

[DESCRIPTION]

[Title of Invention]

INDAZOLE COMPOUND AND PHARMACEUTICAL USE THEREOF

[Technical Field]

5 [0001]

The present invention relates to an indazole compound or a pharmaceutically acceptable salt thereof having hematopoietic prostaglandin D synthase (hereinafter to be abbreviated as "H-PGDS") inhibitory activity, a pharmaceutical composition
10 containing the same, a pharmaceutical use thereof, and the like.

[Background Art]

[0002]

Prostaglandin D synthase (PGDS) is an enzyme that synthesizes prostaglandin D₂ (PGD₂) by using prostaglandin H₂
15 (PGH₂) as a substrate. There are two types of PGDS: hematopoietic PGDS (H-PGDS) and lipocalin-type PGDS (L-PGDS). These two types of enzymes show no homology in amino acid sequence, and are different in tissue distribution and cell localization. H-PGDS is predominantly expressed in mast cells
20 and hematopoietic cells such as neutrophils and macrophages, and is involved in allergy and inflammation. On the other hand, expression of L-PGDS is mainly found in the central nervous system and L-PGDS plays a role in sleep regulation and pain regulation.

25 [0003]

The use of the H-PGDS inhibitor is described below.

(1) Peripheral arterial disease (PAD) and cardiovascular disease (CAD)

In the femoral artery ligation model, which is a PAD
30 model, an increase in lower leg blood flow was observed in H-PGDS knockout mouse as compared with wild-type mouse, suggesting that collateral blood flow pathways are involved in this increase in the lower leg blood flow (Patent Document 1). In addition, it has been reported that some PAD patients having
35 well-developed collateral blood flow pathways show higher

walking function (Non-patent Document 1). Furthermore,
collateral blood flow pathways are also present in the heart,
and some CAD patients having well-developed collateral blood
flow pathways have been reported to show better prognosis (Non-
5 patent Document 2). Based on these findings, H-PGDS inhibitors
are expected to achieve therapeutic effects on PAD and CAD by
increasing the blood flow to lower legs and heart via
collateral blood flow pathways. PAD is classified into mild
intermittent claudication (IC: Intermittent Claudication) and
10 severe comprehensive chronic limb threatening ischemia (CLTI:
Chronic Limb Threatening Ischemia), and H-PGDS inhibitors are
expected to provide therapeutic drugs for these disease
conditions (Non-patent Documents 8, 9).

Peripheral arterial disease is also called chronic
15 arterial occlusive disease or arteriosclerosis obliterans.
[0004]

(2) Allergic asthma and chronic obstructive pulmonary disease

It has been reported that the D-prostanoid (DP) receptor,
which is the receptor for PGD₂, and the chemo-triggered
20 receptor-like molecule (CRTH2) receptor expressed in Th2 cells
are involved in allergic asthma and chronic obstructive
pulmonary diseases (COPD). In an asthma model, reduced
allergic asthma symptoms such as reduced infiltration of
eosinophils and lymphocytes into the lungs and decreased airway
25 hyperresponsiveness have been found in DP receptor knockout
mice, as compared with wild-type mice (Non-patent Document 3).
It has also been reported that PGD₂ exacerbates inflammation by
recruiting eosinophils into the airways via the CRTH2 receptor
(Non-patent Document 4), and that CRTH2 receptor inhibitors
30 show bronchial inflammation improving effects in COPD model
mouse (Non-patent Document 5). From these findings, H-PGDS
inhibitors are expected to show therapeutic effects on allergic
asthma and COPD by suppressing PGD₂ production and suppressing
inflammation in the airways.

35 [0005]

(3) Duchenne muscular dystrophy

It has been reported that the expression of H-PGDS increases in the muscle tissue of Duchenne muscular dystrophy (DMD) patients and mdx mice, which are DMD model mice (Non-patent Document 6). Furthermore, it has also been reported that the H-PGDS inhibitor HQL-79 suppresses myonecrosis and increases muscle strength in mdx mice (Non-patent Document 7). From these findings, H-PGDS inhibitors may also show therapeutic effects on DMD.

10 (4) Allergic rhinitis

In an animal model of allergic rhinitis, it has been reported that the PGD2 concentration in nasal lavage fluid increases and the administration of an H-PGDS inhibitor improves nasal obstruction (Non-patent Document 10). From the above results, H-PGDS inhibitors are considered to provide therapeutic agents for allergic rhinitis.

(5) Sarcopenia

In sarcopenia model animals, a muscle atrophy suppressive action by the administration of H-PGDS inhibitors has been reported (Patent Document 2). From the above results, H-PGDS inhibitors are considered to provide therapeutic agents for sarcopenia.

[Document List]

[Patent Document]

25 [0006]

[Patent Document 1] WO 2011/052628

[Patent Document 2] WO 2019/203296

[Non-patent Document]

[0007]

30 [Non-patent Document 1] McDermott MM, et al., JACC Cardiovasc Imaging. 2013 Jun; 6(6):687-94.

[Non-patent Document 2] Steg PG, et al., Circulation. 2010 Jun 29; 121(25):2724-30.

[Non-patent Document 3] Matsuoka T, et al., Science. 2000 Mar 35 17; 287(5460):2013-7.

[Non-patent Document 4] George L, et al., Ther Adv Chronic Dis. 2016 Jan; 7(1):34-51.

[Non-patent Document 5] Sargent C, et al., Br J Pharmacol 7 (2009): 003P.

5 [Non-patent Document 6] Okinaga T, et al., Acta Neuropathol. 2002 Oct; 104(4):377-84.

[Non-patent Document 7] Mohri I, et al., Am J Pathol. 2009 May; 174(5):1735-44.

[Non-patent Document 8] Hamburg NM, et al., Circulation J 2017;
10 81:281-289

[Non-patent Document 9] Tran B, Heart 2021; 107: 1835-1843

[Non-patent Document 10] Kajiwara D, et al., European Journal of Pharmacology 667 (2011) 389-395.

[Summary of Invention]

15 [0008]

The present invention provides an indazole compound having H-PGDS inhibitory activity or a pharmaceutically acceptable salt thereof, a pharmaceutical composition containing the same, a pharmaceutical use thereof, and the like.

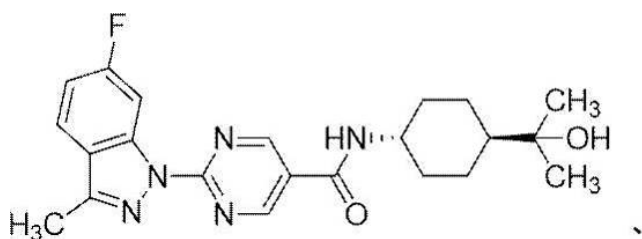
20 Accordingly, the present invention provides the following.

[0009]

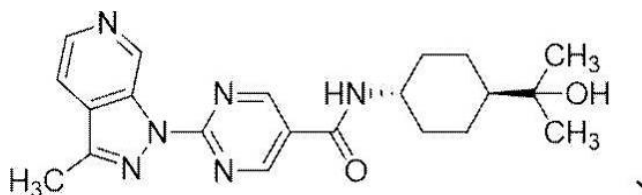
[Item 1]

A compound selected from the group consisting of the following structural formulas:

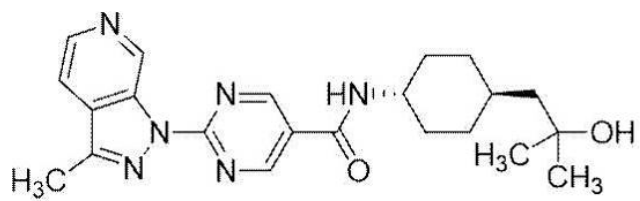
25 [0010]



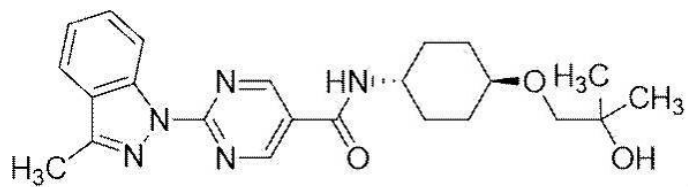
[0011]



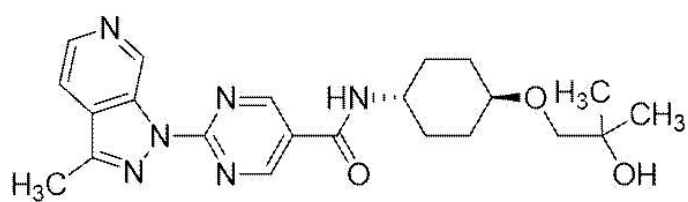
[0012]



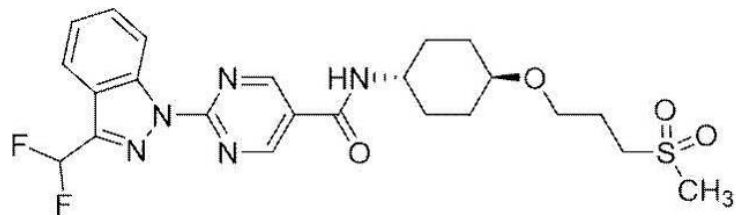
[0013]



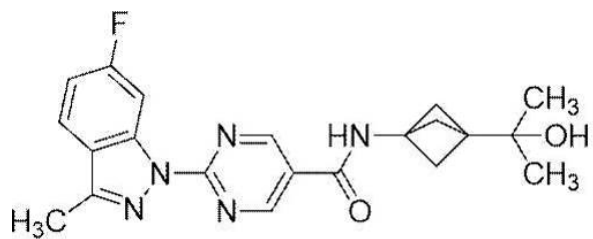
5 [0014]



[0015]

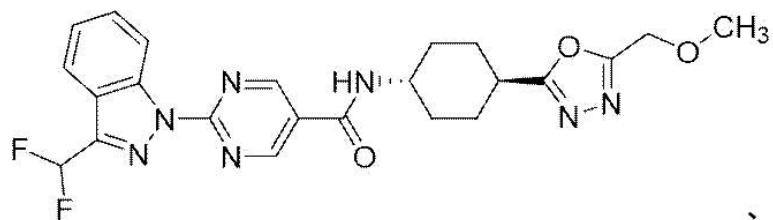


[0016]

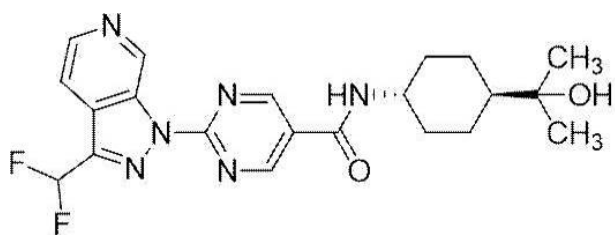


10

[0017]

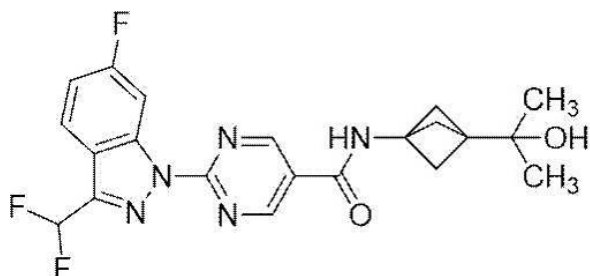


[0018]



and

[0019]



[0020]

5 or a pharmaceutically acceptable salt thereof.

[0021]

[Item 2]

A pharmaceutical composition comprising the compound of Item 1 or a pharmaceutically acceptable salt thereof, and a
10 pharmaceutically acceptable carrier.

[0022]

[Item 3]

An H-PGDS inhibitor comprising the compound of Item 1 or a pharmaceutically acceptable salt thereof.

15 [0023]

[Item 4]

A therapeutic or prophylactic agent for a disease selected from the group consisting of peripheral arterial diseases, cardiovascular diseases, allergic asthma, chronic
20 obstructive pulmonary diseases, and Duchenne muscular dystrophy, the agent comprising the compound of Item 1 or a pharmaceutically acceptable salt thereof.

[0024]

[Item 5]

25 A method for inhibiting H-PGDS in a mammal, comprising administering a pharmaceutically effective amount of the

compound of Item 1 or a pharmaceutically acceptable salt thereof to the mammal.

[0025]

[Item 6]

5 A method for treating or preventing a disease selected from the group consisting of peripheral arterial diseases, cardiovascular diseases, allergic asthma, chronic obstructive pulmonary diseases, and Duchenne muscular dystrophy in a mammal, comprising administering a pharmaceutically effective amount of
10 the compound of Item 1 or a pharmaceutically acceptable salt thereof to the mammal.

[0026]

[Item 7]

 Use of the compound of Item 1 or a pharmaceutically
15 acceptable salt thereof in producing an H-PGDS inhibitor.

[0027]

[Item 8]

 Use of the compound of Item 1 or a pharmaceutically acceptable salt thereof in producing a therapeutic or
20 prophylactic agent for a disease selected from the group consisting of peripheral arterial diseases, cardiovascular diseases, allergic asthma, chronic obstructive pulmonary diseases, and Duchenne muscular dystrophy.

[0028]

25 [Item 9]

 The compound of Item 1 or a pharmaceutically acceptable salt thereof for use in inhibiting H-PGDS.

[0029]

[Item 10]

30 The compound of Item 1 or a pharmaceutically acceptable salt thereof for use in the treatment or prophylaxis of a disease selected from the group consisting of peripheral arterial diseases, cardiovascular diseases, allergic asthma, chronic obstructive pulmonary diseases, and Duchenne muscular
35 dystrophy.

[0030]

[Item 11]

A commercial package comprising the pharmaceutical composition of Item 2 and a written matter associated therewith, the written matter stating that the pharmaceutical composition can be used for treatment or prophylaxis of a disease selected from the group consisting of peripheral arterial diseases, cardiovascular diseases, allergic asthma, chronic obstructive pulmonary diseases, and Duchenne muscular dystrophy.

10 [0031]

[Item 12]

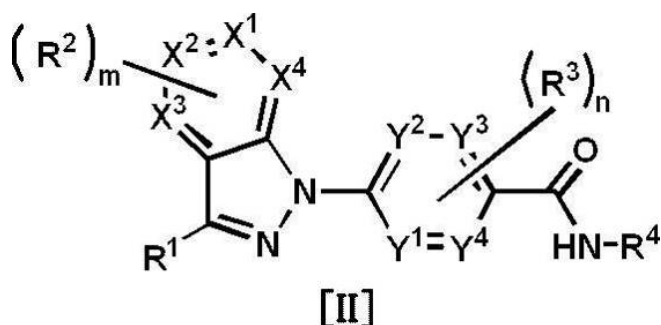
A kit comprising the pharmaceutical composition of Item 2 and a written matter associated therewith, the written matter stating that the pharmaceutical composition can be used for treatment or prophylaxis of a disease selected from the group consisting of peripheral arterial diseases, cardiovascular diseases, allergic asthma, chronic obstructive pulmonary diseases, and Duchenne muscular dystrophy.

[0032]

20 [Item 1A]

A compound of the formula [II]:

[0033]



[0034]

25 wherein

X^1 , X^2 , X^3 , X^4 , Y^1 , Y^2 , Y^3 and Y^4 are each independently a carbon or a nitrogen atom (wherein the total number of the nitrogen atoms for X^1 , X^2 , X^3 and X^4 is 0 or 1, and the total number of the nitrogen atoms for Y^1 , Y^2 , Y^3 and Y^4 is 0, 1 or 2),

30 m is 0, 1 or 2,

n is 0, 1 or 2,

R¹ is

- (1) hydroxy,
- (2) cyano,
- 5 (3) C₁₋₄ alkyl (wherein the alkyl is optionally substituted by hydroxy or C₁₋₄ alkoxy),
- (4) C₁₋₄ alkoxy,
- (5) halogen,
- (6) C₁₋₄ haloalkyl, or
- 10 (7) C₃₋₆ cycloalkyl,

R² in the number of m are each independently

- (1) cyano,
- (2) C₁₋₄ alkyl,
- (3) C₁₋₄ alkoxy,
- 15 (4) halogen, or
- (5) C₁₋₄ haloalkyl,

R³ in the number of n are each independently

- (1) C₁₋₄ alkyl,
- (2) C₁₋₄ alkoxy, or
- 20 (3) halogen, and

R⁴ is

- (1) ring Cy [wherein the ring Cy is

(a) C₄₋₆ cycloalkyl (wherein the cycloalkyl is optionally substituted by 1 or 2 substituents independently selected from
25 the group consisting of

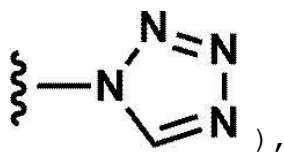
- (I) hydroxy,
- (II) cyano,
- (III) oxo,
- (IV) C₁₋₆ alkyl (wherein the alkyl is optionally

30 substituted by

- (i) hydroxy,
- (ii) carboxy,
- (iii) -CONH₂,
- (iv) -CO-C₁₋₄ alkoxy,
- 35 (v) -SO₂-C₁₋₄ alkyl, or

(vi) a group represented by the formula:

[0035]



[0036]

5 (V) C₁₋₆ alkoxy (wherein the alkoxy is optionally substituted by hydroxy or -SO₂-C₁₋₄ alkyl),

(VI) carboxy,

(VII) -CO-NR⁵R⁶ [wherein R⁵ and R⁶ are each independently C₁₋₄ alkyl (wherein the alkyl is optionally substituted by C₁₋₄ alkoxy), or R⁵ and R⁶ optionally form, together with the
10 nitrogen atom bonded thereto, 4- to 6-membered heterocycloalkyl containing 1 or 2 hetero atoms independently selected from the group consisting of nitrogen and oxygen atoms {wherein the heterocycloalkyl is optionally substituted by 1 or 2
15 substituents independently selected from the group consisting of

(i) hydroxy, and

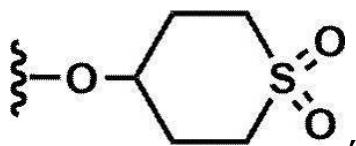
(ii) C₁₋₆ alkyl (wherein the alkyl is optionally substituted by hydroxy)}],

20 (VIII) -NR⁷R⁸ {wherein R⁷ and R⁸ are each independently C₁₋₄ alkyl or -CO-C₁₋₆ alkyl (wherein the alkyl is optionally substituted by cyano)}],

(IX) -O-C₁₋₆ haloalkyl,

(X) a group represented by the formula:

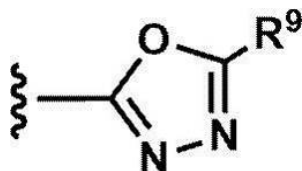
25 [0037]



[0038]

(XI) a group represented by the formula:

[0039]

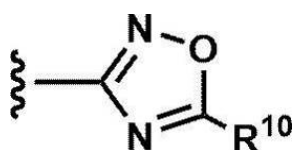


[0040]

{wherein R⁹ is C₁₋₄ alkyl (wherein the alkyl is optionally substituted by C₁₋₄ alkoxy)}, and

5 (XII) a group represented by the formula:

[0041]



[0042]

(wherein R¹⁰ is C₁₋₄ alkyl)),

10 (b) C₅₋₈ bridged cycloalkyl {wherein the bridged cycloalkyl is optionally substituted by

(I) hydroxy,

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

15 (i) hydroxy,

(ii) carboxy,

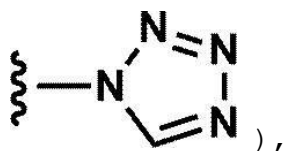
(iii) -CONH₂,

(iv) -CO-C₁₋₄ alkoxy,

(v) -SO₂-C₁₋₄ alkyl, or

20 (vi) a group represented by the formula:

[0043]



[0044]

(III) C₁₋₆ alkoxy (wherein the alkoxy is optionally substituted by hydroxy or -SO₂-C₁₋₄ alkyl),

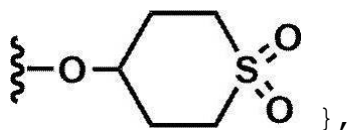
(IV) carboxy,

(V) -CO-C₁₋₄ alkoxy,

(VI) -O-C₁₋₆ haloalkyl, or

(VII) a group represented by the formula:

[0045]



[0046]

5 (c) 5- or 6-membered heterocycloalkyl containing one nitrogen atom [wherein the heterocycloalkyl is optionally substituted by 1 to 3 substituents independently selected from the group consisting of

(I) oxo,

10 (II) C₁₋₆ alkyl,

(III) -CO-R¹¹ {wherein R¹¹ is

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

(A) hydroxy,

15 (B) cyano, or

(C) C₁₋₄ alkoxy),

(ii) C₁₋₆ alkoxy,

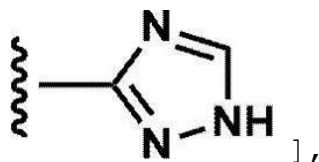
(iii) C₁₋₆ haloalkyl,

(iv) C₃₋₆ cycloalkyl (wherein the cycloalkyl is
20 optionally substituted by halogen), or

(v) 4- to 6-membered heterocycloalkyl containing one oxygen atom (wherein the heterocycloalkyl is optionally substituted by halogen)}, and

(IV) a group represented by the formula:

25 [0047]



[0048]

(d) 8-membered bridged heterocycloalkyl containing one nitrogen atom {wherein the bridged heterocycloalkyl is
30 optionally substituted by -CO-R¹¹},

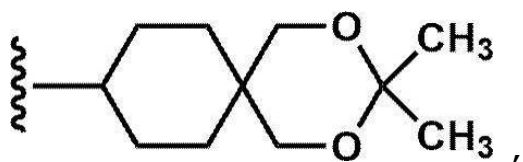
(e) 7- to 11-membered spiro heterocycloalkyl containing

one nitrogen atom {wherein the spiro heterocycloalkyl is optionally substituted by -CO-R¹¹},

(f) 6- to 9-membered saturated or partially unsaturated fused ring group containing 1 or 2 nitrogen atoms (wherein the
5 fused ring group is optionally substituted by -CO-R¹¹),

(g) a group represented by the formula:

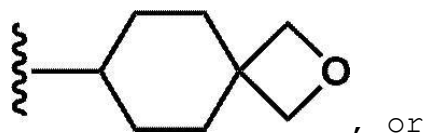
[0049]



[0050]

10 (h) a group represented by the formula:

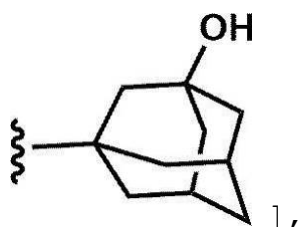
[0051]



[0052]

(i) a group represented by the formula:

15 [0053]



[0054]

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

(a) C₃₋₆ cycloalkyl (wherein the cycloalkyl is optionally
20 substituted by 1 or 2 substituents independently selected from the group consisting of hydroxy and C₁₋₄ alkyl optionally substituted by hydroxy), or

(b) phenyl}, or

(3) C₁₋₄ haloalkyl (wherein the haloalkyl is optionally
25 substituted by C₃₋₆ cycloalkyl optionally substituted by hydroxy)],

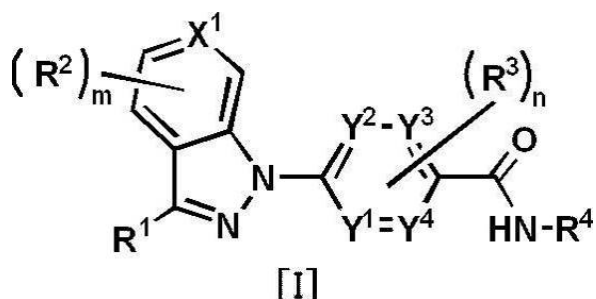
or a pharmaceutically acceptable salt thereof.

[0055]

[Item 2A]

The compound of Item 1A, which is represented by the formula [I]:

5 [0056]



[0057]

(wherein each symbol is as defined for Item 1A),
or a pharmaceutically acceptable salt thereof.

10 [0058]

[Item 3A]

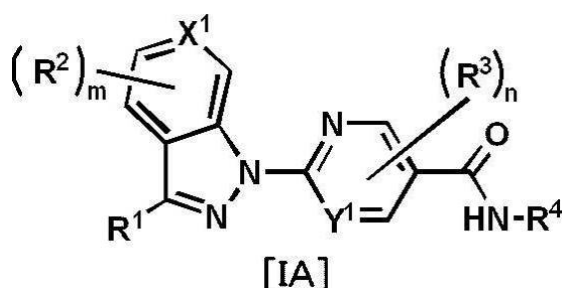
The compound of Item 1A or 2A, wherein the total number of the nitrogen atoms for Y¹, Y², Y³ and Y⁴ is 1 or 2, or a pharmaceutically acceptable salt thereof.

15 [0059]

[Item 4A]

The compound of Item 1A, which is represented by the formula [IA]:

[0060]



20

[0061]

(wherein each symbol is as defined for Item 1A),
or a pharmaceutically acceptable salt thereof.

[0062]

25 [Item 5A]

The compound of any one of Items 1A to 4A, wherein R³ is halogen, or a pharmaceutically acceptable salt thereof.

[0063]

[Item 6A]

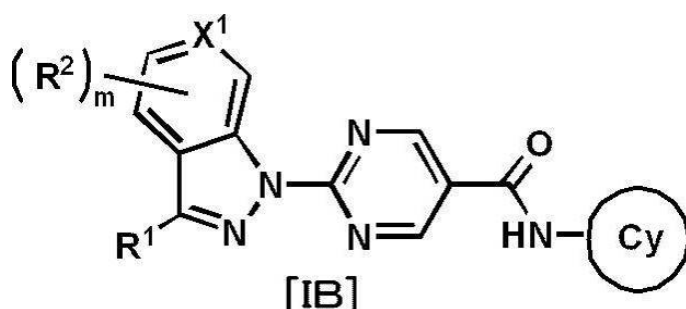
- 5 The compound of any one of Items 1A to 5A, wherein R⁴ is ring Cy, or a pharmaceutically acceptable salt thereof.

[0064]

[Item 7A]

10 The compound of Item 1A, which is represented by the formula [IB]:

[0065]



[0066]

(wherein each symbol is as defined for Item 1A),

- 15 or a pharmaceutically acceptable salt thereof.

[0067]

[Item 8A]

- 20 The compound of any one of Items 1A to 7A, wherein R¹ is
(1) C₁₋₄ alkyl (wherein the alkyl is optionally substituted by
hydroxy or C₁₋₄ alkoxy),

(2) C₁₋₄ alkoxy,

(3) halogen, or

(4) C₁₋₄ haloalkyl,

or a pharmaceutically acceptable salt thereof.

25 [0068]

[Item 9A]

The compound of any one of Items 1A to 8A, wherein R² is halogen, or a pharmaceutically acceptable salt thereof.

[0069]

30 [Item 10A]

The compound of any one of Items 1A to 9A, wherein ring Cy is

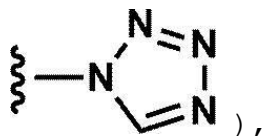
(1) C₄₋₆ cycloalkyl (wherein the cycloalkyl is optionally substituted by 1 or 2 substituents independently selected from the group consisting of

- (a) hydroxy,
- (b) cyano,
- (c) oxo,
- (d) C₁₋₆ alkyl (wherein the alkyl is optionally

substituted by

- (I) hydroxy,
- (II) carboxy,
- (III) -CONH₂,
- (IV) -CO-C₁₋₄ alkoxy,
- (V) -SO₂-C₁₋₄ alkyl, or
- (VI) a group represented by the formula:

[0070]



[0071]

(e) C₁₋₆ alkoxy (wherein the alkoxy is optionally substituted by hydroxy or -SO₂-C₁₋₄ alkyl),

(f) carboxy,

(g) -CO-NR⁵R⁶ [wherein R⁵ and R⁶ are each independently C₁₋₄ alkyl (wherein the alkyl is optionally substituted by C₁₋₄ alkoxy), or R⁵ and R⁶ optionally form, together with the nitrogen atom bonded thereto, 4- to 6-membered heterocycloalkyl containing 1 or 2 hetero atoms independently selected from the group consisting of nitrogen and oxygen atoms {wherein the heterocycloalkyl is optionally substituted by 1 or 2 substituents independently selected from the group consisting of

- (I) hydroxy, and
- (II) C₁₋₆ alkyl (wherein the alkyl is optionally

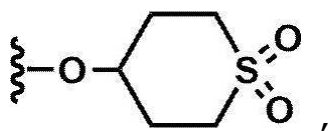
substituted by hydroxy) }],

(h) $-NR^7R^8$ {wherein R^7 and R^8 are each independently C_{1-4} alkyl, or $-CO-C_{1-6}$ alkyl (wherein the alkyl is optionally substituted by cyano)},

5 (i) $-O-C_{1-6}$ haloalkyl,

(j) a group represented by the formula:

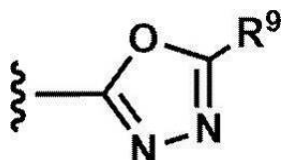
[0072]



[0073]

10 (k) a group represented by the formula:

[0074]

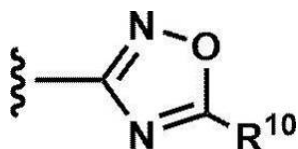


[0075]

15 {wherein R^9 is C_{1-4} alkyl (wherein the alkyl is optionally substituted by C_{1-4} alkoxy)}, and

(m) a group represented by the formula:

[0076]



20

[0077]

wherein R^{10} is C_{1-4} alkyl)),

(2) C_{5-8} bridged cycloalkyl {wherein the bridged cycloalkyl is optionally substituted by

25 (a) hydroxy,

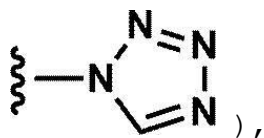
(b) C_{1-6} alkyl (wherein the alkyl is optionally substituted by

(I) hydroxy,

(II) carboxy,

- (III) $-\text{CONH}_2$,
- (IV) $-\text{CO}-\text{C}_{1-4}$ alkoxy,
- (V) $-\text{SO}_2-\text{C}_{1-4}$ alkyl, or
- (VI) a group represented by the formula:

5 [0078]

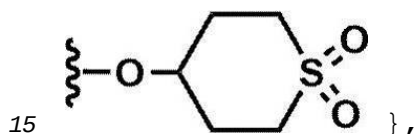


[0079]

(c) C_{1-6} alkoxy (wherein the alkoxy is optionally substituted by hydroxy or $-\text{SO}_2-\text{C}_{1-4}$ alkyl),

- 10 (d) carboxy,
- (e) $-\text{CO}-\text{C}_{1-4}$ alkoxy,
- (f) $-\text{O}-\text{C}_{1-6}$ haloalkyl, or
- (g) a group represented by the formula:

[0080]



[0081]

(3) 5- or 6-membered heterocycloalkyl containing one nitrogen atom [wherein the heterocycloalkyl is optionally substituted by 1 to 3 substituents independently selected from the group

20 consisting of

- (a) oxo,
- (b) C_{1-6} alkyl,
- (c) $-\text{CO}-\text{R}^{11}$ {wherein R^{11} is

25 (I) C_{1-6} alkyl (wherein the alkyl is optionally substituted by

- (i) hydroxy,
- (ii) cyano, or
- (iii) C_{1-4} alkoxy),

(II) C_{1-6} alkoxy,

30 (III) C_{1-6} haloalkyl,

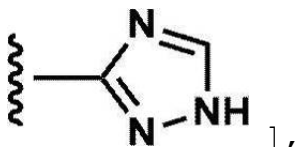
(IV) C_{3-6} cycloalkyl (wherein the cycloalkyl is

optionally substituted by halogen), or

(V) 4- to 6-membered heterocycloalkyl containing one oxygen atom (wherein the heterocycloalkyl is optionally substituted by halogen)}, and

5 (d) a group represented by the formula:

[0082]



[0083]

(4) 8-membered bridged heterocycloalkyl containing one nitrogen
10 atom {wherein the bridged heterocycloalkyl is optionally substituted by $-\text{CO}-\text{R}^{11}$ },

(5) 7- to 11-membered spiro heterocycloalkyl containing one nitrogen atom {wherein the spiro heterocycloalkyl is optionally substituted by $-\text{CO}-\text{R}^{11}$ }, or

15 (6) a 6- to 9-membered saturated or partially unsaturated fused ring group containing 1 or 2 nitrogen atoms (wherein the fused ring group is optionally substituted by $-\text{CO}-\text{R}^{11}$), or a pharmaceutically acceptable salt thereof.

[0084]

20 [Item 11A]

The compound of any one of Items 1A to 9A, wherein ring Cy is

(1) C_{4-6} cycloalkyl (wherein the cycloalkyl is optionally substituted by 1 or 2 substituents independently selected from
25 the group consisting of

(a) hydroxy,

(b) cyano,

(c) oxo,

(d) C_{1-6} alkyl (wherein the alkyl is optionally
30 substituted by

(I) hydroxy,

(II) carboxy,

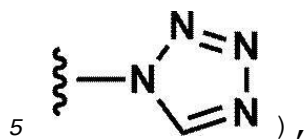
(III) $-\text{CONH}_2$,

(IV) $-\text{CO}-\text{C}_{1-4}$ alkoxy,

(V) $-\text{SO}_2-\text{C}_{1-4}$ alkyl, or

(VI) a group represented by the formula:

[0085]



[0086]

(e) C_{1-6} alkoxy (wherein the alkoxy is optionally substituted by hydroxy or $-\text{SO}_2-\text{C}_{1-4}$ alkyl),

(f) carboxy,

10 (g) $-\text{CO}-\text{NR}^5\text{R}^6$ [wherein R^5 and R^6 are each independently C_{1-4} alkyl (wherein the alkyl is optionally substituted by C_{1-4} alkoxy), or R^5 and R^6 optionally form, together with the nitrogen atom bonded thereto, 4- to 6-membered heterocycloalkyl containing 1 or 2 hetero atoms independently selected from the
15 group consisting of nitrogen and oxygen atoms {wherein the heterocycloalkyl is optionally substituted by 1 or 2 substituents independently selected from the group consisting of

(I) hydroxy, and

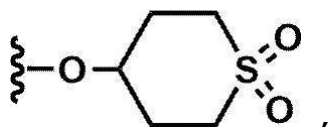
20 (II) C_{1-6} alkyl (wherein the alkyl is optionally substituted by hydroxy)}],

(h) $-\text{NR}^7\text{R}^8$ {wherein R^7 and R^8 are each independently C_{1-4} alkyl, or $-\text{CO}-\text{C}_{1-6}$ alkyl (wherein the alkyl is optionally substituted by cyano)},

25 (i) $-\text{O}-\text{C}_{1-6}$ haloalkyl,

(j) a group represented by the formula:

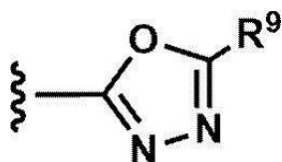
[0087]



[0088]

30 (k) a group represented by the formula:

[0089]

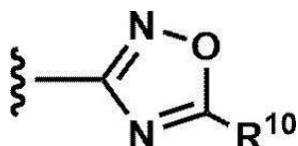


[0090]

{wherein R⁹ is C₁₋₄ alkyl (wherein the alkyl is optionally substituted by C₁₋₄ alkoxy)}, and

5 (m) a group represented by the formula:

[0091]



[0092]

wherein R¹⁰ is C₁₋₄ alkyl)),

10 (2) C₅₋₈ bridged cycloalkyl {wherein the bridged cycloalkyl is optionally substituted by

(a) hydroxy,

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

15 (I) hydroxy,

(II) carboxy,

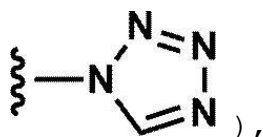
(III) -CONH₂,

(IV) -CO-C₁₋₄ alkoxy,

(V) -SO₂-C₁₋₄ alkyl, or

20 (VI) a group represented by the formula:

[0093]



[0094]

(c) C₁₋₆ alkoxy (wherein the alkoxy is optionally substituted by hydroxy or -SO₂-C₁₋₄ alkyl),

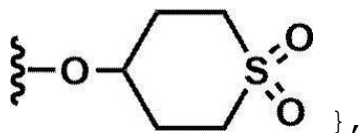
25 (d) carboxy,

(e) -CO-C₁₋₄ alkoxy,

(f) -O-C₁₋₆ haloalkyl, or

(g) a group represented by the formula:

[0095]



[0096]

(3) 5- or 6-membered heterocycloalkyl containing one nitrogen
5 atom [wherein the heterocycloalkyl is optionally substituted by
1 to 3 substituents independently selected from the group
consisting of

(a) oxo,

(b) C₁₋₆ alkyl,

10 (c) -CO-R¹¹ {wherein R¹¹ is

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

(i) hydroxy,

(ii) cyano, or

15 (iii) C₁₋₄ alkoxy),

(II) C₁₋₆ alkoxy,

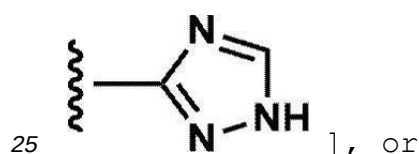
(III) C₁₋₆ haloalkyl,

(IV) C₃₋₆ cycloalkyl (wherein the cycloalkyl is
optionally substituted by halogen), or

20 (V) 4- to 6-membered heterocycloalkyl containing
one oxygen atom (wherein the heterocycloalkyl is optionally
substituted by halogen)}, and

(d) a group represented by the formula:

[0097]



[0098]

(4) 8-membered bridged heterocycloalkyl containing one nitrogen
atom {wherein the bridged heterocycloalkyl is optionally
substituted by -CO-R¹¹},
30 or a pharmaceutically acceptable salt thereof.

[0099]

[Item 12A]

The compound of any one of Items 1A to 9A, wherein ring Cy is

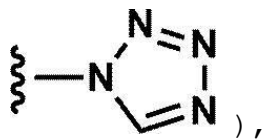
(1) C₄₋₆ cycloalkyl (wherein the cycloalkyl is optionally substituted by 1 or 2 substituents independently selected from the group consisting of

- (a) hydroxy,
- (b) cyano,
- (c) oxo,

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

- (I) hydroxy,
- (II) carboxy,
- (III) -CONH₂,
- (IV) -CO-C₁₋₄ alkoxy,
- (V) -SO₂-C₁₋₄ alkyl, or
- (VI) a group represented by the formula:

[0100]



[0101]

(e) C₁₋₆ alkoxy (wherein the alkoxy is optionally substituted by hydroxy or -SO₂-C₁₋₄ alkyl),

(f) carboxy,

(g) -CO-NR⁵R⁶ [wherein R⁵ and R⁶ are each independently C₁₋₄ alkyl (wherein the alkyl is optionally substituted by C₁₋₄ alkoxy), or R⁵ and R⁶ optionally form, together with the nitrogen atom bonded thereto, 4- to 6-membered heterocycloalkyl containing 1 or 2 hetero atoms independently selected from the group consisting of nitrogen and oxygen atoms {wherein the heterocycloalkyl is optionally substituted by 1 or 2 substituents independently selected from the group consisting of

- (I) hydroxy, and

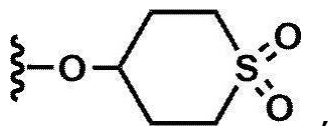
(II) C₁₋₆ alkyl (wherein the alkyl is optionally substituted by hydroxy)}}

(h) -NR⁷R⁸ {wherein R⁷ and R⁸ are each independently C₁₋₄ alkyl, or -CO-C₁₋₆ alkyl (wherein the alkyl is optionally substituted by cyano)},

(i) -O-C₁₋₆ haloalkyl,

(j) a group represented by the formula:

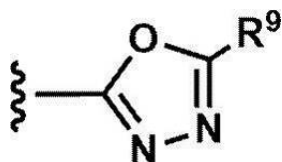
[0102]



10 [0103]

(k) a group represented by the formula:

[0104]

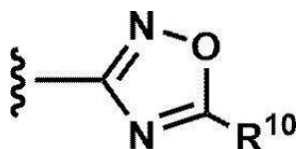


[0105]

15 {wherein R⁹ is C₁₋₄ alkyl (wherein the alkyl is optionally substituted by C₁₋₄ alkoxy)}, and

(m) a group represented by the formula:

[0106]



20 [0107]

wherein R¹⁰ is C₁₋₄ alkyl)), or

(2) C₅₋₈ bridged cycloalkyl {wherein the bridged cycloalkyl is optionally substituted by

(a) hydroxy,

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

(I) hydroxy,

(II) carboxy,

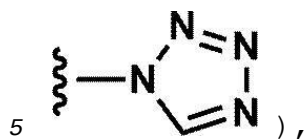
(III) -CONH₂,

(IV) $-\text{CO}-\text{C}_{1-4}$ alkoxy,

(V) $-\text{SO}_2-\text{C}_{1-4}$ alkyl, or

(VI) a group represented by the formula:

[0108]



[0109]

(c) C_{1-6} alkoxy (wherein the alkoxy is optionally substituted by hydroxy or $-\text{SO}_2-\text{C}_{1-4}$ alkyl),

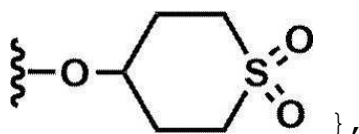
(d) carboxy,

10 (e) $-\text{CO}-\text{C}_{1-4}$ alkoxy,

(f) $-\text{O}-\text{C}_{1-6}$ haloalkyl, or

(g) a group represented by the formula:

[0110]



15 [0111]

or a pharmaceutically acceptable salt thereof.

[0112]

[Item 13A]

The compound of any one of Items 1A to 9A, wherein ring
20 Cy is

(1) cyclohexyl (wherein the cyclohexyl is optionally substituted by 1 or 2 substituents independently selected from the group consisting of

(a) hydroxy,

25 (b) cyano,

(c) oxo,

(d) C_{1-6} alkyl (wherein the alkyl is optionally substituted by

(I) hydroxy,

30 (II) carboxy,

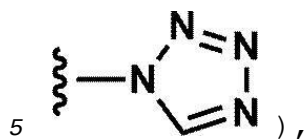
(III) $-\text{CONH}_2$,

(IV) $-\text{CO}-\text{C}_{1-4}$ alkoxy,

(V) $-\text{SO}_2-\text{C}_{1-4}$ alkyl, or

(VI) a group represented by the formula:

[0113]



[0114]

(e) C_{1-6} alkoxy (wherein the alkoxy is optionally substituted by hydroxy or $-\text{SO}_2-\text{C}_{1-4}$ alkyl),

(f) carboxy,

10 (g) $-\text{CO}-\text{NR}^5\text{R}^6$ [wherein R^5 and R^6 are each independently C_{1-4} alkyl (wherein the alkyl is optionally substituted by C_{1-4} alkoxy), or R^5 and R^6 optionally form, together with the nitrogen atom bonded thereto, 4- to 6-membered heterocycloalkyl containing 1 or 2 hetero atoms independently selected from the
15 group consisting of nitrogen and oxygen atoms {wherein the heterocycloalkyl is optionally substituted by 1 or 2 substituents independently selected from the group consisting of

(I) hydroxy, and

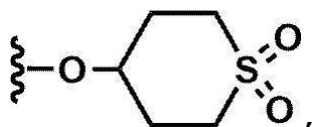
20 (II) C_{1-6} alkyl (wherein the alkyl is optionally substituted by hydroxy)}],

(h) $-\text{NR}^7\text{R}^8$ {wherein R^7 and R^8 are each independently C_{1-4} alkyl, or $-\text{CO}-\text{C}_{1-6}$ alkyl (wherein the alkyl is optionally substituted by cyano)},

25 (i) $-\text{O}-\text{C}_{1-6}$ haloalkyl,

(j) a group represented by the formula:

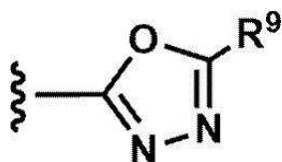
[0115]



[0116]

30 (k) a group represented by the formula:

[0117]

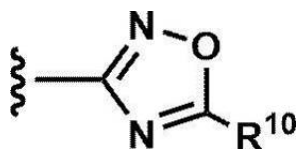


[0118]

{wherein R⁹ is C₁₋₄ alkyl (wherein the alkyl is optionally substituted by C₁₋₄ alkoxy)}, and

5 (m) a group represented by the formula:

[0119]

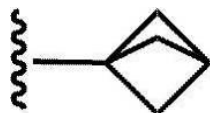


[0120]

wherein R¹⁰ is C₁₋₄ alkyl)), or

10 (2) a group represented by the formula:

[0121]



[0122]

{wherein the group represented by the formula is optionally substituted by

15

(a) hydroxy,

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

(I) hydroxy,

20 (II) carboxy,

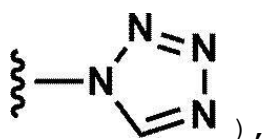
(III) -CONH₂,

(IV) -CO-C₁₋₄ alkoxy,

(V) -SO₂-C₁₋₄ alkyl, or

(VI) a group represented by the formula:

25 [0123]



[0124]

(c) C₁₋₆ alkoxy (wherein the alkoxy is optionally substituted by hydroxy or -SO₂-C₁₋₄ alkyl),

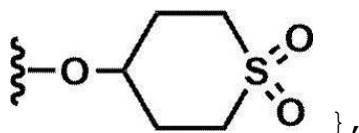
(d) carboxy,

(e) -CO-C₁₋₄ alkoxy,

5 (f) -O-C₁₋₆ haloalkyl, or

(g) a group represented by the formula:

[0125]



[0126]

10 or a pharmaceutically acceptable salt thereof.

[0127]

[Item 14A]

The compound of any one of Items 1A to 9A, wherein ring Cy is

15 (1) a group represented by the formula:

[0128]



[0129]

wherein R¹² and R¹³ are each independently

20 (a) hydrogen,

(b) hydroxy,

(c) cyano,

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

25 (I) hydroxy,

(II) carboxy,

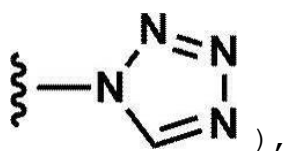
(III) -CONH₂,

(IV) -CO-C₁₋₄ alkoxy,

(V) -SO₂-C₁₋₄ alkyl, or

30 (VI) a group represented by the formula:

[0130]



[0131]

(e) C₁₋₆ alkoxy (wherein the alkoxy is optionally substituted by hydroxy or -SO₂-C₁₋₄ alkyl),

5 (f) carboxy,

(g) -CO-NR⁵R⁶ [wherein R⁵ and R⁶ are each independently C₁₋₄ alkyl (wherein the alkyl is optionally substituted by C₁₋₄ alkoxy), or R⁵ and R⁶ optionally form, together with the nitrogen atom bonded thereto, 4- to 6-membered heterocycloalkyl
10 containing 1 or 2 hetero atoms independently selected from the group consisting of nitrogen and oxygen atoms {wherein the heterocycloalkyl is optionally substituted by 1 or 2 substituents independently selected from the group consisting of

15 (I) hydroxy, and

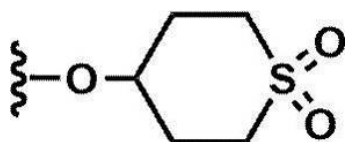
(II) C₁₋₆ alkyl (wherein the alkyl is optionally substituted by hydroxy)}],

(h) -NR⁷R⁸ {wherein R⁷ and R⁸ are each independently C₁₋₄ alkyl or -CO-C₁₋₆ alkyl (wherein the alkyl is optionally
20 substituted by cyano)}],

(i) -O-C₁₋₆ haloalkyl,

(j) a group represented by the formula:

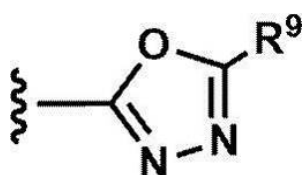
[0132]



25 [0133]

(k) a group represented by the formula:

[0134]

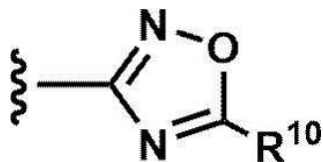


[0135]

{wherein R⁹ is C₁₋₄ alkyl (wherein the alkyl is optionally substituted by C₁₋₄ alkoxy)}, or

(m) a group represented by the formula:

5 [0136]

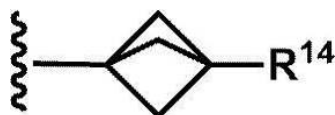


[0137]

wherein R¹⁰ is C₁₋₄ alkyl), or R¹² and R¹³ are optionally joined to form oxo), or

10 (2) a group represented by the formula:

[0138]



[0139]

wherein R¹⁴ is

15 (a) hydrogen,

(b) hydroxy,

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

(I) hydroxy,

20 (II) carboxy,

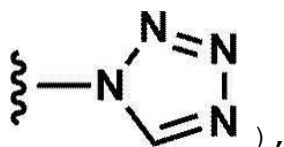
(III) -CONH₂,

(IV) -CO-C₁₋₄ alkoxy,

(V) -SO₂-C₁₋₄ alkyl, or

(VI) a group represented by the formula:

25 [0140]

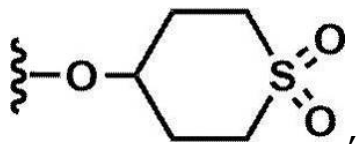


[0141]

(d) C₁₋₆ alkoxy (wherein the alkoxy is optionally substituted by hydroxy or -SO₂-C₁₋₄ alkyl),

- (e) carboxy,
- (f) -CO-C₁₋₄ alkoxy,
- (g) -O-C₁₋₆ haloalkyl, or
- (h) a group represented by the formula:

5 [0142]



[0143]

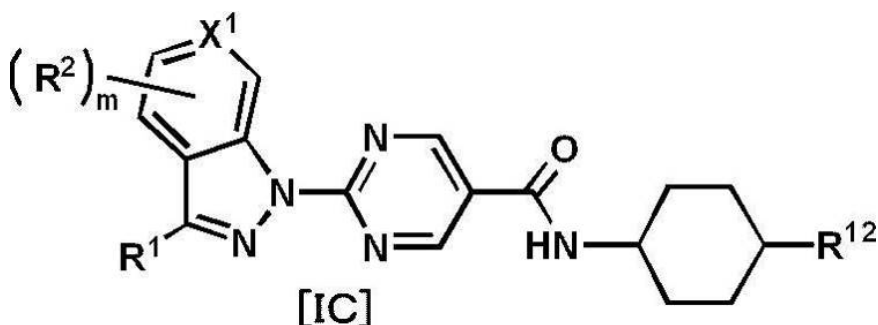
or a pharmaceutically acceptable salt thereof.

[0144]

10 [Item 15A]

The compound of Item 1A or 14A, which is represented by the formula [IC]:

[0145]



15 [0146]

wherein

X¹, R¹, R² and m are as defined for Item 1A, and

R¹² is as defined for Item 14A,

or a pharmaceutically acceptable salt thereof.

20 [0147]

[Item 16A]

The compound of Item 15A, wherein

R¹² is

(1) hydroxy,

25 (2) cyano,

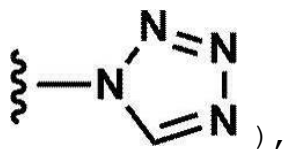
(3) C₁₋₆ alkyl (wherein the alkyl is optionally substituted by

(a) hydroxy,

(b) carboxy,

- (c) $-\text{CONH}_2$,
- (d) $-\text{CO}-\text{C}_{1-4}$ alkoxy,
- (e) $-\text{SO}_2-\text{C}_{1-4}$ alkyl, or
- (f) a group represented by the formula:

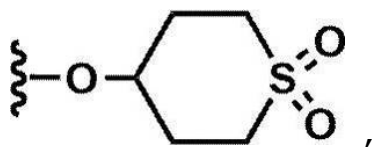
5 [0148]



[0149]

- (4) C_{1-6} alkoxy (wherein the alkoxy is optionally substituted by hydroxy or $-\text{SO}_2-\text{C}_{1-4}$ alkyl),
- 10 (5) $-\text{CO}-\text{NR}^5\text{R}^6$ [wherein R^5 and R^6 form, together with the nitrogen atom bonded thereto, 4- to 6-membered heterocycloalkyl containing 1 or 2 hetero atoms independently selected from the group consisting of nitrogen and oxygen atoms {wherein the heterocycloalkyl is optionally substituted by C_{1-6} alkyl
- 15 (wherein the alkyl is optionally substituted by hydroxy)}],
- (6) $-\text{NR}^7\text{R}^8$ {wherein R^7 and R^8 are each independently C_{1-4} alkyl or $-\text{CO}-\text{C}_{1-6}$ alkyl (wherein the alkyl is optionally substituted by cyano)}},
- (7) a group represented by the formula:

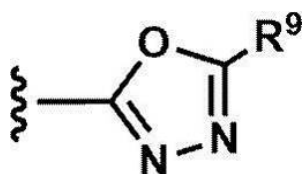
20 [0150]



[0151]

- (8) a group represented by the formula:

[0152]



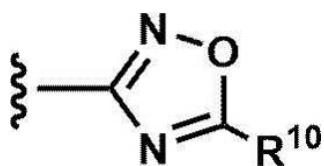
25

[0153]

- {wherein R^9 is C_{1-4} alkyl (wherein the alkyl is optionally substituted by C_{1-4} alkoxy)}}, or

(9) a group represented by the formula:

[0154]



[0155]

5 wherein R¹⁰ is C₁₋₄ alkyl,

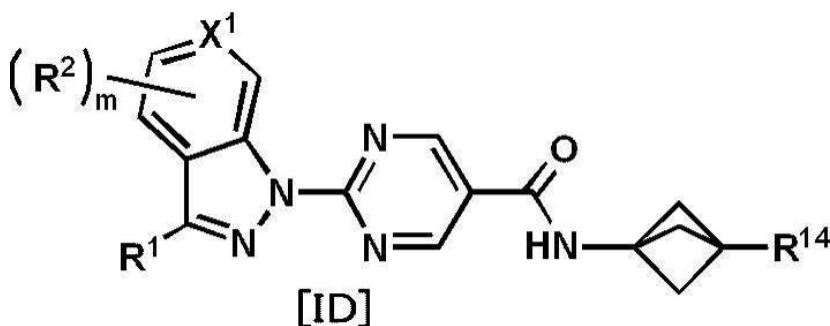
or a pharmaceutically acceptable salt thereof.

[0156]

[Item 17A]

The compound of Item 1A or 14A, which is represented by
10 the formula [ID]:

[0157]



[0158]

15 wherein

X¹, R¹, R² and m are as defined for Item 1A, and

R¹⁴ is as defined for Item 14A,

or a pharmaceutically acceptable salt thereof.

[0159]

20 [Item 18A]

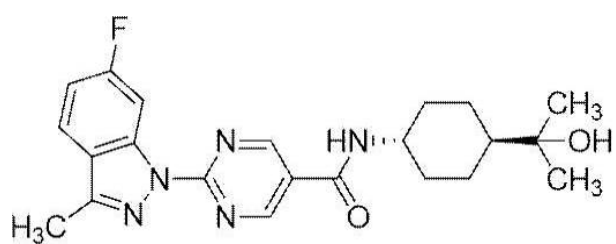
The compound of Item 17A, wherein R¹⁴ is C₁₋₆ alkyl
(wherein the alkyl is optionally substituted by hydroxy), or a
pharmaceutically acceptable salt thereof.

[0160]

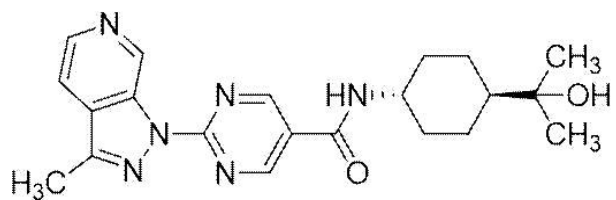
25 [Item 19A]

The compound of Item 1A which is selected from the group
consisting of the following structural formulas:

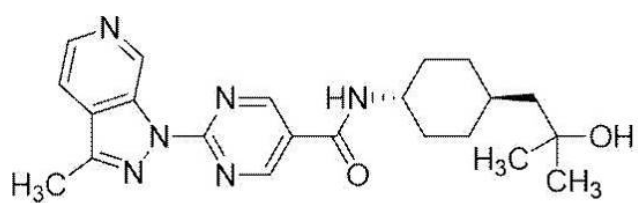
[0161]



[0162]

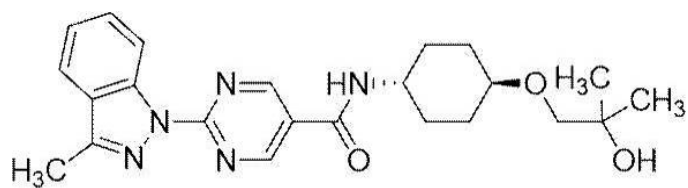


[0163]

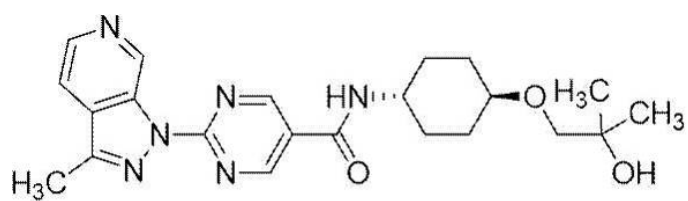


5

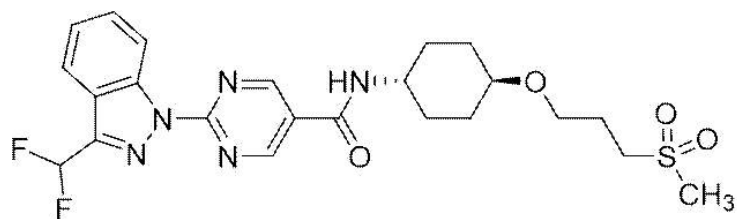
[0164]



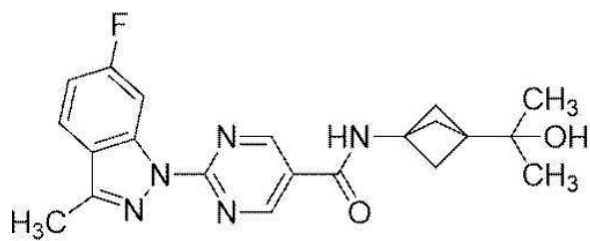
[0165]



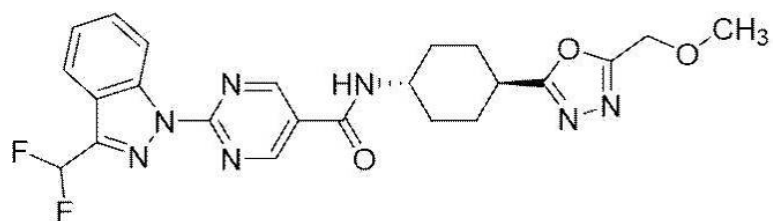
10 [0166]



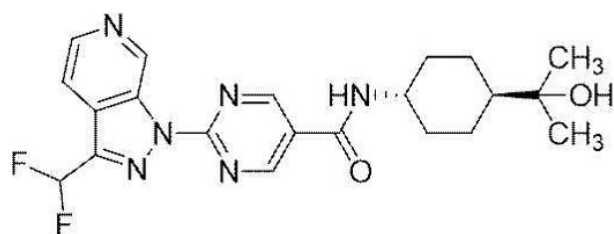
[0167]



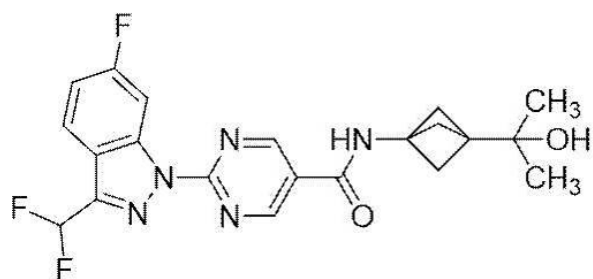
[0168]



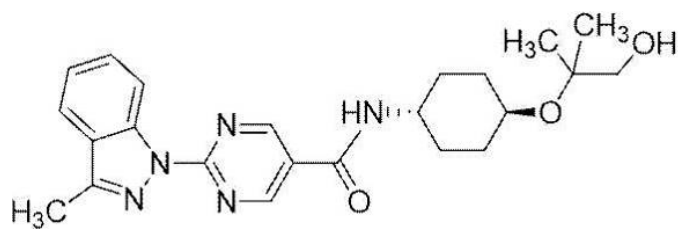
5 [0169]



[0170]



[0171]



10

[0172]

Cc1c2ccccc2nn1-c1ccnc1C(=O)N[C@H]2CCCC[C@H]2O[C@H](C)CO

5 or a pharmaceutically acceptable salt thereof.

[Item 20A]

[0176]

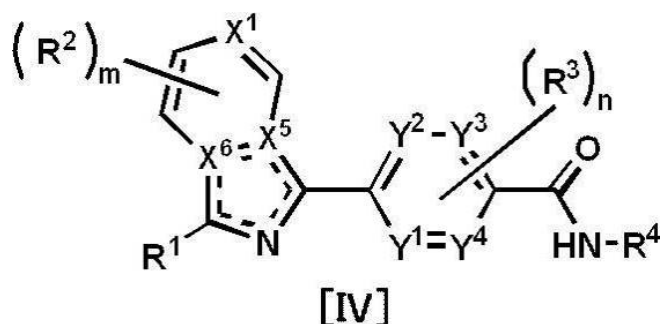


```
{wherein
```

[0178]

A compound of the formula [IV]:

36



[0180]

{wherein

X^1 , X^5 , X^6 , Y^1 , Y^2 , Y^3 and Y^4 are each independently a carbon or
 5 a nitrogen atom (wherein the total number of the nitrogen atoms
 for X^5 and X^6 is 1, and the total number of the nitrogen atoms
 for Y^1 , Y^2 , Y^3 and Y^4 is 0, 1 or 2), and
 other symbols are as defined for Item 1A},
 or a pharmaceutically acceptable salt thereof.

10 [0181]

[Item 22A]

A pharmaceutical composition comprising the compound of
 any one of Items 1A to 21A or a pharmaceutically acceptable
 salt thereof, and a pharmaceutically acceptable carrier.

15 [0182]

[Item 23A]

An H-PGDS inhibitor comprising the compound of any one of
 Items 1A to 21A or a pharmaceutically acceptable salt thereof.

[0183]

20 [Item 24A]

A therapeutic or prophylactic agent for a disease
 selected from the group consisting of peripheral arterial
 diseases, cardiovascular diseases, allergic asthma, chronic
 obstructive pulmonary diseases, and Duchenne muscular dystrophy,
 25 the agent comprising the compound of any one of Items 1A to 21A
 or a pharmaceutically acceptable salt thereof.

[0184]

[Item 25A]

A method for inhibiting H-PGDS in a mammal, comprising
 30 administering a pharmaceutically effective amount of the

compound of any one of Items 1A to 21A or a pharmaceutically acceptable salt thereof to the mammal.

[0185]

[Item 26A]

5 A method for treating or preventing a disease selected from the group consisting of peripheral arterial diseases, cardiovascular diseases, allergic asthma, chronic obstructive pulmonary diseases, and Duchenne muscular dystrophy in a mammal, comprising administering a pharmaceutically effective amount of
10 the compound of any one of Items 1A to 21A or a pharmaceutically acceptable salt thereof to the mammal.

[0186]

[Item 27A]

 Use of the compound of any one of Items 1A to 21A or a
15 pharmaceutically acceptable salt thereof in producing an H-PGDS inhibitor.

[0187]

[Item 28A]

 Use of the compound of any one of Items 1A to 21A or a
20 pharmaceutically acceptable salt thereof in producing a therapeutic or prophylactic agent for a disease selected from the group consisting of peripheral arterial diseases, cardiovascular diseases, allergic asthma, chronic obstructive pulmonary diseases, and Duchenne muscular dystrophy.

25 [0188]

[Item 29A]

 The compound of any one of Items 1A to 21A or a pharmaceutically acceptable salt thereof for use in inhibiting H-PGDS.

30 [0189]

[Item 30A]

 The compound of any one of Items 1A to 21A or a pharmaceutically acceptable salt thereof for use in the treatment or prophylaxis of a disease selected from the group
35 consisting of peripheral arterial diseases, cardiovascular

diseases, allergic asthma, chronic obstructive pulmonary diseases, and Duchenne muscular dystrophy.

[0190]

[Item 31A]

5 A commercial package comprising the pharmaceutical composition of Item 22A and a written matter associated therewith, the written matter stating that the pharmaceutical composition can be used for treatment or prophylaxis of a disease selected from the group consisting of peripheral
10 arterial diseases, cardiovascular diseases, allergic asthma, chronic obstructive pulmonary diseases, and Duchenne muscular dystrophy.

[0191]

[Item 32A]

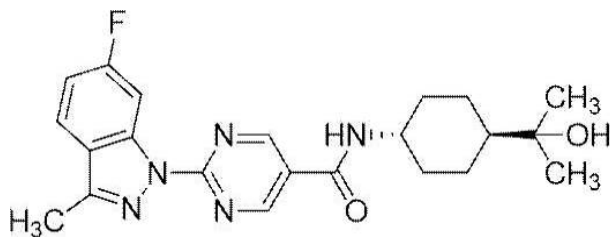
15 A kit comprising the pharmaceutical composition of Item 22A and a written matter associated therewith, the written matter stating that the pharmaceutical composition can be used for treatment or prophylaxis of a disease selected from the group consisting of peripheral arterial diseases, cardiovascular
20 diseases, allergic asthma, chronic obstructive pulmonary diseases, and Duchenne muscular dystrophy.

[0192]

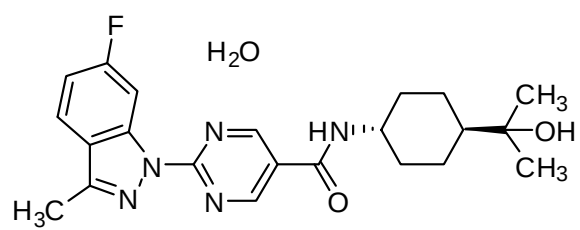
[Item 33A]

 A compound selected from the group consisting of the
25 following structural formulas:

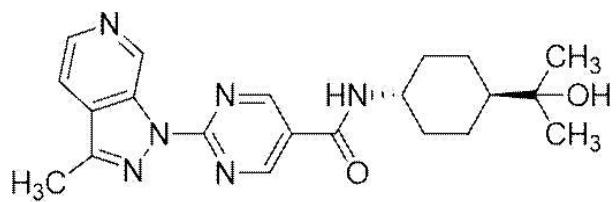
[0193]



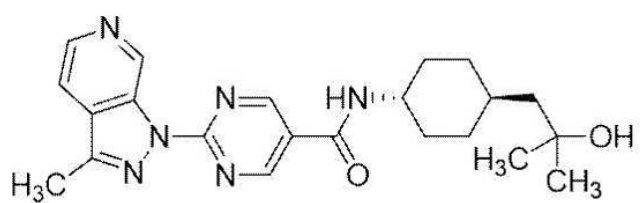
[0194]



[0195]

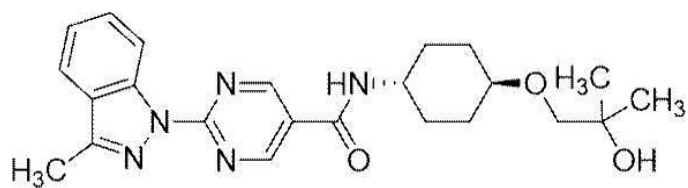


[0196]

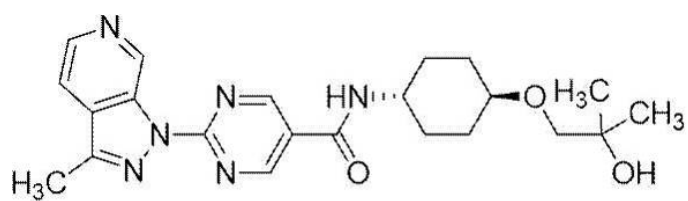


5

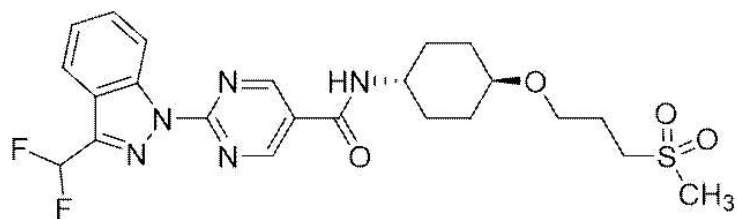
[0197]



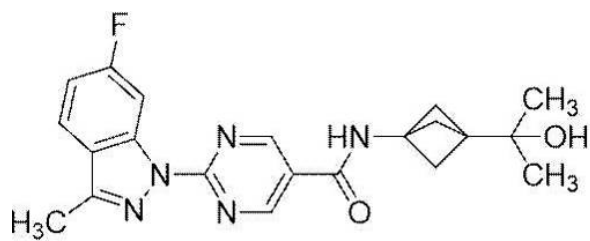
[0198]



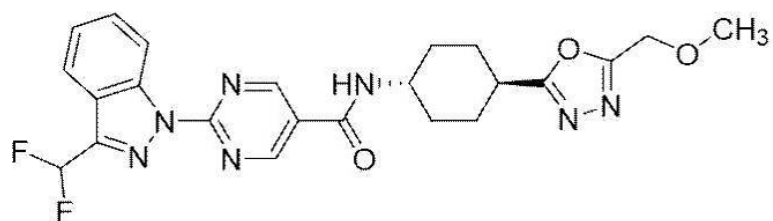
10 [0199]



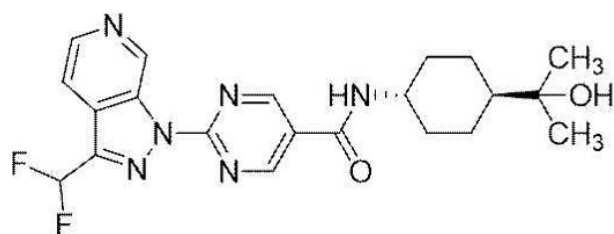
[0200]



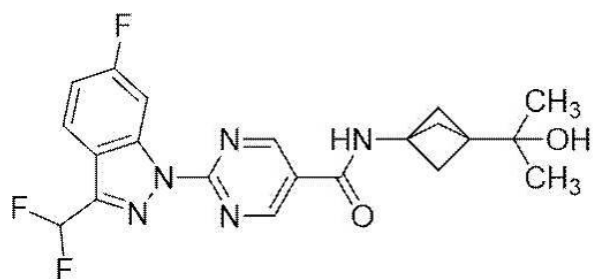
[0201]



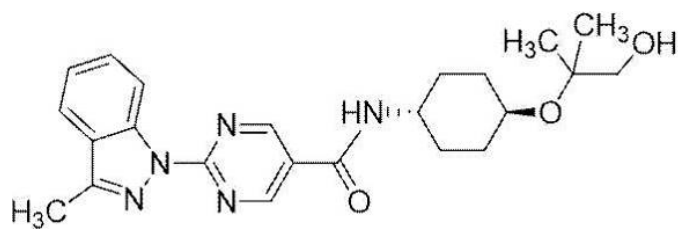
5 [0202]



[0203]

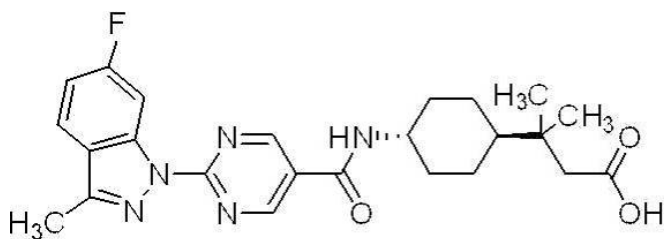


[0204]



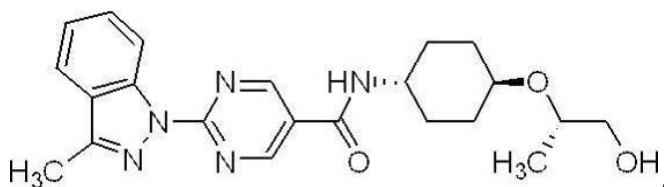
10

[0205]



and

[0206]



[0207]

5 or a pharmaceutically acceptable salt thereof.

[0208]

[Item 34A]

A pharmaceutical composition comprising the compound of any one of Items 1A to 21A and Item 33A or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

[0209]

[Item 35A]

An H-PGDS inhibitor comprising the compound of any one of Items 1A to 21A and Item 33A or a pharmaceutically acceptable salt thereof.

[0210]

[Item 36A]

A therapeutic or prophylactic agent for a disease selected from the group consisting of peripheral arterial diseases, cardiovascular diseases, allergic asthma, chronic obstructive pulmonary diseases, allergic rhinitis, sarcopenia, and Duchenne muscular dystrophy, the agent comprising the compound of any one of Items 1A to 21A and Item 33A or a pharmaceutically acceptable salt thereof.

[0211]

[Item 37A]

The therapeutic or prophylactic agent of Item 36A, wherein the peripheral arterial disease is intermittent claudication or comprehensive severe chronic lower extremity ischemia based on PAD.

5 [0212]

[Item 38A]

A method for inhibiting H-PGDS in a mammal, comprising administering a pharmaceutically effective amount of the compound of any one of Items 1A to 21A and Item 33A or a
10 pharmaceutically acceptable salt thereof to the mammal.

[0213]

[Item 39A]

A method for treating or preventing a disease selected from the group consisting of peripheral arterial diseases,
15 cardiovascular diseases, allergic asthma, chronic obstructive pulmonary diseases, allergic rhinitis, sarcopenia, and Duchenne muscular dystrophy in a mammal, comprising administering a pharmaceutically effective amount of the compound of any one of Items 1A to 21A and Item 33A or a pharmaceutically acceptable
20 salt thereof to the mammal.

[0214]

[Item 40A]

The method of Item 39A, wherein the peripheral arterial disease is intermittent claudication or comprehensive severe
25 chronic lower extremity ischemia based on PAD.

[0215]

[Item 41A]

Use of the compound of any one of Items 1A to 21A and Item 33A or a pharmaceutically acceptable salt thereof in
30 producing an H-PGDS inhibitor.

[0216]

[Item 42A]

Use of the compound of any one of Items 1A to 21A and Item 33A or a pharmaceutically acceptable salt thereof in
35 producing a therapeutic or prophylactic agent for a disease

selected from the group consisting of peripheral arterial diseases, cardiovascular diseases, allergic asthma, chronic obstructive pulmonary diseases, allergic rhinitis, sarcopenia, and Duchenne muscular dystrophy.

5 [0217]

[Item 43A]

The use of Item 42A, wherein the peripheral arterial disease is intermittent claudication or comprehensive severe chronic lower extremity ischemia based on PAD.

10 [0218]

[Item 44A]

The compound of any one of Items 1A to 21A and Item 33A or a pharmaceutically acceptable salt thereof for use in inhibiting H-PGDS.

15 [0219]

[Item 45A]

The compound of any one of Items 1A to 21A and Item 33A and Item 33A or a pharmaceutically acceptable salt thereof for use in the treatment or prophylaxis of a disease selected from
20 the group consisting of peripheral arterial diseases, cardiovascular diseases, allergic asthma, chronic obstructive pulmonary diseases, allergic rhinitis, sarcopenia, and Duchenne muscular dystrophy.

[0220]

25 [Item 46A]

The compound of Item 45A or a pharmaceutically acceptable salt thereof, wherein the peripheral arterial disease is intermittent claudication or comprehensive severe chronic lower extremity ischemia based on PAD.

30 [0221]

[Item 47A]

A commercial package comprising the pharmaceutical composition of Item 34A and a written matter associated therewith, the written matter stating that the pharmaceutical
35 composition can be used for treatment or prophylaxis of a

disease selected from the group consisting of peripheral arterial diseases, cardiovascular diseases, allergic asthma, chronic obstructive pulmonary diseases, allergic rhinitis, sarcopenia, and Duchenne muscular dystrophy.

5 [0222]

[Item 48A]

A kit comprising the pharmaceutical composition of Item 22A and a written matter associated therewith, the written matter stating that the pharmaceutical composition can be used
10 for treatment or prophylaxis of a disease selected from the group consisting of peripheral arterial diseases, cardiovascular diseases, allergic asthma, chronic obstructive pulmonary diseases, allergic rhinitis, sarcopenia, and Duchenne muscular dystrophy.

15 [Description of Embodiments]

[0223]

The definitions of the terms in the present specification are as follows.

[0224]

20 In the chemical formulas, the wavy line shown by the following:

[0225]



[0226]

25 indicates a binding site in the structures or groups represented by the chemical formulas.

[0227]

In the chemical formulas, the bond shown by the following:

30 [0228]

=====

[0229]

is a single bond or a double bond.

[0230]

The "C₁₋₄ alkyl" means a linear or branched chain saturated hydrocarbon group having 1 to 4 carbon atoms. The
5 "C₁₋₄ alkyl" includes methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, and tert-butyl. Preferred "C₁₋₄ alkyl" is methyl, ethyl, or isopropyl. More preferred "C₁₋₄ alkyl" is methyl or ethyl.

[0231]

10 The "C₁₋₆ alkyl" means a linear or branched chain saturated hydrocarbon group having 1 to 6 carbon atoms. The "C₁₋₆ alkyl" includes, for example, methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, tert-butyl, n-pentyl, isopentyl, neopentyl, 2-methylbutyl, 1,1-dimethylpropyl, 1-
15 ethylpropyl, n-hexyl, isohexyl, 1,1-dimethylbutyl, 2,2-dimethylbutyl, 3,3-dimethylbutyl, and 2-ethylbutyl. Preferred "C₁₋₆ alkyl" is methyl, ethyl, isopropyl, isobutyl, tert-butyl, or isopentyl. More preferred "C₁₋₆ alkyl" is methyl, ethyl, isopropyl, isobutyl, or tert-butyl.

20 [0232]

The "C₁₋₄ alkoxy" means a group in which the above-mentioned "C₁₋₄ alkyl" is bonded to an oxygen atom. The "C₁₋₄ alkoxy" includes methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, sec-butoxy, isobutoxy, and tert-butoxy. Preferred "C₁₋₄
25 alkoxy" is methoxy or ethoxy.

[0233]

The "C₁₋₆ alkoxy" means a group in which the above-mentioned "C₁₋₆ alkyl" is bonded to an oxygen atom. The "C₁₋₆ alkoxy" includes, for example, methoxy, ethoxy, n-propoxy,
30 isopropoxy, n-butoxy, sec-butoxy, isobutoxy, tert-butoxy, pentyloxy, isopentyloxy, neopentyloxy, 2-methylbutoxy, 1,1-dimethylpropoxy, 1-ethylpropoxy, hexyloxy, isohexyloxy, 1,1-dimethylbutoxy, 2,2-dimethylbutoxy, 3,3-dimethylbutoxy, and 2-ethylbutoxy. Preferred "C₁₋₆ alkoxy" is methoxy, ethoxy, n-
35 propoxy, isopropoxy, isobutoxy, tert-butoxy, or isopentyloxy.

[0234]

The "halogen" includes, for example, fluorine, chlorine, bromine, and iodine. Preferred "halogen" is fluorine or chlorine.

5 [0235]

The "C₁₋₄ haloalkyl" means the above-mentioned "C₁₋₄ alkyl" substituted by 1 to 7 halogens independently selected from the group of the above-mentioned group of "halogen". The "C₁₋₄ haloalkyl" includes, for example, monofluoromethyl, difluoromethyl, trifluoromethyl, chlorofluoromethyl, 2-fluoroethyl, 2-chloroethyl, 2-bromoethyl, 1,1-difluoroethyl, 2,2-difluoroethyl, 1-fluoro-1-methylethyl, 2,2,2-trifluoro-1-methylethyl, 2,2,2-trifluoroethyl, pentafluoroethyl, 3-fluoropropyl, 3-chloropropyl, 1,1-difluoropropyl, 3,3,3-trifluoropropyl, and 4,4,4-trifluorobutyl. Preferred "C₁₋₄ haloalkyl" is difluoromethyl, trifluoromethyl, or 2,2-difluoroethyl.

[0236]

The "C₁₋₆ haloalkyl" means the above-mentioned "C₁₋₆ alkyl" substituted by 1 to 9 halogens independently selected from the group of the above-mentioned "halogen". The "C₁₋₆ haloalkyl" includes, for example, monofluoromethyl, difluoromethyl, trifluoromethyl, chlorofluoromethyl, 2-fluoroethyl, 2-chloroethyl, 2-bromoethyl, 1,1-difluoroethyl, 2,2-difluoroethyl, 1-fluoro-1-methylethyl, 2,2,2-trifluoro-1-methylethyl, 2,2,2-trifluoroethyl, pentafluoroethyl, 3-fluoropropyl, 3-chloropropyl, 1,1-difluoropropyl, 3,3,3-trifluoropropyl, 4,4,4-trifluorobutyl, 5,5,5-trifluoropentyl, and 6,6,6-trifluorohexyl. Preferred "C₁₋₆ haloalkyl" is difluoromethyl, trifluoromethyl, 1-fluoro-1-methylethyl, or 2,2,2-trifluoroethyl.

[0237]

The "C₄₋₆ cycloalkyl" means a monocyclic saturated hydrocarbon ring group having 4 to 6 carbon atoms. The "C₄₋₆ cycloalkyl" includes, for example, cyclobutyl, cyclopentyl, and cyclohexyl. Preferred "C₄₋₆ cycloalkyl" is cyclobutyl or

cyclohexyl. More preferred "C₄₋₆ cycloalkyl" is cyclohexyl.
[0238]

The "C₃₋₆ cycloalkyl" means a monocyclic saturated hydrocarbon ring group having 3 to 6 carbon atoms. The "C₃₋₆ cycloalkyl" includes, for example, cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl. Preferred "C₃₋₆ cycloalkyl" is cyclopropyl, cyclobutyl, or cyclohexyl.
[0239]

The "4- to 6-membered heterocycloalkyl containing 1 or 2 hetero atoms independently selected from the group consisting of nitrogen and oxygen atoms" means a 4- to 6-membered monocyclic saturated heterocyclic group containing, as a ring-constituting atom besides carbon atom, 1 or 2 hetero atoms independently selected from the group consisting of nitrogen and oxygen. The "4- to 6-membered heterocycloalkyl containing 1 or 2 hetero atoms independently selected from the group consisting of nitrogen and oxygen atoms" includes, for example, azetidiny, oxetanyl, diazetidiny, dioxetanyl, pyrrolidiny, tetrahydrofuranyl, imidazolidiny, pyrazolidiny, oxazolidiny, isoxazolidiny, dioxolanyl, piperidiny, tetrahydropyranyl, 1,3-diazacyclohexanyl, piperaziny, morpholiny, tetrahydro-1,2-oxaziny, and dioxanyl. Preferred "4- to 6-membered heterocycloalkyl containing 1 or 2 hetero atoms independently selected from the group consisting of nitrogen and oxygen atoms" is azetidiny, pyrrolidiny, or morpholiny.
[0240]

The "5- or 6-membered heterocycloalkyl containing one nitrogen atom" means a 5- or 6-membered monocyclic saturated heterocyclic group containing one nitrogen atom as a ring-constituting atom besides carbon atom. The "5- or 6-membered heterocycloalkyl containing one nitrogen atom" includes, for example, pyrrolidiny and piperidiny. Preferred "5- or 6-membered heterocycloalkyl containing one nitrogen atom" is piperidiny.
[0241]

The "4- to 6-membered heterocycloalkyl containing one oxygen atom" means a 4- to 6-membered monocyclic saturated heterocyclic group containing one oxygen atom as a ring-constituting atom besides carbon atom. The "4- to 6-membered heterocycloalkyl containing one oxygen atom" includes, for example, oxetanyl, tetrahydrofuranyl, and tetrahydropyranyl. Preferred "4- to 6-membered heterocycloalkyl containing one oxygen atom" is oxetanyl or tetrahydropyranyl.

[0242]

10 The "C₅₋₈ bridged cycloalkyl" means a 5- to 8-membered, bridged cyclic saturated hydrocarbon group. The "C₅₋₈ bridged cycloalkyl" includes, for example, bicyclo[1.1.1]pentyl, bicyclo[2.2.1]heptyl, and bicyclo[2.2.2]octyl. Preferred "C₅₋₈ bridged cycloalkyl" is bicyclo[1.1.1]pentyl or
15 bicyclo[2.2.2]octyl. More preferred "C₅₋₈ bridged cycloalkyl" is bicyclo[1.1.1]pentyl.

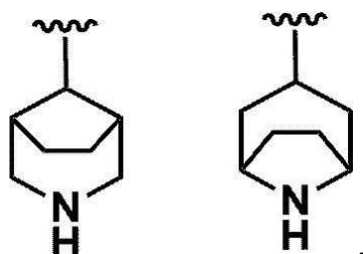
[0243]

The "8-membered bridged heterocycloalkyl containing one nitrogen atom" means a 8-membered bridged saturated
20 heterocyclic group containing one nitrogen atom as a ring-constituting atom besides carbon atom. The "8-membered bridged heterocycloalkyl containing one nitrogen atom" includes, for example,

[0244]

25 the following groups:

[0245]



[0246]

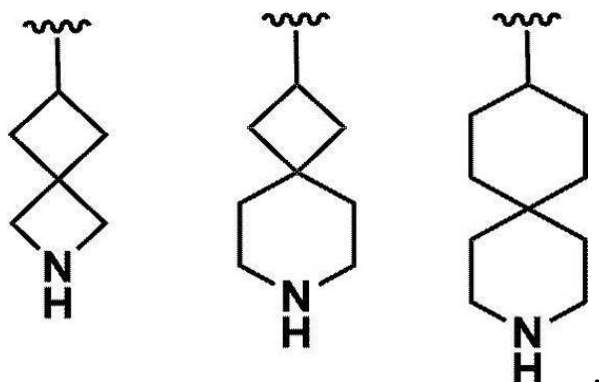
The "7- to 11-membered spiro heterocycloalkyl containing
30 one nitrogen atom" means a 7- to 11-membered spiro-type saturated heterocyclic group containing one nitrogen atom as a

ring-constituting atom besides carbon atom. The "7- to 11-membered spiro heterocycloalkyl containing one nitrogen atom" includes, for example,

[0247]

5 the following groups:

[0248]



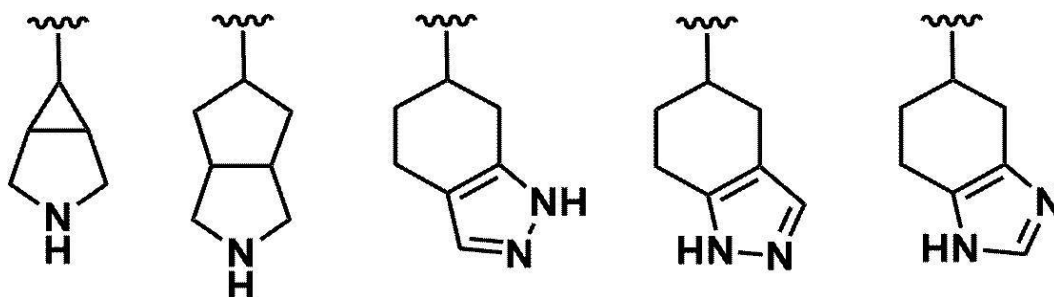
[0249]

The "6- to 9-membered saturated or partially unsaturated fused ring group containing 1 or 2 nitrogen atoms" means a 6-
 10 to 9-membered fused heterocyclic group containing 1 or 2 nitrogen atoms as a ring-constituting atom besides carbon atom, and means a fused ring group containing at least one saturated ring in the ring constituting the fused ring. The "6- to 9-
 15 membered saturated or partially unsaturated fused ring group containing 1 or 2 nitrogen atoms" includes, for example,

[0250]

the following groups:

[0251]



20

[0252]

That α is "optionally substituted" by β means that α is unsubstituted or any substitutable hydrogen of α is replaced

by β . For example, "C₁₋₆ alkyl optionally substituted by hydroxy" means that C₁₋₆ alkyl is unsubstituted or any hydrogen in C₁₋₆ alkyl is replaced by hydroxy.

[0253]

5 Specific embodiments of each substituent of the compound of formula [II] are exemplified below. However, each substituent of the compound of formula [II] is not limited to the specific embodiments. In addition, the compound of the formula [II] also includes an embodiment in which any two or
10 more of the specific embodiments of each substituent are combined.

[0254]

Y¹ is preferably a nitrogen atom.

[0255]

15 Y² is preferably a nitrogen atom.

[0256]

Y³ is preferably a carbon atom.

[0257]

Y⁴ is preferably a carbon atom.

20 [0258]

Preferred embodiment of R¹ is

(1) hydroxy,

(2) C₁₋₄ alkyl (wherein the alkyl is optionally substituted by hydroxy or C₁₋₄ alkoxy),

25 (3) C₁₋₄ alkoxy,

(4) halogen, or

(5) C₁₋₄ haloalkyl.

[0259]

More preferred embodiment of R¹ is

30 (1) C₁₋₄ alkyl (wherein the alkyl is optionally substituted by hydroxy or C₁₋₄ alkoxy),

(2) halogen, or

(3) C₁₋₄ haloalkyl.

[0260]

35 Preferred specific example of R¹ is methyl, fluorine,

chlorine, difluoromethyl, or trifluoromethyl.

[0261]

Preferred embodiments of R^2 in the number of m are each independently halogen.

5 [0262]

Preferred specific examples of R^2 in the number of m include fluorine and chlorine.

[0263]

m is preferably 0 or 1.

10 [0264]

Preferred embodiments of R^3 in the number of n are each independently halogen.

[0265]

Preferred specific examples of R^3 in the number of n
15 include fluorine and chlorine.

[0266]

n is preferably 0 or 1.

[0267]

R^4 is preferably

20 (a) C_{4-6} cycloalkyl (wherein the cycloalkyl is optionally substituted by 1 or 2 substituents independently selected from the group consisting of

(I) hydroxy,

(II) cyano,

25 (III) oxo,

(IV) C_{1-6} alkyl (wherein the alkyl is optionally substituted by

(i) hydroxy,

(ii) carboxy,

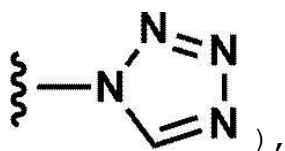
30 (iii) $-CONH_2$,

(iv) $-CO-C_{1-4}$ alkoxy,

(v) $-SO_2-C_{1-4}$ alkyl, or

(vi) a group represented by the formula:

[0268]



[0269]

(V) C₁₋₆ alkoxy (wherein the alkoxy is optionally substituted by hydroxy or -SO₂-C₁₋₄ alkyl),

5 (VI) carboxy,

(VII) -CO-NR⁵R⁶ [wherein R⁵ and R⁶ are each independently C₁₋₄ alkyl (wherein the alkyl is optionally substituted by C₁₋₄ alkoxy), or R⁵ and R⁶ optionally form, together with the nitrogen atom bonded thereto, 4- to 6-membered heterocycloalkyl
10 containing 1 or 2 hetero atoms independently selected from the group consisting of nitrogen and oxygen atoms {wherein the heterocycloalkyl is optionally substituted by 1 or 2 substituents independently selected from the group consisting of

15 (i) hydroxy, and

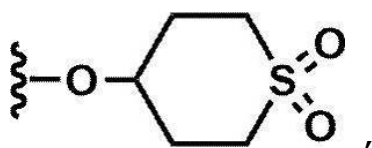
(ii) C₁₋₆ alkyl (wherein the alkyl is optionally substituted by hydroxy)}],

(VIII) -NR⁷R⁸ {wherein R⁷ and R⁸ are each independently C₁₋₄ alkyl or -CO-C₁₋₆ alkyl (wherein the alkyl is optionally
20 substituted by cyano)}],

(IX) -O-C₁₋₆ haloalkyl,

(X) a group represented by the formula:

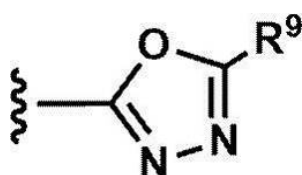
[0270]



25 [0271]

(XI) a group represented by the formula:

[0272]

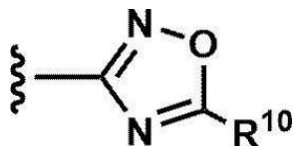


[0273]

{wherein R⁹ is C₁₋₄ alkyl (wherein the alkyl is optionally substituted by C₁₋₄ alkoxy)}, and

(XII) a group represented by the formula:

5 [0274]



[0275]

wherein R¹⁰ is C₁₋₄ alkyl)),

(b) C₅₋₈ bridged cycloalkyl {wherein the bridged
10 cycloalkyl is optionally substituted by

(I) hydroxy,

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

(i) hydroxy,

15 (ii) carboxy,

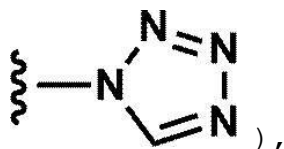
(iii) -CONH₂,

(iv) -CO-C₁₋₄ alkoxy,

(v) -SO₂-C₁₋₄ alkyl, or

(vi) a group represented by the formula:

20 [0276]



[0277]

(III) C₁₋₆ alkoxy (wherein the alkoxy is optionally substituted by hydroxy or -SO₂-C₁₋₄ alkyl),

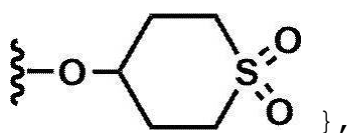
25 (IV) carboxy,

(V) -CO-C₁₋₄ alkoxy,

(VI) -O-C₁₋₆ haloalkyl, or

(VII) a group represented by the formula:

[0278]



[0279]

(c) 5- or 6-membered heterocycloalkyl containing one nitrogen atom [wherein the heterocycloalkyl is

5 (I) oxo,

(II) C₁₋₆ alkyl,

(III) -CO-R¹¹ {wherein R¹¹ is optionally substituted by 1 to 3 substituents independently selected from the group consisting of

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

(A) hydroxy,

(B) cyano, or

(C) C₁₋₄ alkoxy),

15 (ii) C₁₋₆ alkoxy,

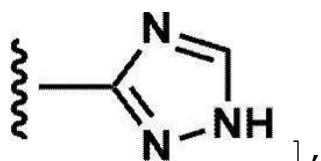
(iii) C₁₋₆ haloalkyl,

(iv) C₃₋₆ cycloalkyl (wherein the cycloalkyl is optionally substituted by halogen), or

(v) 4- to 6-membered heterocycloalkyl containing one
20 oxygen atom (wherein the heterocycloalkyl is optionally substituted by halogen)), and

(IV) a group represented by the formula:

[0280]



25 [0281]

(d) 8-membered bridged heterocycloalkyl containing one nitrogen atom {wherein the bridged heterocycloalkyl is optionally substituted by -CO-R¹¹},

(e) 7- to 11-membered spiro heterocycloalkyl containing
30 one nitrogen atom {wherein the spiro heterocycloalkyl is optionally substituted by -CO-R¹¹}, or

(f) 6- to 9-membered saturated or partially unsaturated fused ring group containing 1 or 2 nitrogen atoms (wherein the fused ring group is optionally substituted by $-\text{CO}-\text{R}^{11}$).

[0282]

5 R^4 is more preferably

(a) C_{4-6} cycloalkyl (wherein the cycloalkyl is optionally substituted by 1 or 2 substituents independently selected from the group consisting of

(I) hydroxy,

10 (II) cyano,

(III) oxo,

(IV) C_{1-6} alkyl (wherein the alkyl is optionally substituted by

(i) hydroxy,

15 (ii) carboxy,

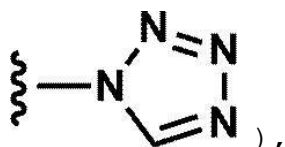
(iii) $-\text{CONH}_2$,

(iv) $-\text{CO}-\text{C}_{1-4}$ alkoxy,

(v) $-\text{SO}_2-\text{C}_{1-4}$ alkyl, or

(vi) a group represented by the formula:

20 [0283]



[0284]

(V) C_{1-6} alkoxy (wherein the alkoxy is optionally substituted by hydroxy or $-\text{SO}_2-\text{C}_{1-4}$ alkyl),

25 (VI) carboxy,

(VII) $-\text{CO}-\text{NR}^5\text{R}^6$ [wherein R^5 and R^6 are each independently C_{1-4} alkyl (wherein the alkyl is optionally substituted by C_{1-4} alkoxy), or R^5 and R^6 optionally form, together with the nitrogen atom bonded thereto, 4- to 6-membered heterocycloalkyl
30 containing 1 or 2 hetero atoms independently selected from the group consisting of nitrogen and oxygen atoms {wherein the heterocycloalkyl is optionally substituted by 1 or 2 substituents independently selected from the group consisting

of

(i) hydroxy, and

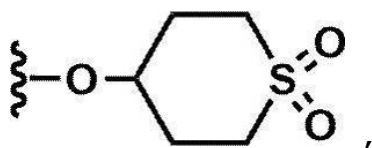
(ii) C₁₋₆ alkyl (wherein the alkyl is optionally substituted by hydroxy)}],

5 (VIII) -NR⁷R⁸ {wherein R⁷ and R⁸ are each independently C₁₋₄ alkyl or -CO-C₁₋₆ alkyl (wherein the alkyl is optionally substituted by cyano)}],

(IX) -O-C₁₋₆ haloalkyl,

(X) a group represented by the formula:

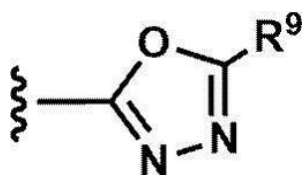
10 [0285]



[0286]

(XI) a group represented by the formula:

[0287]



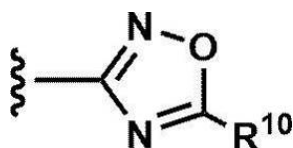
15

[0288]

{wherein R⁹ is C₁₋₄ alkyl (wherein the alkyl is optionally substituted by C₁₋₄ alkoxy)}], and

(XII) a group represented by the formula:

20 [0289]



[0290]

wherein R¹⁰ is C₁₋₄ alkyl)),

25 (b) C₅₋₈ bridged cycloalkyl {wherein the bridged cycloalkyl is optionally substituted by

(I) hydroxy,

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

(i) hydroxy, or
 (ii) $-\text{SO}_2\text{-C}_{1-4}$ alkyl),
 (III) carboxy, or
 (IV) $-\text{CO-C}_{1-4}$ alkoxy},
 5 (c) 5- or 6-membered heterocycloalkyl containing one
 nitrogen atom [wherein the heterocycloalkyl is optionally
 substituted by 1 to 3 substituents independently selected from
 the group consisting of
 (I) oxo,
 10 (II) C_{1-6} alkyl, and
 (III) $-\text{CO-R}^{11}$ {wherein R^{11} is
 (i) C_{1-6} alkyl (wherein the alkyl is optionally
 substituted by
 (A) hydroxy,
 15 (B) cyano, or
 (C) C_{1-4} alkoxy),
 (ii) C_{1-6} alkoxy,
 (iii) C_{1-6} haloalkyl,
 (iv) C_{3-6} cycloalkyl (wherein the cycloalkyl is
 20 optionally substituted by halogen), or
 (v) 4- to 6-membered heterocycloalkyl containing one
 oxygen atom (wherein the heterocycloalkyl is optionally
 substituted by halogen)}],
 (d) 8-membered bridged heterocycloalkyl containing one
 25 nitrogen atom {wherein the bridged heterocycloalkyl is
 optionally substituted by $-\text{CO-R}^{11a}$ {wherein R^{11a} is
 (i) C_{1-6} alkyl (wherein the alkyl is optionally
 substituted by
 (A) hydroxy, or
 30 (B) cyano), or
 (ii) C_{1-6} alkoxy,}},
 (e) 7- to 11-membered spiro heterocycloalkyl containing
 one nitrogen atom {wherein the spiro heterocycloalkyl is
 optionally substituted by $-\text{CO-R}^{11a}$ }, or
 35 (f) 6- to 9-membered saturated or partially unsaturated

fused ring group containing 1 or 2 nitrogen atoms (wherein the fused ring group is optionally substituted by -CO-C₁₋₆ alkyl (wherein the alkyl is optionally substituted by hydroxy)).

[0291]

5 R⁴ is further preferably

(a) C₄₋₆ cycloalkyl (wherein the cycloalkyl is optionally substituted by

(I) hydroxy,

(II) cyano,

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

(i) hydroxy,

(ii) carboxy,

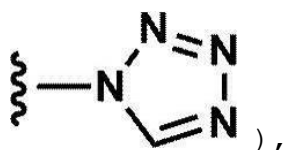
(iii) -CONH₂,

15 (iv) -CO-C₁₋₄ alkoxy,

(v) -SO₂-C₁₋₄ alkyl, or

(vi) a group represented by the formula:

[0292]



20 [0293]

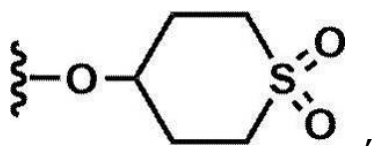
(IV) C₁₋₆ alkoxy (wherein the alkoxy is optionally substituted by hydroxy or -SO₂-C₁₋₄ alkyl),

(V) -CO-NR⁵R⁶ [wherein R⁵ and R⁶ form, together with the nitrogen atom bonded thereto, 4- to 6-membered heterocycloalkyl
25 containing 1 or 2 hetero atoms independently selected from the group consisting of nitrogen and oxygen atoms {wherein the heterocycloalkyl is optionally substituted by C₁₋₆ alkyl (wherein the alkyl is optionally substituted by hydroxy)}],

(VI) -NR⁷R⁸ {wherein R⁷ and R⁸ are each independently C₁₋₄
30 alkyl or -CO-C₁₋₆ alkyl (wherein the alkyl is optionally substituted by cyano)},

(VII) a group represented by the formula:

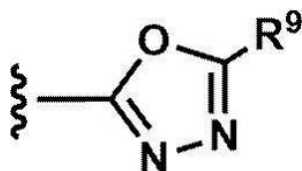
[0294]



[0295]

(VIII) a group represented by the formula:

[0296]



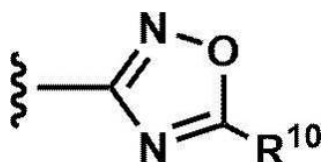
5

[0297]

{wherein R⁹ is C₁₋₄ alkyl (wherein the alkyl is optionally substituted by C₁₋₄ alkoxy)}, or

(IX) a group represented by the formula:

10 [0298]



[0299]

wherein R¹⁰ is C₁₋₄ alkyl)),

(b) C₅₋₈ bridged cycloalkyl {wherein the bridged
15 cycloalkyl is optionally substituted by C₁₋₆ alkyl (wherein the alkyl is optionally substituted by hydroxy)},

(c) 5- or 6-membered heterocycloalkyl containing one nitrogen atom [wherein the heterocycloalkyl is optionally substituted by -CO-R¹¹ {wherein R¹¹ is

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

(A) hydroxy,

(B) cyano, or

(C) C₁₋₄ alkoxy),

25 (ii) C₁₋₆ alkoxy,

(iii) C₁₋₆ haloalkyl,

(iv) C₃₋₆ cycloalkyl (wherein the cycloalkyl is optionally substituted by halogen), or

(v) 4- to 6-membered heterocycloalkyl containing one oxygen atom (wherein the heterocycloalkyl is optionally substituted by halogen)}], or

(d) 8-membered bridged heterocycloalkyl containing one
5 nitrogen atom {wherein the bridged heterocycloalkyl is optionally substituted by -CO-C₁₋₆ alkyl (wherein the alkyl is optionally substituted by

(A) hydroxy, or

(B) cyano)}.

10 [0300]

Specific embodiments of each substituent of the compound of formula [I] are exemplified below. However, each substituent of the compound of formula [I] is not limited to the specific embodiments. In addition, the compound of the
15 formula [I] also includes an embodiment in which any two or more of the specific embodiments of each substituent are combined.

[0301]

Y¹ is preferably a nitrogen atom.

20 [0302]

Y² is preferably a nitrogen atom.

[0303]

Y³ is preferably a carbon atom.

[0304]

25 Y⁴ is preferably a carbon atom.

[0305]

Preferred embodiment of R¹ is

(1) hydroxy,

(2) C₁₋₄ alkyl (wherein the alkyl is optionally substituted by
30 hydroxy or C₁₋₄ alkoxy),

(3) C₁₋₄ alkoxy,

(4) halogen, or

(5) C₁₋₄ haloalkyl.

[0306]

35 More preferred embodiment of R¹ is

- (1) C₁₋₄ alkyl (wherein the alkyl is optionally substituted by hydroxy or C₁₋₄ alkoxy),
(2) halogen, or
(3) C₁₋₄ haloalkyl.

5 [0307]

Preferred specific example of R¹ is methyl, fluorine, chlorine, difluoromethyl, or trifluoromethyl.

[0308]

Preferred embodiments of R² in the number of m are each
10 independently halogen.

[0309]

Preferred specific examples of R² in the number of m include fluorine and chlorine.

[0310]

15 m is preferably 0 or 1.

[0311]

Preferred embodiments of R³ in the number of n are each independently halogen.

[0312]

20 Preferred specific examples of R³ in the number of n include fluorine and chlorine.

[0313]

n is preferably 0 or 1.

[0314]

25 R⁴ is preferably

(a) C₄₋₆ cycloalkyl (wherein the cycloalkyl is optionally substituted by 1 or 2 substituents independently selected from the group consisting of

(I) hydroxy,

30 (II) cyano,

(III) oxo,

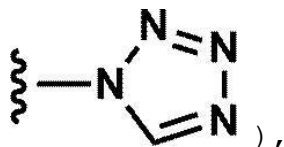
(IV) C₁₋₆ alkyl (wherein the alkyl is optionally substituted by

(i) hydroxy,

35 (ii) carboxy,

- (iii) $-\text{CONH}_2$,
- (iv) $-\text{CO}-\text{C}_{1-4}$ alkoxy,
- (v) $-\text{SO}_2-\text{C}_{1-4}$ alkyl, or
- (vi) a group represented by the formula:

5 [0315]



[0316]

(V) C_{1-6} alkoxy (wherein the alkoxy is optionally substituted by hydroxy or $-\text{SO}_2-\text{C}_{1-4}$ alkyl),

10 (VI) carboxy,

(VII) $-\text{CO}-\text{NR}^5\text{R}^6$ [wherein R^5 and R^6 are each independently C_{1-4} alkyl (wherein the alkyl is optionally substituted by C_{1-4} alkoxy), or R^5 and R^6 optionally form, together with the nitrogen atom bonded thereto, 4- to 6-membered heterocycloalkyl
 15 containing 1 or 2 hetero atoms independently selected from the group consisting of nitrogen and oxygen atoms {wherein the heterocycloalkyl is optionally substituted by 1 or 2 substituents independently selected from the group consisting of

20 (i) hydroxy, and

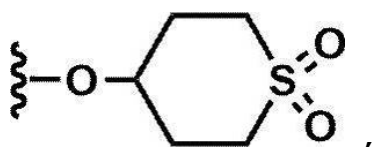
(ii) C_{1-6} alkyl (wherein the alkyl is optionally substituted by hydroxy)}],

(VIII) $-\text{NR}^7\text{R}^8$ {wherein R^7 and R^8 are each independently C_{1-4} alkyl or $-\text{CO}-\text{C}_{1-6}$ alkyl (wherein the alkyl is optionally
 25 substituted by cyano)}],

(IX) $-\text{O}-\text{C}_{1-6}$ haloalkyl,

(X) a group represented by the formula:

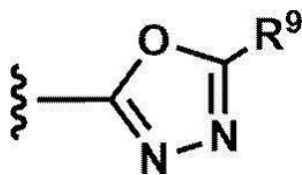
[0317]



30 [0318]

(XI) a group represented by the formula:

[0319]

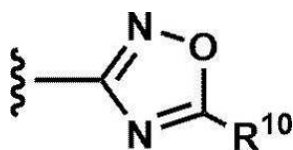


[0320]

{wherein R⁹ is C₁₋₄ alkyl (wherein the alkyl is optionally
5 substituted by C₁₋₄ alkoxy)}, and

(XII) a group represented by the formula:

[0321]



[0322]

10 wherein R¹⁰ is C₁₋₄ alkyl)),

(b) C₅₋₈ bridged cycloalkyl {wherein the bridged
cycloalkyl is optionally substituted by

(I) hydroxy,

(II) C₁₋₆ alkyl (wherein the alkyl is optionally

15 substituted by

(i) hydroxy,

(ii) carboxy,

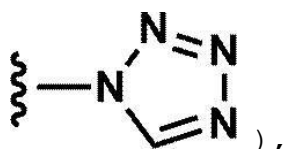
(iii) -CONH₂,

(iv) -CO-C₁₋₄ alkoxy,

20 (v) -SO₂-C₁₋₄ alkyl, or

(vi) a group represented by the formula:

[0323]



[0324]

25 (III) C₁₋₆ alkoxy (wherein the alkoxy is optionally
substituted by hydroxy or -SO₂-C₁₋₄ alkyl),

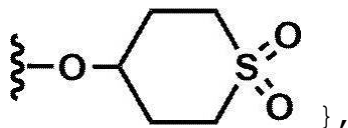
(IV) carboxy,

(V) -CO-C₁₋₄ alkoxy,

(VI) -O-C₁₋₆ haloalkyl, or

(VII) a group represented by the formula:

[0325]



5 [0326]

(c) 5- or 6-membered heterocycloalkyl containing one nitrogen atom [wherein the heterocycloalkyl is optionally substituted by 1 to 3 substituents independently selected from the group consisting of

10

(I) oxo,

(II) C₁₋₆ alkyl,

(III) -CO-R¹¹ {wherein R¹¹ is

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

15

(A) hydroxy,

(B) cyano, or

(C) C₁₋₄ alkoxy),

(ii) C₁₋₆ alkoxy,

(iii) C₁₋₆ haloalkyl,

20

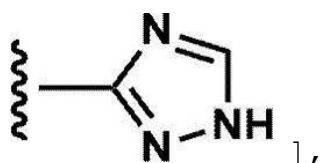
(iv) C₃₋₆ cycloalkyl (wherein the cycloalkyl is optionally substituted by halogen), or

(v) 4- to 6-membered heterocycloalkyl containing one oxygen atom (wherein the heterocycloalkyl is optionally substituted by halogen)}, and

25

(IV) a group represented by the formula:

[0327]



[0328]

(d) 8-membered bridged heterocycloalkyl containing one
30 nitrogen atom {wherein the bridged heterocycloalkyl is optionally substituted by -CO-R¹¹} ,

(e) 7- to 11-membered spiro heterocycloalkyl containing one nitrogen atom {wherein the spiro heterocycloalkyl is optionally substituted by -CO-R¹¹}, or

(f) 6- to 9-membered saturated or partially unsaturated fused ring group containing 1 or 2 nitrogen atoms (wherein the fused ring group is optionally substituted by -CO-R¹¹).

[0329]

R⁴ is more preferably

(a) C₄₋₆ cycloalkyl (wherein the cycloalkyl is optionally substituted by 1 or 2 substituents independently selected from the group consisting of

(I) hydroxy,

(II) cyano,

(III) oxo,

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

(i) hydroxy,

(ii) carboxy,

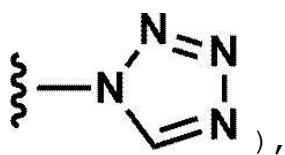
(iii) -CONH₂,

(iv) -CO-C₁₋₄ alkoxy,

(v) -SO₂-C₁₋₄ alkyl, or

(vi) a group represented by the formula:

[0330]



[0331]

(V) C₁₋₆ alkoxy (wherein the alkoxy is optionally substituted by hydroxy or -SO₂-C₁₋₄ alkyl),

(VI) carboxy,

(VII) -CO-NR⁵R⁶ [wherein R⁵ and R⁶ are each independently C₁₋₄ alkyl (wherein the alkyl is optionally substituted by C₁₋₄ alkoxy), or R⁵ and R⁶ optionally form, together with the nitrogen atom bonded thereto, 4- to 6-membered heterocycloalkyl containing 1 or 2 hetero atoms independently selected from the

group consisting of nitrogen and oxygen atoms {wherein the heterocycloalkyl is optionally substituted by 1 or 2 substituents independently selected from the group consisting of

5 (i) hydroxy, and

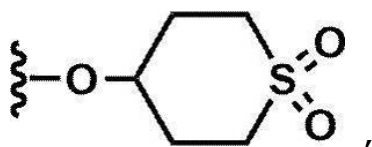
(ii) C₁₋₆ alkyl (wherein the alkyl is optionally substituted by hydroxy)}],

(VIII) -NR⁷R⁸ {wherein R⁷ and R⁸ are each independently C₁₋₄ alkyl or -CO-C₁₋₆ alkyl (wherein the alkyl is optionally
10 substituted by cyano)}],

(IX) -O-C₁₋₆ haloalkyl,

(X) a group represented by the formula:

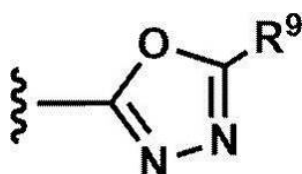
[0332]



15 [0333]

(XI) a group represented by the formula:

[0334]

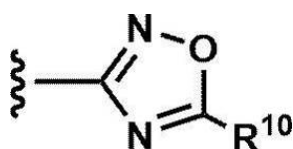


[0335]

20 {wherein R⁹ is C₁₋₄ alkyl (wherein the alkyl is optionally substituted by C₁₋₄ alkoxy)}], and

(XII) a group represented by the formula:

[0336]



25 [0337]

wherein R¹⁰ is C₁₋₄ alkyl)),

(b) C₅₋₈ bridged cycloalkyl {wherein the bridged cycloalkyl is optionally substituted by

(I) hydroxy,

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

(i) hydroxy, or

5 (ii) -SO₂-C₁₋₄ alkyl),

(III) carboxy, or

(IV) -CO-C₁₋₄ alkoxy},

(c) 5- or 6-membered heterocycloalkyl containing one nitrogen atom [wherein the heterocycloalkyl is optionally

10 substituted by 1 to 3 substituents independently selected from the group consisting of

(I) oxo,

(II) C₁₋₆ alkyl, and

(III) -CO-R¹¹ {wherein R¹¹ is

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

(A) hydroxy,

(B) cyano, or

(C) C₁₋₄ alkoxy),

20 (ii) C₁₋₆ alkoxy,

(iii) C₁₋₆ haloalkyl,

(iv) C₃₋₆ cycloalkyl (wherein the cycloalkyl is optionally substituted by halogen), or

(v) 4- to 6-membered heterocycloalkyl containing one

25 oxygen atom (wherein the heterocycloalkyl is optionally substituted by halogen))],

(d) 8-membered bridged heterocycloalkyl containing one nitrogen atom {wherein the bridged heterocycloalkyl is optionally substituted by -CO-R^{11a} {wherein R^{11a} is

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

(A) hydroxy, or

(B) cyano), or

(ii) C₁₋₆ alkoxy,}},

35 (e) 7- to 11-membered spiro heterocycloalkyl containing

one nitrogen atom {wherein the spiro heterocycloalkyl is optionally substituted by -CO-R^{11a}}, or

(f) 6- to 9-membered saturated or partially unsaturated fused ring group containing 1 or 2 nitrogen atoms (wherein the fused ring group is optionally substituted by -CO-C₁₋₆ alkyl (wherein the alkyl is optionally substituted by hydroxy)).

[0338]

R⁴ is further preferably

(a) C₄₋₆ cycloalkyl (wherein the cycloalkyl is optionally substituted by

(I) hydroxy,

(II) cyano,

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

(i) hydroxy,

(ii) carboxy,

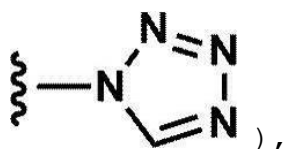
(iii) -CONH₂,

(iv) -CO-C₁₋₄ alkoxy,

(v) -SO₂-C₁₋₄ alkyl, or

(vi) a group represented by the formula:

[0339]



[0340]

(IV) C₁₋₆ alkoxy (wherein the alkoxy is optionally substituted by hydroxy or -SO₂-C₁₋₄ alkyl),

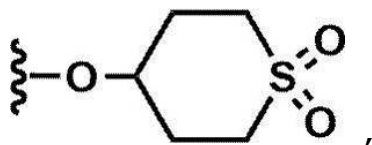
(V) -CO-NR⁵R⁶ [wherein R⁵ and R⁶ form, together with the nitrogen atom bonded thereto, 4- to 6-membered heterocycloalkyl containing 1 or 2 hetero atoms independently selected from the group consisting of nitrogen and oxygen atoms {wherein the heterocycloalkyl is optionally substituted by C₁₋₆ alkyl (wherein the alkyl is optionally substituted by hydroxy)}],

(VI) -NR⁷R⁸ {wherein R⁷ and R⁸ are each independently C₁₋₄ alkyl or -CO-C₁₋₆ alkyl (wherein the alkyl is optionally

substituted by cyano)),

(VII) a group represented by the formula:

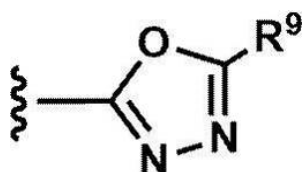
[0341]



5 [0342]

(VIII) a group represented by the formula:

[0343]

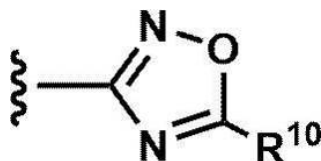


[0344]

10 {wherein R⁹ is C₁₋₄ alkyl (wherein the alkyl is optionally substituted by C₁₋₄ alkoxy)}, or

(IX) a group represented by the formula:

[0345]



15

[0346]

wherein R¹⁰ is C₁₋₄ alkyl)),

(b) C₅₋₈ bridged cycloalkyl {wherein the bridged cycloalkyl is optionally substituted by C₁₋₆ alkyl (wherein the
20 alkyl is optionally substituted by hydroxy)},

(c) 5- or 6-membered heterocycloalkyl containing one nitrogen atom [wherein the heterocycloalkyl is optionally substituted by -CO-R¹¹ {wherein R¹¹ is

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

- (A) hydroxy,
- (B) cyano, or
- (C) C₁₋₄ alkoxy),

(ii) C₁₋₆ alkoxy,
(iii) C₁₋₆ haloalkyl,
(iv) C₃₋₆ cycloalkyl (wherein the cycloalkyl is optionally substituted by halogen), or

5 (v) 4- to 6-membered heterocycloalkyl containing one oxygen atom (wherein the heterocycloalkyl is optionally substituted by halogen)}], or

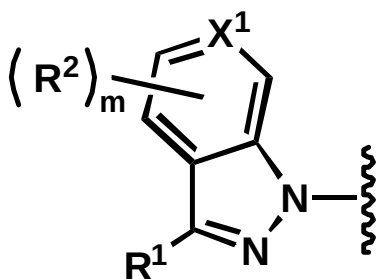
(d) 8-membered bridged heterocycloalkyl containing one nitrogen atom {wherein the bridged heterocycloalkyl is
10 optionally substituted by -CO-C₁₋₆ alkyl (wherein the alkyl is optionally substituted by

(A) hydroxy, or
(B) cyano)}.

[0347]

15 In a partial structure represented by the formula:

[0348]



[0349]

in the formula [I], preferably,

20 X^1 is carbon or a nitrogen atom;

m is 0 or 1;

R^1 is

(1) hydroxy,

(2) C₁₋₄ alkyl (wherein the alkyl is optionally substituted by
25 hydroxy or C₁₋₄ alkoxy),

(3) C₁₋₄ alkoxy,

(4) halogen, or

(5) C₁₋₄ haloalkyl; and

R^2 in the number of m are each independently halogen,

30 [0350]

more preferably,

X¹ is carbon or a nitrogen atom;

m is 0 or 1;

R¹ is

- 5 (1) C₁₋₄ alkyl (wherein the alkyl is optionally substituted by hydroxy or C₁₋₄ alkoxy),
(2) halogen, or
(3) C₁₋₄ haloalkyl; and

R² in the number of m are each independently halogen.

10 [0351]

Specific embodiments of each substituent of the compound of formula [III] are exemplified below. However, each substituent of the compound of formula [III] is not limited to the specific embodiments. In addition, the compound of the
15 formula [III] also includes an embodiment in which any two or more of the specific embodiments of each substituent are combined.

[0352]

Preferred embodiment of R¹ is

- 20 (1) C₁₋₄ alkyl,
(2) C₁₋₄ haloalkyl, or
(3) C₃₋₆ cycloalkyl.

[0353]

More preferred embodiment of R¹ is C₁₋₄ alkyl.

25 [0354]

Specific preferable example of R¹ is methyl.

[0355]

Preferred embodiments of R² in the number of m are each independently

- 30 (1) cyano,
(2) C₁₋₄ alkyl,
(3) C₁₋₄ alkoxy, or
(4) halogen.

[0356]

35 More preferred embodiments of R² in the number of m are

each independently halogen.

[0357]

Preferred specific examples of R^2 in the number of m include fluorine and chlorine.

5 [0358]

m is preferably 0 or 1.

[0359]

Preferred embodiments of R^3 in the number of n are each independently halogen.

10 [0360]

Preferred specific examples of R^3 in the number of n include fluorine and chlorine.

[0361]

R^4 is preferably

15 (a) C_{4-6} cycloalkyl (wherein the cycloalkyl is optionally substituted by 1 or 2 substituents independently selected from the group consisting of

(I) hydroxy,

(II) cyano,

20 (III) oxo,

(IV) C_{1-6} alkyl (wherein the alkyl is optionally substituted by

(i) hydroxy,

(ii) carboxy,

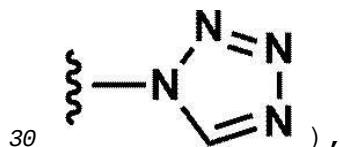
25 (iii) $-CONH_2$,

(iv) $-CO-C_{1-4}$ alkoxy,

(v) $-SO_2-C_{1-4}$ alkyl, or

(vi) a group represented by the formula:

[0362]



[0363]

(V) C_{1-6} alkoxy (wherein the alkoxy is optionally substituted by hydroxy or $-SO_2-C_{1-4}$ alkyl),

(VI) carboxy,

(VII) $-\text{CO}-\text{NR}^5\text{R}^6$ [wherein R^5 and R^6 are each independently C_{1-4} alkyl (wherein the alkyl is optionally substituted by C_{1-4} alkoxy), or R^5 and R^6 optionally form, together with the
5 nitrogen atom bonded thereto, 4- to 6-membered heterocycloalkyl containing 1 or 2 hetero atoms independently selected from the group consisting of nitrogen and oxygen atoms {wherein the heterocycloalkyl is optionally substituted by 1 or 2
10 substituents independently selected from the group consisting

(i) hydroxy, and

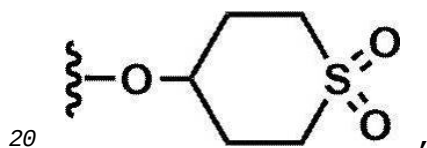
(ii) C_{1-6} alkyl (wherein the alkyl is optionally substituted by hydroxy)}],

(VIII) $-\text{NR}^7\text{R}^8$ {wherein R^7 and R^8 are each independently
15 C_{1-4} alkyl or $-\text{CO}-\text{C}_{1-6}$ alkyl (wherein the alkyl is optionally substituted by cyano)}],

(IX) $-\text{O}-\text{C}_{1-6}$ haloalkyl,

(X) a group represented by the formula:

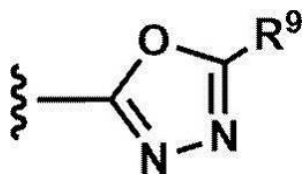
[0364]



[0365]

(XI) a group represented by the formula:

[0366]

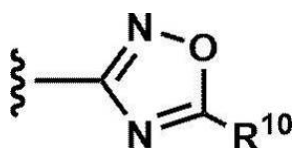


25 [0367]

{wherein R^9 is C_{1-4} alkyl (wherein the alkyl is optionally substituted by C_{1-4} alkoxy)}], and

(XII) a group represented by the formula:

[0368]



[0369]

wherein R¹⁰ is C₁₋₄ alkyl)),

(b) C₅₋₈ bridged cycloalkyl {wherein the bridged
5 cycloalkyl is optionally substituted by

(I) hydroxy,

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

(i) hydroxy,

10 (ii) carboxy,

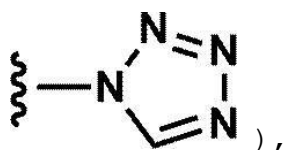
(iii) -CONH₂,

(iv) -CO-C₁₋₄ alkoxy,

(v) -SO₂-C₁₋₄ alkyl, or

(vi) a group represented by the formula:

15 [0370]



[0371]

(III) C₁₋₆ alkoxy (wherein the alkoxy is optionally
substituted by hydroxy or -SO₂-C₁₋₄ alkyl),

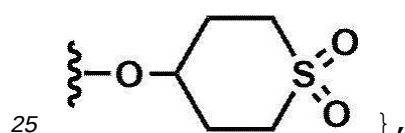
20 (IV) carboxy,

(V) -CO-C₁₋₄ alkoxy,

(VI) -O-C₁₋₆ haloalkyl, or

(VII) a group represented by the formula:

[0372]



[0373]

(c) 5- or 6-membered heterocycloalkyl containing one
nitrogen atom [wherein the heterocycloalkyl is optionally
substituted by 1 to 3 substituents independently selected from

the group consisting of

- (I) oxo,
- (II) C₁₋₆ alkyl,
- (III) -CO-R¹¹ {wherein R¹¹ is

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

- (A) hydroxy,
- (B) cyano, or
- (C) C₁₋₄ alkoxy),

10 (ii) C₁₋₆ alkoxy,

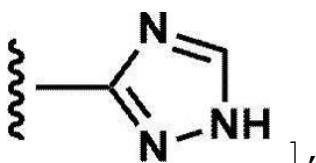
(iii) C₁₋₆ haloalkyl,

(iv) C₃₋₆ cycloalkyl (wherein the cycloalkyl is optionally substituted by halogen), or

(v) 4- to 6-membered heterocycloalkyl containing one
15 oxygen atom (wherein the heterocycloalkyl is optionally substituted by halogen)}, and

(IV) a group represented by the formula:

[0374]



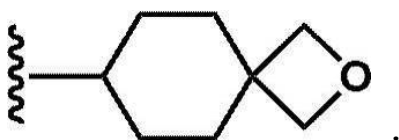
20 [0375]

(d) 6- to 9-membered saturated or partially unsaturated fused ring group containing 1 or 2 nitrogen atoms {wherein the fused ring group is optionally substituted by -CO-R¹¹}, or

[0376]

25 (e) a group represented by the formula:

[0377]



[0378]

R⁴ is more preferably

30 (a) C₄₋₆ cycloalkyl (wherein the cycloalkyl is optionally substituted by 1 or 2 substituents independently selected from

the group consisting of

(I) hydroxy,

(II) cyano,

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

(i) hydroxy,

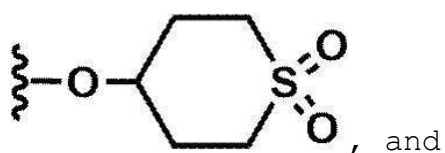
(ii) carboxy, or

(iii) -SO₂-C₁₋₄ alkyl),

(IV) -O-C₁₋₆ haloalkyl,

10 (V) a group represented by the formula:

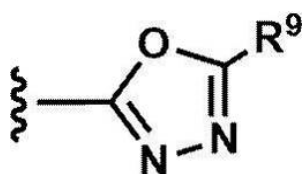
[0379]



[0380]

(VI) a group represented by the formula:

15 [0381]



[0382]

{wherein R⁹ is C₁₋₄ alkyl}},

(b) C₅₋₈ bridged cycloalkyl {wherein the bridged
20 cycloalkyl is optionally substituted by

(I) hydroxy,

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

(i) hydroxy,

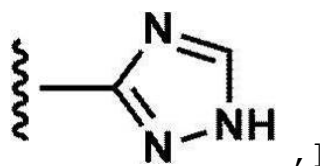
25 (ii) carboxy, or

(iii) -CO-C₁₋₄ alkoxy), or

(III) carboxy},

(c) 5- or 6-membered heterocycloalkyl containing one
nitrogen atom [wherein the heterocycloalkyl is optionally
30 substituted by a group represented by the formula:

[0383]



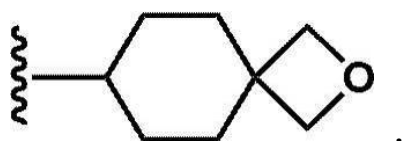
[0384]

(d) 6- to 9-membered saturated or partially unsaturated
5 fused ring group containing 1 or 2 nitrogen atoms, or

[0385]

(e) a group represented by the formula:

[0386]



10 [0387]

Specific embodiments of each substituent of the compound
of formula [IV] are exemplified below. However, each
substituent of the compound of formula [IV] is not limited to
the specific embodiments. In addition, the compound of the
15 formula [IV] also includes an embodiment in which any two or
more of the specific embodiments of each substituent are
combined.

[0388]

Y¹ is preferably a nitrogen atom.

20 [0389]

Y² is preferably a nitrogen atom.

[0390]

Y³ is preferably a carbon atom.

[0391]

25 Y⁴ is preferably a carbon atom.

[0392]

Preferred embodiment of R¹ is C₁₋₄ alkyl.

[0393]

Preferred specific example of R¹ is methyl.

30 [0394]

m is preferably 0.

[0395]

Preferred embodiments of R^3 in the number of n are each independently halogen.

5 [0396]

Preferred specific example of R^3 in the number of n is fluorine.

[0397]

n is preferably 0 or 1.

10 [0398]

R^4 is preferably C_{4-6} cycloalkyl (wherein the cycloalkyl is optionally substituted by 1 or 2 substituents independently selected from the group consisting of

(I) hydroxy,

15 (II) cyano,

(III) oxo,

(IV) C_{1-6} alkyl (wherein the alkyl is optionally substituted by

(i) hydroxy,

20 (ii) carboxy,

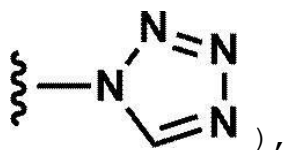
(iii) $-CONH_2$,

(iv) $-CO-C_{1-4}$ alkoxy,

(v) $-SO_2-C_{1-4}$ alkyl, or

(vi) a group represented by the formula:

25 [0399]



[0400]

(V) C_{1-6} alkoxy (wherein the alkoxy is optionally substituted by hydroxy or $-SO_2-C_{1-4}$ alkyl),

30 (VI) carboxy,

(VII) $-CO-NR^5R^6$ [wherein R^5 and R^6 are each independently C_{1-4} alkyl (wherein the alkyl is optionally substituted by C_{1-4} alkoxy), or R^5 and R^6 optionally form, together with the

nitrogen atom bonded thereto, 4- to 6-membered heterocycloalkyl containing 1 or 2 hetero atoms independently selected from the group consisting of nitrogen and oxygen atoms {wherein the heterocycloalkyl is optionally substituted by 1 or 2

5 substituents independently selected from the group consisting of

(i) hydroxy, and

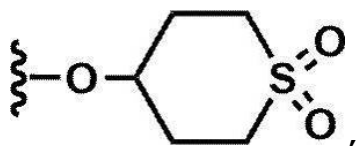
(ii) C₁₋₆ alkyl (wherein the alkyl is optionally substituted by hydroxy)}],

10 (VIII) -NR⁷R⁸ {wherein R⁷ and R⁸ are each independently C₁₋₄ alkyl or -CO-C₁₋₆ alkyl (wherein the alkyl is optionally substituted by cyano)}],

(IX) -O-C₁₋₆ haloalkyl,

(X) a group represented by the formula:

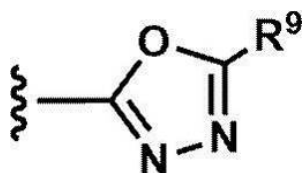
15 [0401]



[0402]

(XI) a group represented by the formula:

[0403]



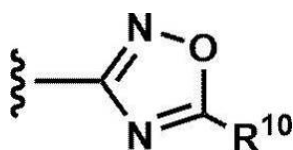
20

[0404]

{wherein R⁹ is C₁₋₄ alkyl (wherein the alkyl is optionally substituted by C₁₋₄ alkoxy)}], and

(XII) a group represented by the formula:

25 [0405]



[0406]

wherein R¹⁰ is C₁₋₄ alkyl)).

[0407]

R⁴ is more preferably C₄₋₆ cycloalkyl (wherein the cycloalkyl is

(I) hydroxy, or

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

(i) hydroxy, or

(ii) carboxy).

[0408]

10 One of the preferred embodiments of the compound of the formula [II] is a compound of the formula [II] wherein X¹, X², X³ and X⁴ are each independently a carbon or a nitrogen atom (wherein the total number of the nitrogen atoms for X¹, X², X³ and X⁴ is 0 or 1);

15 Y¹ and Y² are each a nitrogen atom;

Y³ and Y⁴ are each a carbon atom;

m is 0 or 1;

n is 0 or 1;

R¹ is

20 (1) hydroxy,

(2) C₁₋₄ alkyl (wherein the alkyl is optionally substituted by hydroxy or C₁₋₄ alkoxy),

(3) C₁₋₄ alkoxy,

(4) halogen, or

25 (5) C₁₋₄ haloalkyl;

R² in the number of m are each independently halogen;

R³ in the number of n are each independently halogen;

R⁴ is

(a) C₄₋₆ cycloalkyl (wherein the cycloalkyl is optionally
30 substituted by 1 or 2 substituents independently selected from the group consisting of

(I) hydroxy,

(II) cyano,

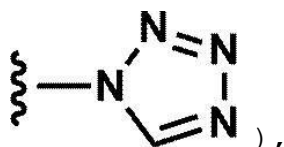
(III) oxo,

35 (IV) C₁₋₆ alkyl (wherein the alkyl is optionally

substituted by

- (i) hydroxy,
- (ii) carboxy,
- (iii) $-\text{CONH}_2$,
- 5 (iv) $-\text{CO}-\text{C}_{1-4}$ alkoxy,
- (v) $-\text{SO}_2-\text{C}_{1-4}$ alkyl, or
- (vi) a group represented by the formula:

[0409]



10 [0410]

(V) C_{1-6} alkoxy (wherein the alkoxy is optionally substituted by hydroxy or $-\text{SO}_2-\text{C}_{1-4}$ alkyl),

(VI) carboxy,

(VII) $-\text{CO}-\text{NR}^5\text{R}^6$ [wherein R^5 and R^6 are each independently
15 C_{1-4} alkyl (wherein the alkyl is optionally substituted by C_{1-4} alkoxy), or R^5 and R^6 optionally form, together with the nitrogen atom bonded thereto, 4- to 6-membered heterocycloalkyl containing 1 or 2 hetero atoms independently selected from the group consisting of nitrogen and oxygen atoms {wherein the
20 heterocycloalkyl is optionally substituted by 1 or 2 substituents independently selected from the group consisting of

(i) hydroxy, and

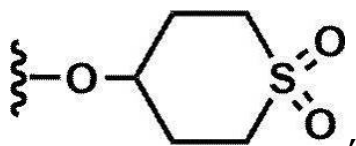
(ii) C_{1-6} alkyl (wherein the alkyl is optionally substituted by hydroxy)}],

(VIII) $-\text{NR}^7\text{R}^8$ {wherein R^7 and R^8 are each independently C_{1-4} alkyl or $-\text{CO}-\text{C}_{1-6}$ alkyl (wherein the alkyl is optionally substituted by cyano)},

(IX) $-\text{O}-\text{C}_{1-6}$ haloalkyl,

30 (X) a group represented by the formula:

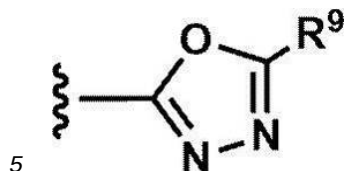
[0411]



[0412]

(XI) a group represented by the formula:

[0413]

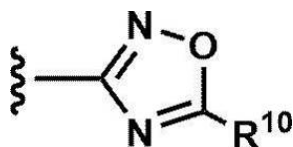


[0414]

{wherein R⁹ is C₁₋₄ alkyl (wherein the alkyl is optionally substituted by C₁₋₄ alkoxy)}, and

(XII) a group represented by the formula:

10 [0415]



[0416]

wherein R¹⁰ is C₁₋₄ alkyl)),

(b) C₅₋₈ bridged cycloalkyl {wherein the bridged
15 cycloalkyl is optionally substituted by

(I) hydroxy,

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

(i) hydroxy,

20 (ii) carboxy,

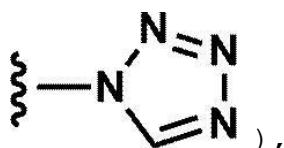
(iii) -CONH₂,

(iv) -CO-C₁₋₄ alkoxy,

(v) -SO₂-C₁₋₄ alkyl, or

(vi) a group represented by the formula:

25 [0417]



[0418]

(III) C₁₋₆ alkoxy (wherein the alkoxy is optionally substituted by hydroxy or -SO₂-C₁₋₄ alkyl),

(IV) carboxy,

5 (V) -CO-C₁₋₄ alkoxy,

(VI) -O-C₁₋₆ haloalkyl, or

(VII) a group represented by the formula:

[0419]



10 [0420]

(c) 5- or 6-membered heterocycloalkyl containing one nitrogen atom [wherein the heterocycloalkyl is optionally substituted by 1 to 3 substituents independently selected from the group consisting of

15 (I) oxo,

(II) C₁₋₆ alkyl,

(III) -CO-R¹¹ {wherein R¹¹ is

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

20 (A) hydroxy,

(B) cyano, or

(C) C₁₋₄ alkoxy),

(ii) C₁₋₆ alkoxy,

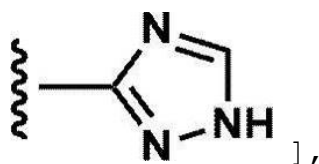
(iii) C₁₋₆ haloalkyl,

25 (iv) C₃₋₆ cycloalkyl (wherein the cycloalkyl is optionally substituted by halogen), or

(v) 4- to 6-membered heterocycloalkyl containing one oxygen atom (wherein the heterocycloalkyl is optionally substituted by halogen)}, and

30 (IV) a group represented by the formula:

[0421]



[0422]

(d) 8-membered bridged heterocycloalkyl containing one nitrogen atom {wherein the bridged heterocycloalkyl is
5 optionally substituted by $-\text{CO}-\text{R}^{11}$ },

(e) 7- to 11-membered spiro heterocycloalkyl containing one nitrogen atom {wherein the spiro heterocycloalkyl is optionally substituted by $-\text{CO}-\text{R}^{11}$ }, or

(f) 6- to 9-membered saturated or partially unsaturated
10 fused ring group containing 1 or 2 nitrogen atoms (wherein the fused ring group is optionally substituted by $-\text{CO}-\text{R}^{11}$).

[0423]

One of the more preferred embodiments of the compound of the formula [II] is a compound of the formula [II] wherein
15 X^1 , X^2 , X^3 and X^4 are each independently a carbon or a nitrogen atom (wherein the total number of the nitrogen atoms for X^1 , X^2 , X^3 and X^4 is 0 or 1);

Y^1 and Y^2 are each a nitrogen atom;

Y^3 and Y^4 are each a carbon atom;

20 m is 0 or 1;

n is 0 or 1;

R^1 is

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

25 (2) halogen, or

(3) C_{1-4} haloalkyl;

R^2 in the number of m are each independently halogen;

R^3 in the number of n are each independently halogen;

R^4 is

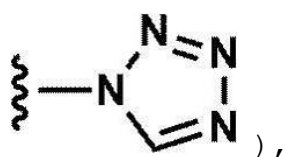
30 (a) C_{4-6} cycloalkyl (wherein the cycloalkyl is optionally substituted by 1 or 2 substituents independently selected from the group consisting of

(I) hydroxy,

(II) cyano,
(III) oxo,
(IV) C₁₋₆ alkyl (wherein the alkyl is optionally substituted by

- 5 (i) hydroxy,
(ii) carboxy,
(iii) -CONH₂,
(iv) -CO-C₁₋₄ alkoxy,
(v) -SO₂-C₁₋₄ alkyl, or
10 (vi) a group represented by the formula:

[0424]



[0425]

- (V) C₁₋₆ alkoxy (wherein the alkoxy is optionally substituted by hydroxy or -SO₂-C₁₋₄ alkyl),
15 (VI) carboxy,
(VII) -CO-NR⁵R⁶ [wherein R⁵ and R⁶ are each independently C₁₋₄ alkyl (wherein the alkyl is optionally substituted by C₁₋₄ alkoxy), or R⁵ and R⁶ optionally form, together with the
20 nitrogen atom bonded thereto, 4- to 6-membered heterocycloalkyl containing 1 or 2 hetero atoms independently selected from the group consisting of nitrogen and oxygen atoms {wherein the heterocycloalkyl is optionally substituted by 1 or 2 substituents independently selected from the group consisting
25 of

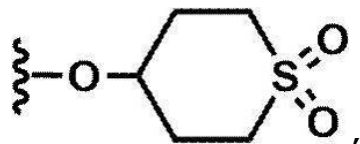
- (i) hydroxy, and
(ii) C₁₋₆ alkyl (wherein the alkyl is optionally substituted by hydroxy)}],

- (VIII) -NR⁷R⁸ {wherein R⁷ and R⁸ are each independently
30 C₁₋₄ alkyl or -CO-C₁₋₆ alkyl (wherein the alkyl is optionally substituted by cyano)},

(IX) -O-C₁₋₆ haloalkyl,

(X) a group represented by the formula:

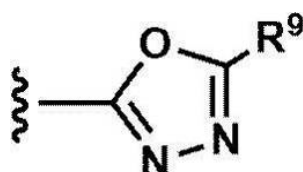
[0426]



[0427]

(XI) a group represented by the formula:

5 [0428]

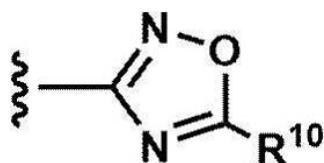


[0429]

{wherein R⁹ is C₁₋₄ alkyl (wherein the alkyl is optionally substituted by C₁₋₄ alkoxy)}, and

10 (XII) a group represented by the formula:

[0430]



[0431]

wherein R¹⁰ is C₁₋₄ alkyl)),

15 (b) C₅₋₈ bridged cycloalkyl {wherein the bridged cycloalkyl is optionally substituted by

(I) hydroxy,

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

20 (i) hydroxy, or

(ii) -SO₂-C₁₋₄ alkyl),

(III) carboxy, or

(IV) -CO-C₁₋₄ alkoxy},

(c) 5- or 6-membered heterocycloalkyl containing one
25 nitrogen atom [wherein the heterocycloalkyl is optionally substituted by 1 to 3 substituents independently selected from the group consisting of

(I) oxo,

- (II) C₁₋₆ alkyl, and
(III) -CO-R¹¹ {wherein R¹¹ is
(i) C₁₋₆ alkyl (wherein the alkyl is optionally substituted by
5 (A) hydroxy,
(B) cyano, or
(C) C₁₋₄ alkoxy),
(ii) C₁₋₆ alkoxy,
(iii) C₁₋₆ haloalkyl,
10 (iv) C₃₋₆ cycloalkyl (wherein the cycloalkyl is optionally substituted by halogen), or
(v) 4- to 6-membered heterocycloalkyl containing one oxygen atom (wherein the heterocycloalkyl is optionally substituted by halogen)}],
15 (d) 8-membered bridged heterocycloalkyl containing one nitrogen atom {wherein the bridged heterocycloalkyl is -CO-R^{11a} {wherein R^{11a} is optionally substituted by
(i) C₁₋₆ alkyl (wherein the alkyl is optionally substituted by
20 (A) hydroxy, or
(B) cyano), or
(ii) C₁₋₆ alkoxy}}},
(e) 7- to 11-membered spiro heterocycloalkyl containing one nitrogen atom {wherein the spiro heterocycloalkyl is
25 optionally substituted by -CO-R^{11a}}, or
(f) 6- to 9-membered saturated or partially unsaturated fused ring group containing 1 or 2 nitrogen atoms (wherein the fused ring group is optionally substituted by -CO-C₁₋₆ alkyl (wherein the alkyl is optionally substituted by hydroxy)).

30 [0432]

One of the further preferred embodiments of the compound of the formula [II] is a compound of the formula [II] wherein X¹, X², X³ and X⁴ are each independently a carbon or a nitrogen atom (wherein the total number of the nitrogen atoms for X¹, X²,
35 X³ and X⁴ is 0 or 1);

Y¹ and Y² are each a nitrogen atom;

Y³ and Y⁴ are each a carbon atom;

m is 0 or 1;

n is 0 or 1;

5 R¹ is

(1) C₁₋₄ alkyl (wherein the alkyl is optionally substituted by hydroxy or C₁₋₄ alkoxy),

(2) halogen, or

(3) C₁₋₄ haloalkyl;

10 R² in the number of m are each independently halogen;

R³ in the number of n are each independently halogen;

R⁴ is

(a) C₄₋₆ cycloalkyl (wherein the cycloalkyl is optionally substituted by

15 (I) hydroxy,

(II) cyano,

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

(i) hydroxy,

20 (ii) carboxy,

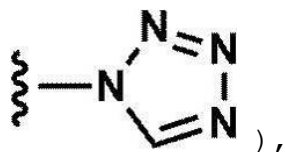
(iii) -CONH₂,

(iv) -CO-C₁₋₄ alkoxy,

(v) -SO₂-C₁₋₄ alkyl, or

(vi) a group represented by the formula:

25 [0433]



[0434]

(IV) C₁₋₆ alkoxy (wherein the alkoxy is optionally substituted by hydroxy or -SO₂-C₁₋₄ alkyl),

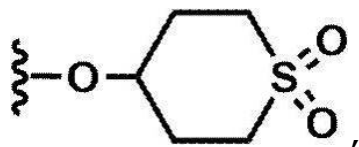
30 (V) -CO-NR⁵R⁶ [wherein R⁵ and R⁶ form, together with the nitrogen atom bonded thereto, 4- to 6-membered heterocycloalkyl containing 1 or 2 hetero atoms independently selected from the group consisting of nitrogen and oxygen atoms {wherein the

heterocycloalkyl is optionally substituted by C₁₋₆ alkyl
(wherein the alkyl is optionally substituted by hydroxy))],

(VI) -NR⁷R⁸ {wherein R⁷ and R⁸ are each independently C₁₋₄
alkyl or -CO-C₁₋₆ alkyl (wherein the alkyl is optionally
5 substituted by cyano)},

(VII) a group represented by the formula:

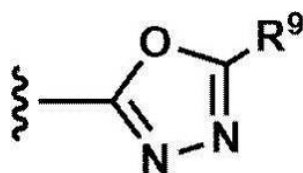
[0435]



[0436]

10 (VIII) a group represented by the formula:

[0437]

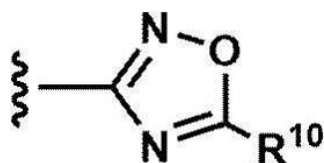


[0438]

{wherein R⁹ is C₁₋₄ alkyl (wherein the alkyl is optionally
15 substituted by C₁₋₄ alkoxy)}, or

(IX) a group represented by the formula:

[0439]



[0440]

20 wherein R¹⁰ is C₁₋₄ alkyl)),

(b) C₅₋₈ bridged cycloalkyl {wherein the bridged
cycloalkyl is optionally substituted by C₁₋₆ alkyl (wherein the
alkyl is optionally substituted by hydroxy)},

(c) 5- or 6-membered heterocycloalkyl containing one
25 nitrogen atom [wherein the heterocycloalkyl is optionally
substituted by -CO-R¹¹ {wherein R¹¹ is

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

(A) hydroxy,
(B) cyano, or
(C) C₁₋₄ alkoxy),
(ii) C₁₋₆ alkoxy,
5 (iii) C₁₋₆ haloalkyl,
(iv) C₃₋₆ cycloalkyl (wherein the cycloalkyl is
optionally substituted by halogen), or
(v) 4- to 6-membered heterocycloalkyl containing one
oxygen atom (wherein the heterocycloalkyl is optionally
10 substituted by halogen)}], or
(d) 8-membered bridged heterocycloalkyl containing one
nitrogen atom {wherein the bridged heterocycloalkyl is
optionally substituted by -CO-C₁₋₆ alkyl (wherein the alkyl is
optionally substituted by
15 (A) hydroxy, or
(B) cyano)}.

[0441]

One of the preferred embodiments of the compound of the
formula [I] is a compound of the formula [I] wherein

20 X¹ is carbon or a nitrogen atom;

Y¹ and Y² are each a nitrogen atom;

Y³ and Y⁴ are each a carbon atom;

m is 0 or 1;

n is 0 or 1;

25 R¹ is

(1) hydroxy,

(2) C₁₋₄ alkyl (wherein the alkyl is optionally substituted by
hydroxy or C₁₋₄ alkoxy),

(3) C₁₋₄ alkoxy,

30 (4) halogen, or

(5) C₁₋₄ haloalkyl;

R² in the number of m are each independently halogen;

R³ in the number of n are each independently halogen;

R⁴ is

35 (a) C₄₋₆ cycloalkyl (wherein the cycloalkyl is optionally

substituted by 1 or 2 substituents independently selected from the group consisting of

(I) hydroxy,

(II) cyano,

5 (III) oxo,

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

(i) hydroxy,

(ii) carboxy,

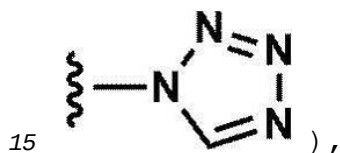
10 (iii) -CONH₂,

(iv) -CO-C₁₋₄ alkoxy,

(v) -SO₂-C₁₋₄ alkyl, or

(vi) a group represented by the formula:

[0442]



[0443]

(V) C₁₋₆ alkoxy (wherein the alkoxy is optionally substituted by hydroxy or -SO₂-C₁₋₄ alkyl),

(VI) carboxy,

20 (VII) -CO-NR⁵R⁶ [wherein R⁵ and R⁶ are each independently C₁₋₄ alkyl (wherein the alkyl is optionally substituted by C₁₋₄ alkoxy), or R⁵ and R⁶ optionally form, together with the nitrogen atom bonded thereto, 4- to 6-membered heterocycloalkyl containing 1 or 2 hetero atoms independently selected from the
25 group consisting of nitrogen and oxygen atoms {wherein the heterocycloalkyl is optionally substituted by 1 or 2 substituents independently selected from the group consisting of

(i) hydroxy, and

30 (ii) C₁₋₆ alkyl (wherein the alkyl is optionally substituted by hydroxy) }],

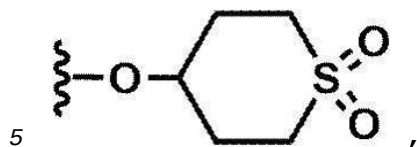
(VIII) -NR⁷R⁸ {wherein R⁷ and R⁸ are each independently C₁₋₄ alkyl or -CO-C₁₋₆ alkyl (wherein the alkyl is optionally

substituted by cyano)),

(IX) -O-C₁₋₆ haloalkyl,

(X) a group represented by the formula:

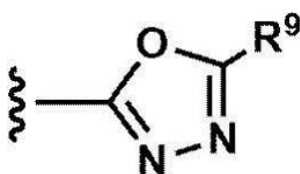
[0444]



[0445]

(XI) a group represented by the formula:

[0446]

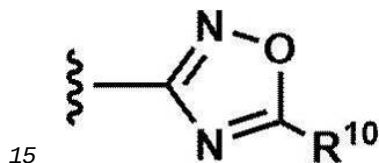


10 [0447]

{wherein R⁹ is C₁₋₄ alkyl (wherein the alkyl is optionally substituted by C₁₋₄ alkoxy)}, and

(XII) a group represented by the formula:

[0448]



[0449]

wherein R¹⁰ is C₁₋₄ alkyl)),

(b) C₅₋₈ bridged cycloalkyl {wherein the bridged cycloalkyl is optionally substituted by

20 (I) hydroxy,

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

(i) hydroxy,

(ii) carboxy,

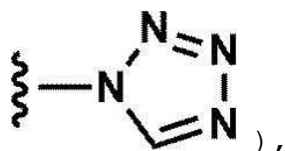
25 (iii) -CONH₂,

(iv) -CO-C₁₋₄ alkoxy,

(v) -SO₂-C₁₋₄ alkyl, or

(vi) a group represented by the formula:

[0450]



[0451]

(III) C₁₋₆ alkoxy (wherein the alkoxy is optionally
5 substituted by hydroxy or -SO₂-C₁₋₄ alkyl),

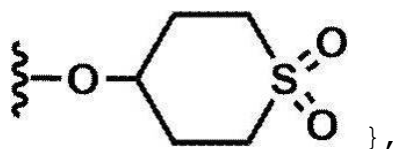
(IV) carboxy,

(V) -CO-C₁₋₄ alkoxy,

(VI) -O-C₁₋₆ haloalkyl, or

(VII) a group represented by the formula:

10 [0452]



[0453]

(c) 5- or 6-membered heterocycloalkyl containing one
nitrogen atom [wherein the heterocycloalkyl is optionally
15 substituted by 1 to 3 substituents independently selected from
the group consisting of

(I) oxo,

(II) C₁₋₆ alkyl,

(III) -CO-R¹¹ {wherein R¹¹ is

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

(A) hydroxy,

(B) cyano, or

(C) C₁₋₄ alkoxy),

25 (ii) C₁₋₆ alkoxy,

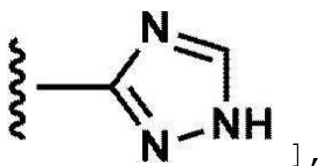
(iii) C₁₋₆ haloalkyl,

(iv) C₃₋₆ cycloalkyl (wherein the cycloalkyl is
optionally substituted by halogen), or

(v) 4- to 6-membered heterocycloalkyl containing one
30 oxygen atom (wherein the heterocycloalkyl is optionally
substituted by halogen)}, and

(IV) a group represented by the formula:

[0454]



[0455]

5 (d) 8-membered bridged heterocycloalkyl containing one nitrogen atom {wherein the bridged heterocycloalkyl is optionally substituted by $-\text{CO}-\text{R}^{11}$ },

(e) 7- to 11-membered spiro heterocycloalkyl containing one nitrogen atom {wherein the spiro heterocycloalkyl is
10 optionally substituted by $-\text{CO}-\text{R}^{11}$ }, or

(f) 6- to 9-membered saturated or partially unsaturated fused ring group containing 1 or 2 nitrogen atoms (wherein the fused ring group is optionally substituted by $-\text{CO}-\text{R}^{11}$).

[0456]

15 One of the more preferred embodiments of the compound of the formula [I] is a compound of the formula [I] wherein X^1 is carbon or a nitrogen atom;
 Y^1 and Y^2 are each a nitrogen atom;
 Y^3 and Y^4 are each a carbon atom;

20 m is 0 or 1;

n is 0 or 1;

R^1 is

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

25 (2) halogen, or

(3) C_{1-4} haloalkyl,;

R^2 in the number of m are each independently halogen;

R^3 in the number of n are each independently halogen;

R^4 is

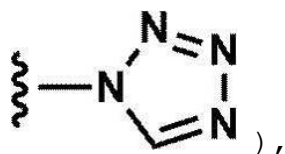
30 (a) C_{4-6} cycloalkyl (wherein the cycloalkyl is optionally substituted by 1 or 2 substituents independently selected from the group consisting of

- (I) hydroxy,
- (II) cyano,
- (III) oxo,
- (IV) C₁₋₆ alkyl (wherein the alkyl is optionally

5 substituted by

- (i) hydroxy,
- (ii) carboxy,
- (iii) -CONH₂,
- (iv) -CO-C₁₋₄ alkoxy,
- 10 (v) -SO₂-C₁₋₄ alkyl, or
- (vi) a group represented by the formula:

[0457]

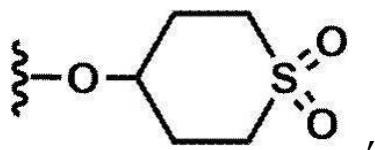


[0458]

- 15 (V) C₁₋₆ alkoxy (wherein the alkoxy is optionally substituted by hydroxy or -SO₂-C₁₋₄ alkyl),
- (VI) carboxy,
- (VII) -CO-NR⁵R⁶ [wherein R⁵ and R⁶ are each independently C₁₋₄ alkyl (wherein the alkyl is optionally substituted by C₁₋₄
- 20 alkoxy), or R⁵ and R⁶ optionally form, together with the nitrogen atom bonded thereto, 4- to 6-membered heterocycloalkyl containing 1 or 2 hetero atoms independently selected from the group consisting of nitrogen and oxygen atoms {wherein the heterocycloalkyl is optionally substituted by 1 or 2
- 25 substituents independently selected from the group consisting of
- (i) hydroxy, and
- (ii) C₁₋₆ alkyl (wherein the alkyl is optionally substituted by hydroxy)}],
- 30 (VIII) -NR⁷R⁸ {wherein R⁷ and R⁸ are each independently C₁₋₄ alkyl or -CO-C₁₋₆ alkyl (wherein the alkyl is optionally substituted by cyano)}],
- (IX) -O-C₁₋₆ haloalkyl,

(X) a group represented by the formula:

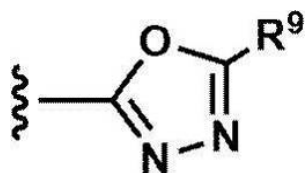
[0459]



[0460]

5 (XI) a group represented by the formula:

[0461]

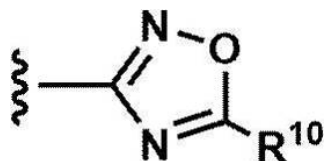


[0462]

{wherein R⁹ is C₁₋₄ alkyl (wherein the alkyl is optionally
10 substituted by C₁₋₄ alkoxy)}, and

(XII) a group represented by the formula:

[0463]



[0464]

15 wherein R¹⁰ is C₁₋₄ alkyl)),

(b) C₅₋₈ bridged cycloalkyl {wherein the bridged
cycloalkyl is optionally substituted by

(I) hydroxy,

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

(i) hydroxy, or

(ii) -SO₂-C₁₋₄ alkyl,)),

(III) carboxy, or

(IV) -CO-C₁₋₄ alkoxy,},

25 (c) 5- or 6-membered heterocycloalkyl containing one
nitrogen atom [wherein the heterocycloalkyl is optionally
substituted by 1 to 3 substituents independently selected from
the group consisting of

(I) oxo,
 (II) C₁₋₆ alkyl, and
 (III) -CO-R¹¹ {wherein R¹¹ is
 (i) C₁₋₆ alkyl (wherein the alkyl is optionally
 5 substituted by
 (A) hydroxy,
 (B) cyano, or
 (C) C₁₋₄ alkoxy),
 (ii) C₁₋₆ alkoxy,
 10 (iii) C₁₋₆ haloalkyl,
 (iv) C₃₋₆ cycloalkyl (wherein the cycloalkyl is
 optionally substituted by halogen), or
 (v) 4- to 6-membered heterocycloalkyl containing one
 oxygen atom (wherein the heterocycloalkyl is optionally
 15 substituted by halogen)}],
 (d) 8-membered bridged heterocycloalkyl containing one
 nitrogen atom {wherein the bridged heterocycloalkyl is
 optionally substituted by -CO-R^{11a} {wherein R^{11a} is
 (i) C₁₋₆ alkyl (wherein the alkyl is optionally
 20 substituted by
 (A) hydroxy, or
 (B) cyano), or
 (ii) C₁₋₆ alkoxy}},
 (e) 7- to 11-membered spiro heterocycloalkyl containing
 25 one nitrogen atom {wherein the spiro heterocycloalkyl is
 optionally substituted by -CO-R^{11a}}, or
 (f) 6- to 9-membered saturated or partially unsaturated
 fused ring group containing 1 or 2 nitrogen atoms (wherein the
 fused ring group is optionally substituted by -CO-C₁₋₆ alkyl
 30 (wherein the alkyl is optionally substituted by hydroxy)).

[0465]

One of the further preferred embodiments of the compound
 of the formula [I] is a compound of the formula [I] wherein
 X¹ is carbon or a nitrogen atom;
 35 Y¹ and Y² are each a nitrogen atom;

Y³ and Y⁴ are each a carbon atom;

m is 0 or 1;

n is 0 or 1;

R¹ is

5 (1) C₁₋₄ alkyl (wherein the alkyl is optionally substituted by hydroxy or C₁₋₄ alkoxy),

(2) halogen, or

(3) C₁₋₄ haloalkyl;

R² in the number of m are each independently halogen;

10 R³ in the number of n are each independently halogen;

R⁴ is

(a) C₄₋₆ cycloalkyl (wherein the cycloalkyl is optionally substituted by

(I) hydroxy,

15 (II) cyano,

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

(i) hydroxy,

(ii) carboxy,

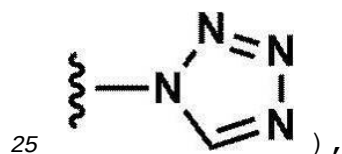
20 (iii) -CONH₂,

(iv) -CO-C₁₋₄ alkoxy,

(v) -SO₂-C₁₋₄ alkyl, or

(vi) a group represented by the formula:

[0466]



[0467]

(IV) C₁₋₆ alkoxy (wherein the alkoxy is optionally substituted by hydroxy or -SO₂-C₁₋₄ alkyl),

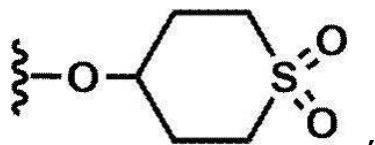
30 (V) -CO-NR⁵R⁶ [wherein R⁵ and R⁶ form, together with the nitrogen atom bonded thereto, 4- to 6-membered heterocycloalkyl containing 1 or 2 hetero atoms independently selected from the group consisting of nitrogen and oxygen atoms {wherein the heterocycloalkyl is optionally substituted by C₁₋₆ alkyl

(wherein the alkyl is optionally substituted by hydroxy))],

(VI) $-NR^7R^8$ {wherein R^7 and R^8 are each independently C_{1-4} alkyl or $-CO-C_{1-6}$ alkyl (wherein the alkyl is optionally substituted by cyano)},

5 (VII) a group represented by the formula:

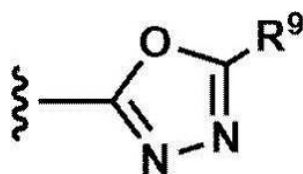
[0468]



[0469]

(VIII) a group represented by the formula:

10 [0470]

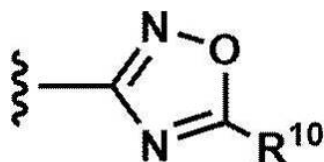


[0471]

{wherein R^9 is C_{1-4} alkyl (wherein the alkyl is optionally substituted by C_{1-4} alkoxy)}, or

15 (IX) a group represented by the formula:

[0472]



[0473]

20 wherein R^{10} is C_{1-4} alkyl)),

(b) C_{5-8} bridged cycloalkyl {wherein the bridged cycloalkyl is optionally substituted by C_{1-6} alkyl (wherein the alkyl is optionally substituted by hydroxy)},

(c) 5- or 6-membered heterocycloalkyl containing one
25 nitrogen atom [wherein the heterocycloalkyl is optionally substituted by $-CO-R^{11}$ {wherein R^{11} is

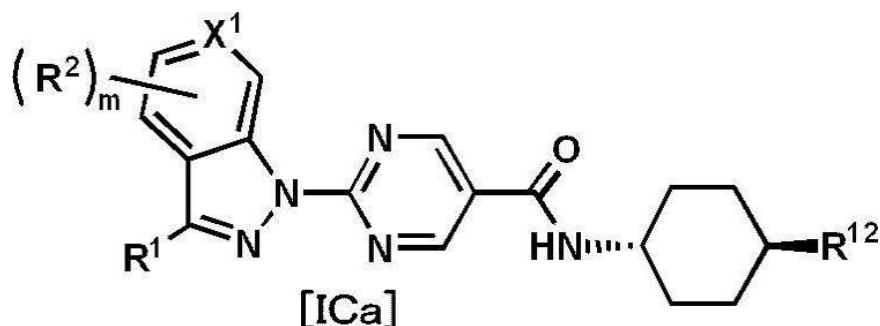
(i) C_{1-6} alkyl (wherein the alkyl is optionally substituted by

- (A) hydroxy,
 (B) cyano, or
 (C) C₁₋₄ alkoxy),
 (ii) C₁₋₆ alkoxy,
 5 (iii) C₁₋₆ haloalkyl,
 (iv) C₃₋₆ cycloalkyl (wherein the cycloalkyl is
 optionally substituted by halogen), or
 (v) 4- to 6-membered heterocycloalkyl containing one
 oxygen atom (wherein the heterocycloalkyl is optionally
 10 substituted by halogen) }], or
 (d) 8-membered bridged heterocycloalkyl containing one
 nitrogen atom {wherein the bridged heterocycloalkyl is
 optionally substituted by -CO-C₁₋₆ alkyl (wherein the alkyl is
 optionally substituted by
 15 (A) hydroxy, or
 (B) cyano)}.

[0474]

One of the preferred embodiments of the compound of the
 formula [IC] is a compound represented by the formula [ICa]:

20 [0475]



[0476]

wherein X¹, R¹, R², R¹² and m are as defined above.

[0477]

- 25 One of the more preferred embodiments of the compound of
 the formula [IC] is a compound of the formula [ICa], wherein
 X¹, R¹, R² and m are as defined above:

R¹² is

- (1) hydroxy,
 30 (2) cyano,

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

(a) hydroxy,

(b) carboxy,

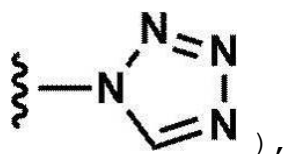
(c) -CONH₂,

5 (d) -CO-C₁₋₄ alkoxy,

(e) -SO₂-C₁₋₄ alkyl, or

(f) a group represented by the formula:

[0478]



10 [0479]

(4) C₁₋₆ alkoxy (wherein the alkoxy is optionally substituted by hydroxy or -SO₂-C₁₋₄ alkyl),

(5) -CO-NR⁵R⁶ [wherein R⁵ and R⁶ form, together with the nitrogen atom bonded thereto, 4- to 6-membered heterocycloalkyl

15 containing 1 or 2 hetero atoms independently selected from the group consisting of nitrogen and oxygen atoms {wherein the heterocycloalkyl is optionally substituted by C₁₋₆ alkyl

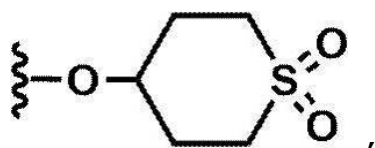
(wherein the alkyl is optionally substituted by hydroxy)}],

(6) -NR⁷R⁸ {wherein R⁷ and R⁸ are each independently C₁₋₄ alkyl

20 or -CO-C₁₋₆ alkyl (wherein the alkyl is optionally substituted by cyano)}],

(7) a group represented by the formula:

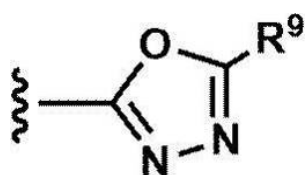
[0480]



25 [0481]

(8) a group represented by the formula:

[0482]

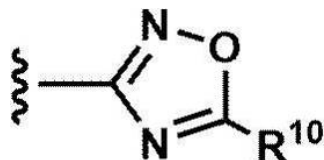


[0483]

{wherein R⁹ is C₁₋₄ alkyl (wherein the alkyl is optionally substituted by C₁₋₄ alkoxy)}, or

(9) a group represented by the formula:

5 [0484]



[0485]

wherein R¹⁰ is C₁₋₄ alkyl).

10 [0486]

One of the preferred embodiments of the compound of the formula [III] is a compound of the formula [III] wherein X¹, X², X³, X⁴, Y¹, Y², Y³ and Y⁴ are each independently a carbon or a nitrogen atom (wherein the total number of the nitrogen atoms for X¹, X², X³ and X⁴ is 0 or 1, and the total number of the nitrogen atoms for Y¹, Y², Y³ and Y⁴ is 0, 1 or 2);

m is 0 or 1;

n is 0, 1 or 2;

R¹ is

20 (1) C₁₋₄ alkyl,

(2) C₁₋₄ haloalkyl, or

(3) C₃₋₆ cycloalkyl;

R² in the number of m are each independently

(1) cyano,

25 (2) C₁₋₄ alkyl,

(3) C₁₋₄ alkoxy, or

(4) halogen;

R³ in the number of n are each independently halogen;

R⁴ is

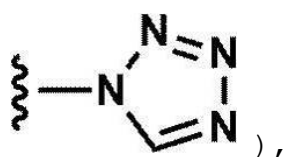
30 (a) C₄₋₆ cycloalkyl (wherein the cycloalkyl is optionally substituted by 1 or 2 substituents independently selected from the group consisting of

(I) hydroxy,

(II) cyano,
(III) oxo,
(IV) C₁₋₆ alkyl (wherein the alkyl is optionally substituted by

- 5 (i) hydroxy,
(ii) carboxy,
(iii) -CONH₂,
(iv) -CO-C₁₋₄ alkoxy,
(v) -SO₂-C₁₋₄ alkyl, or
10 (vi) a group represented by the formula:

[0487]



[0488]

- (V) C₁₋₆ alkoxy (wherein the alkoxy is optionally substituted by hydroxy or -SO₂-C₁₋₄ alkyl),
15 (VI) carboxy,
(VII) -CO-NR⁵R⁶ [wherein R⁵ and R⁶ are each independently C₁₋₄ alkyl (wherein the alkyl is optionally substituted by C₁₋₄ alkoxy), or R⁵ and R⁶ optionally form, together with the
20 nitrogen atom bonded thereto, 4- to 6-membered heterocycloalkyl containing 1 or 2 hetero atoms independently selected from the group consisting of nitrogen and oxygen atoms {wherein the heterocycloalkyl is optionally substituted by 1 or 2 substituents independently selected from the group consisting
25 of

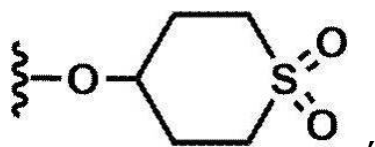
- (i) hydroxy, and
(ii) C₁₋₆ alkyl (wherein the alkyl is optionally substituted by hydroxy)}],

- (VIII) -NR⁷R⁸ {wherein R⁷ and R⁸ are each independently
30 C₁₋₄ alkyl or -CO-C₁₋₆ alkyl (wherein the alkyl is optionally substituted by cyano)},

(IX) -O-C₁₋₆ haloalkyl,

(X) a group represented by the formula:

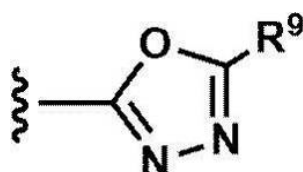
[0489]



[0490]

(XI) a group represented by the formula:

5 [0491]

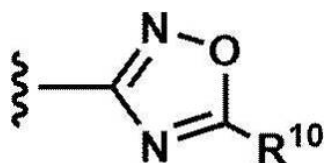


[0492]

{wherein R⁹ is C₁₋₄ alkyl (wherein the alkyl is optionally substituted by C₁₋₄ alkoxy)}, and

10 (XII) a group represented by the formula:

[0493]



[0494]

wherein R¹⁰ is C₁₋₄ alkyl)),

15 (b) C₅₋₈ bridged cycloalkyl {wherein the bridged cycloalkyl is optionally substituted by

(I) hydroxy,

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

20 (i) hydroxy,

(ii) carboxy,

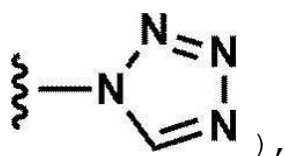
(iii) -CONH₂,

(iv) -CO-C₁₋₄ alkoxy,

(v) -SO₂-C₁₋₄ alkyl, or

25 (vi) a group represented by the formula:

[0495]



[0496]

(III) C₁₋₆ alkoxy (wherein the alkoxy is optionally substituted by hydroxy or -SO₂-C₁₋₄ alkyl),

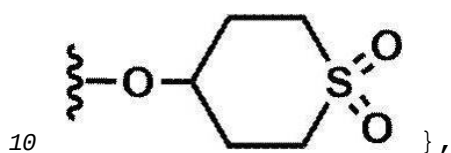
5 (IV) carboxy,

(V) -CO-C₁₋₄ alkoxy,

(VI) -O-C₁₋₆ haloalkyl, or

(VII) a group represented by the formula:

[0497]



[0498]

(c) 5- or 6-membered heterocycloalkyl containing one nitrogen atom [wherein the heterocycloalkyl is optionally substituted by 1 to 3 substituents independently selected from
15 the group consisting of

(I) oxo,

(II) C₁₋₆ alkyl,

(III) -CO-R¹¹ {wherein R¹¹ is

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

(A) hydroxy,

(B) cyano, or

(C) C₁₋₄ alkoxy),

(ii) C₁₋₆ alkoxy,

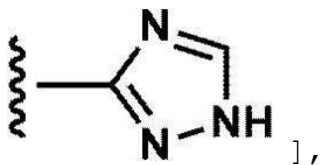
25 (iii) C₁₋₆ haloalkyl,

(iv) C₃₋₆ cycloalkyl (wherein the cycloalkyl is optionally substituted by halogen), or

(v) 4- to 6-membered heterocycloalkyl containing one oxygen atom (wherein the heterocycloalkyl is optionally
30 substituted by halogen)}, and

(IV) a group represented by the formula:

[0499]



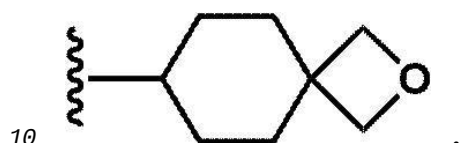
[0500]

(d) a 6- to 9-membered saturated or partially unsaturated
5 fused ring group containing 1 or 2 nitrogen atoms (wherein the
fused ring group is optionally substituted by $-\text{CO}-\text{R}^{11}$), or

[0501]

(e) a group represented by the formula:

[0502]



[0503]

One of the more preferred embodiments of the compound of
the formula [III] is a compound of the formula [III] wherein
 X^1 , X^2 , X^3 , X^4 , Y^1 , Y^2 , Y^3 and Y^4 are each independently a carbon
15 or a nitrogen atom (wherein the total number of the nitrogen
atoms for X^1 , X^2 , X^3 and X^4 is 0 or 1, and the total number of
the nitrogen atoms for Y^1 , Y^2 , Y^3 and Y^4 is 0, 1 or 2);

m is 0 or 1;

n is 0, 1 or 2;

20 R^1 is C_{1-4} alkyl;

R^2 in the number of m are each independently halogen;

R^3 in the number of n are each independently halogen;

R^4 is

(a) C_{4-6} cycloalkyl (wherein the cycloalkyl is optionally
25 substituted by 1 or 2 substituents independently selected from
the group consisting of

(I) hydroxy,

(II) cyano,

(III) C_{1-6} alkyl (wherein the alkyl is optionally
30 substituted by

- (i) hydroxy,
- (ii) carboxy, or
- (iii) $-\text{SO}_2\text{-C}_{1-4}$ alkyl,),
- (IV) $-\text{O-C}_{1-6}$ haloalkyl,

5 (V) a group represented by the formula:

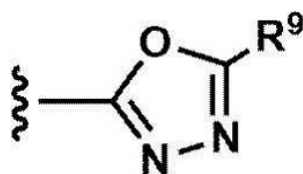
[0504]



[0505]

(VI) a group represented by the formula:

10 [0506]



[0507]

{wherein R^9 is C_{1-4} alkyl}},

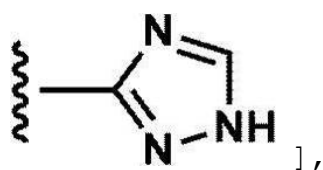
(b) C_{5-8} bridged cycloalkyl {wherein the bridged
15 cycloalkyl is optionally substituted by

- (I) hydroxy,
- (II) C_{1-6} alkyl (wherein the alkyl is optionally substituted by

- (i) hydroxy,
- 20 (ii) carboxy, or
- (iii) $-\text{CO-C}_{1-4}$ alkoxy), or
- (III) carboxy},

(c) 5- or 6-membered heterocycloalkyl containing one nitrogen atom [wherein the heterocycloalkyl is optionally
25 substituted by a group represented by the formula:

[0508]



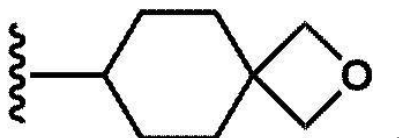
[0509]

(d) a 6- to 9-membered saturated or partially unsaturated fused ring group containing 1 or 2 nitrogen atoms, or

[0510]

5 (e) a group represented by the formula:

[0511]



[0512]

One of the preferred embodiments of the compound of the
10 formula [IV] is a compound of the formula [IV] wherein
 X^1 , X^5 and X^6 are each independently a carbon or a nitrogen atom
(wherein the total number of the nitrogen atoms for X^5 and X^6
is 1);

Y^1 and Y^2 are each a nitrogen atom;

15 Y^3 and Y^4 are each a carbon atom;

m is 0;

n is 0 or 1;

R^1 is C_{1-4} alkyl;

R^3 in the number of n are each independently halogen;

20 R^4 is C_{4-6} cycloalkyl (wherein the cycloalkyl is optionally
substituted by 1 or 2 substituents independently selected from
the group consisting of

(I) hydroxy,

(II) cyano,

25 (III) oxo,

(IV) C_{1-6} alkyl (wherein the alkyl is optionally
substituted by

(i) hydroxy,

(ii) carboxy,

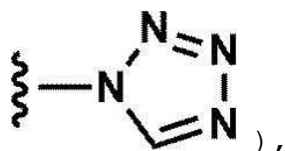
30 (iii) $-CONH_2$,

(iv) $-CO-C_{1-4}$ alkoxy,

(v) $-SO_2-C_{1-4}$ alkyl, or

(vi) a group represented by the formula:

[0513]



[0514]

(V) C₁₋₆ alkoxy (wherein the alkoxy is optionally substituted by hydroxy or -SO₂-C₁₋₄ alkyl),

(VI) carboxy,

(VII) -CO-NR⁵R⁶ [wherein R⁵ and R⁶ are each independently C₁₋₄ alkyl (wherein the alkyl is optionally substituted by C₁₋₄ alkoxy), or R⁵ and R⁶ optionally form, together with the nitrogen atom bonded thereto, 4- to 6-membered heterocycloalkyl containing 1 or 2 hetero atoms independently selected from the group consisting of nitrogen and oxygen atoms {wherein the heterocycloalkyl is optionally substituted by 1 or 2 substituents independently selected from the group consisting

of

(i) hydroxy, and

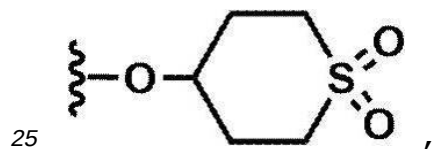
(ii) C₁₋₆ alkyl (wherein the alkyl is optionally substituted by hydroxy)}],

(VIII) -NR⁷R⁸ {wherein R⁷ and R⁸ are each independently C₁₋₄ alkyl or -CO-C₁₋₆ alkyl (wherein the alkyl is optionally substituted by cyano)},

(IX) -O-C₁₋₆ haloalkyl,

(X) a group represented by the formula:

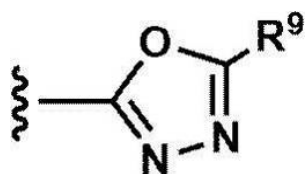
[0515]



[0516]

(XI) a group represented by the formula:

[0517]

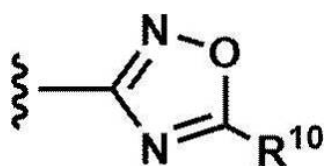


[0518]

{wherein R⁹ is C₁₋₄ alkyl (wherein the alkyl is optionally substituted by C₁₋₄ alkoxy)}, and

5 (XII) a group represented by the formula:

[0519]



[0520]

wherein R¹⁰ is C₁₋₄ alkyl)).

10 [0521]

One of the more preferred embodiments of the compound of the formula [IV] is a compound of the formula [IV] wherein X¹, X⁵ and X⁶ are each independently a carbon or a nitrogen atom (wherein the total number of the nitrogen atoms for X⁵ and X⁶

15 is 1);

Y¹ and Y² are each a nitrogen atom;

Y³ and Y⁴ are each a carbon atom;

m is 0;

n is 0 or 1;

20 R¹ is C₁₋₄ alkyl;

R³ in the number of n are each independently halogen;

R⁴ is C₄₋₆ cycloalkyl (wherein the cycloalkyl is optionally substituted by

(I) hydroxy, or

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

(i) hydroxy, or

(ii) carboxy)).

[0522]

30 The "pharmaceutically acceptable salt" may be any salt

known in the art that does not accompany excessive toxicity. Specifically, salts with inorganic acids, salts with organic acid, salts with inorganic bases, salts with organic bases and the like can be mentioned. Various forms of pharmaceutically acceptable salts are well-known in the pertinent technical field and are described, for example, in the following reference documents:

- (a) Berge et al., J. Pharm. Sci., 66, p1-19 (1977),
- (b) Stahl et al., "Handbook of Pharmaceutical Salts: Properties, Selection, and Use" (Wiley-VCH, Weinheim, Germany, 2002),
- (c) Paulekuhn et al., J. Med. Chem., 50, p6665-6672 (2007).

Pharmaceutically acceptable salts of the compound of the present invention can be each obtained by reacting the compound of the present invention with an inorganic acid, an organic acid, an inorganic base, or an organic base according to a method known per se.

[0523]

Examples of the salt with inorganic acid include salts with hydrofluoric acid, hydrochloric acid, hydrobromic acid, hydroiodic acid, nitric acid, phosphoric acid, and sulfuric acid.

Examples of the salt with organic acid include salts with acetic acid, adipic acid, alginic acid, 4-aminosalicylic acid, anhydromethylenecitric acid, benzoic acid, benzenesulfonic acid, calcium edetate, camphoric acid, 10-camphorsulfonic acid, carbonic acid, citric acid, edetic acid, ethane-1,2-disulfonic acid, dodecylsulfuric acid, ethanesulfonic acid, fumaric acid, glucoheptonic acid, gluconic acid, glucuronic acid, glycolylarsanilic acid, hexylresorcinic acid, hydroxy-naphthoic 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-naphthoic acid, 1,5-naphthalene disulfonic 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-toluenesulfonic acid, undecanoic acid, aspartic acid, and
5 glutamic acid.

[0524]

Examples of the salt with inorganic base include salts with lithium, sodium, potassium, magnesium, calcium, barium, aluminum, zinc, bismuth, and ammonium.

10 [0525]

Examples of the salt with organic base include salts with arecoline, betaine, choline, clemizole, ethylenediamine, N-methylglucamine, N-benzylphenethylamine, tris(hydroxymethyl)methylamine, arginine, and lysine.

15 [0526]

Preferred embodiments of the "pharmaceutically acceptable salt" are as follows.

Examples of the salts with inorganic acid include salts with hydrochloric acid, nitric acid, sulfuric acid, phosphoric
20 acid, and hydrobromic acid.

Examples of the salts with organic acid include 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,
25 oleic acid, pamoic acid, methanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, and 2-hydroxy-1-ethanesulfonic acid.

Examples of the salts with inorganic base include salts with sodium, potassium, calcium, magnesium, and zinc.

30 Examples of the salts with organic base include salts with tris(hydroxymethyl)methylamine, N-methylglucamine, and lysine.

[0527]

The compound of the present invention or a
35 pharmaceutically acceptable salt thereof may exist as a solvate

thereof. The "solvate" refers to the compound of the present invention or a pharmaceutically acceptable salt thereof with which a solvent molecule is coordinated, and also includes hydrates. Such solvates are preferably pharmaceutically acceptable solvates. Such solvates include, for example, hydrate, ethanol solvate, dimethylsulfoxide-solvate, and the like of the compound of the present invention or a pharmaceutically acceptable salt thereof.

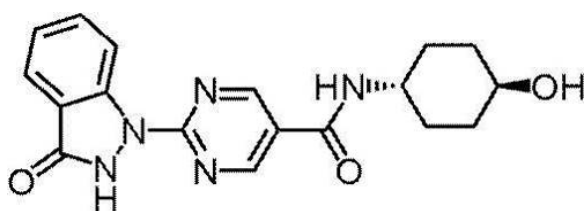
[0528]

Specific examples include hemihydrate, monohydrate, dihydrate or mono ethanol solvate of the compound of the present invention or a monohydrate of a sodium salt of the compound of the present invention, 2/3 ethanol solvate of dihydrochloride of the compound of the present invention, and the like. These solvates can be obtained according to conventional methods.

[0529]

The compound of the present invention may exist as a tautomer. In this case, the compound of the present invention can be a single tautomer or a mixture of individual tautomers. For example, the structure represented by the following formula:

[0530]

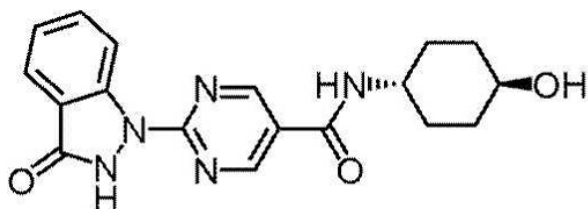


[0531]

is, unless otherwise indicated, present as

(1)

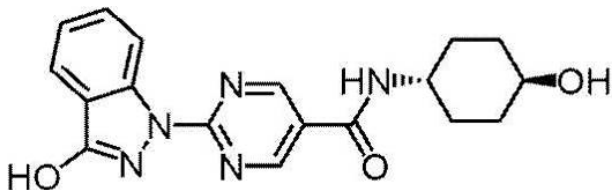
[0532]



[0533]

(2)

[0534]



5

or

[0535]

(3) a mixture of these.

[0536]

The compound of the present invention may have a carbon
10 double bond. In this case, the compound of the present
invention can be present as E form, Z form, or a mixture of E
form and Z form.

[0537]

The compound of the present invention may contain a
15 stereoisomer that should be recognized as a cis/trans isomer.
In this case, the compound of the present invention can be
present as a cis form, a trans form, or a mixture of a cis form
and a trans form.

[0538]

20 The compound of the present invention may contain one or
more asymmetric carbons. In this case, the compound of the
present invention may be present as a single enantiomer, a
single diastereomer, a mixture of enantiomers or a mixture of
diastereomers.

25 [0539]

The compound of the present invention may be present as
an atropisomer. In this case, the compound of the present

invention may be present as an individual atropisomer or a mixture of atropisomers.

[0540]

The compound of the present invention may simultaneously
5 contain plural structural characteristics that produce the above-mentioned isomers. Moreover, the compound of the present invention may contain the above-mentioned isomers at any ratio.

[0541]

In the absence of other reference such as annotation and
10 the like, the formulae, chemical structures and compound names indicated in the present specification without specifying the stereochemistry thereof encompass all the above-mentioned isomers that may exist.

[0542]

15 A diastereomeric mixture can be separated into each diastereomer by conventional methods such as chromatography, crystallization and the like. In addition, each diastereomer can also be formed by using a stereochemically single starting material, or by a synthetic method using a stereoselective
20 reaction.

[0543]

An enantiomeric mixture can be separated into each single enantiomer by a method well-known in the pertinent technical field.

25 For example, from a diastereomeric mixture formed by reacting a mixture of enantiomers with a compound known as a chiral auxiliary, which is a substantially pure enantiomer, the isomer ratio can be increased or a single substantially pure diastereomer can be separated from the diastereomeric mixture.
30 The separated diastereomer can be converted to a desired enantiomer by removing the added chiral auxiliary by a cleavage reaction. Alternatively, a mixture of enantiomers can be directly separated by a chromatographic method using a chiral stationary phase, as is well-known in the pertinent technical
35 field. Alternatively, either enantiomer can be obtained by

using substantially pure optically active starting materials or by stereoselective synthesis (asymmetric induction) of a prochiral intermediate using a chiral auxiliary and an asymmetric catalyst.

5 [0544]

The absolute steric configuration can be determined based on the X-ray crystal analysis of the resultant crystalline product or intermediate. In this case, a resultant crystalline product or intermediate derivatized with a reagent having an
10 asymmetric center with a known steric configuration may be used where necessary.

[0545]

The compound of the present invention may be labeled with an isotope element ($^2\text{H}(\text{D})$, ^3H , ^{14}C , ^{18}F , ^{35}S , etc.). For example,
15 when the compound of the formula [I] has a methyl group, the methyl group is replaced with $-\text{CD}_3$ group, and the thus-obtained compound is also encompassed in the present invention.

[0546]

As the compound of the present invention or a
20 pharmaceutically acceptable salt thereof, the compound of the present invention or a pharmaceutically acceptable salt thereof, each of which is substantially purified, is preferred. More preferred is the compound of the present invention or a pharmaceutically acceptable salt thereof, each of which is
25 purified to a chemical purity of not less than 80%.

[0547]

The pharmaceutical composition of the present invention may be produced according to a method known in the technical field of pharmaceutical preparations, by mixing the compound of
30 the present invention or a pharmaceutically acceptable salt thereof with a suitable amount of at least one kind of pharmaceutically acceptable carrier and the like as appropriate. While the content of the compound of the present invention or a pharmaceutically acceptable salt thereof in the pharmaceutical
35 composition varies depending on the dosage form, dose and the

like, it is, for example, 0.1 to 100 wt% of the whole composition.

[0548]

The dosage form of a pharmaceutical composition
5 containing the compound of the present invention or a
pharmaceutically acceptable salt thereof (hereinafter also to
be referred to as "the pharmaceutical composition of the
present invention" in the present specification) include oral
preparations such as tablet, capsule, granule, powder, troche,
10 syrup, emulsion, suspension and the like, and parenteral agents
such as external preparation, suppository, injection, eye drop,
nasal preparations, pulmonary preparation and the like.

[0549]

Examples of the "pharmaceutically acceptable carrier"
15 include various organic or inorganic carrier substances
conventionally used as preparation materials, for example,
excipient, disintegrant, binder, fluidizer, lubricant, and the
like for solid preparations, solvent, solubilizing agent,
suspending agent, isotonicity agent, buffering agent, soothing
20 agent and the like for liquid preparations, and base,
emulsifier, wetting agent, stabilizer, stabilizing agent,
dispersing agent, plasticizer, pH regulator, absorption
promoter, gelling agent, antiseptic, filler, dissolving agent,
solubilizing agent, suspending agent, and the like for
25 semisolid preparations. Where necessary, moreover, additives
such as preservative, antioxidant, colorant, sweetening agent,
and the like may be used.

[0550]

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

Examples of the "disintegrant" include carmellose,
35 carmellose calcium, carmellose sodium, sodium carboxymethyl

starch, croscarmellose sodium, crospovidone, low-substituted hydroxypropyl cellulose, hydroxypropylmethylcellulose, crystalline cellulose, and the like.

Examples of the "binder" include hydroxypropyl cellulose, 5 hydroxypropylmethylcellulose, povidone, crystalline cellulose, sucrose, dextrin, starch, gelatin, carmellose sodium, gum arabic, and the like.

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

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

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

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

Examples of the "suspending agent" include benzalkonium chloride, carmellose, hydroxypropylcellulose, propylene glycol, 20 povidone, methylcellulose, glycerol monostearate, and the like.

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

Examples of the "buffering agent" include sodium hydrogen phosphate, sodium acetate, sodium carbonate, sodium citrate, and 25 the like.

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

Examples of the "base" include water, animal and vegetable oils (olive oil, corn oil, peanut oil, sesame oil, 30 castor oil, etc.), lower alcohols (ethanol, propanol, propylene glycol, 1,3-butyleneglycol, phenol, etc.), higher fatty acid and ester thereof, waxes, higher alcohol, polyhydric alcohol, hydrocarbons (white petrolatum, liquid paraffin, paraffin, etc.), hydrophilic petrolatum, purified lanolin, absorption 35 ointment, hydrolyzed lanolin, hydrophilic ointment, starch,

pullulan, gum arabic, gum tragacanth, gelatin, dextran, cellulose derivative (methyl cellulose, carboxymethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, etc.), synthetic polymers (carboxyvinyl polymer, sodium polyacrylate, 5 polyvinyl alcohol, polyvinylpyrrolidone, etc.), propylene glycol, macrogol (macrogol 200-600, etc.), and combinations of two or more kinds thereof.

Examples of the "preservative" include ethyl parahydroxybenzoate, chlorobutanol, benzyl alcohol, sodium 10 dehydroacetate, sorbic acid, and the like.

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

Examples of the "colorant" include food colors (e.g., Food Color Red No. 2 or 3, Food Color yellow No. 4 or 5, etc.), β - 15 carotene, and the like.

Examples of the "sweetening agent" include saccharin sodium, dipotassium glycyrrhizinate, aspartame, and the like. [0551]

The pharmaceutical composition of the present invention 20 can be administered orally or parenterally (topical, rectal, intravenous administration, intramuscular, subcutaneous, etc.) to human as well as mammals other than human (e.g., mouse, rat, hamster, guinea pig, rabbit, cat, dog, swine, bovine, horse, sheep, monkey, etc.). The dose of the compound of the present 25 invention or a pharmaceutically acceptable salt thereof (hereinafter also to be referred to as a "pharmaceutically effective amount" in the present specification) may appropriately vary depending on the subject of administration, administration route, target disease, symptoms, severity of the 30 disease, and combinations of these. For example, the daily dose for oral administration to an adult patient is generally within the range of about 0.01 mg to 1 g, based on the compound of the present invention as the active ingredient. This amount can be administered in one to several portions.

35 [0552]

Since the compound of the present invention or a pharmaceutically acceptable salt thereof has an H-PGDS inhibitory action, it is useful for the treatment and/or prophylaxis of various diseases or conditions that can be
5 expected to be improved by regulation of H-PGDS activity. Examples of the various diseases or conditions that can be expected to be improved by regulation of H-PGDS activity include peripheral arterial diseases (e.g., intermittent claudication and comprehensive severe chronic lower extremity
10 ischemia), cardiovascular diseases, allergic asthma, chronic obstructive pulmonary diseases, allergic rhinitis, sarcopenia, and Duchenne muscular dystrophy.

[0553]

To "inhibit H-PGDS" means to inhibit the function of H-
15 PGDS and eliminate or attenuate the activity. For example, it means to inhibit the function of H-PGDS based on the below-mentioned Experimental Example 1. To "inhibit H-PGDS", human H-PGDS is preferably inhibited.

[0554]

20 The "H-PGDS inhibitor" means a substance that inhibits the function of H-PGDS. For example, an H-PGDS inhibitor is expected to be useful for the treatment and/or prophylaxis of a disease selected from the group consisting of peripheral arterial diseases (e.g., intermittent claudication and
25 comprehensive severe chronic lower extremity ischemia), cardiovascular diseases, allergic asthma, chronic obstructive pulmonary diseases, allergic rhinitis, sarcopenia, and Duchenne muscular dystrophy.

[0555]

30 In the present specification, the "treatment" includes improvement of symptoms, prevention of aggravation, maintenance of remission, prevention of relapse, and further, prevention of recurrence.

In the present specification, "prophylaxis" means
35 suppression of the onset of symptoms.

[0556]

Unless there is a contradiction between one embodiment disclosed in a certain part of the specification and embodiments disclosed in other parts, any combination of two or
5 more of thereof is intended to be encompassed in the present invention.

[0557]

Preferred specific embodiment of the active ingredient in the H-PGDS inhibitor or pharmaceutical composition of the
10 present invention is the compound of the present invention or a pharmaceutically acceptable salt thereof.

[0558]

[General production methods of the compound of the present invention or a pharmaceutically acceptable salt thereof]

15 A general method for producing the compound of the formula [I] or a pharmaceutically acceptable salt thereof, the compound of the formula [II] or a pharmaceutically acceptable salt thereof, the compound of the formula [III] or a pharmaceutically acceptable salt thereof, or the compound of
20 formula [IV] or a pharmaceutically acceptable salt thereof is exemplified below. However, the production method of the compound of the formula [I] or a pharmaceutically acceptable salt thereof, the compound of the formula [II] or a pharmaceutically acceptable salt thereof, the compound of the
25 formula [III] or a pharmaceutically acceptable salt thereof, or the compound of the formula [IV] or a pharmaceutically acceptable salt thereof is not limited thereto.

[0559]

The compound obtained in each step can be isolated and/or
30 purified as necessary by known methods such as distillation, recrystallization, and column chromatography. In some cases, the compound can proceed to the next step without isolation and/or purification.

[0560]

35 In the present specification, the room temperature refers

to a temperature in the state where the temperature is not controlled, and one embodiment is 1°C to 40°C.

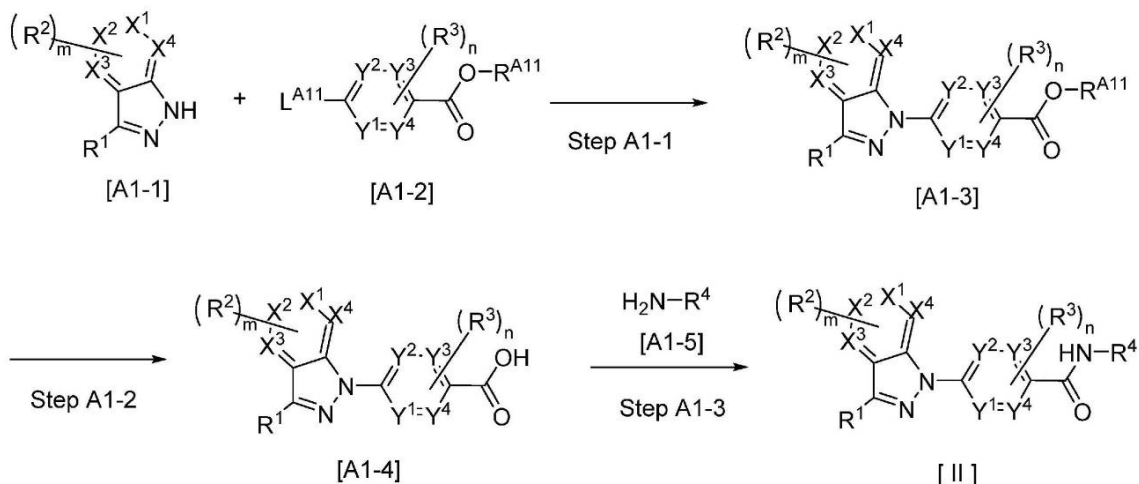
[0561]

Production method A1: Production method of compound [II] or a

5 salt thereof

Compound [II] or a salt thereof can be produced, for example, by production method A1 shown below:

[0562]



10 [0563]

wherein

X^1 , X^2 , X^3 , X^4 , Y^1 , Y^2 , Y^3 and Y^4 are each independently a carbon or a nitrogen atom (wherein the total number of the nitrogen atoms for X^1 , X^2 , X^3 and X^4 is 0 or 1, and the total number of

15 the nitrogen atoms for Y^1 , Y^2 , Y^3 and Y^4 is 0, 1 or 2),

R^{A11} is a carboxy-protecting group (e.g., methyl, ethyl and tert-butyl),

L^{A11} is a leaving group {for example, halogen, boronic acid, and boronic acid ester (e.g., boronic acid pinacol ester)}, and

20 R^1 , R^2 , R^3 , R^4 , m and n are as defined above.

[0564]

(Step A1-1)

Compound [A1-3] or a salt thereof can be obtained by reacting compound [A1-1] or a salt thereof with compound [A1-2] or a salt thereof in a solvent in the presence of a base by

25 adding a metal catalyst as necessary.

[0565]

Examples of the solvent include tetrahydrofuran, N,N-dimethylformamide, N,N-dimethylacetamide, dimethyl sulfoxide, dichloromethane and mixed solvents thereof. Preferred solvent
5 is N,N-dimethylformamide.

[0566]

Examples of the base include potassium tert-butoxide, potassium carbonate, cesium carbonate and pyridine. Preferred base is potassium carbonate.

10 [0567]

Examples of the metal catalyst include copper iodide (I) and copper acetate (II).

[0568]

The reaction temperature is, for example, 20°C to 120°C,
15 preferably 20°C to 90°C.

[0569]

Compound [A1-1] or a salt thereof may be a commercially available product, or produced from a commercially available product by a known method.

20 [0570]

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

[0571]

25 (Step A1-2)

Compound [A1-4] or a salt thereof can be produced by removing R^{A11} of compound [A1-3] or a salt thereof by a deprotection reaction. The deprotection reaction may be carried out under conditions suitable for the kind of R^{A11}. For
30 example, when R^{A11} is ethyl, compound [A1-4] or a salt thereof can be produced by hydrolyzing compound [A1-3] or a salt thereof in a solvent in the presence of a base.

[0572]

Examples of the base include lithium
35 hydroxide monohydrate, sodium hydroxide, and potassium

hydroxide.

[0573]

Examples of the solvent include methanol, tetrahydrofuran, water, and mixed solvents thereof. Preferred solvent is a
5 mixed solvent of tetrahydrofuran and water.

[0574]

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

[0575]

10 (Step A1-3)

Compound [II] or a salt thereof can be produced by reacting compound [A1-4] or a salt thereof with compound [A1-5] or a salt thereof in a solvent in the presence of a condensing agent and a base.

15 [0576]

Examples of the condensing agent include dicyclohexylcarbodiimide (DCC), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (WSC·HCl), diisopropyl carbodiimide, 1,1'-carbonyldiimidazole (CDI), 1-
20 hydroxy-7-azabenzotriazole, O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (HATU), hexafluorophosphoric acid (benzotriazol-1-yl-oxo)tripyrrolidinophosphonium (PyBOP), (1-cyano-2-ethoxy-2-oxoethylideneaminoxy)dimethylaminomorpholinocarbenium
25 hexafluorophosphate (COMU), and diphenylphosphoryl azide. Preferred condensing agent is 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (WSC·HCl).

[0577]

Examples of the base include triethylamine and N,N-
30 diisopropylethylamine. Preferred base is triethylamine.

[0578]

Examples of the solvent include tetrahydrofuran, N,N-dimethylformamide, N,N-dimethylacetamide, dimethyl sulfoxide, acetonitrile, and mixed solvents thereof. Preferred solvent is
35 N,N-dimethylformamide.

[0579]

The reaction temperature is, for example, 20°C to 30°C.

[0580]

Compound [A1-5] or a salt thereof may be a commercially available product, or produced from a commercially available product by a known method. For example, it can be obtained by the below-mentioned production methods B1 to B4.

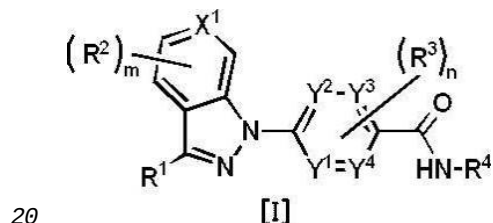
[0581]

Compound [II] or a salt thereof may also be produced by performing this production method by using, instead of compound [A1-5] or a salt thereof, a compound having a functional group or a protected functional group or a salt thereof that can be converted to compound [A1-5] or a salt thereof by a known reaction to obtain a compound corresponding to compound [II] or a salt thereof, and converting the functional group thereof.

[0582]

Production method A1a: Production method of compound [I] or a salt thereof

[0583]



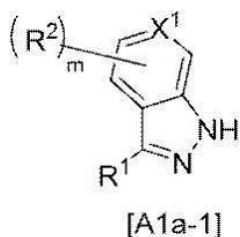
[0584]

wherein each symbol is as defined above.

[0585]

Compound [I] or a salt thereof can be produced by performing production method A1 by using compound [A1a-1] or a salt thereof instead of compound [A1-1] or a salt thereof:

[0586]



[0587]

wherein each symbol is as defined above.

[0588]

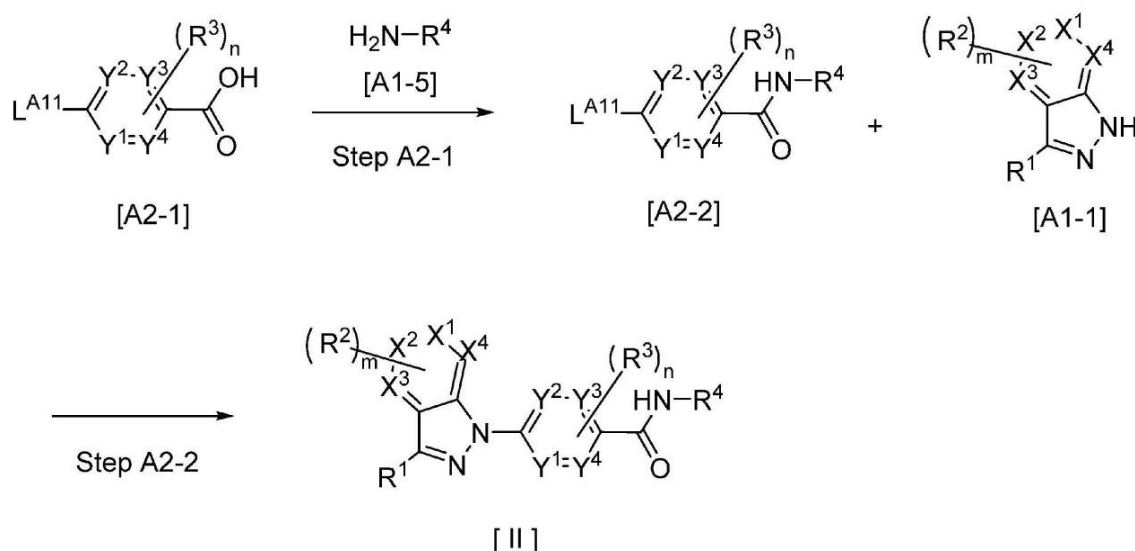
Compound [A1a-1] or a salt thereof may be a commercially available product, or produced from a commercially available product by a known method.

[0589]

Production method A2: Another method for producing compound [II] or a salt thereof

Compound [II] or a salt thereof can also be produced by, for example, the following production method A2.

[0590]



[0591]

wherein

X^1 , X^2 , X^3 , X^4 , Y^1 , Y^2 , Y^3 and Y^4 are each independently a carbon or a nitrogen atom (wherein the total number of the nitrogen atoms for X^1 , X^2 , X^3 and X^4 is 0 or 1, and the total number of the nitrogen atoms for Y^1 , Y^2 , Y^3 and Y^4 is 0, 1 or 2), and

L^{A11} , R^1 , R^2 , R^3 , R^4 , m and n are as defined above.

[0592]

(Step A2-1)

Compound [A2-2] or a salt thereof can be produced by reacting compound [A2-1] or a salt thereof with compound [A1-5] or a salt thereof, according to step A1-3.

[0593]

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

5 [0594]

(Step A2-2)

Compound [II] or a salt thereof can be produced by reacting compound [A2-2] or a salt thereof with compound [A1-1] or a salt thereof according to step A1-1.

10 [0595]

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

[0596]

15 Compound [II] or a salt thereof may also be produced by performing this production method by using, instead of compound [A1-5] or a salt thereof, a compound having a functional group or a protected functional group or a salt thereof that can be converted to compound [A1-5] or a salt thereof by a known
20 reaction to obtain a compound corresponding to compound [II] or a salt thereof, and converting the functional group thereof.

[0597]

Production method A2a: Another method for producing compound [I] or a salt thereof

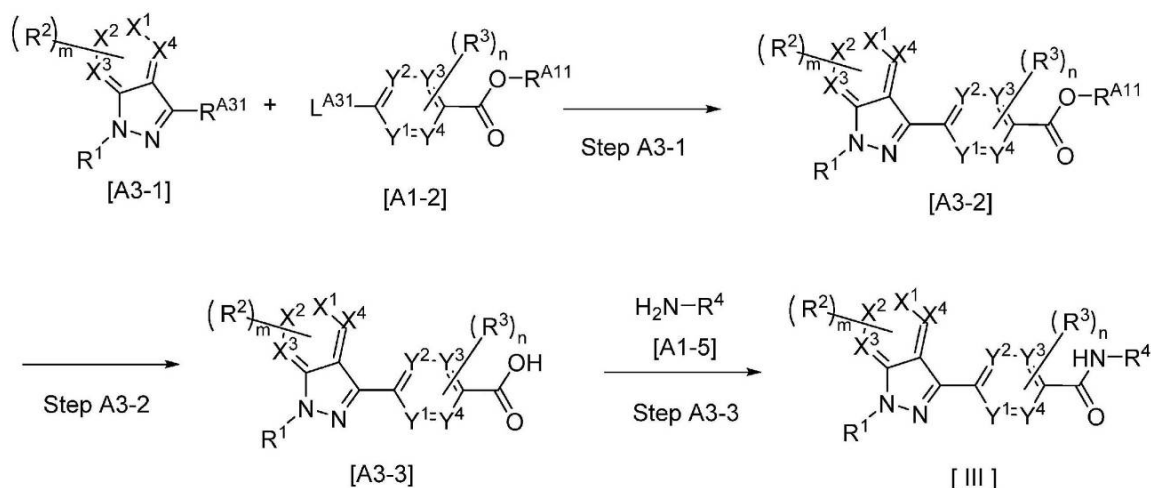
25 Compound [I] or a salt thereof can be produced by performing production method A2 by using compound [A1a-1] or a salt thereof instead of Compound [A1-1] or a salt thereof:

[0598]

Production method A3: Production method of compound [III] or a
30 salt thereof

Compound [III] or a salt thereof can be produced, for example, by the following production method A3.

[0599]



[0600]

wherein

X^1 , X^2 , X^3 , X^4 , Y^1 , Y^2 , Y^3 and Y^4 are each independently a carbon
 5 or a nitrogen atom (wherein the total number of the nitrogen
 atoms for X^1 , X^2 , X^3 and X^4 is 0 or 1, and the total number of
 the nitrogen atoms for Y^1 , Y^2 , Y^3 and Y^4 is 0, 1 or 2),
 L^{A31} is a leaving group {for example, halogen, boronic acid, and
 boronic acid ester (e.g., boronic acid pinacol ester)},
 10 R^{A31} is halogen, boronic acid, or boronic acid ester (e.g.,
 boronic acid pinacol ester)} (wherein when L^{A31} is halogen, R^{A31}
 is boronic acid or boronic acid ester, and when L^{A31} is boronic
 acid or boronic acid ester, R^{A31} is halogen), and
 R^1 , R^2 , R^3 , R^4 , R^{A11} , m and n are as defined above.

15 [0601]

(Step A3-1)

Compound [A3-2] or a salt thereof can be obtained by
 reacting compound [A3-1] or a salt thereof with compound [A1-2]
 or a salt thereof in a solvent in the presence of a base and a
 20 catalyst.

[0602]

Examples of the solvent include toluene, 1,4-dioxane,
 tetrahydrofuran, 1,2-dimethoxyethane, cyclopentyl methyl ether,
 N,N-dimethylformamide, N,N-dimethylacetamide, acetonitrile, and
 25 mixed solvents thereof with water. Preferred solvent is a
 mixed solvent of 1,2-dimethoxyethane and water.

[0603]

Examples of the base include potassium phosphate, sodium carbonate, sodium hydrogen carbonate, potassium carbonate, and tetrabutylammonium acetate. Preferred base is potassium
5 phosphate.

[0604]

Examples of the catalyst include palladium acetate, tetrakis triphenylphosphine palladium, bis(triphenylphosphine) palladium dichloride,
10 (bis(diphenylphosphino)ferrocene)palladium dichloride-dichloromethane complex, and (2-dicyclohexylphosphino-2',4',6'-triisopropyl-1,1'-biphenyl)[2-(2'-amino-1,1'-biphenyl)]palladium(II) methanesulfonate. Preferred catalyst
is (bis(diphenylphosphino)ferrocene)palladium dichloride-
15 dichloromethane complex.

[0605]

The reaction temperature is, for example, 70°C to 100°C.

[0606]

Compound [A3-1] or a salt thereof may be a commercially
20 available product, or produced from a commercially available product by a known method.

[0607]

(Step A3-2)

Compound [A3-3] or a salt thereof can be produced by
25 reacting compound [A3-2] or a salt thereof according to step A1-2.

[0608]

(Step A3-3)

Compound [III] or a salt thereof can be produced by
30 reacting compound [A3-3] or a salt thereof with compound [A1-5] or a salt thereof, according to step A1-3.

[0609]

Compound [III] or a salt thereof may also be produced by performing this production method by using, instead of compound
35 [A1-5] or a salt thereof, a compound having a functional group

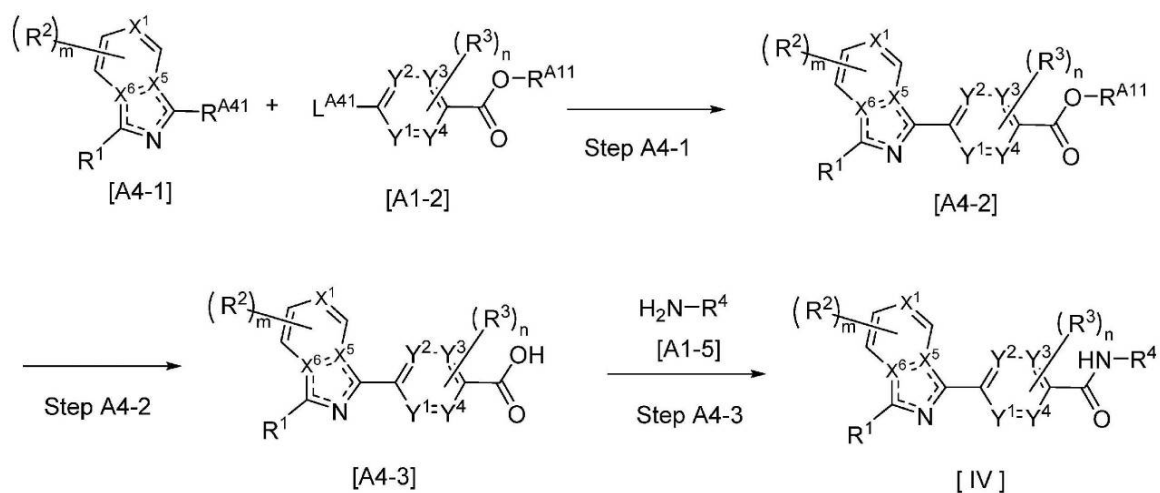
or a protected functional group or a salt thereof that can be converted to compound [A1-5] or a salt thereof by a known reaction to obtain a compound corresponding to compound [III] or a salt thereof, and converting the functional group thereof.

5 [0610]

Production method A4: Production method of compound [IV] or a salt thereof

Compound [IV] or a salt thereof can be produced, for example, by the following production method A4.

10 [0611]



[0612]

wherein

X^1 , X^5 , X^6 , Y^1 , Y^2 , Y^3 and Y^4 are each independently a carbon or
15 a nitrogen atom (wherein the total number of the nitrogen atoms for X^5 and X^6 is 1, and the total number of the nitrogen atoms for Y^1 , Y^2 , Y^3 and Y^4 is 0, 1 or 2),

L^{A41} is a leaving group {for example, halogen, boronic acid, and boronic acid ester (e.g., boronic acid pinacol ester)},

20 R^{A41} is hydrogen, halogen, boronic acid, or boronic acid ester (e.g., boronic acid pinacol ester)} (wherein when L^{A41} is halogen, R^{A41} is hydrogen, boronic acid or boronic acid ester, and when L^{A41} is boronic acid or boronic acid ester, R^{A41} is hydrogen or halogen), and

25 R^1 , R^2 , R^3 , R^4 , R^{A11} , m and n are as defined above.

[0613]

(Step A4-1)

Compound [A4-2] or a salt thereof can be produced by reacting compound [A4-1] or a salt thereof with compound [A1-2] or a salt thereof, according to step A3-1.

5 [0614]

Compound [A4-1] or a salt thereof may be a commercially available product, or produced from a commercially available product by a known method.

[0615]

10 (Step A4-2)

Compound [A4-3] or a salt thereof can be produced by reacting compound [A4-2] or a salt thereof according to step A1-2.

[0616]

15 (Step A4-3)

Compound [IV] or a salt thereof can be produced by reacting compound [A4-3] or a salt thereof with compound [A1-5] or a salt thereof, according to step A1-3.

[0617]

20 Compound [IV] or a salt thereof may also be produced by performing this production method by using, instead of compound [A1-5] or a salt thereof, a compound having a functional group or a protected functional group or a salt thereof that can be converted to compound [A1-5] or a salt thereof by a known
25 reaction to obtain a compound corresponding to compound [IV] or a salt thereof, and converting the functional group thereof.

[0618]

Production method B: Production method of compound [A1-5] or a salt thereof

30 [0619]

$\text{H}_2\text{N}-\text{R}^4$

[A1-5]

[0620]

wherein R^4 is as defined above.

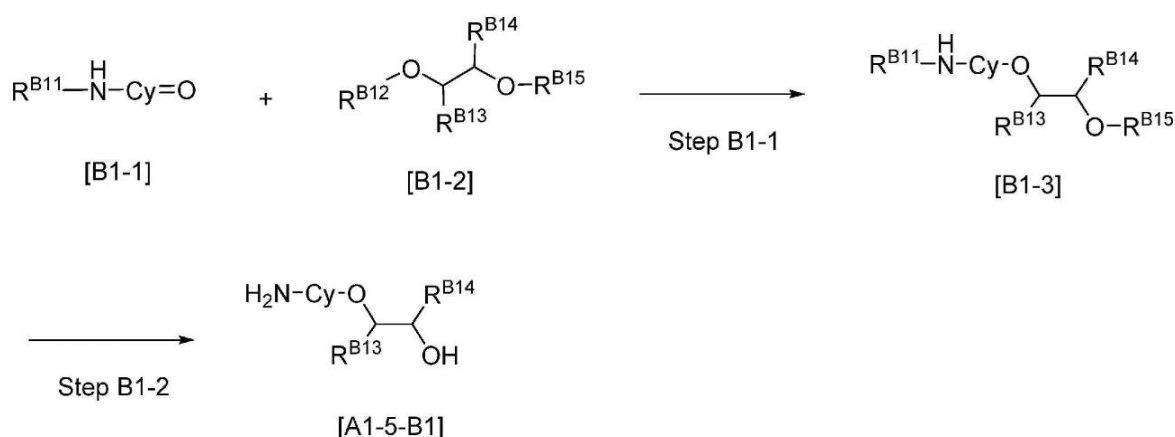
[0621]

In one embodiment, [A1-5] or a salt thereof can be obtained by the following production methods B1 to B4. In any production method, the starting material may be a commercially available product, or produced from a commercially available product by a known method.

[0622]

Production method B1: Production method of compound [A1-5-B1] or a salt thereof

10 [0623]



[0624]

wherein

R^{B11} is an amino-protecting group (e.g., benzyloxycarbonyl),
15 R^{B12} is a hydroxy-protecting group (e.g., trimethylsilyl),
 R^{B13} and R^{B14} are each independently hydrogen or C_{1-4} alkyl,
 R^{B15} is a hydroxy-protecting group (e.g., benzyl),
 $\text{Cy}=\text{O}$ is a group in which two hydrogens on the same carbon atom constituting ring Cy are substituted by oxo, and
20 ring Cy is as defined above.

[0625]

(Step B1-1)

Compound [B1-3] or a salt thereof can be produced by reacting compound [B1-1] or a salt thereof with compound [B1-2] or a salt thereof in a solvent in the presence of an acid and a
25 reducing agent.

[0626]

Examples of the acid include trimethylsilyl trifluoromethanesulfonate.

[0627]

Examples of the reducing agent include triethylsilane and
5 trimethylsilane. Preferred reducing agent is triethylsilane.

[0628]

Examples of the solvent include acetonitrile and dichloromethane. Preferred solvent is acetonitrile.

[0629]

10 The reaction temperature is, for example, 0°C to 10°C.

[0630]

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

15 [0631]

Compound [B1-2] or a salt thereof, commercially available product, or produced from a commercially available product by a known method.

[0632]

20 (Step B1-2)

Compound [A1-5-B1] or a salt thereof can be produced by removing R^{B11} and R^{B15} of compound [B1-3] or a salt thereof by a deprotection reaction. The deprotection reaction can be carried out under conditions suitable for the kind of each of
25 R^{B11} and R^{B15} . For example, when R^{B11} is benzyloxycarbonyl and R^{B15} is benzyl, compound [A1-5-B1] or a salt thereof can be obtained by subjecting compound [B1-3] or a salt thereof to a catalytic hydrogenation reaction. For example, compound [A1-5-B1] or a salt thereof can be obtained by reacting compound [B1-
30 2] or a salt thereof in a solvent under a hydrogen atmosphere in the presence of a catalyst.

[0633]

Examples of the solvent include methanol, ethanol, tetrahydrofuran, ethyl acetate, acetic acid, and mixed solvents
35 thereof. Preferred solvent is methanol.

[0634]

The pressure of hydrogen gas is, for example, 1 to 10 atm, preferably 1 to 4 atm.

[0635]

- 5 Examples of the catalyst include palladium-carbon and palladium hydroxide-carbon. Preferred catalyst is palladium hydroxide-carbon.

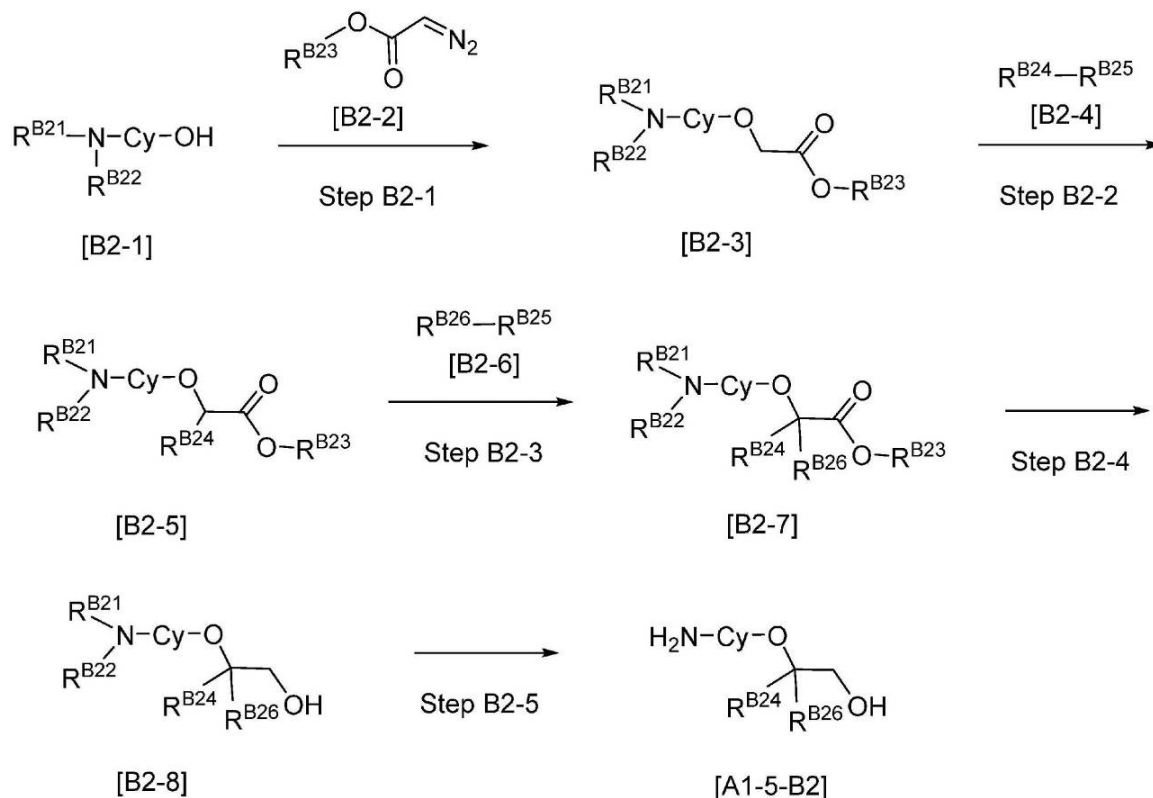
[0636]

The reaction temperature is, for example, 20°C to 30°C.

10 [0637]

Production method B2: Production method of compound [A1-5-B2] or a salt thereof

[0638]



15 [0639]

wherein

R^{B21} and R^{B22} are each independently an amino-protecting group (e.g., benzyl),

R^{B23} , R^{B24} and R^{B26} are each independently C_{1-4} alkyl,

20 R^{B25} are each independently halogen, and

ring Cy is as defined above.

[0640]

(Step B2-1)

Compound [B2-3] or a salt thereof can be obtained by
5 reacting compound [B2-1] or a salt thereof with compound [B2-2]
in a solvent in the presence of a metal catalyst.

[0641]

Examples of the solvent include dichloromethane.

[0642]

10 Examples of the metal catalyst include rhodium (II)
acetate and rhodium (II) octanoate. Preferred metal catalyst
is rhodium (II) acetate.

[0643]

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

15 [0644]

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

[0645]

20 Compound [B2-2] may be a commercially available product,
or produced from a commercially available product by a known
method.

[0646]

(Step B2-2)

25 Compound [B2-5] or a salt thereof can be obtained by
reacting compound [B2-3] or a salt thereof with compound [B2-4]
in a solvent in the presence of a base.

[0647]

Examples of the solvent include diethyl ether,
30 tetrahydrofuran, dimethoxyethane, benzene, toluene,
hexamethylphosphoric triamide, and mixed solvents thereof.
Preferred solvent is tetrahydrofuran.

[0648]

Examples of the base include potassium hexamethyl
35 disilazide, sodium hexamethyl disilazide, lithium hexamethyl

disilazide, and lithium diisopropylamide.

[0649]

The reaction temperature is, for example, -78°C to 30°C.

[0650]

5 Compound [B2-4] may be a commercially available product, or produced from a commercially available product by a known method.

[0651]

(Step B2-3)

10 Compound [B2-7] or a salt thereof can be obtained by reacting compound [B2-5] or a salt thereof with compound [B2-6], according to step B2-2.

[0652]

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

[0653]

(Step B2-4)

20 Compound [B2-8] or a salt thereof can be produced by reducing compound [B2-7] or a salt thereof in a solvent.

[0654]

Examples of the reducing agent include lithium aluminum hydride and sodium borohydride. Preferred reducing agent is lithium aluminum hydride.

25 [0655]

Examples of the solvent include tetrahydrofuran.

[0656]

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

30 [0657]

(Step B2-5)

Compound [A1-5-B2] or a salt thereof can be produced by removing R^{B21} and R^{B22} of compound [B2-8] or a salt thereof by a deprotection reaction. The deprotection reaction can be
35 carried out under conditions suitable for the kind of each of

R^{B21} and R^{B22}. For example, when R^{B21} and R^{B22} are each benzyl, compound [A1-5-B2] or a salt thereof can be obtained by reacting compound [B2-8] or a salt thereof in a solvent under a hydrogen atmosphere in the presence of a catalyst.

5 [0658]

Examples of the solvent include methanol, ethanol, tetrahydrofuran, ethyl acetate, acetic acid, and mixed solvents thereof. Preferred solvent is a mixed solvent of methanol and tetrahydrofuran.

10 [0659]

The pressure of hydrogen gas is, for example, 1 to 10 atm, preferably 1 to 4 atm.

[0660]

Examples of the catalyst include palladium-carbon and
15 palladium hydroxide-carbon. Preferred catalyst is palladium hydroxide-carbon.

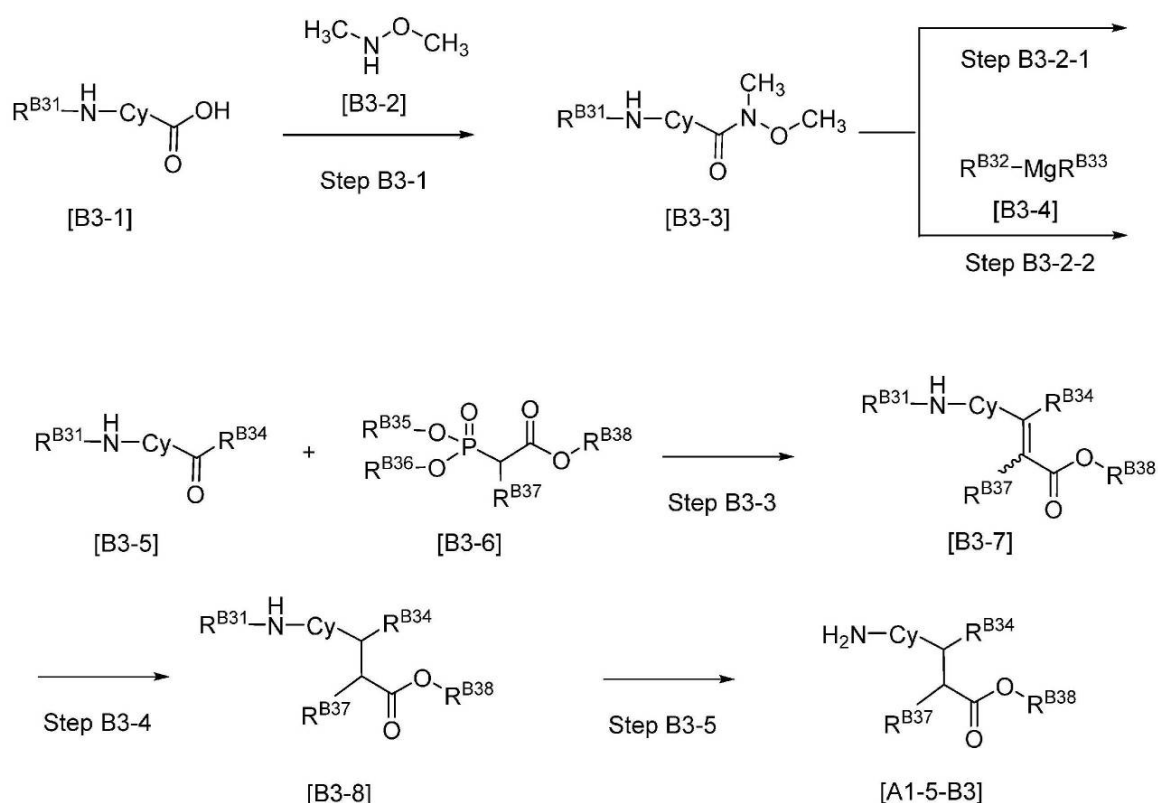
[0661]

The reaction temperature is, for example, 20°C to 30°C.

[0662]

20 Production method B3: Production method of compound [A1-5-B3]
or a salt thereof

[0663]



[0664]

wherein

- R^{B31} is an amino-protecting group (e.g., tert-butoxycarbonyl or
 5 benzyloxycarbonyl, preferably tert-butoxycarbonyl),
 R^{B32} and R^{B38} are each independently C_{1-4} alkyl,
 R^{B33} is halogen,
 R^{B34} , R^{B35} , R^{B36} and R^{B37} are each independently hydrogen or C_{1-4}
 alkyl, and
 10 ring Cy is as defined above.

[0665]

(Step B3-1)

Compound [B3-3] or a salt thereof can be obtained by
 reacting compound [B3-1] or a salt thereof with compound [B3-2]
 15 or a salt thereof in a solvent in the presence of a condensing
 agent and a base.

[0666]

Examples of the solvent include 1,4-dioxane,
 tetrahydrofuran, diethyl ether, 1,2-dimethoxyethane,
 20 cyclopentyl methyl ether, toluene, hexane, xylene,

dichloromethane, chloroform, N,N-dimethylformamide, N,N-dimethylacetamide, dimethyl sulfoxide, acetonitrile, pyridine, and mixed solvents thereof. Preferred solvent is N,N-dimethylformamide.

5 [0667]

Examples of the condensing agent include dicyclohexylcarbodiimide (DCC), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (WSC·HCl), diisopropyl carbodiimide, 1,1'-carbonyldiimidazole (CDI), O-(7-
10 azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (HATU), hexafluorophosphoric acid (benzotriazol-1-yloxy)tripyrrolidinophosphonium (PyBOP), (1-cyano-2-ethoxy-2-oxoethylideneaminoxy)dimethylaminomorpholinocarbenium
15 hexafluorophosphate (COMU), and diphenylphosphoryl azide. Preferred condensing agent is 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (WSC·HCl).
[0668]

Examples of the base include pyridine, triethylamine, and
20 N,N-diisopropylethylamine. Preferred base is N,N-diisopropylethylamine.
[0669]

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

25 [0670]

Compound [B3-1] or a salt thereof may be a commercially available product, or produced from a commercially available product by a known method.
[0671]

30 Compound [B3-2] or a salt thereof may be a commercially available product, or produced from a commercially available product by a known method.
[0672]

(Step B3-2-1)

35 When R^{B34} is hydrogen, compound [B3-5] or a salt thereof

can be obtained by reducing compound [B3-3] or a salt thereof in a solvent.

[0673]

Examples of the solvent include 1,4-dioxane,
5 tetrahydrofuran, diethyl ether, 1,2-dimethoxyethane, cyclopentyl methyl ether, and mixed solvents thereof. Preferred solvent is tetrahydrofuran.

[0674]

Examples of the reducing agent include diisobutylaluminum
10 hydride and lithium aluminum hydride. Preferred reducing agent is lithium aluminum hydride.

[0675]

The reaction temperature is, for example, -78°C to 40°C, preferably -78°C to 0°C.

15 [0676]

(Step B3-2-2)

When R^{B34} is C_{1-4} alkyl, compound [B3-5] or a salt thereof can be obtained by reacting compound [B3-3] or a salt thereof with compound [B3-4] in a solvent.

20 [0677]

Examples of the solvent include 1,4-dioxane, tetrahydrofuran, diethyl ether, 1,2-dimethoxyethane, cyclopentyl methyl ether, and mixed solvents thereof. Preferred solvent is tetrahydrofuran.

25 [0678]

The reaction temperature is, for example, -78°C to 40°C, preferably 0°C to 20°C.

[0679]

Compound [B3-4] may be a commercially available product,
30 or produced from a commercially available product by a known method.

[0680]

(Step B3-3)

Compound [B3-7] or a salt thereof can be obtained by
35 reacting compound [B3-5] or a salt thereof with compound [B3-6]

or a salt thereof in a solvent in the presence of a base.

[0681]

Examples of the solvent include tetrahydrofuran, dimethoxyethane, benzene, toluene, methanol, ethanol, and mixed
5 solvents thereof. Preferred solvent is tetrahydrofuran.

[0682]

Examples of the base include sodium hydride, sodium methoxide, sodium ethoxide, and n-butyllithium. Preferred base is sodium hydride.

10 [0683]

The reaction temperature is, for example, -78°C to 100°C, preferably 0°C to 70°C.

[0684]

Compound [B3-6] or a salt thereof may be a commercially
15 available product, or produced from a commercially available product by a known method.

[0685]

(Step B3-4)

Compound [B3-8] or a salt thereof can be obtained by
20 subjecting compound [B3-7] or a salt thereof to a catalytic hydrogenation reaction. For example, compound [B3-8] or a salt thereof can be obtained by reacting compound [B3-7] or a salt thereof in a solvent under a hydrogen atmosphere in the presence of a catalyst.

25 [0686]

Examples of the solvent include methanol, ethanol, tetrahydrofuran, ethyl acetate, acetic acid, and mixed solvents thereof. Preferred solvent is a mixed solvent of methanol and tetrahydrofuran.

30 [0687]

The pressure of hydrogen gas is, for example, 1 to 10 atm, preferably 1 to 4 atm.

[0688]

Examples of the catalyst include palladium-carbon and
35 palladium hydroxide-carbon. Preferred palladium catalyst is

palladium-carbon.

[0689]

The reaction temperature is, for example, 0°C to 70°C, preferably 0°C to 40°C.

5 [0690]

(Step B3-5)

Compound [A1-5-B3] or a salt thereof can be produced by removing R^{B31} of compound [B3-8] or a salt thereof by a deprotection reaction. The deprotection reaction can be

10 carried out under conditions suitable for the kind of R^{B31}. For example, when R^{B31} is tert-butoxycarbonyl, compound [A1-5-B3] or a salt thereof can be obtained by reacting compound [B3-8] or a salt thereof with an acid in a solvent.

[0691]

15 Examples of the solvent include ethyl acetate, 1,4-dioxane, methanol, cyclopentyl methyl ether, and mixed solvents thereof. Preferred solvent is ethyl acetate, methanol, or a mixed solvent thereof.

[0692]

20 Examples of the acid include hydrogen chloride, sulfuric acid, and trifluoroacetic acid. Preferred acid is hydrogen chloride.

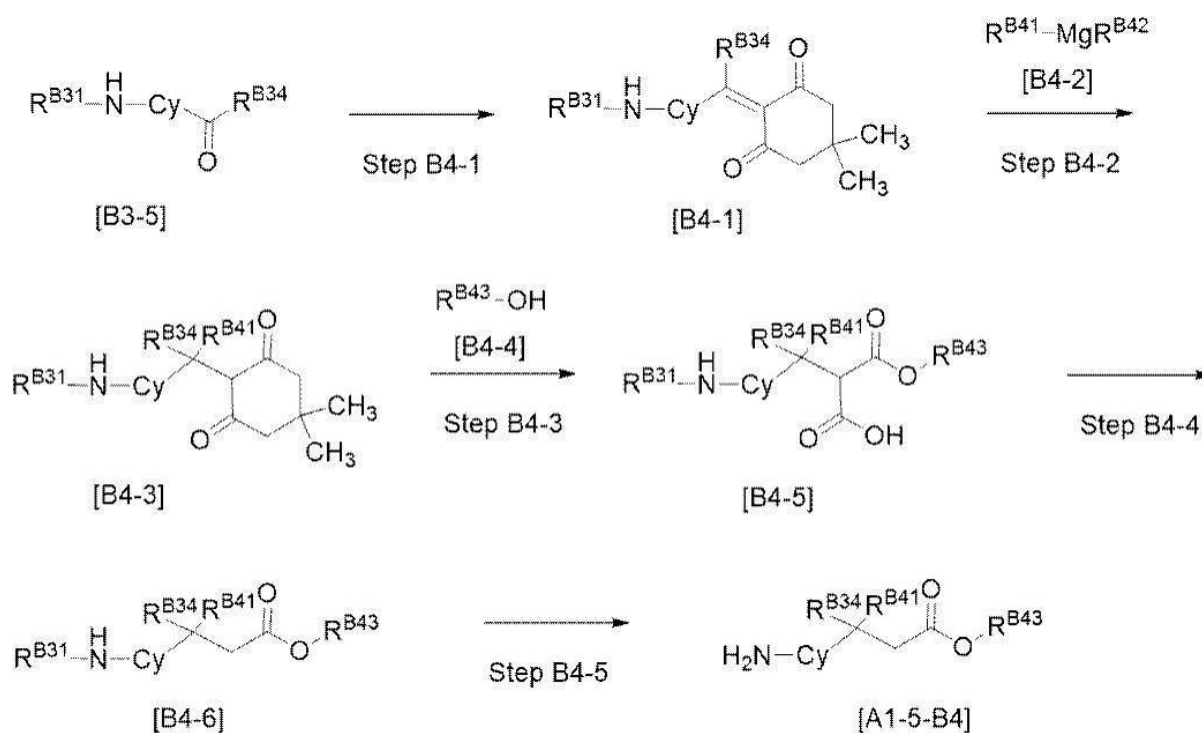
[0693]

The reaction temperature is, for example, 0°C to 50°C, preferably 0°C to 30°C.

25 [0694]

Production method B4: Production method of compound [A1-5-B4] or a salt thereof

[0695]



[0696]

wherein

R^{B41} and R^{B43} are each independently C_{1-4} alkyl,

5 R^{B42} is halogen, and

R^{B31} , R^{B34} and ring Cy are as defined above.

[0697]

(Step B4-1)

Compound [B4-1] or a salt thereof can be obtained by
 10 reacting compound [B3-5] or a salt thereof with Meldrum's acid
 in a solvent in the presence of Lewis acid and a base.

[0698]

Examples of the solvent include benzene, toluene,
 dichloromethane, chloroform, tetrahydrofuran, and mixed
 15 solvents thereof. Preferred solvent is tetrahydrofuran.

[0699]

Examples of the Lewis acid include titanium tetrachloride.

[0700]

Examples of the base include piperidine, morpholine, and
 20 pyridine. Preferred base is pyridine.

[0701]

The reaction temperature is, for example, $0^{\circ}C$ to $50^{\circ}C$,

preferably 0°C to 30°C.

[0702]

Compound [B3-5] or a salt thereof can be obtained according to production method B3, step B3-1, and step B3-2-1
5 or B3-2-2.

[0703]

(Step B4-2)

Compound [B4-3] or a salt thereof can be obtained by reacting compound [B4-1] or a salt thereof with compound [B4-2]
10 in a solvent. When R^{B34} is C₁₋₄ alkyl, it is preferable to add copper(I) bromide to the reaction system.

[0704]

Examples of the solvent include diethyl ether, tetrahydrofuran, dimethoxyethane, and mixed solvents thereof.
15 Preferred solvent is tetrahydrofuran.

[0705]

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

[0706]

Compound [B4-2] may be a commercially available product,
20 or produced from a commercially available product by a known method.

[0707]

(Step B4-3)

Compound [B4-5] or a salt thereof can be obtained by
25 reacting compound [B4-3] or a salt thereof in solvent [B4-4].

[0708]

Examples of the solvent [B4-4] include methanol, ethanol, and tert-butyl alcohol. Preferred solvent [B4-4] is methanol.

[0709]

30 The reaction temperature is, for example, 20°C to 110°C, preferably 60°C to 100°C.

[0710]

(Step B4-4)

Compound [B4-6] or a salt thereof can be obtained by
35 reacting compound [B4-5] or a salt thereof in a solvent in the

presence of sodium chloride.

[0711]

Examples of the solvent include dimethyl sulfoxide, water,
and mixed solvents thereof. Preferred solvent is a mixed
5 solvent of dimethyl sulfoxide and water.

[0712]

The reaction temperature is, for example, 100°C to 160°C,
preferably 120°C to 150°C.

[0713]

10 (Step B4-5)

Compound [A1-5-B4] or a salt thereof can be produced by
removing R^{B31} of compound [B4-6] or a salt thereof by a
deprotection reaction according to step B3-5.

[Examples]

15 [0714]

The method for producing the compound of the present
invention or a pharmaceutically acceptable salt thereof is
specifically described below. However, the production method
of the compound of the present invention or a pharmaceutically
20 acceptable salt thereof is not limited to the following.

[0715]

The compound obtained in each step can be isolated and/or
purified as necessary by known methods such as distillation,
recrystallization, and column chromatography. In some cases,
25 the compound can proceed to the next step without isolation
and/or purification.

[0716]

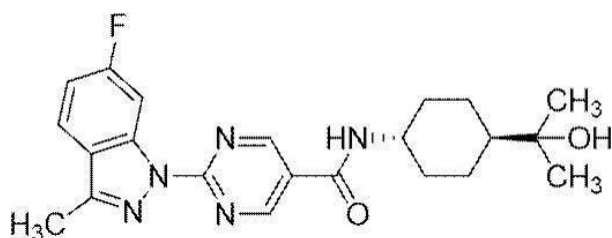
In the present specification, the room temperature refers
to a temperature in the state where the temperature is not
30 controlled, and one embodiment is 1°C to 40°C.

NMR was measured at 400 MHz.

[0717]

[Production Example 1] Example 1: Production of 2-(6-fluoro-3-
methyl-1H-indazol-1-yl)-N-(trans-4-(2-hydroxypropan-2-
35 yl)cyclohexyl)pyrimidine-5-carboxamide

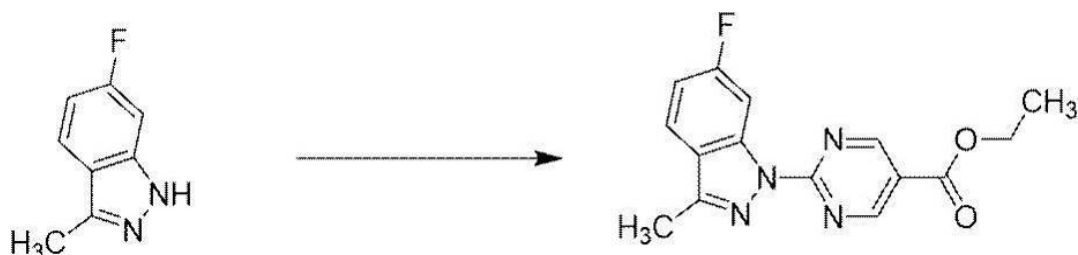
[0718]



[0719]

Step 1-1: Ethyl 2-(6-fluoro-3-methyl-1H-indazol-1-yl)pyrimidine-5-carboxylate

[0720]



[0721]

A suspension of 6-fluoro-3-methyl-1H-indazole (200 mg), ethyl 2-chloropyrimidine-carboxylate (161 mg) and cesium carbonate (698 mg) in N,N-dimethylformamide (2.0 mL) was stirred at 90°C for 4 hr. To the reaction mixture was added water at room temperature, and the precipitated solid was collected by filtration and dried under reduced pressure at 70°C to give the title compound (158 mg).
¹H-NMR (DMSO-D₆) δ: 9.28 (2H, s), 8.42 (1H, dd, J = 10.5, 2.2 Hz), 7.94 (1H, dd, J = 8.2, 5.2 Hz), 7.30 (1H, ddd, J = 10.5, 8.2, 2.2 Hz), 4.40 (2H, q, J = 7.2 Hz), 2.61 (3H, s), 1.37 (3H, t, J = 7.2 Hz).

[0722]

Step 1-2: 2-(6-Fluoro-3-methyl-1H-indazol-1-yl)pyrimidine-5-carboxylic acid

[0723]



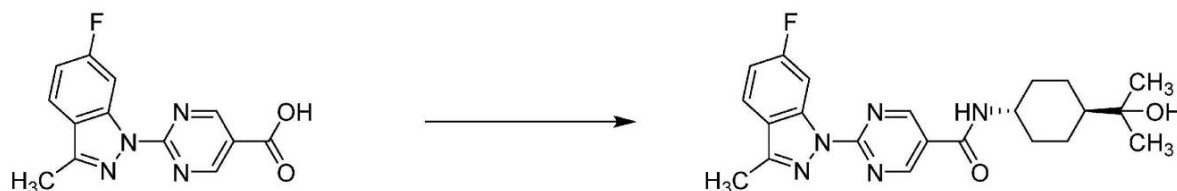
[0724]

To a suspension of ethyl 2-(6-fluoro-3-methyl-1H-indazol-1-yl)pyrimidine-5-carboxylate (158 mg) in
 5 methanol/tetrahydrofuran (2.37 mL,
 methanol/tetrahydrofuran=1/2) was added 4 M aqueous sodium
 hydroxide solution (0.263 mL) at room temperature, and the
 mixture was stirred for 2 hr. To the reaction mixture were
 added 2 M hydrochloric acid (0.526 mL) and water at room
 10 temperature, and the precipitated solid was collected by
 filtration and dried under reduced pressure at 70°C to give a
 crude product (65.6 mg) containing the title compound.

[0725]

Step 1-3: 2-(6-Fluoro-3-methyl-1H-indazol-1-yl)-N-(trans-4-(2-
 15 hydroxypropan-2-yl)cyclohexyl)pyrimidine-5-carboxamide

[0726]



[0727]

To a suspension of a crude product (30 mg) containing 2-
 20 (6-fluoro-3-methyl-1H-indazol-1-yl)pyrimidine-5-carboxylic acid,
 2-(trans-4-aminocyclohexyl)propan-2-ol (22.53 mg) and
 triethylamine (0.023 mL) in N,N-dimethylformamide (0.6 mL) were
 added 1-hydroxy-7-azabenzotriazole (4.5 mg) and 1-ethyl-3-(3-
 dimethylaminopropyl)carbodiimide hydrochloride (31.7 mg) at
 25 room temperature, and the mixture was stirred for 30 min, left
 standing overnight, and further stirred for 6 hr. To the
 reaction mixture were added water and ethyl acetate at room

temperature, and the layers were separated. The aqueous layer was extracted once with ethyl acetate. The combined organic layer was washed twice with water and concentrated under reduced pressure. To the residue was added ethyl acetate, and
5 slurry purification was performed. The solid was collected by filtration and dried under reduced pressure at 70°C to give the title compound (8.5 mg).

¹H-NMR (DMSO-D₆)δ: 9.23 (2H, s), 8.54 (1H, d, J = 8.2 Hz), 8.40 (1H, dd, J = 10.2, 2.0 Hz), 7.94 (1H, dd, J = 8.6, 5.6 Hz),
10 7.29 (1H, ddd, J = 10.2, 8.6, 2.0 Hz), 4.05 (1H, br s), 3.81-3.68 (1H, m), 2.61 (3H, s), 1.96 (2H, d, J = 10.5 Hz), 1.86 (2H, d, J = 10.5 Hz), 1.40-1.26 (2H, m), 1.25-1.00 (3H, m), 1.06 (6H, s). MS (M+H):412 MS (M-H):410

[0728]

15 Step 1-4: 2-(6-Fluoro-3-methyl-1H-indazol-1-yl)pyrimidine-5-carboxylic acid

[0729]



[0730]

20 To a suspension of ethyl 2-(6-fluoro-3-methyl-1H-indazol-1-yl)pyrimidine-5-carboxylate (177.68 g) synthesized in the same manner as in step 1-1 in tetrahydrofuran/water (2.132 L, tetrahydrofuran/water=2/1) was added dropwise 4 M aqueous lithium hydroxide solution (192 mL) at room temperature, and
25 the mixture was stirred under a nitrogen stream for 2 hr. To the reaction mixture were successively added dropwise 2 M hydrochloric acid (385 mL) and water (1060 mL) at room temperature, and the mixture was stirred for 6 hr and left standing overnight. The precipitated solid was collected by
30 filtration, washed with water (1440 mL), air dried for 3 days, and dried under reduced pressure at 60°C to give the title

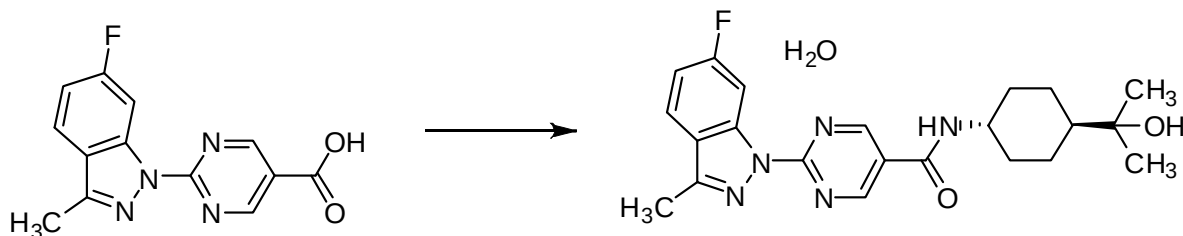
compound (166.22 g).

[0731]

Step 1-5: 2-(6-Fluoro-3-methyl-1H-indazol-1-yl)-N-(trans-4-(2-hydroxypropan-2-yl)cyclohexyl)pyrimidine-5-carboxamide

5 monohydrate

[0732]



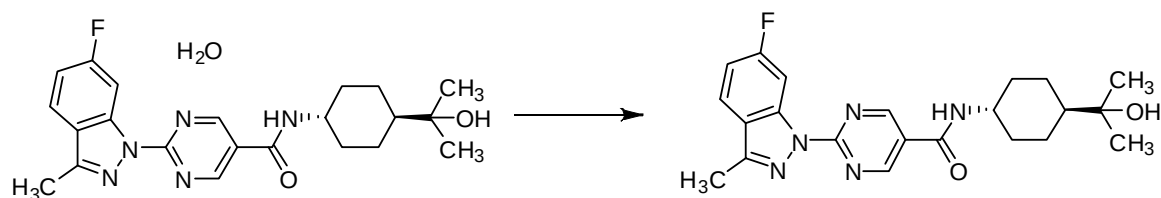
[0733]

To a suspension of 2-(6-fluoro-3-methyl-1H-indazol-1-yl)pyrimidine-5-carboxylic acid (150 g), 2-(trans-4-aminocyclohexyl)propan-2-ol (104 g) and 1-hydroxy-7-azabenzotriazole (75 g) in N,N-dimethylformamide (1.95 L) were added triethylamine (115 mL), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (158 g) and N,N-dimethylformamide (75 mL) at room temperature, and the mixture was stirred under a nitrogen stream for 5 hr. To the reaction mixture were added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (52.8 g) and N,N-dimethylformamide (75 mL) at room temperature, and the mixture was stirred under a nitrogen stream overnight. To the reaction mixture was added dropwise 5.0 wt% aqueous sodium hydrogen carbonate solution (4.2 L) at room temperature, and the mixture was stirred for 2 hr. The solid was collected by filtration, washed with water (1.5 L), air dried for 2 days, and dried under reduced pressure at 60°C to give the title compound as crystals (α crystal, 219.92 g).

[0734]

Step 1-6: 2-(6-Fluoro-3-methyl-1H-indazol-1-yl)-N-(trans-4-(2-hydroxypropan-2-yl)cyclohexyl)pyrimidine-5-carboxamide

30 [0735]



[0736]

A suspension of 2-(6-fluoro-3-methyl-1H-indazol-1-yl)-N-(trans-4-(2-hydroxypropan-2-yl)cyclohexyl)pyrimidine-5-carboxamide monohydrate crystal (α crystal, 37.4 g) in acetonitrile (748 mL) was stirred for 2 days under an argon atmosphere at room temperature. The precipitated solid was collected by pressure filtration with nitrogen and dried under reduced pressure at 60°C to give the title compound as crystals (β crystal, 34.42 g).

[0737]

Step 1-7: 2-(6-Fluoro-3-methyl-1H-indazol-1-yl)-N-(trans-4-(2-hydroxypropan-2-yl)cyclohexyl)pyrimidine-5-carboxamide monohydrate

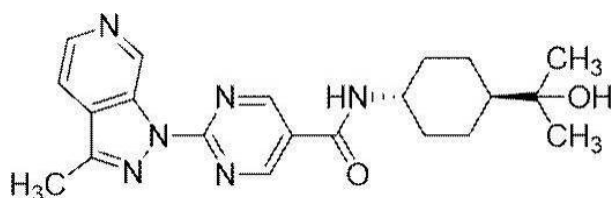
[0738]

A suspension of 2-(6-fluoro-3-methyl-1H-indazol-1-yl)-N-(trans-4-(2-hydroxypropan-2-yl)cyclohexyl)pyrimidine-5-carboxamide monohydrate crystal (α crystal, 500 mg) in tetrahydrofuran/water (6.0 mL, tetrahydrofuran/water=5/1) was stirred at 75°C until it became a solution. To the reaction mixture was added dropwise water (4.0 mL) at the same temperature, and the mixture was stirred for 30 min, cooled to room temperature, and stirred for 1 hr. To the reaction mixture was added dropwise water (5.0 mL) at room temperature, and the mixture was stirred for 3 hr. The precipitated solid was collected by filtration and dried under reduced pressure to give the title compound as crystals (γ crystal, 466.6 mg).

[0739]

[Production Example 2] Example 2: Production of N-(trans-4-(2-hydroxy-2-methylpropyl)cyclohexyl)-2-(3-methyl-1H-pyrazolo[3,4-c]pyridin-1-yl)pyrimidine-5-carboxamide

[0740]



[0741]

Step 2-1: tert-Butyl 2-chloropyrimidine-5-carboxylate

[0742]



[0743]

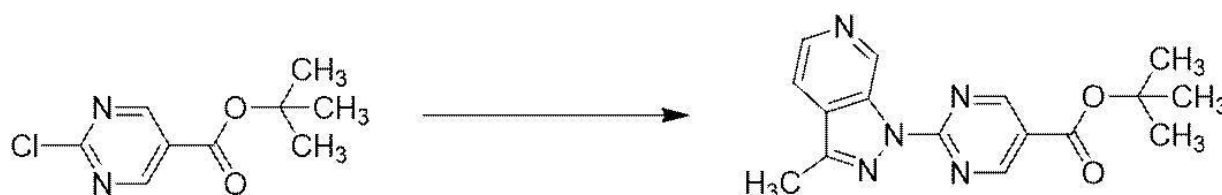
To a solution of 2-chloropyrimidine-5-carboxylic acid (2.0 g) and N,N-dimethyl-4-aminopyridine (0.462 g) in tert-butyl alcohol/chloroform (30 mL, tert-butyl
 10 alcohol/chloroform=2/1) was added di-tert-butyl bicarbonate (5.51 g) at room temperature, and the mixture was stirred at 60°C for 90 min and left standing overnight. To the reaction mixture was added ethyl acetate at room temperature, and the organic layer was washed successively with saturated aqueous
 15 sodium hydrogen carbonate, aqueous citric acid solution and saturated brine. The organic layer was dried over sodium sulfate, sodium sulfate was removed by filtration, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluent: n-
 20 hexane/ethyl acetate) to give the title compound (990 mg).

¹H-NMR (DMSO-D₆) δ: 9.13 (2H, s), 1.57 (9H, s).

[0744]

Step 2-2: tert-Butyl 2-(3-methyl-1H-pyrazolo[3,4-c]pyridin-1-yl)pyrimidine-5-carboxylate

25 [0745]

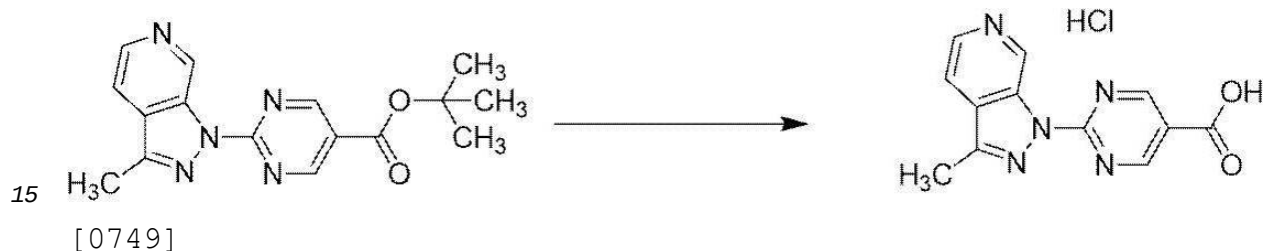


[0746]

A suspension of tert-butyl 2-chloropyrimidine-5-carboxylate (100 mg), 3-methyl-1H-pyrazolo[3,4-c]pyridine (62 mg) and cesium carbonate (182 mg) in N,N-dimethylformamide (1.0 mL) was stirred at room temperature for 30 min and left standing overnight. To the reaction mixture was added water at room temperature, and the precipitated solid was collected by filtration and dried under reduced pressure at 70°C to give the title compound (130 mg).

¹H-NMR (DMSO-D₆) δ: 10.01 (1H, s), 9.29 (2H, s), 8.55 (1H, d, J = 5.2 Hz), 7.95 (1H, d, J = 5.2 Hz), 2.67 (3H, s), 1.61 (9H, s).
[0747]

Step 2-3: 2-(3-Methyl-1H-pyrazolo[3,4-c]pyridin-1-yl)pyrimidine-5-carboxylic acid monohydrochloride
[0748]

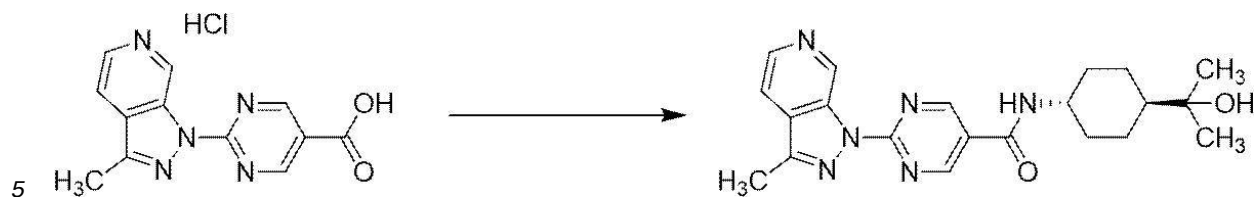


To a suspension of tert-butyl 2-(3-methyl-1H-pyrazolo[3,4-c]pyridin-1-yl)pyrimidine-5-carboxylate (130 mg) in ethyl acetate (0.26 mL) was added 4 M hydrogen chloride/ethyl acetate solution (1.3 mL) at room temperature, and the mixture was stirred for 6 hr and left standing overnight. The reaction mixture was concentrated under reduced pressure. To the residue was added trifluoroacetic acid (0.65 mL) at room temperature, and the mixture was stirred for 5 hr and left standing overnight. To the reaction mixture was added 4 M hydrogen chloride/ethyl acetate solution at room temperature, and the precipitated solid was collected by filtration, and dried under reduced pressure at 70°C to give the title compound (97.8 mg).

30 ¹H-NMR (DMSO-D₆) δ: 13.73 (1H, br s), 10.06 (1H, s), 9.34 (2H, s), 8.62 (1H, d, J = 5.5 Hz), 8.15-8.08 (1H, m), 2.70 (3H, s).
[0750]

Step 2-4: N-(Trans-4-(2-hydroxy-2-methylpropyl)cyclohexyl)-2-(3-methyl-1H-pyrazolo[3,4-c]pyridin-1-yl)pyrimidine-5-carboxamide

[0751]



[0752]

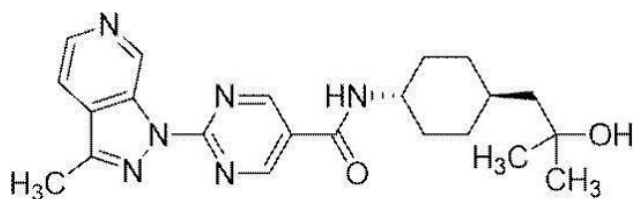
To a suspension of 2-(3-methyl-1H-pyrazolo[3,4-c]pyridin-1-yl)pyrimidine-5-carboxylic acid monohydrochloride (30 mg), 2-(trans-4-aminocyclohexyl)propan-2-ol (19.41 mg), 1-hydroxy-7-azabenzotriazole (4.2 mg) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (29.6 mg) in N,N-dimethylformamide (0.6 mL) was added triethylamine (0.0215 mL) at room temperature, and the mixture was stirred for 45 min and left standing overnight. The reaction mixture was purified by reversed-phase silica gel column chromatography (eluent: water/acetonitrile=95/5 to 0/100) to give the title compound (35.1 mg).

¹H-NMR (DMSO-D₆) δ: 9.99 (1H, s), 9.28 (2H, s), 8.58 (1H, d, J = 7.6 Hz), 8.53 (1H, d, J = 5.3 Hz), 7.94 (1H, d, J = 5.3 Hz), 4.05 (1H, br s), 3.81-3.68 (1H, m), 2.66 (3H, s), 1.97 (2H, d, J = 10.2 Hz), 1.86 (2H, d, J = 10.2 Hz), 1.40-1.26 (2H, m), 1.25-1.03 (3H, m), 1.06 (6H, s). MS (M+H):395 MS (M-H):393

[0753]

[Production Example 3] Example 3: Production of N-(trans-4-(2-hydroxy-2-methylpropyl)cyclohexyl)-2-(3-methyl-1H-pyrazolo[3,4-c]pyridin-1-yl)pyrimidine-5-carboxamide

[0754]



[0755]

Step 3-1: tert-Butyl 2-chloropyrimidine-5-carboxylate
[0756]

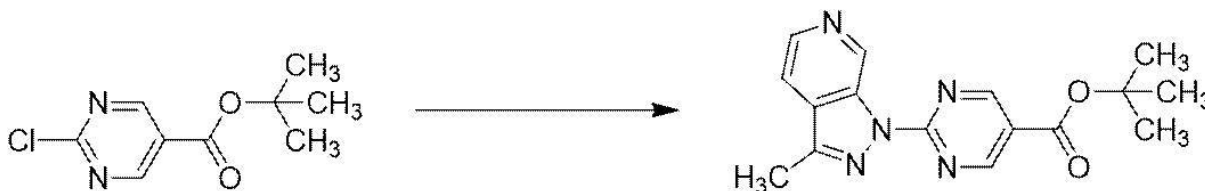


[0757]

5 To a solution of 2-chloropyrimidine-5-carboxylic acid (2.0 g) and N,N-dimethyl-4-aminopyridine (0.462 g) in tert-butyl alcohol/chloroform (30 mL, tert-butyl alcohol/chloroform=2/1) was added di-tert-butyl bicarbonate (5.51 g) at room temperature, and the mixture was stirred at
10 60°C for 90 min and left standing overnight. To the reaction mixture was added ethyl acetate at room temperature, and the organic layer was washed successively with saturated aqueous sodium hydrogen carbonate, aqueous citric acid solution and saturated brine. The organic layer was dried over sodium
15 sulfate, sodium sulfate was removed by filtration, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluent: n-hexane/ethyl acetate) to give the title compound (990 mg).
¹H-NMR (DMSO-D₆) δ: 9.13 (2H, s), 1.57 (9H, s).

20 [0758]

Step 3-2: tert-Butyl 2-(3-methyl-1H-pyrazolo[3,4-c]pyridin-1-yl)pyrimidine-5-carboxylate
[0759]



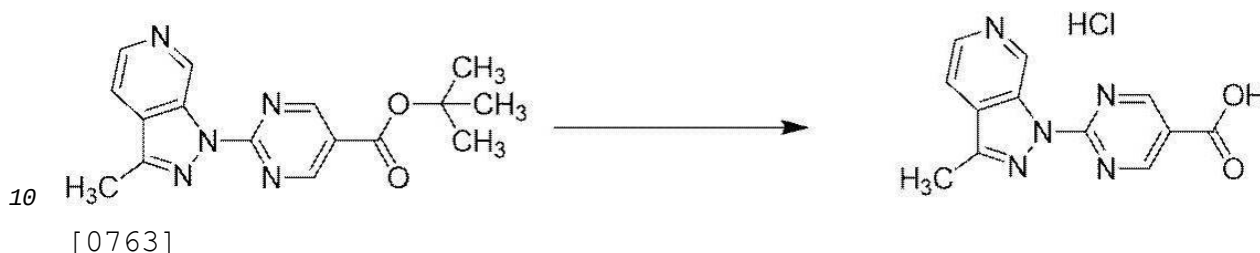
25 [0760]

A suspension of tert-butyl 2-chloropyrimidine-5-carboxylate (100 mg), 3-methyl-1H-pyrazolo[3,4-c]pyridine (62 mg) and cesium carbonate (182 mg) in N,N-dimethylformamide (1.0 mL) was stirred at room temperature for 30 min and left
30 standing overnight. To the reaction mixture was added water at

room temperature, and the precipitated solid was collected by filtration and dried under reduced pressure at 70°C to give the title compound (130 mg).

¹H-NMR (DMSO-D₆) δ: 10.01 (1H, s), 9.29 (2H, s), 8.55 (1H, d, J = 5.2 Hz), 7.95 (1H, d, J = 5.2 Hz), 2.67 (3H, s), 1.61 (9H, s).
[0761]

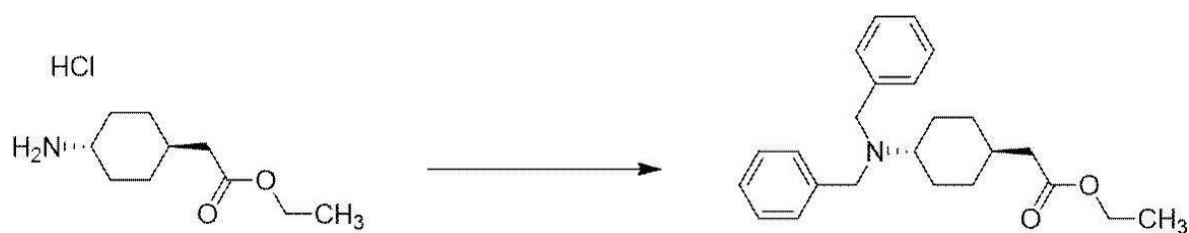
Step 3-3: 2-(3-Methyl-1H-pyrazolo[3,4-c]pyridin-1-yl)pyrimidine-5-carboxylic acid monohydrochloride
[0762]



To a suspension of tert-butyl 2-(3-methyl-1H-pyrazolo[3,4-c]pyridin-1-yl)pyrimidine-5-carboxylate (130 mg) in ethyl acetate (0.26 mL) was added 4 M hydrogen
15 chloride/ethyl acetate solution (1.3 mL) at room temperature, and the mixture was stirred for 6 hr and left standing overnight. The reaction mixture was concentrated under reduced pressure. To the residue was added trifluoroacetic acid (0.65 mL) at room temperature, and the mixture was stirred for 5 hr
20 and left standing overnight. To the reaction mixture was added 4 M hydrogen chloride/ethyl acetate solution at room temperature, and the precipitated solid was collected by filtration and dried under reduced pressure at 70°C to give the title compound (97.8 mg).

25 ¹H-NMR (DMSO-D₆) δ: 13.73 (1H, br s), 10.06 (1H, s), 9.34 (2H, s), 8.62 (1H, d, J = 5.5 Hz), 8.15-8.08 (1H, m), 2.70 (3H, s).
[0764]

Step 3-4: Ethyl 2-(trans-4-(dibenzylamino)cyclohexyl)acetate
[0765]



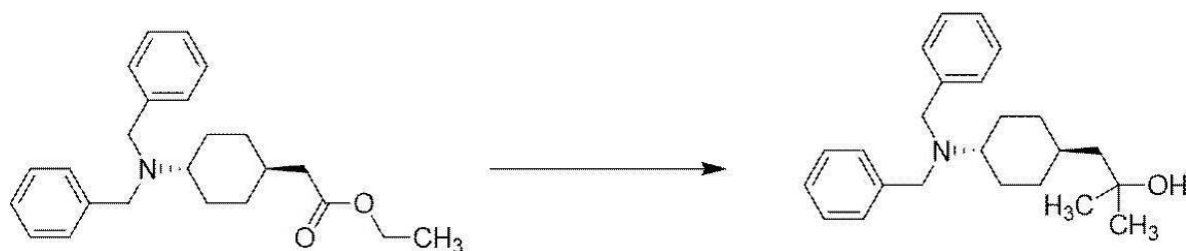
[0766]

To a suspension of ethyl 2-(trans-4-aminocyclohexyl)acetate monohydrochloride (3.0 g) and potassium carbonate (5.99 g) in acetonitrile (30 mL) was added benzyl bromide (3.4 mL) at room temperature, and the mixture was stirred overnight. To the reaction mixture were added water (30 mL) and ethyl acetate (30 mL) at room temperature, and the layers were separated. The aqueous layer was extracted with ethyl acetate (10 mL). The combined organic layer was washed with saturated brine, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluent: n-hexane/ethyl acetate=96/4 to 74/26) to give a crude product (5.068 g) containing the title compound.

15 [0767]

Step 3-5: 1-(Trans-4-(dibenzylamino)cyclohexyl)-2-methylpropan-2-ol

[0768]



20 [0769]

To a solution of the crude product containing ethyl 2-(trans-4-(dibenzylamino)cyclohexyl)acetate crude product (3.847 g) in tetrahydrofuran (20 mL) was added 3.0 M tetrahydrofuran solution (11 mL) of methylmagnesium bromide under ice-cooling, and the mixture was allowed to gradually return to room temperature and stirred overnight. To the reaction mixture were added saturated aqueous ammonium chloride solution (15 mL)

and ethyl acetate (20 mL) under ice-cooling. After partitioning, the organic layer was washed with saturated brine, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluent: n-hexane/ethyl acetate=94/6 to 53/47) to give the title compound (1.45 g).

¹H-NMR (DMSO-D₆) δ: 7.35-7.26 (8H, m), 7.21-7.17 (2H, m), 3.96 (1H, s), 3.57 (4H, s), 2.38-2.31 (1H, m), 1.85-1.76 (4H, m), 1.42-1.31 (3H, m), 1.21-1.15 (2H, m), 1.06 (6H, s), 0.82-0.73 (2H, m).

[0770]

Step 3-6: 1-(Trans-4-aminocyclohexyl)-2-methylpropan-2-ol

[0771]



[0772]

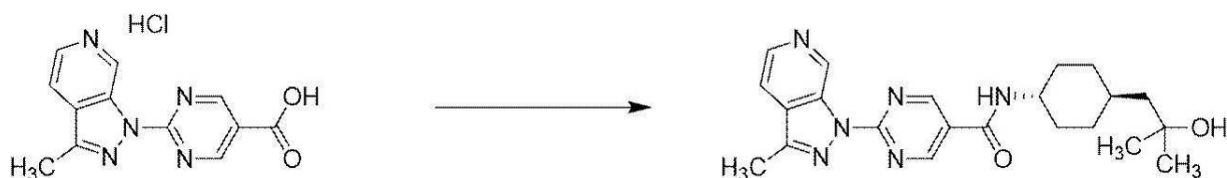
To a solution of 1-(trans-4-(dibenzylamino)cyclohexyl)-2-methylpropan-2-ol (1.45 g) in methanol (20 mL) was added 20% palladium hydroxide-carbon (368 mg) at room temperature. Under 1 atm hydrogen atmosphere, the mixture was stirred at room temperature overnight. The reaction mixture was filtered through celite, and the filtrate was concentrated under reduced pressure to give the title compound (692 mg).

¹H-NMR (DMSO-D₆) δ: 3.98 (1H, br s), 2.44-2.37 (1H, m), 1.76-1.67 (4H, m), 1.47 (2H, br s), 1.34-1.22 (4H, m), 1.07 (6H, s), 0.99-0.84 (3H, m).

[0773]

Step 3-7: N-(Trans-4-(2-hydroxy-2-methylpropyl)cyclohexyl)-2-(3-methyl-1H-pyrazolo[3,4-c]pyridin-1-yl)pyrimidine-5-carboxamide

[0774]



[0775]

To a suspension of 2-(3-methyl-1H-pyrazolo[3,4-c]pyridin-1-yl)pyrimidine-5-carboxylic acid monohydrochloride (30 mg), 1-
 5 (trans-4-aminocyclohexyl)-2-methylpropan-2-ol (21.14 mg), 1-hydroxy-7-azabenzotriazole (4.5 mg) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (31.7 mg) in N,N-dimethylformamide (0.6 mL) was added triethylamine (0.0215 mL) at room temperature, and the mixture was stirred for 45 min
 10 and left standing overnight. The reaction mixture was purified by reversed-phase silica gel column chromatography (eluent: water/acetonitrile=95/5 to 0/100) to give the title compound (22.4 mg).

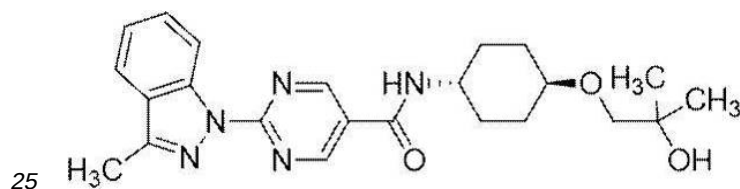
¹H-NMR (DMSO-D₆) δ: 9.99 (1H, s), 9.27 (2H, s), 8.56 (1H, d, J = 7.6 Hz), 8.53 (1H, d, J = 5.3 Hz), 7.94 (1H, d, J = 5.3 Hz), 4.04 (1H, br s), 3.82-3.69 (1H, m), 2.66 (3H, s), 1.88 (4H, d, J = 10.6 Hz), 1.50-1.22 (5H, m), 1.21-0.98 (2H, m), 1.11 (6H, s).

MS (M+H): 409 MS (M-H): 407

20 [0776]

[Production Example 4] Example 4: Production of N-(trans-4-(2-hydroxy-2-methylpropoxy)cyclohexyl)-2-(3-methyl-1H-indazol-1-yl)pyrimidine-5-carboxamide

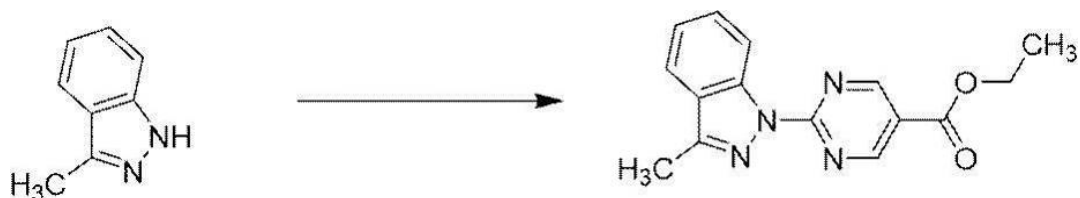
[0777]



[0778]

Step 4-1: Ethyl 2-(3-methyl-1H-indazol-1-yl)pyrimidine-5-carboxylate

[0779]



[0780]

A suspension of 3-methyl-1H-indazole (5.0 g), ethyl 2-chloropyrimidine-carboxylate (8.47 g) and cesium carbonate (24.65 g) in N,N-dimethylformamide (25 mL) was stirred at 90°C for 3 hr. To the reaction mixture were added water, ethyl acetate and chloroform at room temperature, and the layers were separated. The aqueous layer was extracted once with ethyl acetate. The combined organic layer was washed with saturated brine, and dried over magnesium sulfate. Magnesium sulfate was removed by filtration, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluent: n-hexane/ethyl acetate=85/15 to 0/100) to give a crude product (9.5 g) containing the title compound. To the crude product (9.5 g) containing the title compound was added n-hexane/ethyl acetate (30 mL, n-hexane/ethyl acetate=1/2), and slurry purification was performed. The solid was collected by filtration and dried under reduced pressure to give a crude product (7.8 g) containing the title compound. A solution of the crude product (7.8 g) containing the title compound in chloroform was purified by silica gel column chromatography (eluent: chloroform) to give the title compound (6.4 g).

¹H-NMR (DMSO-D₆) δ: 9.26 (2H, s), 8.69-8.67 (1H, m), 7.90-7.88 (1H, m), 7.66-7.62 (1H, m), 7.43-7.39 (1H, m), 4.39 (2H, q, J = 7.1 Hz), 2.62 (3H, s), 1.37 (3H, t, J = 7.2 Hz).

[0781]

Step 4-2: 2-(3-Methyl-1H-indazol-1-yl)pyrimidine-5-carboxylic acid

[0782]



[0783]

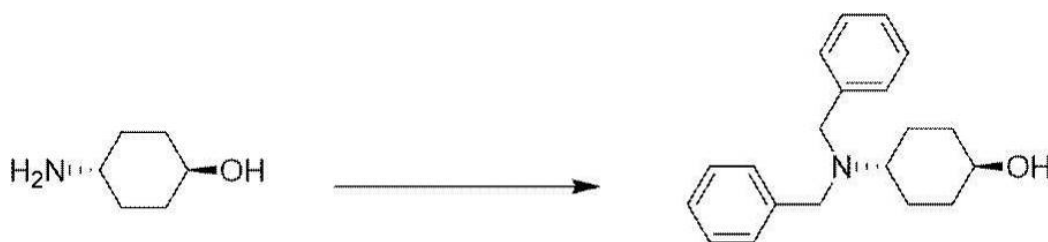
To a solution of ethyl 2-(3-methyl-1H-indazol-1-yl)pyrimidine-5-carboxylate (3.0 g) in tetrahydrofuran (60 mL) was added 2 M aqueous sodium hydroxide solution (15.94 mL) at room temperature, and the mixture was stirred for 3 hr. To the reaction mixture was added 2 M aqueous sodium hydroxide solution (5.31 mL) at room temperature, and the mixture was stirred for 1 hr and left standing overnight. To the reaction mixture was added 2 M hydrochloric acid (21.25 mL) at room temperature, and the mixture was stirred for 30 min. To the reaction mixture was added water at room temperature, and the mixture was stirred for 30 min. The precipitated solid was collected by filtration and dried under reduced pressure to give the title compound (2.47 g).

$^1\text{H-NMR}$ ($\text{DMSO-}D_6$) δ : 13.64 (1H, br s), 9.26 (2H, s), 8.70 (1H, d, $J = 8.2$ Hz), 7.89 (1H, d, $J = 7.5$ Hz), 7.66-7.62 (1H, m), 7.41 (1H, t, $J = 7.5$ Hz), 2.62 (3H, s).

[0784]

Step 4-3: Trans-4-(dibenzylamino)cyclohexan-1-ol

[0785]



[0786]

To a suspension of trans-4-aminocyclohexan-1-ol (5.0 g) and potassium carbonate (13.2 g) in acetonitrile (80 mL) was added benzyl bromide (10.9 mL) at room temperature, and the mixture was stirred overnight. To the reaction mixture was added water (100 mL) at room temperature, and the precipitated

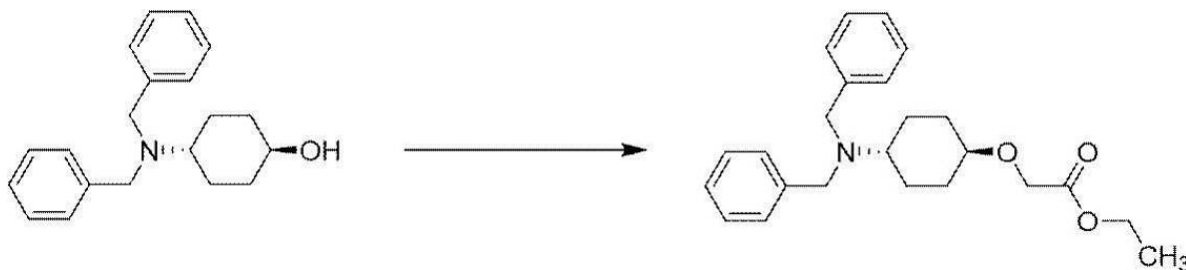
solid was collected by filtration, washed three times with water (40 mL), and dried under reduced pressure at 80°C to give the title compound (12.88 g). The title compound (10.38 g) was obtained from the starting material, trans-4-aminocyclohexan-1-ol (5.0 g), by a similar production method.

¹H-NMR (DMSO-D₆) δ: 7.35-7.27 (8H, m), 7.21-7.17 (2H, m), 4.43 (1H, br s), 3.55 (4H, s), 3.36-3.29 (1H, m), 2.39-2.31 (1H, m), 1.83-1.76 (4H, m), 1.43-1.37 (2H, m), 1.03-0.93 (2H, m).

[0787]

10 Step 4-4: Ethyl 2-{[trans-4-(dibenzylamino)cyclohexyl]oxy}acetate

[0788]



[0789]

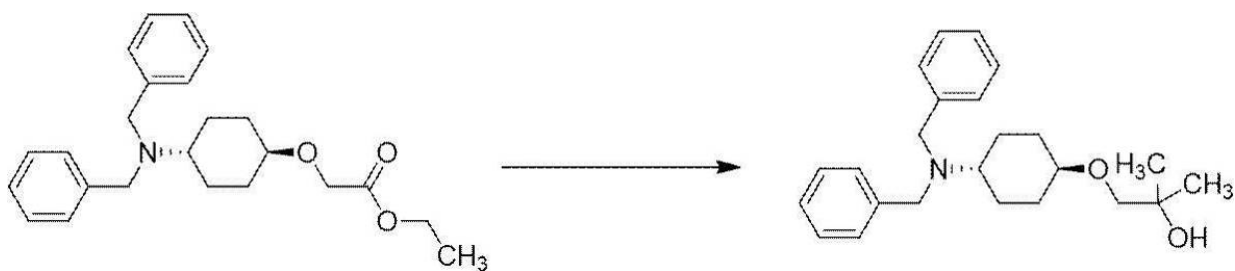
15 To a solution of trans-4-(dibenzylamino)cyclohexan-1-ol (5.0 g) in dichloromethane (50 mL) was added rhodium (II) acetate dimer (22.4 mg) at room temperature, 15 wt% ethyl diazoacetate/toluene solution (57.5 mL) was added dropwise over 2 hr, and the mixture was stirred for 2 hr. The reaction mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluent: n-hexane/ethyl acetate=93/7 to 40/60) to give the title compound (5.779 g).

25 ¹H-NMR (CDCl₃) δ: 7.38-7.32 (4H, m), 7.31-7.24 (4H, m), 7.23-7.17 (2H, m), 4.20 (2H, q, J = 7.4 Hz), 4.07 (2H, s), 3.60 (4H, s), 3.32-3.20 (1H, m), 2.58-2.47 (1H, m), 2.13-2.05 (2H, m), 1.96-1.87 (2H, m), 1.43-1.16 (7H, m).

[0790]

Step 4-5: 1-{[Trans-4-(dibenzylamino)cyclohexyl]oxy}-2-methylpropan-2-ol

[0791]



[0792]

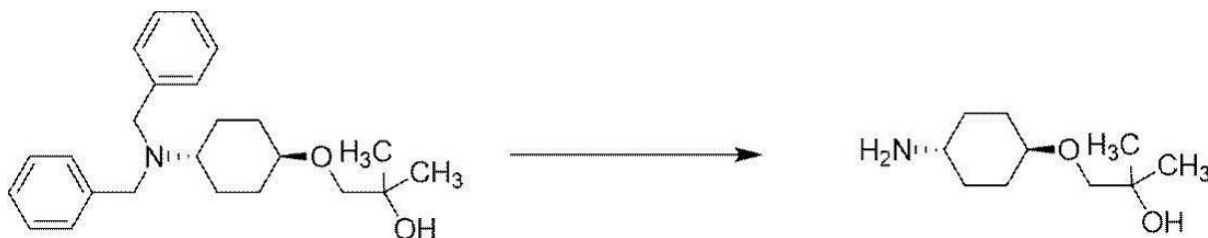
To a solution of ethyl 2-([trans-4-(dibenzylamino)cyclohexyl]oxy)acetate (5.779 g) in tetrahydrofuran (57.8 mL) was added 1.02 M tetrahydrofuran solution (44.6 mL) of methylmagnesium bromide under ice-cooling, and the mixture was stirred at the same temperature for 2 hr. To the reaction mixture was added saturated aqueous ammonium chloride solution under ice-cooling. To the reaction mixture was added ethyl acetate at room temperature, and the layers were separated. The aqueous layer was extracted once with ethyl acetate. The combined organic layer was washed successively with water and saturated brine, and dried over sodium sulfate. Sodium sulfate was removed by filtration, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluent: n-hexane/ethyl acetate=93/7 to 40/60) to give the title compound (4.04 g).

$^1\text{H-NMR}$ (CDCl_3) δ : 7.38-7.33 (4H, m), 7.32-7.25 (4H, m), 7.23-7.17 (2H, m), 3.60 (4H, s), 3.24 (2H, s), 3.22-3.12 (1H, m), 2.57-2.47 (1H, m), 2.33 (1H, s), 2.10-2.01 (2H, m), 1.96-1.86 (2H, m), 1.43-1.33 (2H, m), 1.20-1.10 (8H, m).

[0793]

Step 4-6: 1-((Trans-4-aminocyclohexyl)oxy)-2-methylpropan-2-ol

[0794]



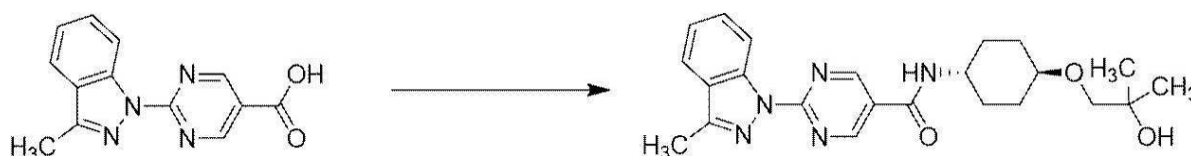
[0795]

To a solution of 1-{[trans-4-(dibenzylamino)cyclohexyl]oxy}-2-methylpropan-2-ol (3.715 g) in methanol/tetrahydrofuran (40 mL, methanol/tetrahydrofuran=1/1) was added 20% palladium hydroxide-carbon (310 mg) at room temperature. Under 1 atm hydrogen atmosphere, the mixture was stirred at room temperature overnight. The reaction mixture was filtered through celite, and the filtrate was concentrated under reduced pressure to give the title compound (1.926 g).
¹H-NMR (DMSO-D₆) δ: 4.17 (1H, br s), 3.18-3.11 (2H, m), 2.55-2.48 (2H, m), 1.92-1.86 (2H, m), 1.75-1.68 (2H, m), 1.47 (2H, br s), 1.20-1.09 (2H, m), 1.06-0.96 (2H, m), 1.04 (6H, s).

[0796]

Step 4-7: N-(Trans-4-(2-hydroxy-2-methylpropoxy)cyclohexyl)-2-(3-methyl-1H-indazol-1-yl)pyrimidine-5-carboxamide

15 [0797]



[0798]

A suspension of 2-(3-methyl-1H-indazol-1-yl)pyrimidine-5-carboxylic acid (30 mg), 1-((trans-4-aminocyclohexyl)oxy)-2-methylpropan-2-ol (27 mg), 1-hydroxy-7-azabenzotriazole (16 mg) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (35 mg) in N,N-dimethylformamide (1.0 mL) was stirred overnight. To the reaction mixture were added saturated aqueous sodium hydrogen carbonate (2.0 mL) and water (3.0 mL) at room temperature, and the precipitated solid was collected by filtration and dried under reduced pressure to give the title compound (44.8 mg).

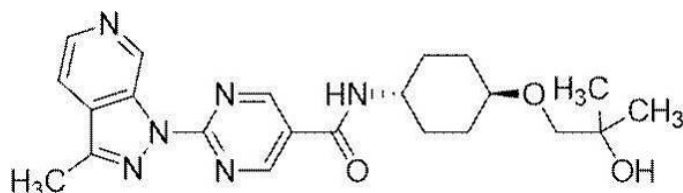
¹H-NMR (DMSO-D₆) δ: 9.22 (2H, s), 8.67 (1H, d, J = 8.6 Hz), 8.53 (1H, d, J = 7.6 Hz), 7.89 (1H, d, J = 7.9 Hz), 7.65-7.61 (1H, m), 7.42-7.38 (1H, m), 4.22 (1H, s), 3.85-3.76 (1H, m), 3.29-3.22 (1H, m), 3.19 (2H, s), 2.62 (3H, s), 2.06-2.01 (2H, m), 1.95-1.91 (2H, m), 1.45-1.23 (4H, m), 1.08 (6H, s).

MS (M+H) : 424 MS (M-H) : 422

[0799]

[Production Example 5] Example 5: Production of N-(trans-4-(2-hydroxy-2-methylpropyl)cyclohexyl)-2-(3-methyl-1H-pyrazolo[3,4-c]pyridin-1-yl)pyrimidine-5-carboxamide

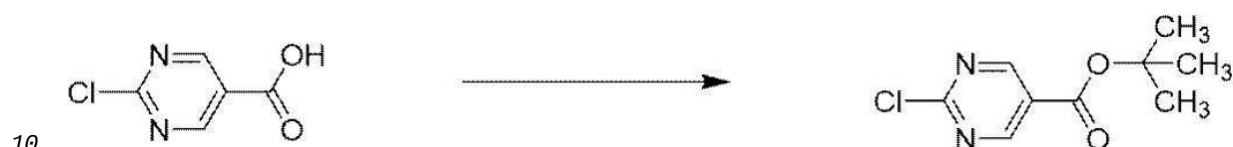
5 [0800]



[0801]

Step 5-1: tert-Butyl 2-chloropyrimidine-5-carboxylate

[0802]



[0803]

To a solution of 2-chloropyrimidine-5-carboxylic acid (2.0 g) and N,N-dimethyl-4-aminopyridine (0.462 g) in tert-butyl alcohol/chloroform (30 mL, tert-butyl

15 alcohol/chloroform=2/1) was added di-tert-butyl bicarbonate (5.51 g) at room temperature, and the mixture was stirred at 60°C for 90 min and left standing overnight. To the reaction mixture was added ethyl acetate at room temperature, and the organic layer was washed successively with saturated aqueous

20 sodium hydrogen carbonate, aqueous citric acid solution and saturated brine. The organic layer was dried over sodium sulfate, sodium sulfate was removed by filtration, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluent: n-

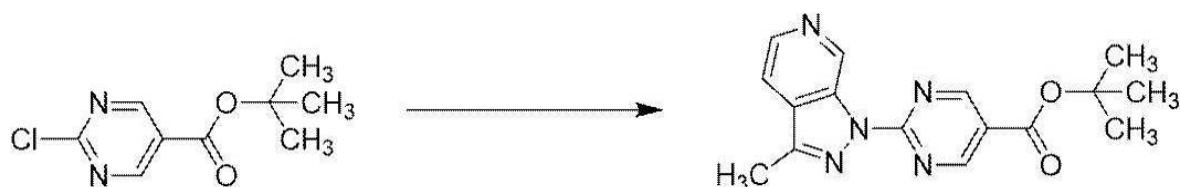
25 hexane/ethyl acetate) to give the title compound (990 mg).

¹H-NMR (DMSO-D₆) δ: 9.13 (2H, s), 1.57 (9H, s).

[0804]

Step 5-2: tert-Butyl 2-(3-methyl-1H-pyrazolo[3,4-c]pyridin-1-yl)pyrimidine-5-carboxylate

30 [0805]



[0806]

A suspension of tert-butyl 2-chloropyrimidine-5-carboxylate (500 mg), 3-methyl-1H-pyrazolo[3,4-c]pyridine (310 mg) and cesium carbonate (911 mg) in N,N-dimethylformamide (5.0 mL) was stirred at room temperature for 1 hr and left standing overnight. To the reaction mixture was added water at room temperature, and the precipitated solid was collected by filtration and dried under reduced pressure at 70°C to give the title compound (618 mg).

¹H-NMR (DMSO-D₆) δ: 10.01 (1H, s), 9.29 (2H, s), 8.55 (1H, d, J = 5.3 Hz), 7.95 (1H, dd, J = 5.3, 0.9 Hz), 2.67 (3H, s), 1.60 (9H, s).

[0807]

Step 5-3: 2-(3-Methyl-1H-pyrazolo[3,4-c]pyridin-1-yl)pyrimidine-5-carboxylic acid monohydrochloride

[0808]



[0809]

A solution of tert-butyl 2-(3-methyl-1H-pyrazolo[3,4-c]pyridin-1-yl)pyrimidine-5-carboxylate (618 mg) in trifluoroacetic acid (3.09 mL) was stirred for 2 hr and left standing overnight. To the reaction mixture was added 4 M hydrogen chloride/ethyl acetate solution at room temperature, and the mixture was stirred for 1 hr. The precipitated solid was collected by filtration, and dried under reduced pressure at 70°C to give the title compound (563 mg).

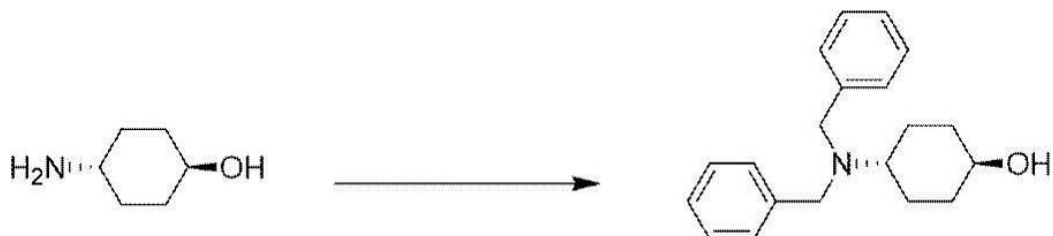
¹H-NMR (DMSO-D₆) δ: 13.77 (1H, br s), 10.08 (1H, s), 9.35 (2H, s), 8.66 (1H, d, J = 5.2 Hz), 8.23 (1H, d, J = 5.2 Hz), 2.72

(3H, s).

[0810]

Step 5-4: Trans-4-(dibenzylamino)cyclohexan-1-ol

[0811]



[0812]

To a suspension of trans-4-aminocyclohexan-1-ol (5.0 g) and potassium carbonate (13.2 g) in acetonitrile (80 mL) was added benzyl bromide (10.9 mL) at room temperature, and the mixture was stirred overnight. To the reaction mixture was added water (100 mL) at room temperature, and the precipitated solid was collected by filtration, washed 3 times with water (40 mL), and dried under reduced pressure at 80°C to give the title compound (12.88 g).

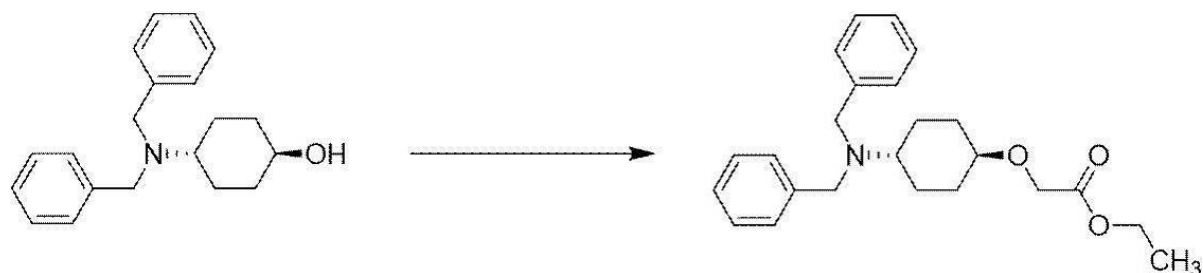
15 $^1\text{H-NMR}$ (DMSO- D_6) δ : 7.35–7.27 (8H, m), 7.21–7.17 (2H, m), 4.43 (1H, br s), 3.55 (4H, s), 3.36–3.29 (1H, m), 2.39–2.31 (1H, m), 1.83–1.76 (4H, m), 1.43–1.37 (2H, m), 1.03–0.93 (2H, m).

[0813]

Step 5-5: ethyl 2-{[trans-4-

20 (dibenzylamino)cyclohexyl]oxy}acetate

[0814]



[0815]

To a solution of trans-4-(dibenzylamino)cyclohexan-1-ol (5.0 g) in dichloromethane (50 mL) was added rhodium (II) acetate dimer (22.4 mg) at room temperature, 15 wt% ethyl diazoacetate/toluene solution (57.5 mL) was added dropwise over

2 hr, and the mixture was stirred for 2 hr. The reaction mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluent: n-hexane/ethyl acetate=93/7 to 40/60) to give the title compound

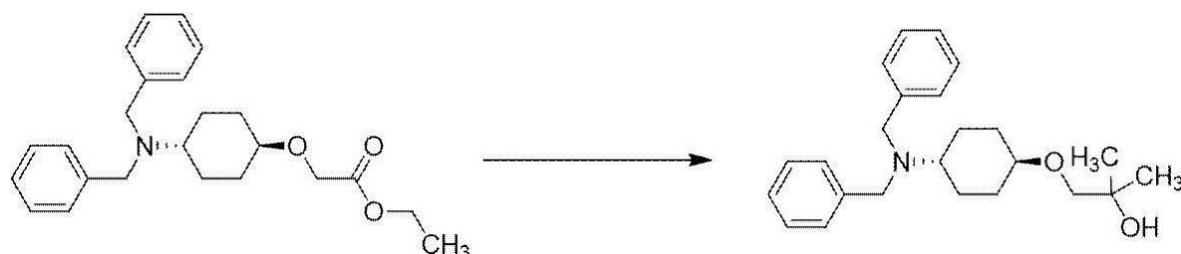
5 (5.779 g).

$^1\text{H-NMR}$ (CDCl_3) δ : 7.38-7.32 (4H, m), 7.31-7.24 (4H, m), 7.23-7.17 (2H, m), 4.20 (2H, q, $J = 7.4$ Hz), 4.07 (2H, s), 3.60 (4H, s), 3.32-3.20 (1H, m), 2.58-2.47 (1H, m), 2.13-2.05 (2H, m), 1.96-1.87 (2H, m), 1.43-1.16 (7H, m).

10 [0816]

Step 5-6: 1-{[Trans-4-(dibenzylamino)cyclohexyl]oxy}-2-methylpropan-2-ol

[0817]



15 [0818]

To a solution of ethyl 2-{[trans-4-(dibenzylamino)cyclohexyl]oxy}acetate (5.779 g) in tetrahydrofuran (57.8 mL) was added 1.02 M tetrahydrofuran solution (44.6 mL) of methylmagnesium bromide under ice-cooling, and the mixture was stirred at the same temperature for 2 hr. To the reaction mixture was added saturated aqueous ammonium chloride solution under ice-cooling. To the reaction mixture was added ethyl acetate at room temperature. After partitioning, the aqueous layer was extracted once with ethyl acetate. The combined organic layer was washed successively with water and saturated brine, and dried over sodium sulfate. Sodium sulfate was removed by filtration, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluent: n-hexane/ethyl acetate=93/7 to 40/60) to give the title compound (4.04 g).

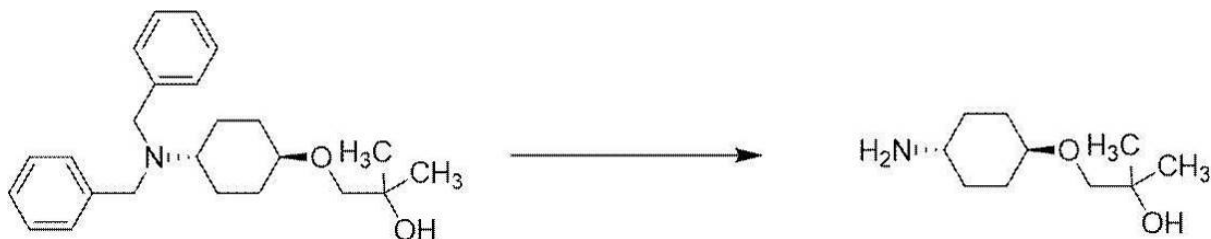
30

$^1\text{H-NMR}$ (CDCl_3) δ : 7.38-7.33 (4H, m), 7.32-7.25 (4H, m), 7.23-

7.17 (2H, m), 3.60 (4H, s), 3.24 (2H, s), 3.22-3.12 (1H, m),
2.57-2.47 (1H, m), 2.33 (1H, s), 2.10-2.01 (2H, m), 1.96-1.86
(2H, m), 1.43-1.33 (2H, m), 1.20-1.10 (8H, m).

[0819]

5 Step 5-7: 1-((Trans-4-aminocyclohexyl)oxy)-2-methylpropan-2-ol
[0820]



[0821]

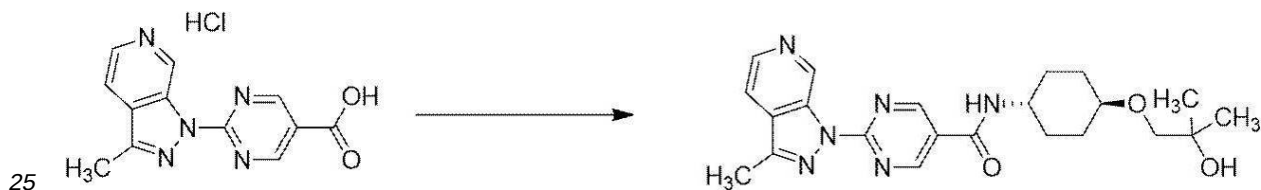
To a solution of 1-{[trans-4-
10 (dibenzylamino)cyclohexyl]oxy}-2-methylpropan-2-ol (3.715 g) in
methanol (20 mL) was added 20% palladium hydroxide-carbon (310
mg) at room temperature. Under 1 atm hydrogen atmosphere, the
mixture was stirred at room temperature overnight. The
reaction mixture was filtered through celite, and the filtrate
15 was concentrated under reduced pressure to give the title
compound (1.926 g).

¹H-NMR (DMSO-D₆) δ: 4.17 (1H, br s), 3.18-3.11 (2H, m), 2.55-
2.48 (2H, m), 1.92-1.86 (2H, m), 1.75-1.68 (2H, m), 1.47 (2H,
br s), 1.20-1.09 (2H, m), 1.06-0.96 (2H, m), 1.04 (6H, s).

20 [0822]

Step 5-8: N-(Trans-4-(2-hydroxy-2-methylpropyl)cyclohexyl)-2-
(3-methyl-1H-pyrazolo[3,4-c]pyridin-1-yl)pyrimidine-5-
carboxamide

[0823]



[0824]

To a suspension of 2-(3-methyl-1H-pyrazolo[3,4-c]pyridin-
1-yl)pyrimidine-5-carboxylic acid monohydrochloride (30 mg), 1-

((trans-4-aminocyclohexyl)oxy)-2-methylpropan-2-ol (23.11 mg), 1-hydroxy-7-azabenzotriazole (4.2 mg) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (29.6 mg) in N,N-dimethylformamide (0.6 mL) was added triethylamine (0.0215 mL) at room temperature, and the mixture was stirred for 2 hr and left standing overnight. To the reaction mixture was added water at room temperature, and the precipitated solid was collected by filtration and dried under reduced pressure at 70°C to give the title compound (41.4 mg).

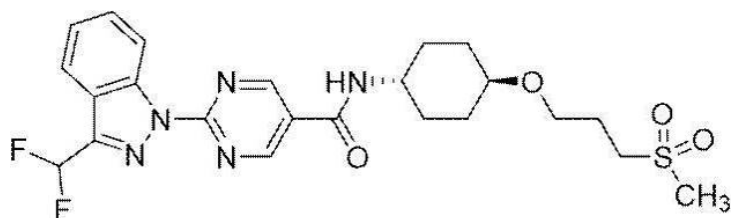
¹H-NMR (DMSO-D₆) δ: 9.99 (1H, s), 9.27 (2H, s), 8.58 (1H, d, J = 7.5 Hz), 8.54 (1H, d, J = 5.2 Hz), 7.94 (1H, d, J = 5.2 Hz), 4.20 (1H, br s), 3.87-3.74 (1H, m), 3.51-3.22 (1H, m), 3.19 (2H, s), 2.67 (3H, s), 2.04 (2H, d, J = 10.5 Hz), 1.93 (2H, d, J = 10.5 Hz), 1.48-1.20 (4H, m), 1.07 (6H, s).

MS (M+H) : 425 MS (M-H) : 423

[0825]

[Production Example 6] Example 6: Production of 2-(3-(difluoromethyl)-1H-indazol-1-yl)-N-(trans-4-(3-(methylsulfonyl)propoxy)cyclohexyl)pyrimidine-5-carboxamide

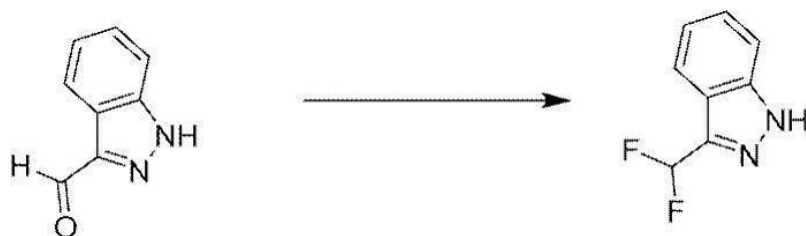
[0826]



[0827]

Step 6-1: 3-(Difluoromethyl)-1H-indazole

[0828]



25

[0829]

To a solution of 1H-indazole-3-carbaldehyde (1.5 g) in dichloromethane (10 mL) was added N,N-diethylaminosulfur

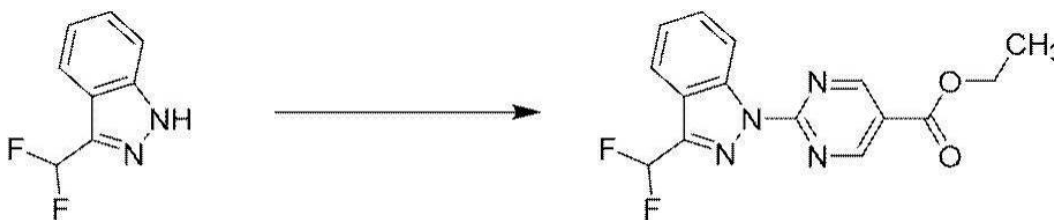
trifluoride (2.71 mL) under ice-cooling, and the mixture was allowed to gradually return to room temperature and stirred for 5 hr. To the reaction mixture was added dropwise saturated aqueous sodium hydrogen carbonate under ice-cooling, ethyl acetate was added, and the layers were separated. The aqueous layer was extracted once with ethyl acetate. The combined organic layer was washed with saturated brine, and dried over magnesium sulfate. Magnesium sulfate was removed by filtration, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluent: n-hexane/ethyl acetate=95/5 to 80/20) and silica gel column chromatography (eluent: n-hexane/ethyl acetate=100/0 to 85/15) to give the title compound (343 mg). The title compound (673 mg) was obtained from the starting material, 1H-indazole-3-carboxaldehyde, by a similar production method.

¹H-NMR (DMSO-D₆) δ: 13.59 (1H, s), 7.84 (1H, d, J = 8.2 Hz), 7.64 (1H, d, J = 9.0 Hz), 7.46 (1H, t, J = 7.5 Hz), 7.34 (1H, t, J = 53.9 Hz), 7.25 (1H, t, J = 7.5 Hz).

[0830]

Step 6-2: Ethyl 2-(3-(difluoromethyl)-1H-indazol-1-yl)pyrimidine-5-carboxylate

[0831]



[0832]

A suspension of 3-(difluoromethyl)-1H-indazole (0.95 g), ethyl 2-chloropyrimidine-carboxylate (1.1 g) and cesium carbonate (2.2 g) in N,N-dimethylformamide (10 mL) was stirred at room temperature for 4 hr. To the reaction mixture was added water under ice-cooling, and the mixture was stirred for 1 hr. The precipitated solid was collected by filtration and dried under reduced pressure to give the title compound (1.73 g).

^1H -NMR (DMSO- D_6) δ : 9.38 (2H, s), 8.81 (1H, d, J = 8.6 Hz), 8.01 (1H, d, J = 8.1 Hz), 7.77 (1H, t, J = 8.4 Hz), 7.57 (1H, t, J = 54.0 Hz), 7.54 (1H, t, J = 7.6 Hz), 4.42 (2H, q, J = 7.1 Hz), 1.38 (3H, t, J = 7.1 Hz).

5 [0833]

Step 6-3: 2-(3-(Difluoromethyl)-1H-indazol-1-yl)pyrimidine-5-carboxylic acid

[0834]



10 [0835]

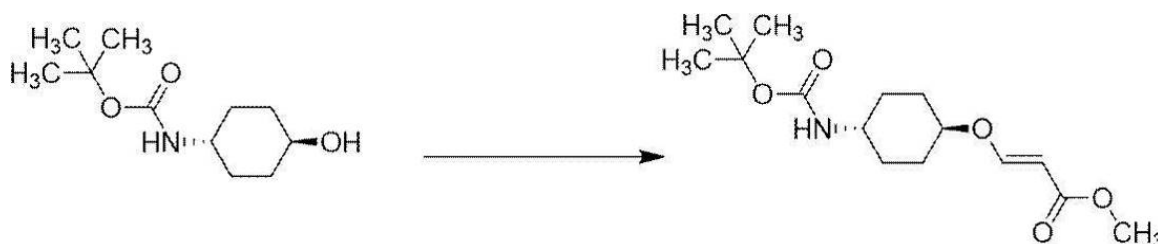
To a solution of ethyl 2-(3-(difluoromethyl)-1H-indazol-1-yl)pyrimidine-5-carboxylate (1.73 g) in tetrahydrofuran (10 mL) was added 2 M aqueous sodium hydroxide solution (5.03 mL) under ice-cooling, and the mixture was allowed to gradually
15 return to room temperature and stirred for 6 hr. To the reaction mixture was added 2 M hydrochloric acid (5.0 mL) under ice-cooling, and the mixture was stirred for 1 hr. The precipitated solid was collected by filtration and dried under reduced pressure to give the title compound (1.45 g).

20 ^1H -NMR (DMSO- D_6) δ : 13.80 (1H, br s), 9.35 (2H, s), 8.82 (1H, d, J = 8.5 Hz), 8.01 (1H, d, J = 7.9 Hz), 7.78-7.74 (1H, m), 7.56 (1H, t, J = 54.0 Hz), 7.56-7.51 (1H, m).

[0836]

Step 6-4: Methyl (E)-3-((trans-4-((tert-butoxycarbonyl)amino)cyclohexyl)oxy)acrylate

25 [0837]



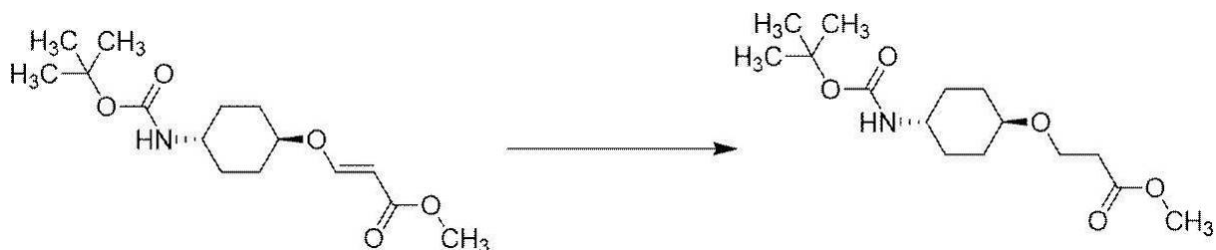
[0838]

To a suspension of tert-butyl (trans-4-hydroxycyclohexyl)carbamate (5.0 g) and 1,4-diazabicyclo[2,2,2]octane (0.261 g) in tetrahydrofuran (50 mL) was added dropwise methyl propiolate (1.935 mL) at room temperature, and the mixture was stirred for 1 hr and left standing overnight. To the reaction mixture was added ethyl acetate at room temperature, and the organic layer was washed successively twice with saturated aqueous ammonium chloride solution and once with saturated brine. The organic layer was dried over sodium sulfate, sodium sulfate was removed by filtration, and the filtrate was concentrated under reduced pressure to give a crude product (7.42 g) containing the title compound.

[0839]

Step 6-5: Methyl 3-((trans-4-((tert-butoxycarbonyl)amino)cyclohexyl)oxy)propionate

[0840]



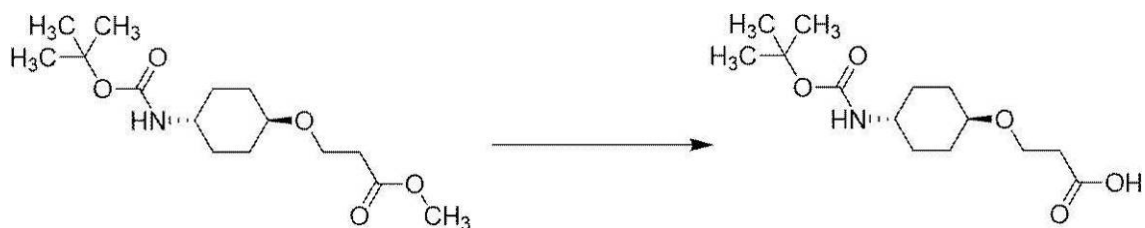
[0841]

To a solution of a crude product (2.0 g) containing methyl (E)-3-((trans-4-((tert-butoxycarbonyl)amino)cyclohexyl)oxy)acrylate in methanol (9.37 mL) was added 10% palladium-carbon (187 mg) at room temperature. Under 1 atm hydrogen atmosphere, the mixture was stirred at room temperature for 3 hr. The reaction mixture was filtered through celite, and the filtrate was concentrated under reduced pressure to give a crude product (1.71 g) containing the title compound.

[0842]

Step 6-6: 3-((Trans-4-((tert-butoxycarbonyl)amino)cyclohexyl)oxy)propionic acid

[0843]



[0844]

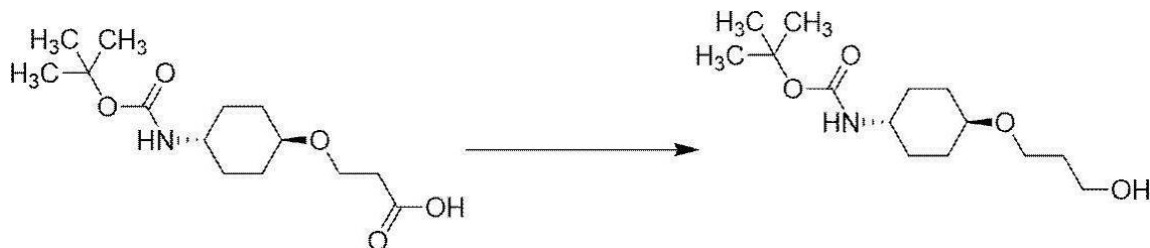
To a solution of a crude product (0.974 mg) containing
5 methyl 3-((trans-4-((tert-butoxycarbonyl)amino)cyclohexyl)oxy)propionate in methanol
(9.14 mL) was added 4 M aqueous sodium hydroxide solution (1.13
mL) at room temperature, and the mixture was stirred for 45 min
and left standing overnight. The reaction mixture was
10 concentrated under reduced pressure. To the residue were added
water and ethyl acetate, the layers were separated, to the
aqueous layer was added 2 M hydrochloric acid (2.4 mL), and the
mixture was extracted twice with ethyl acetate. The combined
organic layer was washed with saturated brine, and dried over
15 sodium sulfate. Sodium sulfate was removed by filtration, and
the filtrate was concentrated under reduced pressure to give
the title compound (0.94 g).

$^1\text{H-NMR}$ (DMSO- D_6) δ : 12.04 (1H, br s), 6.69 (1H, d, $J = 7.4$ Hz),
3.58 (2H, t, $J = 6.4$ Hz), 3.22-3.10 (2H, m), 2.39 (2H, t, $J =$
20 6.4 Hz), 1.94-1.85 (2H, m), 1.79-1.70 (2H, m), 1.37 (9H, s),
1.24-1.07 (4H, m).

[0845]

Step 6-7: tert-Butyl (trans-4-(3-
hydroxypropoxy)cyclohexyl)carbamate

25 [0846]



[0847]

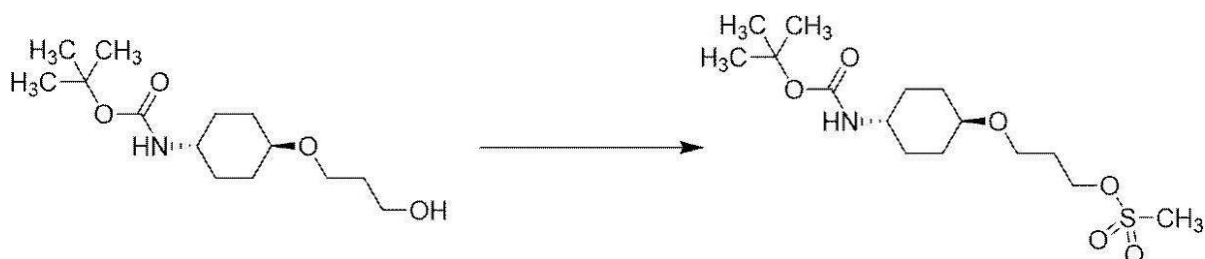
To a solution of 3-((trans-4-((tert-butoxycarbonyl)amino)cyclohexyl)oxy)propionic acid (0.94 g) and triethylamine (0.384 mL) in tetrahydrofuran (7.548 mL) was added isobutyl chloroformate (0.362 mL) under ice-cooling, and the mixture was stirred for 30 min. The reaction mixture was filtered to remove insoluble materials. To the filtrate was added dropwise sodium borohydride (0.298 g)/0.05 M aqueous sodium hydroxide solution (0.3774 mL) under ice-cooling. The mixture was stirred for 2 hr, allowed to gradually return to room temperature, and stirred for 90 min. To the reaction mixture were added saturated aqueous sodium hydrogen carbonate, water and ethyl acetate, and the layers were separated. The aqueous layer was extracted with ethyl acetate. The combined organic layer was washed successively with water and saturated brine, and dried over sodium sulfate. Sodium sulfate was removed by filtration, and the filtrate was concentrated under reduced pressure to give the title compound (0.774 g).

¹H-NMR (DMSO-D₆) δ: 6.68 (1H, d, J = 7.9 Hz), 4.32 (1H, t, J = 5.1 Hz), 3.46-3.38 (4H, m), 3.23-3.05 (2H, m), 1.95-1.86 (2H, m), 1.80-1.70 (2H, m), 1.65-1.55 (2H, m), 1.37 (9H, s), 1.22-1.04 (4H, m).

[0848]

Step 6-8: 3-((Trans-4-((tert-butylbutoxycarbonyl)amino)cyclohexyl)oxy)propylmethanesulfonate

[0849]



[0850]

To a solution of tert-butyl (trans-4-(3-hydroxypropoxy)cyclohexyl)carbamate (370 mg) and triethylamine (0.238 mL) in tetrahydrofuran (1.55 mL) was added methanesulfonic anhydride (297 mg) under ice-cooling. The

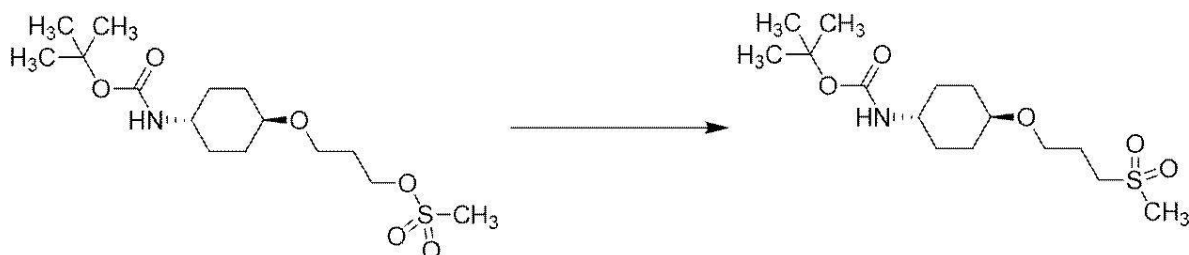
mixture was allowed to gradually return to room temperature, and stirred for 90 min. To the reaction mixture were added water and ethyl acetate at room temperature, and the layers were separated. The aqueous layer was extracted with ethyl
 5 acetate. The combined organic layer was washed successively with saturated aqueous sodium hydrogen carbonate and saturated brine, and dried over sodium sulfate. Sodium sulfate was removed by filtration, and the filtrate was concentrated under reduced pressure to give the title compound (420 mg).

10 $^1\text{H-NMR}$ (DMSO-D_6) δ : 6.70 (1H, d, $J = 7.2$ Hz), 4.23 (2H, t, $J = 6.4$ Hz), 3.46 (2H, t, $J = 6.2$ Hz), 3.23-3.06 (2H, m), 3.15 (3H, s), 1.97-1.81 (4H, m), 1.80-1.69 (2H, m), 1.37 (9H, s), 1.23-1.05 (4H, m).

[0851]

15 Step 6-9: tert-Butyl (trans-4-(3-(methanesulfonyl)propoxy)cyclohexyl)carbamate

[0852]



[0853]

20 A suspension of 3-((trans-4-((tert-butoxycarbonyl)amino)cyclohexyl)oxy)propyl methanesulfonate (420 mg), sodium methanesulfinate (242 mg) and sodium iodide (186 mg) in N,N -dimethylformamide (1.987 mL) was stirred at 70°C for 1 hr, and at 100°C for 3 hr. To the reaction mixture
 25 was added water at room temperature, and the precipitated solid was collected by filtration, and dried under reduced pressure at 60°C to give the title compound (220 mg). Step 6-8 and step 6-9 were separately performed to give the title compound (47.2 mg).

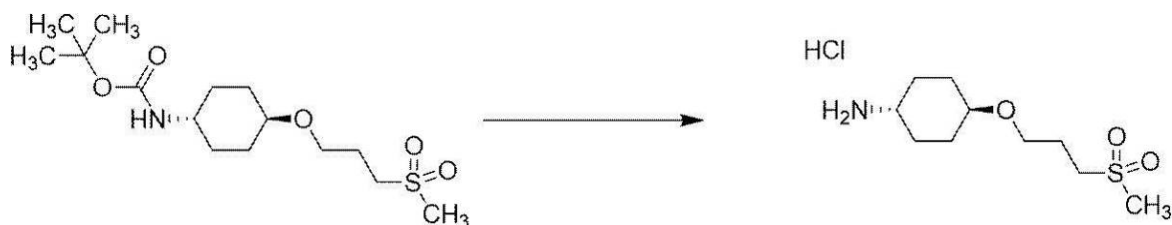
30 $^1\text{H-NMR}$ (DMSO-D_6) δ : 6.70 (1H, d, $J = 7.5$ Hz), 3.47 (2H, t, $J = 6.4$ Hz), 3.24-3.06 (4H, m), 2.97 (3H, s), 1.98-1.81 (4H, m),

1.81-1.67 (2H, m), 1.37 (9H, s), 1.23-1.07 (4H, m).

[0854]

Step 6-10: Trans-4-(3-(methylsulfonyl)propoxy)cyclohexan-1-amine monohydrochloride

5 [0855]



[0856]

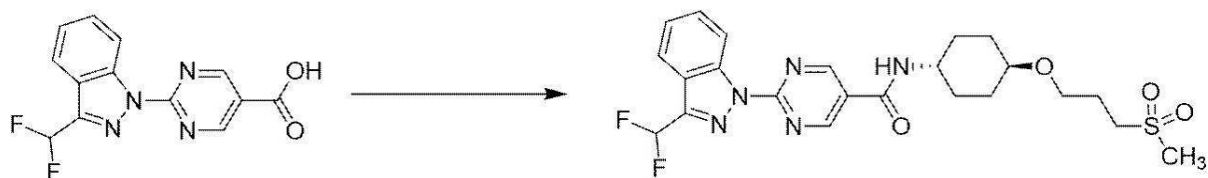
To a suspension of tert-butyl (trans-4-(3-(methylsulfonyl)propoxy)cyclohexyl)carbamate (253 mg) in ethyl acetate (1.265 mL) was added 4 M hydrogen chloride/ethyl acetate solution (1.265 mL) at room temperature, and the mixture was stirred for 2 hr and left standing overnight. The precipitated solid was collected by filtration, washed with ethyl acetate, and dried under reduced pressure at 60°C for 1 hr to give the title compound (202 mg).

¹H-NMR (DMSO-D₆) δ: 7.87 (3H, br s), 3.50 (2H, t, J = 6.2 Hz), 3.24-3.15 (1H, m), 3.14-3.07 (2H, m), 3.03-2.91 (1H, m), 2.97 (3H, s), 2.04-1.82 (6H, m), 1.40-1.27 (2H, m), 1.26-1.13 (2H, m).

20 [0857]

Step 6-11: 2-(3-(Difluoromethyl)-1H-indazol-1-yl)-N-(trans-4-(3-(methylsulfonyl)propoxy)cyclohexyl)pyrimidine-5-carboxamide

[0858]



25 [0859]

To a suspension of 2-(3-(difluoromethyl)-1H-indazol-1-yl)pyrimidine-5-carboxylic acid (30 mg), trans-4-(3-(methylsulfonyl)propoxy)cyclohexan-1-amine monohydrochloride

(33.7 mg) and triethylamine (0.0261 mL) in N,N-dimethylformamide (0.5 mL) were added 1-hydroxy-7-azabenzotriazole (4.22 mg) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (29.7 mg) at room temperature, and the mixture was stirred overnight. To the reaction mixture was added water at room temperature, and the precipitated solid was collected by filtration and dried under reduced pressure. The solid was dissolved in dimethyl sulfoxide and purified by reversed-phase silica gel column chromatography (eluent: water/acetonitrile=95/5 to 0/100) to give the title compound (38.5 mg).

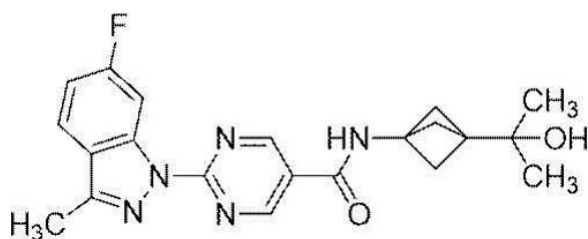
¹H-NMR (DMSO-D₆) δ: 9.30 (2H, s), 8.78 (1H, d, J = 8.6 Hz), 8.63 (1H, d, J = 7.5 Hz), 8.00 (1H, d, J = 8.1 Hz), 7.75 (1H, t, J = 8.1 Hz), 7.56 (1H, t, J = 53.9 Hz), 7.52 (1H, t, J = 7.5 Hz), 3.86-3.76 (1H, m), 3.53 (2H, t, J = 6.2 Hz), 3.30-3.25 (1H, m), 3.16-3.11 (2H, m), 2.99 (3H, s), 2.07-2.02 (2H, m), 1.97-1.87 (4H, m), 1.46-1.36 (2H, m), 1.33-1.23 (2H, m).

MS (M+H): 508 MS (M-H): 506

[0860]

[Production Example 7] Example 7: Production of 2-(6-fluoro-3-methyl-1H-indazol-1-yl)-N-(3-(2-hydroxypropan-2-yl)bicyclo[1.1.1]pentan-1-yl)pyrimidine-5-carboxamide

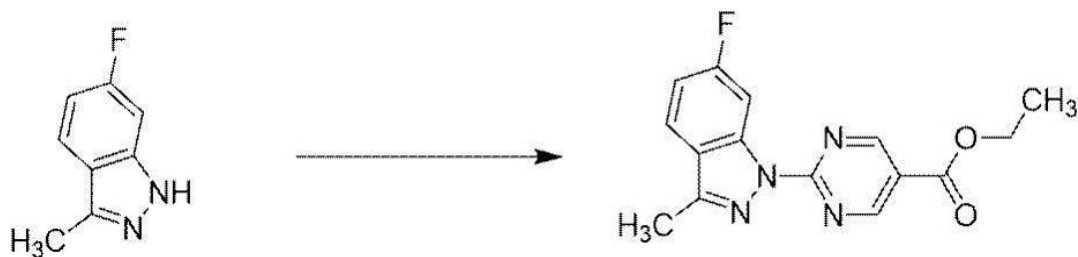
[0861]



[0862]

Step 7-1: Ethyl 2-(6-fluoro-3-methyl-1H-indazol-1-yl)pyrimidine-5-carboxylate

[0863]



[0864]

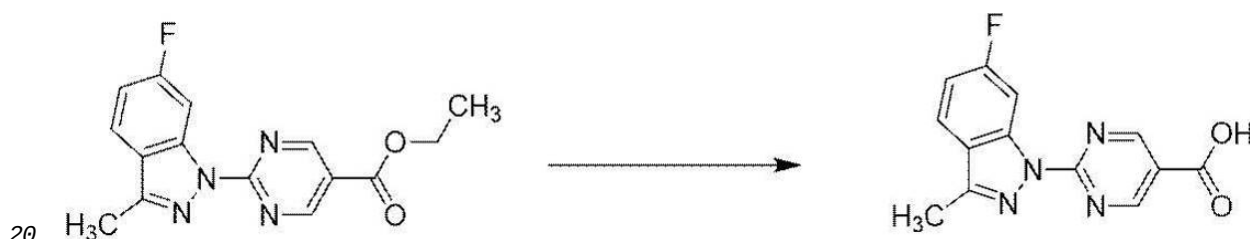
A suspension of 6-fluoro-3-methyl-1H-indazole (1.5 g), ethyl 2-chloropyrimidine-carboxylate (2.05 g) and cesium carbonate (6.51 g) in N,N-dimethylformamide (10 mL) was stirred for 3 hr and left standing overnight at room temperature. To the reaction mixture was added water at room temperature, and the precipitated solid was collected by filtration, and dried under reduced pressure. The solid was dissolved in chloroform, and purified by silica gel column chromatography (eluent: chloroform) to give the title compound (2.65 g).

¹H-NMR (DMSO-D₆) δ: 9.30 (2H, s), 8.44 (1H, dd, J = 10.4, 2.1 Hz), 7.95 (1H, dd, J = 8.8, 5.3 Hz), 7.31 (1H, td, J = 8.9, 2.2 Hz), 4.40 (2H, q, J = 7.1 Hz), 2.61 (3H, s), 1.37 (3H, t, J = 7.1 Hz).

[0865]

Step 7-2: 2-(6-Fluoro-3-methyl-1H-indazol-1-yl)pyrimidine-5-carboxylic acid

[0866]



[0867]

To a solution of ethyl 2-(6-fluoro-3-methyl-1H-indazol-1-yl)pyrimidine-5-carboxylate (2.65 g) in tetrahydrofuran (53 mL) was added 2 M aqueous sodium hydroxide solution (13.24 mL) at room temperature, and the mixture was stirred for 3 hr and left standing overnight. To the reaction mixture was added 2 M aqueous sodium hydroxide solution (4.41 mL) at room temperature,

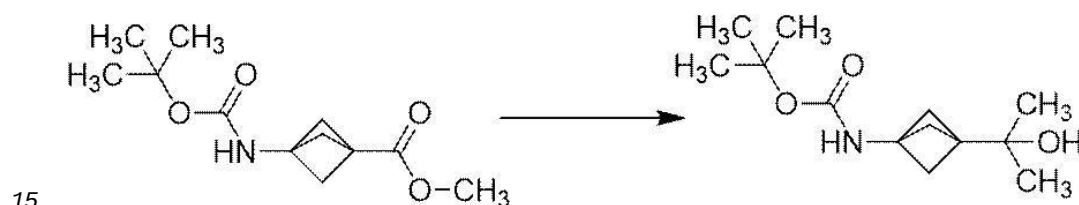
and the mixture was stirred for 1 hr. To the reaction mixture was added 2 M hydrochloric acid (17.65 mL) at room temperature. The mixture was stirred for 30 min and left standing overnight, and concentrated under reduced pressure. To the residue was
5 added water, and the mixture was stirred for 30 min, and the precipitated solid was collected by filtration and dried under reduced pressure to give the title compound (2.38 g).

¹H-NMR (DMSO-D₆) δ: 13.68 (1H, br s), 9.27 (2H, s), 8.44 (1H, dd, J = 10.5, 2.2 Hz), 7.95 (1H, dd, J = 9.0, 5.2 Hz), 7.31 (1H,
10 td, J = 8.6, 2.0 Hz), 2.61 (3H, s).

[0868]

Step 7-3: tert-Butyl (3-(2-hydroxypropan-2-yl)bicyclo[1.1.1]pentan-1-yl)carbamate

[0869]



[0870]

To a solution of methyl 3-((tert-butoxycarbonyl)amino)bicyclo[1.1.1]pentane-1-carboxylate (2.0 g) in tetrahydrofuran (10 mL) were added 1.02 M tetrahydrofuran
20 solution (33 mL) of methylmagnesium bromide under ice-cooling, and the mixture was stirred at the same temperature for 1 hr, allowed to gradually return to room temperature, and stirred for 2 hr. To the reaction mixture was added saturated aqueous ammonium chloride solution (40 mL) under ice-cooling. To the
25 reaction mixture was added ethyl acetate at room temperature (40 mL), and the layers were separated. The aqueous layer was extracted once with ethyl acetate (10 mL). The combined organic layer was washed with saturated brine and dried over sodium sulfate. Sodium sulfate was removed by filtration, and
30 the filtrate was concentrated under reduced pressure to give the title compound (2.0 g).

¹H-NMR (DMSO-D₆) δ: 7.34 (1H, br s), 4.07 (1H, br s), 1.70 (6H,

s), 1.37 (9H, s), 1.02 (6H, s).

[0871]

Step 7-4: 2-(3-Aminobicyclo[1.1.1]pentan-1-yl)propan-2-ol
monohydrochloride

5 [0872]



[0873]

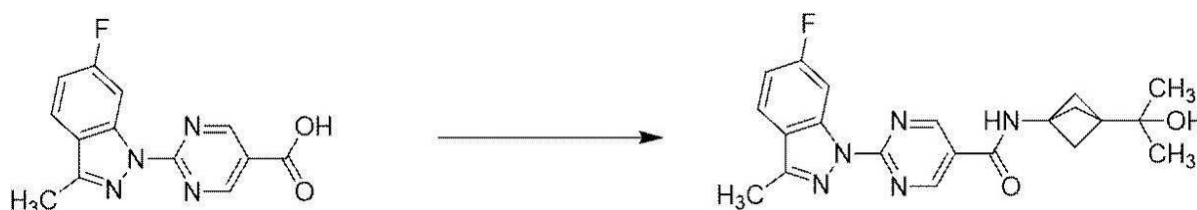
To a solution of tert-butyl (3-(2-hydroxypropan-2-yl)bicyclo[1.1.1]pentan-1-yl)carbamate (414 mg) in ethyl
10 acetate (4.0 mL) was added 4 M hydrogen chloride/ethyl acetate
solution (4.0 mL) at room temperature, and the mixture was
stirred overnight. To the reaction mixture was added ethyl
acetate at room temperature (10 mL), and the precipitated solid
was collected by filtration and dried under reduced pressure
15 to give the title compound (271 mg).

¹H-NMR (DMSO-D₆) δ: 8.79 (3H, br s), 4.21 (1H, br s), 1.80 (6H, s), 1.05 (6H, s).

[0874]

Step 7-5: 2-(6-Fluoro-3-methyl-1H-indazol-1-yl)-N-(3-(2-
20 hydroxypropan-2-yl)bicyclo[1.1.1]pentan-1-yl)pyrimidine-5-
carboxamide

[0875]



[0876]

25 To a suspension of 2-(6-fluoro-3-methyl-1H-indazol-1-yl)pyrimidine-5-carboxylic acid (30 mg), 2-(3-aminobicyclo[1.1.1]pentan-1-yl)propan-2-ol monohydrochloride (28 mg), 1-hydroxy-7-azabenzotriazole (16 mg) and 1-ethyl-3-(3-

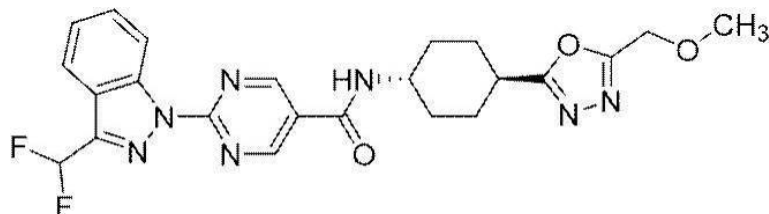
dimethylaminopropyl)carbodiimide hydrochloride (36 mg) in N,N-dimethylformamide (1.0 mL) was added triethylamine (0.030 mL) at room temperature, and the mixture was stirred overnight. To the reaction mixture were added saturated aqueous sodium hydrogen carbonate (2.0 mL) and water (3.0 mL) at room temperature, and the precipitated solid was collected by filtration and dried under reduced pressure to give the title compound (42.7 mg).

¹H-NMR (DMSO-D₆) δ: 9.24 (1H, br s), 9.22 (2H, s), 8.39 (1H, dd, J = 10.3, 2.2 Hz), 7.94 (1H, dd, J = 8.8, 5.3 Hz), 7.32-7.26 (1H, m), 4.20 (1H, s), 2.61 (3H, s), 1.96 (6H, s), 1.09 (6H, s). MS (M+H): 396 MS (M-H): 394

[0877]

[Production Example 8] Example 8: Production of 2-(3-(difluoromethyl)-1H-indazol-1-yl)-N-(trans-4-(5-(methoxymethyl)-1,3,4-oxadiazol-2-yl)cyclohexyl)pyrimidine-5-carboxamide

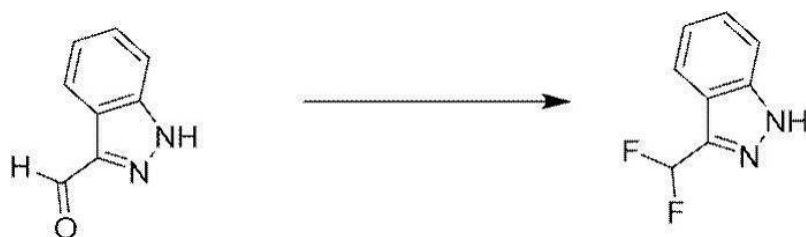
[0878]



[0879]

Step 8-1: 3-(Difluoromethyl)-1H-indazole

[0880]



[0881]

To a solution of 1H-indazole-3-carbaldehyde (1.5 g) in dichloromethane (10 mL) was added N,N-diethylaminosulfur trifluoride (2.71 mL) under ice-cooling, and the mixture was allowed to gradually return to room temperature and stirred for

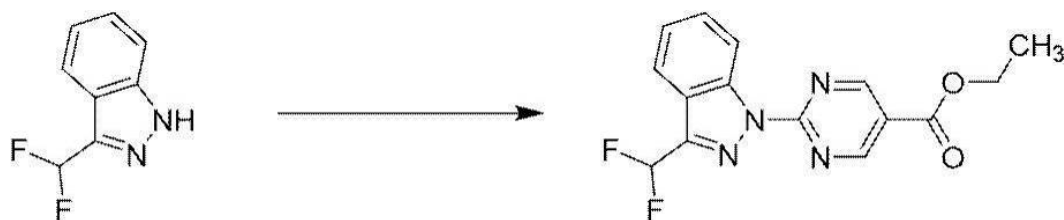
5 hr. To the reaction mixture was added dropwise saturated aqueous sodium hydrogen carbonate under ice-cooling, and ethyl acetate was added. The layers were separated, and the aqueous layer was extracted once with ethyl acetate. The combined
5 organic layer was washed with saturated brine and dried over magnesium sulfate. Magnesium sulfate was removed by filtration, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluent: n-hexane/ethyl acetate=95/5 to 80/20) and silica gel
10 column chromatography (eluent: n-hexane/ethyl acetate=100/0 to 85/15) to give the title compound (343 mg). The title compound (673 mg) was obtained from the starting material, 1H-indazole-3-carboxaldehyde, by a similar production method.

¹H-NMR (DMSO-D₆) δ: 13.59 (1H, s), 7.84 (1H, d, J = 8.2 Hz),
15 7.64 (1H, d, J = 9.0 Hz), 7.46 (1H, t, J = 7.5 Hz), 7.34 (1H, t, J = 53.9 Hz), 7.25 (1H, t, J = 7.5 Hz).

[0882]

Step 8-2: Ethyl 2-(3-(difluoromethyl)-1H-indazol-1-yl)pyrimidine-5-carboxylate

20 [0883]



[0884]

A suspension of 3-(difluoromethyl)-1H-indazole (0.95 g), ethyl 2-chloropyrimidine-carboxylate (1.1 g) and cesium
25 carbonate (2.2 g) in N,N-dimethylformamide (10 mL) was stirred at room temperature for 4 hr. To the reaction mixture was added water at room temperature and the mixture was stirred for 1 hr. The precipitated solid was collected by filtration and dried under reduced pressure to give the title compound (1.73
30 g).

¹H-NMR (DMSO-D₆) δ: 9.38 (2H, s), 8.81 (1H, d, J = 8.6 Hz),
8.01 (1H, d, J = 8.1 Hz), 7.77 (1H, t, J = 8.4 Hz), 7.57 (1H, t,

J = 54.0 Hz), 7.54 (1H, t, J = 7.6 Hz), 4.42 (2H, q, J = 7.1 Hz), 1.38 (3H, t, J = 7.1 Hz).

[0885]

Step 8-3: 2-(3-(Difluoromethyl)-1H-indazol-1-yl)pyrimidine-5-
5 carboxylic acid

[0886]



[0887]

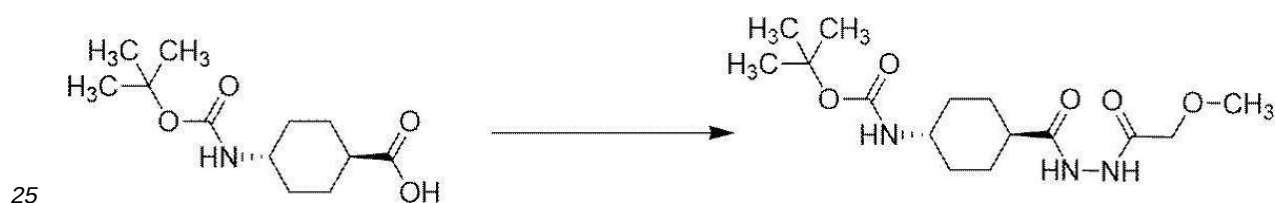
To a solution of ethyl 2-(3-(difluoromethyl)-1H-indazol-
10 1-yl)pyrimidine-5-carboxylate (1.73 g) in tetrahydrofuran (10 mL) was added 2 M aqueous sodium hydroxide solution (5.03 mL) under ice-cooling, and the mixture was allowed to gradually return to room temperature and stirred for 6 hr. To the
reaction mixture was added 2 M hydrochloric acid (5.0 mL) at
15 room temperature, and the mixture was stirred for 1 hr. The precipitated solid was collected by filtration and dried under reduced pressure to give the title compound (1.45 g).

¹H-NMR (DMSO-D₆) δ: 13.80 (1H, br s), 9.35 (2H, s), 8.82 (1H, d, J = 8.5 Hz), 8.01 (1H, d, J = 7.9 Hz), 7.78-7.74 (1H, m), 7.56
20 (1H, t, J = 54.0 Hz), 7.56-7.51 (1H, m).

[0888]

Step 8-4: tert-Butyl (trans-4-(2-(2-methoxyacetyl)hydrazine-1-carbonyl)cyclohexyl)carbamate

[0889]



[0890]

To trans-4-((tert-butoxycarbonyl)amino)cyclohexane-1-carboxylic acid (800 mg), methoxyacetic acid hydrazide (411 mg),

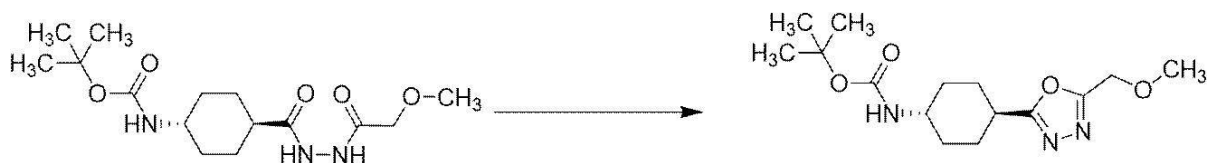
1-hydroxy-7-azabenzotriazole (134 mg) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (819 mg) were added N,N-dimethylformamide (10 mL) and triethylamine (732 mg) in a water bath, and the mixture was stirred for 10 min and
 5 stirred at room temperature overnight. To the reaction mixture was added water (20 mL) at room temperature, and the mixture was stirred for 1 hr. The precipitated solid was collected by filtration and dried under reduced pressure to give the title compound (650 mg).

10 ¹H-NMR (DMSO-D₆) δ: 9.64 (2H, d, J = 7.5 Hz), 6.71 (1H, d, J = 7.5 Hz), 3.87 (2H, s), 3.31 (3H, s), 3.22-3.09 (1H, m), 2.14-2.01 (1H, m), 1.85-1.68 (4H, br m), 1.46-1.30 (11H, m), 1.21-1.09 (2H, m).

[0891]

15 Step 8-5: tert-Butyl (trans-4-(5-(methoxymethyl)-1,3,4-oxadiazol-2-yl)cyclohexyl)carbamate

[0892]



[0893]

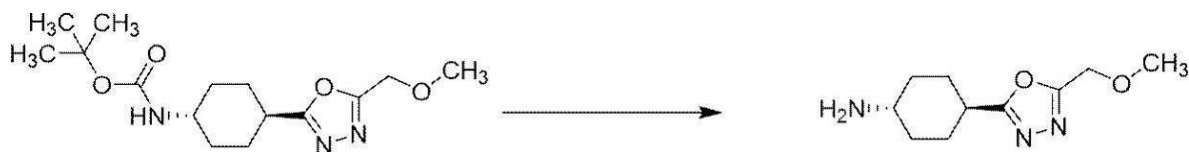
20 To a solution of tert-butyl (trans-4-(2-(2-methoxyacetyl)hydrazine -1-carbonyl)cyclohexyl)carbamate (650 mg), hexachloroethane (701 mg) and diisopropylethylamine (1.054 mL) in acetonitrile (12 mL) was added two divided portions of triphenylphosphine (725 mg) under ice-cooling, and the mixture
 25 was stirred for 15 min. The mixture was stirred at room temperature for 30 min and then at 70°C for 3 hr. To the reaction mixture were added hexachloroethane (350 mg), diisopropylethylamine (0.5 mL) and triphenylphosphine (370 mg) in a water bath, and the mixture was stirred at 80°C for 2 hr.
 30 To the reaction mixture were added toluene and water in a water bath, and the layers were separated. The organic layer was washed successively with 5 wt% aqueous potassium hydrogen sulfate solution and saturated brine, and concentrated under

reduced pressure. To the residue was added ethyl acetate at room temperature, insoluble material was removed by filtration, and the residue was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluent: n-hexane/ethyl acetate=34/66) to give crude product (480 mg) containing the title compound.

[0894]

Step 8-6: Trans-4-(5-(methoxymethyl)-1,3,4-oxadiazol-2-yl)cyclohexan-1-amine

10 [0895]



[0896]

To a solution of a crude product (480 mg) containing tert-butyl (trans-4-(5-(methoxymethyl)-1,3,4-oxadiazol-2-yl)cyclohexyl)carbamate in ethyl acetate (1.0 mL) was added trifluoroacetic acid (1.5 mL) at room temperature, and the mixture was stirred for 3 hr. To the reaction mixture was added trifluoroacetic acid (5.0 mL) at room temperature, and the mixture was stirred at 40°C for 1 hr. The reaction mixture was concentrated under reduced pressure, and ethyl acetate and Wakogel (registered trade mark) 50NH₂ (1.5 g) were added to the residue. The mixture was stirred for 30 min and filtered through celite, and the filtrate was concentrated under reduced pressure. The residue was purified by Bond Elut SCX (Agilent technologies) (eluent: methanol to 1 M ammonia/methanol solution) to give a crude product (190 mg) containing the title compound.

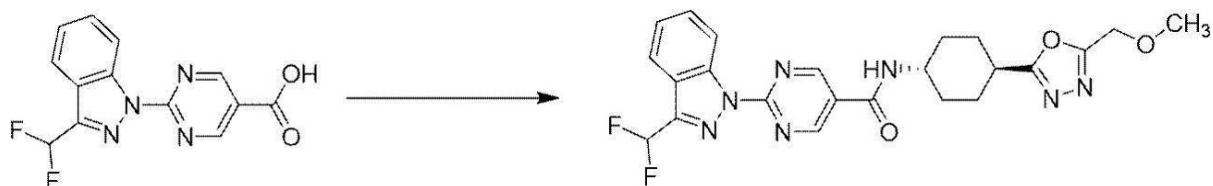
25

[0897]

Step 8-7: 2-(3-(Difluoromethyl)-1H-indazol-1-yl)-N-(trans-4-(5-(methoxymethyl)-1,3,4-oxadiazol-2-yl)cyclohexyl)pyrimidine-5-carboxamide

30

[0898]



[0899]

A suspension of a crude product (51 mg) containing trans-4-(5-(methoxymethyl)-1,3,4-oxadiazol-2-yl)cyclohexan-1-amine,
 5 2-(3-(difluoromethyl)-1H-indazol-1-yl)pyrimidine-5-carboxylic acid (50 mg), triethylamine (52.3 mg), 1-hydroxy-7-azabenzotriazole (25.8 mg) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (49.5 mg) in N,N-dimethylformamide (1.2 mL) was stirred overnight at room
 10 temperature. To the reaction mixture was added water at room temperature, and the precipitated solid was collected by filtration, and dried under reduced pressure. To this solid was added n-hexane/ethyl acetate (n-hexane/ethyl acetate=1/1) solution, and slurry purification was performed. The solid was
 15 collected by filtration, and dried under reduced pressure. The solid was dissolved in methanol and purified by amino silica gel column chromatography (eluent: ethyl acetate/methanol=100/0 to 97/3) to give a crude product containing the title compound. To the crude product containing the title compound was added
 20 ethyl acetate, and the mixture was slurry purified. The solid was collected by filtration and dried under reduced pressure to give the title compound (22 mg).

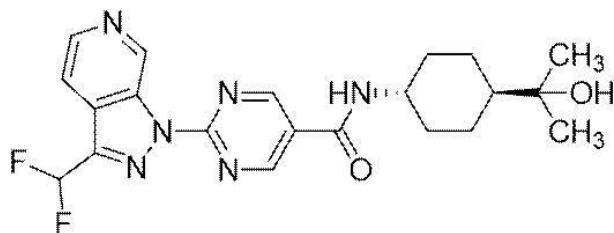
¹H-NMR (DMSO-D₆) δ: 9.33 (2H, s), 8.79 (1H, d, J = 5.1 Hz), 8.74 (1H, d, J = 7.6 Hz), 8.01 (1H, d, J = 8.1 Hz), 7.78-7.74
 25 (1H, m), 7.57 (1H, t, J = 53.0 Hz), 7.56-7.49 (1H, m), 4.63 (2H, s), 3.95-3.85 (1H, m), 3.35 (3H, s), 3.06-2.96 (1H, m), 2.24-2.22 (2H, br m), 2.18-2.16 (2H, br m), 1.75-1.46 (4H, m).

MS (M+H): 484 MS (M-H): 482

[0900]

30 [Production Example 9] Example 9: 2-(3-(difluoromethyl)-1H-pyrazolo[3,4-c]pyridin-1-yl)-N-(trans-4-(2-hydroxypropan-2-yl)cyclohexyl)pyrimidine-5-carboxamide

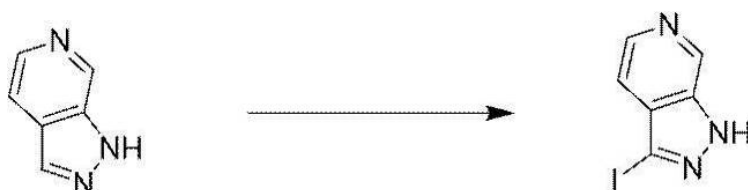
[0901]



[0902]

Step 9-1: 3-Iodo-1H-pyrazolo[3,4-c]pyridine

5 [0903]



[0904]

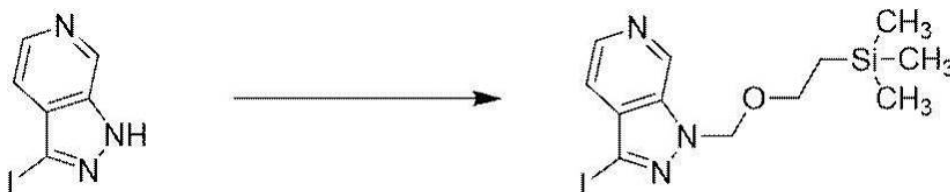
To a suspension of 1H-pyrazolo[3,4-c]pyridine (4.95 g) and potassium carbonate (17.23 g) in N,N-dimethylformamide
10 (49.5 mL) was added iodine (10.55 g) under ice-cooling, and the mixture was stirred at room temperature for 3 hr. The reaction mixture was added to 10 wt% aqueous sodium thiosulfate solution (300 mL), and the mixture was stirred at room temperature for 1 hr. The precipitated solid was collected by filtration and
15 dried under reduced pressure to give the title compound (8.66 g).

¹H-NMR (DMSO-D₆) δ: 14.06 (1H, s), 9.05 (1H, s), 8.30 (1H, d, J = 6.0 Hz), 7.45 (1H, d, J = 6.0 Hz).

[0905]

20 Step 9-2: 3-Iodo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazolo[3,4-c]pyridine

[0906]



[0907]

25 To a suspension of sodium hydride (0.612 g, 60 wt% oil

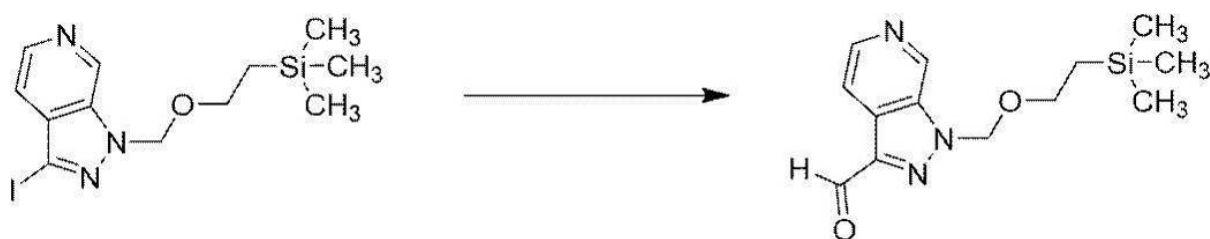
dispersion) in N,N-dimethylformamide (10 mL) was added dropwise N,N-dimethylformamide (30 mL) solution of 3-iodo-1H-pyrazolo[3,4-c]pyridine (3.0 g) under ice-cooling, and the mixture was stirred at the same temperature for 1 hr. To the
5 reaction mixture was added 2-(chloromethoxy)ethyltrimethylsilane (2.7 mL) under ice-cooling, and the mixture was stirred at room temperature for 2 hr. The reaction mixture and ethyl acetate were added to water (60 mL) at room temperature. The layers were separated, and the
10 aqueous layer was extracted once with ethyl acetate. The combined organic layer was washed successively with water and saturated brine, and dried over sodium sulfate. Sodium sulfate was removed by filtration, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel
15 column chromatography (eluent: n-hexane/ethyl acetate=90/10 to 50/50) to give the title compound (2.55 g).

$^1\text{H-NMR}$ ($\text{DMSO-}D_6$) δ : 9.26 (1H, s), 8.38 (1H, d, $J = 6.0$ Hz), 7.49 (1H, d, $J = 6.0$ Hz), 5.88 (2H, s), 3.54 (2H, t, $J = 7.9$ Hz), 0.80 (2H, t, $J = 7.9$ Hz), -0.12 (9H, s).

20 [0908]

Step 9-3: 1-((2-(Trimethylsilyl)ethoxy)methyl)-1H-pyrazolo[3,4-c]pyridine-3-carbaldehyde

[0909]



25 [0910]

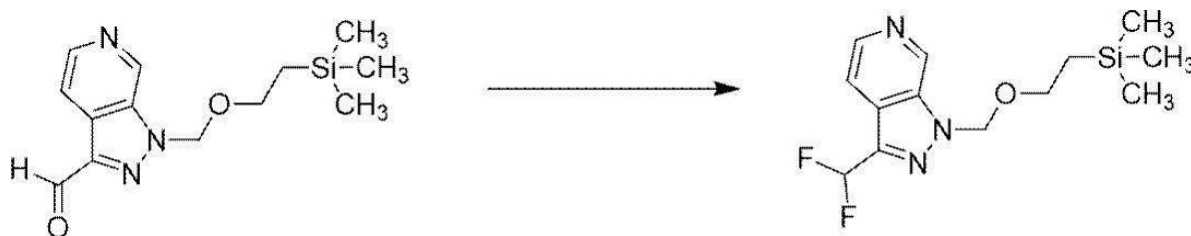
To a solution of 3-iodo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazolo[3,4-c]pyridine (1.1 g) in tetrahydrofuran (20 mL) was added dropwise 2.0 M tetrahydrofuran solution (2.198 mL) of isopropylmagnesium
30 chloride under ice-salt bath cooling, and the mixture was stirred for 1 hr. At the same temperature, N,N-

dimethylformamide (0.908 mL) was added and the mixture was stirred for 2 hr. To the reaction mixture was added saturated aqueous ammonium chloride solution at the same temperature. Ethyl acetate was added thereto at room temperature, and the
5 layers were separated. The organic layer was washed successively with water and saturated brine, and dried over sodium sulfate. Sodium sulfate was removed by filtration, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography
10 (eluent: n-hexane/ethyl acetate=90/10 to 0/100) to give the title compound (0.26 g).

$^1\text{H-NMR}$ ($\text{DMSO-}d_6$) δ : 10.42 (1H, s), 9.44 (1H, s), 8.42 (1H, d, J = 6.0 Hz), 8.05 (1H, d, J = 6.0 Hz), 6.22 (2H, s), 3.64 (2H, t, J = 7.9 Hz), 0.85 (2H, t, J = 7.9 Hz), -0.10 (9H, s).

15 [0911]

Step 9-4: 3-(Difluoromethyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazolo[3,4-c]pyridine
[0912]



20 [0913]

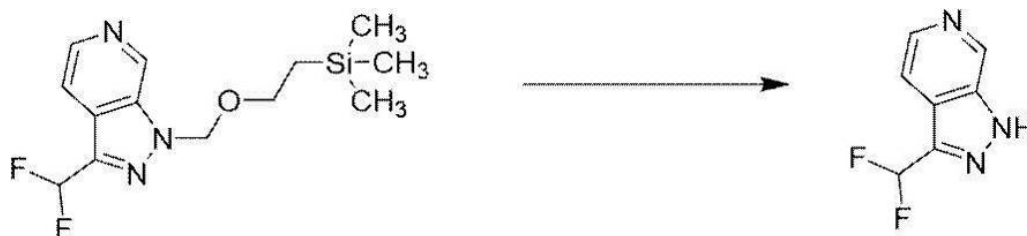
To a solution of 1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazolo[3,4-c]pyridine-3-carbaldehyde (260 mg) in dichloromethane (5.0 mL) was added dropwise Deoxo-Fluor (registered trade mark) (0.518 mL) under ice-cooling. The
25 mixture was stirred at the same temperature for 1 hr, and at room temperature for 4 hr. To the reaction mixture was slowly added saturated aqueous sodium hydrogen carbonate under ice-cooling. To the reaction mixture was added ethyl acetate at room temperature, and the organic layer was washed successively
30 with water and saturated brine. The organic layer was dried over sodium sulfate, sodium sulfate was removed by filtration,

and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluent: n-hexane/ethyl acetate=90/10 to 0/100) to give the title compound (260 mg).

5 ¹H-NMR (DMSO-D₆) δ: 9.34 (1H, s), 8.25 (1H, d, J = 5.4 Hz), 7.75 (1H, d, J = 5.4 Hz), 7.75 (1H, t, J = 52.5 Hz), 5.99 (2H, s), 3.59 (2H, t, J = 7.9 Hz), 0.86 (2H, t, J = 7.9 Hz), -0.08 (9H, s).

[0914]

10 Step 9-5: 3-(Difluoromethyl)-1H-pyrazolo[3,4-c]pyridine
[0915]



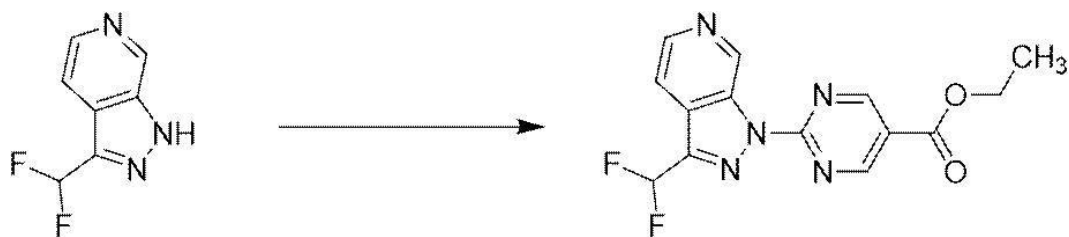
[0916]

To a solution of 3-(difluoromethyl)-1-((2-(
15 (trimethylsilyl)ethoxy)methyl)-1H-pyrazolo[3,4-c]pyridine (260 mg) in dichloromethane (1.5 mL) was added trifluoroacetic acid (1.5 mL) at room temperature, and the mixture was stirred overnight. The reaction mixture was concentrated under reduced pressure, and chloroform and triethylamine (0.182 mL) was added
20 to the residue. The mixture was purified by silica gel column chromatography {eluent: n-hexane/ethyl acetate (containing 5% 2 M ammonia/methanol solution)=90/10 to 0/100} to give a crude product (83 mg) containing the title compound.

[0917]

25 Step 9-6: Ethyl 2-(3-(difluoromethyl)-1H-pyrazolo[3,4-c]pyridin-1-yl)pyrimidine-5-carboxylate

[0918]



[0919]

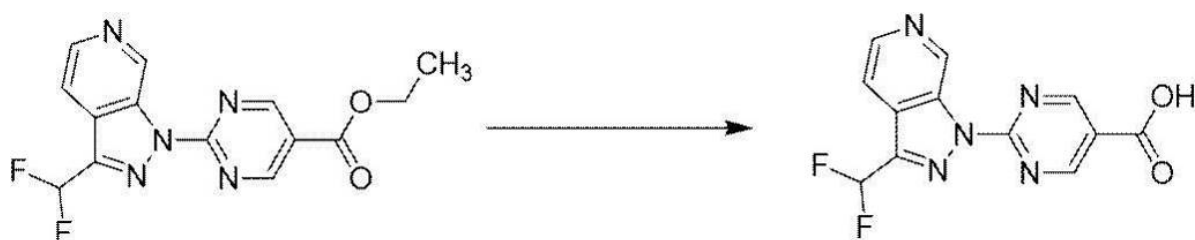
A suspension of a crude product (54 mg) containing 3-(difluoromethyl)-1H-pyrazolo[3,4-c]pyridine, ethyl 2-chloropyrimidine-carboxylate (59.6 mg) and cesium carbonate (156 mg) in N,N-dimethylformamide (0.6 mL) was stirred at room temperature for 1 hr. To the reaction mixture was added water at room temperature, and the precipitated solid was collected by filtration, washed with water, and dried under reduced pressure. The solid was purified by silica gel column chromatography (eluent: n-hexane/ethyl acetate=80/20 to 0/100) to give the title compound (70 mg).

¹H-NMR (DMSO-D₆) δ: 10.13 (1H, d, J = 1.2 Hz), 9.42 (2H, s), 8.63 (1H, d, J = 5.4 Hz), 8.00 (1H, d, J = 5.4 Hz), 7.63 (1H, t, J = 53.1 Hz), 4.42 (2H, q, J = 7.1 Hz), 1.37 (3H, t, J = 7.1 Hz).

[0920]

Step 9-7: 2-(3-(Difluoromethyl)-1H-pyrazolo[3,4-c]pyridin-1-yl)pyrimidine-5-carboxylic acid

[0921]



[0922]

To a solution of ethyl 2-(3-(difluoromethyl)-1H-pyrazolo[3,4-c]pyridin-1-yl)pyrimidine-5-carboxylate (70 mg) in tetrahydrofuran (1.0 mL) was added 2 M aqueous sodium hydroxide solution (0.329 mL) at room temperature, and the mixture was stirred overnight. To the reaction mixture was added 1 M

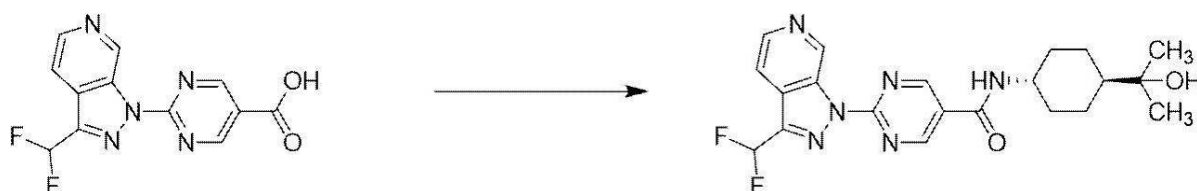
hydrochloric acid (0.658 mL) at room temperature, and the mixture was stirred for 1 hr. The precipitated solid was collected by filtration, washed with water, and dried under reduced pressure to give the title compound (33 mg).

5 $^1\text{H-NMR}$ ($\text{DMSO-}d_6$) δ : 13.88 (1H, br s), 10.15 (1H, s), 9.41 (2H, s), 8.64 (1H, d, $J = 5.4$ Hz), 8.01 (1H, d, $J = 5.4$ Hz), 7.64 (1H, t, $J = 53.1$ Hz).

[0923]

Step 9-8: 2-(3-(difluoromethyl)-1H-pyrazolo[3,4-c]pyridin-1-yl)-N-(trans-4-(2-hydroxypropan-2-yl)cyclohexyl)pyrimidine-5-
10 carboxamide

[0924]



[0925]

15 To a suspension of 2-(3-(difluoromethyl)-1H-pyrazolo[3,4-c]pyridin-1-yl)pyrimidine-5-carboxylic acid (33 mg) and 2-(trans-4-aminocyclohexyl)propan-2-ol (26.7 mg) in *N,N*-dimethylformamide (0.33 mL) were added triethylamine (0.0237 mL), 1-hydroxy-7-azabenzotriazole (15.42 mg) and 1-ethyl-3-(3-
20 dimethylaminopropyl)carbodiimide hydrochloride (26.1 mg) at room temperature, and the mixture was stirred overnight. To the reaction mixture were added water (2.0 mL) and saturated aqueous sodium hydrogen carbonate (1.0 mL) at room temperature, and the mixture was stirred for 1 hr. The precipitated solid
25 was collected by filtration, washed with water, and dried under reduced pressure to give the title compound (42 mg).

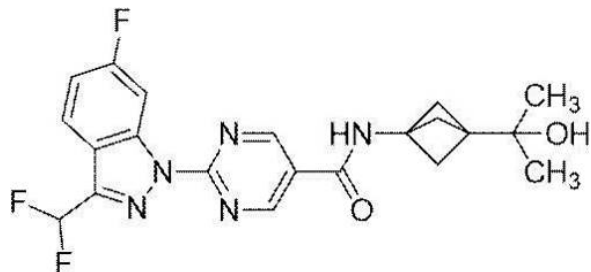
$^1\text{H-NMR}$ ($\text{DMSO-}d_6$) δ : 10.12 (1H, s), 9.35 (2H, s), 8.67 (1H, d, $J = 7.5$ Hz), 8.62 (1H, d, $J = 5.4$ Hz), 8.00 (1H, d, $J = 5.4$ Hz), 7.64 (1H, t, $J = 53.3$ Hz), 4.06 (1H, s), 3.81-3.70 (1H, m),
30 1.99-1.85 (4H, m), 1.38-1.28 (2H, m), 1.22-1.11 (3H, m), 1.05 (6H, s).

MS ($M+H$): 431 MS ($M-H$): 429

[0926]

[Production Example 10] Example 10: 2-(3-(difluoromethyl)-6-fluoro-1H-indazol-1-yl)-N-(3-(2-hydroxypropan-2-yl)bicyclo[1.1.1]pentan-1-yl)pyrimidine-5-carboxamide

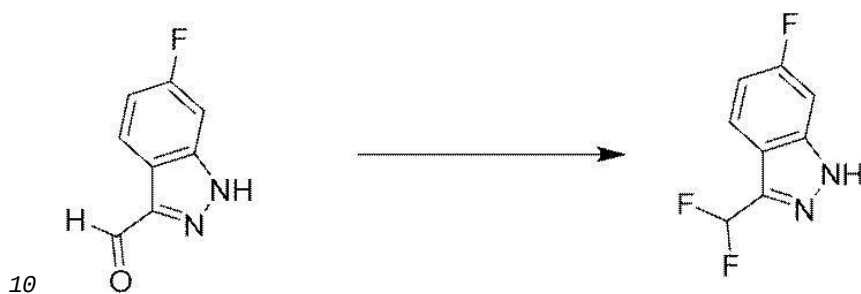
5 [0927]



[0928]

Step 10-1: 3-(Difluoromethyl)-6-fluoro-1H-indazole

[0929]



10

[0930]

To a suspension of 6-fluoro-1H-indazole-3-carbaldehyde (500 mg) in dichloromethane (15 mL) was added N,N-diethylaminosulfur trifluoride (0.805 mL) under ice-cooling, and the mixture was allowed to gradually return to room temperature and stirred for 4 hr. To the reaction mixture were added saturated aqueous sodium hydrogen carbonate (10 mL) and water (5 mL) under ice-cooling. To the reaction mixture was added chloroform at room temperature, and the layers were separated. The organic layer was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluent: n-hexane/ethyl acetate=92/8 to 34/66) to give a crude product (205 mg) containing the title compound.

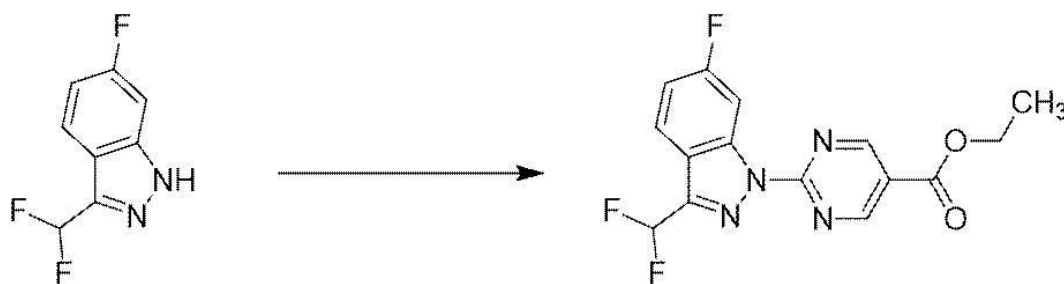
15

20

[0931]

25 Step 10-2: Ethyl 2-(3-(difluoromethyl)-6-fluoro-1H-indazol-1-yl)pyrimidine-5-carboxylate

[0932]



[0933]

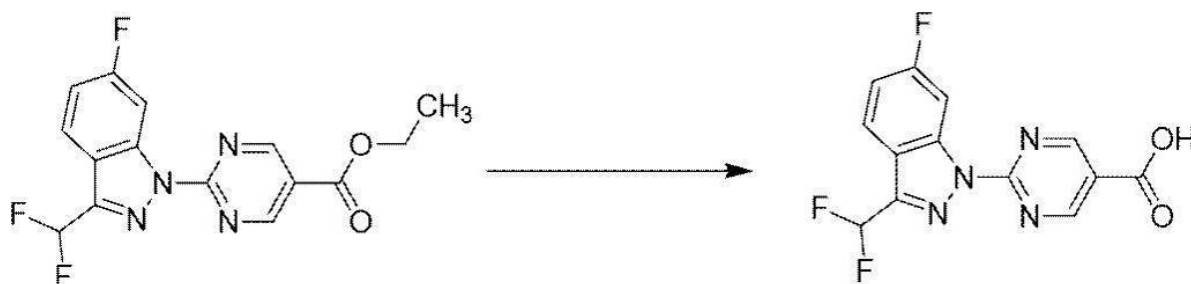
A suspension of a crude product (205 mg) containing 3-(difluoromethyl)-6-fluoro-1H-indazole, ethyl 2-chloropyrimidine-carboxylate (206 mg) and cesium carbonate (456 mg) in N,N-dimethylformamide (4.0 mL) was stirred at 60°C for 5 hr. To the reaction mixture was added water (25 mL) at room temperature, and the precipitated solid was collected by
10 filtration, and dried under reduced pressure. The solid was dissolved in chloroform and purified twice by silica gel column chromatography (eluent: n-hexane/ethyl acetate=92/8 to 34/66) to give the title compound (275 mg).

¹H-NMR (DMSO-D₆) δ: 9.39 (2H, s), 8.57 (1H, dd, J = 10.4, 2.3
15 Hz), 8.05 (1H, dd, J = 8.8, 5.3 Hz), 7.57 (1H, t, J = 53.4 Hz), 7.48-7.42 (1H, m), 4.42 (2H, q, J = 7.2 Hz), 1.38 (3H, t, J = 7.2 Hz).

[0934]

Step 10-3: 2-(3-(Difluoromethyl)-6-fluoro-1H-indazol-1-yl)pyrimidine-5-carboxylic acid
20

[0935]



[0936]

To a suspension of ethyl 2-(3-(difluoromethyl)-6-fluoro-1H-indazol-1-yl)pyrimidine-5-carboxylate (275 mg) in
25

tetrahydrofuran (10 mL) was added 2 M aqueous sodium hydroxide solution (0.85 mL) at room temperature, and the mixture was stirred for 8 hr. To the reaction mixture were added 1 M hydrochloric acid (1.7 mL) and water (15 mL) at room

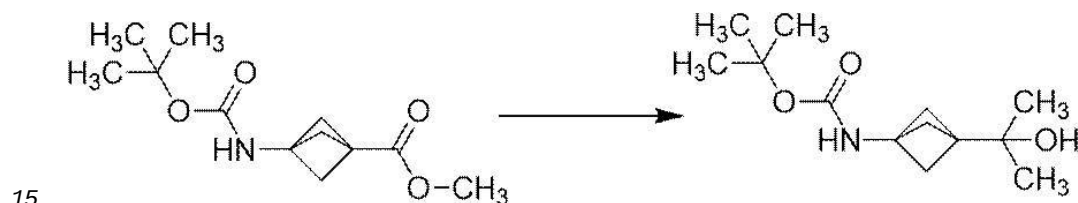
5 temperature, and the mixture was left standing overnight. The precipitated solid was collected by filtration and dried under reduced pressure to give the title compound (210 mg).

¹H-NMR (DMSO-D₆) δ: 13.84 (1H, br s), 9.36 (2H, s), 8.56 (1H, dd, J = 10.2, 2.3 Hz), 8.04 (1H, dd, J = 8.8, 5.3 Hz), 7.56 (1H, t, J = 53.2 Hz), 7.47-7.42 (1H, m).

[0937]

Step 10-4: tert-Butyl (3-(2-hydroxypropan-2-yl)bicyclo[1.1.1]pentan-1-yl)carbamate

[0938]



[0939]

To a solution of methyl 3-((tert-butoxycarbonyl)amino)bicyclo[1.1.1]pentane-1-carboxylate (2.0 g) in tetrahydrofuran (10 mL) was added 1.02 M tetrahydrofuran solution (33 mL) of methylmagnesium bromide under ice-cooling. The mixture was stirred at the same temperature for 1 hr, allowed to gradually return to room temperature, and stirred for 2 hr. To the reaction mixture was added saturated aqueous ammonium chloride solution (40 mL) under ice-cooling. To the reaction mixture was added ethyl acetate (40 mL) at room temperature, the layers were separated, and the aqueous layer was extracted once with ethyl acetate (10 mL). The combined organic layer was washed with saturated brine, and dried over sodium sulfate. Sodium sulfate was removed by filtration, and the filtrate was concentrated under reduced pressure to give the title compound (2.0 g).

30 ¹H-NMR (DMSO-D₆) δ: 7.34 (1H, br s), 4.07 (1H, br s), 1.70 (6H,

s), 1.37 (9H, s), 1.02 (6H, s).

[0940]

Step 10-5: 2-(3-Aminobicyclo[1.1.1]pentan-1-yl)propan-2-ol
monohydrochloride

5 [0941]



[0942]

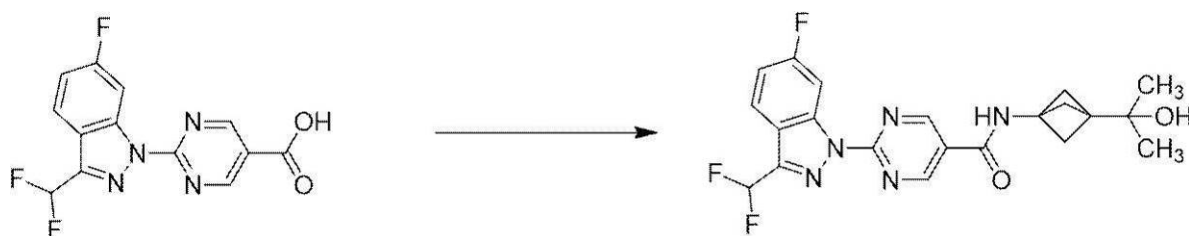
To a solution of tert-butyl (3-(2-hydroxypropan-2-yl)bicyclo[1.1.1]pentan-1-yl)carbamate (414 mg) in ethyl
10 acetate (4.0 mL) was added 4 M hydrogen chloride/ethyl acetate
solution (4.0 mL) at room temperature, and the mixture was
stirred overnight. To the reaction mixture was added ethyl
acetate (10 mL) at room temperature, and the precipitated solid
was collected by filtration and dried under reduced pressure to
15 give the title compound (271 mg).

¹H-NMR (DMSO-D₆) δ: 8.79 (3H, br s), 4.21 (1H, br s), 1.80 (6H, s), 1.05 (6H, s).

[0943]

Step 10-6: 2-(3-(Difluoromethyl)-6-fluoro-1H-indazol-1-yl)-N-
20 (3-(2-hydroxypropan-2-yl)bicyclo[1.1.1]pentan-1-yl)pyrimidine-
5-carboxamide

[0944]



[0945]

25 To a suspension of 2-(3-(difluoromethyl)-6-fluoro-1H-
indazol-1-yl)pyrimidine-5-carboxylic acid (62 mg), 2-(3-
aminobicyclo[1.1.1]pentan-1-yl)propan-2-ol monohydrochloride

(48 mg), 1-hydroxy-7-azabenzotriazole (31 mg) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (49 mg) in N,N-dimethylformamide (1.0 mL) was added triethylamine (0.050 mL) at room temperature, and the mixture was stirred overnight. To the reaction mixture were added saturated aqueous sodium hydrogen carbonate (1.0 mL) and water (12 mL) at room temperature, and the precipitated solid was collected by filtration and dried under reduced pressure to give the title compound (74.5 mg).

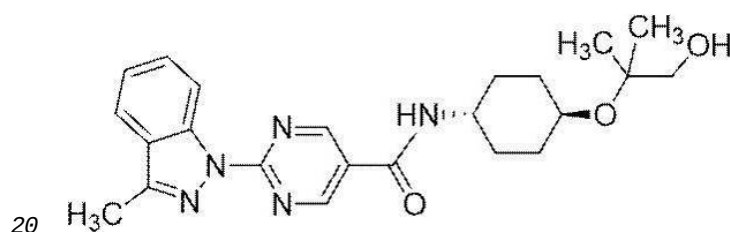
¹H-NMR (DMSO-D₆) δ: 9.33 (1H, br s), 9.30 (2H, s), 8.52 (1H, dd, J = 10.3, 2.2 Hz), 8.04 (1H, dd, J = 8.8, 5.3 Hz), 7.56 (1H, t, J = 53.2 Hz), 7.46-7.41 (1H, m), 4.21 (1H, s), 1.96 (6H, s), 1.09 (6H, s).

MS (M+H): 432 MS (M-H): 430

[0946]

[Production Example 11] Example 229: Production of N-(trans-4-(1-hydroxy-2-methylpropoxy)cyclohexyl)-2-(3-methyl-1H-indazol-1-yl)pyrimidine-5-carboxamide

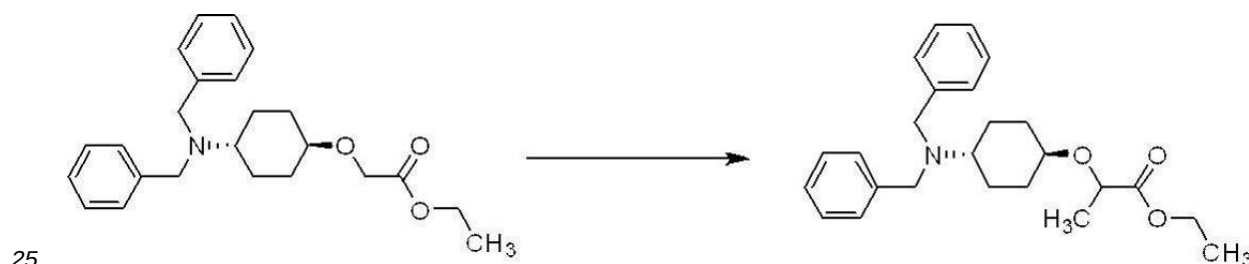
[0947]



[0948]

Step 11-1: Ethyl 2-{[trans-4-(dibenzylamino)cyclohexyl]oxy}-propionate

[0949]



[0950]

To 1.13 M n-hexane solution (7.81 mL) of lithium

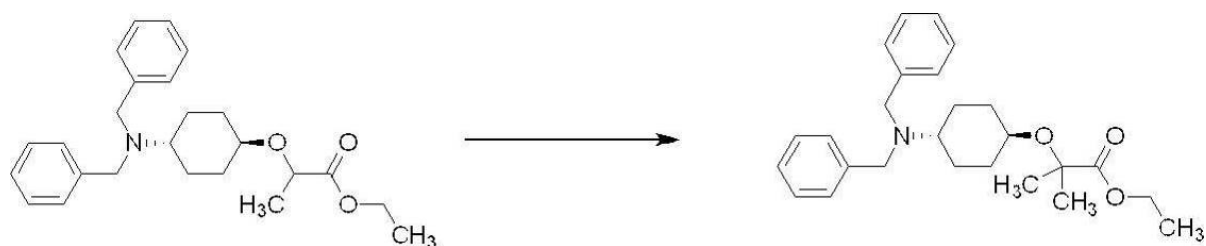
bis(trimethylsilyl)amide was added dropwise at -78°C tetrahydrofuran (15.3 mL) solution of 2-{{trans-4-(dibenzylamino)cyclohexyl}oxy}ethyl acetate (1.53 g) synthesized in the same manner as in Production Example 4, step 5 4-4, and the mixture was stirred at the same temperature for 20 min. To the reaction mixture was added dropwise methyl iodide (1.003 mL) at the same temperature. The mixture was stirred for 1 hr, allowed to gradually return to room temperature, and left standing overnight. To the reaction mixture were added 10 water and ethyl acetate. The layers were separated, and the aqueous layer was extracted once with ethyl acetate. The combined organic layer was concentrated under reduced pressure. The residue was purified by silica gel chromatography (eluent: n-hexane/ethyl acetate=98/2 to 80/20) to give the title 15 compound (422 mg).

¹H-NMR (DMSO-D₆) δ: 7.33-7.26 (8H, m), 7.23-7.16 (2H, m), 4.13-4.00 (3H, m), 3.55 (4H, s), 3.25-3.15 (1H, m), 2.44-2.31 (1H, m), 2.07-1.88 (2H, m), 1.85-1.73 (2H, m), 1.46-1.30 (2H, m), 1.25-1.13 (6H, m), 1.10-0.88 (2H, m).

20 [0951]

Step 11-2: Ethyl 2-{{trans-4-(dibenzylamino)cyclohexyl}oxy}-2-methylpropionate

[0952]



25 [0953]

To 2.0 M tetrahydrofuran/n-heptane/ethylbenzene solution (1.174 mL) of lithium diisopropylamide was added dropwise at -78°C tetrahydrofuran (4.22 mL) solution of ethyl 2-{{trans-4-(dibenzylamino)cyclohexyl}oxy}propionate (422 mg), and the 30 mixture was stirred at the same temperature for 30 min. To the reaction mixture was added dropwise methyl iodide (0.267 mL) at

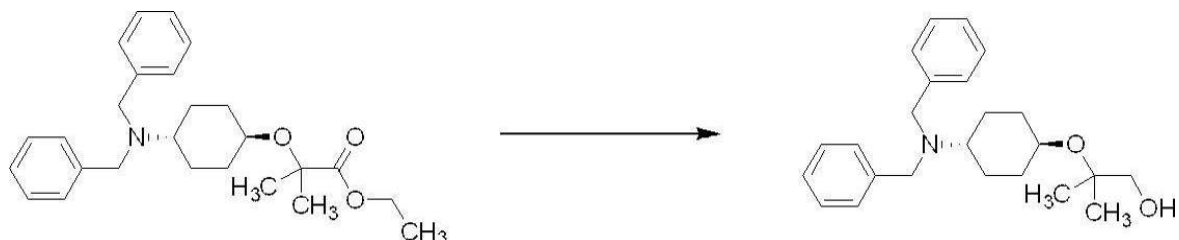
the same temperature, hexamethylphosphoric triamide (0.204 mL) was added, and the mixture was stirred for 40 min. The reaction mixture was allowed to gradually return to room temperature, stirred for 1 hr, and left standing overnight. To the reaction mixture were added water and ethyl acetate. The layers were separated, and the aqueous layer was extracted once with ethyl acetate. The combined organic layer was concentrated under reduced pressure. The residue was purified by silica gel chromatography (eluent: n-hexane/ethyl acetate=98/2 to 78/22) to give the title compound (388 mg).

¹H-NMR (DMSO-D₆) δ: 7.36-7.24 (8H, m), 7.23-7.16 (2H, m), 4.09 (2H, q, J = 7.2 Hz), 3.55 (4H, s), 3.27-3.20 (1H, m), 2.37-2.30 (1H, m), 1.95-1.84 (2H, m), 1.81-1.71 (2H, m), 1.50-1.35 (2H, m), 1.29 (6H, s), 1.19 (3H, t, J = 7.0 Hz), 1.11-0.97 (2H, m).

[0954]

Step 11-3: 2-{[Trans-4-(dibenzylamino)cyclohexyl]oxy}-2-methylpropan-1-ol

[0955]



[0956]

To a suspension of lithium aluminum hydride (76 mg) in tetrahydrofuran (3.88 mL) was added dropwise tetrahydrofuran (1.94 mL) solution of ethyl 2-{[trans-4-(dibenzylamino)cyclohexyl]oxy}-2-methylpropionate (388 mg) under ice-cooling. The mixture was allowed to gradually return to room temperature, stirred for 1 hr, and left standing overnight. To the reaction mixture were successively added water (0.076 mL), 4 M aqueous sodium hydroxide solution (0.076 mL) and water (0.228 mL) under ice-cooling. The mixture was filtered through celite, and the filtrate was concentrated under reduced pressure to give the title compound (329 mg).

¹H-NMR (DMSO-D₆) δ: 7.36-7.25 (8H, m), 7.22-7.16 (2H, m), 4.45 (1H, t, J = 5.5 Hz), 3.55 (4H, s), 3.49-3.34 (1H, m), 3.16 (2H, d, J = 5.5 Hz), 2.39-2.30 (1H, m), 1.86-1.71 (4H, m), 1.51-1.39 (2H, m), 1.12-0.93 (8H, m).

5 [0957]

Step 11-4: 2-((Trans-4-aminocyclohexyl)oxy)-2-methylpropan-1-ol
[0958]



[0959]

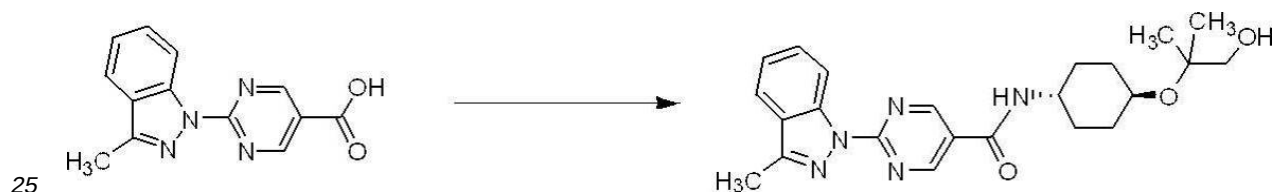
10 To a solution of 2-{[trans-4-(dibenzylamino)cyclohexyl]oxy}-2-methylpropan-1-ol (150 mg) in tetrahydrofuran/methanol (1.5 mL, tetrahydrofuran/methanol=1/1) was added 20% palladium hydroxide-carbon (15 mg) at room temperature. Under 1 atm hydrogen, the mixture was stirred at
15 room temperature overnight. The reaction mixture was filtered through celite, and the filtrate was concentrated under reduced pressure to give the title compound (68.8 mg).

¹H-NMR (DMSO-D₆) δ: 4.46 (1H, t, J = 5.1 Hz), 3.48-3.35 (2H, m), 3.17 (2H, d, J = 5.1 Hz), 2.25-1.91 (2H, m), 1.77-1.63 (4H, m),
20 1.25-0.96 (10H, m).

[0960]

Step 11-5: N-(Trans-4-(1-hydroxy-2-methylpropoxy)cyclohexyl)-2-(3-methyl-1H-indazol-1-yl)pyrimidine-5-carboxamide

[0961]



25

[0962]

A suspension of 2-(3-methyl-1H-indazol-1-yl)pyrimidine-5-carboxylic acid (30 mg) synthesized in the same manner as in

Production Example 4, step 4-2, 2-((trans-4-aminocyclohexyl)oxy)-2-methylpropan-1-ol (24.31 mg), 1-hydroxy-7-azabenzotriazole (4.82 mg) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (33.9 mg) in
5 N,N-dimethylformamide (0.6 mL) was stirred for 3 hr. To the reaction mixture was added water (3.0 mL) at room temperature, and the precipitated solid was collected by filtration, washed with water, and dried under reduced pressure at 70°C to give a crude product (41.6 mg) containing the title compound. The
10 crude product was purified by reversed-phase silica gel chromatography (eluent: water/acetonitrile=95/5 to 0/100) to give the title compound (23.9 mg).

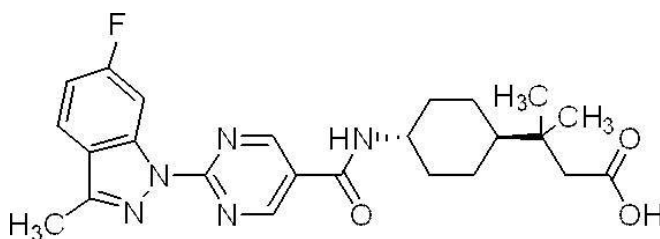
¹H-NMR (DMSO-D₆) δ: 9.21 (2H, s), 8.67 (1H, d, J = 8.3 Hz), 8.51 (1H, d, J = 7.4 Hz), 7.89 (1H, d, J = 7.6 Hz), 7.63 (1H, dd, J = 8.3, 7.5 Hz), 7.40 (1H, dd, J = 7.6, 7.5 Hz), 4.53 (1H, br s), 3.82-3.67 (1H, m), 3.58-3.45 (1H, m), 3.22 (2H, s), 2.62 (3H, s), 1.97-1.76 (4H, m), 1.51-1.22 (4H, m), 1.09 (6H, s).

MS (M+H): 424 MS (M-H): 422

[0963]

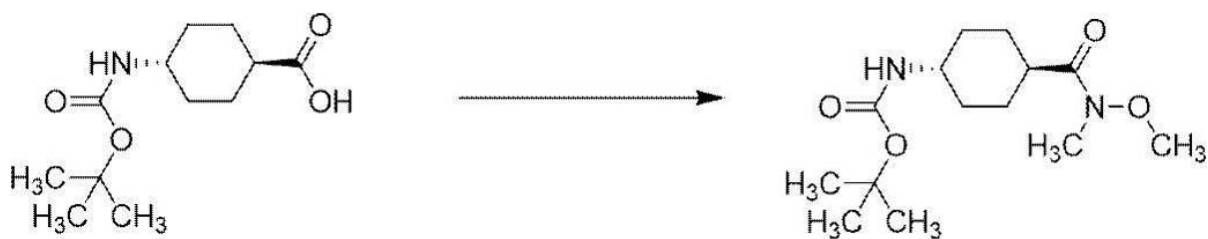
20 [Production Example 12] Example 241: Production of 3-(trans-4-(2-(6-fluoro3-methyl-1H-indazol-1-yl)pyrimidine-5-carboxamide)cyclohexyl)-3-methylbutyric acid

[0964]



25 [0965]

Step 12-1: tert-Butyl {trans-4-[methoxy(methyl) carbamoyl]cyclohexyl}carbamate
[0966]



[0967]

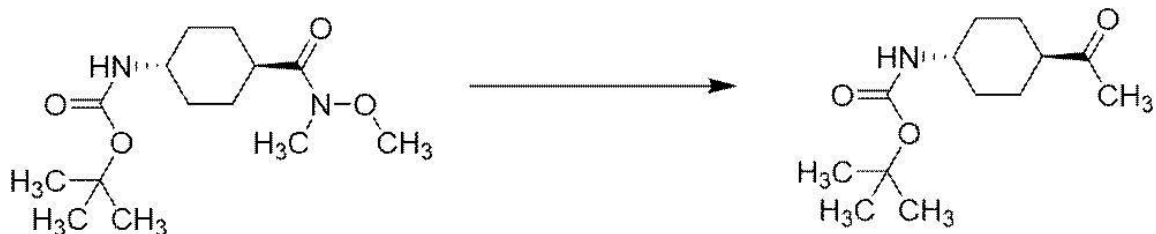
Under a nitrogen atmosphere, to a solution of trans-4-
 [(tert-butoxycarbonyl)amino]cyclohexanecarboxylic acid (25.0 g),
 5 N,O-dimethylhydroxylamine hydrochloride (13.1 g) and N,N-
 diisopropylethylamine (23.3 mL) in N,N-dimethylformamide (250
 mL) were successively added portions of 1-hydroxy-1H-
 benzotriazole monohydrate (20.5 g) and 1-ethyl-3-(3-
 dimethylaminopropyl)carbodiimide hydrochloride (25.7 g) under
 10 water cooling, and the mixture was stirred for 7 days. To the
 reaction mixture was added dropwise saturated aqueous sodium
 hydrogen carbonate/water (250 mL, saturated aqueous sodium
 hydrogen carbonate/water = 1/2) at room temperature, and the
 mixture was stirred. The precipitated solid was collected by
 15 filtration, washed with water (300 mL), and dried under reduced
 pressure to give the title compound (24.45 g).

¹H-NMR (CDCl₃) δ: 4.40-4.33 (1H, m), 3.69 (3H, s), 3.48-3.39
 (1H, m), 3.17 (3H, s), 2.64-2.57 (1H, m), 2.11-2.07 (2H, m),
 1.86-1.81 (2H, m), 1.67-1.57 (2H, m), 1.44 (9H, s), 1.14 (2H,
 20 ddd, J = 24.9, 12.7, 3.4 Hz).

[0968]

Step 12-2: tert-Butyl (trans-4-acetylcyclohexyl)carbamate

[0969]



25 [0970]

Under an argon atmosphere, to a solution of tert-butyl
 {trans-4-[methoxy(methyl)carbamoyl]cyclohexyl}carbamate (3.0 g)

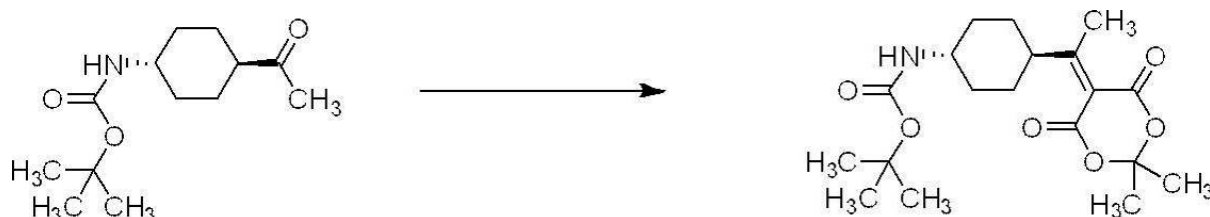
in tetrahydrofuran (20 mL) was added 1.02 M tetrahydrofuran solution (22.6 mL) of methylmagnesium bromide under ice-cooling, and the mixture was stirred for 3 hr. To the reaction mixture were added saturated aqueous ammonium chloride solution (20 mL),
 5 water (10 mL) and ethyl acetate (30 mL) under ice-cooling, and the layers were separated. The aqueous layer was extracted once with ethyl acetate (20 mL). The combined organic layer was washed successively with water and saturated brine, and dried over sodium sulfate. Sodium sulfate was removed by
 10 filtration, and the filtrate was concentrated under reduced pressure to give the title compound (2.464 g).

$^1\text{H-NMR}$ ($\text{DMSO-}d_6$) δ : 6.72 (1H, d, $J = 7.9$ Hz), 3.17-3.07 (1H, m), 2.27-2.20 (1H, m), 2.08 (3H, s), 1.87-1.76 (4H, m), 1.37 (9H, s), 1.26-1.09 (4H, m).

15 [0971]

Step 12-3: tert-Butyl (trans-4-(1-(2,2-dimethyl-4,6-dioxo-1,3-dioxan-5-ylidene)ethyl)cyclohexyl)carbamate

[0972]



20 [0973]

A 1.0 M dichloromethane solution (31 mL) of titanium tetrachloride (IV) was added to tetrahydrofuran (20 mL) under ice-cooling. To the reaction mixture were added tetrahydrofuran (28 mL) solution of tert-butyl (trans-4-
 25 acetylcyclohexyl)carbamate (2.464 g) and 2,2-dimethyl-1,3-dioxane-4,6-dione (1.619 g), and pyridine (4.54 mL) under ice-cooling. The mixture was allowed to gradually return to room temperature and stirred overnight. To the reaction mixture were added saturated aqueous ammonium chloride solution (30 mL),
 30 water (15 mL) and ethyl acetate (60 mL) at room temperature. After partitioning, the organic layer was washed successively with water and saturated brine, and concentrated under reduced

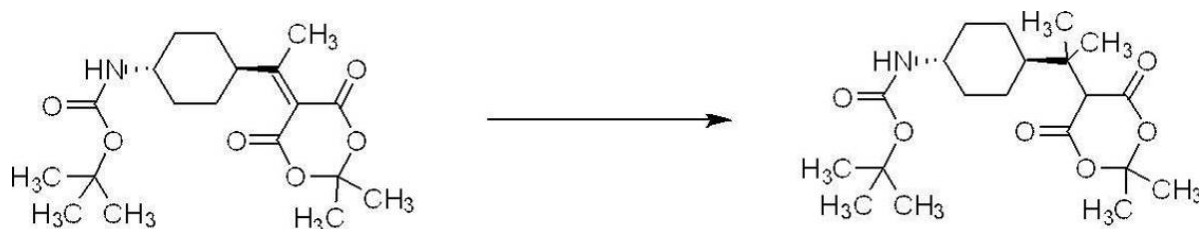
pressure. To the residue were added ethyl acetate (3.0 mL), n-hexane (30 mL) and water (10 mL) and the mixture was slurry stirred for 1 hr. The solid was collected by filtration and dried under reduced pressure to give the title compound (2.254 g).

$^1\text{H-NMR}$ (DMSO-D_6) δ : 6.75 (1H, d, $J = 8.1$ Hz), 3.42–3.35 (1H, m), 3.32–3.22 (1H, m), 2.29 (3H, s), 1.85–1.81 (2H, m), 1.67 (6H, s), 1.60–1.49 (4H, m), 1.38 (9H, s), 1.24–1.14 (2H, m).

[0974]

Step 12-4: tert-Butyl (trans-4-(2-(2,2-dimethyl-4,6-dioxo-1,3-dioxan-5-yl)propan-2-yl)cyclohexyl)carbamate

[0975]



[0976]

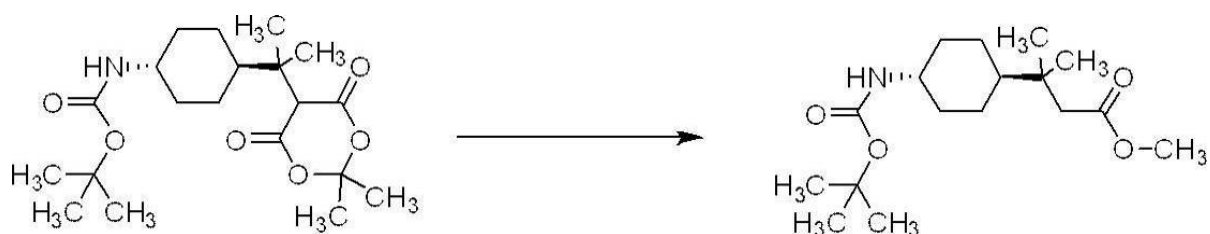
To a solution of copper(I) bromide (2.64 g) in tetrahydrofuran (20 mL) was added 1.0 M tetrahydrofuran solution (37 mL) of methyllmagnesium bromide under ice-cooling. To the reaction mixture was added tetrahydrofuran (40 mL) solution of tert-butyl (trans-4-(1-(2,2-dimethyl-4,6-dioxo-1,3-dioxan-5-ylidene)ethyl)cyclohexyl)carbamate (2.254 g) under ice-cooling. The mixture was stirred for 90 min, allowed to gradually return to room temperature, and stirred for 90 min. To the reaction mixture were added saturated aqueous ammonium chloride solution (60 mL) and ethyl acetate (80 mL) at room temperature. After partitioning, the organic layer was washed with saturated brine, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluent: n-hexane/ethyl acetate=92/8 to 34/66) to give the title compound (217 mg).

$^1\text{H-NMR}$ (DMSO-D_6) δ : 6.66 (1H, d, $J = 7.9$ Hz), 3.81 (1H, s), 3.12 (1H, m), 1.82–1.77 (2H, m), 1.73 (3H, s), 1.69–1.60 (3H,

m), 1.65 (3H, s), 1.37 (9H, s), 1.13-1.02 (4H, m), 1.02 (6H, s).
[0977]

Step 12-5: Methyl 3-(trans-4-((tert-butoxycarbonyl)amino)cyclohexyl)-3-methylbutyrate

5 [0978]



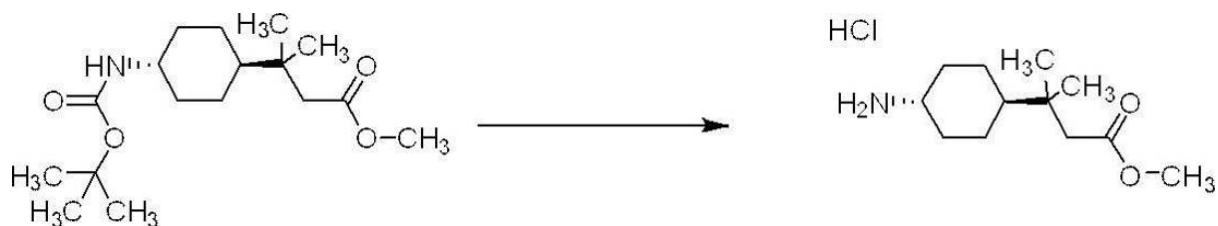
[0979]

A solution of tert-butyl (trans-4-(2-(2,2-dimethyl-4,6-dioxo-1,3-dioxan-5-yl)propan-2-yl)cyclohexyl)carbamate (205 mg)
10 in methanol (6.0 mL) was stirred at 80°C for 8 hr and left standing overnight. The reaction mixture was concentrated under reduced pressure. To the residue were added dimethyl sulfoxide (2.0 mL), water (0.2 mL) and sodium chloride (70 mg), and the mixture was stirred at 140°C for 7 hr. To the reaction
15 mixture were added water (15 mL) and ethyl acetate (15 mL) at room temperature, and the layers were separated. The aqueous layer was extracted once with ethyl acetate (5.0 mL). The combined organic layer was washed successively with water, and saturated brine, and the residue was concentrated under reduced
20 pressure to give a crude product (179 mg) containing the title compound.

[0980]

Step 12-6: Methyl 3-(trans-4-aminocyclohexyl)-3-methylbutyrate monohydrochloride

25 [0981]



[0982]

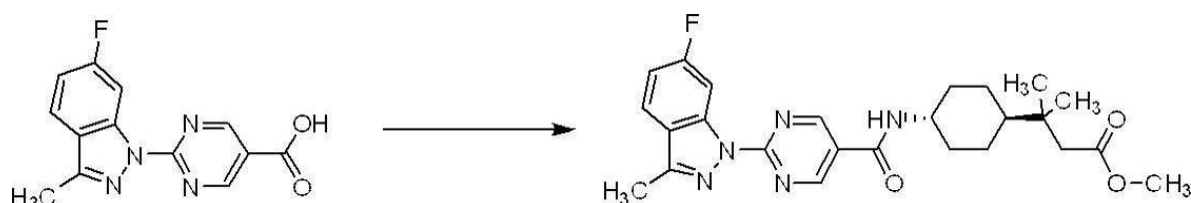
To a solution of a crude product (179 mg) containing

methyl 3-(trans-4-((tert-butoxycarbonyl)amino)cyclohexyl)-3-methylbutyrate in ethyl acetate (2.0 mL) was added 4 M hydrogen chloride/ethyl acetate (2.0 mL) solution at room temperature, and the mixture was stirred overnight. The reaction mixture
5 was concentrated under reduced pressure to give the title compound (131 mg).

¹H-NMR (DMSO-D₆) δ: 7.95 (3H, br s), 3.57 (3H, s), 2.92-2.85 (1H, m), 2.21 (2H, s), 1.99-1.96 (2H, m), 1.77-1.74 (2H, m), 1.33-0.96 (5H, m), 0.90 (6H, s).

10 [0983]

Step 12-7: Methyl 3-(trans-4-(2-(6-fluoro-3-methyl-1H-indazol-1-yl)pyrimidine-5-carboxyamido)cyclohexyl)-3-methylbutyrate
[0984]

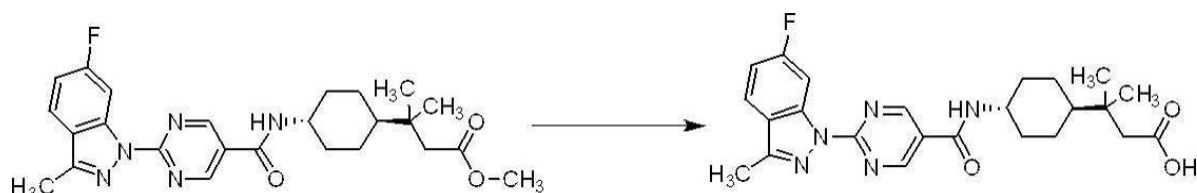


15 [0985]

To a suspension of 2-(6-fluoro-3-methyl-1H-indazol-1-yl)pyrimidine-5-carboxylic acid (50 mg) synthesized in the same manner as in Production Example 1, step 1-2, methyl 3-(trans-4-aminocyclohexyl)-3-methylbutyrate monohydrochloride (55 mg), 1-
20 hydroxy-7-azabenzotriazole (25 mg) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (55 mg) in N,N-dimethylformamide (1.5 mL) was added triethylamine (0.040 mL) at room temperature, and the mixture was stirred overnight. To the reaction mixture were successively added saturated aqueous
25 sodium hydrogen carbonate (2.0 mL) and water (3.0 mL) at room temperature, and the precipitated solid was collected by filtration and dried under reduced pressure to give a crude product (77 mg) containing the title compound.

[0986]

30 Step 12-8: 3-(Trans-4-(2-(6-fluoro-3-methyl-1H-indazol-1-yl)pyrimidine-5-carboxyamido)cyclohexyl)-3-methylbutyric acid
[0987]



[0988]

A suspension of a crude product (30 mg) containing methyl 3-(trans-4-(2-(6-fluoro-3-methyl-1H-indazol-1-yl)pyrimidine-5-carboxamido)cyclohexyl)-3-methylbutyrate, sodium iodide (67 mg) and chlorotrimethylsilane (0.05 mL) in acetonitrile (2.0 mL) was stirred at 85°C for 7 hr. To the reaction mixture were added sodium iodide (63 mg) and chlorotrimethylsilane (0.05 mL) at room temperature, and the mixture was stirred at 85°C for 9 hr. To the reaction mixture were successively added water (4.0 mL) and 1 M hydrochloric acid (0.5 mL) at room temperature, and the solid was collected by filtration. The solid was dissolved in dimethyl sulfoxide, and purified by reversed-phase silica gel chromatography (eluent: water/acetonitrile=90/10 to 0/100) to give the title compound (7.3 mg).

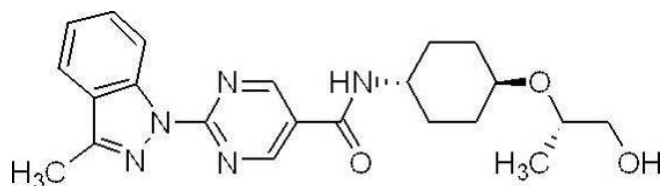
¹H-NMR (DMSO-D₆) δ: 9.27-9.26 (2H, m), 8.83-8.73 (1H, br m), 8.40 (1H, dd, J = 10.4, 2.3 Hz), 7.94 (1H, dd, J = 8.7, 5.4 Hz), 7.31-7.26 (1H, m), 3.75-3.65 (1H, m), 2.61 (3H, s), 1.94-1.90 (2H, m), 1.86-1.83 (2H, m), 1.85 (2H, s), 1.48-1.41 (1H, m), 1.36-1.27 (2H, m), 1.11-1.02 (2H, m), 0.91 (6H, s).

MS (M+H): 454 MS (M-H): 452

[0989]

[Production Example 13] Example 306: Production of N-(trans-4-(((S)-1-hydroxypropan-2-yl)oxy)cyclohexyl)-2-(3-methyl-1H-indazol-1-yl)pyrimidine-5-carboxamide

[0990]



[0991]

Step 13-1: (S)-((1-(Benzyloxy)propan-2-yl)oxy)trimethylsilane

[0992]



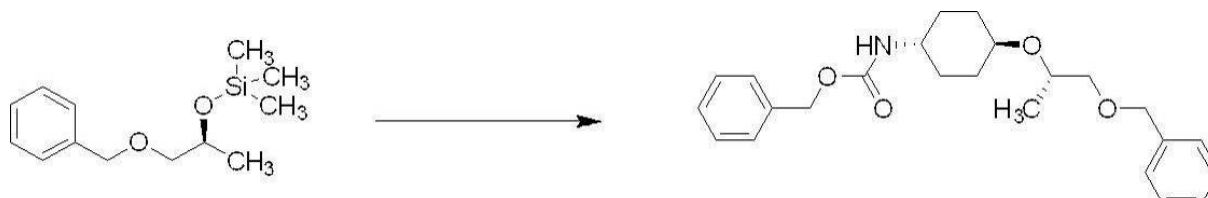
[0993]

To a solution of (S)-1-benzyloxy-2-propanol (500 mg) and
5 triethylamine (0.922 mL) in tetrahydrofuran (5.0 mL) was added
trimethylsilyl chloride (0.408 mL) in a water bath, and the
mixture was stirred and left standing overnight. To the
reaction mixture was added n-hexane/ethyl acetate (n-
hexane/ethyl acetate=10/1) at room temperature, and the mixture
10 was stirred. The insoluble material was filtered off, and the
filtrate was concentrated to give a crude product (767.8 mg)
containing the title compound.

[0994]

Step 13-2: Benzyl (trans-4-(((S)-1-(benzyloxy)propan-2-
15 yl)oxy)cyclohexyl)carbamate

[0995]



[0996]

To a solution of a crude product (767.8 mg) containing
20 (S)-((1-(benzyloxy)propan-2-yl)oxy)trimethylsilane, benzyl (4-
oxocyclohexyl)carbamate (1481 mg) and triethylsilane (1045 mg)
in acetonitrile (20 mL) was added dropwise acetonitrile (2.0
mL) solution of trimethylsilyl trifluoromethanesulfonate (1.094
mL) under ice-cooling, and the mixture was stirred at the same
25 temperature for 3 hr. To the reaction mixture were added 1 M
hydrochloric acid and ethyl acetate, and the layers were
separated. The organic layer was washed with saturated brine.
The organic layer was dried over sodium sulfate, sodium sulfate
was removed by filtration, and the filtrate was concentrated

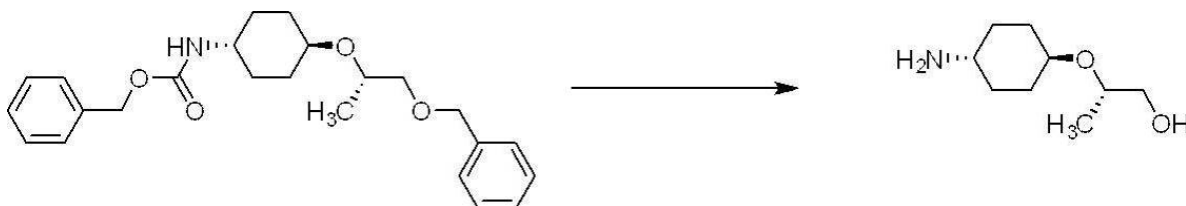
under reduced pressure. The residue was purified by silica gel chromatography (eluent: n-hexane/ethyl acetate=80/20 to 76/24) to give the title compound (504.5 mg).

¹H-NMR (DMSO-D₆) δ: 7.39-7.26 (10H, m), 7.17 (1H, d, J = 7.6 Hz), 4.99 (2H, s), 4.48 (2H, s), 3.74-3.65 (1H, m), 3.40-3.23 (4H, m), 1.91-1.85 (2H, m), 1.82-1.75 (2H, m), 1.21-1.14 (4H, m), 1.04 (3H, d, J = 6.3 Hz).

[0997]

Step 13-3: (S)-2-((Trans-4-aminocyclohexyl)oxy)propan-1-ol

10 [0998]



[0999]

To a solution of benzyl (trans-4-((S)-1-(benzyloxy)propan-2-yl)oxy)cyclohexyl carbamate (504 mg) in methanol (10 mL) was added 20% palladium hydroxide-carbon (178 mg) at room temperature. Under 4 atm hydrogen, the mixture was stirred overnight at room temperature. The reaction mixture was filtered through celite, and the filtrate was concentrated under reduced pressure. To a solution of the residue in methanol (10 mL) was added 20% palladium hydroxide-carbon (178 mg) at room temperature. Under 4 atm hydrogen, the mixture was stirred at room temperature for 2 days. The reaction mixture was filtered through celite, and the filtrate was concentrated under reduced pressure. The residue was purified by Bond Elut SCX (Agilent technologies) (eluent: methanol, 1 M ammonia/methanol solution) to give the title compound (176 mg).

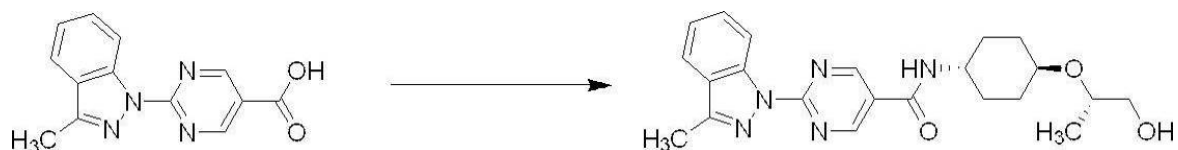
¹H-NMR (DMSO-D₆) δ: 4.45 (1H, br s), 3.49-3.42 (1H, m), 3.34-3.14 (4H, m), 1.85-1.70 (4H, m), 1.61 (2H, br s), 1.18-0.95 (4H, m), 0.99 (3H, d, J = 5.0 Hz).

30 [1000]

Step 13-4: N-(Trans-4-((S)-1-hydroxypropan-2-yl)oxy)cyclohexyl)-2-(3-methyl-1H-indazol-1-yl)pyrimidine-5-

carboxamide

[1001]



[1002]

5 To a suspension of 2-(3-methyl-1H-indazol-1-yl)pyrimidine-5-carboxylic acid (40 mg) synthesized in the same manner as in Production Example 4, step 4-2, and (S)-2-((trans-4-aminocyclohexyl)oxy)propan-1-ol (32.7 mg) in N,N-dimethylformamide (0.6 mL) were successively added

10 triethylamine (0.0329 mL), 1-hydroxy-7-azabenzotriazole (21.41 mg) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (36.2 mg) at room temperature, and the mixture was stirred at the same temperature for 20 hr. To the reaction mixture was added water (0.6 mL) at room temperature, and the

15 mixture was purified by reversed-phase silica gel chromatography (eluent: water (containing 0.1% formic acid)/acetonitrile=100/0 to 60/40) and concentrated. The precipitated solid was collected by filtration, washed with water, and dried under reduced pressure to give the title

20 compound (46.2 mg).

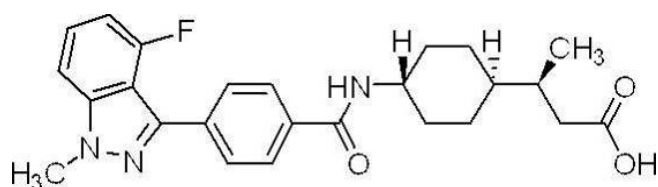
¹H-NMR (DMSO-D₆) δ: 9.20 (2H, s), 8.66 (1H, d, J = 8.3 Hz), 8.51 (1H, d, J = 7.4 Hz), 7.87 (1H, d, J = 7.9 Hz), 7.63-7.60 (1H, m), 7.39-7.37 (1H, m), 4.48 (1H, t, J = 5.8 Hz), 3.80-3.73 (1H, m), 3.52-3.48 (1H, m), 3.39-3.31 (2H, m), 3.23-3.17 (1H, m), 2.61 (3H, s), 1.97-1.89 (4H, m), 1.43-1.20 (4H, m), 1.02 (3H, d, J = 6.2 Hz).

MS (M+H): 410 MS (M-H): 408

[1003]

[Production Example 14] Example 335: Production of (S)-3-(trans-4-(4-(4-fluoro-1-methyl-1H-indazol-3-yl)benzamido)cyclohexyl)butanoic acid

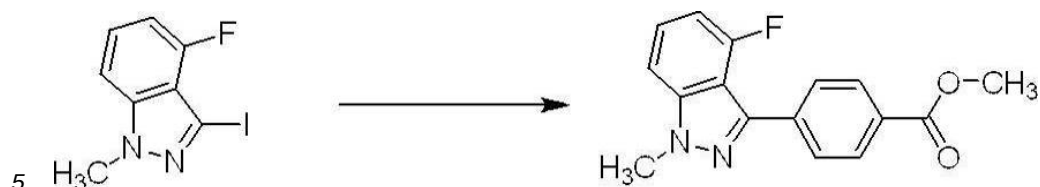
[1004]



[1005]

Step 14-1: Methyl 4-(4-fluoro-1-methyl-1H-indazol-3-yl)benzoate

[1006]



[1007]

Under a nitrogen atmosphere, a suspension of 4-bromo-1H-pyrrolo[3,2-c]pyridine (202 mg), (4-(methoxycarbonyl)phenyl)boronic acid (359 mg), potassium
 10 phosphate (769 mg) and [1,1'-bis(di-tert-butylphosphino)ferrocene]palladium(II) dichloride-dichloromethane adduct (74 mg) in 1,2-dimethoxyethane/water (5.0 mL, 1,2-dimethoxyethane/water=4/1) was stirred under microwave irradiation at 100°C for 45 min. The reaction
 15 mixture was purified by silica gel chromatography (eluent: n-hexane/ethyl acetate=100/0 to 70/30) to give a crude product (352 mg) containing the title compound.

[1008]

Step 14-2: 4-(4-Fluoro-1-methyl-1H-indazol-3-yl)benzoic acid

20 [1009]



[1010]

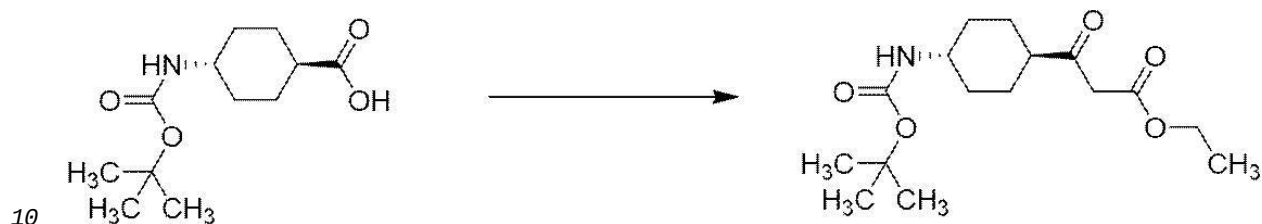
A solution of a crude product (352 mg) containing methyl 4-(4-fluoro-1-methyl-1H-indazol-3-yl)benzoate in methanol (3.0
 25 mL) was stirred under microwave irradiation at 100°C for 20 min. To the reaction mixture was added 1 M hydrochloric acid at room

temperature until a solid was precipitated. The precipitated solid was collected by filtration, and dried under reduced pressure at 60°C to give a crude product (315 mg) containing the title compound.

5 [1011]

Step 14-3: Ethyl 3-(trans-4-((tert-butoxycarbonyl)amino)cyclohexyl)-3-oxopropionate (assumed to be enol-keto 1/9 mixture)

[1012]



[1013]

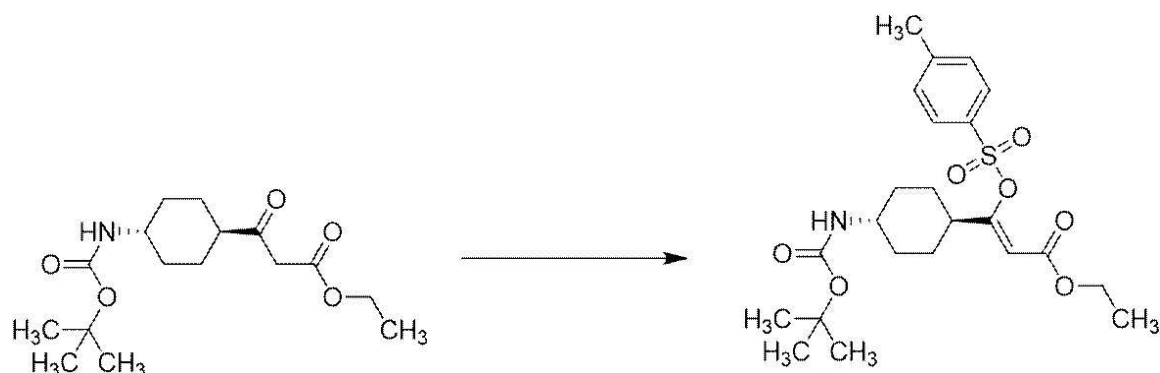
Under a nitrogen atmosphere, to a solution of trans-4-[(tert-butoxycarbonyl)amino]cyclohexanecarboxylic acid (200 g) in tetrahydrofuran (900 mL) was added 1,1'-carbonyldiimidazole
15 (140 g) in portions over 7 min at room temperature while rinsing in with tetrahydrofuran (100 mL). After stirring for 1.5 hr, at room temperature, potassium ethyl malonate (196 g) was added in portions over 2 min, and magnesium chloride (110 g) was added in portions over 2 min while rinsing in with
20 tetrahydrofuran (200 mL). The reaction mixture was stirred at room temperature for 26 hr. To the reaction mixture was added 20 wt% aqueous citric acid solution (1000 mL) at room temperature, and the mixture was stirred for 20 min. Ethyl acetate (1000 mL) was added thereto, and the layers were
25 separated. The organic layer was washed successively with 10 wt% aqueous citric acid solution (1000 mL), water (1000 mL), 7.5 wt% aqueous sodium hydrogen carbonate solution (1000 mL), and saturated brine (1000 mL). The organic layer was dried over sodium sulfate, sodium sulfate was removed by filtration,
30 and the filtrate was concentrated under reduced pressure. The residue was dissolved by adding n-hexane/ethyl acetate (800 mL,

n-hexane/ethyl acetate=1/3), and insoluble material was filtered off. The filtrate was concentrated under reduced pressure and dried under reduced pressure to give the title compound (247 g).

5 $^1\text{H-NMR}$ (CDCl_3) δ : 12.14 (0.1H, s), 4.95 (0.1H, s), 4.36 (1H, br s), 4.19 (2H, q, $J = 7.1$ Hz), 3.47 (1.8H, s), 3.40 (1H, br s), 2.49-2.33 (0.9H, m), 2.16-2.05 (2H, m), 2.01-1.93 (2H, m), 1.93-1.89 (0.1H, m), 1.53-1.36 (11H, m), 1.27 (3H, t, $J = 7.2$ Hz), 1.17-1.07 (2H, m).

10 [1014]

Step 14-4: Ethyl (Z)-3-(trans-4-((tert-butoxycarbonyl)amino)cyclohexyl)-3-(tosyloxy)acrylate
[1015]



15 [1016]

Under a nitrogen atmosphere, to a solution of ethyl 3-(trans-4-((tert-butoxycarbonyl)amino)cyclohexyl)-3-oxopropionate (234.4 g) in acetonitrile/toluene (937 mL, acetonitrile/toluene=1/3) were added tetramethylethylenediamine
20 (169 mL) and lithium chloride (47.5 g) at room temperature, and the mixture was stirred for 30 min. To the reaction mixture was added dropwise acetonitrile/toluene (468 mL, acetonitrile/toluene=1/3) solution of p-toluenesulfonylchloride (214 g) under ice-cooling over 20 min, while rinsing in with
25 acetonitrile/toluene (4118 mL, acetonitrile/toluene=1/3). After stirring for 2 hr, 5.0 wt% aqueous sodium hydrogen carbonate solution (1172 mL) was added dropwise over 1 min under ice-cooling. To the reaction mixture was added toluene (937 mL), and the layers were separated. The organic layer was

washed successively with water (234 mL) and saturated brine (1172 mL). The organic layer was dried over sodium sulfate (234 g), CARBORAFFIN-20 (23 g) was added thereto, and sodium sulfate and CARBORAFFIN-20 were removed by filtration, and the mixture was concentrated under reduced pressure. To the residue was added ethyl acetate (200 mL), and the filtrate was dissolved at 85°C, and ethyl acetate (150 mL) was added. n-Hexane (1050 mL) was added dropwise at 50°C, and the seed crystal was added at 40°C. To this suspension was added dropwise n-hexane (2100 mL) at 40°C. The mixture was stirred at the same temperature for 2 hr, allowed to gradually return to room temperature, and stirred for 15 hr. The precipitated solid was collected by filtration, washed with n-hexane/ethyl acetate (500 mL, n-hexane/ethyl acetate=19/1), and dried under reduced pressure to give the title compound (302 g).

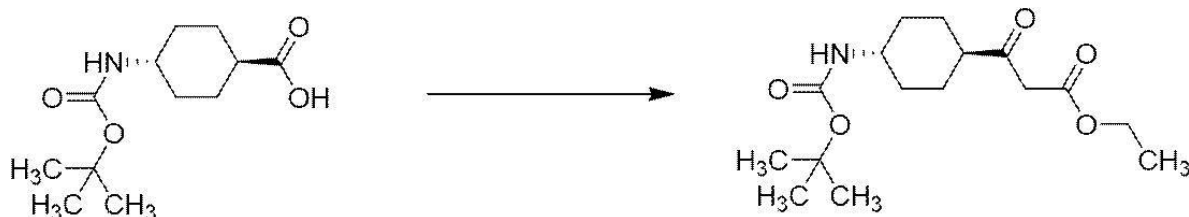
[1017]

Synthesis of seed crystal of the title compound (ethyl (Z)-3-{trans-4-[(tert-butoxycarbonyl)amino]cyclohexyl}-3-(p-toluenesulfonyloxy)acrylate)

[1018]

Step 14-4-1: Ethyl 3-(trans-4-((tert-butoxycarbonyl)amino)cyclohexyl)-3-oxopropionate

[1019]



[1020]

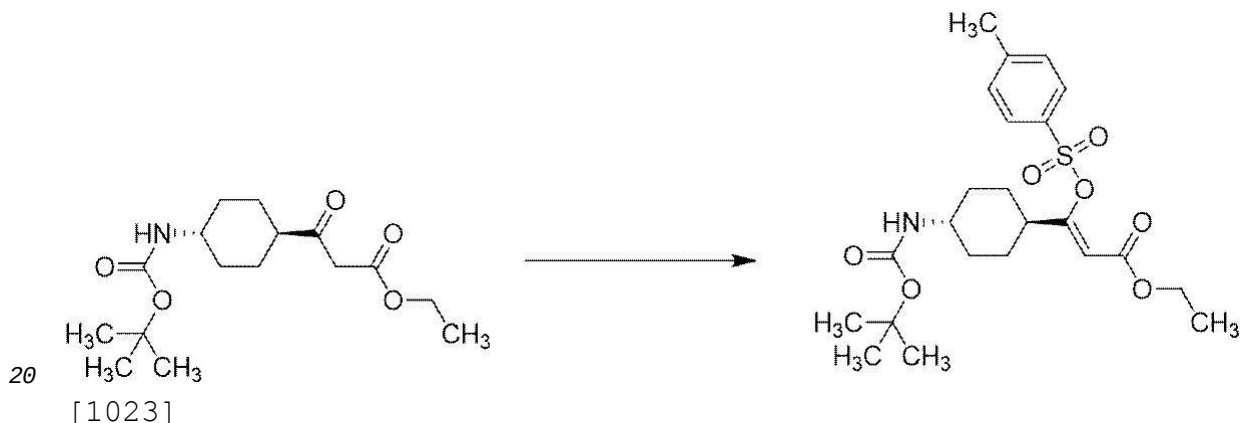
To a solution of trans-4-((tert-butoxycarbonyl)amino)cyclohexanecarboxylic acid (1.0 g) in tetrahydrofuran (5 mL) was added 1,1'-carbonyldiimidazole (700 mg) at room temperature, and the mixture was stirred for 1 hr. Potassium ethyl malonate (839 mg) and magnesium chloride (470 mg) were added at room temperature, and the mixture was stirred at room temperature for 1 hr, and at 70°C for 3 hr. To the

reaction mixture was added 10 wt% aqueous citric acid solution (5.0 mL) at room temperature, and the mixture was stirred for 15 min. Ethyl acetate (5.0 mL) was added thereto, and the layers were separated. The organic layer was washed successively once with 10 wt% aqueous citric acid solution (5.0 mL), once with water (5.0 mL), three times with saturated aqueous sodium hydrogen carbonate solution (3.0 mL), and once with saturated brine. The organic layer was dried over sodium sulfate. Sodium sulfate was removed by filtration, and the filtrate was concentrated under reduced pressure. To the residue was dissolved by adding n-hexane/ethyl acetate (n-hexane/ethyl acetate=1/2), and insoluble material was filtered off. The filtrate was concentrated under reduced pressure and dried under reduced pressure to give a crude product (1.16 g) containing the title compound.

[1021]

Step 14-4-2: Ethyl (Z)-3-(trans-4-((tert-butoxycarbonyl)amino)cyclohexyl)-3-(tosyloxy)acrylate

[1022]



To a solution of ethyl 3-(trans-4-((tert-butoxycarbonyl)amino)cyclohexyl)-3-oxopropionate (1.15 g) in acetonitrile (9.26 mL) were added lithium chloride (235 mg) and tetramethylethylenediamine (0.829 mL) at room temperature, and the mixture was stirred for 15 min. To the reaction mixture was added dropwise acetonitrile (2.3 mL) solution of p-toluenesulfonylchloride (1.056 g) under ice-cooling, and the mixture was stirred for 1 hr. To the reaction mixture were

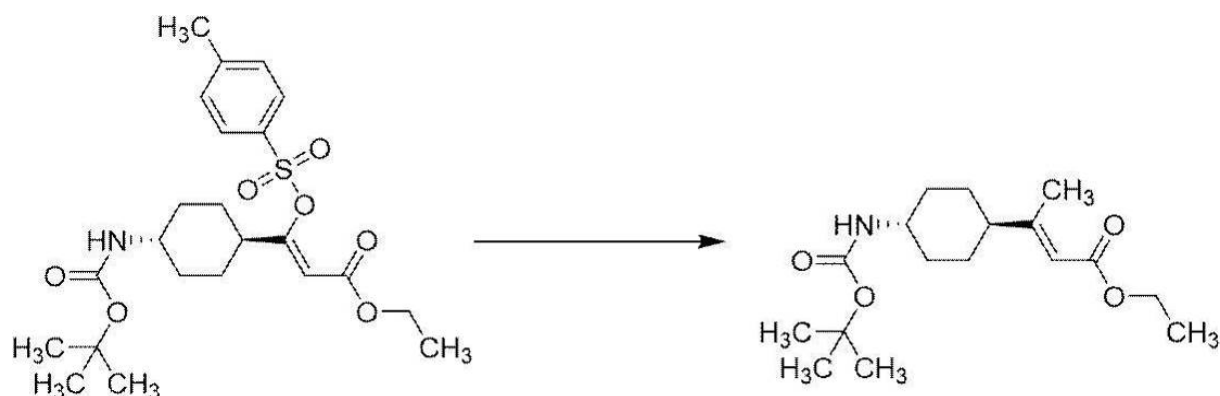
added water (16 mL) and toluene (16 mL), and the layers were separated. The organic layer was washed successively with water, saturated aqueous sodium hydrogen carbonate, and saturated brine. The organic layer was dried over sodium sulfate (234 g), sodium sulfate was removed by filtration, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel chromatography (eluent: n-hexane/ethyl acetate=85/15 to 65/35) to give the title compound (1.40 g).

¹H-NMR (CDCl₃) δ: 7.93-7.86 (2H, m), 7.38-7.31 (2H, m), 5.52-5.49 (1H, m), 4.34 (1H, br s), 4.05 (2H, q, J = 7.1 Hz), 3.36 (1H, br s), 2.46 (3H, s), 2.39-2.28 (1H, m), 2.10-1.98 (4H, m), 1.43 (9H, s), 1.29-1.15 (5H, m), 1.13-1.00 (2H, m).

[1024]

Step 14-5: Ethyl (E)-3-(trans-4-((tert-butoxycarbonyl)amino)cyclohexyl)-2-butenate

[1025]



[1026]

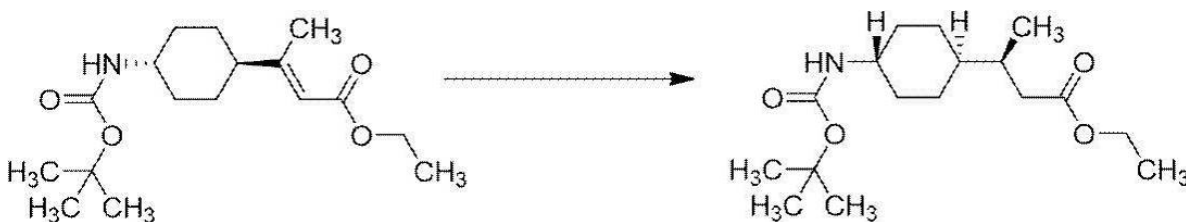
To a solution of ethyl (Z)-3-(trans-4-((tert-butoxycarbonyl)amino)cyclohexyl)-3-(tosyloxy)acrylate (210 g) in tetrahydrofuran (1050 mL) was added iron chloride (III) (3.64 g) under sodium chloride/ice-cooling, and 1.0 M tetrahydrofuran solution (1229 mL) of methylmagnesium bromide was added dropwise. To the reaction mixture was added 10 wt% aqueous citric acid solution (1000 mL) under sodium chloride/ice-cooling, and the mixture was stirred at room temperature for 1 hr. Ethyl acetate (840 mL) was added thereto,

and the layers were separated. The organic layer was washed successively with 5.0 wt% aqueous sodium hydrogen carbonate solution (1050 mL), water (1050 mL), and saturated brine (1050 mL). The organic layer was dried over sodium sulfate (210 g), CARBORAFFIN-20 (21 g) was added thereto, sodium sulfate and CARBORAFFIN-20 were removed by filtration, and the filtrate was concentrated under reduced pressure. The residue was dissolved by adding n-hexane/ethyl acetate (1600 mL, n-hexane/ethyl acetate=9/1) at 85°C, and the mixture was allowed to gradually return to room temperature and stirred for 15 hr. The precipitated solid was collected by filtration, washed with n-hexane/ethyl acetate (400 mL, n-hexane/ethyl acetate=19/1), and dried under reduced pressure to give a crude product (100 g) containing the title compound. The crude products (40 g and 60 g) containing the title compound were purified by silica gel chromatography (eluent: n-hexane/ethyl acetate=95/5 to 50/50) to give the title compound (44.09 g).

¹H-NMR (CDCl₃) δ: 5.65 (1H, s), 4.37 (1H, br s), 4.14 (2H, q, J = 7.1 Hz), 3.39 (1H, br s), 2.13 (3H, d, J = 1.2 Hz), 2.12-2.03 (2H, m), 1.99-1.88 (1H, m), 1.84-1.74 (2H, m), 1.44 (9H, s), 1.42-1.30 (2H, m), 1.27 (3H, t, J = 7.2 Hz), 1.20-1.06 (2H, m). [1027]

Step 14-6: Ethyl (S)-3-(trans-4-((tert-butoxycarbonyl)amino)cyclohexyl)butanoate

[1028]



[1029]

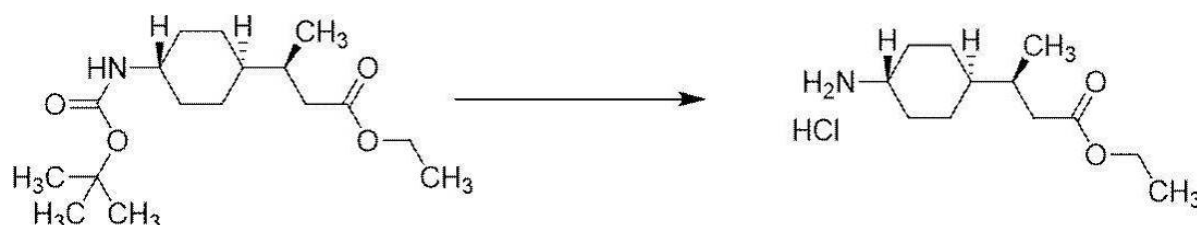
Under a nitrogen atmosphere, a solution of bis[η-(2,5-nornornadiene)]rhodium (I) tetrafluoroborate (0.36 g) and (R)-1-[(Sp)-2-(di-tert-butylphosphino)ferrocenyl]ethyl bis(2-methylphenyl)phosphine (CAS No.: 849924-76-1) (0.583 g) in methanol (120 mL) was stirred at room temperature for 1 hr. To

the reaction mixture was added a solution of ethyl (E)-3-(trans-4-((tert-butoxycarbonyl)amino)cyclohexyl)-2-butenate (30 g) in methanol (210 mL) at room temperature, and the mixture was stirred under 3.9 atm hydrogen for 2 days. The reaction mixture was concentrated under reduced pressure. It was combined with a concentrate obtained from ethyl (E)-3-(trans-4-((tert-butoxycarbonyl)amino)cyclohexyl)-2-butenate (14 g) by a similar production method to give a crude product (46 g) containing the title compound.

10 [1030]

Step 14-7: Ethyl (S)-3-(trans-4-aminocyclohexyl)butanoate hydrochloride

[1031]



15 [1032]

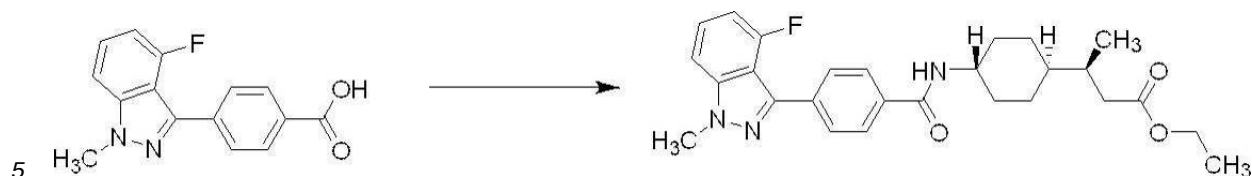
To a solution of a crude product (100 g) containing ethyl (S)-3-(trans-4-((tert-butoxycarbonyl)amino)cyclohexyl)butanoate synthesized in the same manner as in step 14-6 in ethyl acetate (100 mL) was added dropwise 4 M hydrogen chloride/ethyl acetate (500 mL) solution under ice-cooling over 10 min. The mixture was allowed to gradually return to room temperature and stirred for 90 min. To the reaction mixture was added n-hexane (300 mL) and the mixture was stirred for 30 min. The precipitated solid was collected by filtration, washed with n-hexane/ethyl acetate (100 mL, n-hexane/ethyl acetate=9/1), and dried under reduced pressure to give the title compound (56.8 g).

¹H-NMR (DMSO-D₆) δ: 7.87 (3H, br s), 4.05 (2H, q, J = 7.1 Hz), 2.89 (1H, tt, J = 11.7, 3.8 Hz), 2.35 (1H, dd, J = 14.9, 5.2 Hz), 2.05 (1H, dd, J = 15.0, 9.0 Hz), 2.00-1.87 (2H, m), 1.83-1.71 (1H, m), 1.71-1.59 (2H, m), 1.33-1.20 (2H, m), 1.17 (3H, t, J = 7.2 Hz), 1.14-0.96 (3H, m), 0.83 (3H, d, J = 6.7 Hz).

[1033]

Step 14-8: Ethyl (S)-3-(trans-4-(4-(4-fluoro-1-methyl-1H-indazol-3-yl)benzamido)cyclohexyl)butanoate

[1034]



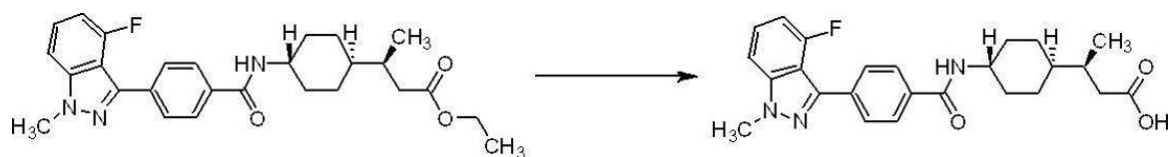
[1035]

To a suspension of a crude product (50 mg) containing 4-(4-fluoro-1-methyl-1H-indazol-3-yl)benzoic acid, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (42.6 mg), 1-hydroxy-1H-benzotriazole monohydrate (31.2 mg), and ethyl (S)-3-(trans-4-aminocyclohexyl)butanoate hydrochloride (50.8 mg) in N,N-dimethylformamide (1.5 mL) was added triethylamine (0.064 mL) at room temperature, and the mixture was stirred for 3 hr. To the reaction mixture was added water at room temperature until a solid was precipitated, and the precipitated solid was collected by filtration and dried under reduced pressure to give a crude product (110 mg) containing the title compound.

[1036]

Step 14-9: (S)-3-(Trans-4-(4-(4-fluoro-1-methyl-1H-indazol-3-yl)benzamido)cyclohexyl)butanoic acid

[1037]



[1038]

To a solution of a crude product (86.6 mg) containing ethyl (S)-3-(trans-4-(4-(4-fluoro-1-methyl-1H-indazol-3-yl)benzamido)cyclohexyl)butanoate in tetrahydrofuran/methanol (3 mL, tetrahydrofuran/methanol=1/2) was added 2 M aqueous sodium hydroxide solution (0.463 mL) at room temperature, and the mixture was stirred under microwave irradiation at 100°C for 20 min. To the reaction mixture was added 2 M hydrochloric

acid (0.463 mL) at room temperature, and the precipitated solid was collected by filtration, and dried under reduced pressure at 60°C to give the title compound (68.7 mg).

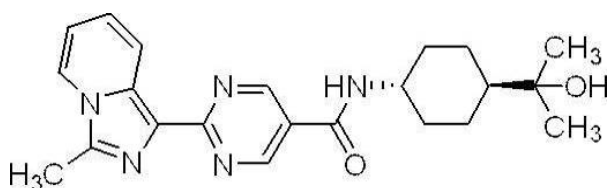
¹H-NMR (DMSO-D₆) δ: 11.98 (1H, br s), 8.30-8.24 (1H, m), 8.06-8.01 (2H, m), 8.00-7.95 (2H, m), 7.93-7.88 (1H, m), 7.81-7.76 (1H, m), 7.43-7.36 (1H, m), 4.14 (3H, s), 3.80-3.68 (1H, m), 2.35-2.27 (1H, m), 2.04-1.95 (1H, m), 1.94-1.86 (2H, m), 1.84-1.74 (1H, m), 1.73-1.65 (2H, m), 1.42-1.27 (2H, m), 1.25-1.06 (3H, m), 0.89-0.85 (3H, m).

10 MS (M+H): 438 MS (M-H): 436

[1039]

[Production Example 15] Example 426: Production of N-(trans-4-(2-hydroxypropan-2-yl)cyclohexyl)-2-(3-methylimidazo[1,5-a]pyridin-1-yl)pyrimidine-5-carboxamide

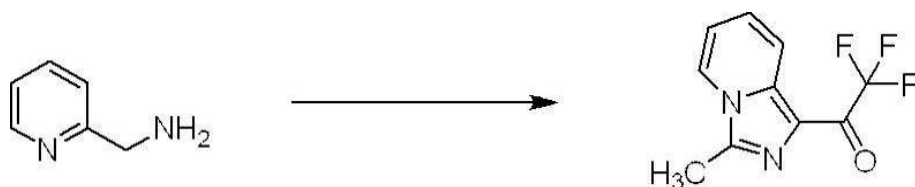
15 [1040]



[1041]

Step 15-1: 2,2,2-Trifluoro-1-(3-methylimidazo[1,5-a]pyridin-1-yl)ethan-1-one

20 [1042]



[1043]

To a solution of 2-picolylamine (2.098 g) and pyridine (6.2 mL) in chloroform (15 mL) was added dropwise acetyl chloride (1.4 mL) under ice-cooling, and the mixture was stirred at the same temperature for 20 min. To the reaction mixture was added dropwise trifluoroacetic anhydride (5.5 mL) under ice-cooling, and the mixture was stirred at room temperature overnight. To the reaction mixture was added

saturated aqueous sodium hydrogen carbonate (60 mL) at room temperature, and the layers were separated. The aqueous layer was extracted once with chloroform (15 mL). The combined organic layer was concentrated under reduced pressure, and
5 toluene (30 mL) was added to the residue. The mixture was concentrated under reduced pressure, and the residue was purified by silica gel chromatography (eluent: n-hexane/ethyl acetate=84/16 to 0/100) to give a crude product (1.98 g) containing the title compound.

10 [1044]

Step 15-2: 3-Methylimidazo[1,5-a]pyridine-1-carboxylic acid
[1045]



[1046]

15 To a solution of a crude product (1.98 g) containing 2,2,2-trifluoro-1-(3-methylimidazo[1,5-a]pyridin-1-yl)ethan-1-one in methanol (20 mL) was added 2 M aqueous sodium hydroxide solution (20 mL) at room temperature, and the mixture was stirred at 80°C for 7 hr. To the reaction mixture was added 6
20 M hydrochloric acid (6.6 mL) at room temperature, and methanol contained in the reaction mixture was concentrated under reduced pressure. To the residue was added 1 M hydrochloric acid (7.0 mL) at room temperature, and the precipitated solid was collected by filtration and dried under reduced pressure to
25 give the title compound (811 mg).

¹H-NMR (DMSO-D₆) δ: 8.43-8.39 (1H, m), 8.04-8.01 (1H, m), 7.35-7.28 (1H, m), 7.09-7.03 (1H, m), 2.70 (3H, s).

[1047]

Step 15-3: 3-Methylimidazo[1,5-a]pyridine-1-carboxamide

30 [1048]



[1049]

A mixture of 3-methylimidazo[1,5-a]pyridine-1-carboxylic acid (510 mg) and thionyl chloride (3.0 mL) was stirred at 70°C for 7 hr, and left standing overnight at room temperature. The reaction mixture was concentrated under reduced pressure, and 28% aqueous ammonia solution (5.0 mL) was added to the obtained residue under ice-cooling. The mixture was warmed to room temperature and stirred overnight. The precipitated solid was collected by filtration, washed with water, and dried under reduced pressure to give a crude product (352 mg) containing the title compound.

[1050]

Step 15-4: 3-Methylimidazo[1,5-a]pyridine-1-carbonitrile

[1051]



[1052]

To a solution of a crude product (352 mg) containing 3-methylimidazo[1,5-a]pyridine-1-carboxamide and triethylamine (0.65 mL) in chloroform (5.0 mL) was added trifluoroacetic anhydride (0.37 mL) under ice-cooling, and the mixture was allowed to gradually return to room temperature and stirred overnight. To the reaction mixture were added triethylamine (0.33 mL) and trifluoroacetic acid (0.20 mL) under ice-cooling, and the mixture was allowed to gradually return to room temperature and stirred overnight. To the reaction mixture was added saturated aqueous sodium hydrogen carbonate (5.0 mL), and the layers were separated. The organic layer was concentrated under reduced pressure. The residue was purified by silica gel

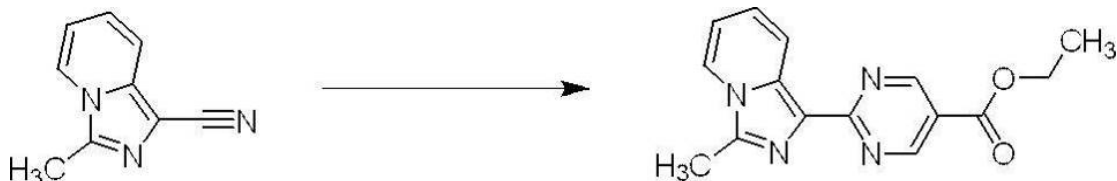
chromatography (eluent: n-hexane/ethyl acetate=88/12 to 0/100) to give the title compound (254 mg).

$^1\text{H-NMR}$ ($\text{DMSO-}D_6$) δ : 8.41-8.39 (1H, m), 7.76-7.73 (1H, m), 7.29-7.25 (1H, m), 7.02-6.98 (1H, m), 2.64 (3H, s).

5 [1053]

Step 15-5: Ethyl 2-(3-methylimidazo[1,5-a]pyridin-1-yl)pyrimidine-5-carboxylate

[1054]



10 [1055]

To a solution of 3-methylimidazo[1,5-a]pyridine-1-carbonitrile (254 mg) in methanol (7 mL) were added 5.0 M methanol solution (0.032 mL) of sodium methoxide at room temperature, and the mixture was stirred at the same temperature for 5 hr. To the reaction mixture was added 5.0 M methanol solution (0.32 mL) of sodium methoxide at room temperature, and the mixture was stirred at room temperature overnight. To the reaction mixture was added 5.0 M methanol solution (0.32 mL) of sodium methoxide at room temperature, and the mixture was stirred at room temperature overnight. This step was repeated twice. To the reaction mixture was added ammonium chloride (463 mg) at room temperature, and the mixture was stirred for 72 hr. The mixture was filtered through celite, and concentrated under reduced pressure. To the residue were successively added N,N-dimethylformamide (4.0 mL), potassium carbonate (675 mg) and ethyl 2-formyl-3-oxopropionate (0.611 mL) at room temperature, and the mixture was stirred at 100°C for 7 hr. To the reaction mixture were added ethyl acetate (20 mL) and water (15 mL) at room temperature, and the layers were separated. The aqueous layer was extracted once with ethyl acetate (10 mL). The combined organic layer was washed successively with water and saturated brine, dried over sodium

15
20
25
30

sulfate, and concentrated under reduced pressure. The residue was purified twice by silica gel chromatography (eluent: n-hexane/acetone=66/34 to 34/66, then chloroform/methanol=90/10) to give the title compound (230 mg).

5 $^1\text{H-NMR}$ (DMSO-D_6) δ : 9.16 (2H, s), 8.55-8.53 (1H, m), 8.35 (1H, d, $J = 6.5$ Hz), 7.28-7.24 (1H, m), 7.00-6.96 (1H, m), 4.40-4.34 (2H, m), 2.70 (3H, s), 1.38-1.34 (3H, m).

[1056]

Step 15-6: 2-(3-Methylimidazo[1,5-a]pyridin-1-yl)pyrimidine-5-
10 carboxylic acid

[1057]



[1058]

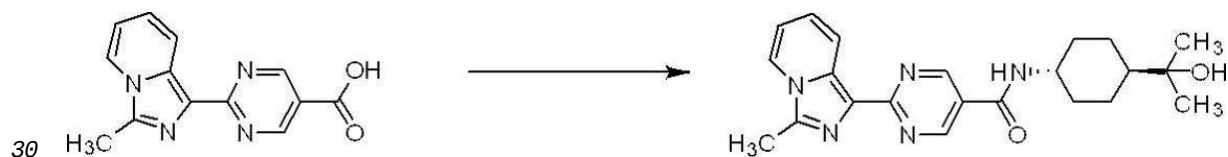
To a suspension of ethyl 2-(3-methylimidazo[1,5-
15 a]pyridin-1-yl)pyrimidine-5-carboxylate (180 mg) in methanol (3.0 mL) was added 2 M aqueous sodium hydroxide solution (0.7 mL) at room temperature, and the mixture was stirred overnight. To the reaction mixture were successively added 1 M hydrochloric acid (1.4 mL) and water (15.0 mL) at room
20 temperature, and the precipitated solid was collected by filtration and dried under reduced pressure to give the title compound (82 mg).

$^1\text{H-NMR}$ (DMSO-D_6) δ : 13.54 (1H, br s), 9.21 (2H, s), 8.55 (1H, d, $J = 9.2$ Hz), 8.46-8.44 (1H, m), 7.39-7.35 (1H, m), 7.12-7.08
25 (1H, m), 2.78 (3H, s).

[1059]

Step 15-7: N-(Trans-4-(2-hydroxypropan-2-yl)cyclohexyl)-2-(3-methylimidazo[1,5-a]pyridin-1-yl)pyrimidine-5-carboxamide

[1060]



[1061]

A suspension of 2-(3-methylimidazo[1,5-a]pyridin-1-yl)pyrimidine-5-carboxylic acid (30 mg), 2-(trans-4-aminocyclohexyl)propan-2-ol (25 mg), 1-hydroxy-7-azabenzotriazole (16 mg) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (36 mg) in N,N-dimethylformamide (1.0 mL) was stirred at room temperature overnight. To the reaction mixture were added saturated aqueous sodium hydrogen carbonate (2.0 mL) and water (3.0 mL) at room temperature, and the precipitated solid was collected by filtration and dried under reduced pressure to give the title compound (31.4 mg).

¹H-NMR (DMSO-D₆) δ: 9.13 (2H, s), 8.51 (1H, d, J = 8.8 Hz), 8.44 (1H, d, J = 7.9 Hz), 8.32 (1H, d, J = 6.7 Hz), 7.23-7.19 (1H, m), 6.97-6.93 (1H, m), 4.04 (1H, br s), 3.78-3.68 (1H, m), 2.70 (3H, s), 1.97-1.91 (2H, m), 1.88-1.82 (2H, m), 1.36-1.09 (5H, m), 1.05 (6H, s).

MS (M+H): 394 MS (M-H): 438

[1062]

Other Example compounds were obtained by a method similar to the above-mentioned production methods and Production Examples, or using a known method as necessary. The structural formula and property data of each Example compound are shown in the following Table 1.

25

[1063]

[Table 1-1]

Ex.No.	structural formula	¹ H-NMR (400 MHz)	MS (positive)	MS (negative)	Comments
1		¹ H-NMR (DMSO-D ₆) δ: 9.23 (2H, s), 8.54 (1H, d, J = 8.2 Hz), 8.40 (1H, dd, J = 10.2, 2.0 Hz), 7.94 (1H, dd, J = 8.6, 5.6 Hz), 7.29 (1H, ddd, J = 10.2, 8.6, 2.0 Hz), 4.05 (1H, br s), 3.81-3.68 (1H, m), 2.61 (3H, s), 1.96 (2H, d, J = 10.5 Hz), 1.86 (2H, d, J = 10.5 Hz), 1.40-1.26 (2H, m), 1.25-1.00 (3H, m), 1.06 (6H, s).	412	410	
2		¹ H-NMR (DMSO-D ₆) δ: 9.99 (1H, s), 9.28 (2H, s), 8.58 (1H, d, J = 7.6 Hz), 8.53 (1H, d, J = 5.3 Hz), 7.94 (1H, d, J = 5.3 Hz), 4.05 (1H, br s), 3.81-3.68 (1H, m), 2.66 (3H, s), 1.97 (2H, d, J = 10.2 Hz), 1.86 (2H, d, J = 10.2 Hz), 1.40-1.26 (2H, m), 1.25-1.03 (3H, m), 1.06 (6H, s).	395	393	
3		¹ H-NMR (DMSO-D ₆) δ: 9.99 (1H, s), 9.27 (2H, s), 8.56 (1H, d, J = 7.6 Hz), 8.53 (1H, d, J = 5.3 Hz), 7.94 (1H, d, J = 5.3 Hz), 4.04 (1H, br s), 3.82-3.69 (1H, m), 2.66 (3H, s), 1.88 (4H, d, J = 10.6 Hz), 1.50-1.22 (5H, m), 1.21-0.98 (2H, m), 1.11 (6H, s).	409	407	
4		¹ H-NMR (DMSO-D ₆) δ: 9.22 (2H, s), 8.67 (1H, d, J = 8.6 Hz), 8.53 (1H, d, J = 7.6 Hz), 7.89 (1H, d, J = 7.9 Hz), 7.65-7.61 (1H, m), 7.42-7.38 (1H, m), 4.22 (1H, s), 3.85-3.76 (1H, m), 3.29-3.22 (1H, m), 3.19 (2H, s), 2.62 (3H, s), 2.06-2.01 (2H, m), 1.95-1.91 (2H, m), 1.45-1.23 (4H, m), 1.08 (6H, s).	424	422	
5		¹ H-NMR (DMSO-D ₆) δ: 9.99 (1H, s), 9.27 (2H, s), 8.58 (1H, d, J = 7.5 Hz), 8.54 (1H, d, J = 5.2 Hz), 7.94 (1H, d, J = 5.2 Hz), 4.20 (1H, br s), 3.87-3.74 (1H, m), 3.51-3.22 (1H, m), 3.19 (2H, s), 2.67 (3H, s), 2.04 (2H, d, J = 10.5 Hz), 1.93 (2H, d, J = 10.5 Hz), 1.48-1.20 (4H, m), 1.07 (6H, s).	425	423	
6		¹ H-NMR (DMSO-D ₆) δ: 9.30 (2H, s), 8.78 (1H, d, J = 8.6 Hz), 8.63 (1H, d, J = 7.5 Hz), 8.00 (1H, d, J = 8.1 Hz), 7.75 (1H, t, J = 8.1 Hz), 7.56 (1H, t, J = 53.9 Hz), 7.52 (1H, t, J = 7.5 Hz), 3.86-3.76 (1H, m), 3.53 (2H, t, J = 6.2 Hz), 3.30-3.25 (1H, m), 3.16-3.11 (2H, m), 2.99 (3H, s), 2.07-2.02 (2H, m), 1.97-1.87 (4H, m), 1.46-1.36 (2H, m), 1.33-1.23 (2H, m).	508	506	
7		¹ H-NMR (DMSO-D ₆) δ: 9.24 (1H, br s), 9.22 (2H, s), 8.39 (1H, dd, J = 10.3, 2.2 Hz), 7.94 (1H, dd, J = 8.8, 5.3 Hz), 7.32-7.26 (1H, m), 4.20 (1H, s), 2.61 (3H, s), 1.96 (6H, s), 1.09 (6H, s).	396	394	
8		¹ H-NMR (DMSO-D ₆) δ: 9.33 (2H, s), 8.79 (1H, d, J = 5.1 Hz), 8.74 (1H, d, J = 7.6 Hz), 8.01 (1H, d, J = 8.1 Hz), 7.78-7.74 (1H, m), 7.57 (1H, t, J = 53.0 Hz), 7.56-7.49 (1H, m), 4.63 (2H, s), 3.95-3.85 (1H, m), 3.35 (3H, s), 3.06-2.96 (1H, m), 2.24-2.22 (2H, br m), 2.18-2.16 (2H, br m), 1.75-1.46 (4H, m).	484	482	

[1064]

[Table 1-2]

Ex.No.	structural formula	¹ H-NMR (400 MHz)	MS (positive)	MS (negative)	Comments
9		¹ H-NMR (DMSO-D ₆) δ: 10.12 (1H, s), 9.35 (2H, s), 8.67 (1H, d, J = 7.5 Hz), 8.62 (1H, d, J = 5.4 Hz), 8.00 (1H, d, J = 5.4 Hz), 7.64 (1H, t, J = 53.3 Hz), 4.06 (1H, s), 3.81-3.70 (1H, m), 1.99-1.85 (4H, m), 1.38-1.28 (2H, m), 1.22-1.11 (3H, m), 1.05 (6H, s).	431	429	
10		¹ H-NMR (DMSO-D ₆) δ: 9.33 (1H, brs), 9.30 (2H, s), 8.52 (1H, dd, J = 10.3, 2.2 Hz), 8.04 (1H, dd, J = 8.8, 5.3 Hz), 7.56 (1H, t, J = 53.2 Hz), 7.46-7.41 (1H, m), 4.21 (1H, s), 1.96 (6H, s), 1.09 (6H, s).	432	430	
11		¹ H-NMR (DMSO-D ₆) δ: 8.28 (1H, d, J = 7.9 Hz), 8.06-8.02 (2H, m), 7.92-7.83 (4H, m), 7.55-7.51 (1H, m), 7.31-7.27 (1H, m), 3.83-3.76 (1H, m), 2.61 (3H, s), 1.87-1.83 (2H, m), 1.77-1.74 (2H, m), 1.65-1.60 (1H, m), 1.40-1.27 (4H, m), 1.20-1.10 (1H, m).	334	Not Detected	
12		¹ H-NMR (DMSO-D ₆) δ: 11.99 (1H, s), 8.28 (1H, d, J = 8.1 Hz), 8.05-8.02 (2H, m), 7.92-7.83 (4H, m), 7.55-7.51 (1H, m), 7.31-7.27 (1H, m), 3.79-3.70 (1H, m), 2.60 (3H, s), 2.32 (1H, dd, J = 15.0, 5.2 Hz), 2.00 (1H, dd, J = 15.0, 9.0 Hz), 1.93-1.88 (2H, m), 1.82-1.76 (1H, m), 1.70-1.68 (2H, m), 1.40-1.29 (2H, m), 1.24-1.06 (3H, m), 0.88 (3H, d, J = 6.7 Hz).	420	Not Detected	optically active form (S)
13		¹ H-NMR (DMSO-D ₆) δ: 9.08 (1H, d, J = 2.5 Hz), 8.43 (1H, d, J = 8.8 Hz), 8.39 (1H, dd, J = 8.4, 2.4 Hz), 8.19 (1H, d, J = 8.6 Hz), 7.97 (1H, d, J = 8.6 Hz), 7.91 (1H, d, J = 8.3 Hz), 7.59-7.55 (1H, m), 7.35-7.31 (1H, m), 4.56 (1H, d, J = 4.4 Hz), 3.81-3.73 (1H, m), 3.44-3.38 (1H, m), 2.62 (3H, s), 1.88-1.80 (4H, m), 1.54-1.44 (2H, m), 1.32-1.23 (2H, m).	351	Not Detected	
14		¹ H-NMR (DMSO-D ₆) δ: 8.96 (1H, dd, J = 2.3, 0.7 Hz), 8.76-8.73 (1H, m), 8.37-8.33 (2H, m), 8.00 (1H, dd, J = 8.7, 0.6 Hz), 7.87 (1H, dt, J = 8.1, 0.9 Hz), 7.62-7.58 (1H, m), 7.35 (1H, td, J = 16.0, 8.0 Hz), 4.56 (1H, d, J = 4.4 Hz), 3.80-3.71 (1H, m), 3.46-3.37 (1H, m), 2.62 (3H, s), 1.88-1.85 (4H, m), 1.44-1.34 (2H, m), 1.31-1.21 (2H, m).	351	349	
15		¹ H-NMR (DMSO-D ₆) δ: 8.97-8.96 (1H, m), 8.75 (1H, d, J = 8.3 Hz), 8.38-8.34 (2H, m), 8.00 (1H, d, J = 8.8 Hz), 7.87 (1H, d, J = 8.1 Hz), 7.62-7.58 (1H, m), 7.37-7.33 (1H, m), 4.04 (1H, s), 3.78-3.69 (1H, m), 2.62 (3H, s), 1.96-1.91 (2H, m), 1.87-1.83 (2H, m), 1.37-1.28 (2H, m), 1.23-1.05 (3H, m), 1.05 (6H, s).	393	391	
16		¹ H-NMR (DMSO-D ₆) δ: 8.99 (1H, d, J = 2.2 Hz), 8.82 (1H, d, J = 8.2 Hz), 8.44-8.39 (2H, m), 8.00 (1H, d, J = 8.2 Hz), 7.85 (1H, d, J = 8.2 Hz), 7.76-7.72 (1H, m), 7.50-7.48 (1H, m), 4.56 (1H, d, J = 4.5 Hz), 3.80-3.72 (1H, m), 3.45-3.40 (1H, m), 1.88-1.86 (4H, m), 1.39-1.26 (4H, m).	371	369	

[1065]

[Table 1-3]

Ex.No.	structural formula	¹ H-NMR (400 MHz)	MS (positive)	MS (negative)	Comments
17		¹ H-NMR (DMSO-D ₆) δ: 9.00 (1H, d, J = 2.2 Hz), 8.82 (1H, d, J = 8.2 Hz), 8.45-8.40 (2H, m), 8.00 (1H, d, J = 9.0 Hz), 7.85 (1H, d, J = 7.5 Hz), 7.76-7.72 (1H, m), 7.49 (1H, t, J = 7.5 Hz), 4.04 (1H, s), 3.76-3.72 (1H, m), 1.94-1.85 (4H, m), 1.37-1.09 (5H, m), 1.05 (6H, s).	413	411	
18		¹ H-NMR (DMSO-D ₆) δ: 9.22 (2H, s), 8.67 (1H, d, J = 8.2 Hz), 8.51 (1H, d, J = 7.5 Hz), 7.89 (1H, d, J = 7.5 Hz), 7.65-7.61 (1H, m), 7.42-7.38 (1H, m), 4.58 (1H, d, J = 4.5 Hz), 3.81-3.72 (1H, m), 3.46-3.38 (1H, m), 2.62 (3H, s), 1.90-1.87 (4H, m), 1.44-1.35 (2H, m), 1.31-1.22 (2H, m).	352	350	
19		¹ H-NMR (DMSO-D ₆) δ: 9.22 (2H, s), 8.67 (1H, d, J = 8.5 Hz), 8.53 (1H, d, J = 7.8 Hz), 7.89 (1H, d, J = 8.0 Hz), 7.65-7.61 (1H, m), 7.42-7.38 (1H, m), 4.05 (1H, s), 3.78-3.70 (1H, m), 2.62 (3H, s), 1.98-1.94 (2H, m), 1.88-1.84 (2H, m), 1.37-1.28 (2H, m), 1.24-1.06 (3H, m), 1.06 (6H, s).	394	392	
20		¹ H-NMR (DMSO-D ₆) δ: 9.11 (1H, d, J = 2.3 Hz), 8.57 (1H, d, J = 8.6 Hz), 8.50 (1H, dd, J = 8.3, 2.5 Hz), 8.28 (1H, d, J = 8.6 Hz), 8.09-8.06 (2H, m), 7.76-7.72 (1H, m), 7.59 (1H, t, J = 7.7 Hz), 4.57 (1H, d, J = 4.4 Hz), 3.84-3.74 (1H, m), 3.45-3.38 (1H, m), 1.88-1.80 (4H, m), 1.56-1.46 (2H, m), 1.32-1.23 (2H, m).	362	360	
21		¹ H-NMR (DMSO-D ₆) δ: 8.97 (1H, d, J = 1.5 Hz), 8.80 (1H, d, J = 9.0 Hz), 8.40-8.37 (2H, m), 7.90-7.86 (2H, m), 7.74 (1H, t, J = 7.9 Hz), 7.45 (1H, t, J = 7.5 Hz), 4.56 (1H, d, J = 3.7 Hz), 3.78-3.72 (1H, m), 3.46-3.35 (1H, m), 1.89-1.84 (4H, m), 1.41-1.23 (4H, m).	355	353	
22		¹ H-NMR (DMSO-D ₆) δ: 8.98 (1H, d, J = 1.5 Hz), 8.80 (1H, d, J = 9.0 Hz), 8.42-8.38 (2H, m), 7.90-7.86 (2H, m), 7.74 (1H, t, J = 7.9 Hz), 7.46 (1H, t, J = 7.5 Hz), 4.04 (1H, s), 3.76-3.70 (1H, m), 1.93-1.85 (4H, m), 1.37-1.09 (5H, m), 1.05 (6H, s).	397	395	
23		¹ H-NMR (DMSO-D ₆) δ: 9.25 (2H, s), 8.73 (1H, d, J = 8.8 Hz), 8.55 (1H, d, J = 7.6 Hz), 7.85 (1H, d, J = 8.1 Hz), 7.75 (1H, t, J = 7.6 Hz), 7.51 (1H, t, J = 7.6 Hz), 4.56 (1H, d, J = 4.4 Hz), 3.78-3.72 (1H, m), 3.44-3.39 (1H, m), 1.88-1.85 (4H, m), 1.37-1.27 (4H, m).	372	370	
24		¹ H-NMR (DMSO-D ₆) δ: 9.26 (2H, s), 8.74 (1H, d, J = 8.8 Hz), 8.57 (1H, d, J = 7.4 Hz), 7.85 (1H, d, J = 7.9 Hz), 7.76 (1H, t, J = 7.9 Hz), 7.51 (1H, t, J = 7.5 Hz), 4.03 (1H, s), 3.74-3.69 (1H, m), 1.95-1.85 (4H, m), 1.32-1.12 (5H, m), 1.04 (6H, s).	414	412	

[1066]

[Table 1-4]

Ex.No.	structural formula	¹ H-NMR (400 MHz)	MS (positive)	MS (negative)	Comments
25		¹ H-NMR (DMSO-D ₆) δ : 9.34 (2H, s), 8.82 (1H, d, J = 8.2 Hz), 8.65 (1H, d, J = 7.5 Hz), 8.06 (1H, d, J = 8.2 Hz), 7.83 (1H, t, J = 8.2 Hz), 7.62 (1H, t, J = 8.2 Hz), 4.58 (1H, d, J = 4.5 Hz), 3.85-3.71 (1H, m), 3.49-3.38 (1H, m), 1.96-1.83 (4H, m), 1.47-1.20 (4H, m).	363	361	
26		¹ H-NMR (DMSO-D ₆) δ : 9.23 (2H, s), 8.74 (1H, d, J = 8.2 Hz), 8.53 (1H, d, J = 7.5 Hz), 7.93 (1H, d, J = 7.5 Hz), 7.77 (1H, t, J = 7.5 Hz), 7.50 (1H, t, J = 7.5 Hz), 4.58 (1H, d, J = 3.7 Hz), 3.78-3.73 (1H, m), 3.46-3.39 (1H, m), 1.92-1.85 (4H, m), 1.41-1.25 (4H, m).	356	354	
27		¹ H-NMR (DMSO-D ₆) δ : 9.18 (2H, s), 8.68 (1H, d, J = 8.2 Hz), 8.46 (1H, d, J = 7.5 Hz), 7.78 (1H, d, J = 8.2 Hz), 7.67 (1H, t, J = 7.9 Hz), 7.38 (1H, t, J = 7.5 Hz), 4.58 (1H, d, J = 4.5 Hz), 4.17 (3H, s), 3.77-3.72 (1H, m), 3.46-3.41 (1H, m), 1.89-1.87 (4H, m), 1.39-1.27 (4H, m).	368	366	
28		¹ H-NMR (DMSO-D ₆) δ : 9.24 (2H, s), 8.74 (1H, d, J = 8.2 Hz), 8.55 (1H, d, J = 8.2 Hz), 7.92 (1H, d, J = 8.2 Hz), 7.77 (1H, t, J = 8.2 Hz), 7.50 (1H, t, J = 8.2 Hz), 4.05 (1H, s), 3.78-3.70 (1H, m), 1.99-1.84 (4H, m), 1.36-1.10 (5H, m), 1.08 (6H, d, J = 17.2 Hz).	398	396	
29		¹ H-NMR (DMSO-D ₆) δ : 9.99 (1H, s), 9.27 (2H, s), 8.55 (1H, d, J = 7.9 Hz), 8.53 (1H, d, J = 5.5 Hz), 7.94 (1H, d, J = 5.3 Hz), 4.57 (1H, br s), 3.83-3.70 (1H, m), 3.49-3.38 (1H, m), 2.66 (3H, s), 1.96-1.80 (4H, m), 1.48-1.17 (4H, m).	353	351	
30		¹ H-NMR (DMSO-D ₆) δ : 9.08 (1H, d, J = 2.5 Hz), 8.43 (1H, d, J = 8.6 Hz), 8.39 (1H, dd, J = 8.4, 2.7 Hz), 8.20 (1H, d, J = 8.6 Hz), 7.97 (1H, d, J = 8.6 Hz), 7.91 (1H, d, J = 8.1 Hz), 7.59-7.55 (1H, m), 7.35-7.31 (1H, m), 4.04 (1H, s), 3.79-3.71 (1H, m), 2.62 (3H, s), 1.92-1.83 (4H, m), 1.47-1.38 (2H, m), 1.24-1.01 (3H, m), 1.05 (6H, s).	393	Not Detected	
31		¹ H-NMR (DMSO-D ₆) δ : 9.22 (2H, s), 8.58 (1H, d, J = 7.6 Hz), 7.72 (1H, dd, J = 7.4, 1.2 Hz), 7.45-7.34 (2H, m), 4.57 (1H, d, J = 4.4 Hz), 3.80-3.71 (1H, m), 3.46-3.38 (1H, m), 2.61 (3H, s), 1.91-1.85 (4H, m), 1.43-1.21 (4H, m).	370	368	
32		¹ H-NMR (DMSO-D ₆) δ : 9.19 (2H, s), 8.68 (1H, d, J = 9.0 Hz), 8.48 (1H, d, J = 7.5 Hz), 7.78 (1H, d, J = 7.5 Hz), 7.67 (1H, t, J = 7.5 Hz), 7.38 (1H, t, J = 7.5 Hz), 4.17 (3H, s), 4.05 (1H, s), 3.79-3.68 (1H, m), 1.99-1.84 (4H, m), 1.36-1.09 (5H, m), 1.06 (6H, s).	410	408	

[1067]

[Table 1-5]

Ex.No.	structural formula	¹ H-NMR (400 MHz)	MS (positive)	MS (negative)	Comments
33		¹ H-NMR (DMSO-D ₆) δ: 9.22 (2H, s), 8.68 (1H, d, J = 8.2 Hz), 8.51 (1H, d, J = 7.5 Hz), 7.92 (1H, d, J = 8.2 Hz), 7.62 (1H, t, J = 7.9 Hz), 7.39 (1H, t, J = 7.5 Hz), 4.58 (1H, d, J = 4.5 Hz), 3.81-3.72 (1H, m), 3.47-3.39 (1H, m), 3.05 (2H, q, J = 7.5 Hz), 1.91-1.85 (4H, m), 1.44-1.35 (2H, m), 1.39 (3H, t, J = 7.5 Hz), 1.31-1.23 (2H, m).	366	364	
34		¹ H-NMR (DMSO-D ₆) δ: 9.20 (2H, s), 8.68 (1H, d, J = 9.0 Hz), 8.49 (1H, d, J = 8.2 Hz), 7.98 (1H, d, J = 8.2 Hz), 7.63 (1H, t, J = 7.5 Hz), 7.40 (1H, t, J = 7.5 Hz), 4.57 (1H, d, J = 4.5 Hz), 3.79-3.71 (1H, m), 3.47-3.39 (1H, m), 2.49-2.42 (1H, m), 1.90-1.86 (4H, m), 1.44-1.34 (2H, m), 1.31-1.22 (2H, m), 1.15-1.13 (4H, m).	378	376	
35		¹ H-NMR (DMSO-D ₆) δ: 9.23 (2H, s), 8.52 (1H, d, J = 7.5 Hz), 8.41 (1H, dd, J = 10.5, 2.2 Hz), 7.95 (1H, dd, J = 8.2, 5.2 Hz), 7.30 (1H, ddd, J = 8.2, 8.2, 2.2 Hz), 4.58 (1H, br s), 3.83-3.70 (1H, m), 3.48-3.39 (1H, m), 2.61 (3H, s), 1.95-1.82 (4H, m), 1.46-1.20 (4H, m).	370	368	
36		¹ H-NMR (DMSO-D ₆) δ: 9.21 (2H, s), 8.68 (1H, dd, J = 9.0, 4.5 Hz), 8.52 (1H, d, J = 7.5 Hz), 7.74 (1H, dd, J = 9.0, 2.2 Hz), 7.52 (1H, ddd, J = 9.0, 9.0, 2.2 Hz), 4.58 (1H, br s), 3.83-3.70 (1H, m), 3.48-3.37 (1H, m), 2.60 (3H, s), 1.95-1.83 (4H, m), 1.47-1.20 (4H, m).	370	368	
37		¹ H-NMR (DMSO-D ₆) δ: 8.93 (1H, d, J = 1.5 Hz), 8.57-8.55 (2H, m), 7.86 (1H, d, J = 7.5 Hz), 7.76 (1H, d, J = 8.2 Hz), 7.50 (1H, t, J = 7.5 Hz), 7.31 (1H, t, J = 7.5 Hz), 4.57 (1H, d, J = 4.5 Hz), 3.80-3.72 (1H, m), 3.46-3.37 (1H, m), 2.60 (3H, s), 1.89-1.86 (4H, m), 1.43-1.22 (4H, m).	385	383	
38		¹ H-NMR (DMSO-D ₆) δ: 8.94 (1H, s), 8.59-8.57 (2H, m), 7.86 (1H, d, J = 8.2 Hz), 7.77 (1H, d, J = 9.0 Hz), 7.52-7.50 (1H, m), 7.31 (1H, t, J = 7.5 Hz), 4.05 (1H, s), 3.77-3.70 (1H, m), 2.60 (3H, s), 1.97-1.84 (4H, m), 1.37-1.10 (5H, m), 1.06 (6H, s).	427	425	
39		¹ H-NMR (DMSO-D ₆) δ: 8.97 (1H, s), 8.46 (1H, d, J = 10.5 Hz), 8.40-8.32 (2H, m), 7.99 (1H, d, J = 9.0 Hz), 7.93 (1H, dd, J = 9.0, 5.2 Hz), 7.25 (1H, t, J = 9.0 Hz), 4.56 (1H, d, J = 4.5 Hz), 3.81-3.69 (1H, m), 3.48-3.35 (1H, m), 2.61 (3H, s), 1.92-1.80 (4H, br m), 1.46-1.19 (4H, m).	369	367	
40		¹ H-NMR (DMSO-D ₆) δ: 8.98 (1H, s), 8.46 (1H, d, J = 9.7 Hz), 8.38 (2H, t, J = 6.7 Hz), 7.99 (1H, d, J = 8.2 Hz), 7.93 (1H, dd, J = 8.6, 5.6 Hz), 7.25 (1H, t, J = 8.6 Hz), 4.04 (1H, s), 3.80-3.67 (1H, m), 2.61 (3H, s), 1.99-1.89 (2H, br m), 1.89-1.79 (2H, br m), 1.40-1.25 (2H, br m), 1.25-1.00 (9H, br m).	411	409	

[1068]

[Table 1-6]

Ex.No.	structural formula	¹ H-NMR (400 MHz)	MS (positive)	MS (negative)	Comments
41		¹ H-NMR (DMSO-D ₆) δ: 8.92 (1H, d, J = 1.6 Hz), 8.43 (1H, d, J = 7.6 Hz), 8.37 (1H, dd, J = 8.6, 2.3 Hz), 7.88 (1H, d, J = 8.3 Hz), 7.70 (1H, d, J = 7.9 Hz), 7.41-7.36 (1H, m), 7.32 (1H, td, J = 7.9, 4.2 Hz), 4.56 (1H, d, J = 4.4 Hz), 3.79-3.71 (1H, m), 3.45-3.37 (1H, m), 2.61 (3H, s), 1.89-1.85 (4H, m), 1.44-1.34 (2H, m), 1.31-1.21 (2H, m).	369	367	
42		¹ H-NMR (DMSO-D ₆) δ: 9.23 (2H, s), 8.54 (1H, d, J = 7.5 Hz), 8.49 (1H, d, J = 9.0 Hz), 7.63-7.61 (1H, m), 7.18-7.15 (1H, m), 4.58 (1H, s), 3.81-3.70 (1H, m), 3.47-3.37 (1H, m), 2.70 (3H, s), 1.90-1.87 (4H, m), 1.44-1.23 (4H, m).	370	368	
43		¹ H-NMR (DMSO-D ₆) δ: 9.24 (2H, s), 8.56 (1H, d, J = 7.5 Hz), 8.50 (1H, d, J = 9.0 Hz), 7.63-7.61 (1H, m), 7.18-7.16 (1H, m), 4.05 (1H, s), 3.77-3.70 (1H, m), 2.70 (3H, s), 1.96-1.86 (4H, m), 1.37-1.10 (5H, m), 1.06 (6H, s).	412	410	
44		¹ H-NMR (DMSO-D ₆) δ: 8.39 (1H, d, J = 7.5 Hz), 7.96 (1H, d, J = 12.0 Hz), 7.88 (2H, t, J = 13.1 Hz), 7.75 (1H, t, J = 8.2 Hz), 7.49 (1H, t, J = 7.5 Hz), 7.40 (1H, dd, J = 9.0, 3.7 Hz), 7.28 (1H, t, J = 7.5 Hz), 4.57 (1H, d, J = 4.5 Hz), 3.81-3.70 (1H, m), 3.46-3.36 (1H, m), 2.60 (3H, s), 1.92-1.78 (4H, br m), 1.46-1.33 (2H, br m), 1.32-1.20 (2H, br m).	368	366	
45		¹ H-NMR (DMSO-D ₆) δ: 8.41 (1H, d, J = 8.2 Hz), 7.97 (1H, d, J = 12.0 Hz), 7.92-7.84 (2H, m), 7.76 (1H, t, J = 7.9 Hz), 7.50 (1H, t, J = 7.5 Hz), 7.40 (1H, dd, J = 9.0, 3.7 Hz), 7.28 (1H, t, J = 7.5 Hz), 4.04 (1H, s), 3.79-3.68 (1H, m), 2.60 (3H, s), 1.98-1.80 (4H, br m), 1.40-1.26 (2H, br m), 1.23-1.03 (9H, br m).	410	408	
46		¹ H-NMR (DMSO-D ₆) δ: 9.34 (2H, s), 8.82 (1H, d, J = 8.8 Hz), 8.65 (1H, d, J = 7.6 Hz), 8.00-7.98 (1H, m), 7.83-7.79 (1H, m), 7.61-7.57 (1H, m), 4.05 (1H, s), 3.79-3.72 (1H, m), 2.00-1.96 (2H, m), 1.88-1.85 (2H, m), 1.38-1.28 (2H, m), 1.25-1.02 (3H, m), 1.06 (6H, s).	448	446	
47		¹ H-NMR (DMSO-D ₆) δ: 8.80 (1H, d, J = 2.2 Hz), 8.39 (1H, d, J = 7.5 Hz), 8.27 (1H, d, J = 2.2 Hz), 7.95 (1H, d, J = 7.5 Hz), 7.84 (1H, d, J = 7.5 Hz), 7.48 (1H, t, J = 7.5 Hz), 7.29 (1H, t, J = 7.5 Hz), 4.56 (1H, d, J = 4.5 Hz), 3.81-3.72 (1H, m), 3.46-3.38 (1H, m), 2.59 (3H, s), 2.52 (3H, s), 1.88-1.86 (4H, m), 1.43-1.22 (4H, m).	365	363	
48		¹ H-NMR (DMSO-D ₆) δ: 8.81 (1H, s), 8.41 (1H, d, J = 7.5 Hz), 8.28 (1H, s), 7.95 (1H, d, J = 9.0 Hz), 7.84 (1H, d, J = 7.5 Hz), 7.49 (1H, t, J = 7.5 Hz), 7.29 (1H, t, J = 7.5 Hz), 4.04 (1H, s), 3.78-3.70 (1H, m), 2.60 (3H, s), 2.52 (3H, s), 1.94-1.85 (4H, m), 1.37-1.09 (5H, m), 1.06 (6H, s).	407	405	

[1069]

[Table 1-7]

Ex.No.	structural formula	¹ H-NMR (400 MHz)	MS (positive)	MS (negative)	Comments
49		¹ H-NMR (DMSO-D ₆) δ: 8.96 (1H, d, J = 2.2 Hz), 8.56 (1H, d, J = 9.0 Hz), 8.40-8.36 (2H, m), 8.01 (1H, d, J = 8.2 Hz), 7.58 (1H, td, J = 8.2, 5.7 Hz), 7.12 (1H, dd, J = 10.5, 8.2 Hz), 4.56 (1H, d, J = 4.5 Hz), 3.79-3.72 (1H, m), 3.45-3.38 (1H, m), 2.70 (3H, s), 1.88-1.85 (4H, m), 1.43-1.22 (4H, m).	369	367	
50		¹ H-NMR (DMSO-D ₆) δ: 8.98 (1H, s), 8.57 (1H, d, J = 9.0 Hz), 8.41-8.38 (2H, m), 8.01 (1H, d, J = 9.0 Hz), 7.58 (1H, q, J = 7.2 Hz), 7.12 (1H, dd, J = 10.5, 7.2 Hz), 4.04 (1H, s), 3.77-3.70 (1H, m), 2.70 (3H, s), 1.95-1.84 (4H, m), 1.37-1.09 (5H, m), 1.05 (6H, s).	411	409	
51		¹ H-NMR (DMSO-D ₆) δ: 9.23 (2H, s), 8.66 (1H, d, J = 8.6 Hz), 8.54 (1H, d, J = 7.6 Hz), 7.61-7.57 (1H, m), 7.42 (1H, d, J = 7.6 Hz), 4.58 (1H, d, J = 4.6 Hz), 3.81-3.71 (1H, m), 3.47-3.38 (1H, m), 2.78 (3H, s), 1.90-1.87 (4H, m), 1.44-1.35 (2H, m), 1.31-1.22 (2H, m).	386	384	
52		¹ H-NMR (DMSO-D ₆) δ: 9.06 (1H, d, J = 3.0 Hz), 8.50 (1H, d, J = 8.2 Hz), 8.42 (1H, dd, J = 9.0, 3.0 Hz), 8.22 (1H, d, J = 8.2 Hz), 8.03 (1H, d, J = 8.2 Hz), 7.87 (1H, d, J = 8.2 Hz), 7.70-7.68 (1H, m), 7.47-7.46 (1H, m), 4.57 (1H, d, J = 3.7 Hz), 3.82-3.73 (1H, m), 3.45-3.38 (1H, m), 1.87-1.80 (4H, m), 1.55-1.46 (2H, m), 1.31-1.23 (2H, m).	371	369	
53		¹ H-NMR (DMSO-D ₆) δ: 9.07 (1H, s), 8.50 (1H, d, J = 8.2 Hz), 8.42 (1H, d, J = 8.2 Hz), 8.23 (1H, d, J = 8.2 Hz), 8.03 (1H, d, J = 8.2 Hz), 7.87 (1H, d, J = 8.2 Hz), 7.69 (1H, t, J = 8.2 Hz), 7.46 (1H, t, J = 8.2 Hz), 4.04 (1H, s), 3.79-3.70 (1H, m), 1.91-1.83 (4H, m), 1.48-1.39 (2H, m), 1.24-1.09 (3H, m), 1.05 (6H, s).	413	411	
54		¹ H-NMR (DMSO-D ₆) δ: 8.84 (1H, s), 8.47 (1H, d, J = 7.5 Hz), 8.35-8.33 (1H, m), 8.20 (1H, d, J = 9.0 Hz), 7.88 (1H, d, J = 8.2 Hz), 7.56 (1H, t, J = 8.2 Hz), 7.35 (1H, dd, J = 9.0, 8.2 Hz), 4.57 (1H, d, J = 4.5 Hz), 3.80-3.70 (1H, m), 3.47-3.37 (1H, m), 2.60 (3H, s), 1.89-1.86 (4H, m), 1.43-1.22 (4H, m).	369	367	
55		¹ H-NMR (DMSO-D ₆) δ: 8.85 (1H, s), 8.49 (1H, d, J = 7.5 Hz), 8.35 (1H, d, J = 12.0 Hz), 8.20 (1H, d, J = 8.2 Hz), 7.88 (1H, d, J = 7.5 Hz), 7.56 (1H, t, J = 7.9 Hz), 7.36 (1H, t, J = 7.5 Hz), 4.05 (1H, s), 3.78-3.70 (1H, m), 2.61 (3H, s), 1.96-1.84 (4H, m), 1.37-1.10 (5H, m), 1.06 (6H, s).	411	409	
56		¹ H-NMR (DMSO-D ₆) δ: 9.24 (2H, s), 8.68 (1H, d, J = 8.2 Hz), 8.54 (1H, d, J = 7.5 Hz), 7.89 (1H, d, J = 7.5 Hz), 7.63 (1H, t, J = 7.1 Hz), 7.40 (1H, t, J = 7.5 Hz), 4.41 (1H, d, J = 3.0 Hz), 3.89-3.79 (2H, m), 2.62 (3H, s), 1.84-1.69 (4H, m), 1.62-1.48 (4H, m).	352	350	

[1070]

[Table 1-8]

Ex.No.	structural formula	¹ H-NMR (400 MHz)	MS (positive)	MS (negative)	Comments
57		¹ H-NMR (DMSO-D ₆) δ: 8.95 (2H, s), 8.48 (1H, d, J = 8.8 Hz), 8.27-8.19 (1H, m), 7.46 (1H, d, J = 7.9 Hz), 7.29 (1H, dd, J = 8.8, 7.9 Hz), 7.07 (1H, dd, J = 7.9, 7.9 Hz), 4.55 (1H, d, J = 4.4 Hz), 3.79-3.65 (1H, m), 3.46-3.37 (1H, m), 1.93-1.79 (4H, m), 1.45-1.18 (4H, m).	354	352	
58		¹ H-NMR (DMSO-D ₆) δ: 9.24 (2H, s), 8.55 (1H, d, J = 7.6 Hz), 8.28 (1H, dd, J = 10.1, 2.0 Hz), 7.30 (1H, td, J = 10.1, 1.8 Hz), 4.58 (1H, d, J = 4.4 Hz), 3.80-3.72 (1H, m), 3.47-3.39 (1H, m), 2.67 (3H, s), 1.90-1.86 (4H, m), 1.44-1.35 (2H, m), 1.31-1.23 (2H, m).	388	386	
59		¹ H-NMR (DMSO-D ₆) δ: 9.24 (2H, s), 8.72 (1H, d, J = 1.8 Hz), 8.51 (1H, d, J = 7.8 Hz), 7.93 (1H, d, J = 8.5 Hz), 7.45 (1H, dd, J = 8.3, 1.8 Hz), 4.58 (1H, d, J = 4.5 Hz), 3.79-3.71 (1H, m), 3.47-3.38 (1H, m), 2.61 (3H, s), 1.90-1.86 (4H, m), 1.43-1.34 (2H, m), 1.31-1.22 (2H, m).	386	384	
60		¹ H-NMR (DMSO-D ₆) δ: 10.07 (1H, s), 9.31 (2H, s), 8.63 (1H, d, J = 6.0 Hz), 8.61 (1H, d, J = 7.5 Hz), 7.92 (1H, d, J = 6.0 Hz), 4.58 (1H, d, J = 4.5 Hz), 3.82-3.71 (1H, m), 3.48-3.39 (1H, m), 1.90-1.87 (4H, m), 1.44-1.23 (4H, m).	373	371	
61		¹ H-NMR (DMSO-D ₆) δ: 9.11 (2H, s), 8.39 (1H, d, J = 7.6 Hz), 8.32 (1H, dd, J = 10.8, 2.0 Hz), 7.85-7.76 (1H, m), 7.12 (1H, t, J = 8.8 Hz), 4.58 (1H, br s), 3.81-3.69 (1H, m), 3.50-3.18 (1H, m), 1.93-1.80 (4H, m), 1.46-1.17 (4H, m).	372	370	
62		¹ H-NMR (DMSO-D ₆) δ: 8.99 (1H, d, J = 1.5 Hz), 8.79 (1H, s), 8.36 (2H, d, J = 7.5 Hz), 7.99 (1H, d, J = 9.0 Hz), 7.91 (1H, d, J = 8.2 Hz), 7.40 (1H, d, J = 8.2 Hz), 4.57 (1H, br s), 3.80-3.71 (1H, m), 3.45-3.39 (1H, m), 2.62 (3H, s), 1.89-1.84 (4H, m), 1.43-1.34 (2H, m), 1.31-1.21 (2H, m).	385	383	
63		¹ H-NMR (DMSO-D ₆) δ: 9.23 (2H, s), 8.58 (1H, d, J = 8.2 Hz), 7.75 (1H, dd, J = 9.0, 4.5 Hz), 7.47 (1H, td, J = 9.3, 6.0 Hz), 4.58 (1H, d, J = 3.7 Hz), 3.80-3.72 (1H, m), 3.47-3.39 (1H, m), 2.60 (3H, s), 1.90-1.87 (4H, m), 1.44-1.34 (2H, m), 1.31-1.23 (2H, m).	388	386	
64		¹ H-NMR (DMSO-D ₆) δ: 9.26 (2H, s), 9.10 (1H, s), 8.55 (1H, d, J = 7.5 Hz), 8.13 (1H, d, J = 8.2 Hz), 7.78 (1H, d, J = 8.2 Hz), 4.58 (1H, d, J = 3.7 Hz), 3.81-3.71 (1H, m), 3.46-3.39 (1H, m), 2.67 (3H, s), 1.90-1.87 (4H, m), 1.44-1.23 (4H, m).	377	375	

[1071]

[Table 1-9]

Ex.No.	structural formula	¹ H-NMR (400 MHz)	MS (positive)	MS (negative)	Comments
65		¹ H-NMR (DMSO-D ₆) δ: 9.09-8.93 (2H, m), 8.36-8.24 (1H, m), 8.22-8.12 (1H, m), 7.59-7.48 (1H, m), 7.09-6.97 (1H, m), 4.02 (1H, s), 3.71-3.57 (1H, m), 1.97-1.74 (4H, m), 1.33-1.07 (5H, m), 1.04 (6H, s).	414	412	
66		¹ H-NMR (DMSO-D ₆) δ: 10.16 (1H, s), 9.37 (2H, s), 8.68-8.67 (2H, m), 8.02 (1H, d, J = 5.2 Hz), 4.58 (1H, d, J = 4.5 Hz), 3.82-3.74 (1H, m), 3.47-3.39 (1H, m), 1.91-1.88 (4H, m), 1.45-1.24 (4H, m).	407	405	
67		¹ H NMR (DMSO D ₆) δ: 9.22 (2H, s), 8.49 (1H, d, J = 7.6 Hz), 8.20 (1H, d, J = 2.2 Hz), 7.75 (1H, d, J = 8.8 Hz), 7.01 (1H, dd, J = 8.8, 2.2 Hz), 4.57 (1H, d, J = 3.9 Hz), 3.90 (3H, s), 3.81-3.71 (1H, m), 3.47-3.38 (1H, m), 2.55 (3H, s), 1.89-1.86 (4H, m), 1.43-1.22 (4H, m).	382	380	
68		¹ H-NMR (DMSO-D ₆) δ: 9.27 (2H, s), 9.02-9.02 (1H, m), 8.50 (1H, d, J = 7.6 Hz), 8.15 (1H, d, J = 8.4 Hz), 7.72 (1H, dd, J = 8.4, 1.3 Hz), 4.58 (1H, br s), 3.80-3.72 (1H, m), 3.46-3.39 (1H, m), 2.68 (3H, s), 1.90-1.87 (4H, m), 1.43-1.23 (4H, m).	420	418	
69		¹ H NMR (DMSO D ₆) δ: 8.84 (1H, s), 8.48 (1H, d, J = 8.2 Hz), 8.35 (1H, d, J = 12.0 Hz), 7.97 (1H, dd, J = 9.7, 2.2 Hz), 7.93 (1H, dd, J = 9.0, 5.2 Hz), 7.28-7.22 (1H, m), 4.57 (1H, d, J = 4.5 Hz), 3.80-3.71 (1H, m), 3.46-3.38 (1H, m), 2.59 (3H, s), 1.88-1.86 (4H, m), 1.43-1.22 (4H, m).	387	385	
70		¹ H-NMR (DMSO-D ₆) δ: 8.85 (1H, s), 8.50 (1H, d, J = 8.2 Hz), 8.36 (1H, d, J = 12.0 Hz), 8.00-7.92 (2H, m), 7.27-7.23 (1H, m), 4.05 (1H, s), 3.79-3.70 (1H, m), 2.60 (3H, s), 1.96-1.84 (4H, m), 1.36-1.09 (5H, m), 1.06 (6H, s).	429	427	
71		¹ H-NMR (DMSO-D ₆) δ: 8.84 (1H, s), 8.48 (1H, d, J = 7.5 Hz), 8.35 (1H, d, J = 12.0 Hz), 7.99-7.92 (2H, m), 7.27-7.23 (1H, m), 4.57 (1H, d, J = 4.5 Hz), 3.80-3.71 (1H, m), 3.46-3.38 (1H, m), 2.59 (3H, s), 1.89-1.86 (4H, m), 1.43-1.22 (4H, m).	387	385	
72		¹ H-NMR (DMSO-D ₆) δ: 8.85 (1H, s), 8.49 (1H, d, J = 8.2 Hz), 8.36 (1H, d, J = 12.0 Hz), 7.99-7.92 (2H, m), 7.27-7.22 (1H, m), 4.05 (1H, s), 3.77-3.69 (1H, m), 2.59 (3H, s), 1.96-1.84 (4H, m), 1.38-1.06 (5H, m), 1.05 (6H, s).	429	427	

[1072]

[Table 1-10]

Ex.No.	structural formula	¹ H-NMR (400 MHz)	MS (positive)	MS (negative)	Comments
73		¹ H-NMR (DMSO-D ₆) δ: 11.93 (1H, br s), 8.78 (1H, s), 8.45-8.33 (1H, m), 8.25 (1H, d, J = 12.0 Hz), 8.10-7.93 (1H, m), 7.89-7.73 (1H, m), 7.27-7.06 (1H, m), 4.56 (1H, d, J = 3.7 Hz), 3.82-3.66 (1H, m), 3.48-3.36 (1H, m), 1.96-1.74 (4H, m), 1.46-1.13 (4H, m).	389	387	
74		¹ H-NMR (DMSO-D ₆) δ: 12.73 (1H, s), 8.36-8.25 (3H, m), 7.52 (1H, d, J = 8.2 Hz), 7.40 (2H, t, J = 7.9 Hz), 7.08 (1H, t, J = 7.5 Hz), 4.55 (1H, d, J = 3.7 Hz), 3.76-3.64 (1H, m), 3.44-3.34 (1H, m), 1.90-1.77 (4H, m), 1.42-1.16 (4H, m).	371	369	
75		¹ H-NMR (DMSO-D ₆) δ: 9.20 (2H, s), 8.50 (1H, d, J = 7.6 Hz), 8.22 (1H, d, J = 8.3 Hz), 7.51 (1H, t, J = 8.2 Hz), 6.84 (1H, d, J = 7.9 Hz), 4.57 (1H, d, J = 4.2 Hz), 3.96 (3H, s), 3.82-3.69 (1H, m), 3.48-3.37 (1H, m), 2.66 (3H, s), 1.93-1.82 (4H, m), 1.47-1.17 (4H, m).	382	380	
76		¹ H-NMR (DMSO-D ₆) δ: 12.73 (1H, s), 8.38-8.26 (3H, m), 7.52 (1H, d, J = 8.6 Hz), 7.40 (2H, t, J = 7.6 Hz), 7.08 (1H, t, J = 7.5 Hz), 4.03 (1H, br s), 3.75-3.61 (1H, m), 1.96-1.77 (4H, m), 1.35-1.06 (5H, m), 1.04 (6H, s).	413	411	
77		¹ H-NMR (DMSO-D ₆) δ: 9.26 (2H, s), 9.07 (1H, d, J = 7.2 Hz), 8.57 (1H, d, J = 7.6 Hz), 7.85-7.77 (2H, m), 4.58 (1H, d, J = 4.4 Hz), 3.83-3.71 (1H, m), 3.48-3.37 (1H, m), 2.68 (3H, s), 1.95-1.82 (4H, m), 1.48-1.17 (4H, m).	420	418	
78		¹ H-NMR (DMSO-D ₆) δ: 9.30 (2H, s), 8.78 (1H, d, J = 9.0 Hz), 8.60 (1H, d, J = 8.2 Hz), 8.00 (1H, d, J = 8.2 Hz), 7.75 (1H, t, J = 7.9 Hz), 7.70-7.42 (2H, m), 4.58 (1H, d, J = 4.5 Hz), 3.81-3.73 (1H, m), 3.46-3.39 (1H, m), 1.90-1.87 (4H, m), 1.44-1.35 (2H, m), 1.31-1.23 (2H, m).	388	386	
79		¹ H-NMR (DMSO-D ₆) δ: 8.97 (1H, d, J = 2.2 Hz), 8.49-8.44 (2H, m), 8.36 (1H, dd, J = 8.2, 2.2 Hz), 8.00 (1H, d, J = 8.2 Hz), 7.93 (1H, dd, J = 8.2, 5.2 Hz), 7.25 (1H, td, J = 9.0, 2.2 Hz), 3.90-3.78 (1H, m), 2.76-2.67 (1H, m), 2.61 (3H, s), 2.13-2.04 (2H, m), 1.95-1.87 (2H, m), 1.70-1.58 (0H, m), 1.45-1.35 (2H, m).	378	376	
80		¹ H-NMR (DMSO-D ₆) δ: 8.97 (1H, d, J = 2.2 Hz), 8.48-8.35 (3H, m), 8.00 (1H, d, J = 8.2 Hz), 7.93 (1H, dd, J = 9.0, 5.2 Hz), 7.25 (1H, td, J = 9.0, 2.2 Hz), 3.84-3.73 (2H, m), 3.43-3.35 (1H, m), 3.15-3.01 (4H, m), 2.62 (3H, s), 2.08-1.87 (8H, m), 1.47-1.24 (4H, m).	501	499	

[1073]

[Table 1-11]

Ex.No.	structural formula	¹ H-NMR (400 MHz)	MS (positive)	MS (negative)	Comments
81		¹ H-NMR (DMSO-D ₆) δ: 8.98 (1H, d, J = 2.2 Hz), 8.49-8.42 (2H, m), 8.37 (1H, dd, J = 8.2, 2.2 Hz), 8.00 (1H, d, J = 8.2 Hz), 7.93 (1H, dd, J = 9.0, 5.2 Hz), 7.25 (1H, td, J = 9.0, 2.2 Hz), 3.82-3.72 (1H, m), 3.09 (2H, d, J = 6.0 Hz), 2.99 (3H, s), 2.62 (3H, s), 2.01-1.87 (5H, m), 1.46-1.35 (2H, m), 1.28-1.16 (2H, m).	445	443	
82		¹ H-NMR (DMSO-D ₆) δ: 8.82 (1H, s), 8.56 (1H, d, J = 7.5 Hz), 8.38 (1H, d, J = 10.5 Hz), 7.73 (1H, d, J = 8.2 Hz), 7.40-7.28 (2H, m), 4.57 (1H, s), 3.79-3.71 (1H, m), 3.46-3.39 (1H, m), 2.61 (3H, s), 1.89-1.87 (4H, m), 1.43-1.22 (4H, m).	387	385	
83		¹ H-NMR (DMSO-D ₆) δ: 9.25 (2H, s), 8.70 (1H, d, J = 8.8 Hz), 8.54 (1H, d, J = 7.9 Hz), 7.95 (1H, d, J = 7.9 Hz), 7.68-7.62 (1H, m), 7.42 (1H, td, J = 7.6, 0.7 Hz), 4.87 (2H, s), 4.58 (1H, d, J = 4.4 Hz), 3.83-3.71 (1H, m), 3.49-3.38 (1H, m), 3.38 (3H, s), 1.93-1.85 (4H, br m), 1.45-1.33 (2H, br m), 1.33-1.21 (2H, br m).	382	380	
84		¹ H-NMR (DMSO-D ₆) δ: 9.23 (2H, s), 8.69 (1H, d, J = 8.6 Hz), 8.52 (1H, d, J = 7.6 Hz), 8.02 (1H, d, J = 7.9 Hz), 7.65-7.61 (1H, m), 7.40 (1H, t, J = 7.2 Hz), 5.57 (1H, t, J = 6.0 Hz), 4.90 (2H, d, J = 5.8 Hz), 4.57 (1H, d, J = 4.4 Hz), 3.81-3.71 (1H, m), 3.48-3.38 (1H, m), 1.93-1.82 (4H, br m), 1.46-1.33 (2H, br m), 1.33-1.21 (2H, br m).	368	366	
85		¹ H-NMR (DMSO-D ₆) δ: 9.25 (2H, s), 9.01 (1H, d, J = 8.2 Hz), 8.57 (1H, d, J = 8.2 Hz), 7.94 (1H, d, J = 6.7 Hz), 7.79 (1H, t, J = 7.9 Hz), 4.59 (1H, d, J = 4.5 Hz), 3.82-3.70 (1H, m), 3.49-3.39 (1H, m), 2.79 (3H, s), 1.95-1.83 (4H, m), 1.49-1.19 (4H, m).	377	375	
86		¹ H-NMR (DMSO-D ₆) δ: 8.58 (1H, d, J = 1.8 Hz), 8.47 (1H, d, J = 7.6 Hz), 8.05 (1H, d, J = 1.8 Hz), 7.81 (1H, d, J = 8.3 Hz), 7.47 (1H, d, J = 8.1 Hz), 7.42 (1H, ddd, J = 8.3, 8.3, 1.9 Hz), 7.24 (1H, ddd, J = 8.3, 8.1, 1.9 Hz), 4.58 (1H, br s), 3.90 (3H, s), 3.84-3.73 (1H, m), 3.48-3.38 (1H, m), 2.57 (3H, s), 1.94-1.83 (4H, m), 1.50-1.20 (4H, m).	381	379	
87		¹ H-NMR (DMSO-D ₆) δ: 8.59 (1H, d, J = 1.8 Hz), 8.50 (1H, d, J = 7.9 Hz), 8.06 (1H, d, J = 1.8 Hz), 7.81 (1H, d, J = 7.9 Hz), 7.46 (1H, t, J = 7.9 Hz), 7.42 (1H, td, J = 7.9, 1.5 Hz), 7.24 (1H, ddd, J = 7.9, 7.9, 1.5 Hz), 4.05 (1H, s), 3.91 (3H, s), 3.85-3.71 (1H, m), 2.57 (3H, s), 2.02-1.81 (4H, m), 1.41-1.09 (5H, m), 1.06 (6H, s).	423	421	
88		¹ H-NMR (DMSO-D ₆) δ: 9.21 (2H, s), 8.52 (1H, d, J = 7.9 Hz), 8.23 (1H, d, J = 8.2 Hz), 7.51 (1H, dd, J = 8.2, 8.2 Hz), 6.84 (1H, d, J = 8.2 Hz), 4.05 (1H, br s), 3.96 (3H, s), 3.80-3.67 (1H, m), 2.66 (3H, s), 2.01-1.80 (4H, m), 1.39-1.08 (5H, m), 1.05 (6H, s).	424	422	

[1074]

[Table 1-12]

Ex.No.	structural formula	¹ H-NMR (400 MHz)	MS (positive)	MS (negative)	Comments
89		¹ H-NMR (DMSO-D ₆) δ: 9.03 (2H, s), 8.40 (1H, d, J = 6.9 Hz), 8.33 (1H, d, J = 8.3 Hz), 7.26 (1H, ddd, J = 8.3, 8.3, 5.4 Hz), 6.74 (1H, dd, J = 9.6, 8.3 Hz), 4.56 (1H, d, J = 4.4 Hz), 3.79-3.67 (1H, m), 3.48-3.38 (1H, m), 1.93-1.79 (4H, m), 1.50-1.16 (4H, m).	372	370	
90		¹ H-NMR (DMSO-D ₆) δ: 8.82 (1H, d, J = 1.2 Hz), 8.47 (1H, d, J = 7.6 Hz), 8.33 (1H, dd, J = 11.8, 1.8 Hz), 7.68 (1H, d, J = 8.3 Hz), 7.43 (1H, t, J = 8.1 Hz), 6.77 (1H, d, J = 7.9 Hz), 4.56 (1H, br s), 3.95 (3H, s), 3.81-3.70 (1H, m), 3.47-3.38 (1H, m), 2.65 (3H, s), 1.93-1.81 (4H, m), 1.46-1.19 (4H, m).	399	397	
91		¹ H-NMR (DMSO-D ₆) δ: 8.83 (1H, d, J = 1.4 Hz), 8.49 (1H, d, J = 7.9 Hz), 8.34 (1H, dd, J = 11.8, 1.8 Hz), 7.68 (1H, d, J = 8.3 Hz), 7.43 (1H, t, J = 8.2 Hz), 6.77 (1H, d, J = 7.9 Hz), 4.04 (1H, s), 3.95 (3H, s), 3.79-3.67 (1H, m), 2.65 (3H, s), 2.00-1.80 (4H, m), 1.39-1.08 (5H, m), 1.05 (6H, s).	441	439	
92		¹ H-NMR (DMSO-D ₆) δ: 9.27 (2H, s), 8.64 (1H, d, J = 7.9 Hz), 7.89 (1H, dd, J = 7.9, 0.9 Hz), 7.63 (1H, dd, J = 7.6, 0.9 Hz), 7.38-7.34 (1H, m), 4.58 (1H, d, J = 4.2 Hz), 3.81-3.72 (1H, m), 3.46-3.38 (1H, m), 2.60 (3H, s), 1.92-1.86 (4H, m), 1.44-1.22 (4H, m).	386	384	
93		¹ H-NMR (DMSO-D ₆) δ: 9.28 (2H, s), 8.67 (1H, d, J = 7.9 Hz), 7.90 (1H, dd, J = 8.0, 0.9 Hz), 7.64 (1H, dd, J = 7.6, 0.9 Hz), 7.38-7.34 (1H, m), 4.05 (1H, s), 3.79-3.69 (1H, m), 2.60 (3H, s), 1.99-1.95 (2H, m), 1.88-1.84 (2H, m), 1.37-1.04 (5H, m), 1.06 (6H, s).	428	426	
94		¹ H-NMR (DMSO-D ₆) δ: 9.29 (2H, s), 8.66 (1H, d, J = 7.9 Hz), 8.29 (1H, dd, J = 8.0, 1.0 Hz), 8.14 (1H, dd, J = 7.5, 1.0 Hz), 7.56-7.52 (1H, m), 4.58 (1H, d, J = 4.6 Hz), 3.82-3.73 (1H, m), 3.46-3.38 (1H, m), 2.66 (3H, d, J = 8.8 Hz), 1.92-1.85 (4H, m), 1.45-1.35 (2H, m), 1.32-1.22 (2H, m).	377	375	
95		¹ H-NMR (DMSO-D ₆) δ: 9.30 (2H, s), 8.68 (1H, d, J = 7.6 Hz), 8.29 (1H, dd, J = 7.9, 1.1 Hz), 8.14 (1H, dd, J = 7.4, 1.1 Hz), 7.56-7.52 (1H, m), 4.05 (1H, s), 3.81-3.71 (1H, m), 2.65 (3H, s), 1.99-1.95 (2H, m), 1.89-1.83 (2H, m), 1.38-1.28 (2H, m), 1.25-1.02 (3H, m), 1.06 (6H, s).	419	417	
96		¹ H-NMR (DMSO-D ₆) δ: 9.67 (1H, d, J = 1.5 Hz), 8.88 (1H, d, J = 1.5 Hz), 8.51-8.48 (2H, m), 8.38 (1H, dd, J = 12.0, 1.5 Hz), 7.93-7.92 (1H, m), 4.58 (1H, d, J = 4.5 Hz), 3.80-3.72 (1H, m), 3.46-3.39 (1H, m), 2.65 (3H, s), 1.89-1.86 (4H, m), 1.44-1.35 (2H, m), 1.32-1.22 (2H, m).	370	368	

[1075]

[Table 1-13]

Ex.No.	structural formula	¹ H-NMR (400 MHz)	MS (positive)	MS (negative)	Comments
97		¹ H-NMR (DMSO-D ₆) δ : 9.67 (1H, s), 8.89 (1H, s), 8.52 (1H, d, J = 7.5 Hz), 8.49 (1H, d, J = 6.0 Hz), 8.39 (1H, d, J = 12.0 Hz), 7.93 (1H, d, J = 5.2 Hz), 4.05 (1H, s), 3.78-3.70 (1H, m), 2.65 (3H, s), 1.97-1.93 (2H, m), 1.88-1.84 (2H, m), 1.37-1.28 (2H, m), 1.24-1.02 (3H, m), 1.06 (6H, s).	412	410	
98		¹ H-NMR (DMSO-D ₆) δ : 9.31 (2H, s), 8.78 (1H, d, J = 8.6 Hz), 8.62 (1H, d, J = 7.6 Hz), 8.00 (1H, d, J = 8.1 Hz), 7.75 (1H, t, J = 7.9 Hz), 7.56 (1H, t, J = 53.4 Hz), 7.52 (1H, t, J = 7.5 Hz), 4.05 (1H, s), 3.79-3.71 (1H, m), 1.99-1.95 (2H, m), 1.88-1.84 (2H, m), 1.38-1.28 (2H, m), 1.24-1.07 (3H, m), 1.06 (6H, s).	430	428	
99		¹ H-NMR (DMSO-D ₆) δ : 8.40 (1H, d, J = 7.5 Hz), 7.96 (1H, d, J = 12.0 Hz), 7.93-7.87 (2H, m), 7.76 (1H, t, J = 7.9 Hz), 7.23 (1H, d, J = 9.7 Hz), 7.16 (1H, t, J = 9.3 Hz), 4.57 (1H, d, J = 4.5 Hz), 3.81-3.70 (1H, m), 3.47-3.37 (1H, m), 2.58 (3H, s), 1.92-1.80 (4H, br m), 1.46-1.34 (2H, br m), 1.32-1.20 (2H, br m).	386	384	
100		¹ H-NMR (DMSO-D ₆) δ : 8.41 (1H, d, J = 8.2 Hz), 7.97 (1H, d, J = 12.0 Hz), 7.94-7.87 (2H, m), 7.76 (1H, t, J = 7.9 Hz), 7.23 (1H, d, J = 9.7 Hz), 7.16 (1H, t, J = 9.3 Hz), 4.04 (1H, s), 3.79-3.68 (1H, m), 2.59 (3H, s), 1.96-1.81 (4H, br m), 1.39-1.28 (2H, br m), 1.22-1.03 (9H, br m).	428	426	
101		¹ H-NMR (DMSO-D ₆) δ : 9.20 (2H, s), 8.53 (1H, d, J = 7.9 Hz), 8.50 (1H, d, J = 10.5 Hz), 7.46 (1H, dd, J = 7.9, 7.9 Hz), 7.12 (1H, d, J = 7.9 Hz), 3.83-3.70 (1H, m), 3.49-3.26 (2H, m), 2.75 (3H, s), 2.72 (3H, s), 1.93-1.83 (4H, m), 1.46-1.20 (4H, m).	366	364	
102		¹ H-NMR (DMSO-D ₆) δ : 9.98 (1H, d, J = 1.2 Hz), 9.27 (2H, s), 8.58 (1H, d, J = 7.6 Hz), 8.53 (1H, d, J = 5.3 Hz), 7.94 (1H, dd, J = 5.3, 1.2 Hz), 3.86-3.75 (1H, m), 3.47 (2H, q, J = 7.0 Hz), 3.38-3.20 (1H, m), 2.66 (3H, s), 2.08-1.88 (4H, m), 1.47-1.20 (4H, m), 1.10 (3H, t, J = 7.0 Hz).	381	379	
103		¹ H-NMR (DMSO-D ₆) δ : 9.21 (2H, s), 8.56 (1H, d, J = 8.3 Hz), 8.50 (1H, d, J = 7.6 Hz), 7.51 (1H, dd, J = 8.3, 7.4 Hz), 7.17 (1H, d, J = 7.4 Hz), 3.82-3.71 (1H, m), 3.54 (1H, br s), 3.46-3.38 (1H, m), 3.09 (2H, q, J = 7.6 Hz), 2.75 (3H, s), 1.93-1.83 (4H, m), 1.46-1.22 (4H, m), 1.30 (3H, t, J = 7.6 Hz).	380	378	
104		¹ H-NMR (DMSO-D ₆) δ : 13.38 (1H, s), 8.99 (2H, s), 8.43 (1H, d, J = 7.6 Hz), 7.31-7.20 (2H, m), 7.05 (1H, td, J = 7.9, 4.2 Hz), 4.55 (1H, d, J = 4.4 Hz), 3.78-3.65 (1H, m), 3.46-3.35 (1H, m), 1.92-1.77 (4H, m), 1.44-1.15 (4H, m).	372	370	

[1076]

[Table 1-14]

Ex.No.	structural formula	¹ H-NMR (400 MHz)	MS (positive)	MS (negative)	Comments
105		¹ H-NMR (DMSO-D ₆) δ: 9.23 (2H, s), 8.54 (1H, d, J = 7.6 Hz), 8.40 (1H, dd, J = 10.4, 2.3 Hz), 7.94 (1H, dd, J = 8.7, 5.4 Hz), 7.32-7.27 (1H, m), 4.22 (1H, s), 3.85-3.76 (1H, m), 3.32-3.22 (1H, m), 3.19 (2H, s), 2.61 (3H, s), 2.06-2.01 (2H, m), 1.95-1.91 (2H, m), 1.45-1.35 (2H, m), 1.32-1.23 (2H, m), 1.07 (6H, s).	442	440	
106		¹ H-NMR (DMSO-D ₆) δ: 9.33 (2H, s), 8.82 (1H, d, J = 8.6 Hz), 8.64 (1H, d, J = 7.6 Hz), 7.99 (1H, d, J = 8.1 Hz), 7.83-7.79 (1H, m), 7.61-7.57 (1H, m), 4.59 (1H, d, J = 4.4 Hz), 3.83-3.73 (1H, m), 3.48-3.40 (1H, m), 1.92-1.87 (4H, m), 1.46-1.35 (2H, m), 1.33-1.23 (2H, m).	406	404	
107		¹ H-NMR (DMSO-D ₆) δ: 9.77 (1H, s), 8.96 (1H, s), 8.64 (1H, d, J = 5.2 Hz), 8.61 (1H, d, J = 7.5 Hz), 8.51 (1H, d, J = 12.0 Hz), 8.01 (1H, d, J = 5.2 Hz), 4.59 (1H, s), 3.82-3.74 (1H, m), 3.46-3.39 (1H, m), 1.90-1.87 (4H, m), 1.45-1.23 (4H, m).	424	422	
108		¹ H-NMR (DMSO-D ₆) δ: 9.18 (1H, d, J = 1.5 Hz), 8.60 (1H, d, J = 6.0 Hz), 8.50 (1H, d, J = 7.5 Hz), 8.07 (1H, d, J = 11.2 Hz), 8.03-7.96 (3H, m), 3.80-3.73 (1H, m), 3.45-3.39 (1H, m), 1.88-1.86 (4H, m), 1.45-1.22 (4H, m).	423	421	
109		¹ H-NMR (DMSO-D ₆) δ: 9.77 (1H, s), 8.97 (1H, s), 8.65-8.62 (2H, m), 8.51 (1H, d, J = 11.2 Hz), 8.01 (1H, d, J = 5.2 Hz), 4.05 (1H, s), 3.80-3.72 (1H, m), 1.98-1.85 (4H, m), 1.38-1.10 (5H, m), 1.06 (6H, s).	466	464	
110		¹ H-NMR (DMSO-D ₆) δ: 8.74 (1H, s), 8.68 (1H, d, J = 8.3 Hz), 8.44 (1H, d, J = 7.9 Hz), 7.87 (1H, d, J = 8.1 Hz), 7.61 (1H, t, J = 7.9 Hz), 7.37 (1H, t, J = 7.5 Hz), 4.56 (1H, d, J = 4.4 Hz), 3.74-3.68 (1H, m), 3.46-3.38 (1H, m), 2.64 (3H, s), 2.61 (3H, s), 1.92-1.85 (4H, m), 1.37-1.22 (4H, m).	366	364	
111		¹ H-NMR (DMSO-D ₆) δ: 8.75 (1H, s), 8.68 (1H, d, J = 8.6 Hz), 8.45 (1H, d, J = 7.9 Hz), 7.87 (1H, d, J = 7.9 Hz), 7.61 (1H, t, J = 7.7 Hz), 7.38 (1H, t, J = 7.5 Hz), 4.04 (1H, s), 3.72-3.65 (1H, m), 2.65 (3H, s), 2.61 (3H, s), 2.00-1.96 (2H, m), 1.86-1.84 (2H, m), 1.30-1.08 (5H, m), 1.05 (6H, s).	408	406	
112		¹ H-NMR (DMSO-D ₆) δ: 8.84 (1H, d, J = 1.6 Hz), 8.50 (1H, d, J = 7.6 Hz), 8.37 (1H, dd, J = 11.8, 1.6 Hz), 7.81 (1H, dd, J = 9.5, 1.8 Hz), 7.23 (1H, td, J = 10.0, 1.7 Hz), 4.57 (1H, d, J = 4.4 Hz), 3.79-3.72 (1H, m), 3.46-3.38 (1H, m), 2.65 (3H, s), 1.89-1.85 (4H, m), 1.44-1.34 (2H, m), 1.31-1.22 (2H, m).	405	403	

[1077]

[Table 1-15]

Ex.No.	structural formula	¹ H-NMR (400 MHz)	MS (positive)	MS (negative)	Comments
113		¹ H-NMR (DMSO-D ₆) δ: 8.85 (1H, d, J = 1.2 Hz), 8.52 (1H, d, J = 7.6 Hz), 8.38 (1H, dd, J = 11.7, 1.7 Hz), 7.81 (1H, dd, J = 9.5, 1.8 Hz), 7.24 (1H, td, J = 10.0, 1.8 Hz), 4.05 (1H, s), 3.77-3.70 (1H, m), 2.66 (3H, s), 1.96-1.93 (2H, m), 1.87-1.84 (2H, m), 1.37-1.27 (2H, m), 1.23-1.05 (3H, m), 1.05 (6H, s).	447	445	
114		¹ H-NMR (DMSO-D ₆) δ: 9.33 (2H, s), 8.83-8.81 (1H, m), 8.70 (1H, d, J = 7.6 Hz), 8.00-7.97 (1H, m), 7.83-7.79 (1H, m), 7.61-7.57 (1H, m), 3.92-3.82 (1H, m), 2.78-2.71 (1H, m), 2.12-2.07 (2H, m), 1.97-1.92 (2H, m), 1.71-1.61 (2H, m), 1.47-1.37 (2H, m).	415	413	
115		¹ H-NMR (DMSO-D ₆) δ: 9.34 (2H, s), 8.83 (1H, d, J = 8.8 Hz), 8.72 (1H, d, J = 7.2 Hz), 8.01-7.98 (1H, m), 7.84-7.80 (1H, m), 7.61-7.57 (1H, m), 4.08-3.90 (1H, br m), 3.89-3.71 (2H, m), 2.92-2.83 (2H, m), 1.99-1.95 (1H, m), 1.80-1.75 (1H, m), 1.62-1.53 (1H, m), 1.50-1.42 (1H, m), 1.40 (9H, s).	491	489	
116		¹ H-NMR (DMSO-D ₆) δ: 9.34 (2H, s), 8.82 (1H, d, J = 8.8 Hz), 8.70 (1H, d, J = 7.6 Hz), 8.00-7.97 (1H, m), 7.83-7.79 (1H, m), 7.61-7.57 (1H, m), 3.84-3.75 (1H, m), 3.10 (2H, d, J = 6.2 Hz), 3.00 (3H, s), 2.02-1.88 (5H, m), 1.46-1.37 (2H, m), 1.29-1.20 (2H, m).	482	480	
117		¹ H-NMR (DMSO-D ₆) δ: 9.46 (2H, s), 9.24 (1H, br s), 9.21-9.18 (1H, m), 8.98 (1H, br s), 8.83 (1H, d, J = 8.8 Hz), 8.01-7.98 (1H, m), 7.84-7.80 (1H, m), 7.62-7.58 (1H, m), 4.31-4.13 (1H, m), 3.37-3.24 (1H, m), 3.19-3.12 (1H, m), 3.02-2.90 (2H, m), 2.00-1.89 (2H, m), 1.78-1.58 (2H, m).	391	389	racemate
118		¹ H-NMR (DMSO-D ₆) δ: 9.33 (2H, s), 8.82 (1H, d, J = 8.8 Hz), 8.66 (1H, d, J = 7.6 Hz), 8.00-7.98 (1H, m), 7.83-7.79 (1H, m), 7.61-7.57 (1H, m), 4.54 (1H, t, J = 5.4 Hz), 3.86-3.77 (1H, m), 3.51-3.44 (4H, m), 3.31-3.25 (1H, m), 2.07-2.03 (2H, m), 1.96-1.92 (2H, m), 1.46-1.36 (2H, m), 1.32-1.23 (2H, m).	450	448	
119		¹ H-NMR (DMSO-D ₆) δ: 9.34 (1H, s), 9.33 (1H, s), 8.84-8.81 (1.5H, m), 8.76 (0.5H, d, J = 7.4 Hz), 8.00-7.98 (1H, m), 7.84-7.79 (1H, m), 7.61-7.57 (1H, m), 4.60-4.53 (1H, m), 4.37-4.33 (0.5H, m), 4.17-4.07 (2H, m), 3.98-3.85 (1.5H, m), 3.77-3.73 (0.5H, m), 3.62-3.57 (0.5H, m), 3.12-2.97 (1.5H, m), 2.81-2.76 (0.5H, m), 2.02-1.98 (1H, m), 1.83-1.78 (1H, m), 1.74-1.43 (2H, m).	449	447	racemate
120		¹ H-NMR (DMSO-D ₆) δ: 9.32 (2H, s), 8.79 (1H, d, J = 8.6 Hz), 8.73 (1H, d, J = 7.6 Hz), 8.01 (1H, d, J = 8.1 Hz), 7.76 (1H, dt, J = 10.9, 3.9 Hz), 7.57 (1H, t, J = 53.2 Hz), 7.53 (1H, t, J = 7.3 Hz), 3.92-3.85 (1H, m), 2.93 (1H, tt, J = 11.8, 3.5 Hz), 2.47 (3H, s), 2.18-2.11 (2H, br m), 2.08-2.00 (2H, br m), 1.69-1.47 (4H, m).	454	452	

[1078]

[Table 1-16]

Ex.No.	structural formula	¹ H-NMR (400 MHz)	MS (positive)	MS (negative)	Comments
121		¹ H-NMR (DMSO-D ₆) δ: 9.31 (2H, s), 8.78 (1H, d, J = 9.0 Hz), 8.67 (1H, d, J = 7.5 Hz), 8.01 (1H, d, J = 7.5 Hz), 7.75 (1H, t, J = 7.9 Hz), 7.56 (1H, t, J = 53.9 Hz), 7.52 (1H, t, J = 7.5 Hz), 3.85-3.74 (1H, m), 3.09 (2H, d, J = 6.7 Hz), 3.00 (3H, s), 2.05-1.85 (5H, br m), 1.48-1.35 (2H, br m), 1.31-1.17 (2H, br m).	464	462	
122		¹ H-NMR (DMSO-D ₆) δ: 9.30 (2H, s), 8.78 (1H, d, J = 8.2 Hz), 8.67 (1H, d, J = 7.5 Hz), 8.00 (1H, d, J = 8.2 Hz), 7.75 (1H, t, J = 7.9 Hz), 7.56 (1H, t, J = 53.9 Hz), 7.52 (1H, t, J = 7.9 Hz), 3.92-3.81 (1H, m), 2.77-2.71 (1H, m), 2.13-2.05 (2H, br m), 1.99-1.90 (2H, br m), 1.71-1.61 (2H, br m), 1.46-1.37 (2H, br m).	397	395	
123		¹ H-NMR (DMSO-D ₆) δ: 9.30 (2H, s), 8.78 (1H, d, J = 9.0 Hz), 8.62 (1H, d, J = 7.5 Hz), 8.00 (1H, d, J = 8.2 Hz), 7.75 (1H, t, J = 7.9 Hz), 7.56 (1H, t, J = 53.1 Hz), 7.52 (1H, t, J = 7.9 Hz), 4.22 (1H, s), 3.86-3.76 (1H, m), 3.30-3.22 (1H, m), 3.19 (2H, s), 2.08-2.00 (2H, br m), 1.98-1.90 (2H, br m), 1.47-1.34 (2H, br m), 1.34-1.22 (2H, br m), 1.07 (6H, s).	460	458	
124		¹ H-NMR (DMSO-D ₆) δ: 9.30 (2H, s), 8.78 (1H, d, J = 8.2 Hz), 8.63 (1H, d, J = 7.5 Hz), 8.00 (1H, d, J = 8.2 Hz), 7.75 (1H, t, J = 7.9 Hz), 7.56 (1H, t, J = 53.1 Hz), 7.52 (1H, t, J = 7.9 Hz), 4.54 (1H, t, J = 5.2 Hz), 3.87-3.76 (1H, m), 3.52-3.42 (4H, m), 3.30-3.23 (1H, m), 2.10-2.00 (2H, br m), 1.98-1.90 (2H, br m), 1.48-1.34 (2H, br m), 1.33-1.22 (2H, br m).	432	430	
125		¹ H-NMR (DMSO-D ₆) δ: 9.21 (2H, s), 8.98 (1H, s), 8.67 (1H, d, J = 8.6 Hz), 8.57 (1H, d, J = 7.6 Hz), 7.89 (1H, d, J = 7.9 Hz), 7.63 (1H, ddd, J = 8.6, 7.4, 1.2 Hz), 7.39 (1H, dd, J = 7.9, 7.4 Hz), 4.63 (2H, d, J = 6.9 Hz), 3.84-3.71 (1H, m), 2.62 (3H, s), 2.03-1.88 (3H, m), 1.67-1.57 (2H, m), 1.42-1.14 (4H, m).	418	416	
126		¹ H-NMR (DMSO-D ₆) δ: 9.23 (2H, s), 8.59 (1H, d, J = 7.6 Hz), 8.40 (1H, dd, J = 10.4, 2.3 Hz), 7.94 (1H, dd, J = 9.0, 5.4 Hz), 7.29 (1H, ddd, J = 9.0, 9.0, 2.3 Hz), 3.91-3.80 (1H, m), 2.79-2.69 (1H, m), 2.61 (3H, s), 2.14-2.04 (2H, m), 1.97-1.89 (2H, m), 1.73-1.59 (2H, m), 1.49-1.34 (2H, m).	379	377	
127		¹ H-NMR (DMSO-D ₆) δ: 9.24 (2H, s), 8.59 (1H, d, J = 7.9 Hz), 8.41 (1H, dd, J = 10.4, 2.3 Hz), 7.95 (1H, dd, J = 9.0, 5.4 Hz), 7.29 (1H, ddd, J = 9.0, 9.0, 2.3 Hz), 3.86-3.71 (1H, m), 3.09 (2H, d, J = 6.2 Hz), 2.99 (3H, s), 2.61 (3H, s), 2.05-1.85 (4H, m), 1.49-1.17 (5H, m).	446	444	
128		¹ H-NMR (DMSO-D ₆) δ: 9.23 (2H, s), 8.98 (1H, s), 8.58 (1H, d, J = 7.9 Hz), 8.40 (1H, dd, J = 10.4, 2.3 Hz), 7.94 (1H, dd, J = 9.0, 5.3 Hz), 7.29 (1H, ddd, J = 9.0, 9.0, 2.3 Hz), 4.63 (2H, d, J = 7.2 Hz), 3.84-3.72 (1H, m), 2.61 (3H, s), 2.04-1.88 (3H, m), 1.66-1.56 (2H, m), 1.42-1.14 (4H, m).	436	434	

[1079]

[Table 1-17]

Ex.No.	structural formula	¹ H-NMR (400 MHz)	MS (positive)	MS (negative)	Comments
129		¹ H-NMR (DMSO-D ₆) δ: 9.25 (2H, s), 8.65 (1H, d, J = 7.6 Hz), 8.41 (1H, dd, J = 10.5, 2.0 Hz), 7.95 (1H, dd, J = 8.9, 5.3 Hz), 7.30 (1H, ddd, J = 8.9, 8.9, 2.0 Hz), 3.94-3.81 (1H, m), 2.97-2.88 (1H, m), 2.61 (3H, s), 2.47 (3H, s), 2.20-1.98 (4H, m), 1.71-1.45 (4H, m).	436	434	
130		¹ H-NMR (DMSO-D ₆) δ: 9.23 (2H, s), 8.55 (1H, d, J = 7.6 Hz), 8.40 (1H, dd, J = 10.4, 2.3 Hz), 7.95 (1H, dd, J = 9.0, 5.4 Hz), 7.29 (1H, ddd, J = 9.0, 9.0, 2.3 Hz), 4.54 (1H, t, J = 5.3 Hz), 3.86-3.74 (1H, m), 3.52-3.42 (4H, m), 3.29-3.22 (1H, m), 2.61 (3H, s), 2.10-1.87 (4H, m), 1.47-1.20 (4H, m).	414	412	
131		¹ H-NMR (DMSO-D ₆) δ: 9.25 (2H, s), 8.92 (1H, d, J = 6.9 Hz), 8.41 (1H, dd, J = 10.3, 2.2 Hz), 7.95 (1H, dd, J = 8.9, 5.4 Hz), 7.30 (1H, ddd, J = 8.9, 8.9, 2.2 Hz), 4.42-4.29 (1H, m), 4.25 (1H, br s), 2.61 (3H, s), 2.40-2.21 (3H, m), 2.12-2.00 (2H, m), 1.06 (6H, s).	384	382	
132		¹ H-NMR (DMSO-D ₆) δ: 9.23 (2H, s), 8.55 (1H, d, J = 7.5 Hz), 8.40 (1H, d, J = 9.7 Hz), 7.94 (1H, dd, J = 9.0, 5.2 Hz), 7.29 (1H, dd, J = 9.0, 9.0 Hz), 3.86-3.73 (1H, m), 3.25 (3H, s), 3.19-3.10 (1H, m), 2.61 (3H, s), 2.10-1.83 (4H, m), 1.49-1.15 (4H, m).	384	382	
133		¹ H-NMR (DMSO-D ₆) δ: 9.25 (2H, s), 8.87 (1H, d, J = 6.0 Hz), 8.41 (1H, dd, J = 10.1, 1.9 Hz), 7.95 (1H, dd, J = 8.8, 5.6 Hz), 7.30 (1H, ddd, J = 8.8, 8.8, 1.9 Hz), 4.53-4.41 (1H, m), 3.66-3.52 (1H, m), 3.50-3.39 (1H, m), 3.39-3.17 (2H, m), 2.61 (3H, s), 2.21-2.08 (1H, m), 2.01-1.87 (1H, m), 1.42 (9H, s).	441	439	optically active form (R)
134		¹ H-NMR (DMSO-D ₆) δ: 9.24 (2H, s), 8.60 (1H, d, J = 7.6 Hz), 7.75 (1H, dd, J = 8.6, 4.2 Hz), 7.51-7.44 (1H, m), 4.05 (1H, s), 3.77-3.69 (1H, m), 2.60 (3H, s), 1.98-1.94 (2H, m), 1.88-1.84 (2H, m), 1.36-1.27 (2H, m), 1.24-1.01 (3H, m), 1.05 (6H, s).	430	428	
135		¹ H-NMR (DMSO-D ₆) δ: 9.24 (2H, s), 8.72 (1H, d, J = 1.8 Hz), 8.53 (1H, d, J = 7.6 Hz), 7.93 (1H, d, J = 8.3 Hz), 7.45 (1H, dd, J = 8.3, 1.8 Hz), 4.05 (1H, s), 3.78-3.70 (1H, m), 2.61 (3H, s), 1.99-1.94 (2H, m), 1.88-1.84 (2H, m), 1.37-1.27 (2H, m), 1.24-1.06 (3H, m), 1.06 (6H, s).	428	426	
136		¹ H-NMR (DMSO-D ₆) δ: 8.83 (1H, d, J = 1.5 Hz), 8.57 (1H, d, J = 7.6 Hz), 8.40 (1H, dd, J = 10.6, 1.8 Hz), 7.76 (1H, dd, J = 8.8, 4.1 Hz), 7.45-7.38 (1H, m), 4.03 (1H, s), 3.78-3.69 (1H, m), 2.59 (3H, s), 1.97-1.94 (2H, m), 1.87-1.84 (2H, m), 1.37-1.27 (2H, m), 1.23-1.05 (3H, m), 1.05 (6H, s).	447	445	

[1080]

[Table 1-18]

Ex.No.	structural formula	¹ H-NMR (400 MHz)	MS (positive)	MS (negative)	Comments
137		¹ H-NMR (DMSO-D ₆) δ: 9.22 (2H, s), 8.67 (1H, d, J = 8.6 Hz), 8.57 (1H, d, J = 7.4 Hz), 7.89 (1H, d, J = 7.9 Hz), 7.65-7.61 (1H, m), 7.40 (1H, t, J = 7.5 Hz), 3.90-3.80 (1H, m), 2.78-2.69 (1H, m), 2.62 (3H, s), 2.12-2.05 (2H, m), 1.97-1.89 (2H, m), 1.71-1.58 (2H, m), 1.47-1.35 (2H, m).	361	359	
138		¹ H-NMR (DMSO-D ₆) δ: 9.22 (2H, s), 8.69-8.66 (1H, m), 8.57 (1H, d, J = 7.6 Hz), 7.91-7.87 (1H, m), 7.65-7.61 (1H, m), 7.42-7.38 (1H, m), 3.82-3.73 (1H, m), 3.09 (2H, d, J = 6.2 Hz), 2.99 (3H, s), 2.62 (3H, s), 2.03-1.86 (5H, m), 1.47-1.35 (2H, m), 1.30-1.18 (2H, m).	428	426	
139		¹ H-NMR (DMSO-D ₆) δ: 9.22 (2H, s), 8.70-8.66 (1H, m), 8.54 (1H, d, J = 7.6 Hz), 7.90-7.87 (1H, m), 7.65-7.61 (1H, m), 7.42-7.38 (1H, m), 3.84-3.74 (2H, m), 3.46-3.36 (1H, m), 3.14-3.01 (4H, m), 2.62 (3H, s), 2.11-1.89 (8H, m), 1.48-1.25 (4H, m).	484	482	
140		¹ H-NMR (DMSO-D ₆) δ: 9.24 (2H, s), 8.71-8.61 (2H, m), 7.92-7.87 (1H, m), 7.65-7.61 (1H, m), 7.42-7.38 (1H, m), 3.92-3.83 (1H, m), 2.97-2.88 (1H, m), 2.62 (3H, s), 2.47 (3H, s), 2.17-2.11 (2H, m), 2.07-2.00 (2H, m), 1.68-1.47 (4H, m).	418	416	
141		¹ H-NMR (DMSO-D ₆) δ: 9.22 (2H, s), 8.67 (1H, d, J = 8.3 Hz), 8.53 (1H, d, J = 7.6 Hz), 7.89 (1H, d, J = 7.9 Hz), 7.63 (1H, t, J = 7.6 Hz), 7.40 (1H, t, J = 7.5 Hz), 3.84-3.75 (1H, m), 3.47 (2H, q, J = 7.0 Hz), 3.28-3.20 (1H, m), 2.62 (3H, s), 2.06-1.99 (2H, m), 1.96-1.89 (2H, m), 1.45-1.34 (2H, m), 1.31-1.20 (2H, m), 1.10 (3H, t, J = 6.9 Hz).	380	378	
142		¹ H-NMR (DMSO-D ₆) δ: 9.22 (2H, s), 8.67 (1H, d, J = 8.3 Hz), 8.53 (1H, d, J = 7.9 Hz), 7.89 (1H, d, J = 7.9 Hz), 7.65-7.61 (1H, m), 7.42-7.38 (1H, m), 4.54 (1H, t, J = 5.3 Hz), 3.84-3.76 (1H, m), 3.51-3.43 (4H, m), 3.31-3.24 (1H, m), 2.62 (3H, s), 2.08-2.01 (2H, m), 1.96-1.89 (2H, m), 1.45-1.34 (2H, m), 1.31-1.21 (2H, m).	396	394	
143		¹ H-NMR (DMSO-D ₆) δ: 9.23 (2H, s), 8.60 (1H, d, J = 8.2 Hz), 7.75 (1H, dd, J = 8.6, 4.1 Hz), 7.51-7.44 (1H, m), 4.21 (1H, s), 3.83-3.76 (1H, m), 3.30-3.23 (1H, m), 3.18 (2H, s), 2.60 (3H, s), 2.04-1.91 (4H, m), 1.44-1.23 (4H, m), 1.07 (6H, s).	460	458	
144		¹ H-NMR (DMSO-D ₆) δ: 9.23 (2H, s), 8.61 (1H, d, J = 7.5 Hz), 7.75 (1H, dd, J = 9.0, 4.5 Hz), 7.51-7.44 (1H, m), 4.54 (1H, t, J = 4.9 Hz), 3.85-3.75 (1H, m), 3.50-3.43 (4H, m), 3.29-3.23 (1H, m), 2.60 (3H, s), 2.05-1.91 (4H, m), 1.44-1.22 (4H, m).	432	430	

[1081]

[Table 1-19]

Ex.No.	structural formula	¹ H-NMR (400 MHz)	MS (positive)	MS (negative)	Comments
145		¹ H-NMR (DMSO-D ₆) δ: 9.23 (2H, s), 8.59 (1H, d, J = 8.2 Hz), 7.77-7.74 (1H, m), 7.51-7.44 (1H, m), 4.04 (1H, s), 3.79-3.68 (1H, m), 2.60 (3H, s), 1.89-1.87 (4H, m), 1.45-1.28 (5H, m), 1.11 (6H, s), 1.10-1.02 (2H, m).	444	442	
146		¹ H-NMR (DMSO-D ₆) δ: 9.34 (2H, s), 8.82 (1H, d, J = 8.6 Hz), 8.67 (1H, d, J = 7.6 Hz), 8.00-7.97 (1H, m), 7.83-7.79 (1H, m), 7.61-7.57 (1H, m), 4.42 (1H, t, J = 5.3 Hz), 3.83-3.73 (1H, m), 3.27-3.23 (2H, m), 1.97-1.93 (2H, m), 1.84-1.80 (2H, m), 1.41-1.31 (3H, m), 1.07-0.97 (2H, m).	420	418	
147		¹ H-NMR (DMSO-D ₆) δ: 9.37 (2H, s), 9.18 (1H, d, J = 8.1 Hz), 8.85-8.82 (1H, m), 8.00-7.96 (2H, m), 7.84-7.79 (1H, m), 7.61-7.57 (1H, m), 4.66-4.59 (1H, m), 3.26-3.31 (2H, m), 2.47-2.40 (1H, m), 2.10-2.00 (1H, m).	391	389	optically active form (S)
148		¹ H-NMR (DMSO-D ₆) δ: 9.37 (2H, s), 9.18 (1H, d, J = 8.1 Hz), 8.85-8.82 (1H, m), 8.00-7.96 (2H, m), 7.84-7.79 (1H, m), 7.61-7.57 (1H, m), 4.66-4.59 (1H, m), 3.26-3.31 (2H, m), 2.47-2.40 (1H, m), 2.10-2.00 (1H, m).	391	389	optically active form (R)
149		¹ H-NMR (DMSO-D ₆) δ: 9.24 (2H, s), 8.68 (1H, d, J = 8.2 Hz), 8.64 (1H, d, J = 7.5 Hz), 7.89 (1H, d, J = 8.2 Hz), 7.63 (1H, t, J = 7.5 Hz), 7.40 (1H, t, J = 7.5 Hz), 3.93-3.82 (1H, m), 2.82-2.73 (1H, m), 2.63 (3H, s), 2.56 (3H, s), 2.12-1.98 (4H, br m), 1.65-1.48 (4H, m).	418	416	
150		¹ H-NMR (DMSO-D ₆) δ: 9.25 (2H, s), 8.65 (1H, d, J = 7.5 Hz), 8.41 (1H, dd, J = 10.1, 1.9 Hz), 7.94 (1H, dd, J = 8.6, 5.6 Hz), 7.29 (1H, td, J = 8.8, 1.7 Hz), 3.93-3.81 (1H, m), 2.82-2.74 (1H, m), 2.61 (3H, s), 2.56 (3H, s), 2.11-1.99 (4H, br m), 1.65-1.48 (4H, m).	436	434	
151		¹ H-NMR (DMSO-D ₆) δ: 9.32 (2H, s), 8.79 (1H, d, J = 8.2 Hz), 8.73 (1H, d, J = 7.5 Hz), 8.01 (1H, d, J = 8.2 Hz), 7.76 (1H, t, J = 7.9 Hz), 7.57 (1H, t, J = 53.1 Hz), 7.53 (1H, t, J = 7.5 Hz), 3.94-3.83 (1H, m), 2.83-2.74 (1H, m), 2.57 (3H, s), 2.11-2.00 (4H, br m), 1.66-1.48 (4H, m).	454	452	
152		¹ H-NMR (DMSO-D ₆) δ: 9.22 (2H, s), 8.64 (1H, d, J = 7.6 Hz), 7.75-7.72 (1H, m), 7.49-7.43 (1H, m), 3.80-3.72 (1H, m), 3.07 (2H, d, J = 6.2 Hz), 2.98 (3H, s), 2.59 (3H, s), 1.99-1.90 (5H, m), 1.43-1.17 (4H, m).	464	462	

[1082]

[Table 1-20]

Ex.No.	structural formula	¹ H-NMR (400 MHz)	MS (positive)	MS (negative)	Comments
153		¹ H-NMR (DMSO-D ₆) δ: 9.22 (2H, s), 8.71 (1H, d, J = 1.8 Hz), 8.51 (1H, d, J = 7.6 Hz), 7.92 (1H, d, J = 8.6 Hz), 7.43 (1H, dd, J = 8.4, 1.7 Hz), 4.20 (1H, s), 3.84-3.73 (1H, m), 3.27-3.21 (1H, m), 3.17 (2H, s), 2.60 (3H, s), 2.03-1.90 (4H, m), 1.43-1.21 (4H, m), 1.06 (6H, s).	458	456	
154		¹ H-NMR (DMSO-D ₆) δ: 9.22 (2H, s), 8.70 (1H, d, J = 1.7 Hz), 8.52 (1H, d, J = 7.6 Hz), 7.91 (1H, d, J = 8.6 Hz), 7.43 (1H, dd, J = 8.6, 1.7 Hz), 4.53 (1H, t, J = 5.4 Hz), 3.82-3.74 (1H, m), 3.49-3.40 (4H, m), 3.27-3.22 (1H, m), 2.60 (3H, s), 2.04-1.90 (4H, m), 1.43-1.21 (4H, m).	430	428	
155		¹ H-NMR (DMSO-D ₆) δ: 9.23 (2H, s), 8.71 (1H, dd, J = 1.8, 0.6 Hz), 8.56 (1H, d, J = 7.6 Hz), 7.92 (1H, dd, J = 8.3, 0.6 Hz), 7.43 (1H, dd, J = 8.3, 1.8 Hz), 3.80-3.72 (1H, m), 3.07 (2H, d, J = 6.2 Hz), 2.98 (3H, s), 2.60 (3H, s), 1.99-1.90 (5H, m), 1.43-1.17 (4H, m).	462	460	
156		¹ H-NMR (DMSO-D ₆) δ: 9.23 (2H, s), 8.68 (1H, d, J = 8.2 Hz), 8.55 (1H, d, J = 7.5 Hz), 7.89 (1H, d, J = 8.2 Hz), 7.63 (1H, t, J = 7.5 Hz), 7.40 (1H, t, J = 7.5 Hz), 4.41 (1H, t, J = 5.2 Hz), 3.81-3.73 (1H, m), 3.25 (2H, t, J = 5.6 Hz), 2.62 (3H, s), 1.98-1.90 (2H, m), 1.85-1.77 (2H, m), 1.41-1.29 (3H, m), 1.08-0.95 (2H, m).	366	364	
157		¹ H-NMR (DMSO-D ₆) δ: 9.28 (2H, s), 9.13 (1H, d, J = 8.2 Hz), 8.68 (1H, d, J = 8.2 Hz), 7.89 (1H, d, J = 7.5 Hz), 7.63 (1H, t, J = 7.5 Hz), 7.46-7.39 (3H, m), 7.39-7.33 (2H, m), 7.28-7.23 (1H, m), 5.25-5.18 (1H, m), 2.63 (3H, s), 1.53 (3H, d, J = 6.7 Hz).	358	356	opti- cally active form (R)
158		¹ H-NMR (DMSO-D ₆) δ: 9.28 (2H, s), 9.13 (1H, d, J = 8.2 Hz), 8.68 (1H, d, J = 8.2 Hz), 7.89 (1H, d, J = 8.2 Hz), 7.63 (1H, t, J = 7.5 Hz), 7.46-7.39 (3H, m), 7.39-7.33 (2H, m), 7.28-7.23 (1H, m), 5.25-5.18 (1H, m), 2.63 (3H, s), 1.53 (3H, d, J = 6.7 Hz).	358	356	opti- cally active form (S)
159		¹ H-NMR (DMSO-D ₆) δ: 9.15 (2H, s), 8.66 (1H, d, J = 9.0 Hz), 8.01 (1H, s), 7.88 (1H, d, J = 7.5 Hz), 7.62 (1H, t, J = 7.9 Hz), 7.39 (1H, t, J = 7.5 Hz), 4.32 (1H, s), 2.61 (3H, s), 2.08-2.04 (6H, m), 1.66-1.62 (6H, m).	378	376	
160		¹ H-NMR (DMSO-D ₆) δ: 9.16 (2H, s), 8.39 (1H, dd, J = 10.5, 2.2 Hz), 8.02 (1H, s), 7.94 (1H, dd, J = 8.2, 5.2 Hz), 7.29 (1H, td, J = 8.6, 2.0 Hz), 4.32 (1H, s), 2.61 (3H, s), 2.08-2.04 (6H, m), 1.66-1.62 (6H, m).	396	394	

[1083]

[Table 1-21]

Ex.No.	structural formula	¹ H-NMR (400 MHz)	MS (positive)	MS (negative)	Comments
161		¹ H-NMR (DMSO-D ₆) δ: 9.23 (2H, s), 8.68 (1H, d, J = 8.6 Hz), 8.61 (1H, d, J = 7.4 Hz), 7.89 (1H, d, J = 8.1 Hz), 7.65-7.61 (1H, m), 7.42-7.38 (1H, m), 5.39 (1H, s), 4.84-4.33 (2H, br m), 4.13-4.06 (1H, m), 3.19-2.76 (2H, br m), 2.62 (3H, s), 1.92-1.88 (2H, m), 1.54-1.43 (2H, m), 1.34 (6H, s).	423	421	
162		¹ H-NMR (DMSO-D ₆) δ: 9.23 (2H, s), 8.68 (1H, d, J = 8.6 Hz), 8.63 (1H, d, J = 7.6 Hz), 7.89 (1H, d, J = 7.9 Hz), 7.65-7.61 (1H, m), 7.42-7.38 (1H, m), 4.54 (1H, t, J = 5.5 Hz), 4.34-4.30 (1H, m), 4.14-4.06 (3H, m), 3.75-3.72 (1H, m), 3.14-3.08 (1H, m), 2.88-2.82 (1H, m), 2.62 (3H, s), 1.93-1.89 (2H, m), 1.55-1.39 (2H, m).	395	393	
163		¹ H-NMR (DMSO-D ₆) δ: 9.23 (2H, d, J = 4.2 Hz), 8.68 (1.5H, d, J = 8.3 Hz), 8.63 (0.5H, d, J = 7.4 Hz), 7.89 (1H, d, J = 7.9 Hz), 7.66-7.62 (1H, m), 7.42-7.38 (1H, m), 4.58-4.52 (1H, m), 4.36-4.33 (0.5H, m), 4.14-4.08 (2H, m), 4.00-3.94 (0.5H, m), 3.90-3.84 (1H, m), 3.75-3.72 (0.5H, m), 3.61-3.57 (0.5H, m), 3.06-2.98 (1.5H, m), 2.78-2.72 (0.5H, m), 2.63 (3H, s), 2.00-1.97 (1H, m), 1.81-1.77 (1H, m), 1.70-1.43 (2H, m).	395	393	optically active form (S)
164		¹ H NMR (DMSO D ₆) δ: 9.25 (2H, d, J = 1.2 Hz), 8.87 (1H, dd, J = 12.8, 6.4 Hz), 8.41 (1H, dd, J = 10.5, 2.2 Hz), 7.95 (1H, dd, J = 8.8, 5.3 Hz), 7.30 (1H, td, J = 8.8, 2.3 Hz), 4.63-4.42 (1H, m), 4.03 (1H, s), 4.00 (1H, s), 3.75-3.61 (1H, m), 3.59-3.40 (4H, m), 2.61 (3H, s), 2.27-1.88 (2H, m).	399	397	optically active form (R)
165		¹ H-NMR (DMSO-D ₆) δ: 9.25 (2H, s), 8.87 (1H, d, J = 6.0 Hz), 8.41 (1H, dd, J = 10.1, 1.9 Hz), 7.95 (1H, dd, J = 8.8, 5.6 Hz), 7.30 (1H, ddd, J = 8.8, 8.8, 1.9 Hz), 4.53-4.41 (1H, m), 3.66-3.52 (1H, m), 3.50-3.39 (1H, m), 3.39-3.17 (2H, m), 2.61 (3H, s), 2.21-2.08 (1H, m), 2.01-1.87 (1H, m), 1.42 (9H, s).	441	439	optically active form (S)
166		¹ H-NMR (DMSO-D ₆) δ: 9.25 (2H, d, J = 2.5 Hz), 8.84 (1H, d, J = 6.2 Hz), 8.41 (1H, dd, J = 10.4, 2.3 Hz), 7.95 (1H, dd, J = 8.8, 5.3 Hz), 7.30 (1H, td, J = 9.0, 2.3 Hz), 5.17 (1H, s), 4.53-4.37 (1H, m), 4.15-4.06 (0.5H, m), 4.00-3.84 (1H, m), 3.79-3.54 (1.5H, m), 3.46-3.34 (1H, m), 2.61 (3H, s), 2.24-1.94 (1.5H, m), 1.92-1.79 (0.5H, m), 1.36-1.25 (6H, m).	427	425	optically active form (R)
167		¹ H-NMR (DMSO-D ₆) δ: 9.25 (2H, s), 8.87 (1H, dd, J = 11.9, 5.7 Hz), 8.41 (1H, dd, J = 10.4, 2.3 Hz), 7.95 (1H, t, J = 7.1 Hz), 7.30 (1H, td, J = 8.9, 2.1 Hz), 4.63-4.43 (2H, m), 4.06-3.97 (2H, m), 3.75-3.62 (1H, m), 3.59-3.40 (3H, m), 2.61 (3H, s), 2.28-1.89 (2H, m).	399	397	optically active form (S)
168		¹ H-NMR (DMSO-D ₆) δ: 9.24 (2H, s), 8.61 (1H, d, J = 7.2 Hz), 8.41 (1H, dd, J = 10.4, 2.3 Hz), 7.95 (1H, dd, J = 9.0, 5.3 Hz), 7.30 (1H, ddd, J = 9.0, 9.0, 2.3 Hz), 4.10-3.62 (3H, m), 2.93-2.81 (1H, m), 2.61 (3H, s), 2.00-1.89 (1H, m), 1.83-1.72 (1H, m), 1.62-1.50 (1H, m), 1.49-1.29 (2H, m), 1.40 (9H, s).	455	453	optically active form (R)

[1084]

[Table 1-22]

Ex.No.	structural formula	¹ H-NMR (400 MHz)	MS (positive)	MS (negative)	Comments
169		¹ H-NMR (DMSO-D ₆) δ: 9.23 (2H, s), 8.55 (1H, d, J = 7.6 Hz), 8.40 (1H, dd, J = 10.4, 2.1 Hz), 7.94 (1H, dd, J = 8.9, 5.4 Hz), 7.29 (1H, ddd, J = 8.9, 8.9, 2.1 Hz), 3.86-3.74 (1H, m), 3.53 (2H, t, J = 6.2 Hz), 3.34-3.22 (1H, m), 3.18-3.09 (2H, m), 2.99 (3H, s), 2.61 (3H, s), 2.09-1.99 (2H, m), 1.98-1.84 (4H, m), 1.47-1.21 (4H, m).	490	488	
170		¹ H-NMR (DMSO-D ₆) δ: 9.22 (2H, s), 8.68 (1H, d, J = 8.6 Hz), 8.54 (1H, d, J = 7.9 Hz), 7.89 (1H, d, J = 8.1 Hz), 7.63 (1H, t, J = 7.7 Hz), 7.40 (1H, t, J = 7.5 Hz), 3.86-3.76 (1H, m), 3.71 (2H, s), 3.45 (2H, s), 2.62 (3H, s), 1.89-1.81 (2H, br m), 1.78-1.69 (2H, br m), 1.50-1.38 (2H, m), 1.33 (6H, s), 1.21-1.11 (2H, m).	436	434	
171		¹ H-NMR (DMSO-D ₆) δ: 9.22 (2H, s), 8.68 (1H, d, J = 8.5 Hz), 8.54 (1H, d, J = 7.6 Hz), 7.89 (1H, d, J = 7.6 Hz), 7.63 (1H, t, J = 7.4 Hz), 7.40 (1H, t, J = 7.6 Hz), 4.33 (2H, br s), 3.82-3.70 (1H, m), 3.43 (2H, s), 3.20 (2H, s), 2.62 (3H, s), 1.74-1.64 (2H, br m), 1.61-1.43 (4H, br m), 1.28-1.15 (2H, m).	396	394	
172		¹ H-NMR (DMSO-D ₆) δ: 9.31 (2H, s), 8.78 (1H, d, J = 8.6 Hz), 8.64 (1H, d, J = 7.9 Hz), 8.00 (1H, d, J = 8.1 Hz), 7.78-7.73 (1H, m), 7.56 (1H, t, J = 53.4 Hz), 7.55-7.50 (1H, m), 3.80 (1H, tt, J = 11.9, 3.9 Hz), 3.18-3.11 (2H, m), 2.96 (3H, s), 1.98-1.90 (2H, br m), 1.86-1.78 (2H, br m), 1.67-1.58 (2H, m), 1.43-1.30 (3H, br m), 1.15-1.02 (2H, br m).	478	476	
173		¹ H-NMR (DMSO-D ₆) δ: 9.99 (1H, s), 9.28 (2H, s), 8.57 (1H, d, J = 8.1 Hz), 8.54 (1H, d, J = 5.3 Hz), 7.95 (1H, d, J = 5.3 Hz), 4.06 (2H, q, J = 7.1 Hz), 3.83-3.70 (1H, m), 2.67 (3H, s), 2.22 (2H, s), 2.04-1.93 (2H, m), 1.85-1.76 (2H, m), 1.39-1.07 (5H, m), 1.20 (3H, t, J = 7.1 Hz), 0.95 (6H, s).	465	463	
174		¹ H-NMR (DMSO-D ₆) δ: 9.24 (2H, d, J = 3.9 Hz), 8.70 (0.5H, d, J = 7.9 Hz), 8.64 (0.5H, d, J = 7.9 Hz), 8.41 (1H, dd, J = 10.4, 2.3 Hz), 7.95 (1H, dd, J = 8.9, 5.3 Hz), 7.30 (1H, ddd, J = 8.9, 8.9, 2.3 Hz), 4.60-4.50 (1H, m), 4.38-4.30 (0.5H, m), 4.19-4.04 (2H, m), 4.00-3.80 (1.5H, m), 3.77-3.69 (0.5H, m), 3.63-3.54 (0.5H, m), 3.12-2.93 (1.5H, m), 2.80-2.71 (0.5H, m), 2.62 (3H, s), 2.04-1.93 (1H, m), 1.84-1.75 (1H, m), 1.73-1.41 (2H, m).	413	411	optically active form (R)
175		¹ H-NMR (DMSO-D ₆) δ: 9.24 (2H, s), 8.63 (1H, d, J = 7.6 Hz), 8.41 (1H, dd, J = 10.4, 2.3 Hz), 7.95 (1H, dd, J = 8.9, 5.4 Hz), 7.30 (1H, ddd, J = 8.9, 8.9, 2.3 Hz), 5.39 (1H, s), 5.02-4.07 (2H, m), 3.95-3.81 (1H, m), 3.17-2.58 (2H, m), 2.62 (3H, s), 2.05-1.94 (1H, m), 1.83-1.72 (1H, m), 1.68-1.55 (1H, m), 1.53-1.42 (1H, m), 1.41-1.30 (6H, m).	441	439	optically active form (R)
176		¹ H-NMR (DMSO-D ₆) δ: 9.17 (2H, s), 8.40 (1H, dd, J = 10.4, 2.1 Hz), 8.10 (1H, br s), 7.94 (1H, dd, J = 8.8, 5.4 Hz), 7.29 (1H, ddd, J = 8.8, 8.8, 2.1 Hz), 3.59 (3H, s), 2.61 (3H, s), 2.06-1.96 (6H, m), 1.89-1.80 (6H, m).	438	436	

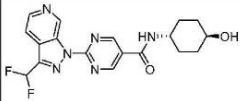
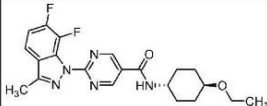
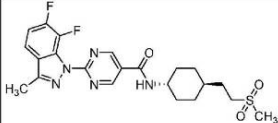
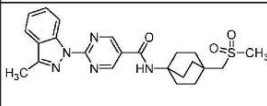
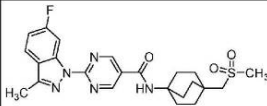
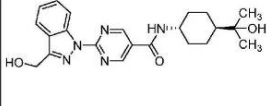
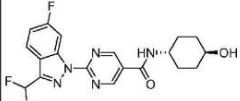
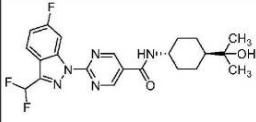
[1085]

[Table 1-23]

Ex.No.	structural formula	¹ H-NMR (400 MHz)	MS (positive)	MS (negative)	Comments
177		¹ H-NMR (DMSO-D ₆) δ: 9.16 (2H, s), 8.67 (1H, d, J = 8.6 Hz), 8.09 (1H, br s), 7.89 (1H, d, J = 7.9 Hz), 7.63 (1H, dd, J = 8.6, 7.4 Hz), 7.39 (1H, dd, J = 7.9, 7.4 Hz), 3.59 (3H, s), 2.62 (3H, s), 2.05-1.96 (6H, m), 1.89-1.80 (6H, m).	420	418	
178		¹ H-NMR (DMSO-D ₆) δ: 9.98 (1H, s), 9.22 (2H, s), 8.53 (1H, d, J = 5.3 Hz), 8.13 (1H, s), 7.94 (1H, dd, J = 5.3, 1.2 Hz), 3.59 (3H, s), 2.66 (3H, s), 2.07-1.96 (6H, m), 1.90-1.80 (6H, m).	421	419	
179		¹ H-NMR (DMSO-D ₆) δ: 9.22 (2H, s), 8.67 (1H, d, J = 8.3 Hz), 8.54 (1H, d, J = 7.6 Hz), 7.89 (1H, d, J = 7.9 Hz), 7.63 (1H, dd, J = 8.3, 7.5 Hz), 7.40 (1H, dd, J = 7.9, 7.5 Hz), 3.87-3.74 (1H, m), 3.53 (2H, t, J = 6.1 Hz), 3.30-3.22 (1H, m), 3.14 (2H, t, J = 7.9 Hz), 2.99 (3H, s), 2.62 (3H, s), 2.08-1.99 (2H, m), 1.97-1.85 (4H, m), 1.49-1.20 (4H, m).	472	470	
180		¹ H-NMR (DMSO-D ₆) δ: 9.22 (2H, s), 8.58 (1H, d, J = 7.9 Hz), 8.40 (1H, dd, J = 10.4, 2.1 Hz), 7.94 (1H, dd, J = 8.9, 5.3 Hz), 7.29 (1H, ddd, J = 8.9, 8.9, 2.1 Hz), 4.49-4.34 (1H, m), 4.18-4.07 (2H, m), 2.61 (3H, s), 2.02-1.53 (8H, m), 1.44 (9H, s).	481	479	exo form
181		¹ H-NMR (DMSO-D ₆) δ: 9.24-9.22 (2H, m), 8.70-8.59 (2H, m), 7.89 (1H, d, J = 8.1 Hz), 7.63 (1H, t, J = 7.6 Hz), 7.40 (1H, t, J = 7.4 Hz), 4.59-4.50 (1H, m), 4.36-3.57 (5H, m), 3.11-2.72 (2H, m), 2.62 (3H, s), 2.02-1.95 (1H, m), 1.83-1.76 (1H, m), 1.73-1.40 (2H, m).	395	393	optically active form (R)
182		¹ H-NMR (DMSO-D ₆) δ: 9.23 (2H, s), 8.68 (1H, d, J = 8.5 Hz), 8.61 (1H, d, J = 7.6 Hz), 7.89 (1H, d, J = 8.1 Hz), 7.64 (1H, t, J = 7.6 Hz), 7.40 (1H, t, J = 7.4 Hz), 5.39 (1H, s), 4.90-4.15 (2H, br m), 3.96-3.83 (1H, m), 3.13-2.69 (2H, br m), 2.62 (3H, s), 2.04-1.95 (1H, m), 1.82-1.72 (1H, m), 1.68-1.28 (8H, m).	423	421	optically active form (R)
183		¹ H-NMR (DMSO-D ₆) δ: 9.22 (2H, s), 8.68 (1H, d, J = 8.5 Hz), 8.54 (1H, d, J = 8.1 Hz), 7.89 (1H, d, J = 8.1 Hz), 7.63 (1H, t, J = 7.9 Hz), 7.40 (1H, t, J = 7.6 Hz), 3.84-3.74 (1H, m), 3.17-3.12 (2H, m), 2.96 (3H, s), 2.62 (3H, s), 1.97-1.90 (2H, m), 1.85-1.78 (2H, m), 1.67-1.58 (2H, m), 1.43-1.30 (3H, m), 1.15-1.01 (2H, m).	442	440	
184		¹ H-NMR (DMSO-D ₆) δ: 9.23 (2H, s), 8.55 (1H, d, J = 7.6 Hz), 8.43-8.38 (1H, m), 7.97-7.92 (1H, m), 7.32-7.26 (1H, m), 3.84-3.73 (1H, m), 3.18-3.10 (2H, m), 2.96 (3H, s), 2.61 (3H, s), 1.97-1.89 (2H, m), 1.86-1.76 (2H, m), 1.66-1.58 (2H, m), 1.43-1.30 (3H, m), 1.15-1.01 (2H, m).	460	458	

[1086]

[Table 1-24]

Ex.No.	structural formula	¹ H-NMR (400 MHz)	MS (positive)	MS (negative)	Comments
185		¹ H-NMR (DMSO-D ₆) δ: 10.12 (1H, s), 9.35 (2H, s), 8.65-8.62 (2H, m), 8.00 (1H, d, J = 5.8 Hz), 7.64 (1H, t, J = 53.0 Hz), 4.58 (1H, s), 3.83-3.71 (1H, m), 3.49-3.40 (1H, m), 1.90-1.88 (4H, m), 1.44-1.23 (4H, m).	389	387	
186		¹ H-NMR (DMSO-D ₆) δ: 9.23 (2H, s), 8.61 (1H, d, J = 7.6 Hz), 7.77-7.74 (1H, m), 7.51-7.44 (1H, m), 3.84-3.75 (1H, m), 3.47 (2H, q, J = 7.0 Hz), 3.27-3.21 (1H, m), 2.60 (3H, s), 2.04-1.91 (4H, m), 1.44-1.20 (4H, m), 1.10 (3H, t, J = 7.0 Hz).	416	414	
187		¹ H-NMR (DMSO-D ₆) δ: 9.24 (2H, s), 8.62 (1H, d, J = 7.6 Hz), 7.77-7.74 (1H, m), 7.51-7.45 (1H, m), 3.82-3.74 (1H, m), 3.16-3.12 (2H, m), 2.96 (3H, s), 2.60 (3H, s), 1.94-1.79 (4H, m), 1.65-1.59 (2H, m), 1.39-1.31 (3H, m), 1.12-1.03 (2H, m).	478	476	
188		¹ H-NMR (DMSO-D ₆) δ: 9.17 (2H, s), 8.67 (1H, d, J = 8.6 Hz), 8.04 (1H, s), 7.88 (1H, d, J = 7.9 Hz), 7.65-7.60 (1H, m), 7.39 (1H, t, J = 7.3 Hz), 3.07 (2H, s), 2.95 (3H, s), 2.62 (3H, s), 2.01-1.97 (6H, m), 1.82-1.78 (6H, m).	454	452	
189		¹ H-NMR (DMSO-D ₆) δ: 9.18 (2H, s), 8.39 (1H, dd, J = 10.4, 2.3 Hz), 8.06 (1H, s), 7.94 (1H, dd, J = 8.7, 5.4 Hz), 7.29 (1H, td, J = 8.9, 2.3 Hz), 3.07 (2H, s), 2.95 (3H, s), 2.61 (3H, s), 2.01-1.97 (6H, m), 1.82-1.78 (6H, m).	472	470	
190		¹ H-NMR (DMSO-D ₆) δ: 9.24 (2H, s), 8.69 (1H, d, J = 8.6 Hz), 8.55 (1H, d, J = 7.9 Hz), 8.02 (1H, d, J = 7.9 Hz), 7.65-7.61 (1H, m), 7.40 (1H, t, J = 7.2 Hz), 5.57 (1H, t, J = 6.0 Hz), 4.90 (2H, d, J = 6.0 Hz), 4.05 (1H, s), 3.78-3.70 (1H, m), 1.98-1.94 (2H, m), 1.88-1.84 (2H, m), 1.36-1.27 (2H, m), 1.24-1.09 (3H, m), 1.06 (6H, s).	410	408	
191		¹ H-NMR (DMSO-D ₆) δ: 9.30 (2H, s), 8.61 (1H, d, J = 7.4 Hz), 8.54-8.50 (1H, m), 8.04 (1H, dd, J = 8.7, 5.2 Hz), 7.56 (1H, t, J = 53.6 Hz), 7.46-7.41 (1H, m), 4.58 (1H, d, J = 4.6 Hz), 3.81-3.73 (1H, m), 3.47-3.40 (1H, m), 1.90-1.88 (4H, m), 1.45-1.33 (2H, m), 1.32-1.23 (2H, m).	406	404	
192		¹ H-NMR (DMSO-D ₆) δ: 9.31 (2H, s), 8.63 (1H, d, J = 7.6 Hz), 8.54-8.50 (1H, m), 8.04 (1H, dd, J = 8.6, 5.3 Hz), 7.56 (1H, t, J = 53.2 Hz), 7.46-7.40 (1H, m), 4.05 (1H, br s), 3.80-3.70 (1H, m), 1.99-1.95 (2H, m), 1.88-1.84 (2H, m), 1.37-1.06 (5H, m), 1.06 (6H, s).	448	446	

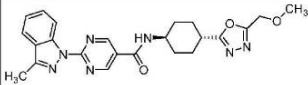
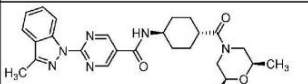
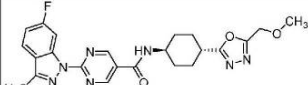
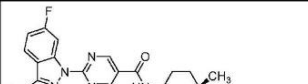
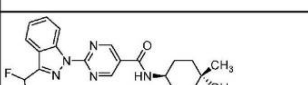
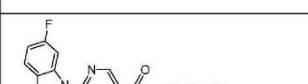
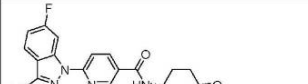
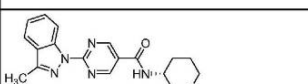
[1087]

[Table 1-25]

Ex.No.	structural formula	¹ H-NMR (400 MHz)	MS (positive)	MS (negative)	Comments
193		¹ H-NMR (DMSO-D ₆) δ: 9.30 (2H, s), 8.63 (1H, d, J = 7.6 Hz), 8.54-8.50 (1H, m), 8.06-8.02 (1H, m), 7.56 (1H, t, J = 53.2 Hz), 7.46-7.40 (1H, m), 4.54 (1H, t, J = 5.1 Hz), 3.84-3.77 (1H, m), 3.49-3.40 (4H, m), 3.31-3.24 (1H, m), 2.07-2.02 (2H, m), 1.96-1.91 (2H, m), 1.45-1.36 (2H, m), 1.32-1.22 (2H, m).	450	448	
194		¹ H-NMR (DMSO-D ₆) δ: 9.30 (2H, d, J = 0.7 Hz), 8.63 (1H, d, J = 7.6 Hz), 8.54-8.51 (1H, m), 8.04 (1H, dd, J = 8.8, 5.3 Hz), 7.56 (1H, t, J = 53.2 Hz), 7.45-7.41 (1H, m), 4.21 (1H, s), 3.86-3.76 (1H, m), 3.19 (2H, s), 3.31-3.22 (1H, m), 2.06-2.01 (2H, m), 1.96-1.91 (2H, m), 1.45-1.23 (4H, m), 1.07 (6H, s).	478	476	
195		¹ H-NMR (DMSO-D ₆) δ: 9.30 (1H, s), 9.29 (1H, s), 8.78 (1H, d, J = 8.1 Hz), 8.71 (1H, d, J = 8.3 Hz), 7.99 (1H, d, J = 8.1 Hz), 7.74 (1H, t, J = 8.1 Hz), 7.55 (1H, t, J = 53.0 Hz), 7.51 (2H, t, J = 8.1 Hz), 4.57-4.51 (1H, m), 4.35-3.56 (4H, m), 3.10-2.63 (2H, m), 1.99-1.43 (4H, m).	431	429	
196		¹ H-NMR (DMSO-D ₆) δ: 9.30 (2H, s), 8.77 (1H, d, J = 8.1 Hz), 8.69 (1H, d, J = 7.4 Hz), 7.99 (1H, d, J = 8.1 Hz), 7.74 (1H, t, J = 8.1 Hz), 7.55 (1H, t, J = 53.0 Hz), 7.51 (1H, t, J = 8.1 Hz), 5.38 (1H, s), 3.94-3.81 (1H, m), 3.02-2.28 (4H, m), 2.00-1.97 (1H, m), 1.77-1.48 (3H, m), 1.36 (3H, s), 1.33 (3H, s).	459	457	
197		¹ H-NMR (DMSO-D ₆) δ: 9.23 (2H, s), 8.68 (1H, d, J = 8.6 Hz), 8.59 (1H, d, J = 7.0 Hz), 7.89 (1H, d, J = 7.5 Hz), 7.63 (1H, t, J = 7.8 Hz), 7.40 (1H, t, J = 7.3 Hz), 3.83-3.73 (1H, m), 3.61-3.41 (8H, br m), 2.62 (3H, s), 2.61-2.53 (1H, br m), 2.00-1.92 (2H, br m), 1.80-1.72 (2H, br m), 1.56-1.37 (4H, m).	449	447	
198		¹ H-NMR (DMSO-D ₆) δ: 9.23 (2H, s), 8.60 (1H, d, J = 7.5 Hz), 8.41 (1H, d, J = 10.2 Hz), 7.94 (1H, dd, J = 8.6, 5.4 Hz), 7.29 (1H, t, J = 9.2 Hz), 3.84-3.72 (1H, m), 3.62-3.41 (8H, br m), 2.61 (3H, s), 2.60-2.54 (1H, br m), 1.99-1.91 (2H, br m), 1.80-1.72 (2H, br m), 1.56-1.37 (4H, m).	467	465	
199		¹ H-NMR (DMSO-D ₆) δ: 9.31 (2H, s), 8.79 (1H, d, J = 8.6 Hz), 8.69 (1H, d, J = 7.5 Hz), 8.01 (1H, d, J = 8.1 Hz), 7.75 (1H, t, J = 7.8 Hz), 7.57 (1H, t, J = 53.3 Hz), 7.53 (1H, t, J = 7.5 Hz), 3.83-3.74 (1H, m), 3.61-3.41 (8H, br m), 2.63-2.54 (1H, m), 2.01-1.92 (2H, br m), 1.81-1.72 (2H, br m), 1.56-1.38 (4H, m).	485	483	
200		¹ H-NMR (DMSO-D ₆) δ: 9.22 (2H, s), 8.68 (1H, d, J = 8.3 Hz), 8.59-8.53 (1H, br m), 7.89 (1H, d, J = 7.9 Hz), 7.63 (1H, t, J = 7.7 Hz), 7.40 (1H, t, J = 7.5 Hz), 4.97 (0.4H, t, J = 5.5 Hz), 4.74 (0.6H, t, J = 5.5 Hz), 3.98-3.91 (1H, m), 3.83-3.73 (1H, m), 3.53-3.45 (2H, br m), 3.40-3.28 (1H, m), 3.27-3.19 (1H, m), 2.62 (3H, s), 2.55-2.52 (0.4H, m), 2.42-2.32 (0.6H, m), 2.00-1.33 (12H, br m).	463	461	optically active form (S)

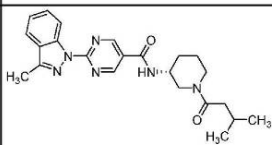
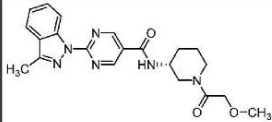
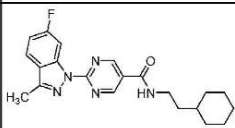
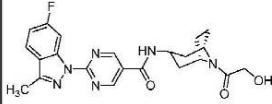
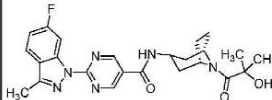
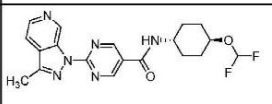
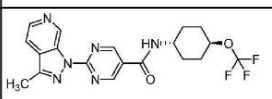
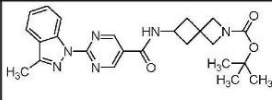
[1088]

[Table 1-26]

Ex.No.	structural formula	¹ H-NMR (400 MHz)	MS (positive)	MS (negative)	Comments
201		¹ H-NMR (DMSO-D ₆) δ: 9.24 (2H, s), 8.68 (1H, d, J = 8.6 Hz), 8.64 (1H, d, J = 7.6 Hz), 7.89 (1H, d, J = 7.9 Hz), 7.63 (1H, t, J = 7.7 Hz), 7.40 (1H, t, J = 7.5 Hz), 4.63 (2H, s), 3.92-3.85 (1H, m), 3.35 (3H, s), 3.00 (1H, tt, J = 11.7, 3.5 Hz), 2.63 (3H, s), 2.21-2.13 (2H, br m), 2.08-2.01 (2H, br m), 1.72-1.60 (2H, m), 1.60-1.48 (2H, m).	448	446	
202		¹ H-NMR (DMSO-D ₆) δ: 9.22 (2H, s), 8.68 (1H, d, J = 8.6 Hz), 8.58 (1H, d, J = 7.4 Hz), 7.89 (1H, d, J = 8.1 Hz), 7.63 (1H, t, J = 7.7 Hz), 7.40 (1H, t, J = 7.4 Hz), 4.27 (1H, d, J = 12.9 Hz), 3.87 (1H, d, J = 13.4 Hz), 3.82-3.71 (1H, br m), 3.53-3.36 (2H, br m), 2.76-2.67 (1H, m), 2.66-2.56 (4H, br m), 2.25-2.15 (1H, br m), 2.00-1.91 (2H, br m), 1.79-1.69 (2H, br m), 1.57-1.39 (4H, br m), 1.13 (3H, d, J = 6.0 Hz), 1.09 (3H, d, J = 6.0 Hz).	477	475	
203		¹ H-NMR (DMSO-D ₆) δ: 9.25 (2H, s), 8.65 (1H, d, J = 7.4 Hz), 8.41 (1H, d, J = 10.4 Hz), 7.95 (1H, t, J = 6.2 Hz), 7.30 (1H, t, J = 8.9 Hz), 4.63 (2H, s), 3.94-3.84 (1H, br m), 3.35 (3H, s), 3.05-2.96 (1H, m), 2.62 (3H, s), 2.21-2.13 (2H, br m), 2.09-2.01 (2H, br m), 1.60-1.72 (2H, m), 1.60-1.48 (2H, m).	466	464	
204		¹ H-NMR (DMSO-D ₆) δ: 9.22 (2H, s), 8.49 (1H, d, J = 7.5 Hz), 8.43-8.38 (1H, m), 7.97-7.92 (1H, m), 7.33-7.26 (1H, m), 4.30 (1H, s), 3.91-3.81 (1H, m), 2.61 (3H, s), 1.87-1.78 (2H, m), 1.67-1.59 (2H, m), 1.54-1.42 (4H, m), 1.17 (3H, s).	384	382	
205		¹ H-NMR (DMSO-D ₆) δ: 9.30 (2H, s), 8.79 (1H, d, J = 8.6 Hz), 8.57 (1H, d, J = 7.5 Hz), 8.00 (1H, d, J = 8.1 Hz), 7.75 (1H, t, J = 7.5 Hz), 7.57 (1H, t, J = 53.3 Hz), 7.52 (2H, t, J = 7.5 Hz), 4.42-4.19 (1H, m), 3.92-3.82 (1H, m), 1.90-1.78 (2H, m), 1.67-1.59 (2H, m), 1.55-1.42 (4H, m), 1.18 (3H, s).	402	400	
206		¹ H-NMR (DMSO-D ₆) δ: 9.25 (2H, s), 8.56 (1H, d, J = 8.1 Hz), 8.40 (1H, dd, J = 10.2, 2.2 Hz), 7.94 (1H, dd, J = 8.6, 5.4 Hz), 7.29 (1H, td, J = 9.0, 2.3 Hz), 4.09 (1H, s), 3.82-3.73 (1H, m), 2.61 (3H, s), 1.83-1.71 (2H, m), 1.66-1.57 (4H, m), 1.43-1.34 (2H, m), 1.13 (3H, s).	384	382	
207		¹ H-NMR (DMSO-D ₆) δ: 8.98-8.96 (1H, m), 8.49-8.44 (1H, m), 8.42-8.34 (2H, m), 7.99 (1H, d, J = 8.8 Hz), 7.93 (1H, dd, J = 8.7, 5.4 Hz), 7.27-7.23 (1H, m), 4.54 (1H, t, J = 5.2 Hz), 3.83-3.75 (1H, m), 3.52-3.42 (4H, m), 3.30-3.22 (1H, m), 2.61 (3H, s), 2.07-2.00 (2H, m), 1.95-1.86 (2H, m), 1.45-1.34 (2H, m), 1.31-1.20 (2H, m).	413	411	
208		¹ H-NMR (DMSO-D ₆) δ: 9.25-9.21 (2.0H, m), 8.68-8.60 (2.0H, m), 7.89 (1.0H, d, J = 8.1 Hz), 7.64 (1.0H, t, J = 7.5 Hz), 7.40 (1.0H, t, J = 7.5 Hz), 4.86 (1.0H, d, J = 7.5 Hz), 4.46-4.39 (0.5H, m), 4.13-4.06 (0.5H, m), 4.04-3.98 (0.5H, m), 3.92-3.78 (1.5H, m), 3.16-3.03 (1.0H, m), 2.92-2.84 (0.5H, m), 2.78-2.68 (0.5H, m), 2.62 (3.0H, s), 2.48-2.45 (2.0H, m), 2.04-1.94 (1.0H, m), 1.83-1.74 (1.0H, m), 1.72-1.34 (1.0H, m), 1.22-1.14 (6.0H, m).	437	435	optically active form (R)

[1089]

[Table 1-27]

Ex.No.	structural formula	¹ H-NMR (400 MHz)	MS (positive)	MS (negative)	Comments
209		¹ H-NMR (DMSO-D ₆) δ: 9.27-9.21 (2H, m), 8.69-8.60 (2H, m), 7.89 (1H, d, J = 8.1 Hz), 7.64 (1H, t, J = 7.8 Hz), 7.40 (1H, t, J = 7.5 Hz), 4.45-3.75 (3H, m), 3.10-2.98 (1H, m), 2.83-2.65 (1H, m), 2.62 (3H, s), 2.32-1.98 (4H, m), 1.79-1.41 (3H, m), 0.97-0.86 (6H, m).	421	419	optically active form (R)
210		¹ H-NMR (DMSO-D ₆) δ: 9.25-9.20 (2H, m), 8.72-8.61 (2H, m), 7.89 (1H, d, J = 8.1 Hz), 7.63 (1H, t, J = 7.8 Hz), 7.40 (1H, t, J = 7.5 Hz), 4.37-3.61 (5H, m), 3.32-3.26 (3H, m), 3.11-2.67 (2H, m), 2.62 (3H, s), 2.03-1.94 (1H, m), 1.85-1.75 (1H, m), 1.71-1.38 (2H, m).	409	407	optically active form (R)
211		¹ H-NMR (DMSO-D ₆) δ: 9.23 (2H, s), 8.74 (1H, t, J = 5.4 Hz), 8.41 (1H, dd, J = 10.4, 2.3 Hz), 7.94 (1H, dd, J = 8.7, 5.4 Hz), 7.29 (1H, td, J = 8.9, 2.1 Hz), 3.39-3.32 (2H, m), 2.61 (3H, s), 1.79-1.59 (5H, m), 1.51-1.43 (2H, m), 1.41-1.30 (1H, m), 1.28-1.12 (3H, m), 0.97-0.88 (2H, m).	382	380	
212		¹ H NMR (DMSO D ₆) δ: 9.22 (2H, s), 8.57 (1H, d, J = 7.6 Hz), 8.40 (1H, d, J = 9.7 Hz), 7.99-7.90 (1H, m), 7.30 (1H, t, J = 8.9 Hz), 4.66 (1H, t, J = 5.1 Hz), 4.60-4.51 (1H, m), 4.50-4.40 (1H, m), 4.32-4.23 (1H, m), 4.14 (1H, dd, J = 15.0, 5.5 Hz), 4.01 (1H, dd, J = 15.3, 5.5 Hz), 2.61 (3H, s), 2.12-1.56 (8H, m).	439	437	exo form
213		¹ H NMR (DMSO D ₆) δ: 9.23 (2H, s), 8.58 (1H, d, J = 7.6 Hz), 8.40 (1H, d, J = 10.2 Hz), 7.94 (1H, dd, J = 8.9, 5.5 Hz), 7.29 (1H, dd, J = 8.9, 8.9 Hz), 5.25 (1H, br s), 5.19-5.03 (1H, m), 4.69-4.53 (1H, m), 4.52-4.36 (1H, m), 2.61 (3H, s), 2.10-1.57 (8H, m), 1.34 (6H, s).	467	465	exo form
214		¹ H-NMR (DMSO-D ₆) δ: 9.98 (1H, s), 9.27 (2H, s), 8.60 (1H, d, J = 7.2 Hz), 8.53 (1H, d, J = 5.1 Hz), 7.94 (1H, d, J = 5.1 Hz), 6.73 (1H, t, J = 76.5 Hz), 4.15-4.02 (1H, m), 3.92-3.76 (1H, m), 2.66 (3H, s), 2.11-1.87 (4H, m), 1.62-1.38 (4H, m).	403	401	
215		¹ H-NMR (DMSO-D ₆) δ: 9.99 (1H, s), 9.28 (2H, s), 8.64 (1H, d, J = 7.4 Hz), 8.53 (1H, d, J = 5.3 Hz), 7.94 (1H, d, J = 5.3 Hz), 4.48-4.36 (1H, m), 3.93-3.79 (1H, m), 2.66 (3H, s), 2.17-1.91 (4H, m), 1.73-1.43 (4H, m).	421	419	
216		¹ H-NMR (DMSO-D ₆) δ: 9.22 (2H, s), 8.90 (1H, d, J = 6.9 Hz), 8.67 (1H, d, J = 8.6 Hz), 7.89 (1H, d, J = 7.9 Hz), 7.63 (1H, dd, J = 8.6, 7.5 Hz), 7.40 (1H, dd, J = 7.9, 7.5 Hz), 4.38-4.25 (1H, m), 3.94 (2H, s), 3.82 (2H, s), 2.62 (3H, s), 2.60-2.52 (2H, m), 2.32-2.23 (2H, m), 1.38 (9H, s).	449	447	

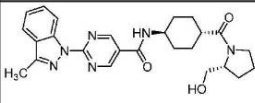
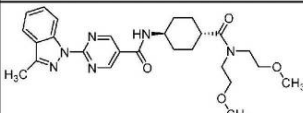
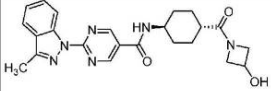
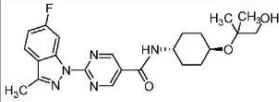
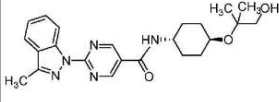
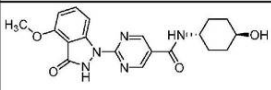
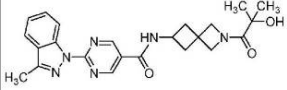
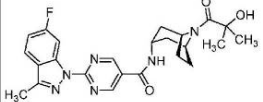
[1090]

[Table 1-28]

Ex.No.	structural formula	¹ H-NMR (400 MHz)	MS (positive)	MS (negative)	Comments
217		¹ H-NMR (DMSO-D ₆) δ: 9.01 (2H, s), 8.45-8.24 (2H, m), 7.43-7.21 (1H, m), 6.91-6.66 (1H, m), 4.04 (1H, s), 3.78-3.65 (1H, m), 2.01-1.78 (4H, m), 1.43-1.08 (5H, m), 1.05 (6H, s).	414	412	
218		¹ H-NMR (DMSO-D ₆) δ: 9.32-8.85 (2H, m), 8.41-8.26 (1H, m), 8.20-7.74 (1H, m), 7.46-7.19 (1H, m), 6.95-6.70 (1H, m), 3.07 (2H, s), 2.95 (3H, s), 2.15-1.91 (6H, m), 1.90-1.71 (6H, m).	474	472	
219		¹ H-NMR (DMSO-D ₆) δ: 9.19-9.00 (2H, m), 8.54-8.32 (2H, m), 7.44-7.28 (1H, m), 6.91-6.79 (1H, m), 3.83-3.70 (1H, m), 3.47 (2H, q, J = 6.9 Hz), 3.27-3.18 (1H, m), 2.08-1.97 (2H, m), 1.95-1.83 (2H, m), 1.52-1.32 (2H, m), 1.32-1.17 (2H, m), 1.10 (3H, t, J = 6.9 Hz).	400	398	
220		¹ H-NMR (DMSO-D ₆) δ: 9.05 (2H, s), 8.46-8.30 (2H, m), 7.37-7.24 (1H, m), 6.86-6.73 (1H, m), 3.78-3.64 (1H, m), 3.16 (2H, s), 2.97 (3H, s), 1.91-1.73 (4H, m), 1.49-1.30 (5H, m), 1.21-1.02 (2H, m), 1.15 (6H, s).	504	502	
221		¹ H-NMR (DMSO-D ₆) δ: 9.23 (2H, s), 8.68 (1H, d, J = 8.6 Hz), 8.62 (1H, d, J = 7.5 Hz), 7.89 (1H, d, J = 7.5 Hz), 7.63 (1H, t, J = 7.8 Hz), 7.40 (1H, t, J = 7.5 Hz), 4.89 (1H, s), 4.42 (1H, d, J = 13.5 Hz), 4.13-4.01 (2H, m), 3.21-3.14 (1H, m), 2.81-2.74 (1H, m), 2.62 (3H, s), 2.54-2.43 (2H, m), 1.93-1.87 (2H, m), 1.56-1.34 (2H, m), 1.19 (6H, s).	437	435	
222		¹ H-NMR (DMSO-D ₆) δ: 9.24 (2H, s), 8.63 (1H, d, J = 7.5 Hz), 8.40 (1H, dd, J = 10.2, 2.2 Hz), 7.94 (1H, dd, J = 8.6, 5.4 Hz), 7.29 (1H, td, J = 9.0, 2.3 Hz), 5.40 (1H, s), 4.86-4.32 (2H, br m), 4.13-4.05 (1H, m), 3.26-2.73 (2H, br m), 2.61 (3H, s), 1.92-1.88 (2H, m), 1.54-1.43 (2H, m), 1.34 (6H, s).	441	439	
223		¹ H-NMR (DMSO-D ₆) δ: 9.32 (2H, s), 8.79 (1H, d, J = 8.6 Hz), 8.71 (1H, d, J = 7.5 Hz), 8.00 (1H, d, J = 8.1 Hz), 7.76 (1H, t, J = 7.8 Hz), 7.57 (1H, t, J = 53.3 Hz), 7.52 (1H, t, J = 7.5 Hz), 5.40 (1H, s), 4.88-4.29 (2H, br m), 4.15-4.07 (1H, m), 3.25-2.73 (2H, br m), 1.93-1.89 (2H, m), 1.53-1.46 (2H, m), 1.34 (6H, s).	459	457	
224		¹ H-NMR (DMSO-D ₆) δ: 9.22 (1H, d, J = 5.5 Hz), 9.21 (2H, s), 8.68-8.66 (1H, m), 7.90-7.87 (1H, m), 7.65-7.61 (1H, m), 7.42-7.38 (1H, m), 4.20 (1H, s), 2.62 (3H, s), 1.96 (6H, s), 1.09 (6H, s).	378	376	

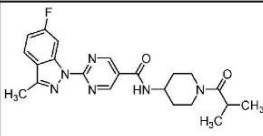
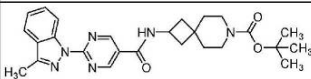
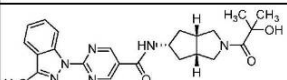
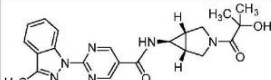
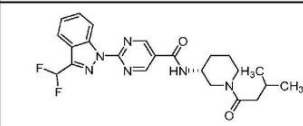
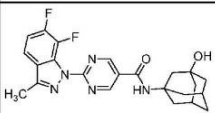
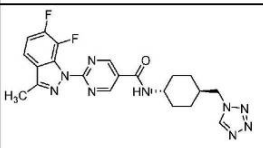
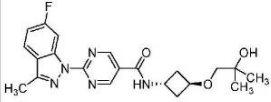
[1091]

[Table 1-29]

Ex.No.	structural formula	¹ H-NMR (400 MHz)	MS (positive)	MS (negative)	Comments
225		¹ H-NMR (DMSO-D ₆) δ: 9.22 (2H, s), 8.68 (1H, d, J = 8.3 Hz), 8.59-8.53 (1H, br m), 7.89 (1H, d, J = 7.9 Hz), 7.63 (1H, t, J = 7.7 Hz), 7.40 (1H, t, J = 7.5 Hz), 4.97 (OH, t, J = 5.5 Hz), 4.74 (1H, t, J = 5.5 Hz), 3.98-3.91 (1H, m), 3.83-3.73 (1H, m), 3.53-3.45 (2H, br m), 3.40-3.28 (1H, m), 3.27-3.19 (1H, m), 2.62 (3H, s), 2.55-2.52 (OH, m), 2.42-2.32 (1H, m), 2.00-1.33 (12H, br m).	463	461	optically active form (R)
226		¹ H-NMR (DMSO-D ₆) δ: 9.22 (2H, s), 8.68 (1H, d, J = 8.6 Hz), 8.55 (1H, d, J = 7.6 Hz), 7.89 (1H, d, J = 7.9 Hz), 7.66-7.60 (1H, m), 7.40 (1H, t, J = 7.4 Hz), 3.84-3.73 (1H, br m), 3.55 (2H, t, J = 5.2 Hz), 3.50-3.36 (6H, br m), 3.28 (3H, s), 3.24 (3H, s), 2.65-2.56 (4H, br m), 1.99-1.91 (2H, br m), 1.76-1.69 (2H, br m), 1.54-1.37 (4H, m).	495	493	
227		¹ H-NMR (DMSO-D ₆) δ: 9.22 (2H, s), 8.67 (1H, d, J = 8.3 Hz), 8.56 (1H, d, J = 7.6 Hz), 7.89 (1H, d, J = 7.9 Hz), 7.63 (1H, t, J = 7.9 Hz), 7.40 (1H, t, J = 7.5 Hz), 5.69 (1H, br s), 4.44 (1H, br s), 4.35 (1H, t, J = 7.4 Hz), 4.01 (1H, t, J = 7.6 Hz), 3.89 (1H, dd, J = 9.0, 3.7 Hz), 3.82-3.70 (1H, br m), 3.56 (1H, dd, J = 9.2, 3.5 Hz), 2.62 (3H, s), 2.22-2.13 (1H, br m), 2.01-1.90 (2H, br m), 1.81-1.68 (2H, br m), 1.50-1.32 (4H, br m).	435	433	
228		¹ H-NMR (DMSO-D ₆) δ: 9.22 (2H, s), 8.52 (1H, d, J = 7.6 Hz), 8.41 (1H, dd, J = 10.4, 2.3 Hz), 7.95 (1H, dd, J = 8.9, 5.3 Hz), 7.29 (1H, td, J = 8.9, 2.3 Hz), 4.53 (1H, br s), 3.80-3.68 (1H, m), 3.56-3.46 (1H, m), 3.21 (2H, d, J = 8.8 Hz), 2.61 (3H, s), 1.94-1.77 (4H, m), 1.49-1.22 (4H, m), 1.09 (6H, s).	442	440	
229		¹ H-NMR (DMSO-D ₆) δ: 9.21 (2H, s), 8.67 (1H, d, J = 8.3 Hz), 8.51 (1H, d, J = 7.4 Hz), 7.89 (1H, d, J = 7.6 Hz), 7.63 (1H, dd, J = 8.3, 7.5 Hz), 7.40 (1H, dd, J = 7.6, 7.5 Hz), 4.53 (1H, br s), 3.82-3.67 (1H, m), 3.58-3.45 (1H, m), 3.22 (2H, s), 2.62 (3H, s), 1.97-1.76 (4H, m), 1.51-1.22 (4H, m), 1.09 (6H, s).	424	422	
230		¹ H-NMR (DMSO-D ₆) δ: 9.02 (2H, br s), 8.35 (1H, br s), 8.15 (1H, d, J = 8.1 Hz), 7.20 (1H, t, J = 8.1 Hz), 6.58 (1H, d, J = 7.5 Hz), 4.57 (1H, br s), 3.84 (3H, s), 3.79-3.66 (1H, m), 3.49-3.39 (1H, m), 1.94-1.78 (4H, m), 1.52-1.16 (4H, m).	384	382	
231		¹ H-NMR (DMSO-D ₆) δ: 9.22 (2H, s), 8.92 (1H, d, J = 6.9 Hz), 8.68 (1H, d, J = 8.6 Hz), 7.89 (1H, d, J = 8.1 Hz), 7.63 (1H, dd, J = 8.6, 7.5 Hz), 7.40 (1H, dd, J = 8.1, 7.5 Hz), 5.02 (1H, d, J = 6.9 Hz), 4.47 (1H, s), 4.40-4.27 (1H, m), 4.35 (1H, s), 3.94 (1H, s), 3.83 (1H, s), 2.62 (3H, s), 2.60-2.52 (2H, m), 2.35-2.23 (2H, m), 1.23 (6H, s).	435	433	
232		¹ H-NMR (DMSO-D ₆) δ: 9.18 (2H, s), 8.48 (1H, d, J = 4.6 Hz), 8.44 (1H, dd, J = 10.2, 2.1 Hz), 7.95 (1H, dd, J = 8.9, 5.3 Hz), 7.30 (1H, ddd, J = 8.9, 8.9, 2.1 Hz), 5.27 (1H, br s), 5.08-4.94 (1H, m), 4.62-4.48 (1H, m), 4.09-3.97 (1H, m), 2.62 (3H, s), 2.35-1.70 (8H, m), 1.41-1.23 (6H, m).	467	465	endo form

[1092]

[Table 1-30]

Ex.No.	structural formula	¹ H-NMR (400 MHz)	MS (positive)	MS (negative)	Comments
233		¹ H-NMR (DMSO-D ₆) δ: 9.24 (2H, s), 8.62 (1H, d, J = 7.6 Hz), 8.41 (1H, dd, J = 10.5, 2.2 Hz), 7.95 (1H, dd, J = 8.9, 5.3 Hz), 7.30 (1H, ddd, J = 8.9, 8.9, 2.2 Hz), 4.43-4.32 (1H, m), 4.16-4.05 (1H, m), 4.03-3.93 (1H, m), 3.25-3.13 (1H, m), 2.97-2.86 (1H, m), 2.80-2.69 (1H, m), 2.61 (3H, s), 1.99-1.83 (2H, m), 1.56-1.32 (2H, m), 1.07-0.96 (6H, m).	425	423	
234		¹ H-NMR (DMSO-D ₆) δ: 9.23 (2H, s), 8.91 (1H, d, J = 7.2 Hz), 8.68 (1H, d, J = 8.6 Hz), 7.89 (1H, d, J = 8.1 Hz), 7.63 (1H, ddd, J = 8.6, 7.4, 1.9 Hz), 7.40 (1H, dd, J = 8.1, 7.4 Hz), 4.51-4.39 (1H, m), 3.33-3.27 (2H, m), 3.26-3.19 (2H, m), 2.62 (3H, s), 2.30-2.21 (2H, m), 1.91-1.83 (2H, m), 1.55 (2H, t, J = 5.5 Hz), 1.49 (2H, t, J = 5.5 Hz), 1.39 (9H, s).	477	475	
235		¹ H-NMR (DMSO-D ₆) δ: 9.22 (2H, s), 8.73 (1H, d, J = 7.4 Hz), 8.67 (1H, d, J = 8.6 Hz), 7.89 (1H, d, J = 7.9 Hz), 7.63 (1H, t, J = 7.7 Hz), 7.40 (1H, t, J = 7.5 Hz), 5.16 (1H, s), 4.39-4.26 (1H, m), 3.99-3.66 (2H, m), 3.57-3.38 (2H, m), 2.71-2.42 (2H, m), 2.62 (3H, s), 2.36-2.14 (2H, m), 1.52-1.37 (2H, m), 1.31 (6H, s).	449	447	cis form
236		¹ H-NMR (DMSO-D ₆) δ: 9.20 (2H, s), 8.86 (1H, d, J = 3.9 Hz), 8.67 (1H, d, J = 8.6 Hz), 7.89 (1H, d, J = 7.6 Hz), 7.63 (1H, dd, J = 8.6, 7.4 Hz), 7.40 (1H, dd, J = 7.6, 7.4 Hz), 5.22 (1H, s), 4.43-4.32 (1H, m), 3.86-3.77 (1H, m), 3.72-3.60 (1H, m), 3.43-3.35 (1H, m), 3.34-3.27 (1H, m), 2.62 (3H, s), 2.00-1.90 (1H, m), 1.84-1.74 (1H, m), 1.28 (6H, s).	421	419	trans form
237		¹ H-NMR (DMSO-D ₆) δ: 9.31 (1H, s), 9.29 (1H, s), 8.78 (1H, d, J = 7.9 Hz), 8.69 (1H, d, J = 7.6 Hz), 7.99 (1H, d, J = 7.9 Hz), 7.75 (1H, t, J = 7.9 Hz), 7.55 (1H, t, J = 53.0 Hz), 7.51 (1H, t, J = 7.9 Hz), 4.40-3.76 (3H, m), 3.08-2.62 (2H, m), 2.20-1.95 (3H, m), 1.78-1.37 (4H, m), 0.91-0.85 (6H, m).	457	455	
238		¹ H-NMR (DMSO-D ₆) δ: 9.17 (2H, s), 8.16 (1H, s), 7.75-7.72 (1H, m), 7.49-7.42 (1H, m), 4.53 (1H, s), 2.58 (3H, s), 2.19-2.17 (2H, br m), 2.01-1.92 (6H, m), 1.60-1.45 (6H, m).	440	438	
239		¹ H-NMR (DMSO-D ₆) δ: 9.21 (2H, s), 8.97 (1H, s), 8.63 (1H, d, J = 7.9 Hz), 7.75-7.72 (1H, m), 7.49-7.43 (1H, m), 4.61 (2H, d, J = 6.9 Hz), 3.80-3.70 (1H, m), 2.58 (3H, s), 1.97-1.90 (3H, m), 1.61-1.58 (2H, m), 1.37-1.14 (4H, m).	454	452	
240		¹ H-NMR (DMSO-D ₆) δ: 9.25 (2H, s), 8.97 (1H, d, J = 6.5 Hz), 8.41 (1H, dd, J = 10.2, 2.2 Hz), 7.95 (1H, dd, J = 8.6, 5.4 Hz), 7.30 (1H, td, J = 8.9, 2.2 Hz), 4.50-4.45 (1H, m), 4.32 (1H, s), 4.19-4.14 (1H, m), 3.07 (2H, s), 2.61 (3H, s), 2.32-2.29 (4H, m), 1.10 (6H, s).	414	412	

[1093]

[Table 1-31]

Ex.No.	structural formula	¹ H-NMR (400 MHz)	MS (positive)	MS (negative)	Comments
241		¹ H-NMR (DMSO-D ₆) δ: 9.27-9.26 (2H, m), 8.83-8.73 (1H, br m), 8.40 (1H, dd, J = 10.4, 2.3 Hz), 7.94 (1H, dd, J = 8.7, 5.4 Hz), 7.31-7.26 (1H, m), 3.75-3.65 (1H, m), 2.61 (3H, s), 1.94-1.90 (2H, m), 1.86-1.83 (2H, m), 1.85 (2H, s), 1.48-1.41 (1H, m), 1.36-1.27 (2H, m), 1.11-1.02 (2H, m), 0.91 (6H, s).	454	452	
242		¹ H-NMR (DMSO-D ₆) δ: 9.25 (2H, s), 9.04 (1H, d, J = 8.0 Hz), 8.68 (1H, d, J = 8.6 Hz), 8.10 (1H, s), 7.89 (1H, d, J = 8.0 Hz), 7.66-7.62 (1H, m), 7.42-7.38 (1H, m), 4.81-4.74 (1H, m), 2.62 (3H, s), 2.31 (1H, dd, J = 12.1, 8.8 Hz), 1.88 (1H, dd, J = 12.1, 10.9 Hz), 1.29 (3H, s), 1.25 (3H, s).	365	363	racemate
243		¹ H-NMR (DMSO-D ₆) δ: 9.26 (2H, s), 9.05 (1H, d, J = 8.1 Hz), 8.41 (1H, dd, J = 10.4, 2.3 Hz), 8.11 (1H, br s), 7.94 (1H, dd, J = 8.7, 5.4 Hz), 7.32-7.27 (1H, m), 4.81-4.74 (1H, m), 2.61 (3H, s), 2.31 (1H, dd, J = 12.3, 8.8 Hz), 1.88 (1H, dd, J = 12.3, 10.9 Hz), 1.29 (3H, s), 1.25 (3H, s).	383	381	racemate
244		¹ H-NMR (DMSO-D ₆) δ: 9.23 (2H, s), 8.92 (1H, d, J = 7.2 Hz), 8.68 (1H, d, J = 8.6 Hz), 7.89 (1H, d, J = 8.1 Hz), 7.64 (1H, ddd, J = 8.6, 7.5, 1.9 Hz), 7.40 (1H, dd, J = 8.1, 7.5 Hz), 5.33 (1H, s), 4.54-4.40 (1H, m), 3.97-3.36 (4H, m), 2.62 (3H, s), 2.32-2.23 (2H, m), 1.94-1.86 (2H, m), 1.66-1.49 (4H, m), 1.31 (6H, s).	463	461	
245		¹ H-NMR (DMSO-D ₆) δ: 9.24 (2H, s), 8.62 (1H, d, J = 7.4 Hz), 8.41 (1H, dd, J = 10.4, 2.1 Hz), 7.95 (1H, dd, J = 8.9, 5.3 Hz), 7.30 (1H, ddd, J = 8.9, 8.9, 2.1 Hz), 4.11-3.88 (3H, m), 3.61 (3H, s), 3.09-2.87 (2H, m), 2.61 (3H, s), 1.92-1.81 (2H, m), 1.54-1.39 (2H, m).	413	411	
246		¹ H-NMR (DMSO-D ₆) δ: 9.24 (2H, s), 8.61 (1H, d, J = 7.6 Hz), 8.41 (1H, dd, J = 10.4, 2.3 Hz), 7.95 (1H, dd, J = 8.9, 5.4 Hz), 7.30 (1H, ddd, J = 8.9, 8.9, 2.3 Hz), 4.83-4.74 (1H, m), 4.10-3.89 (3H, m), 3.05-2.84 (2H, m), 2.61 (3H, s), 1.94-1.81 (2H, m), 1.54-1.38 (2H, m), 1.20 (6H, d, J = 6.2 Hz).	441	439	
247		¹ H-NMR (DMSO-D ₆) δ: 9.22 (2H, s), 8.67 (1H, d, J = 8.6 Hz), 8.53 (1H, d, J = 7.6 Hz), 7.89 (1H, d, J = 7.9 Hz), 7.65-7.61 (1H, m), 7.42-7.38 (1H, m), 4.49 (1H, t, J = 5.8 Hz), 3.82-3.74 (1H, m), 3.42-3.32 (3H, m), 3.25-3.19 (1H, m), 2.62 (3H, s), 2.03-1.87 (4H, br m), 1.46-1.33 (2H, br m), 1.33-1.21 (2H, br m), 1.04 (3H, d, J = 6.2 Hz).	410	408	optically active form (R)
248		¹ H-NMR (DMSO-D ₆) δ: 9.23 (2H, s), 8.54 (1H, d, J = 7.6 Hz), 8.40 (1H, dd, J = 10.3, 2.2 Hz), 7.94 (1H, dd, J = 8.7, 5.4 Hz), 7.29 (1H, td, J = 8.9, 2.2 Hz), 4.49 (1H, t, J = 5.8 Hz), 3.81-3.74 (1H, m), 3.56-3.47 (1H, m), 3.42-3.30 (2H, m), 3.25-3.18 (1H, m), 2.61 (3H, s), 2.03-1.88 (4H, br m), 1.46-1.20 (4H, br m), 1.04 (3H, d, J = 6.0 Hz).	428	426	optically active form (R)

[1094]

[Table 1-32]

Ex.No.	structural formula	¹ H-NMR (400 MHz)	MS (positive)	MS (negative)	Comments
249		¹ H-NMR (DMSO-D ₆) δ: 9.30 (2H, s), 8.78 (1H, d, J = 8.6 Hz), 8.62 (1H, d, J = 7.6 Hz), 8.00 (1H, d, J = 8.1 Hz), 7.78-7.73 (1H, m), 7.56 (1H, t, J = 53.4 Hz), 7.55-7.50 (1H, m), 4.50 (1H, t, J = 5.8 Hz), 3.85-3.73 (1H, m), 3.56-3.47 (1H, m), 3.42-3.32 (2H, m), 3.26-3.18 (1H, m), 2.03-1.89 (4H, br m), 1.47-1.34 (2H, m), 1.33-1.21 (2H, m), 1.04 (3H, d, J = 6.0 Hz).	446	444	opti- cally active form (R)
250		¹ H-NMR (DMSO-D ₆) δ: 9.22 (2H, s), 8.67 (1H, d, J = 8.6 Hz), 8.55 (1H, d, J = 7.6 Hz), 7.89 (1H, d, J = 7.9 Hz), 7.65-7.61 (1H, m), 7.42-7.38 (1H, m), 7.25 (1H, br s), 6.72 (1H, br s), 3.80-3.73 (1H, m), 2.62 (3H, s), 1.97 (2H, d, J = 6.9 Hz), 1.93-1.89 (2H, m), 1.78-1.74 (2H, m), 1.69-1.62 (1H, m), 1.40-1.32 (2H, m), 1.10-1.01 (2H, m).	393	391	
251		¹ H-NMR (DMSO-D ₆) δ: 9.23 (2H, s), 8.61-8.55 (1H, br m), 8.41 (1H, dd, J = 10.4, 2.3 Hz), 7.95 (1H, dd, J = 8.8, 5.3 Hz), 7.29 (1H, td, J = 8.9, 2.2 Hz), 4.97 (0.4H, t, J = 5.7 Hz), 4.74 (0.6H, t, J = 5.7 Hz), 3.99-3.91 (1H, m), 3.83-3.72 (1H, m), 3.54-3.45 (2H, m), 3.39-3.31 (1H, m), 3.28-3.19 (1H, m), 2.61 (3H, s), 2.55-2.52 (0.4H, br m), 2.42-2.33 (0.6H, br m), 2.00-1.35 (12H, br m).	481	479	opti- cally active form (R)
252		¹ H-NMR (DMSO-D ₆) δ: 9.30 (2H, s), 8.79 (1H, d, J = 8.8 Hz), 8.68-8.63 (1H, br m), 8.00 (1H, d, J = 8.1 Hz), 7.78-7.72 (1H, m), 7.56 (1H, t, J = 53.4 Hz), 7.52 (1H, t, J = 7.5 Hz), 4.97 (0.4H, t, J = 5.7 Hz), 4.74 (0.6H, t, J = 5.7 Hz), 3.99-3.91 (1H, m), 3.85-3.73 (1H, m), 3.53-3.45 (2H, m), 3.38-3.32 (1H, m), 3.27-3.20 (1H, m), 2.58-2.51 (0.4H, br m), 2.42-2.32 (0.6H, br m), 2.01-1.37 (12H, br m).	499	497	opti- cally active form (R)
253		¹ H-NMR (DMSO-D ₆) δ: 9.23 (2H, t, J = 15.7 Hz), 8.53 (1H, d, J = 7.9 Hz), 8.40 (1H, dd, J = 10.4, 2.2 Hz), 7.94 (1H, dd, J = 8.9, 5.3 Hz), 7.32-7.27 (1H, m), 7.19 (1H, br s), 6.66 (1H, br s), 3.79-3.69 (1H, m), 2.61 (3H, s), 1.99-1.94 (2H, m), 1.98 (2H, s), 1.98-1.95 (2H, m), 1.36-1.19 (3H, m), 1.16-1.06 (2H, m), 0.94 (6H, s).	453	451	
254		¹ H-NMR (DMSO-D ₆) δ: 9.32 (2H, s), 8.72 (1H, d, J = 7.6 Hz), 8.53 (1H, dd, J = 10.2, 2.3 Hz), 8.05 (1H, dd, J = 8.8, 5.3 Hz), 7.56 (1H, t, J = 53.4 Hz), 7.46-7.41 (1H, m), 5.40 (1H, s), 4.90-4.25 (2H, br m), 4.16-4.06 (1H, m), 3.31-3.06 (2H, br m), 1.92-1.90 (2H, m), 1.57-1.42 (2H, m), 1.34 (6H, s).	477	475	
255		¹ H-NMR (DMSO-D ₆) δ: 9.32 (1H, br s), 9.30 (2H, s), 8.78 (1H, d, J = 8.6 Hz), 8.01-7.99 (1H, m), 7.77-7.73 (1H, m), 7.56 (1H, t, J = 53.4 Hz), 7.54-7.50 (1H, m), 4.21 (1H, s), 1.97 (6H, s), 1.09 (6H, s).	414	412	
256		¹ H-NMR (DMSO-D ₆) δ: 9.99 (1H, s), 9.28 (2H, s), 8.59 (1H, br s), 8.53 (1H, d, J = 5.5 Hz), 7.94 (1H, d, J = 5.5 Hz), 3.81-3.69 (1H, m), 2.66 (3H, s), 2.10 (2H, s), 2.02-1.92 (2H, m), 1.87-1.76 (2H, m), 1.41-1.26 (3H, m), 1.21-1.09 (2H, m), 0.97 (6H, s).	437	435	

[1095]

[Table 1-33]

Ex.No.	structural formula	¹ H-NMR (400 MHz)	MS (positive)	MS (negative)	Comments
257		¹ H-NMR (DMSO-D ₆) δ: 9.22 (2H, s), 8.67 (1H, d, J = 8.6 Hz), 8.57 (1H, d, J = 7.5 Hz), 7.89 (1H, d, J = 8.1 Hz), 7.63 (1H, dd, J = 8.6, 7.5 Hz), 7.40 (1H, dd, J = 8.1, 7.5 Hz), 4.23 (1H, t, J = 7.5 Hz), 4.16-4.07 (1H, m), 4.07-3.96 (1H, m), 3.87-3.28 (2H, m), 2.62 (3H, s), 2.27-2.14 (2H, m), 2.02-1.87 (3H, m), 1.85-1.69 (2H, m), 1.56-1.30 (4H, m), 1.10 (3H, s), 0.97 (3H, s).	477	475	optically active form (S)
258		¹ H-NMR (DMSO-D ₆) δ: 9.23 (2H, s), 8.77-8.73 (1H, m), 8.43-8.38 (1H, m), 7.97-7.92 (1H, m), 7.32-7.26 (1H, m), 4.45 (1H, d, J = 4.3 Hz), 3.37-3.29 (3H, m), 2.61 (3H, s), 1.86-1.71 (4H, m), 1.48-1.42 (2H, m), 1.31-1.22 (1H, m), 1.19-1.07 (2H, m), 1.00-0.88 (2H, m).	398	396	
259		¹ H-NMR (DMSO-D ₆) δ: 9.28 (2H, s), 9.10-9.06 (1H, m), 8.44-8.39 (1H, m), 7.97-7.92 (1H, m), 7.33-7.27 (1H, m), 4.58 (1H, d, J = 4.3 Hz), 3.83 (2H, td, J = 15.4, 5.9 Hz), 3.39-3.32 (1H, m), 2.61 (3H, s), 1.94-1.82 (5H, m), 1.29-1.10 (4H, m).	434	432	
260		¹ H-NMR (DMSO-D ₆) δ: 9.25 (2H, s), 8.63 (1H, d, J = 7.0 Hz), 8.41 (1H, d, J = 10.8 Hz), 7.97-7.93 (1H, m), 7.32-7.27 (1H, m), 4.53 (1H, t, J = 5.9 Hz), 4.30-4.26 (2H, m), 4.16-4.05 (1H, m), 3.44-3.43 (2H, m), 3.00-2.94 (2H, m), 2.61 (3H, s), 1.92-1.89 (2H, m), 1.50-1.42 (2H, m), 1.18 (6H, s).	455	453	
261		¹ H-NMR (DMSO-D ₆) δ: 9.25 (2H, s), 8.64 (1H, d, J = 7.5 Hz), 8.41 (1H, d, J = 10.2 Hz), 7.97-7.93 (1H, m), 7.32-7.28 (1H, m), 4.32-4.29 (1H, m), 4.17-4.04 (3H, m), 3.83-3.80 (1H, m), 3.31 (3H, s), 3.17-3.09 (1H, m), 2.83-2.76 (1H, m), 2.61 (3H, s), 1.94-1.89 (2H, m), 1.57-1.36 (2H, m).	427	425	
262		¹ H-NMR (DMSO-D ₆) δ: 9.25 (2H, s), 8.68 (1H, d, J = 7.5 Hz), 8.42-8.39 (1H, m), 7.95 (1H, dd, J = 8.6, 4.8 Hz), 7.32-7.27 (1H, m), 4.34-4.11 (3H, m), 3.25-2.67 (2H, m), 2.61 (3H, s), 1.99-1.96 (2H, m), 1.67-1.55 (2H, m), 1.55 (6H, s).	450	448	
263		¹ H-NMR (DMSO-D ₆) δ: 9.24 (2H, s), 8.64 (1H, d, J = 7.5 Hz), 8.41 (1H, d, J = 9.2 Hz), 7.97-7.93 (1H, m), 7.32-7.27 (1H, m), 4.72-4.11 (3H, m), 3.17 (3H, s), 3.16-3.14 (1H, m), 2.74-2.72 (1H, m), 2.61 (3H, s), 1.94-1.92 (2H, m), 1.62-1.36 (2H, m), 1.35 (6H, s).	455	453	
264		¹ H-NMR (DMSO-D ₆) δ: 9.23 (2H, s), 8.68 (1H, d, J = 8.1 Hz), 8.57 (1H, d, J = 7.5 Hz), 7.89 (1H, d, J = 8.1 Hz), 7.63 (1H, dd, J = 8.1, 7.5 Hz), 7.40 (1H, dd, J = 8.1, 7.5 Hz), 4.34-4.22 (0.6H, m), 3.90-3.76 (1H, m), 3.67-3.56 (0.4H, m), 2.83 (1.8H, s), 2.70 (1.2H, s), 2.62 (3H, s), 2.06 (1.2H, s), 2.03-1.92 (2H, m), 1.98 (1.8H, s), 1.82-1.38 (6H, m).	407	405	

[1096]

[Table 1-34]

Ex.No.	structural formula	¹ H-NMR (400 MHz)	MS (positive)	MS (negative)	Comments
265		¹ H-NMR (DMSO-D ₆) δ: 9.23 (2H, s), 8.68 (1H, d, J = 8.1 Hz), 8.59 (1H, d, J = 7.5 Hz), 7.89 (1H, d, J = 8.1 Hz), 7.63 (1H, dd, J = 8.1, 7.6 Hz), 7.40 (1H, dd, J = 8.1, 7.6 Hz), 5.59 (1H, br s), 4.00 (1H, t, J = 6.5 Hz), 3.85-3.72 (2H, m), 3.50-3.20 (2H, m), 2.62 (3H, s), 2.05-1.83 (5H, m), 1.82-1.62 (3H, m), 1.57-1.33 (4H, m), 1.03 (3H, s), 0.98 (3H, s).	491	489	optically active form (S)
266		¹ H-NMR (DMSO-D ₆) δ: 9.16 (2H, s), 8.67 (1H, d, J = 8.6 Hz), 8.00 (1H, s), 7.88 (1H, d, J = 8.1 Hz), 7.62 (1H, dd, J = 8.6, 7.5 Hz), 7.39 (1H, dd, J = 8.1, 7.5 Hz), 3.87 (1H, br s), 2.62 (3H, s), 1.92 (6H, t, J = 7.8 Hz), 1.57 (6H, t, J = 7.8 Hz), 1.01 (6H, s).	420	418	
267		¹ H-NMR (DMSO-D ₆) δ: 9.98 (1H, s), 9.22 (2H, s), 8.53 (1H, d, J = 5.4 Hz), 8.05 (1H, br s), 7.94 (1H, d, J = 5.4 Hz), 3.87 (1H, br s), 2.66 (3H, s), 1.93 (6H, t, J = 7.8 Hz), 1.57 (6H, t, J = 7.8 Hz), 1.01 (6H, s).	421	419	
268		¹ H-NMR (DMSO-D ₆) δ: 9.23 (2H, s), 8.68 (1H, d, J = 8.1 Hz), 8.59 (1H, d, J = 7.5 Hz), 7.89 (1H, d, J = 8.1 Hz), 7.63 (1H, dd, J = 8.1, 7.6 Hz), 7.40 (1H, dd, J = 8.1, 7.6 Hz), 5.59 (1H, br s), 4.00 (1H, t, J = 6.5 Hz), 3.85-3.72 (2H, m), 3.50-3.20 (2H, m), 2.62 (3H, s), 2.05-1.83 (5H, m), 1.82-1.62 (3H, m), 1.57-1.33 (4H, m), 1.03 (3H, s), 0.98 (3H, s).	491	489	optically active form (R)
269		¹ H-NMR (DMSO-D ₆) δ: 9.16 (2H, s), 8.67 (1H, d, J = 8.6 Hz), 8.00 (1H, br s), 7.88 (1H, d, J = 8.1 Hz), 7.62 (1H, dd, J = 8.6, 7.3 Hz), 7.39 (1H, dd, J = 8.1, 7.3 Hz), 3.49 (1H, br s), 3.05 (2H, s), 2.62 (3H, s), 1.96 (6H, t, J = 8.1 Hz), 1.46 (6H, t, J = 8.1 Hz).	392	390	
270		¹ H-NMR (DMSO-D ₆) δ: 9.23 (2H, s), 8.74 (1H, t, J = 5.4 Hz), 8.41 (1H, dd, J = 10.8, 2.2 Hz), 7.94 (1H, dd, J = 8.6, 5.4 Hz), 7.32-7.27 (1H, m), 4.43 (1H, t, J = 5.7 Hz), 3.78 (1H, s), 3.38-3.33 (2H, m), 3.13 (2H, d, J = 5.4 Hz), 2.61 (3H, s), 1.57-1.21 (11H, m).	428	426	
271		¹ H-NMR (DMSO-D ₆) δ: 9.22 (2H, s), 8.67 (1H, d, J = 8.1 Hz), 8.53 (1H, d, J = 7.4 Hz), 7.89 (1H, d, J = 8.1 Hz), 7.63 (1H, t, J = 7.9 Hz), 7.40 (1H, t, J = 7.4 Hz), 4.49 (1H, d, J = 4.4 Hz), 3.85-3.75 (1H, m), 3.73-3.64 (1H, m), 3.35-3.29 (1H, m), 3.29-3.19 (2H, m), 2.62 (3H, s), 2.08-2.00 (2H, br m), 1.97-1.89 (2H, br m), 1.46-1.33 (2H, m), 1.33-1.21 (2H, m), 1.04 (3H, d, J = 6.0 Hz).	410	408	optically active form (R)
272		¹ H-NMR (DMSO-D ₆) δ: 9.23 (2H, s), 8.54 (1H, d, J = 7.6 Hz), 8.40 (1H, dd, J = 10.4, 2.3 Hz), 7.94 (1H, dd, J = 8.7, 5.4 Hz), 7.29 (1H, td, J = 8.9, 2.3 Hz), 4.49 (1H, d, J = 4.6 Hz), 3.85-3.74 (1H, m), 3.73-3.64 (1H, m), 3.35-3.30 (1H, m), 3.29-3.18 (2H, m), 2.61 (3H, s), 2.07-2.00 (2H, br m), 1.96-1.88 (2H, br m), 1.46-1.33 (2H, m), 1.32-1.20 (2H, m), 1.04 (3H, d, J = 6.2 Hz).	428	426	optically active form (R)

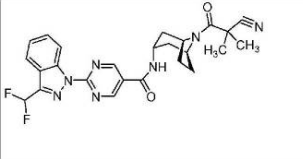
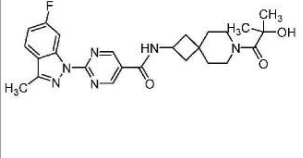
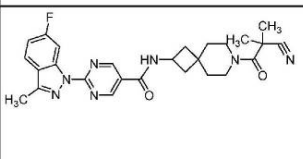
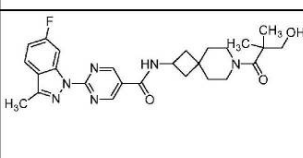
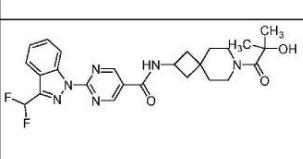
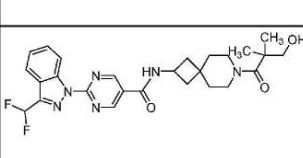
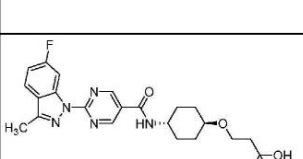
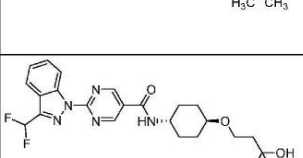
[1097]

[Table 1-35]

Ex.No.	structural formula	¹ H-NMR (400 MHz)	MS (positive)	MS (negative)	Comments
273		¹ H-NMR (DMSO-D ₆) δ: 9.30 (2H, s), 8.78 (1H, d, J = 8.6 Hz), 8.63 (1H, d, J = 7.6 Hz), 8.00 (1H, d, J = 8.1 Hz), 7.75 (1H, t, J = 7.9 Hz), 7.56 (1H, t, J = 53.4 Hz), 7.52 (1H, t, J = 7.6 Hz), 4.49 (1H, d, J = 4.6 Hz), 3.86-3.75 (1H, m), 3.74-3.63 (1H, m), 3.35-3.29 (1H, m), 3.28-3.19 (2H, m), 2.08-2.00 (2H, br m), 1.98-1.89 (2H, br m), 1.46-1.35 (2H, m), 1.33-1.22 (2H, m), 1.04 (3H, d, J = 6.2 Hz).	446	444	optically active form (R)
274		¹ H-NMR (DMSO-D ₆) δ: 9.23 (2H, s), 8.62 (1H, d, J = 7.9 Hz), 8.39 (1H, dd, J = 10.3, 2.2 Hz), 7.93 (1H, dd, J = 8.8, 5.3 Hz), 7.31-7.25 (1H, m), 4.31-4.28 (2H, m), 4.18-4.08 (1H, m), 3.27-3.13 (1H, m), 2.96-2.76 (1H, m), 2.60 (3H, s), 1.94-1.92 (2H, m), 1.55 (6H, d, J = 22.0 Hz), 1.52-1.41 (2H, m).	443	441	
275		¹ H-NMR (DMSO-D ₆) δ: 9.25 (2H, s), 8.65 (1H, d, J = 7.6 Hz), 8.41 (1H, dd, J = 10.4, 2.3 Hz), 7.95 (1H, dd, J = 8.8, 5.3 Hz), 7.30 (1H, td, J = 8.8, 2.3 Hz), 4.25-4.15 (3H, m), 3.22-2.98 (2H, m), 2.61 (3H, s), 1.98-1.96 (2H, m), 1.59-1.46 (2H, m), 1.33-1.13 (4H, m).	441	439	
276		¹ H-NMR (DMSO-D ₆) δ: 9.24 (2H, s), 8.63 (1H, d, J = 7.6 Hz), 8.41 (1H, dd, J = 10.3, 2.2 Hz), 7.95 (1H, dd, J = 8.8, 5.2 Hz), 7.30 (1H, td, J = 8.8, 2.2 Hz), 4.35-4.32 (1H, m), 4.12-4.03 (1H, m), 3.87-3.83 (1H, m), 3.21-3.15 (1H, m), 2.78-2.72 (1H, m), 2.62 (3H, s), 2.03 (3H, s), 1.94-1.85 (2H, m), 1.54-1.36 (2H, m).	397	395	
277		¹ H-NMR (DMSO-D ₆) δ: 12.09 (1H, br s), 9.23 (2H, s), 8.56 (1H, d, J = 7.6 Hz), 8.40 (1H, dd, J = 10.4, 2.3 Hz), 7.94 (1H, dd, J = 8.9, 5.3 Hz), 7.29 (1H, td, J = 8.9, 2.3 Hz), 3.79-3.70 (1H, m), 2.61 (3H, s), 1.99-1.95 (2H, m), 1.68-1.65 (2H, m), 1.58-1.51 (1H, m), 1.39-1.30 (2H, m), 1.21-1.09 (2H, m), 1.05 (6H, s).	440	438	
278		¹ H-NMR (DMSO-D ₆) δ: 9.24 (2H, s), 8.60 (1H, d, J = 7.4 Hz), 8.41 (1H, dd, J = 10.4, 2.3 Hz), 7.94 (1H, dd, J = 8.7, 5.4 Hz), 7.32-7.27 (1H, m), 5.59 (1H, s), 4.01-3.98 (1H, m), 3.81-3.74 (2H, m), 3.43-3.36 (1H, m), 2.61 (3H, s), 2.57-2.45 (1H, m), 1.99-1.84 (5H, m), 1.66-1.81 (3H, m), 1.56-1.38 (4H, m), 1.13 (0.4H, s), 1.08 (0.4H, s), 1.03 (2.6H, s), 0.98 (2.6H, s).	509	507	optically active form (S)
279		¹ H-NMR (DMSO-D ₆) δ: 9.31 (2H, s), 8.79 (1H, d, J = 8.6 Hz), 8.68 (1H, d, J = 7.4 Hz), 8.01 (1H, d, J = 7.9 Hz), 7.77-7.73 (1H, m), 7.57 (1H, t, J = 53.2 Hz), 7.54-7.51 (1H, m), 5.59 (1H, s), 4.02-3.98 (1H, m), 3.82-3.75 (2H, m), 3.43-3.36 (1H, m), 2.57-2.46 (1H, m), 2.01-1.84 (5H, m), 1.80-1.66 (3H, m), 1.56-1.36 (4H, m), 1.13 (0.3H, s), 1.08 (0.3H, s), 1.03 (2.7H, s), 0.98 (2.7H, s).	527	525	optically active form (S)
280		¹ H-NMR (DMSO-D ₆) δ: 9.19 (2H, s), 8.54 (1H, d, J = 4.0 Hz), 8.44 (1H, d, J = 10.3 Hz), 7.95 (1H, dd, J = 9.0, 5.4 Hz), 7.30 (1H, dd, J = 9.0, 9.0 Hz), 4.77-4.52 (2H, m), 4.11-3.99 (1H, m), 2.62 (3H, s), 2.38-1.77 (8H, m), 1.53 (6H, s).	476	474	endo form

[1098]

[Table 1-36]

Ex.No.	structural formula	¹ H-NMR (400 MHz)	MS (positive)	MS (negative)	Comments
281		¹ H-NMR (DMSO-D ₆) δ: 9.27 (2H, s), 8.81 (1H, d, J = 8.5 Hz), 8.62 (1H, d, J = 4.5 Hz), 8.01 (1H, d, J = 8.1 Hz), 7.76 (1H, dd, J = 8.5, 7.9 Hz), 7.57 (1H, t, J = 53.4 Hz), 7.53 (1H, dd, J = 8.1, 7.9 Hz), 4.78-4.53 (2H, m), 4.13-4.02 (1H, m), 2.43-1.79 (8H, m), 1.54 (6H, s).	494	492	endo form
282		¹ H-NMR (DMSO-D ₆) δ: 9.25 (2H, s), 8.94 (1H, d, J = 7.2 Hz), 8.41 (1H, dd, J = 10.3, 1.8 Hz), 7.95 (1H, dd, J = 8.5, 5.4 Hz), 7.30 (1H, ddd, J = 8.5, 8.5, 1.8 Hz), 5.33 (1H, s), 4.53-4.41 (1H, m), 4.00-3.36 (4H, m), 2.62 (3H, s), 2.27 (2H, t, J = 10.3 Hz), 1.89 (2H, t, J = 10.3 Hz), 1.67-1.44 (4H, m), 1.31 (6H, s).	481	479	
283		¹ H-NMR (DMSO-D ₆) δ: 9.25 (2H, s), 8.95 (1H, d, J = 7.2 Hz), 8.41 (1H, dd, J = 10.3, 2.2 Hz), 7.95 (1H, dd, J = 8.8, 5.2 Hz), 7.30 (1H, ddd, J = 8.8, 8.8, 2.2 Hz), 4.53-4.41 (1H, m), 3.75-3.41 (4H, m), 2.62 (3H, s), 2.30 (2H, t, J = 10.1 Hz), 1.92 (2H, t, J = 10.1 Hz), 1.74-1.55 (4H, m), 1.52 (6H, s).	490	488	
284		¹ H-NMR (DMSO-D ₆) δ: 9.25 (2H, s), 8.94 (1H, d, J = 7.6 Hz), 8.41 (1H, dd, J = 10.3, 2.2 Hz), 7.95 (1H, dd, J = 8.5, 5.4 Hz), 7.30 (1H, ddd, J = 8.5, 8.5, 2.2 Hz), 4.53-4.41 (2H, m), 3.55-3.37 (6H, m), 2.62 (3H, s), 2.27 (2H, t, J = 10.3 Hz), 1.89 (2H, t, J = 10.1 Hz), 1.63-1.48 (4H, m), 1.15 (6H, s).	495	493	
285		¹ H-NMR (DMSO-D ₆) δ: 9.32 (2H, s), 9.02 (1H, d, J = 7.2 Hz), 8.79 (1H, d, J = 8.5 Hz), 8.01 (1H, d, J = 8.1 Hz), 7.76 (1H, dd, J = 8.5, 7.6 Hz), 7.57 (1H, t, J = 53.4 Hz), 7.53 (1H, dd, J = 8.1, 7.6 Hz), 5.34 (1H, s), 4.55-4.41 (1H, m), 4.02-3.37 (4H, m), 2.29 (2H, t, J = 10.1 Hz), 1.90 (2H, t, J = 9.9 Hz), 1.69-1.44 (4H, m), 1.31 (6H, s).	499	497	
286		¹ H-NMR (DMSO-D ₆) δ: 9.32 (2H, s), 9.02 (1H, d, J = 7.2 Hz), 8.79 (1H, d, J = 8.5 Hz), 8.01 (1H, d, J = 8.1 Hz), 7.76 (1H, dd, J = 8.5, 7.9 Hz), 7.57 (1H, t, J = 53.4 Hz), 7.53 (1H, dd, J = 8.1, 7.9 Hz), 4.54-4.40 (2H, m), 3.58-3.37 (6H, m), 2.28 (2H, t, J = 10.1 Hz), 1.90 (2H, t, J = 10.3 Hz), 1.59 (2H, t, J = 5.2 Hz), 1.53 (2H, t, J = 5.2 Hz), 1.15 (6H, s).	513	511	
287		¹ H-NMR (DMSO-D ₆) δ: 9.23 (2H, s), 8.55 (1H, d, J = 7.6 Hz), 8.40 (1H, dd, J = 10.5, 2.5 Hz), 7.94 (1H, dd, J = 8.5, 5.4 Hz), 7.29 (1H, td, J = 8.9, 2.4 Hz), 4.17 (1H, s), 3.84-3.76 (1H, m), 3.53 (2H, t, J = 7.2 Hz), 3.27-3.20 (1H, m), 2.61 (3H, s), 2.07-1.99 (2H, m), 1.96-1.88 (2H, m), 1.61 (2H, t, J = 7.2 Hz), 1.47-1.34 (2H, m), 1.32-1.19 (2H, m), 1.10 (6H, s).	456	454	
288		¹ H-NMR (DMSO-D ₆) δ: 9.30 (2H, s), 8.78 (1H, d, J = 8.5 Hz), 8.63 (1H, d, J = 7.6 Hz), 8.00 (1H, d, J = 8.1 Hz), 7.75 (1H, t, J = 7.9 Hz), 7.56 (1H, t, J = 53.2 Hz), 7.52 (1H, t, J = 7.4 Hz), 4.17 (1H, s), 3.85-3.76 (1H, m), 3.53 (2H, t, J = 7.2 Hz), 3.28-3.20 (1H, m), 2.07-1.99 (2H, m), 1.96-1.90 (2H, m), 1.61 (2H, t, J = 7.2 Hz), 1.45-1.36 (2H, m), 1.32-1.21 (2H, m), 1.10 (6H, s).	474	472	

[1099]

[Table 1-37]

Ex.No.	structural formula	¹ H-NMR (400 MHz)	MS (positive)	MS (negative)	Comments
289		¹ H-NMR (DMSO-D ₆) δ: 9.17 (2H, s), 8.39 (1H, dd, J = 10.5, 2.0 Hz), 8.01 (1H, br s), 7.94 (1H, dd, J = 8.9, 5.6 Hz), 7.29 (1H, ddd, J = 8.9, 8.9, 2.0 Hz), 4.36 (1H, br s), 3.05 (2H, s), 2.61 (3H, s), 1.95 (6H, t, J = 7.9 Hz), 1.46 (6H, t, J = 7.9 Hz).	410	408	
290		¹ H-NMR (DMSO-D ₆) δ: 9.25 (2H, s), 8.78 (1H, d, J = 9.0 Hz), 8.10 (1H, br s), 8.00 (1H, d, J = 8.1 Hz), 7.75 (1H, dd, J = 9.0, 7.6 Hz), 7.56 (1H, t, J = 53.4 Hz), 7.52 (1H, dd, J = 8.1, 7.6 Hz), 4.37 (1H, br s), 3.05 (2H, s), 1.96 (6H, t, J = 7.9 Hz), 1.46 (6H, t, J = 7.9 Hz).	428	426	
291		¹ H-NMR (DMSO-D ₆) δ: 9.18 (2H, s), 8.49 (1H, d, J = 4.5 Hz), 8.43 (1H, dd, J = 10.3, 1.8 Hz), 7.95 (1H, dd, J = 8.8, 5.2 Hz), 7.30 (1H, ddd, J = 8.8, 8.8, 1.8 Hz), 4.64-4.51 (2H, m), 4.55 (1H, t, J = 5.8 Hz), 4.05-3.95 (1H, m), 3.43 (2H, d, J = 5.8 Hz), 2.61 (3H, s), 2.22-2.01 (4H, m), 1.96-1.80 (4H, m), 1.15 (6H, s).	481	479	endo form
292		¹ H-NMR (DMSO-D ₆) δ: 9.32 (2H, s), 9.03 (1H, d, J = 7.2 Hz), 8.79 (1H, d, J = 8.5 Hz), 8.01 (1H, d, J = 7.6 Hz), 7.76 (1H, dd, J = 8.5, 7.6 Hz), 7.57 (1H, t, J = 53.4 Hz), 7.53 (1H, dd, J = 7.6, 7.6 Hz), 4.54-4.43 (1H, m), 3.77-3.40 (4H, m), 2.32 (2H, t, J = 10.5 Hz), 1.93 (2H, t, J = 10.5 Hz), 1.75-1.57 (4H, m), 1.53 (6H, s).	508	506	
293		¹ H-NMR (DMSO-D ₆) δ: 9.25 (2H, s), 8.65 (1H, d, J = 7.6 Hz), 8.41 (1H, dd, J = 9.9, 2.1 Hz), 7.95 (1H, dd, J = 8.5, 5.4 Hz), 7.30 (1H, td, J = 8.5, 2.1 Hz), 4.35-4.31 (1H, m), 4.17-4.03 (1H, m), 3.89-3.86 (1H, m), 3.77-3.61 (2H, m), 3.23-3.17 (1H, m), 2.86-2.81 (1H, m), 2.61 (3H, s), 1.93-1.89 (2H, m), 1.58-1.38 (2H, m).	465	463	
294		¹ H-NMR (DMSO-D ₆) δ: 9.24 (2H, d, J = 0.9 Hz), 8.63 (1H, d, J = 7.6 Hz), 8.41 (1H, dd, J = 10.3, 2.1 Hz), 7.95 (1H, dd, J = 8.5, 5.4 Hz), 7.30 (1H, td, J = 8.5, 2.1 Hz), 4.38-4.35 (1H, m), 4.15-4.00 (1H, m), 3.86-3.84 (2H, m), 3.44-3.37 (2H, m), 3.23-3.16 (1H, m), 2.97-2.89 (1H, m), 2.78-2.72 (1H, m), 2.61 (3H, s), 1.96-1.86 (3H, m), 1.66-1.38 (6H, m).	467	465	
295		¹ H-NMR (DMSO-D ₆) δ: 9.24 (2H, s), 8.64 (1H, d, J = 6.7 Hz), 8.42-8.40 (1H, m), 7.97-7.93 (1H, m), 7.32-7.28 (1H, m), 4.33-4.16 (3H, m), 3.79-3.63 (4H, m), 3.29-3.22 (1H, m), 2.98-2.82 (1H, m), 2.61 (3H, s), 2.14-1.97 (6H, m), 1.61-1.42 (2H, m).	485	483	
296		¹ H-NMR (DMSO-D ₆) δ: 9.24 (2H, s), 8.63 (1H, d, J = 7.6 Hz), 8.41 (1H, dd, J = 10.5, 2.1 Hz), 7.95 (1H, dd, J = 8.8, 5.6 Hz), 7.30 (1H, td, J = 8.8, 2.1 Hz), 4.75-4.64 (4H, m), 4.36-4.33 (1H, m), 4.20-4.04 (2H, m), 3.45-3.42 (1H, m), 3.10-3.04 (1H, m), 2.86-2.80 (1H, m), 2.61 (3H, s), 1.94-1.86 (2H, m), 1.46-1.38 (2H, m).	439	437	

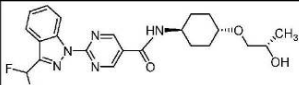
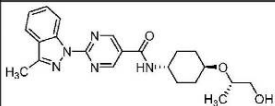
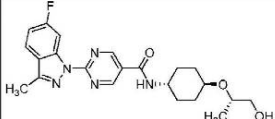
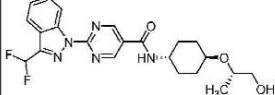
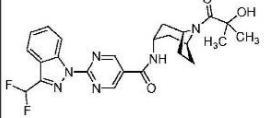
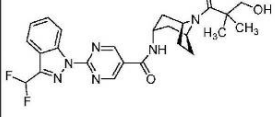
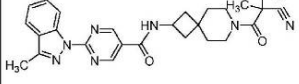
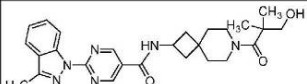
[1100]

[Table 1-38]

Ex.No.	structural formula	¹ H-NMR (400 MHz)	MS (positive)	MS (negative)	Comments
297		¹ H-NMR (DMSO-D ₆) δ: 9.24 (2H, s), 8.63 (1H, d, J = 7.6 Hz), 8.40 (1H, dd, J = 10.1, 2.0 Hz), 7.95 (1H, dd, J = 8.5, 5.4 Hz), 7.29 (1H, td, J = 8.5, 2.0 Hz), 4.34-4.30 (1H, m), 4.13 (1H, d, J = 6.7 Hz), 3.83-3.80 (1H, m), 3.24-3.18 (1H, m), 2.94-2.88 (1H, m), 2.70-2.62 (2H, m), 2.61 (3H, s), 2.44-2.32 (2H, m), 1.95-1.84 (3H, m), 1.56-1.44 (3H, m).	455	453	
298		¹ H-NMR (DMSO-D ₆) δ: 9.32 (2H, s), 9.06 (1H, d, J = 6.7 Hz), 8.79 (1H, d, J = 9.0 Hz), 8.01 (1H, d, J = 7.6 Hz), 7.76 (1H, t, J = 7.9 Hz), 7.57 (1H, t, J = 53.4 Hz), 7.53 (1H, t, J = 7.4 Hz), 4.54-4.44 (1H, m), 4.33 (1H, br s), 4.20-4.14 (1H, m), 3.08 (2H, s), 2.34-2.30 (4H, m), 1.10 (6H, s).	432	430	
299		¹ H-NMR (DMSO-D ₆) δ: 9.22 (2H, s), 8.67 (1H, d, J = 8.5 Hz), 8.54 (1H, d, J = 7.6 Hz), 7.89 (1H, d, J = 8.1 Hz), 7.63 (1H, t, J = 7.9 Hz), 7.40 (1H, t, J = 7.4 Hz), 4.17 (1H, s), 3.85-3.74 (1H, m), 3.53 (2H, t, J = 7.2 Hz), 3.28-3.18 (1H, m), 2.62 (3H, s), 2.07-1.99 (2H, m), 1.97-1.88 (2H, m), 1.61 (2H, t, J = 7.2 Hz), 1.47-1.34 (2H, m), 1.32-1.19 (2H, m), 1.10 (6H, s).	438	436	
300		¹ H-NMR (DMSO-D ₆) δ: 9.23 (2H, s), 8.58 (1H, d, J = 7.6 Hz), 8.40 (1H, dd, J = 10.4, 2.2 Hz), 7.94 (1H, dd, J = 8.8, 5.3 Hz), 7.29 (1H, td, J = 8.8, 2.2 Hz), 3.81-3.73 (1H, m), 3.34 (1H, br s), 2.61 (3H, s), 2.12-2.06 (1H, m), 1.97-1.93 (4H, m), 1.46-1.32 (4H, m).	398	396	
301		¹ H-NMR (DMSO-D ₆) δ: 12.03 (1H, br s), 9.23 (2H, s), 8.56 (1H, d, J = 7.9 Hz), 8.40 (1H, dd, J = 10.4, 2.3 Hz), 7.94 (1H, dd, J = 8.8, 5.3 Hz), 7.29 (1H, td, J = 8.9, 2.3 Hz), 3.82-3.73 (1H, m), 2.61 (3H, s), 2.14 (2H, d, J = 7.4 Hz), 1.94-1.90 (2H, m), 1.80-1.77 (2H, m), 1.71-1.61 (1H, m), 1.42-1.32 (2H, m), 1.15-1.06 (2H, m).	412	410	
302		¹ H-NMR (DMSO-D ₆) δ: 12.06 (1H, br s), 9.17 (2H, s), 8.39 (1H, dd, J = 10.4, 2.3 Hz), 8.08 (1H, s), 7.94 (1H, dd, J = 8.8, 5.4 Hz), 7.29 (1H, td, J = 8.8, 2.3 Hz), 2.61 (3H, s), 2.02-1.98 (6H, m), 1.84-1.80 (6H, m).	424	422	
303		¹ H-NMR (DMSO-D ₆) δ: 9.22 (2H, s), 8.67 (1H, d, J = 8.1 Hz), 8.53 (1H, d, J = 7.4 Hz), 7.89 (1H, d, J = 8.1 Hz), 7.63 (1H, t, J = 7.9 Hz), 7.40 (1H, t, J = 7.4 Hz), 4.49 (1H, d, J = 4.4 Hz), 3.85-3.75 (1H, m), 3.73-3.64 (1H, m), 3.35-3.29 (1H, m), 3.29-3.19 (2H, m), 2.62 (3H, s), 2.08-2.00 (2H, br m), 1.97-1.89 (2H, br m), 1.46-1.33 (2H, m), 1.33-1.21 (2H, m), 1.04 (3H, d, J = 6.0 Hz).	410	408	optically active form (S)
304		¹ H-NMR (DMSO-D ₆) δ: 9.23 (2H, s), 8.54 (1H, d, J = 7.6 Hz), 8.40 (1H, dd, J = 10.4, 2.3 Hz), 7.94 (1H, dd, J = 8.7, 5.4 Hz), 7.29 (1H, td, J = 8.9, 2.3 Hz), 4.49 (1H, d, J = 4.6 Hz), 3.85-3.74 (1H, m), 3.73-3.64 (1H, m), 3.35-3.30 (1H, m), 3.29-3.18 (2H, m), 2.61 (3H, s), 2.07-2.00 (2H, br m), 1.96-1.88 (2H, br m), 1.46-1.33 (2H, m), 1.32-1.20 (2H, m), 1.04 (3H, d, J = 6.2 Hz).	428	426	optically active form (S)

[1101]

[Table 1-39]

Ex.No.	structural formula	¹ H-NMR (400 MHz)	MS (positive)	MS (negative)	Comments
305		¹ H-NMR (DMSO-D ₆) δ: 9.30 (2H, s), 8.78 (1H, d, J = 8.6 Hz), 8.63 (1H, d, J = 7.6 Hz), 8.00 (1H, d, J = 8.1 Hz), 7.75 (1H, t, J = 7.9 Hz), 7.56 (1H, t, J = 53.4 Hz), 7.52 (1H, t, J = 7.6 Hz), 4.49 (1H, d, J = 4.6 Hz), 3.86-3.75 (1H, m), 3.74-3.63 (1H, m), 3.35-3.29 (1H, m), 3.28-3.19 (2H, m), 2.08-2.00 (2H, br m), 1.98-1.89 (2H, br m), 1.46-1.35 (2H, m), 1.33-1.22 (2H, m), 1.04 (3H, d, J = 6.2 Hz).	446	444	optically active form (S)
306		¹ H-NMR (DMSO-D ₆) δ: 9.20 (2H, s), 8.66 (1H, d, J = 8.3 Hz), 8.51 (1H, d, J = 7.4 Hz), 7.87 (1H, d, J = 7.9 Hz), 7.63-7.60 (1H, m), 7.39-7.37 (1H, m), 4.48 (1H, t, J = 5.8 Hz), 3.80-3.73 (1H, m), 3.52-3.48 (1H, m), 3.39-3.31 (2H, m), 3.23-3.17 (1H, m), 2.61 (3H, s), 1.97-1.89 (4H, m), 1.43-1.20 (4H, m), 1.02 (3H, d, J = 6.2 Hz).	410	408	optically active form (S)
307		¹ H NMR (DMSO-D ₆) δ: 9.21 (2H, s), 8.52 (1H, d, J = 7.6 Hz), 8.39 (1H, dd, J = 10.4, 2.2 Hz), 7.93 (1H, dd, J = 8.8, 5.3 Hz), 7.28 (1H, td, J = 8.8, 2.2 Hz), 4.48 (1H, t, J = 5.8 Hz), 3.80-3.71 (1H, m), 3.53-3.46 (1H, m), 3.40-3.30 (2H, m), 3.23-3.17 (1H, m), 2.60 (3H, s), 2.01-1.89 (4H, m), 1.42-1.19 (4H, m), 1.02 (3H, d, J = 6.0 Hz).	428	426	optically active form (S)
308		¹ H-NMR (DMSO-D ₆) δ: 9.28 (2H, s), 8.77 (1H, d, J = 8.6 Hz), 8.60 (1H, d, J = 7.6 Hz), 7.99 (1H, d, J = 8.1 Hz), 7.76-7.72 (1H, m), 7.55 (1H, t, J = 52.0 Hz), 7.52-7.50 (1H, m), 4.48 (1H, t, J = 5.8 Hz), 3.81-3.74 (1H, m), 3.53-3.48 (1H, m), 3.37-3.33 (2H, m), 3.23-3.17 (1H, m), 2.01-1.89 (4H, m), 1.43-1.19 (4H, m), 1.02 (3H, d, J = 6.0 Hz).	446	444	optically active form (S)
309		¹ H NMR (DMSO-D ₆) δ: 9.25 (2H, s), 8.81 (1H, d, J = 8.6 Hz), 8.55 (1H, d, J = 4.6 Hz), 8.01 (1H, d, J = 8.1 Hz), 7.76 (1H, dd, J = 8.6, 7.9 Hz), 7.57 (1H, t, J = 53.4 Hz), 7.53 (1H, dd, J = 8.1, 7.9 Hz), 5.27 (1H, s), 5.10-4.97 (1H, m), 4.61-4.49 (1H, m), 4.10-3.99 (1H, m), 2.35-1.72 (8H, m), 1.40-1.25 (6H, m).	485	483	endo form
310		¹ H-NMR (DMSO-D ₆) δ: 9.26 (2H, s), 8.81 (1H, d, J = 8.6 Hz), 8.57 (1H, d, J = 4.6 Hz), 8.01 (1H, d, J = 7.9 Hz), 7.76 (1H, ddd, J = 8.6, 7.9, 2.0 Hz), 7.57 (1H, t, J = 53.4 Hz), 7.53 (1H, dd, J = 7.9, 7.9 Hz), 4.63-4.51 (2H, m), 4.55 (1H, t, J = 5.8 Hz), 4.07-3.96 (1H, m), 3.43 (2H, d, J = 5.8 Hz), 2.23-2.02 (4H, m), 1.95-1.79 (4H, m), 1.15 (6H, s).	499	497	endo form
311		¹ H NMR (DMSO-D ₆) δ: 9.24 (2H, s), 8.94 (1H, d, J = 7.2 Hz), 8.68 (1H, d, J = 8.6 Hz), 7.89 (1H, d, J = 7.9 Hz), 7.63 (1H, dd, J = 8.6, 7.7 Hz), 7.40 (1H, dd, J = 7.9, 7.7 Hz), 4.53-4.39 (1H, m), 3.76-3.36 (4H, m), 2.62 (3H, s), 2.30 (2H, t, J = 10.2 Hz), 1.92 (2H, t, J = 10.2 Hz), 1.75-1.56 (4H, m), 1.52 (6H, s).	472	470	
312		¹ H NMR (DMSO-D ₆) δ: 9.23 (2H, s), 8.93 (1H, d, J = 7.4 Hz), 8.68 (1H, d, J = 8.3 Hz), 7.89 (1H, d, J = 7.9 Hz), 7.63 (1H, ddd, J = 8.3, 7.9, 2.1 Hz), 7.40 (1H, dd, J = 7.9, 7.9 Hz), 4.52-4.40 (1H, m), 4.48 (1H, t, J = 5.9 Hz), 3.55-3.47 (2H, m), 3.46-3.38 (2H, m), 3.40 (2H, d, J = 5.9 Hz), 2.62 (3H, s), 2.27 (2H, t, J = 10.3 Hz), 1.89 (2H, t, J = 10.3 Hz), 1.59 (2H, t, J = 5.3 Hz), 1.53 (2H, t, J = 5.3 Hz), 1.15 (6H, s).	477	475	

[1102]

[Table 1-40]

Ex.No.	structural formula	¹ H-NMR (400 MHz)	MS (positive)	MS (negative)	Comments
313		¹ H-NMR (DMSO-D ₆) δ: 9.23 (2H, s), 8.68 (1H, d, J = 8.5 Hz), 8.58 (1H, d, J = 8.1 Hz), 7.89 (1H, d, J = 8.1 Hz), 7.64 (1H, dd, J = 8.5, 7.6 Hz), 7.40 (1H, dd, J = 8.1, 7.6 Hz), 4.23 (0.5H, s), 4.07-3.78 (1.5H, m), 3.10 (1H, s), 2.78 (2H, s), 2.62 (3H, s), 2.11-1.58 (6H, m), 1.58-1.42 (2H, m), 1.54 (6H, s).	460	458	
314		¹ H-NMR (DMSO-D ₆) δ: 9.25 (2H, s), 8.60 (1H, d, J = 8.1 Hz), 8.41 (1H, dd, J = 10.3, 2.2 Hz), 7.95 (1H, dd, J = 8.5, 5.4 Hz), 7.30 (1H, ddd, J = 8.5, 8.5, 2.2 Hz), 4.23 (0.5H, s), 4.07-3.78 (1.5H, m), 3.10 (1H, s), 2.78 (2H, s), 2.61 (3H, s), 2.10-1.66 (6H, m), 1.65-1.41 (2H, m), 1.54 (6H, s).	478	476	
315		¹ H-NMR (DMSO-D ₆) δ: 9.32 (2H, d, J = 0.9 Hz), 8.78 (1H, d, J = 8.2 Hz), 8.72 (1H, d, J = 7.2 Hz), 8.01 (1H, d, J = 8.2 Hz), 7.76 (1H, t, J = 8.2 Hz), 7.57 (1H, t, J = 53.0 Hz), 7.53 (1H, t, J = 8.2 Hz), 4.53 (1H, t, J = 5.8 Hz), 4.30-4.27 (2H, m), 4.15-4.06 (1H, m), 3.44 (2H, d, J = 5.8 Hz), 3.00-2.94 (2H, m), 1.93-1.91 (2H, m), 1.49-1.45 (2H, m), 1.18 (6H, s).	473	471	
316		¹ H-NMR (DMSO-D ₆) δ: 9.25 (2H, s), 8.69-8.67 (2H, m), 7.89 (1H, d, J = 7.9 Hz), 7.66-7.61 (1H, m), 7.40 (1H, t, J = 7.5 Hz), 4.38-4.30 (1H, m), 2.62 (3H, s), 2.58-2.50 (2H, m), 2.37-2.31 (2H, m), 2.18-2.13 (2H, m), 1.89-1.79 (2H, m).	350	348	
317		¹ H-NMR (DMSO-D ₆) δ: 8.27 (1H, d, J = 8.1 Hz), 8.12 (1H, dt, J = 8.3, 0.9 Hz), 8.07-8.04 (2H, m), 8.00-7.97 (2H, m), 7.73-7.71 (1H, m), 7.50-7.46 (1H, m), 7.30-7.26 (1H, m), 4.13 (3H, s), 3.83-3.76 (1H, m), 1.86-1.74 (4H, m), 1.64-1.61 (1H, m), 1.40-1.27 (4H, m), 1.18-1.14 (1H, m).	334	Not Detected	
318		¹ H-NMR (DMSO-D ₆) δ: 8.13-8.08 (1H, m), 8.05-8.00 (2H, m), 7.94-7.88 (2H, m), 7.74-7.66 (2H, m), 7.51-7.45 (1H, m), 7.30-7.24 (1H, m), 4.13 (3H, s), 4.10-4.02 (2H, m), 2.00-1.90 (6H, m), 2.50-2.40 (1H, m), 1.90-1.80 (1H, m), 1.68-1.57 (1H, m), 1.53-1.38 (6H, m), 1.22-1.15 (3H, m), 0.81-0.75 (3H, m).	474	472	optically active form (R)
319		¹ H-NMR (DMSO-D ₆) δ: 8.29-8.23 (1H, m), 8.14-8.10 (1H, m), 8.08-8.03 (2H, m), 8.01-7.95 (2H, m), 7.75-7.70 (1H, m), 7.52-7.45 (1H, m), 7.31-7.24 (1H, m), 4.13 (3H, s), 4.03 (1H, s), 3.79-3.66 (1H, m), 1.96-1.80 (4H, m), 1.40-1.26 (2H, m), 1.25-1.07 (3H, m), 1.05 (6H, s).	392	Not Detected	
320		¹ H-NMR (DMSO-D ₆) δ: 11.98 (1H, br s), 8.13-8.08 (1H, m), 8.05-8.00 (2H, m), 7.95-7.88 (2H, m), 7.75-7.67 (2H, m), 7.51-7.45 (1H, m), 7.30-7.24 (1H, m), 4.13 (3H, s), 2.43-2.36 (1H, m), 2.00-1.89 (6H, m), 1.80-1.72 (1H, m), 1.65-1.55 (1H, m), 1.54-1.37 (6H, m), 0.82-0.77 (3H, m).	446	444	optically active form (R)

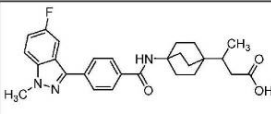
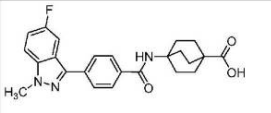
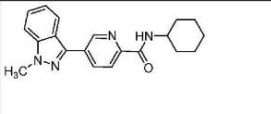
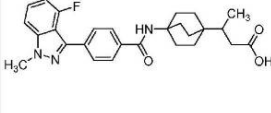
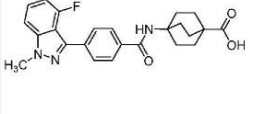
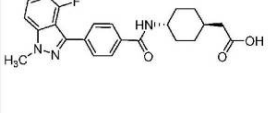
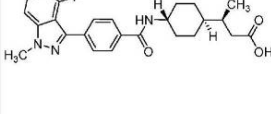
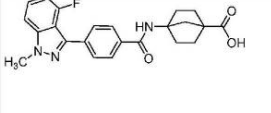
[1103]

[Table 1-41]

Ex.No.	structural formula	¹ H-NMR (400 MHz)	MS (positive)	MS (negative)	Comments
321		¹ H-NMR (DMSO-D ₆) δ: 12.04 (1H, br s), 8.13-8.08 (1H, m), 8.05-8.00 (2H, m), 7.93-7.89 (2H, m), 7.76-7.70 (2H, m), 7.51-7.45 (1H, m), 7.30-7.24 (1H, m), 4.13 (3H, s), 2.04-1.96 (6H, m), 1.85-1.77 (6H, m).	404	402	
322		¹ H-NMR (DMSO-D ₆) δ: 8.15 (2H, d, J = 7.2 Hz), 7.98-7.89 (5H, m), 6.93 (1H, ddd, J = 9.2, 6.5, 0.9 Hz), 6.78-6.74 (1H, m), 3.83-3.74 (1H, m), 2.65 (3H, t, J = 16.0 Hz), 1.91-1.74 (4H, m), 1.64-1.60 (1H, m), 1.40-1.26 (4H, m), 1.19-1.09 (1H, m).	334	Not Detected	
323		¹ H-NMR (DMSO-D ₆) δ: 8.28-8.22 (1H, m), 7.99-7.89 (4H, m), 7.59-7.54 (1H, m), 7.51-7.43 (1H, m), 7.05-6.98 (1H, m), 4.15 (3H, s), 4.03 (1H, s), 3.79-3.66 (1H, m), 1.96-1.79 (4H, m), 1.40-1.25 (2H, m), 1.24-1.07 (3H, m), 1.05 (6H, s).	410	Not Detected	
324		¹ H-NMR (DMSO-D ₆) δ: 8.67-8.63 (2H, m), 8.32-8.27 (1H, m), 8.12-8.08 (2H, m), 8.02-7.97 (2H, m), 7.38-7.33 (1H, m), 4.15 (3H, s), 3.85-3.73 (1H, m), 1.90-1.81 (2H, m), 1.81-1.70 (2H, m), 1.68-1.57 (1H, m), 1.38-1.24 (4H, m), 1.21-1.09 (1H, m).	335	Not Detected	
325		¹ H NMR (DMSO D ₆) δ: 8.69-8.66 (1H, m), 8.58-8.53 (2H, m), 8.26-8.21 (2H, m), 8.00-7.95 (2H, m), 7.53-7.47 (1H, m), 4.17 (3H, s), 3.85-3.73 (1H, m), 1.91-1.80 (2H, m), 1.79-1.70 (2H, m), 1.68-1.58 (1H, m), 1.40-1.27 (4H, m), 1.22-1.08 (1H, m).	335	Not Detected	
326		¹ H NMR (DMSO D ₆) δ: 8.31-8.25 (1H, m), 8.17-8.11 (1H, m), 8.06-8.01 (2H, m), 8.00-7.95 (2H, m), 7.65-7.60 (1H, m), 7.18-7.11 (1H, m), 4.09 (3H, s), 3.84-3.74 (1H, m), 1.89-1.80 (2H, m), 1.79-1.69 (2H, m), 1.67-1.58 (1H, m), 1.40-1.28 (4H, m), 1.21-1.08 (1H, m).	352	Not Detected	
327		¹ H-NMR (DMSO-D ₆) δ: 8.30-8.25 (1H, m), 8.06-8.02 (2H, m), 8.00-7.95 (2H, m), 7.92-7.88 (1H, m), 7.81-7.76 (1H, m), 7.43-7.36 (1H, m), 4.14 (3H, s), 3.84-3.74 (1H, m), 1.88-1.80 (2H, m), 1.78-1.70 (2H, m), 1.66-1.58 (1H, m), 1.39-1.28 (4H, m), 1.20-1.09 (1H, m).	352	Not Detected	
328		¹ H-NMR (DMSO-D ₆) δ: 8.29-8.23 (1H, m), 7.98-7.89 (4H, m), 7.59-7.54 (1H, m), 7.50-7.42 (1H, m), 7.05-6.98 (1H, m), 4.14 (3H, s), 3.85-3.72 (1H, m), 1.89-1.81 (2H, m), 1.78-1.70 (2H, m), 1.67-1.57 (1H, m), 1.39-1.27 (4H, m), 1.21-1.08 (1H, m).	352	350	

[1104]

[Table 1-42]

Ex.No.	structural formula	¹ H-NMR (400 MHz)	MS (positive)	MS (negative)	Comments
329		¹ H-NMR (DMSO-D ₆) δ: 11.98 (1H, br s), 7.91-7.87 (4H, m), 7.70-7.67 (1H, m), 7.58-7.54 (1H, m), 7.50-7.42 (1H, m), 7.04-6.97 (1H, m), 4.14 (3H, s), 2.43-2.31 (1H, m), 1.98-1.89 (6H, m), 1.81-1.70 (1H, m), 1.66-1.54 (1H, m), 1.53-1.37 (6H, m), 0.81-0.76 (3H, m).	464	462	optically active form (R)
330		¹ H-NMR (DMSO-D ₆) δ: 12.02 (1H, br s), 7.90-7.88 (4H, m), 7.76-7.74 (1H, m), 7.58-7.54 (1H, m), 7.50-7.43 (1H, m), 7.04-6.97 (1H, m), 4.14 (3H, s), 2.03-1.94 (6H, m), 1.84-1.76 (6H, m).	422	420	
331		¹ H-NMR (DMSO-D ₆) δ: 9.24-9.19 (1H, m), 8.58-8.53 (1H, m), 8.51-8.45 (1H, m), 8.19-8.12 (2H, m), 7.80-7.74 (1H, m), 7.55-7.48 (1H, m), 7.34-7.27 (1H, m), 4.17 (3H, s), 3.88-3.76 (1H, m), 1.88-1.79 (2H, m), 1.79-1.68 (2H, m), 1.66-1.56 (1H, m), 1.50-1.27 (4H, m), 1.25-1.11 (1H, m).	335	Not Detected	
332		¹ H-NMR (DMSO-D ₆) δ: 11.96 (1H, br s), 8.03-7.98 (2H, m), 7.92-7.85 (3H, m), 7.81-7.76 (1H, m), 7.70-7.67 (1H, m), 7.43-7.36 (1H, m), 4.14 (3H, s), 2.43-2.31 (1H, m), 1.99-1.90 (6H, m), 1.80-1.72 (1H, m), 1.64-1.55 (1H, m), 1.52-1.37 (6H, m), 0.81-0.77 (3H, m).	464	462	optically active form (R)
333		¹ H-NMR (DMSO-D ₆) δ: 12.09-11.95 (1H, m), 8.03-7.99 (2H, m), 7.93-7.85 (3H, m), 7.81-7.73 (2H, m), 7.43-7.36 (1H, m), 4.14 (3H, s), 2.03-1.95 (6H, m), 1.84-1.76 (6H, m).	422	420	
334		¹ H-NMR (DMSO-D ₆) δ: 12.01 (1H, br s), 8.31-8.26 (1H, m), 8.06-8.02 (2H, m), 7.99-7.95 (2H, m), 7.92-7.88 (1H, m), 7.81-7.77 (1H, m), 7.43-7.36 (1H, m), 4.14 (3H, s), 3.82-3.68 (1H, m), 2.15-2.11 (2H, m), 1.91-1.82 (2H, m), 1.82-1.73 (2H, m), 1.69-1.57 (1H, m), 1.46-1.31 (2H, m), 1.16-1.00 (2H, m).	410	408	
335		¹ H-NMR (DMSO-D ₆) δ: 11.98 (1H, br s), 8.30-8.24 (1H, m), 8.06-8.01 (2H, m), 8.00-7.95 (2H, m), 7.93-7.88 (1H, m), 7.81-7.76 (1H, m), 7.43-7.36 (1H, m), 4.14 (3H, s), 3.80-3.68 (1H, m), 2.35-2.27 (1H, m), 2.04-1.95 (1H, m), 1.94-1.86 (2H, m), 1.84-1.74 (1H, m), 1.73-1.65 (2H, m), 1.42-1.27 (2H, m), 1.25-1.06 (3H, m), 0.89-0.85 (3H, m).	438	436	optically active form (S)
336		¹ H-NMR (DMSO-D ₆) δ: 12.12 (1H, br s), 8.54-8.51 (1H, m), 8.06-8.01 (2H, m), 7.99-7.94 (2H, m), 7.93-7.87 (1H, m), 7.82-7.76 (1H, m), 7.43-7.36 (1H, m), 4.14 (3H, s), 2.02-1.96 (6H, m), 1.96-1.85 (2H, m), 1.69-1.60 (2H, m).	408	406	

[1105]

[Table 1-43]

Ex.No.	structural formula	¹ H-NMR (400 MHz)	MS (positive)	MS (negative)	Comments
337		¹ H-NMR (DMSO-D ₆) δ: 12.04 (1H, br s), 8.12-8.08 (1H, m), 8.05-8.00 (2H, m), 7.94-7.89 (2H, m), 7.78-7.73 (2H, m), 7.49-7.43 (1H, m), 7.29-7.23 (1H, m), 4.57-4.49 (2H, m), 2.04-1.95 (6H, m), 1.85-1.77 (6H, m), 1.49-1.42 (3H, m).	418	416	
338		¹ H-NMR (DMSO-D ₆) δ: 8.31-8.26 (1H, m), 7.96-7.90 (2H, m), 7.75-7.68 (3H, m), 7.48-7.41 (1H, m), 7.28-7.23 (1H, m), 4.14 (3H, s), 3.85-3.72 (1H, m), 1.90-1.81 (2H, m), 1.79-1.70 (2H, m), 1.67-1.57 (1H, m), 1.40-1.26 (4H, m), 1.22-1.09 (1H, m).	368	Not Detected	
339		¹ H-NMR (DMSO-D ₆) δ: 8.32-8.25 (1H, m), 7.96-7.91 (2H, m), 7.67-7.61 (2H, m), 7.53-7.48 (1H, m), 7.36-7.30 (1H, m), 6.95-6.92 (1H, m), 4.08 (3H, s), 3.86-3.74 (1H, m), 2.31 (3H, s), 1.89-1.81 (2H, m), 1.79-1.70 (2H, m), 1.66-1.58 (1H, m), 1.38-1.27 (4H, m), 1.20-1.09 (1H, m).	348	Not Detected	
340		¹ H-NMR (DMSO-D ₆) δ: 8.28-8.22 (1H, m), 8.06-8.01 (2H, m), 8.00-7.94 (2H, m), 7.90-7.87 (1H, m), 7.63-7.59 (1H, m), 7.33-7.28 (1H, m), 4.10 (3H, s), 3.85-3.73 (1H, m), 2.47 (3H, s), 1.90-1.79 (2H, m), 1.79-1.70 (2H, m), 1.68-1.58 (1H, m), 1.39-1.26 (4H, m), 1.22-1.08 (1H, m).	348	Not Detected	
341		¹ H-NMR (DMSO-D ₆) δ: 8.41-8.37 (1H, m), 8.21-7.90 (3H, m), 7.79-7.75 (1H, m), 7.74-7.68 (2H, m), 7.63-7.58 (1H, m), 7.48-7.42 (1H, m), 7.25-7.19 (1H, m), 3.87-3.75 (1H, m), 1.90-1.81 (2H, m), 1.80-1.71 (2H, m), 1.67-1.59 (1H, m), 1.41-1.25 (4H, m), 1.22-1.08 (1H, m).	370	Not Detected	
342		¹ H-NMR (DMSO-D ₆) δ: 9.14-9.10 (1H, m), 8.61-8.56 (1H, m), 8.46-8.39 (1H, m), 8.30-8.25 (1H, m), 8.21-8.16 (1H, m), 7.76-7.71 (1H, m), 7.51-7.46 (1H, m), 7.33-7.27 (1H, m), 4.16 (3H, s), 3.85-3.74 (1H, m), 1.91-1.82 (2H, m), 1.81-1.70 (2H, m), 1.67-1.58 (1H, m), 1.39-1.26 (4H, m), 1.22-1.08 (1H, m).	335	Not Detected	
343		¹ H-NMR (DMSO-D ₆) δ: 8.28 (1H, d, J = 7.9 Hz), 8.17-8.15 (1H, m), 7.92-7.88 (1H, m), 7.79-7.75 (2H, m), 7.62-7.58 (1H, m), 6.92 (1H, ddd, J = 9.2, 6.5, 0.9 Hz), 6.79-6.76 (1H, m), 3.83-3.74 (1H, m), 2.67 (3H, s), 1.86-1.73 (4H, m), 1.64-1.60 (1H, m), 1.38-1.23 (4H, m), 1.19-1.09 (1H, m).	352	Not Detected	
344		¹ H-NMR (DMSO-D ₆) δ: 8.26 (1H, d, J = 7.9 Hz), 8.11-8.09 (1H, m), 8.06-8.03 (2H, m), 8.00-7.97 (2H, m), 7.80-7.77 (1H, m), 7.47-7.43 (1H, m), 7.28-7.24 (1H, m), 5.13-5.03 (1H, m), 3.85-3.75 (1H, m), 1.88-1.72 (4H, m), 1.65-1.60 (1H, m), 1.56 (6H, d, J = 6.7 Hz), 1.40-1.27 (4H, m), 1.20-1.10 (1H, m).	362	Not Detected	

[Table 1-44]

270

[1107]

[Table 1-45]

Ex.No.	structural formula	¹ H-NMR (400 MHz)	MS (positive)	MS (negative)	Comments
353		¹ H-NMR (DMSO-D ₆) δ : 9.26 (2H, s), 8.57-8.53 (2H, m), 7.78 (1H, d, J = 8.6 Hz), 7.53-7.49 (1H, m), 7.36-7.32 (1H, m), 4.58 (1H, d, J = 4.4 Hz), 4.21 (3H, s), 3.81-3.72 (1H, m), 3.47-3.39 (1H, m), 1.90-1.87 (4H, m), 1.45-1.35 (2H, m), 1.31-1.23 (2H, m).	352	350	
354		¹ H-NMR (DMSO-D ₆) δ : 9.27 (2H, s), 8.59-8.54 (2H, m), 7.78 (1H, d, J = 8.6 Hz), 7.53-7.49 (1H, m), 7.37-7.33 (1H, m), 4.21 (3H, s), 4.05 (1H, s), 3.79-3.71 (1H, m), 1.99-1.95 (2H, m), 1.88-1.84 (2H, m), 1.38-1.28 (2H, m), 1.24-1.08 (3H, m), 1.06 (6H, s).	394	392	
355		¹ H-NMR (DMSO-D ₆) δ : 9.13 (1H, d, J = 1.6 Hz), 8.40 (1H, dd, J = 8.2, 2.2 Hz), 8.33 (1H, d, J = 8.6 Hz), 8.21 (1H, d, J = 7.2 Hz), 8.05-8.00 (2H, m), 7.03-6.99 (1H, m), 6.83-6.80 (1H, m), 4.56 (1H, d, J = 4.2 Hz), 3.80-3.70 (1H, m), 3.46-3.38 (1H, m), 2.67 (3H, s), 1.88-1.80 (4H, m), 1.53-1.43 (2H, m), 1.32-1.22 (2H, m).	351	Not Detected	
356		¹ H-NMR (DMSO-D ₆) δ : 9.13 (1H, d, J = 1.8 Hz), 8.40 (1H, dd, J = 8.3, 2.3 Hz), 8.34 (1H, d, J = 8.6 Hz), 8.21 (1H, d, J = 7.2 Hz), 8.05 (1H, d, J = 8.3 Hz), 8.03-8.01 (1H, m), 7.03-6.99 (1H, m), 6.83-6.80 (1H, m), 4.04 (1H, s), 3.77-3.68 (1H, m), 2.67 (3H, s), 1.91-1.82 (4H, m), 1.45-1.36 (2H, m), 1.24-1.03 (3H, m), 1.05 (6H, s).	393	Not Detected	
357		¹ H-NMR (DMSO-D ₆) δ : 9.18 (1H, d, J = 0.9 Hz), 8.55-8.52 (1H, m), 8.44 (1H, d, J = 8.8 Hz), 8.14 (1H, d, J = 8.1 Hz), 7.96-7.93 (1H, m), 7.83 (1H, dd, J = 9.1, 4.3 Hz), 7.45-7.40 (1H, m), 4.57 (1H, d, J = 4.4 Hz), 4.17 (3H, s), 3.81-3.73 (1H, m), 3.45-3.38 (1H, m), 1.88-1.80 (4H, m), 1.55-1.44 (2H, m), 1.32-1.22 (2H, m).	369	Not Detected	
358		¹ H-NMR (DMSO-D ₆) δ : 9.18 (1H, d, J = 2.1 Hz), 8.53 (1H, dd, J = 8.0, 2.1 Hz), 8.46 (1H, d, J = 8.6 Hz), 8.18-8.14 (2H, m), 7.67 (1H, dd, J = 9.7, 2.1 Hz), 7.20-7.15 (1H, m), 4.57 (1H, d, J = 4.4 Hz), 4.12 (3H, s), 3.81-3.73 (1H, m), 3.45-3.39 (1H, m), 1.88-1.80 (4H, m), 1.55-1.45 (2H, m), 1.32-1.22 (2H, m).	369	Not Detected	
359		¹ H-NMR (DMSO-D ₆) δ : 9.18 (1H, d, J = 2.1 Hz), 8.53 (1H, dd, J = 8.2, 1.7 Hz), 8.44 (1H, d, J = 8.6 Hz), 8.14 (1H, d, J = 8.2 Hz), 7.97-7.94 (1H, m), 7.83 (1H, dd, J = 9.1, 4.3 Hz), 7.45-7.40 (1H, m), 4.17 (3H, s), 4.04 (1H, s), 3.79-3.71 (1H, m), 1.92-1.83 (4H, m), 1.47-1.37 (2H, m), 1.25-1.01 (3H, m), 1.05 (6H, s).	411	Not Detected	
360		¹ H-NMR (DMSO-D ₆) δ : 9.21 (1H, d, J = 2.2 Hz), 8.54 (1H, dd, J = 8.2, 2.2 Hz), 8.45 (1H, d, J = 9.0 Hz), 8.15 (2H, t, J = 8.2 Hz), 7.81 (1H, d, J = 8.2 Hz), 7.50 (1H, t, J = 8.2 Hz), 7.30 (1H, t, J = 7.1 Hz), 4.56 (2H, q, J = 7.1 Hz), 4.56 (1H, s), 3.80-3.78 (1H, m), 3.45-3.36 (1H, m), 1.88-1.78 (4H, m), 1.54-1.45 (2H, m), 1.47 (3H, t, J = 7.1 Hz), 1.32-1.23 (2H, m).	365	363	

[1108]

[Table 1-46]

Ex.No.	structural formula	¹ H-NMR (400 MHz)	MS (positive)	MS (negative)	Comments
361		¹ H-NMR (DMSO-D ₆) δ: 9.21 (1H, d, J = 2.2 Hz), 8.54 (1H, dd, J = 8.2, 2.2 Hz), 8.46 (1H, d, J = 8.2 Hz), 8.16-8.14 (2H, m), 7.81 (1H, d, J = 9.0 Hz), 7.50 (1H, t, J = 7.5 Hz), 7.30 (1H, t, J = 7.5 Hz), 4.57 (2H, q, J = 7.2 Hz), 4.04 (1H, s), 3.77-3.71 (1H, m), 1.91-1.81 (4H, m), 1.47 (3H, t, J = 7.2 Hz), 1.47-1.38 (2H, m), 1.24-1.10 (3H, m), 1.05 (6H, s).	407	Not Detected	
362		¹ H-NMR (DMSO-D ₆) δ: 9.07 (1H, d, J = 2.1 Hz), 8.49 (1H, d, J = 8.6 Hz), 8.40 (1H, dd, J = 8.1, 2.1 Hz), 8.11 (1H, d, J = 8.1 Hz), 7.41 (1H, t, J = 8.1 Hz), 7.28 (1H, d, J = 8.6 Hz), 6.71 (1H, d, J = 7.6 Hz), 4.56 (1H, d, J = 4.4 Hz), 4.10 (3H, s), 3.90 (3H, s), 3.81-3.74 (1H, m), 3.44-3.38 (1H, m), 1.88-1.80 (4H, m), 1.56 1.45 (2H, m), 1.32 1.23 (2H, m).	381	Not Detected	
363		¹ H-NMR (DMSO-D ₆) δ: 9.20 (1H, d, J = 2.1 Hz), 8.52 (1H, dd, J = 8.2, 2.1 Hz), 8.44 (1H, d, J = 8.6 Hz), 8.15 (1H, d, J = 8.2 Hz), 7.68 (1H, d, J = 9.1 Hz), 7.45 (1H, d, J = 2.3 Hz), 7.16 (1H, dd, J = 9.1, 2.3 Hz), 4.57 (1H, d, J = 4.4 Hz), 4.13 (3H, s), 3.88 (3H, s), 3.81-3.76 (1H, m), 3.45-3.39 (1H, m), 1.88-1.81 (4H, m), 1.54-1.44 (2H, m), 1.32-1.22 (2H, m).	381	Not Detected	
364		¹ H-NMR (DMSO-D ₆) δ: 9.08 (1H, s), 8.51 (1H, d, J = 8.6 Hz), 8.40 (1H, d, J = 8.3 Hz), 8.15 (1H, d, J = 8.1 Hz), 7.61 (1H, d, J = 8.3 Hz), 7.53 7.47 (1H, m), 7.06 (1H, dd, J = 11.6, 7.6 Hz), 4.56 (1H, br s), 4.18 (3H, s), 3.81-3.73 (1H, m), 3.45-3.37 (1H, m), 1.88 1.79 (4H, m), 1.56 1.45 (2H, m), 1.32 1.22 (2H, m).	369	Not Detected	
365		¹ H-NMR (DMSO-D ₆) δ: 9.21 (1H, s), 8.55 (1H, dd, J = 8.1, 2.1 Hz), 8.46 (1H, d, J = 8.7 Hz), 8.17-8.14 (2H, m), 7.77 (1H, d, J = 8.7 Hz), 7.54 7.50 (1H, m), 7.33 7.29 (1H, m), 4.17 (3H, s), 4.04 (1H, s), 3.79-3.70 (1H, m), 1.92-1.83 (4H, m), 1.47-1.38 (2H, m), 1.24 1.05 (3H, m), 1.05 (6H, s).	393	Not Detected	
366		¹ H-NMR (DMSO-D ₆) δ: 9.24 (2H, s), 8.71 (1H, d, J = 4.4 Hz), 8.55 (1H, d, J = 7.9 Hz), 8.38 (1H, d, J = 7.9 Hz), 7.43 (1H, dd, J = 7.9, 4.4 Hz), 4.57 (1H, d, J = 4.2 Hz), 3.83-3.70 (1H, m), 3.49-3.37 (1H, m), 2.63 (3H, s), 1.97-1.82 (4H, m), 1.47-1.17 (4H, m).	353	351	
367		¹ H-NMR (DMSO-D ₆) δ: 9.24 (2H, s), 8.96 (1H, d, J = 8.6 Hz), 8.71 (1H, d, J = 4.4 Hz), 8.54 (1H, d, J = 7.6 Hz), 7.65 (1H, dd, J = 8.6, 4.4 Hz), 4.57 (1H, d, J = 3.9 Hz), 3.83-3.65 (1H, m), 3.51-3.38 (1H, m), 2.66 (3H, s), 1.96-1.82 (4H, m), 1.47-1.19 (4H, m).	353	351	
368		¹ H-NMR (DMSO-D ₆) δ: 9.29 (1H, d, J = 1.1 Hz), 9.23 (1H, dd, J = 2.2, 0.7 Hz), 8.57 (1H, dd, J = 8.2, 2.2 Hz), 8.46 (1H, d, J = 8.6 Hz), 8.39 (1H, d, J = 5.8 Hz), 8.17 (1H, dd, J = 8.2, 0.7 Hz), 8.13 (1H, dd, J = 5.8, 1.1 Hz), 4.57 (1H, d, J = 4.4 Hz), 4.29 (3H, s), 3.83-3.73 (1H, m), 3.46-3.38 (1H, m), 1.89-1.81 (4H, m), 1.55-1.45 (2H, m), 1.33-1.22 (2H, m).	352	Not Detected	

[1109]

[Table 1-47]

Ex.No.	structural formula	¹ H-NMR (400 MHz)	MS (positive)	MS (negative)	Comments
369		¹ H-NMR (DMSO-D ₆) δ: 9.27 (2H, s), 8.58 (1H, d, J = 7.5 Hz), 8.36 (1H, d, J = 7.5 Hz), 7.35-7.26 (2H, m), 4.58 (1H, d, J = 4.5 Hz), 4.33 (3H, s), 3.81-3.73 (1H, m), 3.46-3.39 (1H, m), 1.90-1.87 (4H, m), 1.44-1.35 (2H, m), 1.31-1.23 (2H, m).	370	368	
370		¹ H-NMR (DMSO-D ₆) δ: 9.63-9.61 (1H, br m), 9.00-8.97 (1H, m), 8.71-8.69 (1H, br m), 8.48-8.46 (1H, m), 8.30-8.27 (1H, m), 8.20-8.17 (1H, m), 7.56-7.52 (1H, m), 4.58-4.55 (1H, br m), 4.20 (3H, s), 3.82-3.73 (1H, m), 3.46-3.38 (1H, m), 1.90-1.78 (4H, m), 1.55-1.45 (2H, m), 1.32-1.23 (2H, m).	352	Not Detected	
371		¹ H-NMR (DMSO-D ₆) δ: 9.22 (1H, s), 8.79 (1H, s), 8.63-8.60 (1H, m), 8.46 (1H, d, J = 8.1 Hz), 8.15 (1H, d, J = 8.3 Hz), 7.97 (1H, d, J = 9.0 Hz), 7.84 (1H, d, J = 8.3 Hz), 4.57 (1H, d, J = 4.2 Hz), 4.21 (3H, s), 3.83-3.73 (1H, m), 3.46-3.39 (1H, m), 1.88-1.81 (4H, m), 1.55-1.45 (2H, m), 1.33-1.23 (2H, m).	376	420	
372		¹ H-NMR (DMSO-D ₆) δ: 9.26 (2H, s), 8.56 (1H, d, J = 7.4 Hz), 8.19 (1H, dd, J = 9.4, 2.4 Hz), 7.85 (1H, dd, J = 9.2, 4.4 Hz), 7.43 (1H, td, J = 9.1, 2.3 Hz), 4.57 (1H, d, J = 4.4 Hz), 4.22 (3H, s), 3.82-3.72 (1H, m), 3.46-3.39 (1H, m), 1.90-1.87 (4H, m), 1.44-1.35 (2H, m), 1.31-1.22 (2H, m).	370	368	
373		¹ H-NMR (DMSO-D ₆) δ: 9.25 (2H, s), 8.59 (1H, d, J = 7.9 Hz), 7.61 (1H, d, J = 8.3 Hz), 7.49 (1H, td, J = 8.0, 4.6 Hz), 7.04 (1H, dd, J = 11.0, 7.7 Hz), 4.57 (1H, d, J = 4.4 Hz), 4.20 (3H, s), 3.80-3.72 (1H, m), 3.45-3.39 (1H, m), 1.90-1.87 (4H, m), 1.43-1.35 (2H, m), 1.31-1.22 (2H, m).	370	368	
374		¹ H-NMR (DMSO-D ₆) δ: 9.25 (2H, s), 9.23 (1H, s), 8.65 (1H, d, J = 5.8 Hz), 8.56 (1H, d, J = 7.4 Hz), 8.50 (1H, d, J = 5.8 Hz), 4.57 (1H, d, J = 3.7 Hz), 3.84-3.70 (1H, m), 3.33-3.21 (1H, m), 2.70 (3H, s), 1.93-1.84 (4H, m), 1.46-1.20 (4H, m).	353	351	
375		¹ H-NMR (DMSO-D ₆) δ: 9.45 (1H, d, J = 1.6 Hz), 9.21 (1H, d, J = 2.0 Hz), 8.55 (1H, dd, J = 8.2, 2.0 Hz), 8.41 (1H, d, J = 8.8 Hz), 8.22 (1H, dd, J = 5.0, 1.6 Hz), 8.09 (1H, d, J = 8.2 Hz), 7.67 (1H, d, J = 5.0 Hz), 4.56 (1H, d, J = 4.4 Hz), 3.80-3.72 (1H, m), 3.45-3.38 (1H, m), 2.70 (3H, s), 1.88-1.80 (4H, m), 1.54-1.44 (2H, m), 1.32-1.23 (2H, m).	352	Not Detected	
376		¹ H-NMR (DMSO-D ₆) δ: 9.08 (1H, d, J = 1.6 Hz), 8.53 (1H, d, J = 7.4 Hz), 8.46 (1H, d, J = 8.6 Hz), 8.43 (1H, dd, J = 8.2, 2.2 Hz), 8.13 (1H, d, J = 8.2 Hz), 7.69-7.66 (1H, m), 6.86-6.82 (1H, m), 6.77-6.74 (1H, m), 4.56 (1H, d, J = 4.4 Hz), 3.82-3.72 (1H, m), 3.46-3.37 (1H, m), 2.51 (3H, s), 1.88-1.79 (4H, m), 1.55-1.45 (2H, m), 1.32-1.22 (2H, m).	351	Not Detected	

[1110]

[Table 1-48]

Ex.No.	structural formula	¹ H-NMR (400 MHz)	MS (positive)	MS (negative)	Comments
377		¹ H-NMR (DMSO-D ₆) δ: 9.08 (1H, d, J = 2.2 Hz), 8.54 (1H, d, J = 7.2 Hz), 8.47 (1H, d, J = 8.2 Hz), 8.43 (1H, dd, J = 8.2, 2.2 Hz), 8.13 (1H, d, J = 8.2 Hz), 7.68 (1H, d, J = 9.0 Hz), 6.84 (1H, dd, J = 9.0, 6.2 Hz), 6.78-6.74 (1H, m), 4.04 (1H, s), 3.79-3.70 (1H, m), 2.51 (3H, s), 1.91-1.82 (4H, m), 1.47-1.38 (2H, m), 1.24-1.05 (3H, m), 1.05 (6H, s).	393	Not Detected	
378		¹ H-NMR (DMSO-D ₆) δ: 9.08 (1H, d, J = 1.5 Hz), 8.54 (1H, d, J = 8.2 Hz), 8.43 (1H, d, J = 1.5 Hz), 8.17 (1H, d, J = 7.5 Hz), 7.76 (1H, d, J = 7.5 Hz), 7.49 (1H, t, J = 7.5 Hz), 7.27 (1H, t, J = 7.5 Hz), 4.57 (1H, s), 4.18 (3H, s), 3.79-3.71 (1H, m), 3.46-3.38 (1H, m), 1.89-1.86 (4H, m), 1.43-1.22 (4H, m).	385	383	
379		¹ H-NMR (DMSO-D ₆) δ: 9.09 (1H, d, J = 1.5 Hz), 8.56 (1H, d, J = 8.2 Hz), 8.44 (1H, d, J = 1.5 Hz), 8.17 (1H, d, J = 7.9 Hz), 7.76 (1H, d, J = 7.9 Hz), 7.49 (1H, t, J = 7.9 Hz), 7.28 (1H, t, J = 7.9 Hz), 4.18 (3H, s), 4.04 (1H, s), 3.77-3.68 (1H, m), 1.97-1.84 (4H, m), 1.37-1.09 (5H, m), 1.06 (6H, s).	427	425	
380		¹ H-NMR (DMSO-D ₆) δ: 9.27 (2H, s), 8.58 (1H, d, J = 7.9 Hz), 8.19 (1H, dd, J = 9.5, 2.3 Hz), 7.85 (1H, dd, J = 9.1, 4.3 Hz), 7.43 (1H, td, J = 9.0, 2.5 Hz), 4.22 (3H, s), 4.05 (1H, s), 3.79-3.70 (1H, m), 1.99-1.94 (2H, m), 1.88-1.84 (2H, m), 1.37-1.28 (2H, m), 1.24-1.09 (3H, m), 1.06 (6H, s).	412	410	
381		¹ H-NMR (DMSO-D ₆) δ: 8.35 (1H, d, J = 7.5 Hz), 7.90-7.82 (3H, m), 7.78 (1H, dd, J = 8.2, 3.0 Hz), 7.73 (1H, d, J = 8.2 Hz), 7.48 (1H, t, J = 7.9 Hz), 7.25 (1H, t, J = 7.5 Hz), 4.56 (1H, d, J = 4.5 Hz), 4.15 (3H, s), 3.81-3.69 (1H, m), 3.47-3.38 (1H, m), 1.91-1.80 (4H, br m), 1.46-1.33 (2H, br m), 1.32-1.20 (2H, br m).	368	366	
382		¹ H-NMR (DMSO-D ₆) δ: 8.37 (1H, d, J = 7.5 Hz), 7.91-7.82 (3H, m), 7.78 (1H, dd, J = 8.2, 3.0 Hz), 7.73 (1H, d, J = 9.0 Hz), 7.48 (1H, t, J = 7.9 Hz), 7.25 (1H, t, J = 7.9 Hz), 4.15 (3H, s), 4.04 (1H, s), 3.79-3.68 (1H, m), 1.96-1.80 (4H, br m), 1.39-1.26 (2H, br m), 1.24-1.02 (9H, m).	410	408	
383		¹ H-NMR (DMSO-D ₆) δ: 9.19 (1H, dd, J = 2.2, 0.8 Hz), 8.52 (1H, dd, J = 8.2, 2.2 Hz), 8.43 (1H, d, J = 8.3 Hz), 8.15 (1H, dd, J = 8.2, 0.8 Hz), 7.92 (1H, s), 7.65 (1H, d, J = 8.6 Hz), 7.36-7.33 (1H, m), 4.56 (1H, d, J = 4.4 Hz), 4.13 (3H, s), 3.82-3.72 (1H, m), 3.46-3.38 (1H, m), 2.48 (3H, s), 1.88-1.81 (4H, m), 1.55-1.44 (2H, m), 1.32-1.22 (2H, m).	365	Not Detected	
384		¹ H-NMR (DMSO-D ₆) δ: 9.20 (1H, dd, J = 2.3, 0.7 Hz), 8.53 (1H, dd, J = 8.2, 2.3 Hz), 8.43 (1H, d, J = 8.6 Hz), 8.15 (1H, dd, J = 8.2, 0.7 Hz), 7.93 (1H, s), 7.65 (1H, d, J = 8.6 Hz), 7.36-7.33 (1H, m), 4.13 (3H, s), 4.04 (1H, s), 3.79-3.71 (1H, m), 2.48 (3H, s), 1.93-1.83 (4H, m), 1.47-1.37 (2H, m), 1.24-1.01 (3H, m), 1.05 (6H, s).	407	Not Detected	

[1111]

[Table 1-49]

Ex.No.	structural formula	¹ H-NMR (400 MHz)	MS (positive)	MS (negative)	Comments
385		¹ H-NMR (DMSO-D ₆) δ: 9.49 (1H, d, J = 0.9 Hz), 9.27-9.26 (1H, m), 8.64 (1H, dd, J = 8.2, 2.1 Hz), 8.50-8.48 (2H, m), 8.18 (1H, d, J = 8.2 Hz), 7.79 (1H, dd, J = 6.0, 1.2 Hz), 4.56 (1H, d, J = 4.4 Hz), 4.18 (3H, s), 3.82-3.74 (1H, m), 3.46-3.38 (1H, m), 1.88-1.80 (4H, m), 1.56-1.45 (2H, m), 1.32-1.22 (2H, m).	352	Not Detected	
386		¹ H-NMR (DMSO-D ₆) δ: 9.85-9.83 (1H, m), 9.05-9.05 (1H, m), 8.38 (1H, d, J = 7.6 Hz), 8.26-8.26 (2H, m), 7.77-7.74 (1H, m), 6.99-6.91 (2H, m), 4.56 (1H, d, J = 4.4 Hz), 3.80-3.71 (1H, m), 3.45-3.37 (1H, m), 2.53 (3H, s), 1.90-1.83 (4H, m), 1.44-1.21 (4H, m).	351	349	
387		¹ H-NMR (DMSO-D ₆) δ: 9.85-9.83 (1H, m), 9.06 (1H, t, J = 1.5 Hz), 8.39 (1H, d, J = 8.1 Hz), 8.29-8.24 (2H, m), 7.77-7.74 (1H, m), 6.99-6.91 (2H, m), 4.04 (1H, s), 3.78-3.68 (1H, m), 2.53 (3H, s), 1.95-1.91 (2H, m), 1.87-1.83 (2H, m), 1.37-1.27 (2H, m), 1.23-1.01 (3H, m), 1.05 (6H, s).	393	437	
388		¹ H-NMR (DMSO-D ₆) δ: 8.98 (1H, s), 8.42 (1H, d, J = 8.2 Hz), 8.37 (1H, d, J = 7.5 Hz), 8.14 (1H, s), 7.72 (1H, d, J = 8.2 Hz), 7.47 (1H, t, J = 8.2 Hz), 7.25 (1H, t, J = 8.2 Hz), 4.56 (1H, d, J = 3.7 Hz), 4.16 (3H, s), 3.80-3.71 (1H, m), 3.46-3.37 (1H, m), 2.73 (3H, s), 1.88-1.86 (4H, m), 1.44-1.22 (4H, m).	365	363	
389		¹ H-NMR (DMSO-D ₆) δ: 8.99 (1H, d, J = 1.5 Hz), 8.42 (1H, d, J = 8.2 Hz), 8.39 (1H, d, J = 7.5 Hz), 8.15 (1H, d, J = 1.5 Hz), 7.72 (1H, d, J = 8.2 Hz), 7.47 (1H, t, J = 8.2 Hz), 7.26 (1H, t, J = 8.2 Hz), 4.16 (3H, s), 4.04 (1H, s), 3.78-3.70 (1H, m), 2.73 (3H, s), 1.95-1.84 (4H, m), 1.37-1.09 (5H, m), 1.06 (6H, s).	407	405	
390		¹ H-NMR (DMSO-D ₆) δ: 9.11 (1H, dd, J = 2.3, 0.7 Hz), 8.40 (1H, d, J = 7.9 Hz), 8.27 (1H, dd, J = 8.3, 2.3 Hz), 8.23 (1H, dd, J = 9.5, 2.3 Hz), 8.16 (1H, dd, J = 8.3, 0.7 Hz), 7.81 (1H, dd, J = 9.1, 4.3 Hz), 7.43-7.38 (1H, m), 4.56 (1H, br s), 4.18 (3H, s), 3.80-3.71 (1H, m), 3.44-3.38 (1H, m), 1.89-1.84 (4H, m), 1.45-1.34 (2H, m), 1.31-1.21 (2H, m).	369	413	
391		¹ H-NMR (DMSO-D ₆) δ: 9.01 (1H, s), 8.48 (1H, d, J = 7.5 Hz), 8.44 (1H, d, J = 8.2 Hz), 8.20 (1H, d, J = 11.2 Hz), 7.76 (1H, d, J = 7.5 Hz), 7.50 (1H, t, J = 7.5 Hz), 7.30 (1H, t, J = 7.5 Hz), 4.57 (1H, d, J = 4.5 Hz), 4.18 (3H, s), 3.80-3.72 (1H, m), 3.45-3.37 (1H, m), 1.89-1.86 (4H, m), 1.44-1.22 (4H, m).	369	367	
392		¹ H-NMR (DMSO-D ₆) δ: 9.02 (1H, s), 8.50 (1H, d, J = 7.5 Hz), 8.44 (1H, d, J = 8.2 Hz), 8.22 (1H, d, J = 12.0 Hz), 7.77 (1H, d, J = 7.5 Hz), 7.50 (1H, t, J = 7.5 Hz), 7.31 (1H, t, J = 7.5 Hz), 4.18 (3H, s), 4.05 (1H, s), 3.78-3.70 (1H, m), 1.96-1.84 (4H, m), 1.37-1.10 (5H, m), 1.06 (6H, s).	411	409	

[1112]

[Table 1-50]

Ex.No.	structural formula	¹ H-NMR (400 MHz)	MS (positive)	MS (negative)	Comments
393		¹ H-NMR (DMSO-D ₆) δ: 9.12 (1H, dd, J = 2.3, 0.8 Hz), 8.42 (1H, d, J = 7.9 Hz), 8.28 (1H, dd, J = 8.3, 2.3 Hz), 8.24 (1H, dd, J = 9.4, 2.3 Hz), 8.17 (1H, dd, J = 8.3, 0.7 Hz), 7.81 (1H, dd, J = 9.1, 4.3 Hz), 7.43-7.38 (1H, m), 4.18 (3H, s), 4.04 (1H, br s), 3.79-3.69 (1H, m), 1.96-1.92 (2H, m), 1.87-1.83 (2H, m), 1.38-1.27 (2H, m), 1.24-1.02 (3H, m), 1.06 (6H, s).	411	455	
394		¹ H-NMR (DMSO-D ₆) δ: 8.36 (1H, d, J = 7.5 Hz), 7.91-7.78 (4H, m), 7.53-7.48 (1H, br m), 7.40 (1H, td, J = 9.0, 2.2 Hz), 4.56 (1H, d, J = 4.5 Hz), 4.16 (3H, s), 3.80-3.69 (1H, m), 3.46-3.36 (1H, m), 1.91-1.80 (4H, br m), 1.46-1.33 (2H, br m), 1.32-1.20 (2H, br m).	386	384	
395		¹ H-NMR (DMSO-D ₆) δ: 8.37 (1H, d, J = 8.2 Hz), 7.91-7.78 (4H, m), 7.53-7.48 (1H, br m), 7.40 (1H, td, J = 9.7, 2.2 Hz), 4.16 (3H, s), 4.04 (1H, s), 3.79-3.67 (1H, br m), 1.97-1.80 (4H, br m), 1.39-1.26 (2H, br m), 1.23-1.02 (9H, br m).	428	426	
396		¹ H-NMR (DMSO-D ₆) δ: 8.43 (1H, d, J = 7.6 Hz), 7.90-7.79 (4H, m), 7.50 (1H, dt, J = 9.3, 2.7 Hz), 7.40 (1H, td, J = 9.1, 2.5 Hz), 4.16 (3H, s), 3.89-3.78 (1H, m), 2.70 (1H, t, J = 11.6, 3.5 Hz), 2.12-2.04 (2H, br m), 1.93-1.86 (2H, br m), 1.70-1.58 (2H, br m), 1.46-1.35 (2H, br m).	395	393	
397		¹ H-NMR (DMSO-D ₆) δ: 8.42 (1H, d, J = 7.9 Hz), 7.91-7.78 (4H, m), 7.51 (1H, dt, J = 9.6, 2.6 Hz), 7.40 (1H, td, J = 9.1, 2.4 Hz), 4.16 (3H, s), 3.82-3.71 (1H, m), 3.09 (2H, d, J = 6.2 Hz), 2.99 (3H, s), 2.03-1.95 (2H, br m), 1.94-1.84 (3H, br m), 1.47-1.35 (2H, br m), 1.28-1.16 (2H, br m).	462	460	
398		¹ H-NMR (DMSO-D ₆) δ: 8.39 (1H, d, J = 7.5 Hz), 7.91-7.78 (4H, m), 7.53-7.47 (1H, br m), 7.40 (1H, td, J = 9.0, 1.5 Hz), 4.16 (3H, s), 3.83-3.74 (2H, m), 3.43-3.34 (1H, m), 3.14-3.00 (4H, m), 2.10-1.95 (6H, br m), 1.93-1.85 (2H, br m), 1.48-1.36 (2H, br m), 1.35-1.23 (2H, br m).	518	516	
399		¹ H-NMR (DMSO-D ₆) δ: 8.33 (1H, d, J = 7.9 Hz), 7.91-7.77 (4H, m), 7.50 (1H, dt, J = 9.5, 2.8 Hz), 7.40 (1H, td, J = 9.1, 2.5 Hz), 4.35 (2H, s), 4.24 (2H, s), 4.16 (3H, s), 3.83-3.71 (1H, m), 2.14-2.05 (2H, br m), 1.82-1.73 (2H, br m), 1.58-1.47 (2H, br m), 1.40-1.28 (2H, br m).	412	410	
400		¹ H-NMR (DMSO-D ₆) δ: 8.41 (1H, d, J = 7.9 Hz), 7.91-7.78 (4H, m), 7.50 (1H, dt, J = 9.5, 2.6 Hz), 7.40 (1H, td, J = 9.1, 2.4 Hz), 6.73 (1H, t, J = 76.6 Hz), 4.16 (3H, s), 4.10-4.02 (1H, m), 3.87-3.77 (1H, m), 2.07-1.99 (2H, br m), 1.96-1.88 (2H, br m), 1.57-1.40 (4H, br m).	436	434	

[1113]

[Table 1-51]

Ex.No.	structural formula	¹ H-NMR (400 MHz)	MS (positive)	MS (negative)	Comments
401		¹ H-NMR (DMSO-D ₆) δ : 8.72 (1H, d, J = 7.5 Hz), 7.92-7.78 (4H, m), 7.54-7.48 (1H, br m), 7.40 (1H, td, J = 9.0, 1.5 Hz), 4.60 (1H, t, J = 5.2 Hz), 4.48 (1H, t, J = 5.2 Hz), 4.43-4.31 (1H, m), 4.16 (3H, s), 3.45 (2H, d, J = 5.2 Hz), 3.38 (2H, d, J = 5.2 Hz), 2.09 (2H, t, J = 10.5 Hz), 1.90 (2H, t, J = 10.1 Hz).	402	400	
402		¹ H-NMR (DMSO-D ₆) δ : 8.36 (1H, d, J = 7.5 Hz), 7.83-7.76 (2H, m), 7.71 (1H, t, J = 7.5 Hz), 7.58 (1H, d, J = 9.0 Hz), 7.51-7.43 (1H, m), 6.97 (1H, dd, J = 10.8, 7.9 Hz), 4.56 (1H, d, J = 4.5 Hz), 4.15 (3H, s), 3.80-3.69 (1H, m), 3.47-3.36 (1H, m), 1.92-1.80 (4H, br m), 1.45-1.33 (2H, br m), 1.32-1.20 (2H, br m).	386	Not Detected	
403		¹ H-NMR (DMSO-D ₆) δ : 8.38 (1H, d, J = 8.2 Hz), 7.85-7.77 (2H, m), 7.71 (1H, t, J = 7.5 Hz), 7.58 (1H, d, J = 8.2 Hz), 7.51-7.43 (1H, m), 6.97 (1H, dd, J = 11.2, 7.5 Hz), 4.15 (3H, s), 4.04 (1H, s), 3.78-3.66 (1H, m), 1.97-1.80 (4H, br m), 1.39-1.26 (2H, br m), 1.22-1.02 (9H, br m).	428	426	
404		¹ H-NMR (DMSO-D ₆) δ : 8.37 (1H, d, J = 7.5 Hz), 7.79 (1H, dd, J = 8.2, 2.2 Hz), 7.75 (1H, d, J = 9.0 Hz), 7.66 (1H, t, J = 7.1 Hz), 7.52-7.44 (2H, m), 7.27 (1H, t, J = 7.5 Hz), 4.56 (1H, d, J = 4.5 Hz), 4.16 (3H, s), 3.76-3.66 (1H, m), 3.46-3.37 (1H, m), 1.91-1.82 (4H, br m), 1.38-1.21 (4H, m).	386	384	
405		¹ H-NMR (DMSO-D ₆) δ : 8.37 (1H, d, J = 7.5 Hz), 7.80 (1H, dd, J = 8.2, 3.0 Hz), 7.75 (1H, d, J = 8.2 Hz), 7.66 (1H, t, J = 7.1 Hz), 7.53-7.44 (2H, m), 7.27 (1H, t, J = 7.5 Hz), 4.16 (3H, s), 4.04 (1H, s), 3.74-3.63 (1H, m), 1.99-1.90 (2H, br m), 1.88-1.80 (2H, br m), 1.33-1.21 (2H, br m), 1.20-1.01 (9H, br m).	428	426	
406		¹ H-NMR (DMSO-D ₆) δ : 8.29 (1H, d, J = 8.2 Hz), 7.78 (1H, dd, J = 8.2, 3.0 Hz), 7.75 (1H, d, J = 9.0 Hz), 7.64 (1H, dd, J = 10.1, 5.6 Hz), 7.56 (1H, dd, J = 10.5, 6.0 Hz), 7.49 (1H, t, J = 7.9 Hz), 7.26 (1H, t, J = 7.9 Hz), 4.56 (1H, d, J = 4.5 Hz), 4.16 (3H, s), 3.76-3.65 (1H, m), 3.46-3.36 (1H, m), 1.91-1.81 (4H, br m), 1.41-1.19 (4H, m).	386	384	
407		¹ H-NMR (DMSO-D ₆) δ : 8.30 (1H, d, J = 8.2 Hz), 7.79 (1H, dd, J = 8.2, 3.7 Hz), 7.75 (1H, d, J = 8.2 Hz), 7.65 (1H, dd, J = 10.1, 5.6 Hz), 7.57 (1H, dd, J = 10.5, 6.0 Hz), 7.49 (1H, t, J = 7.9 Hz), 7.26 (1H, t, J = 7.5 Hz), 4.16 (3H, s), 4.04 (1H, s), 3.74-3.62 (1H, m), 1.99-1.90 (2H, br m), 1.88-1.79 (2H, br m), 1.33-1.21 (2H, br m), 1.19-1.03 (9H, br m).	428	426	
408		¹ H-NMR (DMSO-D ₆) δ : 8.38 (1H, d, J = 7.9 Hz), 7.91 (1H, dd, J = 7.2, 4.4 Hz), 7.87-7.85 (2H, m), 7.80-7.76 (1H, m), 7.66-7.63 (1H, m), 6.83-6.79 (1H, m), 6.72-6.69 (1H, m), 4.56 (1H, d, J = 4.4 Hz), 3.80-3.70 (1H, m), 3.45-3.37 (1H, m), 2.50 (3H, s), 1.89-1.82 (4H, m), 1.45-1.35 (2H, m), 1.31-1.20 (2H, m).	368	412	

[1114]

[Table 1-52]

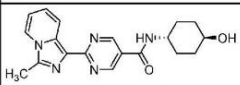
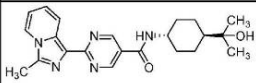
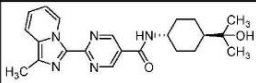
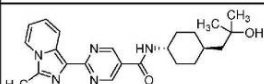
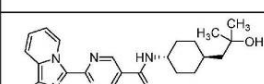
Ex.No.	structural formula	¹ H-NMR (400 MHz)	MS (positive)	MS (negative)	Comments
409		¹ H-NMR (DMSO-D ₆) δ: 8.40 (1H, d, J = 7.9 Hz), 7.92-7.89 (1H, m), 7.88-7.85 (2H, m), 7.80-7.76 (1H, m), 7.66-7.63 (1H, m), 6.81 (1H, dd, J = 9.2, 6.2 Hz), 6.72-6.69 (1H, m), 4.04 (1H, s), 3.78-3.68 (1H, m), 2.50 (3H, s), 1.94-1.90 (2H, m), 1.87-1.83 (2H, m), 1.38-1.04 (5H, m), 1.05 (6H, s).	410	454	
410		¹ H-NMR (DMSO-D ₆) δ: 8.04 (1H, d, J = 7.5 Hz), 7.78 (1H, d, J = 5.2 Hz), 7.73 (1H, d, J = 8.2 Hz), 7.63 (1H, d, J = 11.2 Hz), 7.48 (1H, t, J = 7.5 Hz), 7.41 (1H, d, J = 6.0 Hz), 7.24 (1H, t, J = 7.5 Hz), 4.56 (1H, d, J = 3.7 Hz), 4.16 (3H, s), 3.94 (3H, s), 3.79-3.68 (1H, m), 3.48-3.39 (1H, m), 1.93-1.80 (4H, br m), 1.42-1.20 (4H, br m).	398	442	
411		¹ H-NMR (DMSO-D ₆) δ: 8.03 (1H, d, J = 8.2 Hz), 7.78 (1H, dd, J = 8.2, 3.0 Hz), 7.73 (1H, d, J = 9.0 Hz), 7.63 (1H, d, J = 11.2 Hz), 7.48 (1H, t, J = 7.9 Hz), 7.41 (1H, d, J = 6.0 Hz), 7.24 (1H, t, J = 7.5 Hz), 4.16 (3H, s), 4.04 (1H, s), 3.95 (3H, s), 3.74-3.64 (1H, m), 2.01-1.92 (2H, br m), 1.88-1.79 (2H, br m), 1.33-1.02 (11H, m).	440	484	
412		¹ H-NMR (DMSO-D ₆) δ: 8.43 (1H, d, J = 7.5 Hz), 7.75 (3H, d, J = 8.2 Hz), 7.59 (1H, d, J = 8.2 Hz), 7.49 (1H, t, J = 7.5 Hz), 7.23 (1H, t, J = 7.5 Hz), 4.57 (1H, d, J = 3.7 Hz), 4.16 (3H, s), 3.80-3.69 (1H, m), 3.46-3.36 (1H, m), 1.93-1.81 (4H, br m), 1.46-1.33 (2H, br m), 1.32-1.20 (2H, br m).	386	384	
413		¹ H-NMR (DMSO-D ₆) δ: 8.45 (1H, d, J = 7.5 Hz), 7.76 (3H, d, J = 9.0 Hz), 7.59 (1H, d, J = 8.2 Hz), 7.49 (1H, t, J = 7.9 Hz), 7.23 (1H, t, J = 7.5 Hz), 4.16 (3H, s), 4.05 (1H, s), 3.78-3.67 (1H, m), 1.98-1.89 (2H, br m), 1.89-1.81 (2H, br m), 1.39-1.26 (2H, br m), 1.24-1.01 (9H, br m).	428	426	
414		¹ H-NMR (DMSO-D ₆) δ: 8.25 (1H, d, J = 7.9 Hz), 7.64 (2H, t, J = 8.3 Hz), 7.60-7.52 (3H, m), 7.41 (1H, t, J = 7.7 Hz), 7.15 (1H, t, J = 7.5 Hz), 4.56 (1H, d, J = 4.4 Hz), 4.10 (3H, s), 3.86 (3H, s), 3.82-3.72 (1H, m), 3.47-3.36 (1H, m), 1.92-1.81 (4H, br m), 1.48-1.35 (2H, br m), 1.33-1.21 (2H, br m).	380	378	
415		¹ H-NMR (DMSO-D ₆) δ: 8.27 (1H, d, J = 8.1 Hz), 7.64 (2H, t, J = 7.9 Hz), 7.61-7.53 (3H, m), 7.44-7.39 (1H, m), 7.18-7.12 (1H, m), 4.10 (3H, s), 4.04 (1H, s), 3.86 (3H, s), 3.81-3.70 (1H, m), 1.97-1.89 (2H, br m), 1.89-1.82 (2H, br m), 1.42-1.28 (2H, br m), 1.25-1.03 (9H, br m).	422	420	
416		¹ H-NMR (DMSO-D ₆) δ: 8.49 (1H, d, J = 8.2 Hz), 7.92-7.79 (4H, m), 7.51 (1H, d, J = 9.0 Hz), 7.41 (1H, t, J = 9.0 Hz), 4.17 (3H, s), 3.92-3.81 (1H, m), 2.95-2.86 (1H, m), 2.47 (3H, s), 2.18-2.09 (2H, br m), 2.04-1.96 (2H, br m), 1.69-1.46 (4H, m).	452	450	

[Table 1-53]

279

[1116]

[Table 1-54]

Ex.No.	structural formula	¹ H-NMR (400 MHz)	MS (positive)	MS (negative)	Comments
425		¹ H-NMR (DMSO-D ₆) δ: 9.11 (2H, s), 8.50 (1H, d, J = 9.1 Hz), 8.41 (1H, d, J = 7.6 Hz), 8.31 (1H, d, J = 7.2 Hz), 7.19 (1H, dd, J = 9.1, 6.5 Hz), 6.95-6.91 (1H, m), 4.57 (1H, d, J = 4.4 Hz), 3.79-3.70 (1H, m), 3.46-3.37 (1H, m), 2.68 (3H, s), 1.90-1.83 (4H, m), 1.43-1.21 (4H, m).	352	396	
426		¹ H-NMR (DMSO-D ₆) δ: 9.13 (2H, s), 8.51 (1H, d, J = 8.8 Hz), 8.44 (1H, d, J = 7.9 Hz), 8.32 (1H, d, J = 6.7 Hz), 7.23-7.19 (1H, m), 6.97-6.93 (1H, m), 4.04 (1H, br s), 3.78-3.68 (1H, m), 2.70 (3H, s), 1.97-1.91 (2H, m), 1.88-1.82 (2H, m), 1.36-1.09 (5H, m), 1.05 (6H, s).	394	438	
427		¹ H-NMR (DMSO-D ₆) δ: 9.79 (1H, d, J = 6.9 Hz), 9.23 (2H, s), 8.54 (1H, d, J = 7.9 Hz), 7.83 (1H, d, J = 8.8 Hz), 7.11-7.02 (2H, m), 4.05 (1H, s), 3.79-3.69 (1H, m), 2.55 (3H, s), 1.98-1.94 (2H, m), 1.89-1.83 (2H, m), 1.37-1.23 (2H, m), 1.24-1.02 (3H, m), 1.06 (6H, s).	394	392	
428		¹ H-NMR (DMSO-D ₆) δ: 9.11 (2H, s), 8.52-8.49 (1H, m), 8.41 (1H, d, J = 7.9 Hz), 8.31 (1H, d, J = 7.2 Hz), 7.21-7.17 (1H, m), 6.95-6.91 (1H, m), 4.04 (1H, s), 3.78-3.68 (1H, m), 2.69 (3H, s), 1.90-1.84 (4H, m), 1.46-1.26 (3H, m), 1.29 (2H, d, J = 5.3 Hz), 1.11 (6H, s), 1.14-0.95 (2H, m).	408	452	
429		¹ H-NMR (DMSO-D ₆) δ: 9.79 (1H, d, J = 6.9 Hz), 9.22 (2H, s), 8.53 (1H, d, J = 7.6 Hz), 7.83 (1H, d, J = 8.8 Hz), 7.11-7.01 (2H, m), 4.04 (1H, s), 3.79-3.70 (1H, m), 2.55 (3H, s), 1.90-1.85 (4H, m), 1.46-1.23 (3H, m), 1.29 (2H, d, J = 5.1 Hz), 1.11 (6H, s), 1.14-1.00 (2H, m).	408	406	

[1117]

5 Experimental Example 1: Measurement of human H-PGDS binding inhibitory activity

The H-PGDS binding inhibitory activity of the test compound was measured by AlphaLISA antagonistic assay. A specific protocol is as follows.

- 10 In an AlphaPlate-384 Shallow well plate (Cat. 6008350, PerkinElmer) were added and mixed 240 nL/well of DMSO solution as a compound solution or a solvent control, 3 μL/well (final concentration: 45 nmol/L) of biotinylated H-PGDS inhibitor (see below for the production method) diluted with 2%(v/v) DMSO-
- 15 containing Assay Buffer (50 mM HEPES-NaOH (pH 7.5), 2 mM GSH, 150 mM NaCl, 2 mM MgCl₂, 0.005% Surfactant P20), and 2 μL/well (final concentration: 0.3 nmol/L) of His-tagged human H-PGDS (Cat. ATGP1557, ATgen) diluted with Assay Buffer. As a blank, 2 μL/well of Assay Buffer was added instead of His-tagged human

H-PGDS. This plate was allowed to stand at room temperature for 60 min, and Nickel Chelate AlphaLISA Acceptor Beads (Cat. AL108C, Perkin Elmer) at 5 µL/well (final concentration: 20 µg/mL) were added and mixed. After allowing to stand at room temperature for 30 min under shading, AlphaScreen Streptavidin donor beads (Cat. 6760002S, Perkin Elmer) were added at 5 µL/well (final concentration: 30 µg/mL) and mixed. After allowing to stand at room temperature for 60 min under shading, AlphaLISA signals (excitation wavelength: 680 nm, measurement wavelength: 615 nm) were measured using Enspire (Perkin Elmer).

The H-PGDS binding inhibitory activity (inhibitory rate) of each test compound was calculated as follows, and the IC₅₀ value was calculated from the inhibitory rate at two concentrations sandwiching 50%.

[1118]

$$\text{inhibitory rate (\%)} = \left(1 - \frac{\text{fluorescence of test compound well} - \text{fluorescence of blank well}}{\text{fluorescence of solvent control well} - \text{fluorescence of blank well}} \right) \times 100$$

[1119]

The results of human H-PGDS binding inhibitory activity are shown in the following Table 2.

[1120]

[Table 2-1]

Example No.	human H-PGDS binding inhibitor activity IC ₅₀ (nM)	Example No.	human H-PGDS binding inhibitor activity IC ₅₀ (nM)	Example No.	human H-PGDS binding inhibitor activity IC ₅₀ (nM)
1	3	41	374	81	32
2	30	42	200	82	359
3	21	43	15	83	9%*
4	5	44	541	84	418
5	60	45	85	85	48%*
6	3	46	10	86	9%*
7	11	47	25%*	87	8%*
8	6	48	423	88	497
9	13	49	589	89	373
10	6	50	74	90	6%*
11	171	51	155	91	39%*
12	31	52	36%*	92	42%*
13	578	53	322	93	280
14	159	54	41	94	871
15	12	55	3	95	144
16	372	56	54	96	490
17	27	57	372	97	33
18	45	58	172	98	2
19	4	59	68	99	487
20	11%*	60	503	100	74
21	885	61	491	101	328
22	129	62	319	102	55
23	53	63	152	103	473
24	3	64	827	104	15%*
25	973	65	289	105	5
26	166	66	42%*	106	131
27	225	67	18%*	107	21%*
28	13	68	8%*	108	10%*
29	262	69	27	109	492
30	49	70	3	110	37%*
31	167	71	29	111	222
32	19	72	3	112	481
33	415	73	9%*	113	42
34	42%*	74	7%*	114	113
35	33	75	22%*	115	138
36	772	76	7%*	116	33
37	684	77	32%*	117	39%*
38	81	78	15	118	31
39	71	79	54	119	244
40	7	80	17	120	15

*Inhibition rate (%) at 1000 nM

[1121]

[Table 2-2]

Example No.	human H-PGDS binding inhibitor activity IC ₅₀ (nM)	Example No.	human H-PGDS binding inhibitor activity IC ₅₀ (nM)	Example No.	human H-PGDS binding inhibitor activity IC ₅₀ (nM)
121	6	161	30	201	19
122	16	162	81	202	53
123	4	163	41%**	203	13
124	8	164	25%**	204	14
125	14	165	48	205	8
126	19	166	22%**	206	37
127	10	167	30%**	207	18
128	5	168	12	208	26
129	17	169	7	209	10
130	8	170	4	210	23
131	33	171	47	211	22
132	6	172	3	212	47%**
133	96	173	14	213	42
134	19	174	19	214	40
135	6	175	32	215	37
136	48	176	4	216	31
137	33	177	8	217	373
138	18	178	60	218	405
139	7	179	11	219	421
140	25	180	52	220	596
141	6	181	26	221	69
142	16	182	36	222	17
143	24	183	6	223	10
144	41	184	5	224	12
145	10	185	236	225	7
146	50	186	19	226	34
147	258	187	22	227	34
148	349	188	15	228	3
149	19	189	6	229	3
150	14	190	21	230	25%**
151	10	191	11	231	62
152	46	192	2	232	29
153	18	193	3	233	10
154	72	194	3	234	8
155	31	195	11	235	41%**
156	17	196	14	236	53
157	544	197	19	237	5
158	155	198	13	238	81
159	26	199	8	239	19
160	20	200	16	240	33

**Inhibition rate (%) at 100 nM

[1122]

[Table 2-3]

Example No.	human H-PGDS binding inhibitor activity IC ₅₀ (nM)	Example No.	human H-PGDS binding inhibitor activity IC ₅₀ (nM)	Example No.	human H-PGDS binding inhibitor activity IC ₅₀ (nM)
241	2	281	15	321	143
242	49%**	282	17	322	335
243	88	283	9	323	32
244	17	284	11	324	21%*
245	12	285	12	325	30%*
246	13	286	8	326	22%*
247	5	287	12	327	146
248	4	288	7	328	417
249	3	289	9	329	34
250	19	290	3	330	289
251	6	291	8	331	352
252	5	292	5	332	7
253	2	293	43	333	66
254	14	294	67	334	186
255	7	295	7	335	15
256	22	296	60	336	39%**
257	27	297	51%***	337	46%*
258	36	298	31	338	36%*
259	17	299	14	339	48%*
260	11	300	57	340	46%*
261	63	301	41	341	25%*
262	10	302	28	342	207
263	26	303	13	343	145
264	27	304	9	344	23%*
265	13	305	7	345	32%*
266	3	306	12	346	26
267	16	307	8	347	100
268	3	308	6	348	585
269	9	309	20	349	63
270	38	310	7	350	546
271	13	311	11	351	39
272	9	312	13	352	39
273	5	313	19	353	136
274	5	314	14	354	13
275	7	315	5	355	589
276	36	316	60	356	51
277	4	317	176	357	478
278	10	318	56	358	14%*
279	8	319	30	359	50
280	20	320	10	360	32%*

*Inhibition rate (%) at 1000 nM; **Inhibition rate (%) at 100 nM; ***Inhibition rate (%) at 3 nM

[1123]

[Table 2-4]

Example No.	human H-PGDS binding inhibitory activity IC ₅₀ (nM)	Example No.	human H-PGDS binding inhibitory activity IC ₅₀ (nM)
361	293	401	453
362	13%*	402	510
363	13%*	403	101
364	413	404	37%*
365	39	405	338
366	19%*	406	33%*
367	45%*	407	443
368	8%*	408	510
369	520	409	107
370	21%*	410	16%*
371	11%*	411	21%*
372	50	412	506
373	957	413	152
374	43%*	414	12%*
375	4%*	415	13%*
376	556	416	144
377	57	417	150
378	589	418	325
379	75	419	109
380	3	420	401
381	238	421	238
382	25	422	267
383	25%*	423	461
384	386	424	16%*
385	7%*	425	31%**
386	56	426	27
387	6	427	7
388	19%*	428	25
389	663	429	6
390	308		
391	142		
392	6		
393	46		
394	181		
395	23		
396	129		
397	51		
398	37		
399	93		
400	56		

*Inhibition rate (%) at 1000 nM; **Inhibition rate (%) at 100 nM

[1124]

Production of biotinylated H-PGDS inhibitor

The biotinylated H-PGDS inhibitor used in Experimental Example 1 was produced by biotinylating the H-PGDS inhibitor produced by the following steps. The H-PGDS inhibitor subjected to biotinylation may be any of enantiomers A and B described later, and enantiomer B was used in this Experimental Example.

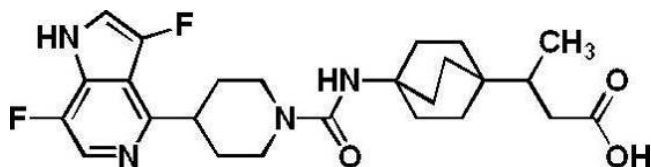
[1125]

10 Production of H-PGDS inhibitor (3-{4-[4-(3,7-difluoro-1H-pyrrolo[3,2-c]pyridin-4-yl)piperidine-1-carboxamido]bicyclo[2.2.2]octan-1-yl}butyric acid)

[1126]

The title compound represented by the following formula:

15 [1127]



[1128]

has an asymmetric carbon at the β -position of the carboxy group.

In this Production Example, asymmetric reduction is performed using a chiral phosphine ligand in the following step 10A or step 10B. A compound obtained using R-Sp form as the chiral phosphine ligand is referred to as enantiomer A, and a compound obtained using S-Rp form is referred to as enantiomer B.

25 [1129]

Step 1: tert-Butyl 4-(7-fluoro-1H-pyrrolo [3,2-c]pyridin-4-yl)-3,6-dihydropyridine-1(2H)-carboxylate

[1130]



30 [1131]

Under an argon atmosphere, to a solution of 4-bromo-7-

fluoro-1H-pyrrolo[3,2-c]pyridine (4.5 g) and tert-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate (9.6 g) in toluene/ethanol (42 mL, toluene/ethanol=2.5/1) were added 2 M aqueous sodium carbonate solution (21 mL) and [1,1'-bis(di-tert-butylphosphino)ferrocene]palladium(II) dichloride-dichloromethane adduct (1.7 g) at room temperature, and the mixture was stirred at 100°C overnight. The reaction mixture was filtered through celite, and water and ethyl acetate were added thereto. After partitioning, the organic layer was washed with saturated brine. The organic layer was dried over sodium sulfate, sodium sulfate was removed by filtration, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluent: n-hexane/ethyl acetate=70/30 to 35/65) to give the title compound (6.3 g).

¹H-NMR (DMSO-D₆) δ: 1.44 (9H, s), 2.68-2.71 (2H, m), 3.54-3.58 (2H, m), 4.08-4.11 (2H, m), 6.49-6.51 (1H, m), 6.86-6.88 (1H, m), 7.55-7.57 (1H, m), 8.10 (1H, d, J = 2.1 Hz), 12.20 (1H, br s).

[1132]

Step 2: tert-Butyl 4-(7-fluoro-1H-pyrrolo[3,2-c]pyridin-4-yl)piperidine-1-carboxylate

[1133]



[1134]

To a solution of tert-butyl 4-(7-fluoro-1H-pyrrolo[3,2-c]pyridin-4-yl)-3,6-dihydropyridine-1(2H)-carboxylate (6.3 g) in tetrahydrofuran/methanol (63 mL, tetrahydrofuran/methanol=1/1) was added 10% palladium-carbon (1.3 g) at room temperature, and the mixture was stirred overnight under 1 atm hydrogen atmosphere. The reaction mixture was filtered through celite, and the filtrate was

concentrated under reduced pressure to give the title compound (6.3 g).

¹H-NMR (DMSO-D₆) δ: 1.42 (9H, s), 1.70-1.80 (4H, m), 2.83-2.99 (2H, m), 3.26-3.36 (1H, m), 4.04-4.10 (2H, m), 6.75-6.77 (1H, m), 7.49-7.51 (1H, m), 8.03 (1H, d, J = 2.7 Hz), 12.09 (1H, br s).

[1135]

Step 3: tert-Butyl 4-(3,7-difluoro-1H-pyrrolo[3,2-c]pyridin-4-yl)piperidine-1-carboxylate

10 [1136]



[1137]

Under an argon atmosphere, to a suspension of tert-butyl 4-(7-fluoro-1H-pyrrolo[3,2-c]pyridin-4-yl)piperidine-1-carboxylate (3.3 g) in acetonitrile (33 mL) was added acetic acid (6.6 mL) at room temperature. To the reaction mixture was added N-fluoro-N'-(chloromethyl)triethylenediamine bis(tetrafluoroborate) (5.5 g) in several divided portions at room temperature, and the mixture was stirred for 2 hr. The reaction mixture was added dropwise to saturated aqueous sodium hydrogen carbonate solution (120 mL) over 10 min at room temperature. To the reaction mixture was added sodium dithionite (2.5 g) at room temperature, and the mixture was stirred for 30 min. To the reaction mixture was added ethyl acetate and, after partitioning, the organic layer was washed with saturated brine. The organic layer was dried over sodium sulfate, sodium sulfate was removed by filtration, and the filtrate was concentrated under reduced pressure. The residue was purified twice by silica gel column chromatography (eluent: n-hexane/ethyl acetate=80/20 to 50/50) to give the title compound (0.99 g).

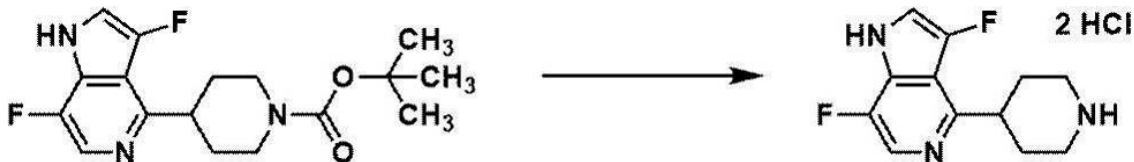
25 ¹H-NMR (CDCl₃) δ: 1.48 (9H, s), 1.87-1.97 (4H, m), 2.84-2.94 (2H, m), 3.35-3.43 (1H, m), 4.22-4.34 (2H, m), 7.06 (1H, t, J =

2.8 Hz), 8.11 (1H, d, J = 2.7 Hz), 8.22 (1H, br s).

[1138]

Step 4: 3,7-Difluoro-4-(piperidin-4-yl)-1H-pyrrolo[3,2-c]pyridine dihydrochloride

5 [1139]



[1140]

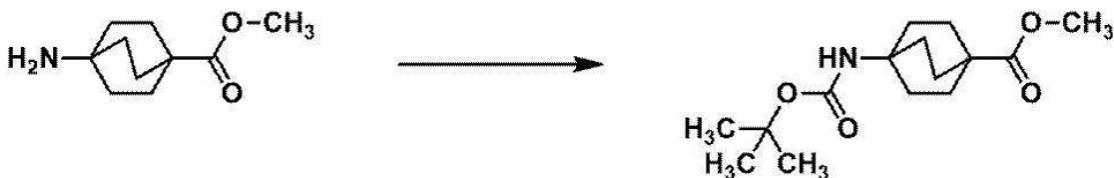
To a solution of tert-butyl 4-(3,7-difluoro-1H-pyrrolo[3,2-c]pyridin-4-yl)piperidine-1-carboxylate (0.99 g) in
10 ethyl acetate (5.0 mL) was added 4 M hydrogen chloride/ethyl acetate (9.9 mL) solution at room temperature, and the mixture was stirred for 3 hr. To the reaction mixture was added ethyl acetate (5.0 mL) at room temperature, and the mixture was stirred for 1 hr. The precipitated solid was collected by
15 filtration and dried under reduced pressure to give the title compound (0.78 g).

¹H-NMR (DMSO-D₆) δ: 1.99-2.20 (4H, m), 3.04-3.13 (2H, m), 3.37-3.43 (2H, m), 3.53-3.60 (1H, m), 7.76 (1H, s), 8.27 (1H, s), 8.80 (1H, br s), 9.05 (1H, br s), 12.56 (1H, br s).

20 [1141]

Step 5: Methyl 4-[(tert-butoxycarbonyl)amino]bicyclo[2.2.2]octane-1-carboxylate

[1142]



25 [1143]

To a suspension of methyl 4-aminobicyclo[2.2.2]octane-1-carboxylate (25 g) and triethylamine (23 mL) in tetrahydrofuran (250 mL) was added di-tert-butyl bicarbonate (38 mL) at room temperature, and the mixture was stirred for 15 hr. The
30 reaction mixture was concentrated under reduced pressure, and

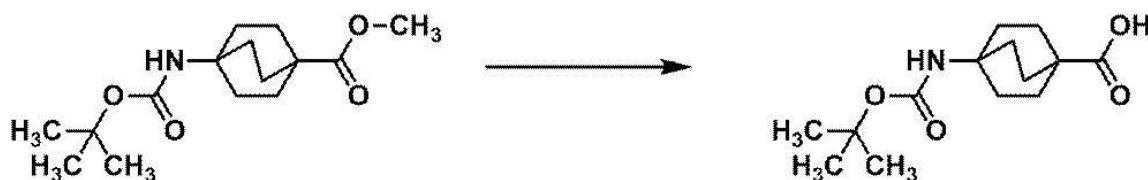
n-hexane/ethyl acetate (100 mL, n-hexane/ethyl acetate=90/10) was added to the residue. The precipitated solid was collected by filtration, washed with n-hexane/ethyl acetate (60 mL, n-hexane/ethyl acetate=90/10), and dried under reduced pressure to give the title compound (37 g).

$^1\text{H-NMR}$ (DMSO-D_6) δ : 1.35 (9H, s), 1.73 (12H, s), 3.55 (3H, s), 6.44 (1H, br s).

[1144]

Step 6: 4-[(tert-Butoxycarbonyl)amino]bicyclo[2.2.2]octane-1-carboxylic acid

[1145]



[1146]

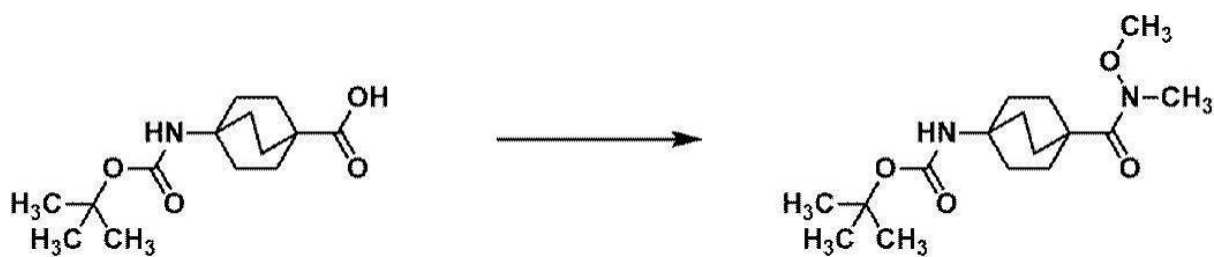
To a suspension of methyl 4-[(tert-butoxycarbonyl)amino]bicyclo[2.2.2]octane-1-carboxylate (37 g) in tetrahydrofuran/methanol (370 mL, tetrahydrofuran/methanol=1/1) was added 2 M aqueous sodium hydroxide solution (130 mL) at room temperature, and the mixture was stirred at 60°C for 4 hr. To the reaction mixture was added 2 M hydrochloric acid (130 mL) under ice-cooling, and the mixture was stirred for 1 hr. The precipitated solid was collected by filtration and dried under reduced pressure to give the title compound (27 g).

$^1\text{H-NMR}$ (DMSO-D_6) δ : 1.35 (9H, s), 1.72 (12H, s), 6.41 (1H, br s), 11.98 (1H, s).

[1147]

Step 7: tert-Butyl {4-[methoxy(methyl)carbamoyl]bicyclo[2.2.2]octan-1-yl}carbamate

[1148]



[1149]

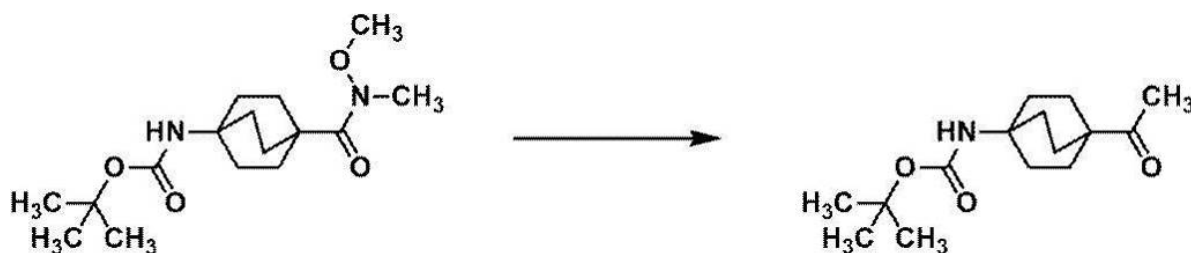
Under an argon atmosphere, to a solution of 4-[(tert-butoxycarbonyl)amino]bicyclo[2.2.2]octane-1-carboxylic acid (10 g) in N,N-dimethylformamide (100 mL) were added O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (17 g), N,O-dimethylhydroxylamine hydrochloride (4.4 g) and N,N-diisopropylethylamine (16 mL) at room temperature, and the mixture was stirred for 4 hr. To the reaction mixture were added N,N-diisopropylethylamine (2.6 mL) and N,O-dimethylhydroxylamine hydrochloride (1.5 g) at room temperature, and the mixture was stirred for 18 hr. To the reaction mixture were added water (100 mL) and ethyl acetate (200 mL) at room temperature. After partitioning, the organic layer was washed successively with water (200 mL), saturated aqueous sodium hydrogen carbonate solution (100 mL) and saturated brine (50 mL). The organic layer was dried over sodium sulfate, sodium sulfate was removed by filtration, and the filtrate was concentrated under reduced pressure to give the title compound (12 g).

$^1\text{H-NMR}$ (CDCl_3) δ : 1.42 (9H, s), 1.82-1.87 (6H, m), 1.95-1.99 (6H, m), 3.14 (3H, s), 3.64 (3H, s), 4.35 (1H, br s).

[1150]

Step 8: tert-Butyl (4-acetylbicyclo[2.2.2]octan-1-yl)carbamate

[1151]



[1152]

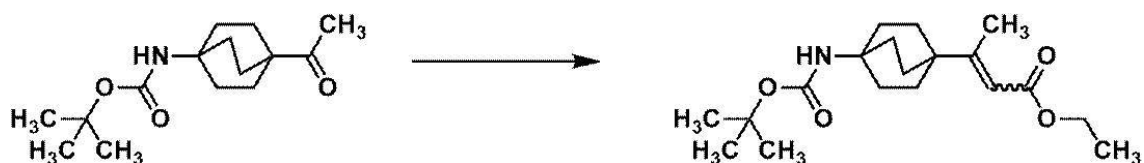
Under an argon atmosphere, to a solution of tert-butyl {4-[methoxy(methyl)carbamoyl]bicyclo[2.2.2]octan-1-yl}carbamate (8.0 g) in tetrahydrofuran (80 mL) was added dropwise 1.1 M tetrahydrofuran (57 mL) solution of methylmagnesium bromide over 15 min under ice-cooling, and the mixture was stirred for 40 min. To the reaction mixture was added 0.95 M tetrahydrofuran (22 mL) solution of methylmagnesium bromide under ice-cooling, and the mixture was stirred at the same temperature for 30 min and at room temperature for 2.5 hr. To the reaction mixture were added 10 wt% aqueous citric acid solution and ethyl acetate (100 mL) at room temperature. After partitioning, the organic layer was washed with saturated brine. The organic layer was dried over sodium sulfate, sodium sulfate was removed by filtration, and the filtrate was concentrated under reduced pressure. To the residue was added n-hexane/ethyl acetate (13 mL, n-hexane/ethyl acetate=2/1), and the mixture was stirred. The precipitated solid was collected by filtration, washed with n-hexane/ethyl acetate (n-hexane/ethyl acetate=10/1) and dried under reduced pressure to give the title compound (2.5 g). In addition, the filtrate was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (eluent: n-hexane/ethyl acetate=95/5 to 60/40) to give the title compound (3.6 g).

¹H-NMR (CDCl₃) δ: 1.42 (9H, s), 1.78-1.83 (6H, m), 1.84-1.89 (6H, m), 2.08 (3H, s), 4.35 (1H, br s).

[1153]

Step 9: Ethyl 3-{4-[(tert-butoxycarbonyl)amino]bicyclo[2.2.2]octan-1-yl}-2-butenate

[1154]



[1155]

Under an argon atmosphere, to a suspension of sodium

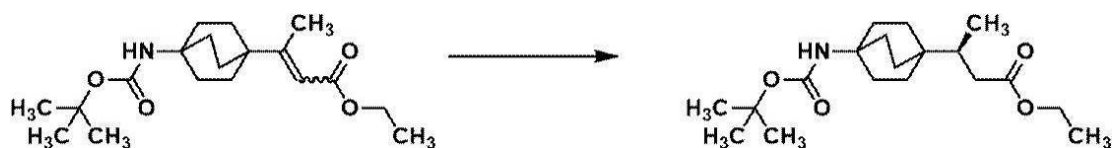
hydride (1.8 g, 60 wt% oil dispersion) in tetrahydrofuran (60 mL) was added dropwise tetrahydrofuran (6.0 mL) solution of triethyl phosphonoacetate (10 g) over 20 min under ice-cooling, and the mixture was stirred for 1 hr. To the reaction mixture
 5 was added dropwise tetrahydrofuran (30 mL) solution of tert-butyl (4-acetylbicyclo[2.2.2]octan-1-yl)carbamate (6.0 g) over 10 min under ice-cooling. The reaction mixture was stirred at room temperature for 3 hr and at 50°C for 15 hr. To the reaction mixture were added saturated aqueous ammonium chloride
 10 solution (100 mL) and ethyl acetate (200 mL) at room temperature. After partitioning, the organic layer was washed with saturated brine (50 mL). The organic layer was dried over sodium sulfate, sodium sulfate was removed by filtration, and the filtrate was concentrated under reduced pressure. The
 15 residue was purified by silica gel column chromatography (eluent: n-hexane/ethyl acetate=95/5 to 60/40) to give the title compound (4.1 g).

¹H-NMR (CDCl₃) δ: 1.27 (3H, t, J = 7.2 Hz), 1.42 (9H, s), 1.68-1.72 (6H, m), 1.85-1.88 (6H, m), 2.10 (3H, s), 4.13 (2H, q, J =
 20 7.2 Hz), 4.34 (1H, br s), 5.63 (1H, s).

[1156]

Step 10A: Ethyl (S)-3-{4-[(tert-butoxycarbonyl)amino]bicyclo[2.2.2]octan-1-yl}butyrate (enantiomer A)

25 [1157]



[1158]

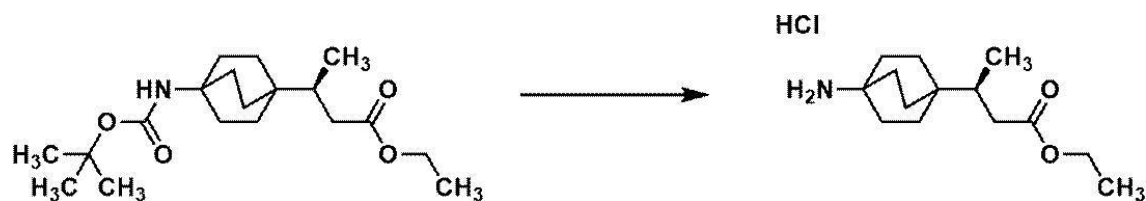
Under an argon atmosphere, a solution of bis[η-(2,5-norbornadiene)]rhodium (I) tetrafluoroborate (28 mg) and (R)-1-
 30 [(Sp)-2-(di-tert-butylphosphino)ferrocenyl]ethyl bis(2-methylphenyl)phosphine (R-Sp form) (CAS No.: 849924-76-1) (42 mg) in methanol (1.5 mL) was stirred at room temperature for 1 hr. To the reaction mixture was added a solution of ethyl 3-

{4-[(tert-butoxycarbonyl)amino]bicyclo[2.2.2]octan-1-yl}-2-butenate (0.50 g) in methanol (4.0 mL) at room temperature, and the mixture was stirred under 4 atm hydrogen atmosphere for 60 hr. The reaction mixture was concentrated under reduced
 5 pressure, and the residue was purified by silica gel column chromatography (eluent: n-hexane/ethyl acetate=98/2 to 80/20) to give the title compound (0.46 g).

¹H-NMR (CDCl₃) δ: 0.81 (3H, d, J = 6.7 Hz), 1.25 (3H, t, J = 7.2 Hz), 1.41-1.48 (6H, m), 1.42 (9H, s), 1.68-1.74 (1H, m),
 10 1.76-1.81 (6H, m), 1.87 (1H, dd, J = 14.6, 10.9 Hz), 2.41 (1H, dd, J = 14.6, 3.2 Hz), 4.12 (2H, q, J = 7.2 Hz), 4.30 (1H, s).
 [1159]

Step 11A: Ethyl (S)-3-(4-aminobicyclo[2.2.2]octan-1-yl)butyrate monohydrochloride (enantiomer A)

15 [1160]



[1161]

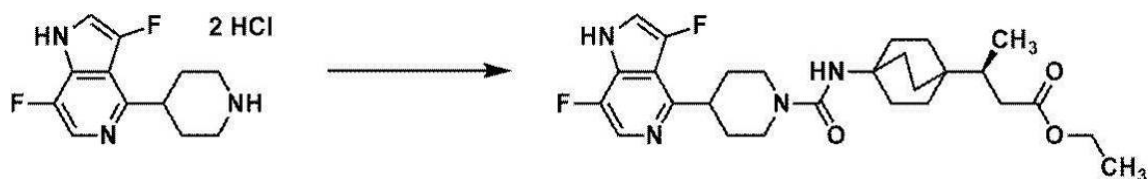
To ethyl (S)-3-{4-[(tert-butoxycarbonyl)amino]bicyclo[2.2.2]octan-1-yl}butyrate
 20 (enantiomer A) (0.46 g) was added 4 M hydrogen chloride/ethyl acetate (4.6 mL) solution at room temperature, and the mixture was stirred for 2 hr. The reaction mixture was concentrated under reduced pressure and azeotropically distilled with toluene to give the title compound (0.36 g).

25 ¹H-NMR (DMSO-D₆) δ: 0.75 (3H, d, J = 6.7 Hz), 1.17 (3H, t, J = 7.1 Hz), 1.38-1.50 (6H, m), 1.59-1.68 (7H, m), 1.83 (1H, dd, J = 14.9, 10.6 Hz), 2.42 (1H, dd, J = 14.9, 3.1 Hz), 4.05 (2H, q, J = 7.1 Hz), 7.86-8.04 (3H, m).

[1162]

30 Step 12A: Ethyl (S)-3-{4-[4-(3,7-difluoro-1H-pyrrolo[3,2-c]pyridin-4-yl)piperidine-1-carboxamido]bicyclo[2.2.2]octan-1-yl}butyrate (enantiomer A)

[1163]



[1164]

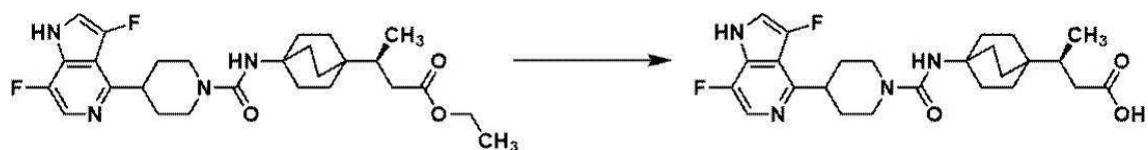
Under an argon atmosphere, to a solution of triphosgene
5 (36 mg) in tetrahydrofuran (1.5 mL) was added dropwise a
suspension of ethyl (S)-3-(4-aminobicyclo[2.2.2]octan-1-
yl)butyrate monohydrochloride (enantiomer A) (0.10 g) and N,N-
diisopropylethylamine (0.14 mL) in tetrahydrofuran (3.0 mL)
under ice-cooling, and the mixture was stirred for 1 hr. To
10 the reaction mixture were added N,N-diisopropylethylamine (0.16
mL), water (0.45 mL) and 3,7-difluoro-4-(piperidin-4-yl)-1H-
pyrrolo[3,2-c]pyridine dihydrochloride (80 mg) under ice-
cooling, and the mixture was stirred at room temperature for 15
hr. The reaction mixture was concentrated under reduced
15 pressure and purified by silica gel column chromatography
(eluent: n-hexane/ethyl acetate=85/15 to 30/70) to give the
title compound (0.12 g).

¹H-NMR (CDCl₃) δ: 0.83 (3H, d, J = 6.7 Hz), 1.25 (3H, t, J =
7.1 Hz), 1.46-1.51 (6H, m), 1.71-1.73 (1H, m), 1.85-1.97 (11H,
20 m), 2.44 (1H, dd, J = 14.8, 3.2 Hz), 2.88-2.96 (2H, m), 3.33-
3.41 (1H, m), 4.00-4.05 (2H, m), 4.12 (2H, q, J = 7.2 Hz), 4.20
(1H, s), 7.06 (1H, t, J = 2.9 Hz), 8.10 (1H, d, J = 2.8 Hz),
8.31 (1H, br s).

[1165]

25 Step 13A: (S)-3-{4-[4-(3,7-Difluoro-1H-pyrrolo[3,2-c]pyridin-4-
yl)piperidine-1-carboxamido]bicyclo[2.2.2]octan-1-yl}butyric
acid (enantiomer A)

[1166]



30 [1167]

To a solution of ethyl (S)-3-{4-[4-(3,7-difluoro-1H-pyrrolo[3,2-c]pyridin-4-yl)piperidine-1-carboxamido]bicyclo[2.2.2]octan-1-yl}butyrate (enantiomer A) (0.12 g) in tetrahydrofuran/methanol (2.4 mL, 5 tetrahydrofuran/methanol=1/1) was added 2 M aqueous sodium hydroxide solution (0.59 mL) at room temperature, and the mixture was stirred at 65°C for 2 hr. To the reaction mixture were added 2 M hydrochloric acid (0.59 mL), water and ethyl acetate under ice-cooling. After partitioning, the organic 10 layer was washed with saturated brine. The organic layer was dried over sodium sulfate, sodium sulfate was removed by filtration, and the filtrate was concentrated under reduced pressure to give the title compound (0.094 g).

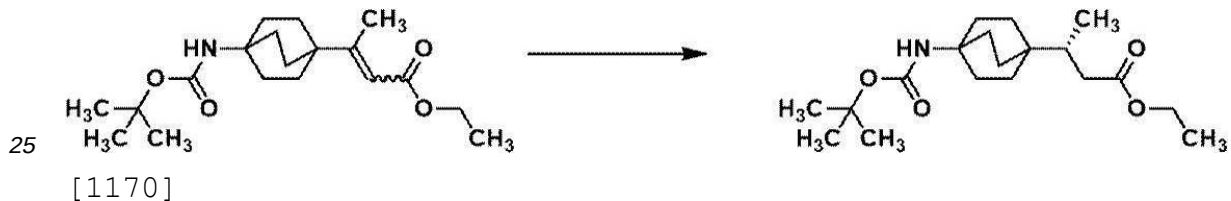
¹H-NMR (DMSO-D₆) δ: 0.76 (3H, d, J = 6.7 Hz), 1.31-1.46 (6H, m), 15 1.50-1.61 (1H, m), 1.67-1.82 (11H, m), 2.33-2.39 (1H, m), 2.68-2.77 (2H, m), 3.21-3.29 (1H, m), 4.03-4.09 (2H, m), 5.60 (1H, s), 7.54 (1H, d, J = 2.5 Hz), 8.08 (1H, d, J = 3.0 Hz), 11.95 (2H, br s).

MS (M+H): 475 MS (M-H): 473

20 [1168]

Step 10B: Ethyl (R)-3-{4-[(tert-butoxycarbonyl)amino]bicyclo[2.2.2]octan-1-yl}butyrate (enantiomer B)

[1169]

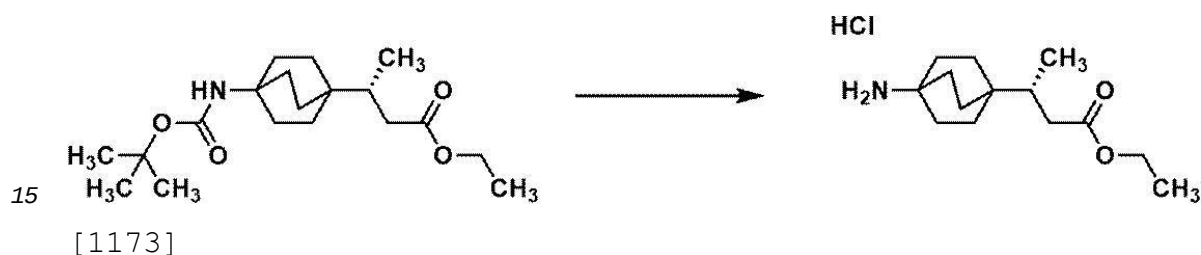


Under an argon atmosphere, a solution of bis[η-(2,5-norbornadiene)]rhodium (I) tetrafluoroborate (28 mg) and (S)-1-[(Rp)-2-(di-tert-butylphosphino)ferrocenyl]ethyl bis(2- 30 methylphenyl)phosphine (S-Rp form) (CAS No.: 849924-77-2) (45 mg) in methanol (1.5 mL) was stirred at room temperature for 1 hr. To the reaction mixture was added a solution of ethyl 3-{4-[(tert-butoxycarbonyl)amino]bicyclo[2.2.2]octan-1-yl}-2-

butenoate (0.50 g) in methanol (4.0 mL) at room temperature, and the mixture was stirred under a 4 atm hydrogen atmosphere for 65 hr. The reaction mixture was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (eluent: n-hexane/ethyl acetate=98/2 to 80/20) to give the title compound (0.54 g).

¹H-NMR (CDCl₃) δ: 0.81 (3H, d, J = 6.7 Hz), 1.25 (3H, t, J = 7.2 Hz), 1.41-1.48 (6H, m), 1.42 (9H, s), 1.68-1.74 (1H, m), 1.76-1.81 (6H, m), 1.87 (1H, dd, J = 14.6, 10.9 Hz), 2.41 (1H, dd, J = 14.6, 3.2 Hz), 4.12 (2H, q, J = 7.2 Hz), 4.30 (1H, s).
[1171]

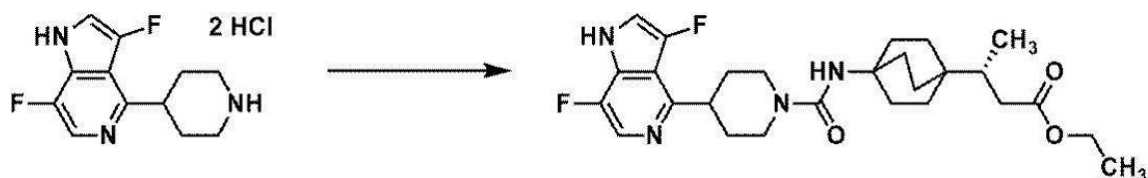
Step 11B: Ethyl (R)-3-(4-aminobicyclo[2.2.2]octan-1-yl)butyrate monohydrochloride (enantiomer B)
[1172]



To ethyl (R)-3-{4-[(tert-butoxycarbonyl)amino]bicyclo[2.2.2]octan-1-yl}butyrate (enantiomer B) (0.54 g) was added 4 M hydrogen chloride/ethyl acetate (4.8 mL) solution at room temperature, and the mixture was stirred for 3 hr. The reaction mixture was concentrated under reduced pressure and azeotropically distilled with toluene to give the title compound (0.36 g).

¹H-NMR (CDCl₃) δ: 0.82 (3H, d, J = 5.3 Hz), 1.23-1.27 (3H, m), 1.48-1.55 (6H, m), 1.73-1.79 (1H, m), 1.85-1.93 (7H, m), 2.38 (1H, d, J = 14.8 Hz), 4.09-4.15 (2H, m), 8.23 (3H, br s).
[1174]

Step 12B: Ethyl (R)-3-{4-[4-(3,7-difluoro-1H-pyrrolo[3,2-c]pyridin-4-yl)piperidine-1-carboxamido]bicyclo[2.2.2]octan-1-yl}butyrate (enantiomer B)
[1175]



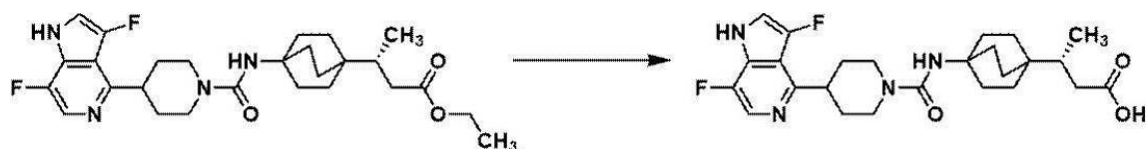
[1176]

Under an argon atmosphere, to a solution of triphosgene (36 mg) in tetrahydrofuran (0.8 mL) was added dropwise a suspension of ethyl (R)-3-(4-aminobicyclo[2.2.2]octan-1-yl)butyrate monohydrochloride (enantiomer B) (100 mg) and N,N-diisopropylethylamine (0.14 mL) in tetrahydrofuran (1.6 mL) under ice-cooling, and the mixture was stirred for 1 hr. To the reaction mixture were added N,N-diisopropylethylamine (0.16 mL), 3,7-difluoro-4-(piperidin-4-yl)-1H-pyrrolo[3,2-c]pyridine dihydrochloride (80 mg) and water (0.24 mL) under ice-cooling, and the mixture was stirred at room temperature for 15 hr. The reaction mixture was concentrated, and the residue was purified by silica gel column chromatography (eluent: n-hexane/ethyl acetate=80/20 to 0/100) to give the title compound (62 mg).
¹H-NMR (CDCl₃) δ: 0.83 (3H, d, J = 6.7 Hz), 1.25 (3H, t, J = 7.1 Hz), 1.46-1.51 (6H, m), 1.71-1.73 (1H, m), 1.85-1.97 (11H, m), 2.44 (1H, dd, J = 14.8, 3.2 Hz), 2.88-2.96 (2H, m), 3.33-3.41 (1H, m), 4.00-4.05 (2H, m), 4.12 (2H, q, J = 7.2 Hz), 4.20 (1H, s), 7.06 (1H, t, J = 2.9 Hz), 8.10 (1H, d, J = 2.8 Hz), 8.19 (1H, br s).

[1177]

Step 13B: (R)-3-{4-[4-(3,7-Difluoro-1H-pyrrolo[3,2-c]pyridin-4-yl)piperidine-1-carboxamido]bicyclo[2.2.2]octan-1-yl}butyric acid (enantiomer B)

[1178]



[1179]

To a solution of ethyl (R)-3-{4-[4-(3,7-difluoro-1H-pyrrolo[3,2-c]pyridin-4-yl)piperidine-1-

carboxamido]bicyclo[2.2.2]octan-1-yl}butyrate (enantiomer B)
(62 mg) in tetrahydrofuran/methanol (1.2 mL,
tetrahydrofuran/methanol=1/1) was added 2 M aqueous sodium
hydroxide solution (0.31 mL) at room temperature, and the
5 mixture was stirred at 65°C for 2 hr. To the reaction mixture
were added 2 M hydrochloric acid (0.31 mL) and ethyl acetate at
room temperature. After partitioning, the organic layer was
washed with saturated brine. The organic layer was dried over
sodium sulfate, sodium sulfate was removed by filtration, and
10 the filtrate was concentrated under reduced pressure to give
the title compound (48 mg).

¹H-NMR (DMSO-D₆) δ: 0.74 (3H, d, J = 6.7 Hz), 1.30-1.40 (6H, m),
1.51-1.58 (1H, m), 1.66-1.79 (11H, m), 2.31-2.37 (1H, m), 2.65-
2.74 (2H, m), 3.21-3.27 (1H, m), 4.01-4.06 (2H, m), 5.59 (1H,
15 s), 7.52-7.53 (1H, m), 8.06 (1H, d, J = 3.0 Hz), 11.90-11.97
(2H, m).

MS (M+H): 475 MS (M-H): 473

[1180]

Biotinylation of H-PGDS inhibitor ((R)-3-{4-[4-(3,7-difluoro-
20 1H-pyrrolo[3,2-c]pyridin-4-yl)piperidine-1-
carboxamido]bicyclo[2.2.2]octan-1-yl}butyric acid) (enantiomer
B)

[1181]

To a solution of (R)-3-{4-[4-(3,7-difluoro-1H-
25 pyrrolo[3,2-c]pyridin-4-yl)piperidine-1-
carboxamido]bicyclo[2.2.2]octan-1-yl}butyric acid (enantiomer
B) (10 mg) and N-(35-amino-3,6,9,12,15,18,21,24,27,30,33-
undecaoxapentatriacontyl)-5-(2-oxohexahydro-1H-thieno[3,4-
d]imidazol-4-yl)pentanamide (16.25 mg) in N,N-dimethylformamide
30 (0.5 mL) were added 1-ethyl-3-(3-
dimethylaminopropyl)carbodiimide hydrochloride (4.85 mg) and
1H-benzo[d][1,2,3]triazol-1-ol hydrate at room temperature, and
the mixture was left standing overnight. The reaction mixture
was purified by silica gel reversed-phase column chromatography
35 (eluent: water/trifluoroacetic acid/acetonitrile) and

lyophilized. The residue was added to VariPure IPE column (manufactured by Agilent) and eluted with methanol. The eluate was concentrated under reduced pressure and dried under reduced pressure to give the title compound (14 mg).

5 [1182]

Measurement of human H-PGDS inhibitory activity of compound ((R)-3-{4-[4-(3,7-difluoro-1H-pyrrolo[3,2-c]pyridin-4-yl)piperidine-1-carboxamido]bicyclo[2.2.2]octan-1-yl}butyric acid) (enantiomer B)

10 [1183]

(1) Preparation of human H-PGDS purified fraction

Using the human H-PGDS expression plasmid DNA (pET28b/hH-PGDS) as a template, PCR (Polymerase Chain Reaction) was performed to amplify a DNA fragment containing human H-PGDS with a NotI recognition cleavage sequence immediately before the translation initiation codon and a BamHI recognition cleavage sequence immediately below the translation end codon. The purified DNA fragment was fused to pET15b (manufactured by Merck KGaA, model number 69661) digested with NotI and BamHI, by using In-Fusion HD Cloning Kit (manufactured by Takara Bio Inc., model number 639649). Human H-PGDS expression plasmid DNA was isolated from Escherichia coli DH5 α (manufactured by TOYOBO, model number DNA-903) transformed with the obtained In-Fusion reaction product. The base sequence of human H-PGDS cloned into the vector was determined by the Dye Terminator method using BigDye Terminator v3.1 Cycle Sequencing Kit (manufactured by Applied Biosystems, model number 4337456). The determined sequence was identical to the sequence of the protein translation region of human H-PGDS (Accession number NM_014485.2) registered in the NCBI Reference Database.

[1184]

Escherichia coli BL21 (DE3) (Merck KGaA, model number 69450-4) transformed with human H-PGDS-expressing plasmid DNA was cultured at 37°C using 2 $\times$ YT medium (manufactured by Becton Dickinson, model number 244020) until the optical concentration

at 620 nm reached 0.6 or higher, and then cultured at 30°C for 6 hr in the presence of 1 mmol/L isopropyl β -D-1-thiogalactopyranoside. After completion of the culture, bacterial cells were collected and suspended in Homogenate Buffer (PBS(-), cOmplete (registered trade mark), EDTA-free (F. Hoffmann-La Roche Ltd, model number 1873580)). Using an Ultrasonic disruptor UD-201 (manufactured by TOMY DIGITAL BIOLOGY CO., LTD.), the bacterial cells suspended for 15 seconds at out put:4, duty cycle:50 were disrupted, and this operation was repeated three times. After removing the precipitate by centrifugation (13,100×g, 15 min, 4°C) and ammonium sulfate was added to the supernatant to 40% saturation and stirred at 4°C for 1 hr or more. After removing the precipitate by centrifugation (13,100×g, 10 min, 4°C), ammonium sulfate was added to the supernatant to 60% saturation, and the mixture was stirred at 4°C for 1 hr or more. Thereafter, the precipitate obtained by centrifugation was suspended in PBS(-) and dialyzed twice for 2 hr or more against a dialysis fluid (50 mmol/L potassium phosphate (pH 6.0), 150 mmol/L NaCl, 1 mmol/L MgCl₂). The supernatant fraction obtained by centrifuging (21,100×g, 10 min, 4°C) the sample after dialysis was added to a Glutathione Sepharose 4B column (manufactured by GE Healthcare, model number 17075604). After washing the column with the dialysis fluid, human H-PGDS was eluted with the eluent (5 mmol/L Tris-HCl (pH 8.0), 150 mmol/L NaCl, 1 mmol/L MgCl₂, 15 mmol/L Glutathione). Glutathione Sepharose 4B column eluate was added to a gel filtration column (Superdex-200 30/100 GL (manufactured by GE HealthCare, model number 17-5175-01)), and eluted with gel filtration Buffer (5 mmol/L Tris-HCl (pH 8.0), 150 mmol/L NaCl, 1 mmol/L MgCl₂). Eluted fractions were collected and used as human H-PGDS purified fractions.

[1185]

The protein concentration of the human H-PGDS purified fraction was measured with Pierce 660nm Protein Assay Reagent

(manufactured by Thermo Fisher Scientific Inc., model number 22660). Purified fractions were stored at -80°C after rapid freezing using liquid nitrogen. Human H-PGDS was detected by Western blotting using a rabbit anti-H-PGDS polyclonal antibody
5 (manufactured by LifeSpan BioSciences, Inc, model number LS-B6886).

[1186]

(2) Evaluation of human H-PGDS inhibitory activity

Calculation of the H-PGDS inhibitory activity of a
10 compound was performed according to the following protocol attached to Prostaglandin D Synthase Inhibitor Screening Assay Kit (Cat. No. 10006595, Cayman Chemical Company) and Prostaglandin D2 Express ELISA Kit (Cat. No. 512041, Cayman Chemical Company). Human recombinant H-PGDS prepared as
15 described above was used.

[1187]

In a 96 well V-bottom plate (Cat. No. 3363, Costar) were added and mixed lightly 10 µL/well of DMSO solution (10 % v/v) diluted with Assay buffer (0.1 mol/L Tris-HCl, pH 8.0) as a
20 compound solution or a solvent control diluted with Assay buffer, 10 µL/well of MgCl₂ solution at a final concentration of 2 mmol/L, 10 µL/well of GSH solution at a final concentration of 0.8 mmol/L, and human recombinant H-PGDS at a final concentration of 1.6 µg/mL, or 10 µL/well of Assay buffer
25 as a blank. This plate was allowed to stand at room temperature for 10 min, 10 µL/well of PGH₂ at a final concentration of 50 µmol/L was added to initiate an enzyme reaction, and the reaction was carried out for 1 min while mixing with a plate mixer. After the enzyme reaction, 0.5
30 mol/L of HCl was added at 10 µL/well to discontinue the reaction. Furthermore, a FeCl₂ solution dissolved in 0.1 mol/L hydrochloric acid to a concentration of 0.4 mg/mL was added at 10 µL/well to perform reduction of PGH₂. This enzyme reaction solution was diluted 4000-fold with EIA buffer, and the diluted
35 enzyme reaction solution was added to an ELISA plate at 50

5 $\mu\text{L}/\text{well}$. Prostaglandin D2 Express AChE Tracer and
 Prostaglandin D2 Express EIA Monoclonal Antibody were added to
 this plate at 50 $\mu\text{L}/\text{well}$ each. As a Non-Specific Binding
 sample (NSB), 100 $\mu\text{L}/\text{well}$ of EIA buffer and 50 $\mu\text{L}/\text{well}$ of
 10 Prostaglandin D2 Express AChE Tracer were added in another well,
 and 50 $\mu\text{L}/\text{well}$ of EIA buffer and 50 $\mu\text{L}/\text{well}$ of Prostaglandin D2
 Express AChE Tracer, and 50 $\mu\text{L}/\text{well}$ of prostaglandin D2 Express
 EIA Monoclonal Antibody were added as B0 samples. This plate
 was reacted for 2 hr while mixing with a plate mixer. After
 15 completion of the reaction, the reaction solution was removed
 and Wash buffer was added at 200 $\mu\text{L}/\text{well}$. This process was
 repeated 5 times to wash the plate. After washing the plate,
 200 $\mu\text{L}/\text{well}$ of Ellman's Reagent was added to all wells, and the
 mixture was reacted for 30 min in shading while mixing with a
 15 plate mixer. After completion of the reaction, the absorbance
 at 420 nm was measured using a microplate reader.

The H-PGDS binding inhibitory activity (inhibitory rate)
 of the compound was calculated as follows, and the IC_{50} value
 for H-PGDS activity was calculated from the inhibitory rate at
 20 two concentrations sandwiching 50%.
 [1188]

$$\begin{aligned}
 & \text{inhibitory rate (\%)} = \left[1 - \frac{\begin{array}{cc} \text{B}^1/\text{B0}^2 & \text{B}^1/\text{B0}^2 \\ \text{of blank} & \text{of compound} \end{array}}{\begin{array}{cc} \text{B}^1/\text{B0}^2 & \text{B}^1/\text{B0}^2 \\ \text{of blank} & \text{of solvent control} \end{array}} \right] \times 100 \\
 & \text{25}
 \end{aligned}$$

30 *1: B = OD_{420} of each well - OD_{420} of NSB

*2: B0 = OD_{420} of B0 - OD_{420} of NSB

[1189]

Also, the human H-PGDS inhibitory activity (IC_{50} value)
 35 was calculated for the compound (enantiomer A) according to the
 above-mentioned method.

[1190]

The evaluation results of each compound are shown in the following Table 3.

[1191]

[Table 3]

compound		human H-PGDS inhibitory activity IC ₅₀ (nM)
(3-{4-[4-(3,7-difluoro-1H-pyrrolo[3,2-c]pyridin-4-yl)piperidine-1-carboxamido]-bicyclo[2.2.2]octan-1-yl}-butyric acid)	enantiomer A	5
	enantiomer B	6

5

[1192]

Formulation Examples of the present invention include the following formulations. However, the present invention is not limited by these Formulation Examples.

10 [1193]

Formulation Example 1: Production of capsule

- 1) compound of Example 1 30 mg
- 2) microcrystalline cellulose 10 mg
- 3) lactose 19 mg
- 15 4) magnesium stearate 1 mg

1), 2), 3) and 4) are mixed and filled in a gelatin capsule.

[1194]

Formulation Example 2: Production of tablet

- 20 1) compound of Example 1 10 g
- 2) lactose 50 g
- 3) cornstarch 15 g
- 4) carmellose calcium 44 g
- 5) magnesium stearate 1 g

25 A total amount of 1), 2) and 3) and 30 g of 4) are kneaded with water, vacuum dried, and sieved. The sieved powder is mixed with 14 g of 4) and 1 g of 5), and the mixture is punched with a tableting machine. As a result, 1000 tablets containing 10 mg of the compound of Example 1 per tablet are

obtained.

[Industrial Applicability]

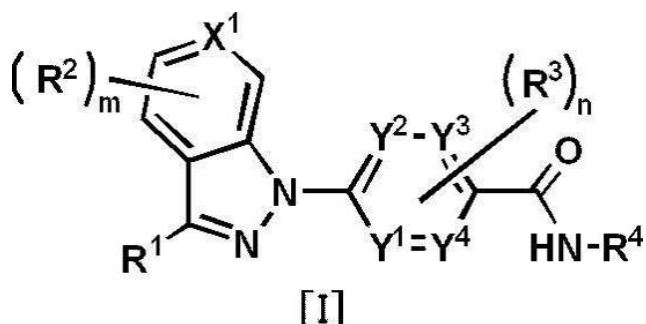
[1195]

The compound of the present invention or a
5 pharmaceutically acceptable salt thereof has H-PGDS inhibitory
activity, and is useful for the treatment and/or prophylaxis of
a disease selected from the group consisting of peripheral
arterial diseases (e.g., intermittent claudication and
comprehensive severe chronic lower extremity ischemia),
10 cardiovascular diseases, allergic asthma, chronic obstructive
pulmonary diseases, allergic rhinitis, sarcopenia, and Duchenne
muscular dystrophy.

[CLAIMS]

[Claim 1]

A compound of the formula [I]:



wherein

X^1 , Y^1 , Y^2 , Y^3 and Y^4 are each independently a carbon or a
nitrogen atom (wherein the total number of the nitrogen atoms
10 for Y^1 , Y^2 , Y^3 and Y^4 is 0, 1 or 2),

m is 0, 1 or 2,

n is 0, 1 or 2,

R^1 is

- (1) hydroxy,
15 (2) cyano,
(3) C_{1-4} alkyl (wherein the alkyl is optionally substituted by
hydroxy or C_{1-4} alkoxy),
(4) C_{1-4} alkoxy,
(5) halogen,
20 (6) C_{1-4} haloalkyl, or
(7) C_{3-6} cycloalkyl,

R^2 in the number of m are each independently

- (1) cyano,
(2) C_{1-4} alkyl,
25 (3) C_{1-4} alkoxy,
(4) halogen, or
(5) C_{1-4} haloalkyl,

R^3 in the number of n are each independently

- (1) C_{1-4} alkyl,
30 (2) C_{1-4} alkoxy, or

(3) halogen, and

R⁴ is

(1) ring Cy [wherein the ring Cy is

(a) C₄₋₆ cycloalkyl (wherein the cycloalkyl is optionally
5 substituted by 1 or 2 substituents independently selected from
the group consisting of

(I) hydroxy,

(II) cyano,

(III) oxo,

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

(i) hydroxy,

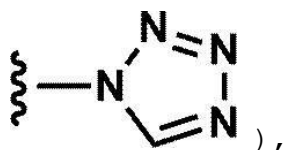
(ii) carboxy,

(iii) -CONH₂,

15 (iv) -CO-C₁₋₄ alkoxy,

(v) -SO₂-C₁₋₄ alkyl, or

(vi) a group represented by the formula:



(V) C₁₋₆ alkoxy (wherein the alkoxy is optionally
substituted by hydroxy or -SO₂-C₁₋₄ alkyl),

(VI) carboxy,

(VII) -CO-NR⁵R⁶ [wherein R⁵ and R⁶ are each independently
25 C₁₋₄ alkyl (wherein the alkyl is optionally substituted by C₁₋₄
alkoxy), or R⁵ and R⁶ optionally form, together with the
nitrogen atom bonded thereto, 4- to 6-membered heterocycloalkyl
containing 1 or 2 hetero atoms independently selected from the
group consisting of nitrogen and oxygen atoms {wherein the
30 heterocycloalkyl is optionally substituted by 1 or 2
substituents independently selected from the group consisting
of

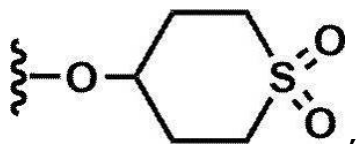
(i) hydroxy, and

(ii) C₁₋₆ alkyl (wherein the alkyl is optionally substituted by hydroxy)}],

(VIII) -NR⁷R⁸ {wherein R⁷ and R⁸ are each independently C₁₋₄ alkyl or -CO-C₁₋₆ alkyl (wherein the alkyl is optionally substituted by cyano)}],

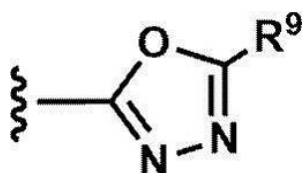
(IX) -O-C₁₋₆ haloalkyl,

(X) a group represented by the formula:



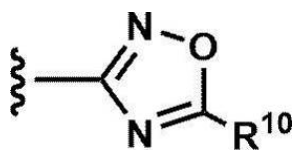
10

(XI) a group represented by the formula:



15 {wherein R⁹ is C₁₋₄ alkyl (wherein the alkyl is optionally substituted by C₁₋₄ alkoxy)}], and

(XII) a group represented by the formula:



20

wherein R¹⁰ is C₁₋₄ alkyl)),

(b) C₅₋₈ bridged cycloalkyl {wherein the bridged cycloalkyl is optionally substituted by

(I) hydroxy,

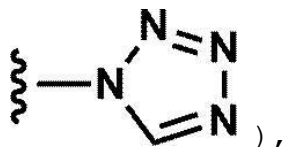
25 (II) C₁₋₆ alkyl (wherein the alkyl is optionally substituted by

(i) hydroxy,

(ii) carboxy,

- (iii) $-\text{CONH}_2$,
- (iv) $-\text{CO}-\text{C}_{1-4}$ alkoxy,
- (v) $-\text{SO}_2-\text{C}_{1-4}$ alkyl, or
- (vi) a group represented by the formula:

5

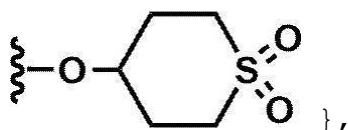


(III) C_{1-6} alkoxy (wherein the alkoxy is optionally substituted by hydroxy or $-\text{SO}_2-\text{C}_{1-4}$ alkyl),

10

- (IV) carboxy,
- (V) $-\text{CO}-\text{C}_{1-4}$ alkoxy,
- (VI) $-\text{O}-\text{C}_{1-6}$ haloalkyl, or
- (VII) a group represented by the formula:

15



20

(c) 5- or 6-membered heterocycloalkyl containing one nitrogen atom [wherein the heterocycloalkyl is optionally substituted by 1 to 3 substituents independently selected from the group consisting of

- (I) oxo,
- (II) C_{1-6} alkyl,
- (III) $-\text{CO}-\text{R}^{11}$ {wherein R^{11} is

25 substituted by

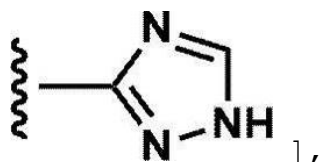
- (A) hydroxy,
- (B) cyano, or
- (C) C_{1-4} alkoxy),
- (ii) C_{1-6} alkoxy,
- (iii) C_{1-6} haloalkyl,
- (iv) C_{3-6} cycloalkyl (wherein the cycloalkyl is

30

optionally substituted by halogen), or

(v) 4- to 6-membered heterocycloalkyl containing one oxygen atom (wherein the heterocycloalkyl is optionally substituted by halogen)}, and

5 (IV) a group represented by the formula:

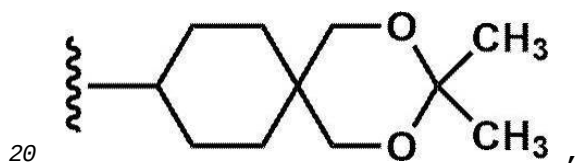


(d) 8-membered bridged heterocycloalkyl containing one
10 nitrogen atom {wherein the bridged heterocycloalkyl is optionally substituted by -CO-R^{11} },

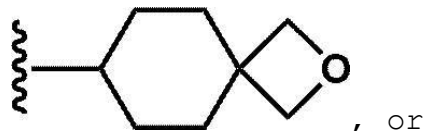
(e) 7- to 11-membered spiro heterocycloalkyl containing one nitrogen atom {wherein the spiro heterocycloalkyl is optionally substituted by -CO-R^{11} },

15 (f) 6- to 9-membered saturated or partially unsaturated fused ring group containing 1 or 2 nitrogen atoms (wherein the fused ring group is optionally substituted by -CO-R^{11}),

(g) a group represented by the formula:



(h) a group represented by the formula:



25 (i) a group represented by the formula:

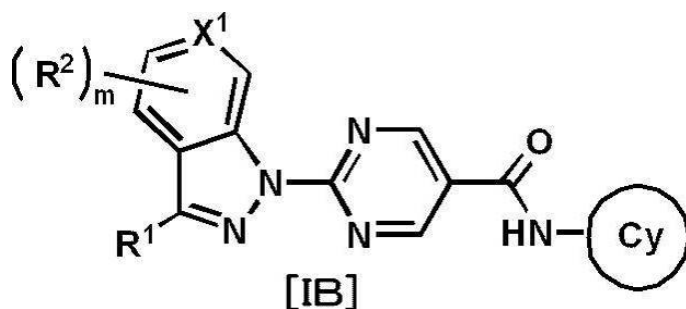
halogen, or a pharmaceutically acceptable salt thereof.

[Claim 5]

The compound of any one of Claims 1 to 4, wherein R⁴ is ring Cy, or a pharmaceutically acceptable salt thereof.

5 [Claim 6]

The compound of Claim 1, which is represented by the formula [IB]:



10

(wherein each symbol is as defined for Claim 1),
or a pharmaceutically acceptable salt thereof.

[Claim 7]

The compound of any one of Claims 1 to 6, wherein R¹ is
15 (1) C₁₋₄ alkyl (wherein the alkyl is optionally substituted by
hydroxy or C₁₋₄ alkoxy),

(2) C₁₋₄ alkoxy,

(3) halogen, or

(4) C₁₋₄ haloalkyl,

20 or a pharmaceutically acceptable salt thereof.

[Claim 8]

The compound of any one of Claims 1 to 7, wherein R² is
halogen, or a pharmaceutically acceptable salt thereof.

[Claim 9]

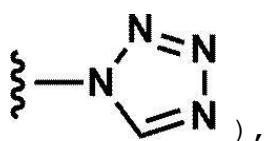
25 The compound of any one of Claims 1 to 8, wherein ring Cy
is

(1) C₄₋₆ cycloalkyl (wherein the cycloalkyl is optionally
substituted by 1 or 2 substituents independently selected from
the group consisting of

30 (a) hydroxy,

(b) cyano,
(c) oxo,
(d) C₁₋₆ alkyl (wherein the alkyl is optionally substituted by

- 5 (I) hydroxy,
(II) carboxy,
(III) -CONH₂,
(IV) -CO-C₁₋₄ alkoxy,
(V) -SO₂-C₁₋₄ alkyl, or
10 (VI) a group represented by the formula:

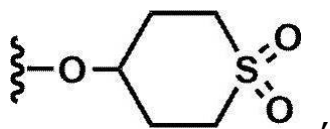


- (e) C₁₋₆ alkoxy (wherein the alkoxy is optionally substituted by hydroxy or -SO₂-C₁₋₄ alkyl),
15 (f) carboxy,
(g) -CO-NR⁵R⁶ [wherein R⁵ and R⁶ are each independently C₁₋₄ alkyl (wherein the alkyl is optionally substituted by C₁₋₄ alkoxy), or R⁵ and R⁶ optionally form, together with the
20 nitrogen atom bonded thereto, 4- to 6-membered heterocycloalkyl containing 1 or 2 hetero atoms independently selected from the group consisting of nitrogen and oxygen atoms {wherein the heterocycloalkyl is optionally substituted by 1 or 2 substituents independently selected from the group consisting
25 of

(I) hydroxy, and
(II) C₁₋₆ alkyl (wherein the alkyl is optionally substituted by hydroxy)}],

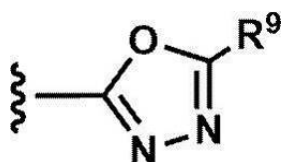
- (h) -NR⁷R⁸ {wherein R⁷ and R⁸ are each independently C₁₋₄ alkyl, or -CO-C₁₋₆ alkyl (wherein the alkyl is optionally substituted by cyano)},
30

(i) -O-C₁₋₆ haloalkyl,
(j) a group represented by the formula:



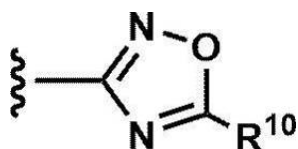
(k) a group represented by the formula:

5



{wherein R⁹ is C₁₋₄ alkyl (wherein the alkyl is optionally substituted by C₁₋₄ alkoxy)}, and

10 (m) a group represented by the formula:



wherein R¹⁰ is C₁₋₄ alkyl)),

15 (2) C₅₋₈ bridged cycloalkyl {wherein the bridged cycloalkyl is optionally substituted by

(a) hydroxy,

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

20 (I) hydroxy,

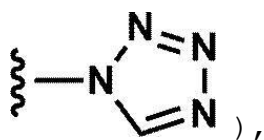
(II) carboxy,

(III) -CONH₂,

(IV) -CO-C₁₋₄ alkoxy,

(V) -SO₂-C₁₋₄ alkyl, or

25 (VI) a group represented by the formula:



(c) C₁₋₆ alkoxy (wherein the alkoxy is optionally substituted by hydroxy or -SO₂-C₁₋₄ alkyl),

(d) carboxy,

5 (e) -CO-C₁₋₄ alkoxy,

(f) -O-C₁₋₆ haloalkyl, or

(g) a group represented by the formula:



10

(3) 5- or 6-membered heterocycloalkyl containing one nitrogen atom [wherein the heterocycloalkyl is optionally substituted by 1 to 3 substituents independently selected from the group consisting of

15 (a) oxo,

(b) C₁₋₆ alkyl,

(c) -CO-R¹¹ {wherein R¹¹ is

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

20 (i) hydroxy,

(ii) cyano, or

(iii) C₁₋₄ alkoxy),

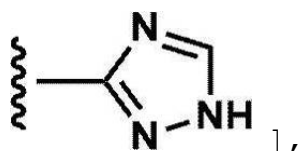
(II) C₁₋₆ alkoxy,

(III) C₁₋₆ haloalkyl,

25 (IV) C₃₋₆ cycloalkyl (wherein the cycloalkyl is optionally substituted by halogen), or

(V) 4- to 6-membered heterocycloalkyl containing one oxygen atom (wherein the heterocycloalkyl is optionally substituted by halogen)}, and

30 (d) a group represented by the formula:



(4) 8-membered bridged heterocycloalkyl containing one nitrogen atom {wherein the bridged heterocycloalkyl is optionally substituted by $-\text{CO}-\text{R}^{11}$ },

(5) 7- to 11-membered spiro heterocycloalkyl containing one nitrogen atom {wherein the spiro heterocycloalkyl is optionally substituted by $-\text{CO}-\text{R}^{11}$ }, or

(6) a 6- to 9-membered saturated or partially unsaturated fused ring group containing 1 or 2 nitrogen atoms (wherein the fused ring group is optionally substituted by $-\text{CO}-\text{R}^{11}$), or a pharmaceutically acceptable salt thereof.

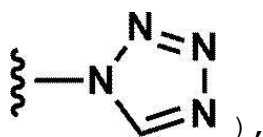
[Claim 10]

The compound of any one of Claims 1 to 9, wherein ring Cy is

(1) C_{4-6} cycloalkyl (wherein the cycloalkyl is optionally substituted by 1 or 2 substituents independently selected from the group consisting of

- (a) hydroxy,
- (b) cyano,
- (c) oxo,
- (d) C_{1-6} alkyl (wherein the alkyl is optionally substituted by

- (I) hydroxy,
- (II) carboxy,
- (III) $-\text{CONH}_2$,
- (IV) $-\text{CO}-\text{C}_{1-4}$ alkoxy,
- (V) $-\text{SO}_2-\text{C}_{1-4}$ alkyl, or
- (VI) a group represented by the formula:



(e) C₁₋₆ alkoxy (wherein the alkoxy is optionally substituted by hydroxy or -SO₂-C₁₋₄ alkyl),

(f) carboxy,

5 (g) -CO-NR⁵R⁶ [wherein R⁵ and R⁶ are each independently C₁₋₄ alkyl (wherein the alkyl is optionally substituted by C₁₋₄ alkoxy), or R⁵ and R⁶ optionally form, together with the nitrogen atom bonded thereto, 4- to 6-membered heterocycloalkyl containing 1 or 2 hetero atoms independently selected from the
10 group consisting of nitrogen and oxygen atoms {wherein the heterocycloalkyl is optionally substituted by 1 or 2 substituents independently selected from the group consisting of

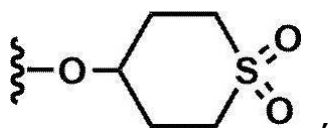
(I) hydroxy, and

15 (II) C₁₋₆ alkyl (wherein the alkyl is optionally substituted by hydroxy)}],

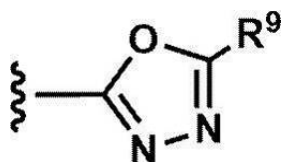
(h) -NR⁷R⁸ {wherein R⁷ and R⁸ are each independently C₁₋₄ alkyl, or -CO-C₁₋₆ alkyl (wherein the alkyl is optionally substituted by cyano)},

20 (i) -O-C₁₋₆ haloalkyl,

(j) a group represented by the formula:

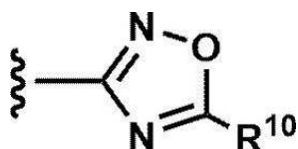


25 (k) a group represented by the formula:



{wherein R⁹ is C₁₋₄ alkyl (wherein the alkyl is optionally substituted by C₁₋₄ alkoxy)}, and
30

(m) a group represented by the formula:



wherein R¹⁰ is C₁₋₄ alkyl)),

5 (2) C₅₋₈ bridged cycloalkyl {wherein the bridged cycloalkyl is optionally substituted by

(a) hydroxy,

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

10 (I) hydroxy,

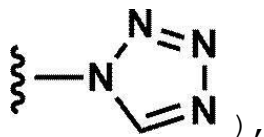
(II) carboxy,

(III) -CONH₂,

(IV) -CO-C₁₋₄ alkoxy,

(V) -SO₂-C₁₋₄ alkyl, or

15 (VI) a group represented by the formula:



(c) C₁₋₆ alkoxy (wherein the alkoxy is optionally substituted by hydroxy or -SO₂-C₁₋₄ alkyl),

20 (d) carboxy,

(e) -CO-C₁₋₄ alkoxy,

(f) -O-C₁₋₆ haloalkyl, or

(g) a group represented by the formula:

25



(3) 5- or 6-membered heterocycloalkyl containing one nitrogen atom [wherein the heterocycloalkyl is optionally substituted by

1 to 3 substituents independently selected from the group consisting of

(a) oxo,

(b) C₁₋₆ alkyl,

5 (c) -CO-R¹¹ {wherein R¹¹ is

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

(i) hydroxy,

(ii) cyano, or

10 (iii) C₁₋₄ alkoxy),

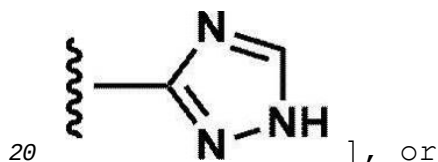
(II) C₁₋₆ alkoxy,

(III) C₁₋₆ haloalkyl,

(IV) C₃₋₆ cycloalkyl (wherein the cycloalkyl is optionally substituted by halogen), or

15 (V) 4- to 6-membered heterocycloalkyl containing one oxygen atom (wherein the heterocycloalkyl is optionally substituted by halogen)}, and

(d) a group represented by the formula:



(4) 8-membered bridged heterocycloalkyl containing one nitrogen atom {wherein the bridged heterocycloalkyl is optionally substituted by -CO-R¹¹},

25 or a pharmaceutically acceptable salt thereof.

[Claim 11]

The compound of any one of Claims 1 to 8, wherein ring Cy is

(1) C₄₋₆ cycloalkyl (wherein the cycloalkyl is optionally substituted by 1 or 2 substituents independently selected from the group consisting of

(a) hydroxy,

(b) cyano,

(c) oxo,

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

(I) hydroxy,

5 (II) carboxy,

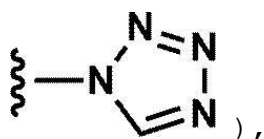
(III) -CONH₂,

(IV) -CO-C₁₋₄ alkoxy,

(V) -SO₂-C₁₋₄ alkyl, or

(VI) a group represented by the formula:

10



(e) C₁₋₆ alkoxy (wherein the alkoxy is optionally substituted by hydroxy or -SO₂-C₁₋₄ alkyl),

15 (f) carboxy,

(g) -CO-NR⁵R⁶ [wherein R⁵ and R⁶ are each independently C₁₋₄ alkyl (wherein the alkyl is optionally substituted by C₁₋₄ alkoxy), or R⁵ and R⁶ optionally form, together with the nitrogen atom bonded thereto, 4- to 6-membered heterocycloalkyl
20 containing 1 or 2 hetero atoms independently selected from the group consisting of nitrogen and oxygen atoms {wherein the heterocycloalkyl is optionally substituted by 1 or 2 substituents independently selected from the group consisting of

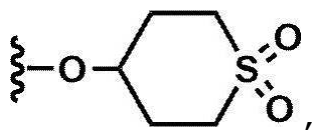
25 (I) hydroxy, and

(II) C₁₋₆ alkyl (wherein the alkyl is optionally substituted by hydroxy) }],

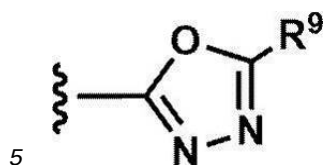
(h) -NR⁷R⁸ {wherein R⁷ and R⁸ are each independently C₁₋₄ alkyl, or -CO-C₁₋₆ alkyl (wherein the alkyl is optionally
30 substituted by cyano) },

(i) -O-C₁₋₆ haloalkyl,

(j) a group represented by the formula:



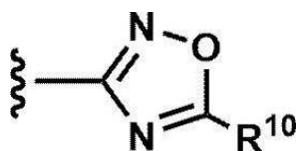
(k) a group represented by the formula:



{wherein R⁹ is C₁₋₄ alkyl (wherein the alkyl is optionally substituted by C₁₋₄ alkoxy)}, and

(m) a group represented by the formula:

10



wherein R¹⁰ is C₁₋₄ alkyl)), or

(2) C₅₋₈ bridged cycloalkyl {wherein the bridged cycloalkyl is
15 optionally substituted by

(a) hydroxy,

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

(I) hydroxy,

20 (II) carboxy,

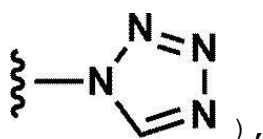
(III) -CONH₂,

(IV) -CO-C₁₋₄ alkoxy,

(V) -SO₂-C₁₋₄ alkyl, or

(VI) a group represented by the formula:

25



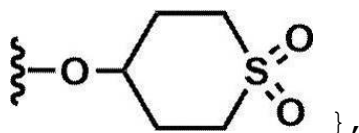
(c) C₁₋₆ alkoxy (wherein the alkoxy is optionally substituted by hydroxy or -SO₂-C₁₋₄ alkyl),

(d) carboxy,

(e) -CO-C₁₋₄ alkoxy,

5 (f) -O-C₁₋₆ haloalkyl, or

(g) a group represented by the formula:



10 or a pharmaceutically acceptable salt thereof.

[Claim 12]

The compound of any one of Claims 1 to 8, wherein ring Cy is

(1) cyclohexyl (wherein the cyclohexyl is optionally substituted by 1 or 2 substituents independently selected from the group consisting of

(a) hydroxy,

(b) cyano,

(c) oxo,

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

(I) hydroxy,

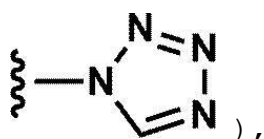
(II) carboxy,

(III) -CONH₂,

25 (IV) -CO-C₁₋₄ alkoxy,

(V) -SO₂-C₁₋₄ alkyl, or

(VI) a group represented by the formula:



30

(e) C₁₋₆ alkoxy (wherein the alkoxy is optionally

substituted by hydroxy or $-\text{SO}_2\text{-C}_{1-4}$ alkyl),

(f) carboxy,

(g) $-\text{CO-NR}^5\text{R}^6$ [wherein R^5 and R^6 are each independently C_{1-4} alkyl (wherein the alkyl is optionally substituted by C_{1-4} alkoxy), or R^5 and R^6 optionally form, together with the nitrogen atom bonded thereto, 4- to 6-membered heterocycloalkyl containing 1 or 2 hetero atoms independently selected from the group consisting of nitrogen and oxygen atoms {wherein the heterocycloalkyl is optionally substituted by 1 or 2 substituents independently selected from the group consisting of

(I) hydroxy, and

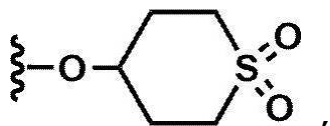
(II) C_{1-6} alkyl (wherein the alkyl is optionally substituted by hydroxy)}],

(h) $-\text{NR}^7\text{R}^8$ {wherein R^7 and R^8 are each independently C_{1-4} alkyl, or $-\text{CO-C}_{1-6}$ alkyl (wherein the alkyl is optionally substituted by cyano)},

(i) $-\text{O-C}_{1-6}$ haloalkyl,

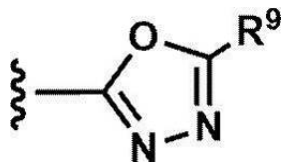
(j) a group represented by the formula:

20



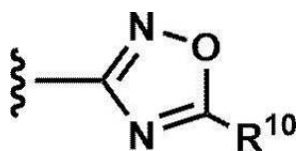
(k) a group represented by the formula:

25



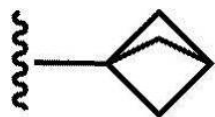
{wherein R^9 is C_{1-4} alkyl (wherein the alkyl is optionally substituted by C_{1-4} alkoxy)}, and

(m) a group represented by the formula:



wherein R^{10} is C_{1-4} alkyl)), or

5 (2) a group represented by the formula:



{wherein the group represented by the formula is optionally substituted by

(a) hydroxy,

10 (b) C_{1-6} alkyl (wherein the alkyl is optionally substituted by

(I) hydroxy,

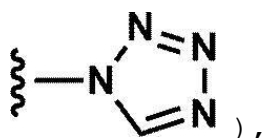
(II) carboxy,

(III) $-CONH_2$,

15 (IV) $-CO-C_{1-4}$ alkoxy,

(V) $-SO_2-C_{1-4}$ alkyl, or

(VI) a group represented by the formula:



20

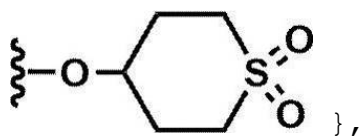
(c) C_{1-6} alkoxy (wherein the alkoxy is optionally substituted by hydroxy or $-SO_2-C_{1-4}$ alkyl),

(d) carboxy,

(e) $-CO-C_{1-4}$ alkoxy,

25 (f) $-O-C_{1-6}$ haloalkyl, or

(g) a group represented by the formula:



or a pharmaceutically acceptable salt thereof.

[Claim 13]

5 The compound of any one of Claims 1 to 8, wherein ring Cy is

(1) a group represented by the formula:



10

wherein R^{12} and R^{13} are each independently

(a) hydrogen,

(b) hydroxy,

(c) cyano,

15 (d) C_{1-6} alkyl (wherein the alkyl is optionally substituted by

(I) hydroxy,

(II) carboxy,

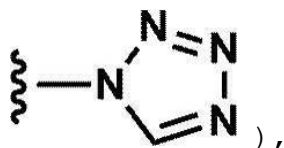
(III) $-CONH_2$,

20

(IV) $-CO-C_{1-4}$ alkoxy,

(V) $-SO_2-C_{1-4}$ alkyl, or

(VI) a group represented by the formula:



25

(e) C_{1-6} alkoxy (wherein the alkoxy is optionally substituted by hydroxy or $-SO_2-C_{1-4}$ alkyl),

(f) carboxy,

(g) $-CO-NR^5R^6$ [wherein R^5 and R^6 are each independently C_1 -

4 alkyl (wherein the alkyl is optionally substituted by C₁₋₄
alkoxy), or R⁵ and R⁶ optionally form, together with the
nitrogen atom bonded thereto, 4- to 6-membered heterocycloalkyl
containing 1 or 2 hetero atoms independently selected from the
5 group consisting of nitrogen and oxygen atoms {wherein the
heterocycloalkyl is optionally substituted by 1 or 2
substituents independently selected from the group consisting
of

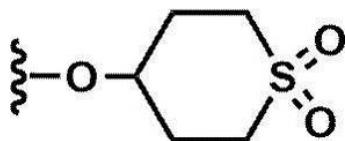
(I) hydroxy, and

10 (II) C₁₋₆ alkyl (wherein the alkyl is optionally
substituted by hydroxy)}],

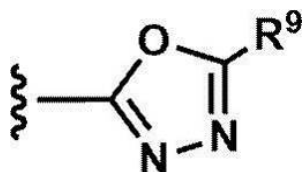
(h) -NR⁷R⁸ {wherein R⁷ and R⁸ are each independently C₁₋₄
alkyl or -CO-C₁₋₆ alkyl (wherein the alkyl is optionally
substituted by cyano)},

15 (i) -O-C₁₋₆ haloalkyl,

(j) a group represented by the formula:

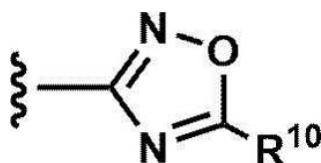


20 (k) a group represented by the formula:



{wherein R⁹ is C₁₋₄ alkyl (wherein the alkyl is optionally
25 substituted by C₁₋₄ alkoxy)}, or

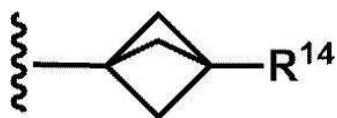
(m) a group represented by the formula:



wherein R^{10} is C_{1-4} alkyl), or R^{12} and R^{13} are optionally joined to form oxo), or

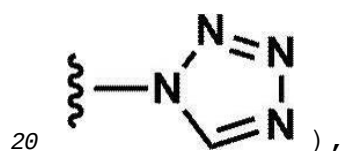
(2) a group represented by the formula:

5

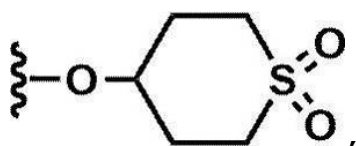


wherein R^{14} is

- (a) hydrogen,
- 10 (b) hydroxy,
- (c) C_{1-6} alkyl (wherein the alkyl is optionally substituted by
 - (I) hydroxy,
 - (II) carboxy,
 - 15 (III) $-\text{CONH}_2$,
 - (IV) $-\text{CO}-C_{1-4}$ alkoxy,
 - (V) $-\text{SO}_2-C_{1-4}$ alkyl, or
 - (VI) a group represented by the formula:



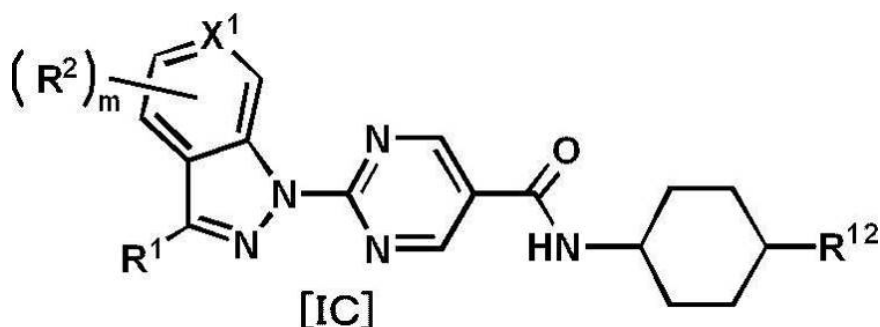
- (d) C_{1-6} alkoxy (wherein the alkoxy is optionally substituted by hydroxy or $-\text{SO}_2-C_{1-4}$ alkyl),
- (e) carboxy,
- 25 (f) $-\text{CO}-C_{1-4}$ alkoxy,
- (g) $-\text{O}-C_{1-6}$ haloalkyl, or
- (h) a group represented by the formula:



or a pharmaceutically acceptable salt thereof.

[Claim 14]

The compound of Claim 1 or 13, which is represented by
5 the formula [IC]:



wherein

10 X¹, R¹, R² and m are as defined for Claim 1, and
R¹² is as defined for Claim 13,
or a pharmaceutically acceptable salt thereof.

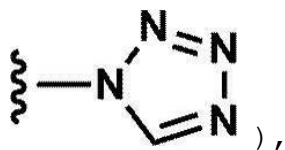
[Claim 15]

The compound of Claim 14, wherein

15 R¹² is

- (1) hydroxy,
- (2) cyano,
- (3) C₁₋₆ alkyl (wherein the alkyl is optionally substituted by
 - (a) hydroxy,
 - (b) carboxy,
 - (c) -CONH₂,
 - (d) -CO-C₁₋₄ alkoxy,
 - (e) -SO₂-C₁₋₄ alkyl, or
 - (f) a group represented by the formula:

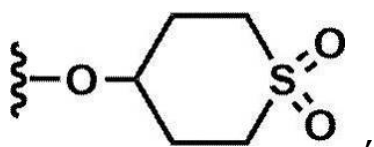
25



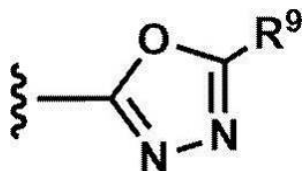
(4) C₁₋₆ alkoxy (wherein the alkoxy is optionally substituted by

hydroxy or -SO₂-C₁₋₄ alkyl),

- (5) -CO-NR⁵R⁶ [wherein R⁵ and R⁶ form, together with the nitrogen atom bonded thereto, 4- to 6-membered heterocycloalkyl containing 1 or 2 hetero atoms independently selected from the group consisting of nitrogen and oxygen atoms {wherein the heterocycloalkyl is optionally substituted by C₁₋₆ alkyl (wherein the alkyl is optionally substituted by hydroxy)}],
- (6) -NR⁷R⁸ {wherein R⁷ and R⁸ are each independently C₁₋₄ alkyl or -CO-C₁₋₆ alkyl (wherein the alkyl is optionally substituted by cyano)},
- (7) a group represented by the formula:

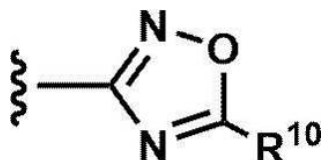


- (8) a group represented by the formula:



- {wherein R⁹ is C₁₋₄ alkyl (wherein the alkyl is optionally substituted by C₁₋₄ alkoxy)}, or

- (9) a group represented by the formula:

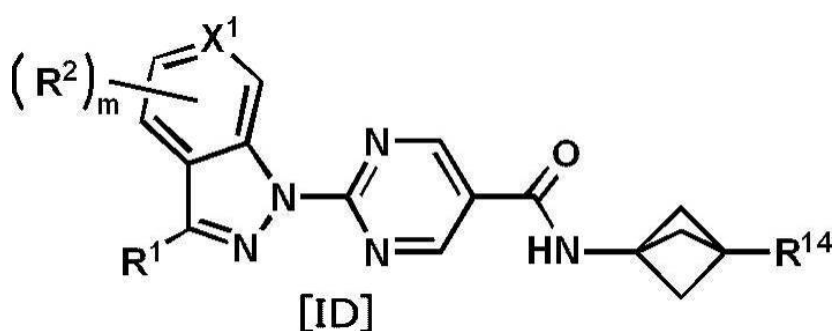


- wherein R¹⁰ is C₁₋₄ alkyl,
or a pharmaceutically acceptable salt thereof.

[Claim 16]

The compound of Claim 1 or 13, which is represented by

the formula [ID]:



5 wherein

X^1 , R^1 , R^2 and m are as defined for Claim 1, and

R^{14} is as defined for Claim 13,

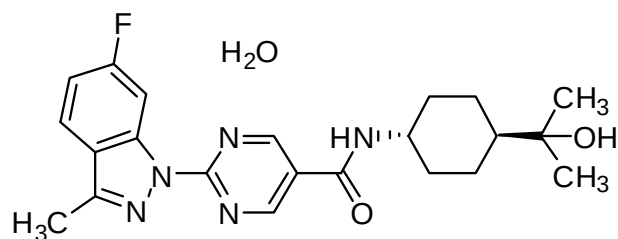
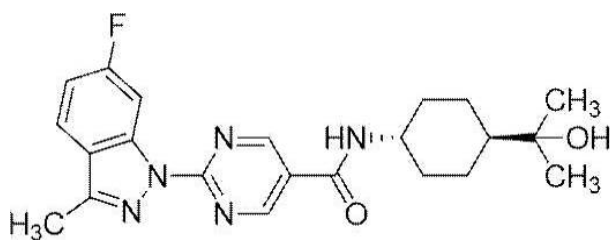
or a pharmaceutically acceptable salt thereof.

[Claim 17]

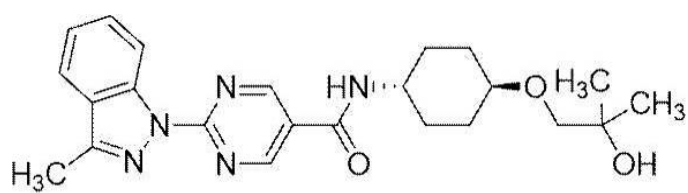
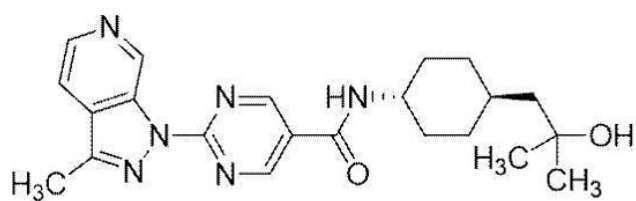
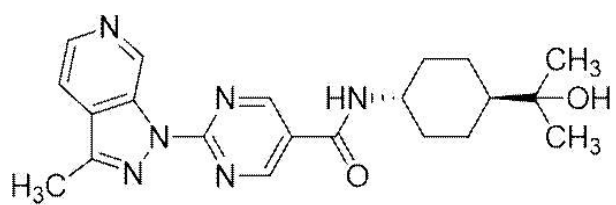
10 The compound of Claim 16, wherein R^{14} is C_{1-6} alkyl
(wherein the alkyl is optionally substituted by hydroxy), or a
pharmaceutically acceptable salt thereof.

[Claim 18]

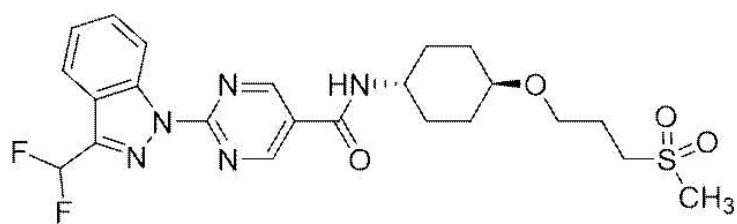
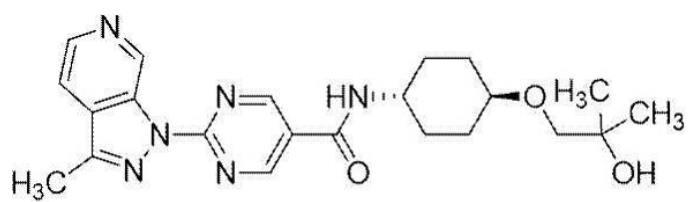
A compound selected from the group consisting of the
15 following structural formulas:



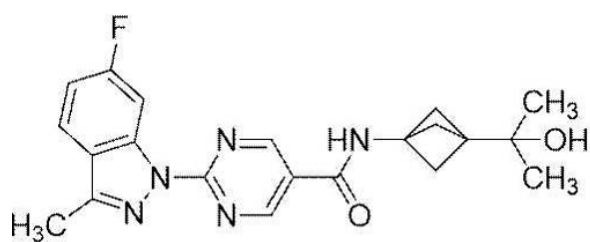
20

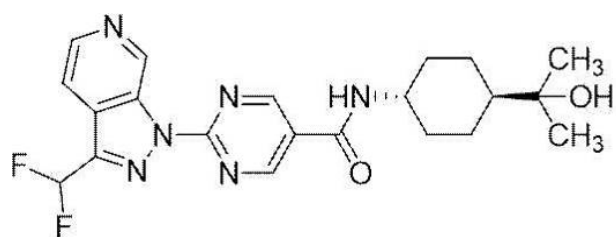
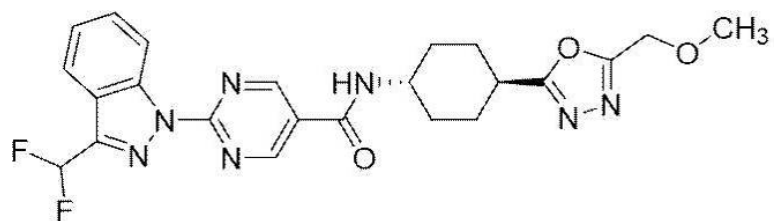


5

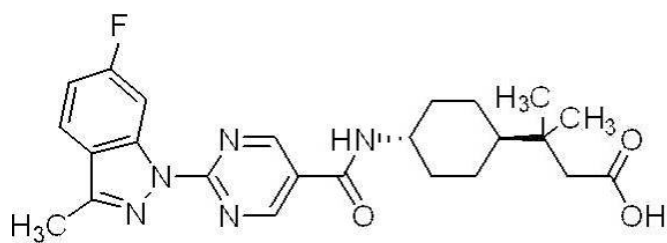
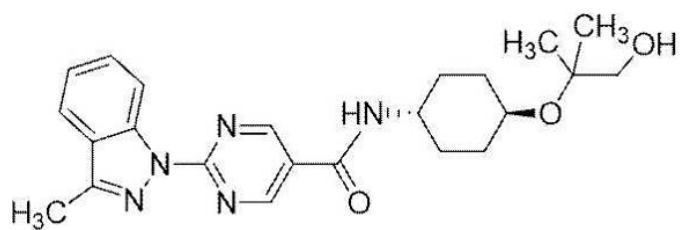
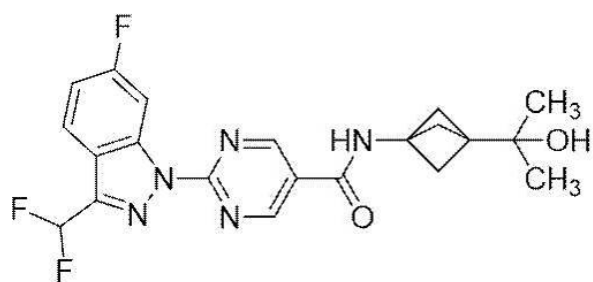


10



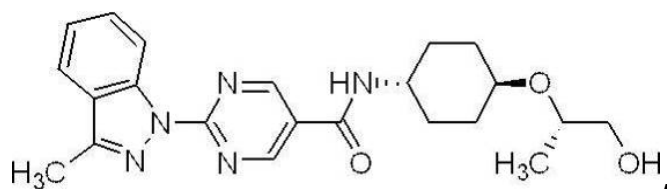


5



and

10



or a pharmaceutically acceptable salt thereof.

[Claim 19]

5 A pharmaceutical composition comprising the compound of any one of Claims 1 to 18 or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

[Claim 20]

 An H-PGDS inhibitor comprising the compound of any one of
10 Claims 1 to 18 or a pharmaceutically acceptable salt thereof.

[Claim 21]

 A therapeutic or prophylactic agent for a disease selected from the group consisting of peripheral arterial diseases, cardiovascular diseases, allergic asthma, chronic
15 obstructive pulmonary diseases, allergic rhinitis, sarcopenia, and Duchenne muscular dystrophy, the agent comprising the compound of any one of Claims 1 to 18 or a pharmaceutically acceptable salt thereof.

[Claim 22]

20 The therapeutic or prophylactic agent of Claim 21, wherein the peripheral arterial disease is intermittent claudication or comprehensive severe chronic lower extremity ischemia based on PAD.

[Claim 23]

25 A method for inhibiting H-PGDS in a mammal, comprising administering a pharmaceutically effective amount of the compound of any one of Claims 1 to 18 or a pharmaceutically acceptable salt thereof to the mammal.

[Claim 24]

30 A method for treating or preventing a disease selected from the group consisting of peripheral arterial diseases, cardiovascular diseases, allergic asthma, chronic obstructive

pulmonary diseases, allergic rhinitis, sarcopenia, and Duchenne muscular dystrophy in a mammal, comprising administering a pharmaceutically effective amount of the compound of any one of Claims 1 to 18 or a pharmaceutically acceptable salt thereof to
5 the mammal.

[Claim 25]

The method of Claim 24, wherein the peripheral arterial disease is intermittent claudication or comprehensive severe chronic lower extremity ischemia based on PAD.

10 [Claim 26]

Use of the compound of any one of Claims 1 to 18 or a pharmaceutically acceptable salt thereof in producing an H-PGDS inhibitor.

[Claim 27]

15 Use of the compound of any one of Claims 1 to 18 or a pharmaceutically acceptable salt thereof in producing a therapeutic or prophylactic agent for a disease selected from the group consisting of peripheral arterial diseases, cardiovascular diseases, allergic asthma, chronic obstructive
20 pulmonary diseases, allergic rhinitis, sarcopenia, and Duchenne muscular dystrophy.

[Claim 28]

The use of Claim 27, wherein the peripheral arterial disease is intermittent claudication or comprehensive severe
25 chronic lower extremity ischemia based on PAD.

[Claim 29]

The compound of any one of Claims 1 to 18 or a pharmaceutically acceptable salt thereof for use in inhibiting H-PGDS.

30 [Claim 30]

The compound of 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 peripheral arterial diseases, cardiovascular
35 diseases, allergic asthma, chronic obstructive pulmonary

diseases, allergic rhinitis, sarcopenia, and Duchenne muscular dystrophy.

[Claim 31]

The compound of Claim 30 or a pharmaceutically acceptable
5 salt thereof, wherein the peripheral arterial disease is
intermittent claudication or comprehensive severe chronic lower
extremity ischemia based on PAD.