

DESCRIPTION

Title of the Invention: DIHYDROOXADIAZINONE COMPOUND AND PHARMACEUTICAL USE THEREOF

5 Technical Field

[0001]

The present invention relates to a dihydrooxadiazinone compound or a pharmaceutically acceptable salt thereof having a phospholipase D (hereinafter to be referred to as "PLD")
10 inhibitory activity, a pharmaceutical composition comprising the same, and a pharmaceutical use thereof, and the like.

Background Art

[0002]

Three important factors for thrombus formation are said
15 to be changes in blood components, changes in properties of vascular wall, and changes in blood flow. Arterial blood flow is laminar, faster in the center and slower near the vascular wall. The shear stress generated by this velocity difference exerts a strong influence on platelets flowing near the
20 vascular wall, and enhances the platelet aggregation ability. Thrombus formation in arteries is largely triggered by arteriosclerotic plaque rupture. The reaction of the platelet membrane receptor with collagen in the subendothelial tissue exposed with arteriosclerotic plaque rupture, or von Willebrand
25 factor (vWF) adhering to the collagen, triggers platelet activation signalling, which in turn causes platelet aggregation, thereby initiating thrombus formation. Thus, platelet aggregation initiated at the site of plaque rupture in coronary arteries and cerebral arteries may cause rapid
30 thrombotic occlusion, resulting in the development of myocardial infarction and stroke. At the site of atherosclerotic stenosis, and the like, where these pathologies are thought to occur, it is assumed that extremely high shear stress is generated. Recent studies using an in vitro flow
35 chamber incorporating a blood flow environment have revealed

that platelet adhesion and aggregation mechanisms differ depending on the shear stress. Under high shear stress, platelet adhesion and aggregation reactions proceed by mechanisms completely different from the classical concepts
5 established in conventional static systems and closed stirring experimental systems (Non-Patent Documents 1, 2, 3 and 4).
[0003]

The primary role of thrombus formation in vivo is a hemostatic mechanism to prevent blood leakage. As the first
10 step in hemostatic mechanism, platelets adhere to the site of damaged vascular wall (primary hemostasis). The next step following platelet adhesion is platelet aggregation reaction. Platelets firmly adhering to the damaged vascular wall capture and combine with platelets supplied through the bloodstream one
15 after another, resulting in spatial growth of the platelet thrombus. There are many factors that activate platelets and induce platelet aggregation. Regardless of the type of triggering factor, the final reaction is cross-linking of platelets to each other by binding of fibrinogen or vWF to
20 activated integrin $\alpha\text{IIb}\beta 3$ (glycoprotein GPIIb/IIIa, GPIIb/IIIa) on the platelet membrane. Since all of existing anti-platelet drugs represented by aspirin and clopidogrel have an action of inhibiting signals leading to platelet activation and impairing the primary hemostatic function, the drugs carry a bleeding
25 risk as an extension of their anti-thrombotic action (Non-Patent Document 5). As mentioned above, thrombus formation at the site of atheromatous stenosis may be mainly caused by platelet adhesion and aggregation due to high shear stress. Therefore, drugs that can inhibit only platelet aggregation
30 reaction under high shear stress are expected to have a lower bleeding risk than existing drugs.

[0004]

PLD1 and PLD2 are known as major isoforms of PLD. PLD1 is encoded by the gene of the same name, and its expression has
35 been confirmed throughout the human body. PLD1 is a

phospholipid-metabolizing enzyme that hydrolyzes a biomembrane-constituting phospholipid, phosphatidylcholine (PC) to produce phosphatidic acid (PA). Since PA produced by PLD1 acts as a signaling molecule, PLD1 is thought to regulate various cellular functions via PA. In addition, PLD2 exists as an enzyme that hydrolyzes PC into PA and choline in cells like PLD1. PLD2 is also encoded by the gene of the same name, and its expression has also been confirmed throughout the human body. PLD activity confirmed in mammalian cells and tissues is thought to be due to these PLD1 and PLD2 (Non-Patent Document 6).

[0005]

As a result of phenotypic analysis using PLD1 knockout mice, it was clarified that the mice exhibit an anti-thrombotic effect without showing a bleeding risk. In addition, as a result of phenotypic analysis using PLD1/2 dual knockout mice, it was shown that, in addition to the phenotype of PLD1 knockout mice, they also have an inhibitory effect on α -granule secretion from platelets. As a result of analysis using these mouse-derived platelets, it was shown that suppression of PLD1 and PLD2 inhibits platelet aggregation under high shear stress, but does not affect platelet aggregation induced by soluble agonists, which are shown to inhibit by existing anti-platelet drugs (Non-Patent Documents 7 and 8).

[0006]

Both PLD1 and PLD2 are reported to contribute to various phenomena such as cell proliferation, survival, metabolism, migration and membrane fusion (Non-Patent Documents 9, 10 and 11). Activation of PLD1 and PLD2 is thought to contribute to multiple pathologies including cancers (Non-Patent Documents 12 and 13), and their expression and increased activity have been detected in various human cancers in the colon, breast, stomach, thyroid, brain, kidney, uterine smooth muscle and the like (Non-Patent Documents 11, 12 and 13). In addition, there are many reports that PLD1 and PLD2 enzymes are directly

involved in transformation and tumorigenesis in various cancer types such as breast cancer, ovarian cancer, lung cancer, colorectal cancer, kidney cancer, pancreatic cancer, prostate cancer, and brain tumor (Non-Patent Documents 11, 12 and 13).

5 In studies using PLD1 and PLD2 knockout mice and their respective inhibitors, it has been confirmed that the growth of tumor tissue is suppressed (Non-Patent Documents 13 and 14).
[0007]

In view of the above, PLD inhibitors are considered to be
10 therapeutic agents (e.g., drugs for secondary prevention, drugs for relapse prevention, drugs for exacerbation prevention, etc.) or prophylactic agents for thrombosis (e.g., arterial thrombosis, acute coronary syndrome, stable angina, unstable angina, non-ST elevation myocardial infarction, ST elevation
15 myocardial infarction, ischemic stroke, non-cardioembolic stroke, atherosclerotic stroke, cryptogenic stroke, embolic stroke of undetermined source (ESUS), lacunar stroke, transient ischemic attack, peripheral arterial disease, etc.), and thrombosis during perioperative and postoperative periods
20 associated with revascularization (coronary artery bypass graft, percutaneous coronary intervention, carotid endarterectomy, carotid artery stenting, thrombolysis, lower extremity revascularization, etc.) or aortic valve replacement (surgical aortic valve replacement, transcatheter aortic valve
25 replacement, etc.). Moreover, PLD inhibitors are also considered to be useful as therapeutic agents for cancers (e.g., breast cancer, ovarian cancer, lung cancer, colorectal cancer, kidney cancer, pancreatic cancer, prostate cancer, brain tumor, etc.).

30 Document List

Non-Patent Document

[0008]

[Non-Patent Document 1] Cell. 1996 Jan 26; 84(2): 289-297

[Non-Patent Document 2] J Thromb Haemost. 2014; 12(3): 418-420

35 [Non-Patent Document 3] Nat Med. 2009 Jun; 15(6): 665-673

[Non-Patent Document 4] The Journal of Japanese College of Angiology. 2011; 51(3): 275-281

[Non-Patent Document 5] Thromb Haemost. 2010 Jun; 103(6):1128-1135

5 [Non-Patent Document 6] Chem Rev. 2011 Oct 12;111(10):6064-119.

[Non-Patent Document 7] Sci Signal. 2010 Jan 5; 3(103): ra1

[Non-Patent Document 8] J Thromb Haemost. 2012 Nov;10(11):2361-72

[Non-Patent Document 9] J Biol Chem. 2014 Aug 15; 289(33):

10 22567-22574

[Non-Patent Document 10] J Biol Chem. 2014 Aug 15;289(33):22557-22566.

[Non-Patent Document 11] J Biol Chem. 2014; 289(33): 22575-22582

15 [Non-Patent Document 12] Pharmacol Rev. 2014 Oct; 66(4): 1033-1079

[Non-Patent Document 13] Nat Rev Drug Discov. 2017 May; 16(5):351-367

[Non-Patent Document 14] Adv Biol Regul. 2018 Jan;67:134-140.

20 **Summary of Invention**

[0009]

The present invention provides a dihydrooxadiazinone compound or a pharmaceutically acceptable salt thereof having a PLD inhibitory activity, a pharmaceutical composition
25 comprising the same, and a pharmaceutical use thereof.

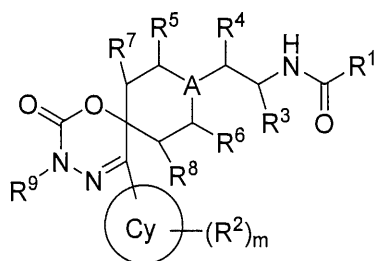
Accordingly, the present invention includes the embodiments exemplified below.

[0010]

[Item 1]

30 A compound represented by Formula [I] or a pharmaceutically acceptable salt thereof:

[0011]



[I]

[0012]

wherein

A is CR¹⁰ or N;

5 Cy is

(1) C₆₋₁₀ aryl,

(2) 5- or 6-membered heteroaryl containing one or two nitrogen atoms as a ring constituting atom, besides carbon atom, or

(3) a 9- or 10-membered partially unsaturated fused cyclic group containing one or two oxygen atoms as a ring constituting atom, besides carbon atom;

R¹ is

(1) C₁₋₆ alkyl wherein the alkyl is optionally substituted by

(a) hydroxy,

15 (b) cyano,

(c) SO₂R¹¹ wherein R¹¹ is C₁₋₄ alkyl, or

(d) NHCOR¹² wherein R¹² is C₁₋₄ alkyl,

(2) C₂₋₄ alkenyl wherein the alkenyl is optionally substituted by NR¹³R¹⁴ wherein R¹³ and R¹⁴ are each independently hydrogen or

20 C₁₋₄ alkyl,

(3) C₁₋₄ haloalkyl,

(4) C₁₋₆ alkoxy wherein the alkoxy is optionally substituted by phenyl,

(5) NR¹⁵R¹⁶ wherein R¹⁵ and R¹⁶ are each independently

25 (a) hydrogen,

(b) C₁₋₄ alkyl wherein the alkyl is optionally substituted by

(i) phenyl wherein the phenyl is optionally substituted by halogen, or

(ii) pyridyl,

- (c) C₁₋₄ alkoxy, or
- (d) C₃₋₄ cycloalkyl,
- (6) COR¹⁷ wherein R¹⁷ is C₁₋₄ alkyl,
- (7) CONR¹⁸R¹⁹ wherein R¹⁸ and R¹⁹ are each independently
 - 5 (a) hydrogen,
 - (b) C₁₋₄ alkyl,
 - (c) C₃₋₄ cycloalkyl, or
 - (d) C₅₋₈ bridged cycloalkyl,
- (8) C₃₋₄ cycloalkyl wherein the cycloalkyl is optionally
 - 10 substituted by
 - (a) hydroxy,
 - (b) halogen, or
 - (c) phenyl,
 - (9) 4 to 7-membered heterocycloalkyl containing one or two
 - 15 heteroatoms selected from the group consisting of nitrogen and oxygen atoms as a ring constituting atom, besides carbon atom, wherein the heterocycloalkyl is optionally substituted by
 - (a) hydroxy,
 - (b) oxo,
 - 20 (c) NR²⁰R²¹ wherein R²⁰ and R²¹ are each independently hydrogen or C₁₋₄ alkyl, or
 - (d) phenyl,
 - (10) 6 to 11-membered spiro heterocycloalkyl containing one or two heteroatoms selected from the group consisting of nitrogen and oxygen atoms as a ring constituting atom, besides carbon
 - 25 atom,
 - (11) phenyl wherein the phenyl is optionally substituted by one or two halogens,
 - (12) 5 to 10-membered heteroaryl containing 1 to 3 heteroatoms
 - 30 selected from the group consisting of nitrogen and oxygen atoms as a ring constituting atom, besides carbon atom, wherein the heteroaryl is optionally substituted by one or two R²², or
 - (13) a 8 to 10-membered saturated or partially unsaturated fused cyclic group containing 1 to 4 heteroatoms selected from
 - 35 the group consisting of nitrogen and oxygen atoms as a ring

constituting atom, besides carbon atom, wherein the fused cyclic group is optionally substituted by C₁₋₄ haloalkyl; R² in the number of m are each independently

- (1) hydroxy,
- 5 (2) cyano,
- (3) halogen,
- (4) C₁₋₆ alkyl wherein the alkyl is optionally substituted by
 - (a) hydroxy, or
 - (b) C₃₋₄ cycloalkyl,
- 10 (5) C₂₋₄ alkenyl wherein the alkenyl is optionally substituted by C₁₋₄ alkoxy,
- (6) C₁₋₄ haloalkyl,
- (7) C₁₋₄ alkoxy wherein the alkoxy is optionally substituted by 1 to 3 substituents selected from the group consisting of
 - 15 (a) hydroxy, and
 - (b) halogen,
- (8) SR²³ wherein R²³ is C₁₋₄ alkyl,
- (9) COR²⁴ wherein R²⁴ is hydroxy or C₁₋₄ alkyl,
- (10) CONR²⁵R²⁶ wherein R²⁵ and R²⁶ are each independently
 - 20 (a) hydrogen,
 - (b) C₁₋₆ alkyl, or
 - (c) C₃₋₄ cycloalkyl,
- (11) SO₂R²⁷ wherein R²⁷ is C₁₋₆ alkyl,
- (12) C₃₋₄ cycloalkyl,
- 25 (13) 4 to 7-membered heterocycloalkyl containing one or two heteroatoms selected from the group consisting of nitrogen and oxygen atoms as a ring constituting atom, besides carbon atom, wherein the heterocycloalkyl is optionally substituted by one or two substituents selected from the group consisting of
 - 30 (a) halogen,
 - (b) C₁₋₄ alkyl, and
 - (c) C₁₋₄ haloalkyl,
- (14) 5 to 9-membered bridged heterocycloalkyl containing one or two heteroatoms selected from the group consisting of nitrogen

and oxygen atoms as a ring constituting atom, besides carbon atom,

(15) 6 to 11-membered spiro heterocycloalkyl containing one or two heteroatoms selected from the group consisting of nitrogen and oxygen atoms as a ring constituting atom, besides carbon atom, or

(16) phenyl;

R³, R⁴, R⁵ and R⁶ are each independently hydrogen or C₁₋₄ alkyl; R⁷ and R⁸ are both hydrogens, or R⁷ and R⁸ are bonded to each other to form a cyclopentane ring together with the carbon atoms to which they are bonded;

R⁹ is hydrogen or CONHR²⁸ wherein R²⁸ is C₃₋₄ cycloalkyl;

R¹⁰ is

(1) hydrogen,

(2) hydroxy, or

(3) halogen;

one or two R²² are each independently

(1) halogen,

(2) C₁₋₄ alkyl,

(3) C₁₋₄ haloalkyl,

(4) C₁₋₄ alkoxy,

(5) NHCOR²⁹ wherein R²⁹ is C₁₋₄ alkyl, or

(6) SO₂R³⁰ wherein R³⁰ is C₁₋₄ alkyl; and

m is 0, 1, 2 or 3.

[0013]

[Item 2]

The compound according to Item 1 or a pharmaceutically acceptable salt thereof, wherein R⁹ is hydrogen.

[0014]

[Item 3]

The compound according to Item 1 or 2, or a pharmaceutically acceptable salt thereof, wherein A is N.

[0015]

[Item 4]

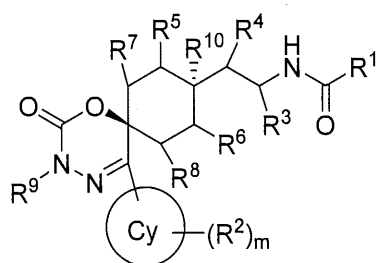
The compound according to Item 1 or 2, or a pharmaceutically acceptable salt thereof, wherein A is CR¹⁰ wherein R¹⁰ is as defined in Item 1.

[0016]

5 [Item 5]

The compound according to Item 4, or a pharmaceutically acceptable salt thereof, which is represented by Formula [II]:

[0017]



[II]

10 [0018]

wherein

Cy, R¹, R², R³, R⁴, R⁵, R⁶, R⁷, R⁸, R⁹, R¹⁰ and m are as defined in Item 1.

[0019]

15 [Item 6]

The compound according to any one of Items 1 to 5, or a pharmaceutically acceptable salt thereof, wherein R³ is C₁₋₄ alkyl.

[0020]

20 [Item 7]

A pharmaceutical composition comprising a compound as defined in any one of Items 1 to 6, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

25 [0021]

[Item 8]

A PLD1 inhibitor comprising a compound as defined in any one of Items 1 to 6, or a pharmaceutically acceptable salt thereof.

[0022]

[Item 9]

An agent for the treatment or prophylaxis of a disease selected from the group consisting of thrombosis and cancer,
5 comprising a compound as defined in any one of Items 1 to 6, or a pharmaceutically acceptable salt thereof.

[0023]

[Item 10]

A method for inhibiting PLD1 in a mammal, comprising
10 administering a therapeutically effective amount of a compound as defined in any one of Items 1 to 6, or a pharmaceutically acceptable salt thereof to the mammal.

[0024]

[Item 11]

15 A method for treating or preventing a disease selected from the group consisting of thrombosis and cancer in a mammal, comprising administering a therapeutically effective amount of a compound as defined in any one of Items 1 to 6, or a pharmaceutically acceptable salt thereof to the mammal.

20 [0025]

[Item 12]

Use of a compound as defined in any one of Items 1 to 6, or a pharmaceutically acceptable salt thereof, for the manufacture of a PLD1 inhibitor.

25 [0026]

[Item 13]

Use of a compound as defined in any one of Items 1 to 6, or a pharmaceutically acceptable salt thereof, for the manufacture of an agent for the treatment or prophylaxis of a
30 disease selected from the group consisting of thrombosis and cancer.

[0027]

[Item 14]

A compound as defined in any one of Items 1 to 6, or a pharmaceutically acceptable salt thereof, for use in the inhibition of PLD1.

[0028]

5 [Item 15]

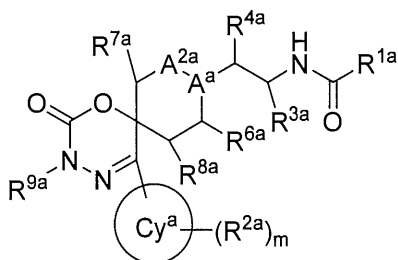
A compound as defined in any one of Items 1 to 6, or a pharmaceutically acceptable salt thereof, for use in the treatment or prophylaxis of a disease selected from the group consisting of thrombosis and cancer.

10 [0029]

[Item 1a]

A compound represented by Formula [Ia] or a pharmaceutically acceptable salt thereof:

[0030]



15 [Ia]

[0031]

wherein

A^a is CR^{10a} or N;

A^{2a} is CR^{5a} or O;

20 Cy^a is

(1) C₆₋₁₀ aryl,

(2) 5 to 10-membered heteroaryl containing one or two nitrogen atoms as a ring constituting atom, besides carbon atom, or

(3) a 9- or 10-membered partially unsaturated fused cyclic group containing one or two oxygen atoms as a ring constituting atom, besides carbon atom;

R^{1a} is

(1) C₁₋₆ alkyl wherein the alkyl is optionally substituted by

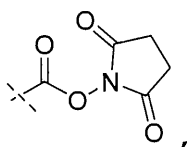
(a) hydroxy,

- (b) cyano,
- (c) SO_2R^{11} wherein R^{11} is C_{1-4} alkyl, or
- (d) NHCOR^{12} wherein R^{12} is C_{1-4} alkyl,

(2) C_{2-4} alkenyl wherein the alkenyl is optionally substituted
 5 by 1 to 3 of

- (a) $\text{NR}^{13}\text{R}^{14}$ wherein R^{13} and R^{14} are each independently hydrogen or C_{1-4} alkyl,
- (b) halogen,
- (c) COR^{35a} wherein R^{35a} is hydroxy or C_{1-4} alkoxy,
- 10 (d) $\text{CONR}^{36a}\text{R}^{37a}$ wherein R^{36a} and R^{37a} are each independently hydrogen or C_{1-4} alkyl, or
- (e) a partial structural formula:

[0032]



15 [0033]

- (3) C_{1-4} haloalkyl wherein the haloalkyl is optionally substituted by hydroxy,
- (4) C_{1-6} alkoxy wherein the alkoxy is optionally substituted by phenyl,
- 20 (5) $\text{NR}^{15}\text{R}^{16}$ wherein R^{15} and R^{16} are each independently
 - (a) hydrogen,
 - (b) C_{1-4} alkyl wherein the alkyl is optionally substituted by
 - (i) phenyl wherein the phenyl is optionally substituted by halogen, or
 - 25 (ii) pyridyl,
 - (c) C_{1-4} alkoxy, or
 - (d) C_{3-4} cycloalkyl,
- (6) COR^{17a} wherein R^{17a} is C_{1-4} alkyl or hydroxy,
- (7) $\text{CONR}^{18a}\text{R}^{19a}$ wherein R^{18a} and R^{19a} are each independently
 - 30 (a) hydrogen,
 - (b) C_{1-4} alkyl wherein the alkyl is optionally substituted by hydroxy,
 - (c) C_{3-4} cycloalkyl,

- (d) C₅₋₈ bridged cycloalkyl,
 - (e) C₁₋₄ haloalkyl, or
 - (f) C₁₋₄ alkoxy,
- 5 (8) C₃₋₄ cycloalkyl wherein the cycloalkyl is optionally substituted by
- (a) hydroxy,
 - (b) halogen, or
 - (c) phenyl,
- 10 (9) 4 to 7-membered heterocycloalkyl containing one or two heteroatoms selected from the group consisting of nitrogen and oxygen atoms as a ring constituting atom, besides carbon atom, wherein the heterocycloalkyl is optionally substituted by
- (a) hydroxy,
 - (b) oxo,
 - 15 (c) NR²⁰R²¹ wherein R²⁰ and R²¹ are each independently hydrogen or C₁₋₄ alkyl, or
 - (d) phenyl,
- (10) 6 to 11-membered spiro heterocycloalkyl containing one or two heteroatoms selected from the group consisting of nitrogen
- 20 and oxygen atoms as a ring constituting atom, besides carbon atom,
- (11) phenyl wherein the phenyl is optionally substituted by one or two of
- (a) halogen, or
 - 25 (b) C₁₋₄ haloalkyl,
- (12) 5 to 10-membered heteroaryl containing 1 to 3 heteroatoms selected from the group consisting of nitrogen and oxygen atoms as a ring constituting atom, besides carbon atom, wherein the heteroaryl is optionally substituted by one or two R^{22a},
- 30 (13) a 8 to 10-membered saturated or partially unsaturated fused cyclic group containing 1 to 4 heteroatoms selected from the group consisting of nitrogen and oxygen atoms as a ring constituting atom, besides carbon atom, wherein the fused cyclic group is optionally substituted by C₁₋₄ haloalkyl, or

(14) a 5 to 7-membered partially unsaturated cyclic group containing one or two nitrogen atoms as a ring constituting atom, besides carbon atom, wherein the partially unsaturated cyclic group is optionally substituted by an oxo group and C₁₋₄ alkyl;

R^{2a} in the number of m are each independently

- (1) hydroxy,
- (2) cyano,
- (3) halogen,
- 10 (4) C₁₋₆ alkyl wherein the alkyl is optionally substituted by
 - (a) hydroxy, or
 - (b) C₃₋₄ cycloalkyl,
- (5) C₂₋₄ alkenyl wherein the alkenyl is optionally substituted by C₁₋₄ alkoxy,
- 15 (6) C₁₋₄ haloalkyl,
- (7) C₁₋₄ alkoxy wherein the alkoxy is optionally substituted by 1 to 3 substituents selected from the group consisting of
 - (a) hydroxy, and
 - (b) halogen,
- 20 (8) SR^{23a} wherein R^{23a} is C₁₋₄ alkyl or C₁₋₄ haloalkyl,
- (9) COR^{24a} wherein R^{24a} is
 - (a) hydroxy,
 - (b) C₁₋₄ alkyl, or
 - (c) C₁₋₄ alkoxy,
- 25 (10) CONR^{25a}R^{26a} wherein R^{25a} and R^{26a} are each independently
 - (a) hydrogen,
 - (b) C₁₋₆ alkyl, or
 - (c) C₃₋₄ cycloalkyl, or

R^{25a} and R^{26a} are bonded to each other to form 4 to 7-membered heterocycloalkyl together with the nitrogen atom to which they are bonded, wherein the heterocycloalkyl contains one or two heteroatoms selected from the group consisting of nitrogen and oxygen atoms as a ring constituting atom, besides carbon atom, and is optionally substituted by one or two halogens,

35 (11) SO₂R²⁷ wherein R²⁷ is C₁₋₆ alkyl,

- (12) C₃₋₄ cycloalkyl,
- (13) 4 to 7-membered heterocycloalkyl containing one or two heteroatoms selected from the group consisting of nitrogen and oxygen atoms as a ring constituting atom, besides carbon atom,
5 wherein the heterocycloalkyl is optionally substituted by one or two substituents selected from the group consisting of
- (a) halogen,
 - (b) C₁₋₄ alkyl, and
 - (c) C₁₋₄ haloalkyl,
- 10 (14) 5 to 9-membered bridged heterocycloalkyl containing one or two heteroatoms selected from the group consisting of nitrogen and oxygen atoms as a ring constituting atom, besides carbon atom,
- (15) 6 to 11-membered spiro heterocycloalkyl containing one or
15 two heteroatoms selected from the group consisting of nitrogen and oxygen atoms as a ring constituting atom, besides carbon atom, or
- (16) phenyl;
- R^{3a} is
- 20 (1) hydrogen,
- (2) C₁₋₄ alkyl, or
- (3) C₁₋₄ haloalkyl;
- R^{4a} is
- (1) hydrogen,
- 25 (2) C₁₋₄ alkyl, or
- (3) cyano;
- R^{5a} is hydrogen or C₁₋₄ alkyl;
- the combination of R^{6a}, R^{7a} and R^{8a} is
- (1) a combination where R^{6a} is hydrogen or C₁₋₄ alkyl, and R^{7a}
30 and R^{8a} are both hydrogens,
- (2) a combination where R^{6a} is hydrogen or C₁₋₄ alkyl, and R^{7a} and R^{8a} are bonded to each other to form a cyclopentane ring together with the spiro carbon atom and the carbon atoms to which they are bonded, or

(3) a combination where R^{6a} and R^{7a} are bonded to each other to form a cyclopentane ring together with the spiro carbon atom and the carbon atoms to which they are bonded, and R^{8a} is hydrogen;

5 R^{9a} is

- (1) hydrogen,
- (2) CONHR²⁸ wherein R²⁸ is C₃₋₄ cycloalkyl, or
- (3) C₁₋₄ alkyl;

R^{10a} is

10 (1) hydrogen,

(2) hydroxy,

(3) halogen,

(4) C₁₋₄ alkyl,

(5) cyano, or

15 (6) C₁₋₄ alkoxy;

one or two R^{22a} are each independently

(1) halogen,

(2) C₁₋₄ alkyl,

(3) C₁₋₄ haloalkyl,

20 (4) C₁₋₄ alkoxy,

(5) NHCOR²⁹ wherein R²⁹ is C₁₋₄ alkyl,

(6) SO₂R³⁰ wherein R³⁰ is C₁₋₄ alkyl,

(7) cyano, or

(8) C₃₋₄ cycloalkyl; and

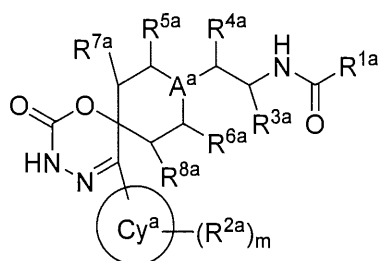
25 m is 0, 1, 2 or 3.

[0034]

[Item 2a]

The compound according to Item 1a or a pharmaceutically acceptable salt thereof, which is represented by Formula [IIa]:

30 [0035]



[IIa]

[0036]

wherein

A^a, Cy^a, R^{1a}, R^{2a}, R^{3a}, R^{4a}, R^{5a}, R^{6a}, R^{7a}, R^{8a} and m are as defined
 5 in Item 1a.

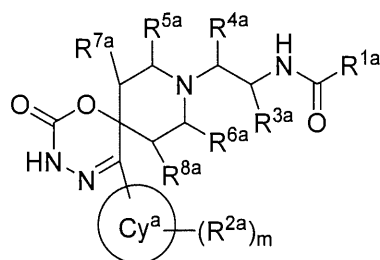
[0037]

[Item 3a]

The compound according to Item 1a or a pharmaceutically
 acceptable salt thereof, which is represented by Formula

10 [IIIa]:

[0038]



[IIIa]

[0039]

wherein

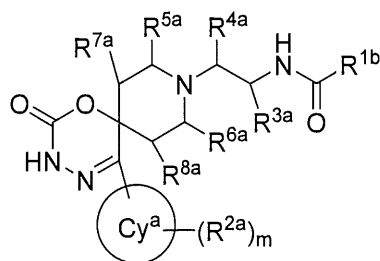
15 Cy^a, R^{1a}, R^{2a}, R^{3a}, R^{4a}, R^{5a}, R^{6a}, R^{7a}, R^{8a} and m are as defined in
 Item 1a.

[0040]

[Item 4a]

The compound according to Item 1a or a pharmaceutically
 20 acceptable salt thereof, which is represented by Formula [IVa]:

[0041]



[IVa]

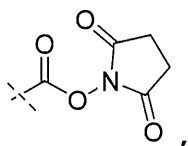
[0042]

wherein

R^{1b} is

- 5 (1) C₁₋₆ alkyl wherein the alkyl is optionally substituted by
 - (a) hydroxy,
 - (b) cyano,
 - (c) SO₂R¹¹ wherein R¹¹ is C₁₋₄ alkyl, or
 - (d) NHCOR¹² wherein R¹² is C₁₋₄ alkyl,
- 10 (2) C₂₋₄ alkenyl wherein the alkenyl is optionally substituted by 1 to 3 of
 - (a) NR¹³R¹⁴ wherein R¹³ and R¹⁴ are each independently hydrogen or C₁₋₄ alkyl,
 - (b) halogen,
 - 15 (c) COR^{35a} wherein R^{35a} is hydroxy or C₁₋₄ alkoxy,
 - (d) CONR^{36a}R^{37a} wherein R^{36a} and R^{37a} are each independently hydrogen or C₁₋₄ alkyl, or
 - (e) a partial structural formula:

[0043]



[0044]

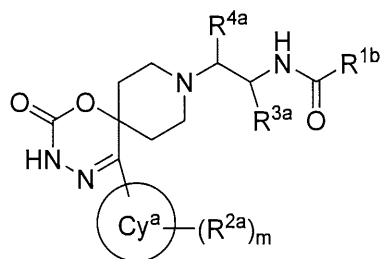
- (3) C₁₋₆ alkoxy wherein the alkoxy is optionally substituted by phenyl,
- (4) NR¹⁵R¹⁶ wherein R¹⁵ and R¹⁶ are each independently
 - 25 (a) hydrogen,
 - (b) C₁₋₄ alkyl wherein the alkyl is optionally substituted by

(i) phenyl wherein the phenyl is optionally substituted by halogen, or
(ii) pyridyl,
(c) C₁₋₄ alkoxy, or
5 (d) C₃₋₄ cycloalkyl,
(5) CONR^{18a}R^{19a} wherein R^{18a} and R^{19a} are each independently
(a) hydrogen,
(b) C₁₋₄ alkyl wherein the alkyl is optionally substituted by hydroxy,
10 (c) C₃₋₄ cycloalkyl,
(d) C₅₋₈ bridged cycloalkyl,
(e) C₁₋₄ haloalkyl, or
(f) C₁₋₄ alkoxy,
(6) 6 to 11-membered spiro heterocycloalkyl containing one or
15 two heteroatoms selected from the group consisting of nitrogen and oxygen atoms as a ring constituting atom, besides carbon atom,
(7) 5 to 10-membered heteroaryl containing 1 to 3 heteroatoms selected from the group consisting of nitrogen and oxygen atoms
20 as a ring constituting atom, besides carbon atom, wherein the heteroaryl is optionally substituted by one or two R^{22a},
(8) a 8 to 10-membered saturated or partially unsaturated fused cyclic group containing 1 to 4 heteroatoms selected from the group consisting of nitrogen and oxygen atoms as a ring
25 constituting atom, besides carbon atom, wherein the fused cyclic group is optionally substituted by C₁₋₄ haloalkyl, or
(9) a 5 to 7-membered partially unsaturated cyclic group containing one or two nitrogen atoms as a ring constituting atom, besides carbon atom, wherein the partially unsaturated
30 cyclic group is optionally substituted by an oxo group and C₁₋₄ alkyl; and
Cy^a, R^{2a}, R^{3a}, R^{4a}, R^{5a}, R^{6a}, R^{7a}, R^{8a}, R^{22a} and m are as defined in Item 1a.

[0045]

35 [Item 5a]

The compound according to Item 4a or a pharmaceutically acceptable salt thereof, which is represented by Formula [Va]:
[0046]



[Va]

5 [0047]

wherein

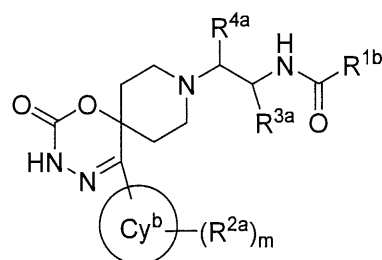
Cy^a, R^{2a}, R^{3a}, R^{4a} and m are as defined in Item 1a; and

R^{1b} is as defined in Item 4a.

[0048]

10 [Item 6a]

The compound according to Item 4a or a pharmaceutically acceptable salt thereof, which is represented by Formula [VIa]:
[0049]



[VIa]

15 [0050]

wherein

Cy^b is

(1) C₆₋₁₀ aryl, or

(2) 5- or 6-membered heteroaryl containing one or two nitrogen

20 atoms as a ring constituting atom, besides carbon atom;

R^{1b} is as defined in Item 4a; and

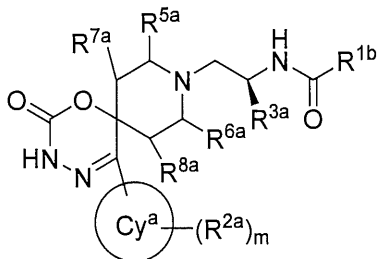
R^{2a}, R^{3a}, R^{4a} and m are as defined in Item 1a.

[0051]

[Item 7a]

The compound according to Item 4a or a pharmaceutically acceptable salt thereof, which is represented by Formula [VIIa]:

[0052]



[VIIa]

[0053]

wherein

Cy^a , R^{2a} , R^{3a} , R^{5a} , R^{6a} , R^{7a} , R^{8a} and m are as defined in Item 1a;

and

R^{1b} is as defined in Item 4a.

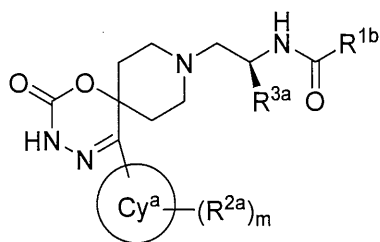
[0054]

[Item 8a]

The compound according to Item 4a or a pharmaceutically acceptable salt thereof, which is represented by Formula

[VIIIa]:

[0055]



[VIIIa]

[0056]

wherein

Cy^a , R^{2a} , R^{3a} and m are as defined in Item 1a; and

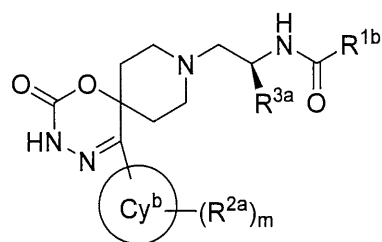
R^{1b} is as defined in Item 4a.

[0057]

[Item 9a]

The compound according to Item 6a or a pharmaceutically acceptable salt thereof, which is represented by Formula [IXa]:

[0058]



[IXa]

[0059]

wherein

5 Cy^b is as defined in Item 6a;

R^{1b} is as defined in Item 4a; and

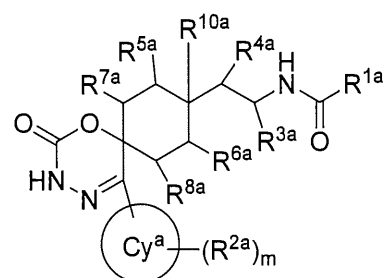
R^{2a}, R^{3a} and m are as defined in Item 1a.

[0060]

[Item 10a]

10 The compound according to Item 1a or a pharmaceutically acceptable salt thereof, which is represented by Formula [Xa]:

[0061]



[Xa]

[0062]

15 wherein

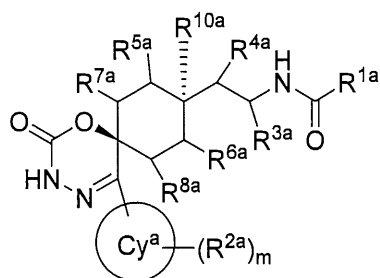
Cy^a, R^{1a}, R^{2a}, R^{3a}, R^{4a}, R^{5a}, R^{6a}, R^{7a}, R^{8a}, R^{10a} and m are as defined in Item 1a.

[0063]

[Item 11a]

20 The compound according to Item 1a or a pharmaceutically acceptable salt thereof, which is represented by Formula [XIa]:

[0064]



[XIa]

[0065]

wherein

Cy^a, R^{1a}, R^{2a}, R^{3a}, R^{4a}, R^{5a}, R^{6a}, R^{7a}, R^{8a}, R^{10a} and m are as
 5 defined in Item 1a.

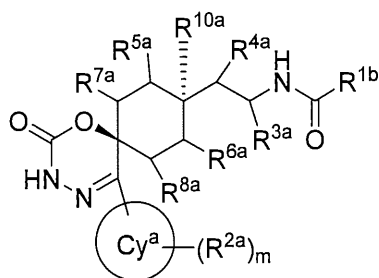
[0066]

[Item 12a]

The compound according to Item 1a or a pharmaceutically
 acceptable salt thereof, which is represented by Formula

10 [XIIa]:

[0067]



[XIIa]

[0068]

wherein

15 R^{1b} is

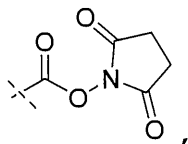
- (1) C₁₋₆ alkyl wherein the alkyl is optionally substituted by
 - (a) hydroxy,
 - (b) cyano,
 - (c) SO₂R¹¹ wherein R¹¹ is C₁₋₄ alkyl, or

20 (d) NHCOR¹² wherein R¹² is C₁₋₄ alkyl,

- (2) C₂₋₄ alkenyl wherein the alkenyl is optionally substituted
 by 1 to 3 of

- (a) $\text{NR}^{13}\text{R}^{14}$ wherein R^{13} and R^{14} are each independently hydrogen or C_{1-4} alkyl,
- (b) halogen,
- (c) $\text{COR}^{35\text{a}}$ wherein $\text{R}^{35\text{a}}$ is hydroxy or C_{1-4} alkoxy,
- 5 (d) $\text{CONR}^{36\text{a}}\text{R}^{37\text{a}}$ wherein $\text{R}^{36\text{a}}$ and $\text{R}^{37\text{a}}$ are each independently hydrogen or C_{1-4} alkyl, or
- (e) a partial structural formula:

[0069]



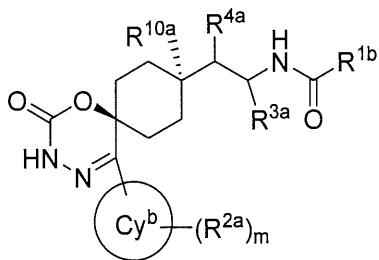
10 [0070]

- (3) C_{1-6} alkoxy wherein the alkoxy is optionally substituted by phenyl,
- (4) $\text{NR}^{15}\text{R}^{16}$ wherein R^{15} and R^{16} are each independently
 - (a) hydrogen,
 - 15 (b) C_{1-4} alkyl wherein the alkyl is optionally substituted by
 - (i) phenyl wherein the phenyl is optionally substituted by halogen, or
 - (ii) pyridyl,
 - (c) C_{1-4} alkoxy, or
 - 20 (d) C_{3-4} cycloalkyl,
- (5) $\text{CONR}^{18\text{a}}\text{R}^{19\text{a}}$ wherein $\text{R}^{18\text{a}}$ and $\text{R}^{19\text{a}}$ are each independently
 - (a) hydrogen,
 - (b) C_{1-4} alkyl wherein the alkyl is optionally substituted by hydroxy,
 - 25 (c) C_{3-4} cycloalkyl,
 - (d) C_{5-8} bridged cycloalkyl,
 - (e) C_{1-4} haloalkyl, or
 - (f) C_{1-4} alkoxy,
- (6) 6 to 11-membered spiro heterocycloalkyl containing one or
 - 30 two heteroatoms selected from the group consisting of nitrogen and oxygen atoms as a ring constituting atom, besides carbon atom,

The compound according to Item 12a or a pharmaceutically acceptable salt thereof, which is represented by Formula

[XIVa]:

[0075]



[XIVa]

[0076]

wherein

Cy^b is

(1) C₆₋₁₀ aryl, or

(2) 5- or 6-membered heteroaryl containing one or two nitrogen atoms as a ring constituting atom, besides carbon atom;

R^{1b} is as defined in Item 12a; and

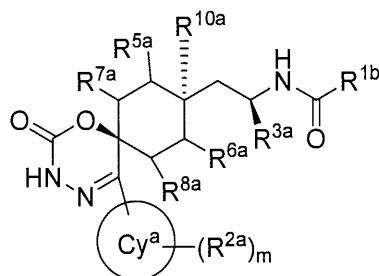
R^{2a}, R^{3a}, R^{4a}, R^{10a} and m are as defined in Item 1a.

[0077]

[Item 15a]

The compound according to Item 12a or a pharmaceutically acceptable salt thereof, which is represented by Formula [XVa]:

[0078]



[XVa]

[0079]

wherein

Cy^a, R^{2a}, R^{3a}, R^{5a}, R^{6a}, R^{7a}, R^{8a}, R^{10a} and m are as defined in Item 1a; and

R^{1b} is as defined in Item 12a.

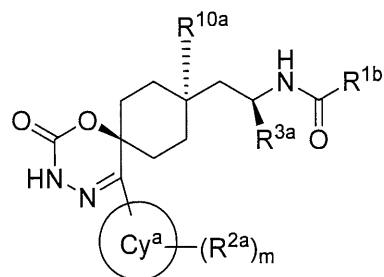
[0080]

[Item 16a]

The compound according to Item 12a or a pharmaceutically
5 acceptable salt thereof, which is represented by Formula

[XVIa]:

[0081]



[XVIa]

[0082]

10 wherein

Cy^a, R^{2a}, R^{3a}, R^{10a} and m are as defined in Item 1a; and

R^{1b} is as defined in Item 12a.

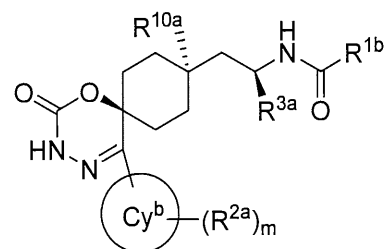
[0083]

[Item 17a]

15 The compound according to Item 14a or a pharmaceutically
acceptable salt thereof, which is represented by Formula

[XVIIa]:

[0084]



[XVIIa]

20 [0085]

wherein

Cy^b is as defined in Item 14a;

R^{1b} is as defined in Item 12a; and

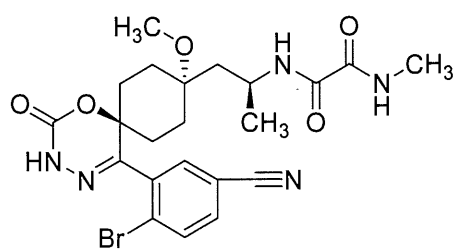
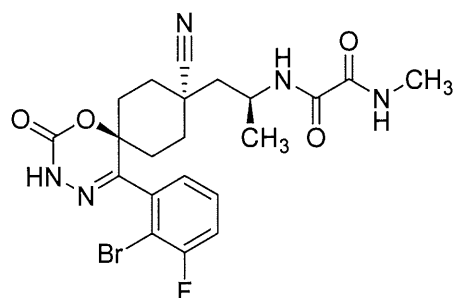
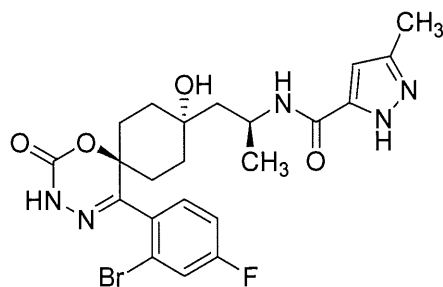
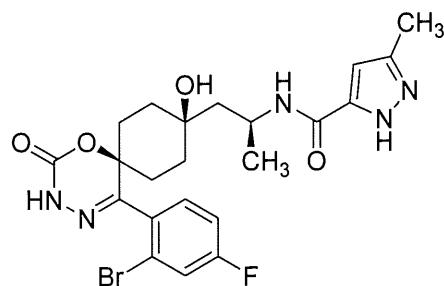
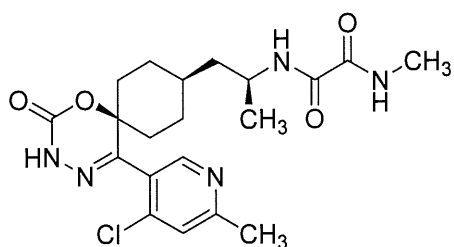
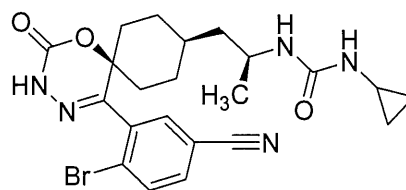
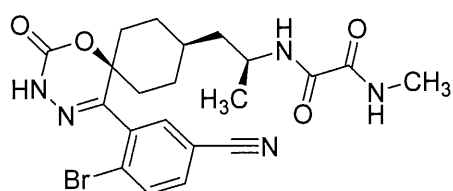
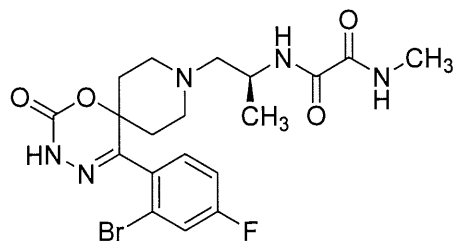
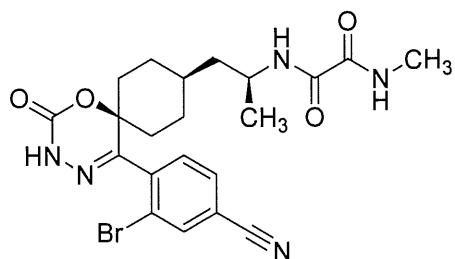
R^{2a}, R^{3a}, R^{10a} and m are as defined in Item 1a.

[0086]

[Item 18a]

A compound selected from the group consisting of compounds represented by the following formulae:

5 [0087]



and

[0088]

or a pharmaceutically acceptable salt thereof.

[0089]

[Item 19a]

5 A pharmaceutical composition comprising a compound as defined in any one of Items 1a to 18a, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

[0090]

[Item 20a]

10 A pharmaceutical composition comprising a compound as defined in any one of Items 1a to 18a, or a pharmaceutically acceptable salt thereof, in combination with one or more other drugs, and a pharmaceutically acceptable carrier.

[0091]

15 [Item 21a]

A PLD inhibitor comprising a compound as defined in any one of Items 1a to 18a, or a pharmaceutically acceptable salt thereof.

[0092]

20 [Item 22a]

A PLD1 inhibitor comprising a compound as defined in any one of Items 1a to 18a, or a pharmaceutically acceptable salt thereof.

[0093]

25 [Item 23a]

A PLD1/2 inhibitor comprising a compound as defined in any one of Items 1a to 18a, or a pharmaceutically acceptable salt thereof.

[0094]

30 [Item 24a]

An agent for the treatment or prophylaxis of a disease selected from the group consisting of thrombosis and cancer, comprising a compound as defined in any one of Items 1a to 18a, or a pharmaceutically acceptable salt thereof.

35 [0095]

[Item 25a]

An agent for the treatment or prophylaxis of a disease selected from the group consisting of thrombosis and cancer, comprising a compound as defined in any one of Items 1a to 18a,
5 or a pharmaceutically acceptable salt thereof, in combination with one or more other drugs.

[0096]

[Item 26a]

A method for inhibiting PLD in a mammal, comprising
10 administering a therapeutically effective amount of a compound as defined in any one of Items 1a to 18a, or a pharmaceutically acceptable salt thereof to the mammal.

[0097]

[Item 27a]

15 A method for inhibiting PLD1 in a mammal, comprising administering a therapeutically effective amount of a compound as defined in any one of Items 1a to 18a, or a pharmaceutically acceptable salt thereof to the mammal.

[0098]

20 [Item 28a]

A method for inhibiting PLD1/2 in a mammal, comprising administering a therapeutically effective amount of a compound as defined in any one of Items 1a to 18a, or a pharmaceutically acceptable salt thereof to the mammal.

25 [0099]

[Item 29a]

A method for treating or preventing a disease selected from the group consisting of thrombosis and cancer in a mammal, comprising administering a therapeutically effective amount of
30 a compound as defined in any one of Items 1a to 18a, or a pharmaceutically acceptable salt thereof to the mammal.

[0100]

[Item 30a]

A method for treating or preventing a disease selected
35 from the group consisting of thrombosis and cancer in a mammal,

comprising administering a therapeutically effective amount of a compound as defined in any one of Items 1a to 18a, or a pharmaceutically acceptable salt thereof, in combination with one or more other drugs, to the mammal.

5 [0101]

[Item 31a]

Use of a compound as defined in any one of Items 1a to 18a, or a pharmaceutically acceptable salt thereof, for the manufacture of a PLD inhibitor.

10 [0102]

[Item 32a]

Use of a compound as defined in any one of Items 1a to 18a, or a pharmaceutically acceptable salt thereof, for the manufacture of a PLD1 inhibitor.

15 [0103]

[Item 33a]

Use of a compound as defined in any one of Items 1a to 18a, or a pharmaceutically acceptable salt thereof, for the manufacture of a PLD1/2 inhibitor.

20 [0104]

[Item 34a]

Use of a compound as defined in any one of Items 1a to 18a, or a pharmaceutically acceptable salt thereof, for the manufacture of an agent for the treatment or prophylaxis of a
25 disease selected from the group consisting of thrombosis and cancer.

[0105]

[Item 35a]

Use of a compound as defined in any one of Items 1a to
30 18a, or a pharmaceutically acceptable salt thereof, in combination with one or more other drugs, for the manufacture of an agent for the treatment or prophylaxis of a disease selected from the group consisting of thrombosis and cancer.

[0106]

35 [Item 36a]

A compound as defined in any one of Items 1a to 18a, or a pharmaceutically acceptable salt thereof, for use in the inhibition of PLD.

5 [0107]

[Item 37a]

A compound as defined in any one of Items 1a to 18a, or a pharmaceutically acceptable salt thereof, for use in the inhibition of PLD1.

10 [0108]

[Item 38a]

A compound as defined in any one of Items 1a to 18a, or a pharmaceutically acceptable salt thereof, for use in the inhibition of PLD1/2.

15 [0109]

[Item 39a]

A compound as defined in any one of Items 1a to 18a, or a pharmaceutically acceptable salt thereof, for use in the treatment or prophylaxis of a disease selected from the group
20 consisting of thrombosis and cancer.

[0110]

[Item 40a]

A compound as defined in any one of Items 1a to 18a, or a pharmaceutically acceptable salt thereof, in combination with
25 one or more other drugs, for use in the treatment or prophylaxis of a disease selected from the group consisting of thrombosis and cancer.

Effect of the Invention

[0111]

30 Since the compound represented by Formula [I] or Formula [Ia] or a pharmaceutically acceptable salt thereof of the present invention has a PLD inhibitory activity, it may be useful for the treatment or prophylaxis of thrombosis and cancer.

35 **Embodiments of the Invention**

[0112]

The definitions of the terms used herein are as follows.

[0113]

Examples of the "halogen" include fluorine, chlorine,
5 bromine and iodine.

[0114]

The "C₁₋₄ alkyl" means a linear or branched saturated hydrocarbon group having 1 to 4 carbon atoms. Examples of the "C₁₋₄ alkyl" include methyl, ethyl, n-propyl, isopropyl, n-
10 butyl, sec-butyl, isobutyl, and tert-butyl. The preferred "C₁₋₄ alkyl" are methyl, ethyl, n-propyl, n-butyl, isobutyl, and tert-butyl.

[0115]

The "C₁₋₆ alkyl" means a linear or branched saturated
15 hydrocarbon group having 1 to 6 carbon atoms. Examples of the "C₁₋₆ alkyl" include methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, tert-butyl, n-pentyl, isopentyl, neo-pentyl, 1,1-dimethylpropyl, 1,2-dimethylpropyl, 1-ethylpropyl, n-hexyl, isohexyl, 1-ethyl-2-methylpropyl, and
20 3,3-dimethylbutyl. The preferred "C₁₋₆ alkyl" are methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, and tert-butyl.

[0116]

The "C₂₋₄ alkenyl" means a linear or branched hydrocarbon group having 2 to 4 carbon atoms and a carbon-carbon double
25 bond. Examples of the "C₂₋₄ alkenyl" include vinyl, allyl, prop-1-en-1-yl, prop-1-en-2-yl, 2-methylprop-1-ene-yl, but-3-en-1-yl, but-2-en-1-yl, and but-2-en-2-yl. The preferred "C₂₋₄ alkenyl" are vinyl, prop-1-en-1-yl, and 2-methylprop-1-ene-yl.

[0117]

30 The "C₁₋₄ haloalkyl" means the above-mentioned "C₁₋₄ alkyl" substituted by 1 to 5 halogen independently selected from the group consisting of the above-mentioned "halogen". Examples of the "C₁₋₄ haloalkyl" include monofluoromethyl, difluoromethyl, trifluoromethyl, 2-fluoroethyl, 2-chloroethyl, 2-bromoethyl,
35 1,1-difluoroethyl, 1-fluoro-1-methylethyl, 2,2-difluoroethyl,

2,2,2-trifluoroethyl, pentafluoroethyl, 3,3,3-trifluoropropyl, and 4,4,4-trifluorobutyl. The preferred "C₁₋₄ haloalkyl" are difluoromethyl, trifluoromethyl, 2,2-difluoroethyl, 2,2,2-trifluoroethyl, and 3,3,3-trifluoropropyl.

5 [0118]

The "C₁₋₄ alkoxy" means a group wherein the above-mentioned "C₁₋₄ alkyl" is bonded to an oxygen atom. Examples of the "C₁₋₄ alkoxy" include methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, sec-butoxy, isobutoxy, and tert-butoxy.

10 The preferred "C₁₋₄ alkoxy" are methoxy, ethoxy, n-propoxy, isobutoxy, and tert-butoxy.

[0119]

The "C₁₋₆ alkoxy" means a group wherein the above-mentioned "C₁₋₆ alkyl" is bonded to an oxygen atom. Examples of
15 the "C₁₋₆ alkoxy" include methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, sec-butoxy, isobutoxy, tert-butoxy, n-pentyloxy, (3-methylbutan-2-yl)oxy, and n-hexyloxy. The preferred "C₁₋₆ alkoxy" are methoxy, ethoxy, n-propoxy, isobutoxy, and tert-butoxy.

20 [0120]

The "C₃₋₄ cycloalkyl" means a monocyclic saturated hydrocarbon group having 3 or 4 carbon atoms. Examples of the "C₃₋₄ cycloalkyl" include cyclopropyl, and cyclobutyl. The preferred "C₃₋₄ cycloalkyl" is cyclopropyl.

25 [0121]

The "C₅₋₈ bridged cycloalkyl" means a 5 to 8-membered bridged cyclic saturated hydrocarbon group. Examples of the "C₅₋₈ bridged cycloalkyl" include bicyclo[1.1.1]pentyl, bicyclo[2.2.1]heptyl, and bicyclo[2.2.2]octyl. The preferred
30 "C₅₋₈ bridged cycloalkyl" is bicyclo[1.1.1]pentyl.

[0122]

The "C₆₋₁₀ aryl" means an aromatic hydrocarbon group having 6 to 10 carbon atoms. Examples of the "C₆₋₁₀ aryl" include phenyl and naphthyl. The preferred "C₆₋₁₀ aryl" is
35 phenyl.

[0123]

The "4 to 7-membered heterocycloalkyl containing one or two heteroatoms selected from the group consisting of nitrogen and oxygen atoms as a ring constituting atom, besides carbon atom" means a 4 to 7-membered saturated heterocyclic group containing one or two of nitrogen and oxygen atoms as a ring constituting atom, besides carbon atom. Examples of the "4 to 7-membered heterocycloalkyl containing one or two heteroatoms selected from the group consisting of nitrogen and oxygen atoms as a ring constituting atom, besides carbon atom" include azetidiny, oxetanyl, pyrrolidinyl, tetrahydrofuryl, piperidyl, tetrahydropyranyl, dioxanyl, piperazinyl, morpholinyl, and azepanyl. The preferred "4 to 7-membered heterocycloalkyl containing one or two heteroatoms selected from the group consisting of nitrogen and oxygen atoms as a ring constituting atom, besides carbon atom" are azetidiny, oxetanyl, pyrrolidinyl, tetrahydrofuryl, piperidyl, dioxanyl, and morpholinyl.

[0124]

The "5 to 9-membered bridged heterocycloalkyl containing one or two heteroatoms selected from the group consisting of nitrogen and oxygen atoms as a ring constituting atom, besides carbon atom" means a 5 to 9-membered bridged heterocyclic group containing one or two of nitrogen and oxygen atoms as a ring constituting atom, besides carbon atom. Examples of the "5 to 9-membered bridged heterocycloalkyl containing one or two heteroatoms selected from the group consisting of nitrogen and oxygen atoms as a ring constituting atom, besides carbon atom" include 6-azabicyclo[3.1.1]heptyl, 7-azabicyclo[2.2.1]heptyl, 3-oxa-6-azabicyclo[3.1.1]heptyl, 2-oxa-5-azabicyclo[2.2.1]heptyl, and 8-oxa-3-azabicyclo[3.2.1]octyl. The preferred "5 to 9-membered bridged heterocycloalkyl containing one or two heteroatoms selected from the group consisting of nitrogen and oxygen atoms as a ring constituting

atom, besides carbon atom" are 2-oxa-5-azabicyclo[2.2.1]heptyl, and 8-oxa-3-azabicyclo[3.2.1]octyl.

[0125]

The "6 to 11-membered spiro heterocycloalkyl containing
5 one or two heteroatoms selected from the group consisting of
nitrogen and oxygen atoms as a ring constituting atom, besides
carbon atom" means a 6 to 11-membered spiro heterocyclic group
containing one or two of nitrogen and oxygen atoms as a ring
constituting atom, besides carbon atom. Examples of the "6 to
10 11-membered spiro heterocycloalkyl containing one or two
heteroatoms selected from the group consisting of nitrogen and
oxygen atoms as a ring constituting atom, besides carbon atom"
include 2-azaspiro[3.3]heptyl, 2-oxa-6-azaspiro[3.3]heptyl, 5-
azaspiro[2.4]heptyl, 4-oxa-7-azaspiro[2.5]octyl, 2,8-
15 diazaspiro[4.5]decyl, and 3-oxa-9-azaspiro[5.5]undecyl. The
preferred "6 to 11-membered spiro heterocycloalkyl containing
one or two heteroatoms selected from the group consisting of
nitrogen and oxygen atoms as a ring constituting atom, besides
carbon atom" are 2-oxa-6-azaspiro[3.3]heptyl, 5-
20 azaspiro[2.4]heptyl, and 4-oxa-7-azaspiro[2.5]octyl.

[0126]

The "5- or 6-membered heteroaryl containing one or two
nitrogen atoms as a ring constituting atom, besides carbon
atom" means a 5- or 6-membered aromatic heterocyclic group
25 containing one or two nitrogen atoms as a ring constituting
atom, besides carbon atom. Examples of the "5- or 6-membered
heteroaryl containing one or two nitrogen atoms as a ring
constituting atom, besides carbon atom" include pyrrolyl,
imidazolyl, pyrazolyl, pyridyl, pyrazinyl, pyrimidinyl and
30 pyridazinyl. The preferred "5- or 6-membered heteroaryl
containing one or two nitrogen atoms as a ring constituting
atom, besides carbon atom" are pyrrolyl, imidazolyl, pyrazolyl,
pyridyl, pyrazinyl, pyrimidinyl, and pyridazinyl.

[0127]

The "5 to 10-membered heteroaryl containing one or two nitrogen atoms as a ring constituting atom, besides carbon atom" means a 5 to 10-membered aromatic heterocyclic group containing one or two nitrogen atoms as a ring constituting atom, besides carbon atom. Examples of the "5 to 10-membered heteroaryl containing one or two nitrogen atoms as a ring constituting atom, besides carbon atom" include pyrrolyl, imidazolyl, pyrazolyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, indolyl, benzimidazolyl, indazolyl, indolizinyl, imidazo[1,2-a]pyridyl, pyrazolo[1,5-a]pyridyl, quinolyl, isoquinolyl, and quinoxalyl. The preferred "5 to 10-membered heteroaryl containing one or two nitrogen atoms as a ring constituting atom, besides carbon atom" are pyrrolyl, imidazolyl, pyrazolyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, and pyrazolo[1,5-a]pyridyl.

[0128]

The "5 to 10-membered heteroaryl containing 1 to 3 heteroatoms selected from the group consisting of nitrogen and oxygen atoms as a ring constituting atom, besides carbon atom" means a 5 to 10-membered aromatic heterocyclic group containing 1 to 3 of nitrogen and oxygen atoms as a ring constituting atom, besides carbon atom. Examples of the "5 to 10-membered heteroaryl containing 1 to 3 heteroatoms selected from the group consisting of nitrogen and oxygen atoms as a ring constituting atom, besides carbon atom" include pyrrolyl, furyl, imidazolyl, pyrazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, oxazolyl, isoxazolyl, 1,2,4-oxadiazolyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, triazinyl, indolyl, benzofuranyl, benzimidazolyl, indazolyl, benzoxazolyl, benzisoxazolyl, indolizinyl, imidazo[1,2-a]pyridyl, pyrazolo[1,5-a]pyridyl, quinolyl, isoquinolyl, and quinoxalyl. The preferred "5 to 10-membered heteroaryl containing 1 to 3 heteroatoms selected from the group consisting of nitrogen and oxygen atoms as a ring constituting atom, besides carbon atom" are pyrrolyl, imidazolyl, pyrazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl,

isoxazolyl, 1,2,4-oxadiazolyl, pyridyl, pyrimidinyl, pyridazinyl, pyrazinyl, indolyl, benzofuranyl, benzimidazolyl, indoliziny, imidazo[1,2-a]pyridyl, and pyrazolo[1,5-a]pyridyl. [0129]

5 The "5 to 7-membered partially unsaturated cyclic group containing one or two nitrogen atoms as a ring constituting atom, besides carbon atom" means a 5 to 7-membered partially unsaturated cyclic group containing one or two nitrogen atoms as a ring constituting atom, besides carbon atom. Examples of
10 the "5 to 7-membered partially unsaturated cyclic group containing one or two nitrogen atoms as a ring constituting atom, besides carbon atom" include dihydropyrrolyl, dihydropyridyl, and dihydropyrimidinyl. The preferred "5 to 7-membered partially unsaturated cyclic group containing one or
15 two nitrogen atoms as a ring constituting atom, besides carbon atom" is dihydropyridyl. [0130]

 The "8 to 10-membered saturated or partially unsaturated fused cyclic group containing 1 to 4 heteroatoms selected from
20 the group consisting of nitrogen and oxygen atoms as a ring constituting atom, besides carbon atom" means a 8 to 10-membered fused heterocyclic group containing 1 to 4 heteroatoms selected from the group consisting of nitrogen and oxygen atoms as a ring constituting atom, besides carbon atom and containing
25 at least one saturated ring as a constituent ring in the fused ring. Examples of the "8 to 10-membered saturated or partially unsaturated fused cyclic group containing 1 to 4 heteroatoms selected from the group consisting of nitrogen and oxygen atoms as a ring constituting atom, besides carbon atom" include
30 octahydro-2H-isoindolyl, dihydrobenzofuranyl, benzo[d][1,3]dioxolyl, isoindolyl, dihydroisoquinolyl, dihydro-1,6-naphthyridinyl, dihydro-1,7-naphthyridinyl, dihydroisoxazolo[4,3-c]pyridyl, dihydropyrazolo[1,5-a]pyrazinyl, and dihydrotriazolo[1,5-a]pyrazinyl. [0131]
35

The "9- or 10-membered partially unsaturated fused cyclic group containing one or two oxygen atoms as a ring constituting atom, besides carbon atom" means a 9- or 10-membered fused heterocyclic group containing one or two oxygen atoms as a ring
5 constituting atom, besides carbon atom, and containing at least one saturated ring as a constituent ring in the fused ring. Examples of the "9- or 10-membered partially unsaturated fused cyclic group containing one or two oxygen atoms as a ring constituting atom, besides carbon atom" include 2,3-
10 dihydrobenzo[b][1,4]dioxiranyl, dihydrobenzofuranyl, and benzo[d][1,3]dioxolyl. The preferred "9- or 10-membered partially unsaturated fused cyclic group containing one or two oxygen atoms as a ring constituting atom, besides carbon atom" are dihydrobenzofuranyl, and benzo[d][1,3]dioxolyl.
15 [0132]

The expression that Substituent α is "optionally substituted" by Substituent β means that Substituent α is unsubstituted, or substituted by Substituent β at any substitutable position thereof (any hydrogen is replaced with
20 Substituent β). For example, the "C₁₋₆ alkyl optionally substituted by hydroxy" means that C₁₋₆ alkyl is unsubstituted, or substituted by hydroxy at any substitutable position thereof.
[0133]

25 Specific embodiments of each substituent of the compound of Formula [I] (hereinafter, also to be referred to as "Compound [I]") and the compound of Formula [Ia] (hereinafter, also to be referred to as "Compound [Ia]") are exemplified below. Each group of Compound [I] and Compound [Ia] is not
30 limited to its specific embodiments, and Compound [I] and Compound [Ia] also includes combinations of two or more embodiments selected appropriately from the specific embodiments of each substituent.

First, specific embodiments of each substituent of
35 Compound [I] are exemplified below.

[0134]

A is preferably CR¹⁰ wherein R¹⁰ is hydrogen, hydroxy, or halogen.

[0135]

5 Cy is preferably

(1) C₆₋₁₀ aryl, or

(2) 5- or 6-membered heteroaryl containing one or two nitrogen atoms as a ring constituting atom, besides carbon atom.

[0136]

10 R³ is preferably C₁₋₄ alkyl.

[0137]

R⁴ is preferably hydrogen.

[0138]

R⁵ is preferably hydrogen.

15 [0139]

R⁶ is preferably hydrogen.

[0140]

R⁷ and R⁸ are preferably both hydrogens.

[0141]

20 R⁹ is preferably hydrogen.

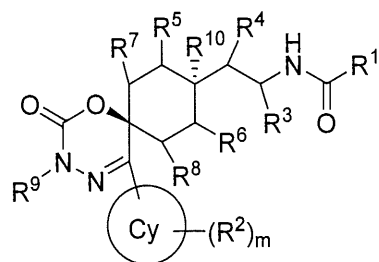
[0142]

m is preferably one or two.

[0143]

One of preferred embodiments of Compound [I] is a
25 compound represented by Formula [II]:

[0144]



[II]

[0145]

wherein

Cy is

- (1) C₆₋₁₀ aryl, or
- (2) 5- or 6-membered heteroaryl containing one or two nitrogen atoms as a ring constituting atom, besides carbon atom;

5 R¹ is

- (1) C₁₋₆ alkyl wherein the alkyl is optionally substituted by
 - (a) hydroxy,
 - (b) cyano,
 - (c) SO₂R¹¹ wherein R¹¹ is C₁₋₄ alkyl, or

10 (d) NHCOR¹² wherein R¹² is C₁₋₄ alkyl,

- (2) C₂₋₄ alkenyl wherein the alkenyl is optionally substituted by NR¹³R¹⁴ wherein R¹³ and R¹⁴ are each independently hydrogen or C₁₋₄ alkyl,

- (3) C₁₋₄ haloalkyl,

15 (4) C₁₋₆ alkoxy wherein the alkoxy is optionally substituted by phenyl,

- (5) NR¹⁵R¹⁶ wherein R¹⁵ and R¹⁶ are each independently

- (a) hydrogen,

- (b) C₁₋₄ alkyl wherein the alkyl is optionally substituted by

20 (i) phenyl wherein the phenyl is optionally substituted by halogen, or

- (ii) pyridyl,

- (c) C₁₋₄ alkoxy, or

- (d) C₃₋₄ cycloalkyl,

25 (6) COR¹⁷ wherein R¹⁷ is C₁₋₄ alkyl,

- (7) CONR¹⁸R¹⁹ wherein R¹⁸ and R¹⁹ are each independently

- (a) hydrogen,

- (b) C₁₋₄ alkyl,

- (c) C₃₋₄ cycloalkyl, or

30 (d) C₅₋₈ bridged cycloalkyl,

- (8) C₃₋₄ cycloalkyl wherein the cycloalkyl is optionally substituted by

- (a) hydroxy,

- (b) halogen, or

35 (c) phenyl,

- (9) 4 to 7-membered heterocycloalkyl containing one or two heteroatoms selected from the group consisting of nitrogen and oxygen atoms as a ring constituting atom, besides carbon atom, wherein the heterocycloalkyl is optionally substituted by
- 5 (a) hydroxy,
(b) oxo,
(c) $\text{NR}^{20}\text{R}^{21}$ wherein R^{20} and R^{21} are each independently hydrogen or C_{1-4} alkyl, or
(d) phenyl,
- 10 (10) 6 to 11-membered spiro heterocycloalkyl containing one or two heteroatoms selected from the group consisting of nitrogen and oxygen atoms as a ring constituting atom, besides carbon atom,
(11) phenyl wherein the phenyl is optionally substituted by one
15 or two halogens,
(12) 5 to 10-membered heteroaryl containing 1 to 3 heteroatoms selected from the group consisting of nitrogen and oxygen atoms as a ring constituting atom, besides carbon atom, wherein the heteroaryl is optionally substituted by one or two R^{22} , or
20 (13) a 8 to 10-membered saturated or partially unsaturated fused cyclic group containing 1 to 4 heteroatoms selected from the group consisting of nitrogen and oxygen atoms as a ring constituting atom, besides carbon atom, wherein the fused cyclic group is optionally substituted by C_{1-4} haloalkyl;
25 R^2 in the number of m are each independently
(1) hydroxy,
(2) cyano,
(3) halogen,
(4) C_{1-6} alkyl wherein the alkyl is optionally substituted by
30 (a) hydroxy, or
(b) C_{3-4} cycloalkyl,
(5) C_{2-4} alkenyl wherein the alkenyl is optionally substituted by C_{1-4} alkoxy,
(6) C_{1-4} haloalkyl,

- (7) C₁₋₄ alkoxy wherein the alkoxy is optionally substituted by 1 to 3 substituents selected from the group consisting of
- (a) hydroxy, and
 - (b) halogen,
- 5 (8) SR²³ wherein R²³ is C₁₋₄ alkyl,
- (9) COR²⁴ wherein R²⁴ is hydroxy or C₁₋₄ alkyl,
- (10) CONR²⁵R²⁶ wherein R²⁵ and R²⁶ are each independently
- (a) hydrogen,
 - (b) C₁₋₆ alkyl, or
 - 10 (c) C₃₋₄ cycloalkyl,
- (11) SO₂R²⁷ wherein R²⁷ is C₁₋₆ alkyl,
- (12) C₃₋₄ cycloalkyl,
- (13) 4 to 7-membered heterocycloalkyl containing one or two heteroatoms selected from the group consisting of nitrogen and
- 15 oxygen atoms as a ring constituting atom, besides carbon atom, wherein the heterocycloalkyl is optionally substituted by one or two substituents selected from the group consisting of
- (a) halogen,
 - (b) C₁₋₄ alkyl, and
 - 20 (c) C₁₋₄ haloalkyl,
- (14) 5 to 9-membered bridged heterocycloalkyl containing one or two heteroatoms selected from the group consisting of nitrogen and oxygen atoms as a ring constituting atom, besides carbon atom,
- 25 (15) 6 to 11-membered spiro heterocycloalkyl containing one or two heteroatoms selected from the group consisting of nitrogen and oxygen atoms as a ring constituting atom, besides carbon atom, or
- (16) phenyl;
- 30 R³ is C₁₋₄ alkyl;
- R⁴, R⁵, R⁶, R⁷, R⁸ and R⁹ are all hydrogen;
- R¹⁰ is
- (1) hydrogen,
 - (2) hydroxy, or
 - 35 (3) halogen;

one or two R²² are each independently

(1) halogen,

(2) C₁₋₄ alkyl,

(3) C₁₋₄ haloalkyl,

5 (4) C₁₋₄ alkoxy,

(5) NHCOR²⁹ wherein R²⁹ is C₁₋₄ alkyl, or

(6) SO₂R³⁰ wherein R³⁰ is C₁₋₄ alkyl; and

m is one or two.

[0146]

10 Preferred specific embodiments of Compound [I] include the compounds of Examples 1 to 339 listed in Table 1-1 to Table 1-43 described later.

[0147]

Next, specific embodiments of each substituent of
15 Compound [Ia] are exemplified below. Compound [Ia] includes Compound [I].

[0148]

A^a is preferably CR^{10a}.

In another embodiment, A^a is preferably N.

20 A^{2a} is preferably CR^{5a}.

[0149]

Cy^a is preferably

(1) C₆₋₁₀ aryl, or

(2) 5- or 6-membered heteroaryl containing one or two nitrogen
25 atoms as a ring constituting atom, besides carbon atom.

[0150]

R^{1a} is preferably

(1) C₁₋₆ alkyl wherein the alkyl is optionally substituted by

(a) hydroxy,

30 (b) cyano,

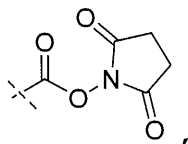
(c) SO₂R¹¹ wherein R¹¹ is C₁₋₄ alkyl, or

(d) NHCOR¹² wherein R¹² is C₁₋₄ alkyl,

(2) C₂₋₄ alkenyl wherein the alkenyl is optionally substituted
by 1 to 3 of

- (a) $\text{NR}^{13}\text{R}^{14}$ wherein R^{13} and R^{14} are each independently hydrogen or C_{1-4} alkyl,
- (b) halogen,
- (c) COR^{35a} wherein R^{35a} is hydroxy or C_{1-4} alkoxy,
- 5 (d) $\text{CONR}^{36a}\text{R}^{37a}$ wherein R^{36a} and R^{37a} are each independently hydrogen or C_{1-4} alkyl, or
- (e) a partial structural formula:

[0151]



10 [0152]

- (3) C_{1-6} alkoxy wherein the alkoxy is optionally substituted by phenyl,
- (4) $\text{NR}^{15}\text{R}^{16}$ wherein R^{15} and R^{16} are each independently
 - (a) hydrogen,
 - 15 (b) C_{1-4} alkyl wherein the alkyl is optionally substituted by
 - (i) phenyl wherein the phenyl is optionally substituted by halogen, or
 - (ii) pyridyl,
 - (c) C_{1-4} alkoxy, or
 - 20 (d) C_{3-4} cycloalkyl,
- (5) $\text{CONR}^{18a}\text{R}^{19a}$ wherein R^{18a} and R^{19a} are each independently
 - (a) hydrogen,
 - (b) C_{1-4} alkyl wherein the alkyl is optionally substituted by hydroxy,
 - 25 (c) C_{3-4} cycloalkyl,
 - (d) C_{5-8} bridged cycloalkyl,
 - (e) C_{1-4} haloalkyl, or
 - (f) C_{1-4} alkoxy,
 - (6) 6 to 11-membered spiro heterocycloalkyl containing one or
 - 30 two heteroatoms selected from the group consisting of nitrogen and oxygen atoms as a ring constituting atom, besides carbon atom,

(7) 5 to 10-membered heteroaryl containing 1 to 3 heteroatoms selected from the group consisting of nitrogen and oxygen atoms as a ring constituting atom, besides carbon atom, wherein the heteroaryl is optionally substituted by one or two R^{22a} wherein
5 each R^{22a} is as defined above,

(8) a 8 to 10-membered saturated or partially unsaturated fused cyclic group containing 1 to 4 heteroatoms selected from the group consisting of nitrogen and oxygen atoms as a ring constituting atom, besides carbon atom, wherein the fused
10 cyclic group is optionally substituted by C_{1-4} haloalkyl, or

(9) a 5 to 7-membered partially unsaturated cyclic group containing one or two nitrogen atoms as a ring constituting atom, besides carbon atom, wherein the partially unsaturated cyclic group is optionally substituted by an oxo group and C_{1-4}
15 alkyl.

[0153]

In another embodiment, R^{1a} is preferably

(1) $NR^{15}R^{16}$ wherein R^{15} and R^{16} are each independently

(a) hydrogen,

20 (b) C_{1-4} alkyl wherein the alkyl is optionally substituted by
(i) phenyl wherein the phenyl is optionally substituted by halogen, or

(ii) pyridyl,

(c) C_{1-4} alkoxy, or

25 (d) C_{3-4} cycloalkyl,

(2) $CONR^{18a}R^{19a}$ wherein R^{18a} and R^{19a} are each independently

(a) hydrogen,

(b) C_{1-4} alkyl wherein the alkyl is optionally substituted by hydroxy,

30 (c) C_{3-4} cycloalkyl,

(d) C_{5-8} bridged cycloalkyl,

(e) C_{1-4} haloalkyl, or

(f) C_{1-4} alkoxy, or

(3) 5 to 10-membered heteroaryl containing 1 to 3 heteroatoms
35 selected from the group consisting of nitrogen and oxygen atoms

as a ring constituting atom, besides carbon atom, wherein the heteroaryl is optionally substituted by one or two R^{22a} wherein each R^{22a} is as defined above.

[0154]

5 R^{2a} in the number of m are each independently preferably

(1) cyano,

(2) halogen, or

(3) C₁₋₆ alkyl wherein the alkyl is optionally substituted by

(a) hydroxy, or

10 (b) C₃₋₄ cycloalkyl.

[0155]

R^{3a} is preferably C₁₋₄ alkyl.

In another embodiment, R^{3a} is preferably methyl.

[0156]

15 R^{4a} is preferably hydrogen.

[0157]

R^{5a} is preferably hydrogen.

[0158]

The combination of R^{6a}, R^{7a} and R^{8a} is preferably

20 (1) a combination where R^{6a} is hydrogen, and R^{7a} and R^{8a} are both hydrogens,

(2) a combination where R^{6a} is hydrogen, and R^{7a} and R^{8a} are bonded to each other to form a cyclopentane ring together with the spiro carbon atom and the carbon atoms to which they are

25 bonded, or

(3) a combination where R^{6a} and R^{7a} are bonded to each other to form a cyclopentane ring together with the spiro carbon atom and the carbon atoms to which they are bonded, and R^{8a} is hydrogen.

30 In another embodiment, R^{6a}, R^{7a} and R^{8a} are preferably all hydrogen.

[0159]

R^{9a} is preferably hydrogen.

[0160]

35 R^{10a} is preferably

- (1) hydrogen,
- (2) hydroxy, or
- (3) cyano.

[0161]

5 One or two R^{2a} are each independently preferably

- (1) halogen,
- (2) C_{1-4} alkyl,
- (3) C_{1-4} haloalkyl,
- (4) C_{1-4} alkoxy,
- 10 (5) $NHCOR^{29}$ wherein R^{29} is C_{1-4} alkyl,
- (6) cyano, or
- (7) C_{3-4} cycloalkyl.

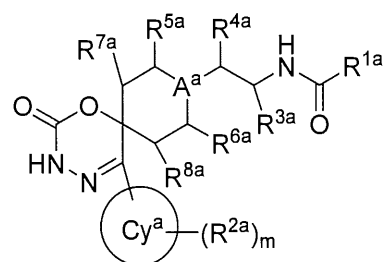
[0162]

m is preferably one or two.

15 [0163]

One of preferred embodiments of Compound [Ia] is a compound represented by Formula [IIa]:

[0164]



[IIa]

20 [0165]

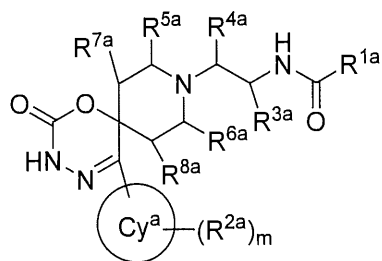
wherein

A^a , Cy^a , R^{1a} , R^{2a} , R^{3a} , R^{4a} , R^{5a} , R^{6a} , R^{7a} , R^{8a} and m are as defined above.

[0166]

25 Another preferred embodiment of Compound [Ia] is a compound represented by Formula [IIIa]:

[0167]



[IIIa]

[0168]

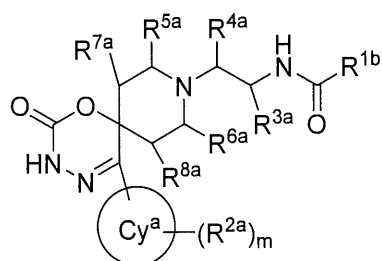
wherein

Cy^a, R^{1a}, R^{2a}, R^{3a}, R^{4a}, R^{5a}, R^{6a}, R^{7a}, R^{8a} and m are as defined
5 above.

[0169]

Another preferred embodiment of Compound [Ia] is a
compound represented by Formula [IVa]:

[0170]



[IVa]

10

[0171]

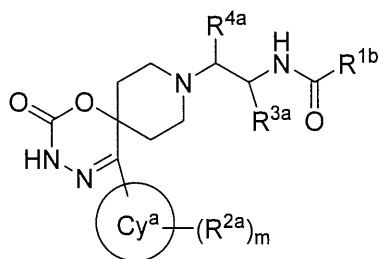
wherein

Cy^a, R^{1b}, R^{2a}, R^{3a}, R^{4a}, R^{5a}, R^{6a}, R^{7a}, R^{8a} and m are as defined
above.

15 [0172]

Another preferred embodiment of Compound [Ia] is a
compound represented by Formula [Va]:

[0173]



[Va]

[0174]

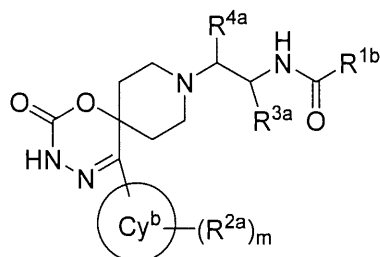
wherein

Cy^a, R^{1b}, R^{2a}, R^{3a}, R^{4a} and m are as defined above.

5 [0175]

Another preferred embodiment of Compound [Ia] is a compound represented by Formula [VIa]:

[0176]



[VIa]

10 [0177]

wherein

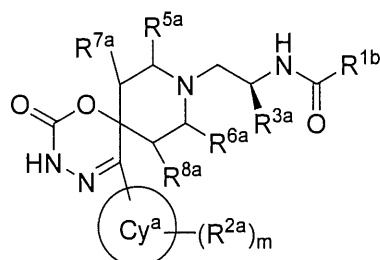
Cy^b, R^{1b}, R^{2a}, R^{3a}, R^{4a} and m are as defined above.

[0178]

Another preferred embodiment of Compound [Ia] is a compound represented by Formula [VIIa]:

15 [0179]

[0179]



[VIIa]

[0180]

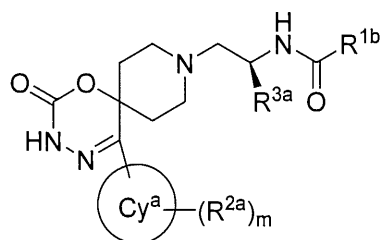
wherein

Cy^a, R^{1b}, R^{2a}, R^{3a}, R^{5a}, R^{6a}, R^{7a}, R^{8a} and m are as defined above.

[0181]

Another preferred embodiment of Compound [Ia] is a compound represented by Formula [VIIIa]:

5 [0182]



[VIIIa]

[0183]

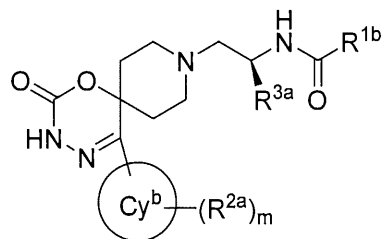
wherein

Cy^a, R^{1b}, R^{2a}, R^{3a} and m are as defined above.

10 [0184]

Another preferred embodiment of Compound [Ia] is a compound represented by Formula [IXa]:

[0185]



[IXa]

15 [0186]

wherein

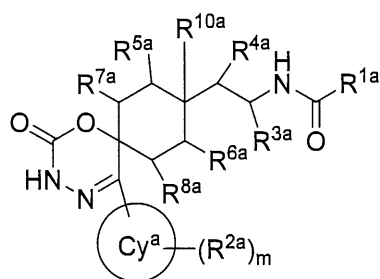
Cy^b, R^{1b}, R^{2a}, R^{3a} and m are as defined above.

[0187]

Another preferred embodiment of Compound [Ia] is a compound represented by Formula [Xa]:

20 [0188]

[0188]



[Xa]

[0189]

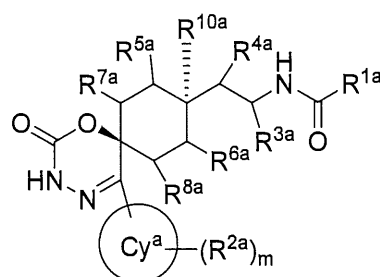
wherein

Cy^a, R^{1a}, R^{2a}, R^{3a}, R^{4a}, R^{5a}, R^{6a}, R^{7a}, R^{8a}, R^{10a} and m are as
5 defined above.

[0190]

Another preferred embodiment of Compound [Ia] is a compound represented by Formula [XIa]:

[0191]



[XIa]

10

[0192]

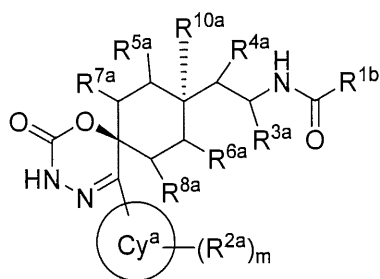
wherein

Cy^a, R^{1a}, R^{2a}, R^{3a}, R^{4a}, R^{5a}, R^{6a}, R^{7a}, R^{8a}, R^{10a} and m are as
defined above.

15 [0193]

Another preferred embodiment of Compound [Ia] is a compound represented by Formula [XIIa]:

[0194]



[XIIa]

[0195]

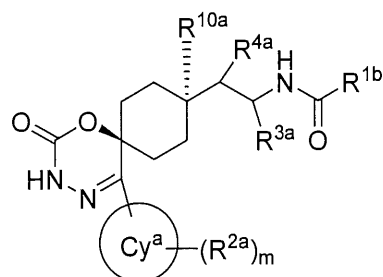
wherein

Cy^a, R^{1b}, R^{2a}, R^{3a}, R^{4a}, R^{5a}, R^{6a}, R^{7a}, R^{8a}, R^{10a} and m are as
 5 defined above.

[0196]

Another preferred embodiment of Compound [Ia] is a
 compound represented by Formula [XIIIa]:

[0197]



[XIIIa]

10

[0198]

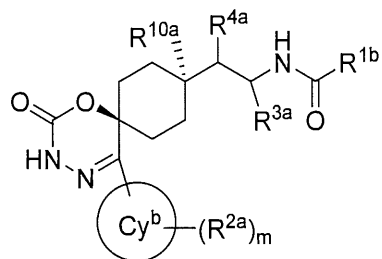
wherein

Cy^a, R^{1b}, R^{2a}, R^{3a}, R^{4a}, R^{10a} and m are as defined above.

[0199]

15 Another preferred embodiment of Compound [Ia] is a
 compound represented by Formula [XIVa]:

[0200]



[XIVa]

[0201]

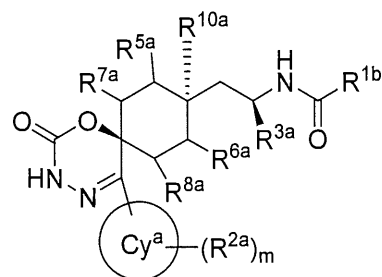
wherein

Cy^b, R^{1b}, R^{2a}, R^{3a}, R^{4a}, R^{10a} and m are as defined above.

5 [0202]

Another preferred embodiment of Compound [Ia] is a compound represented by Formula [XVa]:

[0203]



[XVa]

10 [0204]

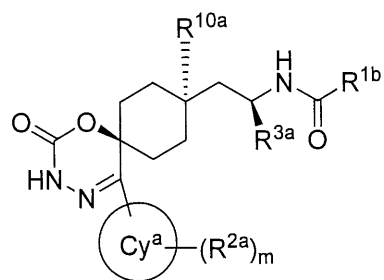
wherein

Cy^a, R^{1b}, R^{2a}, R^{3a}, R^{5a}, R^{6a}, R^{7a}, R^{8a}, R^{10a} and m are as defined above.

[0205]

15 Another preferred embodiment of Compound [Ia] is a compound represented by Formula [XVIa]:

[0206]



[XVIa]

[0207]

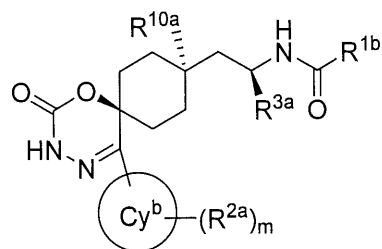
wherein

Cy^a, R^{1b}, R^{2a}, R^{3a}, R^{10a} and m are as defined above.

5 [0208]

Another preferred embodiment of Compound [Ia] is a compound represented by Formula [XVIIa]:

[0209]



[XVIIa]

10 [0210]

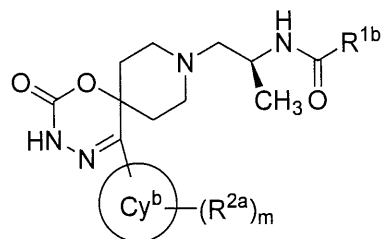
wherein

Cy^b, R^{1b}, R^{2a}, R^{3a}, R^{10a} and m are as defined above.

[0211]

Another preferred embodiment of Compound [Ia] is a compound represented by Formula [XVIIIa]:

[0212]



[XVIIIa]

[0213]

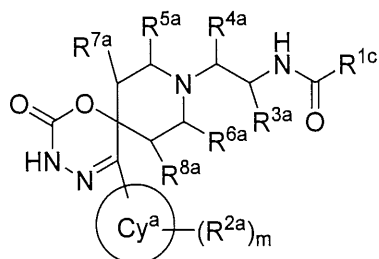
wherein

Cy^b, R^{1b}, R^{2a} and m are as defined above.

[0214]

Another preferred embodiment of Compound [Ia] is a compound represented by Formula [XIXa]:

5 [0215]



[XIXa]

[0216]

wherein

R^{1c} is

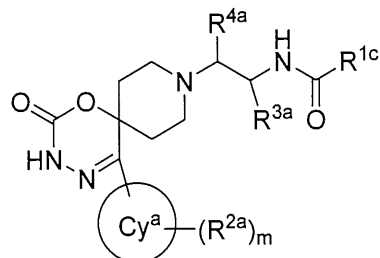
- 10 (1) C₁₋₄ haloalkyl wherein the haloalkyl is optionally substituted by hydroxy,
(2) COR^{17a} wherein R^{17a} is C₁₋₄ alkyl or hydroxy,
(3) C₃₋₄ cycloalkyl wherein the cycloalkyl is optionally substituted by
15 (a) hydroxy,
(b) halogen, or
(c) phenyl,
(4) 4 to 7-membered heterocycloalkyl containing one or two heteroatoms selected from the group consisting of nitrogen and
20 oxygen atoms as a ring constituting atom, besides carbon atom, wherein the heterocycloalkyl is optionally substituted by
(a) hydroxy,
(b) oxo,
(c) NR²⁰R²¹ wherein R²⁰ and R²¹ are each independently
25 hydrogen or C₁₋₄ alkyl, or
(d) phenyl, or
(5) phenyl wherein the phenyl is optionally substituted by one or two of
(a) halogen, or

(b) C₁₋₄ haloalkyl, and
Cy^a, R^{2a}, R^{3a}, R^{4a}, R^{5a}, R^{6a}, R^{7a}, R^{8a} and m are as defined above.

[0217]

Another preferred embodiment of Compound [Ia] is a
5 compound represented by Formula [XXa]:

[0218]



[XXa]

[0219]

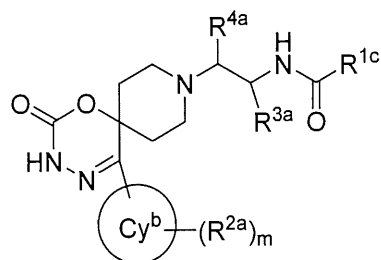
wherein

10 Cy^a, R^{1c}, R^{2a}, R^{3a}, R^{4a} and m are as defined above.

[0220]

Another preferred embodiment of Compound [Ia] is a
compound represented by Formula [XXIa]:

[0221]



[XXIa]

15

[0222]

wherein

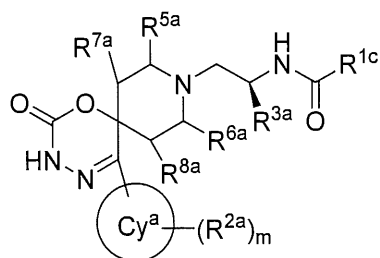
Cy^b, R^{1c}, R^{2a}, R^{3a}, R^{4a} and m are as defined above.

[0223]

20

Another preferred embodiment of Compound [Ia] is a
compound represented by Formula [XXIIa]:

[0224]



[XXIIa]

[0225]

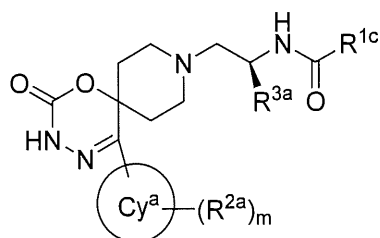
wherein

Cy^a, R^{1c}, R^{2a}, R^{3a}, R^{5a}, R^{6a}, R^{7a}, R^{8a} and m are as defined above.

5 [0226]

Another preferred embodiment of Compound [Ia] is a compound represented by Formula [XXIIIa]:

[0227]



[XXIIIa]

10 [0228]

wherein

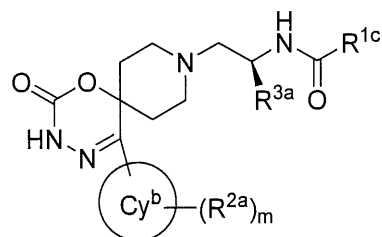
Cy^a, R^{1c}, R^{2a}, R^{3a} and m are as defined above.

[0229]

Another preferred embodiment of Compound [Ia] is a compound represented by Formula [XXIVa]:

15

[0230]



[XXIVa]

[0231]

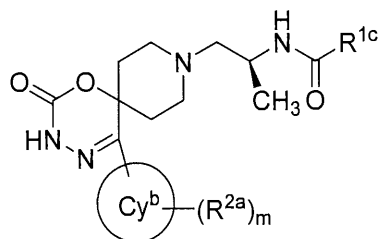
wherein

Cy^b, R^{1c}, R^{2a}, R^{3a} and m are as defined above.

[0232]

Another preferred embodiment of Compound [Ia] is a compound represented by Formula [XXVa]:

5 [0233]



[XXVa]

[0234]

wherein

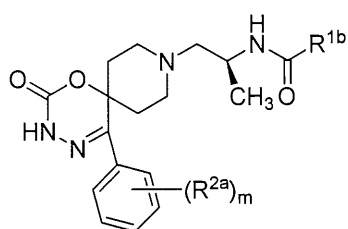
Cy^b, R^{1c}, R^{2a} and m are as defined above.

10 [0235]

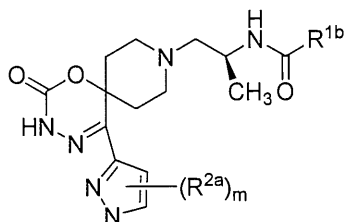
Another preferred embodiment of Compound [Ia] is a compound represented by Formula [XXVIa-1], Formula [XXVIa-2], Formula [XXVIa-3], Formula [XXVIa-4], Formula [XXVIa-5], Formula [XXVIa-6], Formula [XXVIa-7], Formula [XXVIa-8], or

15 Formula [XXVIa-9]:

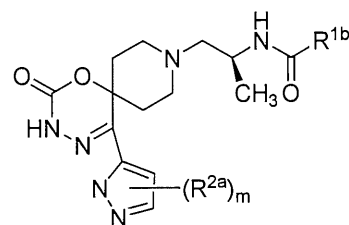
[0236]



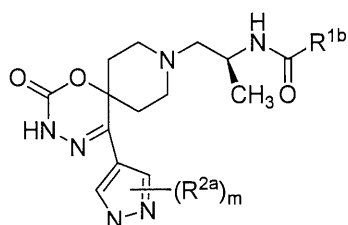
[XXVIa-1]



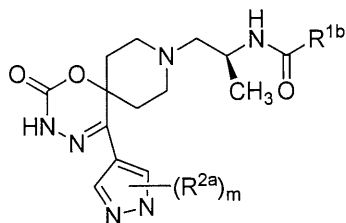
[XXVIa-2]



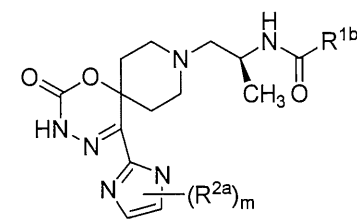
[XXVIa-3]



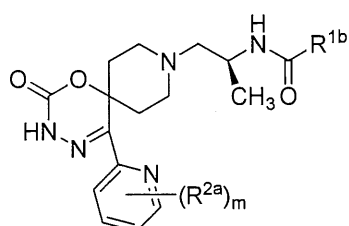
[XXVIa-4]



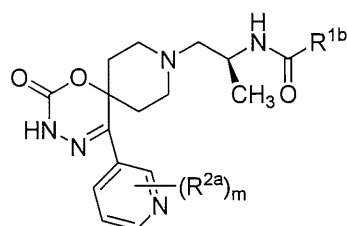
[XXVIa-5]



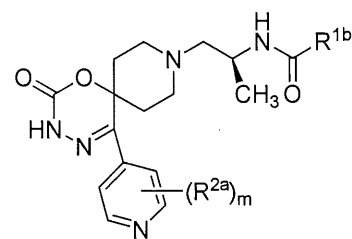
[XXVIa-6]



[XXVIa-7]



[XXVIa-8]



[XXVIa-9]

[0237]

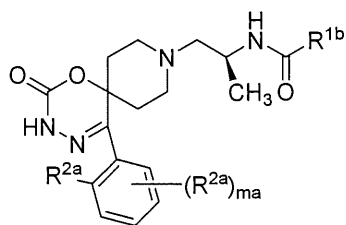
wherein

R^{1b}, R^{2a} and m are as defined above.

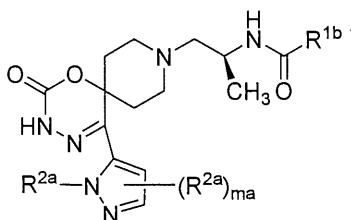
5 [0238]

Another preferred embodiment of Compound [Ia] is a compound represented by Formula [XXVIIa-1], Formula [XXVIIa-2], Formula [XXVIIa-3], Formula [XXVIIa-4], Formula [XXVIIa-5], Formula [XXVIIa-6], Formula, [XXVIIa-7], Formula [XXVIIa-8],
 10 Formula [XXVIIa-9], Formula [XXVIIa-10], or Formula [XXVIIa-11]:

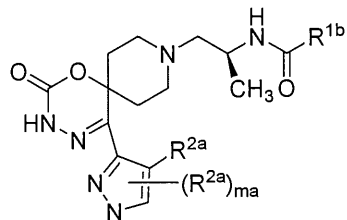
[0239]



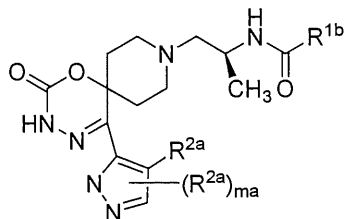
[XXVIIa-1]



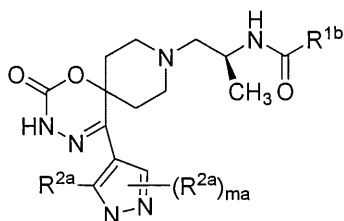
[XXVIIa-2]



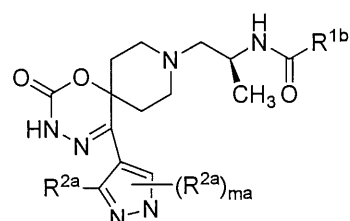
[XXVIIa-3]



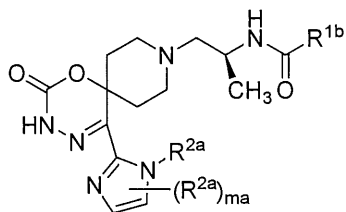
[XXVIIa-4]



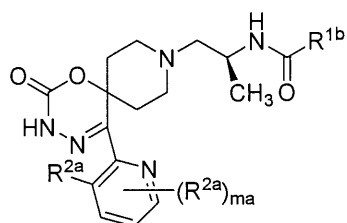
[XXVIIa-5]



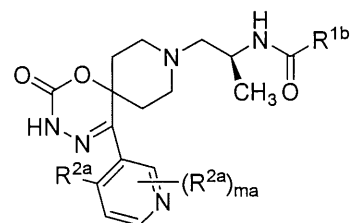
[XXVIIa-6]



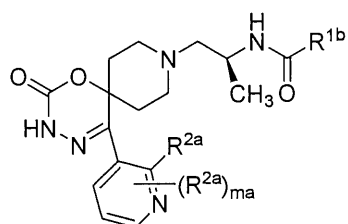
[XXVIIa-7]



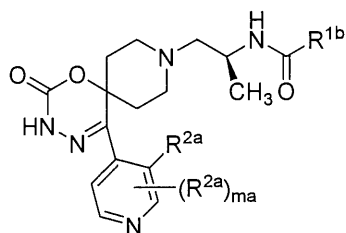
[XXVIIa-8]



[XXVIIa-9]



[XXVIIa-10]



[XXVIIa-11]

[0240]

wherein

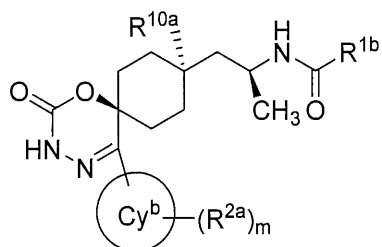
ma is 0, one or two, and

5 R^{1b} and R^{2a} are as defined above.

[0241]

Another preferred embodiment of Compound [Ia] is a compound represented by Formula [XXVIIIa]:

[0242]



[XXVIIIa]

[0243]

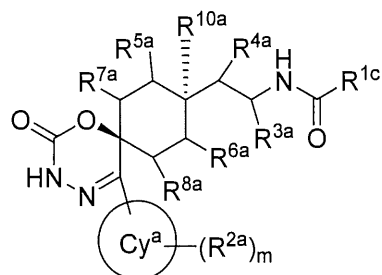
wherein

Cy^b, R^{1b}, R^{2a}, R^{10a} and m are as defined above.

5 [0244]

Another preferred embodiment of Compound [Ia] is a compound represented by Formula [XXIXa]:

[0245]



[XXIXa]

10 [0246]

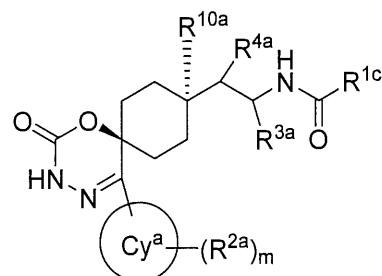
wherein

Cy^a, R^{1c}, R^{2a}, R^{3a}, R^{4a}, R^{5a}, R^{6a}, R^{7a}, R^{8a}, R^{10a} and m are as defined above.

[0247]

15 Another preferred embodiment of Compound [Ia] is a compound represented by Formula [XXXa]:

[0248]



[XXXa]

[0249]

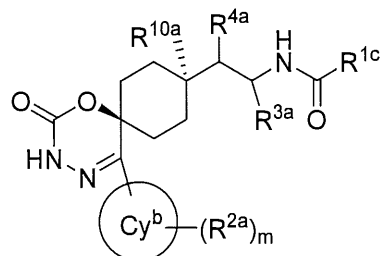
wherein

Cy^a, R^{1c}, R^{2a}, R^{3a}, R^{4a}, R^{10a} and m are as defined above.

[0250]

5 Another preferred embodiment of Compound [Ia] is a compound represented by Formula [XXXIa]:

[0251]



[XXXIa]

[0252]

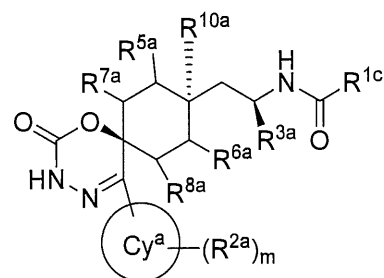
10 wherein

Cy^b, R^{1c}, R^{2a}, R^{3a}, R^{4a}, R^{10a} and m are as defined above.

[0253]

Another preferred embodiment of Compound [Ia] is a compound represented by Formula [XXXIIa]:

15 [0254]



[XXXIIa]

[0255]

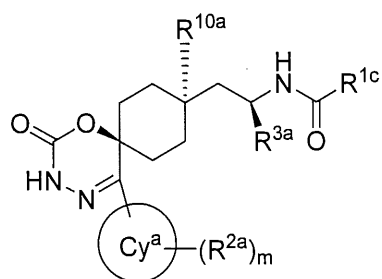
wherein

Cy^a, R^{1c}, R^{2a}, R^{3a}, R^{5a}, R^{6a}, R^{7a}, R^{8a}, R^{10a} and m are as defined
20 above.

[0256]

Another preferred embodiment of Compound [Ia] is a compound represented by Formula [XXXIIIa]:

[0257]



[XXXIIIa]

[0258]

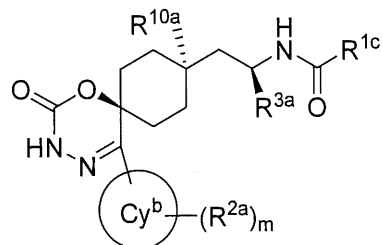
wherein

- 5 Cy^a , R^{1c} , R^{2a} , R^{3a} , R^{10a} and m are as defined above.

[0259]

Another preferred embodiment of Compound [Ia] is a compound represented by Formula [XXXIVa]:

[0260]



[XXXIVa]

10

[0261]

wherein

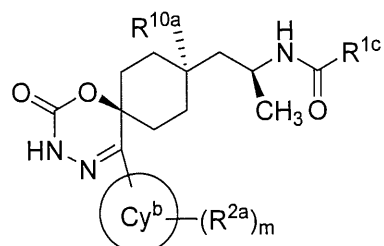
Cy^b , R^{1c} , R^{2a} , R^{3a} , R^{10a} and m are as defined above.

[0262]

15

Another preferred embodiment of Compound [Ia] is a compound represented by Formula [XXXVa]:

[0263]



[XXXVa]

[0264]

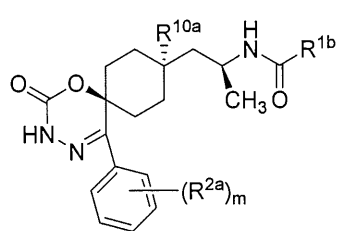
wherein

Cy^b, R^{1c}, R^{2a}, R^{10a} and m are as defined above.

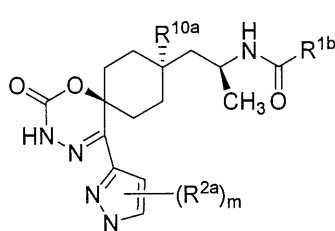
[0265]

5 Another preferred embodiment of Compound [Ia] is a compound represented by Formula [XXXVIa-1], Formula [XXXVIa-2], Formula [XXXVIa-3], Formula [XXXVIa-4], Formula [XXXVIa-5], Formula [XXXVIa-6], Formula [XXXVIa-7], Formula [XXXVIa-8], or Formula [XXXVIa-9]:

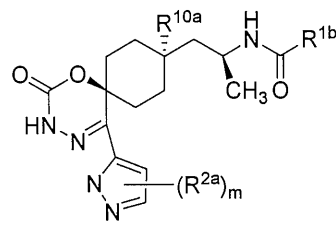
10 [0266]



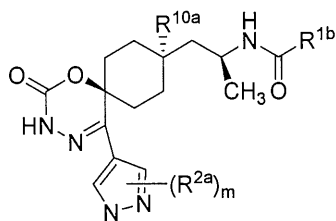
[XXXVIa-1]



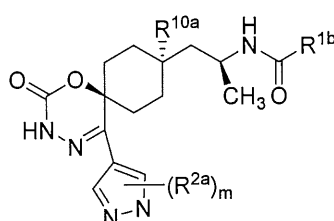
[XXXVIa-2]



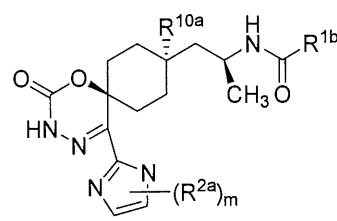
[XXXVIa-3]



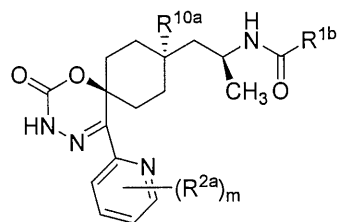
[XXXVIa-4]



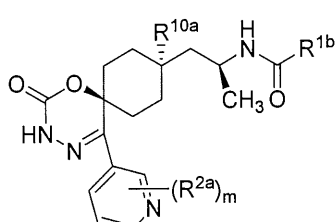
[XXXVIa-5]



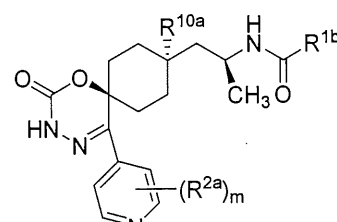
[XXXVIa-6]



[XXXVIa-7]



[XXXVIa-8]



[XXXVIa-9]

[0267]

wherein

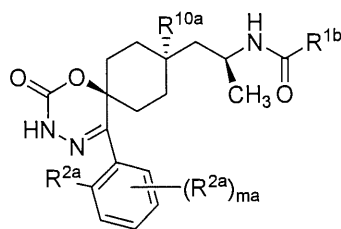
R^{1b}, R^{2a}, R^{10a} and m are as defined above.

15 [0268]

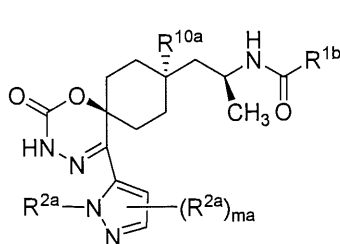
Another preferred embodiment of Compound [Ia] is a compound represented by Formula [XXXVIIa-1], Formula [XXXVIIa-

2], Formula [XXXVIIa-3], Formula [XXXVIIa-4], Formula [XXXVIIa-5], Formula [XXXVIIa-6], Formula [XXXVIIa-7], Formula [XXXVIIa-8], Formula [XXXVIIa-9], Formula [XXXVIIa-10], or Formula [XXXVIIa-11]:

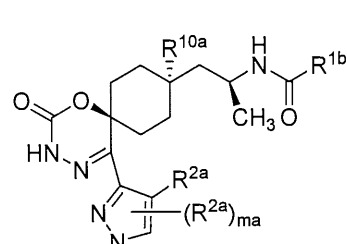
5 [0269]



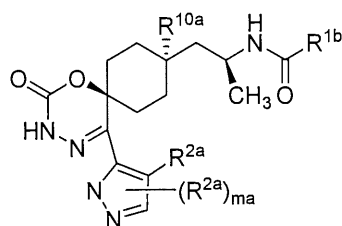
[XXXVIIa-1]



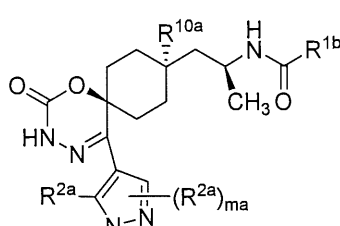
[XXXVIIa-2]



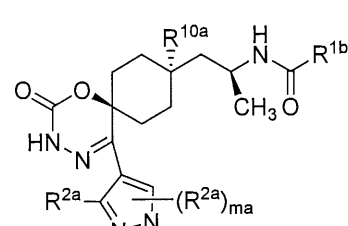
[XXXVIIa-3]



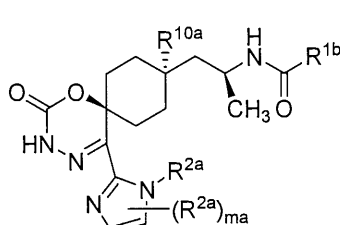
[XXXVIIa-4]



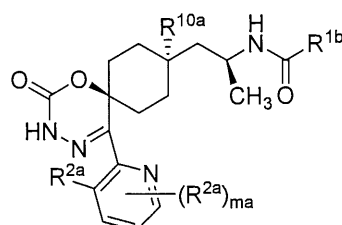
[XXXVIIa-5]



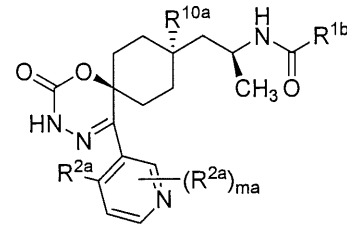
[XXXVIIa-6]



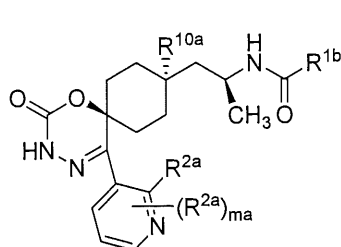
[XXXVIIa-7]



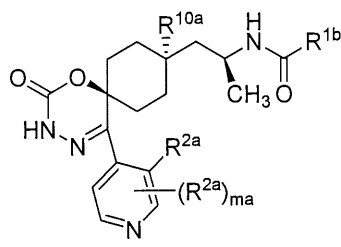
[XXXVIIa-8]



[XXXVIIa-9]



[XXXVIIa-10]



[XXXVIIa-11]

[0270]

wherein

R^{1b}, R^{2a}, R^{10a} and ma are as defined above.

10 [0271]

Preferred specific embodiments of Compound [Ia] include the compounds of Examples 1 to 339 and Examples 2-001 to 2-172 listed in Table 1-1 to Table 1-61 described later.

[0272]

5 The "pharmaceutically acceptable salt" may be any salt known in the art as long as it is not associated with undue toxicity. Specific examples thereof include salts with inorganic acid, salts with organic acid, salts with inorganic base, and salts with organic base. Various forms of
10 pharmaceutically acceptable salts are well known in the art, and they are described in the following documents.
(a) Berge et al., J. Pharm. Sci., 66, p 1-19 (1977),
(b) Stahl et al., "Handbook of Pharmaceutical Salt: Properties, Selection, and Use" (Wiley-VCH, Weinheim, Germany, 2002),
15 (c) Paulekuhn et al., J. Med. Chem., 50, p 6665-6672 (2007)

The pharmaceutically acceptable salt can be obtained by reacting Compound [I] or Compound [Ia] with an inorganic acid, an organic acid, an inorganic base or an organic base according to a known method.

20 [0273]

Examples of the salt with inorganic acid include salts with hydrofluoric acid, hydrochloric acid, hydrobromic acid, hydriodic acid, nitric acid, phosphoric acid and sulfuric acid. Preferred are salts with hydrochloric acid, nitric acid,
25 sulfuric acid, phosphoric acid and hydrobromic acid.

[0274]

Examples of the salt with organic acid include salts with acetic acid, adipic acid, alginic acid, 4-aminosalicylic acid, anhydromethylenecitric acid, benzoic acid, benzenesulfonic
30 acid, calcium edetate, camphoric acid, camphor-10-sulfonic acid, carbonic acid, citric acid, edetic acid, ethane-1,2-disulfonic acid, dodecylsulfuric acid, ethanesulfonic acid, fumaric acid, glucoheptonic acid, gluconic acid, glucuronic acid, glucoheptonic acid, glycolylarsanilic acid,
35 hexylresorcinoic acid, hydroxynaphthoic acid, 2-hydroxy-1-

ethanesulfonic acid, lactic acid, lactobionic acid, malic acid, maleic acid, mandelic acid, methanesulfonic acid, methylsulfuric acid, methylnitric acid, methylenebis(salicylic acid), galactaric acid, naphthalene-2-sulfonic acid, 2-
5 naphthoic acid, 1,5-naphthalenedisulfonic acid, oleic acid, oxalic acid, pamoic acid, pantothenic acid, pectic acid, picric acid, propionic acid, polygalacturonic acid, salicylic acid, stearic acid, succinic acid, tannic acid, tartaric acid, teoclic acid, thiocyanic acid, trifluoroacetic acid, p-
10 toluenesulfonic acid, undecanoic acid, aspartic acid and glutamic acid. Preferred are salts with oxalic acid, maleic acid, citric acid, fumaric acid, lactic acid, malic acid, succinic acid, tartaric acid, acetic acid, trifluoroacetic acid, benzoic acid, glucuronic acid, oleic acid, pamoic acid,
15 methanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid and 2-hydroxy-1-ethanesulfonic acid.

[0275]

Examples of the salt with inorganic base include salts with lithium, sodium, potassium, magnesium, calcium, barium,
20 aluminium, zinc, bismass and ammonium. Preferred are salts with sodium, potassium, calcium, magnesium and zinc.

[0276]

Examples of the salt with organic base include salts with arecoline, betaine, choline, clemizole, ethylene diamine, N-
25 methylglucamine, N-benzyl phenethylamine, tris(hydroxymethyl)methylamine, arginine and lysine. Preferred are salts with tris(hydroxymethyl)methylamine, N-methylglucamine and lysine.

[0277]

30 Compound [I] or Compound [Ia] or a pharmaceutically acceptable salt thereof may be present as a solvate. The term "solvate" refers to Compound [I] or Compound [Ia] or a pharmaceutically acceptable salt thereof with which a solvent molecule is coordinated. The solvate may be any
35 pharmaceutically acceptable solvate, and include hydrates,

ethanolates, acetic acid solvate, dimethyl sulfoxidates or the like of Compound [I] or Compound [Ia] or a pharmaceutically acceptable salt thereof.

Specific examples include semihydrate, monohydrate,
5 dihydrate, mono acetic acid solvate and monoethanolate of Compound [I] or Compound [Ia], monohydrate of sodium salt of Compound [I] or Compound [Ia], and 2/3 ethanolate of monohydrochloride of Compound [I] or Compound [Ia]. These solvates can be obtained according to a known method.

10 [0278]

Compound [I] or Compound [Ia] may be present as a tautomer. In this case, Compound [I] or Compound [Ia] can be a single tautomer or a mixture thereof.

Compound [I] or Compound [Ia] may have a carbon-carbon
15 double bond. In this case, Compound [I] or Compound [Ia] can be present as an E form, a Z form, or a mixture thereof.

Compound [I] or Compound [Ia] may be present as a stereoisomer that should be recognized as a cis/trans isomer. In this case, Compound [I] or Compound [Ia] can be present as a
20 cis form, a trans form, or a mixture thereof.

[0279]

Compound [I] or Compound [Ia] may contain one or more asymmetric carbons. In this case, Compound [I] or Compound [Ia] may be present as a single enantiomer, a single
25 diastereomer, a mixture of enantiomers or a mixture of diastereomers.

Compound [I] or Compound [Ia] may be present as an atropisomer. In this case, Compound [I] or Compound [Ia] may be present as a single atropisomer or a mixture thereof.

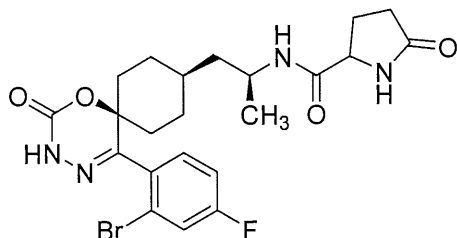
30 Compound [I] or Compound [Ia] may simultaneously contain a plurality of structural features that give rise to the above-mentioned isomers. Moreover, Compound [I] or Compound [Ia] may contain the above-mentioned isomers at any ratio.

[0280]

The formulae, chemical structures and compound names indicated herein without specifying the stereochemistry thereof includes all of the above isomers that may be present, unless otherwise noted. For example, the structure represented by

5 formula:

[0281]

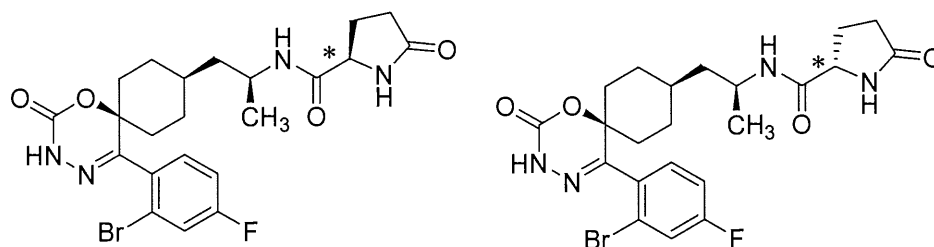


[0282]

includes all of

- 10 (1) a mixture of two diastereomers (the stereochemistry of the asymmetric carbon marked with * is S or R) represented by the following formula:

[0283]



15 [0284]

(2) a diastereomer where the stereochemistry of the asymmetric carbon marked with * is S, and

(3) a diastereomer where the stereochemistry of the asymmetric carbon marked with * is R,

20 unless otherwise noted.

[0285]

A diastereomeric mixture can be separated into each diastereomer by conventional methods such as chromatography and crystallization. Alternatively, each diastereomer can also be

25 produced by using a stereochemically single starting material, or by a synthesis method employing a stereoselective reaction.

[0286]

An enantiomeric mixture can be separated into each single enantiomer by a method well known in the art. For example, first, a diastereomeric mixture can be prepared by reacting an enantiomeric mixture with a substantially pure enantiomer
5 compound known as a chiral auxiliary. Next, the obtained diastereomeric mixture can be separated into a single diastereomer having high isomer ratio or a substantially pure single diastereomer by a conventional method such as fractional crystallization and chromatography. Finally, the separated
10 diastereomer can be converted to a desired enantiomer by removing the added chiral auxiliary by cleavage. Moreover, an enantiomeric mixture can also be directly separated by a chromatography method using a chiral solid phase well known in the art. Alternatively, one of enantiomers can also be
15 obtained by using a substantially pure optically active starting material or by employing stereoselective synthesis (asymmetric induction) of a prochiral intermediate using a chiral auxiliary and an asymmetric catalyst.

[0287]

20 The absolute steric configuration can be determined by the X-ray crystal analysis of the crystalline product or intermediate. In this case, a crystalline product or intermediate derivatized with a reagent having an asymmetric center with a known steric configuration may be used if
25 necessary.

[0288]

Compound [I] or Compound [Ia] may be labeled with an isotope [$^2\text{H(D)}$, ^3H , ^{11}C , ^{13}C , ^{14}C , ^{13}N , ^{15}N , ^{15}O , ^{18}O , ^{18}F , ^{35}S , ^{123}I etc.]. For example, when Compound [I] or Compound [Ia] has
30 methyl, the methyl can be replaced by $-\text{CD}_3$. Such labeled Compound [I] or Compound [Ia] is also included in the present invention. Compound [I] or Compound [Ia] labeled with an isotope may be useful for medicaments, pharmacokinetic studies, in vitro and/or in vivo assays, and/or diagnostics (e.g.
35 positron emission tomography (PET), single photon emission

computed tomography (SPECT)). Compound [I] or Compound [Ia] labeled with an isotope can be produced using an isotope-labelling reagent instead of a non-isotope-labelling reagent, according to known methods or the methods described here.

5 [0289]

Compound [I] or Compound [Ia] or a pharmaceutically acceptable salt thereof is preferably substantially purified, Compound [I] or Compound [Ia] or a pharmaceutically acceptable salt thereof. Further preferably, it is Compound [I] or
10 Compound [Ia] or a pharmaceutically acceptable salt thereof that is purified to a purity of 80% or more.

[0290]

The pharmaceutical composition of the present invention may be produced by appropriately admixing a therapeutically
15 effective amount of an active ingredient (e.g., Compound [I] or Compound [Ia] or a pharmaceutically acceptable salt thereof) with at least one kind of a pharmaceutically acceptable carrier and the like, according to a method known in the art of pharmaceutical preparations. The content of the active
20 ingredient in the pharmaceutical composition varies depending on the dosage form, the dose, and the like. It is, for example, 0.1 to 100 wt% of the whole composition.

[0291]

Examples of the dosage form of the pharmaceutical
25 composition containing Compound [I] or Compound [Ia] or a pharmaceutically acceptable salt thereof include oral preparations such as tablet, capsule, granule, powder, troche, syrup, emulsion and suspension, and parenteral preparations such as external preparation, suppository, injection, eye drop,
30 nasal preparations and pulmonary preparation.

[0292]

Examples of the "pharmaceutically acceptable carrier" include various organic or inorganic carrier substances conventionally used as preparation materials, and specifically
35 include excipient, disintegrant, binder, glidant, lubricant and

the like for solid preparations; solvent, solubilizing agent, suspending agent, isotonicity agent, buffering agent, soothing agent and the like for liquid preparations; and base, emulsifier, moistening agent, stabilizer, stabilizing agent, 5 dispersant, plasticizer, pH adjuster, absorption enhancer, gelling agent, preservative, filler, solvent, solubilizing agent, suspending agent and the like for semi-solid preparations. Where necessary, additives such as preservative, antioxidant, colorant, sweetening agent and the like may be 10 used.

[0293]

Examples of the "excipient" include lactose, sucrose, D-mannitol, D-sorbitol, corn starch, dextrin, microcrystalline cellulose, crystalline cellulose, carmellose, carmellose 15 calcium, sodium carboxymethyl starch, low-substituted hydroxypropylcellulose, gum arabic and the like.

Examples of the "disintegrant" include carmellose, carmellose calcium, carmellose sodium, sodium carboxymethyl starch, croscarmellose sodium, crospovidone, low-substituted 20 hydroxypropylcellulose, hydroxypropylmethylcellulose, crystalline cellulose and the like.

Examples of the "binder" include hydroxypropylcellulose, hydroxypropylmethylcellulose, povidone, crystalline cellulose, sucrose, dextrin, starch, gelatin, carmellose sodium, gum 25 arabic and the like.

Examples of the "glidant" include light anhydrous silicic acid, magnesium stearate and the like.

Examples of the "lubricant" include magnesium stearate, calcium stearate, talc and the like.

30 Examples of the "solvent" include purified water, ethanol, propylene glycol, macrogol, sesame oil, corn oil, olive oil and the like.

Examples of the "solubilizing agent" include propylene glycol, D-mannitol, benzyl benzoate, ethanol, triethanolamine, 35 sodium carbonate, sodium citrate and the like.

Examples of the "suspending agent" include benzalkonium chloride, carmellose, hydroxypropylcellulose, propylene glycol, povidone, methylcellulose, glycerol monostearate and the like.

Examples of the "isotonic agent" include glucose, D-
5 sorbitol, sodium chloride, D-mannitol and the like.

Examples of the "buffering agent" include sodium hydrogenphosphate, sodium acetate, sodium carbonate, sodium citrate and the like.

Examples of the "soothing agent" include benzyl alcohol
10 and the like.

Examples of the "base" include water, animal and vegetable oils (olive oil, corn oil, arachis oil, sesame oil, castor oil etc.), lower alcohols (ethanol, propanol, propylene glycol, 1,3-butylene glycol, phenol etc.), higher fatty acids
15 and esters thereof, wax, higher alcohols, polyalcohols, hydrocarbons (white vaseline, liquid paraffin, paraffin etc.), hydrophilic vaseline, purified lanolin, absorptive ointment, hydrous lanolin, hydrophilic ointment, starch, pullulan, gum arabic, tragacanth gum, gelatin, dextran, cellulose derivatives
20 (methyl cellulose, carboxymethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose etc.), synthetic polymers (carboxyvinyl polymer, sodium polyacrylate, polyvinyl alcohol, polyvinyl pyrrolidone etc.), propylene glycol, Macrogol (Macrogol 200 to 600), and combinations of two or more types
25 thereof.

Examples of the "preservative" include ethyl parahydroxybenzoate, chlorobutanol, benzyl alcohol, sodium dehydroacetate, sorbic acid and the like.

Examples of the "antioxidant" include sodium sulfite,
30 ascorbic acid and the like.

Examples of the "colorant" include food colors (Food Color Red No. 2 or 3, and Food Color Yellow No. 4 or 5 etc.), β -carotene and the like.

Examples of the "sweetening agent" include saccharin
35 sodium, dipotassium glycyrrhizinate, aspartame and the like.

[0294]

The pharmaceutical composition can be administered orally or parenterally (topically, rectally, intravenously, intramuscularly, and subcutaneously etc.) to human as well as
5 mammals other than human (mouse, rat, hamster, guinea pig, rabbit, cat, dog, swine, bovine, horse, sheep, monkey etc.). The dose (hereinafter, also to be referred to as "therapeutically effective amount") varies depending on administration subject, administration route, target disease,
10 symptom, severity of disease, dosage form and the like. For example, when administered orally to a human (adult patient) (body weight 60 kg), the lower limit of the therapeutically effective amount is, for example, about 0.01 mg, about 0.1 mg, about 0.5 mg, about 1 mg, about 10 mg, about 20 mg or about 50
15 mg per day, and the upper limit of the therapeutically effective amount is, for example, about 1 mg, about 5 mg, about 10 mg, about 20 mg, about 50 mg, about 100 mg, about 200 mg, about 500 mg or about 1000 mg per day. This amount can be administered in once, twice, three or more times a day.

20 [0295]

The expression "inhibiting PLD" means to eliminate or attenuate the activity of PLD by inhibiting its function. For example, it means to inhibit the function as PLD based on the conditions in the below-mentioned Experimental Example 1 and/or
25 Experimental Example 2. Inhibition of the function of PLD or elimination or attenuation of the activity of PLD is preferably performed in human clinical indications.

One embodiment of the "inhibiting PLD" is "inhibiting PLD1"

30 The expression "inhibiting PLD1" means to eliminate or attenuate the activity of PLD1 by inhibiting its function. For example, it means to inhibit the function as PLD1 based on the conditions in the below-mentioned Experimental Example 1 and/or Experimental Example 2. Inhibition of the function of PLD1 or

elimination or attenuation of the activity of PLD1 is preferably performed in human clinical indications.

One embodiment of the "inhibiting PLD" is "inhibiting PLD1/2"

5 The expression "inhibiting PLD1/2" means to eliminate or attenuate the activities of PLD1 and PLD2 by inhibiting their functions. For example, it means to inhibit the functions as PLD1 and PLD2 based on the conditions in the below-mentioned Experimental Example 1 and/or Experimental Example 2.

10 Inhibition of the functions of PLD1 and PLD2 or elimination or attenuation of the activities of PLD1 and PLD2 is preferably performed in human clinical indications.

[0296]

15 The "inhibiting PLD" is preferably "inhibiting human PLD".

[0297]

 The "PLD inhibitor" means a substance that binds to PLD and inhibits the function of PLD. The "PLD inhibitor" is preferably "human PLD inhibitor".

20 One embodiment of the "PLD inhibitor" is "PLD1 inhibitor".

 The "PLD1 inhibitor" means a substance that binds to PLD1 and inhibits the function of PLD1. The "PLD1 inhibitor" is preferably "human PLD1 inhibitor".

25 One embodiment of the "PLD inhibitor" is "PLD1/2 inhibitor".

 The "PLD1/2 inhibitor" means a substance that binds to PLD1 and PLD2 and inhibits the functions of PLD1 and PLD2. The "PLD1/2 inhibitor" is preferably "human PLD1/2 inhibitor".

30 [0298]

 Compound [I] or Compound [Ia] or a pharmaceutically acceptable salt thereof has a PLD inhibitory activity, and may be useful for the treatment and/or prophylaxis of various diseases or conditions expected to be improved by controlling
35 PLD activity. Examples of various diseases or conditions

expected to be improved by controlling PLD activity include thrombosis (e.g., arterial thrombosis, acute coronary syndrome, stable angina, unstable angina, non-ST elevation myocardial infarction, ST elevation myocardial infarction, ischemic stroke, non-cardioembolic stroke, atherosclerotic stroke, cryptogenic stroke, embolic stroke of undetermined source (ESUS), lacunar stroke, transient ischemic attack, peripheral arterial disease, etc.), thrombosis during perioperative and postoperative periods associated with revascularization (coronary artery bypass graft, percutaneous coronary intervention, carotid endarterectomy, carotid artery stenting, thrombolysis, lower extremity revascularization, etc.) or aortic valve replacement (surgical aortic valve replacement, transcatheter aortic valve replacement, etc.), and cancers (e.g., breast cancer, ovarian cancer, lung cancer, colorectal cancer, kidney cancer, pancreatic cancer, prostate cancer, brain tumor, etc.).

[0299]

As used herein, the term "treatment" includes improvement of symptoms, prevention of severity, maintenance of remission, prevention of exacerbation, secondary prevention and prevention of relapse.

[0300]

As used herein, the term "prophylaxis" includes suppressing the onset of symptoms.

[0301]

In some embodiments, the PLD inhibitor or pharmaceutical composition may be provided in the form of a kit (administration, treatment and/or prevention kits, etc.), a package (packaging good, etc.) and a medicine set (and/or a container), associated therewith a written matter stating that it can or should be used for the prophylaxis or treatment of the above-mentioned diseases. Such kit, package and medicine set may contain one or more containers filled with PLD inhibitor and/or other medicines or drugs (or components).

Examples of such kit, package and medicine set include commercial kits, commercial packages and commercial medicines, which are appropriately directed to the treatment and/or prevention of target diseases. Examples of the written matter
5 contained therein include precautions or package inserts in the form directed by the government organization which regulates manufacture, use or sale of pharmaceutical or biological products, which show the approval of the government organization about manufacture, use or sale of the products
10 related to human administration. In the above-mentioned kit, package and medicine set, packed products may also be included, and structures constructed for suitable administration step may also be included, and structures constructed to achieve more preferred medical treatment and/or prevention, including
15 treatment and/or prevention of the target diseases, may also be included.

[0302]

Compound [I] or Compound [Ia] or a pharmaceutically acceptable salt thereof of the present invention can be used in
20 combination with one or a plurality of other medicaments (hereinafter to be also referred to as "concomitant drug") (hereinafter to be referred to as combined use), as long as the medicinal effects thereof are not impaired. The administration period is not limited, and they may be administered to an
25 administration subject simultaneously or at given intervals. In addition, the combination of Compound [I] or Compound [Ia] or pharmaceutically acceptable salt thereof and the concomitant drug can also be administered as a single preparation. The administration form of the concomitant drug is not particularly
30 limited, and it is only required that Compound [I] or Compound [Ia] or a pharmaceutically acceptable salt thereof of the present invention is combined with a concomitant drug.

The dose of the concomitant drug can be appropriately selected based on the dose used in clinical practice. The ratio
35 of Compound [I] or Compound [Ia] or a pharmaceutically

production methods can be selected appropriately from the above "pharmaceutically acceptable salt".

The compound obtained in each step can be, if necessary, isolated or purified according to a method known per se such as
5 distillation, recrystallization and column chromatography, or directly used in the next step without isolation or purification.

As used herein, the room temperature refers to a temperature in an uncontrolled state, and one embodiment
10 includes 1°C to 40°C.

[0306]

The abbreviations used are as follows.

THF: tetrahydrofuran

DMF: N,N-dimethylformamide

15 CDCl₃: deuteration chloroform

Pt-C: platinum-activated carbon

Pd-C: palladium-activated carbon

DMSO: dimethyl sulfoxide

LiHMDS: lithium bis(trimethylsilyl)amide

20 NaHMDS: sodium bis(trimethylsilyl)amide

TBAF: tetra-n-butylammonium fluoride

DBU: diazabicycloundecene

CDI: 1,1'-carbonyldiimidazole

WSC: 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide

25 hydrochloride

HATU: 1-[bis(dimethylamino)methylene]-1H-1,2,3-triazole[4,5-b]pyridinium 3-oxide hexafluorophosphate

DMT-MM: 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride

30 HOAt: 1-hydroxy-7-azabenzotriazole

DMAP: 4-dimethylaminopyridine

CPME: cyclopentyl methyl ether

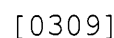
DMA: dimethylacetamide

Boc₂O: di-tert-butyl dicarbonate

35 LDA: lithium diisopropylamide

Production Method A1: production method of Compound [I] or a salt thereof

[0308]



10 A, Cy, R¹, R², R³, R⁴, R⁵, R⁶, R⁷, R⁸, R⁹ and m are as defined
above, and
L¹¹ is hydroxy or a leaving group (for example, halogen, etc.).

(Step A1-1)

For example, when L¹¹ is halogen, Compound [I] or a salt thereof can be produced by reacting Compound [A1-1] or a salt thereof with Compound [A1-2] or a salt thereof in the presence of a base, in a solvent.

25 Examples of the solvent include DMF, acetonitrile, THF
and the like. The preferred solvent is DMF.

82

Alternatively, for example, when L¹¹ is hydroxy, Compound [I] or a salt thereof can also be produced by reacting Compound [A1-1] or a salt thereof with Compound [A1-2] or a salt thereof in the presence of a condensing agent and a base, in a solvent.

5 Examples of the base include triethylamine, N,N-diisopropylethylamine and the like. The preferred base is N,N-diisopropylethylamine.

 Examples of the condensing agent include WSC, HATU, DMT-MM and the like. The preferred condensing agent is WSC or
10 HATU.

 Examples of the solvent include DMF, acetonitrile, methanol, THF and the like. The preferred solvent is DMF.

 The reaction temperature is, for example, 0°C to 60°C, preferably 20°C to 40°C.

15 Compound [A1-1] or a salt thereof may be a commercially available product, or can be produced from a commercially available product by a known method, for example, it can be also produced according to Production Methods B1 and B2 described below.

20 Compound [A1-2] or a salt thereof may be a commercially available product, or can be produced from a commercially available product by a known method.

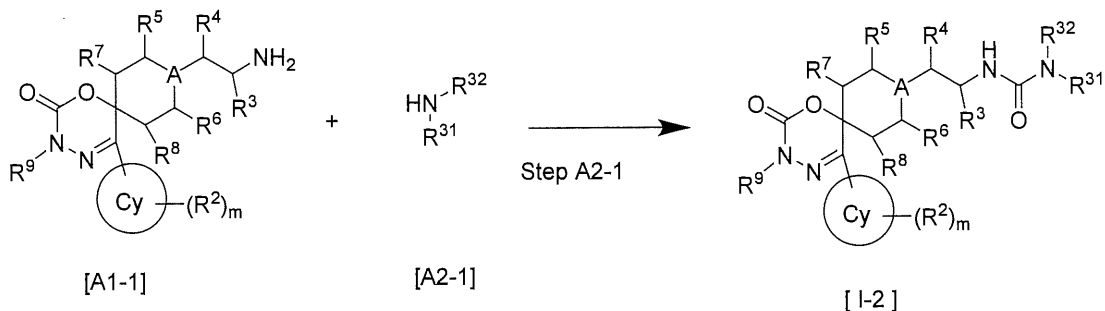
 Alternatively, Compound [I] or a salt thereof can also be produced by carrying out this production method using compound
25 or a salt thereof having a functional group or a protected functional group on Cy that can be converted to R² by a known reaction, instead of Compound [A1-1] or a salt thereof to obtain a compound corresponding to Compound [I], or a salt thereof, and then converting the functional group of the
30 compound or salt thereof to R².

[0311]

Production Method A2: production method of Compound [I-2] or a salt thereof

Compound [I] or a salt thereof wherein R^1 is $NR^{31}R^{32}$,
i.e., Compound [I-2] or a salt thereof, can be produced, for
example, according to the following Production Method A2.

[0312]



[0313]

wherein

A, Cy, R^2 , R^3 , R^4 , R^5 , R^6 , R^7 , R^8 , R^9 and m are as defined above,
and

R^{31} and R^{32} are each independently

- (1) hydrogen,
- (2) C_{1-4} alkyl wherein the alkyl is optionally substituted by
 - (a) phenyl wherein the phenyl is optionally substituted by halogen, or
 - (b) pyridyl,
- (3) C_{1-4} alkoxy, or
- (4) C_{3-4} cycloalkyl, or

R^{31} and R^{32} are bonded to each other to form, together with the
nitrogen atoms to which they are bonded,

- (5) 4 to 7-membered heterocycloalkyl containing one or two
heteroatoms selected from the group consisting of nitrogen and
oxygen atoms as a ring constituting atom, besides carbon atom,
wherein the heterocycloalkyl is optionally substituted by
 - (a) hydroxy,
 - (b) oxo,
 - (c) $NR^{20}R^{21}$ wherein R^{20} and R^{21} are each independently
hydrogen or C_{1-4} alkyl, or
 - (d) phenyl,

- (6) 6 to 11-membered spiro heterocycloalkyl containing one or
two heteroatoms selected from the group consisting of nitrogen

and oxygen atoms as a ring constituting atom, besides carbon atom, or

(7) a 8 to 10-membered saturated or partially unsaturated fused cyclic group containing 1 to 4 heteroatoms selected from the group consisting of nitrogen and oxygen atoms as a ring constituting atom, besides carbon atom, wherein the fused cyclic group is optionally substituted by C₁₋₄ haloalkyl.

[0314]

(Step A2-1)

10 Compound [I-2] or a salt thereof can be produced by reacting Compound [A1-1] or a salt thereof with Compound [A2-1] or a salt thereof in the presence of an ureating agent and a base, in a solvent.

15 Examples of the ureating agent include CDI, triphosgene and the like. The preferred ureating agent is CDI.

Examples of the base include N-methylmorpholine, triethylamine, N,N-diisopropylethylamine and the like. The preferred base is N-methylmorpholine.

20 Examples of the solvent include THF, acetonitrile, DMF, water, mixed solvent thereof and the like. The preferred solvent is THF or a mixed solvent of THF and water.

The reaction temperature is, for example, 0°C to 80°C, preferably 30°C to 60°C.

25 Compound [A2-1] or a salt thereof may be a commercially available product, or can be produced from a commercially available product by a known method.

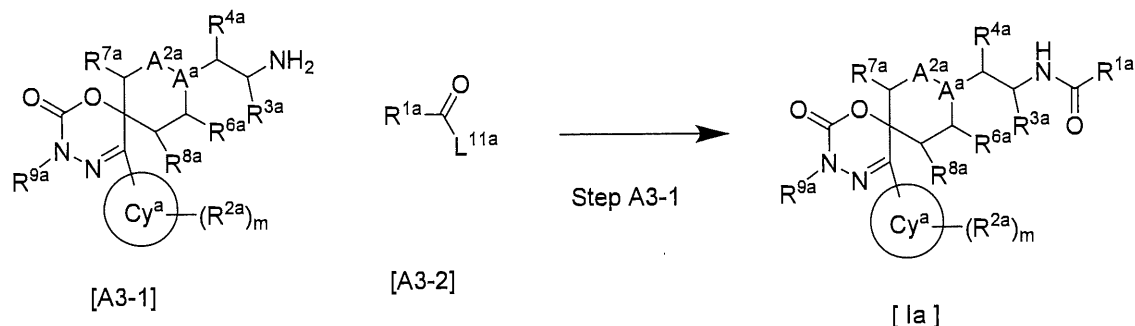
Alternatively, Compound [I-2] or a salt thereof can also be produced by carrying out this production method using compound or a salt thereof having a functional group or a protected functional group on Cy that can be converted to R² by a known reaction, instead of Compound [A1-1] or a salt thereof to obtain a compound corresponding to Compound [I-2], or a salt thereof, and then converting the functional group of the compound or salt thereof to R².

35 [0315]

Production Method A3: production method of Compound [Ia] or a salt thereof

Compound [Ia] or a salt thereof can be produced, for example, according to the following Production Method A3.

5 [0316]



[0317]

wherein

A^a, A^{2a}, Cy^a, R^{1a}, R^{2a}, R^{3a}, R^{4a}, R^{6a}, R^{7a}, R^{8a}, R^{9a} and m are as

10 defined above, and

L^{11a} is hydroxy or a leaving group (for example, halogen, etc.).

[0318]

(Step A3-1)

Compound [I] or a salt thereof can be produced by
15 reacting Compound [A3-1] or a salt thereof with Compound [A3-2]
or a salt thereof.

For example, when L^{11a} is halogen, Compound [Ia] or a salt thereof can be produced by reacting Compound [A3-1] or a salt thereof with Compound [A3-2] or a salt thereof in the presence
20 of a base, in a solvent.

Examples of the base include triethylamine, N,N-diisopropylethylamine and the like. The preferred base is N,N-diisopropylethylamine.

Examples of the solvent include DMF, acetonitrile, THF
25 and the like. The preferred solvent is DMF.

The reaction temperature is, for example, 0°C to 60°C, preferably 20°C to 40°C.

Alternatively, for example, when L^{11a} is hydroxy, Compound [Ia] or a salt thereof can also be produced by reacting

Compound [A3-1] or a salt thereof with Compound [A3-2] or a salt thereof in the presence of a condensing agent and a base, in a solvent.

Examples of the base include triethylamine, N,N-
5 diisopropylethylamine and the like. The preferred base is N,N-diisopropylethylamine.

Examples of the condensing agent include WSC, HATU, DMT-MM and the like. The preferred condensing agent is WSC or HATU.

10 Examples of the solvent include DMF, acetonitrile, methanol, THF and the like. The preferred solvent is DMF.

The reaction temperature is, for example, 0°C to 60°C, preferably 20°C to 40°C.

Compound [A3-1] or a salt thereof may be a commercially
15 available product, or can be produced from a commercially available product by a known method, for example, it can be also produced according to Production Methods B3 and B4 described below.

Compound [A3-2] or a salt thereof may be a commercially
20 available product, or can be produced from a commercially available product by a known method.

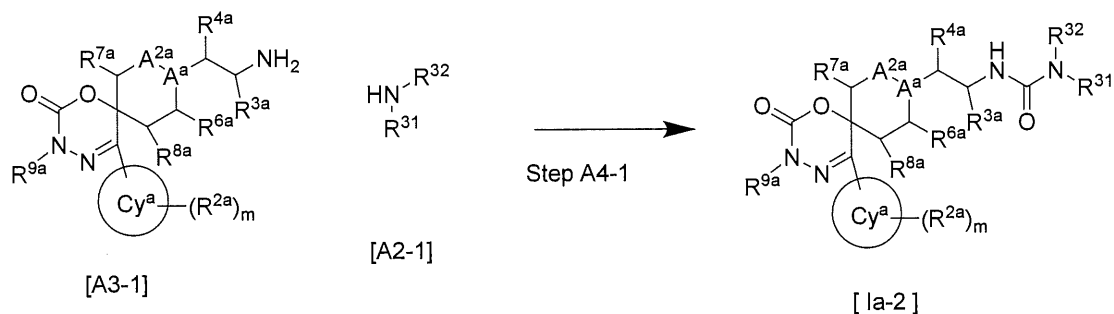
Alternatively, Compound [Ia] or a salt thereof can also be produced by carrying out this production method using compound or a salt thereof having a functional group or a
25 protected functional group on Cy^a that can be converted to R^{2a} by a known reaction, instead of Compound [A3-1] or a salt thereof to obtain a compound corresponding to Compound [Ia], or a salt thereof, and then converting the functional group of the compound or salt thereof to R^{2a}.

30 [0319]

Production Method A4: production method of Compound [Ia-2] or a salt thereof

Compound [Ia] or a salt thereof wherein R^{1a} is NR³¹R³²,
i.e., Compound [Ia-2] or a salt thereof, can be produced, for
35 example, according to the following Production Method A4.

[0320]



[0321]

wherein

5 A^a, Cy^a, R^{2a}, R^{3a}, R^{4a}, R^{5a}, R^{6a}, R^{7a}, R^{8a}, R^{9a}, R³¹, R³² and m are as defined above.

(Step A4-1)

Compound [Ia-2] or a salt thereof can be produced by reacting Compound [A3-1] or a salt thereof with Compound [A2-1] or a salt thereof in the presence of an ureating agent and a base, in a solvent.

Examples of the ureating agent include CDI, triphosgene and the like. The preferred ureating agent is CDI.

15 Examples of the base include N-methylmorpholine, triethylamine, N,N-diisopropylethylamine and the like. The preferred base is N-methylmorpholine.

Examples of the solvent include THF, acetonitrile, DMF, water, mixed solvent thereof and the like. The preferred solvent is THF or a mixed solvent of THF and water.

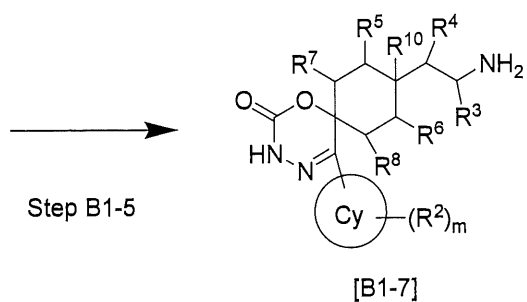
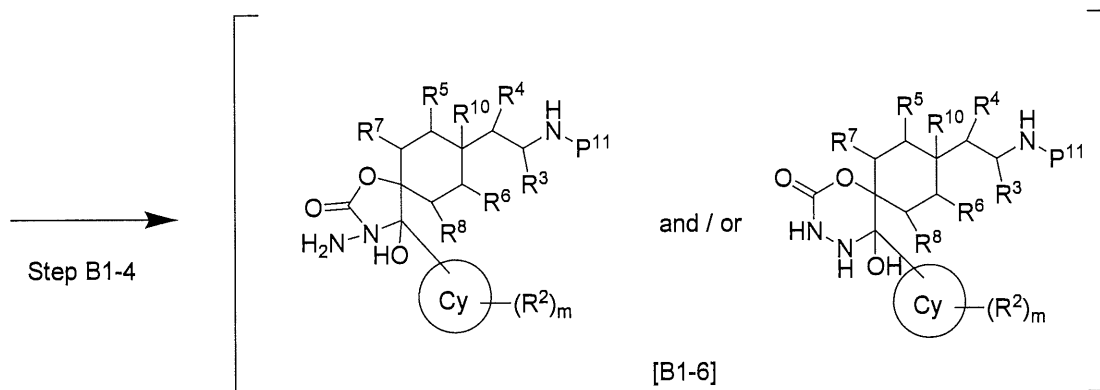
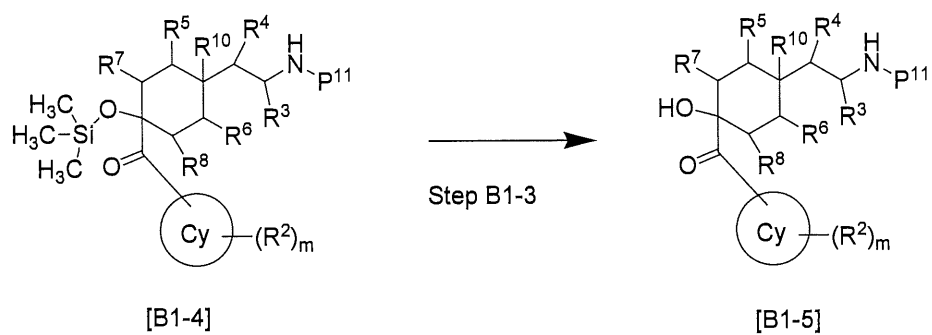
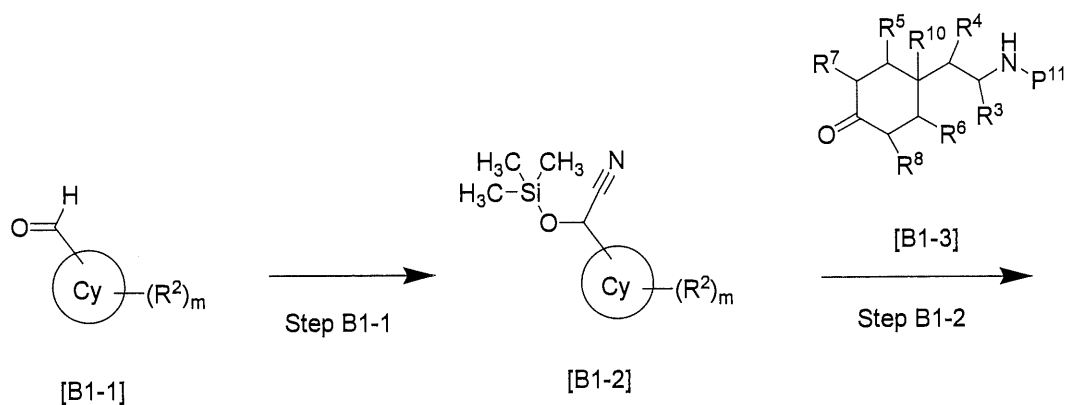
20 The reaction temperature is, for example, 0°C to 80°C, preferably 30°C to 60°C.

Alternatively, Compound [Ia-2] or a salt thereof can also be produced by carrying out this production method using compound or a salt thereof having a functional group or a protected functional group on Cy^a that can be converted to R^{2a} by a known reaction, instead of Compound [A3-1] or a salt thereof to obtain a compound corresponding to Compound [Ia-2], or a salt thereof, and then converting the functional group of the compound or salt thereof to R^{2a}.

30 [0322]

Production Method B1: production method of Compound [B1-7] or a salt thereof

Compound [A1-1] or a salt thereof (used in Production Methods A1 and A2) wherein A is CR¹⁰ and R⁹ is hydrogen, i.e.,
5 Compound [B1-7] or a salt thereof, can be produced, for example, according to the following Production Method B1.
[0323]



[0324]

wherein

Cy, R², R³, R⁴, R⁵, R⁶, R⁷, R⁸, R¹⁰ and m are as defined above,

5 and

P¹¹ is a protecting group for amine (for example, tert-butoxycarbonyl, benzyloxycarbonyl, etc.).

[0325]

(Step B1-1)

5 Compound [B1-2] or a salt thereof can be produced by reacting Compound [B1-1] or a salt thereof with trimethylsilylcyanide in the presence of a catalyst, in a solvent.

10 Examples of the catalyst include lithium chloride, DMAP and the like. The preferred catalyst is lithium chloride or DMAP.

 Examples of the solvent include THF, acetonitrile and the like. The preferred solvent is THF.

15 The reaction temperature is, for example, 0°C to 60°C, preferably 15°C to 30°C.

 Compound [B1-1] or a salt thereof may be a commercially available product, or can be produced from a commercially available product by a known method.

[0326]

20 (Step B1-2)

 Compound [B1-4] or a salt thereof can be produced by reacting Compound [B1-2] or a salt thereof with Compound [B1-3] or a salt thereof in the presence of a catalyst and a base, in a solvent. Step B1-1 and Step B1-2 can also be carried out in
25 one-pot.

 Examples of the catalyst include lithium chloride, DMAP and the like. The preferred catalyst is lithium chloride or DMAP.

30 Examples of the base include LiHMDS, NaHMDS, LDA, n-butyllithium and the like. The preferred base is LiHMDS or NaHMDS.

 Examples of the solvent include THF, n-hexane, toluene and the like. The preferred solvent is THF or toluene.

35 The reaction temperature is, for example, -100°C to 0°C, preferably -78°C to -50°C.

Compound [B1-3] or a salt thereof may be a commercially available product, or can be produced from a commercially available product by a known method, for example, it can be also produced according to Production Method C1 described
5 below.

[0327]

(Step B1-3)

Compound [B1-5] or a salt thereof can be produced by reacting Compound [B1-4] or a salt thereof in the presence of a
10 desilylating agent and an acid, in a solvent.

Examples of the desilylating agent include TBAF, hydrogen fluoride-pyridine and the like. The preferred desilylating agent is TBAF.

Examples of the acid include acetic acid and the like.
15 The preferred acid is acetic acid.

Examples of the solvent include THF, acetonitrile and the like. The preferred solvent is THF.

The reaction temperature is, for example, 0°C to 60°C, preferably 15°C to 30°C.

20 [0328]

(Step B1-4)

Compound [B1-6] or a salt thereof can be produced by reacting Compound [B1-5] or a salt thereof in the presence of a base, CDI and hydrazine monohydrate, in a solvent.

25 Examples of the base include DBU, N-methylimidazole and the like. The preferred base is DBU.

Examples of the solvent include THF, DMF, acetonitrile and the like. The preferred solvent is THF or DMF.

The reaction temperature is, for example, 0°C to 60°C,
30 preferably 20°C to 40°C.

[0329]

(Step B1-5)

Compound [B1-7] or a salt thereof can be produced by reacting Compound [B1-6] or a salt thereof in the presence of
35 an acid, in a solvent.

Examples of the acid include hydrochloric acid, acetic acid and the like. The preferred acid is hydrochloric acid.

Examples of the solvent include THF, water, toluene and the like. The preferred solvent is THF.

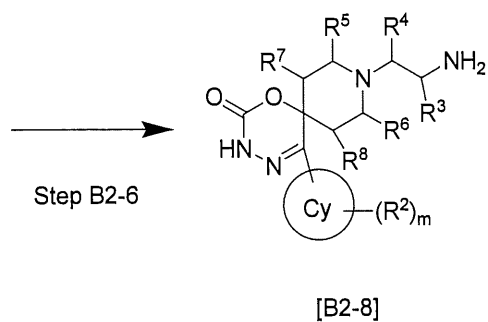
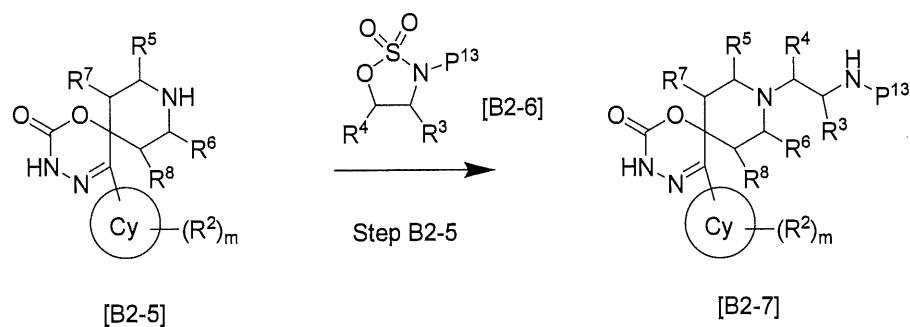
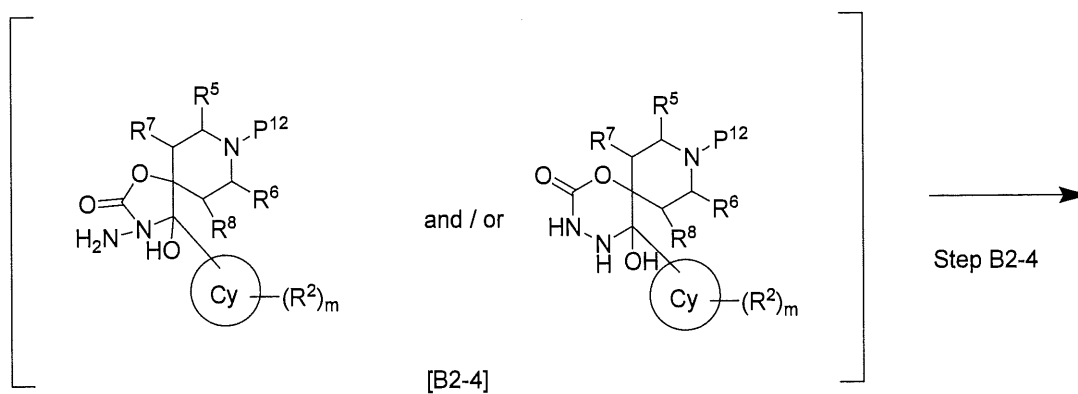
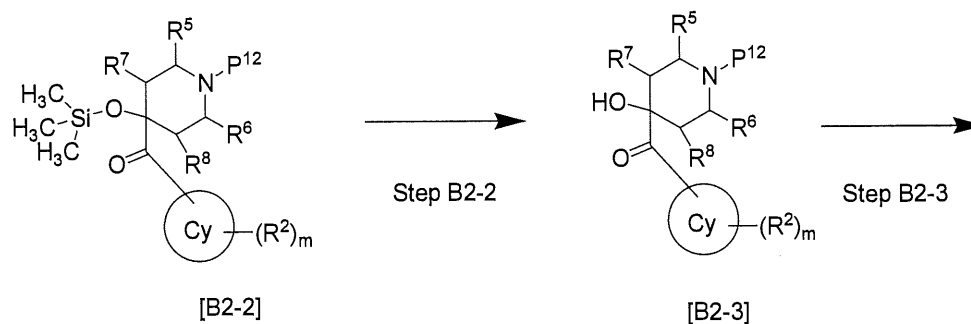
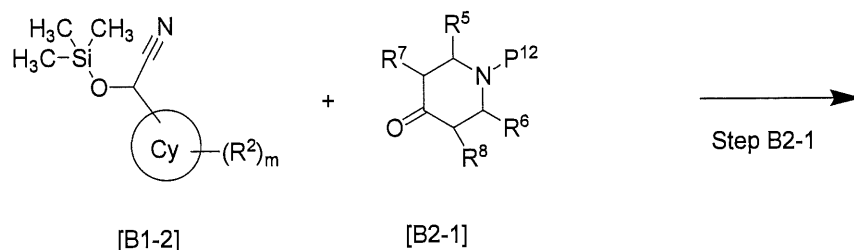
5 The reaction temperature is, for example, 15°C to 120°C, preferably 20°C to 60°C.

Alternatively, Compound [B1-7] or a salt thereof can also be produced by carrying out this production method using compound or a salt thereof having a functional group or a
10 protected functional group on Cy that can be converted to R² by a known reaction, instead of Compound [B1-1] or a salt thereof to obtain a compound corresponding to Compound [B1-7], or a salt thereof, and then converting the functional group of the compound or salt thereof to R².

15 [0330]

Production Method B2: production method of Compound [B2-8] or a salt thereof

Compound [A1-1] or a salt thereof (used in Production Methods A1 and A2) wherein A is N and R⁹ is hydrogen, i.e.,
20 Compound [B2-8] or a salt thereof, can be produced, for example, according to the following Production Method B2.
[0331]



[0332]

wherein

Cy, R², R³, R⁴, R⁵, R⁶, R⁷, R⁸ and m are as defined above, and P¹² and P¹³ are each independently a protecting group for amine (for example, tert-butoxycarbonyl, etc.).

[0333]

5 (Step B2-1)

Compound [B2-2] or a salt thereof can be produced by reacting Compound [B1-2] or a salt thereof with Compound [B2-1] or a salt thereof according to Step B1-2.

Compound [B2-1] or a salt thereof may be a commercially
10 available product, or can be produced from a commercially available product by a known method.

[0334]

(Step B2-2)

Compound [B2-3] or a salt thereof can be produced by
15 reacting Compound [B2-2] or a salt thereof according to Step B1-3.

[0335]

(Step B2-3)

Compound [B2-4] or a salt thereof can be produced by
20 reacting Compound [B2-3] or a salt thereof according to Step B1-4.

[0336]

(Step B2-4)

Compound [B2-5] or a salt thereof can be produced by
25 reacting Compound [B2-4] or a salt thereof according to Step B1-5.

[0337]

(Step B2-5)

Compound [B2-7] or a salt thereof can be produced by
30 reacting Compound [B2-5] or a salt thereof with Compound [B2-6] or a salt thereof in the presence of a base, in a solvent.

Examples of the base include triethylamine, N,N-diisopropylethylamine and the like. The preferred base is triethylamine.

Examples of the solvent include methanol, acetonitrile, THF and the like. The preferred solvent is methanol.

The reaction temperature is, for example, 0°C to 60°C, preferably 20°C to 40°C.

5 Compound [B2-6] or a salt thereof may be a commercially available product, or can be produced from a commercially available product by a known method.

[0338]

(Step B2-6)

10 Compound [B2-8] or a salt thereof can be produced by removing the protecting group P¹³ of Compound [B2-7] or a salt thereof employing a deprotection reaction. The deprotection reaction can be carried out under a condition suitable for the type of P¹³.

15 For example, when P¹³ is tert-butoxycarbonyl, Compound [B2-8] or a salt thereof can be produced by reacting Compound [B2-7] or a salt thereof with an acid in a solvent.

Examples of the acid include hydrochloric acid, trifluoroacetic acid and the like. The preferred acid is
20 hydrochloric acid.

Examples of the solvent include CPME, ethyl acetate and the like. The preferred solvent is CPME or ethyl acetate.

The reaction temperature is, for example, 0°C to 60°C, preferably 20°C to 40°C.

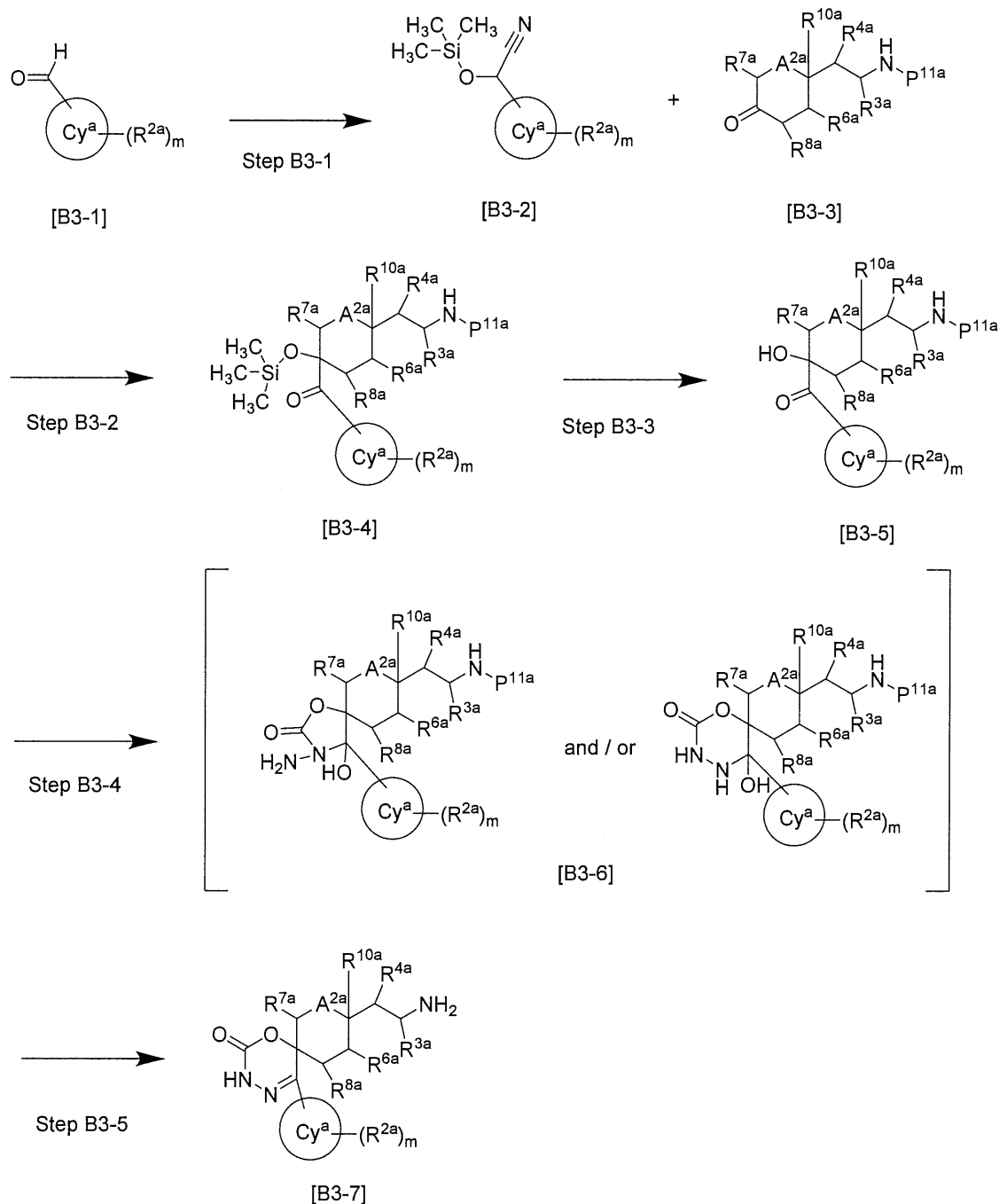
25 Alternatively, Compound [B2-8] or a salt thereof can also be produced by carrying out this production method using compound or a salt thereof having a functional group or a protected functional group on Cy that can be converted to R² by a known reaction, instead of Compound [B1-2] or a salt thereof
30 to obtain a compound corresponding to Compound [B2-8], or a salt thereof, and then converting the functional group of the compound or salt thereof to R².

[0339]

Production Method B3: production method of Compound [B3-7] or a
35 salt thereof

Compound [A3-1] or a salt thereof (used in Production Methods A3 and A4) wherein A^a is CR^{10a} and R^{9a} is hydrogen, i.e., Compound [B3-7] or a salt thereof, can be produced, for example, according to the following Production Method B3.

5 [0340]



[0341]

wherein

A^{2a}, Cy^a, R^{2a}, R^{3a}, R^{4a}, R^{6a}, R^{7a}, R^{8a}, R^{10a} and m are as defined

10 above, and

P^{11a} is a protecting group for amine (for example, tert-butoxycarbonyl, benzyloxycarbonyl, etc.).

[0342]

(Step B3-1)

5 Compound [B3-2] or a salt thereof can be produced by reacting Compound [B3-1] or a salt thereof with trimethylsilylcyanide in the presence of a catalyst, in a solvent.

 Examples of the catalyst include lithium chloride, DMAP
10 and the like. The preferred catalyst is lithium chloride or DMAP.

 Examples of the solvent include THF, acetonitrile and the like. The preferred solvent is THF.

 The reaction temperature is, for example, 0°C to 60°C,
15 preferably 15°C to 30°C.

 Compound [B3-1] or a salt thereof may be a commercially available product, or can be produced from a commercially available product by a known method.

[0343]

20 (Step B3-2)

 Compound [B3-4] or a salt thereof can be produced by reacting Compound [B3-2] or a salt thereof with Compound [B3-3] or a salt thereof in the presence of a catalyst and a base, in a solvent. Step B3-1 and Step B3-2 can also be carried out in
25 one-pot.

 Examples of the catalyst include lithium chloride, DMAP and the like. The preferred catalyst is lithium chloride or DMAP.

 Examples of the base include LiHMDS, NaHMDS, LDA, n-butyllithium and the like. The preferred base is LiHMDS or
30 NaHMDS.

 Examples of the solvent include THF, n-hexane, toluene and the like. The preferred solvent is THF or toluene.

 The reaction temperature is, for example, -100°C to 0°C,
35 preferably -78°C to -50°C.

Compound [B3-3] or a salt thereof may be a commercially available product, or can be produced from a commercially available product by a known method, for example, it can be also produced according to Production Method C2 described
5 below.

[0344]

(Step B3-3)

Compound [B3-5] or a salt thereof can be produced by reacting Compound [B3-4] or a salt thereof in the presence of a
10 desilylating agent and an acid, in a solvent.

Examples of the desilylating agent include TBAF, hydrogen fluoride-pyridine and the like. The preferred desilylating agent is TBAF.

Examples of the acid include acetic acid and the like.
15 The preferred acid is acetic acid.

Examples of the solvent include THF, acetonitrile and the like. The preferred solvent is THF.

The reaction temperature is, for example, 0°C to 60°C, preferably 15°C to 30°C.

20 [0345]

(Step B3-4)

Compound [B3-6] or a salt thereof can be produced by reacting Compound [B3-5] or a salt thereof in the presence of a base, CDI and hydrazine monohydrate, in a solvent.

25 Examples of the base include DBU, N-methylimidazole and the like. The preferred base is DBU.

Examples of the solvent include THF, DMF, acetonitrile and the like. The preferred solvent is THF or DMF.

The reaction temperature is, for example, 0°C to 60°C,
30 preferably 20°C to 40°C.

[0346]

(Step B3-5)

Compound [B3-7] or a salt thereof can be produced by reacting Compound [B3-6] or a salt thereof in the presence of
35 an acid, in a solvent.

Examples of the acid include hydrochloric acid, acetic acid and the like. The preferred acid is hydrochloric acid.

Examples of the solvent include THF, water, toluene and the like. The preferred solvent is THF.

5 The reaction temperature is, for example, 15°C to 120°C, preferably 20°C to 60°C.

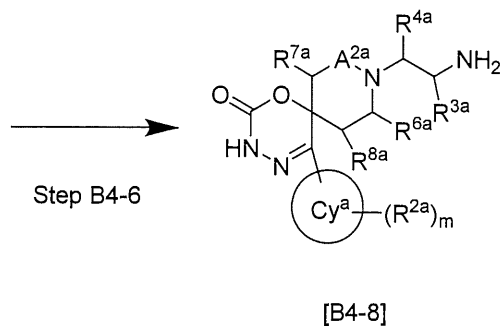
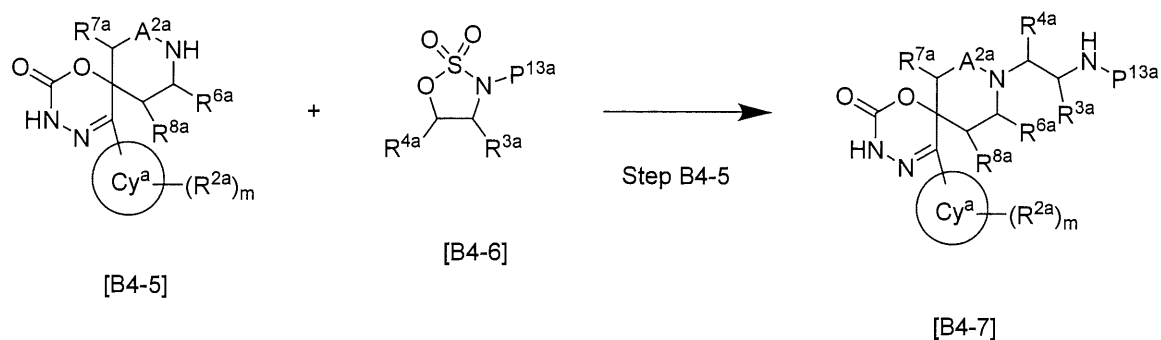
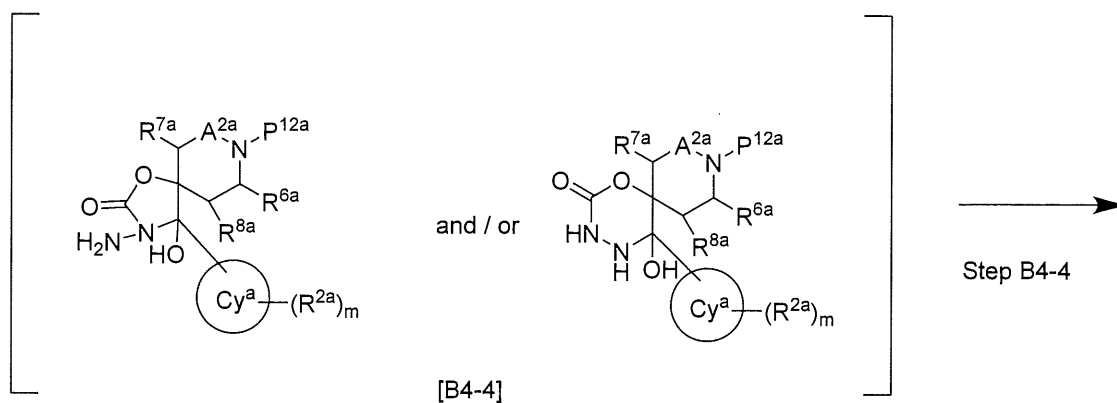
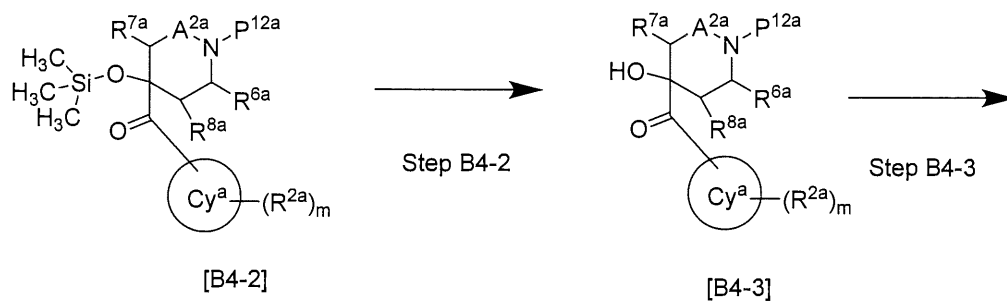
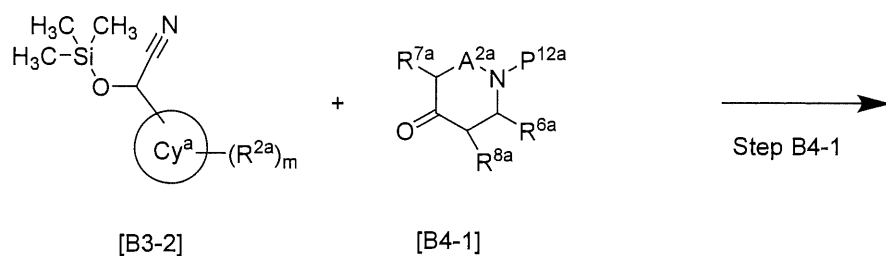
Alternatively, Compound [B3-7] or a salt thereof can also be produced by carrying out this production method using compound or a salt thereof having a functional group or a
10 protected functional group on Cy^a that can be converted to R^{2a} by a known reaction, instead of Compound [B3-1] or a salt thereof to obtain a compound corresponding to Compound [B3-7], or a salt thereof, and then converting the functional group of the compound or salt thereof to R^{2a}.

15 [0347]

Production Method B4: production method of Compound [B4-8] or a salt thereof

Compound [A3-1] or a salt thereof (used in Production Methods A3 and A4) wherein A^a is N and R^{9a} is hydrogen, i.e.,
20 Compound [B4-8] or a salt thereof, can be produced, for example, according to the following Production Method B4.

[0348]



[0349]

wherein

A^{2a}, Cy^a, R^{2a}, R^{3a}, R^{4a}, R^{6a}, R^{7a}, R^{8a} and m are as defined above,
and

P^{12a} and P^{13a} are each independently a protecting group for amine
5 (for example, tert-butoxycarbonyl, benzyloxycarbonyl, etc.).

[0350]

(Step B4-1)

Compound [B4-2] or a salt thereof can be produced by
reacting Compound [B3-2] or a salt thereof with Compound [B4-1]
10 or a salt thereof according to Step B3-2.

Compound [B4-1] or a salt thereof may be a commercially
available product, or can be produced from a commercially
available product by a known method.

[0351]

15 (Step B4-2)

Compound [B4-3] or a salt thereof can be produced by
reacting Compound [B4-2] or a salt thereof according to Step
B3-3.

[0352]

20 (Step B4-3)

Compound [B4-4] or a salt thereof can be produced by
reacting Compound [B4-3] or a salt thereof according to Step
B3-4.

[0353]

25 (Step B4-4)

Compound [B4-5] or a salt thereof can be produced by
reacting Compound [B4-4] or a salt thereof according to Step
B3-5.

[0354]

30 (Step B4-5)

Compound [B4-7] or a salt thereof can be produced by
reacting Compound [B4-5] or a salt thereof with Compound [B4-6]
or a salt thereof in the presence of a base, in a solvent.

Examples of the base include triethylamine, N,N-diisopropylethylamine and the like. The preferred base is triethylamine.

Examples of the solvent include methanol, acetonitrile,
5 THF and the like. The preferred solvent is methanol.

The reaction temperature is, for example, 0°C to 60°C, preferably 20°C to 40°C.

Compound [B4-6] or a salt thereof may be a commercially available product, or can be produced from a commercially
10 available product by a known method.

[0355]

(Step B4-6)

Compound [B4-8] or a salt thereof can be produced by removing the protecting group P^{13a} of Compound [B4-7] or a salt
15 thereof employing a deprotection reaction. The deprotection reaction can be carried out under a condition suitable for the type of P^{13a}.

For example, when P^{13a} is tert-butoxycarbonyl, Compound [B4-8] or a salt thereof can be produced by reacting Compound
20 [B4-7] or a salt thereof with an acid in a solvent.

Examples of the acid include hydrochloric acid, trifluoroacetic acid and the like. The preferred acid is hydrochloric acid.

Examples of the solvent include CPME, ethyl acetate and
25 the like. The preferred solvent is CPME or ethyl acetate.

The reaction temperature is, for example, 0°C to 60°C, preferably 20°C to 40°C.

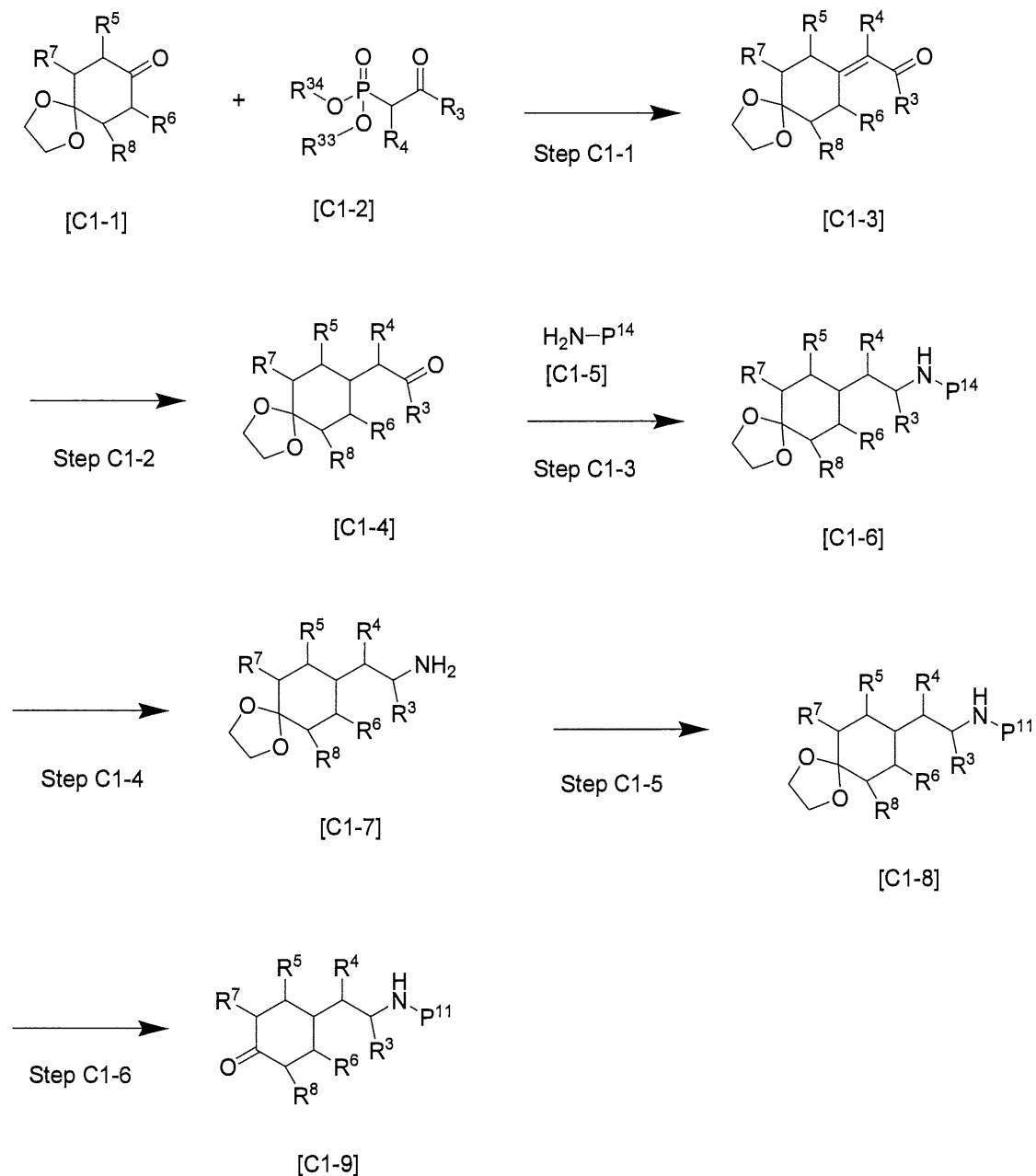
Alternatively, Compound [B4-8] or a salt thereof can also be produced by carrying out this production method using
30 compound or a salt thereof having a functional group or a protected functional group on Cy^a that can be converted to R^{2a} by a known reaction, instead of Compound [B3-2] or a salt thereof to obtain a compound corresponding to Compound [B4-8], or a salt thereof, and then converting the functional group of
35 the compound or salt thereof to R^{2a}.

[0356]

Production Method C1: production method of Compound [C1-9] or a salt thereof

Compound [B1-3] or a salt thereof (used in Production
5 Method B1) wherein R¹⁰ is hydrogen, i.e., Compound [C1-9] or a salt thereof, can be produced, for example, according to the following Production Method C1.

[0357]



10 [0358]

wherein

R³, R⁴, R⁵, R⁶, R⁷, R⁸ and P¹¹ are as defined above,

R³³ and R³⁴ are each independently C₁₋₄ alkyl, and
P¹⁴ is a protecting group for amine (for example, benzyl, (S)-
1-phenylethyl, etc.).

[0359]

5 (Step C1-1)

Compound [C1-3] or a salt thereof can be produced by
reacting Compound [C1-1] or a salt thereof with Compound [C1-2]
or a salt thereof in the presence of a base, in a solvent.

Examples of the base include sodium ethoxide, sodium
10 hydride, DBU and the like. The preferred base is sodium
ethoxide.

Examples of the solvent include ethanol, THF, DMF and the
like. The preferred solvent is ethanol.

The reaction temperature is, for example, 0°C to 60°C,
15 preferably 20°C to 40°C.

Compound [C1-1] or a salt thereof may be a commercially
available product, or can be produced from a commercially
available product by a known method.

Compound [C1-2] or a salt thereof may be a commercially
20 available product, or can be produced from a commercially
available product by a known method.

[0360]

(Step C1-2)

Compound [C1-4] or a salt thereof can be produced by
25 subjecting Compound [C1-3] or a salt thereof to catalytic
hydrogenation in the presence of a metal catalyst, in a
solvent.

Examples of the metal catalyst include Pd-C, Pt-C,
palladium hydroxide and the like. The preferred metal catalyst
30 is Pd-C or palladium hydroxide.

Examples of the solvent include methanol, ethanol, THF
and the like. The preferred solvent is THF.

The reaction temperature is, for example, 0°C to 60°C,
preferably 20°C to 40°C.

35 [0361]

(Step C1-3)

Compound [C1-6] or a salt thereof can be produced by
subjecting Compound [C1-4] or a salt thereof to a reductive
amination reaction with Compound [C1-5] or a salt thereof in a
5 solvent. The reductive amination reaction includes, for
example, a reaction using an acid and a reducing agent.

Examples of the reducing agent include sodium
triacetoxyborohydride, sodium cyanoborohydride, sodium
borohydride and the like. The preferred reducing agent is
10 sodium triacetoxyborohydride.

Examples of the acid include acetic acid, trifluoroacetic
acid, hydrochloric acid and the like. The preferred acid is
acetic acid.

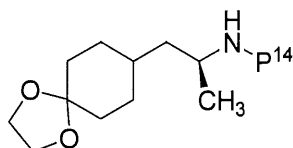
Examples of the solvent include THF, chloroform, toluene,
15 N-methylpyrrolidone and the like. The preferred solvent is
THF.

The reaction temperature is, for example, 0°C to 60°C,
preferably 20°C to 40°C.

Compound [C1-5] or a salt thereof may be a commercially
20 available product, or can be produced from a commercially
available product by a known method.

Compound [C1-6] or a salt thereof wherein R³ is methyl,
and R⁴, R⁵, R⁶, R⁷ and R⁸ are all hydrogens, i.e., the following
Compound [C1-10]

25 [0362]



[C1-10]

[0363]

wherein

P¹⁴ are as defined above,

30 or a salt thereof can be produced by, for example, carrying out
Step C1-3 using (S)-1-phenethylamine as Compound [C1-5] or a

salt thereof, and stirring the obtained diastereomeric mixture or a salt thereof in a solvent, and then collecting the precipitated solid by filtration.

Examples of the solvent include toluene, THF, ethyl acetate and the like. The preferred solvent is ethyl acetate.
[0364]

(Step C1-4)

Compound [C1-7] or a salt thereof can be produced by removing the protecting group P^{14} of Compound [C1-6] or a salt thereof employing a deprotection reaction. The deprotection reaction can be carried out under a condition suitable for the type of P^{14} .

For example, when P^{14} is (S)-1-phenylethyl, Compound [C1-7] or a salt thereof can be produced by reacting Compound [C1-6] or a salt thereof according to Step C1-2.
[0365]

(Step C1-5)

Compound [C1-8] or a salt thereof can be produced by introducing the protecting group P^{11} to Compound [C1-7] or a salt thereof. The introduction of the protecting group can be carried out under a condition suitable for the type of P^{11} .

For example, when P^{11} is tert-butoxycarbonyl, Compound [C1-8] or a salt thereof can be produced by reacting Compound [C1-7] or a salt thereof with the corresponding carbamating agent in a solvent. Bases may be added according to conditions.

Examples of the corresponding carbamating agent include Boc_2O and the like. The preferred corresponding carbamating agent is Boc_2O .

Examples of the base include sodium hydroxide, sodium bicarbonate and the like.

Examples of the solvent include THF, water, mixed solvent thereof and the like. The preferred solvent is a mixed solvent of THF and water.

The reaction temperature is, for example, 0°C to 60°C, preferably 20°C to 40°C.

[0366]

(Step C1-6)

5 Compound [C1-9] or a salt thereof can be produced by reacting Compound [C1-8] or a salt thereof in the presence of a catalyst, in a solvent.

Examples of the catalyst include trifluoroacetic acid, p-toluenesulfonic acid, p-toluenesulfonic acid pyridine salt and
10 the like. The preferred catalyst is p-toluenesulfonic acid pyridine salt.

Examples of the solvent include THF, acetone, water, mixed solvent thereof and the like. The preferred solvent is a mixed solvent of acetone and water.

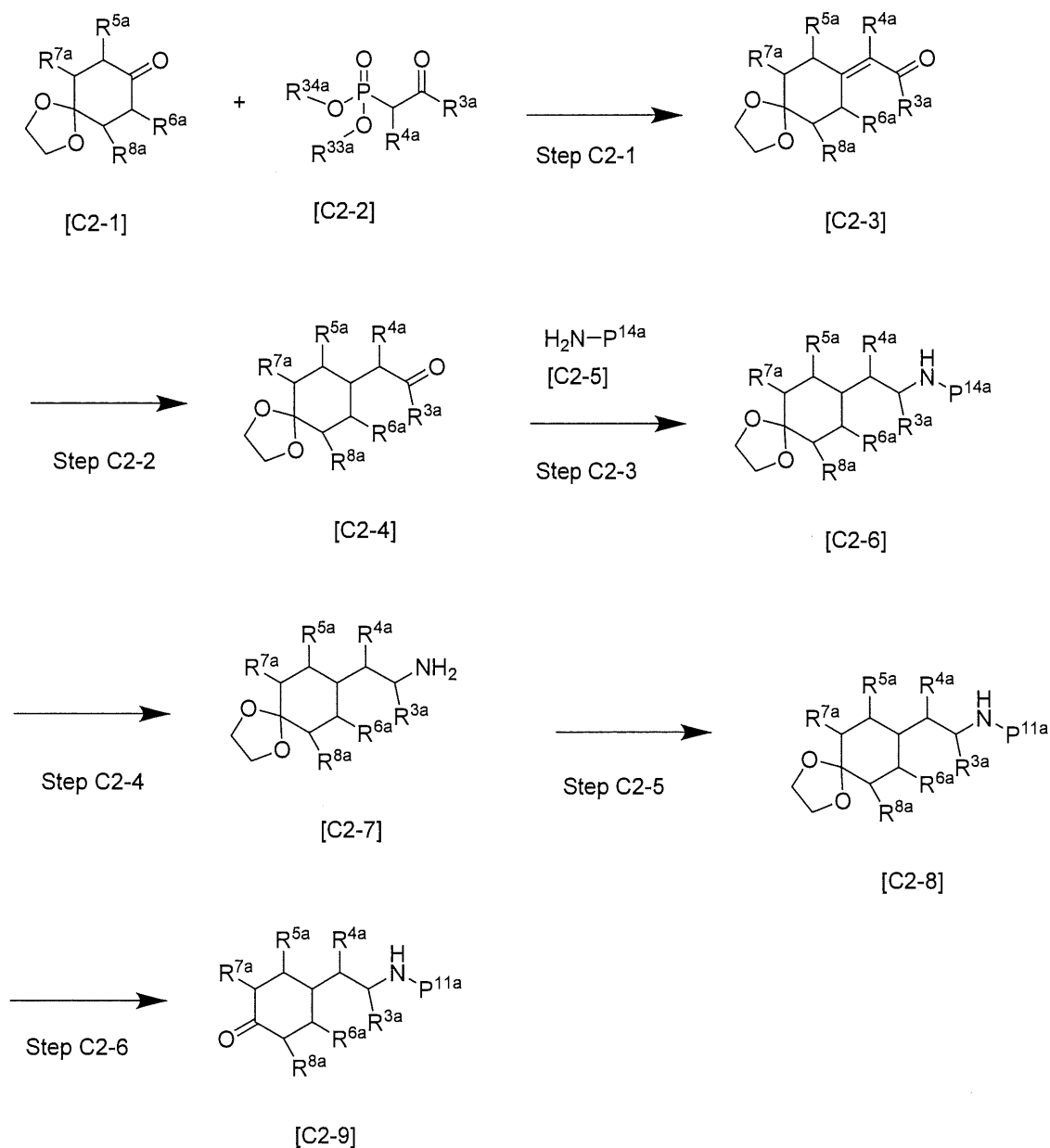
15 The reaction temperature is, for example, 20°C to 100°C, preferably 40°C to 80°C.

[0367]

Production Method C2: production method of Compound [C2-9] or a salt thereof

20 Compound [B3-3] or a salt thereof (used in Production Method B3) wherein R^{10a} is hydrogen and A^{2a} is CR^{5a}, i.e., Compound [C2-9] or a salt thereof, can be produced, for example, according to the following Production Method C2.

[0368]



[0369]

wherein

R^{3a}, R^{4a}, R^{5a}, R^{6a}, R^{7a}, R^{8a} and P^{11a} are as defined above,

5 R^{33a} and R^{34a} are each independently C₁₋₄ alkyl, and

P^{14a} is a protecting group for amine (for example, benzyl, (S)-1-phenylethyl, etc.).

[0370]

(Step C2-1)

10 Compound [C2-3] or a salt thereof can be produced by reacting Compound [C2-1] or a salt thereof with Compound [C2-2] or a salt thereof in the presence of a base, in a solvent.

Examples of the base include sodium ethoxide, sodium hydride, DBU and the like. The preferred base is sodium ethoxide.

Examples of the solvent include ethanol, THF, DMF and the
5 like. The preferred solvent is ethanol.

The reaction temperature is, for example, 0°C to 60°C, preferably 20°C to 40°C.

Compound [C2-1] or a salt thereof may be a commercially available product, or can be produced from a commercially
10 available product by a known method.

Compound [C2-2] or a salt thereof may be a commercially available product, or can be produced from a commercially available product by a known method.

[0371]

15 (Step C2-2)

Compound [C2-4] or a salt thereof can be produced by subjecting Compound [C2-3] or a salt thereof to catalytic hydrogenation in the presence of a metal catalyst, in a solvent.

20 Examples of the metal catalyst include Pd-C, Pt-C, palladium hydroxide and the like. The preferred metal catalyst is Pd-C or palladium hydroxide.

Examples of the solvent include methanol, ethanol, THF and the like. The preferred solvent is THF.

25 The reaction temperature is, for example, 0°C to 60°C, preferably 20°C to 40°C.

[0372]

(Step C2-3)

Compound [C2-6] or a salt thereof can be produced by
30 subjecting Compound [C2-4] or a salt thereof to a reductive amination reaction with Compound [C2-5] or a salt thereof in a solvent. The reductive amination reaction includes, for example, a reaction using an acid and a reducing agent.

Examples of the reducing agent include sodium
35 triacetoxymethylborohydride, sodium cyanoborohydride, sodium

borohydride and the like. The preferred reducing agent is sodium triacetoxyborohydride.

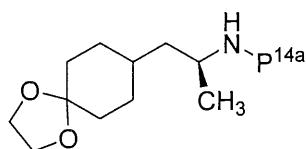
Examples of the acid include acetic acid, trifluoroacetic acid, hydrochloric acid and the like. The preferred acid is
5 acetic acid.

Examples of the solvent include THF, chloroform, toluene, N-methylpyrrolidone and the like. The preferred solvent is THF.

The reaction temperature is, for example, 0°C to 60°C,
10 preferably 20°C to 40°C.

Compound [C2-5] or a salt thereof may be a commercially available product, or can be produced from a commercially available product by a known method.

Compound [C2-6] or a salt thereof wherein R^{3a} is methyl,
15 and R^{4a}, R^{5a}, R^{6a}, R^{7a} and R^{8a} are all hydrogens, i.e., the following Compound [C2-10]
[0373]



[C2-10]

[0374]

20 wherein

P^{14a} are as defined above

or a salt thereof can be produced by, for example, carrying out Step C2-3 using (S)-1-phenethylamine as Compound [C2-5] or a salt thereof, and stirring the obtained diastereomeric mixture
25 or a salt thereof in a solvent, and then collecting the precipitated solid by filtration.

Examples of the solvent include toluene, THF, ethyl acetate and the like. The preferred solvent is ethyl acetate.
[0375]

30 (Step C2-4)

Compound [C2-7] or a salt thereof can be produced by removing the protecting group P^{14a} of Compound [C2-6] or a salt thereof employing a deprotection reaction. The deprotection reaction can be carried out under a condition suitable for the
5 type of P^{14a}.

For example, when P^{14a} is (S)-1-phenylethyl, Compound [C2-7] or a salt thereof can be produced by reacting Compound [C2-6] or a salt thereof according to Step C2-2.

[0376]

10 (Step C2-5)

Compound [C2-8] or a salt thereof can be produced by introducing the protecting group P^{11a} to Compound [C2-7] or a salt thereof. The introduction of the protecting group can be carried out under a condition suitable for the type of P^{11a}.

15 For example, when P^{11a} is tert-butoxycarbonyl, Compound [C2-8] or a salt thereof can be produced by reacting Compound [C2-7] or a salt thereof with the corresponding carbamating agent in a solvent. Bases may be added according to conditions.

20 Examples of the corresponding carbamating agent include Boc₂O and the like. The preferred corresponding carbamating agent is Boc₂O.

Examples of the base include sodium hydroxide, sodium bicarbonate and the like.

25 Examples of the solvent include THF, water, mixed solvent thereof and the like. The preferred solvent is a mixed solvent of THF and water.

The reaction temperature is, for example, 0°C to 60°C, preferably 20°C to 40°C.

30 [0377]

(Step C2-6)

Compound [C2-9] or a salt thereof can be produced by reacting Compound [C2-8] or a salt thereof in the presence of a catalyst in a solvent.

Examples of the catalyst include trifluoroacetic acid, p-toluenesulfonic acid, p-toluenesulfonic acid pyridine salt and the like. The preferred catalyst is p-toluenesulfonic acid pyridine salt.

5 Examples of the solvent include THF, acetone, water, mixed solvent thereof and the like. The preferred solvent is a mixed solvent of acetone and water.

The reaction temperature is, for example, 20°C to 100°C, preferably 40°C to 80°C.

10 **Examples**

[0378]

Next, the production method of Compound [I] or Compound [Ia] or a pharmaceutically acceptable salt thereof of the present invention will be concretely explained with reference
15 to the following Production Examples. However, the production method of Compound [I] or Compound [Ia] or a pharmaceutically acceptable salt thereof of the present invention should not be limited to such production examples.

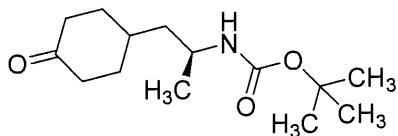
The compound obtained in each step can be, if necessary,
20 isolated or purified according to a method known per se such as distillation, recrystallization and column chromatography, or directly used in the next step without isolation or purification.

As used herein, the room temperature refers to a
25 temperature in an uncontrolled state, and one embodiment includes 1°C to 40°C.

[0379]

[Production Example 1]: Synthesis of tert-butyl (S)-(1-(4-oxocyclohexyl)propan-2-yl)carbamate

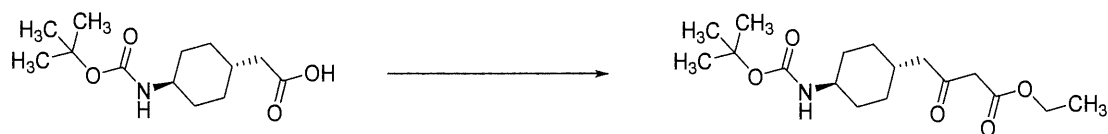
30 [0380]



[0381]

(1) ethyl 4-(trans-4-((tert-butoxycarbonyl)amino)cyclohexyl)-3-oxobutanoate

[0382]



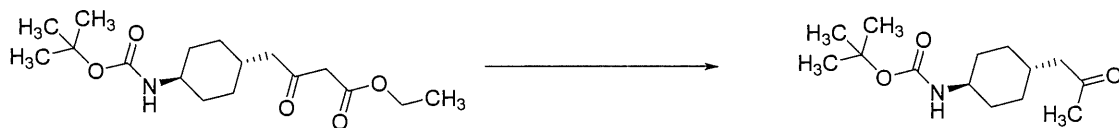
5 [0383]

Under argon atmosphere, to a solution of 2-(trans-4-((tert-butoxycarbonyl)amino)cyclohexyl)acetic acid (1.4 kg) in THF (6.2 kg) was added dropwise a solution of carbonyldiimidazole (1 kg) in DMF (4.7 kg) at room temperature, and the mixture was stirred. The washing with DMF (0.7 kg) is combined therewith, and the mixture was stirred for 3 hr. Monoethyl potassium malonate (1.3 kg) was added thereto, and then magnesium chloride (0.6 kg) was added thereto in divided portions. After stirring all day, water (4.2 kg) and 6M hydrochloric acid (3.1 kg) were added thereto at an internal temperature of 5°C, and the mixture was stirred at room temperature for 1 hr. Toluene (6.1 kg) was added thereto, the mixture was subjected to extraction, and the aqueous layer was subjected to re-extraction with toluene (2.4 kg). The combined organic layers were washed twice with 20% brine (7 kg). The organic layer was concentrated under reduced pressure, followed by azeotropy with methanol (2.2 kg). To the obtained residue was added methanol (3.3 kg) to give a methanol solution. The above methanol solution was combined with a methanol solution obtained by the same procedures from 2-(trans-4-((tert-butoxycarbonyl)amino)cyclohexyl)acetic acid (8 kg) to give a methanol solution (34 kg) of the title compound. A part of it was concentrated to give an NMR sample.

¹H-NMR (CDCl₃) δ: 4.44-4.31 (1H, m), 4.19 (2H, q, J = 7.1 Hz), 3.46-3.27 (1H, m), 3.40 (2H, s), 2.43 (2H, d, J = 6.3 Hz), 2.04-1.93 (2H, m), 1.88-1.69 (3H, m), 1.44 (9H, s), 1.28 (3H, t, J = 7.1 Hz), 1.19-0.97 (4H, m).

[0384]

(2) tert-butyl (trans-4-(2-oxopropyl)cyclohexyl)carbamate
[0385]



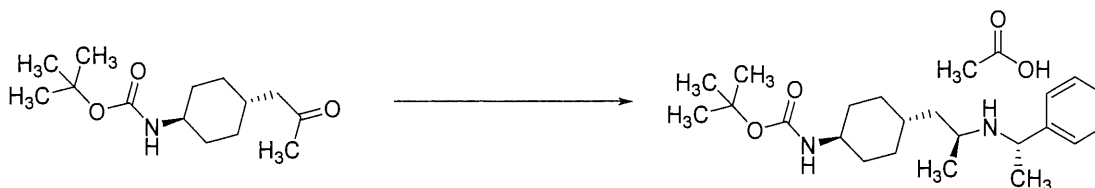
[0386]

5 The methanol solution obtained in (1) (34 kg) of ethyl 4-(trans-4-((tert-butoxycarbonyl)amino)cyclohexyl)-3-oxobutanoate was warmed to 35°C, 4M aqueous sodium hydroxide solution (20 kg) was added thereto, and the mixture was stirred. After stirring at 40°C for 2 hr, a solution of citric acid (8.4 kg)
10 in water (19 kg) was added dropwise thereto at 45°C. Ethyl acetate (25 kg) was added thereto, the mixture was stirred for 20 min, and a solution of citric acid (8.4 kg) in water (19 kg) was added dropwise thereto. After stirring for 3 hr, the mixture was allowed to cool to room temperature, ethyl acetate
15 (25 kg) was added thereto, and the mixture was subjected to liquid separation. The organic layer was washed with 10% brine (47 kg), and concentrated under reduced pressure. Ethyl acetate (17 kg) was added thereto, and the mixture was concentrated under reduced pressure to give the title compound
20 (8.1 kg) in 87% yield.

¹H-NMR (CDCl₃) δ: 4.36 (1H, br s), 3.35 (1H, br s), 2.31 (2H, d, J = 6.4 Hz), 2.12 (3H, s), 2.02-1.95 (2H, m), 1.83-1.71 (3H, m), 1.44 (9H, s), 1.18-0.95 (4H, m).

[0387]

25 (3) tert-butyl (trans-4-((S)-2-(((S)-1-phenylethyl)amino)propyl)cyclohexyl)carbamate acetate
[0388]



[0389]

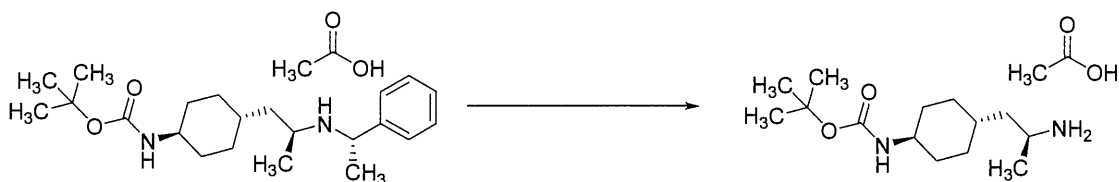
A solution of tert-butyl (trans-4-(2-oxopropyl)cyclohexyl)carbamate obtained in (2) (8.1 kg) in methanol (67 kg) was prepared, and under Ar atmosphere, (S)-1-phenethylamine (4.4 kg), acetic acid (1.2 kg) and a suspension
 5 of 2% Pt-C (0.42 kg) in water (1.7 kg) were added thereto at room temperature, and the mixture was stirred. The mixture was stirred under hydrogen atmosphere (4 atm) at 40°C for 20 hr. After cooling to room temperature, the 2% Pt-C was removed by filtration with KC flock (registered trademark) as a filter
 10 aid, and washed twice with methanol (15 kg). The obtained solution was concentrated under reduced pressure, isopropyl alcohol (20 kg) was added thereto, and the mixture was concentrated under reduced pressure. The same operation was performed again, and to the obtained solid was added isopropyl
 15 alcohol (43 kg) to prepare a suspension. This suspension was heated to 70°C, and acetic acid (1 kg) was added dropwise thereto. After stirring for 2 hr, the mixture was allowed to cool to room temperature, and stirred for 17 hr. The mixture was stirred for additional 2 hr at an internal temperature of
 20 5°C, and the obtained solid was collected by filtration, washed with ice-cooled isopropyl alcohol (20 kg), and dried at 30°C for 19 hr to give the title compound (9 kg) in 65% yield.

¹H-NMR (DMSO-D₆) δ: 7.35-7.25 (4H, m), 7.21-7.15 (1H, m), 6.62 (1H, d, J = 7.5 Hz), 3.80 (1H, q, J = 6.5 Hz), 3.17-3.01 (1H, m), 2.48-2.38 (1H, m), 1.90 (3H, s), 1.77-1.59 (3H, m), 1.54-1.28 (11H, m), 1.23-0.66 (12H, m).

[0390]

(4) tert-butyl (S)-(trans-4-(2-aminopropyl)cyclohexyl)carbamate acetate

30 [0391]



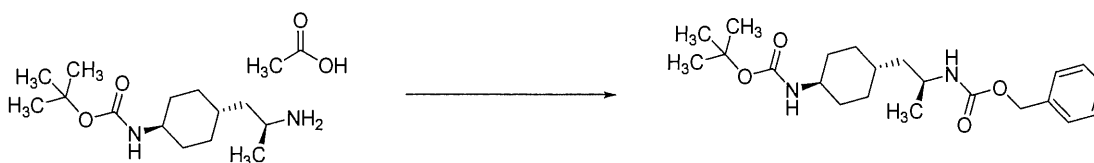
[0392]

To a solution of tert-butyl (trans-4-((S)-2-((S)-1-phenylethyl)amino)propyl)cyclohexyl)carbamate acetate obtained in (3) (8.9 kg) in methanol (85 kg) was added a suspension of 5% Pd-C (PE type) (0.89 kg) in water (1.8 kg) under Ar

5 atmosphere at room temperature, and the mixture was stirred. The mixture was stirred under hydrogen atmosphere (4 atm) at 35°C for 2 hr. After gradually cooling to room temperature, the 5% Pd-C was removed by filtration with KC flock (registered trademark) as a filter aid, and washed with methanol (21 kg).
10 The filtrate was concentrated under reduced pressure, followed by azeotropy with acetonitrile (21 kg). To the obtained solid was added methanol (42 kg) to give a methanol solution of the title compound. A part of it was concentrated to give an NMR sample.

15 ¹H-NMR (DMSO-D₆) δ: 6.71-6.64 (1H, m), 6.14 (3H, br s), 3.21-3.02 (1H, m), 2.99-2.86 (1H, m), 1.84-1.58 (7H, m), 1.37 (9H, s), 1.32-1.04 (5H, m), 1.03-0.96 (3H, m), 0.94-0.75 (2H, m).
[0393]

(5) benzyl (S)-(1-(trans-4-((tert-butoxycarbonyl)amino)cyclohexyl)propan-2-yl)carbamate
20 [0394]



[0395]

To a solution of tert-butyl (S)-(trans-4-(2-aminopropyl)cyclohexyl)carbamate acetate (obtained in the same manner as in (4)) (218 g) in DMF (1080 ml) was added triethylamine (100 ml) at room temperature, and the mixture was stirred. Under water-cooling, N-carbobenzoxysuccinimide (179 g) was added thereto, and the mixture was stirred at room
30 temperature for 6 hr. Under water-cooling, water (2160 ml) was added thereto, and the mixture was stirred for 1 hr. The obtained solid was collected by filtration, washed with water

(1200 ml), and dried at room temperature for 48 hr to give seed crystals (257 g) of the title compound in 97% yield.

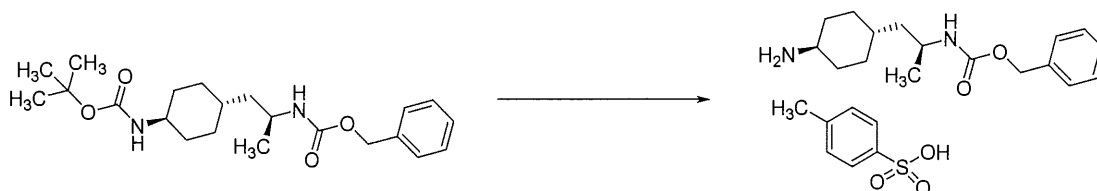
To a methanol solution obtained in (4) of tert-butyl (S)-(trans-4-(2-aminopropyl)cyclohexyl)carbamate acetate were added
5 triethylamine (5.1 kg) and a solution of N-carbobenzoxysuccinimide (5.8 kg) in acetonitrile (14 kg) at 10°C, and the mixture was stirred. The washing with acetonitrile (3.5 kg) is combined therewith, and the mixture was stirred for 3 hr. Water (8.9 kg) was added thereto, the
10 seed crystals obtained in the same manner as above were added thereto, and the mixture was stirred for 2 hr. The obtained solid was collected by filtration, washed with 50% methanol aqueous solution (24 kg), and dried for 69 hr to give the title compound (8 kg) in 97% yield.

15 ¹H-NMR (DMSO-D₆) δ: 7.41-7.27 (5H, m), 7.06 (1H, d, J = 8.2 Hz), 6.66 (1H, d, J = 8.2 Hz), 5.03 (1H, d, J = 12.0 Hz), 4.98 (1H, d, J = 12.0 Hz), 3.66-3.52 (1H, m), 3.19-3.03 (1H, m), 1.80-1.51 (4H, m), 1.43-1.26 (1H, m), 1.37 (9H, s), 1.23-0.75 (6H, m), 1.01 (3H, d, J = 6.7 Hz).

20 [0396]

(6) benzyl (S)-(1-(trans-4-aminocyclohexyl)propan-2-yl)carbamate p-toluenesulfonate

[0397]



25 [0398]

A suspension of benzyl (S)-(1-(trans-4-((tert-butoxycarbonyl)amino)cyclohexyl)propan-2-yl)carbamate (obtained in the same manner as in (5)) (257 g) in ethyl acetate (2570 ml) was heated to 80°C, p-toluenesulfonic acid monohydrate (188
30 g) was added thereto, and the mixture was stirred for 3 hr. After gradually cooling to room temperature, the mixture was allowed to stand all day. The obtained solid was collected by

filtration, and washed with ethyl acetate (236 ml). The solid was dried at 50°C for 8 hr dried under reduced pressure, and then dried under reduced pressure at room temperature all day to give seed crystals (281 g) of the title compound in 92%
5 yield.

A suspension of benzyl (S)-(1-(trans-4-((tert-butoxycarbonyl)amino)cyclohexyl)propan-2-yl)carbamate obtained in (5) (8 kg) in ethyl acetate (58 kg) was prepared, p-toluenesulfonic acid monohydrate (5.1 kg) was added thereto at
10 room temperature, and the mixture was stirred. The washing with ethyl acetate (1.4 kg) is combined therewith, and the mixture was stirred for 1 hr. the seed crystals obtained in the same manner as above were added thereto, and the mixture was stirred for 1 hr, warmed to 55°C, and stirred for 4 hr.
15 After gradually cooling to room temperature, the mixture was stirred for 14 hr. The obtained solid was collected by filtration, washed with ethyl acetate (22 kg), and dried at 50°C for 23 hr to give the title compound (9 kg) in 96% yield. ¹H-NMR (DMSO-D₆) δ: 7.67 (3H, br s), 7.47 (2H, d, J = 8.2 Hz),
20 7.41-7.28 (5H, m), 7.14-7.06 (3H, m), 5.02 (1H, d, J = 12.7 Hz), 4.98 (1H, d, J = 12.7 Hz), 3.66-3.53 (1H, m), 2.98-2.83 (1H, m), 2.29 (3H, s), 1.95-1.60 (4H, m), 1.39-0.81 (7H, m), 1.02 (3H, d, J = 6.7 Hz).

[0399]

25 (7) benzyl (S)-(1-trans-(4-aminocyclohexyl)propan-2-yl)carbamate

[0400]



[0401]

30 To a solution of benzyl (S)-(1-(trans-4-aminocyclohexyl)propan-2-yl)carbamate p-toluenesulfonate

obtained in (6) (30 g) in 2-methyl-tetrahydrofuran (120 ml) was added 4M aqueous sodium hydroxide solution (17 ml) at room temperature, and the mixture was stirred for 1.5 hr. Water (120 ml) was added thereto, the mixture was subjected to
5 extraction, and the organic layer was washed with water (120 ml, twice) and saturated brine (120 ml), and dried over sodium sulfate. The sodium sulfate was removed by filtration, and the filtrate was concentrated under reduced pressure. Methanol (90 ml) was added thereto, and the mixture was concentrated under
10 reduced pressure to give the title compound (18 g) in 96% yield.

¹H-NMR (DMSO-D₆) δ: 7.41-7.25 (5H, m), 7.05 (1H, d, J = 8.5 Hz), 5.03 (1H, d, J = 12.5 Hz), 4.97 (1H, d, J = 12.5 Hz), 3.68-3.50 (1H, m), 2.46-2.33 (1H, m), 1.81-0.71 (13H, m), 1.01
15 (3H, d, J = 6.5 Hz).

[0402]

(8) benzyl (S)-(1-(4-oxocyclohexyl)propan-2-yl)carbamate

[0403]



20 [0404]

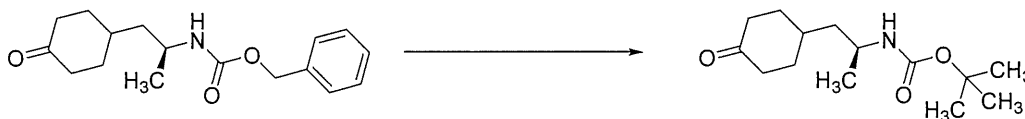
To a solution of benzyl (S)-(1-trans-(4-aminocyclohexyl)propan-2-yl)carbamate obtained in (7) (18 g) in methanol (90 ml) was added 3,5-di-tert-butyl-1,2-benzoquinone (14 g) at room temperature, and the mixture was stirred for 1.5
25 hr. Water (18 ml), acetone (72 ml) and DOWEX (45 g) were added thereto, and the mixture was stirred for 1.5 hr. Additional DOWEX (9 g) was added thereto, and the mixture was stirred for 30 min. The mixture was filtered with ethyl acetate, and the filtrate was concentrated under reduced pressure. Ethyl
30 acetate (72 ml) and water (36 ml) were added thereto, the mixture was subjected to extraction, and the organic layer was dried over sodium sulfate. The sodium sulfate was removed by filtration, and the filtrate was concentrated under reduced pressure. Ethyl acetate (36 ml) and silica gel (18 g) were

added thereto, and the mixture was stirred for 30 min. The mixture was filtered with ethyl acetate, and the filtrate was concentrated under reduced pressure. To the obtained residue was added diisopropyl ether (18 ml), and the mixture was warmed
5 to an internal temperature of 48°C. Heptane (72 ml) was added dropwise thereto, and the mixture was stirred for 1.5 hr. The obtained solid was collected by filtration, washed with heptane, and dried under reduced pressure at 60°C for 3 hr and then at room temperature all day to give the title compound (15
10 g) in 83% yield.

¹H-NMR (DMSO-D₆) δ: 7.41-7.25 (5H, m), 7.15 (1H, d, J = 8.6 Hz), 5.03 (1H, d, J = 12.4 Hz), 4.99 (1H, d, J = 12.4 Hz), 3.70-3.55 (1H, m), 2.40-2.10 (4H, m), 2.08-1.66 (3H, m), 1.49-1.18 (4H, m), 1.06 (3H, d, J = 6.5 Hz).

15 [0405]

(9) tert-butyl (S)-(1-(4-oxocyclohexyl)propan-2-yl)carbamate
[0406]



[0407]

20 To a solution of benzyl (S)-(1-(4-oxocyclohexyl)propan-2-yl)carbamate obtained in (8) (15 g) in methanol (145 ml) were added 10% Pd-C (1.5 g) and Boc₂O (12 g) under argon atmosphere at room temperature. The mixture was stirred under hydrogen atmosphere (1 atm) for 4 hr. After purging with nitrogen, the
25 10% Pd-C was removed by Celite filtration, and washed with methanol. The filtrate was concentrated under reduced pressure, to the obtained residue was added acetone (27 ml), and the mixture was stirred at room temperature. Water (82 ml) was added thereto, and the mixture was stirred all day. The
30 obtained solid was collected by filtration, washed with water, and dried under reduced pressure at 60°C for 3 hr and then at room temperature all day to give the title compound (12 g) in 88% yield. The same procedures as in (7)-(9) above were

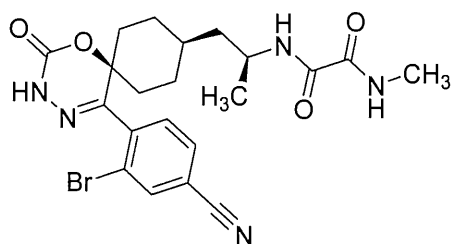
performed with benzyl (S)-(1-(trans-4-aminocyclohexyl)propan-2-yl)carbamate p-toluenesulfonate (211 g) to give the title compound (60 g).

1H-NMR (DMSO-D6) δ : 6.65 (1H, d, J = 8.6 Hz), 3.63-3.46 (1H, m), 2.42-2.10 (4H, m), 2.08-1.97 (1H, m), 1.94-1.83 (1H, m), 1.80-1.66 (1H, m), 1.46-1.16 (4H, m), 1.38 (9H, s), 1.02 (3H, d, J = 6.5 Hz).

[0408]

[Production Example 2]: Synthesis of N¹-((S)-1-(cis-5-(2-bromo-4-cyanophenyl)-2-oxo-1-oxa-3,4-diazaspiro[5.5]undec-4-en-9-yl)propan-2-yl)-N²-methyloxamide (Example 57)

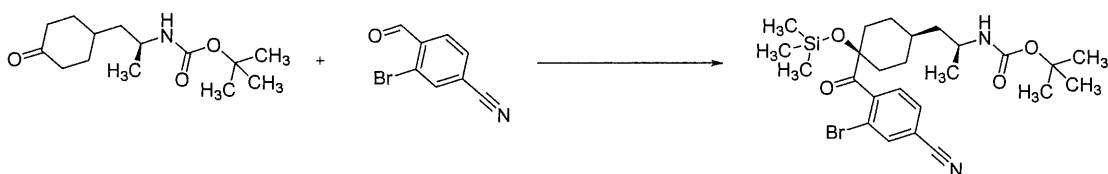
[0409]



[0410]

(1) tert-butyl ((S)-1-(cis-4-(2-bromo-4-cyanobenzoyl)-4-((trimethylsilyl)oxy)cyclohexyl)propan-2-yl)carbamate

[0411]



[0412]

To a solution of 3-bromo-4-formylbenzonitrile (2.1 g) in THF (4 ml) were added lithium chloride (0.043 g) and trimethylsilylcyanide (1.5 ml) at room temperature, and the mixture was stirred at room temperature for 1 hr. THF (26 ml) was added thereto, and the mixture was cooled to -78°C. 1M NaHMDS-THF solution (10.2 ml) was added thereto, and the mixture was stirred for 3 min. A solution of tert-butyl (S)-(1-(4-oxocyclohexyl)propan-2-yl)carbamate (obtained in the same manner as in (9) of [Production Example 1]) (2 g) in THF (10

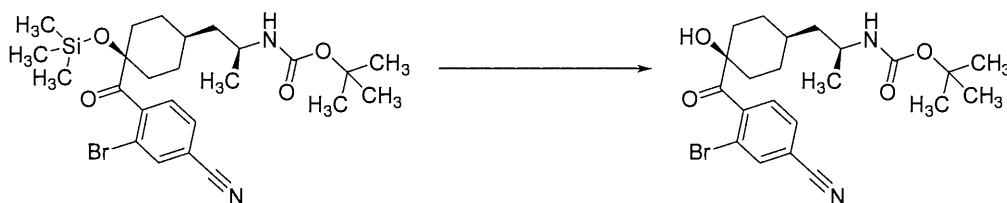
ml) was added thereto, and the mixture was stirred for 30 min, and warmed to -10°C over 1 hr. Water and ethyl acetate were added thereto, and the mixture was subjected to extraction. The aqueous layer was subjected to re-extraction twice with
 5 ethyl acetate, and the combined organic layers were washed with saturated brine, and dried over sodium sulfate. The sodium sulfate was removed by filtration, and the filtrate was concentrated under reduced pressure. The obtained residue was purified by silica gel chromatography (developing solvent:
 10 ethyl acetate/n-hexane) to give the title compound (1.2 g) in 28% yield.

¹H-NMR (CDCl₃) δ: 7.89 (1H, s), 7.62 (1H, d, J = 8.1 Hz), 7.39 (1H, d, J = 8.1 Hz), 4.30-4.15 (1H, m), 3.84-3.56 (1H, m), 2.01-1.92 (2H, m), 1.86-1.70 (3H, m), 1.64-1.52 (1H, m), 1.43
 15 (9H, s), 1.40-1.18 (5H, m), 1.11 (3H, d, J = 6.5 Hz), 0.04 (9H, s).

[0413]

(2) tert-butyl ((S)-1-(cis-4-(2-bromo-4-cyanobenzoyl)-4-hydroxycyclohexyl)propan-2-yl)carbamate

20 [0414]



[0415]

To a solution of tert-butyl ((S)-1-(cis-4-(2-bromo-4-cyanobenzoyl)-4-((trimethylsilyl)oxy)cyclohexyl)propan-2-yl)carbamate obtained in (1) and the same compound obtained in
 25 the same manner as above (total 1.4 g) in THF (2.7 ml) were added acetic acid (0.42 ml) and 1M TBAF-THF solution (3.7 ml) at room temperature, and the mixture was stirred for 15 min. Saturated aqueous ammonium chloride solution, water and ethyl
 30 acetate were added thereto, and the mixture was subjected to extraction. The aqueous layer was subjected to re-extraction twice with ethyl acetate, and the combined organic layers were

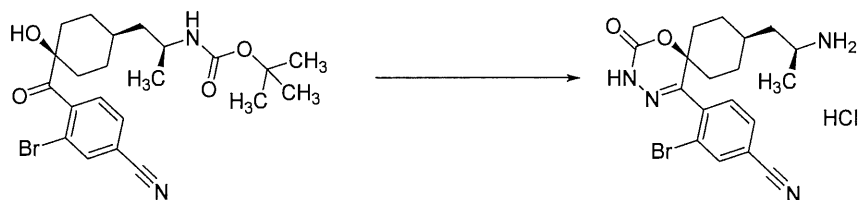
washed with saturated aqueous sodium bicarbonate solution and saturated brine, and dried over sodium sulfate. The sodium sulfate was removed by filtration, and the filtrate was concentrated under reduced pressure. The obtained residue was purified by silica gel chromatography (developing solvent: ethyl acetate/n-hexane) to give the title compound (1.1 g) in 93% yield.

¹H-NMR (CDCl₃) δ: 7.89 (1H, s), 7.65 (1H, d, J = 8.1 Hz), 7.32 (1H, d, J = 7.5 Hz), 4.30-4.17 (1H, m), 3.84-3.67 (1H, m), 2.66 (1H, s), 1.93-1.74 (5H, m), 1.69-1.60 (1H, m), 1.50-1.22 (5H, m), 1.43 (9H, s), 1.10 (3H, d, J = 5.9 Hz).

[0416]

(3) 4-(cis-9-((S)-2-aminopropyl)-2-oxo-1-oxa-3,4-diazaspiro[5.5]undec-4-en-5-yl)-3-bromobenzonitrile hydrochloride

[0417]



[0418]

To a solution of tert-butyl ((S)-1-(cis-4-(2-bromo-4-cyanobenzoyl)-4-hydroxycyclohexyl)propan-2-yl)carbamate obtained in (2) (1.1 g) in THF (11 ml) were added DBU (0.052 ml) and CDI (0.55 g) at room temperature, and the mixture was stirred for 1 hr. Hydrazine monohydrate was added thereto, and the mixture was stirred for 30 min. 10% Aqueous citric acid solution and ethyl acetate were added thereto, and the mixture was subjected to extraction. The aqueous layer was subjected to re-extraction twice with ethyl acetate, and the combined organic layers were washed with saturated brine, and dried over sodium sulfate. The sodium sulfate was removed by filtration, and the filtrate was concentrated under reduced pressure. The obtained residue was purified by silica gel chromatography (developing solvent: ethyl acetate/n-hexane, ethyl

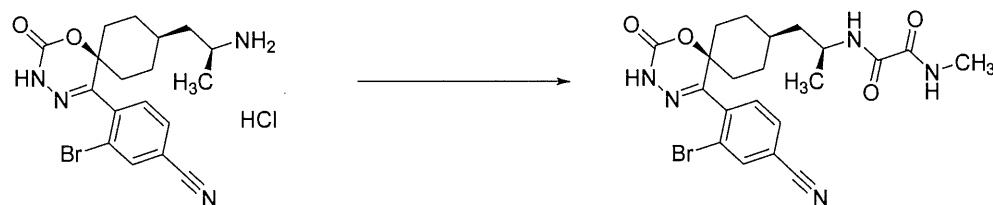
acetate/methanol). To the obtained solid were added THF (6.5 ml) and 6M hydrochloric acid (3.2 ml) at room temperature, and the mixture was stirred all day and then at 50°C for 5 hr. The reaction solution was concentrated under reduced pressure,
 5 followed by azeotropy twice with THF (2 ml) to give the title compound (0.61 g).

¹H-NMR (DMSO-D₆) δ: 11.37 (1H, s), 8.39 (1H, s), 7.99 (1H, d, J = 8.1 Hz), 7.90-7.72 (3H, m), 7.70 (1H, d, J = 8.1 Hz), 3.27-3.13 (1H, m), 2.23-2.10 (2H, m), 1.62-1.17 (9H, m), 1.13 (3H,
 10 d, J = 5.4 Hz).

[0419]

(4) N¹-((S)-1-(cis-5-(2-bromo-4-cyanophenyl)-2-oxo-1-oxa-3,4-diazaspiro[5.5]undec-4-en-9-yl)propan-2-yl)-N²-methyloxamide

[0420]



15

[0421]

To a solution of 4-(cis-9-((S)-2-aminopropyl)-2-oxo-1-oxa-3,4-diazaspiro[5.5]undec-4-en-5-yl)-3-bromobenzonitrile hydrochloride obtained in (3) (0.57 g) in DMF (8.4 ml) were
 20 added 2-methylamino-2-oxoacetic acid (0.24 g), HOAt (0.33 g) and N,N-diisopropylethylamine (1.0 ml) at room temperature. WSC (0.47 g) was added thereto, and the mixture was stirred at room temperature all day. Water, saturated aqueous sodium bicarbonate solution and ethyl acetate were added thereto, and
 25 the mixture was subjected to extraction. The aqueous layer was subjected to re-extraction twice with ethyl acetate, and the combined organic layers were washed with saturated brine, and dried over sodium sulfate. The sodium sulfate was removed by filtration, and the filtrate was concentrated under reduced
 30 pressure. The residue was subjected to azeotropy twice with toluene (10 ml), and the obtained residue was purified by silica gel chromatography (developing solvent: ethyl acetate/n-

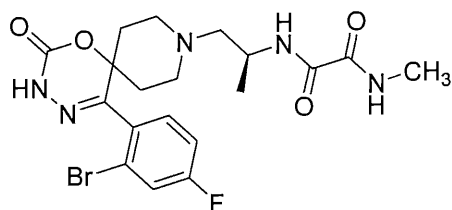
hexane), and then reverse-phase silica gel chromatography (developing solvent: acetonitrile/water). The obtained solid was subjected to recrystallization in ethyl acetate (8.4 ml)/isopropyl ether (8.4 ml) at 50°C, and the mixture was stirred at room temperature all day. The obtained suspension was filtered, and the obtained solid was washed threetimes with a mixed solvent (1 ml) of ice-cooled ethyl acetate:isopropyl ether=1:1, and dried under reduced pressure at 50°C for 4 hr to give the title compound (0.30 g) in 57% yield.

¹H-NMR (CDCl₃) δ: 8.24 (1H, s), 7.97 (1H, d, J = 1.6 Hz), 7.68 (1H, dd, J = 7.9, 1.6 Hz), 7.44-7.39 (1H, m), 7.33 (1H, d, J = 7.9 Hz), 7.18-7.14 (1H, m), 4.08-4.00 (1H, m), 2.89 (3H, d, J = 5.3 Hz), 2.34-2.28 (2H, m), 1.79-1.72 (1H, m), 1.60-1.51 (2H, m), 1.50-1.31 (5H, m), 1.30-1.21 (1H, m), 1.16 (3H, d, J = 6.5 Hz).

[0422]

[Production Example 3]: Synthesis of (S)-N¹-(1-(5-(2-bromo-4-fluorophenyl)-2-oxo-1-oxa-3,4,9-triazaspiro[5.5]undec-4-en-9-yl)propan-2-yl)-N²-methyloxamide (Example 179)

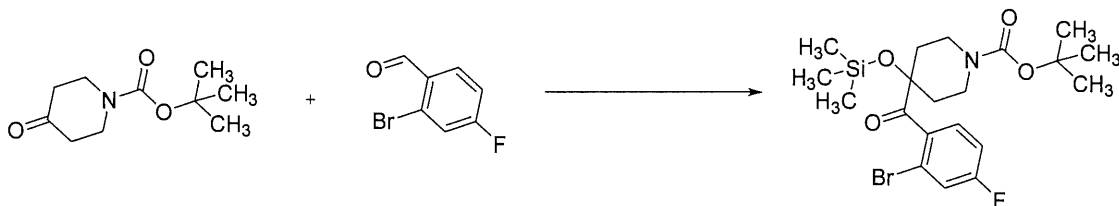
[0423]



[0424]

(1) tert-butyl 4-(2-bromo-4-fluorobenzoyl)-4-((trimethylsilyl)oxy)piperidine-1-carboxylate

[0425]



[0426]

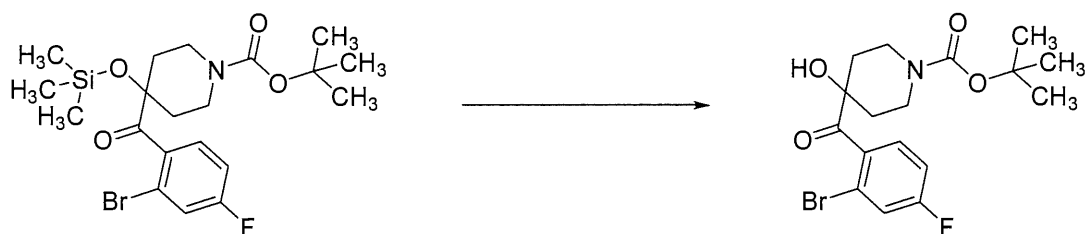
To a solution of 2-bromo-4-fluorobenzaldehyde (1.2 ml) and DMAP (0.015 g) in acetonitrile (20 ml) was added trimethylsilylcyanide (1.5 ml) at room temperature, and the mixture was stirred for 3 hr. The reaction solution was concentrated, THF (18 ml) was added thereto, and the mixture was cooled to -78°C. 1.1M LiHMDS-n-hexane solution (10 ml) was added thereto, and the mixture was stirred for 30 min. A solution of tert-butyl 4-oxopiperidine-1-carboxylate (2 g) in THF (9 ml) was added thereto, and the mixture was stirred for 1 hr. 2M Hydrochloric acid (12 ml) was added thereto, and the mixture was stirred at room temperature all day. The reaction solution was ice-cooled, 2M aqueous sodium hydroxide solution (12.5 ml) was added thereto, and the mixture was stirred at room temperature for 30 min. Water and ethyl acetate were added thereto, and the mixture was subjected to extraction. The aqueous layer was subjected to re-extraction with ethyl acetate, and the combined organic layers were dried over magnesium sulfate. The magnesium sulfate was removed by filtration, and the filtrate was concentrated under reduced pressure. The obtained residue was purified by silica gel chromatography (developing solvent: ethyl acetate/n-hexane=15/85 to 35/65) to give the title compound (1.8 g) in 34% yield.

¹H-NMR (DMSO-D₆) δ: 7.74 (1H, dd, J = 8.7, 2.4 Hz), 7.62 (1H, dd, J = 8.6, 6.0 Hz), 7.38 (1H, td, J = 8.6, 2.5 Hz), 3.66 (2H, dt, J = 13.9, 4.0 Hz), 3.24-3.14 (2H, m), 1.92-1.83 (2H, m), 1.82-1.75 (2H, m), 1.38 (9H, s), 0.06 (9H, s).

[0427]

(2) tert-butyl 4-(2-bromo-4-fluorobenzoyl)-4-hydroxypiperidine-1-carboxylate

[0428]



[0429]

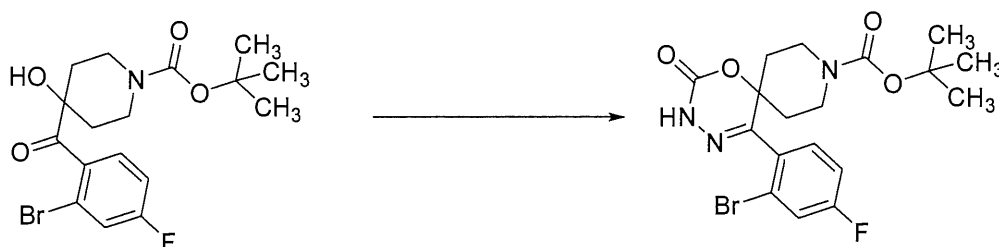
To a solution of tert-butyl 4-(2-bromo-4-fluorobenzoyl)-4-((trimethylsilyl)oxy)piperidine-1-carboxylate obtained in (1) (1.0 g) in THF (8.8 ml) was added 1M TBAF-THF solution (1.9 ml) at room temperature, and the mixture was stirred for 1 hr. Saturated aqueous ammonium chloride solution and ethyl acetate were added thereto, and the mixture was subjected to extraction. The organic layer was concentrated under reduced pressure, and the obtained residue was purified by silica gel chromatography (developing solvent: ethyl acetate/n-hexane=20/80 to 40/60) to give the title compound (0.74 g) in 92% yield.

¹H-NMR (DMSO-D₆) δ: 7.67 (1H, dd, J = 8.8, 2.5 Hz), 7.58 (1H, dd, J = 8.6, 6.0 Hz), 7.34 (1H, td, J = 8.6, 2.4 Hz), 5.70 (1H, s), 3.84-3.73 (2H, m), 3.15-2.92 (2H, m), 1.81-1.66 (4H, m), 1.40 (9H, s).

[0430]

(3) tert-butyl 5-(2-bromo-4-fluorophenyl)-2-oxo-1-oxa-3,4,9-triazaspiro[5.5]undec-4-ene-9-carboxylate

[0431]



[0432]

To a solution of tert-butyl 4-(2-bromo-4-fluorobenzoyl)-4-hydroxypiperidine-1-carboxylate obtained in (2) (0.74 g) in THF (6.9 ml) were added DBU (0.026 ml) and CDI (0.42 g) at room temperature, and the mixture was stirred for 1 hr. Hydrazine

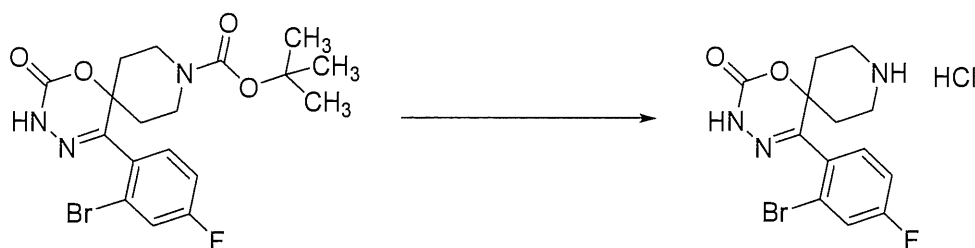
monohydrate (0.25 ml) was added thereto, and the mixture was stirred for 1 hr. 1M Hydrochloric acid and ethyl acetate were added thereto, and the mixture was subjected to extraction. The aqueous layer was subjected to re-extraction with ethyl
 5 acetate, and the combined organic layers were washed with saturated aqueous sodium bicarbonate solution and saturated brine, and dried over magnesium sulfate. The sodium sulfate was removed by filtration, and the filtrate was concentrated under reduced pressure. To the obtained residue were added THF
 10 (7.3 ml) and 6M hydrochloric acid (3.7 ml) at room temperature, and the mixture was stirred for 20 hr. The mixture was neutralized with 4M aqueous sodium hydroxide solution (6.0 ml), Boc₂O (0.44 ml) was added thereto, and the mixture was stirred for 1 hr. Ethyl acetate was added thereto, and the mixture was
 15 subjected to extraction. The organic layer was concentrated under reduced pressure, and the obtained residue was purified by silica gel chromatography (developing solvent: ethyl acetate/n-hexane=30/70 to 50/50) to give the title compound (0.60 g) in 79% yield.

20 ¹H-NMR (DMSO-D₆) δ: 11.35 (1H, s), 7.76 (1H, dd, J = 8.6, 2.5 Hz), 7.57 (1H, dd, J = 8.7, 5.9 Hz), 7.36 (1H, td, J = 8.5, 2.6 Hz), 3.90-3.78 (2H, m), 3.10-2.91 (2H, m), 2.16-2.06 (2H, m), 1.59-1.46 (2H, m), 1.35 (9H, s).

[0433]

25 (4) 5-(2-bromo-4-fluorophenyl)-1-oxa-3,4,9-triazaspiro[5.5]undec-4-en-2-one hydrochloride

[0434]



[0435]

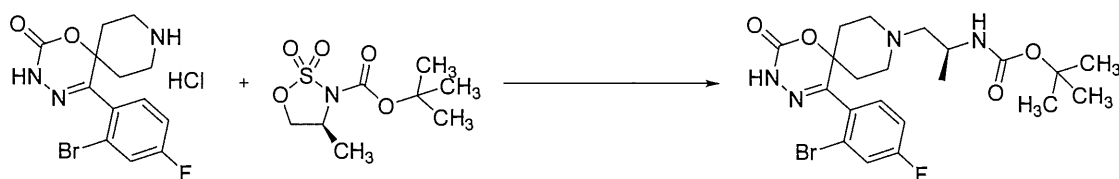
30 To tert-butyl 5-(2-bromo-4-fluorophenyl)-2-oxo-1-oxa-3,4,9-triazaspiro[5,5]undec-4-ene-9-carboxylate obtained in (3)

(0.60 g) was added 4M hydrogen chloride-CPME solution (5.6 ml) at room temperature, and the mixture was stirred for 3 hr. The obtained reaction solution was concentrated under reduced pressure to give the title compound (0.53 g) in 100% yield.

5 ¹H-NMR (DMSO-D₆) δ: 11.48 (1H, s), 8.87-8.70 (1H, m), 8.56-8.40 (1H, m), 7.81 (1H, dd, J = 8.6, 2.5 Hz), 7.61 (1H, dd, J = 8.7, 5.9 Hz), 7.44 (1H, td, J = 8.5, 2.6 Hz), 3.28-3.20 (2H, m), 3.11-2.99 (2H, m), 2.36-2.26 (2H, m), 1.99-1.85 (2H, m).

[0436]

10 (5) tert-butyl (S)-(1-(5-(2-bromo-4-fluorophenyl)-2-oxo-1-oxa-3,4,9-triazaspiro[5.5]undec-4-en-9-yl)propan-2-yl)carbamate
[0437]



[0438]

15 To a solution of 5-(2-bromo-4-fluorophenyl)-1-oxa-3,4,9-triazaspiro[5.5]undec-4-en-2-one hydrochloride obtained in (4) (0.53 g) in methanol (5.3 ml) were added triethylamine (0.89 ml) and tert-butyl (S)-4-methyl-1,2,3-oxathiazolidine-3-carboxylate 2,2-dioxide (0.36 g) under ice-cooled, and the
20 mixture was stirred for 5 hr. The methanol was evaporated, THF (5.3 ml), water (5.3 ml) and potassium hydrogen sulfate (0.52 g) were added thereto, and the mixture was stirred at room temperature for 2 days. Saturated aqueous sodium bicarbonate solution and ethyl acetate were added thereto, and the mixture
25 was subjected to extraction. The organic layer was concentrated under reduced pressure, and the obtained residue was purified by thin layer chromatography (developing solvent: ethyl acetate/n-hexane=67/33) to give the title compound (0.57 g) in 84% yield.

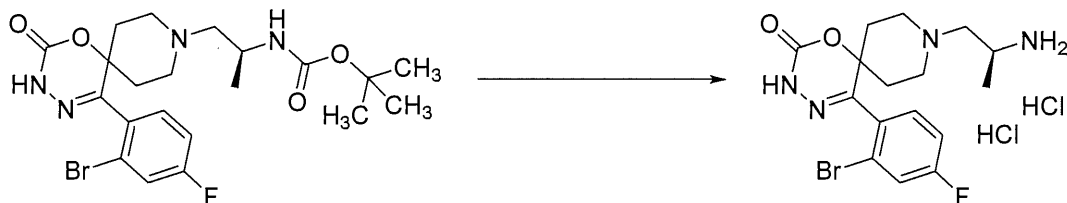
30 ¹H-NMR (DMSO-D₆) δ: 11.24 (1H, s), 7.75 (1H, dd, J = 8.7, 2.7 Hz), 7.53 (1H, dd, J = 8.6, 6.0 Hz), 7.36 (1H, td, J = 8.5, 2.6 Hz), 6.45-6.38 (1H, m), 3.64-3.51 (1H, m), 2.81-2.71 (1H, m),

2.63-2.57 (1H, m), 2.35-2.24 (1H, m), 2.24-2.01 (5H, m), 1.68-1.44 (2H, m), 1.28 (9H, s), 0.94 (3H, d, J = 6.5 Hz).

[0439]

(6) (S)-9-(2-aminopropyl)-5-(2-bromo-4-fluorophenyl)-1-oxa-3,4,9-triazaspiro[5.5]undec-4-en-2-one dihydrochloride

[0440]



[0441]

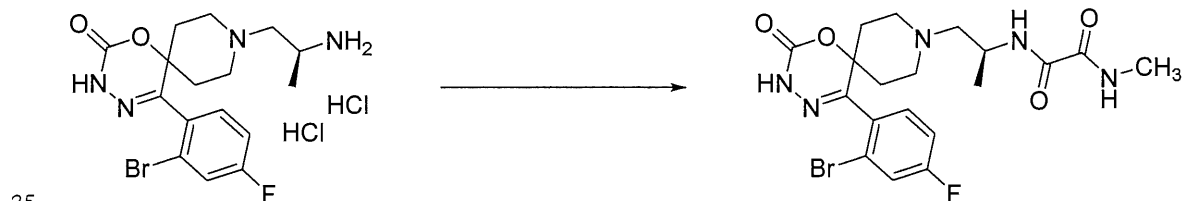
To tert-butyl (S)-(1-(5-(2-bromo-4-fluorophenyl)-2-oxo-1-oxa-3,4,9-triazaspiro[5.5]undec-4-en-9-yl)propan-2-yl)carbamate obtained in (5) (0.12 g) was added 4M hydrogen chloride-CPME solution (1.1 ml) at room temperature, and the mixture was stirred for 3 hr. The obtained reaction solution was concentrated under reduced pressure to give the title compound (0.13 g).

¹H-NMR (DMSO-D₆) δ: 11.59-11.30 (1H, m), 10.86-10.59 (1H, m), 8.46-8.13 (2H, m), 7.79 (1H, dd, J = 8.6, 2.5 Hz), 7.58 (1H, dd, J = 8.6, 6.0 Hz), 7.41 (1H, td, J = 8.5, 2.5 Hz), 3.90-3.53 (5H, m), 3.49-3.30 (1H, m), 2.44-2.10 (4H, m), 1.68-1.42 (2H, m), 1.31-1.13 (3H, m).

[0442]

(7) (S)-N¹-(1-(5-(2-bromo-4-fluorophenyl)-2-oxo-1-oxa-3,4,9-triazaspiro[5.5]undec-4-en-9-yl)propan-2-yl)-N²-methyloxamide

[0443]



[0444]

To a solution of (S)-9-(2-aminopropyl)-5-(2-bromo-4-fluorophenyl)-1-oxa-3,4,9-triazaspiro[5.5]undec-4-en-2-one dihydrochloride obtained in (6) (0.04 g) in acetonitrile (0.34

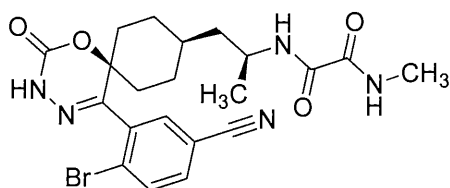
ml) were added 2-methylamino-2-oxoacetic acid (0.014 g), HOAt (0.018 g) and N,N-diisopropylethylamine (0.059 ml) at room temperature. WSC (0.026 g) was added thereto, and the mixture was stirred at room temperature for 3 hr. Saturated aqueous sodium bicarbonate solution and ethyl acetate were added thereto, and the mixture was subjected to extraction. The organic layer was concentrated under reduced pressure, and the obtained residue was purified by thin layer chromatography (developing solvent: ethyl acetate) to give the title compound (0.029 g) in 87% yield.

¹H-NMR (DMSO-D₆) δ: 11.25 (1H, s), 8.63 (1H, q, J = 4.7 Hz), 8.35 (1H, d, J = 8.8 Hz), 7.75 (1H, dd, J = 8.6, 2.5 Hz), 7.54 (1H, dd, J = 8.6, 5.8 Hz), 7.36 (1H, td, J = 8.6, 2.5 Hz), 3.96-3.89 (1H, m), 2.72-2.60 (2H, m), 2.64 (3H, d, J = 4.7 Hz), 2.42 (1H, dd, J = 12.5, 8.3 Hz), 2.33-2.19 (3H, m), 2.10-2.02 (2H, m), 1.64-1.48 (2H, m), 1.04 (3H, d, J = 6.5 Hz).

[0445]

[Production Example 4]: Synthesis of N¹-((S)-1-(cis-5-(2-bromo-5-cyanophenyl)-2-oxo-1-oxa-3,4-diazaspiro[5.5]undec-4-en-9-yl)propan-2-yl)-N²-methyloxamide (Example 198)

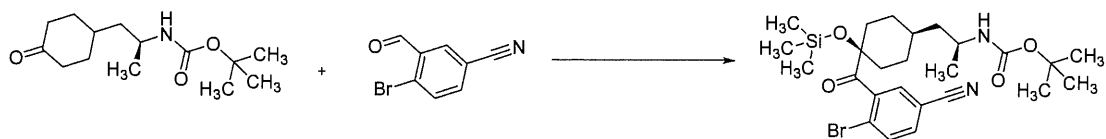
[0446]



[0447]

(1) tert-butyl ((S)-1-(cis-4-(2-bromo-5-cyanobenzoyl)-4-((trimethylsilyl)oxy)cyclohexyl)propan-2-yl)carbamate

[0448]



[0449]

To a solution of 4-bromo-3-formylbenzonitrile (54 g) and lithium chloride (1.1 g) in THF (350 ml) was added

trimethylsilylcyanoide (34 ml) under water-cooling, and the mixture was stirred for 1 hr. The mixture was cooled to -78°C, 1.1M LiHMDS-n-hexane solution (225 ml) was added thereto, and the mixture was stirred for 2 hr. The mixture was warmed to -
 5 60°C, a solution of tert-butyl (S)-(1-(4-oxocyclohexyl)propan-2-yl)carbamate (obtained in (9) of [Production Example 1]) (50 g) in THF (100 ml) was added thereto, and the mixture was stirred for 1.5 hr. Acetic acid (15 ml) was added thereto, the mixture was warmed to -20°C, and water (250 ml) was added
 10 thereto. After stirring at room temperature for 10 min, water (250 ml) and toluene (500 ml) were added thereto, and the mixture was subjected to extraction. The organic layer was washed with water (500 ml, threetimes) and 20% brine (500 ml), and dried over sodium sulfate. The sodium sulfate was removed
 15 by filtration, and the filtrate was concentrated under reduced pressure at room temperature to give the title compound (150 g) containing small amount of toluene.

¹H-NMR (DMSO-D₆) δ: 8.01-7.98 (1H, m), 7.96 (1H, d, J = 8.3 Hz), 7.89-7.85 (1H, m), 6.59 (1H, d, J = 8.6 Hz), 3.62-3.48
 20 (1H, m), 2.01-1.91 (2H, m), 1.77-1.50 (4H, m), 1.40-1.07 (5H, m), 1.36 (9H, s), 0.99 (3H, d, J = 6.5 Hz), 0.00 (9H, s).

[0450]

(2) tert-butyl ((S)-1-(cis-4-(2-bromo-5-cyanobenzoyl)-4-hydroxycyclohexyl)propan-2-yl)carbamate

25 [0451]



[0452]

To tert-butyl ((S)-1-(cis-4-(2-bromo-5-cyanobenzoyl)-4-((trimethylsilyl)oxy)cyclohexyl)propan-2-yl)carbamate obtained
 30 in (1) (150 g) were added THF (310 ml), acetic acid (14 ml) and 1M TBAF-THF solution (230 ml) at room temperature, and the mixture was stirred at room temperature for 1.5 hr. Water (500 ml) and toluene (500 ml) were added thereto, and the mixture

was subjected to extraction. The obtained organic layer was washed with 5% aqueous sodium bicarbonate solution (500 ml), water (500 ml) and saturated brine (500 ml), and dried over sodium sulfate. The sodium sulfate was removed by filtration, and the filtrate was concentrated under reduced pressure. Methanol (150 ml) was added thereto, and the mixture was concentrated again under reduced pressure. To the obtained residue were added methanol (270 ml) and water (90 ml), and the mixture was stirred for two days. Under ice-cooled, the mixture was stirred again all day, and the obtained solid was collected by filtration. The solid was washed with a mixed solvent of ice-cooled methanol (68 ml) and water (22 ml), and dried under reduced pressure at 60°C for 3 hr and then at room temperature all day to give the title compound (52 g) in 58% yield.

¹H-NMR (DMSO-D₆) δ: 7.92-7.88 (2H, m), 7.83-7.79 (1H, m), 6.59 (1H, d, J = 8.1 Hz), 5.28 (1H, s), 3.64-3.48 (1H, m), 1.88-1.78 (2H, m), 1.71-1.09 (9H, m), 1.38 (9H, s), 0.99 (3H, d, J = 6.5 Hz).

[0453]

(3) 3-(cis-9-((S)-2-aminopropyl)-2-oxo-1-oxa-3,4-diazaspiro[5.5]undec-4-en-5-yl)-4-bromobenzonitrile
[0454]



[0455]

To a solution of tert-butyl ((S)-1-(cis-4-(2-bromo-5-cyanobenzoyl)-4-hydroxycyclohexyl)propan-2-yl)carbamate obtained in (2) (48 g) in THF (240 ml) were added DBU (2.4 ml) and CDI (25 g) at room temperature, and the mixture was stirred for 1 hr. Hydrazine monohydrate (10 ml) was added thereto, and the mixture was stirred for 30 min. Water (240 ml) and ethyl acetate (240 ml) were added thereto, and the mixture was

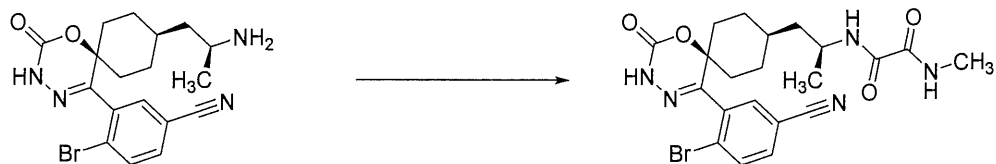
subjected to extraction. The obtained organic layer was washed with 10% aqueous citric acid solution (240 ml), water (240 ml) and 20% brine (240 ml), and dried over sodium sulfate. The sodium sulfate was removed by filtration, and the filtrate was concentrated under reduced pressure. To the obtained residue was added ethyl acetate (530 ml), and the mixture was stirred at room temperature for 1 hr. The solid was removed by filtration, and the filtrate was concentrated under reduced pressure. To concentrate were added THF (240 ml) and 6M hydrochloric acid (120 ml) at room temperature, and the mixture was stirred at 50°C for 5 hr. The mixture was gradually cooled to room temperature, water (242 ml) and 8M aqueous sodium hydroxide solution (91 ml) were added thereto, and the mixture was stirred for 5 min. THF (120 ml) and toluene (240 ml) were added thereto, and the mixture was subjected to extraction. The aqueous layer was subjected to re-extraction with THF (96 ml) and toluene (120 ml). The combined organic layers were washed with 20% brine (240 ml), and dried over sodium sulfate. The sodium sulfate was removed by filtration, and the filtrate was concentrated under reduced pressure. Ethyl acetate (144 ml) was added thereto, and the mixture was concentrated again under reduced pressure. To the obtained residue was added ethyl acetate (54 ml) at room temperature, and the mixture was stirred all day. The obtained solid was collected by filtration, washed with ice-cooled ethyl acetate (36 ml), and dried under reduced pressure 60°C for 3 hr and then at room temperature all day to give the title compound (32 g) in 89% yield.

¹H-NMR (DMSO-D₆) δ: 11.29 (1H, br s), 8.04-7.96 (2H, m), 7.91-7.84 (1H, m), 2.87-2.75 (1H, m), 2.19-2.05 (2H, m), 1.80-1.03 (11H, m), 0.92 (3H, d, J = 5.9 Hz).

[0456]

(4) N¹-((S)-1-(cis-5-(2-bromo-5-cyanophenyl)-2-oxo-1-oxa-3,4-diazaspiro[5.5]undec-4-en-9-yl)propan-2-yl)-N²-methyloxamide

[0457]



[0458]

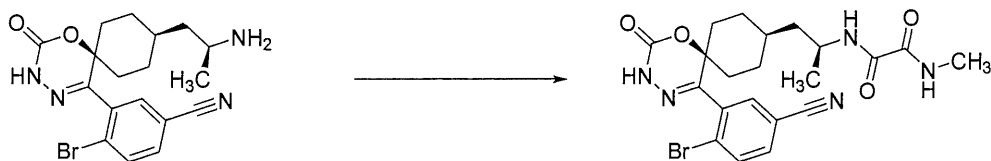
To a solution of 3-(cis-9-((S)-2-aminopropyl)-2-oxo-1-oxa-3,4-diazaspiro[5.5]undec-4-en-5-yl)-4-bromobenzonitrile (obtained in the same manner as in (3)) (0.02 g) in DMF (0.5 ml) were added 2-methylamino-2-oxoacetic acid (0.008 g), HOAt (0.007 g), WSC (0.014 g) and N,N-diisopropylethylamine (0.026 ml) at room temperature, and the mixture was stirred all day. Water and ethyl acetate were added thereto, and the mixture was subjected to extraction. The aqueous layer was subjected to re-extraction with ethyl acetate. The combined organic layers were washed with water and saturated brine, and dried over sodium sulfate. The sodium sulfate was removed by filtration, and the filtrate was concentrated under reduced pressure. The residue was purified by thin layer chromatography (developing solvent: ethyl acetate) to give the title compound (0.021 g) in 87% yield.

¹H-NMR (DMSO-D₆) δ: 11.29 (1H, s), 8.65-8.59 (1H, m), 8.41 (1H, d, J = 9.0 Hz), 8.00 (1H, d, J = 1.8 Hz), 7.98 (1H, d, J = 8.3 Hz), 7.86 (1H, dd, J = 8.3, 1.8 Hz), 3.98-3.85 (1H, m), 2.64 (3H, d, J = 4.9 Hz), 2.16-2.04 (2H, m), 1.69-1.59 (1H, m), 1.59-1.13 (8H, m), 1.06 (3H, d, J = 6.5 Hz).

[0459]

(5) crystal of N¹-((S)-1-(cis-5-(2-bromo-5-cyanophenyl)-2-oxo-1-oxa-3,4-diazaspiro[5.5]undec-4-en-9-yl)propan-2-yl)-N²-methyloxamide

[0460]



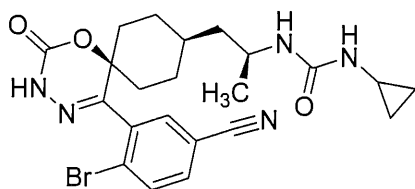
[0461]

Under nitrogen atmosphere, to a solution of 3-(cis-9-
((S)-2-aminopropyl)-2-oxo-1-oxa-3,4-diazaspiro[5.5]undec-4-en-
5-yl)-4-bromobenzonitrile (obtained in the same manner as in
(3)) (42 g), 2-methylamino-2-oxoacetic acid (13 g) and WSC (24
5 g) in DMF (210 ml) was added HOAt (7.1 g) at room temperature,
and the mixture was stirred for 1 hr. 5% Aqueous sodium
bicarbonate solution (420 ml) and ethyl acetate (420 ml) were
added thereto, and the mixture was subjected to extraction.
The aqueous layer was subjected to re-extraction with ethyl
10 acetate (210 ml), and the combined organic layers were washed
with 5% aqueous sodium bicarbonate solution (210 ml), water
(210 ml×2) and saturated brine (210 ml). Sodium sulfate and
activated carbon (1.3 g) were added thereto, the mixture was
stirred for 1.5 hr, and the solid was removed by filtration.
15 The obtained solution was concentrated under reduced pressure,
and to the obtained amorphous solid was added DMF (115 ml).
The obtained solution was concentrated under reduced pressure,
the ethyl acetate was evaporated, and the obtained solution was
subjected to dust removal filtration, followed by washing with
20 DMF (139 ml). To the obtained DMF solution was added water
(150 ml) at room temperature. After confirming the solid
precipitation, water (612 ml) was added dropwise thereto, and
the obtained suspension was stirred at room temperature for 5
days. The suspension was warmed to 50°C, stirred overnight,
25 and allowed to cool to room temperature. The suspension was
filtered, and the solid was washed with water. The obtained
wet crystals were air-dried overnight, and then dried under
reduced pressure at 60°C for 3 hr to give the title compound
(45 g).

30 [0462]

[Production Example 5]: Synthesis of 1-((S)-1-(cis-5-(2-bromo-
5-cyanophenyl)-2-oxo-1-oxa-3,4-diazaspiro[5.5]undec-4-en-9-
yl)propan-2-yl)-3-cyclopropylurea (Example 222)

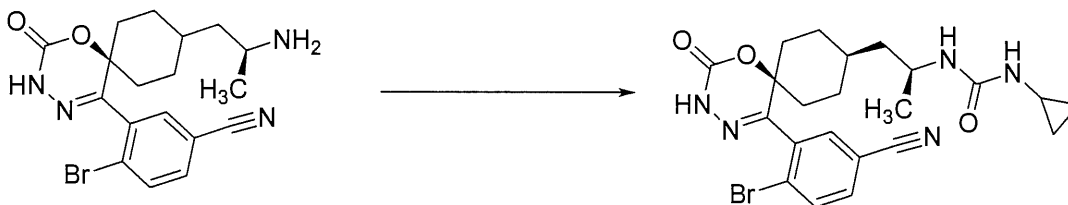
[0463]



[0464]

(1) 1-((S)-1-(cis-5-(2-bromo-5-cyanophenyl)-2-oxo-1-oxa-3,4-diazaspiro[5.5]undec-4-en-9-yl)propan-2-yl)-3-cyclopropylurea

5 [0465]



[0466]

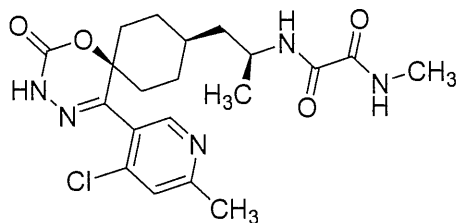
To a solution of 3-(cis-9-((S)-2-aminopropyl)-2-oxo-1-oxa-3,4-diazaspiro[5.5]undec-4-en-5-yl)-4-bromobenzonitrile
 10 (obtained in the same manner as in (3) of [Production Example 4]) (0.020 g) in THF (0.4 ml) was added cyclopropylisocyanate (0.005 ml) at room temperature, and the mixture was stirred for 3 hr. Water and ethyl acetate were added thereto, and the mixture was subjected to extraction. The aqueous layer was
 15 subjected to re-extraction with ethyl acetate, and the combined organic layers were washed with water and saturated brine, and dried over sodium sulfate. The sodium sulfate was removed by filtration, and the filtrate was concentrated under reduced pressure. The obtained residue was purified by thin layer
 20 chromatography (developing solvent: ethyl acetate) to give the title compound (0.019 g) in 79% yield.

¹H-NMR (DMSO-D₆) δ: 11.30 (1H, s), 8.03 (1H, d, J = 1.8 Hz), 7.99 (1H, d, J = 8.3 Hz), 7.87 (1H, dd, J = 8.4, 2.0 Hz), 5.89 (1H, d, J = 2.8 Hz), 5.46 (1H, d, J = 8.6 Hz), 3.72-3.61 (1H, m), 2.40-2.31 (1H, m), 2.19-2.07 (2H, m), 1.70-1.57 (1H, m), 1.56-1.06 (8H, m), 0.97 (3H, d, J = 6.5 Hz), 0.56-0.46 (2H, m), 0.31-0.22 (2H, m).

[0467]

[Production Example 6]: Synthesis of N¹-((S)-1-(cis-5-(4-chloro-6-methylpyridin-3-yl)-2-oxo-1-oxa-3,4-diazaspiro[5.5]undec-4-en-9-yl)propan-2-yl)-N²-methyloxamide (Example 230)

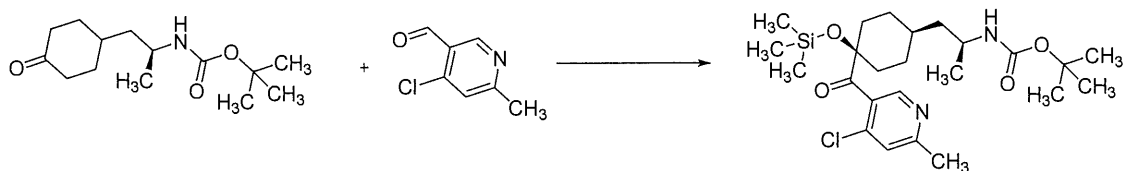
5 [0468]



[0469]

(1) tert-butyl ((S)-1-(cis-4-(4-chloro-6-methylnicotinoyl)-4-((trimethylsilyl)oxy)cyclohexyl)propan-2-yl)carbamate

10 [0470]



[0471]

To a mixture of 4-chloro-6-methylnicotinaldehyde (0.55 g) and lithium chloride (0.015 g) was added trimethylsilylcyanide (0.55 ml), and the mixture was stirred at room temperature for 15 10 min. THF (7 ml) was added thereto, and the mixture was cooled to -78°C. 1M NaHMDS-THF solution (1.9 ml) was added thereto, and the mixture was stirred for 5 min. tert-Butyl ((S)-1-(4-oxocyclohexyl)propan-2-yl)carbamate (obtained in the 20 same manner as in (9) of [Production Example 1]) (0.7 g) was added thereto, and the mixture was stirred for 30 min, and warmed to 0°C over 1 hr. Water and ethyl acetate were added thereto, and the mixture was subjected to extraction. The aqueous layer was subjected to re-extraction twice with ethyl 25 acetate, and the combined organic layers were washed with saturated brine, and dried over sodium sulfate. The sodium sulfate was removed by filtration, and the filtrate was concentrated under reduced pressure. The obtained residue was

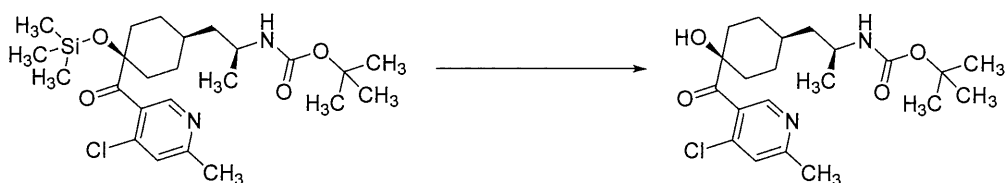
purified by silica gel chromatography (developing solvent: ethyl acetate/n-hexane) to give the title compound (1.1 g) in 83% yield.

¹H-NMR (CDCl₃) δ: 8.58 (1H, s), 7.25 (1H, s), 4.32-4.15 (1H, m), 3.84-3.65 (1H, m), 2.57 (3H, s), 1.99-1.88 (2H, m), 1.83-1.68 (3H, m), 1.66-1.55 (1H, m), 1.43 (9H, s), 1.41-1.21 (5H, m), 1.11 (3H, d, J = 6.5 Hz), 0.06 (9H, s).

[0472]

(2) tert-butyl ((S)-1-(cis-4-(4-chloro-6-methylnicotinoyl)-4-hydroxycyclohexyl)propan-2-yl)carbamate

[0473]



[0474]

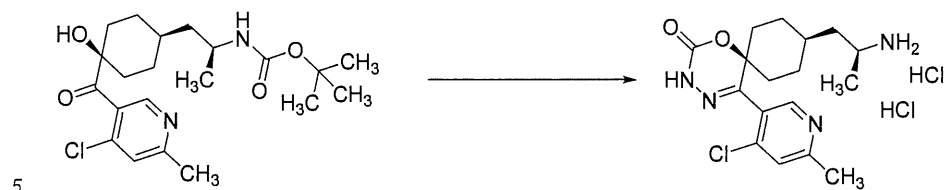
To a solution of tert-butyl ((S)-1-(cis-4-(4-chloro-6-methylnicotinoyl)-4-((trimethylsilyl)oxy)cyclohexyl)propan-2-yl)carbamate obtained in (1) (1.1 g) in THF (2.2 ml) were added acetic acid (0.39 ml) and 1M TBAF-THF solution (3.4 ml) at room temperature, and the mixture was stirred for 15 min, and allowed to stand all day. Saturated aqueous ammonium chloride solution, water and ethyl acetate were added thereto, and the mixture was subjected to extraction. The aqueous layer was subjected to re-extraction twice with ethyl acetate, and the combined organic layers were washed with saturated brine, and dried over sodium sulfate. The sodium sulfate was removed by filtration, and the filtrate was concentrated under reduced pressure. The obtained residue was purified by silica gel chromatography (developing solvent: ethyl acetate/n-hexane) to give the title compound (0.80 g) in 86% yield.

¹H-NMR (CDCl₃) δ: 8.39 (1H, s), 7.26 (1H, s), 4.29-4.16 (1H, m), 3.83-3.65 (1H, m), 2.93 (1H, s), 2.58 (3H, s), 1.87-1.73 (5H, m), 1.67-1.59 (1H, m), 1.43 (9H, s), 1.41-1.22 (5H, m), 1.10 (3H, d, J = 6.5 Hz).

[0475]

(3) cis-9-((S)-2-aminopropyl)-5-(4-chloro-6-methylpyridin-3-yl)-1-oxa-3,4-diazaspiro[5.5]undec-4-en-2-one dihydrochloride

[0476]



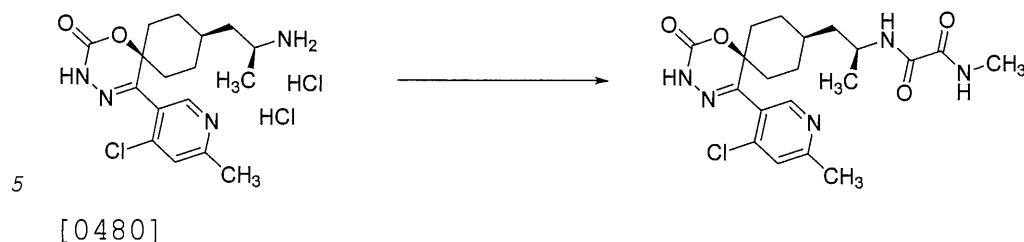
[0477]

To a solution of tert-butyl ((S)-1-(cis-4-(4-chloro-6-methylnicotinoyl)-4-hydroxycyclohexyl)propan-2-yl)carbamate obtained in (2) (0.8 g) in THF (8 ml) were added DBU (0.044 ml) and CDI (0.47 g) at room temperature, and the mixture was stirred for 1 hr. Hydrazine monohydrate (0.19 ml) was added thereto, and the mixture was stirred for 1 hr. 10% Aqueous citric acid solution and ethyl acetate were added thereto, and the mixture was subjected to extraction. The aqueous layer was subjected to re-extraction twice with ethyl acetate, and the combined organic layers were washed with saturated brine, and dried over sodium sulfate. The sodium sulfate was removed by filtration, and the filtrate was concentrated under reduced pressure. The obtained residue was purified by silica gel chromatography (developing solvent: ethyl acetate/n-hexane). To the obtained solid were added THF (9.0 ml) and 6M hydrochloric acid (4.5 ml) at room temperature, and the mixture was stirred all day and then at 50°C for 6 hr. The reaction solution was concentrated under reduced pressure, followed by azeotropy twice with THF (10 ml) to give the title compound (0.98 g).

¹H-NMR (DMSO-D₆) δ: 11.40 (1H, s), 8.64 (1H, s), 8.08-7.97 (3H, m), 7.81 (1H, s), 3.25-3.14 (1H, m), 2.59 (3H, s), 2.18-2.08 (2H, m), 1.62-1.19 (9H, m), 1.15 (3H, d, J = 6.5 Hz).

[0478]

(4) N¹-((S)-1-(cis-5-(4-chloro-6-methylpyridin-3-yl)-2-oxo-1-oxa-3,4-diazaspiro[5.5]undec-4-en-9-yl)propan-2-yl)-N²-methyloxamide
[0479]



To a solution of cis-9-((S)-2-aminopropyl)-5-(4-chloro-6-methylpyridin-3-yl)-1-oxa-3,4-diazaspiro[5.5]undec-4-en-2-one dihydrochloride obtained in (3) (0.1 g) in DMF (1.5 ml) were
10 added 2-methylamino-2-oxoacetic acid (0.045 g), HOAt (0.062 g) and N,N-diisopropylethylamine (0.23 ml) at room temperature. WSC (0.087 g) was added thereto, and the mixture was stirred at room temperature for 15 min, and allowed to stand all day. Water, saturated aqueous sodium bicarbonate solution and ethyl
15 acetate were added thereto, and the mixture was subjected to extraction. The aqueous layer was subjected to re-extraction twice with ethyl acetate, and the combined organic layers were washed with saturated brine, and dried over sodium sulfate. The sodium sulfate was removed by filtration, and the filtrate
20 was concentrated under reduced pressure, followed by azeotropy with toluene (5 ml). The obtained residue was purified by silica gel chromatography (developing solvent: ethyl acetate/n-hexane) to give the title compound (0.067 g) in 71% yield.

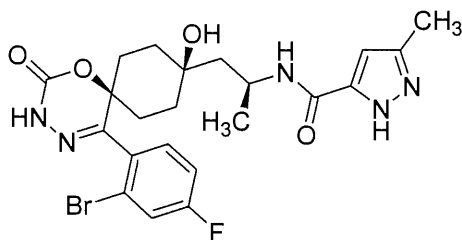
¹H-NMR (DMSO-D₆) δ: 11.28 (1H, s), 8.62 (1H, q, J = 4.8 Hz),
25 8.48 (1H, s), 8.41 (1H, d, J = 9.2 Hz), 7.58 (1H, s), 3.98-3.83 (1H, m), 2.64 (3H, d, J = 4.8 Hz), 2.51 (3H, s), 2.15-2.02 (2H, m), 1.71-1.59 (1H, m), 1.57-1.15 (8H, m), 1.05 (3H, d, J = 6.5 Hz).

[0481]

30 [Production Example 7]: Synthesis of N-((S)-1-(cis-5-(2-bromo-4-fluorophenyl)-9-hydroxy-2-oxo-1-oxa-3,4-diazaspiro[5.5]undec-

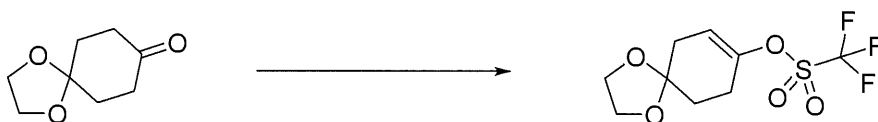
4-en-9-yl)propan-2-yl)-3-methyl-1H-pyrazole-5-carboxamide
(Example 320)

[0482]



5 [0483]

(1) 1,4-dioxaspiro[4.5]dec-7-en-8-yl trifluoromethanesulfonate
[0484]



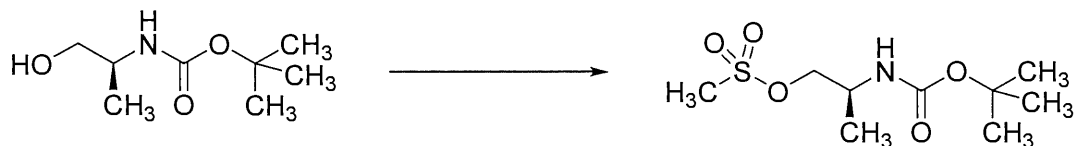
[0485]

10 A solution of 1,4-dioxaspiro[4.5]decan-8-one (5 g) in THF (50 ml) was cooled to -78°C , 1.1M LiHMDS-n-hexane solution (31 ml) was added thereto, and the mixture was stirred for 10 min. The mixture was warmed to 0°C , stirred for 20 min, and cooled to -78°C , and Comins reagent (14 g) was added thereto. The
15 mixture was stirred for 30 min, warmed to 0°C , and stirred for additional 1.5 hr. Saturated aqueous sodium bicarbonate solution, water and ethyl acetate were added thereto, and the mixture was subjected to extraction. The aqueous layer was subjected to re-extraction with ethyl acetate, and the combined
20 organic layers were washed with saturated brine, and dried over sodium sulfate. The sodium sulfate was removed by filtration, and the filtrate was concentrated under reduced pressure. The obtained residue was purified by silica gel chromatography (developing solvent: ethyl acetate/n-hexane) to give the title
25 compound (7.5 g) in 81% yield.

$^1\text{H-NMR}$ (CDCl_3) δ : 5.69-5.65 (1H, m), 4.00 (4H, t, $J = 2.4$ Hz), 2.54 (2H, t, $J = 6.5$ Hz), 2.41 (2H, d, $J = 2.7$ Hz), 1.91 (2H, t, $J = 6.7$ Hz).

[0486]

(2) (S)-2-((tert-butoxycarbonyl)amino)propyl methanesulfonate
[0487]



[0488]

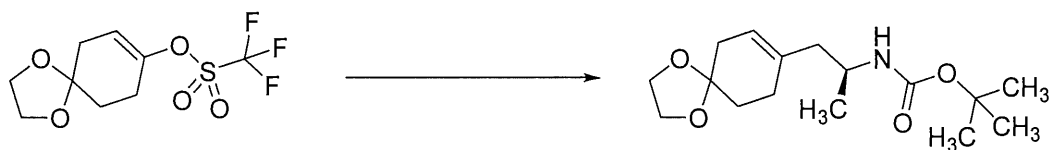
5 To a solution of tert-butyl (S)-(1-hydroxypropan-2-yl)carbamate (10 g) in THF (100 ml) was added triethylamine (16 ml) at room temperature. The mixture was cooled to 0°C, methanesulfonic anhydride (11 g) was added thereto, and the mixture was stirred at room temperature for 15 min. The
10 reaction solution was concentrated under reduced pressure, and the obtained residue was purified by silica gel chromatography (developing solvent: ethyl acetate/n-hexane) to give the title compound (13.7 g) in 95% yield.

1H-NMR (CDCl₃) δ: 4.68-4.49 (1H, m), 4.28-4.19 (1H, m), 4.15
15 (1H, dd, J = 9.7, 4.3 Hz), 4.04-3.88 (1H, m), 3.04 (3H, s), 1.45 (9H, s), 1.24 (3H, d, J = 7.0 Hz).

[0489]

(3) tert-butyl (S)-(1-(1,4-dioxaspiro[4.5]dec-7-en-8-yl)propan-2-yl)carbamate

20 [0490]



[0491]

To a solution of 1,4-dioxaspiro[4.5]dec-7-en-8-yl trifluoromethanesulfonate obtained in (1) (5 g) in DMA (100 ml)
25 were added (S)-2-((tert-butoxycarbonyl)amino)propyl methanesulfonate obtained in (2) (7.9 g), nickel(II) iodide (0.093 ml), 2,2':6',2''-terpyridine (0.61 g), manganese (2.9 g) and sodium iodide (1.3 g) at room temperature, and the mixture was stirred at 80°C for 1.5 hr. Water and ethyl acetate were
30 added thereto at room temperature, and the mixture was subjected to extraction. The aqueous layer was subjected to

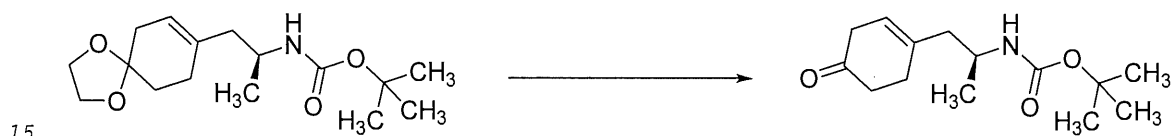
re-extraction twice with ethyl acetate, and the combined organic layers were washed with saturated brine, and dried over sodium sulfate. The sodium sulfate was removed by filtration, and the filtrate was concentrated under reduced pressure. The
5 obtained residue was purified by silica gel chromatography (developing solvent: ethyl acetate/n-hexane) to give the title compound (1.9 g) in 37% yield.

¹H-NMR (CDCl₃) δ: 5.34 (1H, s), 4.40-4.21 (1H, m), 3.97 (4H, s), 3.88-3.71 (1H, m), 2.30-1.98 (6H, m), 1.75 (2H, t, J = 6.5
10 Hz), 1.43 (9H, s), 1.10 (3H, d, J = 6.5 Hz).

[0492]

(4) tert-butyl (S)-(1-(4-oxocyclohex-1-en-1-yl)propan-2-yl)carbamate

[0493]



[0494]

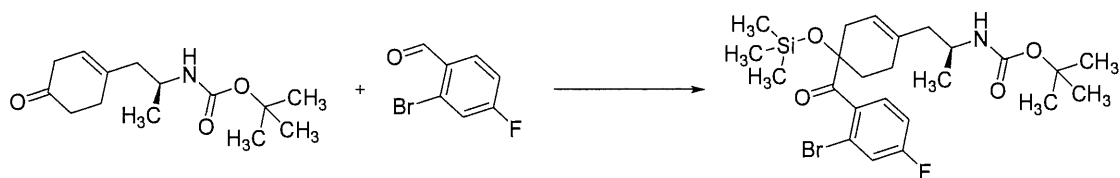
To a solution of tert-butyl (S)-(1-(1,4-dioxaspiro[4,5]dec-7-en-8-yl)propan-2-yl)carbamate obtained in (3) (0.5 g) in water (2 ml) was added acetic acid (8 ml) at
20 room temperature, and the mixture was stirred for 15 min, and allowed to stand all day. The reaction solution was concentrated under reduced pressure, followed by azeotropy threetimes with toluene (2 ml), and the obtained residue was purified by silica gel chromatography (developing solvent:
25 ethyl acetate/n-hexane) to give the title compound (0.37 g) in 87% yield.

¹H-NMR (CDCl₃) δ: 5.49 (1H, s), 4.37-4.22 (1H, m), 3.91-3.76 (1H, m), 2.85 (2H, s), 2.60-2.30 (4H, m), 2.22-2.09 (2H, m), 1.42 (9H, s), 1.14 (3H, d, J = 6.5 Hz).

30 [0495]

(5) tert-butyl ((2S)-1-(4-(2-bromo-4-fluorobenzoyl)-4-((trimethylsilyl)oxy)cyclohex-1-en-1-yl)propan-2-yl)carbamate

[0496]



[0497]

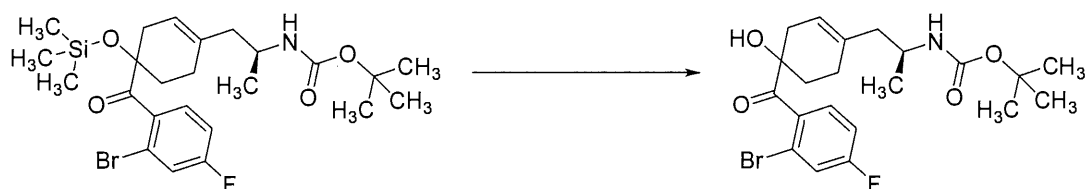
To 2-bromo-4-fluorobenzaldehyde (0.16 g) and lithium chloride (0.003 g) was added trimethylcyanide (0.12 ml) at room
 5 temperature, and the mixture was stirred for 10 min. THF (1.5 ml) was added thereto, and the mixture was cooled to -78°C . 1M NaHMDS-THF solution (0.77 ml) was added thereto, and the mixture was stirred for 5 min. tert-Butyl (S)-(1-(4-oxocyclohex-1-en-1-yl)propan-2-yl)carbamate obtained in (4)
 10 (0.15 g) was added to the reaction solution, and the mixture was stirred for 30 min. The mixture was warmed to 0°C over 1 hr, water and ethyl acetate were added thereto, and the mixture was subjected to extraction. The aqueous layer was subjected to re-extraction twice with ethyl acetate, and the combined
 15 organic layers were washed with saturated brine, and dried over sodium sulfate. The sodium sulfate was removed by filtration, and the filtrate was concentrated under reduced pressure. The obtained residue was purified by silica gel chromatography (developing solvent: ethyl acetate/n-hexane) to give the title
 20 compound (0.22 g) in 66% yield.

$^1\text{H-NMR}$ (CDCl_3) δ : 7.65 (0.3H, dd, $J = 8.6, 6.5$ Hz), 7.56 (0.7H, dd, $J = 8.1, 6.5$ Hz), 7.36 (1H, d, $J = 8.1$ Hz), 7.04 (1H, t, $J = 8.4$ Hz), 5.36 (1H, s), 4.37-4.21 (1H, m), 3.88-3.74 (1H, m), 2.81-2.67 (1H, m), 2.34-1.92 (7H, m), 1.45 (3H, s), 1.43 (6H, s), 1.14 (2.1H, d, $J = 6.5$ Hz), 1.12 (0.9H, d, $J = 6.5$ Hz),
 25 0.01 (6.3H, s), 0.00 (2.7H, s).

[0498]

(6) tert-butyl ((2S)-1-(4-(2-bromo-4-fluorobenzoyl)-4-hydroxycyclohex-1-en-1-yl)propan-2-yl)carbamate

30 [0499]



[0500]

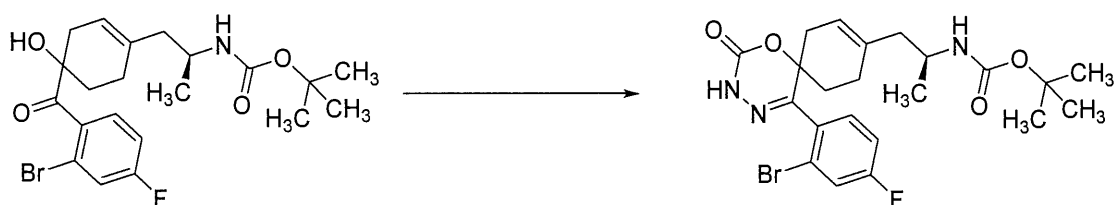
To a solution of tert-butyl ((2S)-1-(4-(2-bromo-4-fluorobenzoyl)-4-((trimethylsilyl)oxy)cyclohex-1-en-1-yl)propan-2-yl)carbamate obtained in (5) (0.22 g) in THF (0.41 ml) were added acetic acid (0.067 ml) and 1M TBAF-THF solution (0.59 ml) at room temperature, and the mixture was stirred for 15 min, and allowed to stand at room temperature all day. Saturated aqueous ammonium chloride solution, water and ethyl acetate were added thereto, and the mixture was subjected to extraction. The aqueous layer was subjected to re-extraction twice with ethyl acetate, and the combined organic layers were washed with saturated aqueous sodium bicarbonate solution and saturated brine, and dried over sodium sulfate. The sodium sulfate was removed by filtration, and the filtrate was concentrated under reduced pressure. The obtained residue was purified by silica gel chromatography (developing solvent: ethyl acetate/n-hexane) to give the title compound (0.17 g) in 66% yield.

¹H-NMR (CDCl₃) δ: 7.50-7.41 (0.3H, m), 7.40-7.29 (1.7H, m), 7.12-6.96 (1H, m), 5.43-5.35 (1H, m), 4.37-4.18 (1H, m), 4.01 (0.3H, s), 3.90-3.73 (1H, m), 3.10 (0.7H, s), 2.82-2.50 (1H, m), 2.30-1.88 (7H, m), 1.39-1.38 (2.7H, s), 1.37-1.35 (6.3H, s), 1.14 (0.9H, d, J = 7.5 Hz), 1.12 (2.1H, d, J = 6.5 Hz).

[0501]

(7) tert-butyl ((2S)-1-(5-(2-bromo-4-fluorophenyl)-2-oxo-1-oxa-3,4-diazaspiro[5.5]undeca-4,8-dien-9-yl)propan-2-yl)carbamate

[0502]



[0503]

To a solution of tert-butyl ((2S)-1-(4-(2-bromo-4-fluorobenzoyl)-4-hydroxycyclohex-1-en-1-yl)propan-2-yl)carbamate obtained in (6) (0.17 g) in THF (1.7 ml) were
5 added DBU (0.009 ml) and CDI (0.093 g) at room temperature, and the mixture was stirred for 30 min. Hydrazine monohydrate (0.037 ml) was added thereto, and the mixture was stirred at room temperature for 30 min. 10% Aqueous citric acid solution and ethyl acetate were added thereto, and the mixture was
10 subjected to extraction. The aqueous layer was subjected to re-extraction twice with ethyl acetate, and the combined organic layers were washed with saturated brine, and dried over sodium sulfate. The sodium sulfate was removed by filtration, and the filtrate was concentrated under reduced pressure. The
15 obtained residue was purified by silica gel chromatography (developing solvent: ethyl acetate/n-hexane). To the obtained solid were added THF (1.5 ml) and 6M hydrochloric acid (0.73 ml) at room temperature, and the mixture was stirred for 15 min, and allowed to stand all day. The mixture was stirred at
20 50°C for 1.5 hr, and the reaction solution was concentrated under reduced pressure, followed by azeotropy twice with THF (2 ml). To the obtained solid were added saturated aqueous sodium bicarbonate solution (0.65 mL), THF (1.3 ml), water (0.65 ml) and Boc₂O (0.19 ml) at room temperature, and the mixture was
25 stirred all day. Water and ethyl acetate were added thereto, and the mixture was subjected to extraction. The aqueous layer was subjected to re-extraction twice with ethyl acetate, and the combined organic layers were washed with saturated brine, and dried over sodium sulfate. The sodium sulfate was removed
30 by filtration, and the filtrate was concentrated under reduced pressure. The obtained residue was purified by silica gel chromatography (developing solvent: ethyl acetate/n-hexane) to give the title compound (0.12 g) in 88% yield.

¹H-NMR (CDCl₃) δ: 8.13 (1H, s), 7.44-7.39 (1H, m), 7.24-7.16
35 (1H, m), 7.13-7.02 (1H, m), 5.31-5.18 (1H, m), 4.40-4.14 (1H,

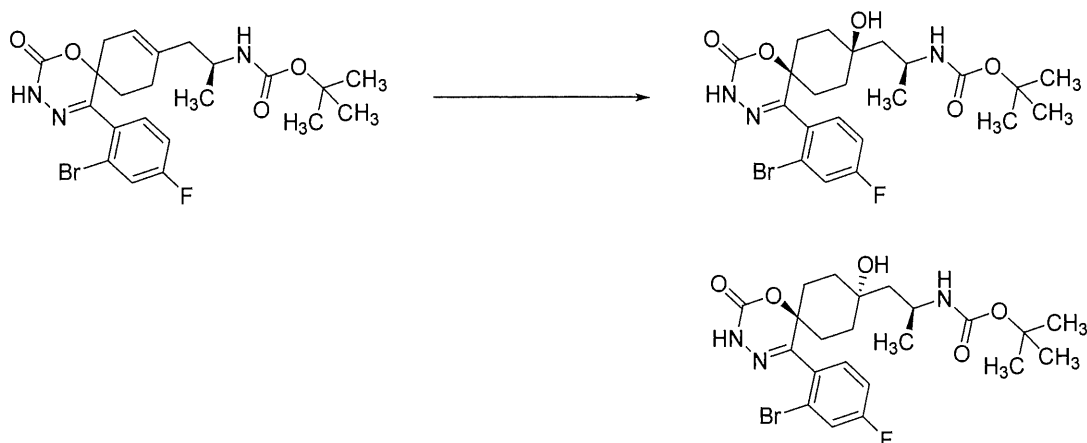
m), 3.86-3.67 (1H, m), 2.71-2.60 (1H, m), 2.44-2.08 (4H, m), 2.07-1.91 (2H, m), 1.78-1.66 (1H, m), 1.43 (2.7H, s), 1.32 (6.3H, s), 1.12 (0.9H, d, J = 7.0 Hz), 1.07 (2.1H, d, J = 7.0 Hz).

5 [0504]

(8) tert-butyl ((S)-1-(cis-5-(2-bromo-4-fluorophenyl)-9-hydroxy-2-oxo-1-oxa-3,4-diazaspiro[5.5]undec-4-en-9-yl)propan-2-yl)carbamate (cis isomer), and tert-butyl ((S)-1-(trans-5-(2-bromo-4-fluorophenyl)-9-hydroxy-2-oxo-1-oxa-3,4-

10 diazaspiro[5.5]undec-4-en-9-yl)propan-2-yl)carbamate (trans isomer)

[0505]



[0506]

15 To a solution of tert-butyl ((2S)-1-(5-(2-bromo-4-fluorophenyl)-2-oxo-1-oxa-3,4-diazaspiro[5.5]undeca-4,8-dien-9-yl)propan-2-yl)carbamate obtained in (7) (0.12 g) in THF (1.8 ml) were added cobalt(II) acetyl acetone (0.063 g) and phenylsilane (0.30 ml) at room temperature, and the mixture was
20 stirred under oxygen atmosphere all day. Saturated aqueous sodium thiosulfate solution, water and ethyl acetate were added thereto, and the mixture was subjected to extraction. The aqueous layer was subjected to re-extraction twice with ethyl acetate, and the combined organic layers were washed with
25 saturated brine, and dried over sodium sulfate. The sodium sulfate was removed by filtration, and the filtrate was concentrated under reduced pressure. The obtained residue was

purified by silica gel chromatography (developing solvent: ethyl acetate/n-hexane) to give a cis isomer (0.047 g) of the title compound in 27% yield, and a trans isomer (0.060 g) of the title compound in 30% yield.

5 (cis isomer)

¹H-NMR (CDCl₃) δ: 8.22-8.08 (1H, m), 7.43 (1H, dd, J = 8.1, 2.2 Hz), 7.27-7.22 (1H, m), 7.11 (1H, td, J = 8.1, 2.5 Hz), 4.63 (1H, d, J = 6.5 Hz), 3.81-3.67 (1H, m), 2.32-2.22 (2H, m), 2.19 (1H, s), 2.00-1.84 (3H, m), 1.84-1.48 (5H, m), 1.42 (9H, s),

10 1.15 (3H, d, J = 6.5 Hz).

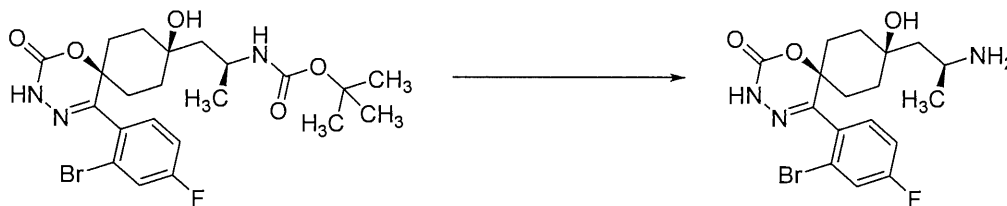
(trans isomer)

¹H-NMR (CDCl₃) δ: 8.10 (1H, s), 7.40 (1H, dd, J = 8.1, 2.2 Hz), 7.28-7.22 (1H, m), 7.10 (1H, t, J = 8.6 Hz), 4.59-4.44 (1H, m), 3.99-3.81 (1H, m), 3.81-3.66 (1H, m), 2.19 (1H, s), 2.15-2.03 (1H, m), 2.03-1.89 (2H, m), 1.85-1.73 (2H, m), 1.73-1.50 (4H, m), 1.41 (9H, s), 1.17 (3H, d, J = 7.0 Hz).

[0507]

(9) cis-9-((S)-2-aminopropyl)-5-(2-bromo-4-fluorophenyl)-9-hydroxy-1-oxa-3,4-diazaspiro[5.5]undec-4-en-2-one

20 [0508]



[0509]

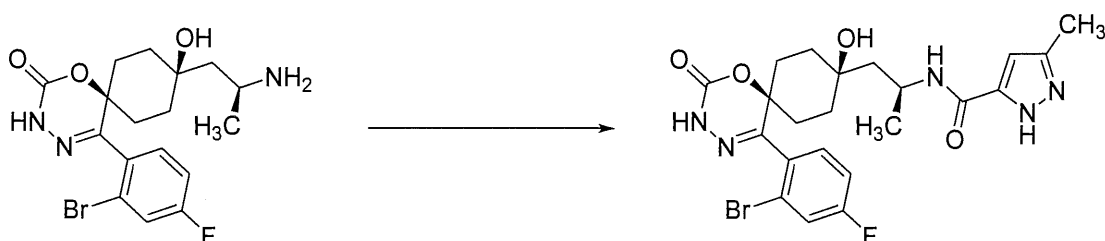
To a solution of tert-butyl ((S)-1-(cis-5-(2-bromo-4-fluorophenyl)-9-hydroxy-2-oxo-1-oxa-3,4-diazaspiro[5.5]undec-4-en-9-yl)propan-2-yl)carbamate obtained in (8) (0.039 g) in chloroform (0.39 ml) was added trifluoroacetic acid (0.39 ml) at room temperature, and the mixture was stirred for 30 min. The reaction solution was concentrated under reduced pressure, and the residue was purified by silica gel chromatography (InertSep (registered trademark) SCX, developing solvent: methanol/2M ammonia-methanol solution) to give the title compound (0.030 g) in 85% yield.

1H-NMR (DMSO-D6) δ : 11.30-11.21 (1H, m), 7.75 (1H, dd, J = 8.6, 2.7 Hz), 7.56 (1H, dd, J = 8.9, 5.7 Hz), 7.40-7.32 (1H, m), 2.97-2.85 (1H, m), 2.10-1.97 (2H, m), 1.81-1.27 (9H, m), 1.09-0.99 (2H, m), 0.96 (3H, d, J = 6.5 Hz).

5 [0510]

(10) N-((S)-1-(cis-5-(2-bromo-4-fluorophenyl)-9-hydroxy-2-oxo-1-oxa-3,4-diazaspiro[5.5]undec-4-en-9-yl)propan-2-yl)-3-methyl-1H-pyrazole-5-carboxamide

[0511]



10

[0512]

To a solution of cis-9-((S)-2-aminopropyl)-5-(2-bromo-4-fluorophenyl)-9-hydroxy-1-oxa-3,4-diazaspiro[5.5]undec-4-en-2-one obtained in (9) (0.013 g) in DMF (0.2 ml) were added 3-methyl-1H-pyrazole-5-carboxylic acid (0.005 g), HOAt (0.006 g) and N,N-diisopropylethylamine (0.017 ml) at room temperature. WSC (0.008 g) was added thereto, and the mixture was stirred at room temperature for 15 min, and allowed to stand all day. Water, saturated aqueous sodium bicarbonate solution and ethyl acetate were added thereto, and the mixture was subjected to extraction. The aqueous layer was subjected to re-extraction twice with ethyl acetate, and the combined organic layers were washed with saturated brine, and dried over sodium sulfate. The sodium sulfate was removed by filtration, and the filtrate was concentrated under reduced pressure, followed by azeotropy twice with toluene (2 ml). The obtained residue was purified by silica gel chromatography (developing solvent: ethyl acetate/n-hexane) and then reverse-phase silica gel chromatography (developing solvent: acetonitrile/water) to give the title compound (0.004 g) in 26% yield.

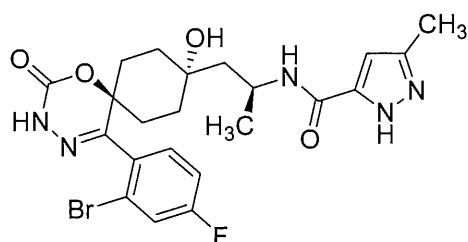
30

1H-NMR (DMSO-D6) δ : 12.81 (1H, s), 11.24 (1H, s), 7.90-7.79 (1H, m), 7.74 (1H, d, J = 8.1 Hz), 7.59-7.48 (1H, m), 7.39-7.26 (1H, m), 6.29 (1H, s), 4.59 (1H, s), 4.07-3.93 (1H, m), 2.25 (3H, s), 2.11-1.94 (2H, m), 1.78-1.28 (8H, m), 1.12 (3H, d, J = 5.9 Hz).

[0513]

[Production Example 8]: Synthesis of N-((S)-1-(trans-5-(2-bromo-4-fluorophenyl)-9-hydroxy-2-oxo-1-oxa-3,4-diazaspiro[5,5]undec-4-en-9-yl)propan-2-yl)-3-methyl-1H-pyrazole-5-carboxamide (Example 322)

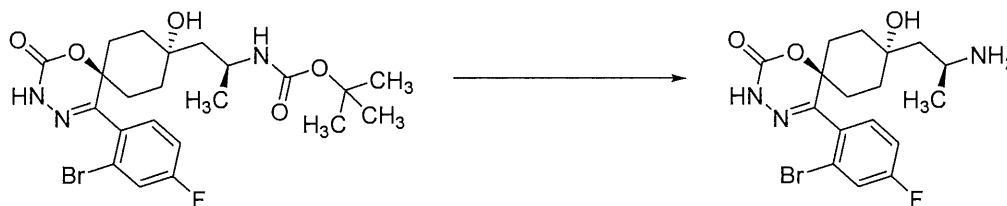
[0514]



[0515]

(1) trans-9-((S)-2-aminopropyl)-5-(2-bromo-4-fluorophenyl)-9-hydroxy-1-oxa-3,4-diazaspiro[5.5]undec-4-en-2-one

[0516]



[0517]

To a solution of tert-butyl ((S)-1-(trans-5-(2-bromo-4-fluorophenyl)-9-hydroxy-2-oxo-1-oxa-3,4-diazaspiro[5,5]undec-4-en-9-yl)propan-2-yl)carbamate (obtained in (8) of [Production Example 7]) (0.056 g) in chloroform (0.44 ml) was added trifluoroacetic acid (0.44 ml) at room temperature, and the mixture was stirred for 30 min. The reaction solution was concentrated under reduced pressure, and the residue was purified by silica gel chromatography (InertSep (registered trademark) SCX, developing solvent: methanol/2M ammonia-

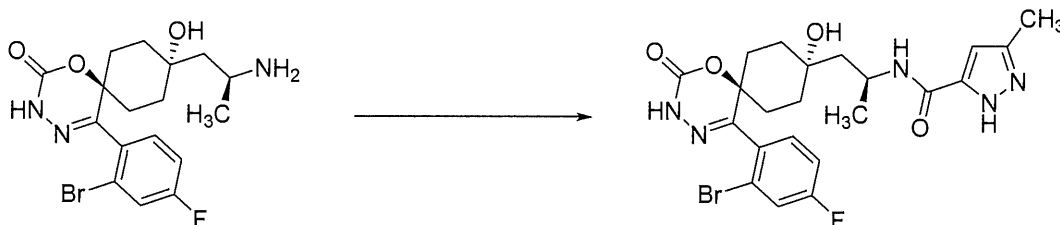
methanol solution) to give the title compound (0.036 g) in 100% yield.

LC-MS(M+1): 414

[0518]

- 5 (2) N-((S)-1-(trans-5-(2-bromo-4-fluorophenyl)-9-hydroxy-2-oxo-1-oxa-3,4-diazaspiro[5.5]undec-4-en-9-yl)propan-2-yl)-3-methyl-1H-pyrazole-5-carboxamide

[0519]



10 [0520]

To a solution of trans-9-((S)-2-aminopropyl)-5-(2-bromo-4-fluorophenyl)-9-hydroxy-1-oxa-3,4-diazaspiro[5,5]undec-4-en-2-one obtained in (1) (0.016 g) in DMF (0.24 ml) were added 3-methyl-1H-pyrazole-5-carboxylic acid (0.006 g), HOAt (0.007 g)
15 and N,N-diisopropylethylamine (0.020 ml) at room temperature. WSC (0.010 g) was added thereto, and the mixture was stirred at room temperature for 15 min, and allowed to stand all day. Water, saturated aqueous sodium bicarbonate solution and ethyl acetate were added thereto, and the mixture was subjected to
20 extraction. The aqueous layer was subjected to re-extraction twice with ethyl acetate, and the combined organic layers were washed with saturated brine, and dried over sodium sulfate. The sodium sulfate was removed by filtration, and the filtrate was concentrated under reduced pressure, followed by azeotropy
25 twice with toluene (2 ml). The obtained residue was purified by silica gel chromatography (developing solvent: ethyl acetate/n-hexane) and then reverse-phase silica gel chromatography (developing solvent: acetonitrile/water) to give the title compound (0.007 g) in 34% yield.

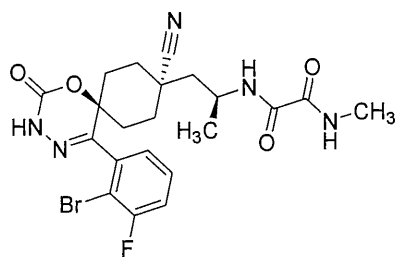
30 ¹H-NMR (DMSO-D₆) δ: 12.80 (1H, s), 11.18 (1H, s), 7.85 (1H, d, J = 7.5 Hz), 7.74 (1H, dd, J = 8.6, 2.7 Hz), 7.51 (1H, dd, J =

8.6, 5.9 Hz), 7.37 (1H, ddd, J = 8.6, 8.1, 2.7 Hz), 6.31 (1H, s), 4.25-4.08 (1H, m), 4.21 (1H, s), 2.24 (3H, s), 1.97-1.82 (2H, m), 1.82-1.66 (3H, m), 1.66-1.34 (5H, m), 1.12 (3H, d, J = 6.5 Hz).

5 [0521]

[Production Example 9]: Synthesis of N¹-((S)-1-(trans-5-(2-bromo-3-fluorophenyl)-9-cyano-2-oxo-1-oxa-3,4-diazaspiro[5.5]undec-4-en-9-yl)propan-2-yl)-N²-methyloxamide (Example 2-153)

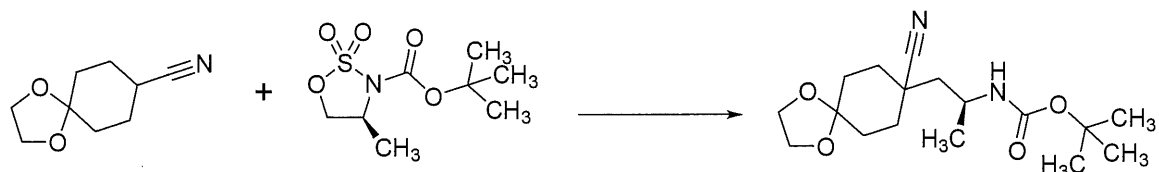
10 [0522]



[0523]

(1) tert-butyl (S)-(1-(8-cyano-1,4-dioxaspiro[4.5]decan-8-yl)propan-2-yl)carbamate

15 [0524]



[0525]

A solution of 1,4-dioxaspiro[4.5]decane-8-carbonitrile (7.5 g) in THF (75 ml) was cooled to -78°C, 1.11M LDA-THF/n-hexane solution (48.5 ml) was added thereto, and the mixture was stirred for 1 hr. tert-Butyl (S)-4-methyl-1,2,3-oxathiazolidine-3-carboxylate 2,2-dioxide (12.8 g) was added thereto, and the mixture was warmed to 0°C, and stirred for 1 hr. 1M Hydrochloric acid (135 ml) was added thereto, and the mixture was stirred at room temperature for 30 min. Ethyl acetate and water were added thereto, and the mixture was subjected to extraction. The organic layer was washed with saturated brine, and dried over sodium sulfate. The sodium

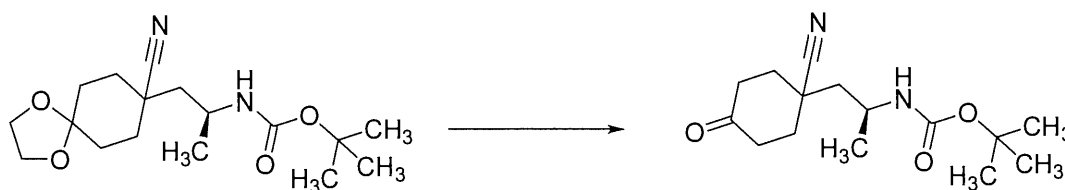
sulfate was removed by filtration, and the filtrate was concentrated under reduced pressure. The obtained residue was purified by silica gel chromatography (developing solvent: ethyl acetate/n-hexane=25/75 to 55/45), and the fractions were concentrated under reduced pressure to give the title compound (14.3 g) in 98% yield.

¹H-NMR (DMSO-D₆) δ: 6.78 (1H, d, J = 8.6 Hz), 3.87 (4H, s), 3.78-3.63 (1H, m), 2.06-1.44 (10H, m), 1.37 (9H, s), 1.06 (3H, d, J = 6.5 Hz).

[0526]

(2) tert-butyl (S)-(1-(1-cyano-4-oxocyclohexyl)propan-2-yl)carbamate

[0527]



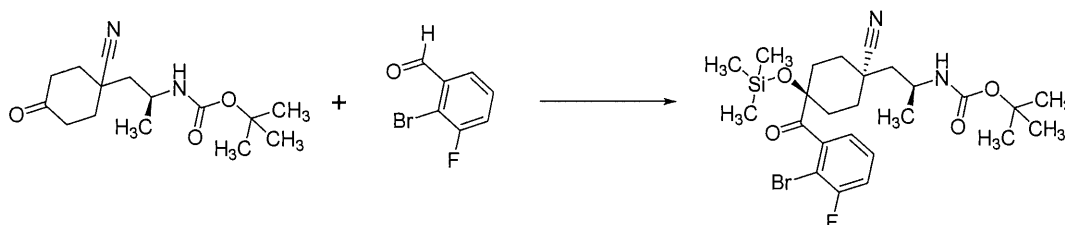
[0528]

To a solution of tert-butyl (S)-(1-(8-cyano-1,4-dioxaspiro[4.5]decan-8-yl)propan-2-yl)carbamate obtained in (1) (10.9 g) in THF (54.5 ml) was added 6M hydrochloric acid (28 ml) at room temperature, and the mixture was stirred at 60°C for 6 hr. After standing at room temperature for 3 days, 10M aqueous sodium hydroxide solution (16.8 ml) and Boc₂O (23.4 ml) were added thereto, and the mixture was stirred for 2 hr. Ethyl acetate and water were added thereto, and the mixture was subjected to extraction. The organic layer was washed with saturated brine, and dried over sodium sulfate. The sodium sulfate was removed by filtration, and the filtrate was concentrated under reduced pressure. The obtained residue was purified by silica gel chromatography (developing solvent: ethyl acetate/n-hexane=30/70 to 65/35), and the fractions were concentrated under reduced pressure to give the title compound (5.59 g) in 59% yield.

1H-NMR (DMSO-D6) δ : 6.84 (1H, d, J = 9.2 Hz), 3.83-3.67 (1H, m), 2.55-2.39 (2H, m), 2.36-2.10 (4H, m), 1.92-1.75 (3H, m), 1.65 (1H, dd, J = 14.3, 3.5 Hz), 1.38 (9H, s), 1.09 (3H, d, J = 6.5 Hz).

5 [0529]

(3) tert-butyl ((S)-1-(trans-4-(2-bromo-3-fluorobenzoyl)-1-cyano-4-((trimethylsilyl)oxy)cyclohexyl)propan-2-yl)carbamate [0530]



10 [0531]

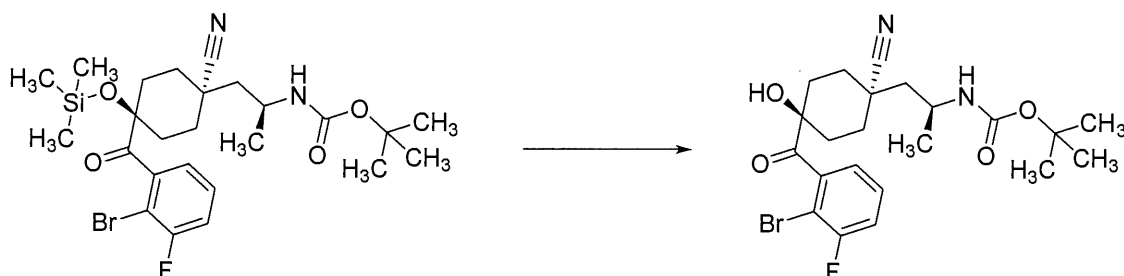
Under argon atmosphere, to a solution of 2-bromo-3-fluorobenzaldehyde (0.38 g) and lithium chloride (0.008 g) in THF (0.8 ml) was added trimethylsilylcyanide (0.27 ml) at room temperature, and the mixture was stirred for 30 min. THF (5.2 ml) was added thereto, and the mixture was cooled to -78°C, and stirred for 5 min. 1.13M LiHMDS-n-hexane solution (1.6 ml) was added thereto, and the mixture was stirred for 10 min. tert-Butyl (S)-(1-(1-cyano-4-oxocyclohexyl)propan-2-yl)carbamate obtained in (2) (0.40 g) was added thereto, and the mixture was stirred for 30 min. Then, and the mixture was warmed to 0°C over 1 hr, water and ethyl acetate were added thereto, and the mixture was subjected to extraction. The organic layer was washed with saturated brine, and dried over sodium sulfate. The sodium sulfate was removed by filtration, and the filtrate was concentrated under reduced pressure. The obtained residue was purified by silica gel chromatography (developing solvent: ethyl acetate/n-hexane=3/97 to 30/70), and the fractions were concentrated under reduced pressure to give the title compound (0.62 g) in 78% yield.

¹H-NMR (DMSO-D₆) δ: 7.59-7.41 (2H, m), 7.39-7.33 (1H, m), 6.84 (1H, d, J = 8.6 Hz), 3.82-3.67 (1H, m), 2.07-1.49 (10H, m), 1.37 (9H, s), 1.08 (3H, d, J = 6.5 Hz), 0.04 (9H, s).

[0532]

- 5 (4) tert-butyl ((S)-1-(trans-4-(2-bromo-3-fluorobenzoyl)-1-cyano-4-hydroxycyclohexyl)propan-2-yl)carbamate

[0533]



[0534]

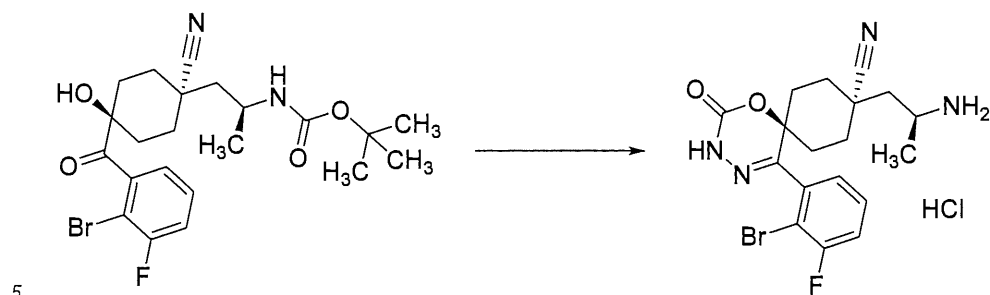
- 10 To a solution of tert-butyl ((S)-1-(trans-4-(2-bromo-3-fluorobenzoyl)-1-cyano-4-
((trimethylsilyl)oxy)cyclohexyl)propan-2-yl)carbamate obtained
in (3) (0.62 g) in THF (3.1 ml) were added acetic acid (0.19
ml) and 1M TBAF-THF solution (1.7 ml) at room temperature, and
15 the mixture was stirred for 2 hr. Saturated aqueous sodium
bicarbonate solution and ethyl acetate were added thereto, the
mixture was subjected to extraction, and the organic layer was
dried over sodium sulfate. The sodium sulfate was removed by
filtration, and the filtrate was concentrated under reduced
20 pressure. The obtained residue was purified by silica gel
chromatography (developing solvent: ethyl acetate/n-
hexane=30/70 to 60/40), and the fractions were concentrated
under reduced pressure to give the title compound (0.25 g) in
46% yield.

- 25 ¹H-NMR (DMSO-D₆) δ: 7.55-7.39 (2H, m), 7.32-7.27 (1H, m), 6.81 (1H, d, J = 8.6 Hz), 5.53 (1H, s), 3.83-3.69 (1H, m), 2.02-1.49 (10H, m), 1.37 (9H, s), 1.07 (3H, d, J = 6.5 Hz).

[0535]

(5) trans-9-((S)-2-aminopropyl)-5-(2-bromo-3-fluorophenyl)-2-oxo-1-oxa-3,4-diazaspiro[5.5]undec-4-ene-9-carbonitrile hydrochloride

[0536]



[0537]

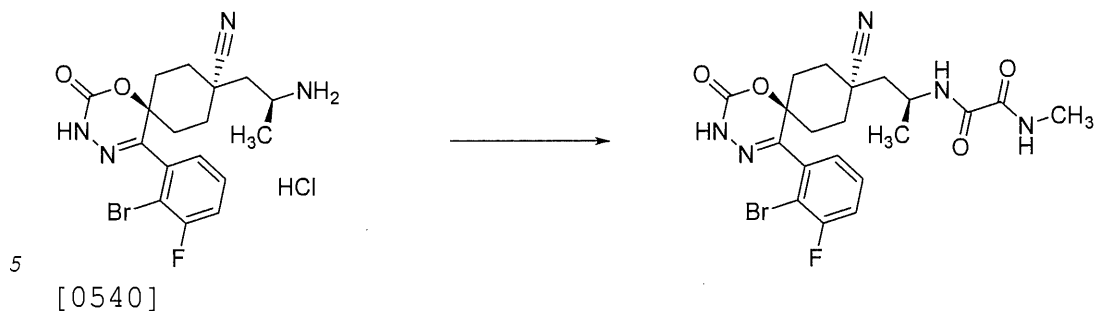
To a solution of tert-butyl ((S)-1-(trans-4-(2-bromo-3-fluorobenzoyl)-1-cyano-4-hydroxycyclohexyl)propan-2-yl)carbamate obtained in (4) (0.25 g) in THF (2.5 ml) were
 10 added CDI (0.13 g) and DBU (0.012 ml) at room temperature, and the mixture was stirred for 30 min. Hydrazine monohydrate (0.069 ml) was added, and the mixture was stirred for 30 min. 10% Aqueous citric acid solution and ethyl acetate were added thereto, and the mixture was subjected to extraction. The
 15 organic layer was dried over sodium sulfate, the sodium sulfate was removed by filtration, and the filtrate was concentrated under reduced pressure. The obtained residue was purified by silica gel chromatography (developing solvent: ethyl acetate/n-hexane=50/50 to 90/10), and the fractions were concentrated
 20 under reduced pressure. To the obtained solid were added THF (2.3 ml) and 6M hydrochloric acid (1.1 ml), and the mixture was stirred at 50°C for 2 hr. The reaction solution was concentrated under reduced pressure, followed by azeotropy with THF to give the title compound (0.17 g) in 72% yield.

25 ¹H-NMR (DMSO-D₆) δ: 11.45 (1H, s), 7.93 (3H, br s), 7.62-7.50 (2H, m), 7.42-7.36 (1H, m), 3.44-3.34 (1H, m), 2.31-2.19 (2H, m), 2.03-1.81 (4H, m), 1.78-1.58 (4H, m), 1.31 (3H, d, J = 6.5 Hz).

[0538]

(6) N¹-((S)-1-(trans-5-(2-bromo-3-fluorophenyl)-9-cyano-2-oxo-1-oxa-3,4-diazaspiro[5.5]undec-4-en-9-yl)propan-2-yl)-N²-methyloxamide

[0539]



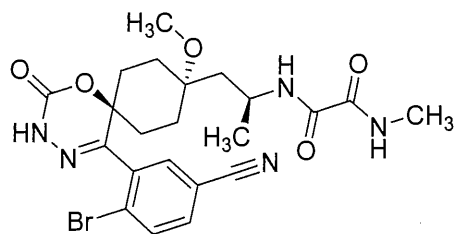
To a solution of trans-9-((S)-2-aminopropyl)-5-(2-bromo-3-fluorophenyl)-2-oxo-1-oxa-3,4-diazaspiro[5.5]undec-4-ene-9-carbonitrile hydrochloride obtained in (5) (0.025 g) in DMF
 10 (0.4 ml) were added 2-methylamino-2-oxoacetic acid (0.007 g), N,N-diisopropylethylamine (0.048 ml) and HATU (0.025 g) at room temperature, and the mixture was stirred for 1 hr. The reaction solution was purified by reverse-phase silica gel chromatography (developing solvent: acetonitrile/water=5/95 to
 15 70/30) and then thin layer chromatography (developing solvent: ethyl acetate), and the fractions were concentrated under reduced pressure to give the title compound (0.018 g) in 65% yield.

1H-NMR (DMSO-D₆) δ: 11.39 (1H, s), 8.72 (1H, d, J = 9.2 Hz),
 20 8.63-8.57 (1H, m), 7.58-7.47 (2H, m), 7.38-7.34 (1H, m), 4.17-4.04 (1H, m), 2.64 (3H, d, J = 4.8 Hz), 2.27-1.95 (4H, m), 1.81-1.53 (6H, m), 1.12 (3H, d, J = 6.5 Hz).

[0541]

[Production Example 10]: Synthesis of N¹-((S)-1-(trans-5-(2-bromo-5-cyanophenyl)-9-methoxy-2-oxo-1-oxa-3,4-diazaspiro[5.5]undec-4-en-9-yl)propan-2-yl)-N²-methyloxamide (Example 2-123)

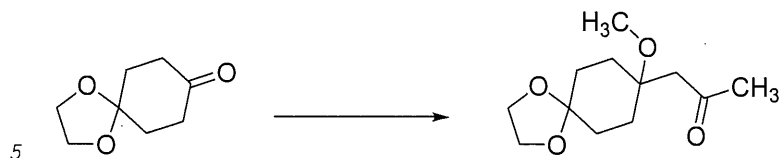
[0542]



[0543]

(1) 1-(8-methoxy-1,4-dioxaspiro[4.5]decan-8-yl)propan-2-one

[0544]



[0545]

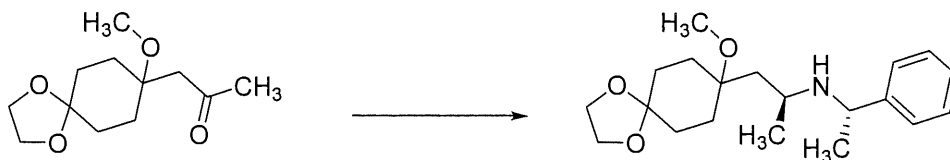
To a solution of 1,4-dioxaspiro[4.5]decan-8-one (5.0 g) in methanol (50 ml) were added dimethyl (2-oxopropyl)phosphonate (5.9 g) and 28% sodium methoxide-methanol solution (23.5 ml) at room temperature, and the mixture was stirred all day. Water (20 ml) was added thereto, and the mixture was concentrated under reduced pressure to evaporate the methanol. The mixture was diluted with ethyl acetate, and washed with saturated brine. The obtained organic layer was dried over sodium sulfate, the sodium sulfate was removed by filtration, and the filtrate was concentrated under reduced pressure. The obtained residue was purified by silica gel chromatography (developing solvent: ethyl acetate/n-hexane=20/80 to 50/50), and the fractions were concentrated under reduced pressure to give the title compound (2.1 g) in 28% yield.

¹H-NMR (DMSO-D₆) δ: 3.83 (4H, s), 3.15 (3H, s), 2.57 (2H, s), 2.11 (3H, s), 1.78-1.68 (2H, m), 1.66-1.41 (6H, m).

[0546]

25 (2) (S)-1-(8-methoxy-1,4-dioxaspiro[4.5]decan-8-yl)-N-((S)-1-phenylethyl)propan-2-amine

[0547]



[0548]

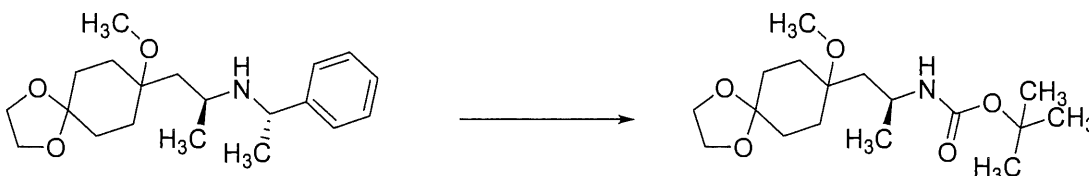
To a solution of 1-(8-methoxy-1,4-dioxaspiro[4.5]decan-8-yl)propan-2-one obtained in (1) (2.1 g) in THF (31 ml) were
 5 added (S)-1-phenethylamine (1.3 ml), acetic acid (0.52 ml) and sodium triacetoxyborohydride (3.6 g) at room temperature, and the mixture was stirred for 3 hr. Under ice-cooled, 4M aqueous sodium hydroxide solution (11.3 ml) and water were added thereto, and the mixture was diluted with ethyl acetate. The
 10 obtained organic layer was washed with saturated brine. The organic layer was dried over sodium sulfate, the sodium sulfate was removed by filtration, and the filtrate was concentrated under reduced pressure. The obtained residue was purified by silica gel chromatography (developing solvent: methanol/ethyl
 15 acetate/n-hexane=0/25/75 to 0/100/0 to 5/95/0), and the fractions were concentrated under reduced pressure to give the title compound (1.4 g) in 46% yield.

¹H-NMR (DMSO-D₆) δ: 7.36-7.23 (4H, m), 7.20-7.15 (1H, m), 3.82 (4H, s), 3.78 (1H, q, J = 6.7 Hz), 3.04 (3H, s), 2.66-2.56 (1H, m), 1.89-1.29 (11H, m), 1.24-1.10 (3H, m), 0.90 (3H, d, J = 6.6 Hz).

[0549]

(3) tert-butyl (S)-(1-(8-methoxy-1,4-dioxaspiro[4.5]decan-8-yl)propan-2-yl)carbamate

25 [0550]



[0551]

To a solution of (S)-1-(8-methoxy-1,4-dioxaspiro[4.5]decan-8-yl)-N-((S)-1-phenylethyl)propan-2-amine

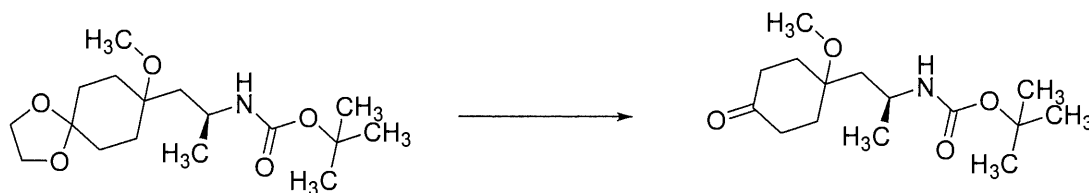
obtained in (2) (1.4 g) in THF (14 ml) were added acetic acid (0.48 ml) and 20% palladium hydroxide-activated carbon at room temperature, and the mixture was stirred under hydrogen atmosphere (1 atm) all day. The reaction solution was filtered
 5 through Celite, followed by washing with THF (14 ml). To the obtained THF solution were added water (4.8 ml), sodium bicarbonate (1.1 g) and Boc_2O (1.1 ml) at room temperature, and the mixture was stirred for 2 hr. The mixture was diluted with ethyl acetate, and washed with saturated brine. The obtained
 10 organic layer was dried over sodium sulfate, the sodium sulfate was removed by filtration, and the filtrate was concentrated under reduced pressure. The obtained residue was purified by silica gel chromatography (developing solvent: ethyl acetate/n-hexane=15/85 to 50/50), and the fractions were concentrated
 15 under reduced pressure to give the title compound (1.0 g) in 76% yield.

$^1\text{H-NMR}$ (DMSO-D_6) δ : 6.62 (1H, d, $J = 8.1$ Hz), 3.83 (4H, s), 3.65-3.48 (1H, m), 3.02 (3H, s), 1.79-1.27 (10H, m), 1.36 (9H, s), 1.03 (3H, d, $J = 6.5$ Hz).

20 [0552]

(4) tert-butyl (S)-(1-(1-methoxy-4-oxocyclohexyl)propan-2-yl)carbamate

[0553]



25 [0554]

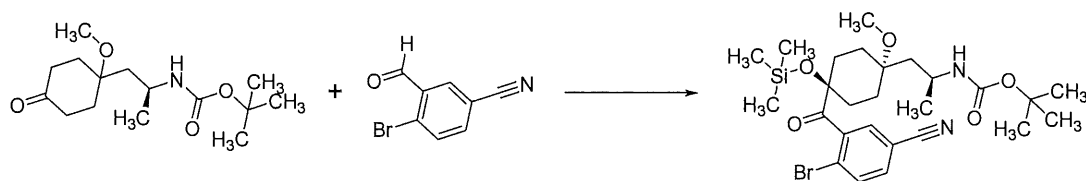
To a solution of tert-butyl (S)-(1-(8-methoxy-1,4-dioxaspiro[4.5]decan-8-yl)propan-2-yl)carbamate obtained in (3) (1.0 g) in a mixed solvent of acetone (10 ml) and water (4.2 ml) was added pyridinium p-toluenesulfonate (0.16 g) at room
 30 temperature, and the mixture was stirred at 60°C for 6 hr. Saturated aqueous sodium bicarbonate solution (5 ml) was added thereto at room temperature, and the acetone was evaporated.

Ethyl acetate was added thereto, and the mixture was subjected to extraction. The obtained organic layer was washed with saturated brine, and dried over sodium sulfate, the sodium sulfate was removed by filtration, and the filtrate was concentrated under reduced pressure. The obtained residue was purified by silica gel chromatography (developing solvent: ethyl acetate/n-hexane=20/80 to 55/45), and the fractions were concentrated under reduced pressure to give the title compound (0.77 g) in 85% yield.

¹H-NMR (DMSO-D₆) δ: 6.68 (1H, d, J = 8.6 Hz), 3.70-3.54 (1H, m), 3.14 (3H, s), 2.48-2.31 (2H, m), 2.11-1.92 (4H, m), 1.78-1.54 (4H, m), 1.36 (9H, s), 1.06 (3H, d, J = 6.5 Hz).

[0555]

(5) tert-butyl ((S)-1-(trans-4-(2-bromo-5-cyanobenzoyl)-1-methoxy-4-((trimethylsilyl)oxy)cyclohexyl)propan-2-yl)carbamate



[0557]

Under argon atmosphere, to a solution of 4-bromo-3-formylbenzonitrile (0.24 g) and lithium chloride (0.005 g) in THF (0.5 ml) was added trimethylsilylcyanide (0.16 ml), and the mixture was stirred at room temperature for 30 min. THF (3.3 ml) was added thereto, and the mixture was cooled to -78°C, and stirred for 5 min. 1.13M LiHMDS-n-hexane solution (1.0 ml) was added thereto, and the mixture was stirred for 10 min. tert-Butyl (S)-1-(1-methoxy-4-oxocyclohexyl)propan-2-ylcarbamate obtained in (4) (0.25 g) was added thereto, and the mixture was stirred for 30 min. Then the mixture was warmed to 0°C over 1 hr, water and ethyl acetate were added thereto, and the mixture was subjected to extraction. The organic layer was washed with saturated brine, and dried over sodium sulfate. The sodium sulfate was removed by filtration, and the filtrate was

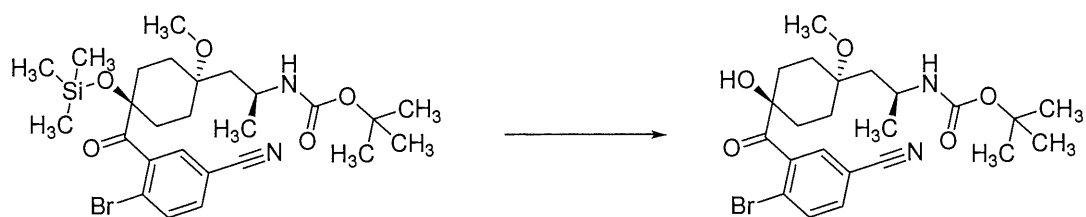
concentrated under reduced pressure. The obtained residue was purified by silica gel chromatography (developing solvent: ethyl acetate/n-hexane=5/95 to 33/67), and the fractions were concentrated under reduced pressure to give the title compound (0.23 g) in 45% yield.

¹H-NMR (DMSO-D₆) δ: 8.05-7.82 (3H, m), 6.69 (1H, d, J = 8.1 Hz), 3.67-3.51 (1H, m), 3.00 (3H, s), 2.01-1.31 (10H, m), 1.36 (9H, s), 1.04 (3H, d, J = 6.5 Hz), 0.00-0.03 (9H, m).

[0558]

(6) tert-butyl ((S)-1-(trans-4-(2-bromo-5-cyanobenzoyl)-4-hydroxy-1-methoxycyclohexyl)propan-2-yl)carbamate

[0559]



[0560]

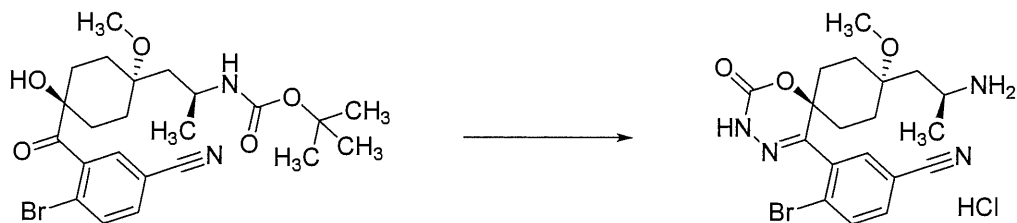
To a solution of tert-butyl ((S)-1-(trans-4-(2-bromo-5-cyanobenzoyl)-1-methoxy-4-((trimethylsilyl)oxy)cyclohexyl)propan-2-yl)carbamate obtained in (5) (0.22 g) in THF (2.2 ml) were added acetic acid (0.067 ml) and 1M TBAF-THF solution (0.58 ml) at room temperature, and the mixture was stirred for 2 hr. Saturated aqueous sodium bicarbonate solution and ethyl acetate were added thereto, and the mixture was subjected to extraction. The organic layer was washed with saturated brine, and dried over sodium sulfate. The sodium sulfate was removed by filtration, and the filtrate was concentrated under reduced pressure. The obtained residue was purified by silica gel chromatography (developing solvent: ethyl acetate/n-hexane=30/70 to 60/40), and the fractions were concentrated under reduced pressure to give the title compound (0.15 g) in 78% yield.

¹H-NMR (DMSO-D₆) δ: 7.93-7.88 (2H, m), 7.84-7.79 (1H, m), 6.64 (1H, d, J = 8.1 Hz), 5.31 (1H, s), 3.69-3.56 (1H, m), 3.04 (3H, s), 1.97-1.31 (10H, m), 1.36 (9H, s), 1.04 (3H, d, J = 6.5 Hz).

[0561]

(7) 3-(trans-9-((S)-2-aminopropyl)-9-methoxy-2-oxo-1-oxa-3,4-diazaspiro[5.5]undec-4-en-5-yl)-4-bromobenzonitrile hydrochloride

5 [0562]



[0563]

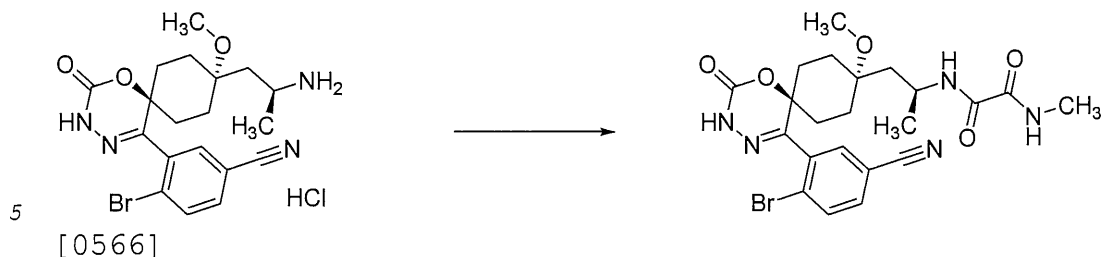
To a solution of tert-butyl ((S)-1-(trans-4-(2-bromo-5-cyanobenzoyl)-4-hydroxy-1-methoxycyclohexyl)propan-2-yl)carbamate obtained in (6) (0.15 g) in THF (1.5 ml) were added CDI (0.073 g) and DBU (0.007 ml), and the mixture was stirred at room temperature for 30 min. Hydrazine monohydrate (0.045 ml) was added thereto, and the mixture was stirred for 30 min. 10% Aqueous citric acid solution and ethyl acetate were added thereto, the mixture was subjected to extraction, and organic layer was dried over sodium sulfate. The sodium sulfate was removed by filtration, and the filtrate was concentrated under reduced pressure. The obtained residue was purified by silica gel chromatography (developing solvent: ethyl acetate/n-hexane=50/50 to 90/10), and the fractions were concentrated under reduced pressure. To the obtained solid were added THF (1.6 ml) and 6M hydrochloric acid (0.8 ml), and the mixture was stirred at 50°C for 2 hr. The mixture was allowed to cool to room temperature, and the reaction solution was concentrated, followed by azeotropy with THF to give the title compound (0.14 g) in 96% yield.

¹H-NMR (DMSO-D₆) δ: 11.38 (1H, s), 8.12-8.08 (1H, m), 8.05-8.00 (1H, m), 7.93-7.86 (1H, m), 7.71 (3H, br s), 3.68-3.49 (1H, m), 2.98 (3H, s), 2.07-1.93 (2H, m), 1.84-1.45 (8H, m), 1.22 (3H, d, J = 6.5 Hz).

[0564]

(8) N¹-((S)-1-(trans-5-(2-bromo-5-cyanophenyl)-9-methoxy-2-oxo-1-oxa-3,4-diazaspiro[5.5]undec-4-en-9-yl)propan-2-yl)-N²-methyloxamide

[0565]



To a solution of 3-(trans-9-((S)-2-aminopropyl)-9-methoxy-2-oxo-1-oxa-3,4-diazaspiro[5.5]undec-4-en-5-yl)-4-bromobenzonitrile hydrochloride obtained in (7) (0.050 g) in
 10 DMF (0.75 ml) were added 2-methylamino-2-oxoacetic acid (0.016 g), N,N-diisopropylethylamine (0.074 ml) and HATU (0.060 g) at room temperature, and the mixture was stirred for 1 hr. The reaction solution was purified by reverse-phase silica gel chromatography (developing solvent: acetonitrile/water=5/95 to
 15 65/35) and then thin layer chromatography (developing solvent: ethyl acetate/n-hexane=67/33), and the fractions were concentrated under reduced pressure to give the title compound (0.049 g) in 89% yield.

1H-NMR (DMSO-D₆) δ: 11.32 (1H, s), 8.65-8.54 (2H, m), 8.09-8.05
 20 (1H, m), 8.03-7.98 (1H, m), 7.91-7.86 (1H, m), 4.01-3.92 (1H, m), 2.92 (3H, s), 2.67-2.63 (3H, m), 1.99-1.42 (10H, m), 1.08 (3H, d, J = 6.5 Hz).

[0567]

The compounds of the other Examples were obtained by
 25 employing the same methods as in the above Production Methods or Production Examples, and, where necessary, known methods. The structural formulae and physical property data of the compounds of Examples 1 to 339 and 2-001 to 2-172 are shown in Table 1-1 to Table 1-61.

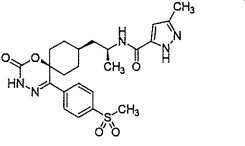
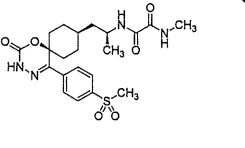
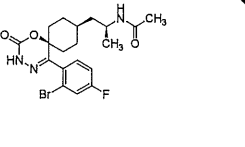
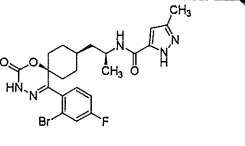
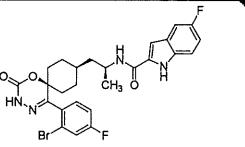
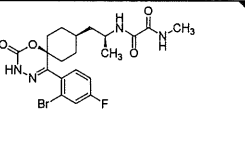
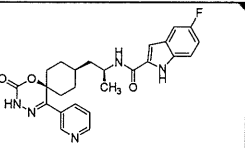
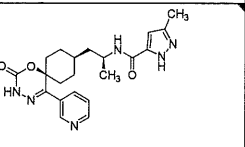
30 [0568]

Table 1-1

Ex. No.	Structure	Notes	¹ H-NMR (400 MHz)	MS (M+1)	MS (M-1)
1			¹ H-NMR (DMSO-D ₆) δ: 11.65 (1H, s), 11.16 (1H, s), 8.17 (1H, d, J = 8.3 Hz), 7.44-7.37 (4H, m), 7.16 (2H, t, J = 8.3 Hz), 7.11 (1H, s), 7.04 (1H, td, J = 8.3, 2.6 Hz), 4.24-4.16 (1H, m), 2.82-2.71 (2H, m), 2.39-2.30 (4H, m), 1.97 (2H, d, J = 13.6 Hz), 1.81 (2H, td, J = 13.6, 5.2 Hz), 1.15 (3H, d, J = 6.5 Hz).	482	480
2			¹ H-NMR (DMSO-D ₆) δ: 11.63 (1H, s), 11.30 (1H, s), 8.20 (1H, d, J = 6.5 Hz), 7.73 (1H, d, J = 6.5 Hz), 7.51 (1H, t, J = 7.6 Hz), 7.42-7.36 (2H, m), 7.30 (1H, t, J = 8.9 Hz), 7.08 (1H, s), 7.03 (1H, t, J = 8.9 Hz), 4.29-4.18 (1H, m), 2.48-2.35 (6H, m), 2.17-2.09 (2H, m), 1.69-1.57 (2H, m), 1.13 (3H, d, J = 6.7 Hz).	560	558
3			¹ H-NMR (DMSO-D ₆) δ: 12.80 (1H, s), 11.26 (1H, s), 7.74 (1H, d, J = 8.0 Hz), 7.58 (1H, d, J = 7.4 Hz), 7.53 (1H, t, J = 7.4 Hz), 7.35 (1H, t, J = 8.0 Hz), 6.29 (1H, s), 4.12-4.02 (1H, m), 2.68 (2H, d, J = 12.3 Hz), 2.44-2.39 (1H, m), 2.33-2.25 (3H, m), 2.24 (3H, s), 2.07 (2H, d, J = 12.3 Hz), 1.55 (2H, s), 1.07 (3H, d, J = 6.2 Hz).	507	505
4			¹ H-NMR (DMSO-D ₆) δ: 11.62 (1H, s), 11.11 (1H, s), 8.20 (1H, d, J = 8.3 Hz), 7.50 (2H, dd, J = 8.8, 5.5 Hz), 7.42-7.36 (2H, m), 7.22 (2H, t, J = 8.8 Hz), 7.12 (1H, d, J = 1.6 Hz), 7.02 (1H, td, J = 8.8, 2.5 Hz), 4.21-4.12 (1H, m), 2.04-1.95 (2H, m), 1.78-1.70 (2H, tm), 1.68-1.61 (1H, m), 1.61-1.51 (2H, m), 1.48-1.23 (4H, m), 1.15 (3H, d, J = 6.5 Hz).	481	479
5			¹ H-NMR (DMSO-D ₆) δ: 12.82 (1H, s), 11.11 (1H, s), 7.62 (1H, s), 7.51 (2H, dd, J = 8.6, 5.3 Hz), 7.23 (2H, dd, J = 8.6, 5.3 Hz), 6.33 (1H, s), 4.12-4.02 (1H, m), 2.24 (3H, s), 2.02-1.95 (2H, m), 1.74-1.66 (2H, m), 1.66-1.60 (1H, m), 1.59-1.50 (2H, m), 1.42-1.22 (4H, m), 1.10 (3H, d, J = 6.2 Hz).	428	426
6			¹ H-NMR (DMSO-D ₆) δ: 11.11 (1H, s), 8.66 (1H, d, J = 5.3 Hz), 8.45 (1H, d, J = 9.2 Hz), 7.52 (2H, dd, J = 8.9, 5.3 Hz), 7.25 (2H, t, J = 8.9 Hz), 3.99-3.89 (1H, m), 2.66 (3H, d, J = 5.3 Hz), 2.02-1.95 (2H, m), 1.74-1.46 (5H, m), 1.35-1.21 (4H, m), 1.08 (3H, d, J = 6.5 Hz).	405	403
7			¹ H-NMR (DMSO-D ₆) δ: 11.12 (1H, s), 8.45 (1H, d, J = 8.3 Hz), 7.76 (1H, d, J = 8.3 Hz), 7.65 (1H, d, J = 8.3 Hz), 7.52 (1H, s), 7.51 (2H, t, J = 7.5 Hz), 7.46 (1H, t, J = 7.5 Hz), 7.33 (1H, t, J = 8.3 Hz), 7.22 (2H, t, J = 8.3 Hz), 4.20-4.10 (1H, m), 2.04-1.94 (2H, m), 1.74-1.53 (5H, m), 1.46-1.26 (4H, m), 1.16 (3H, d, J = 6.5 Hz).	464	462
8			¹ H-NMR (DMSO-D ₆) δ: 11.62 (1H, s), 11.29 (1H, s), 8.20 (1H, d, J = 9.0 Hz), 7.93 (2H, d, J = 8.3 Hz), 7.74 (2H, d, J = 8.3 Hz), 7.42-7.36 (2H, m), 7.13 (1H, d, J = 2.1 Hz), 7.02 (1H, td, J = 9.0, 2.3 Hz), 4.21-4.13 (1H, m), 3.24 (3H, s), 2.08-1.98 (2H, m), 1.78-1.30 (9H, m), 1.16 (3H, d, J = 6.5 Hz).	541	539

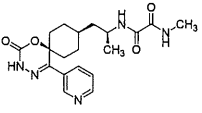
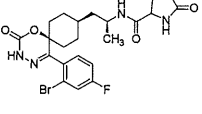
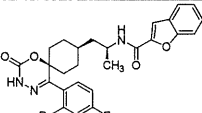
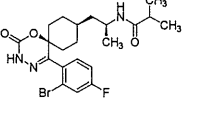
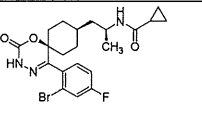
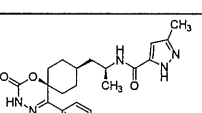
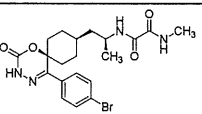
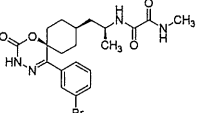
[0569]

Table 1-2

9		1H-NMR (DMSO-D6) δ : 12.83 (1H, s), 11.28 (1H, s), 7.94 (2H, d, J = 8.3 Hz), 7.74 (2H, d, J = 8.3 Hz), 7.63 (1H, d, J = 8.8 Hz), 6.32 (1H, s), 4.12-4.05 (1H, m), 3.25 (3H, s), 2.24 (3H, s), 2.06-1.98 (2H, m), 1.75-1.68 (2H, m), 1.65-1.54 (3H, m), 1.43-1.23 (4H, m), 1.10 (3H, d, J = 6.7 Hz).	488	486
10		1H-NMR (DMSO-D6) δ : 11.29 (1H, s), 8.66 (1H, d, J = 5.1 Hz), 8.46 (1H, q, J = 5.1 Hz), 7.96 (2H, d, J = 8.3 Hz), 7.76 (2H, d, J = 8.3 Hz), 3.98-3.90 (1H, m), 3.27 (3H, s), 2.66 (3H, d, J = 5.1 Hz), 2.06-1.98 (2H, m), 1.77-1.50 (5H, m), 1.38-1.23 (4H, m), 1.08 (3H, d, J = 6.5 Hz).	465	463
11		1H-NMR (DMSO-D6) δ : 11.20 (1H, s), 7.74 (1H, dd, J = 8.4, 2.4 Hz), 7.58-7.50 (2H, m), 7.35 (1H, td, J = 8.4, 2.4 Hz), 3.86-3.76 (1H, m), 2.16-2.08 (2H, m), 1.73 (3H, s), 1.65-1.58 (1H, m), 1.51-1.14 (8H, m), 0.97 (3H, d, J = 6.5 Hz).	440	438
12		1H-NMR (DMSO-D6) δ : 12.96 (0.18H, s), 12.81 (0.82H, s), 11.20 (1H, s), 7.97 (0.18H, d, J = 8.1 Hz), 7.71 (1H, dd, J = 8.6, 2.5 Hz), 7.60 (0.82H, d, J = 8.1 Hz), 7.51 (1H, dd, J = 8.6, 6.0 Hz), 7.31 (1H, td, J = 8.1, 2.5 Hz), 6.59 (0.18H, s), 6.31 (0.82H, s), 4.10-4.00 (1H, m), 2.23 (3H, s), 2.17-2.07 (2H, m), 1.73-1.65 (1H, m), 1.55-1.45 (2H, m), 1.40-1.20 (6H, m), 1.07 (3H, d, J = 6.5 Hz).	506	504
13		1H-NMR (DMSO-D6) δ : 11.60 (1H, s), 11.20 (1H, s), 8.17 (1H, d, J = 8.7 Hz), 7.70 (1H, dd, J = 8.7, 2.7 Hz), 7.49 (1H, dd, J = 8.7, 6.1 Hz), 7.38 (1H, s), 7.40-7.32 (1H, m), 7.30 (1H, td, J = 8.7, 2.7 Hz), 7.10 (1H, s), 7.02 (1H, td, J = 9.2, 2.7 Hz), 4.20-4.08 (1H, m), 2.18-2.08 (2H, m), 1.78-1.70 (1H, m), 1.57-1.49 (2H, m), 1.43-1.23 (6H, m), 1.13 (3H, d, J = 6.5 Hz).	559	557
14		1H-NMR (DMSO-D6) δ : 11.20 (1H, s), 8.64 (1H, q, J = 5.0 Hz), 8.43 (1H, d, J = 8.6 Hz), 7.73 (1H, dd, J = 8.6, 2.5 Hz), 7.52 (1H, dd, J = 8.6, 5.0 Hz), 7.34 (1H, td, J = 8.6, 2.5 Hz), 3.96-3.85 (1H, m), 2.64 (3H, d, J = 5.0 Hz), 2.17-2.05 (2H, m), 1.67-1.63 (1H, m), 1.55-1.15 (8H, m), 1.05 (3H, d, J = 6.5 Hz).	483	481
15		1H-NMR (DMSO-D6) δ : 11.62 (1H, s), 11.25 (1H, s), 8.63 (1H, d, J = 2.4 Hz), 8.62 (1H, dd, J = 4.9, 1.8 Hz), 8.20 (1H, d, J = 8.3 Hz), 7.92 (1H, dt, J = 8.3, 1.8 Hz), 7.44-7.36 (3H, m), 7.12 (1H, d, J = 1.8 Hz), 7.02 (1H, td, J = 9.1, 2.4 Hz), 4.22-4.12 (1H, m), 2.06-1.98 (2H, m), 1.77-1.45 (6H, m), 1.41-1.28 (3H, m), 1.16 (3H, d, J = 6.5 Hz).	464	462
16		1H-NMR (DMSO-D6) δ : 12.82 (1H, s), 11.24 (1H, s), 8.64 (1H, s), 8.63 (1H, dd, J = 4.7, 1.3 Hz), 7.93 (1H, d, J = 8.1 Hz), 7.65-7.58 (1H, m), 7.44 (1H, dd, J = 8.1, 4.7 Hz), 6.32 (1H, s), 4.14-4.04 (1H, m), 2.24 (3H, s), 2.06-1.99 (2H, m), 1.74-1.51 (5H, m), 1.46-1.23 (4H, m), 1.10 (3H, d, J = 6.0 Hz).	411	409

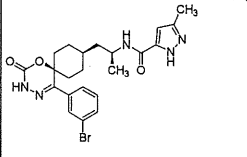
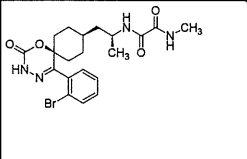
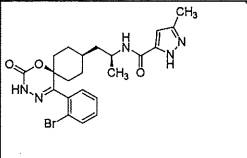
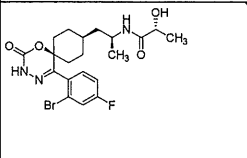
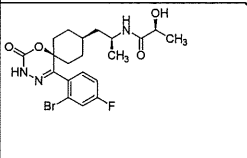
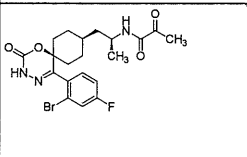
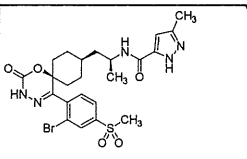
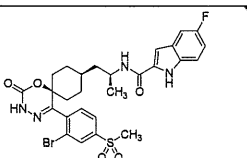
[0570]

Table 1-3

17			¹ H-NMR (DMSO-D ₆) δ: 11.24 (1H, s), 8.67-8.63 (3H, m), 8.44 (1H, d, J = 9.2 Hz), 7.94 (1H, dt, J = 8.0, 1.8 Hz), 7.46 (1H, dd, J = 8.0, 4.7 Hz), 3.97-3.87 (1H, m), 2.65 (3H, d, J = 4.7 Hz), 2.04-1.97 (2H, m), 1.77-1.48 (5H, m), 1.35-1.24 (4H, m), 1.08 (3H, d, J = 6.7 Hz).	388	386
18		Mixture of two diastereomers due to 5-position of pyrrolidone ring	¹ H-NMR (DMSO-D ₆) δ: 11.21 (1H, s), 7.76-7.73 (2H, m), 7.68 (1H, dd, J = 8.6, 4.6 Hz), 7.53 (1H, dd, J = 8.6, 6.0 Hz), 7.36 (1H, tt, J = 8.6, 2.3 Hz), 3.92-3.86 (1H, m), 3.85-3.81 (1H, m), 2.20-2.02 (5H, m), 1.82-1.73 (1H, m), 1.63-1.58 (1H, m), 1.51-1.18 (8H, m), 1.01-0.98 (3H, m).	509	507
19			¹ H-NMR (DMSO-D ₆) δ: 11.20 (1H, s), 8.41 (1H, d, J = 8.6 Hz), 7.75 (1H, d, J = 7.6 Hz), 7.70 (1H, dd, J = 8.6, 2.2 Hz), 7.63 (1H, d, J = 7.6 Hz), 7.50 (1H, dd, J = 8.6, 5.9 Hz), 7.49 (1H, s), 7.45 (1H, td, J = 7.6, 2.2 Hz), 7.33 (1H, t, J = 4.7 Hz), 7.31-7.27 (1H, m), 4.19-4.09 (1H, m), 2.18-2.07 (2H, m), 1.75-1.67 (1H, m), 1.60-1.50 (2H, m), 1.46-1.19 (6H, m), 1.13 (3H, d, J = 6.5 Hz).	542	540
20			¹ H-NMR (DMSO-D ₆) δ: 11.20 (1H, s), 7.74 (1H, dd, J = 8.6, 2.5 Hz), 7.53 (1H, dd, J = 8.6, 6.0 Hz), 7.42 (1H, d, J = 8.4 Hz), 7.35 (1H, td, J = 8.4, 2.5 Hz), 3.86-3.76 (1H, m), 2.30-2.23 (1H, m), 2.16-2.08 (2H, m), 1.63-1.56 (1H, m), 1.53-1.46 (1H, m), 1.43-1.18 (7H, m), 0.97-0.92 (9H, m).	468	466
21			¹ H-NMR (DMSO-D ₆) δ: 11.20 (1H, s), 7.77 (1H, d, J = 7.9 Hz), 7.74 (1H, dd, J = 8.7, 2.5 Hz), 7.54 (1H, dd, J = 8.7, 5.9 Hz), 7.35 (1H, td, J = 8.7, 2.5 Hz), 3.87-3.78 (1H, m), 2.17-2.07 (2H, m), 1.64-1.56 (1H, m), 1.52-1.17 (9H, m), 0.98 (3H, d, J = 6.5 Hz), 0.62-0.56 (4H, m).	466	464
22			¹ H-NMR (DMSO-D ₆) δ: 12.82 (1H, s), 11.15 (1H, s), 7.63-7.59 (1H, m), 7.60 (2H, d, J = 8.6 Hz), 7.41 (2H, d, J = 8.6 Hz), 6.33 (1H, s), 4.07 (1H, s), 2.25 (3H, s), 2.01-1.96 (2H, m), 1.72-1.51 (5H, m), 1.40-1.24 (4H, m), 1.10 (3H, d, J = 6.5 Hz).	488	486
23			¹ H-NMR (DMSO-D ₆) δ: 11.15 (1H, s), 8.65 (1H, q, J = 4.9 Hz), 8.44 (1H, d, J = 9.2 Hz), 7.62 (2H, d, J = 8.6 Hz), 7.43 (2H, d, J = 8.6 Hz), 3.98-3.88 (1H, m), 2.66 (3H, d, J = 4.9 Hz), 2.02-1.95 (2H, m), 1.74-1.47 (5H, m), 1.34-1.21 (4H, m), 1.08 (3H, d, J = 6.5 Hz).	465	463
24			¹ H-NMR (DMSO-D ₆) δ: 11.16 (1H, s), 8.65 (1H, q, J = 4.5 Hz), 8.43 (1H, d, J = 9.0 Hz), 7.66 (1H, d, J = 7.5 Hz), 7.62 (1H, s), 7.50 (1H, d, J = 7.5 Hz), 7.39 (1H, t, J = 7.5 Hz), 3.98-3.88 (1H, m), 2.65 (3H, d, J = 4.5 Hz), 2.03-1.96 (2H, m), 1.83-1.48 (5H, m), 1.33-1.21 (4H, m), 1.08 (3H, d, J = 6.7 Hz).	465	463

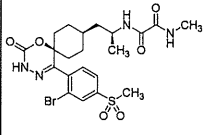
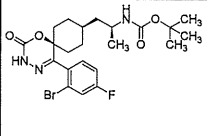
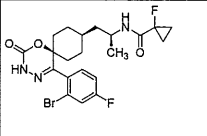
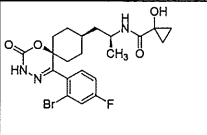
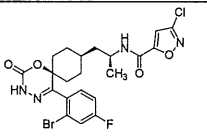
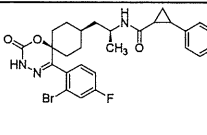
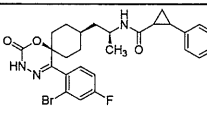
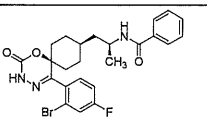
[0571]

Table 1-4

25		1H-NMR (DMSO-D6) δ : 12.81 (1H, s), 11.16 (1H, s), 7.66-7.58 (3H, m), 7.48 (1H, d, J = 7.9 Hz), 7.38 (1H, d, J = 7.9 Hz), 6.32 (1H, s), 4.12-4.02 (1H, m), 2.24 (3H, s), 2.04-1.97 (2H, m), 1.78-1.48 (5H, m), 1.44-1.20 (4H, m), 1.10 (3H, d, J = 6.0 Hz).	488	486
26		1H-NMR (DMSO-D6) δ : 11.16 (1H, s), 8.63 (1H, q, J = 4.8 Hz), 8.41 (1H, d, J = 8.6 Hz), 7.73 (1H, d, J = 8.6 Hz), 7.48-7.37 (3H, m), 3.95-3.85 (1H, m), 2.63 (3H, d, J = 4.8 Hz), 2.18-2.08 (2H, m), 1.69-1.61 (1H, m), 1.54-1.13 (8H, m), 1.05 (3H, d, J = 6.7 Hz).	465	463
27		1H-NMR (DMSO-D6) δ : 12.94 (0.18H, s), 12.80 (0.82H, s), 11.16 (1H, s), 7.94 (0.18H, d, J = 9.0 Hz), 7.72 (1H, d, J = 7.6 Hz), 7.58 (0.82H, d, J = 9.0 Hz), 7.44-7.38 (3H, m), 6.56 (0.18H, s), 6.30 (0.82H, s), 4.10-4.00 (1H, m), 2.23 (3H, s), 2.17-2.08 (2H, m), 1.75-1.63 (1H, m), 1.55-1.45 (2H, m), 1.39-1.20 (6H, m), 1.07 (3H, d, J = 6.0 Hz).	488	486
28		1H-NMR (DMSO-D6) δ : 11.20 (1H, s), 7.74 (1H, dd, J = 8.6, 2.5 Hz), 7.53 (1H, dd, J = 8.6, 6.0 Hz), 7.35 (1H, td, J = 8.6, 2.5 Hz), 7.29 (1H, d, J = 8.6 Hz), 5.35 (1H, d, J = 5.3 Hz), 3.92-3.84 (2H, m), 2.16-2.09 (2H, m), 1.65-1.58 (1H, m), 1.52-1.18 (8H, m), 1.14 (3H, d, J = 6.7 Hz), 1.01 (3H, d, J = 6.5 Hz).	470	468
29		1H-NMR (DMSO-D6) δ : 11.19 (1H, s), 7.74 (1H, dd, J = 8.8, 2.6 Hz), 7.53 (1H, dd, J = 8.6, 6.0 Hz), 7.35 (1H, td, J = 8.6, 2.6 Hz), 7.27 (1H, d, J = 8.8 Hz), 5.32 (1H, d, J = 5.1 Hz), 3.91-3.82 (2H, m), 2.17-2.09 (2H, m), 1.67-1.60 (1H, m), 1.51-1.19 (8H, m), 1.15 (3H, d, J = 6.7 Hz), 1.00 (3H, d, J = 6.5 Hz).	470	468
30		1H-NMR (DMSO-D6) δ : 11.19 (1H, s), 8.27 (1H, d, J = 9.0 Hz), 7.73 (1H, dd, J = 8.6, 2.6 Hz), 7.52 (1H, dd, J = 8.6, 6.1 Hz), 7.34 (1H, td, J = 8.6, 2.6 Hz), 3.91-3.82 (1H, m), 2.30 (3H, s), 2.15-2.08 (2H, m), 1.64-1.59 (1H, m), 1.50-1.18 (8H, m), 1.04 (3H, d, J = 6.5 Hz).	468	466
31		1H-NMR (DMSO-D6) δ : 12.80 (1H, s), 11.31 (1H, s), 8.23 (1H, d, J = 1.8 Hz), 7.95 (1H, dd, J = 8.2, 1.8 Hz), 7.74 (1H, d, J = 8.2 Hz), 7.61-7.56 (1H, m), 6.31-6.29 (1H, m), 4.10-4.02 (1H, m), 3.33 (3H, s), 2.23 (3H, s), 2.20-2.10 (2H, m), 1.73-1.67 (1H, m), 1.55-1.46 (2H, m), 1.45-1.21 (6H, m), 1.07 (3H, d, J = 6.5 Hz).	566	564
32		1H-NMR (DMSO-D6) δ : 11.58 (1H, s), 11.32 (1H, s), 8.22 (1H, d, J = 1.8 Hz), 8.16 (1H, d, J = 8.6 Hz), 7.94 (1H, dd, J = 8.0, 1.8 Hz), 7.72 (1H, d, J = 8.0 Hz), 7.40-7.34 (2H, m), 7.10-7.08 (1H, m), 7.04-6.98 (1H, m), 4.18-4.09 (1H, m), 3.31 (3H, s), 2.20-2.12 (2H, m), 1.77-1.71 (1H, m), 1.57-1.49 (2H, m), 1.47-1.22 (6H, m), 1.13 (3H, d, J = 6.5 Hz).	619	617

[0572]

Table 1-5

33			¹ H-NMR (DMSO-D ₆) δ: 11.31 (1H, s), 8.65-8.60 (1H, m), 8.41 (1H, d, J = 9.2 Hz), 8.25 (1H, d, J = 1.8 Hz), 7.97 (1H, dd, J = 8.1, 1.8 Hz), 7.75 (1H, d, J = 8.1 Hz), 3.95-3.86 (1H, m), 3.34 (3H, s), 2.63 (3H, d, J = 4.9 Hz), 2.17-2.11 (2H, m), 1.69-1.63 (1H, m), 1.56-1.44 (2H, m), 1.40-1.18 (6H, m), 1.05 (3H, d, J = 6.5 Hz).	543	541
34			¹ H-NMR (DMSO-D ₆) δ: 11.20 (1H, s), 7.74 (1H, dd, J = 8.5, 2.5 Hz), 7.53 (1H, dd, J = 8.5, 6.0 Hz), 7.35 (1H, td, J = 8.5, 2.5 Hz), 6.56 (1H, d, J = 9.0 Hz), 3.55-3.45 (1H, m), 2.19-2.08 (2H, m), 1.68-1.60 (1H, m), 1.50-1.12 (8H, m), 1.32 (9H, s), 0.96 (3H, d, J = 6.5 Hz).	498	496
35			¹ H-NMR (DMSO-D ₆) δ: 11.20 (1H, s), 8.05 (1H, d, J = 8.4 Hz), 7.74 (1H, dd, J = 8.4, 2.5 Hz), 7.54 (1H, dd, J = 8.4, 6.1 Hz), 7.36 (1H, td, J = 8.4, 2.5 Hz), 4.00-3.92 (1H, m), 2.18-2.09 (2H, m), 1.65-1.59 (1H, m), 1.51-1.19 (10H, m), 1.16-1.10 (2H, m), 1.06 (3H, d, J = 6.7 Hz).	484	482
36			¹ H-NMR (DMSO-D ₆) δ: 11.20 (1H, s), 7.74 (1H, dd, J = 8.7, 2.5 Hz), 7.54 (1H, dd, J = 8.7, 5.9 Hz), 7.42 (1H, d, J = 8.7 Hz), 7.36 (1H, td, J = 8.7, 2.5 Hz), 6.11 (1H, s), 3.93-3.85 (1H, m), 2.18-2.09 (2H, m), 1.66-1.59 (1H, m), 1.53-1.22 (8H, m), 1.03 (3H, d, J = 6.5 Hz), 0.96 (2H, q, J = 3.8 Hz), 0.77 (2H, q, J = 3.8 Hz).	482	480
37			¹ H-NMR (CDCl ₃) δ: 8.19 (1H, br s), 7.41 (1H, dd, J = 8.1, 2.5 Hz), 7.21-7.17 (1H, m), 7.12-7.07 (1H, m), 6.87 (1H, s), 6.22-6.18 (1H, m), 4.31-4.21 (1H, m), 2.35-2.28 (2H, m), 1.82-1.77 (1H, m), 1.63-1.52 (2H, m), 1.51-1.36 (5H, m), 1.34-1.25 (1H, m), 1.23 (3H, d, J = 6.5 Hz).	527	525
38		Mixture of two diastereomers due to 1,2-positions of cyclopropane ring (relative configuration: trans)	¹ H-NMR (CDCl ₃) δ: 8.12-8.08 (1H, m), 7.43-7.40 (1H, m), 7.30-7.24 (2H, m), 7.23-7.16 (2H, m), 7.13-7.02 (3H, m), 5.29-5.23 (1H, m), 4.16-4.07 (1H, m), 2.47-2.40 (1H, m), 2.35-2.26 (2H, m), 1.80-1.75 (1H, m), 1.62-1.38 (7H, m), 1.37-1.17 (4H, m), 1.14-1.10 (3H, m).	542	540
39		Mixture of two diastereomers due to 1,2-positions of cyclopropane ring (relative configuration: cis)	¹ H-NMR (CDCl ₃) δ: 8.11 (1H, s), 7.50-7.41 (1H, m), 7.23-7.09 (5H, m), 7.08-7.03 (1H, m), 6.90-6.86 (1H, m), 4.97-4.89 (1H, m), 3.89-3.80 (1H, m), 2.44-2.35 (1H, m), 2.27-2.12 (2H, m), 1.91-1.83 (1H, m), 1.69-1.61 (2H, m), 1.50-1.00 (9H, m), 0.94-0.74 (3H, m).	542	540
40			¹ H-NMR (CDCl ₃) δ: 8.15 (1H, s), 7.74-7.71 (2H, m), 7.51-7.38 (4H, m), 7.20-7.16 (1H, m), 7.10-7.05 (1H, m), 5.77 (1H, d, J = 9.0 Hz), 4.38-4.28 (1H, m), 2.33-2.27 (2H, m), 1.90-1.85 (1H, m), 1.62-1.52 (3H, m), 1.51-1.38 (4H, m), 1.37-1.28 (1H, m), 1.22 (3H, d, J = 6.5 Hz).	502	500

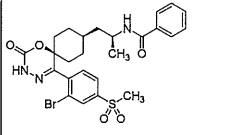
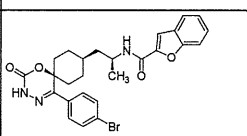
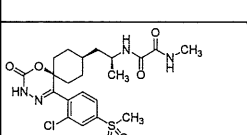
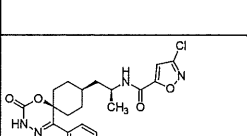
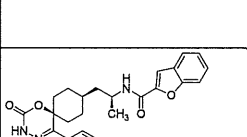
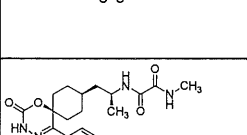
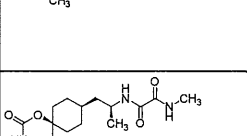
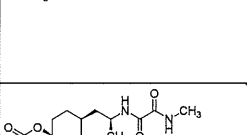
[0573]

Table 1-6

41			¹ H-NMR (CDCl ₃) δ: 8.11 (1H, s), 7.42 (1H, dd, J = 8.1, 2.5 Hz), 7.23-7.19 (1H, m), 7.14-7.09 (1H, m), 5.74-5.70 (1H, m), 4.15-4.07 (1H, m), 3.33 (2H, s), 2.35-2.29 (2H, m), 1.78-1.73 (1H, m), 1.59-1.52 (2H, m), 1.50-1.37 (4H, m), 1.29-1.21 (2H, m), 1.16 (3H, d, J = 6.5 Hz).	465	463
42			¹ H-NMR (CDCl ₃) δ: 8.10 (1H, s), 7.41 (1H, dd, J = 8.1, 2.5 Hz), 7.22-7.18 (1H, m), 7.13-7.07 (1H, m), 5.08-5.02 (1H, m), 4.16-4.08 (1H, m), 2.32-2.27 (2H, m), 2.09 (2H, t, J = 7.5 Hz), 1.84-1.79 (1H, m), 1.67-1.59 (2H, m), 1.57-1.40 (5H, m), 1.33-1.23 (3H, m), 1.10 (3H, d, J = 6.5 Hz), 0.91 (3H, t, J = 7.5 Hz).	468	466
43			¹ H-NMR (CDCl ₃) δ: 8.12 (1H, s), 7.42 (1H, dd, J = 8.2, 2.7 Hz), 7.23-7.20 (1H, m), 7.13-7.09 (1H, m), 5.31-5.28 (1H, m), 4.15-4.07 (1H, m), 3.46-3.31 (2H, m), 2.91 (3H, s), 2.69-2.65 (2H, m), 2.33-2.27 (2H, m), 1.77-1.72 (1H, m), 1.56-1.42 (5H, m), 1.36-1.24 (3H, m), 1.12 (3H, d, J = 6.5 Hz).	532	530
44			¹ H-NMR (DMSO-D ₆) δ: 11.20 (1H, s), 8.66-8.60 (1H, m), 8.41 (1H, d, J = 9.0 Hz), 7.59 (1H, dd, J = 8.8, 2.5 Hz), 7.53 (1H, dd, J = 8.6, 6.1 Hz), 7.30 (1H, td, J = 6.6, 2.8 Hz), 3.97-3.85 (1H, m), 2.64 (3H, d, J = 5.0 Hz), 2.09 (2H, d, J = 13.0 Hz), 1.70-1.12 (9H, m), 1.05 (3H, d, J = 6.5 Hz).	439	437
45			¹ H-NMR (DMSO-D ₆) δ: 12.80 (1H, s), 11.19 (1H, s), 7.63-7.47 (3H, m), 7.28 (1H, td, J = 8.5, 2.2 Hz), 6.30 (1H, s), 4.14-3.99 (1H, m), 2.29-2.04 (5H, m), 1.79-1.16 (9H, m), 1.07 (3H, d, J = 6.5 Hz).	462	460
46			¹ H-NMR (DMSO-D ₆) δ: 11.20 (1H, s), 8.40 (1H, d, J = 8.5 Hz), 7.75 (1H, d, J = 7.8 Hz), 7.63 (1H, d, J = 8.3 Hz), 7.57 (1H, dd, J = 8.8, 2.5 Hz), 7.52 (1H, dd, J = 8.8, 6.0 Hz), 7.49 (1H, d, J = 0.8 Hz), 7.47-7.42 (1H, m), 7.32 (1H, t, J = 7.5 Hz), 7.26 (1H, td, J = 8.5, 2.6 Hz), 4.18-4.08 (1H, m), 2.16-2.05 (2H, m), 1.75-1.66 (1H, m), 1.63-1.21 (8H, m), 1.13 (3H, d, J = 6.5 Hz).	498	496
47			¹ H-NMR (DMSO-D ₆) δ: 11.20 (1H, s), 8.70-8.61 (2H, m), 7.74 (1H, dd, J = 8.0, 2.5 Hz), 7.53 (1H, dd, J = 8.0, 6.6 Hz), 7.36 (1H, td, J = 8.0, 2.5 Hz), 3.18-3.00 (2H, m), 2.64 (3H, d, J = 4.9 Hz), 2.17-2.09 (2H, m), 1.62-1.56 (2H, m), 1.45-1.33 (4H, m), 1.28-1.20 (3H, m).	469	467
48			¹ H-NMR (CDCl ₃) δ: 8.24 (1H, d, J = 1.8 Hz), 8.21 (1H, s), 7.94 (1H, dd, J = 8.1, 1.8 Hz), 7.42 (1H, d, J = 8.1 Hz), 6.86 (1H, s), 6.20-6.17 (1H, m), 4.31-4.22 (1H, m), 3.11 (3H, s), 2.37-2.32 (2H, m), 1.87-1.80 (1H, m), 1.64-1.27 (8H, m), 1.23 (3H, d, J = 6.5 Hz).	587	585

[0574]

Table 1-7

49			¹ H-NMR (CDCl ₃) δ: 8.23 (1H, d, J = 1.8 Hz), 8.18 (1H, s), 7.92 (1H, dd, J = 8.2, 1.8 Hz), 7.73-7.70 (2H, m), 7.52-7.48 (1H, m), 7.45-7.40 (3H, m), 5.78-5.73 (1H, m), 4.38-4.31 (1H, m), 3.10 (3H, s), 2.36-2.30 (2H, m), 1.96-1.90 (1H, m), 1.64-1.49 (2H, m), 1.48-1.26 (6H, m), 1.22 (3H, d, J = 6.7 Hz).	562	560
50			¹ H-NMR (DMSO-D ₆) δ: 11.15 (1H, s), 8.43 (1H, d, J = 9.0 Hz), 7.76 (1H, d, J = 7.3 Hz), 7.65 (1H, d, J = 8.6 Hz), 7.59 (2H, d, J = 8.6 Hz), 7.51 (1H, s), 7.46 (1H, t, J = 7.3 Hz), 7.41 (2H, d, J = 8.6 Hz), 7.33 (1H, t, J = 7.3 Hz), 4.19-4.12 (1H, m), 2.04-1.96 (2H, m), 1.74-1.53 (5H, m), 1.47-1.24 (4H, m), 1.16 (3H, d, J = 6.5 Hz).	524	522
51			¹ H-NMR (DMSO-D ₆) δ: 11.32 (1H, s), 8.65-8.58 (1H, m), 8.41 (1H, d, J = 9.0 Hz), 8.12 (1H, d, J = 1.8 Hz), 7.93 (1H, dd, J = 8.0, 1.8 Hz), 7.78 (1H, d, J = 8.0 Hz), 3.95-3.85 (1H, m), 3.34 (3H, s), 2.63 (3H, d, J = 4.8 Hz), 2.18-2.08 (2H, m), 1.69-1.61 (1H, m), 1.59-1.14 (8H, m), 1.05 (3H, d, J = 6.5 Hz).	499	497
52			¹ H-NMR (DMSO-D ₆) δ: 11.32 (1H, s), 8.77 (1H, d, J = 8.5 Hz), 8.11 (1H, d, J = 1.8 Hz), 7.93 (1H, dd, J = 8.0, 1.8 Hz), 7.78 (1H, d, J = 8.0 Hz), 7.32 (1H, s), 4.12-4.00 (1H, m), 3.33 (3H, s), 2.14 (2H, d, J = 11.3 Hz), 1.66 (1H, d, J = 11.0 Hz), 1.56-1.19 (8H, m), 1.10 (3H, d, J = 6.5 Hz).	543	541
53			¹ H-NMR (DMSO-D ₆) δ: 11.32 (1H, s), 8.40 (1H, d, J = 8.5 Hz), 8.09 (1H, d, J = 1.8 Hz), 7.90 (1H, dd, J = 8.0, 1.8 Hz), 7.75 (2H, t, J = 7.5 Hz), 7.62 (1H, d, J = 8.8 Hz), 7.48 (1H, s), 7.44 (1H, t, J = 7.3 Hz), 7.32 (1H, t, J = 7.3 Hz), 4.15 (1H, bs), 3.36 (3H, s), 2.14 (2H, t, J = 11.0 Hz), 1.71 (1H, d, J = 9.0 Hz), 1.60-1.30 (8H, m), 1.13 (3H, d, J = 6.5 Hz).	558	556
54			¹ H-NMR (DMSO-D ₆) δ: 11.00 (1H, s), 8.64 (1H, q, J = 4.7 Hz), 8.42 (1H, d, J = 9.8 Hz), 7.21 (1H, dd, J = 8.4, 6.8 Hz), 7.01 (1H, dd, J = 9.8, 2.4 Hz), 6.81 (1H, td, J = 8.4, 2.4 Hz), 3.96-3.86 (1H, m), 3.79 (3H, s), 2.64 (3H, d, J = 4.7 Hz), 2.00-1.93 (2H, m), 1.68-1.60 (1H, m), 1.50-1.38 (4H, m), 1.28-1.13 (4H, m), 1.06 (3H, d, J = 6.8 Hz).	435	433
55			¹ H-NMR (DMSO-D ₆) δ: 11.08 (1H, s), 8.62 (1H, q, J = 4.9 Hz), 8.41 (1H, d, J = 9.0 Hz), 7.32 (1H, dd, J = 8.6, 6.0 Hz), 7.17 (1H, dd, J = 10.3, 2.7 Hz), 7.06 (1H, td, J = 8.6, 2.7 Hz), 3.95-3.86 (1H, m), 2.64 (3H, d, J = 4.9 Hz), 2.23 (3H, s), 2.06-1.99 (2H, m), 1.68-1.15 (9H, m), 1.05 (3H, d, J = 6.5 Hz).	419	417
56			¹ H-NMR (DMSO-D ₆) δ: 11.26 (1H, s), 8.64 (1H, q, J = 4.9 Hz), 8.43 (1H, d, J = 9.2 Hz), 7.80 (1H, dd, J = 9.2, 2.5 Hz), 7.71 (1H, dd, J = 8.8, 5.3 Hz), 7.65-7.58 (1H, m), 3.97-3.84 (1H, m), 2.65 (3H, d, J = 4.9 Hz), 2.07-1.88 (2H, m), 1.70-1.60 (1H, m), 1.60-1.14 (8H, m), 1.06 (3H, d, J = 6.5 Hz).	473	471

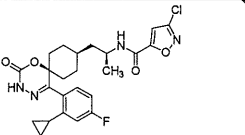
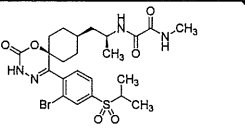
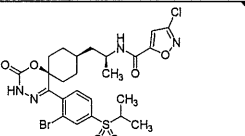
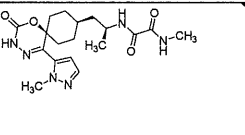
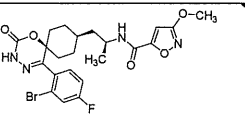
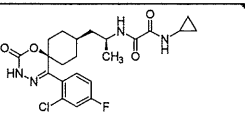
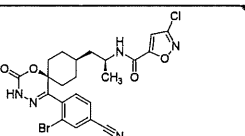
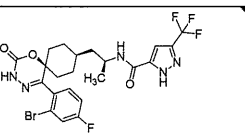
[0575]

Table 1-8

57			¹ H-NMR (CDCl ₃) δ: 8.24 (1H, s), 7.97 (1H, d, J = 1.6 Hz), 7.68 (1H, dd, J = 7.9, 1.6 Hz), 7.44-7.39 (1H, m), 7.33 (1H, d, J = 7.9 Hz), 7.18-7.14 (1H, m), 4.08-4.00 (1H, m), 2.89 (3H, d, J = 5.3 Hz), 2.34-2.28 (2H, m), 1.79-1.72 (1H, m), 1.60-1.51 (2H, m), 1.50-1.31 (5H, m), 1.30-1.21 (1H, m), 1.16 (3H, d, J = 6.5 Hz).	490	488
58			¹ H-NMR (DMSO-D ₆) δ: 11.10 (1H, s), 8.65-8.60 (1H, m), 8.41 (1H, d, J = 9.5 Hz), 7.34 (1H, d, J = 8.6 Hz), 7.28 (1H, d, J = 2.5 Hz), 7.01 (1H, dd, J = 8.6, 2.5 Hz), 3.95-3.85 (1H, m), 3.81 (3H, s), 2.64 (3H, d, J = 4.9 Hz), 2.14-2.05 (2H, m), 1.68-1.62 (1H, m), 1.56-1.11 (8H, m), 1.05 (3H, d, J = 6.5 Hz).	495	493
59			¹ H-NMR (DMSO-D ₆) δ: 11.10 (1H, s), 8.77 (1H, d, J = 8.3 Hz), 7.34 (1H, d, J = 8.6 Hz), 7.32 (1H, s), 7.28 (1H, d, J = 2.5 Hz), 7.00 (1H, dd, J = 8.6, 2.8 Hz), 4.11-4.01 (1H, m), 3.80 (3H, s), 2.15-2.06 (2H, m), 1.69-1.61 (1H, m), 1.55-1.20 (8H, m), 1.11 (3H, d, J = 6.5 Hz).	539	537
60			¹ H-NMR (DMSO-D ₆) δ: 11.21 (1H, s), 8.62 (1H, q, J = 5.2 Hz), 8.41 (1H, d, J = 9.7 Hz), 8.02 (1H, d, J = 1.8 Hz), 7.66 (1H, dd, J = 8.3, 1.8 Hz), 7.41 (1H, d, J = 8.3 Hz), 3.95-3.86 (1H, m), 2.64 (3H, d, J = 5.2 Hz), 2.13-2.06 (2H, m), 1.68-1.61 (1H, m), 1.53-1.15 (8H, m), 1.05 (3H, d, J = 6.5 Hz).	543	541
61			¹ H-NMR (DMSO-D ₆) δ: 11.20 (1H, s), 8.46 (1H, d, J = 8.5 Hz), 7.66 (1H, dd, J = 9.0, 4.3 Hz), 7.57 (2H, dd, J = 8.8, 2.8 Hz), 7.52 (1H, dd, J = 8.6, 6.1 Hz), 7.49 (1H, s), 7.33-7.23 (2H, m), 4.18-4.07 (1H, m), 2.16-2.05 (2H, m), 1.75-1.66 (1H, m), 1.62-1.21 (8H, m), 1.13 (3H, d, J = 6.5 Hz).	516	514
62			¹ H-NMR (DMSO-D ₆) δ: 12.07 (1H, s), 11.20 (1H, s), 8.34 (1H, d, J = 8.5 Hz), 8.24 (1H, s), 7.68 (1H, dd, J = 8.8, 1.8 Hz), 7.61-7.55 (2H, m), 7.51 (1H, dd, J = 8.6, 6.1 Hz), 7.33 (1H, d, J = 1.5 Hz), 7.26 (1H, td, J = 8.6, 2.6 Hz), 4.22-4.10 (1H, m), 3.17 (3H, s), 2.15-2.06 (2H, m), 1.77-1.69 (1H, m), 1.59-1.21 (8H, m), 1.15 (3H, d, J = 6.5 Hz).	575	573
63			¹ H-NMR (DMSO-D ₆) δ: 11.20 (1H, s), 8.77 (1H, d, J = 8.3 Hz), 7.59 (1H, dd, J = 9.0, 2.5 Hz), 7.53 (1H, dd, J = 8.6, 6.1 Hz), 7.32 (1H, s), 7.29 (1H, td, J = 8.5, 2.5 Hz), 4.12-4.01 (1H, m), 2.10 (2H, d, J = 13.0 Hz), 1.69-1.60 (1H, m), 1.57-1.20 (8H, m), 1.11 (3H, d, J = 6.8 Hz).	483	481
64			¹ H-NMR (CDCl ₃) δ: 8.09 (1H, s), 7.44-7.38 (1H, m), 7.18-7.13 (1H, m), 7.08-7.04 (1H, m), 6.90-6.85 (1H, m), 6.52 (1H, dd, J = 10.6, 2.5 Hz), 4.08-3.98 (1H, m), 2.89 (3H, d, J = 5.3 Hz), 2.27-2.19 (2H, m), 1.89-1.82 (1H, m), 1.76-1.70 (1H, m), 1.54-1.35 (7H, m), 1.29-1.21 (1H, m), 1.16 (3H, d, J = 6.5 Hz), 1.06-1.02 (2H, m), 0.75-0.71 (2H, m).	445	443

[0576]

Table 1-9

65			¹ H-NMR (CDCl ₃) δ: 8.07 (1H, s), 7.05 (1H, dd, J = 8.6, 5.8 Hz), 6.89-6.84 (2H, m), 6.52 (1H, dd, J = 10.4, 2.5 Hz), 6.20-6.16 (1H, m), 4.30-4.21 (1H, m), 2.28-2.22 (2H, m), 1.89-1.77 (2H, m), 1.60-1.39 (7H, m), 1.35-1.26 (1H, m), 1.23 (3H, d, J = 6.5 Hz), 1.06-1.02 (2H, m), 0.75-0.71 (2H, m).	489	487
66			¹ H-NMR (CDCl ₃) δ: 8.21 (1H, s), 8.18 (1H, d, J = 1.7 Hz), 7.88 (1H, dd, J = 8.0, 1.7 Hz), 7.43-7.39 (2H, m), 7.17-7.14 (1H, m), 4.11-4.01 (1H, m), 3.29-3.21 (1H, m), 2.89 (3H, d, J = 5.3 Hz), 2.36-2.29 (2H, m), 1.79-1.74 (1H, m), 1.58-1.37 (7H, m), 1.35 (6H, d, J = 7.2 Hz), 1.29-1.21 (1H, m), 1.16 (3H, d, J = 6.5 Hz).	571	569
67			¹ H-NMR (CDCl ₃) δ: 8.19 (1H, s), 8.17 (1H, d, J = 1.8 Hz), 7.87 (1H, dd, J = 8.0, 1.8 Hz), 7.41 (1H, d, J = 8.0 Hz), 6.86 (1H, s), 6.21-6.17 (1H, m), 4.32-4.22 (1H, m), 3.27-3.20 (1H, m), 2.38-2.31 (2H, m), 1.86-1.77 (1H, m), 1.61-1.39 (7H, m), 1.34 (6H, d, J = 6.9 Hz), 1.29-1.21 (4H, m).	615	613
68			¹ H-NMR (DMSO-D ₆) δ: 11.35 (1H, s), 8.68-8.63 (1H, m), 8.44 (1H, d, J = 9.2 Hz), 7.48 (1H, d, J = 1.8 Hz), 6.62 (1H, d, J = 2.1 Hz), 3.97-3.87 (1H, m), 3.81 (3H, s), 2.66 (3H, d, J = 5.1 Hz), 2.03-1.96 (2H, m), 1.77-1.46 (5H, m), 1.37-1.17 (4H, m), 1.08 (3H, d, J = 6.5 Hz).	391	389
69			¹ H-NMR (DMSO-D ₆) δ: 11.19 (1H, s), 8.58 (1H, d, J = 8.3 Hz), 7.72 (1H, dd, J = 8.7, 2.7 Hz), 7.52 (1H, dd, J = 8.6, 6.0 Hz), 7.33 (1H, td, J = 8.5, 2.5 Hz), 6.75 (1H, s), 4.09-3.99 (1H, m), 3.92 (3H, s), 2.16-2.07 (2H, m), 1.69-1.61 (1H, m), 1.55-1.20 (8H, m), 1.09 (3H, d, J = 6.7 Hz).	523	521
70			¹ H-NMR (DMSO-D ₆) δ: 11.20 (1H, s), 8.68 (1H, d, J = 5.2 Hz), 8.41 (1H, d, J = 9.0 Hz), 7.60 (1H, dd, J = 8.6, 2.6 Hz), 7.53 (1H, dd, J = 9.0, 6.0 Hz), 7.30 (1H, td, J = 8.4, 2.6 Hz), 3.93-3.85 (1H, m), 2.77-2.70 (1H, m), 2.12-2.04 (2H, m), 1.68-1.61 (1H, m), 1.54-1.16 (8H, m), 1.05 (3H, d, J = 6.7 Hz), 0.64-0.58 (4H, m).	465	463
71			¹ H-NMR (CDCl ₃) δ: 8.17 (1H, s), 7.96 (1H, d, J = 1.6 Hz), 7.67 (1H, dd, J = 8.0, 1.6 Hz), 7.33 (1H, d, J = 8.0 Hz), 6.86 (1H, s), 6.19-6.15 (1H, m), 4.30-4.22 (1H, m), 2.35-2.31 (2H, m), 1.85-1.79 (1H, m), 1.60-1.25 (8H, m), 1.23 (3H, d, J = 6.5 Hz).	534	532
72			¹ H-NMR (DMSO-D ₆) δ: 14.40-14.28 (1H, m), 11.20 (1H, s), 8.30-8.25 (1H, m), 7.72 (1H, dd, J = 8.7, 2.7 Hz), 7.50 (1H, dd, J = 8.6, 6.0 Hz), 7.32 (1H, td, J = 8.4, 2.5 Hz), 7.26 (1H, s), 4.14-4.03 (1H, m), 2.16-2.07 (2H, m), 1.75-1.67 (1H, m), 1.54-1.21 (8H, m), 1.11 (3H, d, J = 6.5 Hz).	560	558

[0577]

Table 1-10

73			¹ H-NMR (DMSO-D ₆) δ: 11.06 (1H, s), 8.68 (1H, q, J = 5.2 Hz), 8.38 (1H, d, J = 9.0 Hz), 7.78 (2H, d, J = 7.6 Hz), 7.74 (1H, dd, J = 8.1, 2.0 Hz), 7.66 (1H, d, J = 2.0 Hz), 7.51-7.37 (9H, m), 3.90-3.80 (1H, m), 2.67 (3H, d, J = 5.0 Hz), 1.63-1.07 (11H, m), 1.02 (3H, d, J = 6.7 Hz).	539	537
74			¹ H-NMR (DMSO-D ₆) δ: 11.09 (1H, s), 8.63 (1H, q, J = 4.7 Hz), 8.41 (1H, d, J = 9.0 Hz), 7.46-7.36 (2H, m), 7.26-7.15 (2H, m), 3.95-3.85 (1H, m), 2.64 (3H, d, J = 4.7 Hz), 2.43 (3H, s), 2.16-2.07 (2H, m), 1.66-1.60 (1H, m), 1.53-1.37 (3H, m), 1.34-1.13 (5H, m), 1.05 (3H, d, J = 6.5 Hz).	433	431
75			¹ H-NMR (DMSO-D ₆) δ: 11.12 (1H, s), 8.64 (1H, q, J = 4.6 Hz), 8.42 (1H, d, J = 8.8 Hz), 8.07 (1H, d, J = 7.8 Hz), 7.82-7.75 (2H, m), 7.66 (1H, d, J = 7.8 Hz), 3.96-3.86 (1H, m), 3.24 (3H, s), 2.65 (3H, d, J = 4.6 Hz), 2.20-2.09 (2H, m), 1.66-1.45 (4H, m), 1.34-1.17 (5H, m), 1.06 (3H, d, J = 6.7 Hz).	465	463
76			¹ H-NMR (DMSO-D ₆) δ: 11.12 (1H, s), 8.78 (1H, d, J = 8.1 Hz), 8.06 (1H, d, J = 7.6 Hz), 7.77 (2H, dt, J = 18.1, 7.5 Hz), 7.65 (1H, d, J = 6.5 Hz), 7.33 (1H, s), 4.07 (1H, s), 3.24 (3H, s), 2.21-2.06 (2H, m), 1.68-1.42 (4H, m), 1.39-1.20 (5H, m), 1.12 (3H, d, J = 6.2 Hz).	509	507
77			¹ H-NMR (DMSO-D ₆) δ: 11.32 (1H, s), 8.66-8.59 (1H, m), 8.41 (1H, d, J = 9.3 Hz), 8.06 (1H, d, J = 1.8 Hz), 7.90 (1H, dd, J = 8.0, 1.8 Hz), 7.77 (1H, d, J = 8.0 Hz), 3.96-3.84 (1H, m), 3.45-3.39 (2H, m), 2.63 (3H, d, J = 5.3 Hz), 2.16-2.06 (2H, m), 1.69-1.13 (11H, m), 1.05 (3H, d, J = 6.5 Hz), 0.94 (3H, t, J = 7.5 Hz).	527	525
78			¹ H-NMR (DMSO-D ₆) δ: 11.12 (1H, s), 8.78 (1H, d, J = 8.1 Hz), 8.06 (1H, d, J = 7.0 Hz), 7.82-7.72 (2H, m), 7.65 (1H, d, J = 7.0 Hz), 7.33 (1H, s), 4.10-4.02 (1H, m), 3.24 (3H, s), 2.21-2.06 (2H, m), 1.68-1.42 (4H, m), 1.39-1.20 (5H, m), 1.12 (3H, d, J = 6.2 Hz).	509	507
79			¹ H-NMR (DMSO-D ₆) δ: 11.09 (1H, s), 8.76 (1H, d, J = 9.0 Hz), 7.45-7.37 (2H, m), 7.32 (1H, s), 7.25-7.18 (2H, m), 4.10-4.03 (1H, m), 2.43 (3H, s), 2.17-2.09 (2H, m), 1.66-1.61 (1H, m), 1.54-1.21 (8H, m), 1.11 (3H, d, J = 6.5 Hz).	477	475
80			¹ H-NMR (DMSO-D ₆) δ: 11.25 (1H, s), 8.66-8.60 (1H, m), 8.41 (1H, d, J = 9.2 Hz), 7.85-7.83 (1H, m), 7.61 (1H, d, J = 8.3 Hz), 7.51-7.46 (1H, m), 3.95-3.85 (1H, m), 2.64 (3H, d, J = 4.9 Hz), 2.16-2.08 (2H, m), 1.70-1.61 (1H, m), 1.56-1.16 (8H, m), 1.05 (3H, d, J = 6.5 Hz).	549	547

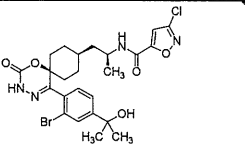
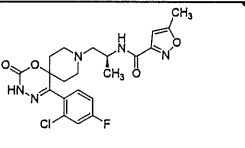
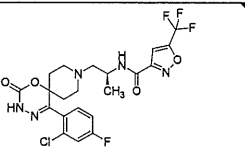
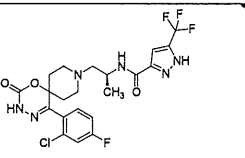
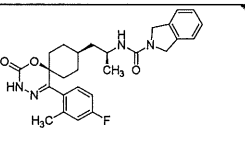
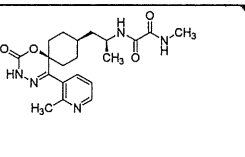
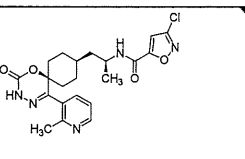
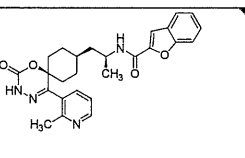
[0578]

Table 1-11

81			¹ H-NMR (DMSO-D ₆) δ: 11.25 (1H, s), 8.77 (1H, d, J = 8.6 Hz), 7.85-7.83 (1H, m), 7.61 (1H, d, J = 8.6 Hz), 7.50-7.46 (1H, m), 7.33-7.31 (1H, m), 4.11-4.01 (1H, m), 2.18-2.09 (2H, m), 1.70-1.62 (1H, m), 1.57-1.21 (8H, m), 1.11 (3H, d, J = 6.5 Hz).	593	591
82			¹ H-NMR (DMSO-D ₆) δ: 11.23 (1H, s), 8.71-8.65 (1H, m), 8.49 (1H, d, J = 9.5 Hz), 7.39 (1H, s), 7.03 (1H, s), 4.01-3.90 (1H, m), 3.98 (2H, d, J = 7.6 Hz), 2.68 (3H, d, J = 4.9 Hz), 2.37-2.20 (2H, m), 1.93-1.82 (2H, m), 1.73-1.64 (1H, m), 1.62-1.45 (2H, m), 1.37-1.15 (5H, m), 1.09 (3H, d, J = 6.5 Hz), 0.52-0.45 (2H, m), 0.37-0.30 (2H, m).	431	429
83			¹ H-NMR (DMSO-D ₆) δ: 11.24 (1H, s), 8.86-8.82 (1H, m), 7.38 (2H, d, J = 9.0 Hz), 7.01 (1H, s), 4.16-4.06 (1H, m), 3.98 (2H, d, J = 7.4 Hz), 2.37-2.22 (2H, m), 1.93-1.84 (2H, m), 1.72-1.65 (1H, m), 1.60-1.50 (2H, m), 1.44-1.17 (5H, m), 1.15 (3H, d, J = 6.9 Hz), 0.51-0.45 (2H, m), 0.37-0.31 (2H, m).	475	473
84			¹ H-NMR (DMSO-D ₆) δ: 11.23 (1H, s), 8.47 (1H, d, J = 8.3 Hz), 7.79-7.75 (1H, m), 7.66 (1H, d, J = 8.6 Hz), 7.54 (1H, s), 7.50-7.43 (1H, m), 7.37 (1H, s), 7.34 (1H, t, J = 8.2 Hz), 6.98 (1H, s), 4.24-4.13 (1H, m), 3.97 (2H, d, J = 7.2 Hz), 2.38-2.21 (2H, m), 1.93-1.85 (2H, m), 1.79-1.69 (1H, m), 1.67-1.51 (2H, m), 1.48-1.14 (5H, m), 1.17 (3H, d, J = 6.2 Hz), 0.51-0.44 (2H, m), 0.36-0.29 (2H, m).	490	488
85			¹ H-NMR (DMSO-D ₆) δ: 11.12 (1H, s), 8.67-8.59 (1H, m), 8.44-8.39 (1H, m), 7.41-7.35 (2H, m), 7.11-7.07 (1H, m), 6.55-6.23 (1H, m), 4.47-4.36 (2H, m), 3.98-3.82 (1H, m), 2.64 (3H, d, J = 4.9 Hz), 2.14-2.05 (2H, m), 1.71-1.61 (1H, m), 1.59-1.10 (8H, m), 1.05 (3H, d, J = 6.5 Hz).	545	543
86			¹ H-NMR (DMSO-D ₆) δ: 11.14 (1H, d, J = 2.3 Hz), 8.65-8.60 (1H, m), 8.41 (1H, d, J = 9.0 Hz), 7.46 (1H, d, J = 2.8 Hz), 7.41 (1H, d, J = 8.1 Hz), 7.14 (1H, dd, J = 8.6, 2.5 Hz), 4.87 (2H, q, J = 8.8 Hz), 3.96-3.85 (1H, m), 2.64 (3H, d, J = 4.6 Hz), 2.15-2.05 (2H, m), 1.70-1.60 (1H, m), 1.58-1.09 (8H, m), 1.05 (3H, d, J = 6.5 Hz).	563	561
87			¹ H-NMR (DMSO-D ₆) δ: 11.24 (1H, s), 8.40 (1H, d, J = 9.2 Hz), 7.82 (1H, d, J = 1.8 Hz), 7.74 (1H, d, J = 8.1 Hz), 7.63 (1H, d, J = 8.3 Hz), 7.59 (1H, d, J = 8.6 Hz), 7.49 (1H, d, J = 0.9 Hz), 7.47-7.42 (2H, m), 7.34-7.30 (1H, m), 4.18-4.07 (1H, m), 2.18-2.09 (2H, m), 1.75-1.66 (1H, m), 1.65-1.20 (8H, m), 1.13 (3H, d, J = 6.7 Hz).	608	606
88			¹ H-NMR (DMSO-D ₆) δ: 11.09 (1H, s), 8.13 (1H, d, J = 8.3 Hz), 7.56-7.48 (2H, m), 7.36-7.30 (2H, m), 7.18 (1H, dd, J = 10.2, 2.8 Hz), 7.08 (1H, td, J = 8.6, 2.8 Hz), 4.08-4.00 (1H, m), 2.24 (3H, s), 2.10-2.02 (2H, m), 1.70-1.63 (1H, m), 1.56-1.23 (8H, m), 1.09 (3H, d, J = 6.5 Hz).	490	488

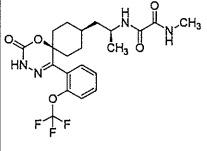
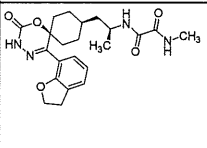
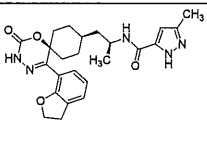
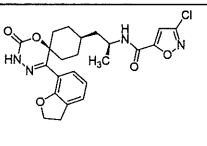
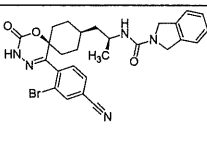
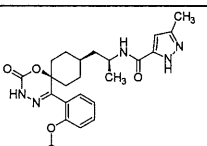
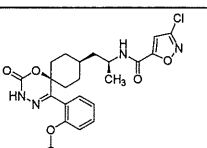
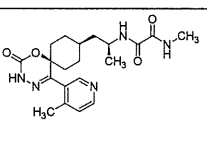
[0579]

Table 1-12

97		1H-NMR (DMSO-D6) δ : 11.14 (1H, s), 8.76 (1H, d, J = 9.0 Hz), 7.78 (1H, s), 7.49 (1H, d, J = 8.2 Hz), 7.35 (1H, d, J = 8.2 Hz), 7.32 (1H, s), 5.22 (1H, s), 4.11-3.99 (1H, m), 2.19-2.07 (2H, m), 1.71-1.60 (1H, m), 1.57-1.20 (8H, m), 1.42 (6H, s), 1.11 (3H, d, J = 6.7 Hz).	567	565
98		1H-NMR (DMSO-D6) δ : 11.25 (1H, s), 8.30 (1H, d, J = 8.5 Hz), 7.62 (1H, dd, J = 9.0, 2.5 Hz), 7.55 (1H, dd, J = 8.6, 6.1 Hz), 7.32 (1H, td, J = 8.5, 2.5 Hz), 6.42 (1H, s), 4.14-4.03 (1H, m), 2.74-2.61 (2H, m), 2.47-2.38 (1H, m), 2.44 (3H, s), 2.36-2.23 (3H, m), 2.10-2.00 (2H, m), 1.62-1.47 (2H, m), 1.07 (3H, d, J = 6.8 Hz).	464	462
99		1H-NMR (DMSO-D6) δ : 11.51 (1H, s), 9.12-9.07 (1H, m), 7.83 (1H, s), 7.72-7.58 (2H, m), 7.45-7.36 (1H, m), 4.56-4.32 (1H, m), 2.55-2.24 (6H, m), 2.12-1.81 (2H, m), 1.67-1.43 (2H, m), 1.21 (3H, d, J = 6.5 Hz).	520 (M+3)	516
100		1H-NMR (DMSO-D6) δ : 14.36 (1H, s), 11.26 (1H, s), 8.26 (1H, d, J = 8.0 Hz), 7.60 (1H, dd, J = 8.8, 2.5 Hz), 7.52 (1H, dd, J = 8.6, 6.1 Hz), 7.29 (1H, td, J = 8.6, 2.6 Hz), 7.23 (1H, s), 4.16-4.06 (1H, m), 2.78-2.64 (2H, m), 2.41 (1H, dd, J = 12.4, 7.6 Hz), 2.36-2.25 (3H, m), 2.05 (2H, d, J = 13.5 Hz), 1.62-1.50 (2H, m), 1.10 (3H, d, J = 6.5 Hz).	517	515
101		1H-NMR (DMSO-D6) δ : 11.08 (1H, s), 7.34-7.24 (5H, m), 7.16 (1H, dd, J = 10.3, 2.7 Hz), 7.04 (1H, td, J = 8.5, 2.5 Hz), 5.88 (1H, d, J = 8.3 Hz), 4.60-4.50 (4H, m), 3.84-3.75 (1H, m), 2.23 (3H, s), 2.09-2.00 (2H, m), 1.69-1.61 (1H, m), 1.55-1.17 (8H, m), 1.04 (3H, d, J = 6.5 Hz).	479	477
102		1H-NMR (DMSO-D6) δ : 11.17 (1H, s), 8.62 (1H, q, J = 4.5 Hz), 8.51 (1H, d, J = 5.2 Hz), 8.41 (1H, d, J = 9.0 Hz), 7.73 (1H, d, J = 7.5 Hz), 7.28 (1H, dd, J = 7.5, 5.2 Hz), 3.97-3.83 (1H, m), 2.64 (3H, d, J = 4.5 Hz), 2.41 (3H, s), 2.14-2.01 (2H, m), 1.71-1.60 (1H, m), 1.58-1.40 (3H, m), 1.40-1.15 (5H, m), 1.05 (3H, d, J = 6.7 Hz).	402	400
103		1H-NMR (DMSO-D6) δ : 11.17 (1H, s), 8.77 (1H, d, J = 8.2 Hz), 8.50 (1H, d, J = 4.5 Hz), 7.72 (1H, d, J = 7.5 Hz), 7.32 (1H, s), 7.27 (1H, dd, J = 7.5, 4.5 Hz), 4.12-4.00 (1H, m), 2.41 (3H, s), 2.14-2.03 (2H, m), 1.71-1.61 (1H, m), 1.56-1.21 (8H, m), 1.11 (3H, d, J = 6.0 Hz).	446	444
104		1H-NMR (DMSO-D6) δ : 11.17 (1H, s), 8.48 (1H, d, J = 3.0 Hz), 8.40 (1H, d, J = 9.0 Hz), 7.74 (1H, d, J = 8.2 Hz), 7.71 (1H, dd, J = 8.2, 1.5 Hz), 7.63 (1H, d, J = 8.2 Hz), 7.49 (1H, s), 7.45 (1H, t, J = 7.5 Hz), 7.32 (1H, t, J = 7.5 Hz), 7.24 (1H, dd, J = 7.9, 4.9 Hz), 4.19-4.07 (1H, m), 2.41 (3H, s), 2.14-2.01 (2H, m), 1.75-1.66 (1H, m), 1.63-1.21 (8H, m), 1.13 (3H, d, J = 6.7 Hz).	461	459

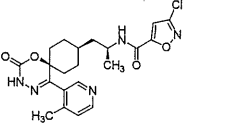
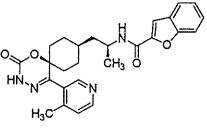
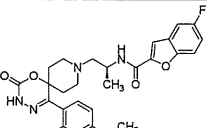
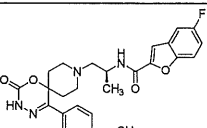
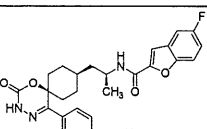
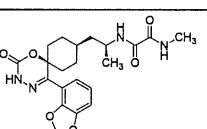
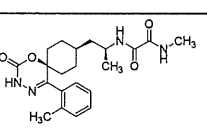
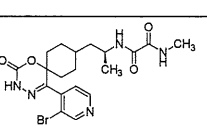
[0581]

Table 1-14

105			¹ H-NMR (DMSO-D ₆) δ: 11.22 (1H, s), 8.63 (1H, q, J = 4.5 Hz), 8.42 (1H, d, J = 9.7 Hz), 7.64-7.58 (1H, m), 7.55-7.43 (3H, m), 3.97-3.83 (1H, m), 2.64 (3H, d, J = 4.5 Hz), 2.07-1.96 (2H, m), 1.71-1.58 (1H, m), 1.58-1.14 (8H, m), 1.05 (3H, d, J = 6.7 Hz).	471	469
106			¹ H-NMR (DMSO-D ₆) δ: 11.03 (1H, s), 8.70-8.65 (1H, m), 8.44 (1H, d, J = 9.0 Hz), 7.31 (1H, d, J = 6.9 Hz), 7.03 (1H, d, J = 7.6 Hz), 6.87 (1H, t, J = 7.5 Hz), 4.57-4.49 (2H, m), 4.00-3.87 (1H, m), 3.21 (2H, t, J = 8.4 Hz), 2.66 (3H, d, J = 4.9 Hz), 1.99-1.87 (2H, m), 1.79-1.42 (5H, m), 1.35-1.14 (4H, m), 1.07 (3H, d, J = 6.7 Hz).	429	427
107			¹ H-NMR (DMSO-D ₆) δ: 12.87-12.77 (1H, m), 11.02 (1H, s), 7.65-7.57 (1H, m), 7.31-7.27 (1H, m), 7.03-7.00 (1H, m), 6.85 (1H, t, J = 7.5 Hz), 6.35-6.29 (1H, m), 4.53-4.39 (2H, m), 4.13-4.02 (1H, m), 3.18 (2H, t, J = 8.7 Hz), 2.29-2.16 (3H, m), 1.98-1.87 (2H, m), 1.76-1.43 (5H, m), 1.33-1.17 (4H, m), 1.09 (3H, d, J = 6.5 Hz).	452	450
108			¹ H-NMR (DMSO-D ₆) δ: 11.03 (1H, s), 8.80 (1H, d, J = 9.0 Hz), 7.35 (1H, s), 7.30 (1H, d, J = 7.4 Hz), 7.02 (1H, d, J = 7.4 Hz), 6.86 (1H, t, J = 7.5 Hz), 4.57-4.43 (2H, m), 4.13-4.01 (1H, m), 3.20 (2H, t, J = 8.7 Hz), 1.99-1.90 (2H, m), 1.77-1.44 (5H, m), 1.37-1.16 (4H, m), 1.13 (3H, d, J = 6.5 Hz).	473	471
109			¹ H-NMR (DMSO-D ₆) δ: 11.30 (1H, s), 8.33 (1H, d, J = 1.4 Hz), 7.92 (1H, dd, J = 7.9, 1.6 Hz), 7.67 (1H, d, J = 7.9 Hz), 7.32-7.25 (4H, m), 5.88 (1H, d, J = 8.1 Hz), 4.61-4.47 (4H, m), 3.86-3.75 (1H, m), 2.20-2.10 (2H, m), 1.73-1.60 (1H, m), 1.58-1.13 (8H, m), 1.04 (3H, d, J = 6.5 Hz).	550	548
110			¹ H-NMR (DMSO-D ₆) δ: 12.80 (1H, s), 11.22 (1H, s), 7.63-7.56 (2H, m), 7.53-7.49 (1H, m), 7.49-7.42 (2H, m), 6.30 (1H, s), 4.12-3.99 (1H, m), 2.23 (3H, s), 2.08-1.96 (2H, m), 1.74-1.62 (1H, m), 1.58-1.18 (8H, m), 1.07 (3H, d, J = 6.7 Hz).	494	492
111			¹ H-NMR (DMSO-D ₆) δ: 11.22 (1H, s), 8.77 (1H, d, J = 8.2 Hz), 7.65-7.56 (1H, m), 7.55-7.42 (3H, m), 7.32 (1H, s), 4.13-3.99 (1H, m), 2.10-1.97 (2H, m), 1.71-1.61 (1H, m), 1.57-1.20 (8H, m), 1.11 (3H, d, J = 6.7 Hz).	515	513
112			¹ H-NMR (DMSO-D ₆) δ: 11.20 (1H, s), 8.62 (1H, q, J = 4.5 Hz), 8.51-8.44 (2H, m), 8.41 (1H, d, J = 9.0 Hz), 7.35 (1H, d, J = 5.2 Hz), 3.98-3.83 (1H, m), 2.64 (3H, d, J = 4.5 Hz), 2.25 (3H, s), 2.13-2.00 (2H, m), 1.72-1.60 (1H, m), 1.58-1.42 (3H, m), 1.42-1.17 (5H, m), 1.06 (3H, d, J = 6.0 Hz).	402	400

[0582]

Table 1-15

113			¹ H-NMR (DMSO-D ₆) δ: 11.21 (1H, s), 8.77 (1H, d, J = 8.2 Hz), 8.47 (1H, d, J = 5.2 Hz), 8.45 (1H, s), 7.35 (1H, d, J = 5.2 Hz), 7.32 (1H, s), 4.13-3.99 (1H, m), 2.25 (3H, s), 2.14-2.00 (2H, m), 1.71-1.59 (1H, m), 1.57-1.20 (8H, m), 1.11 (3H, d, J = 6.7 Hz).	446	444
114			¹ H-NMR (DMSO-D ₆) δ: 11.21 (1H, s), 8.49-8.37 (3H, m), 7.74 (1H, d, J = 8.2 Hz), 7.63 (1H, d, J = 8.2 Hz), 7.49 (1H, s), 7.44 (1H, t, J = 7.9 Hz), 7.37-7.28 (2H, m), 4.21-4.05 (1H, m), 2.24 (3H, s), 2.15-2.02 (2H, m), 1.79-1.65 (1H, m), 1.65-1.20 (8H, m), 1.13 (3H, d, J = 6.7 Hz).	461	459
115			¹ H-NMR (DMSO-D ₆) δ: 11.21 (1H, s), 8.40 (1H, d, J = 8.5 Hz), 7.66 (1H, dd, J = 9.0, 4.0 Hz), 7.58 (1H, dd, J = 8.6, 2.9 Hz), 7.46 (1H, s), 7.40 (1H, d, J = 1.8 Hz), 7.34 (1H, d, J = 8.3 Hz), 7.29 (1H, dd, J = 9.1, 2.9 Hz), 7.22 (1H, dd, J = 8.1, 1.9 Hz), 4.20-4.08 (1H, m), 3.32 (3H, s), 2.78-2.65 (2H, m), 2.49-2.41 (1H, m), 2.37-2.24 (3H, m), 2.09-1.99 (2H, m), 1.64-1.49 (2H, m), 1.11 (3H, d, J = 6.5 Hz).	545	543
116			¹ H-NMR (DMSO-D ₆) δ: 11.37 (1H, s), 8.40 (1H, d, J = 8.5 Hz), 8.12 (1H, d, J = 1.8 Hz), 7.93 (1H, dd, J = 8.3, 1.8 Hz), 7.79 (1H, d, J = 7.8 Hz), 7.68-7.63 (1H, m), 7.60-7.55 (1H, m), 7.44 (1H, s), 7.33-7.26 (1H, m), 4.19-4.08 (1H, m), 3.32 (3H, s), 2.80-2.65 (3H, m), 2.38-2.25 (3H, m), 2.15-2.05 (2H, m), 1.66-1.51 (2H, m), 1.11 (3H, d, J = 6.5 Hz).	577	575
117			¹ H-NMR (DMSO-D ₆) δ: 11.32 (1H, s), 8.46 (1H, d, J = 8.8 Hz), 8.09 (1H, d, J = 1.8 Hz), 7.90 (1H, dd, J = 8.0, 1.8 Hz), 7.76 (1H, d, J = 8.0 Hz), 7.66 (1H, dd, J = 9.1, 4.1 Hz), 7.57 (1H, dd, J = 8.8, 2.5 Hz), 7.48 (1H, s), 7.29 (1H, td, J = 9.1, 2.7 Hz), 4.18-4.06 (1H, m), 3.31 (3H, s), 2.14 (2H, t, J = 9.9 Hz), 1.75-1.67 (1H, m), 1.62-1.21 (8H, m), 1.12 (3H, d, J = 6.5 Hz).	576	574
118			¹ H-NMR (DMSO-D ₆) δ: 11.35 (1H, s), 8.63 (1H, q, J = 4.9 Hz), 8.44 (1H, d, J = 9.2 Hz), 7.51 (1H, dd, J = 6.2, 3.0 Hz), 7.31-7.25 (2H, m), 3.99-3.88 (1H, m), 2.65 (3H, d, J = 4.9 Hz), 2.07-1.98 (2H, m), 1.74-1.46 (5H, m), 1.36-1.18 (4H, m), 1.07 (3H, d, J = 6.5 Hz).	467	465
119			¹ H-NMR (DMSO-D ₆) δ: 11.05 (1H, s), 8.63 (1H, q, J = 4.5 Hz), 8.41 (1H, d, J = 9.0 Hz), 7.38-7.18 (4H, m), 3.98-3.82 (1H, m), 2.64 (3H, d, J = 4.5 Hz), 2.22 (3H, s), 2.10-1.97 (2H, m), 1.70-1.60 (1H, m), 1.58-1.38 (3H, m), 1.38-1.15 (5H, m), 1.05 (3H, d, J = 6.7 Hz).	401	399
120		Mixture (4:1) of two stereoisomers due to 1,4-positions of cyclohexane ring (cis form is presumed to be major.)	¹ H-NMR (DMSO-D ₆) δ: 11.37 (0.2H, s), 11.34 (0.8H, s), 8.91 (0.2H, s), 8.88 (0.8H, s), 8.68-8.58 (2H, m), 8.47-8.43 (0.2H, m), 8.41 (0.8H, d, J = 9.0 Hz), 7.62 (0.2H, d, J = 4.5 Hz), 7.55 (0.8H, d, J = 5.2 Hz), 3.97-3.83 (0.8H, m), 3.82-3.70 (0.2H, m), 2.67-2.65 (0.6H, m), 2.64 (2.4H, d, J = 4.5 Hz), 2.18-2.06 (1.6H, m), 1.91-1.82 (0.4H, m), 1.79-1.13 (9H, m), 1.05 (2.4H, d, J = 6.7 Hz), 1.05-1.01 (0.6H, m).	466	464

[0583]

Table 1-16

121		Mixture (4:1) of two stereoisomers due to 1,4-positions of cyclohexane ring (cis form is presumed to be major.)	¹ H-NMR (DMSO-D ₆) δ: 11.38 (0.2H, s), 11.35 (0.8H, s), 8.91 (0.2H, s), 8.88 (0.8H, s), 8.81-8.78 (0.2H, m), 8.77 (0.8H, d, J = 9.0 Hz), 8.66 (0.2H, d, J = 5.2 Hz), 8.62 (0.8H, d, J = 5.2 Hz), 7.62 (0.2H, d, J = 4.5 Hz), 7.55 (0.8H, d, J = 5.2 Hz), 7.32 (1H, s), 4.13-3.99 (0.8H, m), 3.99-3.85 (0.2H, m), 2.22-2.04 (1.6H, m), 1.93-1.84 (0.4H, m), 1.81-1.59 (2H, m), 1.58-1.19 (7H, m), 1.11 (2.4H, d, J = 6.0 Hz), 1.10-1.07 (0.6H, m).	510	508
122		Mixture (4:1) of two stereoisomers due to 1,4-positions of cyclohexane ring (cis form is presumed to be major.)	¹ H-NMR (DMSO-D ₆) δ: 11.37 (0.2H, s), 11.34 (0.8H, s), 8.91 (0.2H, s), 8.85 (0.8H, s), 8.66 (0.2H, d, J = 4.5 Hz), 8.58 (0.8H, d, J = 5.2 Hz), 8.44-8.41 (0.2H, m), 8.41 (0.8H, d, J = 8.2 Hz), 7.78-7.75 (0.2H, m), 7.74 (0.8H, d, J = 6.7 Hz), 7.66-7.60 (1.2H, m), 7.54 (0.8H, d, J = 5.2 Hz), 7.51-7.41 (2H, m), 7.36-7.29 (1H, m), 4.21-4.06 (0.8H, m), 4.06-3.93 (0.2H, m), 2.19-2.07 (1.6H, m), 1.94-1.84 (0.4H, m), 1.82-1.66 (2H, m), 1.62-1.20 (7H, m), 1.13 (2.4H, d, J = 6.7 Hz), 1.13-1.09 (0.6H, m).	525	523
123			¹ H-NMR (DMSO-D ₆) δ: 11.20 (1H, s), 7.73 (1H, dd, J = 8.2, 2.2 Hz), 7.53 (1H, dd, J = 8.6, 5.6 Hz), 7.42 (1H, d, J = 9.0 Hz), 7.35 (1H, td, J = 8.6, 2.2 Hz), 6.66 (1H, s), 4.69 (1H, d, J = 6.0 Hz), 4.65 (1H, d, J = 6.0 Hz), 4.39 (2H, d, J = 6.0 Hz), 3.98-3.85 (1H, m), 2.17-2.07 (2H, m), 1.68-1.57 (1H, m), 1.53-1.14 (8H, m), 1.01 (3H, d, J = 6.7 Hz).	498	496
124			¹ H-NMR (DMSO-D ₆) δ: 11.20 (1H, s), 7.74 (1H, dd, J = 8.6, 2.6 Hz), 7.52 (1H, dd, J = 9.0, 6.0 Hz), 7.45 (1H, d, J = 9.0 Hz), 7.35 (1H, td, J = 8.6, 2.6 Hz), 4.63 (1H, d, J = 6.0 Hz), 4.59 (1H, d, J = 6.0 Hz), 4.31 (1H, d, J = 6.0 Hz), 4.30 (1H, d, J = 6.0 Hz), 3.97-3.84 (1H, m), 2.99-2.81 (1H, m), 2.18-2.08 (2H, m), 2.05 (3H, s), 1.66-1.57 (1H, m), 1.54-1.16 (8H, m), 1.01 (3H, d, J = 6.0 Hz).	511	509
125		Mixture (4:1) of two stereoisomers due to 1,4-positions of cyclohexane ring (cis form is presumed to be major.)	¹ H-NMR (DMSO-D ₆) δ: 11.28-11.19 (1H, m), 8.69-8.51 (2H, m), 8.51-8.37 (2H, m), 7.40-7.36 (0.2H, m), 7.36-7.31 (0.8H, m), 3.99-3.83 (0.8H, m), 3.83-3.70 (0.2H, m), 2.71-2.60 (3H, m), 2.23 (3H, s), 2.12-2.00 (1.6H, m), 1.89-1.17 (9.4H, m), 1.08-1.02 (3H, m).	402	400
126			¹ H-NMR (DMSO-D ₆) δ: 11.02 (1H, s), 8.63 (1H, q, J = 4.5 Hz), 8.41 (1H, d, J = 9.0 Hz), 7.17 (1H, d, J = 7.5 Hz), 7.12 (1H, d, J = 7.5 Hz), 7.04 (1H, s), 3.98-3.83 (1H, m), 2.64 (3H, d, J = 4.5 Hz), 2.28 (3H, s), 2.16 (3H, s), 2.09-1.98 (2H, m), 1.71-1.58 (1H, m), 1.58-1.39 (3H, m), 1.39-1.14 (5H, m), 1.06 (3H, d, J = 6.7 Hz).	415	413
127			¹ H-NMR (DMSO-D ₆) δ: 12.80 (1H, s), 11.21 (1H, s), 7.61-7.53 (1H, m), 7.42 (1H, d, J = 1.8 Hz), 7.36 (1H, d, J = 8.3 Hz), 7.27 (1H, dd, J = 8.4, 1.9 Hz), 6.29 (1H, s), 4.12-3.99 (1H, m), 2.76-2.64 (2H, m), 2.53 (3H, s), 2.47-2.37 (1H, m), 2.34-2.18 (6H, m), 2.09-2.00 (2H, m), 1.64-1.49 (2H, m), 1.07 (3H, d, J = 6.5 Hz).	491	489
128			¹ H-NMR (DMSO-D ₆) δ: 12.80 (1H, s), 11.38 (1H, s), 8.13 (1H, d, J = 1.8 Hz), 7.95 (1H, dd, J = 8.0, 1.8 Hz), 7.80 (1H, d, J = 8.0 Hz), 7.30-7.20 (1H, m), 6.29 (1H, s), 4.11-3.99 (1H, m), 3.34 (3H, s), 2.81-2.65 (2H, m), 2.48-2.40 (1H, m), 2.35-2.19 (6H, m), 2.13-2.05 (2H, m), 1.64-1.50 (2H, m), 1.06 (3H, d, J = 6.5 Hz).	523	521

[0584]

Table 1-17

129		1H-NMR (DMSO-D6) δ : 11.02 (1H, s), 8.65-8.57 (1H, m), 8.40 (1H, d, J = 8.8 Hz), 7.22 (1H, d, J = 6.9 Hz), 7.13 (1H, t, J = 7.6 Hz), 7.05 (1H, d, J = 7.9 Hz), 3.97-3.83 (1H, m), 2.63 (3H, d, J = 4.9 Hz), 2.26 (3H, s), 2.11 (3H, s), 2.08-1.97 (2H, m), 1.68-1.60 (1H, m), 1.57-1.10 (8H, m), 1.05 (3H, d, J = 6.7 Hz).	415	413
130		1H-NMR (DMSO-D6) δ : 11.10 (1H, s), 8.63 (1H, q, J = 4.9 Hz), 8.41 (1H, d, J = 8.8 Hz), 7.32 (1H, d, J = 8.8 Hz), 7.28 (1H, d, J = 2.5 Hz), 7.01 (1H, dd, J = 8.8, 2.5 Hz), 4.64 (1H, s), 3.95-3.86 (1H, m), 3.77 (2H, s), 2.64 (3H, d, J = 4.9 Hz), 2.13-2.05 (2H, m), 1.66-1.14 (9H, m), 1.19 (6H, s), 1.05 (3H, d, J = 6.5 Hz).	553	551
131		1H-NMR (DMSO-D6) δ : 11.10 (1H, s), 8.77 (1H, d, J = 8.3 Hz), 7.33 (1H, s), 7.32 (1H, d, J = 8.3 Hz), 7.27 (1H, d, J = 2.5 Hz), 7.00 (1H, dd, J = 8.3, 2.5 Hz), 4.63 (1H, s), 4.10-4.02 (1H, m), 3.76 (2H, s), 2.15-2.07 (2H, m), 1.68-1.62 (1H, m), 1.53-1.22 (8H, m), 1.19 (6H, s), 1.11 (3H, d, J = 6.5 Hz).	597	595
132		1H-NMR (DMSO-D6) δ : 11.10 (1H, s), 8.40 (1H, d, J = 8.8 Hz), 7.75 (1H, d, J = 7.9 Hz), 7.63 (1H, d, J = 8.8 Hz), 7.49 (1H, s), 7.45 (1H, t, J = 8.3 Hz), 7.34-7.29 (2H, m), 7.25 (1H, d, J = 2.5 Hz), 6.97 (1H, dd, J = 8.3, 2.5 Hz), 4.61 (1H, s), 4.18-4.09 (1H, m), 3.74 (2H, s), 2.15-2.05 (2H, m), 1.74-1.66 (1H, m), 1.57-1.25 (8H, m), 1.17 (6H, s), 1.13 (3H, d, J = 6.5 Hz).	612	610
133		1H-NMR (DMSO-D6) δ : 11.10 (1H, s), 8.62 (1H, q, J = 4.8 Hz), 8.41 (1H, d, J = 9.0 Hz), 7.30-7.25 (2H, m), 7.06 (1H, td, J = 8.5, 2.5 Hz), 3.95-3.85 (1H, m), 2.87-2.80 (1H, m), 2.64 (3H, d, J = 4.8 Hz), 2.05-1.93 (2H, m), 1.67-1.60 (1H, m), 1.52-1.18 (8H, m), 1.16 (6H, d, J = 6.5 Hz), 1.05 (3H, d, J = 6.5 Hz).	447	445
134		1H-NMR (DMSO-D6) δ : 11.10 (1H, s), 8.77 (1H, d, J = 8.6 Hz), 7.32 (1H, s), 7.29-7.25 (2H, m), 7.05 (1H, td, J = 8.6, 2.5 Hz), 4.09-4.00 (1H, m), 2.87-2.80 (1H, m), 2.08-1.95 (2H, m), 1.68-1.61 (1H, m), 1.53-1.21 (8H, m), 1.16 (6H, d, J = 6.7 Hz), 1.11 (3H, d, J = 6.7 Hz).	491	489
135		1H-NMR (DMSO-D6) δ : 11.18 (1H, s), 8.63 (1H, q, J = 4.7 Hz), 8.42 (1H, d, J = 9.0 Hz), 7.41 (1H, dd, J = 8.6, 5.6 Hz), 7.36 (1H, dd, J = 10.1, 2.6 Hz), 7.15 (1H, td, J = 8.6, 2.6 Hz), 3.97-3.84 (1H, m), 2.79-2.70 (2H, m), 2.64 (3H, d, J = 5.2 Hz), 2.61-2.52 (2H, m), 2.08-1.94 (2H, m), 1.71-1.58 (1H, m), 1.58-1.17 (8H, m), 1.06 (3H, d, J = 6.7 Hz).	501	499
136		1H-NMR (DMSO-D6) δ : 11.08 (1H, s), 7.33 (1H, dd, J = 8.6, 6.0 Hz), 7.18 (1H, dd, J = 10.2, 2.5 Hz), 7.07 (1H, td, J = 8.6, 2.5 Hz), 5.55 (1H, d, J = 8.3 Hz), 3.77-3.68 (1H, m), 3.18-3.11 (4H, m), 2.24 (3H, s), 2.08-2.00 (2H, m), 1.79-1.71 (4H, m), 1.65-1.58 (1H, m), 1.53-1.11 (8H, m), 0.99 (3H, d, J = 6.5 Hz).	431	429

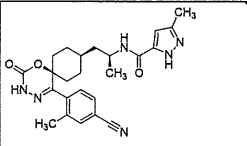
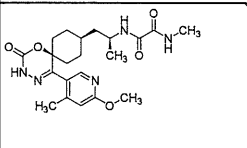
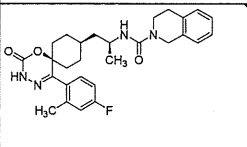
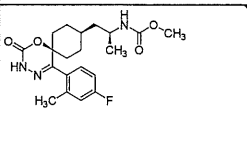
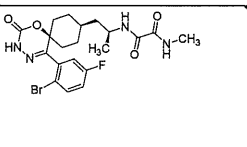
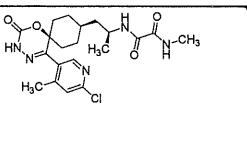
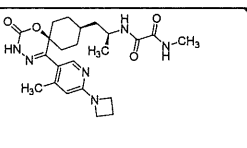
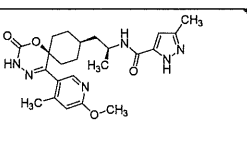
[0585]

Table 1-18

145			¹ H-NMR (DMSO-D ₆) δ: 11.01 (1H, s), 8.65-8.60 (1H, m), 8.41 (1H, d, J = 9.2 Hz), 7.13 (1H, d, J = 7.6 Hz), 7.12-7.10 (1H, m), 7.04 (1H, d, J = 7.6 Hz), 3.95-3.83 (1H, m), 2.64 (3H, d, J = 4.9 Hz), 2.29 (3H, s), 2.18 (3H, s), 2.05-1.97 (2H, m), 1.68-1.60 (1H, m), 1.57-1.10 (8H, m), 1.05 (3H, d, J = 6.5 Hz).	415	413
146			¹ H-NMR (DMSO-D ₆) δ: 13.14 (1H, s), 11.20 (1H, s), 8.61 (1H, d, J = 6.7 Hz), 8.47-8.39 (2H, m), 7.68 (1H, d, J = 6.7 Hz), 7.50 (1H, d, J = 6.7 Hz), 7.34-7.20 (3H, m), 4.22-4.08 (1H, m), 2.23 (3H, s), 2.12-2.00 (2H, m), 1.80-1.69 (1H, m), 1.69-1.57 (1H, m), 1.57-1.20 (7H, m), 1.16 (3H, d, J = 6.0 Hz).	461	459
147			¹ H-NMR (DMSO-D ₆) δ: 11.14 (1H, s), 8.66 (1H, q, J = 4.5 Hz), 8.50-8.41 (2H, m), 7.75 (1H, d, J = 7.9 Hz), 7.35 (1H, dd, J = 7.9, 4.9 Hz), 4.00-3.85 (1H, m), 2.66 (3H, d, J = 4.5 Hz), 2.31 (3H, s), 2.02-1.90 (2H, m), 1.88-1.42 (5H, m), 1.37-1.16 (4H, m), 1.07 (3H, d, J = 6.0 Hz).	402	400
148			¹ H-NMR (DMSO-D ₆) δ: 11.15 (1H, s), 8.80 (1H, d, J = 9.0 Hz), 8.43 (1H, d, J = 4.5 Hz), 7.75 (1H, d, J = 7.5 Hz), 7.39-7.31 (2H, m), 4.15-4.01 (1H, m), 2.30 (3H, s), 2.02-1.92 (2H, m), 1.87-1.71 (2H, m), 1.69-1.61 (1H, m), 1.58-1.46 (2H, m), 1.38-1.21 (4H, m), 1.13 (3H, d, J = 6.7 Hz).	446	444
149			¹ H-NMR (DMSO-D ₆) δ: 11.15 (1H, s), 8.44 (1H, d, J = 8.2 Hz), 8.40 (1H, d, J = 4.5 Hz), 7.76 (1H, d, J = 8.2 Hz), 7.73 (1H, d, J = 8.2 Hz), 7.65 (1H, d, J = 8.2 Hz), 7.51 (1H, s), 7.46 (1H, t, J = 7.9 Hz), 7.38-7.28 (2H, m), 4.23-4.08 (1H, m), 2.30 (3H, s), 2.04-1.92 (2H, m), 1.88-1.65 (3H, m), 1.65-1.47 (2H, m), 1.41-1.21 (4H, m), 1.15 (3H, d, J = 6.0 Hz).	461	459
150		Mixture of three stereoisomers due to octahydro-1H-indole moiety	¹ H-NMR (DMSO-D ₆) δ: 11.08 (1H, s), 7.34 (1H, dd, J = 8.7, 5.9 Hz), 7.18 (1H, dd, J = 10.1, 2.7 Hz), 7.07 (1H, td, J = 8.7, 2.7 Hz), 5.50 (1H, d, J = 8.6 Hz), 3.75-3.66 (1H, m), 3.44-3.35 (2H, m), 2.70-2.61 (2H, m), 2.24 (3H, s), 2.08-2.00 (2H, m), 1.84-1.68 (4H, m), 1.64-1.57 (1H, m), 1.52-1.01 (14H, m), 0.97 (3H, d, J = 6.5 Hz).	485	483
151			¹ H-NMR (DMSO-D ₆) δ: 11.32 (1H, s), 8.65-8.59 (1H, m), 8.60 (1H, s), 8.50 (1H, d, J = 5.5 Hz), 8.41 (1H, d, J = 9.0 Hz), 7.85 (1H, d, J = 5.3 Hz), 3.97-3.84 (1H, m), 2.63 (3H, d, J = 4.9 Hz), 2.17-2.08 (2H, m), 1.71-1.60 (1H, m), 1.58-1.17 (8H, m), 1.05 (3H, d, J = 6.5 Hz).	466	464
152			¹ H-NMR (DMSO-D ₆) δ: 11.21 (1H, s), 8.62 (1H, q, J = 5.2 Hz), 8.41 (1H, d, J = 8.3 Hz), 7.83 (1H, s), 7.71 (1H, d, J = 8.3 Hz), 7.51 (1H, d, J = 8.3 Hz), 3.95-3.85 (1H, m), 2.64 (3H, d, J = 5.2 Hz), 2.27 (3H, s), 2.09-2.01 (2H, m), 1.68-1.61 (1H, m), 1.54-1.37 (3H, m), 1.35-1.16 (5H, m), 1.05 (3H, d, J = 6.7 Hz).	426	424

[0587]

Table 1-20

153		1H-NMR (DMSO-D6) δ : 12.80 (1H, s), 11.20 (1H, s), 7.81 (1H, s), 7.68 (1H, d, J = 8.1 Hz), 7.58 (1H, d, J = 8.1 Hz), 7.50 (1H, d, J = 8.1 Hz), 6.30 (1H, s), 4.09-4.00 (1H, m), 2.26 (3H, s), 2.23 (3H, s), 2.10-2.01 (2H, m), 1.71-1.65 (1H, m), 1.55-1.20 (8H, m), 1.07 (3H, d, J = 6.2 Hz).	449	447
154		1H-NMR (DMSO-D6) δ : 11.13 (1H, s), 8.63 (1H, q, J = 4.5 Hz), 8.41 (1H, d, J = 9.7 Hz), 8.07 (1H, s), 6.77 (1H, s), 3.98-3.83 (1H, m), 3.86 (3H, s), 2.64 (3H, d, J = 4.5 Hz), 2.19 (3H, s), 2.09-1.96 (2H, m), 1.72-1.59 (1H, m), 1.57-1.16 (8H, m), 1.06 (3H, d, J = 6.7 Hz).	432	430
155		1H-NMR (DMSO-D6) δ : 11.08 (1H, s), 7.31 (1H, dd, J = 8.6, 6.0 Hz), 7.21-7.04 (6H, m), 6.12 (1H, d, J = 8.3 Hz), 4.43 (2H, s), 3.84-3.73 (1H, m), 3.57-3.44 (2H, m), 2.75-2.66 (2H, m), 2.23 (3H, s), 2.05-1.97 (2H, m), 1.65-1.14 (9H, m), 1.01 (3H, d, J = 6.7 Hz).	493	491
156		1H-NMR (DMSO-D6) δ : 11.09 (1H, s), 7.34 (1H, dd, J = 8.4, 5.9 Hz), 7.18 (1H, dd, J = 10.1, 2.7 Hz), 7.07 (1H, td, J = 8.4, 2.7 Hz), 6.88 (1H, d, J = 8.6 Hz), 3.59-3.43 (1H, m), 3.47 (3H, s), 2.24 (3H, s), 2.08-2.00 (2H, m), 1.63-1.12 (9H, m), 0.99 (3H, d, J = 6.5 Hz).	392	390
157		1H-NMR (DMSO-D6) δ : 11.22 (1H, s), 8.65-8.59 (1H, m), 8.41 (1H, d, J = 9.0 Hz), 7.77 (1H, dd, J = 8.9, 5.2 Hz), 7.43 (1H, dd, J = 9.0, 3.0 Hz), 7.30 (1H, td, J = 8.6, 3.0 Hz), 3.97-3.83 (1H, m), 2.64 (3H, d, J = 4.9 Hz), 2.19-2.06 (2H, m), 1.70-1.16 (9H, m), 1.06 (3H, d, J = 6.7 Hz).	483	481
158		1H-NMR (DMSO-D6) δ : 11.26 (1H, s), 8.65-8.59 (1H, m), 8.41 (1H, d, J = 9.2 Hz), 8.33 (1H, s), 7.54 (1H, s), 3.98-3.86 (1H, m), 2.64 (3H, d, J = 4.9 Hz), 2.26 (3H, s), 2.10-2.00 (2H, m), 1.70-1.61 (1H, m), 1.58-1.14 (8H, m), 1.06 (3H, d, J = 6.7 Hz).	436	434
159		1H-NMR (DMSO-D6) δ : 11.02 (1H, s), 8.66-8.60 (1H, m), 8.41 (1H, d, J = 9.0 Hz), 7.90 (1H, s), 6.24 (1H, s), 3.98-3.87 (1H, m), 3.94 (4H, t, J = 7.4 Hz), 2.65 (3H, d, J = 5.1 Hz), 2.36-2.27 (2H, m), 2.12 (3H, s), 2.03-1.94 (2H, m), 1.71-1.60 (1H, m), 1.57-1.14 (8H, m), 1.06 (3H, d, J = 6.5 Hz).	457	501 (formic acid adduct)
160		1H-NMR (DMSO-D6) δ : 12.80 (1H, s), 11.13 (1H, s), 8.05 (1H, s), 7.58 (1H, d, J = 8.6 Hz), 6.76 (1H, s), 6.31 (1H, s), 4.14-3.98 (1H, m), 3.84 (3H, s), 2.23 (3H, s), 2.18 (3H, s), 2.07-1.99 (2H, m), 1.73-1.64 (1H, m), 1.57-1.16 (8H, m), 1.08 (3H, d, J = 6.5 Hz).	455	453

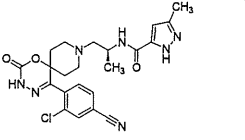
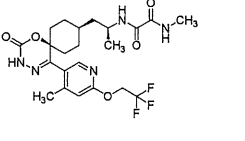
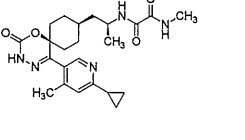
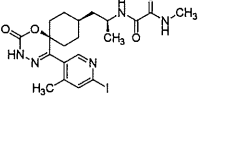
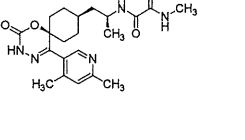
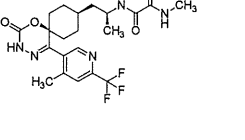
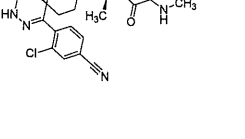
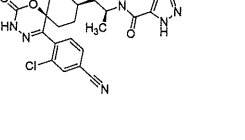
[0588]

Table 1-21

161			¹ H-NMR (DMSO-D ₆) δ: 11.11 (1H, s), 8.62 (1H, q, J = 4.7 Hz), 8.41 (1H, d, J = 9.2 Hz), 7.56 (1H, d, J = 1.8 Hz), 7.43 (1H, dd, J = 8.1, 1.8 Hz), 7.23 (1H, d, J = 8.1 Hz), 3.95-3.86 (1H, m), 2.64 (3H, d, J = 4.7 Hz), 2.22 (3H, s), 2.05-1.98 (2H, m), 1.68-1.63 (1H, m), 1.55-1.36 (3H, m), 1.34-1.15 (5H, m), 1.05 (3H, d, J = 6.5 Hz).	479	477
162			¹ H-NMR (DMSO-D ₆) δ: 11.64 (1H, s), 11.07 (1H, s), 8.64 (1H, q, J = 4.5 Hz), 8.42 (1H, d, J = 9.7 Hz), 7.36 (1H, s), 6.24 (1H, s), 3.99-3.85 (1H, m), 2.65 (3H, d, J = 4.5 Hz), 2.02 (3H, s), 2.02-1.93 (2H, m), 1.71-1.62 (1H, m), 1.59-1.38 (4H, m), 1.33-1.13 (4H, m), 1.07 (3H, d, J = 6.7 Hz).	418	416
163			¹ H-NMR (DMSO-D ₆) δ: 11.07 (1H, s), 8.62 (1H, q, J = 4.7 Hz), 8.41 (1H, d, J = 9.2 Hz), 7.53 (1H, d, J = 1.8 Hz), 7.46 (1H, dd, J = 8.0, 1.8 Hz), 7.25 (1H, d, J = 8.0 Hz), 4.79 (1H, d, J = 2.8 Hz), 4.32 (1H, d, J = 2.8 Hz), 3.95-3.87 (1H, m), 3.90 (2H, q, J = 6.9 Hz), 2.64 (3H, d, J = 4.7 Hz), 2.24 (3H, s), 2.07-1.99 (2H, m), 1.69-1.62 (1H, m), 1.53-1.39 (3H, m), 1.35 (3H, t, J = 6.9 Hz), 1.31-1.15 (5H, m), 1.06 (3H, d, J = 6.9 Hz).	471	469
164			¹ H-NMR (DMSO-D ₆) δ: 11.04 (1H, s), 8.66-8.59 (1H, m), 8.41 (1H, d, J = 9.0 Hz), 7.99 (1H, s), 6.75 (1H, s), 3.97-3.85 (1H, m), 3.71-3.66 (4H, m), 3.50-3.43 (4H, m), 2.64 (3H, d, J = 4.9 Hz), 2.15 (3H, s), 2.04-1.96 (2H, m), 1.69-1.61 (1H, m), 1.57-1.17 (8H, m), 1.06 (3H, d, J = 6.7 Hz).	487	485
165			¹ H-NMR (DMSO-D ₆) δ: 11.00 (1H, s), 8.65-8.60 (1H, m), 8.41 (1H, d, J = 9.2 Hz), 7.92 (1H, s), 6.33 (1H, s), 3.97-3.86 (1H, m), 3.41-3.35 (4H, m), 2.64 (3H, d, J = 4.9 Hz), 2.13 (3H, s), 2.04-1.90 (6H, m), 1.70-1.62 (1H, m), 1.58-1.15 (8H, m), 1.06 (3H, d, J = 6.5 Hz).	471	469
166			¹ H-NMR (DMSO-D ₆) δ: 11.01 (1H, s), 8.66-8.61 (1H, m), 8.41 (1H, d, J = 9.0 Hz), 7.93 (1H, s), 6.71 (1H, s), 3.98-3.86 (1H, m), 3.57-3.49 (4H, m), 2.64 (3H, d, J = 4.9 Hz), 2.13 (3H, s), 2.03-1.95 (2H, m), 1.69-1.18 (15H, m), 1.06 (3H, d, J = 6.5 Hz).	485	483
167			¹ H-NMR (DMSO-D ₆) δ: 11.15 (1H, s), 8.62 (1H, q, J = 4.8 Hz), 8.41 (1H, d, J = 9.2 Hz), 7.89 (1H, d, J = 1.7 Hz), 7.80 (1H, dd, J = 8.1, 1.7 Hz), 7.43 (1H, d, J = 8.1 Hz), 3.95-3.85 (1H, m), 2.63 (3H, d, J = 4.8 Hz), 2.59 (3H, s), 2.30 (3H, s), 2.10-2.02 (2H, m), 1.68-1.61 (1H, m), 1.54-1.41 (3H, m), 1.34-1.17 (5H, m), 1.05 (3H, d, J = 5.8 Hz).	443	441
168			¹ H-NMR (DMSO-D ₆) δ: 11.37 (1H, s), 8.64-8.58 (1H, m), 8.33 (1H, d, J = 8.5 Hz), 8.23 (1H, d, J = 1.5 Hz), 7.93 (1H, dd, J = 8.0, 1.5 Hz), 7.72 (1H, d, J = 8.0 Hz), 3.98-3.87 (1H, m), 2.73-2.59 (2H, m), 2.64 (3H, d, J = 5.0 Hz), 2.42 (1H, dd, J = 12.5, 8.3 Hz), 2.35-2.18 (3H, m), 2.12-2.01 (2H, m), 1.63-1.47 (2H, m), 1.04 (3H, d, J = 6.5 Hz).	447	445

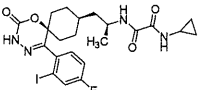
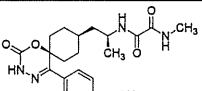
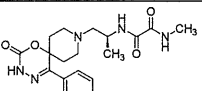
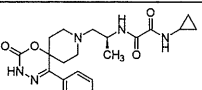
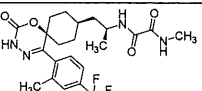
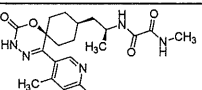
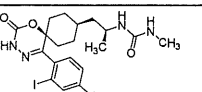
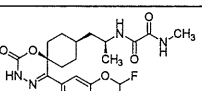
[0589]

Table 1-22

169			¹ H-NMR (DMSO-D ₆) δ: 12.79 (1H, s), 11.36 (1H, s), 8.22 (1H, d, J = 1.3 Hz), 7.91 (1H, dd, J = 8.0, 1.5 Hz), 7.71 (1H, d, J = 8.0 Hz), 7.55 (1H, d, J = 8.0 Hz), 6.28 (1H, s), 4.10-4.00 (1H, m), 2.74-2.64 (2H, m), 2.46-2.38 (1H, m), 2.35-2.14 (6H, m), 2.07 (2H, d, J = 14.3 Hz), 1.61-1.49 (2H, m), 1.06 (3H, d, J = 6.5 Hz).	470	468
170			¹ H-NMR (DMSO-D ₆) δ: 11.18 (1H, s), 8.62 (1H, q, J = 4.9 Hz), 8.41 (1H, d, J = 9.2 Hz), 8.12 (1H, s), 6.97 (1H, s), 5.00 (2H, q, J = 8.9 Hz), 3.99-3.84 (1H, m), 2.64 (3H, d, J = 4.9 Hz), 2.23 (3H, s), 2.10-1.97 (2H, m), 1.71-1.59 (1H, m), 1.57-1.43 (3H, m), 1.42-1.14 (5H, m), 1.06 (3H, d, J = 6.7 Hz).	500	498
171			¹ H-NMR (DMSO-D ₆) δ: 11.14 (1H, s), 8.63 (1H, q, J = 4.9 Hz), 8.40 (1H, d, J = 9.2 Hz), 8.25 (1H, s), 7.24 (1H, s), 3.97-3.84 (1H, m), 2.64 (3H, d, J = 4.9 Hz), 2.19 (3H, s), 2.11-1.97 (3H, m), 1.71-1.60 (1H, m), 1.56-1.41 (3H, m), 1.41-1.15 (5H, m), 1.06 (3H, d, J = 6.5 Hz), 0.99-0.89 (4H, m).	442	440
172			¹ H-NMR (DMSO-D ₆) δ: 11.24 (1H, s), 8.62 (1H, q, J = 4.5 Hz), 8.41 (1H, d, J = 9.0 Hz), 8.25 (1H, s), 7.87 (1H, s), 3.98-3.84 (1H, m), 2.64 (3H, d, J = 4.5 Hz), 2.18 (3H, s), 2.09-1.97 (2H, m), 1.71-1.59 (1H, m), 1.57-1.15 (8H, m), 1.05 (3H, d, J = 6.7 Hz).	528	526
173			¹ H-NMR (DMSO-D ₆) δ: 11.16 (1H, s), 8.66-8.59 (1H, m), 8.40 (1H, d, J = 9.0 Hz), 8.30 (1H, s), 7.21 (1H, s), 3.97-3.83 (1H, m), 2.64 (3H, d, J = 4.9 Hz), 2.44 (3H, s), 2.20 (3H, s), 2.10-1.98 (2H, m), 1.70-1.60 (1H, m), 1.57-1.17 (8H, m), 1.05 (3H, d, J = 6.5 Hz).	416	414
174			¹ H-NMR (DMSO-D ₆) δ: 11.33 (1H, s), 8.69 (1H, s), 8.63 (1H, q, J = 4.5 Hz), 8.41 (1H, d, J = 8.2 Hz), 7.93 (1H, s), 3.98-3.84 (1H, m), 2.64 (3H, d, J = 4.5 Hz), 2.37 (3H, s), 2.14-2.04 (2H, m), 1.72-1.61 (1H, m), 1.58-1.15 (8H, m), 1.06 (3H, d, J = 6.0 Hz).	470	468
175			¹ H-NMR (DMSO-D ₆) δ: 11.32 (1H, s), 8.67-8.59 (1H, m), 8.42 (1H, d, J = 9.2 Hz), 8.22 (1H, d, J = 1.6 Hz), 7.91 (1H, dd, J = 8.1, 1.6 Hz), 7.70 (1H, d, J = 8.1 Hz), 3.95-3.85 (1H, m), 2.64 (3H, d, J = 4.8 Hz), 2.10 (2H, d, J = 11.3 Hz), 1.69-1.62 (1H, m), 1.58-1.15 (8H, m), 1.05 (3H, d, J = 6.5 Hz).	446	444
176			¹ H-NMR (DMSO-D ₆) δ: 12.79 (1H, s), 11.30 (1H, s), 8.19 (1H, s), 7.88 (1H, d, J = 8.3 Hz), 7.69 (1H, d, J = 7.8 Hz), 7.63-7.53 (1H, m), 6.30 (1H, s), 4.12-4.00 (1H, m), 2.27-2.06 (5H, m), 1.90-1.83 (1H, m), 1.75-1.18 (8H, m), 1.07 (3H, d, J = 6.0 Hz).	469	467

[0590]

Table 1-23

177			¹ H-NMR (DMSO-D ₆) δ: 11.19 (1H, s), 8.68 (1H, d, J = 5.3 Hz), 8.42 (1H, d, J = 9.0 Hz), 7.86 (1H, dd, J = 8.4, 2.7 Hz), 7.44 (1H, dd, J = 8.7, 5.9 Hz), 7.33 (1H, td, J = 8.5, 2.6 Hz), 3.95-3.82 (1H, m), 2.78-2.70 (1H, m), 2.16-2.06 (2H, m), 1.69-1.60 (1H, m), 1.59-1.12 (8H, m), 1.05 (3H, d, J = 6.7 Hz), 0.65-0.56 (4H, m).	557	555
178			¹ H-NMR (DMSO-D ₆) δ: 11.02 (1H, s), 8.63 (1H, q, J = 4.9 Hz), 8.41 (1H, d, J = 9.2 Hz), 7.38 (1H, d, J = 1.5 Hz), 7.31 (1H, dd, J = 8.1, 1.5 Hz), 7.17 (1H, d, J = 8.1 Hz), 5.01 (1H, s), 3.95-3.85 (1H, m), 2.63 (3H, d, J = 4.9 Hz), 2.21 (3H, s), 2.06-1.98 (2H, m), 1.68-1.62 (1H, m), 1.54-1.43 (3H, m), 1.42 (6H, s), 1.33-1.16 (5H, m), 1.05 (3H, d, J = 6.5 Hz).	459	457
179			¹ H-NMR (DMSO-D ₆) δ: 11.25 (1H, s), 8.63 (1H, q, J = 4.7 Hz), 8.35 (1H, d, J = 8.8 Hz), 7.75 (1H, dd, J = 8.6, 2.5 Hz), 7.54 (1H, dd, J = 8.6, 5.8 Hz), 7.36 (1H, td, J = 8.6, 2.5 Hz), 3.96-3.89 (1H, m), 2.72-2.60 (2H, m), 2.64 (3H, d, J = 4.7 Hz), 2.42 (1H, dd, J = 12.5, 8.3 Hz), 2.33-2.19 (3H, m), 2.10-2.02 (2H, m), 1.64-1.48 (2H, m), 1.04 (3H, d, J = 6.5 Hz).	484	482
180			¹ H-NMR (DMSO-D ₆) δ: 11.25 (1H, s), 8.68 (1H, d, J = 5.3 Hz), 8.35 (1H, d, J = 8.6 Hz), 7.75 (1H, dd, J = 8.6, 2.6 Hz), 7.54 (1H, dd, J = 8.6, 6.0 Hz), 7.36 (1H, td, J = 8.6, 2.6 Hz), 3.95-3.88 (1H, m), 2.75-2.57 (3H, m), 2.46-2.38 (1H, m), 2.33-2.19 (3H, m), 2.10-2.02 (2H, m), 1.62-1.49 (2H, m), 1.04 (3H, d, J = 6.5 Hz), 0.66-0.56 (4H, m).	510	508
181			¹ H-NMR (DMSO-D ₆) δ: 11.19 (1H, s), 8.66-8.59 (1H, m), 8.41 (1H, d, J = 9.2 Hz), 7.71 (1H, s), 7.59 (1H, d, J = 7.6 Hz), 7.52 (1H, d, J = 7.9 Hz), 3.95-3.85 (1H, m), 2.63 (3H, d, J = 4.9 Hz), 2.31 (3H, s), 2.10-2.02 (2H, m), 1.70-1.60 (1H, m), 1.57-1.14 (8H, m), 1.05 (3H, d, J = 6.7 Hz).	557	555
182			¹ H-NMR (DMSO-D ₆) δ: 11.02 (1H, s), 8.66-8.60 (1H, m), 8.41 (1H, d, J = 9.2 Hz), 7.90 (1H, s), 6.23 (1H, s), 4.06 (2H, t, J = 8.4 Hz), 3.96-3.87 (1H, m), 3.51 (2H, dd, J = 7.9, 5.5 Hz), 2.83-2.72 (1H, m), 2.64 (3H, d, J = 4.9 Hz), 2.11 (3H, s), 2.04-1.94 (2H, m), 1.72-1.60 (1H, m), 1.57-1.14 (8H, m), 1.23 (3H, d, J = 6.7 Hz), 1.06 (3H, d, J = 6.7 Hz).	557	555
183			¹ H-NMR (DMSO-D ₆) δ: 11.20 (1H, s), 7.87 (1H, dd, J = 8.4, 2.7 Hz), 7.46 (1H, dd, J = 8.7, 5.9 Hz), 7.34 (1H, td, J = 8.5, 2.6 Hz), 5.55 (1H, d, J = 8.6 Hz), 5.48 (1H, q, J = 4.5 Hz), 3.69-3.58 (1H, m), 2.50-2.48 (3H, m), 2.18-2.09 (2H, m), 1.67-1.58 (1H, m), 1.54-1.10 (8H, m), 0.96 (3H, d, J = 6.5 Hz).	503	501
184			¹ H-NMR (DMSO-D ₆) δ: 11.23 (1H, s), 8.62 (1H, q, J = 4.5 Hz), 8.42 (1H, d, J = 9.0 Hz), 7.78 (1H, d, J = 9.0 Hz), 7.32 (1H, t, J = 73.7 Hz), 7.28 (1H, d, J = 3.0 Hz), 7.23 (1H, dd, J = 9.0, 3.0 Hz), 3.97-3.83 (1H, m), 2.64 (3H, d, J = 4.5 Hz), 2.19-2.07 (2H, m), 1.70-1.60 (1H, m), 1.57-1.15 (8H, m), 1.06 (3H, d, J = 6.0 Hz).	531	529

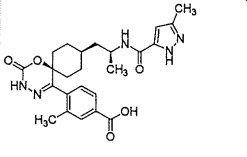
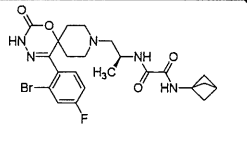
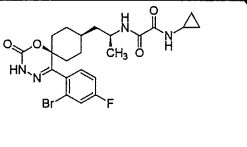
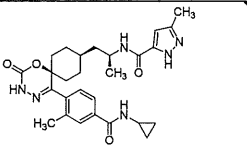
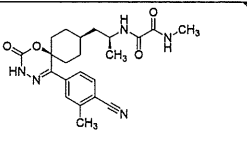
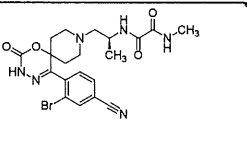
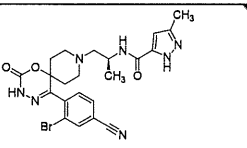
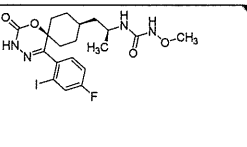
[0591]

Table 1-24

193			¹ H-NMR (DMSO-D ₆) δ: 11.30 (1H, s), 8.67-8.58 (2H, m), 8.41 (1H, d, J = 9.2 Hz), 7.91 (1H, s), 3.99-3.82 (1H, m), 2.70-2.59 (6H, m), 2.34 (3H, s), 2.15-2.02 (2H, m), 1.71-1.60 (1H, m), 1.58-1.42 (3H, m), 1.42-1.16 (5H, m), 1.05 (3H, d, J = 6.5 Hz).	444	442
194			¹ H-NMR (DMSO-D ₆) δ: 11.12 (1H, s), 8.62 (1H, q, J = 4.5 Hz), 8.41 (1H, d, J = 9.0 Hz), 7.35 (1H, d, J = 8.5 Hz), 7.24 (1H, t, J = 74.3 Hz), 7.15 (1H, d, J = 8.1 Hz), 7.06 (1H, s), 3.98-3.83 (1H, m), 2.63 (3H, d, J = 4.5 Hz), 2.19 (3H, s), 2.11-1.98 (2H, m), 1.71-1.59 (1H, m), 1.57-1.39 (3H, m), 1.39-1.16 (5H, m), 1.06 (3H, d, J = 6.7 Hz).	467	465
195			¹ H-NMR (DMSO-D ₆) δ: 11.25 (1H, s), 7.86 (1H, d, J = 2.3 Hz), 7.63 (1H, d, J = 8.6 Hz), 7.50 (1H, d, J = 8.6 Hz), 5.88 (1H, d, J = 2.3 Hz), 5.45 (1H, d, J = 8.3 Hz), 3.70-3.62 (1H, m), 2.38-2.31 (1H, m), 2.18-2.10 (2H, m), 1.68-1.60 (1H, m), 1.53-1.13 (8H, m), 0.97 (3H, d, J = 6.2 Hz), 0.53-0.49 (2H, m), 0.27-0.23 (2H, m).	547	545
196			¹ H-NMR (DMSO-D ₆) δ: 11.41 (1H, s), 8.64-8.57 (1H, m), 8.35 (1H, d, J = 8.3 Hz), 7.68 (1H, dd, J = 8.6, 6.1 Hz), 7.60 (1H, dd, J = 8.8, 2.8 Hz), 7.31 (1H, td, J = 8.6, 2.7 Hz), 3.98-3.86 (1H, m), 2.80-2.72 (1H, m), 2.70-2.31 (7H, m), 2.64 (3H, d, J = 5.0 Hz), 1.63-1.49 (2H, m), 1.18-1.02 (1H, m), 1.07 (3H, d, J = 6.5 Hz), 0.99-0.82 (1H, m).	466	464
197			¹ H-NMR (DMSO-D ₆) δ: 12.77 (1H, s), 11.40 (1H, s), 7.67 (1H, dd, J = 8.6, 6.1 Hz), 7.62-7.57 (2H, m), 7.30 (1H, td, J = 8.6, 2.5 Hz), 6.29 (1H, s), 4.11-3.98 (1H, m), 2.80-2.30 (8H, m), 2.22 (3H, s), 1.68-1.49 (2H, m), 1.18-1.02 (1H, m), 1.11 (3H, d, J = 6.5 Hz), 0.98-0.80 (1H, m).	489	487
198			¹ H-NMR (DMSO-D ₆) δ: 11.29 (1H, s), 8.65-8.59 (1H, m), 8.41 (1H, d, J = 9.0 Hz), 8.00 (1H, d, J = 1.8 Hz), 7.98 (1H, d, J = 8.3 Hz), 7.86 (1H, dd, J = 8.3, 1.8 Hz), 3.98-3.85 (1H, m), 2.64 (3H, d, J = 4.9 Hz), 2.16-2.04 (2H, m), 1.69-1.59 (1H, m), 1.59-1.13 (8H, m), 1.06 (3H, d, J = 6.5 Hz).	490	488
199			¹ H-NMR (DMSO-D ₆) δ: 12.84-12.75 (1H, m), 11.30 (1H, s), 8.32 (1H, d, J = 1.6 Hz), 7.91 (1H, dd, J = 8.0, 1.6 Hz), 7.66 (1H, d, J = 8.1 Hz), 7.59 (1H, d, J = 9.2 Hz), 6.30 (1H, s), 4.11-3.96 (1H, m), 2.23 (3H, s), 2.19-2.07 (2H, m), 1.75-1.63 (1H, m), 1.61-1.15 (8H, m), 1.07 (3H, d, J = 6.5 Hz).	513	511
200			¹ H-NMR (DMSO-D ₆) δ: 10.94 (1H, s), 7.09 (1H, d, J = 8.5 Hz), 6.84 (1H, d, J = 2.3 Hz), 6.78 (1H, dd, J = 8.5, 2.3 Hz), 6.08 (1H, d, J = 7.9 Hz), 3.78-3.76 (1H, m), 3.73 (4H, t, J = 4.7 Hz), 3.49 (4H, t, J = 4.7 Hz), 3.20 (4H, t, J = 4.7 Hz), 3.14 (4H, t, J = 4.7 Hz), 2.18 (3H, s), 2.05-1.97 (2H, m), 1.62-1.56 (1H, m), 1.50-1.35 (4H, m), 1.27-1.14 (4H, m), 0.99 (3H, d, J = 6.5 Hz).	514	512

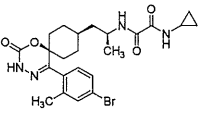
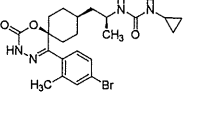
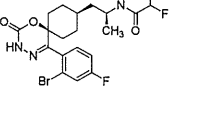
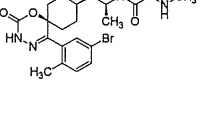
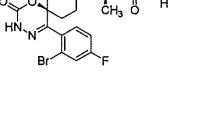
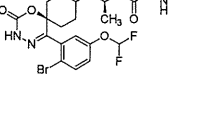
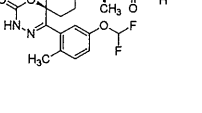
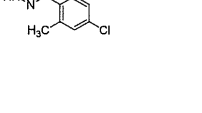
[0593]

Table 1-26

201			¹ H-NMR (DMSO-D ₆) δ: 13.00-12.76 (2H, m), 11.14 (1H, s), 7.85 (1H, s), 7.76 (1H, d, J = 7.9 Hz), 7.68-7.56 (1H, m), 7.38 (1H, d, J = 7.9 Hz), 6.33 (1H, s), 4.10-3.98 (1H, m), 2.27 (3H, s), 2.21 (3H, s), 2.09-2.00 (2H, m), 1.71-1.65 (1H, m), 1.52-1.21 (8H, m), 1.07 (3H, d, J = 6.5 Hz).	468	466
202			¹ H-NMR (DMSO-D ₆) δ: 11.26 (1H, s), 9.15 (1H, s), 8.33 (1H, d, J = 9.0 Hz), 7.75 (1H, dd, J = 8.4, 2.5 Hz), 7.55 (1H, dd, J = 8.4, 6.1 Hz), 7.36 (1H, td, J = 8.4, 2.5 Hz), 3.94-3.87 (1H, m), 2.74-2.60 (2H, m), 2.44-2.38 (2H, m), 2.33-2.20 (3H, m), 2.09-2.03 (2H, m), 2.01 (6H, s), 1.63-1.50 (2H, m), 1.03 (3H, d, J = 6.5 Hz).	536	534
203			¹ H-NMR (DMSO-D ₆) δ: 11.19 (1H, s), 8.68 (1H, d, J = 5.3 Hz), 8.41 (1H, d, J = 8.9 Hz), 7.73 (1H, dd, J = 8.9, 2.4 Hz), 7.52 (1H, dd, J = 8.9, 6.2 Hz), 7.34 (1H, td, J = 8.9, 2.4 Hz), 3.95-3.85 (1H, m), 2.78-2.70 (1H, m), 2.16-2.06 (2H, m), 1.68-1.61 (1H, m), 1.57-1.17 (8H, m), 1.05 (3H, d, J = 6.2 Hz), 0.65-0.58 (4H, m).	509	507
204			¹ H-NMR (DMSO-D ₆) δ: 12.95 (0.15H, s), 12.80 (0.85H, s), 11.11 (1H, s), 8.42 (1H, d, J = 3.9 Hz), 7.93 (0.15H, s), 7.71 (1H, s), 7.62-7.57 (1.85H, m), 7.33 (1H, d, J = 7.9 Hz), 6.56 (0.15H, s), 6.30 (0.85H, s), 4.10-4.00 (1H, m), 2.86-2.80 (1H, m), 2.25 (3H, s), 2.23 (3H, s), 2.08-2.01 (2H, m), 1.71-1.65 (1H, m), 1.53-1.19 (8H, m), 1.07 (3H, d, J = 6.2 Hz), 0.71-0.66 (2H, m), 0.57-0.53 (2H, m).	507	505
205			¹ H-NMR (DMSO-D ₆) δ: 11.25 (1H, s), 8.65 (1H, q, J = 4.9 Hz), 8.44 (1H, d, J = 9.0 Hz), 7.81 (1H, d, J = 8.1 Hz), 7.56 (1H, s), 7.48 (1H, dd, J = 8.1, 1.4 Hz), 3.98-3.87 (1H, m), 2.66 (3H, d, J = 4.9 Hz), 2.51 (3H, s), 2.04-1.94 (2H, m), 1.77-1.46 (5H, m), 1.40-1.19 (4H, m), 1.08 (3H, d, J = 6.5 Hz).	426	424
206			¹ H-NMR (DMSO-D ₆) δ: 11.36 (1H, s), 8.65-8.57 (1H, m), 8.36 (1H, d, J = 1.5 Hz), 8.33 (1H, d, J = 8.8 Hz), 7.96 (1H, dd, J = 8.0, 1.5 Hz), 7.70 (1H, d, J = 8.0 Hz), 3.98-3.87 (1H, m), 2.75-2.58 (2H, m), 2.64 (3H, d, J = 5.0 Hz), 2.42 (1H, dd, J = 12.4, 8.4 Hz), 2.35-2.20 (3H, m), 2.13-2.04 (2H, m), 1.64-1.47 (2H, m), 1.04 (3H, d, J = 6.5 Hz).	491	489
207			¹ H-NMR (DMSO-D ₆) δ: 12.79 (1H, s), 11.35 (1H, s), 8.35 (1H, d, J = 1.5 Hz), 7.95 (1H, dd, J = 8.0, 1.5 Hz), 7.69 (1H, d, J = 7.8 Hz), 7.55 (1H, d, J = 8.5 Hz), 6.28 (1H, s), 4.10-4.00 (1H, m), 2.76-2.64 (2H, m), 2.46-2.37 (1H, m), 2.35-2.20 (6H, m), 2.09 (2H, d, J = 14.3 Hz), 1.63-1.47 (2H, m), 1.06 (3H, d, J = 6.8 Hz).	514	512
208			¹ H-NMR (DMSO-D ₆) δ: 11.20 (1H, s), 8.88 (1H, s), 7.86 (1H, dd, J = 8.6, 2.5 Hz), 7.46 (1H, dd, J = 8.7, 5.9 Hz), 7.34 (1H, td, J = 8.6, 2.5 Hz), 6.49 (1H, d, J = 9.0 Hz), 3.84-3.70 (1H, m), 3.47 (3H, s), 2.19-2.06 (2H, m), 1.73-1.61 (1H, m), 1.57-1.14 (8H, m), 1.03 (3H, d, J = 6.7 Hz).	519	517

[0594]

Table 1-27

209			¹ H-NMR (DMSO-D ₆) δ: 11.11 (1H, s), 8.68 (1H, d, J = 5.3 Hz), 8.41 (1H, d, J = 9.2 Hz), 7.56 (1H, d, J = 1.8 Hz), 7.43 (1H, dd, J = 8.2, 1.8 Hz), 7.23 (1H, d, J = 8.2 Hz), 3.93-3.84 (1H, m), 2.76-2.71 (1H, m), 2.22 (3H, s), 2.06-1.98 (2H, m), 1.68-1.60 (1H, m), 1.54-1.39 (3H, m), 1.36-1.16 (5H, m), 1.05 (3H, d, J = 6.5 Hz), 0.64-0.59 (4H, m).	505	503
210			¹ H-NMR (DMSO-D ₆) δ: 11.12 (1H, s), 7.57 (1H, d, J = 1.6 Hz), 7.44 (1H, dd, J = 8.0, 1.6 Hz), 7.25 (1H, d, J = 8.0 Hz), 5.88 (1H, d, J = 2.3 Hz), 5.45 (1H, d, J = 8.0 Hz), 3.69-3.63 (1H, m), 2.38-2.32 (1H, m), 2.23 (3H, s), 2.08-2.00 (2H, m), 1.66-1.59 (1H, m), 1.51-1.13 (8H, m), 0.97 (3H, d, J = 6.5 Hz), 0.54-0.50 (2H, m), 0.28-0.24 (2H, m).	477	475
211			¹ H-NMR (DMSO-D ₆) δ: 11.20 (1H, s), 8.52 (1H, d, J = 8.8 Hz), 7.73 (1H, dd, J = 8.8, 2.4 Hz), 7.53 (1H, dd, J = 8.8, 6.1 Hz), 7.35 (1H, td, J = 8.8, 2.4 Hz), 6.12 (1H, t, J = 53.8 Hz), 3.95-3.85 (1H, m), 2.18-2.09 (2H, m), 1.65-1.55 (1H, m), 1.51-1.18 (8H, m), 1.05 (3H, d, J = 6.5 Hz).	476	474
212			¹ H-NMR (DMSO-D ₆) δ: 11.13 (1H, s), 8.63 (1H, q, J = 4.8 Hz), 8.41 (1H, d, J = 9.2 Hz), 7.53 (1H, dd, J = 8.2, 2.1 Hz), 7.46 (1H, d, J = 2.1 Hz), 7.27 (1H, d, J = 8.2 Hz), 3.94-3.87 (1H, m), 2.64 (3H, d, J = 4.8 Hz), 2.18 (3H, s), 2.09-2.01 (2H, m), 1.69-1.62 (1H, m), 1.53-1.17 (8H, m), 1.06 (3H, d, J = 6.5 Hz).	479	477
213			¹ H-NMR (DMSO-D ₆) δ: 11.19 (1H, s), 7.96 (1H, t, J = 5.4 Hz), 7.74 (1H, dd, J = 9.4, 1.9 Hz), 7.60-7.49 (2H, m), 7.35 (1H, td, J = 8.4, 2.7 Hz), 3.91-3.78 (1H, m), 3.57 (2H, d, J = 5.4 Hz), 2.20-2.04 (2H, m), 1.79 (3H, s), 1.68-1.56 (1H, m), 1.52-1.12 (8H, m), 0.99 (3H, d, J = 7.0 Hz).	497	495
214			¹ H-NMR (DMSO-D ₆) δ: 12.80 (1H, s), 11.22 (1H, s), 7.77 (1H, d, J = 8.6 Hz), 7.59 (1H, d, J = 9.2 Hz), 7.31 (1H, t, J = 73.5 Hz), 7.27 (1H, s), 7.21 (1H, dd, J = 9.2, 1.6 Hz), 6.30 (1H, s), 4.12-3.98 (1H, m), 2.23 (3H, s), 2.19-2.07 (2H, m), 1.75-1.63 (1H, m), 1.58-1.18 (8H, m), 1.07 (3H, d, J = 6.5 Hz).	554	552
215			¹ H-NMR (DMSO-D ₆) δ: 12.79 (1H, s), 11.12 (1H, s), 7.59 (1H, d, J = 8.1 Hz), 7.34 (1H, d, J = 8.6 Hz), 7.22 (1H, t, J = 74.1 Hz), 7.13 (1H, d, J = 8.6 Hz), 7.06 (1H, s), 6.30 (1H, s), 4.14-3.98 (1H, m), 2.22 (3H, s), 2.19 (3H, s), 2.11-1.99 (2H, m), 1.75-1.61 (1H, m), 1.59-1.16 (8H, m), 1.08 (3H, d, J = 6.5 Hz).	490	488
216			¹ H-NMR (DMSO-D ₆) δ: 11.16 (1H, s), 8.65-8.58 (1H, m), 8.34 (1H, d, J = 8.8 Hz), 7.43 (1H, s), 7.35-7.28 (2H, m), 4.01-3.84 (1H, m), 2.73-2.59 (2H, m), 2.64 (3H, d, J = 4.8 Hz), 2.42 (1H, dd, J = 12.6, 8.4 Hz), 2.35-2.19 (3H, m), 2.22 (3H, s), 2.03-1.95 (2H, m), 1.64-1.45 (2H, m), 1.04 (3H, d, J = 6.5 Hz).	436	434

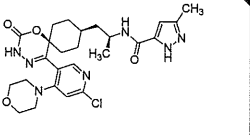
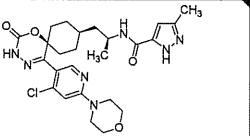
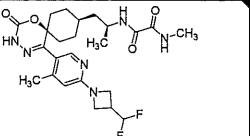
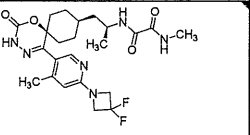
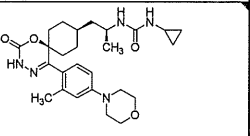
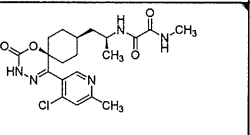
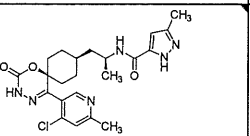
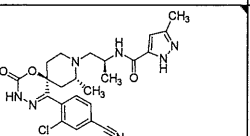
[0595]

Table 1-28

217			¹ H-NMR (DMSO-D ₆) δ: 12.79 (1H, s), 11.16 (1H, s), 7.55 (1H, d, J = 7.5 Hz), 7.42 (1H, s), 7.33-7.25 (2H, m), 6.29 (1H, s), 4.12-3.99 (1H, m), 2.74-2.63 (2H, m), 2.41 (1H, dd, J = 12.3, 8.0 Hz), 2.35-2.14 (9H, m), 1.99 (2H, d, J = 13.5 Hz), 1.62-1.49 (2H, m), 1.07 (3H, d, J = 6.5 Hz).	459	457
218			¹ H-NMR (DMSO-D ₆) δ: 10.94 (1H, s), 8.69 (1H, d, J = 5.3 Hz), 8.41 (1H, d, J = 9.0 Hz), 7.08 (1H, d, J = 9.0 Hz), 6.83 (1H, d, J = 2.3 Hz), 6.78 (1H, dd, J = 9.0, 2.3 Hz), 3.94-3.85 (1H, m), 3.72 (4H, dd, J = 5.5, 4.2 Hz), 3.14 (4H, dd, J = 5.5, 4.2 Hz), 2.76-2.70 (1H, m), 2.17 (3H, s), 2.03-1.95 (2H, m), 1.68-1.61 (1H, m), 1.53-1.16 (8H, m), 1.05 (3H, d, J = 6.5 Hz), 0.63-0.58 (4H, m).	512	510
219			¹ H-NMR (DMSO-D ₆) δ: 11.19 (1H, s), 8.06 (1H, s), 7.78 (1H, s), 7.72 (1H, dd, J = 8.6, 2.5 Hz), 7.65 (1H, d, J = 8.6 Hz), 7.51 (1H, dd, J = 8.6, 6.0 Hz), 7.32 (1H, td, J = 8.6, 2.5 Hz), 4.08-3.99 (1H, m), 3.82 (3H, s), 2.15-2.08 (2H, m), 1.70-1.63 (1H, m), 1.53-1.20 (8H, m), 1.06 (3H, d, J = 6.5 Hz).	506	504
220			¹ H-NMR (DMSO-D ₆) δ: 11.13 (1H, s), 8.68 (1H, d, J = 5.5 Hz), 8.41 (1H, d, J = 9.2 Hz), 8.07 (1H, s), 6.77 (1H, s), 3.95-3.83 (1H, m), 3.86 (3H, s), 2.78-2.69 (1H, m), 2.19 (3H, s), 2.07-1.97 (2H, m), 1.69-1.14 (9H, m), 1.06 (3H, d, J = 6.7 Hz), 0.66-0.56 (4H, m).	458	456
221			¹ H-NMR (DMSO-D ₆) δ: 13.01-12.72 (1H, m), 11.04 (1H, s), 7.97 (1H, s), 7.63-7.55 (1H, m), 6.73 (1H, s), 6.31 (1H, s), 4.13-4.00 (1H, m), 3.67 (4H, t, J = 4.7 Hz), 3.64-3.56 (1H, m), 3.46 (4H, t, J = 4.9 Hz), 2.26-2.19 (2H, m), 2.14 (3H, s), 2.05-1.96 (2H, m), 1.75-1.64 (1H, m), 1.56-1.20 (8H, m), 1.08 (3H, d, J = 6.5 Hz).	510	508
222			¹ H-NMR (DMSO-D ₆) δ: 11.30 (1H, s), 8.03 (1H, d, J = 1.8 Hz), 7.99 (1H, d, J = 8.3 Hz), 7.87 (1H, dd, J = 8.4, 2.0 Hz), 5.89 (1H, d, J = 2.8 Hz), 5.46 (1H, d, J = 8.6 Hz), 3.72-3.61 (1H, m), 2.40-2.31 (1H, m), 2.19-2.07 (2H, m), 1.70-1.57 (1H, m), 1.56-1.06 (8H, m), 0.97 (3H, d, J = 6.5 Hz), 0.56-0.46 (2H, m), 0.31-0.22 (2H, m).	488	486
223			¹ H-NMR (DMSO-D ₆) δ: 12.80 (1H, s), 11.30 (1H, s), 7.86 (1H, s), 7.63-7.54 (1H, m), 6.75 (1H, s), 6.31 (1H, s), 4.12-3.99 (1H, m), 3.71 (2H, t, J = 12.8 Hz), 3.49 (2H, t, J = 7.3 Hz), 2.60-2.51 (2H, m), 2.26-2.05 (1H, m), 2.23 (3H, s), 1.96-1.76 (1H, m), 1.74-1.62 (1H, m), 1.60-1.14 (8H, m), 1.08 (3H, d, J = 6.5 Hz).	550	548
224			¹ H-NMR (DMSO-D ₆) δ: 12.80 (1H, s), 11.15 (1H, s), 8.10 (1H, s), 7.59 (1H, d, J = 8.3 Hz), 6.75 (1H, s), 6.30 (1H, s), 4.11-4.00 (1H, m), 3.86 (2H, t, J = 13.1 Hz), 3.65 (2H, t, J = 7.4 Hz), 2.60-2.50 (2H, m), 2.23 (3H, s), 2.11-1.98 (2H, m), 1.74-1.62 (1H, m), 1.59-1.12 (8H, m), 1.08 (3H, d, J = 6.5 Hz).	550	548

[0596]

Table 1-29

225			¹ H-NMR (DMSO-D ₆) δ: 12.80 (1H, s), 11.25 (1H, s), 7.96 (1H, s), 7.58 (1H, d, J = 8.3 Hz), 7.08 (1H, s), 6.30 (1H, s), 4.11-3.98 (1H, m), 3.61 (4H, t, J = 4.5 Hz), 3.18-3.05 (4H, m), 2.23 (3H, s), 2.13-1.99 (2H, m), 1.72-1.63 (1H, m), 1.55-1.14 (8H, m), 1.08 (3H, d, J = 6.5 Hz).	530	528
226			¹ H-NMR (DMSO-D ₆) δ: 12.80 (1H, s), 11.15 (1H, s), 8.09 (1H, s), 7.59 (1H, d, J = 8.3 Hz), 7.00 (1H, s), 6.31 (1H, s), 4.11-3.99 (1H, m), 3.67 (4H, t, J = 4.7 Hz), 3.51 (4H, t, J = 4.9 Hz), 2.23 (3H, s), 2.10-2.00 (2H, m), 1.73-1.63 (1H, m), 1.57-1.15 (8H, m), 1.08 (3H, d, J = 6.5 Hz).	530	528
227			¹ H-NMR (DMSO-D ₆) δ: 11.08 (1H, s), 8.66-8.60 (1H, m), 8.41 (1H, d, J = 9.2 Hz), 7.95 (1H, s), 6.46-6.37 (1H, m), 6.38 (1H, td, J = 56.4, 4.3 Hz), 4.10 (2H, t, J = 8.3 Hz), 3.97-3.86 (3H, m), 3.32-3.14 (1H, m), 2.64 (3H, d, J = 4.9 Hz), 2.15 (3H, s), 2.05-1.95 (2H, m), 1.71-1.60 (1H, m), 1.59-1.14 (8H, m), 1.06 (3H, d, J = 6.5 Hz).	507	505
228			¹ H-NMR (DMSO-D ₆) δ: 11.08 (1H, s), 8.66-8.60 (1H, m), 8.41 (1H, d, J = 9.2 Hz), 8.01 (1H, s), 6.50 (1H, s), 4.39 (4H, t, J = 12.5 Hz), 3.99-3.85 (1H, m), 2.64 (3H, d, J = 4.9 Hz), 2.16 (3H, s), 2.06-1.98 (2H, m), 1.70-1.60 (1H, m), 1.59-1.15 (8H, m), 1.06 (3H, d, J = 6.7 Hz).	507	505
229			¹ H-NMR (DMSO-D ₆) δ: 10.94 (1H, s), 7.09 (1H, d, J = 8.6 Hz), 6.84 (1H, d, J = 2.7 Hz), 6.78 (1H, dd, J = 8.6, 2.7 Hz), 5.88 (1H, d, J = 2.7 Hz), 5.46 (1H, d, J = 8.6 Hz), 3.73 (4H, dd, J = 5.8, 4.4 Hz), 3.69-3.64 (1H, m), 3.14 (4H, dd, J = 5.8, 4.4 Hz), 2.37-2.33 (1H, m), 2.18 (3H, s), 2.05-1.96 (2H, m), 1.65-1.58 (1H, m), 1.51-1.36 (3H, m), 1.31-1.15 (5H, m), 0.97 (3H, d, J = 6.5 Hz), 0.54-0.50 (2H, m), 0.28-0.23 (2H, m).	484	482
230			¹ H-NMR (DMSO-D ₆) δ: 11.28 (1H, s), 8.62 (1H, q, J = 4.8 Hz), 8.48 (1H, s), 8.41 (1H, d, J = 9.2 Hz), 7.58 (1H, s), 3.98-3.83 (1H, m), 2.64 (3H, d, J = 4.8 Hz), 2.51 (3H, s), 2.15-2.02 (2H, m), 1.71-1.59 (1H, m), 1.57-1.15 (8H, m), 1.05 (3H, d, J = 6.5 Hz).	436	434
231			¹ H-NMR (DMSO-D ₆) δ: 12.80 (1H, s), 11.28 (1H, s), 8.47 (1H, s), 7.65-7.51 (1H, m), 7.56 (1H, s), 6.31 (1H, s), 4.12-4.00 (1H, m), 2.50 (3H, s), 2.22 (3H, s), 2.14-2.02 (2H, m), 1.74-1.63 (1H, m), 1.55-1.15 (8H, m), 1.07 (3H, d, J = 6.7 Hz).	459	457
232			¹ H-NMR (DMSO-D ₆) δ: 12.75 (1H, s), 11.34 (1H, s), 8.21 (1H, s), 7.90 (1H, d, J = 7.5 Hz), 7.68 (1H, d, J = 8.0 Hz), 7.46 (1H, d, J = 8.0 Hz), 6.22 (1H, s), 4.03-3.91 (1H, m), 2.92-2.82 (1H, m), 2.80-2.71 (1H, m), 2.41-2.30 (3H, m), 2.25 (3H, s), 2.00-1.89 (2H, m), 1.83-1.75 (1H, m), 1.68-1.56 (1H, m), 1.08 (3H, d, J = 6.8 Hz), 1.05 (3H, d, J = 6.5 Hz).	484	482

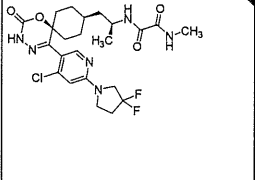
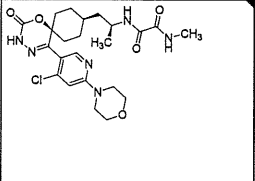
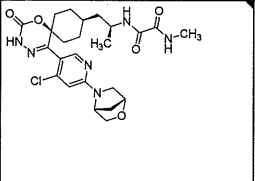
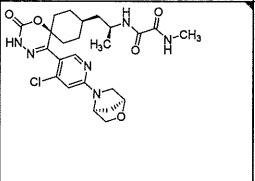
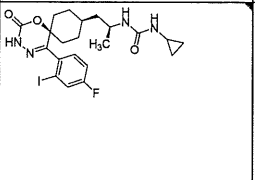
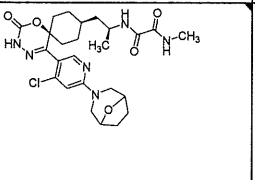
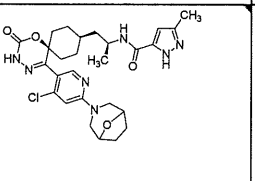
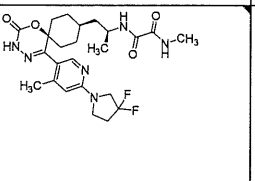
[0597]

Table 1-30

233			¹ H-NMR (DMSO-D ₆) δ: 11.35 (1H, s), 8.60-8.53 (1H, m), 8.28-8.21 (2H, m), 7.92 (1H, dd, J = 8.0, 1.5 Hz), 7.71 (1H, d, J = 8.0 Hz), 3.90-3.76 (1H, m), 2.90-2.82 (1H, m), 2.77-2.69 (1H, m), 2.64 (3H, d, J = 5.0 Hz), 2.40-2.29 (3H, m), 2.00-1.89 (2H, m), 1.85-1.75 (1H, m), 1.63-1.52 (1H, m), 1.07 (3H, d, J = 6.8 Hz), 1.03 (3H, d, J = 6.5 Hz).	461	459
234			¹ H-NMR (DMSO-D ₆) δ: 11.14 (1H, s), 8.08 (1H, s), 7.25-7.18 (2H, m), 7.14-7.08 (1H, m), 6.99-6.94 (1H, m), 6.81 (1H, s), 6.11 (1H, t, J = 6.1 Hz), 5.74 (1H, d, J = 8.8 Hz), 4.24 (1H, dd, J = 15.7, 6.1 Hz), 4.16 (1H, dd, J = 15.7, 6.1 Hz), 3.87 (3H, s), 3.74-3.66 (1H, m), 2.20 (3H, s), 2.10-1.99 (2H, m), 1.68-1.61 (1H, m), 1.52-1.13 (8H, m), 0.99 (3H, d, J = 6.5 Hz).	498	496
235			¹ H-NMR (DMSO-D ₆) δ: 11.14 (1H, s), 8.07 (1H, s), 7.58 (1H, s), 6.78 (1H, s), 6.47 (1H, d, J = 8.1 Hz), 4.62 (2H, s), 4.31 (2H, t, J = 5.4 Hz), 3.85 (3H, s), 3.83-3.72 (3H, m), 2.19 (3H, s), 2.06-1.98 (2H, m), 1.63-1.15 (9H, m), 1.01 (3H, d, J = 6.5 Hz).	497	495
236			¹ H-NMR (DMSO-D ₆) δ: 11.13 (1H, s), 8.06 (1H, s), 7.18-7.05 (4H, m), 6.79 (1H, s), 6.12 (1H, d, J = 8.3 Hz), 4.44 (2H, s), 3.86 (3H, s), 3.83-3.73 (1H, m), 3.61-3.38 (2H, m), 2.81-2.66 (2H, m), 2.19 (3H, s), 2.05-1.96 (2H, m), 1.63-1.56 (1H, m), 1.51-1.14 (8H, m), 1.01 (3H, d, J = 6.5 Hz).	506	504
237			¹ H-NMR (DMSO-D ₆) δ: 11.13 (1H, s), 8.07 (1H, s), 7.36 (1H, d, J = 1.8 Hz), 6.78 (1H, s), 6.40 (1H, d, J = 8.1 Hz), 6.04 (1H, d, J = 1.8 Hz), 4.54 (2H, s), 4.02 (2H, t, J = 5.4 Hz), 3.86 (3H, s), 3.81-3.72 (3H, m), 2.19 (3H, s), 2.06-1.98 (2H, m), 1.63-1.15 (9H, m), 1.01 (3H, d, J = 6.5 Hz).	496	494
238			¹ H-NMR (DMSO-D ₆) δ: 12.80 (1H, s), 11.04 (1H, s), 7.97 (1H, s), 7.63-7.55 (1H, m), 6.46 (1H, s), 6.31 (1H, s), 4.13-4.00 (1H, m), 3.82 (2H, t, J = 13.4 Hz), 3.61 (2H, t, J = 7.3 Hz), 2.59-2.50 (2H, m), 2.23 (3H, s), 2.15 (3H, s), 2.04-1.97 (2H, m), 1.72-1.64 (1H, m), 1.57-1.19 (8H, m), 1.08 (3H, d, J = 6.5 Hz).	530	528
239			¹ H-NMR (DMSO-D ₆) δ: 12.80 (1H, s), 11.13 (1H, s), 8.02 (1H, s), 7.63-7.54 (1H, m), 6.72 (1H, s), 6.31 (1H, s), 4.90 (1H, s), 4.67 (1H, s), 4.12-4.02 (1H, m), 3.76 (1H, d, J = 6.0 Hz), 3.64 (1H, d, J = 7.4 Hz), 3.44 (1H, d, J = 10.2 Hz), 3.32-3.28 (1H, m), 2.23 (3H, s), 2.11-2.00 (2H, m), 1.93-1.82 (2H, m), 1.73-1.64 (1H, m), 1.56-1.16 (8H, m), 1.08 (3H, d, J = 6.5 Hz).	542	540
240			¹ H-NMR (DMSO-D ₆) δ: 12.80 (1H, s), 11.13 (1H, s), 8.02 (1H, s), 7.59 (1H, d, J = 9.0 Hz), 6.80-6.65 (1H, m), 6.31 (1H, s), 4.90 (1H, s), 4.67 (1H, s), 4.13-3.98 (1H, m), 3.76 (1H, d, J = 6.0 Hz), 3.65 (1H, d, J = 7.4 Hz), 3.44 (1H, d, J = 9.0 Hz), 3.32-3.24 (1H, m), 2.23 (3H, s), 2.10-2.00 (2H, m), 1.93-1.81 (2H, m), 1.73-1.65 (1H, m), 1.55-1.15 (8H, m), 1.08 (3H, d, J = 6.5 Hz).	542	540

[0598]

Table 1-31

241			¹ H-NMR (DMSO-D ₆) δ: 11.16 (1H, s), 8.66-8.60 (1H, m), 8.41 (1H, d, J = 9.2 Hz), 8.11 (1H, s), 6.76 (1H, s), 3.95-3.84 (1H, m), 3.88 (2H, t, J = 13.2 Hz), 3.66 (2H, t, J = 7.4 Hz), 2.64 (3H, d, J = 4.9 Hz), 2.61-2.52 (2H, m), 2.10-2.00 (2H, m), 1.71-1.57 (1H, m), 1.57-1.14 (8H, m), 1.06 (3H, d, J = 6.7 Hz).	527	525
242			¹ H-NMR (DMSO-D ₆) δ: 11.15 (1H, s), 8.66-8.60 (1H, m), 8.41 (1H, d, J = 9.2 Hz), 8.10 (1H, s), 7.02 (1H, s), 3.99-3.83 (1H, m), 3.68 (4H, t, J = 4.9 Hz), 3.53 (4H, t, J = 4.7 Hz), 2.64 (3H, d, J = 4.9 Hz), 2.08-2.00 (2H, m), 1.70-1.60 (1H, m), 1.58-1.16 (8H, m), 1.06 (3H, d, J = 6.7 Hz).	507	505
243			¹ H-NMR (DMSO-D ₆) δ: 11.13 (1H, s), 8.67-8.60 (1H, m), 8.41 (1H, d, J = 9.0 Hz), 8.03 (1H, s), 6.79-6.69 (1H, m), 4.91 (1H, s), 4.68 (1H, s), 3.97-3.85 (1H, m), 3.77 (1H, d, J = 7.4 Hz), 3.65 (1H, d, J = 7.4 Hz), 3.48-3.43 (1H, m), 3.33-3.27 (1H, m), 2.64 (3H, d, J = 4.9 Hz), 2.09-1.99 (2H, m), 1.94-1.83 (2H, m), 1.71-1.62 (1H, m), 1.58-1.14 (8H, m), 1.06 (3H, d, J = 6.5 Hz).	519	563 (formic acid adduct)
244			¹ H-NMR (DMSO-D ₆) δ: 11.13 (1H, s), 8.67-8.60 (1H, m), 8.41 (1H, d, J = 9.5 Hz), 8.03 (1H, s), 6.78-6.69 (1H, m), 4.91 (1H, s), 4.68 (1H, s), 3.97-3.85 (1H, m), 3.77 (1H, d, J = 7.4 Hz), 3.65 (1H, d, J = 7.4 Hz), 3.48-3.42 (1H, m), 3.32-3.28 (1H, m), 2.64 (3H, d, J = 4.9 Hz), 2.08-2.00 (2H, m), 1.92-1.83 (2H, m), 1.70-1.61 (1H, m), 1.58-1.16 (8H, m), 1.06 (3H, d, J = 6.5 Hz).	519	563 (formic acid adduct)
245			¹ H-NMR (DMSO-D ₆) δ: 11.20 (1H, s), 7.87 (1H, dd, J = 8.4, 2.7 Hz), 7.46 (1H, dd, J = 8.6, 5.8 Hz), 7.34 (1H, td, J = 8.5, 2.6 Hz), 5.89 (1H, d, J = 2.8 Hz), 5.46 (1H, d, J = 8.3 Hz), 3.72-3.61 (1H, m), 2.40-2.31 (1H, m), 2.19-2.08 (2H, m), 1.69-1.57 (1H, m), 1.55-1.08 (8H, m), 0.97 (3H, d, J = 6.5 Hz), 0.55-0.48 (2H, m), 0.29-0.23 (2H, m).	529	527
246			¹ H-NMR (DMSO-D ₆) δ: 11.14 (1H, s), 8.66-8.61 (1H, m), 8.41 (1H, d, J = 9.2 Hz), 8.07 (1H, s), 6.90 (1H, s), 4.45-4.40 (2H, m), 3.97-3.81 (1H, m), 3.86 (2H, d, J = 11.6 Hz), 3.03-2.96 (1H, m), 2.64 (3H, d, J = 4.9 Hz), 2.09-1.99 (2H, m), 1.87-1.80 (2H, m), 1.75-1.17 (12H, m), 1.06 (3H, d, J = 6.5 Hz).	533	577 (formic acid adduct)
247			¹ H-NMR (DMSO-D ₆) δ: 12.80 (1H, s), 11.14 (1H, s), 8.06 (1H, s), 7.63-7.55 (1H, m), 6.88 (1H, s), 6.31 (1H, s), 4.44-4.39 (2H, m), 4.11-4.00 (1H, m), 3.85 (2H, d, J = 12.5 Hz), 3.02-2.95 (2H, m), 2.23 (3H, s), 2.09-2.01 (2H, m), 1.87-1.64 (5H, m), 1.56-1.17 (8H, m), 1.08 (3H, d, J = 6.5 Hz).	556	554
248			¹ H-NMR (DMSO-D ₆) δ: 11.04 (1H, s), 8.66-8.59 (1H, m), 8.41 (1H, d, J = 9.2 Hz), 7.98 (1H, s), 6.47 (1H, s), 3.96-3.84 (1H, m), 3.84 (2H, t, J = 13.4 Hz), 3.63 (2H, t, J = 7.3 Hz), 2.64 (3H, d, J = 4.9 Hz), 2.60-2.52 (2H, m), 2.16 (3H, s), 2.04-1.96 (2H, m), 1.69-1.60 (1H, m), 1.58-1.14 (8H, m), 1.06 (3H, d, J = 6.7 Hz).	507	505

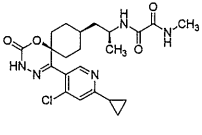
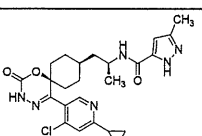
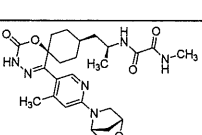
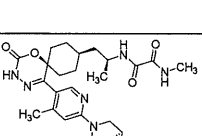
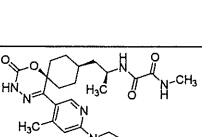
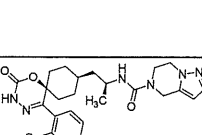
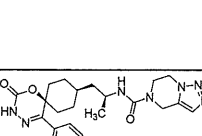
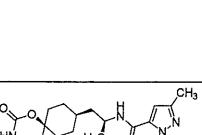
[0599]

Table 1-32

249			¹ H-NMR (DMSO-D ₆) δ: 13.02-12.64 (1H, m), 11.04 (1H, s), 7.91 (1H, s), 7.79-7.49 (1H, m), 6.58-6.24 (2H, m), 4.86 (1H, s), 4.66 (1H, s), 4.13-4.00 (1H, m), 3.76 (1H, d, J = 7.2 Hz), 3.64 (1H, d, J = 7.2 Hz), 3.44 (1H, d, J = 10.2 Hz), 3.24 (1H, d, J = 10.2 Hz), 2.22 (3H, s), 2.13 (3H, s), 2.05-1.96 (2H, m), 1.93-1.80 (2H, m), 1.73-1.63 (1H, m), 1.56-1.16 (8H, m), 1.08 (3H, d, J = 6.5 Hz).	522	520
250			¹ H-NMR (DMSO-D ₆) δ: 12.80 (1H, s), 11.02 (1H, s), 7.91 (1H, s), 7.63-7.54 (1H, m), 6.42 (1H, s), 6.31 (1H, s), 4.85 (1H, s), 4.65 (1H, s), 4.11-4.00 (1H, m), 3.76 (1H, d, J = 7.2 Hz), 3.63 (1H, d, J = 7.2 Hz), 3.43 (1H, d, J = 10.2 Hz), 3.22 (1H, d, J = 10.2 Hz), 2.23 (3H, s), 2.12 (3H, s), 2.05-1.95 (2H, m), 1.91-1.80 (2H, m), 1.72-1.63 (1H, m), 1.57-1.21 (8H, m), 1.08 (3H, d, J = 6.7 Hz).	522	520
251			¹ H-NMR (DMSO-D ₆) δ: 12.80 (1H, s), 11.03 (1H, s), 7.95 (1H, s), 7.59 (1H, d, J = 8.1 Hz), 6.62 (1H, s), 6.31 (1H, s), 4.42 (2H, s), 4.12-3.98 (1H, m), 3.81 (2H, d, J = 12.3 Hz), 2.93 (2H, d, J = 12.3 Hz), 2.23 (3H, s), 2.13 (3H, s), 2.04-1.95 (2H, m), 1.88-1.63 (5H, m), 1.57-1.18 (8H, m), 1.08 (3H, d, J = 6.5 Hz).	536	534
252			¹ H-NMR (DMSO-D ₆) δ: 11.19 (1H, s), 8.84 (1H, d, J = 9.0 Hz), 8.05 (1H, d, J = 8.8 Hz), 7.73 (1H, d, J = 8.8 Hz), 7.70 (1H, dd, J = 8.8, 2.7 Hz), 7.50 (1H, dd, J = 8.8, 6.0 Hz), 7.30 (1H, td, J = 8.8, 2.7 Hz), 4.22-4.13 (1H, m), 2.69 (3H, s), 2.16-2.08 (2H, m), 1.75-1.60 (2H, m), 1.58-1.49 (1H, m), 1.42-1.23 (6H, m), 1.16 (3H, d, J = 6.5 Hz).	518	516
253			¹ H-NMR (DMSO-D ₆) δ: 11.19 (1H, s), 9.01 (1H, d, J = 1.0 Hz), 8.58 (1H, d, J = 1.0 Hz), 8.50 (1H, d, J = 8.6 Hz), 7.71 (1H, dd, J = 8.6, 2.5 Hz), 7.50 (1H, dd, J = 8.6, 6.0 Hz), 7.31 (1H, td, J = 8.6, 2.5 Hz), 4.18-4.11 (1H, m), 2.58 (3H, s), 2.18-2.06 (2H, m), 1.73-1.68 (1H, m), 1.65-1.45 (2H, m), 1.43-1.22 (6H, m), 1.13 (3H, d, J = 6.7 Hz).	518	516
254			¹ H-NMR (DMSO-D ₆) δ: 11.25 (1H, s), 8.05 (1H, s), 7.76 (1H, s), 7.74 (1H, dd, J = 8.6, 2.6 Hz), 7.64 (1H, d, J = 7.4 Hz), 7.54 (1H, dd, J = 8.6, 6.0 Hz), 7.35 (1H, td, J = 8.6, 2.6 Hz), 4.09-4.02 (1H, m), 3.82 (3H, s), 2.73-2.66 (2H, m), 2.40-2.21 (4H, m), 2.11-2.04 (2H, m), 1.63-1.51 (2H, m), 1.05 (3H, d, J = 6.7 Hz).	507	505
255			¹ H-NMR (DMSO-D ₆) δ: 11.25 (1H, s), 8.85 (1H, s), 8.24 (1H, s), 8.03 (1H, d, J = 8.1 Hz), 7.74 (1H, dd, J = 8.6, 2.5 Hz), 7.53 (1H, dd, J = 8.6, 5.9 Hz), 7.34 (1H, td, J = 8.6, 2.5 Hz), 4.13-4.05 (1H, m), 2.75-2.65 (2H, m), 2.41-2.24 (4H, m), 2.12-2.03 (2H, m), 1.63-1.51 (2H, m), 1.08 (3H, d, J = 6.7 Hz).	561	559
256			¹ H-NMR (DMSO-D ₆) δ: 10.99 (1H, s), 8.63 (1H, q, J = 4.9 Hz), 8.41 (1H, d, J = 9.0 Hz), 7.14 (1H, d, J = 8.4 Hz), 6.91 (1H, dd, J = 8.4, 2.3 Hz), 6.70 (1H, d, J = 2.3 Hz), 3.95-3.85 (1H, m), 3.72 (4H, dd, J = 5.6, 4.6 Hz), 3.06 (4H, dd, J = 5.6, 4.6 Hz), 2.64 (3H, d, J = 4.9 Hz), 2.10 (3H, s), 2.09-2.00 (2H, m), 1.69-1.61 (1H, m), 1.52-1.39 (3H, m), 1.32-1.16 (5H, m), 1.06 (3H, d, J = 6.7 Hz).	486	484

[0600]

Table 1-33

265			¹ H-NMR (DMSO-D ₆) δ: 11.27 (1H, s), 8.63 (1H, q, J = 4.8 Hz), 8.413 (1H, d, J = 9.2 Hz), 8.412 (1H, s), 7.62 (1H, s), 3.99-3.83 (1H, m), 2.64 (3H, d, J = 4.8 Hz), 2.23-2.13 (1H, m), 2.13-2.01 (2H, m), 1.72-1.59 (1H, m), 1.57-1.12 (8H, m), 1.05 (3H, d, J = 6.5 Hz), 1.05-0.94 (4H, m).	462	460
266			¹ H-NMR (DMSO-D ₆) δ: 12.80 (1H, s), 11.27 (1H, s), 8.41 (1H, s), 7.67-7.55 (1H, m), 7.61 (1H, s), 6.31 (1H, s), 4.14-3.98 (1H, m), 2.23 (3H, s), 2.21-2.01 (3H, m), 1.76-1.62 (1H, m), 1.58-1.15 (8H, m), 1.07 (3H, d, J = 6.5 Hz), 1.05-0.92 (4H, m).	485	483
267			¹ H-NMR (DMSO-D ₆) δ: 11.02 (1H, s), 8.66-8.61 (1H, m), 8.41 (1H, d, J = 9.5 Hz), 7.92 (1H, s), 6.43 (1H, s), 4.86 (1H, s), 4.66 (1H, s), 3.97-3.87 (1H, m), 3.77 (1H, d, J = 7.4 Hz), 3.64 (1H, d, J = 7.4 Hz), 3.44 (1H, d, J = 10.4 Hz), 3.23 (1H, d, J = 10.4 Hz), 2.64 (3H, d, J = 4.9 Hz), 2.13 (3H, s), 2.04-1.95 (2H, m), 1.93-1.81 (2H, m), 1.73-1.61 (1H, m), 1.58-1.16 (8H, m), 1.06 (3H, d, J = 6.5 Hz).	499	543 (formic acid adduct)
268			¹ H-NMR (DMSO-D ₆) δ: 11.02 (1H, s), 8.66-8.60 (1H, m), 8.41 (1H, d, J = 9.2 Hz), 7.92 (1H, s), 6.44 (1H, s), 4.86 (1H, s), 4.66 (1H, s), 3.98-3.84 (1H, m), 3.77 (1H, d, J = 7.2 Hz), 3.63 (1H, d, J = 7.2 Hz), 3.44 (1H, d, J = 9.9 Hz), 3.23 (1H, d, J = 9.9 Hz), 2.64 (3H, d, J = 4.9 Hz), 2.13 (3H, s), 2.04-1.95 (2H, m), 1.92-1.81 (2H, m), 1.70-1.61 (1H, m), 1.59-1.17 (8H, m), 1.06 (3H, d, J = 6.5 Hz).	499	N.D.
269			¹ H-NMR (DMSO-D ₆) δ: 11.03 (1H, s), 8.66-8.60 (1H, m), 8.41 (1H, d, J = 9.0 Hz), 7.96 (1H, s), 6.63 (1H, s), 4.43 (2H, s), 3.98-3.84 (1H, m), 3.82 (2H, d, J = 12.0 Hz), 2.94 (2H, dd, J = 12.5, 2.3 Hz), 2.64 (3H, d, J = 4.9 Hz), 2.14 (3H, s), 2.03-1.95 (2H, m), 1.87-1.61 (5H, m), 1.60-1.15 (8H, m), 1.06 (3H, d, J = 6.5 Hz).	513	N.D.
270			¹ H-NMR (DMSO-D ₆) δ: 11.30 (1H, s), 8.36 (1H, d, J = 1.6 Hz), 7.96 (1H, dd, J = 7.9, 1.6 Hz), 7.67 (1H, d, J = 7.9 Hz), 7.36 (1H, d, J = 1.8 Hz), 6.39 (1H, d, J = 8.3 Hz), 6.04 (1H, d, J = 1.8 Hz), 4.53 (2H, s), 4.01 (2H, t, J = 5.4 Hz), 3.83-3.69 (3H, m), 2.16-2.06 (2H, m), 1.63-1.55 (1H, m), 1.54-1.12 (8H, m), 1.00 (3H, d, J = 6.5 Hz).	554	552
271			¹ H-NMR (DMSO-D ₆) δ: 11.31 (1H, s), 8.35 (1H, d, J = 1.6 Hz), 7.96 (1H, dd, J = 8.0, 1.5 Hz), 7.67 (1H, d, J = 8.1 Hz), 7.58 (1H, s), 6.47 (1H, d, J = 8.1 Hz), 4.67-4.56 (2H, m), 4.30 (2H, t, J = 5.4 Hz), 3.82-3.72 (3H, m), 2.16-2.08 (2H, m), 1.63-1.56 (1H, m), 1.51-1.13 (8H, m), 1.00 (3H, d, J = 6.5 Hz).	555	553
272			¹ H-NMR (DMSO-D ₆) δ: 12.80 (1H, s), 11.29 (1H, s), 8.00 (1H, d, J = 2.0 Hz), 7.96 (1H, d, J = 8.4 Hz), 7.84 (1H, dd, J = 8.4, 2.0 Hz), 7.63-7.55 (1H, m), 6.31 (1H, s), 4.13-3.98 (1H, m), 2.23 (3H, s), 2.20-2.03 (2H, m), 1.74-1.62 (1H, m), 1.59-1.15 (8H, m), 1.08 (3H, d, J = 6.9 Hz).	513	511

[0602]

Table 1-35

273			¹ H-NMR (DMSO-D ₆) δ: 12.80 (1H, s), 11.08 (1H, s), 7.99 (1H, s), 7.63-7.55 (1H, m), 6.48 (1H, s), 6.31 (1H, s), 4.38 (4H, t, J = 12.5 Hz), 4.11-4.01 (1H, m), 2.23 (3H, s), 2.16 (3H, s), 2.07-1.98 (2H, m), 1.73-1.65 (1H, m), 1.59-1.18 (8H, m), 1.08 (3H, d, J = 6.5 Hz).	516	514
274			¹ H-NMR (DMSO-D ₆) δ: 11.16 (1H, s), 8.66-8.60 (1H, m), 8.41 (1H, d, J = 9.0 Hz), 8.10 (1H, s), 7.16 (1H, s), 3.97-3.86 (1H, m), 3.75 (4H, t, J = 5.7 Hz), 2.64 (3H, d, J = 4.9 Hz), 2.09-1.94 (6H, m), 1.70-1.62 (1H, m), 1.57-1.15 (8H, m), 1.06 (3H, d, J = 6.7 Hz).	541	539
275			¹ H-NMR (DMSO-D ₆) δ: 11.15 (1H, s), 8.10 (1H, s), 7.36 (1H, d, J = 1.8 Hz), 7.03 (1H, s), 6.40 (1H, d, J = 8.3 Hz), 6.04 (1H, s), 4.54 (2H, s), 4.02 (2H, t, J = 5.3 Hz), 3.80-3.73 (3H, m), 3.71-3.65 (4H, m), 3.57-3.49 (4H, m), 2.09-1.99 (2H, m), 1.64-1.55 (1H, m), 1.53-1.14 (8H, m), 1.01 (3H, d, J = 6.7 Hz).	571	569
276			¹ H-NMR (DMSO-D ₆) δ: 11.28 (1H, s), 8.48 (1H, s), 7.59 (1H, s), 7.35 (1H, d, J = 1.3 Hz), 6.39 (1H, d, J = 8.1 Hz), 6.03 (1H, d, J = 1.3 Hz), 4.53 (2H, s), 4.01 (2H, t, J = 5.4 Hz), 3.85-3.68 (3H, m), 2.51 (3H, s), 2.16-2.02 (2H, m), 1.66-1.54 (1H, m), 1.54-1.14 (8H, m), 1.01 (3H, d, J = 6.7 Hz).	500	498
277			¹ H-NMR (DMSO-D ₆) δ: 11.26 (1H, s), 8.42 (1H, s), 7.64 (1H, s), 7.34 (1H, d, J = 0.9 Hz), 6.39 (1H, d, J = 8.1 Hz), 6.03 (1H, d, J = 0.9 Hz), 4.53 (2H, s), 4.01 (2H, t, J = 5.4 Hz), 3.86-3.68 (3H, m), 2.24-2.14 (1H, m), 2.14-2.01 (2H, m), 1.64-1.54 (1H, m), 1.54-1.12 (8H, m), 1.08-0.95 (4H, m), 1.01 (3H, d, J = 6.3 Hz).	526	524
278		Mixture of two diastereomers due to chlorofluoromethyl moiety	¹ H-NMR (DMSO-D ₆) δ: 11.20 (1H, s), 8.42 (1H, d, J = 8.6 Hz), 7.74 (1H, dd, J = 8.6, 2.4 Hz), 7.53 (1H, dd, J = 8.6, 6.2 Hz), 7.35 (1H, td, J = 8.4, 2.4 Hz), 6.63 (1H, d, J = 49.5 Hz), 3.93-3.84 (1H, m), 2.18-2.10 (2H, m), 1.65-1.56 (1H, m), 1.51-1.19 (8H, m), 1.05 (3H, dd, J = 6.2, 4.5 Hz).	492	490
279			¹ H-NMR (DMSO-D ₆) δ: 11.20 (1H, s), 7.73 (2H, dd, J = 8.6, 2.5 Hz), 7.53 (1H, dd, J = 8.6, 6.0 Hz), 7.34 (1H, td, J = 8.6, 2.5 Hz), 6.49 (1H, dt, J = 15.5, 6.1 Hz), 5.96 (1H, d, J = 15.5 Hz), 3.95-3.85 (1H, m), 2.96 (2H, d, J = 6.1 Hz), 2.13 (6H, s), 2.11-2.09 (2H, m), 1.65-1.59 (1H, m), 1.52-1.18 (8H, m), 1.01 (3H, d, J = 6.5 Hz).	509	507
280			¹ H-NMR (DMSO-D ₆) δ: 11.35 (1H, s), 8.63-8.56 (1H, m), 8.30 (1H, d, J = 8.8 Hz), 8.23 (1H, d, J = 1.5 Hz), 7.93 (1H, dd, J = 8.0, 1.5 Hz), 7.73 (1H, d, J = 8.0 Hz), 3.84-3.74 (1H, m), 2.90-2.72 (2H, m), 2.65 (3H, d, J = 4.8 Hz), 2.42 (1H, dd, J = 12.6, 7.6 Hz), 2.35-2.25 (2H, m), 2.00-1.89 (2H, m), 1.87-1.79 (1H, m), 1.69-1.59 (1H, m), 1.05 (3H, d, J = 6.8 Hz), 1.02 (3H, d, J = 6.5 Hz).	461	459

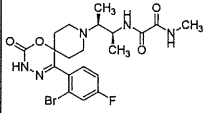
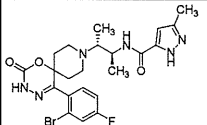
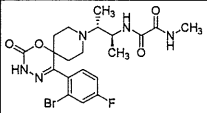
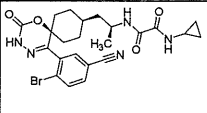
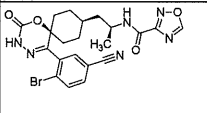
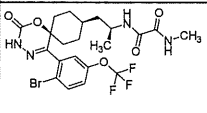
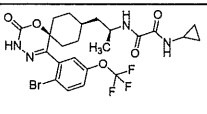
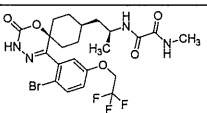
[0603]

Table 1-36

281			¹ H-NMR (DMSO-D ₆) δ: 12.78 (1H, s), 11.35 (1H, s), 8.21 (1H, d, J = 1.5 Hz), 7.91 (1H, d, J = 7.8 Hz), 7.71 (1H, d, J = 7.8 Hz), 7.55-7.47 (1H, m), 6.28 (1H, s), 3.99-3.87 (1H, m), 2.94-2.75 (2H, m), 2.44 (1H, dd, J = 12.6, 7.1 Hz), 2.38-2.13 (7H, m), 2.01-1.90 (2H, m), 1.87-1.79 (1H, m), 1.68-1.58 (1H, m), 1.07 (3H, d, J = 6.8 Hz), 1.05 (3H, d, J = 6.5 Hz).	484	482
282			¹ H-NMR (DMSO-D ₆) δ: 11.19 (1H, s), 7.74 (1H, dd, J = 8.6, 2.5 Hz), 7.54 (1H, dd, J = 8.6, 6.1 Hz), 7.35 (1H, td, J = 8.6, 2.5 Hz), 5.56 (1H, d, J = 8.6 Hz), 3.76-3.69 (1H, m), 3.35-3.31 (2H, m), 3.11-3.02 (2H, m), 2.15-2.10 (2H, m), 1.70 (2H, t, J = 6.8 Hz), 1.65-1.59 (1H, m), 1.52-1.13 (8H, m), 0.99 (3H, d, J = 6.5 Hz), 0.51 (4H, s).	521	519
283			¹ H-NMR (DMSO-D ₆) δ: 11.20 (1H, s), 7.74 (1H, dd, J = 8.6, 2.5 Hz), 7.54 (1H, dd, J = 8.6, 6.1 Hz), 7.35 (1H, td, J = 8.6, 2.5 Hz), 6.02 (1H, d, J = 8.6 Hz), 3.80-3.73 (1H, m), 3.53 (2H, t, J = 4.7 Hz), 3.29-3.16 (4H, m), 2.17-2.09 (2H, m), 1.66-1.60 (1H, m), 1.51-1.13 (8H, m), 0.98 (3H, d, J = 6.5 Hz), 0.60-0.57 (2H, m), 0.49-0.46 (2H, m).	537	535
284			¹ H-NMR (DMSO-D ₆) δ: 11.26 (1H, s), 7.76 (1H, dd, J = 8.7, 2.5 Hz), 7.56 (1H, dd, J = 8.7, 5.9 Hz), 7.37 (1H, td, J = 8.7, 2.5 Hz), 5.52 (1H, d, J = 7.9 Hz), 3.79-3.70 (1H, m), 3.28 (2H, t, J = 6.8 Hz), 3.09-2.98 (2H, m), 2.70-2.62 (2H, m), 2.32-2.17 (4H, m), 2.14-2.02 (2H, m), 1.67 (2H, q, J = 6.2 Hz), 1.61-1.54 (2H, m), 0.99 (3H, d, J = 6.2 Hz), 0.53-0.46 (4H, m).	522	520
285			¹ H-NMR (DMSO-D ₆) δ: 11.30 (1H, s), 8.64 (1H, q, J = 4.8 Hz), 8.60 (1H, d, J = 9.2 Hz), 7.75 (1H, dd, J = 8.6, 2.7 Hz), 7.56 (1H, dd, J = 8.6, 5.9 Hz), 7.37 (1H, ddd, J = 8.6, 8.1, 2.7 Hz), 4.16-3.99 (1H, m), 2.65 (3H, d, J = 4.8 Hz), 2.16-1.97 (3H, m), 1.86-1.52 (7H, m), 1.08 (3H, d, J = 6.5 Hz).	501	499
286			¹ H-NMR (DMSO-D ₆) δ: 12.83 (1H, s), 11.29 (1H, s), 7.81 (1H, d, J = 8.6 Hz), 7.74 (1H, dd, J = 8.6, 2.7 Hz), 7.55 (1H, dd, J = 8.6, 5.9 Hz), 7.36 (1H, ddd, J = 8.6, 8.1, 2.7 Hz), 6.32 (1H, s), 4.29-4.16 (1H, m), 2.24 (3H, s), 2.14-1.95 (3H, m), 1.88-1.53 (7H, m), 1.11 (3H, d, J = 6.5 Hz).	524	522
287			¹ H-NMR (DMSO-D ₆) δ: 11.19 (1H, s), 8.64 (1H, q, J = 4.8 Hz), 8.42 (1H, d, J = 9.2 Hz), 7.81 (1H, s), 7.80 (1H, d, J = 8.1 Hz), 7.53 (1H, d, J = 8.1 Hz), 3.95-3.86 (1H, m), 2.64 (3H, d, J = 4.8 Hz), 2.30 (3H, s), 2.08-2.00 (2H, m), 1.68-1.61 (1H, m), 1.55-1.44 (3H, m), 1.39-1.18 (5H, m), 1.06 (3H, d, J = 6.5 Hz).	426	424
288			¹ H-NMR (DMSO-D ₆) δ: 12.67 (1H, s), 11.21 (1H, s), 7.71 (1H, d, J = 8.6 Hz), 7.50 (1H, d, J = 7.4 Hz), 7.38-7.31 (2H, m), 6.18 (1H, s), 3.78-3.70 (1H, m), 2.72-2.65 (2H, m), 2.58-2.53 (2H, m), 2.36-2.29 (1H, m), 2.26 (3H, s), 2.09-1.92 (2H, m), 1.58-1.48 (1H, m), 1.45-1.35 (1H, m), 1.09 (3H, d, J = 6.5 Hz), 0.92 (3H, d, J = 6.5 Hz).	521	519

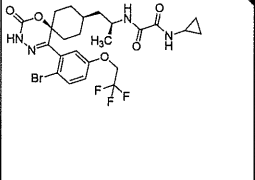
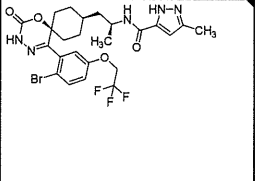
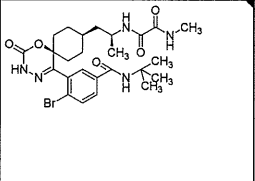
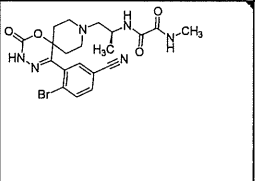
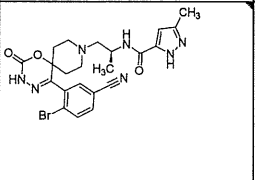
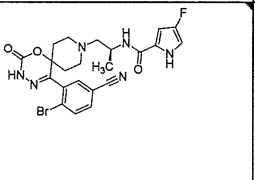
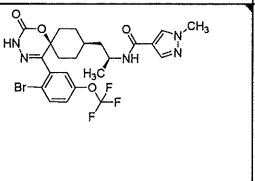
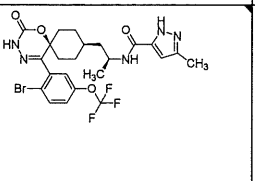
[0604]

Table 1-37

289			¹ H-NMR (DMSO-D ₆) δ: 11.23 (1H, s), 8.56 (1H, d, J = 5.0 Hz), 8.27 (1H, d, J = 7.9 Hz), 7.74 (1H, dd, J = 8.6, 2.5 Hz), 7.47 (1H, dd, J = 8.6, 6.0 Hz), 7.33 (1H, td, J = 8.6, 2.5 Hz), 3.65-3.58 (1H, m), 2.72-2.65 (2H, m), 2.62 (3H, d, J = 5.0 Hz), 2.47-2.41 (2H, m), 2.36-2.28 (1H, m), 2.10-1.95 (2H, m), 1.60-1.40 (2H, m), 1.06 (3H, d, J = 6.5 Hz), 0.90 (3H, d, J = 6.5 Hz).	498	N.D.
290			¹ H-NMR (DMSO-D ₆) δ: 12.83 (1H, s), 11.26 (1H, s), 7.77 (1H, dd, J = 8.6, 2.6 Hz), 7.65 (1H, d, J = 8.1 Hz), 7.57 (1H, dd, J = 8.6, 6.0 Hz), 7.39 (1H, td, J = 8.6, 2.6 Hz), 6.32 (1H, s), 3.98-3.91 (1H, m), 2.79-2.70 (1H, m), 2.60-2.54 (2H, m), 2.46-2.40 (2H, m), 2.24 (3H, s), 2.15-2.05 (2H, m), 1.70-1.50 (2H, m), 1.06 (3H, d, J = 6.3 Hz), 0.86 (3H, d, J = 6.3 Hz).	521	519
291			¹ H-NMR (DMSO-D ₆) δ: 11.26 (1H, s), 8.65 (1H, q, J = 4.9 Hz), 8.46 (1H, d, J = 9.5 Hz), 7.76 (1H, dd, J = 8.6, 2.4 Hz), 7.56 (1H, dd, J = 8.6, 6.0 Hz), 7.38 (1H, td, J = 8.6, 2.4 Hz), 3.82-3.74 (1H, m), 2.77-2.68 (1H, m), 2.65 (3H, d, J = 4.9 Hz), 2.61-2.38 (4H, m), 2.14-2.06 (2H, m), 1.68-1.48 (2H, m), 1.04 (3H, d, J = 6.6 Hz), 0.81 (3H, d, J = 6.6 Hz).	498	N.D.
292			¹ H-NMR (DMSO-D ₆) δ: 11.30 (1H, s), 8.69 (1H, d, J = 5.1 Hz), 8.43 (1H, d, J = 9.2 Hz), 8.00 (1H, d, J = 1.8 Hz), 7.98 (1H, d, J = 8.5 Hz), 7.86 (1H, dd, J = 8.5, 1.8 Hz), 3.95-3.85 (1H, m), 2.76-2.70 (1H, m), 2.15-2.05 (2H, m), 1.68-1.61 (1H, m), 1.56-1.35 (4H, m), 1.33-1.14 (4H, m), 1.06 (3H, d, J = 6.7 Hz), 0.64-0.58 (4H, m).	516	514
293			¹ H-NMR (DMSO-D ₆) δ: 11.31 (1H, s), 9.77 (1H, s), 8.79 (1H, d, J = 8.6 Hz), 8.01 (1H, d, J = 1.6 Hz), 7.97 (1H, d, J = 8.6 Hz), 7.85 (1H, dd, J = 8.4, 1.9 Hz), 4.16-4.05 (1H, m), 2.19-2.06 (2H, m), 1.72-1.64 (1H, m), 1.63-1.18 (8H, m), 1.12 (3H, d, J = 6.5 Hz).	501	499
294			¹ H-NMR (DMSO-D ₆) δ: 11.27 (1H, s), 8.67-8.60 (1H, m), 8.43 (1H, d, J = 9.2 Hz), 7.88 (1H, d, J = 8.6 Hz), 7.56 (1H, d, J = 2.7 Hz), 7.48-7.42 (1H, m), 3.96-3.85 (1H, m), 2.63 (3H, d, J = 4.8 Hz), 2.19-2.08 (2H, m), 1.69-1.62 (1H, m), 1.59-1.12 (8H, m), 1.05 (3H, d, J = 6.5 Hz).	549	547
295			¹ H-NMR (DMSO-D ₆) δ: 11.27 (1H, s), 8.69 (1H, d, J = 5.4 Hz), 8.43 (1H, d, J = 9.2 Hz), 7.88 (1H, d, J = 8.6 Hz), 7.56 (1H, d, J = 2.7 Hz), 7.48-7.42 (1H, m), 3.95-3.83 (1H, m), 2.76-2.70 (1H, m), 2.18-2.07 (2H, m), 1.69-1.60 (1H, m), 1.60-1.12 (8H, m), 1.05 (3H, d, J = 6.5 Hz), 0.66-0.53 (4H, m).	575	573
296			¹ H-NMR (DMSO-D ₆) δ: 11.18 (1H, s), 8.67-8.59 (1H, m), 8.43 (1H, d, J = 9.2 Hz), 7.66 (1H, d, J = 9.2 Hz), 7.13-7.08 (2H, m), 4.90-4.77 (2H, m), 3.97-3.85 (1H, m), 2.63 (3H, d, J = 4.8 Hz), 2.19-2.08 (2H, m), 1.69-1.60 (1H, m), 1.59-1.14 (8H, m), 1.05 (3H, d, J = 6.5 Hz).	563	561

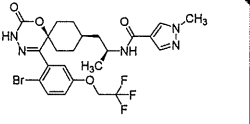
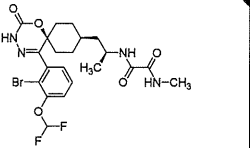
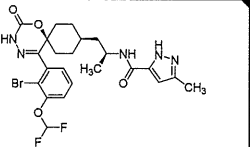
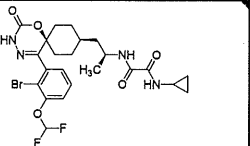
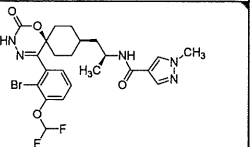
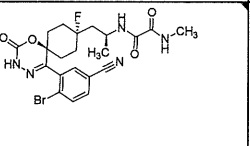
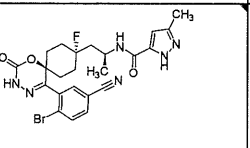
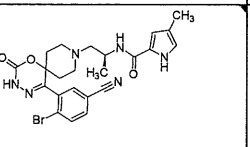
[0605]

Table 1-38

297			¹ H-NMR (DMSO-D ₆) δ: 11.18 (1H, s), 8.69 (1H, d, J = 5.4 Hz), 8.43 (1H, d, J = 9.2 Hz), 7.69-7.64 (1H, m), 7.13-7.07 (2H, m), 4.91-4.77 (2H, m), 3.97-3.83 (1H, m), 2.78-2.68 (1H, m), 2.18-2.07 (2H, m), 1.69-1.61 (1H, m), 1.59-1.14 (8H, m), 1.05 (3H, d, J = 6.5 Hz), 0.66-0.53 (4H, m).	589	587
298			¹ H-NMR (DMSO-D ₆) δ: 12.80 (1H, s), 11.18 (1H, s), 7.65 (1H, d, J = 8.1 Hz), 7.60 (1H, d, J = 8.1 Hz), 7.12-7.06 (2H, m), 6.30 (1H, s), 4.88-4.76 (2H, m), 4.13-4.00 (1H, m), 2.23 (3H, s), 2.19-2.08 (2H, m), 1.73-1.63 (1H, m), 1.57-1.17 (8H, m), 1.07 (3H, d, J = 6.5 Hz).	586	584
299			¹ H-NMR (DMSO-D ₆) δ: 11.21 (1H, s), 8.64-8.58 (1H, m), 8.39 (1H, d, J = 9.0 Hz), 7.91 (1H, s), 7.80 (2H, s), 7.75 (1H, s), 3.95-3.86 (1H, m), 2.63 (3H, d, J = 4.8 Hz), 2.17 (2H, d, J = 13.0 Hz), 1.71-1.64 (1H, m), 1.55-1.15 (8H, m), 1.38 (9H, s), 1.06 (3H, d, J = 6.5 Hz).	564	562
300			¹ H-NMR (DMSO-D ₆) δ: 11.35 (1H, s), 8.64-8.58 (1H, m), 8.35 (1H, d, J = 8.5 Hz), 8.07 (1H, d, J = 2.0 Hz), 8.00 (1H, d, J = 8.5 Hz), 7.88 (1H, dd, J = 8.3, 2.0 Hz), 3.99-3.87 (1H, m), 2.75-2.60 (2H, m), 2.64 (3H, d, J = 5.0 Hz), 2.43 (1H, dd, J = 12.6, 8.1 Hz), 2.35-2.20 (3H, m), 2.14-2.03 (2H, m), 1.75-1.48 (2H, m), 1.05 (3H, d, J = 6.8 Hz).	491	489
301			¹ H-NMR (DMSO-D ₆) δ: 12.79 (1H, s), 11.34 (1H, s), 8.06 (1H, d, J = 1.8 Hz), 7.99 (1H, d, J = 8.3 Hz), 7.87 (1H, dd, J = 8.3, 2.0 Hz), 7.60-7.50 (1H, m), 6.28 (1H, s), 4.15-3.99 (1H, m), 2.70 (2H, t, J = 11.6 Hz), 2.43 (1H, dd, J = 12.3, 7.8 Hz), 2.35-2.15 (6H, m), 2.09 (2H, d, J = 12.8 Hz), 1.69-1.54 (2H, m), 1.07 (3H, d, J = 6.5 Hz).	514	512
302			¹ H-NMR (DMSO-D ₆) δ: 11.46-11.09 (2H, m), 8.06 (1H, d, J = 1.8 Hz), 7.99 (1H, d, J = 8.3 Hz), 7.87 (1H, dd, J = 8.4, 1.9 Hz), 7.64 (1H, d, J = 8.3 Hz), 6.74-6.71 (1H, m), 6.57 (1H, s), 4.12-4.02 (1H, m), 2.77-2.63 (2H, m), 2.39 (1H, dd, J = 12.4, 7.1 Hz), 2.35-2.21 (3H, m), 2.14-2.04 (2H, m), 1.72-1.56 (2H, m), 1.07 (3H, d, J = 6.5 Hz).	517	515
303			¹ H-NMR (DMSO-D ₆) δ: 11.27 (1H, s), 8.05 (1H, s), 7.87 (1H, m), 7.77 (1H, s), 7.65 (1H, m), 7.56 (1H, m), 7.44 (1H, m), 4.04 (1H, s), 3.81 (3H, s), 2.14 (2H, d, J = 12.4 Hz), 1.67 (1H, d, J = 8.6 Hz), 1.52-1.24 (8H, m), 1.06 (3H, d, J = 6.5 Hz).	572	570
304			¹ H-NMR (DMSO-D ₆) δ: 12.80 (1H, s), 11.27 (1H, s), 7.87 (1H, m), 7.60 (1H, d, J = 9.2 Hz), 7.55 (1H, m), 7.43 (1H, d, J = 9.2 Hz), 6.29 (1H, s), 4.05-4.03 (1H, m), 2.23 (3H, s), 2.14 (2H, d, J = 12.4 Hz), 1.70 (1H, s), 1.51-1.25 (8H, m), 1.07 (3H, d, J = 5.9 Hz).	572	570

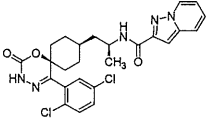
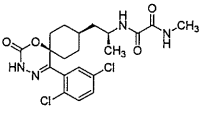
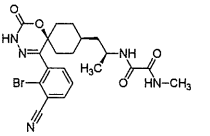
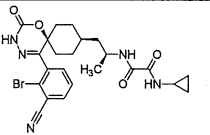
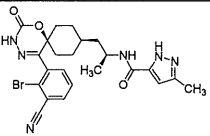
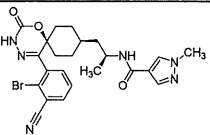
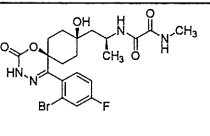
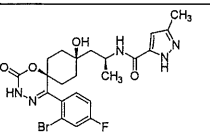
[0606]

Table 1-39

305		1H-NMR (DMSO-D6) δ : 11.18 (1H, s), 8.05 (1H, s), 7.78 (1H, s), 7.67 (1H, s), 7.64 (1H, s), 7.11-7.08 (2H, m), 4.82 (2H, q, J = 8.8 Hz), 4.09-3.96 (1H, m), 3.81 (3H, s), 2.14 (2H, d, J = 11.9 Hz), 1.67 (1H, d, J = 9.7 Hz), 1.51-1.24 (8H, m), 1.06 (3H, d, J = 6.5 Hz).	586	584
306		1H-NMR (DMSO-D6) δ : 11.23 (1H, s), 8.64 (1H, q, J = 4.7 Hz), 8.43 (1H, d, J = 9.2 Hz), 7.51 (1H, t, J = 7.8 Hz), 7.40 (1H, d, J = 8.1 Hz), 7.33 (1H, t, J = 73.8 Hz), 7.32 (1H, d, J = 6.5 Hz), 3.91-3.88 (1H, m), 2.63 (3H, d, J = 4.8 Hz), 2.13 (2H, d, J = 11.9 Hz), 1.64 (1H, s), 1.55-1.17 (8H, m), 1.05 (3H, d, J = 6.5 Hz).	531	529
307		1H-NMR (DMSO-D6) δ : 12.81 (1H, s), 11.22 (1H, s), 7.61 (1H, d, J = 8.6 Hz), 7.51-7.48 (1H, m), 7.38 (1H, d, J = 8.1 Hz), 7.32 (1H, t, J = 73.3 Hz), 7.31 (1H, d, J = 7.3 Hz), 6.30 (1H, s), 4.05 (1H, m), 2.23 (3H, s), 2.13 (2H, d, J = 15.6 Hz), 1.69 (1H, s), 1.49-1.24 (8H, m), 1.07 (3H, d, J = 6.5 Hz).	554	552
308		1H-NMR (DMSO-D6) δ : 11.23 (1H, s), 8.69 (1H, d, J = 5.4 Hz), 8.42 (1H, d, J = 9.2 Hz), 7.52 (1H, t, J = 8.1 Hz), 7.41 (1H, d, J = 8.1 Hz), 7.33 (1H, t, J = 73.3 Hz), 7.32 (1H, d, J = 7.5 Hz), 3.89 (1H, s), 2.74-2.72 (1H, m), 2.13 (2H, d, J = 10.8 Hz), 1.65 (1H, d, J = 7.0 Hz), 1.54-1.20 (8H, m), 1.05 (3H, d, J = 6.5 Hz), 0.62-0.60 (4H, m).	557	555
309		1H-NMR (DMSO-D6) δ : 11.23 (1H, s), 8.05 (1H, s), 7.78 (1H, s), 7.65 (1H, d, J = 8.6 Hz), 7.52-7.48 (1H, m), 7.39 (1H, d, J = 8.6 Hz), 7.32 (1H, t, J = 73.3 Hz), 7.31 (1H, d, J = 3.2 Hz), 4.05-4.01 (1H, m), 3.81 (3H, s), 2.13 (2H, d, J = 9.7 Hz), 1.68 (1H, s), 1.52-1.25 (8H, m), 1.05 (3H, d, J = 6.5 Hz).	554	552
310		1H-NMR (DMSO-D6) δ : 11.40 (1H, s), 8.64 (1H, q, J = 4.8 Hz), 8.61 (1H, d, J = 8.6 Hz), 8.10 (1H, s), 8.01 (1H, d, J = 8.6 Hz), 7.88 (1H, d, J = 8.6 Hz), 4.16-4.01 (1H, m), 2.65 (3H, d, J = 4.8 Hz), 2.16-1.98 (3H, m), 1.86-1.56 (7H, m), 1.08 (3H, d, J = 6.5 Hz).	508	506
311		1H-NMR (DMSO-D6) δ : 12.82 (1H, s), 11.39 (1H, s), 8.09 (1H, s), 8.00 (1H, d, J = 8.6 Hz), 7.87 (1H, d, J = 8.6 Hz), 7.81 (1H, d, J = 8.6 Hz), 6.32 (1H, s), 4.30-4.15 (1H, m), 2.24 (3H, s), 2.15-1.97 (3H, m), 1.89-1.56 (7H, m), 1.11 (3H, d, J = 6.5 Hz).	531	529
312		1H-NMR (DMSO-D6) δ : 11.35 (1H, br s), 10.95 (1H, s), 8.06 (1H, d, J = 1.8 Hz), 7.99 (1H, d, J = 8.3 Hz), 7.87 (1H, dd, J = 8.3, 2.0 Hz), 7.46 (1H, d, J = 8.3 Hz), 6.58 (1H, s), 6.52 (1H, s), 4.11-4.02 (1H, m), 2.78-2.68 (2H, m), 2.40 (1H, dd, J = 12.3, 7.3 Hz), 2.32-2.22 (3H, m), 2.14-2.04 (2H, m), 1.99 (3H, s), 1.73-1.53 (2H, m), 1.06 (3H, d, J = 6.5 Hz).	513	511

[0607]

Table 1-40

313			¹ H-NMR (DMSO-D ₆) δ: 11.24 (1H, s), 8.64 (1H, d, J = 7.2 Hz), 8.07 (1H, d, J = 9.0 Hz), 7.75 (1H, d, J = 9.0 Hz), 7.61-7.57 (2H, m), 7.53 (1H, dd, J = 9.0, 2.4 Hz), 7.27 (1H, dd, J = 9.0, 6.8 Hz), 7.01 (1H, t, J = 6.8 Hz), 6.94 (1H, s), 4.19-4.10 (1H, m), 2.17-2.07 (2H, m), 1.77-1.68 (1H, m), 1.63-1.21 (8H, m), 1.13 (3H, d, J = 6.7 Hz).	514	512
314			¹ H-NMR (DMSO-D ₆) δ: 11.24 (1H, s), 8.64 (1H, q, J = 4.9 Hz), 8.42 (1H, d, J = 9.2 Hz), 7.65-7.55 (3H, m), 3.95-3.86 (1H, m), 2.64 (3H, d, J = 4.9 Hz), 2.16-2.06 (2H, m), 1.71-1.61 (1H, m), 1.57-1.13 (8H, m), 1.06 (3H, d, J = 6.5 Hz).	455	453
315			¹ H-NMR (DMSO-D ₆) δ: 11.32 (1H, s), 8.64 (1H, q, J = 4.8 Hz), 8.43 (1H, d, J = 8.6 Hz), 8.03 (1H, dd, J = 7.8, 1.3 Hz), 7.79 (1H, dd, J = 7.8, 1.3 Hz), 7.65 (1H, t, J = 7.8 Hz), 3.90-3.90 (1H, m), 2.63 (3H, d, J = 4.8 Hz), 2.12 (2H, d, J = 11.9 Hz), 1.64 (1H, s), 1.53-1.21 (8H, m), 1.05 (3H, d, J = 6.5 Hz).	490	488
316			¹ H-NMR (DMSO-D ₆) δ: 11.32 (1H, s), 8.69 (1H, d, J = 5.4 Hz), 8.43 (1H, d, J = 9.2 Hz), 8.04 (1H, dd, J = 7.8, 1.3 Hz), 7.79 (1H, dd, J = 7.8, 1.3 Hz), 7.66 (1H, t, J = 7.8 Hz), 3.90-3.89 (1H, m), 2.75-2.72 (1H, m), 2.11 (2H, d, J = 9.2 Hz), 1.64 (1H, s), 1.55-1.21 (8H, m), 1.05 (3H, d, J = 6.5 Hz), 0.63-0.60 (4H, m).	516	514
317			¹ H-NMR (DMSO-D ₆) δ: 12.81 (1H, s), 11.31 (1H, s), 8.01 (1H, dd, J = 7.8, 1.3 Hz), 7.78 (1H, dd, J = 7.8, 1.3 Hz), 7.63 (1H, br s), 7.61 (1H, s), 6.31 (1H, br s), 4.07-4.05 (1H, m), 2.22 (3H, s), 2.12 (2H, s), 1.69 (1H, d, J = 8.1 Hz), 1.49-1.26 (8H, m), 1.07 (3H, d, J = 6.5 Hz).	513	511
318			¹ H-NMR (DMSO-D ₆) δ: 11.32 (1H, s), 8.05 (1H, s), 8.02 (1H, m), 7.80-7.78 (2H, m), 7.67-7.61 (2H, m), 4.04-4.02 (1H, m), 3.81 (3H, s), 2.13 (2H, d, J = 11.9 Hz), 1.67 (1H, d, J = 9.2 Hz), 1.52-1.23 (8H, m), 1.05 (3H, d, J = 6.5 Hz).	513	511
319			¹ H-NMR (DMSO-D ₆) δ: 11.25 (1H, s), 8.62 (1H, q, J = 4.8 Hz), 8.55 (1H, d, J = 8.1 Hz), 7.74 (1H, dd, J = 8.6, 2.7 Hz), 7.53 (1H, dd, J = 8.6, 5.9 Hz), 7.35 (1H, td, J = 8.6, 2.7 Hz), 4.57 (1H, s), 3.96-3.81 (1H, m), 2.66 (3H, d, J = 4.8 Hz), 2.11-1.94 (2H, m), 1.76-1.29 (8H, m), 1.08 (3H, d, J = 6.5 Hz).	499	497
320			¹ H-NMR (DMSO-D ₆) δ: 12.81 (1H, s), 11.24 (1H, s), 7.90-7.79 (1H, m), 7.74 (1H, d, J = 8.1 Hz), 7.59-7.48 (1H, m), 7.39-7.26 (1H, m), 6.29 (1H, s), 4.59 (1H, s), 4.07-3.93 (1H, m), 2.25 (3H, s), 2.11-1.94 (2H, m), 1.78-1.28 (8H, m), 1.12 (3H, d, J = 5.9 Hz).	522	520

[0608]

Table 1-41

321			¹ H-NMR (DMSO-D ₆) δ: 11.20 (1H, s), 8.63 (1H, q, J = 4.8 Hz), 8.56 (1H, d, J = 7.5 Hz), 7.75 (1H, dd, J = 8.6, 2.7 Hz), 7.52 (1H, dd, J = 8.6, 5.9 Hz), 7.37 (1H, ddd, J = 8.6, 8.1, 2.7 Hz), 4.17 (1H, s), 4.10-3.94 (1H, m), 2.65 (3H, d, J = 4.8 Hz), 1.97-1.85 (2H, m), 1.85-1.66 (3H, m), 1.63-1.33 (5H, m), 1.08 (3H, d, J = 5.9 Hz).	499	497
322			¹ H-NMR (DMSO-D ₆) δ: 12.80 (1H, s), 11.18 (1H, s), 7.85 (1H, d, J = 7.5 Hz), 7.74 (1H, dd, J = 8.6, 2.7 Hz), 7.51 (1H, dd, J = 8.6, 5.9 Hz), 7.37 (1H, ddd, J = 8.6, 8.1, 2.7 Hz), 6.31 (1H, s), 4.25-4.08 (1H, m), 4.21 (1H, s), 2.24 (3H, s), 1.97-1.82 (2H, m), 1.82-1.66 (3H, m), 1.66-1.34 (5H, m), 1.12 (3H, d, J = 6.5 Hz).	522	520
323			¹ H-NMR (DMSO-D ₆) δ: 11.24 (1H, s), 8.22 (1H, dd, J = 7.0, 1.0 Hz), 7.91 (1H, d, J = 1.4 Hz), 7.81 (1H, d, J = 8.4 Hz), 7.61-7.57 (2H, m), 7.53 (1H, dd, J = 8.4, 2.4 Hz), 7.40 (1H, d, J = 9.2 Hz), 6.76 (1H, s), 6.70 (1H, ddd, J = 9.2, 6.5, 1.0 Hz), 6.57 (1H, td, J = 6.5, 1.4 Hz), 4.15-4.05 (1H, m), 2.17-2.08 (2H, m), 1.74-1.66 (1H, m), 1.58-1.21 (8H, m), 1.10 (3H, d, J = 6.5 Hz).	513	511
324			¹ H-NMR (DMSO-D ₆) δ: 11.24 (1H, s), 8.55 (1H, dt, J = 6.9, 1.1 Hz), 8.31 (1H, d, J = 0.6 Hz), 7.97 (1H, d, J = 9.0 Hz), 7.61-7.51 (4H, m), 7.32 (1H, ddd, J = 9.0, 6.9, 1.1 Hz), 6.96 (1H, td, J = 6.9, 1.1 Hz), 4.18-4.08 (1H, m), 2.17-2.07 (2H, m), 1.76-1.68 (1H, m), 1.63-1.20 (8H, m), 1.13 (3H, d, J = 6.7 Hz).	514	512
325			¹ H-NMR (DMSO-D ₆) δ: 11.30 (1H, s), 8.06 (1H, s), 8.00 (1H, d, J = 1.8 Hz), 7.97 (1H, d, J = 8.3 Hz), 7.85 (1H, dd, J = 8.3, 2.1 Hz), 7.78 (1H, d, J = 0.7 Hz), 7.66 (1H, d, J = 8.3 Hz), 4.10-3.96 (1H, m), 3.82 (3H, s), 2.18-2.05 (2H, m), 1.72-1.61 (1H, m), 1.59-1.16 (8H, m), 1.06 (3H, d, J = 6.5 Hz).	513	511
326			¹ H-NMR (DMSO-D ₆) δ: 12.80 (1H, s), 11.43 (1H, s), 8.47 (1H, s), 8.23 (1H, d, J = 7.8 Hz), 7.87 (1H, d, J = 7.8 Hz), 7.62-7.54 (1H, m), 6.30 (1H, s), 4.11-4.01 (1H, m), 2.77-2.66 (2H, m), 2.53-2.37 (1H, m), 2.36-2.16 (6H, m), 2.04-1.88 (2H, m), 1.71-1.53 (2H, m), 1.08 (3H, d, J = 6.5 Hz).	504	502
327			¹ H-NMR (DMSO-D ₆) δ: 11.43 (1H, s), 8.66-8.59 (1H, m), 8.48 (1H, s), 8.35 (1H, d, J = 8.5 Hz), 8.25 (1H, d, J = 8.0 Hz), 7.89 (1H, d, J = 8.0 Hz), 3.99-3.87 (1H, m), 2.76-2.61 (2H, m), 2.65 (3H, d, J = 4.8 Hz), 2.44 (1H, dd, J = 12.5, 8.0 Hz), 2.36-2.20 (3H, m), 2.03-1.90 (2H, m), 1.72-1.52 (2H, m), 1.05 (3H, d, J = 6.5 Hz).	481	479
328			¹ H-NMR (DMSO-D ₆) δ: 11.34 (1H, s), 8.67-8.59 (1H, m), 8.35 (1H, d, J = 8.3 Hz), 8.09 (1H, s), 7.99 (1H, d, J = 8.3 Hz), 7.60 (1H, d, J = 8.3 Hz), 3.99-3.85 (1H, m), 2.74-2.60 (2H, m), 2.65 (3H, d, J = 4.8 Hz), 2.43 (1H, dd, J = 12.6, 7.9 Hz), 2.35-2.20 (3H, m), 2.01-1.84 (2H, m), 1.70-1.53 (2H, m), 1.05 (3H, d, J = 6.5 Hz).	534	532

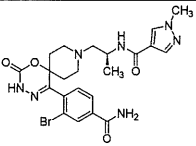
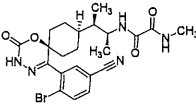
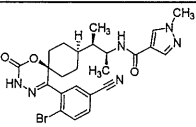
[0609]

Table 1-42

329			¹ H-NMR (DMSO-D ₆) δ: 11.35 (1H, s), 8.66-8.59 (1H, m), 8.41-8.35 (2H, m), 7.97 (1H, dd, J = 7.9, 1.4 Hz), 7.70 (1H, d, J = 8.0 Hz), 3.17-3.00 (2H, m), 2.73 (1H, q, J = 7.5 Hz), 2.68-2.58 (3H, m), 2.65 (3H, d, J = 4.8 Hz), 2.41 (1H, t, J = 11.5 Hz), 2.16-2.06 (2H, m), 1.64-1.47 (2H, m), 0.87 (3H, d, J = 6.8 Hz).	491	489
330			¹ H-NMR (DMSO-D ₆) δ: 11.35 (1H, s), 8.66-8.59 (1H, m), 8.41-8.35 (2H, m), 7.97 (1H, dd, J = 7.9, 1.4 Hz), 7.70 (1H, d, J = 8.0 Hz), 3.17-3.00 (2H, m), 2.73 (1H, q, J = 7.5 Hz), 2.68-2.58 (3H, m), 2.65 (3H, d, J = 4.8 Hz), 2.41 (1H, t, J = 11.5 Hz), 2.16-2.06 (2H, m), 1.64-1.47 (2H, m), 0.87 (3H, d, J = 6.8 Hz).	491	489
331			¹ H-NMR (DMSO-D ₆) δ: 12.82 (1H, br s), 11.29 (1H, br s), 8.08 (1H, d, J = 1.8 Hz), 7.97 (1H, dd, J = 8.5, 1.5 Hz), 7.66-7.55 (1H, m), 7.58 (1H, d, J = 8.5 Hz), 6.34 (1H, s), 4.11-4.01 (1H, m), 2.75-2.65 (2H, m), 2.43 (1H, dd, J = 12.9, 7.6 Hz), 2.35-2.24 (3H, m), 2.24 (3H, s), 2.02-1.86 (2H, m), 1.70-1.54 (2H, m), 1.08 (3H, d, J = 6.5 Hz).	557	555
332			¹ H-NMR (DMSO-D ₆) δ: 12.77 (1H, s), 11.35 (1H, s), 8.37 (1H, s), 7.97 (1H, d, J = 7.8 Hz), 7.68 (2H, d, J = 8.0 Hz), 6.28 (1H, s), 2.80-2.38 (7H, m), 2.25 (3H, s), 2.11 (2H, d, J = 13.3 Hz), 1.65-1.48 (2H, m), 0.90 (3H, d, J = 6.5 Hz).	514	512
333			¹ H-NMR (CDCl ₃) δ: 8.17 (1H, s), 7.47-7.37 (3H, m), 7.24-7.20 (1H, m), 7.13 (1H, td, J = 8.2, 2.5 Hz), 4.00-3.93 (1H, m), 2.89 (3H, d, J = 5.5 Hz), 2.75-2.68 (1H, m), 2.67-2.61 (2H, m), 2.47 (1H, td, J = 12.1, 2.9 Hz), 2.25-2.16 (2H, m), 1.82-1.65 (2H, m), 1.18 (3H, d, J = 6.1 Hz).	486	484
334			¹ H-NMR (DMSO-D ₆) δ: 11.26 (1H, s), 8.05 (1H, s), 7.77-7.72 (2H, m), 7.65 (1H, d, J = 8.3 Hz), 7.54 (1H, dd, J = 8.6, 6.0 Hz), 7.35 (1H, td, J = 8.5, 2.6 Hz), 4.08-4.00 (1H, m), 3.82 (3H, s), 2.74-2.65 (2H, m), 2.35-2.23 (2H, m), 2.12-2.02 (2H, m), 1.64-1.51 (2H, m), 1.05 (3H, d, J = 6.7 Hz).	509	507
335			¹ H-NMR (DMSO-D ₆) δ: 12.77 (1H, s), 11.35 (1H, s), 8.37 (1H, s), 7.97 (1H, d, J = 7.8 Hz), 7.68 (2H, d, J = 8.0 Hz), 6.28 (1H, s), 2.80-2.38 (7H, m), 2.25 (3H, s), 2.11 (2H, d, J = 13.3 Hz), 1.65-1.48 (2H, m), 0.90 (3H, d, J = 6.5 Hz).	514	512
336			¹ H-NMR (DMSO-D ₆) δ: 11.36 (1H, s), 8.36 (1H, s), 8.04 (1H, s), 7.95 (1H, d, J = 8.0 Hz), 7.76 (1H, s), 7.69 (1H, d, J = 7.8 Hz), 7.63 (1H, d, J = 8.0 Hz), 4.13-4.00 (1H, m), 3.83 (3H, s), 2.75-2.65 (2H, m), 2.42-2.20 (4H, m), 2.14-2.05 (2H, m), 1.63-1.51 (2H, m), 1.05 (3H, d, J = 6.8 Hz).	514	512

[0610]

Table 1-43

337			¹ H-NMR (DMSO-D ₆) δ: 11.27 (1H, s), 8.19 (1H, s), 8.15 (1H, s), 8.03 (1H, s), 7.92 (1H, dd, J = 8.0, 1.3 Hz), 7.76 (1H, s), 7.66-7.53 (3H, m), 4.10-3.98 (1H, m), 3.82 (3H, s), 2.74-2.65 (2H, m), 2.41-2.20 (4H, m), 2.14-2.05 (2H, m), 1.65-1.53 (2H, m), 1.06-1.02 (3H, m).	532	530
338			¹ H-NMR (DMSO-D ₆) δ: 11.30 (1H, s), 8.67-8.61 (1H, m), 8.43 (1H, d, J = 9.2 Hz), 8.04-7.97 (2H, m), 7.89-7.85 (1H, m), 3.85-3.75 (1H, m), 2.65 (3H, d, J = 4.3 Hz), 2.24-2.06 (2H, m), 1.59-1.21 (8H, m), 1.02 (3H, d, J = 6.5 Hz), 0.77 (3H, d, J = 7.0 Hz).	504	502
339			¹ H-NMR (DMSO-D ₆) δ: 11.30 (1H, s), 8.07 (1H, s), 8.03-7.96 (2H, m), 7.88-7.83 (1H, m), 7.80 (1H, s), 7.68 (1H, d, J = 8.1 Hz), 4.06-3.97 (1H, m), 3.82 (3H, s), 2.23-2.09 (2H, m), 1.61-1.21 (8H, m), 1.00 (3H, d, J = 7.0 Hz), 0.80 (3H, d, J = 7.0 Hz).	527	525

[0611]

Table 1-44

2-001			¹ H-NMR (DMSO-D ₆) δ: 11.35 (1H, s), 8.58 (1H, s), 8.35 (1H, d, J = 8.8 Hz), 8.07 (1H, d, J = 2.0 Hz), 8.00 (1H, d, J = 8.5 Hz), 7.88 (1H, dd, J = 8.4, 1.9 Hz), 3.99-3.86 (1H, m), 2.75-2.60 (2H, m), 2.43 (1H, dd, J = 12.4, 8.1 Hz), 2.34-2.20 (3H, m), 2.13-2.02 (2H, m), 1.72-1.48 (2H, m), 1.05 (3H, d, J = 6.5 Hz).	494	492
2-002			¹ H-NMR (DMSO-D ₆) δ: 11.35 (2H, s), 8.07 (1H, d, J = 1.8 Hz), 8.00 (1H, d, J = 8.3 Hz), 7.88 (1H, dd, J = 8.4, 1.9 Hz), 7.81 (1H, d, J = 7.8 Hz), 6.31 (1H, s), 4.34-4.22 (1H, m), 3.96-3.83 (1H, m), 2.73-2.63 (2H, m), 2.36-2.22 (4H, m), 2.18 (1H, dd, J = 12.4, 7.1 Hz), 2.14-2.04 (2H, m), 1.72-1.58 (2H, m), 0.99 (3H, d, J = 6.8 Hz).	546	544
2-003			¹ H-NMR (DMSO-D ₆) δ: 11.35 (1H, s), 8.29 (1H, d, J = 7.8 Hz), 8.08 (1H, d, J = 1.8 Hz), 8.00 (1H, d, J = 8.3 Hz), 7.88 (1H, dd, J = 8.4, 1.9 Hz), 6.72-6.69 (2H, m), 4.02-3.90 (1H, m), 2.74-2.63 (2H, m), 2.37-2.20 (4H, m), 2.14-2.05 (2H, m), 1.69-1.55 (2H, m), 1.04 (3H, d, J = 6.5 Hz).	528	526
2-004			¹ H-NMR (DMSO-D ₆) δ: 11.36 (1H, s), 8.59 (1H, s), 8.35 (1H, d, J = 8.3 Hz), 8.19 (1H, d, J = 6.8 Hz), 8.15 (1H, d, J = 9.3 Hz), 4.00-3.89 (1H, m), 2.75-2.60 (3H, m), 2.49-2.40 (1H, m), 2.34-2.20 (2H, m), 2.13-2.00 (2H, m), 1.81-1.59 (2H, m), 1.05 (3H, d, J = 6.5 Hz).	512	510
2-005		mixture of two stereoisomers	¹ H-NMR (DMSO-D ₆) δ: 11.33 (1H, s), 8.67 (1H, d, J = 4.9 Hz), 8.37 (1H, d, J = 7.9 Hz), 7.75 (1H, dd, J = 8.4, 2.4 Hz), 7.60 (1H, dd, J = 8.6, 5.8 Hz), 7.39 (1H, td, J = 8.4, 2.6 Hz), 3.81-3.74 (1H, m), 3.09 (1H, br s), 2.92-2.80 (2H, br m), 2.66 (3H, d, J = 5.1 Hz), 2.59-2.47 (4H, m), 1.99 (1H, br s), 1.80 (1H, br s), 1.64-1.62 (1H, br m), 1.09-1.07 (3H, m).	496	494
2-006			¹ H-NMR (DMSO-D ₆) δ: 11.35 (1H, s), 8.64-8.58 (1H, m), 8.35 (1H, d, J = 8.5 Hz), 8.11 (1H, d, J = 2.0 Hz), 7.99 (1H, dd, J = 8.4, 1.9 Hz), 7.84 (1H, d, J = 8.3 Hz), 3.98-3.86 (1H, m), 2.75-2.60 (2H, m), 2.64 (3H, d, J = 6.5 Hz), 2.43 (1H, dd, J = 12.4, 8.1 Hz), 2.36-2.18 (3H, m), 2.15-1.98 (2H, m), 1.68-1.49 (2H, m), 1.05 (3H, d, J = 6.5 Hz).	447	445
2-007			¹ H-NMR (DMSO-D ₆) δ: 12.78 (1H, s), 11.35 (1H, s), 8.10 (1H, d, J = 2.0 Hz), 7.98 (1H, dd, J = 8.3, 2.0 Hz), 7.83 (1H, d, J = 8.5 Hz), 7.55 (1H, d, J = 8.3 Hz), 6.28 (1H, s), 4.13-4.01 (1H, m), 2.76-2.64 (2H, m), 2.42 (1H, dd, J = 12.3, 7.5 Hz), 2.34-2.26 (3H, m), 2.23 (3H, s), 2.12-2.02 (2H, m), 1.68-1.49 (2H, m), 1.07 (3H, d, J = 6.5 Hz).	470	468
2-008			¹ H-NMR (DMSO) δ: 11.35 (1H, s), 8.58 (1H, s), 8.34 (1H, d, J = 8.8 Hz), 8.11 (1H, d, J = 1.8 Hz), 7.99 (1H, dd, J = 8.5, 2.0 Hz), 7.84 (1H, d, J = 8.5 Hz), 3.96-3.88 (1H, m), 2.75-2.59 (2H, m), 2.43 (1H, dd, J = 12.6, 8.1 Hz), 2.34-2.19 (3H, m), 2.12-2.01 (2H, m), 1.69-1.48 (2H, m), 1.05 (3H, d, J = 6.5 Hz).	450	448
2-009			¹ H-NMR (DMSO-D ₆) δ: 11.33 (1H, s), 8.05 (1H, d, J = 1.8 Hz), 7.99 (1H, dd, J = 8.3, 2.0 Hz), 7.84 (1H, d, J = 8.3 Hz), 7.77 (1H, d, J = 8.8 Hz), 7.05 (1H, d, J = 6.8 Hz), 4.44-4.34 (1H, m), 4.03-3.92 (1H, m), 2.75-2.66 (1H, m), 2.63-2.55 (1H, m), 2.38-1.98 (6H, m), 1.67-1.42 (2H, m), 1.01 (3H, d, J = 6.8 Hz).	488	486
2-010		mixture of two diastereomers	¹ H-NMR (DMSO-D ₆) δ: 11.34 (0.5H, s), 11.31 (0.5H, s), 8.93 (0.5H, d, J = 9.7 Hz), 8.77 (0.5H, q, J = 4.9 Hz), 8.65 (0.5H, q, J = 4.9 Hz), 8.52 (0.5H, d, J = 9.5 Hz), 7.78-7.74 (1H, m), 7.58 (0.5H, dd, J = 8.6, 6.0 Hz), 7.49 (0.5H, dd, J = 8.6, 6.0 Hz), 7.41-7.31 (1H, m), 4.21-4.09 (1H, m), 3.84 (1H, t, J = 10.6 Hz), 2.80-2.54 (6H, m), 2.41-2.30 (1H, m), 2.18-2.07 (2H, m), 1.75-1.60 (1H, m), 1.58-1.40 (1H, m), 1.24 (1.5H, d, J = 6.7 Hz), 1.07 (1.5H, d, J = 6.7 Hz).	509	507

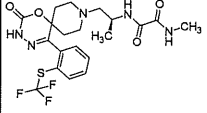
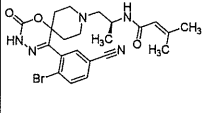
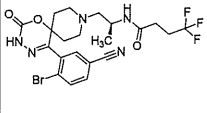
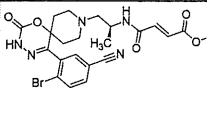
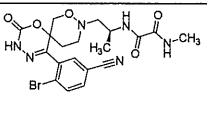
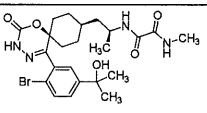
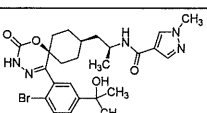
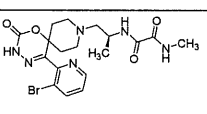
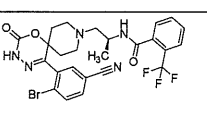
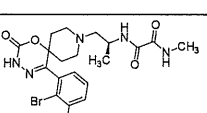
[0612]

Table 1-45

2-011			¹ H-NMR (DMSO-D ₆) δ: 11.26 (1H, s), 8.63 (1H, d, J = 4.9 Hz), 8.36 (1H, d, J = 8.8 Hz), 7.75 (1H, dd, J = 8.6, 2.5 Hz), 7.54 (1H, dd, J = 8.6, 6.0 Hz), 7.36 (1H, td, J = 8.5, 2.6 Hz), 3.96-3.89 (1H, m), 2.72-2.59 (6H, m), 2.44-2.20 (3H, m), 2.10-2.03 (2H, m), 1.59-1.52 (2H, m), 1.04 (3H, d, J = 6.7 Hz).	484	482
2-012			¹ H-NMR (DMSO-D ₆) δ: 12.80 (1H, s), 11.25 (1H, s), 7.74 (1H, dd, J = 8.6, 2.5 Hz), 7.59-7.51 (2H, m), 7.35 (1H, td, J = 8.4, 2.8 Hz), 6.29 (1H, s), 4.11-4.02 (1H, m), 2.75-2.65 (3H, m), 2.46-2.39 (1H, m), 2.33-2.22 (5H, m), 2.11-2.04 (2H, br m), 1.61-1.51 (2H, br m), 1.07 (3H, d, J = 6.5 Hz).	507	505
2-013			¹ H-NMR (DMSO-D ₆) δ: 11.27 (1H, s), 8.69-8.62 (2H, m), 8.48-8.41 (1H, m), 8.26-8.21 (1H, m), 7.47-7.42 (1H, m), 3.97-3.85 (1H, m), 2.65 (3H, d, J = 4.8 Hz), 2.08-2.00 (2H, m), 1.69-1.44 (5H, m), 1.34-1.14 (4H, m), 1.06 (3H, d, J = 6.5 Hz).	466	464
2-014			¹ H-NMR (DMSO-D ₆) δ: 11.18 (1H, s), 8.69-8.63 (1H, m), 8.45 (1H, d, J = 9.2 Hz), 7.62 (1H, d, J = 9.2 Hz), 7.04-6.96 (2H, m), 4.65 (1H, s), 3.99-3.89 (1H, m), 3.78 (2H, s), 2.67 (3H, d, J = 4.9 Hz), 2.22-2.14 (2H, m), 1.73-1.17 (15H, m), 1.09 (3H, d, J = 6.7 Hz).	553	551
2-015			¹ H-NMR (DMSO-D ₆) δ: 11.30 (1H, s), 8.65-8.58 (1H, m), 8.35 (1H, d, J = 8.8 Hz), 7.95 (1H, d, J = 7.3 Hz), 7.81 (1H, d, J = 8.5 Hz), 3.98-3.88 (1H, m), 2.76-2.62 (2H, m), 2.64 (3H, d, J = 5.0 Hz), 2.43 (1H, dd, J = 12.5, 8.0 Hz), 2.35-2.18 (3H, m), 2.12-1.98 (2H, m), 1.68-1.49 (2H, m), 1.05 (3H, d, J = 6.5 Hz).	518	516
2-016			¹ H-NMR (DMSO-D ₆) δ: 12.79 (1H, s), 11.30 (1H, s), 7.95 (1H, d, J = 7.3 Hz), 7.80 (1H, d, J = 8.8 Hz), 7.61-7.50 (1H, m), 6.28 (1H, s), 4.12-4.01 (1H, m), 2.76-2.65 (2H, m), 2.45-2.38 (1H, m), 2.34-2.18 (6H, m), 2.10-2.02 (2H, m), 1.65-1.50 (2H, m), 1.07 (3H, d, J = 6.5 Hz).	541	539
2-017			¹ H-NMR (DMSO-D ₆) δ: 11.38 (1H, s), 9.23 (1H, d, J = 9.0 Hz), 8.78 (1H, q, J = 4.9 Hz), 8.07 (1H, d, J = 1.8 Hz), 8.00 (1H, d, J = 8.3 Hz), 7.88 (1H, dd, J = 8.4, 2.0 Hz), 4.65-4.55 (1H, m), 2.95 (1H, dd, J = 13.1, 9.8 Hz), 2.74-2.58 (7H, m), 2.33-2.26 (1H, m), 2.14-2.05 (2H, br m), 1.68-1.47 (2H, br m).	545	543
2-018			¹ H-NMR (DMSO-D ₆) δ: 11.44 (1H, s), 8.67-8.60 (1H, m), 8.37 (1H, d, J = 8.1 Hz), 7.67-7.62 (1H, m), 7.54-7.41 (2H, m), 3.97-3.87 (1H, m), 2.76-2.60 (2H, m), 2.64 (3H, d, J = 4.8 Hz), 2.46-2.02 (6H, m), 1.72-1.46 (2H, m), 1.05 (3H, d, J = 6.5 Hz).	484	N.D.
2-019			¹ H-NMR (DMSO-D ₆) δ: 11.30 (1H, s), 8.66-8.60 (1H, m), 8.42 (1H, d, J = 9.2 Hz), 7.87-7.82 (1H, m), 7.66-7.61 (3H, m), 3.96-3.86 (1H, m), 2.64 (3H, d, J = 4.8 Hz), 2.08-1.99 (2H, m), 1.72-1.11 (9H, m), 1.06 (3H, d, J = 6.5 Hz).	487	485
2-020			¹ H-NMR (DMSO-D ₆) δ: 11.30 (1H, s), 8.06 (1H, s), 7.87-7.81 (1H, m), 7.78 (1H, s), 7.68-7.59 (4H, m), 4.09-3.98 (1H, m), 3.82 (3H, s), 2.09-2.01 (2H, m), 1.73-1.21 (9H, m), 1.06 (3H, d, J = 6.5 Hz).	510	508

[0613]

Table 1-46

2-021			¹ H-NMR (DMSO-D ₆) δ: 11.36 (1H, s), 8.71-8.59 (1H, m), 8.42-8.33 (1H, m), 7.93-7.83 (1H, m), 7.73-7.61 (3H, m), 4.02-3.87 (1H, m), 2.78-2.60 (2H, m), 2.64 (3H, d, J = 4.8 Hz), 2.43-2.19 (4H, m), 2.10-1.95 (2H, m), 1.75-1.54 (2H, m), 1.15-1.01 (3H, m).	488	486
2-022			¹ H-NMR (DMSO-D ₆) δ: 11.34 (1H, s), 8.07 (1H, d, J = 2.0 Hz), 8.01 (1H, d, J = 8.5 Hz), 7.89 (1H, dd, J = 8.3, 2.0 Hz), 7.41 (1H, d, J = 8.3 Hz), 5.56 (1H, s,), 3.96-3.86 (1H, m), 2.76-2.63 (2H, m), 2.34-2.21 (3H, m), 2.19-2.03 (3H, m), 1.98 (3H, s), 1.74 (3H, s), 1.69-1.51 (2H, m), 0.98 (3H, d, J = 6.5 Hz).	488	486
2-023			¹ H-NMR (DMSO-D ₆) δ: 11.34 (1H, s), 8.07 (1H, d, J = 2.0 Hz), 8.01 (1H, d, J = 8.5 Hz), 7.89 (1H, dd, J = 8.3, 2.0 Hz), 7.41 (1H, d, J = 8.3 Hz), 5.56 (1H, s,), 3.96-3.86 (1H, m), 2.76-2.63 (2H, m), 2.34-2.21 (3H, m), 2.19-2.03 (3H, m), 1.98 (3H, s), 1.74 (3H, s), 1.69-1.51 (2H, m), 0.98 (3H, d, J = 6.5 Hz).	530	528
2-024			¹ H-NMR (DMSO-D ₆) δ: 11.35 (1H, s), 8.36 (1H, d, J = 1.5 Hz), 7.95 (1H, dd, J = 8.0, 1.5 Hz), 7.82 (1H, d, J = 8.5 Hz), 7.70-7.66 (2H, m), 7.47 (1H, d, J = 1.0 Hz), 4.13-4.00 (1H, m), 3.73 (3H, s), 3.48-3.40 (1H, m), 2.75-2.65 (2H, m), 2.40-2.22 (3H, m), 2.14-2.03 (2H, m), 1.64-1.48 (2H, m), 1.08-1.03 (3H, m).	518	516
2-025			¹ H-NMR (DMSO-D ₆) δ: 11.47 (1H, s), 8.68-8.60 (1H, m), 8.53-8.48 (0.5H, m), 8.40-8.35 (0.5H, m), 8.13-8.09 (1H, m), 8.04-7.99 (1H, m), 7.93-7.87 (1H, m), 4.24-4.11 (1H, m), 4.10-3.98 (1H, m), 3.90-3.73 (1H, m), 2.92-2.58 (7H, m), 2.27-2.18 (1H, m), 1.97-1.84 (1H, m), 1.11-1.03 (3H, m).	493	491
2-026			¹ H-NMR (DMSO-D ₆) δ: 11.15 (1H, s), 8.65-8.59 (1H, m), 8.41 (1H, d, J = 9.2 Hz), 7.63 (1H, d, J = 9.2 Hz), 7.47-7.40 (2H, m), 5.19 (1H, s), 3.96-3.82 (1H, m), 2.63 (3H, d, J = 5.4 Hz), 2.20-2.09 (2H, m), 1.71-1.11 (9H, m), 1.41 (6H, s), 1.06 (3H, d, J = 6.5 Hz).	523	521
2-027			¹ H-NMR (DMSO-D ₆) δ: 11.15 (1H, s), 8.04 (1H, s), 7.76 (1H, s), 7.67-7.60 (2H, m), 7.48-7.37 (2H, m), 5.18 (1H, s), 4.09-3.96 (1H, m), 3.81 (3H, s), 2.21-2.09 (2H, m), 1.73-1.15 (9H, m), 1.39 (6H, s), 1.06 (3H, d, J = 4.3 Hz).	546	544
2-028			¹ H-NMR (DMSO-D ₆) δ: 11.36 (1H, s), 8.71-8.65 (2H, m), 8.43-8.39 (1H, m), 8.30-8.27 (1H, m), 7.52-7.47 (1H, m), 4.02-3.92 (1H, m), 2.78-2.61 (2H, m), 2.69 (3H, d, J = 4.9 Hz), 2.55-2.24 (4H, m), 2.06-1.77 (4H, m), 1.09 (3H, d, J = 6.5 Hz).	467	N.D.
2-029			¹ H-NMR (DMSO-D ₆) δ: 11.35 (1H, s), 8.17 (1H, d, J = 8.5 Hz), 8.08 (1H, d, J = 2.0 Hz), 8.01 (1H, d, J = 8.5 Hz), 7.89 (1H, dd, J = 8.5, 2.0 Hz), 7.73 (1H, d, J = 7.5 Hz), 7.70-7.58 (2H, m), 7.41 (1H, d, J = 7.3 Hz), 4.14-4.03 (1H, m), 2.81-2.74 (1H, m), 2.71-2.64 (1H, m), 2.42-2.21 (4H, m), 2.17-2.07 (2H, m), 1.74-1.53 (2H, m), 1.06 (3H, d, J = 6.5 Hz).	578	576
2-030			¹ H-NMR (DMSO-D ₆) δ: 11.30 (1H, s), 8.62 (1H, d, J = 5.1 Hz), 8.35 (1H, d, J = 8.8 Hz), 7.56-7.47 (2H, m), 7.32 (1H, dd, J = 7.3, 1.7 Hz), 3.96-3.88 (1H, m), 2.73-2.60 (5H, m), 2.42 (1H, dd, J = 12.5, 8.1 Hz), 2.33-2.21 (3H, m), 2.11-2.03 (2H, br m), 1.63-1.50 (2H, m), 1.04 (3H, d, J = 6.7 Hz).	484	482

[0614]

Table 1-47

2-031			¹ H-NMR (DMSO-D ₆) δ: 12.79 (1H, s), 11.30 (1H, s), 7.58-7.46 (3H, m), 7.31 (1H, dd, J = 6.8, 2.0 Hz), 6.28 (1H, s), 4.09-4.02 (1H, m), 2.74-2.65 (2H, br m), 2.42 (1H, dd, J = 12.5, 7.4 Hz), 2.33-2.24 (6H, m), 2.11-2.04 (2H, br m), 1.63-1.53 (2H, br m), 1.06 (3H, d, J = 6.7 Hz).	507	505
2-032			¹ H-NMR (DMSO-D ₆) δ: 11.25 (1H, s), 8.65-8.59 (1H, m), 8.43-8.38 (1H, m), 7.94-7.90 (2H, m), 7.86-7.83 (1H, m), 3.96-3.83 (1H, m), 3.87 (3H, s), 2.63 (3H, d, J = 4.8 Hz), 2.21-2.12 (2H, m), 1.71-1.15 (9H, m), 1.05 (3H, d, J = 6.5 Hz).	523	521
2-033			¹ H-NMR (DMSO-D ₆) δ: 11.32 (1H, s), 8.65-8.58 (1H, m), 8.39-8.33 (1H, m), 7.95-7.92 (2H, m), 7.89-7.86 (1H, m), 3.97-3.85 (1H, m), 3.87 (3H, s), 2.75-2.60 (2H, m), 2.62 (3H, d, J = 4.8 Hz), 2.46-2.07 (6H, m), 1.63-1.46 (2H, m), 1.04 (3H, d, J = 7.0 Hz).	524	522
2-034			¹ H-NMR (DMSO-D ₆) δ: 11.20 (1H, s), 8.64-8.58 (1H, m), 8.38-8.33 (1H, m), 7.67-7.63 (1H, m), 7.50-7.45 (1H, m), 7.43-7.40 (1H, m), 5.21 (1H, s), 3.97-3.87 (1H, m), 2.74-2.60 (2H, m), 2.63 (3H, d, J = 4.8 Hz), 2.46-2.02 (6H, m), 1.65-1.48 (2H, m), 1.41 (6H, s), 1.04 (3H, d, J = 6.5 Hz).	524	522
2-035			¹ H-NMR (DMSO-D ₆) δ: 11.23 (1H, s), 8.65-8.57 (2H, m), 8.43-8.38 (1H, m), 7.87-7.80 (2H, m), 7.78-7.76 (1H, m), 3.96-3.84 (1H, m), 2.78 (3H, d, J = 4.3 Hz), 2.63 (3H, d, J = 4.8 Hz), 2.20-2.10 (2H, m), 1.71-1.17 (9H, m), 1.05 (3H, d, J = 6.5 Hz).	522	520
2-036			¹ H-NMR (DMSO-D ₆) δ: 11.21 (1H, s), 8.66-8.60 (1H, m), 8.44-8.38 (1H, m), 7.82-7.78 (1H, m), 7.48-7.45 (1H, m), 7.43-7.39 (1H, m), 3.96-3.85 (1H, m), 2.97 (3H, s), 2.87 (3H, s), 2.64 (3H, d, J = 4.8 Hz), 2.19-2.09 (2H, m), 1.71-1.13 (9H, m), 1.05 (3H, d, J = 6.5 Hz).	536	534
2-037			¹ H-NMR (DMSO-D ₆) δ: 11.29 (1H, s), 8.65-8.57 (2H, m), 8.38-8.34 (1H, m), 7.88-7.83 (2H, m), 7.81-7.78 (1H, m), 3.98-3.89 (1H, m), 2.79 (3H, d, J = 4.3 Hz), 2.75-2.62 (2H, m), 2.63 (3H, d, J = 4.8 Hz), 2.47-2.06 (6H, m), 1.71-1.51 (2H, m), 1.04 (3H, d, J = 6.5 Hz).	523	521
2-038			¹ H-NMR (DMSO-D ₆) δ: 11.27 (1H, s), 8.67-8.58 (1H, m), 8.37-8.31 (1H, m), 7.85-7.80 (1H, m), 7.51-7.48 (1H, m), 7.45-7.40 (1H, m), 3.98-3.87 (1H, m), 2.98 (3H, s), 2.87 (3H, s), 2.74-2.60 (2H, m), 2.64 (3H, d, J = 4.8 Hz), 2.47-2.03 (6H, m), 1.67-1.49 (2H, m), 1.04 (3H, d, J = 6.5 Hz).	537	535
2-039			¹ H-NMR (DMSO-D ₆) δ: 11.30 (1H, s), 8.77 (1H, d, J = 6.9 Hz), 8.61 (1H, t, J = 4.9 Hz), 8.36 (1H, d, J = 8.6 Hz), 8.04 (1H, d, J = 2.3 Hz), 7.28 (1H, dd, J = 6.9, 0.9 Hz), 6.95 (1H, t, J = 7.1 Hz), 6.60 (1H, dd, J = 2.3, 0.9 Hz), 3.96-3.89 (1H, m), 2.73-2.60 (5H, m), 2.42 (1H, dd, J = 12.5, 8.1 Hz), 2.35-2.24 (3H, m), 2.08-2.04 (2H, br m), 1.79-1.66 (2H, m), 1.04 (3H, d, J = 6.7 Hz).	428	426
2-040			¹ H-NMR (DMSO-D ₆) δ: 11.44 (1H, s), 8.72 (1H, d, J = 9.0 Hz), 8.59 (1H, d, J = 4.9 Hz), 8.14 (1H, d, J = 1.8 Hz), 8.03 (1H, d, J = 8.6 Hz), 7.90 (1H, dd, J = 8.3, 2.1 Hz), 4.11 (1H, d, J = 9.7 Hz), 2.64 (3H, d, J = 4.9 Hz), 2.23 (2H, t, J = 11.8 Hz), 2.10-2.04 (1H, m), 2.01-1.97 (1H, m), 1.79-1.56 (6H, m), 1.12 (3H, d, J = 6.7 Hz).	515	513

[0615]

Table 1-48

2-041			¹ H-NMR (DMSO-D ₆) δ: 11.35 (1H, s), 8.31-8.24 (1H, m), 8.15 (1H, d, J = 8.0 Hz), 8.08 (1H, d, J = 2.0 Hz), 8.00 (1H, d, J = 8.3 Hz), 7.87 (1H, dd, J = 8.3, 2.0 Hz), 6.77 (1H, d, J = 15.3 Hz), 6.72 (1H, d, J = 15.3 Hz), 4.02-3.89 (1H, m), 2.71-2.65 (1H, m), 2.67 (3H, d, J = 5.0 Hz), 2.36-2.16 (5H, m), 2.15-2.03 (2H, m), 1.71-1.53 (2H, m), 1.02 (3H, d, J = 6.5 Hz).	517	515
2-042			¹ H-NMR (DMSO-D ₆) δ: 11.35 (1H, s), 8.53-8.45 (1H, m), 8.08 (1H, d, J = 1.8 Hz), 8.00 (1H, d, J = 8.5 Hz), 7.87 (1H, dd, J = 8.4, 2.1 Hz), 7.27 (1H, d, J = 15.5 Hz), 6.77 (1H, d, J = 15.5 Hz), 4.06-3.94 (1H, m), 2.77 (4H, s), 2.73-2.64 (1H, m), 2.41-2.22 (5H, m), 2.18-2.03 (2H, m), 1.71-1.57 (2H, m), 1.06 (3H, d, J = 6.5 Hz).	601	599
2-043			¹ H-NMR (DMSO-D ₆) δ: 11.11 (1H, s), 8.68-8.62 (1H, m), 8.47-8.41 (1H, m), 8.00 (1H, s), 3.99-3.82 (1H, m), 3.85 (3H, s), 2.65 (3H, d, J = 4.8 Hz), 1.97-1.87 (2H, m), 1.81-1.43 (5H, m), 1.35-1.16 (4H, m), 1.07 (3H, d, J = 6.5 Hz).	517	515
2-044			¹ H-NMR (DMSO-D ₆) δ: 11.27 (1H, s), 8.70-8.63 (1H, m), 8.48-8.42 (1H, m), 7.99 (1H, d, J = 8.4 Hz), 7.53 (1H, d, J = 2.4 Hz), 7.32 (1H, dd, J = 8.4, 2.4 Hz), 4.00-3.89 (1H, m), 2.68 (3H, d, J = 4.9 Hz), 2.22-2.13 (2H, m), 1.74-1.17 (9H, m), 1.10 (3H, d, J = 6.5 Hz).	547	545
2-045			¹ H-NMR (DMSO-D ₆) δ: 11.14 (1H, s), 8.70-8.65 (1H, m), 8.44-8.38 (1H, m), 7.66-7.61 (1H, m), 7.48-7.43 (1H, m), 7.42-7.39 (1H, m), 5.19 (1H, s), 3.94-3.84 (1H, m), 2.76-2.67 (1H, m), 2.20-2.09 (2H, m), 1.71-1.11 (9H, m), 1.41 (6H, s), 1.05 (3H, d, J = 6.5 Hz), 0.66-0.55 (4H, m).	549	547
2-046			¹ H-NMR (DMSO-D ₆) δ: 11.11 (1H, s), 8.80 (1H, d, J = 8.1 Hz), 7.99 (1H, s), 7.34 (1H, s), 4.14-4.01 (1H, m), 3.84 (3H, s), 1.98-1.20 (11H, m), 1.13 (3H, d, J = 6.5 Hz).	561	559
2-047			¹ H-NMR (DMSO-D ₆) δ: 11.35 (1H, s), 8.07 (1H, d, J = 2.0 Hz), 8.00 (1H, d, J = 8.5 Hz), 7.87 (1H, dd, J = 8.5, 2.0 Hz), 6.13 (1H, d, J = 12.8 Hz), 6.07-5.98 (1H, m), 3.97-3.89 (1H, m), 2.74-2.67 (2H, m), 2.40-2.20 (4H, m), 2.14-2.04 (2H, m), 1.73-1.58 (2H, m), 1.04 (3H, d, J = 6.5 Hz).	504	502
2-048		Mixture of two diastereomers due to 2-position of furan ring	¹ H-NMR (DMSO-D ₆) δ: 11.34-11.34 (1H, m), 8.09-8.07 (1H, m), 8.04-7.99 (1H, m), 7.92-7.87 (1H, m), 7.37 (0.5H, d, J = 8.8 Hz), 7.23 (0.5H, d, J = 8.8 Hz), 4.16-4.05 (1H, m), 3.97-3.61 (3H, m), 2.76-2.54 (2H, m), 2.41-1.87 (7H, m), 1.81-1.35 (5H, m), 1.00 (3H, d, J = 6.5 Hz).	504	502
2-049		Mixture of two diastereomers due to 2-position of dioxane ring	¹ H-NMR (DMSO-D ₆) δ: 11.36-11.32 (1H, m), 8.09-8.06 (1H, m), 8.03-7.98 (1H, m), 7.91-7.85 (1H, m), 7.44 (0.5H, d, J = 8.6 Hz), 7.36 (0.5H, d, J = 8.6 Hz), 4.00-3.19 (8H, m), 2.73-2.58 (2H, m), 2.40-2.01 (6H, m), 1.72-1.41 (2H, m), 1.00 (3H, d, J = 6.5 Hz).	520	518
2-050			¹ H-NMR (DMSO-D ₆) δ: 11.18 (1H, s), 8.66-8.59 (1H, m), 8.44-8.38 (1H, m), 7.44-7.36 (1H, m), 7.25-7.19 (1H, m), 3.95-3.84 (4H, m), 2.64 (3H, d, J = 4.8 Hz), 2.16-2.06 (2H, m), 1.69-1.12 (9H, m), 1.05 (3H, d, J = 6.5 Hz).	513	511

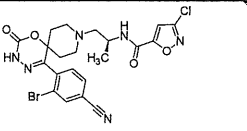
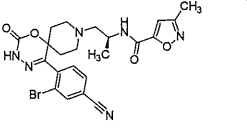
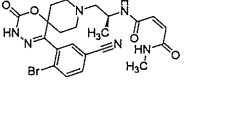
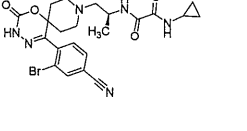
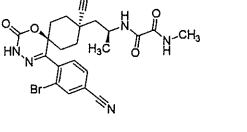
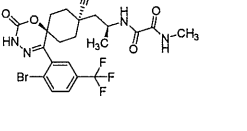
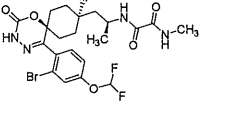
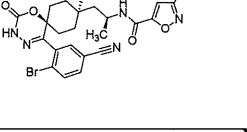
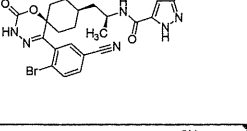
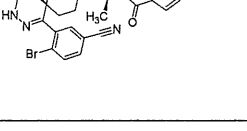
[0616]

Table 1-49

2-051			¹ H-NMR (DMSO-D ₆) δ: 11.30 (1H, s), 8.77 (1H, d, J = 6.9 Hz), 8.61 (1H, t, J = 4.9 Hz), 8.36 (1H, d, J = 8.6 Hz), 8.04 (1H, d, J = 2.3 Hz), 7.28 (1H, dd, J = 6.9, 0.9 Hz), 6.95 (1H, t, J = 7.1 Hz), 6.60 (1H, dd, J = 2.3, 0.9 Hz), 3.96-3.89 (1H, m), 2.73-2.60 (5H, m), 2.42 (1H, dd, J = 12.5, 8.1 Hz), 2.35-2.24 (3H, m), 2.08-2.04 (2H, br m), 1.79-1.66 (2H, m), 1.04 (3H, d, J = 6.7 Hz).	428	426
2-052			¹ H-NMR (DMSO-D ₆) δ: 11.44 (1H, s), 8.72 (1H, d, J = 9.0 Hz), 8.59 (1H, d, J = 4.9 Hz), 8.14 (1H, d, J = 1.8 Hz), 8.03 (1H, d, J = 8.6 Hz), 7.90 (1H, dd, J = 8.3, 2.1 Hz), 4.11 (1H, d, J = 9.7 Hz), 2.64 (3H, d, J = 4.9 Hz), 2.23 (2H, t, J = 11.8 Hz), 2.10-2.04 (1H, m), 2.01-1.97 (1H, m), 1.79-1.56 (6H, m), 1.12 (3H, d, J = 6.7 Hz).	515	513
2-053			¹ H-NMR (DMSO-D ₆) δ: 11.34 (1H, s), 8.06 (1H, d, J = 2.0 Hz), 8.00 (1H, d, J = 8.3 Hz), 7.87 (1H, dd, J = 8.3, 2.0 Hz), 7.83 (1H, d, J = 8.3 Hz), 7.67 (1H, s), 7.48 (1H, d, J = 1.0 Hz), 4.13-4.04 (1H, m), 3.73 (3H, s), 2.77-2.65 (2H, m), 2.41-2.23 (4H, m), 2.14-2.05 (2H, m), 1.68-1.52 (2H, m), 1.07 (3H, d, J = 6.5 Hz).	514	512
2-054			¹ H-NMR (DMSO-D ₆) δ: 11.34 (1H, s), 8.06 (1H, d, J = 2.2 Hz), 8.00 (1H, d, J = 8.5 Hz), 7.90-7.85 (1H, m), 7.58 (1H, s), 7.54 (1H, d, J = 1.0 Hz), 7.48 (1H, d, J = 8.3 Hz), 4.08-4.00 (1H, m), 3.67 (3H, s), 2.74-2.64 (2H, m), 2.43 (1H, dd, J = 12.3, 7.8 Hz), 2.34-2.23 (3H, m), 2.13-2.03 (2H, m), 1.70-1.53 (2H, m), 1.08 (3H, d, J = 6.5 Hz).	514	N.D.
2-055			¹ H-NMR (DMSO-D ₆) δ: 11.37 (1H, s), 8.75-8.70 (1H, m), 8.63-8.57 (1H, m), 7.85-7.80 (1H, m), 7.50-7.30 (2H, m), 7.29-7.24 (1H, m), 4.17-4.07 (1H, m), 2.64 (3H, d, J = 4.8 Hz), 2.28-1.96 (4H, m), 1.81-1.53 (6H, m), 1.12 (3H, d, J = 6.5 Hz).	556	554
2-056			¹ H-NMR (DMSO-D ₆) δ: 11.22 (1H, s), 8.67-8.57 (1H, m), 8.46-8.37 (1H, m), 7.86-7.79 (1H, m), 7.63-7.51 (2H, m), 3.97-3.82 (3H, m), 3.74-3.61 (2H, m), 2.63 (3H, d, J = 4.8 Hz), 2.55-2.36 (2H, m), 2.20-2.09 (2H, m), 1.71-1.14 (9H, m), 1.05 (3H, d, J = 6.5 Hz).	598	596
2-057			¹ H-NMR (CDCl ₃) δ: 8.27 (1H, s), 7.77-7.72 (1H, m), 7.53-7.49 (2H, m), 7.46-7.40 (1H, m), 7.20-7.14 (1H, m), 4.60-4.50 (4H, m), 4.09-3.98 (1H, m), 2.88 (3H, d, J = 5.4 Hz), 2.37-2.27 (2H, m), 1.80-1.33 (9H, m), 1.16 (3H, d, J = 6.5 Hz).	584	582
2-058			¹ H-NMR (DMSO-D ₆) δ: 11.17 (1H, s), 8.69-8.62 (1H, m), 8.49-8.41 (1H, m), 8.09 (1H, s), 6.55-6.23 (1H, m), 4.70-4.58 (2H, m), 3.99-3.87 (1H, m), 2.65 (3H, d, J = 4.8 Hz), 1.98-1.88 (2H, m), 1.84-1.41 (5H, m), 1.35-1.17 (4H, m), 1.07 (3H, d, J = 6.5 Hz).	567	565
2-059			¹ H-NMR (DMSO-D ₆) δ: 11.35 (1H, s), 8.36 (1H, d, J = 1.5 Hz), 7.95 (1H, dd, J = 8.0, 1.5 Hz), 7.82 (1H, d, J = 8.5 Hz), 7.70-7.66 (2H, m), 7.47 (1H, d, J = 1.2 Hz), 4.10-4.01 (1H, m), 3.73 (3H, s), 2.76-2.64 (2H, m), 2.42-2.22 (4H, m), 2.15-2.05 (2H, m), 1.63-1.47 (2H, m), 1.09-1.00 (3H, m).	514	512
2-060			¹ H-NMR (DMSO-D ₆) δ: 11.36 (1H, s), 8.35 (1H, d, J = 1.5 Hz), 7.96 (1H, dd, J = 8.0, 1.5 Hz), 7.69 (1H, d, J = 8.0 Hz), 7.59 (1H, s), 7.54 (1H, d, J = 1.0 Hz), 7.48 (1H, d, J = 8.3 Hz), 4.09-3.97 (1H, m), 3.67 (3H, s), 2.73-2.64 (2H, m), 2.43 (1H, dd, J = 12.4, 7.9 Hz), 2.35-2.22 (3H, m), 2.12-2.03 (2H, m), 1.64-1.48 (2H, m), 1.07 (3H, d, J = 6.5 Hz).	514	512

[0617]

Table 1-50

2-061			¹ H-NMR (DMSO-D ₆) δ: 11.36 (1H, s), 8.71 (1H, d, J = 8.3 Hz), 8.35 (1H, d, J = 1.5 Hz), 7.94 (1H, dd, J = 7.9, 1.6 Hz), 7.68 (1H, d, J = 8.0 Hz), 7.28 (1H, s), 4.14-4.04 (1H, m), 2.76-2.61 (2H, m), 2.46-2.23 (4H, m), 2.12-2.07 (2H, m), 1.58-1.51 (2H, m), 1.09 (3H, d, J = 6.5 Hz).	535	533
2-062			¹ H-NMR (DMSO-D ₆) δ: 11.36 (1H, s), 8.51 (1H, d, J = 8.5 Hz), 8.35 (1H, d, J = 1.5 Hz), 7.95 (1H, dd, J = 8.0, 1.5 Hz), 7.68 (1H, d, J = 8.0 Hz), 6.82 (1H, s), 4.13-4.01 (1H, m), 2.76-2.61 (2H, m), 2.46-2.38 (1H, m), 2.36-2.24 (3H, m), 2.28 (3H, s), 2.12-2.05 (2H, m), 1.61-1.46 (2H, m), 1.08 (3H, d, J = 6.5 Hz).	515	513
2-063			¹ H-NMR (DMSO-D ₆) δ: 11.35 (1H, s), 8.32-7.83 (6H, m), 6.75 (1H, d, J = 5.0 Hz), 4.00-3.84 (1H, m), 2.73-2.64 (1H, m), 2.67 (3H, d, J = 4.8 Hz), 2.35-2.02 (7H, m), 1.70-1.56 (2H, m), 1.02 (3H, d, J = 6.5 Hz).	517	515
2-064			¹ H-NMR (DMSO-D ₆) δ: 11.36 (1H, s), 8.67 (1H, d, J = 5.3 Hz), 8.38-8.31 (2H, m), 7.96 (1H, dd, J = 8.0, 1.5 Hz), 7.70 (1H, d, J = 8.0 Hz), 3.97-3.86 (1H, m), 2.76-2.67 (2H, m), 2.65-2.59 (1H, m), 2.42 (1H, dd, J = 12.5, 8.3 Hz), 2.36-2.19 (3H, m), 2.16-2.03 (2H, m), 1.64-1.48 (2H, m), 1.04 (3H, d, J = 6.5 Hz), 0.68-0.53 (4H, m).	517	515
2-065			¹ H-NMR (DMSO-D ₆) δ: 11.46 (1H, s), 8.73 (1H, d, J = 9.2 Hz), 8.60 (1H, d, J = 4.8 Hz), 8.39 (1H, s), 8.01 (1H, d, J = 8.1 Hz), 7.75 (1H, d, J = 8.1 Hz), 4.12 (1H, br s), 2.64 (3H, d, J = 4.8 Hz), 2.24 (2H, t, J = 10.5 Hz), 2.07 (1H, dd, J = 13.7, 11.0 Hz), 1.99 (1H, br s), 1.79-1.53 (6H, m), 1.12 (3H, d, J = 6.5 Hz).	515	513
2-066			¹ H-NMR (DMSO-D ₆) δ: 11.43 (1H, s), 8.75-8.69 (1H, m), 8.62-8.57 (1H, m), 8.06-8.01 (1H, m), 7.94 (1H, s), 7.83-7.78 (1H, m), 4.16-4.05 (1H, m), 2.65-2.62 (3H, m), 2.33-2.19 (2H, m), 2.11-1.96 (2H, m), 1.81-1.52 (6H, m), 1.12 (3H, d, J = 6.5 Hz).	558	556
2-067			¹ H-NMR (DMSO-D ₆) δ: 11.34 (1H, s), 8.75-8.69 (1H, m), 8.63-8.57 (1H, m), 7.65-7.62 (1H, m), 7.60-7.55 (1H, m), 7.41-7.20 (2H, m), 4.18-4.06 (1H, m), 2.66-2.62 (3H, m), 2.33-2.27 (4H, m), 1.82-1.54 (6H, m), 1.12 (3H, d, J = 6.5 Hz).	556	554
2-068			¹ H-NMR (DMSO-D ₆) δ: 11.44 (1H, s), 9.01 (1H, d, J = 8.6 Hz), 8.16-8.13 (1H, m), 8.04-8.00 (1H, m), 7.91-7.88 (1H, m), 7.30-7.28 (1H, m), 4.35-4.24 (1H, m), 2.32-2.17 (2H, m), 2.07-1.97 (2H, m), 1.87-1.54 (6H, m), 1.20-1.16 (3H, m).	559	557
2-069			¹ H-NMR (DMSO-D ₆) δ: 12.91 (0.25H, s), 12.85 (0.75H, s), 11.29 (1H, s), 8.01-7.93 (2.5H, m), 7.86-7.81 (1H, m), 7.61-7.54 (0.5H, m), 6.49 (0.25H, s), 6.22 (0.75H, s), 4.10-4.00 (1H, m), 2.19-1.79 (3H, m), 1.74-1.14 (9H, m), 1.07 (3H, d, J = 6.5 Hz), 0.98-0.55 (4H, m).	539	537
2-070			¹ H-NMR (DMSO-D ₆) δ: 11.29 (1H, s), 8.01-7.94 (2H, m), 7.86-7.81 (1H, m), 7.74-7.71 (1H, m), 7.68-7.63 (1H, m), 6.57-6.54 (1H, m), 4.12-4.02 (1H, m), 3.88-3.86 (3H, m), 2.17-2.06 (2H, m), 1.73-1.18 (9H, m), 1.08 (3H, d, J = 6.5 Hz).	513	511

[0618]

Table 1-51

2-071			¹ H-NMR (DMSO-D ₆) δ: 11.28 (1H, s), 8.01-7.94 (2H, m), 7.86-7.81 (1H, m), 7.61-7.59 (1H, m), 7.55-7.53 (1H, m), 7.47-7.41 (1H, m), 4.09-3.99 (1H, m), 3.66 (3H, s), 2.16-2.06 (2H, m), 1.74-1.18 (9H, m), 1.07 (3H, d, J = 7.0 Hz).	513	511
2-072			¹ H-NMR (DMSO-D ₆) δ: 12.95-12.82 (1H, m), 11.30 (1H, s), 8.34-8.31 (1H, m), 7.94-7.89 (1H, m), 7.69-7.64 (1H, m), 7.61-7.54 (1H, m), 6.54-6.18 (1H, m), 4.12-3.98 (1H, m), 2.17-2.07 (2H, m), 1.95-1.64 (2H, m), 1.57-1.12 (8H, m), 1.07 (3H, d, J = 5.9 Hz), 0.98-0.56 (4H, m).	539	537
2-073			¹ H-NMR (DMSO-D ₆) δ: 11.28 (1H, s), 8.59 (1H, s), 8.40 (1H, d, J = 9.0 Hz), 8.00 (1H, d, J = 1.8 Hz), 7.98 (1H, d, J = 8.3 Hz), 7.85 (1H, dd, J = 8.3, 1.8 Hz), 3.98-3.85 (1H, m), 2.16-2.04 (2H, m), 1.69-1.59 (1H, m), 1.59-1.13 (8H, m), 1.06 (3H, d, J = 6.5 Hz).	493	491
2-074			¹ H-NMR (DMSO-D ₆) δ: 11.30 (1H, s), 8.65-8.60 (1H, m), 8.47-8.38 (2H, m), 7.00 (1H, s), 3.96-3.84 (1H, m), 3.88 (3H, s), 2.64 (3H, d, J = 4.8 Hz), 2.15-2.06 (2H, m), 1.70-1.15 (9H, m), 1.05 (3H, d, J = 6.5 Hz).	496	494
2-075			¹ H-NMR (DMSO-D ₆) δ: 11.43 (1H, s), 9.09 (1H, s), 8.65-8.58 (1H, m), 8.43-8.38 (1H, m), 8.08 (1H, s), 3.96-3.84 (1H, m), 2.63 (3H, d, J = 4.8 Hz), 2.20-2.11 (2H, m), 1.69-1.16 (9H, m), 1.05 (3H, d, J = 6.5 Hz).	534	532
2-076			¹ H-NMR (DMSO-D ₆) δ: 11.44 (1H, s), 8.72 (1H, d, J = 9.2 Hz), 8.63-8.55 (1H, m), 8.00-7.95 (1H, m), 7.85-7.80 (1H, m), 7.76-7.69 (1H, m), 4.19-4.04 (1H, m), 2.64 (3H, d, J = 4.8 Hz), 2.37-1.92 (4H, m), 1.84-1.35 (6H, m), 1.12 (3H, d, J = 6.5 Hz).	558	556
2-077			¹ H-NMR (DMSO-D ₆) δ: 11.46 (1H, s), 8.75-8.70 (1H, m), 8.63-8.57 (1H, m), 8.49 (1H, s), 7.11 (1H, s), 4.17-4.06 (1H, m), 3.90-3.87 (3H, m), 2.64 (3H, d, J = 3.8 Hz), 2.27-1.97 (4H, m), 1.82-1.53 (6H, m), 1.12 (3H, d, J = 6.5 Hz).	521	519
2-078			¹ H-NMR (DMSO-D ₆) δ: 11.36 (1H, s), 7.86-7.79 (2H, m), 7.61 (1H, s), 7.56 (1H, s), 7.49-7.10 (3H, m), 4.32-4.21 (1H, m), 3.66 (3H, s), 2.29-1.96 (4H, m), 1.88-1.54 (6H, m), 1.14 (3H, d, J = 6.5 Hz).	579	577
2-079			¹ H-NMR (DMSO-D ₆) δ: 11.42 (1H, s), 8.06-8.01 (1H, m), 7.96-7.91 (1H, m), 7.85-7.76 (2H, m), 7.61 (1H, s), 7.55 (1H, s), 4.32-4.20 (1H, m), 3.66 (3H, s), 2.33-1.95 (4H, m), 1.88-1.50 (6H, m), 1.14 (3H, d, J = 7.0 Hz).	581	579
2-080			¹ H-NMR (DMSO-D ₆) δ: 11.41 (1H, s), 8.75-8.70 (1H, m), 8.63-8.57 (1H, m), 7.95-7.90 (1H, m), 7.67-7.64 (1H, m), 7.51-7.46 (1H, m), 4.17-4.05 (1H, m), 2.64 (3H, d, J = 4.8 Hz), 2.30-1.94 (4H, m), 1.81-1.52 (6H, m), 1.12 (3H, d, J = 7.0 Hz).	574	572

[0619]

Table 1-52

2-081			¹ H-NMR (DMSO-D ₆) δ: 11.29 (1H, s), 8.71-8.64 (1H, m), 8.44-8.37 (1H, m), 8.01-7.95 (2H, m), 7.89-7.82 (1H, m), 3.96-3.85 (1H, m), 3.18-3.06 (2H, m), 2.16-2.05 (2H, m), 1.69-1.16 (9H, m), 1.09-0.99 (6H, m).	504	502
2-082			¹ H-NMR (DMSO-D ₆) δ: 11.37 (1H, s), 8.75-8.69 (1H, m), 8.68-8.62 (1H, m), 7.85-7.80 (1H, m), 7.50-7.10 (3H, m), 4.17-4.05 (1H, m), 3.21-3.04 (2H, m), 2.29-1.96 (4H, m), 1.82-1.56 (6H, m), 1.12 (3H, d, J = 6.5 Hz), 1.02 (3H, t, J = 7.3 Hz).	570	568
2-083			¹ H-NMR (DMSO-D ₆) δ: 11.32 (1H, s), 8.66-8.58 (2H, m), 8.45-8.38 (1H, m), 7.10 (1H, s), 6.56-6.24 (1H, m), 4.63-4.51 (2H, m), 3.97-3.84 (1H, m), 2.64 (3H, d, J = 3.8 Hz), 2.16-2.07 (2H, m), 1.71-1.13 (9H, m), 1.06 (3H, d, J = 6.5 Hz).	594	592
2-084			¹ H-NMR (DMSO-D ₆) δ: 11.32 (1H, s), 8.66-8.60 (1H, m), 8.47 (1H, s), 8.44-8.38 (1H, m), 7.14 (1H, s), 6.56-6.24 (1H, m), 4.64-4.52 (2H, m), 3.96-3.85 (1H, m), 2.64 (3H, d, J = 4.8 Hz), 2.15-2.07 (2H, m), 1.70-1.16 (9H, m), 1.05 (3H, d, J = 6.5 Hz).	546	544
2-085			¹ H-NMR (DMSO-D ₆) δ: 11.32 (1H, s), 8.46 (1H, s), 7.60 (1H, s), 7.54 (1H, s), 7.45 (1H, d, J = 9.2 Hz), 7.14 (1H, s), 6.57-6.21 (1H, m), 4.63-4.50 (2H, m), 4.11-3.96 (1H, m), 3.66 (3H, s), 2.17-2.07 (2H, m), 1.76-1.15 (9H, m), 1.07 (3H, d, J = 6.5 Hz).	569	567
2-086			¹ H-NMR (DMSO-D ₆) δ: 11.31 (1H, s), 8.59 (1H, s), 7.61 (1H, s), 7.54 (1H, s), 7.45 (1H, d, J = 8.6 Hz), 7.10 (1H, s), 6.55-6.21 (1H, m), 4.61-4.50 (2H, m), 4.09-3.98 (1H, m), 3.66 (3H, s), 2.17-2.06 (2H, m), 1.75-1.14 (9H, m), 1.07 (3H, d, J = 6.5 Hz).	617	615
2-087			¹ H-NMR (DMSO-D ₆) δ: 11.31 (1H, s), 8.64-8.58 (1H, m), 8.43-8.38 (1H, m), 8.07-8.02 (1H, m), 7.92-7.88 (2H, m), 3.96-3.84 (1H, m), 3.32 (3H, s), 2.63 (3H, d, J = 4.8 Hz), 2.21-2.12 (2H, m), 1.71-1.13 (9H, m), 1.05 (3H, d, J = 6.5 Hz).	543	541
2-088			¹ H-NMR (DMSO-D ₆) δ: 11.34 (1H, s), 8.75-8.69 (1H, m), 8.63-8.57 (1H, m), 7.80-7.75 (1H, m), 7.61-7.55 (1H, s), 7.43-7.36 (1H, m), 4.18-4.06 (1H, m), 2.64 (3H, d, J = 4.8 Hz), 2.26-1.95 (4H, m), 1.81-1.53 (6H, m), 1.12 (3H, d, J = 6.5 Hz).	508	506
2-089			¹ H-NMR (DMSO-D ₆) δ: 11.33 (1H, s), 8.03 (1H, s), 7.86 (1H, d, J = 9.2 Hz), 7.78-7.73 (2H, m), 7.60-7.54 (1H, m), 7.41-7.34 (1H, m), 4.32-4.20 (1H, m), 3.82 (3H, s), 2.27-2.15 (2H, m), 2.03-1.51 (8H, m), 1.12 (3H, d, J = 6.5 Hz).	531	529
2-090			¹ H-NMR (DMSO-D ₆) δ: 11.37 (1H, s), 8.03 (1H, s), 7.90-7.78 (2H, m), 7.76 (1H, s), 7.50-7.08 (3H, m), 4.32-4.20 (1H, m), 3.82 (3H, s), 2.29-2.16 (2H, m), 2.04-1.54 (8H, m), 1.12 (3H, d, J = 6.5 Hz).	579	577

[0620]

Table 1-53

2-091			¹ H-NMR (DMSO-D ₆) δ: 11.31 (1H, s), 8.59 (1H, s), 8.05 (1H, s), 7.78 (1H, s), 7.64 (1H, d, J = 8.1 Hz), 7.10 (1H, s), 6.56-6.21 (1H, m), 4.63-4.49 (2H, m), 4.09-3.94 (1H, m), 3.81 (3H, s), 2.17-2.07 (2H, m), 1.73-1.14 (9H, m), 1.06 (3H, d, J = 5.9 Hz).	617	615
2-092			¹ H-NMR (DMSO-D ₆) δ: 11.45 (1H, s), 8.75-8.70 (1H, m), 8.67-8.63 (1H, m), 8.15-8.13 (1H, m), 8.05-8.01 (1H, m), 7.93-7.88 (1H, m), 4.16-4.04 (1H, m), 2.78-2.69 (1H, m), 2.29-1.94 (4H, m), 1.82-1.53 (6H, m), 1.12 (3H, d, J = 6.5 Hz), 0.64-0.56 (4H, m).	541	539
2-093			¹ H-NMR (DMSO-D ₆) δ: 11.46 (1H, s), 8.75-8.69 (1H, m), 8.67-8.63 (1H, m), 8.49 (1H, s), 7.11 (1H, s), 4.15-4.02 (1H, m), 3.89 (3H, s), 2.77-2.68 (1H, m), 2.27-1.96 (4H, m), 1.82-1.53 (6H, m), 1.12 (3H, d, J = 6.5 Hz), 0.66-0.54 (4H, m).	547	545
2-094			¹ H-NMR (DMSO-D ₆) δ: 11.44 (1H, s), 8.14 (1H, s), 8.04-8.00 (2H, m), 7.91-7.83 (2H, m), 7.76 (1H, s), 4.35-4.19 (1H, m), 3.82 (3H, s), 2.31-2.16 (2H, m), 2.04-1.54 (8H, m), 1.13 (3H, d, J = 6.5 Hz).	538	536
2-095			¹ H-NMR (CDCl ₃) δ: 8.49 (1H, s), 8.34 (1H, s), 7.81 (1H, s), 7.75 (1H, s), 6.62 (1H, s), 5.68 (1H, d, J = 9.7 Hz), 4.59-4.47 (1H, m), 3.92 (3H, s), 3.89 (3H, s), 2.37-2.27 (2H, m), 2.18-1.69 (8H, m), 1.27 (3H, d, J = 6.5 Hz).	544	542
2-096			¹ H-NMR (DMSO-D ₆) δ: 8.35 (1H, d, J = 1.5 Hz), 7.95 (1H, dd, J = 8.0, 1.5 Hz), 7.70 (1H, d, J = 8.0 Hz), 7.42-7.35 (2H, m), 4.10-3.98 (1H, m), 2.74-2.65 (2H, m), 2.46-2.38 (1H, m), 2.34-2.21 (4H, m), 2.24 (3H, s), 2.15-2.04 (2H, m), 1.65-1.51 (2H, m), 1.06 (3H, d, J = 6.5 Hz).	514	512
2-097			¹ H-NMR (DMSO-D ₆) δ: 11.43 (1H, s), 8.02 (1H, s), 7.98-7.94 (1H, m), 7.88-7.79 (2H, m), 7.76 (1H, s), 7.73-7.68 (1H, m), 4.33-4.20 (1H, m), 3.83-3.80 (3H, m), 2.36-2.13 (2H, m), 2.04-1.60 (8H, m), 1.12 (3H, d, J = 6.5 Hz).	581	579
2-098			¹ H-NMR (DMSO-D ₆) δ: 11.38 (1H, s), 8.75-8.70 (1H, m), 8.63-8.57 (1H, m), 7.84-7.79 (1H, m), 7.56-7.51 (1H, m), 7.38-7.30 (1H, m), 4.17-4.06 (1H, m), 2.64 (3H, d, J = 4.8 Hz), 2.27-1.95 (4H, m), 1.81-1.53 (6H, m), 1.12 (3H, d, J = 6.5 Hz).	508	506
2-099			¹ H-NMR (DMSO-D ₆) δ: 11.49 (1H, s), 8.77-8.68 (1H, m), 8.63-8.56 (1H, m), 8.52 (1H, s), 7.25 (1H, s), 6.58-6.24 (1H, m), 4.67-4.54 (2H, m), 4.07-3.97 (1H, m), 2.66 (3H, d, J = 3.8 Hz), 2.08-1.55 (10H, m), 1.11 (3H, d, J = 6.5 Hz).	571	569
2-100			¹ H-NMR (DMSO-D ₆) δ: 11.38 (1H, s), 8.72 (1H, d, J = 9.2 Hz), 8.65 (1H, d, J = 5.4 Hz), 7.84-7.79 (1H, m), 7.56-7.51 (1H, m), 7.38-7.31 (1H, m), 4.16-4.04 (1H, m), 2.78-2.69 (1H, m), 2.27-1.94 (4H, m), 1.82-1.54 (6H, m), 1.12 (3H, d, J = 6.5 Hz), 0.65-0.55 (4H, m).	534	532

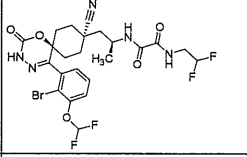
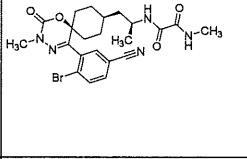
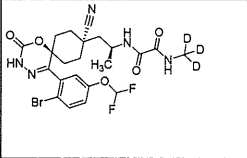
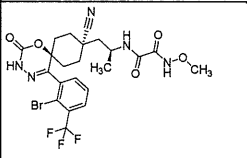
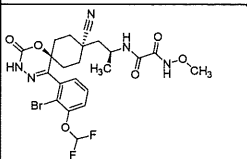
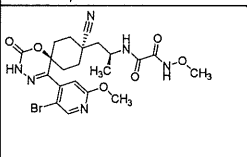
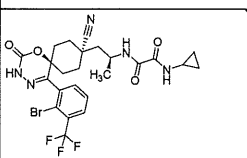
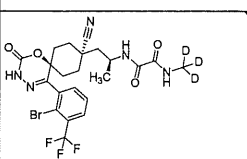
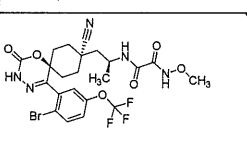
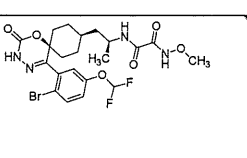
[0621]

Table 1-54

2-101			¹ H-NMR (DMSO-D ₆) δ: 11.49 (1H, s), 8.75-8.68 (1H, m), 8.67-8.60 (1H, m), 8.51 (1H, s), 7.25 (1H, s), 6.58-6.24 (1H, m), 4.67-4.55 (2H, m), 4.07-3.94 (1H, m), 2.80-2.69 (1H, m), 2.08-1.54 (10H, m), 1.10 (3H, d, J = 6.5 Hz), 0.69-0.55 (4H, m).	597	595
2-102			¹ H-NMR (DMSO-D ₆) δ: 11.40 (1H, s), 8.77-8.67 (1H, m), 8.66-8.56 (1H, m), 7.67-7.50 (2H, m), 7.27 (1H, t, J = 71.9 Hz), 4.19-4.05 (1H, m), 2.66-2.62 (3H, m), 2.31-1.93 (4H, m), 1.82-1.50 (6H, m), 1.12 (3H, d, J = 6.5 Hz).	574	572
2-103			¹ H-NMR (DMSO-D ₆) δ: 11.40 (1H, s), 8.72 (1H, d, J = 9.7 Hz), 8.65 (1H, d, J = 4.8 Hz), 7.66-7.59 (1H, m), 7.57-7.51 (1H, m), 7.27 (1H, t, J = 72.2 Hz), 4.17-4.04 (1H, m), 2.77-2.69 (1H, m), 2.27-1.93 (4H, m), 1.82-1.50 (6H, m), 1.12 (3H, d, J = 6.5 Hz), 0.68-0.53 (4H, m).	600	598
2-104			¹ H-NMR (DMSO-D ₆) δ: 11.38 (1H, s), 8.97-8.90 (1H, m), 8.88-8.82 (1H, m), 7.85-7.80 (1H, m), 7.50-7.10 (3H, m), 6.20-5.87 (1H, m), 4.20-4.07 (1H, m), 3.65-3.40 (2H, m), 2.30-1.95 (4H, m), 1.83-1.54 (6H, m), 1.13 (3H, d, J = 6.5 Hz).	606	604
2-105			¹ H-NMR (CDCl ₃) δ: 9.73 (1H, s), 8.34 (1H, s), 7.66 (1H, d, J = 9.2 Hz), 7.39-7.33 (1H, m), 7.15-7.10 (1H, m), 7.02 (1H, d, J = 2.7 Hz), 6.51 (1H, t, J = 72.7 Hz), 4.35-4.22 (1H, m), 3.82 (3H, s), 2.41-2.29 (2H, m), 2.10-1.70 (8H, m), 1.30 (3H, d, J = 6.5 Hz).	572	570
2-106			¹ H-NMR (DMSO-D ₆) δ: 11.46 (1H, s), 8.96-8.91 (1H, m), 8.88-8.82 (1H, m), 8.49 (1H, s), 7.11 (1H, s), 6.21-5.86 (1H, m), 4.18-4.07 (1H, m), 3.88 (3H, s), 3.66-3.39 (2H, m), 2.29-1.95 (4H, m), 1.81-1.55 (6H, m), 1.13 (3H, d, J = 6.5 Hz).	571	569
2-107			¹ H-NMR (DMSO-D ₆) δ: 11.38 (1H, s), 8.75-8.69 (1H, m), 8.67-8.63 (1H, m), 7.85-7.81 (1H, m), 7.52-7.11 (3H, m), 4.16-4.01 (1H, m), 2.78-2.67 (1H, m), 2.29-1.93 (4H, m), 1.86-1.52 (6H, m), 1.12 (3H, d, J = 6.5 Hz), 0.67-0.54 (4H, m).	582	580
2-108			¹ H-NMR (DMSO-D ₆) δ: 11.22 (1H, s), 8.38 (1H, d, J = 8.6 Hz), 7.98 (1H, s), 7.81-7.76 (1H, m), 7.71 (1H, s), 7.53-7.12 (3H, m), 3.95-3.80 (1H, m), 2.21-2.08 (2H, m), 1.70-1.14 (9H, m), 1.05 (3H, d, J = 6.5 Hz).	517	515
2-109			¹ H-NMR (DMSO-D ₆) δ: 11.36 (1H, s), 8.75-8.69 (1H, m), 8.63-8.57 (1H, m), 7.59-7.52 (1H, m), 7.46-7.42 (1H, m), 7.39-7.34 (2H, m), 4.16-4.05 (1H, m), 2.66-2.61 (3H, m), 2.29-1.94 (4H, m), 1.81-1.57 (6H, m), 1.11 (3H, d, J = 4.8 Hz).	556	554
2-110			¹ H-NMR (DMSO-D ₆) δ: 11.37 (1H, s), 8.74-8.69 (1H, m), 8.67-8.63 (1H, m), 7.59-7.53 (1H, m), 7.47-7.42 (1H, m), 7.39-7.35 (2H, m), 4.16-4.03 (1H, m), 2.78-2.68 (1H, m), 2.29-1.93 (4H, m), 1.82-1.55 (6H, m), 1.12 (3H, d, J = 6.5 Hz), 0.67-0.56 (4H, m).	582	580

[0622]

Table 1-55

2-111			¹ H-NMR (DMSO-D ₆) δ: 11.37 (1H, s), 8.97-8.90 (1H, m), 8.88-8.82 (1H, m), 7.59-7.52 (1H, m), 7.47-7.42 (1H, m), 7.39-7.35 (2H, m), 6.20-5.87 (1H, m), 4.20-4.07 (1H, m), 3.64-3.38 (2H, m), 2.30-1.94 (4H, m), 1.83-1.53 (6H, m), 1.13 (3H, d, J = 6.5 Hz).	606	604
2-112			¹ H-NMR (DMSO-D ₆) δ: 8.66-8.59 (1H, m), 8.46-8.38 (1H, m), 8.04-7.96 (2H, m), 7.90-7.84 (1H, m), 3.96-3.85 (1H, m), 3.32 (3H, s), 2.64 (3H, d, J = 4.8 Hz), 2.16-2.05 (2H, m), 1.70-1.38 (4H, m), 1.31-1.14 (5H, m), 1.05 (3H, d, J = 7.0 Hz).	504	N.D.
2-113			¹ H-NMR (DMSO-D ₆) δ: 11.38 (1H, s), 8.72 (1H, d, J = 9.2 Hz), 8.57 (1H, s), 7.85-7.81 (1H, m), 7.50-7.11 (3H, m), 4.16-4.05 (1H, m), 2.28-1.95 (4H, m), 1.81-1.57 (6H, m), 1.12 (3H, d, J = 7.0 Hz).	559	557
2-114			¹ H-NMR (CDCl ₃) δ: 9.77 (1H, s), 8.49 (1H, s), 7.83-7.79 (1H, m), 7.57-7.51 (1H, m), 7.43-7.38 (2H, m), 4.36-4.23 (1H, m), 3.81 (3H, s), 2.45-2.35 (2H, m), 2.09-1.70 (8H, m), 1.29 (3H, d, J = 7.0 Hz).	574	572
2-115			¹ H-NMR (CDCl ₃) δ: 9.84 (1H, s), 8.53 (1H, s), 7.48-7.39 (2H, m), 7.35-7.30 (1H, m), 7.14-7.09 (1H, m), 6.58 (1H, t, J = 72.7 Hz), 4.35-4.22 (1H, m), 3.81 (3H, s), 2.43-2.30 (2H, m), 2.09-1.68 (8H, m), 1.29 (3H, d, J = 7.0 Hz).	572	570
2-116			¹ H-NMR (CDCl ₃) δ: 9.96 (1H, s), 8.77 (1H, s), 8.35 (1H, s), 7.56 (1H, d, J = 9.7 Hz), 6.64 (1H, s), 4.36-4.24 (1H, m), 3.93 (3H, s), 3.82 (3H, s), 2.36-2.29 (2H, m), 2.08-1.70 (8H, m), 1.29 (3H, d, J = 6.5 Hz).	537	535
2-117			¹ H-NMR (DMSO-D ₆) δ: 11.44 (1H, s), 8.74-8.69 (1H, m), 8.67-8.63 (1H, m), 8.00-7.95 (1H, m), 7.85-7.80 (1H, m), 7.76-7.70 (1H, m), 4.16-4.04 (1H, m), 2.78-2.69 (1H, m), 2.34-1.93 (4H, m), 1.84-1.60 (6H, m), 1.12 (3H, d, J = 6.5 Hz), 0.66-0.53 (4H, m).	584	582
2-118			¹ H-NMR (DMSO-D ₆) δ: 11.44 (1H, s), 8.74-8.69 (1H, m), 8.56 (1H, s), 7.99-7.95 (1H, m), 7.84-7.80 (1H, m), 7.75-7.69 (1H, m), 4.15-4.04 (1H, m), 2.33-1.95 (4H, m), 1.81-1.59 (6H, m), 1.11 (3H, d, J = 6.5 Hz).	561	559
2-119			¹ H-NMR (DMSO-D ₆) δ: 12.01 (1H, s), 11.42 (1H, s), 8.86-8.80 (1H, m), 7.96-7.90 (1H, m), 7.67-7.64 (1H, m), 7.51-7.47 (1H, m), 4.17-4.04 (1H, m), 3.59 (3H, s), 2.31-1.95 (4H, m), 1.83-1.52 (6H, m), 1.12 (3H, d, J = 6.6 Hz).	590	588
2-120			¹ H-NMR (DMSO-D ₆) δ: 12.02 (1H, s), 11.23 (1H, s), 8.53 (1H, d, J = 8.1 Hz), 7.79 (1H, d, J = 9.2 Hz), 7.53-7.12 (3H, m), 3.98-3.85 (1H, m), 3.60 (3H, s), 2.20-2.08 (2H, m), 1.70-1.14 (9H, m), 1.05 (3H, d, J = 6.5 Hz).	547	545

[0623]

Table 1-56

2-121			¹ H-NMR (DMSO-D ₆) δ: 11.30 (1H, s), 8.44 (1H, s), 8.42-8.34 (1H, m), 7.99 (1H, s), 7.72 (1H, s), 7.01 (1H, s), 3.94-3.82 (1H, m), 3.88 (3H, s), 2.17-2.06 (2H, m), 1.69-1.15 (9H, m), 1.05 (3H, d, J = 6.5 Hz).	482	480
2-122			¹ H-NMR (DMSO-D ₆) δ: 11.32 (1H, s), 8.47 (1H, s), 8.41-8.34 (1H, m), 7.99 (1H, s), 7.72 (1H, s), 7.15 (1H, s), 6.57-6.25 (1H, m), 4.66-4.52 (2H, m), 3.96-3.82 (1H, m), 2.19-2.07 (2H, m), 1.71-1.15 (9H, m), 1.05 (3H, d, J = 6.5 Hz).	532	530
2-123			¹ H-NMR (DMSO-D ₆) δ: 11.32 (1H, s), 8.65-8.54 (2H, m), 8.09-8.05 (1H, m), 8.03-7.98 (1H, m), 7.91-7.86 (1H, m), 4.01-3.92 (1H, m), 2.92 (3H, s), 2.67-2.63 (3H, m), 1.99-1.42 (10H, m), 1.08 (3H, d, J = 6.5 Hz).	520	518
2-124			¹ H-NMR (DMSO-D ₆) δ: 11.31 (1H, s), 8.65-8.51 (2H, m), 8.00-7.92 (1H, m), 7.80-7.66 (2H, m), 4.04-3.91 (1H, m), 2.90 (3H, s), 2.65 (3H, d, J = 4.8 Hz), 2.01-1.40 (10H, m), 1.08 (3H, d, J = 6.5 Hz).	563	561
2-125			¹ H-NMR (DMSO-D ₆) δ: 11.33 (1H, s), 8.66-8.53 (2H, m), 8.46 (1H, s), 7.03 (1H, s), 4.03-3.91 (1H, m), 3.89 (3H, s), 2.93 (3H, s), 2.65 (3H, d, J = 4.8 Hz), 1.97-1.68 (4H, m), 1.65-1.41 (6H, m), 1.08 (3H, d, J = 6.5 Hz).	526	524
2-126			¹ H-NMR (DMSO-D ₆) δ: 11.33 (1H, s), 8.68-8.64 (1H, m), 8.59-8.54 (1H, m), 8.06 (1H, s), 8.03-7.98 (1H, m), 7.90-7.86 (1H, m), 4.02-3.92 (1H, m), 2.92 (3H, s), 2.78-2.69 (1H, m), 2.00-1.69 (4H, m), 1.64-1.43 (6H, m), 1.08 (3H, d, J = 6.5 Hz), 0.68-0.57 (4H, m).	546	544
2-127			¹ H-NMR (DMSO-D ₆) δ: 11.38 (1H, s), 8.97-8.95 (1H, m), 8.69-8.66 (1H, m), 8.56-8.52 (1H, m), 8.16-8.12 (1H, m), 7.81 (1H, d, J = 8.8 Hz), 7.50-7.46 (1H, m), 7.40-7.38 (1H, m), 7.28 (1H, t, J = 73.6 Hz), 7.27-7.23 (1H, m), 4.41-4.32 (1H, m), 2.31-2.19 (2H, m), 2.08-1.99 (2H, m), 1.88-1.57 (6H, m), 1.20-1.16 (3H, m).	576	574
2-128			¹ H-NMR (DMSO-D ₆) δ: 11.36 (1H, s), 8.78-8.73 (1H, m), 8.64-8.60 (1H, m), 8.03-7.93 (2H, m), 7.82-7.78 (1H, m), 7.60-7.55 (1H, m), 7.39-7.36 (1H, m), 7.28 (1H, t, J = 73.5 Hz), 7.27-7.21 (1H, m), 4.40-4.30 (1H, m), 2.29-1.99 (4H, m), 1.85-1.54 (6H, m), 1.20 (3H, d, J = 6.5 Hz).	576	574
2-129			¹ H-NMR (DMSO-D ₆) δ: 11.31 (1H, s), 8.59-8.53 (2H, m), 7.97-7.93 (1H, m), 7.78-7.66 (2H, m), 4.03-3.90 (1H, m), 2.90 (3H, s), 2.01-1.41 (10H, m), 1.07 (3H, d, J = 6.5 Hz).	566	564
2-130			¹ H-NMR (DMSO-D ₆) δ: 11.33 (1H, s), 8.60-8.54 (2H, m), 8.38-8.35 (1H, m), 8.00-7.95 (1H, m), 7.70-7.66 (1H, m), 4.03-3.90 (1H, m), 2.91 (3H, s), 1.99-1.68 (4H, m), 1.62-1.44 (6H, m), 1.08 (3H, d, J = 6.5 Hz).	523	521

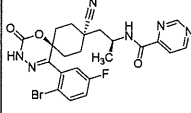
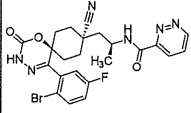
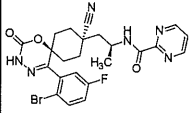
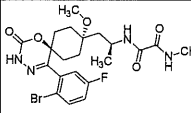
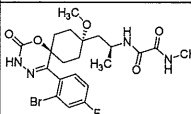
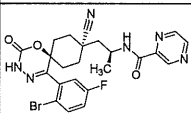
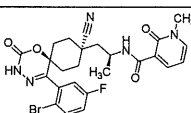
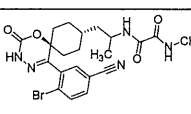
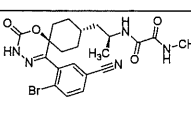
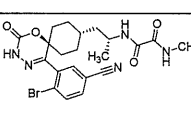
[0624]

Table 1-57

2-131		1H-NMR (DMSO-D6) δ : 11.25 (1H, s), 8.60-8.52 (2H, m), 7.83-7.76 (1H, m), 7.49-7.43 (1H, m), 7.35-7.28 (1H, m), 4.02-3.91 (1H, m), 2.92 (3H, s), 1.99-1.67 (4H, m), 1.64-1.41 (6H, m), 1.08 (3H, d, J = 6.5 Hz).	516	514
2-132		1H-NMR (DMSO-D6) δ : 11.41 (1H, s), 8.73 (1H, d, J = 9.2 Hz), 8.58 (1H, s), 7.92 (1H, d, J = 8.8 Hz), 7.67-7.64 (1H, m), 7.51-7.46 (1H, m), 4.16-4.03 (1H, m), 2.30-1.94 (4H, m), 1.84-1.51 (6H, m), 1.12 (3H, d, J = 6.6 Hz).	577	575
2-133		1H-NMR (DMSO-D6) δ : 11.38 (1H, s), 8.73 (1H, d, J = 9.7 Hz), 8.58 (1H, s), 7.85-7.79 (1H, m), 7.58-7.50 (1H, m), 7.40-7.30 (1H, m), 4.19-4.06 (1H, m), 2.29-1.95 (4H, m), 1.83-1.53 (6H, m), 1.12 (3H, d, J = 6.6 Hz).	511	509
2-134		1H-NMR (DMSO-D6) δ : 11.34 (1H, s), 8.72 (1H, d, J = 9.2 Hz), 8.57 (1H, s), 7.82-7.74 (1H, m), 7.62-7.54 (1H, m), 7.44-7.36 (1H, m), 4.17-4.05 (1H, m), 2.27-2.14 (2H, m), 2.13-1.96 (2H, m), 1.81-1.53 (6H, m), 1.12 (3H, d, J = 6.5 Hz).	511	509
2-135		1H-NMR (DMSO-D6) δ : 11.22 (1H, s), 8.62-8.52 (2H, m), 7.78-7.70 (1H, m), 7.56-7.47 (1H, m), 7.41-7.33 (1H, m), 4.03-3.91 (1H, m), 2.93-2.89 (3H, m), 1.96-1.79 (3H, m), 1.75-1.66 (1H, m), 1.63-1.42 (6H, m), 1.08 (3H, d, J = 6.5 Hz).	516	514
2-136		1H-NMR (DMSO-D6) δ : 11.23 (1H, s), 9.31 (1H, s), 9.04 (1H, d, J = 4.8 Hz), 8.87 (1H, d, J = 8.6 Hz), 8.00 (1H, d, J = 5.4 Hz), 7.81-7.75 (1H, m), 7.48-7.42 (1H, m), 7.35-7.27 (1H, m), 4.28-4.14 (1H, m), 2.95 (3H, s), 2.02-1.86 (3H, m), 1.80-1.73 (1H, m), 1.69-1.46 (6H, m), 1.17 (3H, d, J = 6.5 Hz).	534	532
2-137		1H-NMR (DMSO-D6) δ : 11.23 (1H, s), 9.40-9.37 (1H, m), 9.10 (1H, d, J = 8.6 Hz), 8.20-8.16 (1H, m), 7.91-7.86 (1H, m), 7.81-7.75 (1H, m), 7.47-7.42 (1H, m), 7.34-7.27 (1H, m), 4.34-4.22 (1H, m), 2.96 (3H, s), 2.04-1.48 (10H, m), 1.20 (3H, d, J = 6.5 Hz).	534	532
2-138		1H-NMR (DMSO-D6) δ : 11.40 (1H, s), 8.73 (1H, d, J = 9.2 Hz), 8.57 (1H, s), 7.67-7.59 (1H, m), 7.57-7.51 (1H, m), 7.27 (1H, t, J = 72.2 Hz), 4.18-4.05 (1H, m), 2.29-1.93 (4H, m), 1.83-1.50 (6H, m), 1.12 (3H, d, J = 6.5 Hz).	577	575
2-139		1H-NMR (DMSO-D6) δ : 11.40 (1H, s), 8.73 (1H, d, J = 9.7 Hz), 8.63-8.57 (1H, m), 8.08-8.01 (1H, m), 7.88-7.81 (1H, m), 4.17-4.06 (1H, m), 2.64 (3H, d, J = 4.8 Hz), 2.27-2.15 (2H, m), 2.13-1.96 (2H, m), 1.81-1.55 (6H, m), 1.12 (3H, d, J = 6.5 Hz).	526	524
2-140		1H-NMR (DMSO-D6) δ : 11.40 (1H, s), 8.73 (1H, d, J = 9.7 Hz), 8.57 (1H, s), 8.08-8.01 (1H, m), 7.88-7.81 (1H, m), 4.18-4.06 (1H, m), 2.28-1.93 (4H, m), 1.84-1.55 (6H, m), 1.12 (3H, d, J = 6.5 Hz).	529	527

[0625]

Table 1-58

2-141			¹ H-NMR (DMSO-D ₆) δ: 11.36 (1H, s), 9.30 (1H, s), 9.06-9.00 (2H, m), 8.01-7.97 (1H, m), 7.82-7.76 (1H, m), 7.55-7.49 (1H, m), 7.35-7.28 (1H, m), 4.44-4.28 (1H, m), 2.31-2.01 (4H, m), 1.86-1.52 (6H, m), 1.21 (3H, d, J = 6.5 Hz).	529	527
2-142			¹ H-NMR (DMSO-D ₆) δ: 11.36 (1H, s), 9.38 (1H, d, J = 5.4 Hz), 9.27 (1H, d, J = 9.7 Hz), 8.20-8.15 (1H, m), 7.90-7.85 (1H, m), 7.82-7.77 (1H, m), 7.55-7.49 (1H, m), 7.35-7.28 (1H, m), 4.50-4.36 (1H, m), 2.31-2.03 (4H, m), 1.87-1.54 (6H, m), 1.24 (3H, d, J = 6.5 Hz).	529	527
2-143			¹ H-NMR (DMSO-D ₆) δ: 11.36 (1H, s), 8.94 (2H, d, J = 4.8 Hz), 8.89 (1H, d, J = 9.2 Hz), 7.83-7.77 (1H, m), 7.67-7.63 (1H, m), 7.55-7.50 (1H, m), 7.35-7.28 (1H, m), 4.41-4.30 (1H, m), 2.31-2.01 (4H, m), 1.87-1.55 (6H, m), 1.20 (3H, d, J = 7.0 Hz).	529	527
2-144			¹ H-NMR (DMSO-D ₆) δ: 11.25 (1H, s), 8.65-8.53 (2H, m), 7.84-7.76 (1H, m), 7.49-7.42 (1H, m), 7.36-7.28 (1H, m), 4.02-3.91 (1H, m), 2.92 (3H, d, J = 1.1 Hz), 2.65 (3H, dd, J = 4.8, 1.1 Hz), 1.98-1.66 (4H, m), 1.63-1.40 (6H, m), 1.08 (3H, d, J = 6.5 Hz).	513	511
2-145			¹ H-NMR (DMSO-D ₆) δ: 11.21 (1H, s), 8.65-8.53 (2H, m), 7.76-7.71 (1H, m), 7.55-7.48 (1H, m), 7.40-7.33 (1H, m), 4.03-3.91 (1H, m), 2.91 (3H, d, J = 1.1 Hz), 2.65 (3H, d, J = 4.3 Hz), 1.96-1.67 (4H, m), 1.64-1.41 (6H, m), 1.08 (3H, d, J = 6.5 Hz).	513	511
2-146			¹ H-NMR (DMSO-D ₆) δ: 11.36 (1H, s), 9.16 (1H, s), 8.92 (1H, d, J = 9.7 Hz), 8.86-8.83 (1H, m), 8.72-8.69 (1H, m), 7.83-7.77 (1H, m), 7.55-7.49 (1H, m), 7.35-7.29 (1H, m), 4.45-4.32 (1H, m), 2.35-2.03 (4H, m), 1.85-1.55 (6H, m), 1.21 (3H, d, J = 6.5 Hz).	529	527
2-147			¹ H-NMR (DMSO-D ₆) δ: 11.37 (1H, s), 9.89-9.80 (1H, m), 8.30-8.24 (1H, m), 8.04-7.99 (1H, m), 7.83-7.76 (1H, m), 7.56-7.50 (1H, m), 7.36-7.29 (1H, m), 6.50-6.43 (1H, m), 4.38-4.24 (1H, m), 3.54 (3H, s), 2.29-2.16 (2H, m), 2.09-1.54 (8H, m), 1.21-1.15 (3H, m).	558	556
2-148		racemate	¹ H-NMR (DMSO-D ₆) δ: 11.32 (1H, s), 8.64-8.58 (1H, m), 8.46 (1H, d, J = 9.2 Hz), 8.10 (1H, s), 8.03-7.99 (1H, m), 7.91-7.86 (1H, m), 3.83-3.73 (1H, m), 2.66 (3H, d, J = 4.8 Hz), 1.94-1.55 (7H, m), 1.47-1.15 (4H, m), 1.04 (3H, d, J = 6.6 Hz).	490	488
2-149			¹ H-NMR (DMSO-D ₆) δ: 11.32 (1H, s), 8.64-8.58 (1H, m), 8.46 (1H, d, J = 9.2 Hz), 8.10 (1H, s), 8.03-7.99 (1H, m), 7.91-7.86 (1H, m), 3.83-3.73 (1H, m), 2.66 (3H, d, J = 4.8 Hz), 1.94-1.55 (7H, m), 1.47-1.15 (4H, m), 1.04 (3H, d, J = 6.6 Hz).	490	488
2-150			¹ H-NMR (DMSO-D ₆) δ: 11.32 (1H, s), 8.64-8.58 (1H, m), 8.46 (1H, d, J = 9.2 Hz), 8.10 (1H, s), 8.03-7.99 (1H, m), 7.91-7.86 (1H, m), 3.83-3.73 (1H, m), 2.66 (3H, d, J = 4.8 Hz), 1.94-1.55 (7H, m), 1.47-1.15 (4H, m), 1.04 (3H, d, J = 6.6 Hz).	490	488

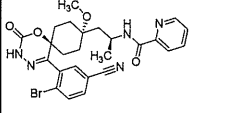
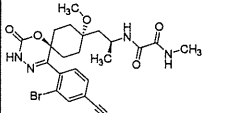
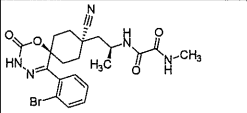
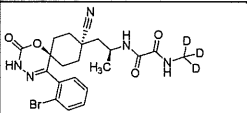
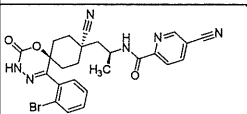
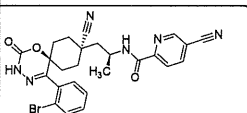
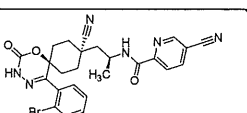
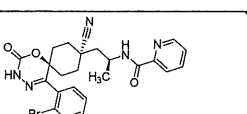
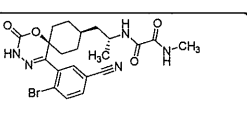
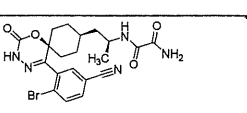
[0626]

Table 1-59

2-151			¹ H-NMR (DMSO-D ₆) δ: 11.27 (1H, s), 8.65-8.52 (2H, m), 8.05-7.97 (1H, m), 7.80-7.72 (1H, m), 4.02-3.91 (1H, m), 2.93 (3H, s), 2.65 (3H, d, J = 4.8 Hz), 1.96-1.69 (4H, m), 1.64-1.41 (6H, m), 1.08 (3H, d, J = 6.5 Hz).	531	529
2-152			¹ H-NMR (DMSO-D ₆) δ: 11.39 (1H, s), 8.72 (1H, d, J = 9.2 Hz), 8.57 (1H, s), 7.59-7.48 (2H, m), 7.39-7.34 (1H, m), 4.17-4.05 (1H, m), 2.28-2.15 (2H, m), 2.13-1.95 (2H, m), 1.82-1.52 (6H, m), 1.12 (3H, d, J = 6.5 Hz).	511	509
2-153			¹ H-NMR (DMSO-D ₆) δ: 11.39 (1H, s), 8.72 (1H, d, J = 9.2 Hz), 8.63-8.57 (1H, m), 7.58-7.47 (2H, m), 7.38-7.34 (1H, m), 4.17-4.04 (1H, m), 2.64 (3H, d, J = 4.8 Hz), 2.27-1.95 (4H, m), 1.81-1.53 (6H, m), 1.12 (3H, d, J = 6.5 Hz).	508	506
2-154			¹ H-NMR (DMSO-D ₆) δ: 11.38 (1H, s), 9.40-9.36 (1H, m), 9.27 (1H, d, J = 9.2 Hz), 8.19-8.15 (1H, m), 7.91-7.85 (1H, m), 7.55-7.45 (2H, m), 7.36-7.31 (1H, m), 4.48-4.35 (1H, m), 2.30-2.03 (4H, m), 1.88-1.52 (6H, m), 1.23 (3H, d, J = 7.0 Hz).	529	527
2-155			¹ H-NMR (DMSO-D ₆) δ: 11.36 (1H, s), 9.39-9.36 (1H, m), 9.27 (1H, d, J = 9.2 Hz), 8.19-8.16 (1H, m), 7.88 (1H, dd, J = 8.6, 4.8 Hz), 7.80 (1H, d, J = 8.6 Hz), 7.39-7.36 (1H, m), 7.28 (1H, t, J = 73.5 Hz), 7.27-7.22 (1H, m), 4.48-4.36 (1H, m), 2.31-2.02 (4H, m), 1.87-1.55 (6H, m), 1.24 (3H, d, J = 6.5 Hz).	577	575
2-156			¹ H-NMR (DMSO-D ₆) δ: 11.33 (1H, s), 9.39-9.36 (1H, m), 9.27 (1H, d, J = 9.2 Hz), 8.20-8.15 (1H, m), 7.88 (1H, dd, J = 8.6, 4.8 Hz), 7.75 (1H, dd, J = 8.6, 2.7 Hz), 7.59-7.53 (1H, m), 7.40-7.33 (1H, m), 4.48-4.36 (1H, m), 2.29-2.02 (4H, m), 1.86-1.52 (6H, m), 1.23 (3H, d, J = 6.5 Hz).	529	527
2-157			¹ H-NMR (DMSO-D ₆) δ: 11.39 (1H, s), 9.40-9.36 (1H, m), 9.27 (1H, d, J = 9.7 Hz), 8.19-8.15 (1H, m), 8.05-7.99 (1H, m), 7.90-7.79 (2H, m), 4.47-4.38 (1H, m), 2.29-2.04 (4H, m), 1.86-1.56 (6H, m), 1.24 (3H, d, J = 6.5 Hz).	547	545
2-158			¹ H-NMR (DMSO-D ₆) δ: 11.27 (1H, s), 8.64-8.53 (2H, m), 7.57-7.46 (2H, m), 7.30 (1H, d, J = 7.0 Hz), 4.04-3.91 (1H, m), 2.91 (3H, s), 2.65 (3H, d, J = 4.8 Hz), 1.96-1.67 (4H, m), 1.65-1.41 (6H, m), 1.08 (3H, d, J = 6.5 Hz).	513	511
2-159			¹ H-NMR (DMSO-D ₆) δ: 11.38 (1H, s), 8.76 (1H, d, J = 9.2 Hz), 8.62 (1H, d, J = 4.3 Hz), 8.03-7.93 (2H, m), 7.59-7.45 (3H, m), 7.36-7.32 (1H, m), 4.41-4.29 (1H, m), 2.29-2.01 (4H, m), 1.87-1.53 (6H, m), 1.20 (3H, d, J = 7.0 Hz).	528	526
2-160			¹ H-NMR (DMSO-D ₆) δ: 11.30 (1H, s), 8.64-8.56 (2H, m), 8.08 (1H, d, J = 1.6 Hz), 8.01-7.97 (1H, m), 7.89-7.85 (1H, m), 4.06-3.96 (1H, m), 2.65 (3H, d, J = 4.8 Hz), 2.03-1.89 (2H, m), 1.76-1.43 (4H, m), 1.27-1.17 (4H, m), 1.06 (3H, d, J = 6.5 Hz), 0.76 (3H, s).	504	502

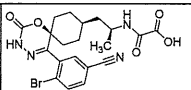
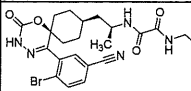
[0627]

Table 1-60

2-161			¹ H-NMR (DMSO-D ₆) δ: 11.31 (1H, s), 8.64-8.57 (2H, m), 8.07-7.94 (4H, m), 7.89-7.85 (1H, m), 7.60-7.55 (1H, m), 4.24-4.14 (1H, m), 2.96 (3H, s), 1.98-1.47 (10H, m), 1.17 (3H, d, J = 6.5 Hz).	540	538
2-162			¹ H-NMR (DMSO-D ₆) δ: 11.33 (1H, s), 8.64-8.53 (2H, m), 8.36 (1H, d, J = 1.6 Hz), 8.00-7.96 (1H, m), 7.68 (1H, d, J = 8.1 Hz), 4.02-3.91 (1H, m), 2.91 (3H, s), 2.65 (3H, d, J = 4.8 Hz), 1.98-1.79 (3H, m), 1.77-1.68 (1H, m), 1.62-1.42 (6H, m), 1.08 (3H, d, J = 7.0 Hz).	520	518
2-163			¹ H-NMR (DMSO-D ₆) δ: 11.31 (1H, s), 8.71 (1H, d, J = 9.7 Hz), 8.63-8.56 (1H, m), 7.77 (1H, d, J = 7.5 Hz), 7.51-7.47 (2H, m), 7.45-7.40 (1H, m), 4.17-4.04 (1H, m), 2.64 (3H, d, J = 4.8 Hz), 2.27-2.16 (2H, m), 2.11-1.95 (2H, m), 1.81-1.52 (6H, m), 1.12 (3H, d, J = 6.5 Hz).	490	488
2-164			¹ H-NMR (DMSO-D ₆) δ: 11.31 (1H, s), 8.71 (1H, d, J = 9.2 Hz), 8.57 (1H, s), 7.77 (1H, d, J = 8.1 Hz), 7.54-7.38 (3H, m), 4.19-4.03 (1H, m), 2.27-2.16 (2H, m), 2.12-1.93 (2H, m), 1.82-1.52 (6H, m), 1.12 (3H, d, J = 6.5 Hz).	493	491
2-165			¹ H-NMR (DMSO-D ₆) δ: 11.30 (1H, s), 9.09 (1H, d, J = 2.2 Hz), 8.99 (1H, d, J = 9.2 Hz), 8.50-8.46 (1H, m), 8.14 (1H, d, J = 8.1 Hz), 7.75 (1H, d, J = 7.5 Hz), 7.48-7.44 (2H, m), 7.43-7.37 (1H, m), 4.41-4.31 (1H, m), 2.29-2.01 (4H, m), 1.84-1.53 (6H, m), 1.20 (3H, d, J = 6.5 Hz).	535	533
2-166			¹ H-NMR (DMSO-D ₆) δ: 11.38 (1H, s), 9.10-9.08 (1H, m), 8.99 (1H, d, J = 9.7 Hz), 8.50-8.46 (1H, m), 8.14 (1H, d, J = 8.1 Hz), 7.55-7.46 (2H, m), 7.36-7.32 (1H, m), 4.41-4.31 (1H, m), 2.28-2.01 (4H, m), 1.83-1.52 (6H, m), 1.20 (3H, d, J = 6.5 Hz).	553	551
2-167			¹ H-NMR (DMSO-D ₆) δ: 11.33 (1H, s), 9.09 (1H, d, J = 2.2 Hz), 8.99 (1H, d, J = 9.7 Hz), 8.50-8.46 (1H, m), 8.16-8.13 (1H, m), 7.75 (1H, dd, J = 8.6, 2.2 Hz), 7.58-7.53 (1H, m), 7.40-7.33 (1H, m), 4.42-4.31 (1H, m), 2.28-2.01 (4H, m), 1.83-1.51 (6H, m), 1.20 (3H, d, J = 7.0 Hz).	553	551
2-168			¹ H-NMR (DMSO-D ₆) δ: 11.29 (1H, s), 8.75 (1H, d, J = 9.7 Hz), 8.61 (1H, d, J = 3.8 Hz), 8.03-7.93 (2H, m), 7.75 (1H, d, J = 8.1 Hz), 7.59-7.54 (1H, m), 7.48-7.44 (2H, m), 7.43-7.36 (1H, m), 4.40-4.29 (1H, m), 2.32-2.01 (4H, m), 1.87-1.52 (6H, m), 1.20 (3H, d, J = 6.5 Hz).	510	508
2-169			¹ H-NMR (DMSO-D ₆) δ: 11.29 (1H, s), 8.65-8.59 (1H, m), 8.41 (1H, d, J = 9.0 Hz), 8.00 (1H, d, J = 1.8 Hz), 7.98 (1H, d, J = 8.3 Hz), 7.86 (1H, dd, J = 8.3, 1.8 Hz), 3.98-3.85 (1H, m), 2.64 (3H, d, J = 4.9 Hz), 2.16-2.04 (2H, m), 1.69-1.59 (1H, m), 1.59-1.13 (8H, m), 1.06 (3H, d, J = 6.5 Hz).	490	488
2-170			¹ H-NMR (DMSO-D ₆) δ: 11.30 (1H, s), 8.39 (1H, d, J = 8.6 Hz), 8.02-7.95 (3H, m), 7.88-7.83 (1H, m), 7.72 (1H, br s), 3.94-3.82 (1H, m), 2.16-2.06 (2H, m), 1.68-1.60 (1H, m), 1.56-1.12 (8H, m), 1.05 (3H, d, J = 6.5 Hz).	476	474

[0628]

Table 1-61

2-171			1H-NMR (DMSO-D6) δ: 11.30 (1H, s), 8.07-7.80 (4H, m), 3.84-3.74 (1H, m), 2.21-2.01 (2H, m), 1.70-1.10 (9H, m), 1.01 (3H, d, J = 6.6 Hz).	477	475
2-172			1H-NMR (DMSO-D6) δ: 11.30 (1H, s), 9.11 (1H, t, J = 6.7 Hz), 8.52 (1H, d, J = 9.2 Hz), 8.00 (1H, d, J = 2.2 Hz), 7.98 (1H, d, J = 8.6 Hz), 7.86 (1H, dd, J = 8.6, 2.2 Hz), 5.65 (1H, t, J = 6.7 Hz), 4.54 (2H, t, J = 6.7 Hz), 3.98-3.86 (1H, m), 2.16-2.06 (2H, m), 1.68-1.16 (9H, m), 1.06 (3H, d, J = 6.5 Hz).	488 (M-17)	504

[0629]

Experimental Example 1: Evaluation of human PLD1 enzyme

5 inhibitory activity

A method for measuring human PLD1 enzyme inhibitory activity using an enzyme in which a FLAG-tag is added to the N-terminus of full-length human PLD1 (1-1036 amino acids) is shown below.

10 1. Production of full-length human PLD1-expression plasmid

DNA fragment in which a FLAG-tag sequence is added to the 5'-end of full-length human PLD1 was amplified by PCR method, using commercially available human PLD1 gene (Promega KK) as a template. The amplified DNA fragment was fused with vector
15 pVL1393 for baculovirus production (Pharmingen) digested with BamHI and EcoRI, using In-Fusion HD Cloning Kit (Takara Bio). The full-length human PLD1-expression plasmid DNA for baculovirus was isolated from Escherichia coli DH5α (TOYOBO) transformed with the obtained In-Fusion reaction product.

20 Next, DNA fragment in which a FLAG-tag sequence is added to the 5'-end of full-length human PLD1 was amplified by PCR method, using the full-length human PLD1-expression plasmid DNA for baculovirus as a template. The amplified DNA fragment was fused with a DNA fragment in which a linker sequence is
25 introduced into pcDNA3.4-TOPO (Life Technologies), using In-Fusion HD Cloning Kit (Takara Bio). The full-length human PLD1-expression plasmid DNA for animal cells was isolated from Escherichia coli DH5α transformed with the obtained In-Fusion reaction product. The base sequence of the full-length human
30 PLD1 cloned into vector was determined by a Dye Terminator

method using BigDye Terminator v3.1 Cycle Sequencing Kit (Applied Biosystems). The determined sequence was a sequence in which the FLAG-tag sequence was inserted at the 5'-end of the full-length human PLD1 (GenBank Accession

5 Number:NM_001130081).

[0630]

2. Production of full-length human PLD1 protein in Expi293F cell expression system

Expi293F cells (Life Technologies) were cultured with
10 shaking using Expi293 Expression Medium (Life Technologies) as a medium at 37°C in the presence of 8% CO₂. The gene introduction reagent PEI was prepared by dissolving Polyethylenimine Max (nominally MW 40,000) (Polysciences) in MilliQ water, adjusting the pH of the solution to 7.0 with NaOH
15 to obtain a 1 mg/mL solution, and then filtering the solution through 0.22 µm filter. The full-length human PLD1-expression plasmid DNA for animal cells was transfected into Expi293F cells using PEI, and after 48 hours of shaking culture, the cells were collected and stored at -80°C.

20 [0631]

3. Purification of full-length human PLD1 protein

To the full-length human PLD1-expressed cells was added a Homogenate buffer (20 mmol/L Na-phosphate pH 7.5, 250 mmol/L NaCl, 1 mmol/L MgCl₂, 1%β-OG, 0.05 mmol/L DTT+complete EDTA-free (Roche Diagnostics K.K.)), and the cells were lysed by
25 Microfluidizer Processor M-110EH (Mizuho Kogyo Co., Ltd.). The lysate was centrifuged at 10,100×g at 4°C for 15 minutes, and the supernatant was collected and filtered through 0.45 µm filter. To the centrifuged supernatant was added ANTI-FLAG M2
30 Affinity Gel (SIGMA-Aldrich) resin equilibrated with a Homogenate buffer, and the mixed solution was stirred at 4°C for 1 hr or more. The mixed solution was loaded onto Poly-Prep column, and the resin was washed with a Wash buffer (20 mmol/L Na-phosphate pH 7.5, 150 mmol/L NaCl, 1 mmol/L MgCl₂, 0.02%
35 Triton, 0.05 mmol/L DTT). A Wash buffer containing 400 µg/mL

DYKDDDDK Peptide (Scrum Inc.) was added to the column to elute the protein bound to the resin. The eluted fractions were subjected to SDS-PAGE followed by CBB staining to identify the fractions containing the full-length human PLD1. The eluted
5 fractions of the full-length human PLD1 were collected and concentrated using Amicon Ultra-15 100k (Merck Millipore). The concentrated fractions were collected, flash-frozen in liquid nitrogen and stored at -80°C.

[0632]

10 4. Evaluation human PLD1 inhibitory activity

A DMSO or test substance solution (the DMSO final concentration: 5%) prepared by diluting DMSO or test substance with an Assay buffer (50 mmol/L HEPES pH 7.5, 80 mmol/L KCl, 3 mmol/L EGTA, 3.6 mmol/L MgCl₂, 0.01% NP-40, 0.1% BSA), and the
15 solution was added to a 384 well Assay Plate (Black, Polystyrene, Non-Treated, Cat No.3573, Corning) by 5 µL/well. A full-length human PLD1 enzyme solution (6 nmol/L) diluted with an Assay buffer was added thereto by 5 µL/well (the Assay buffer was added to blank wells). A 1,2-diheptanoyl-sn-
20 glycerol-3-phosphocholine (Avanti Polar Lipids) substrate solution (6 mmol/L) diluted with an Assay buffer was added thereto by 5 µL/well, and enzymatic reaction was carried out at room temperature for 60 minutes. Immediately before stopping the reaction, a detection solution (200 µmol/L AmplexRed
25 (ThermoFisher), 0.1 U/mL Choline Oxidase (Sigma-Aldrich), 4 U/mL Horseradish peroxidase (ThermoFisher)) containing 4 µmol/L of 5-fluoro-2-indolyl deschlorohalopemide (R&D Systems) as a reaction terminator was prepared with an Assay buffer, the detection solution was added thereto at 5 µL/well to terminate
30 the enzymatic reaction. Immediately after stopping the reaction and 30 minutes after incubation at room temperature, the fluorescence values at Ex: 531 nm/Em: 590 nm were measured by ARVO X5 (PerkinElmer). The inhibition rate was calculated from the change in the fluorescence values immediately after
35 stopping the reaction and after 30 minutes. Data were obtained

by subtracting the average fluorescence value of the blank wells from the average fluorescence value of the treated wells. The inhibition rate at each concentration of the test substance was calculated from the following formula:

5 [0633]

$$100 - (B/A) \times 100$$

A: data of solvent control

B: data of test substance-treatment

10 [0634]

The IC₅₀ value (50% inhibitory concentration) of the test substance was calculated by fitting the inhibition rate at each concentration of the test substance to a logistic curve. The results of the compounds of each example are shown in Tables 2-1 to 2-14 below. For Examples 34, 186, 2-047, 2-099, 2-101, 2-150 and 2-171, the inhibition rate of PLD1 at 10 μM compound is shown, and Example 34 gave 36% inhibition, Example 186 gave 33% inhibition, Example 2-047 gave 32% inhibition, Example 2-099 gave 21% inhibition, Example 2-101 gave 13% inhibition, 20 Examples 2-150 gave 25% inhibition, and Example 2-171 gave 12% inhibition.

[0635]

Experimental Example 2: Evaluation of human PLD2 enzyme inhibitory activity

25 A method for measuring human PLD2 enzyme inhibitory activity using an enzyme in which a FLAG-tag is added to the N-terminus of full-length human PLD2 (1-933 amino acids) is shown below.

1. Production of full-length human PLD2-expression plasmid

30 DNA fragment in which a FLAG-tag sequence is added to the 5'-end of full-length human PLD2 was amplified by PCR method, using commercially available human PLD2 gene (Promega KK) as a template. The amplified DNA fragment was fused with vector pVL1393 for baculovirus production (Pharmlngen) digested with 35 BamHI and EcoRI, using In-Fusion HD Cloning Kit (Takara Bio).

The full-length human PLD2-expression plasmid DNA for baculovirus was isolated from Escherichia coli DH5 α (TOYOBO) transformed with the obtained In-Fusion reaction product.

Next, DNA fragment in which a FLAG-tag sequence is added to the 5'-end of full-length human PLD2 was amplified by PCR method, using the full-length human PLD2-expression plasmid DNA for baculovirus as a template. The amplified DNA fragment was fused with a DNA fragment in which a linker sequence is introduced into pcDNA3.4-TOPO (Life Technologies), using In-Fusion HD Cloning Kit (Takara Bio). The full-length human PLD2-expression plasmid DNA for animal cells was isolated from Escherichia coli DH5 α transformed with the obtained In-Fusion reaction product. The base sequence of the full-length human PLD2 cloned into vector was determined by a Dye Terminator method using BigDye Terminator v3.1 Cycle Sequencing Kit (Applied Biosystems). The determined sequence was a sequence in which the FLAG-tag sequence was inserted at the 5'-end of the full-length human PLD2 (GenBank Accession Number:NM_002663).

[0636]

2. Production of full-length human PLD2 protein in Expi293F cell expression system

Expi293F cells (Life Technologies) were cultured with shaking using Expi293 Expression Medium (Life Technologies) as a medium at 37°C in the presence of 8% CO₂. The gene introduction reagent PEI was prepared by dissolving Polyethylenimine Max (nominally MW 40,000) (Polysciences) in MilliQ water, adjusting the pH of the solution to 7.0 with NaOH to obtain a 1 mg/mL solution, and then filtering the solution through 0.22 μ m filter. The full-length human PLD2-expression plasmid DNA for animal cells was transfected into Expi293F cells using PEI, and after 48 hours of shaking culture, the cells were collected and stored at -80°C.

[0637]

3. Purification of full-length human PLD2 protein

To the full-length human PLD2-expressed cells was added a Homogenate buffer (20 mmol/L Na-phosphate pH 7.5, 250 mmol/L NaCl, 1 mmol/L MgCl₂, 1%β-OG, 0.05 mmol/L DTT+complete EDTA-free (Roche Diagnostics K.K.)), and the cells were lysed by
5 Microfluidizer Processor M-110EH (Mizuho Kogyo Co., Ltd.). The lysate was centrifuged at 10,100×g at 4°C for 15 minutes, and the supernatant was collected and filtered through 0.45 μm filter. To the centrifuged supernatant was added ANTI-FLAG M2 Affinity Gel (SIGMA-Aldrich) resin equilibrated with a
10 Homogenate buffer, and the mixed solution was stirred at 4°C for 1 hr or more. The mixed solution was loaded onto Poly-Prep column, and the resin was washed with a Wash buffer (20 mmol/L Na-phosphate pH 7.5, 150 mmol/L NaCl, 1 mmol/L MgCl₂, 0.02% Triton, 0.05 mmol/L DTT). A Wash buffer containing 400 μg/mL
15 DYKDDDDK Peptide (Scrum Inc.) was added to the column to elute the protein bound to the resin. The eluted fractions were subjected to SDS-PAGE followed by CBB staining to identify the fractions containing the full-length human PLD2. The eluted fractions of the full-length human PLD2 were collected and
20 concentrated using Amicon Ultra-15 100k (Merck Millipore). The concentrated fractions were collected, flash-frozen in liquid nitrogen and stored at -80°C.

[0638]

4. Evaluation human PLD2 inhibitory activity

25 A DMSO or test substance solution (the DMSO final concentration: 5%) prepared by diluting DMSO or test substance with an Assay buffer (50 mmol/L HEPES pH 7.5, 80 mmol/L KCl, 3 mmol/L EGTA, 3.6 mmol/L MgCl₂, 0.01% NP-40, 0.1% BSA), and the solution was added to a 384 well Assay Plate (Black,
30 Polystyrene, Non-Treated, Cat No.3573, Corning) by 5 μL/well. A full-length human PLD2 enzyme solution (6 nmol/L) diluted with an Assay buffer was added thereto by 5 μL/well (the Assay buffer was added to blank wells). A 1,2-diheptanoyl-sn-glycero-3-phosphocholine (Avanti Polar Lipids) substrate
35 solution (6 mmol/L) diluted with an Assay buffer was added

thereto by 5 μ L/well, and enzymatic reaction was carried out at room temperature for 60 minutes. Immediately before stopping the reaction, a detection solution (200 μ mol/L AmplexRed (Thermofisher), 0.1 U/mL Choline Oxidase (Sigma-Aldrich), 4 U/mL Horseradish peroxidase (Thermofisher)) containing 4 μ mol/L of 5-fluoro-2-indolyl deschlorohalopemide (R&D Systems) as a reaction terminator was prepared with an Assay buffer, the detection solution was added thereto at 5 μ L/well to terminate the enzymatic reaction. Immediately after stopping the reaction and 30 minutes after incubation at room temperature, the fluorescence values at Ex: 531 nm/Em: 590 nm were measured by ARVO X5 (PerkinElmer). The inhibition rate was calculated from the change in the fluorescence values immediately after stopping the reaction and after 30 minutes. Data were obtained by subtracting the average fluorescence value of the blank wells from the average fluorescence value of the treated wells. The inhibition rate at each concentration of the test substance was calculated from the following formula:

[0639]

$$100 - (B/A) \times 100$$

A: data of solvent control

B: data of test substance-treatment

[0640]

The IC₅₀ value (50% inhibitory concentration) of the test substance was calculated by fitting the inhibition rate at each concentration of the test substance to a logistic curve. The results of the compounds of each example are shown in Tables 2-1 to 2-14 below. For Examples 34, 186, 2-047, 2-101, 2-112, 2-150 and 2-171, the inhibition rate of PLD2 at 10 μ M compound is shown, and Example 34 gave 17% inhibition, Example 186 gave 18% inhibition, Example 2-047 gave Example 34% inhibition, Example 2-101 gave 28% inhibition, Example 2-112 gave 39% inhibition, Example 2-150 gave 30% inhibition, and Example 2-171 gave 23% inhibition.

[0641]

Table 2-1

Example No.	PLD1 IC ₅₀ (μM)	PLD2 IC ₅₀ (μM)
1	0.033	< 0.010
2	0.020	< 0.010
3	0.027	< 0.010
4	0.036	0.011
5	0.164	0.171
6	0.069	0.120
7	0.030	0.044
8	0.030	0.010
9	0.083	0.056
10	0.092	0.106
11	0.228	0.394
12	< 0.010	< 0.010
13	0.036	< 0.010
14	0.010	< 0.010
15	0.025	< 0.010
16	0.926	0.968
17	0.816	1.044
18	0.852	0.157
19	0.017	0.010
20	1.646	3.769
21	0.307	0.346
22	0.066	0.049
23	0.039	0.051
24	0.041	0.031
25	0.108	0.101
26	< 0.010	< 0.010
27	0.014	0.013
28	0.341	0.303
29	0.999	1.715
30	0.123	0.153
31	0.024	< 0.010
32	0.032	< 0.010
33	0.025	< 0.010
34	36% inhibition at 10μM	17% inhibition at 10μM
35	0.257	0.367
36	0.221	0.137
37	< 0.010	< 0.010
38	0.035	0.088
39	0.093	0.024
40	0.013	< 0.010

[0642]

Table 2-2

41	0.229	0.500
42	0.247	0.261
43	0.221	0.184
44	0.018	< 0.010
45	0.027	0.023
46	0.012	< 0.010
47	0.119	< 0.010
48	0.014	< 0.010
49	0.031	0.011
50	0.033	0.051
51	0.033	0.016
52	0.021	< 0.010
53	0.019	< 0.010
54	0.020	< 0.010
55	0.015	< 0.010
56	0.026	0.017
57	0.016	< 0.010
58	0.014	< 0.010
59	< 0.010	< 0.010
60	< 0.010	< 0.010
61	0.014	0.011
62	0.140	0.223
63	< 0.010	< 0.010
64	0.018	< 0.010
65	< 0.010	< 0.010
66	0.016	< 0.010
67	< 0.010	< 0.010
68	2.028	4.659
69	< 0.010	< 0.010
70	0.028	0.020
71	< 0.010	< 0.010
72	0.034	0.024
73	0.023	0.015
74	< 0.010	< 0.010
75	1.628	1.992
76	0.017	0.017
77	0.026	< 0.010
78	0.350	0.252
79	< 0.010	< 0.010
80	< 0.010	< 0.010

[0643]

Table 2-3

81	0.012	< 0.010
82	0.421	0.358
83	0.259	0.221
84	0.070	0.053
85	0.012	< 0.010
86	0.013	< 0.010
87	0.039	< 0.010
88	0.056	0.065
89	0.038	0.037
90	0.045	0.018
91	0.023	0.015
92	0.026	0.013
93	0.032	< 0.010
94	0.068	0.060
95	8.056	6.165
96	0.018	< 0.010
97	< 0.010	< 0.010
98	0.057	0.078
99	0.241	0.373
100	0.041	0.033
101	< 0.010	< 0.010
102	0.288	0.666
103	0.170	0.379
104	0.075	0.217
105	0.027	0.041
106	0.026	0.048
107	0.085	0.139
108	0.025	0.038
109	0.012	< 0.010
110	0.083	0.099
111	0.017	0.021
112	0.031	0.020
113	0.017	0.013
114	0.013	< 0.010
115	0.015	< 0.010
116	0.043	0.037
117	0.021	0.018
118	0.050	0.073
119	0.011	< 0.010
120	0.012	0.011

[0644]

Table 2-4

121	< 0.010	< 0.010
122	< 0.010	< 0.010
123	0.202	0.502
124	0.638	2.736
125	0.040	0.057
126	0.013	< 0.010
127	0.025	< 0.010
128	0.186	0.060
129	0.018	< 0.010
130	0.018	< 0.010
131	0.010	< 0.010
132	0.014	< 0.010
133	0.029	0.031
134	0.021	0.030
135	0.086	0.033
136	0.155	0.170
137	0.505	1.586
138	0.774	1.396
139	< 0.010	< 0.010
140	< 0.010	< 0.010
141	0.141	0.164
142	0.022	< 0.010
143	0.027	0.025
144	0.011	< 0.010
145	0.017	< 0.010
146	0.020	< 0.010
147	0.032	0.032
148	0.020	0.018
149	0.012	< 0.010
150	0.880	0.640
151	0.018	< 0.010
152	0.023	0.013
153	0.027	0.028
154	0.027	0.014
155	0.014	< 0.010
156	0.236	0.412
157	< 0.010	< 0.010
158	0.027	0.015
159	0.028	< 0.010
160	0.026	0.017

[0645]

Table 2-5

161	0.020	0.013
162	0.322	0.536
163	< 0.010	< 0.010
164	0.038	< 0.010
165	0.019	< 0.010
166	0.019	< 0.010
167	0.020	< 0.010
168	0.056	0.035
169	0.034	0.020
170	0.019	< 0.010
171	0.013	< 0.010
172	0.023	0.012
173	0.029	0.010
174	0.042	0.017
175	0.021	0.015
176	0.029	0.029
177	0.010	< 0.010
178	0.014	0.017
179	0.025	< 0.010
180	0.028	0.012
181	0.013	< 0.010
182	0.019	< 0.010
183	0.042	0.107
184	< 0.010	< 0.010
185	0.068	0.064
186	33% inhibition at 10uM	18% inhibition at 10uM
187	0.222	0.455
188	0.044	0.033
189	0.130	0.140
190	0.642	0.776
191	0.038	< 0.010
192	0.021	< 0.010
193	0.055	0.046
194	< 0.010	< 0.010
195	0.039	0.067
196	0.027	< 0.010
197	0.026	< 0.010
198	0.011	< 0.010
199	0.010	< 0.010
200	0.103	0.082

[0646]

Table 2-6

201	0.328	0.371
202	0.832	1.247
203	0.012	< 0.010
204	0.123	0.146
205	0.035	0.102
206	0.036	0.013
207	0.025	< 0.010
208	0.045	0.224
209	0.018	0.018
210	0.296	1.087
211	0.102	0.429
212	< 0.010	< 0.010
213	0.086	0.115
214	< 0.010	< 0.010
215	< 0.010	< 0.010
216	0.029	0.019
217	0.017	< 0.010
218	0.023	0.013
219	< 0.010	< 0.010
220	0.042	0.033
221	0.016	< 0.010
222	0.059	0.171
223	0.396	0.246
224	0.013	< 0.010
225	0.513	0.203
226	0.018	< 0.010
227	0.019	< 0.010
228	0.028	< 0.010
229	0.197	0.310
230	0.021	< 0.010
231	0.024	0.012
232	2.580	2.132
233	1.861	1.796
234	0.247	0.474
235	0.035	0.013
236	0.015	< 0.010
237	0.034	< 0.010
238	0.012	< 0.010
239	0.018	< 0.010
240	0.013	< 0.010

[0647]

Table 2-7

241	0.017	< 0.010
242	0.016	< 0.010
243	0.024	< 0.010
244	0.019	< 0.010
245	0.040	0.107
246	0.015	< 0.010
247	0.014	< 0.010
248	0.017	< 0.010
249	0.025	< 0.010
250	0.022	< 0.010
251	0.017	< 0.010
252	0.174	0.335
253	0.252	0.324
254	0.029	< 0.010
255	0.032	0.014
256	0.027	< 0.010
257	0.262	0.215
258	0.186	0.249
259	1.450	2.499
260	0.031	< 0.010
261	0.168	0.313
262	0.015	< 0.010
263	2.777	4.499
264	0.036	< 0.010
265	0.013	< 0.010
266	0.015	< 0.010
267	0.026	< 0.010
268	0.030	< 0.010
269	0.018	< 0.010
270	0.017	< 0.010
271	0.018	< 0.010
272	0.015	< 0.010
273	0.019	< 0.010
274	0.017	< 0.010
275	0.025	< 0.010
276	0.021	< 0.010
277	0.017	< 0.010
278	0.246	1.176
279	0.086	0.044
280	0.147	0.316

[0648]

Table 2-8

281	0.169	0.232
282	0.097	0.146
283	0.043	0.048
284	0.061	0.040
285	< 0.010	< 0.010
286	0.014	< 0.010
287	0.013	< 0.010
288	0.026	< 0.010
289	0.018	< 0.010
290	0.122	0.046
291	0.150	0.234
292	0.023	< 0.010
293	0.127	0.325
294	0.011	< 0.010
295	< 0.010	< 0.010
296	0.013	< 0.010
297	0.013	< 0.010
298	0.015	< 0.010
299	0.025	< 0.010
300	0.038	< 0.010
301	0.030	< 0.010
302	0.017	< 0.010
303	0.011	< 0.010
304	< 0.010	< 0.010
305	0.015	< 0.010
306	< 0.010	< 0.010
307	0.013	< 0.010
308	0.015	< 0.010
309	0.015	< 0.010
310	0.014	< 0.010
311	0.015	< 0.010
312	0.029	< 0.010
313	0.023	0.025
314	< 0.010	< 0.010
315	0.025	0.024
316	0.046	0.061
317	0.071	0.065
318	0.037	0.041
319	2.092	0.744
320	3.881	1.577

[0649]

Table 2-9

321	0.042	< 0.010
322	0.030	< 0.010
323	0.010	< 0.010
324	0.020	0.022
325	0.015	< 0.010
326	0.054	0.038
327	0.110	0.051
328	0.048	0.034
329	0.051	< 0.010
330	3.151	0.026
331	0.032	0.022
332	2.595	0.015
333	0.025	< 0.010
334	0.026	< 0.010
335	0.126	< 0.010
336	0.033	< 0.010
337	0.074	0.028
338	0.024	< 0.010
339	0.039	0.010

[0650]

Table 2-10

2-001	0.041	< 0.010
2-002	1.254	1.865
2-003	0.038	0.012
2-004	0.068	< 0.010
2-005	0.433	0.035
2-006	0.056	0.011
2-007	0.028	< 0.010
2-008	0.062	0.011
2-009	2.154	1.037
2-010	1.015	1.258
2-011	2.110	2.943
2-012	2.044	0.245
2-013	0.012	< 0.010
2-014	0.022	< 0.010
2-015	0.026	0.012
2-016	0.019	< 0.010
2-017	0.099	0.045
2-018	0.022	< 0.010
2-019	0.012	< 0.010
2-020	0.021	0.016
2-021	0.027	0.015
2-022	0.738	0.388
2-023	0.102	0.064
2-024	0.046	0.028
2-025	0.219	0.205
2-026	0.012	< 0.010
2-027	0.013	< 0.010
2-028	0.045	0.032
2-029	1.507	8.407
2-030	0.031	0.018
2-031	0.019	< 0.010
2-032	0.011	< 0.010
2-033	0.035	< 0.010
2-034	0.031	0.010
2-035	0.021	< 0.010
2-036	0.017	< 0.010
2-037	0.043	0.013
2-038	0.060	0.011
2-039	0.153	0.264
2-040	0.021	< 0.010

[0651]

Table 2-11

2-041	0.148	0.103
2-042	3.018	0.383
2-043	0.033	0.152
2-044	< 0.010	< 0.010
2-045	0.018	< 0.010
2-046	0.024	0.118
2-047	32% inhibition at 10uM	34% inhibition at 10uM
2-048	0.644	1.014
2-049	1.743	1.443
2-050	0.012	< 0.010
2-051	0.025	< 0.010
2-052	0.021	< 0.010
2-053	0.676	0.245
2-054	0.037	< 0.010
2-055	0.011	< 0.010
2-056	0.017	< 0.010
2-057	0.018	< 0.010
2-058	0.026	0.066
2-059	0.731	0.505
2-060	0.027	0.011
2-061	0.014	< 0.010
2-062	0.025	0.025
2-063	0.173	0.106
2-064	0.027	0.011
2-065	0.021	< 0.010
2-066	0.015	< 0.010
2-067	0.015	< 0.010
2-068	< 0.010	< 0.010
2-069	< 0.010	< 0.010
2-070	0.068	0.038
2-071	0.013	< 0.010
2-072	0.014	0.024
2-073	0.014	0.002
2-074	0.011	< 0.010
2-075	0.016	< 0.010
2-076	0.011	< 0.010
2-077	0.015	< 0.010
2-078	< 0.010	< 0.010
2-079	0.011	0.010
2-080	< 0.010	< 0.010

[0652]

Table 2-12

2-081	< 0.010	< 0.010
2-082	< 0.010	< 0.010
2-083	< 0.010	< 0.010
2-084	0.013	< 0.010
2-085	0.022	< 0.010
2-086	0.015	< 0.010
2-087	0.012	< 0.010
2-088	0.019	< 0.010
2-089	0.018	< 0.010
2-090	0.013	< 0.010
2-091	< 0.010	< 0.010
2-092	0.026	< 0.010
2-093	0.038	0.013
2-094	0.026	< 0.010
2-095	0.035	0.012
2-096	0.055	0.031
2-097	0.020	< 0.010
2-098	0.013	< 0.010
2-099	21% inhibition at 10µM	6.889
2-100	0.015	< 0.010
2-101	13% inhibition at 10µM	28% inhibition at 10µM
2-102	0.014	< 0.010
2-103	0.023	< 0.010
2-104	0.021	0.011
2-105	0.017	< 0.010
2-106	0.073	0.127
2-107	0.011	< 0.010
2-108	< 0.010	< 0.010
2-109	0.011	< 0.010
2-110	0.021	< 0.010
2-111	0.025	0.029
2-112	3.590	39% inhibition at 10µM
2-113	0.014	< 0.010
2-114	0.052	< 0.010
2-115	0.038	< 0.010
2-116	0.081	0.017
2-117	0.030	< 0.010
2-118	0.019	< 0.010
2-119	0.034	< 0.010
2-120	0.021	< 0.010

[0653]

Table 2-13

2-121	0.026	0.021
2-122	0.014	< 0.010
2-123	0.026	< 0.010
2-124	0.022	< 0.010
2-125	0.043	0.016
2-126	0.035	0.014
2-127	< 0.010	< 0.010
2-128	< 0.010	< 0.010
2-129	0.025	< 0.010
2-130	0.032	< 0.010
2-131	0.015	< 0.010
2-132	0.011	< 0.010
2-133	0.014	< 0.010
2-134	0.018	< 0.010
2-135	0.020	< 0.010
2-136	0.017	0.015
2-137	0.029	0.033
2-138	0.014	< 0.010
2-139	0.014	< 0.010
2-140	0.017	< 0.010
2-141	< 0.010	< 0.010
2-142	0.012	< 0.010
2-143	0.262	0.738
2-144	0.012	< 0.010
2-145	0.014	< 0.010
2-146	0.019	0.016
2-147	0.136	0.152
2-148	0.140	0.046
2-149	0.045	0.023
2-150	25% inhibition at 10uM	30% inhibition at 10uM
2-151	0.024	< 0.010
2-152	0.016	< 0.010
2-153	0.016	< 0.010
2-154	0.021	0.017
2-155	< 0.010	< 0.010
2-156	0.013	< 0.010
2-157	0.017	< 0.010
2-158	0.016	< 0.010
2-159	0.015	< 0.010
2-160	0.011	< 0.010

[0654]

Table 2-14

2-161	0.014	< 0.010
2-162	0.021	< 0.010
2-163	< 0.010	< 0.010
2-164	< 0.010	< 0.010
2-165	< 0.010	< 0.010
2-166	0.011	< 0.010
2-167	0.011	< 0.010
2-168	< 0.010	< 0.010
2-169	0.045	0.100
2-170	0.009	0.002
2-171	12% inhibition at 10uM	23% inhibition at 10uM
2-172	0.020	0.003

[0655]

5 The formulation examples of the present invention include the following formulations. However, the present invention is not limited by such formulation examples.

[0656]

Formulation Example 1 (Production of capsule)

- 10 1) Compound of Example 1 30 mg
 2) Microcrystalline cellulose 10 mg
 3) Lactose 19 mg
 4) Magnesium stearate 1 mg

 1), 2), 3) and 4) are mixed and filled in a gelatin capsule.

15 [0657]

Formulation Example 2 (Production of tablet)

- 1) Compound of Example 1 10 g
 2) Lactose 50 g
 3) Corn starch 15 g
20 4) Carmellose calcium 44 g
 5) Magnesium stearate 1 g

 The total amount of 1), 2), 3) and 30 g of 4) are kneaded with water, vacuum dried and then granulated. The granulated powder is mixed with 14 g of 4) and 1 g of 5), and the mixture
25 is tableted by a tableting machine. In this way, 1000 tablets containing 10 mg of the compound of Example 1 per tablet are

obtained.

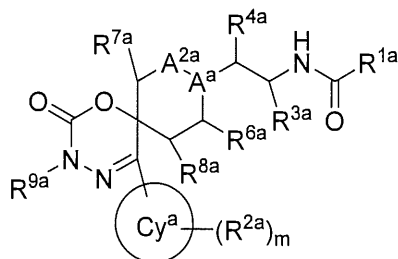
Industrial Applicability

[0658]

- 5 Since Compound [I] or Compound [Ia] or a pharmaceutically acceptable salt thereof of the present invention has a PLD inhibitory activity, it may be useful for the treatment or prophylaxis of thrombosis and cancer.

CLAIMS

1. A compound represented by Formula [Ia] or a pharmaceutically acceptable salt thereof:



[Ia]

wherein

A^a is CR^{10a} or N;

A^{2a} is CR^{5a} or O;

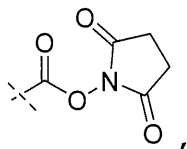
Cy^a is

- (1) C₆₋₁₀ aryl,
- (2) 5 to 10-membered heteroaryl containing one or two nitrogen atoms as a ring constituting atom, besides carbon atom, or
- (3) a 9- or 10-membered partially unsaturated fused cyclic group containing one or two oxygen atoms as a ring constituting atom, besides carbon atom;

R^{1a} is

- (1) C₁₋₆ alkyl wherein the alkyl is optionally substituted by
 - (a) hydroxy,
 - (b) cyano,
 - (c) SO₂R¹¹ wherein R¹¹ is C₁₋₄ alkyl, or
 - (d) NHCOR¹² wherein R¹² is C₁₋₄ alkyl,
- (2) C₂₋₄ alkenyl wherein the alkenyl is optionally substituted by 1 to 3 of
 - (a) NR¹³R¹⁴ wherein R¹³ and R¹⁴ are each independently hydrogen or C₁₋₄ alkyl,
 - (b) halogen,
 - (c) COR^{35a} wherein R^{35a} is hydroxy or C₁₋₄ alkoxy,
 - (d) CONR^{36a}R^{37a} wherein R^{36a} and R^{37a} are each independently hydrogen or C₁₋₄ alkyl, or

(e) a partial structural formula:



- (3) C₁₋₄ haloalkyl wherein the haloalkyl is optionally substituted by hydroxy,
- 5 (4) C₁₋₆ alkoxy wherein the alkoxy is optionally substituted by phenyl,
- (5) NR¹⁵R¹⁶ wherein R¹⁵ and R¹⁶ are each independently
- (a) hydrogen,
- (b) C₁₋₄ alkyl wherein the alkyl is optionally substituted by
- 10 (i) phenyl wherein the phenyl is optionally substituted by halogen, or
- (ii) pyridyl,
- (c) C₁₋₄ alkoxy, or
- (d) C₃₋₄ cycloalkyl,
- 15 (6) COR^{17a} wherein R^{17a} is C₁₋₄ alkyl or hydroxy,
- (7) CONR^{18a}R^{19a} wherein R^{18a} and R^{19a} are each independently
- (a) hydrogen,
- (b) C₁₋₄ alkyl wherein the alkyl is optionally substituted by hydroxy,
- 20 (c) C₃₋₄ cycloalkyl,
- (d) C₅₋₈ bridged cycloalkyl,
- (e) C₁₋₄ haloalkyl, or
- (f) C₁₋₄ alkoxy,
- (8) C₃₋₄ cycloalkyl wherein the cycloalkyl is optionally
- 25 substituted by
- (a) hydroxy,
- (b) halogen, or
- (c) phenyl,
- (9) 4 to 7-membered heterocycloalkyl containing one or two
- 30 heteroatoms selected from the group consisting of nitrogen and oxygen atoms as a ring constituting atom, besides carbon atom, wherein the heterocycloalkyl is optionally substituted by
- (a) hydroxy,

- (b) oxo,
 - (c) $\text{NR}^{20}\text{R}^{21}$ wherein R^{20} and R^{21} are each independently hydrogen or C_{1-4} alkyl, or
 - (d) phenyl,
- 5 (10) 6 to 11-membered spiro heterocycloalkyl containing one or two heteroatoms selected from the group consisting of nitrogen and oxygen atoms as a ring constituting atom, besides carbon atom,
- (11) phenyl wherein the phenyl is optionally substituted by one
- 10 or two of
- (a) halogen, or
 - (b) C_{1-4} haloalkyl,
- (12) 5 to 10-membered heteroaryl containing 1 to 3 heteroatoms selected from the group consisting of nitrogen and oxygen atoms
- 15 as a ring constituting atom, besides carbon atom, wherein the heteroaryl is optionally substituted by one or two R^{22a} ,
- (13) a 8 to 10-membered saturated or partially unsaturated fused cyclic group containing 1 to 4 heteroatoms selected from the group consisting of nitrogen and oxygen atoms as a ring
- 20 constituting atom, besides carbon atom, wherein the fused cyclic group is optionally substituted by C_{1-4} haloalkyl, or
- (14) a 5 to 7-membered partially unsaturated cyclic group containing one or two nitrogen atoms as a ring constituting atom, besides carbon atom, wherein the partially unsaturated
- 25 cyclic group is optionally substituted by an oxo group and C_{1-4} alkyl;
- R^{2a} in the number of m are each independently
- (1) hydroxy,
 - (2) cyano,
- 30 (3) halogen,
- (4) C_{1-6} alkyl wherein the alkyl is optionally substituted by
- (a) hydroxy, or
 - (b) C_{3-4} cycloalkyl,
- (5) C_{2-4} alkenyl wherein the alkenyl is optionally substituted
- 35 by C_{1-4} alkoxy,

- (6) C₁₋₄ haloalkyl,
- (7) C₁₋₄ alkoxy wherein the alkoxy is optionally substituted by 1 to 3 substituents selected from the group consisting of
- (a) hydroxy, and
 - 5 (b) halogen,
- (8) SR^{23a} wherein R^{23a} is C₁₋₄ alkyl or C₁₋₄ haloalkyl,
- (9) COR^{24a} wherein R^{24a} is
- (a) hydroxy,
 - (b) C₁₋₄ alkyl, or
 - 10 (c) C₁₋₄ alkoxy,
- (10) CONR^{25a}R^{26a} wherein R^{25a} and R^{26a} are each independently
- (a) hydrogen,
 - (b) C₁₋₆ alkyl, or
 - (c) C₃₋₄ cycloalkyl, or
- 15 R^{25a} and R^{26a} are bonded to each other to form 4 to 7-membered heterocycloalkyl together with the nitrogen atom to which they are bonded, wherein the heterocycloalkyl contains one or two heteroatoms selected from the group consisting of nitrogen and oxygen atoms as a ring constituting atom, besides carbon atom,
- 20 and is optionally substituted by one or two halogens,
- (11) SO₂R²⁷ wherein R²⁷ is C₁₋₆ alkyl,
- (12) C₃₋₄ cycloalkyl,
- (13) 4 to 7-membered heterocycloalkyl containing one or two heteroatoms selected from the group consisting of nitrogen and
- 25 oxygen atoms as a ring constituting atom, besides carbon atom, wherein the heterocycloalkyl is optionally substituted by one or two substituents selected from the group consisting of
- (a) halogen,
 - (b) C₁₋₄ alkyl, and
 - 30 (c) C₁₋₄ haloalkyl,
- (14) 5 to 9-membered bridged heterocycloalkyl containing one or two heteroatoms selected from the group consisting of nitrogen and oxygen atoms as a ring constituting atom, besides carbon atom,

- (15) 6 to 11-membered spiro heterocycloalkyl containing one or two heteroatoms selected from the group consisting of nitrogen and oxygen atoms as a ring constituting atom, besides carbon atom, or
- 5 (16) phenyl;
- R^{3a} is
- (1) hydrogen,
 - (2) C₁₋₄ alkyl, or
 - (3) C₁₋₄ haloalkyl;
- 10 R^{4a} is
- (1) hydrogen,
 - (2) C₁₋₄ alkyl, or
 - (3) cyano;
- R^{5a} is hydrogen or C₁₋₄ alkyl;
- 15 the combination of R^{6a}, R^{7a} and R^{8a} is
- (1) a combination where R^{6a} is hydrogen or C₁₋₄ alkyl, and R^{7a} and R^{8a} are both hydrogens,
 - (2) a combination where R^{6a} is hydrogen or C₁₋₄ alkyl, and R^{7a} and R^{8a} are bonded to each other to form a cyclopentane ring
 - 20 together with the spiro carbon atom and the carbon atoms to which they are bonded, or
 - (3) a combination where R^{6a} and R^{7a} are bonded to each other to form a cyclopentane ring together with the spiro carbon atom and the carbon atoms to which they are bonded, and R^{8a} is
 - 25 hydrogen;
- R^{9a} is
- (1) hydrogen,
 - (2) CONHR²⁸ wherein R²⁸ is C₃₋₄ cycloalkyl, or
 - (3) C₁₋₄ alkyl;
- 30 R^{10a} is
- (1) hydrogen,
 - (2) hydroxy,
 - (3) halogen,
 - (4) C₁₋₄ alkyl,
 - 35 (5) cyano, or

(6) C₁₋₄ alkoxy;

one or two R^{22a} are each independently

(1) halogen,

(2) C₁₋₄ alkyl,

5 (3) C₁₋₄ haloalkyl,

(4) C₁₋₄ alkoxy,

(5) NHCOR²⁹ wherein R²⁹ is C₁₋₄ alkyl,

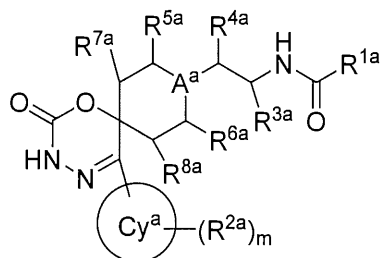
(6) SO₂R³⁰ wherein R³⁰ is C₁₋₄ alkyl,

(7) cyano, or

10 (8) C₃₋₄ cycloalkyl; and

m is 0, 1, 2 or 3.

2. The compound according to Claim 1 or a pharmaceutically acceptable salt thereof, which is represented by Formula [IIa]:

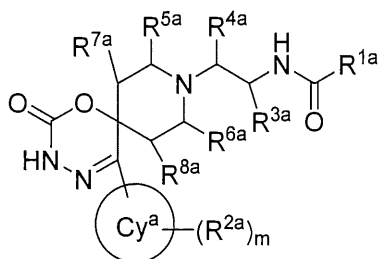


15 [IIa]

wherein

A^a, Cy^a, R^{1a}, R^{2a}, R^{3a}, R^{4a}, R^{5a}, R^{6a}, R^{7a}, R^{8a} and m are as defined in Claim 1.

20 3. The compound according to Claim 1 or a pharmaceutically acceptable salt thereof, which is represented by Formula [IIIa]:

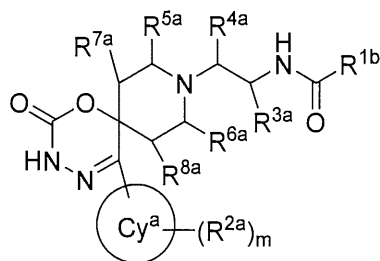


[IIIa]

wherein

Cy^a, R^{1a}, R^{2a}, R^{3a}, R^{4a}, R^{5a}, R^{6a}, R^{7a}, R^{8a} and m are as defined in Claim 1.

- 5 4. The compound according to Claim 1 or a pharmaceutically acceptable salt thereof, which is represented by Formula [IVa]:

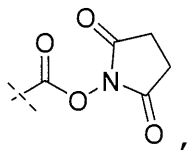


[IVa]

wherein

R^{1b} is

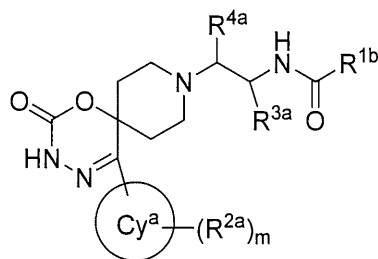
- 10 (1) C₁₋₆ alkyl wherein the alkyl is optionally substituted by
- (a) hydroxy,
 - (b) cyano,
 - (c) SO₂R¹¹ wherein R¹¹ is C₁₋₄ alkyl, or
 - (d) NHCOR¹² wherein R¹² is C₁₋₄ alkyl,
- 15 (2) C₂₋₄ alkenyl wherein the alkenyl is optionally substituted by 1 to 3 of
- (a) NR¹³R¹⁴ wherein R¹³ and R¹⁴ are each independently hydrogen or C₁₋₄ alkyl,
 - (b) halogen,
 - 20 (c) COR^{35a} wherein R^{35a} is hydroxy or C₁₋₄ alkoxy,
 - (d) CONR^{36a}R^{37a} wherein R^{36a} and R^{37a} are each independently hydrogen or C₁₋₄ alkyl, or
 - (e) a partial structural formula:



- 25 (3) C₁₋₆ alkoxy wherein the alkoxy is optionally substituted by phenyl,
- (4) NR¹⁵R¹⁶ wherein R¹⁵ and R¹⁶ are each independently

- (a) hydrogen,
- (b) C₁₋₄ alkyl wherein the alkyl is optionally substituted by
- (i) phenyl wherein the phenyl is optionally substituted
- by halogen, or
- 5 (ii) pyridyl,
- (c) C₁₋₄ alkoxy, or
- (d) C₃₋₄ cycloalkyl,
- (5) CONR^{18a}R^{19a} wherein R^{18a} and R^{19a} are each independently
- (a) hydrogen,
- 10 (b) C₁₋₄ alkyl wherein the alkyl is optionally substituted by
- hydroxy,
- (c) C₃₋₄ cycloalkyl,
- (d) C₅₋₈ bridged cycloalkyl,
- (e) C₁₋₄ haloalkyl, or
- 15 (f) C₁₋₄ alkoxy,
- (6) 6 to 11-membered spiro heterocycloalkyl containing one or
- two heteroatoms selected from the group consisting of nitrogen
- and oxygen atoms as a ring constituting atom, besides carbon
- atom,
- 20 (7) 5 to 10-membered heteroaryl containing 1 to 3 heteroatoms
- selected from the group consisting of nitrogen and oxygen atoms
- as a ring constituting atom, besides carbon atom, wherein the
- heteroaryl is optionally substituted by one or two R^{22a},
- (8) a 8 to 10-membered saturated or partially unsaturated fused
- 25 cyclic group containing 1 to 4 heteroatoms selected from the
- group consisting of nitrogen and oxygen atoms as a ring
- constituting atom, besides carbon atom, wherein the fused
- cyclic group is optionally substituted by C₁₋₄ haloalkyl, or
- (9) a 5 to 7-membered partially unsaturated cyclic group
- 30 containing one or two nitrogen atoms as a ring constituting
- atom, besides carbon atom, wherein the partially unsaturated
- cyclic group is optionally substituted by an oxo group and C₁₋₄
- alkyl; and
- Cy^a, R^{2a}, R^{3a}, R^{4a}, R^{5a}, R^{6a}, R^{7a}, R^{8a}, R^{22a} and m are as defined in
- 35 Claim 1.

5. The compound according to Claim 4 or a pharmaceutically acceptable salt thereof, which is represented by Formula [Va]:

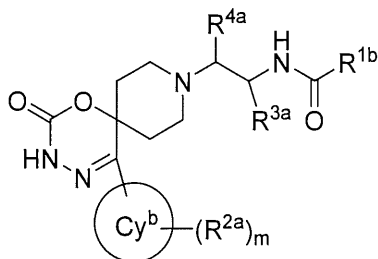


[Va]

5 wherein

Cy^a, R^{2a}, R^{3a}, R^{4a} and m are as defined in Claim 1; and
R^{1b} is as defined in Claim 4.

6. The compound according to Claim 4 or a pharmaceutically acceptable salt thereof, which is represented by Formula [VIa]:



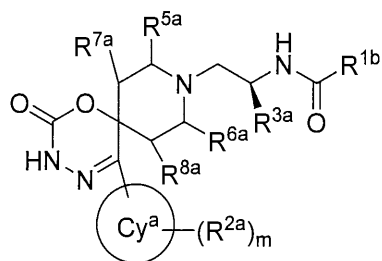
[VIa]

wherein

Cy^b is

- (1) C₆₋₁₀ aryl, or
 - 15 (2) 5- or 6-membered heteroaryl containing one or two nitrogen atoms as a ring constituting atom, besides carbon atom;
- R^{1b} is as defined in Claim 4; and
R^{2a}, R^{3a}, R^{4a} and m are as defined in Claim 1.

20 7. The compound according to Claim 4 or a pharmaceutically acceptable salt thereof, which is represented by Formula [VIIa]:



[VIIa]

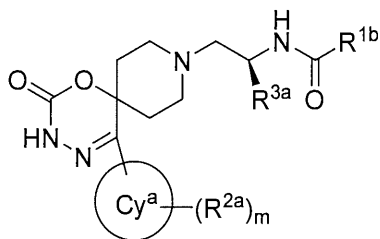
wherein

Cy^a, R^{2a}, R^{3a}, R^{5a}, R^{6a}, R^{7a}, R^{8a} and m are as defined in Claim 1;

and

5 R^{1b} is as defined in Claim 4.

8. The compound according to Claim 4 or a pharmaceutically acceptable salt thereof, which is represented by Formula [VIIIa]:



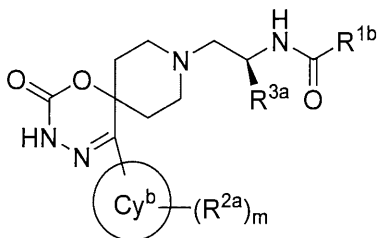
[VIIIa]

wherein

Cy^a, R^{2a}, R^{3a} and m are as defined in Claim 1; and

R^{1b} is as defined in Claim 4.

15 9. The compound according to Claim 6 or a pharmaceutically acceptable salt thereof, which is represented by Formula [IXa]:



[IXa]

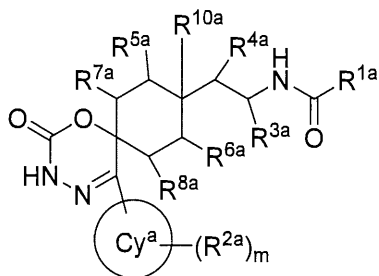
wherein

Cy^b is as defined in Claim 6;

20 R^{1b} is as defined in Claim 4; and

R^{2a}, R^{3a} and m are as defined in Claim 1.

10. The compound according to Claim 1 or a pharmaceutically acceptable salt thereof, which is represented by Formula [Xa]:



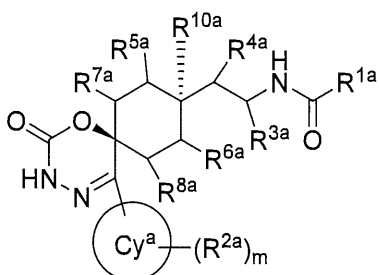
5

[Xa]

wherein

Cy^a, R^{1a}, R^{2a}, R^{3a}, R^{4a}, R^{5a}, R^{6a}, R^{7a}, R^{8a}, R^{10a} and m are as defined in Claim 1.

10 11. The compound according to Claim 1 or a pharmaceutically acceptable salt thereof, which is represented by Formula [XIa]:

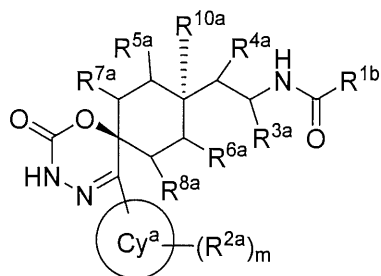


[XIa]

wherein

15 Cy^a, R^{1a}, R^{2a}, R^{3a}, R^{4a}, R^{5a}, R^{6a}, R^{7a}, R^{8a}, R^{10a} and m are as defined in Claim 1.

12. The compound according to Claim 1 or a pharmaceutically acceptable salt thereof, which is represented by Formula [XIIa]:



[XIIa]

wherein

R^{1b} is

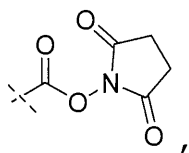
(1) C₁₋₆ alkyl wherein the alkyl is optionally substituted by

- 5 (a) hydroxy,
- (b) cyano,
- (c) SO₂R¹¹ wherein R¹¹ is C₁₋₄ alkyl, or
- (d) NHCOR¹² wherein R¹² is C₁₋₄ alkyl,

(2) C₂₋₄ alkenyl wherein the alkenyl is optionally substituted

10 by 1 to 3 of

- (a) NR¹³R¹⁴ wherein R¹³ and R¹⁴ are each independently hydrogen or C₁₋₄ alkyl,
- (b) halogen,
- (c) COR^{35a} wherein R^{35a} is hydroxy or C₁₋₄ alkoxy,
- 15 (d) CONR^{36a}R^{37a} wherein R^{36a} and R^{37a} are each independently hydrogen or C₁₋₄ alkyl, or
- (e) a partial structural formula:



(3) C₁₋₆ alkoxy wherein the alkoxy is optionally substituted by

20 phenyl,

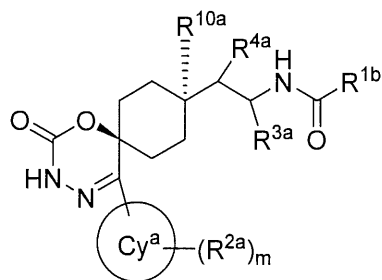
(4) NR¹⁵R¹⁶ wherein R¹⁵ and R¹⁶ are each independently

- (a) hydrogen,
- (b) C₁₋₄ alkyl wherein the alkyl is optionally substituted by
 - (i) phenyl wherein the phenyl is optionally substituted
 - 25 by halogen, or
 - (ii) pyridyl,
- (c) C₁₋₄ alkoxy, or

- (d) C₃₋₄ cycloalkyl,
- (5) CONR^{18a}R^{19a} wherein R^{18a} and R^{19a} are each independently
- (a) hydrogen,
- (b) C₁₋₄ alkyl wherein the alkyl is optionally substituted by
- 5 hydroxy,
- (c) C₃₋₄ cycloalkyl,
- (d) C₅₋₈ bridged cycloalkyl,
- (e) C₁₋₄ haloalkyl, or
- (f) C₁₋₄ alkoxy,
- 10 (6) 6 to 11-membered spiro heterocycloalkyl containing one or two heteroatoms selected from the group consisting of nitrogen and oxygen atoms as a ring constituting atom, besides carbon atom,
- (7) 5 to 10-membered heteroaryl containing 1 to 3 heteroatoms
- 15 selected from the group consisting of nitrogen and oxygen atoms as a ring constituting atom, besides carbon atom, wherein the heteroaryl is optionally substituted by one or two R^{22a},
- (8) a 8 to 10-membered saturated or partially unsaturated fused cyclic group containing 1 to 4 heteroatoms selected from the
- 20 group consisting of nitrogen and oxygen atoms as a ring constituting atom, besides carbon atom, wherein the fused cyclic group is optionally substituted by C₁₋₄ haloalkyl, or
- (9) a 5 to 7-membered partially unsaturated cyclic group containing one or two nitrogen atoms as a ring constituting
- 25 atom, besides carbon atom, wherein the partially unsaturated cyclic group is optionally substituted by an oxo group and C₁₋₄ alkyl; and
- Cy^a, R^{2a}, R^{3a}, R^{4a}, R^{5a}, R^{6a}, R^{7a}, R^{8a}, R^{10a}, R^{22a} and m are as defined in Claim 1.

30

13. The compound according to Claim 12 or a pharmaceutically acceptable salt thereof, which is represented by Formula [XIIIIa]:



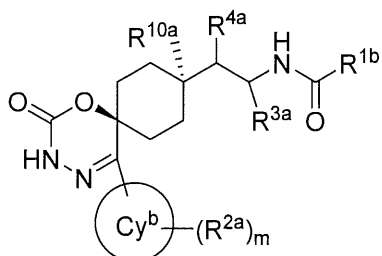
[XIIIa]

wherein

Cy^a, R^{2a}, R^{3a}, R^{4a}, R^{10a} and m are as defined in Claim 1; and R^{1b} is as defined in Claim 12.

5

14. The compound according to Claim 12 or a pharmaceutically acceptable salt thereof, which is represented by Formula [XIVa]:



[XIVa]

10 wherein

Cy^b is

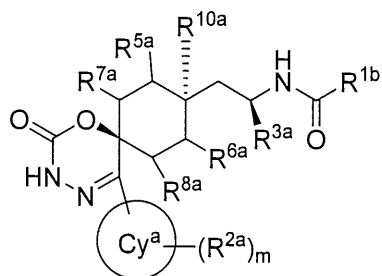
(1) C₆₋₁₀ aryl, or

(2) 5- or 6-membered heteroaryl containing one or two nitrogen atoms as a ring constituting atom, besides carbon atom;

15 R^{1b} is as defined in Claim 12; and

R^{2a}, R^{3a}, R^{4a}, R^{10a} and m are as defined in Claim 1.

15. The compound according to Claim 12 or a pharmaceutically acceptable salt thereof, which is represented by Formula [XVa]:



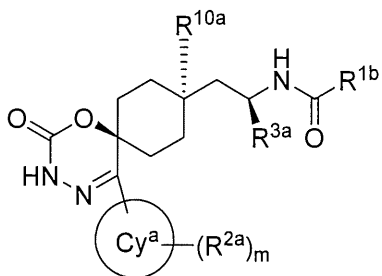
[XVa]

wherein

Cy^a, R^{2a}, R^{3a}, R^{5a}, R^{6a}, R^{7a}, R^{8a}, R^{10a} and m are as defined in Claim 1; and

5 R^{1b} is as defined in Claim 12.

16. The compound according to Claim 12 or a pharmaceutically acceptable salt thereof, which is represented by Formula [XVIa]:



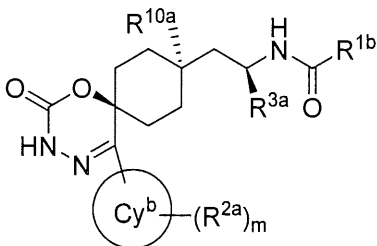
[XVIa]

wherein

Cy^a, R^{2a}, R^{3a}, R^{10a} and m are as defined in Claim 1; and

R^{1b} is as defined in Claim 12.

15 17. The compound according to Claim 14 or a pharmaceutically acceptable salt thereof, which is represented by Formula [XVIIa]:



[XVIIa]

wherein

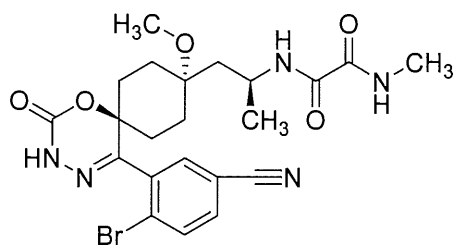
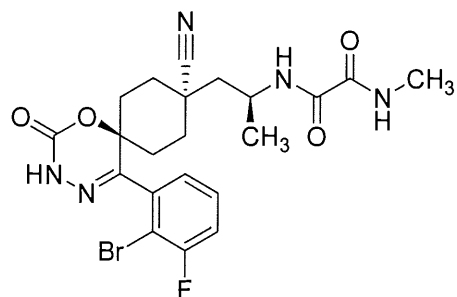
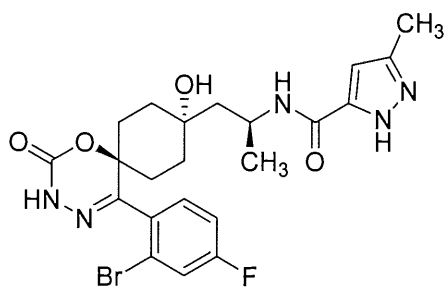
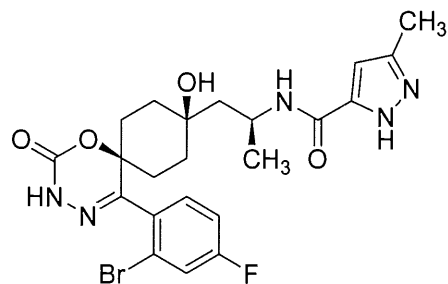
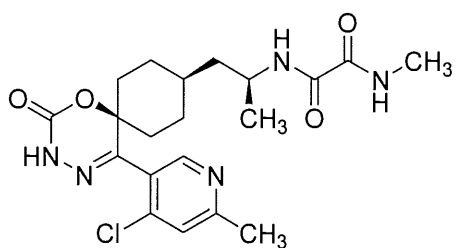
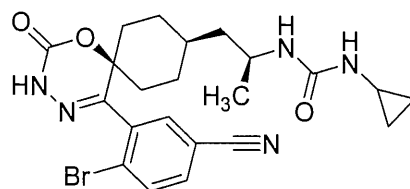
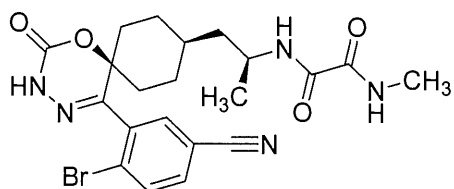
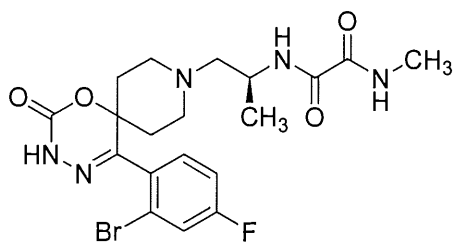
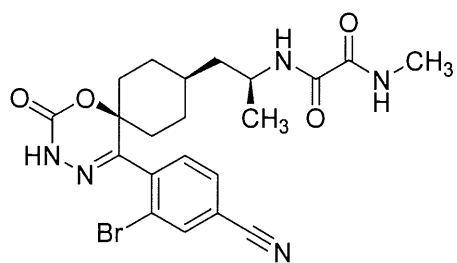
Cy^b is as defined in Claim 14;

R^{1b} is as defined in Claim 12; and

R^{2a}, R^{3a}, R^{10a} and m are as defined in Claim 1.

5

18. A compound selected from the group consisting of compounds represented by the following formulae:



and

or a pharmaceutically acceptable salt thereof.

19. A pharmaceutical composition comprising a compound as
 5 defined in any one of Claims 1 to 18, or a pharmaceutically
 acceptable salt thereof, and a pharmaceutically acceptable
 carrier.

20. A pharmaceutical composition comprising a compound as defined in any one of Claims 1 to 18, or a pharmaceutically acceptable salt thereof, in combination with one or more other
5 drugs, and a pharmaceutically acceptable carrier.

21. A PLD inhibitor comprising a compound as defined in any one of Claims 1 to 18, or a pharmaceutically acceptable salt thereof.

10

22. A PLD1 inhibitor comprising a compound as defined in any one of Claims 1 to 18, or a pharmaceutically acceptable salt thereof.

15 23. A PLD1/2 inhibitor comprising a compound as defined in any one of Claims 1 to 18, or a pharmaceutically acceptable salt thereof.

24. An agent for the treatment or prophylaxis of a disease
20 selected from the group consisting of thrombosis and cancer, comprising a compound as defined in any one of Claims 1 to 18, or a pharmaceutically acceptable salt thereof.

25 25. An agent for the treatment or prophylaxis of a disease selected from the group consisting of thrombosis and cancer, comprising a compound as defined in any one of Claims 1 to 18, or a pharmaceutically acceptable salt thereof, in combination with one or more other drugs.

30 26. A method for inhibiting PLD in a mammal, comprising administering a therapeutically effective amount of a compound as defined in any one of Claims 1 to 18, or a pharmaceutically acceptable salt thereof to the mammal.

27. A method for inhibiting PLD1 in a mammal, comprising administering a therapeutically effective amount of a compound as defined in any one of Claims 1 to 18, or a pharmaceutically acceptable salt thereof to the mammal.

5

28. A method for inhibiting PLD1/2 in a mammal, comprising administering a therapeutically effective amount of a compound as defined in any one of Claims 1 to 18, or a pharmaceutically acceptable salt thereof to the mammal.

10

29. A method for treating or preventing a disease selected from the group consisting of thrombosis and cancer in a mammal, comprising administering a therapeutically effective amount of a compound as defined in any one of Claims 1 to 18, or a
15 pharmaceutically acceptable salt thereof to the mammal.

30. A method for treating or preventing a disease selected from the group consisting of thrombosis and cancer in a mammal, comprising administering a therapeutically effective amount of
20 a compound as defined in any one of Claims 1 to 18, or a pharmaceutically acceptable salt thereof, in combination with one or more other drugs, to the mammal.

31. Use of a compound as defined in any one of Claims 1 to 18,
25 or a pharmaceutically acceptable salt thereof, for the manufacture of a PLD inhibitor.

32. Use of a compound as defined in any one of Claims 1 to 18, or a pharmaceutically acceptable salt thereof, for the
30 manufacture of a PLD1 inhibitor.

33. Use of a compound as defined in any one of Claims 1 to 18, or a pharmaceutically acceptable salt thereof, for the manufacture of a PLD1/2 inhibitor.

35

34. Use of a compound as defined in any one of Claims 1 to 18,
or a pharmaceutically acceptable salt thereof, for the
manufacture of an agent for the treatment or prophylaxis of a
disease selected from the group consisting of thrombosis and
5 cancer.

35. Use of a compound as defined in any one of Claims 1 to 18,
or a pharmaceutically acceptable salt thereof, in combination
with one or more other drugs, for the manufacture of an agent
10 for the treatment or prophylaxis of a disease selected from the
group consisting of thrombosis and cancer.

36. A compound as defined in any one of Claims 1 to 18, or a
pharmaceutically acceptable salt thereof, for use in the
15 inhibition of PLD.

37. A compound as defined in any one of Claims 1 to 18, or a
pharmaceutically acceptable salt thereof, for use in the
inhibition of PLD1.
20

38. A compound as defined in any one of Claims 1 to 18, or a
pharmaceutically acceptable salt thereof, for use in the
inhibition of PLD1/2.

25 39. A compound as defined in any one of Claims 1 to 18, or a
pharmaceutically acceptable salt thereof, for use in the
treatment or prophylaxis of a disease selected from the group
consisting of thrombosis and cancer.

30 40. A compound as defined in any one of Claims 1 to 18, or a
pharmaceutically acceptable salt thereof, in combination with
one or more other drugs, for use in the treatment or
prophylaxis of a disease selected from the group consisting of
thrombosis and cancer.

35