

CYCLOALKYL UREA DERIVATIVE

TECHNICAL FIELD

[0001]

5 The present invention relates to a medicament for
treating or preventing a disease related to orexin receptor,
especially orexin type 2 receptor, comprising a new compound
having a urea structure or a pharmaceutically acceptable
salt thereof as an active ingredient. In more detail, the
10 present invention relates to a medicament for treating or
preventing narcolepsy, idiopathic hypersomnia, hypersomnia,
sleep apnea syndrome, etc.

BACKGROUND ART

15 [0002]

Orexin is a neuropeptide which is specifically produced
in a specific neuron spreading across lateral hypothalamus
and its adjacent region. Orexin is an endogenous ligand of
orexin receptor that is a G-protein-coupled receptor
20 existing mainly in brain, which binds to orexin receptor.
It is known that orexin receptor has two subtypes, type 1
and type 2 (Non-patent Reference 1).

[0003]

It was reported that a narcolepsy-like symptom in a
25 transgenic mouse whose orexin neuron was denatured could be

improved by intraventricular injection of an orexin peptide
(Non-patent Reference 2), and a narcolepsy-like symptom
could be initiated by knocking out prepro-orexin which is a
precursor protein of orexin (Non-patent Reference 3),
5 furthermore the orexin concentration in cerebrospinal fluid
of narcolepsy patients was markedly lowered (Non-patent
Reference 4). Thus, it is suggested that narcolepsy can be
initiated due to lack of orexin.

In addition, it was reported that there was a mutation
10 of orexin 2 receptor in a dog suffering from hereditary
narcolepsy (Non-patent Reference 5), which suggests that
orexin 2 receptor is involved in sleep-wake function.
Furthermore, it was revealed that narcolepsy-like symptom
was initiated in a KO mouse of orexin 2 receptor (Non-patent
15 Reference 6), which strongly suggests that the stimulation
on orexin 2 receptor is involved in sleep-wake function.
Thus, an orexin 2 receptor agonist is expected to be a
hopeful therapy for a patient presenting with hypersomnia-
like symptom such as narcolepsy.

20 [0004]

Recently, a compound having orexin 2 receptor agonistic
action has been reported (Patent Reference 1).

PRIOR ART

25 [0005]

(Patent Reference)

[Patent Literature 1] WO 2017/135306

[0006]

(Non-patent Reference)

5 [Non-patent Literature 1] Cell, Vol.92, 573-585, 1998

[Non-patent Literature 2] Proc. Natl. Acad. Sci. USA,
Vol. 101, 4649-4654, 2004

[Non-patent Literature 3] Cell, Vol. 98, 437-451, 1999

[Non-patent Literature 4] THE LANCET, Vol. 355, 39-40,
10 2000

[Non-patent Literature 5] Cell, Vol. 98, 365-376, 1999

[Non-patent Literature 6] Neuron, Vol. 38, 715-730,
2003

[Non-patent Literature 7] Brain, Vol. 130, 1577-1585,
15 2007

[Non-patent Literature 8] Neuroscience Letters, Vol.
569, 68-73, 2014

SUMMARY OF INVENTION

20 [0007]

(Technical Problem)

The purpose of the present invention may be to provide
a medicament for treating or preventing a disease related to
orexin type 2 receptor, for example, narcolepsy, idiopathic
25 hypersomnia, hypersomnia, sleep apnea syndrome, etc.

[0008]

(Solution to Problem)

The present inventors have extensively studied to reach the above purpose, and then have found that a compound of the following formula (1) or a pharmaceutically acceptable salt thereof (hereinafter, it may be referred to as "the present compound") has therapeutic and preventive effect for a disease related to orexin type 2 receptor, for example, narcolepsy, idiopathic hypersomnia, hypersomnia, sleep apnea syndrome, etc. Based upon the new findings, the present invention has been completed.

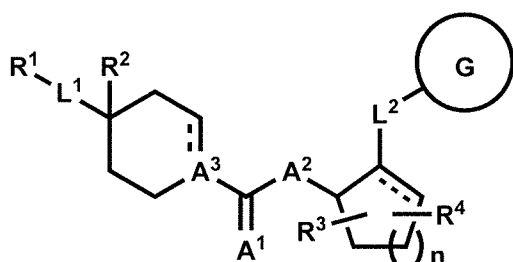
[0009]

The present invention can show as follows.

[0010]

15 (Item A1)

A compound of formula (1):



(1)

or a pharmaceutically acceptable salt thereof

wherein

20 R¹ is optionally-substituted C₆₋₁₀ aromatic carbocycl

group, optionally-substituted 5- to 10-membered aromatic heterocyclyl group, optionally-substituted C₃₋₆ saturated carbocyclyl group, optionally-substituted 4- to 10-membered saturated heterocyclyl group, or cyano;

5 L¹ and L² are each independently single bond, -CH₂-, or oxygen atom;

 R² is hydrogen atom, hydroxy group, halogen atom, cyano, or optionally-substituted C₁₋₄ alkyl; or

 when L¹ is single bond, R¹ and R² may be combined
10 together as a spiro ring to form optionally-substituted C₃₋₆ saturated carbon ring or optionally-substituted 4- to 10-membered saturated heteroring;

 R³ and R⁴ are each independently hydrogen atom, halogen atom, cyano, -(C=O)NR⁵R⁶, carboxy group, -(C=O)O-R⁷,
15 optionally-substituted C₁₋₄ alkyl, or optionally-substituted C₁₋₄ alkoxy, wherein R³ and R⁴ may bind to the same carbon atom if chemically possible; or

 when R³ and R⁴ bind to different ring carbon atoms, R³ and R⁴ may be taken together via C₁₋₆ alkylene to form a fused
20 ring or a bridged ring;

 R⁵ to R⁷ are each independently hydrogen atom, halogen atom, or optionally-substituted C₁₋₄ alkyl;

 n is an integer of 1 or 2;

 Ring G is optionally-substituted C₆₋₁₀ aromatic
25 carbocyclyl group, optionally-substituted 5- to 10-membered

aromatic heterocyclyl group, optionally-substituted C₃₋₆
saturated carbocyclyl group, or optionally-substituted 4- to
10-membered saturated heterocyclyl group;

A¹ is oxygen atom or sulfur atom;

5 A² is oxygen atom or -NH-;

A³ is -CH-, nitrogen atom, or carbon atom; and

the bond accompanied with broken line is each
independently single bond or double bond.

[0011]

10 (Item A2)

The compound of Item A1 or a pharmaceutically acceptable
salt thereof, wherein

in R² - R⁷, the optional substituent of "optionally-
substituted C₁₋₄ alkyl" is the same or different one or more
15 substituents selected from the group consisting of halogen
atom, hydroxy group, C₁₋₄ alkoxy, and C₃₋₇ cycloalkyl; and the
optional substituent of "optionally-substituted C₁₋₄ alkoxy"
is the same or different one or more substituents selected
from the group consisting of halogen atom, hydroxy group,
20 C₁₋₄ alkyl, and C₃₋₇ cycloalkyl;

in R¹, the optional substituent of "optionally-
substituted C₆₋₁₀ aromatic carbocyclyl group", "optionally-
substituted 5- to 10-membered aromatic heterocyclyl group",
"optionally-substituted C₃₋₆ saturated carbocyclyl group",
25 and "optionally-substituted 4- to 10-membered saturated

heterocyclyl group" is each independently at least one substituent selected from the group consisting of hydrogen atom, halogen atom, hydroxy group, C₆₋₁₀ aromatic carbocyclyl group (which may be optionally substituted with the same or different one or more substituents selected from the group consisting of halogen atom, hydroxy group, C₁₋₄ alkyl, C₁₋₄ alkoxy, and C₃₋₇ cycloalkyl), C₁₋₄ alkyl (which may be optionally substituted with the same or different one or more substituents selected from the group consisting of halogen atom, hydroxy group, C₁₋₄ alkoxy, and C₃₋₇ cycloalkyl), C₃₋₇ cycloalkyl (which may be optionally substituted with the same or different one or more substituents selected from the group consisting of halogen atom, hydroxy group, C₁₋₄ alkyl, C₁₋₄ alkoxy, and C₃₋₇ cycloalkyl), C₃₋₇ cycloalkoxy (which may be optionally substituted with the same or different one or more substituents selected from the group consisting of halogen atom, hydroxy group, C₁₋₄ alkyl, C₁₋₄ alkoxy, and C₃₋₇ cycloalkyl), cyano, C₁₋₄ alkoxy (which may be optionally substituted with the same or different one or more substituents selected from the group consisting of halogen atom, hydroxy group, C₁₋₄ alkyl optionally-substituted with the same or different one or more halogen atoms, and C₃₋₇ cycloalkyl), and 5- to 10-membered aromatic heterocyclyl group (which may be optionally substituted with the same or different one or more substituents selected from the group

consisting of halogen atom, hydroxy group, C₁₋₄ alkyl, C₁₋₄ alkoxy, and C₃₋₇ cycloalkyl); and

in Ring G, the optional substituent of "optionally-substituted C₆₋₁₀ aromatic carbocyclyl group", "optionally-substituted 5- to 10-membered aromatic heterocyclyl group",
5 "optionally-substituted C₃₋₆ saturated carbocyclyl group", and "optionally-substituted 4- to 10-membered saturated heterocyclyl group" is each independently at least one substituent selected from the group consisting of halogen atom, C₁₋₆ alkyl (which may be optionally substituted with the same or different one or more substituents selected from the group consisting of halogen atom, hydroxy group, C₁₋₄ alkoxy, and C₃₋₇ cycloalkyl), C₆₋₁₀ aromatic carbocyclyl group (which may be optionally substituted with the same or
10 different one or more substituents selected from the group consisting of halogen atom, hydroxy group, C₁₋₄ alkyl, C₁₋₄ alkoxy, and C₃₋₇ cycloalkyl), C₁₋₄ alkoxy (which may be optionally substituted with the same or different one or more substituents selected from the group consisting of
15 halogen atom, hydroxy group, C₁₋₄ alkyl, and C₃₋₇ cycloalkyl), C₃₋₇ cycloalkyl (which may be optionally substituted with the same or different one or more substituents selected from the group consisting of halogen atom, hydroxy group, C₁₋₄ alkyl, C₁₋₄ alkoxy, and C₃₋₇ cycloalkyl), and C₃₋₇ cycloalkoxy (which
20 may be optionally substituted with the same or different one
25

or more substituents selected from the group consisting of halogen atom, hydroxy group, C₁₋₄ alkyl, C₁₋₄ alkoxy, and C₃₋₇ cycloalkyl); or when there are plural optional substituents, two of them may be taken together via C₁₋₆ alkylene to form
5 a chemically-possible bicyclic structure selected from a fused ring, a spiro ring, and bridged ring.

[0012]

(Item A3)

The compound of Item A1 or A2 or a pharmaceutically
10 acceptable salt thereof, wherein

in R² - R⁷, the optional substituent of "optionally-substituted C₁₋₄ alkyl" is the same or different one or more substituents selected from the group consisting of halogen atom and C₁₋₄ alkoxy; and the optional substituent of
15 "optionally-substituted C₁₋₄ alkoxy" is the same or different one or more substituents selected from the group consisting of halogen atom and C₁₋₄ alkyl;

in R¹, the optional substituent of "optionally-substituted C₆₋₁₀ aromatic carbocyclyl group", "optionally-substituted 5- to 10-membered aromatic heterocyclyl group",
20 "optionally-substituted C₃₋₆ saturated carbocyclyl group", and "optionally-substituted 4- to 10-membered saturated heterocyclyl group" is each independently at least one substituent selected from the group consisting of hydrogen
25 atom, halogen atom, hydroxy group, C₆₋₁₀ aromatic carbocyclyl

group (which may be optionally substituted with the same or different one or more substituents selected from the group consisting of halogen atom, hydroxy group, C₁₋₄ alkyl, C₁₋₄ alkoxy, and C₃₋₇ cycloalkyl), C₁₋₄ alkyl (which may be optionally substituted with the same or different one or more substituents selected from the group consisting of halogen atom, hydroxy group, C₁₋₄ alkoxy, and C₃₋₇ cycloalkyl), C₃₋₇ cycloalkyl (which may be optionally substituted with the same or different one or more substituents selected from the group consisting of halogen atom, hydroxy group, C₁₋₄ alkyl, C₁₋₄ alkoxy, and C₃₋₇ cycloalkyl), cyano, C₁₋₄ alkoxy (which may be optionally substituted with the same or different one or more substituents selected from the group consisting of halogen atom, hydroxy group, C₁₋₄ alkyl optionally-substituted with the same or different one or more halogen atoms, and C₃₋₇ cycloalkyl), and 5- to 10-membered aromatic heterocyclyl group (which may be optionally substituted with the same or different one or more substituents selected from the group consisting of halogen atom, hydroxy group, C₁₋₄ alkyl, C₁₋₄ alkoxy, and C₃₋₇ cycloalkyl); and

in Ring G, the optional substituent of "optionally-substituted C₆₋₁₀ aromatic carbocyclyl group", "optionally-substituted 5- to 10-membered aromatic heterocyclyl group", "optionally-substituted C₃₋₆ saturated carbocyclyl group", and "optionally-substituted 4- to 10-membered saturated

heterocyclyl group" is each independently at least one substituent selected from the group consisting of halogen atom, C₁₋₆ alkyl (which may be optionally substituted with the same or different one or more substituents selected from the group consisting of halogen atom and C₁₋₄ alkoxy), C₆₋₁₀ aromatic carbocyclyl group (which may be optionally substituted with the same or different one or more substituents selected from the group consisting of halogen atom, C₁₋₄ alkyl, and C₁₋₄ alkoxy), C₁₋₄ alkoxy (which may be optionally substituted with the same or different one or more substituents selected from the group consisting of halogen atom and C₁₋₄ alkyl), C₃₋₇ cycloalkyl (which may be optionally substituted with the same or different one or more substituents selected from the group consisting of halogen atom, C₁₋₄ alkyl, and C₁₋₄ alkoxy), and C₃₋₇ cycloalkoxy (which may be optionally substituted with the same or different one or more substituents selected from the group consisting of halogen atom, C₁₋₄ alkyl, and C₁₋₄ alkoxy); or when there are plural optional substituents, two of them may be taken together via C₁₋₆ alkylene to form a chemically-possible bicyclic structure selected from a fused ring, a spiro ring, and bridged ring.

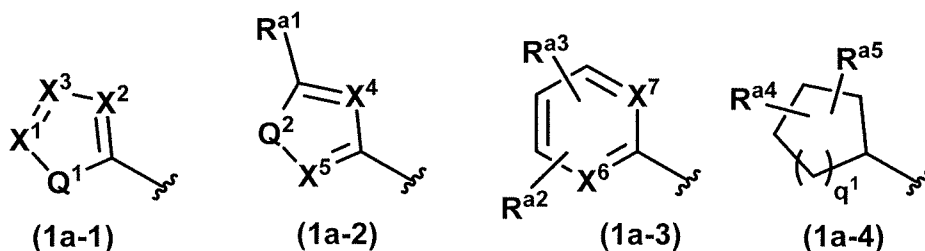
[0013]

(Item A4)

The compound of any one of Items A1 to A3 or a

pharmaceutically acceptable salt thereof, wherein

R¹ is selected from the following formulae (1a-1) to (1a-4):



5 wherein

X¹ - X⁷ are each independently nitrogen atom or CR^{a6};

Q¹ and Q² are oxygen atom, -NR^{a7}-, or sulfur atom;

R^{a1} - R^{a7} are each independently (if there are plural
 CR^{a6}, each R^{a6} is also independently), hydrogen atom, halogen
 10 atom, C₆₋₁₀ aromatic carbocyclyl group (which may be
 optionally substituted with the same or different one or
 more substituents selected from the group consisting of
 halogen atom, hydroxy group, C₁₋₄ alkyl, and C₁₋₄ alkoxy), C₁₋₄
 15 alkyl (which may be optionally substituted with the same
 or different one or more substituents selected from the group
 consisting of halogen atom, hydroxy group, C₁₋₄ alkyl, and
 C₁₋₄ alkoxy), C₃₋₇ cycloalkyl (which may be optionally
 substituted with the same or different one or more
 substituents selected from the group consisting of halogen
 20 atom, hydroxy group, C₁₋₄ alkyl, and C₁₋₄ alkoxy), cyano, C₁₋₄
 alkoxy (which may be optionally substituted with the same or
 different one or more substituents selected from the group

consisting of halogen atom, hydroxy group, C₁₋₄ alkyl, and C₁₋₄ alkoxy), C₃₋₇ cycloalkoxy (which may be optionally substituted with the same or different one or more substituents selected from the group consisting of halogen atom, hydroxy group, C₁₋₄ alkyl, and C₁₋₄ alkoxy), or 5- to 10-membered aromatic heterocyclcyl group; wherein R^{a4} and R^{a5} may bind to the same carbon atom if chemically possible; and when X¹ and X³ are both CR^{a6}, the two R^{a6} may be taken together with the carbon atoms to which they are each attached to form 6-membered carbon ring that is fused with the 5-membered ring comprising X¹, X², and X³; and

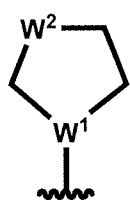
q¹ is an integer of 1 or 2.

[0014]

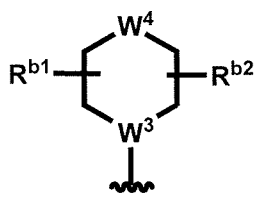
(Item A5)

The compound of any one of Items A1 to A4 or a pharmaceutically acceptable salt thereof, wherein

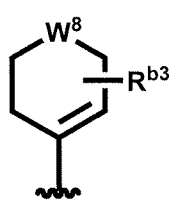
Ring G is selected from the following (1b-1) to (1b-4):



(1b-1)



(1b-2)



(1b-3)



(1b-4)

wherein

W¹, W³, W⁵, W⁶, and W⁷ are each independently nitrogen atom or CR^{b4};

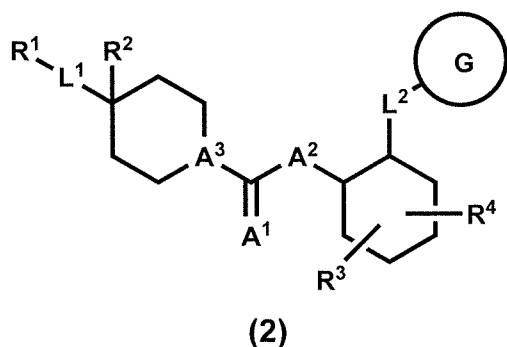
W², W⁴, and W⁸ are NR^{b5}, oxygen atom, or CR^{b6}R^{b7};

R^{b1} - R^{b7} are each independently (if there are plural CR^{b4} , each R^{b4} is also independently), hydrogen atom, C_{1-6} alkyl (which may be optionally substituted with the same or different one or more substituents selected from the group consisting of halogen atom and C_{1-4} alkoxy), C_{6-10} aromatic carbocyclyl group (which may be optionally substituted with the same or different one or more substituents selected from the group consisting of halogen atom, C_{1-4} alkyl, and C_{1-4} alkoxy), C_{1-4} alkoxy (which may be optionally substituted with the same or different one or more substituents selected from the group consisting of halogen atom and C_{1-4} alkyl), C_{3-7} cycloalkyl (which may be optionally substituted with the same or different one or more substituents selected from the group consisting of halogen atom, C_{1-4} alkyl, and C_{1-4} alkoxy), or C_{3-7} cycloalkoxy (which may be optionally substituted with the same or different one or more substituents selected from the group consisting of halogen atom, C_{1-4} alkyl, and C_{1-4} alkoxy); wherein R^{b1} and R^{b2} may bind to the same carbon atom if chemically possible; or R^{b1} and R^{b2} may be taken together via C_{1-6} alkylene to form a chemically-possible bicyclic structure selected from a fused ring, a spiro ring, and bridged ring.

[0015]

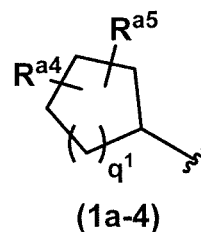
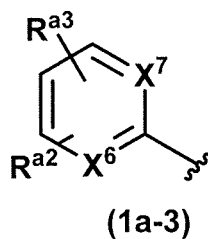
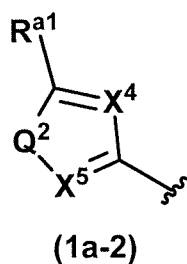
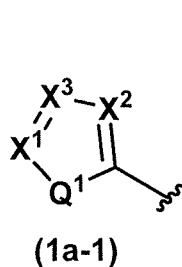
(Item A6)

The compound of any one of Items A1 to A5 of formula (2):



or a pharmaceutically acceptable salt thereof, wherein

R^1 is selected from the following formulae (1a-1) to (1a-4):



wherein

$X^1 - X^7$ are each independently nitrogen atom or CR^{a6} ;

Q^1 and Q^2 are oxygen atom, $-NR^{a7}-$, or sulfur atom;

$R^{a1} - R^{a7}$ are each independently (if there are plural CR^{a6} , each R^{a6} is also independently), hydrogen atom, halogen atom, C_{6-10} aromatic carbocyclyl group (which may be optionally substituted with the same or different one or more substituents selected from the group consisting of halogen atom, hydroxy group, C_{1-4} alkyl, and C_{1-4} alkoxy), C_{1-4} alkyl (which may be optionally substituted with the same or different one or more substituents selected from the group consisting of halogen atom, hydroxy group, C_{1-4} alkyl, and

C₁₋₄ alkoxy), C₃₋₆ cycloalkyl (which may be optionally substituted with the same or different one or more substituents selected from the group consisting of halogen atom, hydroxy group, C₁₋₄ alkyl, and C₁₋₄ alkoxy), cyano, C₁₋₄ alkoxy (which may be optionally substituted with the same or different one or more substituents selected from the group consisting of halogen atom, hydroxy group, C₁₋₄ alkyl, and C₁₋₄ alkoxy), C₃₋₇ cycloalkoxy (which may be optionally substituted with the same or different one or more substituents selected from the group consisting of halogen atom, hydroxy group, C₁₋₄ alkyl, and C₁₋₄ alkoxy), or 5- to 10-membered aromatic heterocyclyl group; wherein R^{a4} and R^{a5} may bind to the same carbon atom if chemically possible; and when X¹ and X³ are both CR^{a6}, the two R^{a6} may be taken together with the carbon atoms to which they are each attached to form 6-membered carbon ring that is fused with the 5-membered ring comprising X¹, X², and X³; and

q¹ is an integer of 1 or 2;

L¹ and L² are each independently single bond, -CH₂-, or oxygen atom;

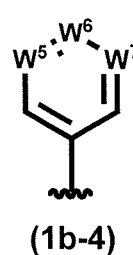
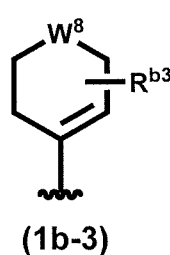
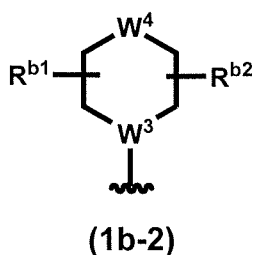
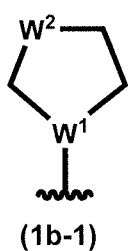
R² is hydrogen atom, hydroxy group, halogen atom, cyano, or optionally-substituted C₁₋₄ alkyl;

R³ and R⁴ are each independently hydrogen atom, halogen atom, C₁₋₄ alkyl (which may be optionally substituted with the same or different one or more substituents selected from

the group consisting of halogen atom, hydroxy group, C₁₋₄ alkoxy, and C₃₋₇ cycloalkyl), or C₁₋₄ alkoxy (which may be optionally substituted with the same or different one or more substituents selected from the group consisting of

5 halogen atom, hydroxy group, C₁₋₄ alkyl, and C₃₋₇ cycloalkyl); wherein R³ and R⁴ may bind to the same carbon atom if chemically possible; and when R³ and R⁴ bind to different carbon atoms on the ring, R³ and R⁴ may be taken together via C₁₋₆ alkylene to form a fused ring or bridged ring;

10 Ring G is selected from the following (1b-1) to (1b-4):



wherein

W¹, W³, W⁵, W⁶, and W⁷ are each independently nitrogen atom or CR^{b4};

15 W², W⁴, and W⁸ are NR^{b5}, oxygen atom or CR^{b6}R^{b7};

R^{b1} - R^{b7} are each independently (if there are plural CR^{b4}, each R^{b4} is also independently), hydrogen atom, C₁₋₆ alkyl (which may be optionally substituted with the same or different one or more substituents selected from the group

20 consisting of halogen atom and C₁₋₄ alkoxy), C₆₋₁₀ aromatic carbocyclyl group (which may be optionally substituted with the same or different one or more substituents selected from

the group consisting of halogen atom, C₁₋₄ alkyl, and C₁₋₄ alkoxy), C₁₋₄ alkoxy (which may be optionally substituted with the same or different one or more substituents selected from the group consisting of halogen atom and C₁₋₄ alkyl),
5 C₃₋₇ cycloalkyl (which may be optionally substituted with the same or different one or more substituents selected from the group consisting of halogen atom, C₁₋₄ alkyl, and C₁₋₄ alkoxy), or C₃₋₇ cycloalkoxy (which may be optionally substituted with the same or different one or more substituents selected from
10 the group consisting of halogen atom, C₁₋₄ alkyl, and C₁₋₄ alkoxy); wherein R^{b1} and R^{b2} may bind to the same carbon atom if chemically possible; or R^{b1} and R^{b2} may be taken together via C₁₋₆ alkylene to form a chemically-possible bicyclic structure selected from a fused ring, a spiro ring, and
15 bridged ring;

A¹ is oxygen atom or sulfur atom;

A² is oxygen atom or -NH-; and

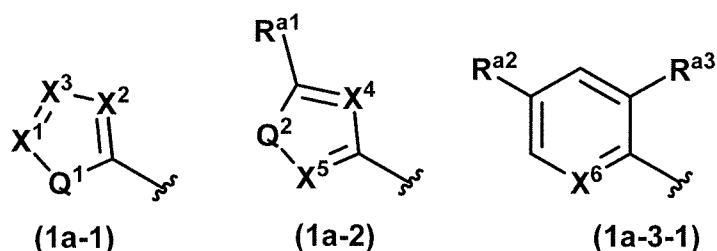
A³ is -CH-, nitrogen atom, or carbon atom.

[0016]

20 (Item A7)

The compound of Item A6 or a pharmaceutically acceptable salt thereof, wherein

R¹ is selected from the following formulae (1a-1), (1a-2), and (1a-3-1):



wherein

$X^1 - X^6$ are each independently nitrogen atom or CR^{a6} ;

Q^1 and Q^2 are oxygen atom, $-NR^{a7}-$, or sulfur atom; and

5 $R^{a1} - R^{a3}$, R^{a6} , and R^{a7} are each independently (if there are plural CR^{a6} , each R^{a6} is also independently), hydrogen atom, halogen atom, C_{6-10} aromatic carbocyclyl group (which may be optionally substituted with the same or different one or more substituents selected from the group consisting of

10 halogen atom, hydroxy group, C_{1-4} alkyl, and C_{1-4} alkoxy), C_{1-4} alkyl (which may be optionally substituted with the same or different one or more substituents selected from the group consisting of halogen atom, hydroxy group, C_{1-4} alkyl, and C_{1-4} alkoxy), C_{3-7} cycloalkyl (which may be optionally

15 substituted with the same or different one or more substituents selected from the group consisting of halogen atom, hydroxy group, C_{1-4} alkyl, and C_{1-4} alkoxy), cyano, C_{1-4} alkoxy (which may be optionally substituted with the same or different one or more substituents selected from the group

20 consisting of halogen atom, hydroxy group, C_{1-4} alkyl, and C_{1-4} alkoxy), C_{3-7} cycloalkoxy (which may be optionally substituted with the same or different one or more

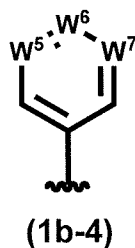
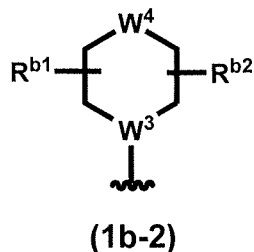
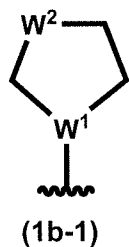
substituents selected from the group consisting of halogen atom, hydroxy group, C₁₋₄ alkyl, and C₁₋₄ alkoxy), or 5- to 10-membered aromatic heterocyclcyl group; wherein when X¹ and X³ are both CR^{a6}, the two R^{a6} may be taken together with the carbon atoms to which they are each attached to form 6-membered carbon ring that is fused with the 5-membered ring comprising X¹, X², and X³.

[0017]

(Item A8)

The compound of Items A6 or A7 or a pharmaceutically acceptable salt thereof, wherein

Ring G is selected from the following (1b-1), (1b-2), and (1b-4):



wherein

W¹, W³, W⁵, W⁶, and W⁷ are each independently nitrogen atom or CR^{b4};

W² and W⁴ are NR^{b5} or CR^{b6}R^{b7}; and

R^{b1}, R^{b2}, and R^{b4} - R^{b7} are each independently (if there are plural CR^{b4}, each R^{b4} is also independently), hydrogen atom, C₁₋₆ alkyl (which may be optionally substituted with the same or different one or more substituents selected from

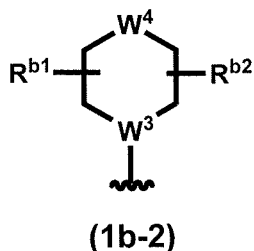
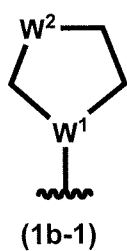
the group consisting of halogen atom and C₁₋₄ alkoxy), C₆₋₁₀ aromatic carbocyclyl group (which may be optionally substituted with the same or different one or more substituents selected from the group consisting of halogen atom, C₁₋₄ alkyl, and C₁₋₄ alkoxy), C₁₋₄ alkoxy (which may be optionally substituted with the same or different one or more substituents selected from the group consisting of halogen atom and C₁₋₄ alkyl), C₃₋₇ cycloalkyl (which may be optionally substituted with the same or different one or more substituents selected from the group consisting of halogen atom, C₁₋₄ alkyl, and C₁₋₄ alkoxy), or C₃₋₇ cycloalkoxy (which may be optionally substituted with the same or different one or more substituents selected from the group consisting of halogen atom, C₁₋₄ alkyl, and C₁₋₄ alkoxy); wherein R^{b1} and R^{b2} may bind to the same carbon atom if chemically possible; or R^{b1} and R^{b2} may be taken together via C₁₋₆ alkylene to form a bridged bicyclic structure.

[0018]

(Item A9)

The compound of any one of Items A6 to A8 or a pharmaceutically acceptable salt thereof, wherein

Ring G is selected from the following (1b-1) and (1b-2):



wherein

W^1 and W^3 are nitrogen atom or CR^{b4} ;

W^2 and W^4 are NR^{b5} or $CR^{b6}R^{b7}$; and

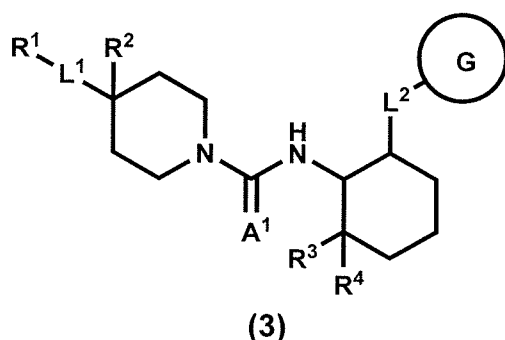
5 R^{b1} , R^{b2} , and $R^{b4} - R^{b7}$ are each independently hydrogen atom, C_{1-6} alkyl (which may be optionally substituted with the same or different one or more substituents selected from the group consisting of halogen atom and C_{1-4} alkoxy), C_{6-10} aromatic carbocyclyl group (which may be optionally substituted with the same or different one or more substituents selected from the group consisting of halogen atom, C_{1-4} alkyl, and C_{1-4} alkoxy), C_{1-4} alkoxy (which may be optionally substituted with the same or different one or more substituents selected from the group consisting of halogen atom and C_{1-4} alkyl), C_{3-7} cycloalkyl (which may be optionally substituted with the same or different one or more substituents selected from the group consisting of halogen atom, C_{1-4} alkyl, and C_{1-4} alkoxy), or C_{3-7} cycloalkoxy (which may be optionally substituted with the same or different one or more substituents selected from the group consisting of halogen atom, C_{1-4} alkyl, and C_{1-4} alkoxy); wherein R^{b1} and R^{b2} may bind to the same carbon atom if

chemically possible; or R^{b1} and R^{b2} may be taken together via C_{1-6} alkylene to form a bridged bicyclic structure.

[0019]

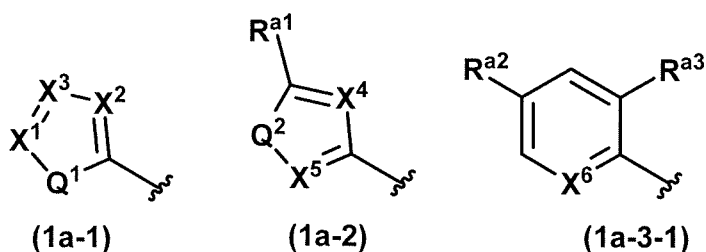
(Item A10)

5 The compound of any one of Items A1 to A9 of formula (3):



or a pharmaceutically acceptable salt thereof, wherein

R^1 is the following formula (1a-1), (1a-2), or (1a-3-1):



wherein

$X^1 - X^6$ are each independently nitrogen atom or CR^{a6} ;

Q^1 and Q^2 are oxygen atom or sulfur atom;

$R^{a1} - R^{a3}$ and R^{a6} are each independently (if there are plural CR^{a6} , each R^{a6} is also independently), hydrogen atom, halogen atom, C_{1-4} alkyl (which may be optionally substituted with the same or different one or more substituents selected from the group consisting of halogen atom, hydroxy group,

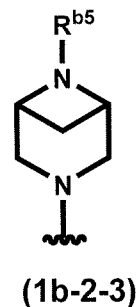
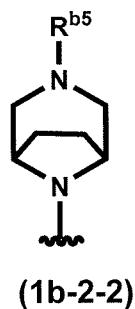
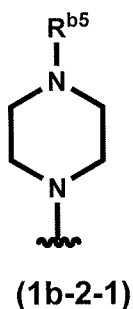
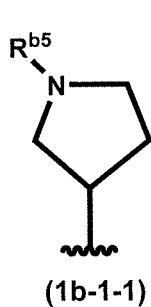
and C₁₋₄ alkoxy), C₃₋₇ cycloalkyl (which may be optionally substituted with the same or different one or more substituents selected from the group consisting of halogen atom, hydroxy group, C₁₋₄ alkyl, and C₁₋₄ alkoxy), cyano, or
 5 C₁₋₄ alkoxy (which may be optionally substituted with the same or different one or more substituents selected from the group consisting of halogen atom, hydroxy group, C₁₋₄ alkyl, and C₁₋₄ alkoxy); wherein when X¹ and X³ are both CR^{a6}, the two R^{a6} may be taken together with the carbon atoms to which
 10 they are each attached to form 6-membered carbon ring that is fused with the 5-membered ring comprising X¹, X², and X³;

L¹ and L² are each independently single bond or oxygen atom;

R² is hydrogen atom, halogen atom, or C₁₋₄ alkyl which
 15 may be optionally substituted with the same or different one or more substituents selected from the group consisting of halogen atom and hydroxy group;

R³ and R⁴ are each independently halogen atom;

20 Ring G is the following (1b-1), (1b-2-1), (1b-2-2), or (1b-2-3):



wherein

R^{b5} is hydrogen atom, or C_{1-6} alkyl which may be optionally substituted with the same or different one or more substituents selected from the group consisting of
5 halogen atom and C_{1-4} alkoxy; and

A^1 is oxygen atom or sulfur atom.

[0020]

(Item A11)

The compound of any one of Items A4 to A10 or a
10 pharmaceutically acceptable salt thereof, wherein

R^1 is formula (1a-2), and

R^{a1} is hydrogen atom, halogen atom, C_{1-4} alkyl (which may be optionally substituted with the same or different one or more substituents selected from the group consisting of
15 halogen atom and C_{1-4} alkoxy), C_{3-7} cycloalkyl (which may be optionally substituted with the same or different one or more substituents selected from the group consisting of halogen atom, hydroxy group, C_{1-4} alkyl, and C_{1-4} alkoxy), or C_{1-4} alkoxy (which may be optionally substituted with the
20 same or different one or more substituents selected from the group consisting of halogen atom and C_{1-4} alkyl).

[0021]

(Item A12)

The compound of Item A10 or A11 or a pharmaceutically
25 acceptable salt thereof, wherein

R¹ is formula (1a-2), and

X⁴ and X⁵ are both nitrogen atom.

[0022]

(Item A13)

5 The compound of any one of Items A10 to A12 or a pharmaceutically acceptable salt thereof, wherein

Ring G is formula (1b-1-1), and

R^{b5} is C₁₋₄ alkyl which may be optionally substituted with the same or different one or more halogen atoms.

10 [0023]

(Item A14)

The compound of any one of Items A10 to A12 or a pharmaceutically acceptable salt thereof, wherein

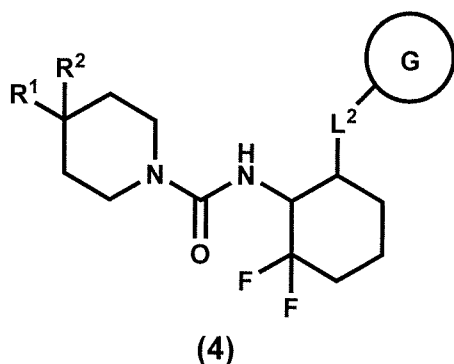
Ring G is formula (1b-2-1), and

15 R^{b5} is hydrogen atom, or C₁₋₄ alkyl which may be optionally substituted with the same or different one or more substituents selected from the group consisting of halogen atom and C₁₋₄ alkoxy.

[0024]

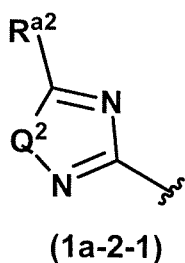
20 (Item A15)

The compound of any one of Items A1 to A12 of formula (4):



or a pharmaceutically acceptable salt thereof, wherein

R^1 is the following (1a-2-1):



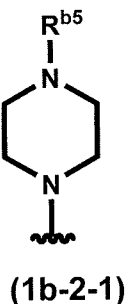
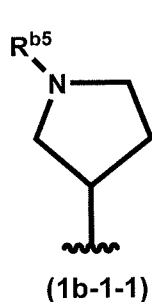
5 wherein

Q^2 is oxygen atom or sulfur atom;

R^{a2} is C_{3-7} cycloalkyl group (which may be optionally substituted with the same or different one or more substituents selected from the group consisting of halogen atom, C_{1-4} alkyl, and C_{1-4} alkoxy) or cycloalkoxy group (which may be optionally substituted with the same or different one or more substituents selected from the group consisting of halogen atom, C_{1-4} alkyl, and C_{1-4} alkoxy);

R^2 is C_{1-4} alkyl;

15 Ring G is the following (1b-1-1) or (1b-2-1):



wherein

R^{b5} is C_{1-4} alkyl which may be optionally substituted with the same or different one or more substituents selected from the group consisting of halogen atom and C_{1-4} alkyl; and

L^2 is single bond or oxygen atom.

[0025]

(Item A16)

The compound of Item A15 or a pharmaceutically acceptable salt thereof, wherein

R^{a2} is C_{3-7} cycloalkyl group which may be optionally substituted with the same or different one or more substituents selected from halogen atoms, and

R^2 is methyl group.

[0026]

(Item A17)

The compound of Item A15 or A16 or a pharmaceutically acceptable salt thereof, wherein

R^{a2} is cyclopropyl group which may be optionally substituted with the same or different one or more substituents selected from halogen atoms, and

R^2 is methyl group.

[0027]

(Item A18)

The compound of any one of Items A15 to A17 or a
5 pharmaceutically acceptable salt thereof, wherein

Ring G is formula (1b-2-1), and

R^{b8} is isopropyl group.

[0028]

(Item A19)

10 The compound of any one of Items A15 to A17 or a
pharmaceutically acceptable salt thereof, wherein

Ring G is formula (1b-1-1),

R^{b5} is isopropyl group, and

L^2 is oxygen atom.

15 [0029]

(Item A20)

The compound of any one of Items A15 to A19 or a
pharmaceutically acceptable salt thereof, wherein Q^2 is
oxygen atom.

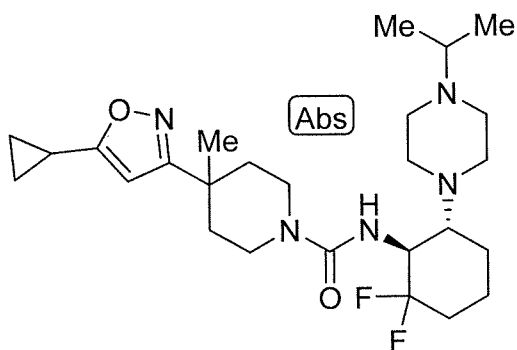
20 [0030]

(Item A21)

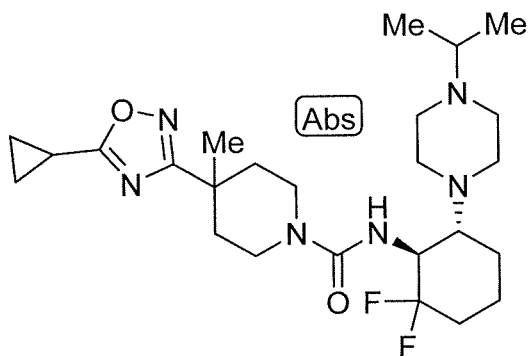
The compound of Item A1 or a pharmaceutically acceptable
salt thereof, which is selected from the following compound
names or structures:

25 Example 22: 4-(5-cyclopropyl-1,2-oxazol-3-yl)-N-

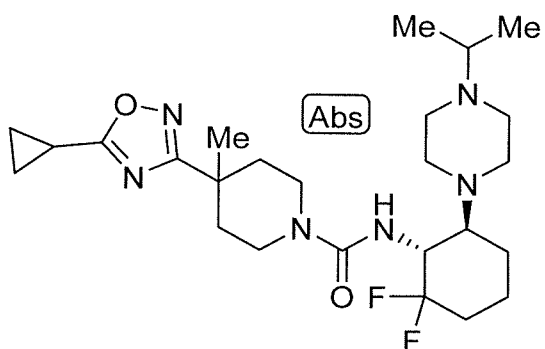
{(1S,6R)-2,2-difluoro-6-[4-(propan-2-yl)piperazin-1-yl]cyclohexyl}-4-methylpiperidine-1-carboxamide



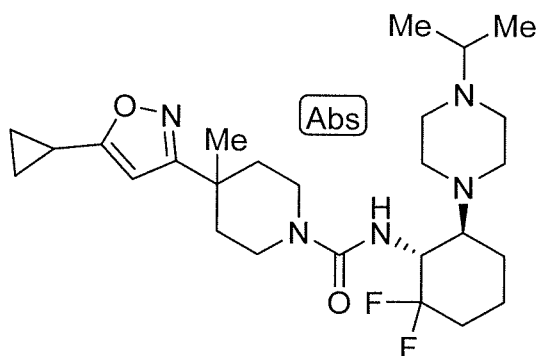
Example 23: 4-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)-N-
{(1S,6R)-2,2-difluoro-6-[4-(propan-2-yl)piperazin-1-
yl]cyclohexyl}-4-methylpiperidine-1-carboxamide



Example 24: 4-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)-N-
{(1R,6S)-2,2-difluoro-6-[4-(propan-2-yl)piperazin-1-
yl]cyclohexyl}-4-methylpiperidine-1-carboxamide

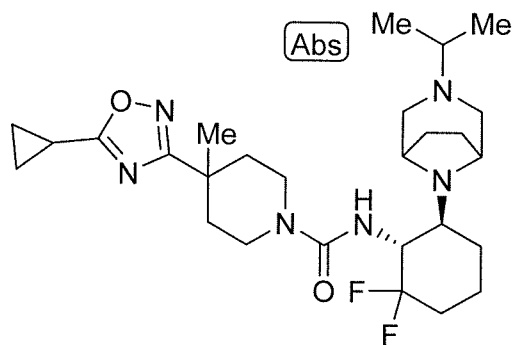


Example 25: 4-(5-cyclopropyl-1,2-oxazol-3-yl)-N-
{(1R,6S)-2,2-difluoro-6-[4-(propan-2-yl)piperazin-1-
yl]cyclohexyl}-4-methylpiperidine-1-carboxamide



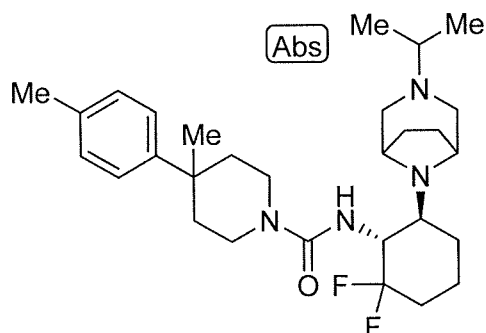
5

Example 62: 4-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)-N-
{(1R,6S)-2,2-difluoro-6-[3-(propan-2-yl)-3,8-
diazabicyclo[3.2.1]octan-8-yl]cyclohexyl}-4-
methylpiperidine-1-carboxamide

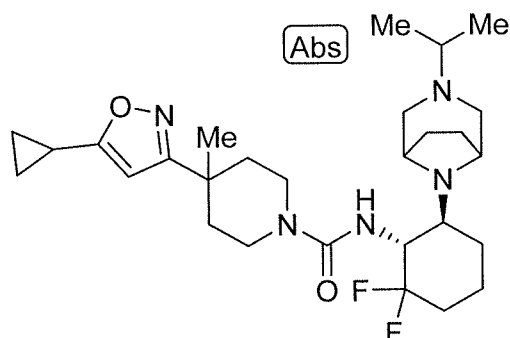


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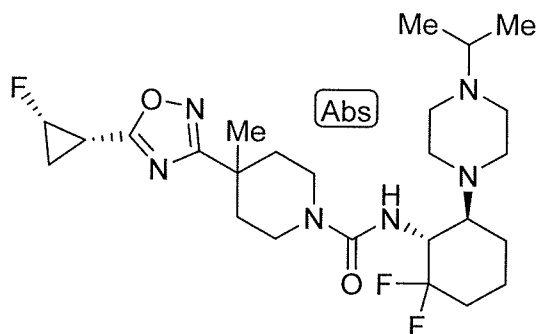
Example 63: N-{(1R,6S)-2,2-difluoro-6-[3-(propan-2-yl)-3,8-diazabicyclo[3.2.1]octan-8-yl]cyclohexyl}-4-methyl-4-(4-methylphenyl)piperidine-1-carboxamide



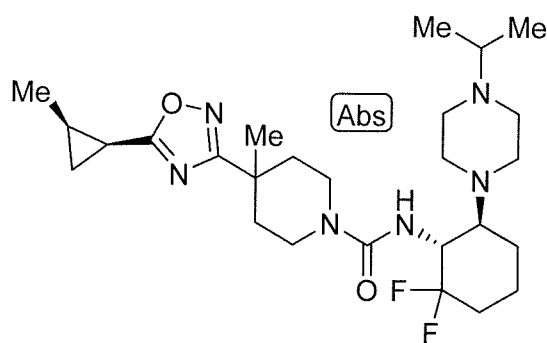
5 Example 65: 4-(5-cyclopropyl-1,2-oxazol-3-yl)-N-{(1R,6S)-2,2-difluoro-6-[3-(propan-2-yl)-3,8-diazabicyclo[3.2.1]octan-8-yl]cyclohexyl}-4-methylpiperidine-1-carboxamide



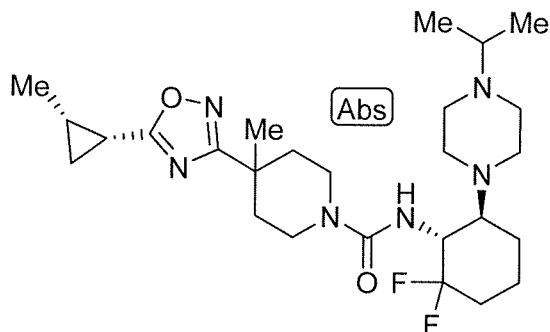
10 Example 66: N-{(1R,6S)-2,2-difluoro-6-[4-(propan-2-yl)piperazin-1-yl]cyclohexyl}-4-{5-[(1S,2S)-2-fluorocyclopropyl]-1,2,4-oxadiazol-3-yl}-4-methylpiperidine-1-carboxamide



Example 68: N-((1R,6S)-2,2-difluoro-6-[4-(propan-2-yl)piperazin-1-yl]cyclohexyl)-4-methyl-4-{5-[(1S,2R)-2-methylcyclopropyl]-1,2,4-oxadiazol-3-yl}piperidine-1-carboxamide

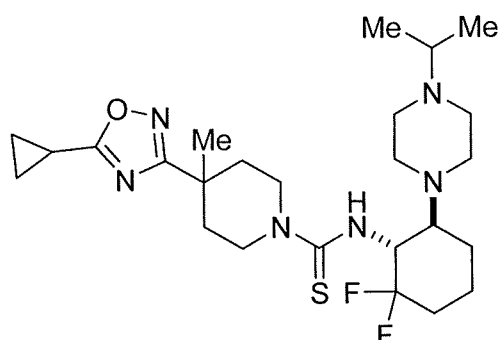


Example 69: N-((1R,6S)-2,2-difluoro-6-[4-(propan-2-yl)piperazin-1-yl]cyclohexyl)-4-methyl-4-{5-[(1R,2S)-2-methylcyclopropyl]-1,2,4-oxadiazol-3-yl}piperidine-1-carboxamide

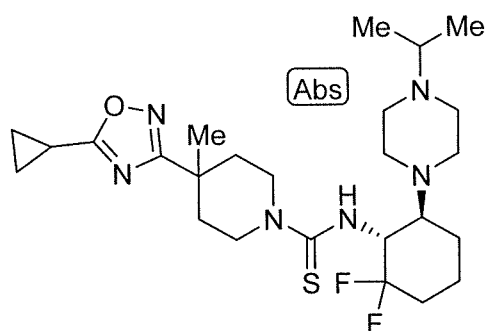


Example 79: *rac*-4-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)-N-((1R,6S)-2,2-difluoro-6-[4-(propan-2-yl)piperazin-1-

yl]cyclohexyl}-4-methylpiperidine-1-carbothioamide



Example 80: 4-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)-N-
 {(1R,6S)-2,2-difluoro-6-[4-(propan-2-yl)piperazin-1-
 5 yl]cyclohexyl}-4-methylpiperidine-1-carbothioamide.

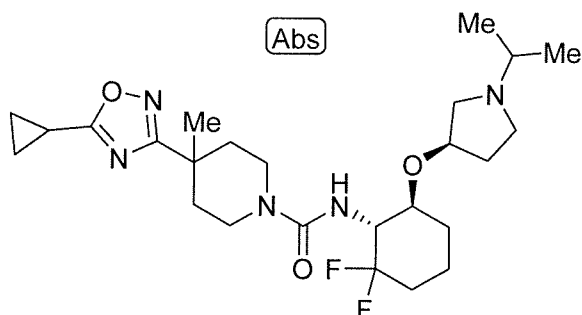


[0031]

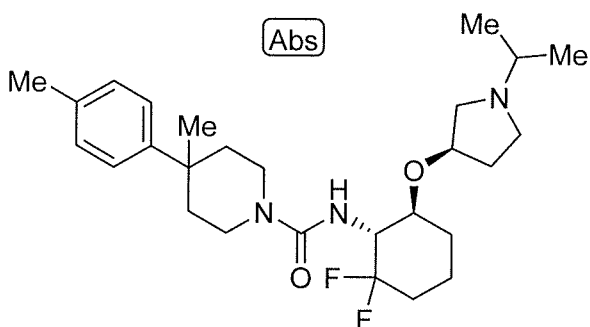
(Item A22)

The compound of Item A1 or a pharmaceutically acceptable
 10 salt thereof, which is selected from the following compound
 names or structures:

Example 64: 4-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)-N-
 [(1R,6S)-2,2-difluoro-6-{[(3R)-1-(propan-2-yl)pyrrolidin-3-
 yl]oxy}cyclohexyl]-4-methylpiperidine-1-carboxamide

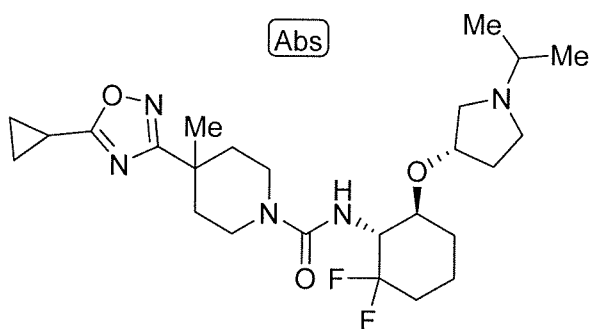


Example 67: N-[(1R,6S)-2,2-difluoro-6-{[(3R)-1-(propan-2-yl)pyrrolidin-3-yl]oxy}cyclohexyl]-4-methyl-4-(4-methylphenyl)piperidine-1-carboxamide



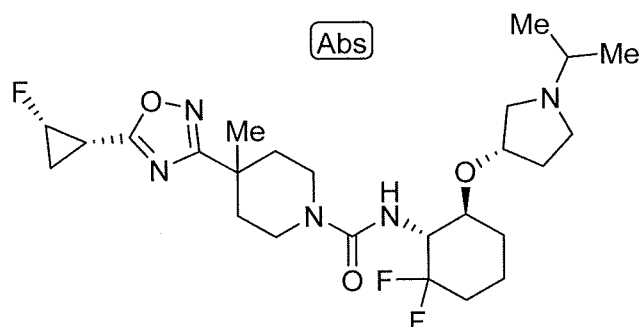
5

Example 71: 4-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)-N-[(1R,6S)-2,2-difluoro-6-{[(3S)-1-(propan-2-yl)pyrrolidin-3-yl]oxy}cyclohexyl]-4-methylpiperidine-1-carboxamide

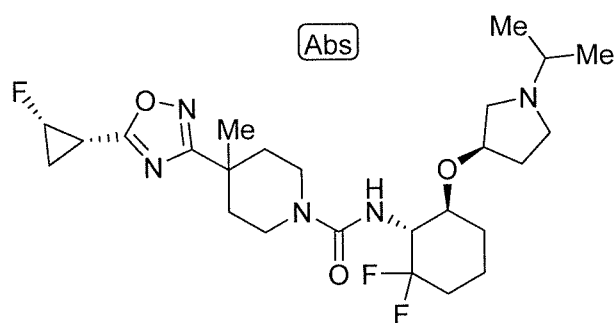


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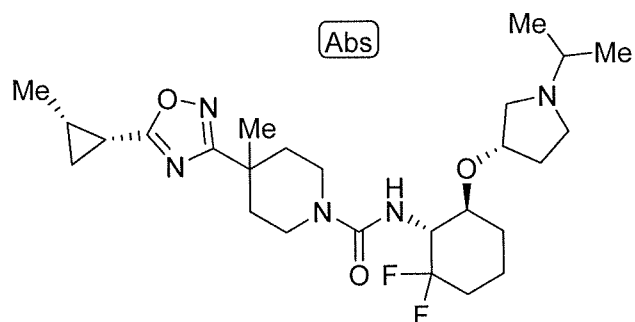
Example 72: N-[(1R,6S)-2,2-difluoro-6-{[(3S)-1-(propan-2-yl)pyrrolidin-3-yl]oxy}cyclohexyl]-4-{5-[(1S,2S)-2-fluorocyclopropyl]-1,2,4-oxadiazol-3-yl}-4-methylpiperidine-1-carboxamide



Example 73: N-[(1R,6S)-2,2-difluoro-6-{[(3R)-1-(propan-2-yl)pyrrolidin-3-yl]oxy}cyclohexyl]-4-{5-[(1S,2S)-2-fluorocyclopropyl]-1,2,4-oxadiazol-3-yl}-4-methylpiperidine-1-carboxamide

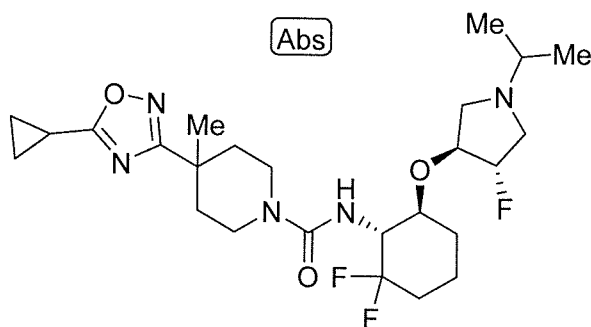


Example 74: N-[(1R,6S)-2,2-difluoro-6-{[(3S)-1-(propan-2-yl)pyrrolidin-3-yl]oxy}cyclohexyl]-4-methyl-4-{5-[(1R,2S)-2-methylcyclopropyl]-1,2,4-oxadiazol-3-yl}piperidine-1-carboxamide

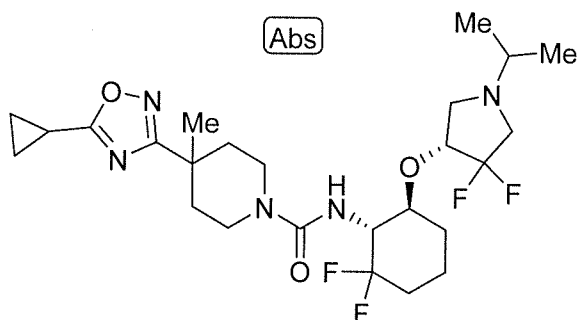


Example 75: 4-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)-N-[(1R,6S)-2,2-difluoro-6-{[(3S,4S)-4-fluoro-1-(propan-2-

yl)pyrrolidin-3-yl]oxy}cyclohexyl]-4-methylpiperidine-1-carboxamide



Example 76: 4-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)-N-
 5 [(1R,6S)-6-{[(3R)-4,4-difluoro-1-(propan-2-yl)pyrrolidin-3-yl]oxy}-2,2-difluorocyclohexyl]-4-methylpiperidine-1-carboxamide.



[0032]

10 (Item A23)

A medicament for treating a disease related to orexin receptor, comprising the compound of any one of Items A1 to A22 or a pharmaceutically acceptable salt thereof.

[0033]

15 (Item A24)

A medicament for treating narcolepsy, idiopathic hypersomnia, hypersomnia, sleep apnea syndrome, narcolepsy

syndrome involving narcolepsy-like symptom, hypersomnia associated with Parkinson's disease, hypersomnia associated with dementia with Lewy body, hypersomnia syndrome involving daytime hypersomnia (e.g. Kleine-Levin syndrome, major depression accompanied by hypersomnia, dementia with Lewy body, Parkinson's disease, progressive supranuclear palsy, Prader-Willi syndrome, Moebius syndrome, hypoventilation syndrome, Niemann-Pick disease type C, brain contusion, cerebral infarction, brain tumor, muscular dystrophy, multiple sclerosis, acute disseminated encephalomyelitis, Guillain-Barre syndrome, Rasmussen's encephalitis, Wernicke's encephalopathy, limbic encephalitis, Hashimoto encephalopathy), coma, loss of consciousness, obesity (e.g. malignant mast cell, extrinsic obesity, hyperinsulinar obesity, hyperplasmic obesity, hypophysial obesity, hypoplasmic obesity, hypothyroid obesity, hypothalamic obesity, symptomatic obesity, childhood obesity, upper body obesity, alimentary obesity, gonadal obesity, systemic mastocytosis, primary obesity, central obesity), insulin resistance syndrome, Alzheimer, impaired consciousness such as coma, side effect or complication caused by anesthesia, sleep disturbance, sleep problem, insomnia, intermittent sleep, night myoclonus, REM sleep interruption, jet lag, jet lag syndrome, sleep disorder of shift workers, dyssomnia, sleep terror, depression, major depression, sleepwalking,

enuresis, sleep disorder, Alzheimer's sundown syndrome,
disease associated with circadian rhythm, fibromyalgia,
condition resulting from decrease in sleeping quality,
bulimia, obsessive eating disorder, obesity-related
5 diseases, hypertension, diabetes, elevated plasma insulin
level/insulin resistance, hyperlipemia, hyperlipidaemia,
endometrial cancer, breast cancer, prostate cancer, colon
cancer, cancer, osteoarthritis, obstructive sleep apnea,
cholelithiasis, gallstone, heart disease, abnormal
10 heartbeat, arrhythmia, myocardial infarction, congestive
heart failure, heart failure, coronary heart disease,
cardiovascular disease, sudden death, polycystic ovary,
craniopharyngioma, Prader-Willi syndrome, Froehlich
syndrome, growth hormone deficiency, normal variant short
15 stature, Turner syndrome, children suffering from acute
lymphoblastic leukemia, syndrome X, reproductive hormone
abnormality, decrease of fecundability, infertility,
hypogonadism in men, sexual/reproductive-function
dysfunction such as hirsutism in women, fetal defect
20 associated with maternity obesity, gastrointestinal motility
disorder such as obesity-related gastroesophageal reflux,
obesity hypoventilation syndrome (Pickwickian syndrome),
respiratory disease such as respiratory distress,
inflammation such as vascular systemic inflammation,
25 arteriosclerosis, hypercholesterolemia, hyperuricemia, low

back pain, gallbladder disease, gout, renal cancer, secondary risk of obesity such as risk of left ventricle hypertrophy, migraine, headache, neuropathic pain, Parkinson's disease, psychosis, schizophrenia, facial
5 flushing, night sweat, disease in genitalium/urinary system, disease associated with sexual function or fecundability, dysthymic disorder, bipolar disorder, bipolar I disorder, bipolar II disorder, cyclothymic disorder, acute stress disorder, agoraphobia, generalized anxiety disorder,
10 obsessive-compulsive disorder, panic attack, panic disorder, posttraumatic stress disorder, separation anxiety disorder, social phobia, anxiety disorder, acute neurological and psychiatric disorder such as cerebral deficiency developed after heart bypass surgery or heart transplant, stroke,
15 ischemic stroke, cerebral ischemia, spinal cord trauma, head injury, periparturient hypoxia, cardiac arrest, hypoglycemic nerve injury, Huntington's disease, amyotrophic lateral sclerosis, multiple sclerosis, eye damage, retinopathy, cognitive impairment, muscle spasm, tremor, epilepsy,
20 disorder associated with muscle spasm, delirium, amnesic disorder, age-associated cognitive decline, schizoaffective disorder, paranoia, drug addiction, movement disorder, chronic fatigue syndrome, fatigue, medication-induced parkinsonian syndrome, Gilles de la Tourette syndrome,
25 chorea, myoclonus, tic, restless legs syndrome, dystonia,

dyskinesia, attention deficit hyperactivity disorder (ADHD),
conduct disorder, urinary incontinence, withdrawal symptom,
trigeminal neuralgia, hearing loss, tinnitus, nerve injury,
retinopathy, macular degeneration, vomiting, cerebral edema,
5 pain, bone pain, arthralgia, toothache, cataplexy, or
traumatic brain injury, comprising the compound of any one
of Items A1 to A22 or a pharmaceutically acceptable salt
thereof.

[0034]

10 (Item A25)

A medicament for treating narcolepsy, idiopathic
hypersomnia, hypersomnia, sleep apnea syndrome, narcolepsy
syndrome involving narcolepsy-like symptom, hypersomnia
associated with Parkinson's disease, or hypersomnia
15 associated with dementia with Lewy body, comprising the
compound of any one of Items A1 to A22 or a pharmaceutically
acceptable salt thereof.

[0035]

(Item A26)

20 A method for treating narcolepsy, idiopathic hypersomnia,
hypersomnia, sleep apnea syndrome, narcolepsy syndrome
involving narcolepsy-like symptom, hypersomnia associated
with Parkinson's disease, or hypersomnia associated with
dementia with Lewy body, comprising administering a
25 therapeutically effective amount of the compound of any one

of Items A1 to A22 or a pharmaceutically acceptable salt thereof to a patient in need thereof.

[0036]

(Item A27)

5 Use of the compound of any one of Items A1 to A22 or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating narcolepsy, idiopathic hypersomnia, hypersomnia, sleep apnea syndrome, narcolepsy syndrome involving narcolepsy-like symptom, hypersomnia
10 associated with Parkinson's disease, or hypersomnia associated with dementia with Lewy body.

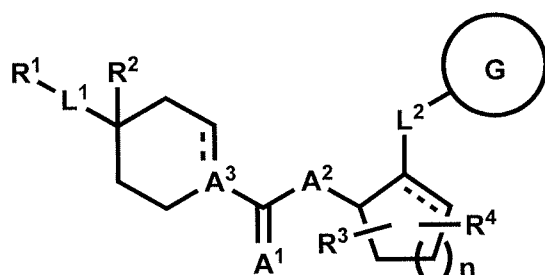
[0037]

The present invention can also show as follows.

[0038]

15 (Item 1)

A compound of formula (1):



(1)

or a pharmaceutically acceptable salt thereof

wherein

20 R¹ is optionally-substituted C₆₋₁₀ aromatic carbocycl

group, optionally-substituted 5- to 10-membered aromatic heterocyclyl group, optionally-substituted C₃₋₆ saturated carbocyclyl group, optionally-substituted 4- to 10-membered saturated heterocyclyl group, or cyano;

5 L¹ and L² are each independently single bond, methylene (which may be optionally substituted with the same or different one or more C₁₋₄ alky), -NR⁸-, -C(=O)-, -OC(=O)-, -SO-, -SO₂-, -S-, or oxygen atom;

10 R² is hydrogen atom, hydroxy group, halogen atom, cyano, or optionally-substituted C₁₋₄ alkyl; or

when L¹ is single bond, R¹ and R² may be combined together as a spiro ring to form optionally-substituted C₃₋₆ saturated carbon ring or optionally-substituted 4- to 10-membered saturated heteroring;

15 R³ and R⁴ are each independently hydrogen atom, halogen atom, cyano, -(C=O)NR⁵R⁶, carboxy group, -(C=O)O-R⁷, optionally-substituted C₁₋₄ alkyl, or optionally-substituted C₁₋₄ alkoxy, wherein R³ and R⁴ may bind to the same carbon atom if chemically possible; or

20 when R³ and R⁴ bind to different ring carbon atoms, R³ and R⁴ may be taken together via C₁₋₆ alkylene to form a fused ring or a bridged ring;

R⁵ to R⁷ are each independently hydrogen atom, halogen atom, or optionally-substituted C₁₋₄ alkyl;

25 R⁸ is each independently hydrogen atom or optionally-

substituted C₁₋₄ alkyl;

n is an integer of 1, 2, 3, or 4;

Ring G is optionally-substituted C₆₋₁₀ aromatic carbocyclyl group, optionally-substituted 5- to 10-membered aromatic heterocyclyl group, optionally-substituted C₃₋₆ saturated carbocyclyl group, or optionally-substituted 4- to 10-membered saturated heterocyclyl group;

A¹ is oxygen atom or sulfur atom;

A² is oxygen atom or -NR⁸-;

10 A³ is -CH-, nitrogen atom, or carbon atom; and

the bond accompanied with broken line is each independently single bond or double bond.

[0039]

(Item 2)

15 The compound of Item 1 or a pharmaceutically acceptable salt thereof, wherein

in R² - R⁸, the optional substituent of "optionally-substituted C₁₋₄ alkyl" is the same or different one or more substituents selected from the group consisting of halogen atom, hydroxy group, C₁₋₄ alkoxy, C₆₋₁₀ aromatic carbocyclyl group, and C₃₋₇ cycloalkyl; and the optional substituent of "optionally-substituted C₁₋₄ alkoxy" is the same or different one or more substituents selected from the group consisting of halogen atom, hydroxy group, C₁₋₄ alkyl, and C₃₋₇ cycloalkyl;

20

25

in R^1 , the optional substituent of "optionally-substituted C_{6-10} aromatic carbocyclyl group", "optionally-substituted 5- to 10-membered aromatic heterocyclyl group", "optionally-substituted C_{3-6} saturated carbocyclyl group", and "optionally-substituted 4- to 10-membered saturated heterocyclyl group" is each independently at least one substituent selected from the group consisting of hydrogen atom, halogen atom, hydroxy group, C_{6-10} aromatic carbocyclyl group (which may be optionally substituted with the same or different one or more substituents selected from the group consisting of halogen atom, hydroxy group, C_{1-4} alkyl, C_{1-4} alkoxy, and C_{3-7} cycloalkyl), C_{1-4} alkyl (which may be optionally substituted with the same or different one or more substituents selected from the group consisting of halogen atom, hydroxy group, C_{1-4} alkoxy, and C_{3-7} cycloalkyl), C_{3-7} cycloalkyl (which may be optionally substituted with the same or different one or more substituents selected from the group consisting of halogen atom, hydroxy group, C_{1-4} alkyl, C_{1-4} alkoxy, and C_{3-7} cycloalkyl), C_{1-6} alkylamino (the alkyl group of which may be optionally substituted with halogen atom, hydroxy group, or C_{3-7} cycloalkyl), C_{3-7} cycloalkoxy (which may be optionally substituted with the same or different one or more substituents selected from the group consisting of halogen atom, hydroxy group, C_{1-4} alkyl, C_{1-4} alkoxy, and C_{3-7} cycloalkyl), cyano, C_{1-4} alkoxy (which may be

optionally substituted with the same or different one or more substituents selected from the group consisting of halogen atom, hydroxy group, C₁₋₄ alkyl optionally-substituted with the same or different one or more halogen atoms, and C₃₋₇ cycloalkyl), and 5- to 10-membered aromatic heterocyclyl group (which may be optionally substituted with the same or different one or more substituents selected from the group consisting of halogen atom, hydroxy group, C₁₋₄ alkyl, C₁₋₄ alkoxy, and C₃₋₇ cycloalkyl); and

in Ring G, the optional substituent of "optionally-substituted C₆₋₁₀ aromatic carbocyclyl group", "optionally-substituted 5- to 10-membered aromatic heterocyclyl group", "optionally-substituted C₃₋₆ saturated carbocyclyl group", and "optionally-substituted 4- to 10-membered saturated heterocyclyl group" is each independently at least one substituent selected from the group consisting of halogen atom, C₁₋₆ alkyl (which may be optionally substituted with the same or different one or more substituents selected from the group consisting of halogen atom, hydroxy group, C₁₋₄ alkoxy, and C₃₋₇ cycloalkyl), C₆₋₁₀ aromatic carbocyclyl group (which may be optionally substituted with the same or different one or more substituents selected from the group consisting of halogen atom, hydroxy group, C₁₋₄ alkyl, C₁₋₄ alkoxy, and C₃₋₇ cycloalkyl), C₁₋₄ alkoxy (which may be optionally substituted with the same or different one or

more substituents selected from the group consisting of halogen atom, hydroxy group, C₁₋₄ alkyl, and C₃₋₇ cycloalkyl), C₁₋₆ alkylamino (the alkyl group of which may be optionally substituted with halogen atom, hydroxy group, or C₃₋₇ cycloalkyl), C₃₋₇ cycloalkyl (which may be optionally substituted with the same or different one or more substituents selected from the group consisting of halogen atom, hydroxy group, C₁₋₄ alkyl, C₁₋₄ alkoxy, and C₃₋₇ cycloalkyl), and C₃₋₇ cycloalkoxy (which may be optionally substituted with the same or different one or more substituents selected from the group consisting of halogen atom, hydroxy group, C₁₋₄ alkyl, C₁₋₄ alkoxy, and C₃₋₇ cycloalkyl); or when there are plural optional substituents, two of them may be taken together via C₁₋₆ alkylene to form a chemically-possible bicyclic structure selected from a fused ring, a spiro ring, and bridged ring.

[0040]

(Item 3)

The compound of Item 1 or 2 or a pharmaceutically acceptable salt thereof, wherein

in R² - R⁷, the optional substituent of "optionally-substituted C₁₋₄ alkyl" is the same or different one or more substituents selected from the group consisting of halogen atom and C₁₋₄ alkoxy; and the optional substituent of "optionally-substituted C₁₋₄ alkoxy" is the same or different

one or more substituents selected from the group consisting of halogen atom and C₁₋₄ alkyl;

in R¹, the optional substituent of "optionally-substituted C₆₋₁₀ aromatic carbocyclyl group", "optionally-substituted 5- to 10-membered aromatic heterocyclyl group",
5 "optionally-substituted C₃₋₆ saturated carbocyclyl group", and "optionally-substituted 4- to 10-membered saturated heterocyclyl group" is each independently at least one substituent selected from the group consisting of hydrogen
10 atom, halogen atom, hydroxy group, C₆₋₁₀ aromatic carbocyclyl group (which may be optionally substituted with the same or different one or more substituents selected from the group consisting of halogen atom, hydroxy group, C₁₋₄ alkyl, C₁₋₄ alkoxy, and C₃₋₇ cycloalkyl), C₁₋₄ alkyl (which may be
15 optionally substituted with the same or different one or more substituents selected from the group consisting of halogen atom, hydroxy group, C₁₋₄ alkoxy, and C₃₋₇ cycloalkyl), C₃₋₇ cycloalkyl (which may be optionally substituted with the same or different one or more substituents selected from the
20 group consisting of halogen atom, hydroxy group, C₁₋₄ alkyl, C₁₋₄ alkoxy, and C₃₋₇ cycloalkyl), cyano, C₁₋₄ alkoxy (which may be optionally substituted with the same or different one or more substituents selected from the group consisting of
25 halogen atom, hydroxy group, C₁₋₄ alkyl optionally-substituted with the same or different one or more halogen

atoms, and C₃₋₇ cycloalkyl), and 5- to 10-membered aromatic heterocyclyl group (which may be optionally substituted with the same or different one or more substituents selected from the group consisting of halogen atom, hydroxy group, C₁₋₄ alkyl, C₁₋₄ alkoxy, and C₃₋₇ cycloalkyl); and

in Ring G, the optional substituent of "optionally-substituted C₆₋₁₀ aromatic carbocyclyl group", "optionally-substituted 5- to 10-membered aromatic heterocyclyl group", "optionally-substituted C₃₋₆ saturated carbocyclyl group", and "optionally-substituted 4- to 10-membered saturated heterocyclyl group" is each independently at least one substituent selected from the group consisting of halogen atom, C₁₋₆ alkyl (which may be optionally substituted with the same or different one or more substituents selected from the group consisting of halogen atom and C₁₋₄ alkoxy), C₆₋₁₀ aromatic carbocyclyl group (which may be optionally substituted with the same or different one or more substituents selected from the group consisting of halogen atom, C₁₋₄ alkyl, and C₁₋₄ alkoxy), C₁₋₄ alkoxy (which may be optionally substituted with the same or different one or more substituents selected from the group consisting of halogen atom and C₁₋₄ alkyl), C₃₋₇ cycloalkyl (which may be optionally substituted with the same or different one or more substituents selected from the group consisting of halogen atom, C₁₋₄ alkyl, and C₁₋₄ alkoxy), C₁₋₆ alkylamino

(the alkyl group of which may be optionally substituted with halogen atom, hydroxy group, or C₃₋₇ cycloalkyl), and C₃₋₇ cycloalkoxy (which may be optionally substituted with the same or different one or more substituents selected from the group consisting of halogen atom, C₁₋₄ alkyl, and C₁₋₄ alkoxy); or when there are plural optional substituents, two of them may be taken together via C₁₋₆ alkylene to form a chemically-possible bicyclic structure selected from a fused ring, a spiro ring, and bridged ring.

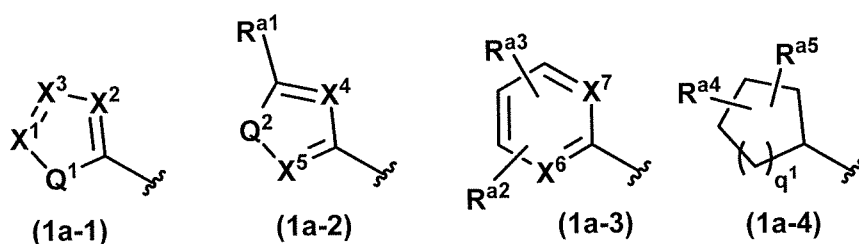
[0041]

(Item 4)

The compound of any one of Items 1 to 3 or a pharmaceutically acceptable salt thereof, wherein

R¹ is selected from the following formulae (1a-1) to

(1a-4):



wherein

X¹ - X⁷ are each independently nitrogen atom or CR^{a6};

Q¹ and Q² are oxygen atom, -NR^{a7}-, or sulfur atom;

R^{a1} - R^{a7} are each independently (if there are plural CR^{a6}, each R^{a6} is also independently), hydrogen atom, halogen atom, C₆₋₁₀ aromatic carbocyclyl group (which may be

optionally substituted with the same or different one or more substituents selected from the group consisting of halogen atom, hydroxy group, C₁₋₄ alkyl, and C₁₋₄ alkoxy), C₁₋₄ alkyl (which may be optionally substituted with the same or different one or more substituents selected from the group consisting of halogen atom, hydroxy group, C₁₋₄ alkyl, and C₁₋₄ alkoxy), C₃₋₇ cycloalkyl (which may be optionally substituted with the same or different one or more substituents selected from the group consisting of halogen atom, hydroxy group, C₁₋₄ alkyl, and C₁₋₄ alkoxy), cyano, C₁₋₄ alkoxy (which may be optionally substituted with the same or different one or more substituents selected from the group consisting of halogen atom, hydroxy group, C₁₋₄ alkyl, and C₁₋₄ alkoxy), C₃₋₇ cycloalkoxy (which may be optionally substituted with the same or different one or more substituents selected from the group consisting of halogen atom, hydroxy group, C₁₋₄ alkyl, and C₁₋₄ alkoxy), or 5- to 10-membered aromatic heterocyclyl group; wherein R^{a4} and R^{a5} may bind to the same carbon atom if chemically possible; and when X¹ and X³ are both CR^{a6}, the two R^{a6} may be taken together with the carbon atoms to which they are each attached to form 6-membered carbon ring that is fused with the 5-membered ring comprising X¹, X², and X³; and

q¹ is an integer of 1 or 2.

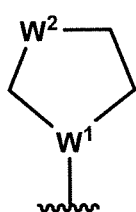
[0042]

(Item 5)

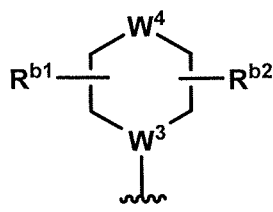
The compound of any one of Items 1 to 4 or a pharmaceutically acceptable salt thereof, wherein

Ring G is selected from the following (1b-1) to (1b-

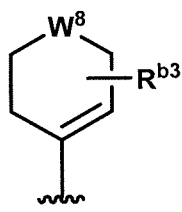
5 14):



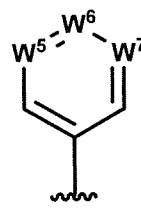
(1b-1)



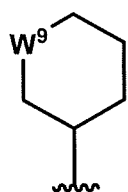
(1b-2)



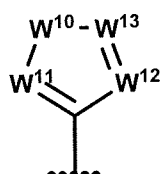
(1b-3)



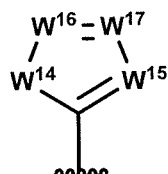
(1b-4)



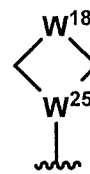
(1b-5)



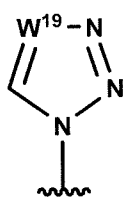
(1b-6)



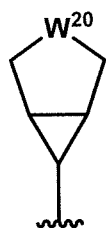
(1b-7)



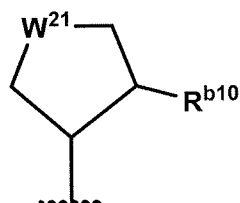
(1b-8)



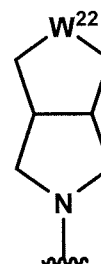
(1b-9)



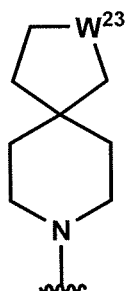
(1b-10)



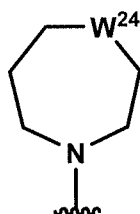
(1b-11)



(1b-12)



(1b-13)



(1b-14)

wherein

W¹, W³, W⁵, W⁶, W⁷, W¹¹, W¹², W¹³, W¹⁵, W¹⁶, W¹⁷, W¹⁹, and W²⁵
are each independently nitrogen atom or CR^{b4};

W², W⁴, W⁸, W⁹, W¹⁰, W¹⁴, W¹⁸, W²⁰, W²¹, W²², W²³, and W²⁴ are
5 NR^{b5}, oxygen atom, or CR^{b6}R^{b7};

R^{b1} - R^{b7} are each independently (if there are plural
CR^{b4}, each R^{b4} is also independently), hydrogen atom, -
N(R^{b8})R^{b9}, C₁₋₆ alkyl (which may be optionally substituted with
the same or different one or more substituents selected from
10 the group consisting of halogen atom, C₃₋₇ cycloalkyl which
may be optionally substituted with the same or different one
or more substituents selected from the group consisting of
halogen atom and C₁₋₄ alkyl (said C₁₋₄ alkyl may be substituted
with halogen atom), and C₁₋₄ alkoxy), C₆₋₁₀ aromatic
15 carbocyclyl group (which may be optionally substituted with
the same or different one or more substituents selected from
the group consisting of halogen atom, C₁₋₄ alkyl, and C₁₋₄
alkoxy), 5- to 10-membered aromatic heterocyclyl group
(which may be optionally substituted with the same or
20 different one or more substituents selected from the group
consisting of halogen atom, C₁₋₄ alkyl, and C₁₋₄ alkoxy), C₁₋₄
alkoxy (which may be optionally substituted with the same or
different one or more substituents selected from the group
consisting of halogen atom and C₁₋₄ alkyl), C₃₋₇ cycloalkyl
25 (which may be optionally substituted with the same or

different one or more substituents selected from the group consisting of halogen atom, C₁₋₄ alkyl, and C₁₋₄ alkoxy), or C₃₋₇ cycloalkoxy (which may be optionally substituted with the same or different one or more substituents selected from the group consisting of halogen atom, C₁₋₄ alkyl, and C₁₋₄ alkoxy); wherein R^{b1} and R^{b2} may bind to the same carbon atom if chemically possible; or R^{b1} and R^{b2} may be taken together via C₁₋₆ alkylene to form a chemically-possible bicyclic structure selected from a fused ring, a spiro ring, and bridged ring; and

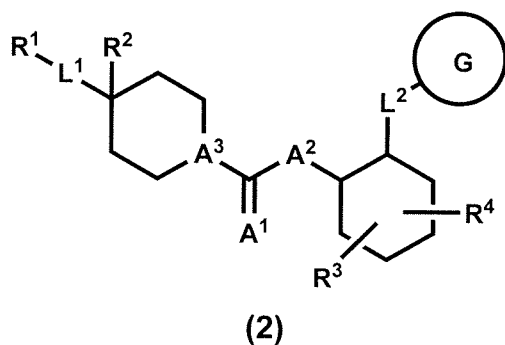
R^{b8} and R^{b9} are each independently hydrogen atom, C₁₋₆ alkyl (which may be optionally substituted with the same or different one or more substituents selected from the group consisting of halogen atom, C₁₋₄ alkoxy, C₃₋₇ cycloalkyl which may be optionally substituted with the same or different one or more substituents selected from the group consisting of halogen atom and C₁₋₄ alkyl (said C₁₋₄ alkyl may be substituted with halogen atom), and 5- to 10-membered aromatic heterocyclyl group), C₁₋₄ alkoxy (which may be optionally substituted with the same or different one or more substituents selected from the group consisting of halogen atom and C₁₋₄ alkyl), 5- to 10-membered aromatic heterocyclyl group (which may be optionally substituted with the same or different one or more substituents selected from the group consisting of halogen atom, C₁₋₄ alkyl, and C₁₋₄ alkoxy), or

C₃₋₇ cycloalkyl (which may be optionally substituted with the same or different one or more substituents selected from the group consisting of halogen atom, hydroxy group, C₁₋₄ alkyl, and C₁₋₄ alkoxy); or R^{b8} and R^{b9} may be taken together with the nitrogen atom to which they are attached to form 3- to 7-membered nitrogen-containing saturated heterocycle.

[0043]

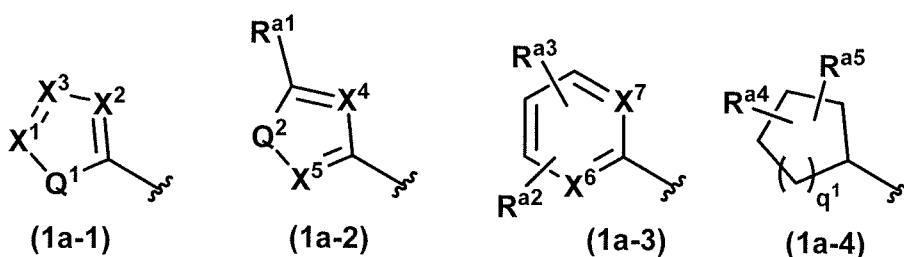
(Item 6)

The compound of any one of Items 1 to 5 of formula (2):



or a pharmaceutically acceptable salt thereof, wherein

R¹ is selected from the following formulae (1a-1) to (1a-4):



wherein

X¹ - X⁷ are each independently nitrogen atom or CR^{a6};

Q¹ and Q² are oxygen atom, -NR^{a7}-, or sulfur atom;

$R^{a1} - R^{a7}$ are each independently (if there are plural CR^{a6} , each R^{a6} is also independently), hydrogen atom, halogen atom, C_{6-10} aromatic carbocyclyl group (which may be optionally substituted with the same or different one or more substituents selected from the group consisting of halogen atom, hydroxy group, C_{1-4} alkyl, and C_{1-4} alkoxy), C_{1-4} alkyl (which may be optionally substituted with the same or different one or more substituents selected from the group consisting of halogen atom, hydroxy group, C_{1-4} alkyl, and C_{1-4} alkoxy), C_{3-6} cycloalkyl (which may be optionally substituted with the same or different one or more substituents selected from the group consisting of halogen atom, hydroxy group, C_{1-4} alkyl, and C_{1-4} alkoxy), cyano, C_{1-4} alkoxy (which may be optionally substituted with the same or different one or more substituents selected from the group consisting of halogen atom, hydroxy group, C_{1-4} alkyl, and C_{1-4} alkoxy), C_{3-7} cycloalkoxy (which may be optionally substituted with the same or different one or more substituents selected from the group consisting of halogen atom, hydroxy group, C_{1-4} alkyl, and C_{1-4} alkoxy), or 5- to 10-membered aromatic heterocyclyl group; wherein R^{a4} and R^{a5} may bind to the same carbon atom if chemically possible; and when X^1 and X^3 are both CR^{a6} , the two R^{a6} may be taken together with the carbon atoms to which they are each attached to form 6-membered carbon ring that is fused with the 5-membered

ring comprising X^1 , X^2 , and X^3 ; and

q^1 is an integer of 1 or 2;

L^1 and L^2 are each independently single bond, $-\text{CH}_2-$, or oxygen atom;

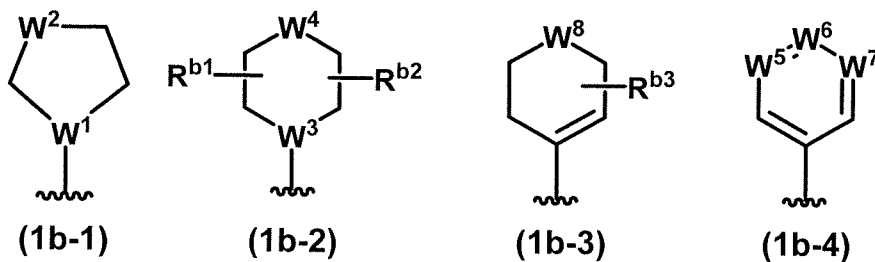
5 R^2 is hydrogen atom, hydroxy group, halogen atom, cyano, or optionally-substituted C_{1-4} alkyl;

R^3 and R^4 are each independently hydrogen atom, halogen atom, C_{1-4} alkyl (which may be optionally substituted with the same or different one or more substituents selected from the group consisting of halogen atom, hydroxy group, C_{1-4} alkoxy, and C_{3-7} cycloalkyl), or C_{1-4} alkoxy (which may be optionally substituted with the same or different one or more substituents selected from the group consisting of halogen atom, hydroxy group, C_{1-4} alkyl, and C_{3-7} cycloalkyl);

10 the group consisting of halogen atom, hydroxy group, C_{1-4} alkoxy, and C_{3-7} cycloalkyl), or C_{1-4} alkoxy (which may be optionally substituted with the same or different one or more substituents selected from the group consisting of halogen atom, hydroxy group, C_{1-4} alkyl, and C_{3-7} cycloalkyl);

15 wherein R^3 and R^4 may bind to the same carbon atom if chemically possible; and when R^3 and R^4 bind to different carbon atoms on the ring, R^3 and R^4 may be taken together via C_{1-6} alkylene to form a fused ring or bridged ring;

Ring G is selected from the following (1b-1) to (1b-4):



wherein

W^1 , W^3 , W^5 , W^6 , and W^7 are each independently nitrogen

atom or CR^{b4};

W², W⁴, and W⁸ are NR^{b5}, oxygen atom or CR^{b6}R^{b7};

R^{b1} - R^{b7} are each independently (if there are plural CR^{b4}, each R^{b4} is also independently), hydrogen atom, C₁₋₆ alkyl (which may be optionally substituted with the same or different one or more substituents selected from the group consisting of halogen atom and C₁₋₄ alkoxy), C₆₋₁₀ aromatic carbocyclyl group (which may be optionally substituted with the same or different one or more substituents selected from the group consisting of halogen atom, C₁₋₄ alkyl, and C₁₋₄ alkoxy), C₁₋₄ alkoxy (which may be optionally substituted with the same or different one or more substituents selected from the group consisting of halogen atom and C₁₋₄ alkyl), C₃₋₇ cycloalkyl (which may be optionally substituted with the same or different one or more substituents selected from the group consisting of halogen atom, C₁₋₄ alkyl, and C₁₋₄ alkoxy), or C₃₋₇ cycloalkoxy (which may be optionally substituted with the same or different one or more substituents selected from the group consisting of halogen atom, C₁₋₄ alkyl, and C₁₋₄ alkoxy); wherein R^{b1} and R^{b2} may bind to the same carbon atom if chemically possible; or R^{b1} and R^{b2} may be taken together via C₁₋₆ alkylene to form a chemically-possible bicyclic structure selected from a fused ring, a spiro ring, and bridged ring;

A¹ is oxygen atom or sulfur atom;

A² is oxygen atom or -NH-; and

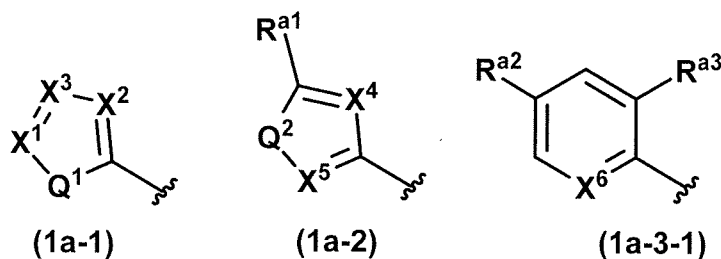
A³ is -CH-, nitrogen atom, or carbon atom.

[0044]

(Item 7)

- 5 The compound of Item 6 or a pharmaceutically acceptable salt thereof, wherein

R¹ is selected from the following formulae (1a-1), (1a-2), and (1a-3-1):



10 wherein

X¹ - X⁶ are each independently nitrogen atom or CR^{a6};

Q¹ and Q² are oxygen atom, -NR^{a7}-, or sulfur atom; and

R^{a1} - R^{a3}, R^{a6}, and R^{a7} are each independently (if there are plural CR^{a6}, each R^{a6} is also independently), hydrogen
 15 atom, halogen atom, C₆₋₁₀ aromatic carbocyclyl group (which may be optionally substituted with the same or different one or more substituents selected from the group consisting of halogen atom, hydroxy group, C₁₋₄ alkyl, and C₁₋₄ alkoxy), C₁₋₄ alkyl (which may be optionally substituted with the same
 20 or different one or more substituents selected from the group consisting of halogen atom, hydroxy group, C₁₋₄ alkyl, and C₁₋₄ alkoxy), C₃₋₇ cycloalkyl (which may be optionally

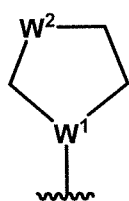
substituted with the same or different one or more substituents selected from the group consisting of halogen atom, hydroxy group, C₁₋₄ alkyl, and C₁₋₄ alkoxy), cyano, C₁₋₄ alkoxy (which may be optionally substituted with the same or different one or more substituents selected from the group consisting of halogen atom, hydroxy group, C₁₋₄ alkyl, and C₁₋₄ alkoxy), C₃₋₇ cycloalkoxy (which may be optionally substituted with the same or different one or more substituents selected from the group consisting of halogen atom, hydroxy group, C₁₋₄ alkyl, and C₁₋₄ alkoxy), or 5- to 10-membered aromatic heterocyclyl group; wherein when X¹ and X³ are both CR^{a6}, the two R^{a6} may be taken together with the carbon atoms to which they are each attached to form 6-membered carbon ring that is fused with the 5-membered ring comprising X¹, X², and X³.

[0045]

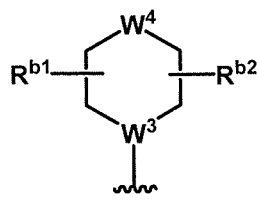
(Item 8)

The compound of Items 6 or 7 or a pharmaceutically acceptable salt thereof, wherein

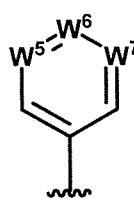
Ring G is selected from the following (1b-1), (1b-2), and (1b-4):



(1b-1)



(1b-2)



(1b-4)

wherein

W^1 , W^3 , W^5 , W^6 , and W^7 are each independently nitrogen atom or CR^{b4} ;

W^2 and W^4 are NR^{b5} or $CR^{b6}R^{b7}$; and

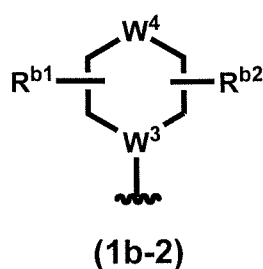
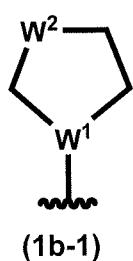
5 R^{b1} , R^{b2} , and $R^{b4} - R^{b7}$ are each independently (if there are plural CR^{b4} , each R^{b4} is also independently), hydrogen atom, C_{1-6} alkyl (which may be optionally substituted with the same or different one or more substituents selected from the group consisting of halogen atom and C_{1-4} alkoxy), C_{6-10}
10 aromatic carbocyclyl group (which may be optionally substituted with the same or different one or more substituents selected from the group consisting of halogen atom, C_{1-4} alkyl, and C_{1-4} alkoxy), C_{1-4} alkoxy (which may be optionally substituted with the same or different one or
15 more substituents selected from the group consisting of halogen atom and C_{1-4} alkyl), C_{3-7} cycloalkyl (which may be optionally substituted with the same or different one or more substituents selected from the group consisting of halogen atom, C_{1-4} alkyl, and C_{1-4} alkoxy), or C_{3-7} cycloalkoxy
20 (which may be optionally substituted with the same or different one or more substituents selected from the group consisting of halogen atom, C_{1-4} alkyl, and C_{1-4} alkoxy); wherein R^{b1} and R^{b2} may bind to the same carbon atom if chemically possible; or R^{b1} and R^{b2} may be taken together via
25 C_{1-6} alkylene to form a bridged bicyclic structure.

[0046]

(Item 9)

The compound of any one of Items 6 to 8 or a pharmaceutically acceptable salt thereof, wherein

5 Ring G is selected from the following (1b-1) and (1b-2):



wherein

W¹ and W³ are nitrogen atom or CR^{b4};

10 W² and W⁴ are NR^{b5} or CR^{b6}R^{b7}; and

R^{b1}, R^{b2}, and R^{b4} - R^{b7} are each independently hydrogen atom, C₁₋₆ alkyl (which may be optionally substituted with the same or different one or more substituents selected from the group consisting of halogen atom and C₁₋₄ alkoxy), C₆₋₁₀ aromatic carbocyclyl group (which may be optionally substituted with the same or different one or more substituents selected from the group consisting of halogen atom, C₁₋₄ alkyl, and C₁₋₄ alkoxy), C₁₋₄ alkoxy (which may be optionally substituted with the same or different one or more substituents selected from the group consisting of halogen atom and C₁₋₄ alkyl), C₃₋₇ cycloalkyl (which may be optionally substituted with the same or different one or

15

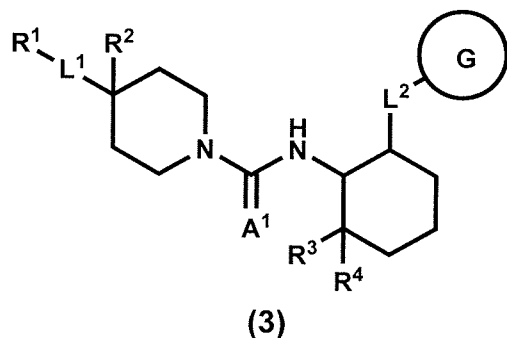
20

more substituents selected from the group consisting of halogen atom, C₁₋₄ alkyl, and C₁₋₄ alkoxy), or C₃₋₇ cycloalkoxy (which may be optionally substituted with the same or different one or more substituents selected from the group consisting of halogen atom, C₁₋₄ alkyl, and C₁₋₄ alkoxy); wherein R^{b1} and R^{b2} may bind to the same carbon atom if chemically possible; or R^{b1} and R^{b2} may be taken together via C₁₋₆ alkylene to form a bridged bicyclic structure.

[0047]

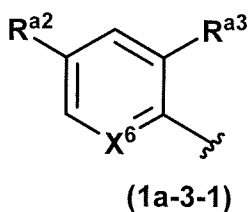
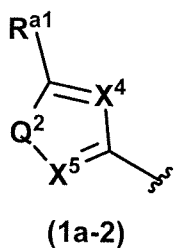
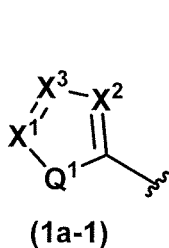
(Item 10)

The compound of any one of Items 1 to 9 of formula (3):



or a pharmaceutically acceptable salt thereof, wherein

R¹ is the following formula (1a-1), (1a-2), or (1a-3-1):



wherein

X¹ - X⁶ are each independently nitrogen atom or CR^{a6};

Q^1 and Q^2 are oxygen atom or sulfur atom;

R^{a1} - R^{a3} and R^{a6} are each independently (if there are plural CR^{a6} , each R^{a6} is also independently), hydrogen atom, halogen atom, C_{1-4} alkyl (which may be optionally substituted
5 with the same or different one or more substituents selected from the group consisting of halogen atom, hydroxy group, and C_{1-4} alkoxy), C_{3-7} cycloalkyl (which may be optionally substituted with the same or different one or more substituents selected from the group consisting of halogen atom, hydroxy group, C_{1-4} alkyl, and C_{1-4} alkoxy), cyano, or
10 C_{1-4} alkoxy (which may be optionally substituted with the same or different one or more substituents selected from the group consisting of halogen atom, hydroxy group, C_{1-4} alkyl, and C_{1-4} alkoxy); wherein when X^1 and X^3 are both CR^{a6} , the
15 two R^{a6} may be taken together with the carbon atoms to which they are each attached to form 6-membered carbon ring that is fused with the 5-membered ring comprising X^1 , X^2 , and X^3 ;

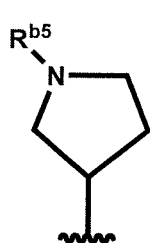
L^1 and L^2 are each independently single bond or oxygen atom;

20 R^2 is hydrogen atom, halogen atom, or C_{1-4} alkyl which may be optionally substituted with the same or different one or more substituents selected from the group consisting of halogen atom and hydroxy group;

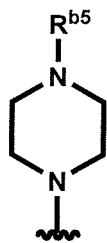
R^3 and R^4 are each independently halogen atom;

25 Ring G is the following (1b-1), (1b-2-1), (1b-2-2), or

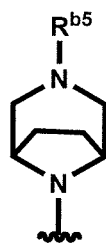
(1b-2-3) :



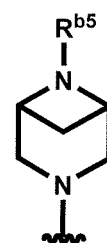
(1b-1-1)



(1b-2-1)



(1b-2-2)



(1b-2-3)

wherein

R^{b5} is hydrogen atom, or C_{1-6} alkyl which may be optionally substituted with the same or different one or more substituents selected from the group consisting of halogen atom and C_{1-4} alkoxy; and

A^1 is oxygen atom or sulfur atom.

[0048]

(Item 11)

The compound of any one of Items 4 to 10 or a pharmaceutically acceptable salt thereof, wherein

R^1 is formula (1a-2), and

R^{a1} is hydrogen atom, halogen atom, C_{1-4} alkyl (which may be optionally substituted with the same or different one or more substituents selected from the group consisting of halogen atom and C_{1-4} alkoxy), C_{3-7} cycloalkyl (which may be optionally substituted with the same or different one or more substituents selected from the group consisting of halogen atom, hydroxy group, C_{1-4} alkyl, and C_{1-4} alkoxy), or C_{1-4} alkoxy (which may be optionally substituted with the

same or different one or more substituents selected from the group consisting of halogen atom and C₁₋₄ alkyl).

[0049]

(Item 12)

5 The compound of Item 10 to 11 or a pharmaceutically acceptable salt thereof, wherein

R¹ is formula (1a-2), and

X⁴ and X⁵ are both nitrogen atom.

[0050]

10 (Item 13)

The compound of any one of Items 10 to 12 or a pharmaceutically acceptable salt thereof, wherein

Ring G is formula (1b-1-1), and

15 R^{b5} is C₁₋₄ alkyl which may be optionally substituted with the same or different one or more substituents selected from halogen atoms.

[0051]

(Item 14)

20 The compound of any one of Items 10 to 12 or a pharmaceutically acceptable salt thereof, wherein

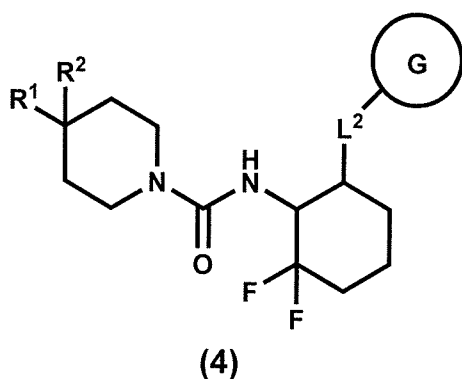
Ring G is formula (1b-2-1), and

25 R^{b5} is hydrogen atom, or C₁₋₄ alkyl which may be optionally substituted with the same or different one or more substituents selected from the group consisting of halogen atom and C₁₋₄ alkoxy.

[0052]

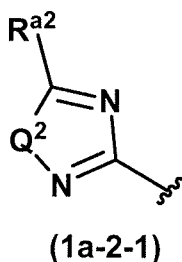
(Item 15)

The compound of any one of Items 1 to 12 of formula (4):



5 or a pharmaceutically acceptable salt thereof, wherein

R^1 is the following (1a-2-1):



wherein

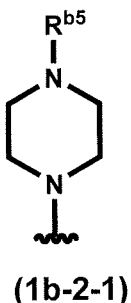
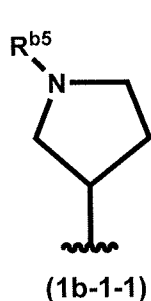
Q^2 is oxygen atom or sulfur atom;

10 R^{a2} is C_{3-7} cycloalkyl group (which may be optionally substituted with the same or different one or more substituents selected from the group consisting of halogen atom, C_{1-4} alkyl, and C_{1-4} alkoxy) or cycloalkoxy group (which may be optionally substituted with the same or different one

15 or more substituents selected from the group consisting of halogen atom, C_{1-4} alkyl, and C_{1-4} alkoxy);

R^2 is C_{1-4} alkyl;

Ring G is the following (1b-1-1) or (1b-2-1):



wherein

R^{b5} is C_{1-4} alkyl which may be optionally substituted
 5 with the same or different one or more substituents selected
 from the group consisting of halogen atom and C_{1-4} alkoxy;
 and

L^2 is single bond or oxygen atom.

[0053]

10 (Item 16)

The compound of Item 15 or a pharmaceutically acceptable
 salt thereof, wherein

R^{a2} is C_{3-7} cycloalkyl group which may be optionally
 substituted with the same or different one or more
 15 substituents selected from halogen atoms, and

R^2 is methyl group.

[0054]

(Item 17)

The compound of Item 15 or 16 or a pharmaceutically
 20 acceptable salt thereof, wherein

R^{a2} is cyclopropyl group which may be optionally

substituted with the same or different one or more substituents selected from halogen atoms, and

R^2 is methyl group.

[0055]

5 (Item 18)

The compound of any one of Items 15 to 17 or a pharmaceutically acceptable salt thereof, wherein

Ring G is formula (1b-2-1), and

R^{b5} is isopropyl group.

10 [0056]

(Item 19)

The compound of any one of Items 15 to 17 or a pharmaceutically acceptable salt thereof, wherein

Ring G is formula (1b-1-1), and

15 R^{b5} is isobutyl group.

[0057]

(Item 20)

The compound of any one of Items 15 to 17 or a pharmaceutically acceptable salt thereof, wherein

20 Ring G is formula (1b-1-1),

R^{b5} is isopropyl group, and

L^2 is oxygen atom.

[0058]

(Item 21)

25 The compound of any one of Items 15 to 20 or a

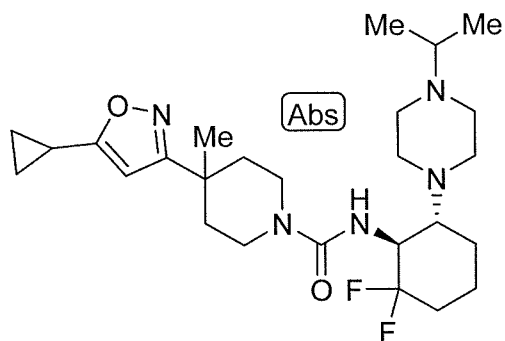
pharmaceutically acceptable salt thereof, wherein Q² is oxygen atom.

[0059]

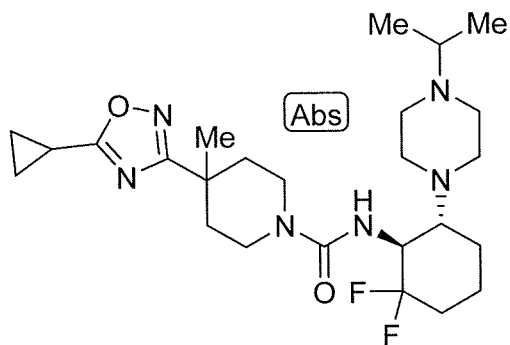
(Item 22)

- 5 The compound of Item 1 or a pharmaceutically acceptable salt thereof, which is selected from the following compound names or structures:

Example 22: 4-(5-cyclopropyl-1,2-oxazol-3-yl)-N-
{(1S,6R)-2,2-difluoro-6-[4-(propan-2-yl)piperazin-1-yl]cyclohexyl}-4-methylpiperidine-1-carboxamide
10



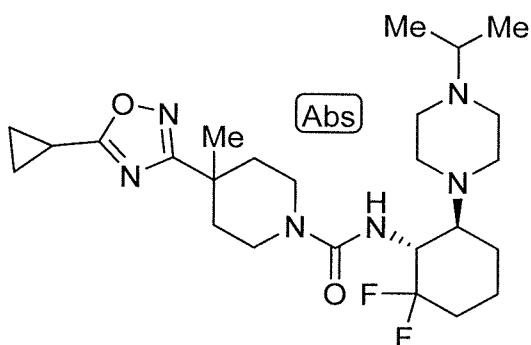
Example 23: 4-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)-N-
{(1S,6R)-2,2-difluoro-6-[4-(propan-2-yl)piperazin-1-yl]cyclohexyl}-4-methylpiperidine-1-carboxamide



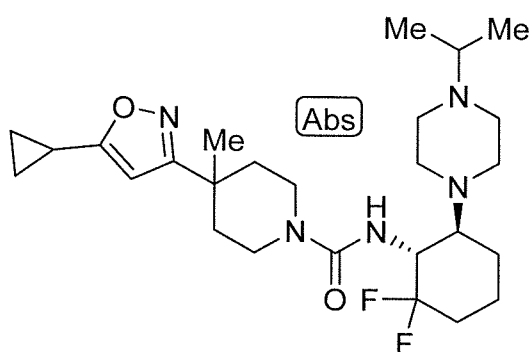
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Example 24: 4-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)-N-

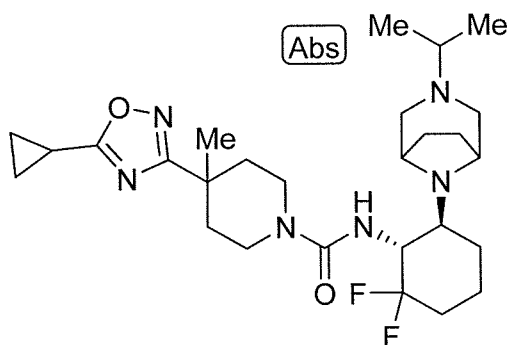
{ (1R, 6S) -2,2-difluoro-6-[4-(propan-2-yl)piperazin-1-yl]cyclohexyl}-4-methylpiperidine-1-carboxamide



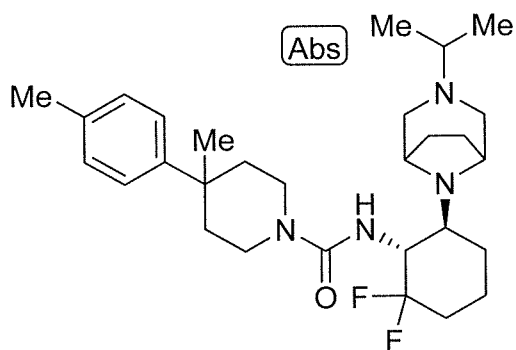
Example 25: 4-(5-cyclopropyl-1,2-oxazol-3-yl)-N-
5 { (1R, 6S) -2,2-difluoro-6-[4-(propan-2-yl)piperazin-1-yl]cyclohexyl}-4-methylpiperidine-1-carboxamide



Example 62: 4-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)-N-
10 { (1R, 6S) -2,2-difluoro-6-[3-(propan-2-yl)-3,8-diazabicyclo[3.2.1]octan-8-yl]cyclohexyl}-4-methylpiperidine-1-carboxamide

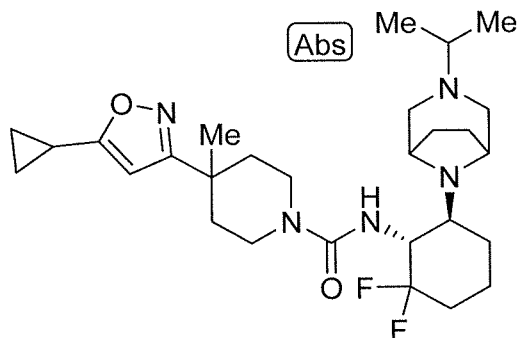


Example 63: N-((1R,6S)-2,2-difluoro-6-[3-(propan-2-yl)-3,8-diazabicyclo[3.2.1]octan-8-yl]cyclohexyl)-4-methyl-4-(4-methylphenyl)piperidine-1-carboxamide



5

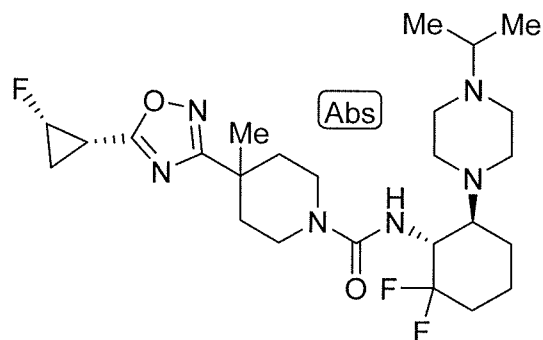
Example 65: 4-(5-cyclopropyl-1,2-oxazol-3-yl)-N-((1R,6S)-2,2-difluoro-6-[3-(propan-2-yl)-3,8-diazabicyclo[3.2.1]octan-8-yl]cyclohexyl)-4-methylpiperidine-1-carboxamide



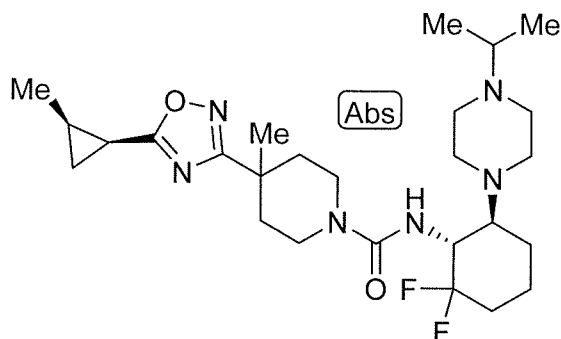
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Example 66: N-((1R,6S)-2,2-difluoro-6-[4-(propan-2-

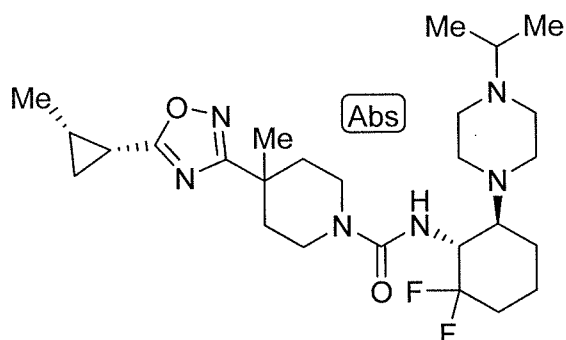
yl)piperazin-1-yl]cyclohexyl}-4-{5-[(1S,2S)-2-fluorocyclopropyl]-1,2,4-oxadiazol-3-yl}-4-methylpiperidine-1-carboxamide



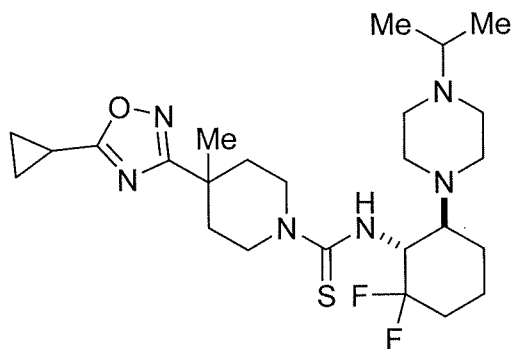
5 Example 68: N-{(1R,6S)-2,2-difluoro-6-[4-(propan-2-yl)piperazin-1-yl]cyclohexyl}-4-methyl-4-{5-[(1S,2R)-2-methylcyclopropyl]-1,2,4-oxadiazol-3-yl}piperidine-1-carboxamide



10 Example 69: N-{(1R,6S)-2,2-difluoro-6-[4-(propan-2-yl)piperazin-1-yl]cyclohexyl}-4-methyl-4-{5-[(1R,2S)-2-methylcyclopropyl]-1,2,4-oxadiazol-3-yl}piperidine-1-carboxamide

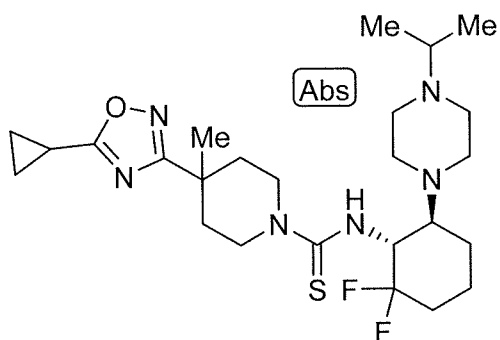


Example 79: *rac*-4-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)-N-((1R,6S)-2,2-difluoro-6-[4-(propan-2-yl)piperazin-1-yl]cyclohexyl)-4-methylpiperidine-1-carbothioamide



5

Example 80: 4-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)-N-((1R,6S)-2,2-difluoro-6-[4-(propan-2-yl)piperazin-1-yl]cyclohexyl)-4-methylpiperidine-1-carbothioamide.



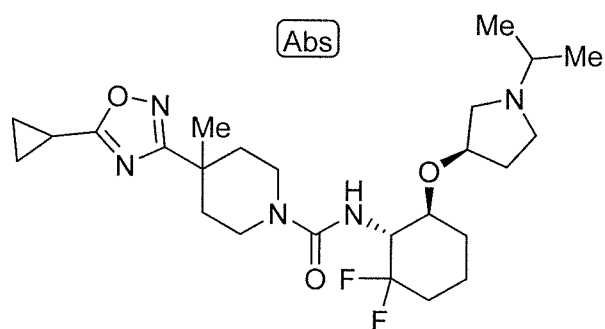
10 [0060]

(Item 23)

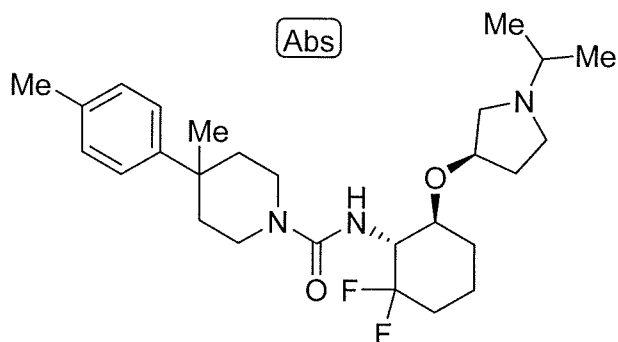
The compound of Item 1 or a pharmaceutically acceptable salt

thereof, which is selected from the following compound names or structures:

Example 64: 4-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)-N-
 [(1R,6S)-2,2-difluoro-6-{[(3R)-1-(propan-2-yl)pyrrolidin-3-yl]oxy}cyclohexyl]-4-methylpiperidine-1-carboxamide
 5

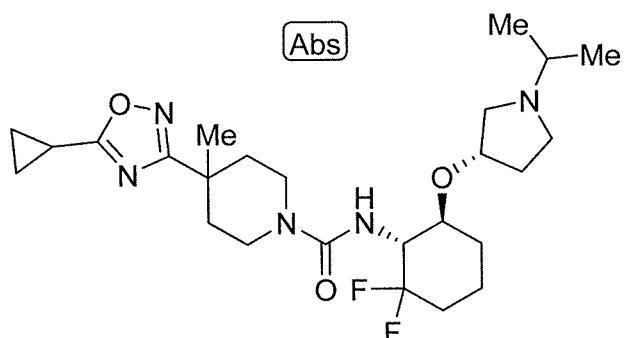


Example 67: N-[(1R,6S)-2,2-difluoro-6-{[(3R)-1-(propan-2-yl)pyrrolidin-3-yl]oxy}cyclohexyl]-4-methyl-4-(4-methylphenyl)piperidine-1-carboxamide

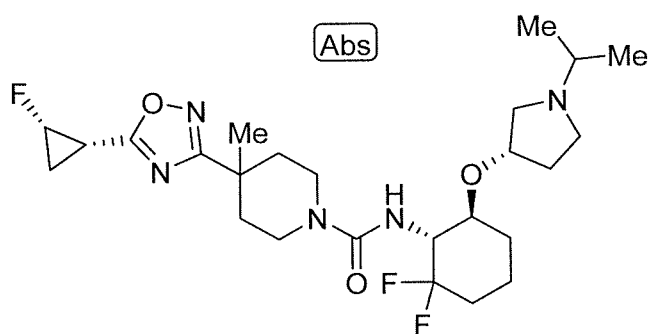


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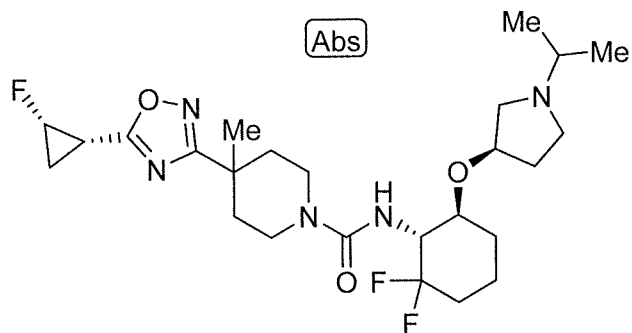
Example 71: 4-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)-N-
 [(1R,6S)-2,2-difluoro-6-{[(3S)-1-(propan-2-yl)pyrrolidin-3-yl]oxy}cyclohexyl]-4-methylpiperidine-1-carboxamide



Example 72: N-[(1R,6S)-2,2-difluoro-6-{[(3S)-1-(propan-2-yl)pyrrolidin-3-yl]oxy}cyclohexyl]-4-{5-[(1S,2S)-2-fluorocyclopropyl]-1,2,4-oxadiazol-3-yl}-4-methylpiperidine-1-carboxamide

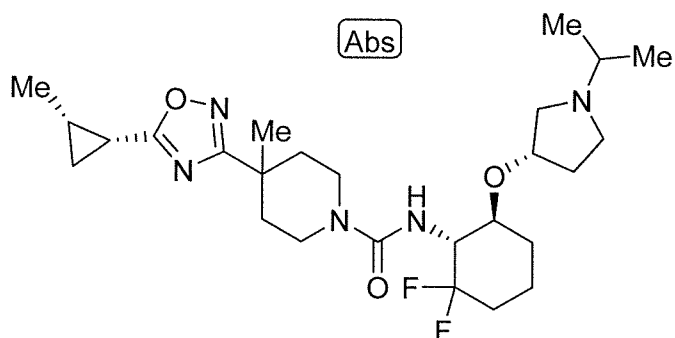


Example 73: N-[(1R,6S)-2,2-difluoro-6-{[(3R)-1-(propan-2-yl)pyrrolidin-3-yl]oxy}cyclohexyl]-4-{5-[(1S,2S)-2-fluorocyclopropyl]-1,2,4-oxadiazol-3-yl}-4-methylpiperidine-1-carboxamide

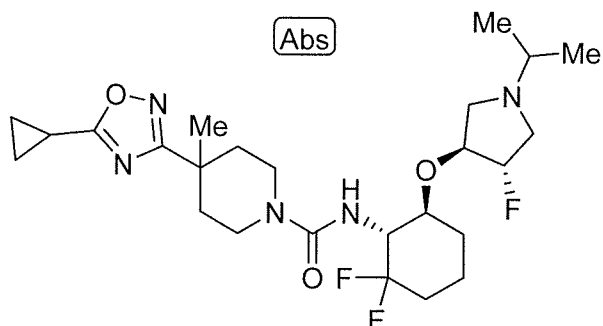


Example 74: N-[(1R,6S)-2,2-difluoro-6-{[(3S)-1-(propan-2-yl)pyrrolidin-3-yl]oxy}cyclohexyl]-4-methyl-4-{5-[(1S,2S)-2-fluorocyclopropyl]-1,2,4-oxadiazol-3-yl}piperidine-1-carboxamide

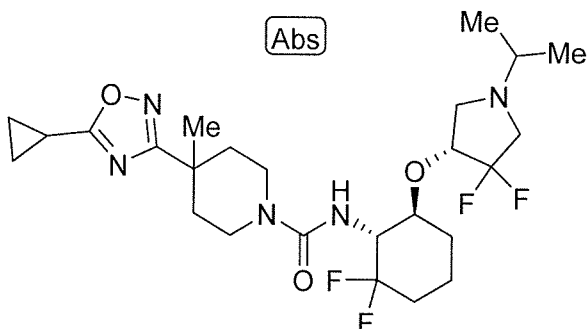
[(1R,2S)-2-methylcyclopropyl]-1,2,4-oxadiazol-3-yl}piperidine-1-carboxamide



Example 75: 4-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)-N-
5 [(1R,6S)-2,2-difluoro-6-{[(3S,4S)-4-fluoro-1-(propan-2-yl)pyrrolidin-3-yl]oxy}cyclohexyl]-4-methylpiperidine-1-carboxamide



Example 76: 4-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)-N-
10 [(1R,6S)-6-{[(3R)-4,4-difluoro-1-(propan-2-yl)pyrrolidin-3-yl]oxy}-2,2-difluorocyclohexyl]-4-methylpiperidine-1-carboxamide.

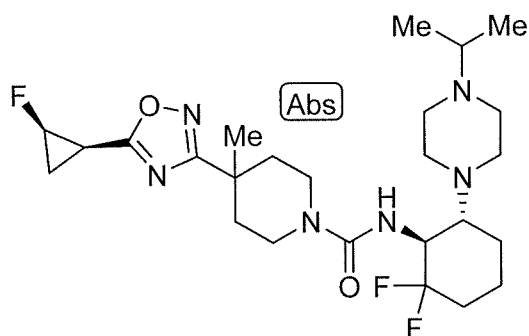


[0061]

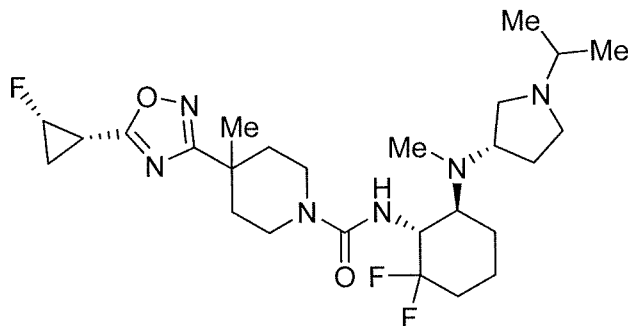
(Item 24)

The compound of Item 1 or a pharmaceutically acceptable salt thereof, which is selected from the following compound names or structures:

Example 82: N-[(1S,6R)-2,2-difluoro-6-[4-(propan-2-yl)piperazin-1-yl]cyclohexyl]-4-{5-[(1R,2R)-2-fluorocyclopropyl]-1,2,4-oxadiazol-3-yl}-4-methylpiperidine-1-carboxamide

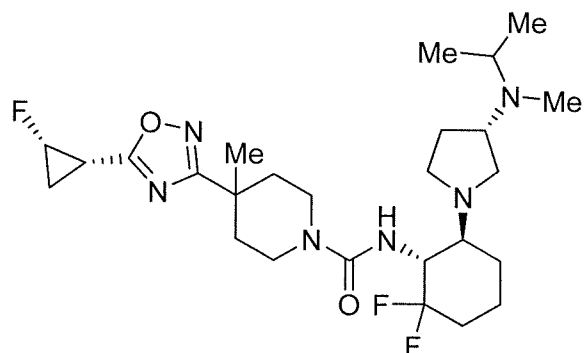


Example 95: N-[(1R,6S)-2,2-difluoro-6-{methyl[(3S)-1-(propan-2-yl)pyrrolidin-3-yl]amino}cyclohexyl]-4-{5-[(1S,2S)-2-fluorocyclopropyl]-1,2,4-oxadiazol-3-yl}-4-methylpiperidine-1-carboxamide

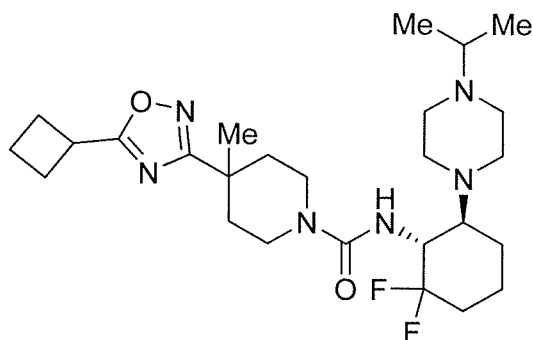


Example 96: N-[(1R,6S)-2,2-difluoro-6-{(3S)-3-[methyl(propan-2-yl)amino]pyrrolidin-1-yl}cyclohexyl]-4-{5-

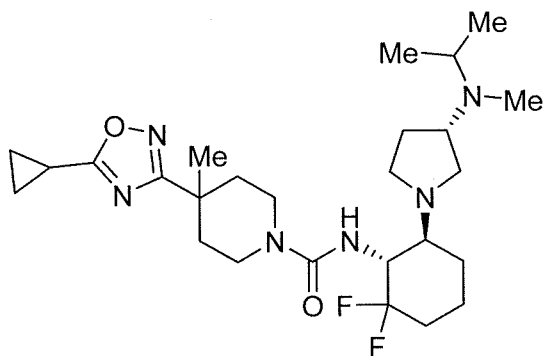
[(1S,2S)-2-fluorocyclopropyl]-1,2,4-oxadiazol-3-yl}-4-methylpiperidine-1-carboxamide



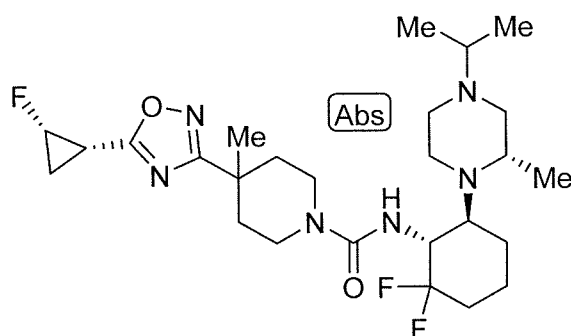
Example 97: 4-(5-cyclobutyl-1,2,4-oxadiazol-3-yl)-N-
5 { (1R,6S)-2,2-difluoro-6-[4-(propan-2-yl)piperazin-1-yl]cyclohexyl}-4-methylpiperidine-1-carboxamide



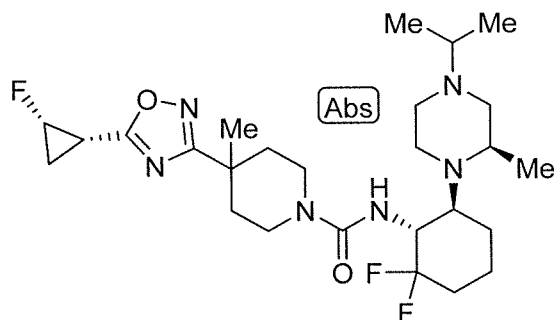
Example 99: 4-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)-N-
10 [(1R,6S)-2,2-difluoro-6-{ (3S)-3-[methyl (propan-2-yl)amino]pyrrolidin-1-yl}cyclohexyl]-4-methylpiperidine-1-carboxamide



Example 110: N-((1R,6S)-2,2-difluoro-6-((2S)-2-methyl-4-(propan-2-yl)piperazin-1-yl)cyclohexyl)-4-((5-((1S,2S)-2-fluorocyclopropyl)-1,2,4-oxadiazol-3-yl)-4-methylpiperidino)-1-carboxamide

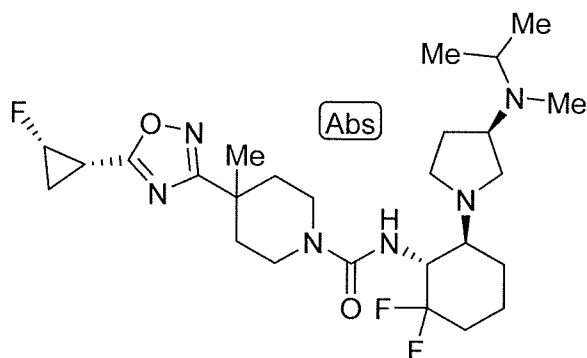


Example 111: N-((1R,6S)-2,2-difluoro-6-((2R)-2-methyl-4-(propan-2-yl)piperazin-1-yl)cyclohexyl)-4-((5-((1S,2S)-2-fluorocyclopropyl)-1,2,4-oxadiazol-3-yl)-4-methylpiperidino)-1-carboxamide

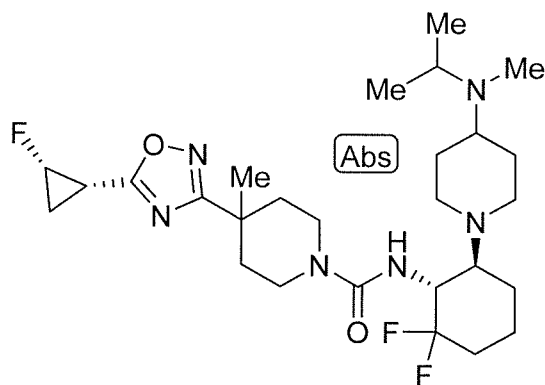


Example 112: N-((1R,6S)-2,2-difluoro-6-((3R)-3-methyl-4-(propan-2-yl)piperazin-1-yl)cyclohexyl)-4-((5-((1S,2S)-2-fluorocyclopropyl)-1,2,4-oxadiazol-3-yl)-4-methylpiperidino)-1-carboxamide

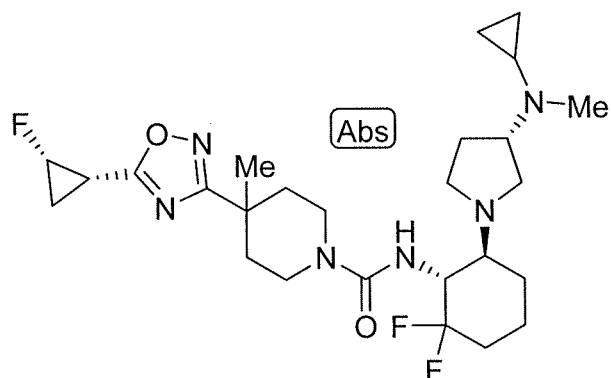
[methyl (propan-2-yl) amino]pyrrolidin-1-yl}cyclohexyl]-4-{5-
 [(1S,2S)-2-fluorocyclopropyl]-1,2,4-oxadiazol-3-yl}-4-
 methylpiperidine-1-carboxamide



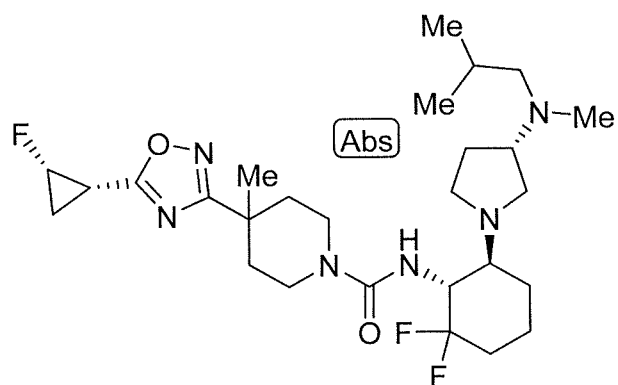
5 Example 114: N-[(1R,6S)-2,2-difluoro-6-{4-
 [methyl (propan-2-yl) amino]piperidin-1-yl}cyclohexyl]-4-{5-
 [(1S,2S)-2-fluorocyclopropyl]-1,2,4-oxadiazol-3-yl}-4-
 methylpiperidine-1-carboxamide



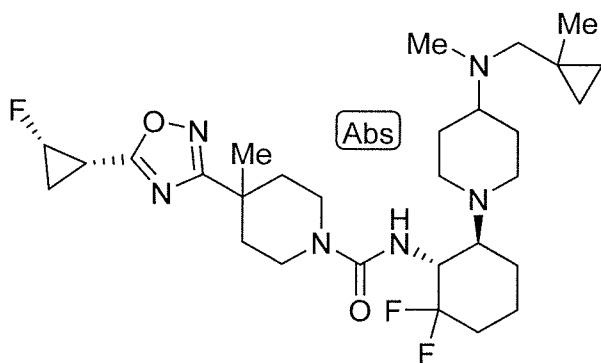
10 Example 115: N-[(1R,6S)-6-{(3S)-3-
 [cyclopropyl (methyl) amino]pyrrolidin-1-yl}-2,2-
 difluorocyclohexyl]-4-{5-[(1S,2S)-2-fluorocyclopropyl]-
 1,2,4-oxadiazol-3-yl}-4-methylpiperidine-1-carboxamide



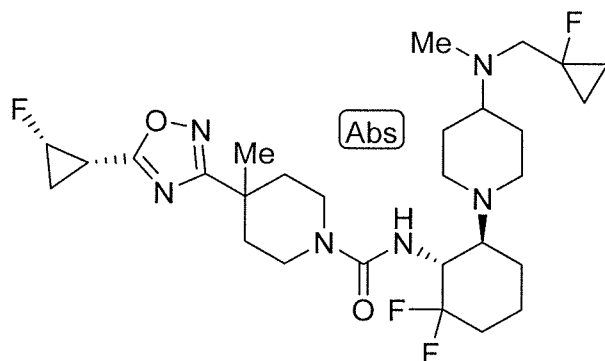
Example 128: N-[(1R,6S)-2,2-difluoro-6-[(3S)-3-
[methyl(2-methylpropyl)amino]pyrrolidin-1-yl]cyclohexyl]-4-
{5-[(1S,2S)-2-fluorocyclopropyl]-1,2,4-oxadiazol-3-yl}-4-
5 methylpiperidine-1-carboxamide



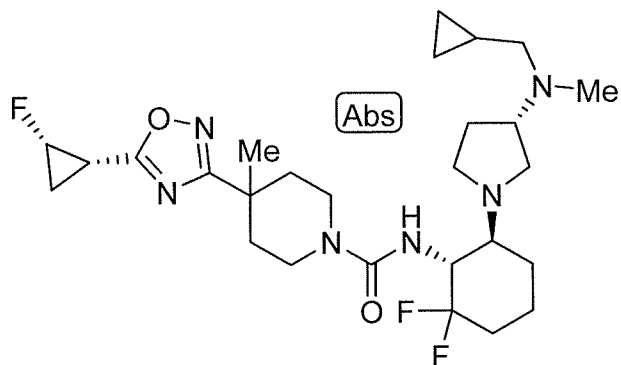
Example 134: N-[(1R,6S)-2,2-difluoro-6-(4-{methyl[(1-
methylcyclopropyl)methyl]amino}piperidin-1-yl)cyclohexyl]-
4-{5-[(1S,2S)-2-fluorocyclopropyl]-1,2,4-oxadiazol-3-yl}-4-
10 methylpiperidine-1-carboxamide



Example 136: N-[(1R,6S)-2,2-difluoro-6-(4-{[(1-fluorocyclopropyl)methyl](methyl)amino}piperidin-1-yl)cyclohexyl]-4-{5-[(1S,2S)-2-fluorocyclopropyl]-1,2,4-oxadiazol-3-yl}-4-methylpiperidine-1-carboxamide



Example 137: N-[(1R,6S)-6-{(3S)-3-[(cyclopropylmethyl)(methyl)amino]pyrrolidin-1-yl}-2,2-difluorocyclohexyl]-4-{5-[(1S,2S)-2-fluorocyclopropyl]-1,2,4-oxadiazol-3-yl}-4-methylpiperidine-1-carboxamide



Example

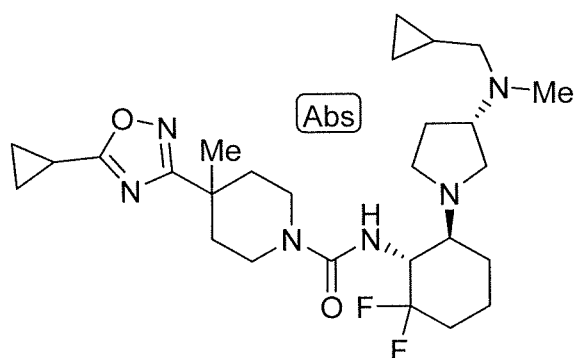
138:

N-[(1R,6S)-6-{(3S)-3-

[(cyclopropylmethyl)(methyl)amino]pyrrolidin-1-yl}-2,2-

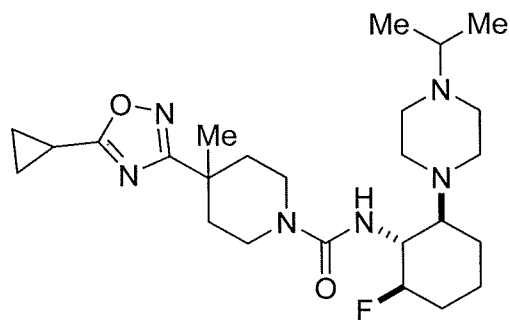
difluorocyclohexyl]-4-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)-

5 4-methylpiperidine-1-carboxamide

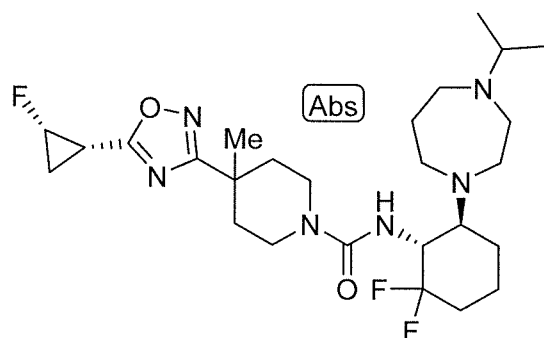
Example 139: *rac*-4-(5-cyclopropyl-1,2,4-oxadiazol-3-

yl)-N-[(1R,2R,6S)-2-fluoro-6-[4-(propan-2-yl)piperazin-1-

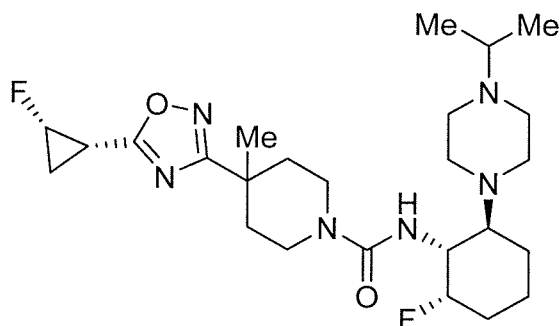
yl]cyclohexyl]-4-methylpiperidine-1-carboxamide



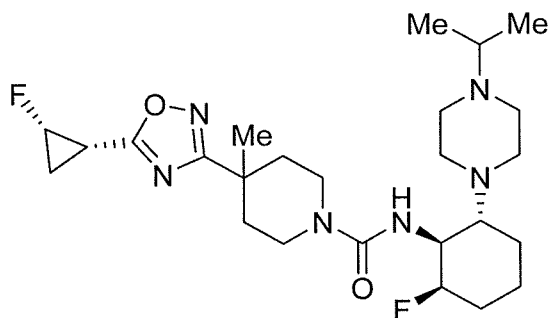
Example 152: N-[(1R,6S)-2,2-difluoro-6-[4-(propan-2-

CN(C(=O)N1CCCCC1)C2=CC=C(C=C2)C3=CC=CC=C3C4=CC=CC=C4C5=CC=CC=C5C6=CC=CC=C6C7=CC=CC=C7C8=CC=CC=C8C9=CC=CC=C9C10=CC=CC=C10C11=CC=CC=C11C12=CC=CC=C12C13=CC=CC=C13C14=CC=CC=C14C15=CC=CC=C15C16=CC=CC=C16C17=CC=CC=C17C18=CC=CC=C18C19=CC=CC=C19C20=CC=CC=C20C21=CC=CC=C21C22=CC=CC=C22C23=CC=CC=C23C24=CC=CC=C24C25=CC=CC=C25C26=CC=CC=C26C27=CC=CC=C27C28=CC=CC=C28C29=CC=CC=C29C30=CC=CC=C30C31=CC=CC=C31C32=CC=CC=C32C33=CC=CC=C33C34=CC=CC=C34C35=CC=CC=C35C36=CC=CC=C36C37=CC=CC=C37C38=CC=CC=C38C39=CC=CC=C39C40=CC=CC=C40C41=CC=CC=C41C42=CC=CC=C42C43=CC=CC=C43C44=CC=CC=C44C45=CC=CC=C45C46=CC=CC=C46C47=CC=CC=C47C48=CC=CC=C48C49=CC=CC=C49C50=CC=CC=C50C51=CC=CC=C51C52=CC=CC=C52C53=CC=CC=C53C54=CC=CC=C54C55=CC=CC=C55C56=CC=CC=C56C57=CC=CC=C57C58=CC=CC=C58C59=CC=CC=C59C60=CC=CC=C60C61=CC=CC=C61C62=CC=CC=C62C63=CC=CC=C63C64=CC=CC=C64C65=CC=CC=C65C66=CC=CC=C66C67=CC=CC=C67C68=CC=CC=C68C69=CC=CC=C69C70=CC=CC=C70C71=CC=CC=C71C72=CC=CC=C72C73=CC=CC=C73C74=CC=CC=C74C75=CC=CC=C75C76=CC=CC=C76C77=CC=CC=C77C78=CC=CC=C78C79=CC=CC=C79C80=CC=CC=C80C81=CC=CC=C81C82=CC=CC=C82C83=CC=CC=C83C84=CC=CC=C84C85=CC=CC=C85C86=CC=CC=C86C87=CC=CC=C87C88=CC=CC=C88C89=CC=CC=C89C90=CC=CC=C90C91=CC=CC=C91C92=CC=CC=C92C93=CC=CC=C93C94=CC=CC=C94C95=CC=CC=C95C96=CC=CC=C96C97=CC=CC=C97C98=CC=CC=C98C99=CC=CC=C99C100=CC=CC=C100C101=CC=CC=C101C102=CC=CC=C102C103=CC=CC=C103C104=CC=CC=C104C105=CC=CC=C105C106=CC=CC=C106C107=CC=CC=C107C108=CC=CC=C108C109=CC=CC=C109C110=CC=CC=C110C111=CC=CC=C111C112=CC=CC=C112C113=CC=CC=C113C114=CC=CC=C114C115=CC=CC=C115C116=CC=CC=C116C117=CC=CC=C117C118=CC=CC=C118C119=CC=CC=C119C120=CC=CC=C120C121=CC=CC=C121C122=CC=CC=C122C123=CC=CC=C123C124=CC=CC=C124C125=CC=CC=C125C126=CC=CC=C126C127=CC=CC=C127C128=CC=CC=C128C129=CC=CC=C129C130=CC=CC=C130C131=CC=CC=C131C132=CC=CC=C132C133=CC=CC=C133C134=CC=CC=C134C135=CC=CC=C135C136=CC=CC=C136C137=CC=CC=C137C138=CC=CC=C138C139=CC=CC=C139C140=CC=CC=C140C141=CC=CC=C141C142=CC=CC=C142C143=CC=CC=C143C144=CC=CC=C144C145=CC=CC=C145C146=CC=CC=C146C147=CC=CC=C147C148=CC=CC=C148C149=CC=CC=C149C150=CC=CC=C150C151=CC=CC=C151C152=CC=CC=C152C153=CC=CC=C153C154=CC=CC=C154C155=CC=CC=C155C156=CC=CC=C156C157=CC=CC=C157C158=CC=CC=C158C159=CC=CC=C159C160=CC=CC=C160C161=CC=CC=C161C162=CC=CC=C162C163=CC=CC=C163C164=CC=CC=C164C165=CC=CC=C165C166=CC=CC=C166C167=CC=CC=C167C168=CC=CC=C168C169=CC=CC=C169C170=CC=CC=C170C171=CC=CC=C171C172=CC=CC=C172C173=CC=CC=C173C174=CC=CC=C174C175=CC=CC=C175C176=CC=CC=C176C177=CC=CC=C177C178=CC=CC=C178C179=CC=CC=C179C180=CC=CC=C180C181=CC=CC=C181C182=CC=CC=C182C183=CC=CC=C183C184=CC=CC=C184C185=CC=CC=C185C186=CC=CC=C186C187=CC=CC=C187C188=CC=CC=C188C189=CC=CC=C189C190=CC=CC=C190C191=CC=CC=C191C192=CC=CC=C192C193=CC=CC=C193C194=CC=CC=C194C195=CC=CC=C195C196=CC=CC=C196C197=CC=CC=C197C198=CC=CC=C198C199=CC=CC=C199C200=CC=CC=C200C201=CC=CC=C201C202=CC=CC=C202C203=CC=CC=C203C204=CC=CC=C204C205=CC=CC=C205C206=CC=CC=C206C207=CC=CC=C207C208=CC=CC=C208C209=CC=CC=C209C210=CC=CC=C210C211=CC=CC=C211C212=CC=CC=C212C213=CC=CC=C213C214=CC=CC=C214C215=CC=CC=C215C216=CC=CC=C216C217=CC=CC=C217C218=CC=CC=C218C219=CC=CC=C219C220=CC=CC=C220C221=CC=CC=C221C222=CC=CC=C222C223=CC=CC=C223C224=CC=CC=C224C225=CC=CC=C225C226=CC=CC=C226C227=CC=CC=C227C228=CC=CC=C228C229=CC=CC=C229C230=CC=CC=C230C231=CC=CC=C231C232=CC=CC=C232C233=CC=CC=C233C234=CC=CC=C234C235=CC=CC=C235C236=CC=CC=C236C237=CC=CC=C237C238=CC=CC=C238C239=CC=CC=C239C240=CC=CC=C240C241=CC=CC=C241C242=CC=CC=C242C243=CC=CC=C243C244=CC=CC=C244C245=CC=CC=C245C246=CC=CC=C246C247=CC=CC=C247C248=CC=CC=C248C249=CC=CC=C249C250=CC=CC=C250C251=CC=CC=C251C252=CC=CC=C252C253=CC=CC=C253C254=CC=CC=C254C255=CC=CC=C255C256=CC=CC=C256C257=CC=CC=C257C258=CC=CC=C258C259=CC=CC=C259C260=CC=CC=C260C261=CC=CC=C261C262=CC=CC=C262C263=CC=CC=C263C264=CC=CC=C264C265=CC=CC=C265C266=CC=CC=C266C267=CC=CC=C267C268=CC=CC=C268C269=CC=CC=C269C270=CC=CC=C270C271=CC=CC=C271C272=CC=CC=C272C273=CC=CC=C273C274=CC=CC=C274C275=CC=CC=C275C276=CC=CC=C276C277=CC=CC=C277C278=CC=CC=C278C279=CC=CC=C279C280=CC=CC=C280C281=CC=CC=C281C282=CC=CC=C282C283=CC=CC=C283C284=CC=CC=C284C285=CC=CC=C285C286=CC=CC=C286C287=CC=CC=C287C288=CC=CC=C288C289=CC=CC=C289C290=CC=CC=C290C291=CC=CC=C291C292=CC=CC=C292C293=CC=CC=C293C294=CC=CC=C294C295=CC=CC=C295C296=CC=CC=C296C297=CC=CC=C297C298=CC=CC=C298C299=CC=CC=C299C300=CC=CC=C300C301=CC=CC=C301C302=CC=CC=C302C303=CC=CC=C303C304=CC=CC=C304C305=CC=CC=C305C306=CC=CC=C306C307=CC=CC=C307C308=CC=CC=C308C309=CC=CC=C309C310=CC=CC=C310C311=CC=CC=C311C312=CC=CC=C312C313=CC=CC=C313C314=CC=CC=C314C315=CC=CC=C315C316=CC=CC=C316C317=CC=CC=C317C318=CC=CC=C318C319=CC=CC=C319C320=CC=CC=C320C321=CC=CC=C321C322=CC=CC=C322C323=CC=CC=C323C324=CC=CC=C324C325=CC=CC=C325C326=CC=CC=C326C327=CC=CC=C327C328=CC=CC=C328C329=CC=CC=C329C330=CC=CC=C330C331=CC=CC=C331C332=CC=CC=C332C333=CC=CC=C333C334=CC=CC=C334C335=CC=CC=C335C336=CC=CC=C336C337=CC=CC=C337C338=CC=CC=C338C339=CC=CC=C339C340=CC=CC=C340C341=CC=CC=C341C342=CC=CC=C342C343=CC=CC=C343C344=CC=CC=C344C345=CC=CC=C345C346=CC=CC=C346C347=CC=CC=C347C348=CC=CC=C348C349=CC=CC=C349C350=CC=CC=C350C351=CC=CC=C351C352=CC=CC=C352C353=CC=CC=C353C354=CC=CC=C354C355=CC=CC=C355C356=CC=CC=C356C357=CC=CC=C357C358=CC=CC=C358C359=CC=CC

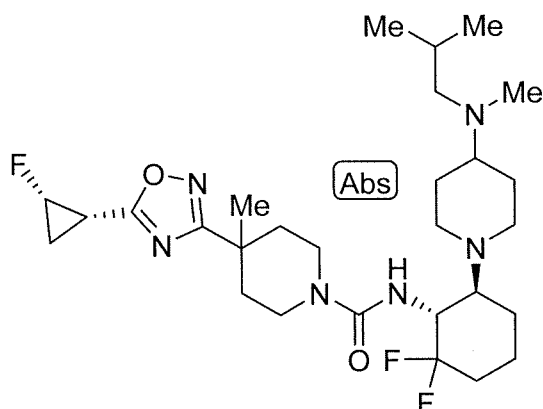
5 Example 156-A: 4-{5-[(1S,2S)-2-fluorocyclopropyl]-
1,2,4-oxadiazol-3-yl}-N-{(1R,2S,6S)-2-fluoro-6-[4-(propan-
2-yl)piperazin-1-yl]cyclohexyl}-4-methylpiperidine-1-
carboxamide



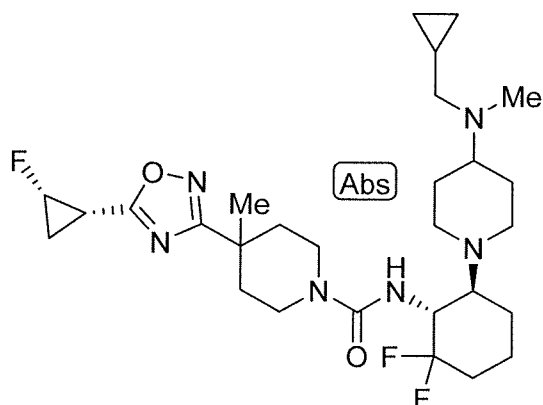
10 Example 156-B: 4-{5-[(1S,2S)-2-fluorocyclopropyl]-
1,2,4-oxadiazol-3-yl}-N-{(1S,2R,6R)-2-fluoro-6-[4-(propan-
2-yl)piperazin-1-yl]cyclohexyl}-4-methylpiperidine-1-
carboxamide



Example 157: N-[(1R,6S)-2,2-difluoro-6-{4-[methyl(2-methylpropyl)amino]piperidin-1-yl}cyclohexyl]-4-{5-[(1S,2S)-2-fluorocyclopropyl]-1,2,4-oxadiazol-3-yl}-4-methylpiperidine-1-carboxamide



Example 158: N-[(1R,6S)-6-{4-[(cyclopropylmethyl)(methyl)amino]piperidin-1-yl}-2,2-difluorocyclohexyl]-4-{5-[(1S,2S)-2-fluorocyclopropyl]-1,2,4-oxadiazol-3-yl}-4-methylpiperidine-1-carboxamide



Example

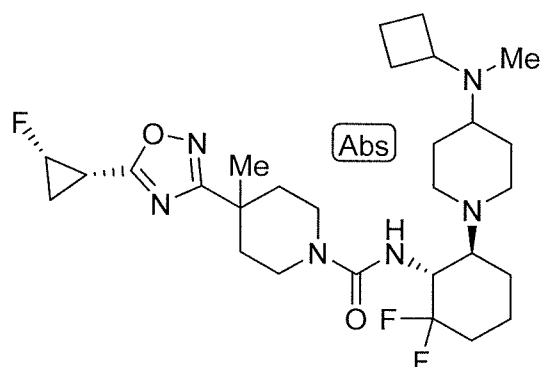
159:

N-[(1R, 6S)-6-{4-

[cyclobutyl(methyl)amino]piperidin-1-yl}-2,2-

difluorocyclohexyl]-4-{5-[(1S, 2S)-2-fluorocyclopropyl]-

1,2,4-oxadiazol-3-yl}-4-methylpiperidine-1-carboxamide



Example

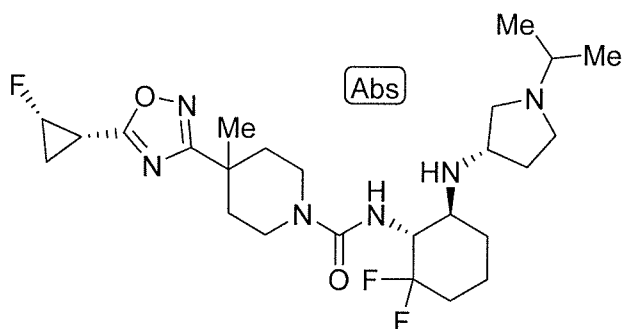
161:

N-[(1R, 6S)-2,2-difluoro-6-{[(3S)-1-

(propan-2-yl)pyrrolidin-3-yl]amino}cyclohexyl]-4-{5-

[(1S, 2S)-2-fluorocyclopropyl]-1,2,4-oxadiazol-3-yl}-4-

methylpiperidine-1-carboxamide

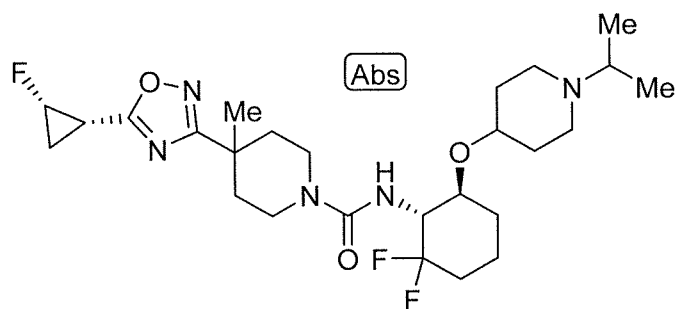


[0062]

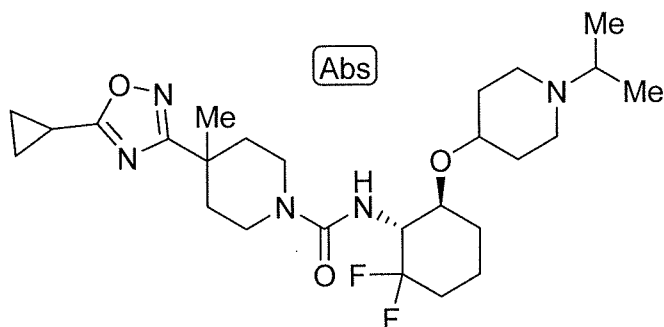
(Item 25)

The compound of Item 1 or a pharmaceutically acceptable salt thereof, which is selected from the following compound names or structures:

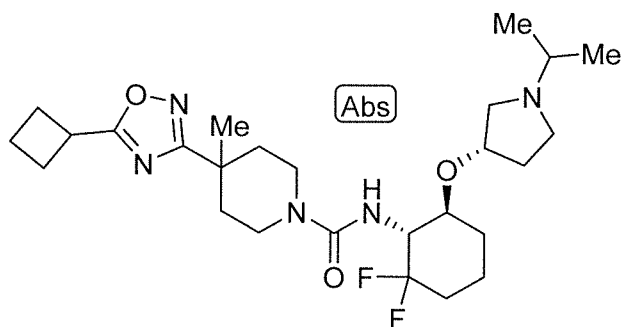
Example 83: N-[(1R,6S)-2,2-difluoro-6-{[1-(propan-2-yl)piperidin-4-yl]oxy}cyclohexyl]-4-{5-[(1S,2S)-2-fluorocyclopropyl]-1,2,4-oxadiazol-3-yl}-4-methylpiperidine-1-carboxamide



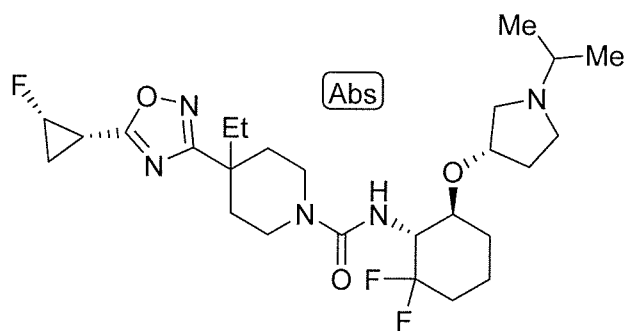
Example 84: 4-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)-N-[(1R,6S)-2,2-difluoro-6-{[1-(propan-2-yl)piperidin-4-yl]oxy}cyclohexyl]-4-methylpiperidine-1-carboxamide



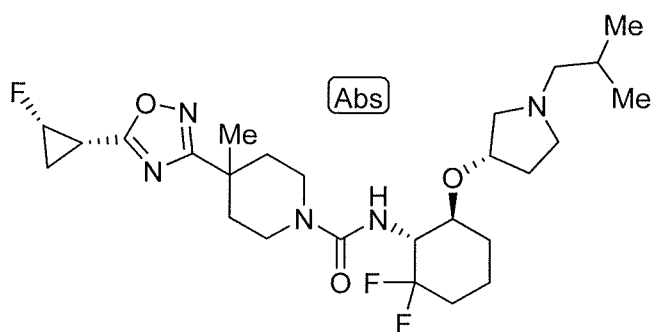
Example 102: 4-(5-cyclobutyl-1,2,4-oxadiazol-3-yl)-N-[(1R,6S)-2,2-difluoro-6-{[(3S)-1-(propan-2-yl)pyrrolidin-3-yl]oxy}cyclohexyl]-4-methylpiperidine-1-carboxamide



Example 103: N-[(1R,6S)-2,2-difluoro-6-{[(3S)-1-(propan-2-yl)pyrrolidin-3-yl]oxy}cyclohexyl]-4-ethyl-4-{5-[(1S,2S)-2-fluorocyclopropyl]-1,2,4-oxadiazol-3-yl}piperidine-1-carboxamide

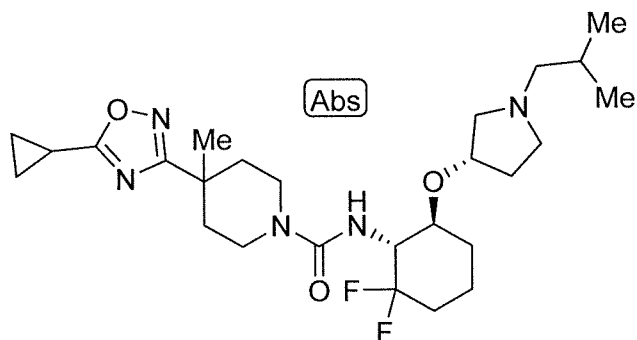


Example 107: N-[(1R,6S)-2,2-difluoro-6-{[(3S)-1-(2-methylpropyl)pyrrolidin-3-yl]oxy}cyclohexyl]-4-{5-[(1S,2S)-2-fluorocyclopropyl]-1,2,4-oxadiazol-3-yl}-4-methylpiperidine-1-carboxamide



Example 116: 4-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)-N-[(1R,6S)-2,2-difluoro-6-{[(3S)-1-(2-methylpropyl)pyrrolidin-3-yl]oxy}cyclohexyl]-4-ethyl-4-{5-[(1S,2S)-2-fluorocyclopropyl]-1,2,4-oxadiazol-3-yl}piperidine-1-carboxamide

methylpropyl)pyrrolidin-3-yl]oxy}cyclohexyl]-4-
methylpiperidine-1-carboxamide

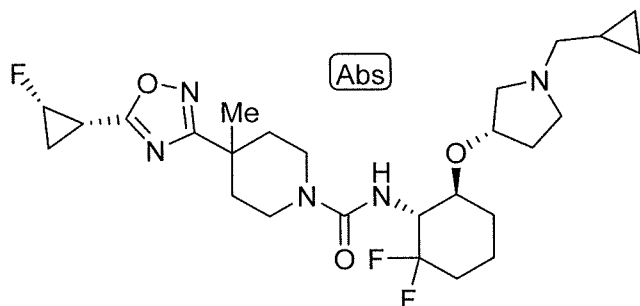


Example

118:

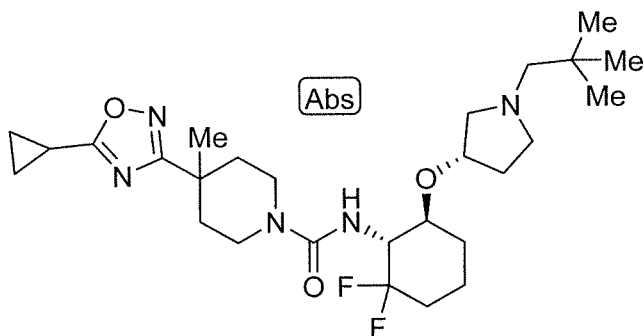
N-[(1R,6S)-6-{[(3S)-1-

(cyclopropylmethyl)pyrrolidin-3-yl]oxy}-2,2-
difluorocyclohexyl]-4-{5-[(1S,2S)-2-fluorocyclopropyl]-
1,2,4-oxadiazol-3-yl}-4-methylpiperidine-1-carboxamide

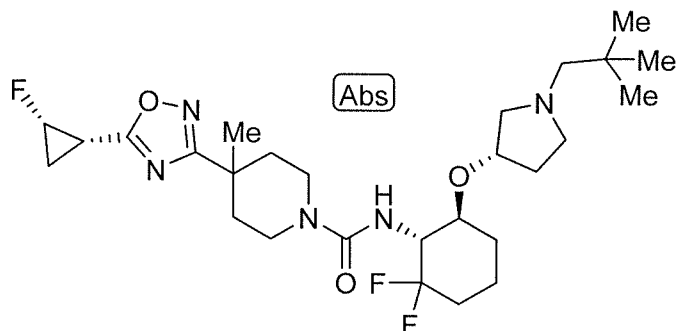


Example 119: 4-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)-N-

[(1R,6S)-6-{[(3S)-1-(2,2-dimethylpropyl)pyrrolidin-3-
yl]oxy}-2,2-difluorocyclohexyl]-4-methylpiperidine-1-
carboxamide

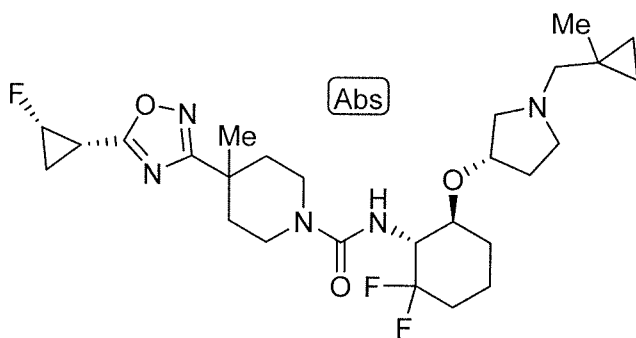


Example 120: N-[(1R,6S)-6-{[(3S)-1-(2,2-dimethylpropyl)pyrrolidin-3-yl]oxy}-2,2-difluorocyclohexyl]-4-{5-[(1S,2S)-2-fluorocyclopropyl]-1,2,4-oxadiazol-3-yl}-4-methylpiperidine-1-carboxamide



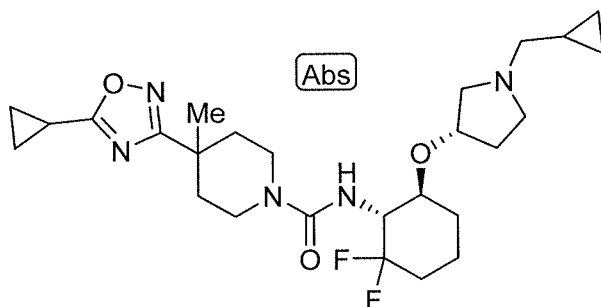
5

Example 121: N-[(1R,6S)-2,2-difluoro-6-({(3S)-1-[(1-methylcyclopropyl)methyl]pyrrolidin-3-yl}oxy)cyclohexyl]-4-{5-[(1S,2S)-2-fluorocyclopropyl]-1,2,4-oxadiazol-3-yl}-4-methylpiperidine-1-carboxamide

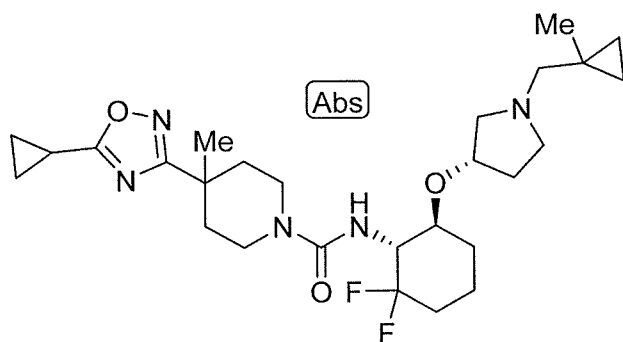


10

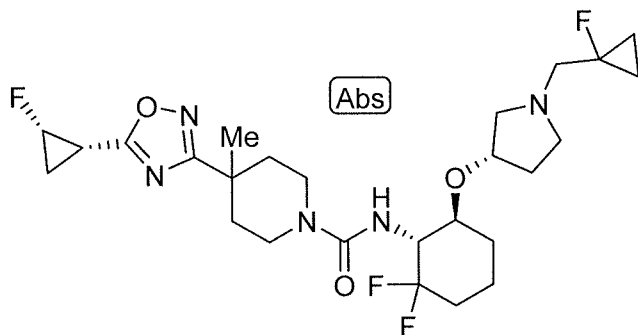
Example 122: N-[(1R,6S)-6-{[(3S)-1-(cyclopropylmethyl)pyrrolidin-3-yl]oxy}-2,2-difluorocyclohexyl]-4-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)-4-methylpiperidine-1-carboxamide



Example 126: 4-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)-N-
 [(1R,6S)-2,2-difluoro-6-({(3S)-1-[(1-
 methylcyclopropyl)methyl]pyrrolidin-3-yl}oxy)cyclohexyl]-4-
 5 methylpiperidine-1-carboxamide

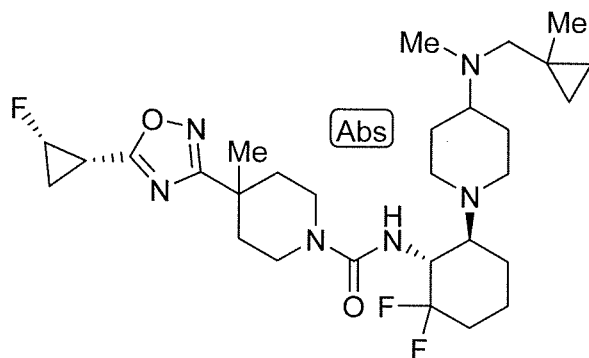


Example 133: N-[(1R,6S)-2,2-difluoro-6-({(3S)-1-[(1-
 fluorocyclopropyl)methyl]pyrrolidin-3-yl}oxy)cyclohexyl]-4-
 {5-[(1S,2S)-2-fluorocyclopropyl]-1,2,4-oxadiazol-3-yl}-4-
 10 methylpiperidine-1-carboxamide

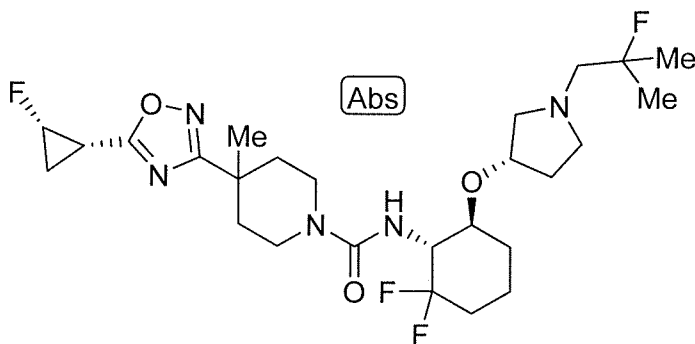


Example 134: N-[(1R,6S)-2,2-difluoro-6-(4-{methyl[(1-
 methylcyclopropyl)methyl]amino}piperidin-1-yl)cyclohexyl]-

4-{5-[(1S,2S)-2-fluorocyclopropyl]-1,2,4-oxadiazol-3-yl}-4-methylpiperidine-1-carboxamide



Example 143: N-[(1R,6S)-2,2-difluoro-6-{[(3S)-1-(2-fluoro-2-methylpropyl)pyrrolidin-3-yl]oxy}cyclohexyl]-4-{5-[(1S,2S)-2-fluorocyclopropyl]-1,2,4-oxadiazol-3-yl}-4-methylpiperidine-1-carboxamide.



[0063]

10 (Item 26)

A medicament for treating a disease related to orexin receptor, comprising the compound of any one of Items 1 to 25 or a pharmaceutically acceptable salt thereof.

[0064]

15 (Item 27)

A medicament for treating narcolepsy, idiopathic hypersomnia, hypersomnia, sleep apnea syndrome, narcolepsy syndrome involving narcolepsy-like symptom, hypersomnia associated with Parkinson's disease, hypersomnia associated with dementia with Lewy body, hypersomnia syndrome involving daytime hypersomnia (e.g. Kleine-Levin syndrome, major depression accompanied by hypersomnia, dementia with Lewy body, Parkinson's disease, progressive supranuclear palsy, Prader-Willi syndrome, Moebius syndrome, hypoventilation syndrome, Niemann-Pick disease type C, brain contusion, cerebral infarction, brain tumor, muscular dystrophy, multiple sclerosis, acute disseminated encephalomyelitis, Guillain-Barre syndrome, Rasmussen's encephalitis, Wernicke's encephalopathy, limbic encephalitis, Hashimoto encephalopathy), coma, loss of consciousness, obesity (e.g. malignant mast cell, extrinsic obesity, hyperinsulinar obesity, hyperplasmic obesity, hypophysial obesity, hypoplasmic obesity, hypothyroid obesity, hypothalamic obesity, symptomatic obesity, childhood obesity, upper body obesity, alimentary obesity, gonadal obesity, systemic mastocytosis, primary obesity, central obesity), insulin resistance syndrome, Alzheimer, impaired consciousness such as coma, side effect or complication caused by anesthesia, sleep disturbance, sleep problem, insomnia, intermittent sleep, night myoclonus, REM sleep interruption, jet lag, jet

lag syndrome, sleep disorder of shift workers, dysomnia, sleep terror, depression, major depression, sleepwalking, enuresis, sleep disorder, Alzheimer's sundown syndrome, disease associated with circadian rhythm, fibromyalgia, condition resulting from decrease in sleeping quality, bulimia, obsessive eating disorder, obesity-related diseases, hypertension, diabetes, elevated plasma insulin level/insulin resistance, hyperlipemia, hyperlipidaemia, endometrial cancer, breast cancer, prostate cancer, colon cancer, cancer, osteoarthritis, obstructive sleep apnea, cholelithiasis, gallstone, heart disease, abnormal heartbeat, arrhythmia, myocardial infarction, congestive heart failure, heart failure, coronary heart disease, cardiovascular disease, sudden death, polycystic ovary, craniopharyngioma, Prader-Willi syndrome, Froehlich syndrome, growth hormone deficiency, normal variant short stature, Turner syndrome, children suffering from acute lymphoblastic leukemia, syndrome X, reproductive hormone abnormality, decrease of fecundability, infertility, hypogonadism in men, sexual/reproductive-function dysfunction such as hirsutism in women, fetal defect associated with maternity obesity, gastrointestinal motility disorder such as obesity-related gastroesophageal reflux, obesity hypoventilation syndrome (Pickwickian syndrome), respiratory disease such as respiratory distress,

inflammation such as vascular systemic inflammation, arteriosclerosis, hypercholesterolemia, hyperuricemia, low back pain, gallbladder disease, gout, renal cancer, secondary risk of obesity such as risk of left ventricle hypertrophy, migraine, headache, neuropathic pain, Parkinson's disease, psychosis, schizophrenia, facial flushing, night sweat, disease in genitalium/urinary system, disease associated with sexual function or fecundability, dysthymic disorder, bipolar disorder, bipolar I disorder, bipolar II disorder, cyclothymic disorder, acute stress disorder, agoraphobia, generalized anxiety disorder, obsessive-compulsive disorder, panic attack, panic disorder, posttraumatic stress disorder, separation anxiety disorder, social phobia, anxiety disorder, acute neurological and psychiatric disorder such as cerebral deficiency developed after heart bypass surgery or heart transplant, stroke, ischemic stroke, cerebral ischemia, spinal cord trauma, head injury, periparturient hypoxia, cardiac arrest, hypoglycemic nerve injury, Huntington's disease, amyotrophic lateral sclerosis, multiple sclerosis, eye damage, retinopathy, cognitive impairment, muscle spasm, tremor, epilepsy, disorder associated with muscle spasm, delirium, amnestic disorder, age-associated cognitive decline, schizoaffective disorder, paranoia, drug addiction, movement disorder, chronic fatigue syndrome, fatigue, medication-induced

parkinsonian syndrome, Gilles de la Tourette syndrome, chorea, myoclonus, tic, restless legs syndrome, dystonia, dyskinesia, attention deficit hyperactivity disorder (ADHD), conduct disorder, urinary incontinence, withdrawal symptom, 5 trigeminal neuralgia, hearing loss, tinnitus, nerve injury, retinopathy, macular degeneration, vomiting, cerebral edema, pain, bone pain, arthralgia, toothache, cataplexy, or traumatic brain injury, comprising the compound of any one of Items 1 to 25 or a pharmaceutically acceptable salt 10 thereof.

[0065]

(Item 28)

A medicament for treating narcolepsy, idiopathic hypersomnia, hypersomnia, sleep apnea syndrome, narcolepsy 15 syndrome involving narcolepsy-like symptom, hypersomnia associated with Parkinson's disease, or hypersomnia associated with dementia with Lewy body, comprising the compound of any one of Items 1 to 25 or a pharmaceutically acceptable salt thereof.

20 [0066]

(Item 29)

A method for treating narcolepsy, idiopathic hypersomnia, hypersomnia, sleep apnea syndrome, narcolepsy syndrome involving narcolepsy-like symptom, hypersomnia associated 25 with Parkinson's disease, or hypersomnia associated with

dementia with Lewy body, comprising administering a therapeutically effective amount of the compound of any one of Items 1 to 25 or a pharmaceutically acceptable salt thereof to a patient in need thereof.

5 [0067]

(Item 30)

Use of the compound of any one of Items 1 to 25 or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating narcolepsy, idiopathic
10 hypersomnia, hypersomnia, sleep apnea syndrome, narcolepsy syndrome involving narcolepsy-like symptom, hypersomnia associated with Parkinson's disease, or hypersomnia associated with dementia with Lewy body.

15 DESCRIPTION OF EMBODIMENTS

[0068]

Hereinafter, the present invention is explained in more detail. In the description, the number of carbon atoms in the definition of "substituents" can indicate, for example,
20 "C₁₋₆". The specific definition "C₁₋₆ alkyl" means an alkyl group having 1 to 6 carbon atoms. In the present description, a substituent group which is not accompanied with "optionally-substituted" or "substituted" means an "unsubstituted" substituent group. For example, "C₁₋₆ alkyl"
25 means "unsubstituted C₁₋₆ alkyl".

[0069]

The substituent groups in the present description may be sometimes expressed without the term "group". In case that "optionally-substituted" is used in the definition of substituent groups, the number of the substituting groups is not limited as long as the substitutions are available, *i.e.*, it is one or more. It means that the possible number of substituting groups is the substitution-available number on carbon atoms or carbon/nitrogen atoms in a substituent group which are acceptable for substitution. Unless otherwise specified, the definition of each substituent group also extends over the case that the substituent group is partially included in another substituent group or the case that the substituent group is attached to another substituent group.

[0070]

Unless otherwise specified, the binding site of substituent groups is not limited as long as the site is available to be bound.

[0071]

The "halogen" includes, for example, fluorine, chlorine, bromine, iodine, and the like. It is preferably fluorine or chlorine.

[0072]

The "C₁₋₄ alkyl" means straight or branched chain saturated hydrocarbon group having 1 to 4 carbon atoms, and

the "C₁₋₆ alkyl" means straight or branched chain saturated hydrocarbon group having 1 to 6 carbon atoms. The "C₁₋₄ alkyl" includes, for example, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, and *tert*-butyl, and
5 the "C₁₋₆ alkyl" includes, for example, pentyl, isopentyl, neopentyl, 1-ethylpropyl, hexyl, and a structural isomer thereof, besides the above C₁₋₄ alkyl. Preferred examples of the "C₁₋₆ alkyl" or "C₁₋₄ alkyl" include methyl, ethyl, propyl, and isopropyl; more preferably methyl and isopropyl.

10 [0073]

The "C₁₋₆ alkylene" means divalent straight or branched chain saturated hydrocarbon group having 1 to 6 carbon atoms. The "C₁₋₆ alkylene" includes preferably "C₁₋₄ alkylene", more preferably "C₁₋₃ alkylene". The "C₁₋₃ alkylene" includes, for
15 example, methylene, ethylene, propylene, trimethylene, and the like. The "C₁₋₄ alkylene" includes, for example, butylene, 1,1-dimethylethylene, 1,2-dimethylethylene, 1-methyltrimethylene, 2-methyltrimethylene, and the like, besides the examples listed in the said "C₁₋₃ alkylene". The
20 "C₁₋₆ alkylene" includes, for example, pentylene, 1,1-dimethyltrimethylene, 1,2-dimethyltrimethylene, 1-methylbutylene, 2-methylbutylene, 1-methylpentylene, 2-methylpentylene, 3-methylpentylene, hexylene, and the like, besides the examples listed in the said "C₁₋₄ alkylene".

25 [0074]

The "C₃₋₇ cycloalkyl" means a non-aromatic cyclic hydrocarbon group (*i.e.*, saturated hydrocarbon group and partially-unsaturated hydrocarbon group) having 3 to 7 carbon atoms, which includes preferably "C₃₋₆ cycloalkyl".

5 The "C₃₋₇ cycloalkyl" also includes a bridged one. The "C₃₋₁₀ cycloalkyl" includes, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclopentenyl, cyclohexenyl, and cycloheptyl.

[0075]

10 The "C₃₋₇ cycloalkyl" also includes a bi-cyclic condensed ring in which the "C₃₋₇ cycloalkyl" is fused with benzene or a 5- or 6-membered ring having one heteroatom selected from nitrogen, sulfur, or oxygen atom, or the same or different and two or more (for example, 2 to 4)
15 heteroatoms thereof (for example, "5- or 6-membered monocyclic heteroaryl" mentioned below, and 5- or 6-membered ring in "4- to 10-membered saturated heterocyclyl" mentioned below).

[0076]

20 The "C₁₋₄ alkoxy" means oxy group substituted with the above "C₁₋₄ alkyl", and the "C₁₋₆ alkoxy" means oxy group substituted with the above "C₁₋₆ alkyl". The "C₁₋₄ alkoxy" includes, for example, methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, sec-butoxy, and *tert*-butoxy. Preferably,
25 the "C₁₋₄ alkoxy" includes methoxy, ethoxy, and isopropoxy.

[0077]

The "C₃₋₇ cycloalkoxy" means oxy group substituted with the above "C₃₋₇ cycloalkyl", which includes preferably "C₃₋₆ cycloalkoxy". The "C₃₋₇ cycloalkoxy" includes, for example,
5 cyclopropyloxy, cyclobutyloxy, cyclopentyloxy, and cyclohexyloxy, and preferably cyclohexyloxy.

[0078]

The "C₆₋₁₀ aromatic carbocyclyl group" means an aromatic hydrocarbon group having 6 to 10 carbon atoms, which is also
10 referred to as "C₆₋₁₀ aryl". More preferably, it is phenyl. The "C₆₋₁₀ aromatic carbocyclyl group" includes, for example, phenyl, 1-naphthyl, and 2-naphthyl.

[0079]

The "C₆₋₁₀ aromatic carbocyclyl group" also includes a
15 condensed ring in which "phenyl" is fused with a 5- or 6-membered ring having one heteroatom selected from nitrogen, sulfur, or oxygen atom, or the same or different and two or more (for example, 2 to 4) heteroatoms thereof (for example, "5- or 6-membered monocyclic aromatic heterocyclyl group"
20 mentioned below, and 5- or 6-membered ring in "4- to 10-membered saturated heterocyclyl" mentioned below), or a 5- to 7-membered cycloalkyl ring (for example, cyclopentane, cyclohexane and cycloheptane).

[0080]

25 The "5- to 10-membered aromatic heterocyclyl group"

means a 5- to 10-membered mono- or multiple-cyclic aromatic group having one heteroatom selected from nitrogen, sulfur, or oxygen atom, or the same or different and two or more (for example, 2 to 4) heteroatoms thereof, besides carbon atoms as the ring atoms, preferably, "5- or 6-membered monocyclic aromatic heterocyclyl group". The "5- or 6-membered monocyclic aromatic heterocyclyl group" means a 5- or 6-membered monocyclic aromatic group within the "5- to 10-membered aromatic heterocyclyl group".

10 [0081]

The multiple-cyclic aromatic heterocyclyl group in the "5- to 10-membered aromatic heterocyclyl group" includes, for example, a condensed ring in which the same or different two monocyclic aromatic heterorings are fused, or a monocyclic aromatic heteroring and an aromatic ring (for example, benzene) or a non-aromatic ring (for example, cyclohexane) are fused.

The "5- to 10-membered aromatic heterocyclyl group" includes, for example, pyrazolyl, imidazolyl, pyridyl, pyrimidinyl, pyrazinyl, and pyridazinyl. Another embodiment includes, preferably, benzofuranyl in which the binding site is on the heteroaryl (furan) ring, pyridyl, pyrimidinyl, pyrazinyl, and pyridazinyl.

[0082]

25 The "C₃₋₆ saturated carbon ring" means a monocyclic

saturated or partially-unsaturated hydrocarbon group having 3 to 6 carbon atoms. The "C₃₋₆ saturated carbon ring" includes, for example, cyclopropane, cyclobutane, cyclopentane, cyclohexane, cyclopropene, cyclobutene, 5 cyclopentene, cyclohexene, and cyclohexadiene, and preferably cyclopropane and cyclobutane.

[0083]

The "4- to 10-membered saturated heteroring" means a monocyclic or bicyclic saturated heteroring composed of 4 to 10 atoms, which has the same or different and one or more (for example, 2 to 4, preferably 2 to 3, more preferably 2) heteroatoms selected from oxygen atom, nitrogen atom, and sulfur atom, besides carbon atoms as the ring atoms. The heteroring may include a partially-unsaturated one, a 15 partially-bridged one, and a partially-spiro one. Preferred one thereof is a 5- or 6-membered saturated heteroring. The bicyclic saturated heteroring also includes a condensed ring of a monocyclic saturated heteroring, and benzene or a 5- or 6-membered monocyclic aromatic heteroring. And, the 20 saturated heteroring may further comprise one or two carbonyl, thiocarbonyl, sulfinyl, or sulfonyl, that is, the saturated heteroring includes, for example, a cyclic group such as lactam, thiolactam, lactone, thiolactone, cyclic imide, cyclic carbamate, and cyclic thiocarbamate, wherein 25 the number of atoms composing 4- to 10-membered ring (*i.e.*,

ring size) or the number of heteroatoms composing hetero ring does not count the oxygen atom in carbonyl, sulfinyl, and sulfonyl, and the sulfur atom in thiocarbonyl. The "4- to 10-membered saturated heteroring" includes preferably

5 monocyclic or bicyclic "4- to 8-membered saturated heteroring", more preferably monocyclic "4- to 6-membered saturated heteroring", and even more preferably monocyclic "5- or 6-membered saturated heteroring". The "4- to 10-membered saturated heteroring" includes, for example,

10 piperazine, oxetanyl, azetidiny, pyran, tetrahydrofuryl, pyrrolidinyl, pyrazolidinyl, imidazolidinyl, piperidinyl, morpholinyl, homopiperidinyl, oxetanyl, thiomorpholinyl, dioxothiomorpholinyl, hexamethyleneiminyl, oxazolidinyl, thiazolidinyl, imidazolidinyl, oxoimidazolidinyl,

15 dioxoimidazolidinyl, oxooxazolidinyl, dioxooxazolidinyl, dioxothiazolidinyl, tetrahydrofuranyl, tetrahydropyran, and tetrahydropyridinyl, and preferably pyran, tetrahydrofuryl, pyrrolidinyl, piperidinyl, piperazinyl, and morpholinyl. The "bicyclic saturated heteroring" includes,

20 for example, dihydroindolyl, dihydroisoindolyl, dihydropurinyl, dihydrothiazolopyrimidinyl, dihydrobenzodioxanyl, isoindolinyl, indazolyl, pyrrolopyridinyl, tetrahydroquinolinyl, decahydroquinolinyl, tetrahydroisoquinolinyl,

25 decahydroisoquinolinyl, tetrahydronaphthyridinyl, and

tetrahydropyrido-azepinyl.

[0084]

The "4- to 6-membered saturated heterocyclyl group" means a monovalent substituent derived from "4- to 6-membered saturated heteroring" which belongs to the above "4- to 10-membered saturated heteroring". It includes preferably azetidiny, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, oxetanyl, tetrahydrofuranyl, and tetrahydropyranyl.

The "3- to 7-membered nitrogen-containing saturated heterocycle" which is formed by taking together R^{b8} and R^{b9} with the nitrogen atom to which they are attached corresponds to the above "4- to 10-membered saturated heteroring" wherein the number of atoms composing the ring is 3 to 7, and one nitrogen atom is included as an atom composing the ring besides carbon atoms.

[0085]

The compound of the present invention includes various hydrate, solvate, and crystal polymorph thereof.

[0086]

The compound of the present invention may include one or more isotope atoms such as D, ³H, ¹¹C, ¹³C, ¹⁴C, ¹³N, ¹⁵N, ¹⁵O, ³⁵S, ¹⁸F, and ¹²⁵I by substitution, and such isotope-substituted compound is also included in the compound of the present invention.

[0087]

The "pharmaceutically acceptable salt" used herein means a pharmaceutically usable acid addition salt and a pharmaceutically usable base addition salt. The

5 "pharmaceutically acceptable salt" includes, but not limited thereto, for example, an acid addition salt such as acetate, propionate, butyrate, formate, trifluoroacetate, maleate, fumarate, tartrate, citrate, stearate, succinate, ethylsuccinate, malonate, lactobionate, gluconate,

10 glucoheptonate, benzoate, methanesulfonate, benzenesulfonate, p-toluenesulfonate (tosylate), laurylsulfate, malate, ascorbate, mandelate, saccharin, xinafoate, pamoate, cinnamate, adipate, cysteine, N-acetylcysteine, hydrochloride, hydrobromide, phosphate,

15 sulfate, hydroiodide, nicotinate, oxalate, picrate, thiocyanate, undecanoate, polyacrylate, and carboxy vinyl polymer; an inorganic base addition salt such as lithium salt, sodium salt, potassium salt, and calcium salt; an organic base addition salt such as morpholine and piperidine;

20 and amino acid addition salt such as aspartate and glutamate.

[0088]

The present compounds can be orally or parenterally administered directly or as a suitable formulation such as drug product, medicament, and pharmaceutical composition.

25 The formulation thereof may include, for example, tablet,

capsule, powder, granule, liquid, suspension, injection, patch, gel patch, and the like, but not limited thereto. The formulation can be prepared with pharmaceutically acceptable additive agents in known means.

5 [0089]

The additive agents can be chosen for any purpose, including an excipient, a disintegrant, a binder, a fluidizer, a lubricant, a coating agent, a solubilizer, a solubilizing agent, a thickener, dispersant, a stabilizing agent, a sweetening agent, a flavor, and the like. Specifically, they include, for example, lactose, mannitol, microcrystalline cellulose, low-substituted hydroxypropylcellulose, cornstarch, partially-pregelatinized starch, carmellose calcium, croscarmellose sodium, hydroxypropylcellulose, hydroxypropyl methylcellulose, polyvinyl alcohol, magnesium stearate, sodium stearyl fumarate, polyethylene glycol, propylene glycol, titanium oxide, talc, and the like.

[0090]

20 The dose of the present compound should be suitably determined depending on subject animal for administration, administration route, target disease, and age, body weight, and condition of patients. For example, in the case of oral administration, about 0.01 mg as minimum to 10000 mg as maximum may be administered a day for an adult in one to

25

several portions.

[0091]

The compound of the present invention has agonist activity for orexin receptor. Thereby, the compound can be
5 a medicament for preventing or treating a disease related to orexin receptor. The disease includes, for example, narcolepsy, idiopathic hypersomnia, hypersomnia, sleep apnea syndrome, narcolepsy syndrome involving narcolepsy-like symptom, hypersomnia associated with Parkinson's disease,
10 hypersomnia associated with dementia with Lewy body, hypersomnia syndrome involving daytime hypersomnia (e.g. Kleine-Levin syndrome, major depression accompanied by hypersomnia, dementia with Lewy body, Parkinson's disease, progressive supranuclear palsy, Prader-Willi syndrome,
15 Moebius syndrome, hypoventilation syndrome, Niemann-Pick disease type C, brain contusion, cerebral infarction, brain tumor, muscular dystrophy, multiple sclerosis, acute disseminated encephalomyelitis, Guillain-Barre syndrome, Rasmussen's encephalitis, Wernicke's encephalopathy, limbic
20 encephalitis, Hashimoto encephalopathy), coma, loss of consciousness, obesity (e.g. malignant mast cell, extrinsic obesity, hyperinsular obesity, hyperplasmic obesity, hypophysial obesity, hypoplastic obesity, hypothyroid obesity, hypothalamic obesity, symptomatic obesity,
25 childhood obesity, upper body obesity, alimentary obesity,

gonadal obesity, systemic mastocytosis, primary obesity, central obesity), insulin resistance syndrome, Alzheimer, impaired consciousness such as coma, side effect or complication caused by anesthesia, sleep disturbance, sleep problem, insomnia, intermittent sleep, night myoclonus, REM sleep interruption, jet lag, jet lag syndrome, sleep disorder of shift workers, dyssomnia, sleep terror, depression, major depression, sleepwalking, enuresis, sleep disorder, Alzheimer's sundown syndrome, disease associated with circadian rhythm, fibromyalgia, condition resulting from decrease in sleeping quality, bulimia, obsessive eating disorder, obesity-related diseases, hypertension, diabetes, elevated plasma insulin level/insulin resistance, hyperlipemia, hyperlipidaemia, endometrial cancer, breast cancer, prostate cancer, colon cancer, cancer, osteoarthritis, obstructive sleep apnea, cholelithiasis, gallstone, heart disease, abnormal heartbeat, arrhythmia, myocardial infarction, congestive heart failure, heart failure, coronary heart disease, cardiovascular disease, sudden death, polycystic ovary, craniopharyngioma, Prader-Willi syndrome, Froehlich syndrome, growth hormone deficiency, normal variant short stature, Turner syndrome, children suffering from acute lymphoblastic leukemia, syndrome X, reproductive hormone abnormality, decrease of fecundability, infertility, hypogonadism in men,

sexual/reproductive-function dysfunction such as hirsutism
in women, fetal defect associated with maternity obesity,
gastrointestinal motility disorder such as obesity-related
gastroesophageal reflux, obesity hypoventilation syndrome
5 (Pickwickian syndrome), respiratory disease such as
respiratory distress, inflammation such as vascular systemic
inflammation, arteriosclerosis, hypercholesterolemia,
hyperuricemia, low back pain, gallbladder disease, gout,
renal cancer, secondary risk of obesity such as risk of left
10 ventricle hypertrophy, migraine, headache, neuropathic pain,
Parkinson's disease, psychosis, schizophrenia, facial
flushing, night sweat, disease in genitalium/urinary system,
disease associated with sexual function or fecundability,
dysthymic disorder, bipolar disorder, bipolar I disorder,
15 bipolar II disorder, cyclothymic disorder, acute stress
disorder, agoraphobia, generalized anxiety disorder,
obsessive-compulsive disorder, panic attack, panic disorder,
posttraumatic stress disorder, separation anxiety disorder,
social phobia, anxiety disorder, acute neurological and
20 psychiatric disorder such as cerebral deficiency developed
after heart bypass surgery or heart transplant, stroke,
ischemic stroke, cerebral ischemia, spinal cord trauma, head
injury, periparturient hypoxia, cardiac arrest, hypoglycemic
nerve injury, Huntington's disease, amyotrophic lateral
25 sclerosis, multiple sclerosis, eye damage, retinopathy,

cognitive impairment, muscle spasm, tremor, epilepsy,
disorder associated with muscle spasm, delirium, amnestic
disorder, age-associated cognitive decline, schizoaffective
disorder, paranoia, drug addiction, movement disorder,
5 chronic fatigue syndrome, fatigue, medication-induced
parkinsonian syndrome, Gilles de la Tourette syndrome,
chorea, myoclonus, tic, restless legs syndrome, dystonia,
dyskinesia, attention deficit hyperactivity disorder (ADHD),
conduct disorder, urinary incontinence, withdrawal symptom,
10 trigeminal neuralgia, hearing loss, tinnitus, nerve injury,
retinopathy, macular degeneration, vomiting, cerebral edema,
pain, bone pain, arthralgia, toothache, cataplexy, and
traumatic brain injury; and preferably narcolepsy,
idiopathic hypersomnia, hypersomnia, sleep apnea syndrome,
15 narcolepsy syndrome involving narcolepsy-like symptom,
hypersomnia associated with Parkinson's disease, and
hypersomnia associated with dementia with Lewy body.

[0092]

Hereinafter, the processes to prepare the compound of
20 the present invention of formula (1) are exemplified along
with examples, but the processes of the present invention
should not be limited to the examples.

[0093]

Preparation Process

25 The compound of the present invention may be synthesized

according to each Preparation Process shown below or its combination with a known synthetic process.

Each compound in the following schemes may exist as a salt thereof, wherein the salt includes, for example, the "pharmaceutically acceptable salt" mentioned above. The following schemes are disclosed as just examples, thus it is also possible to optionally prepare the present compound by a different process based on the knowledge of a skilled person in synthetic organic chemistry field.

[0094]

In each Preparation Process described below, protecting groups can be used as necessary, even if the use of protecting groups is not explicitly stated. And, the protecting groups can be deprotected after a reaction is completed or a series of reactions have been carried out to obtain the desired compound.

[0095]

As such protecting groups, for example, general protecting groups described in *T. W. Greene, and P. G. M. Wuts, "Protective Groups in Organic Synthesis", 3rd Ed., John Wiley & Sons, Inc., New York (1999), and the like* may be used. Examples of amino-protecting groups include, for example, tert-butoxycarbonyl, benzyloxycarbonyl, p-toluenesulfonyl, o-nitrobenzenesulfonyl, tetrahydropyranyl, and the like; examples of hydroxy-protecting groups include,

for example, trialkylsilyl, acetyl, benzyl, tetrahydropyranyl, methoxymethyl, and the like; examples of aldehyde-protecting groups include, for example, dialkylacetal, cyclic alkylacetal, and the like; and
5 examples of carboxyl-protecting groups include, for example, tert-butyl ester, orthoester, amide, and the like.

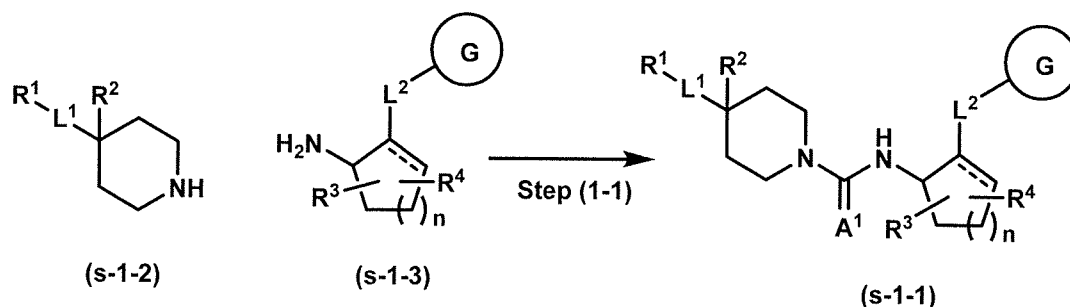
[0096]

The introduction and elimination of protecting groups can be carried out by a method commonly-used in synthetic
10 organic chemistry (for example, see *T. W. Greene, and P. G. M. Wuts, "Protective Groups in Organic Synthesis", 3rd Ed., John Wiley & Sons, Inc., New York (1999)*), or a similar method.

[0097]

15 Preparation Process 1:

In compounds according to formula (1) or a pharmaceutically acceptable salt thereof, the compound of formula (s-1-1) or a pharmaceutically acceptable salt thereof which is a compound of formula (1) wherein A³ is
20 nitrogen atom can be prepared, for example, by the following process.



wherein $R^1 - R^4$, L^1 , L^2 , n , Ring G , A^1 , and the bond accompanied with broken line are as defined in Item 1.

[0098]

5 Step (1-1):

Compound (s-1-1) can be prepared by reacting compound (s-1-2) and compound (s-1-3) in a suitable inert solvent under a reaction condition of urea-binding formulation. The present reaction condition includes, for example, using

10 triphosgene, 4-nitrophenyl chloroformate, 1,1'-carbonyldiimidazole, or thiophosgene. A base is used in the present reaction, and the base used herein includes triethylamine and diisopropylethylamine. The inert solvent includes a halogenated carbon solvent such as chloroform and

15 dichloromethane; a ether solvent such as diethyl ether, THF, and 1,4-dioxane; an aromatic hydrocarbon solvent such as benzene, toluene, and xylene; and an ester solvent such as ethyl acetate and methyl acetate. The reaction time is generally about 1 hour to 24 hours, and the reaction

20 temperature is -20°C to boiling point of a solvent used herein.

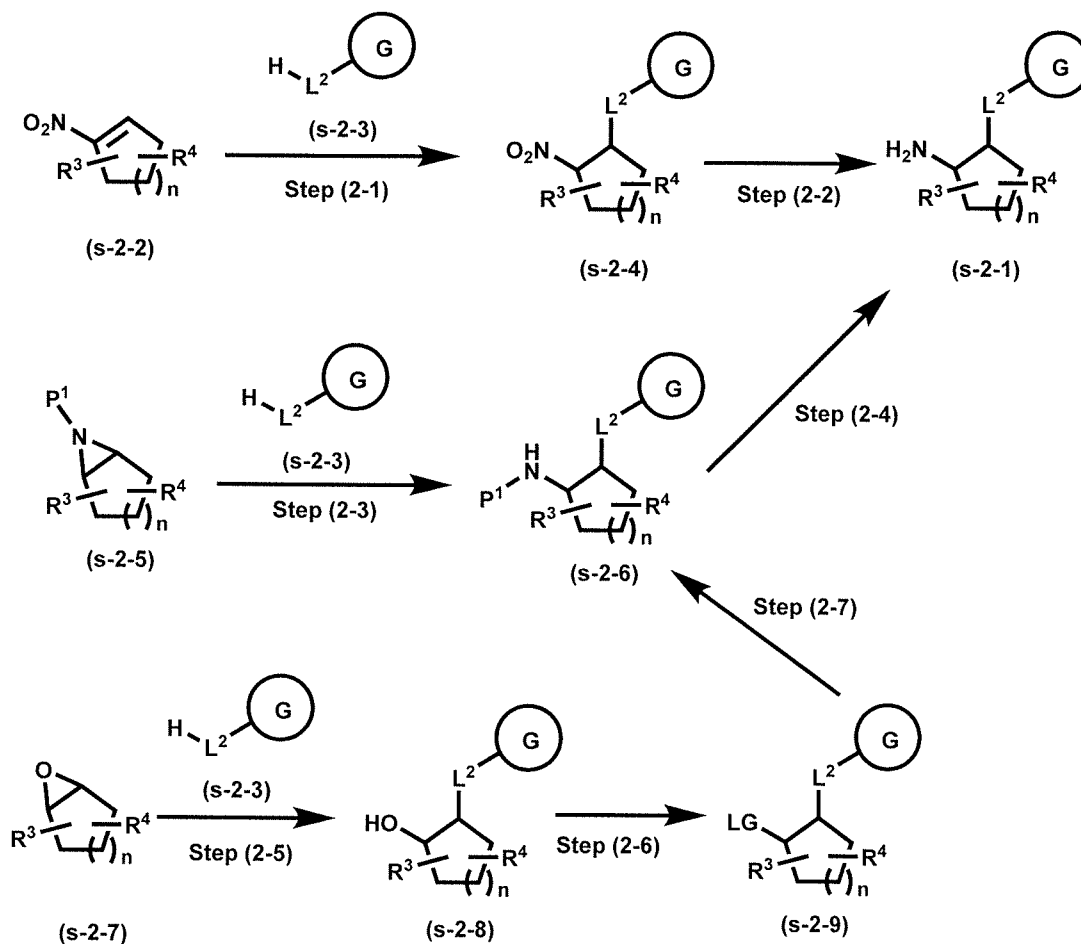
[0099]

In Step (1-1), the intermediate such as an isocyanate may isolated, followed by transforming the intermediate.

[0100]

5 Preparation Process 2:

10 In compounds according to formula (s-1-3), the compound of formula (s-2-1) which is a compound of formula (s-1-3) having no unsaturated bond in the ring can be prepared, for example, by the following process, provided that L^2 is oxygen atom or $-NR^{10}-$, or L^2 is single bond and Ring G is connected to the cycloalkyl via a nitrogen atom therein, wherein R^{10} is H or C_{1-4} alkyl, said definition is used below unless otherwise indicated.



wherein R^3 , R^4 , L^2 , n , and Ring G are as defined in Item 1; P^1 is a suitable protecting group; and LG is a suitable leaving group, said definitions are used below unless
 5 otherwise indicated.

[0101]

Compound (s-2-1) can be prepared from compound (s-2-2) via Step (2-1) and Step (2-2).

[0102]

10 Step (2-1):

Compound (s-2-4) can be prepared by reacting compound (s-2-2) and compound (s-2-3) in a suitable inert solvent

without additives or in the presence of a acid or a base. The acid used herein includes, for example, a protonic acid such as hydrochloric acid, sulfuric acid, phosphoric acid, methanesulfonic acid, benzenesulfonic acid, and p-toluenesulfonic; and a Lewis acid such as zinc(II) chloride, scandium(III) triflate, copper(I) chloride, boron trifluoride, boronic acid, and boronate ester. The base used herein includes, for example, an organic base such as triethylamine, diisopropylethylamine, and DBU; an inorganic base such as sodium hydrogen carbonate, sodium carbonate, and potassium carbonate; a metal alkoxide such as potassium tert-butoxide; an organometallic reagent such as n-butyl lithium and isopropylmagnesium chloride; and a metal amide reagent such as LDA and LHMDs. The inert solvent includes a halogenated carbon solvent such as chloroform and dichloromethane; a ether solvent such as diethyl ether, THF, and 1,4-dioxane; an aromatic hydrocarbon solvent such as benzene, toluene, and xylene; and an ester solvent such as ethyl acetate and methyl acetate. The reaction time is generally about 1 hour to 24 hours, and the reaction temperature is -20°C to boiling point of a solvent used herein.

[0103]

Step (2-2):

Compound (s-2-1) can be prepared by reacting compound

(s-2-4) in a suitable inert solvent or under hydrogen atmosphere as necessary, under a conventional condition of nitro-reduction. The present reaction condition includes, for example, using ferrum, zinc, tin(II) chloride, Raney nickel, palladium carbon, or palladium(II) hydroxide. The inert solvent includes a halogenated carbon solvent such as chloroform and dichloromethane; a ether solvent such as diethyl ether, THF, and 1,4-dioxane; an aromatic hydrocarbon solvent such as benzene, toluene, and xylene; an ester solvent such as ethyl acetate and methyl acetate; and an alcohol solvent such as methanol and ethanol. The reaction time is generally about 1 hour to 24 hours, and the reaction temperature is -20°C to boiling point of a solvent used herein.

[0104]

Compound (s-2-1) can be also prepared from compound (s-2-5) via Step (2-3) and Step (2-4).

[0105]

Step (2-3):

Compound (s-2-6) can be prepared by reacting compound (s-2-5) and compound (s-2-3) in a suitable inert solvent without additives or in the presence of an acid or a base under a conventional condition of aziridine-ring-opening reaction. The acid used herein includes, for example, a protonic acid such as hydrochloric acid, sulfuric acid,

phosphoric acid, methanesulfonic acid, benzenesulfonic acid, and p-toluenesulfonic; and a Lewis acid such as zinc(II) chloride, scandium(III) triflate, copper(I) chloride, boron trifluoride, boronic acid, and boronate ester. The base
5 used herein includes, for example, an organic base such as triethylamine, diisopropylethylamine, and DBU; an inorganic base such as sodium hydrogen carbonate, sodium carbonate, and potassium carbonate; a metal alkoxide such as potassium tert-butoxide; an organometallic reagent such as n-butyl
10 lithium and isopropylmagnesium chloride; and a metal amide reagent such as LDA and LHMDs. The inert solvent includes a halogenated carbon solvent such as chloroform and dichloromethane; a ether solvent such as diethyl ether, THF, and 1,4-dioxane; an aromatic hydrocarbon solvent such as
15 benzene, toluene, and xylene; and an ester solvent such as ethyl acetate and methyl acetate. The reaction time is generally about 1 hour to 24 hours, and the reaction temperature is -20°C to boiling point of a solvent used herein.

20 [0106]

Step (2-4):

Compound (s-2-1) can be prepared by deprotecting compound (s-2-6) in a known manner (for example, a manner described in Protective Groups in Organic Synthesis 3rd
25 Edition (John Wiley & Sons, Inc.), Comprehensive Organic

Transformation, edited by R. C. Larock, VCH publisher Inc., 1989, etc.) or a similar manner thereto.

[0107]

Compound (s-2-1) can be also prepared from compound (s-2-7) via Step (2-5) - Step (2-7), and Step (2-4).

[0108]

Step (2-5):

Compound (s-2-8) can be prepared by reacting compound (s-2-7) and compound (s-2-3) in a suitable inert solvent without additives or in the presence of a acid or a base under a conventional condition of epoxide-ring-opening reaction. The acid used herein includes, for example, a protonic acid such as hydrochloric acid, sulfuric acid, phosphoric acid, methanesulfonic acid, benzenesulfonic acid, and p-toluenesulfonic; and a Lewis acid such as boron trifluoride, zinc(II) chloride, scandium(III) triflate, copper(I) chloride, boronic acid, and boronate ester. The base used herein includes, for example, an organic base such as triethylamine, diisopropylethylamine, and DBU; an inorganic base such as sodium hydrogen carbonate, sodium carbonate, and potassium carbonate; a metal alkoxide such as potassium tert-butoxide; an organometallic reagent such as n-butyl lithium and isopropylmagnesium chloride; and a metal amide reagent such as LDA and LHMDs. The inert solvent includes a halogenated carbon solvent such as chloroform and

dichloromethane; a ether solvent such as diethyl ether, THF, and 1,4-dioxane; an aromatic hydrocarbon solvent such as benzene, toluene, and xylene; and an ester solvent such as ethyl acetate and methyl acetate. The reaction time is generally about 1 hour to 24 hours, and the reaction temperature is -20°C to boiling point of a solvent used herein.

[0109]

Step (2-6):

Compound (s-2-9) can be prepared by reacting compound (s-2-8) in a suitable inert solvent under a conventional condition of transformation reaction from hydroxy group to a leaving group. The present reaction condition includes, for example, using methanesulfonyl chloride, p-toluenesulfonyl chloride, or trifluoromethanesulfonyl chloride. A base is used in the present reaction, and the base used herein includes, for example, an organic base such as triethylamine, diisopropylethylamine, and DBU; an inorganic base such as sodium hydrogen carbonate, sodium carbonate, and potassium carbonate; a metal alkoxide such as potassium *tert*-butoxide; an organometallic reagent such as *n*-butyl lithium and isopropylmagnesium chloride; and a metal amide reagent such as LDA and LHMDs. The inert solvent includes a halogenated carbon solvent such as chloroform and dichloromethane; a ether solvent such as diethyl ether, THF,

and 1,4-dioxane; an aromatic hydrocarbon solvent such as benzene, toluene, and xylene; and an ester solvent such as ethyl acetate and methyl acetate. The reaction time is generally about 1 hour to 24 hours, and the reaction
5 temperature is -20°C to boiling point of a solvent used herein.

[0110]

Step (2-7):

Compound (s-2-6) can be prepared in a general
10 nucleophilic substitution reaction with compound (s-2-9), P^1NH_2 , and a base. The base used herein includes, for example, an organic base such as triethylamine, diisopropylethylamine, and DBU; an inorganic base such as sodium hydrogen carbonate, sodium carbonate, and potassium
15 carbonate; a metal alkoxide such as potassium tert-butoxide; an organometallic reagent such as n-butyl lithium and isopropylmagnesium chloride; and a metal amide reagent such as LDA and LHMDs. The solvent used herein includes a halogenated carbon solvent such as chloroform and
20 dichloromethane; a ether solvent such as diethyl ether, THF, and 1,4-dioxane; an aromatic hydrocarbon solvent such as benzene, toluene, and xylene; and an ester solvent such as ethyl acetate and methyl acetate. The reaction time is generally about 1 hour to 24 hours, and the reaction
25 temperature is -20°C to boiling point of a solvent used

herein.

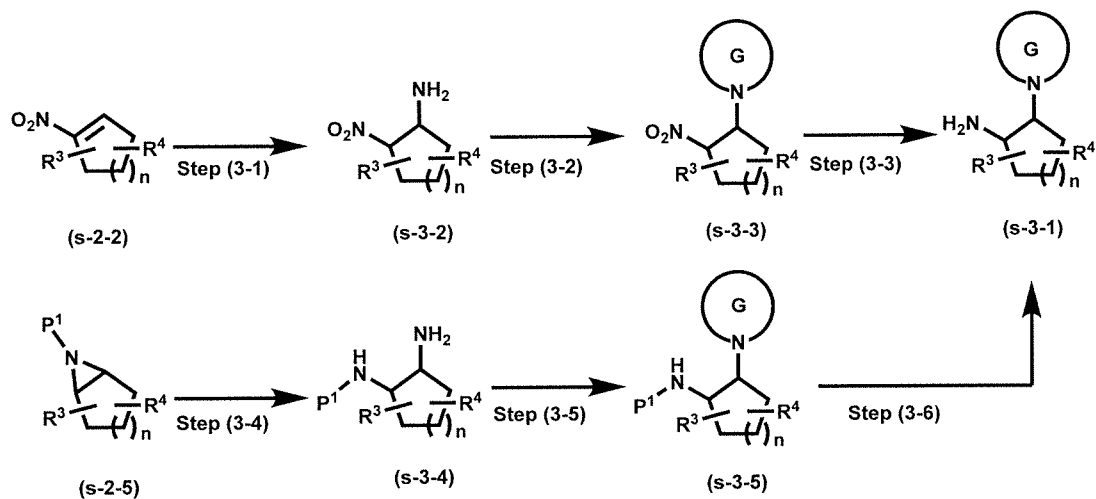
[0111]

Step (2-6) and Step (2-7) may be carried out as one step without isolating the intermediate. And, Step (2-6) and Step (2-7) may be also carried out as one step under Mitsunobu reaction condition.

[0112]

Preparation Process 3-1:

In compounds according to formula (s-2-1), the compound of formula (s-3-1) which is a compound of formula (s-2-1) wherein L^2 is single bond and Ring G binds to cycloalkyl via nitrogen atom therein can be also prepared, for example, by the following process.



wherein R^3 , R^4 , n , and Ring G are as defined in Item 1.

[0113]

Compound (s-3-1) can be prepared from compound (s-2-2) via Step (3-1) - Step (3-3).

[0114]

Step (3-1):

Compound (s-3-2) can be prepared in a similar manner to Step (2-1) with compound (s-2-2) and ammonia or a reagent
5 equal to ammonia that includes a protected-amine reagent which is deprotected after the amination and an azide-inducer which is reduced after the azidation.

[0115]

Step (3-2):

10 Compound (s-3-3) can be prepared in a nitrogen-containing heteroring-formulation with compound (s-3-2). For example, compound (s-3-3) wherein Ring G is piperazine can be prepared by reacting compound (s-3-2) with N-benzyl-bis(2-chloroethyl)amine, followed by deprotection and
15 alkylation.

[0116]

Step (3-3):

Compound (s-3-1) can be prepared in a similar manner to Step (2-2) with compound (s-3-3).

20 [0117]

Compound (s-3-1) can be also prepared from compound (s-2-5) via Step (3-4) - Step (3-6).

[0118]

Step (3-4):

25 Compound (s-3-4) can be prepared in a similar manner to

Step (2-3) with compound (s-2-5) and ammonia or a reagent equal to ammonia that includes a protected-amine reagent which is deprotected after the amination and an azide-inducer which is reduced after the azidation.

5 [0119]

Step (3-5):

Compound (s-3-5) can be prepared in a similar manner to Step (3-2) with compound (s-3-4).

[0120]

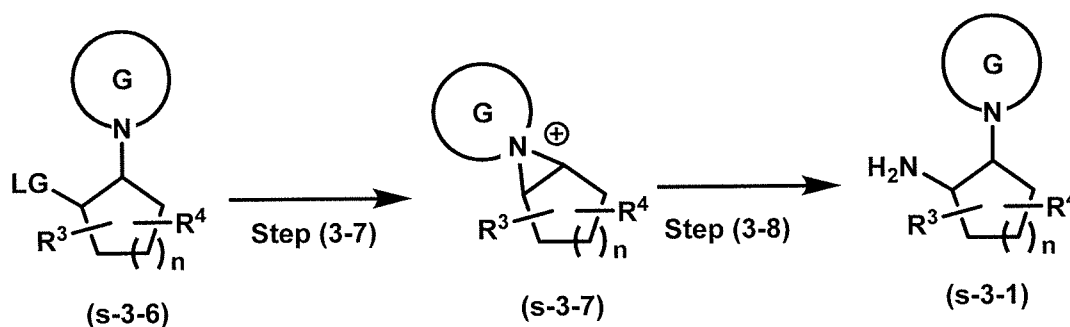
10 Step (3-6):

Compound (s-3-1) can be prepared in a similar deprotection to Step (2-4) with compound (s-3-5).

[0121]

Preparation Process 3-2:

15 The compound according to formula (s-3-1) can be also prepared, for example, by the following process.



wherein R^3 , R^4 , n , and Ring G are as defined in Item 1.

[0122]

20 Compound (s-3-1) can be prepared from compound (s-3-6) via Step (3-7) and Step (3-8).

[0123]

Step (3-7):

Compound (s-3-6) is compound (s-2-9) in Preparation Process 2, wherein L^2 is single bond and Ring G is connected to the cycloalkyl via a nitrogen atom therein. Compound (s-3-7) can be prepared in a general nucleophilic substitution reaction like Step (2-7) with compound (s-3-6) and a conventional base as intramolecular reaction. Compound (s-3-7) may be used in the next step without isolation.

10 [0124]

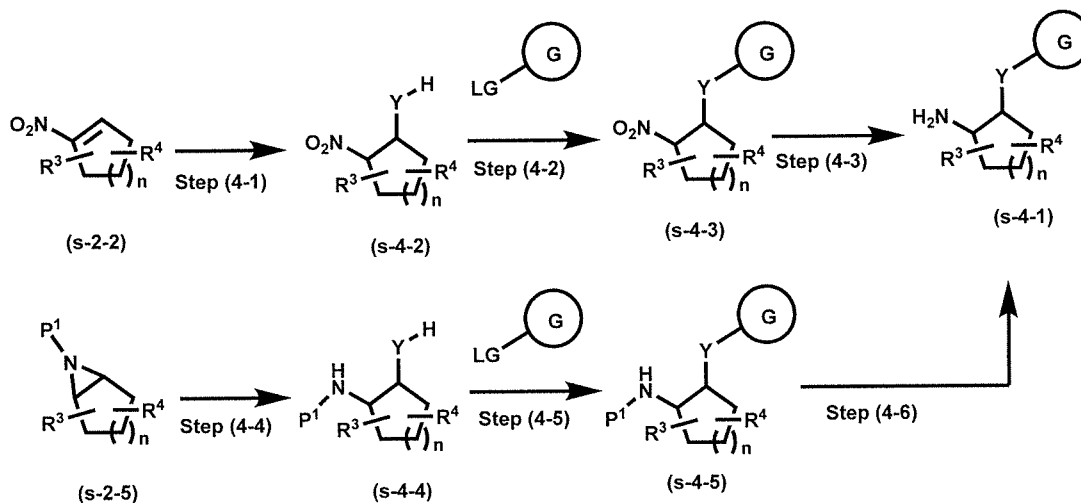
Step (3-8):

Compound (s-3-1) can be prepared in a general ring-opening reaction with compound (s-3-7) and ammonia or a reagent equal to ammonia that includes a protected-amine reagent which is deprotected after the amination and an azide-inducer which is reduced after the azidation.

[0125]

Preparation Process 4:

20 In compounds according to formula (s-2-1), the compound of formula (s-4-1) which is a compound of formula (s-2-1) wherein L^2 is O or NR^{10} can be also prepared, for example, by the following process.



wherein R^3 , R^4 , n , and Ring G are as defined in Item 1; and Y is O or NR^{10} , said definitions are used below unless otherwise indicated.

5 [0126]

Compound (s-4-1) can be prepared from compound (s-2-2) via Step (4-1) - Step (4-3).

[0127]

Step (4-1):

10 Compound (s-4-2) can be prepared by reacting compound (s-2-2) in a similar manner to Step (2-1) with YH_2 or a reagent equal to YH_2 that includes a protected reagent P^2YH which is deprotected after the addition reaction, wherein P^2 is a suitable protecting group, said definition is used below
15 unless otherwise indicated.

[0128]

Step (4-2):

Compound (s-4-3) can be prepared in a general

nucleophilic substitution reaction or aromatic nucleophilic substitution reaction with compound (s-4-2), Ring G accompanied with a leaving group, and a base. The base used herein includes, for example, an organic base such as triethylamine, diisopropylethylamine, and DBU; an inorganic base such as sodium hydrogen carbonate, sodium carbonate, and potassium carbonate; a metal alkoxide such as potassium *tert*-butoxide; an organometallic reagent such as *n*-butyl lithium and isopropylmagnesium chloride; and a metal amide reagent such as LDA and LHMDs. The solvent used herein includes a halogenated carbon solvent such as chloroform and dichloromethane; a ether solvent such as diethyl ether, THF, and 1,4-dioxane; an aromatic hydrocarbon solvent such as benzene, toluene, and xylene; and an ester solvent such as ethyl acetate and methyl acetate. The reaction time is generally about 1 hour to 24 hours, and the reaction temperature is -20°C to boiling point of a solvent used herein.

[0129]

Step (4-3):

Compound (s-4-1) can be prepared in a similar manner to Step (2-2) with compound (s-4-3).

[0130]

Compound (s-4-1) can be also prepared from compound (s-2-5) via Step (4-4) - Step (4-6).

[0131]

Step (4-4):

Compound (s-4-4) can be prepared by reacting compound (s-2-5) in a similar manner to Step (2-3) with YH_2 or a
5 reagent equal to YH_2 that includes a protected reagent P^2YH which is deprotected after the addition reaction.

[0132]

Step (4-5):

Compound (s-4-5) can be prepared in a similar manner to
10 Step (4-2) with compound (s-4-4).

[0133]

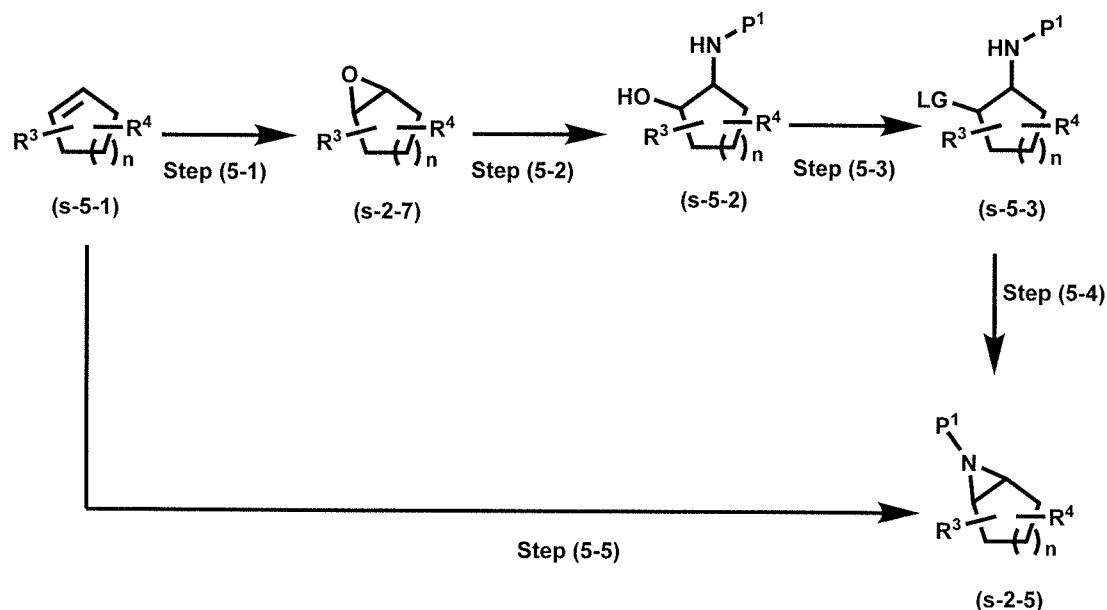
Step (4-6):

Compound (s-4-1) can be prepared in a similar deprotection to Step (2-4) with compound (s-4-5).

15 [0134]

Preparation Process 5:

The compound of formula (s-2-5) can be also prepared, for example, by the following process.



wherein R^3 , R^4 , and n are as defined in Item 1.

[0135]

Compound (s-2-5) can be prepared from compound (s-5-1) via Step (5-1) - Step (5-4).

[0136]

Step (5-1):

Compound (s-2-7) can be prepared by reacting compound (s-5-1) in a suitable inert solvent under a conventional condition of epoxide-formulation. The present reaction condition includes, for example, using an oxidizing agent such as hydrogen peroxide solution, mCPBA, tert-butyl hydroperoxide, and Oxone. In the present reaction, a metal catalyst such as V, Mo, Al, Ti, Fe, Ta, Zr, Nb, W, and Re may be used, as appropriate. The inert solvent includes a halogenated carbon solvent such as chloroform and dichloromethane; an aromatic hydrocarbon solvent such as

benzene, toluene, and xylene; and an ester solvent such as ethyl acetate and methyl acetate. The reaction time is generally about 1 hour to 24 hours, and the reaction temperature is -20°C to boiling point of a solvent used
5 herein.

[0137]

Step (5-2):

Compound (s-5-2) can be prepared in a similar manner to Step (2-5) with compound (s-2-7) and P^1NH_2 in a suitable
10 inert solvent.

[0138]

Step (5-2) may be carried out in a process comprising reacting compound (s-2-7) and ammonia or a reagent equal to ammonia that includes a protected-amine reagent which is
15 deprotected after the amination and an azide-inducer which is reduced after the azidation, and then protecting the product with a protecting group P^1 .

[0139]

Step (5-3):

20 Compound (s-5-3) can be prepared in a similar manner to Step (2-6) with compound (s-5-2) in a suitable inert solvent.

[0140]

Step (5-4):

Compound (s-2-5) can be prepared by reacting compound
25 (s-5-3) in the presence of a base in a suitable inert solvent

under a conventional condition of intramolecular cyclization reaction. The base used herein includes, for example, an organic base such as triethylamine, diisopropylethylamine, and DBU; an inorganic base such as sodium hydrogen carbonate, sodium carbonate, and potassium carbonate; a metal alkoxide such as potassium tert-butoxide; an organometallic reagent such as n-butyl lithium and isopropylmagnesium chloride; and a metal amide reagent such as LDA and LHMDs. The inert solvent includes a halogenated carbon solvent such as chloroform and dichloromethane; an ether solvent such as diethyl ether, THF, and 1,4-dioxane; an aromatic hydrocarbon solvent such as benzene, toluene, and xylene; and an ester solvent such as ethyl acetate and methyl acetate. The reaction time is generally about 1 hour to 24 hours, and the reaction temperature is -20°C to boiling point of a solvent used herein.

[0141]

Step (5-3) and Step (5-4) may be carried out as one step without isolating the intermediate. And, (5-3) and Step (5-4) may be also carried out as one step under Mitsunobu reaction condition.

[0142]

Compound (s-2-5) can be also prepared from compound (s-5-1) via Step (5-5).

[0143]

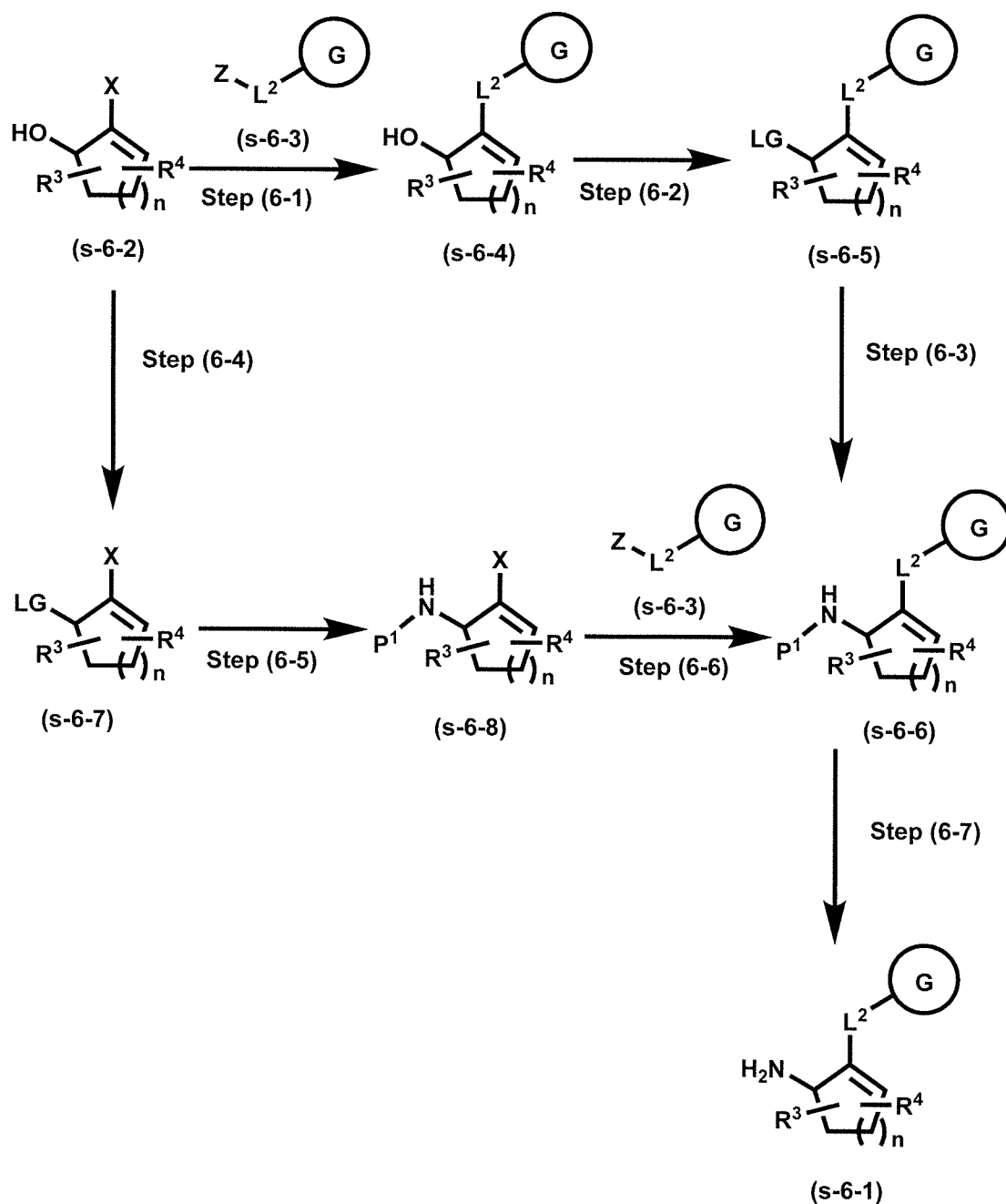
Step (5-5):

Compound (s-2-5) can be prepared by reacting compound (s-5-1) in a suitable inert solvent under a conventional condition of aziridine-ring-formulation reaction. The present reaction condition includes, for example, using P^1NH_2 and an oxidizing agent such as iodosylbenzene in the presence of a metallic catalyst, and using a hydroxylamine derivative $P^1N(H)O-LG$ and a metallic catalyst.

[0144]

10 Preparation Process 6:

In compounds according to formula (s-1-1), the compound of formula (s-6-1) which has an unsaturated bond in the ring can be prepared, for example, by the following process.



wherein R^3 , R^4 , L^2 , n , and Ring G are as defined in Item 1;
 Z is boronic acid, boronate ester, BF_3K , BF_3Na , trialkyl tin,
 zinc halide, or hydrogen atom; and X is halogen.

5 [0145]

Compound (s-6-1) can be prepared from compound (s-6-6)

via Step (6-7). And, compound (s-6-6) can be prepared from compound (s-6-2) via Step (6-1) - Step (6-3), or via Step (6-4) - Step (6-6).

[0146]

5 Step (6-1):

Compound (s-6-4) wherein L^2 is single bond or methylene which may be optionally substituted with the same or different one or more C_{1-4} alkyl can be prepared by reacting compound (s-6-2) with compound (s-6-3) wherein Z is boronic
 10 acid, boronate ester, BF_3K , BF_3Na , trialkyl tin, or zinc halide, in the presence of palladium catalyst and phosphine ligand, and optionally in the presence of a base, in a suitable inert solvent. Compound (s-6-3) is commercially available, or can be prepared according to a known method or
 15 a similar method thereto. The palladium catalyst used herein includes, for example, tetrakis(triphenylphosphine)palladium(0), bis(dibenzylideneacetone)palladium(0), tris(dibenzylideneacetone)dipalladium(0), bis(tri-tert-
 20 butylphosphine)palladium(0), palladium(0) acetate, [1,1-bis(diphenylphosphino)ferrocene]palladium(II) dichloride, and bis(di-tert-butyl(4-dimethylaminophenyl)phosphine)dichloropalladium(II).

The phosphine ligand used herein includes, for example,
 25 o-tolylphosphine, 2-dicyclohexylphosphino-2',6'-

dimethoxybiphenyl (S-Phos), 2-dicyclohexylphosphino-
 2',4',6'-triisopropylbiphenyl (X-Phos), 1,1'-
 bis(diphenylphosphino)ferrocene (DPPF), 1,2-
 bis(diphenylphosphino)ethane (DPPE), 1,3-
 5 bis(diphenylphosphino)propane (DPPP), 1,4-
 bis(diphenylphosphino)butane (DPPB), 2,2'-
 bis(diphenylphosphino)-1,1'-binaphthyl (BINAP), 4,5-
 bis(diphenylphosphino)-9,9-dimethylxanthene (XANT-Phos),
 and bis((2-diphenylphosphino)phenyl) ether (DPE-Phos). The
 10 base used herein includes, for example, sodium carbonate,
 potassium carbonate, cesium carbonate, potassium phosphate,
 sodium hydroxide, and potassium hydroxide. The inert solvent
 includes, for example, 1,4-dioxane, THF, 1,2-
 dimethoxyethane, acetonitrile, water, and a mixture thereof.
 15 The reaction time is generally about 1 hour to 24 hours, and
 the reaction temperature is -20°C to boiling point of a
 solvent used herein.

[0147]

In addition, compound (s-6-4) wherein L^2 is O or NR^{10}
 20 can be also prepared by reacting compound (s-6-2) with
 compound (s-6-3) wherein Z is hydrogen atom in the presence
 of palladium catalyst, phosphine ligand, and a base in a
 suitable inert solvent.

[0148]

25 Step (6-2):

Compound (s-6-5) can be prepared in a similar manner to Step (2-6) with compound (s-6-4).

[0149]

Step (6-3):

5 Compound (s-6-6) can be prepared in a similar manner to Step (2-7) with compound (s-6-5) and P^1NH_2 .

[0150]

10 Step (6-3) may be carried out in a process comprising reacting compound (s-6-5) and ammonia or a reagent equal to ammonia that includes a protected-amine reagent which is deprotected after the amination and an azide-inducer which is reduced after the azidation, and then protecting the product with a protecting group P^1 .

[0151]

15 Step (6-2) and Step (6-3) may be carried out as one step without isolating the intermediate. And, Step (6-2) and Step (6-3) may be also carried out as one step under Mitsunobu reaction condition.

[0152]

20 Step (6-4):

Compound (s-6-7) can be prepared in a similar manner to Step (6-2) with compound (s-6-2).

[0153]

Step (6-5):

25 Compound (s-6-8) can be prepared in a similar manner to

Step (6-3) with compound (s-6-7).

[0154]

Step (6-5) may be carried out in a process comprising reacting compound (s-6-7) and ammonia or a reagent equal to
5 ammonia that includes a protected-amine reagent which is deprotected after the amination and an azide-inducer which is reduced after the azidation, and then protecting the product with a protecting group P¹.

[0155]

10 Step (6-4) and Step (6-5) may be carried out as one step without isolating the intermediate. And, Step (6-4) and Step (6-5) may be also carried out as one step under Mitsunobu reaction condition.

[0156]

15 Step (6-6):

Compound (s-6-6) can be prepared in a similar manner to Step (6-1) with compound (s-6-8).

[0157]

Step (6-7):

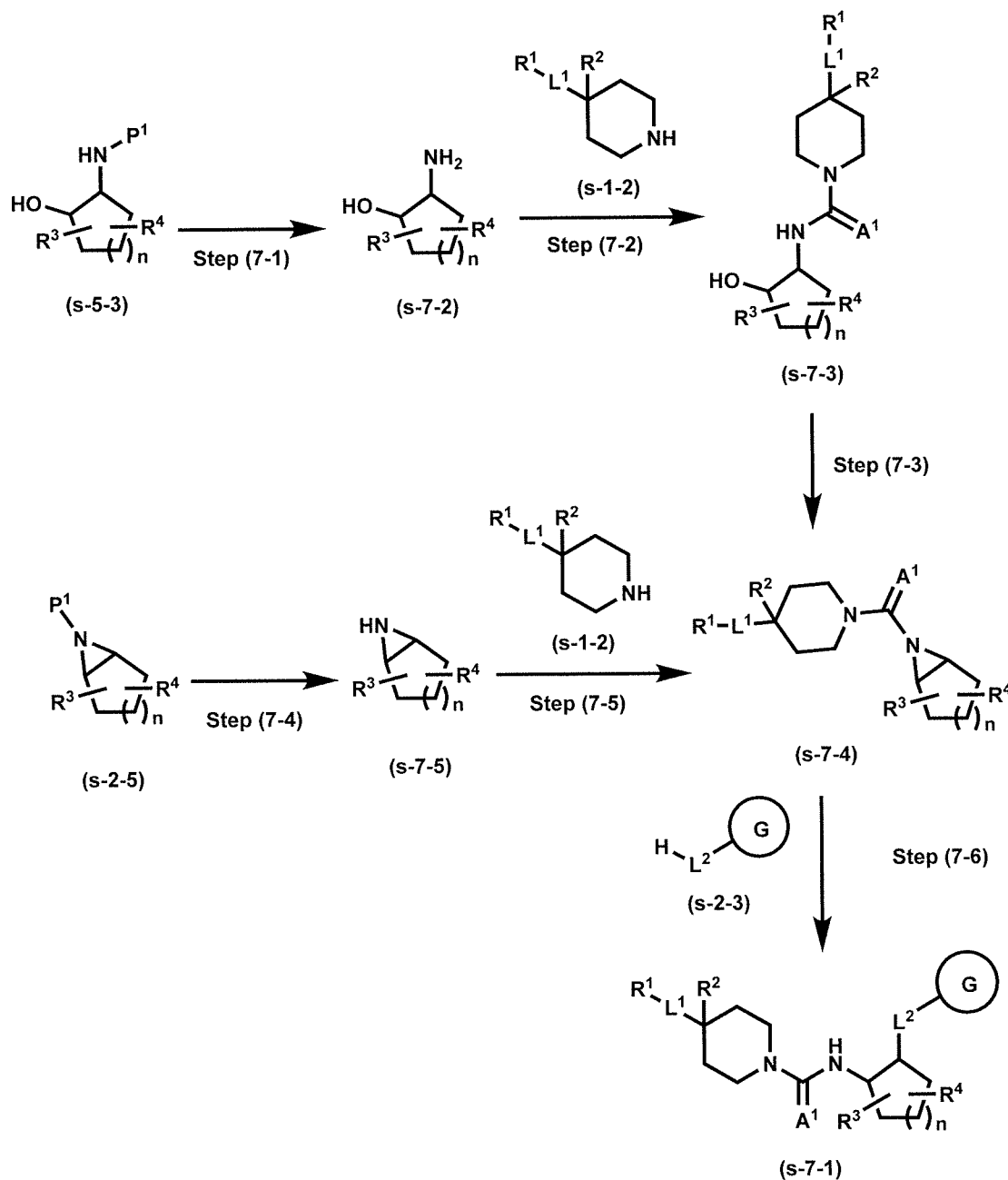
20 Compound (s-6-1) can be prepared in a similar deprotection to Step (2-4) with compound (s-6-6).

[0158]

Preparation Process 7:

In compounds according to formula (s-1-1), the compound
25 of formula (s-7-1) which has no unsaturated bond in the ring

can be prepared, for example, by the following process.



wherein R¹ - R⁴, L¹, L², n, Ring G, and A¹ are as defined in Item 1.

5 [0159]

Compound (s-7-1) can be prepared from compound (s-7-4)

via Step (7-6). And, compound (s-7-4) can be prepared from compound (s-5-3) via Step (7-1) - Step (7-3), or from compound (s-2-5) via Step (7-4) and Step (7-5).

[0160]

5 Step (7-1):

Compound (s-7-2) can be prepared in a similar deprotection to Step (2-4) with compound (s-5-3).

[0161]

Step (7-2):

10 Compound (s-7-3) can be prepared in a similar ureation to Step (1-1) with compound (s-7-2) and compound (s-1-2). In this step, the hydroxy group may be protected and deprotected, if necessary.

[0162]

15 Step (7-3):

Compound (s-7-4) can be prepared in a similar manner to Step (5-3) and Step (5-4) with compound (s-7-3).

[0163]

Step (7-4):

20 Compound (s-7-5) can be prepared in a similar deprotection to Step (2-4) with compound (s-2-5).

[0164]

Step (7-5):

25 Compound (s-7-4) can be prepared in a similar urea formation to Step (1-1) with compound (s-7-5) and compound

(s-1-2) .

[0165]

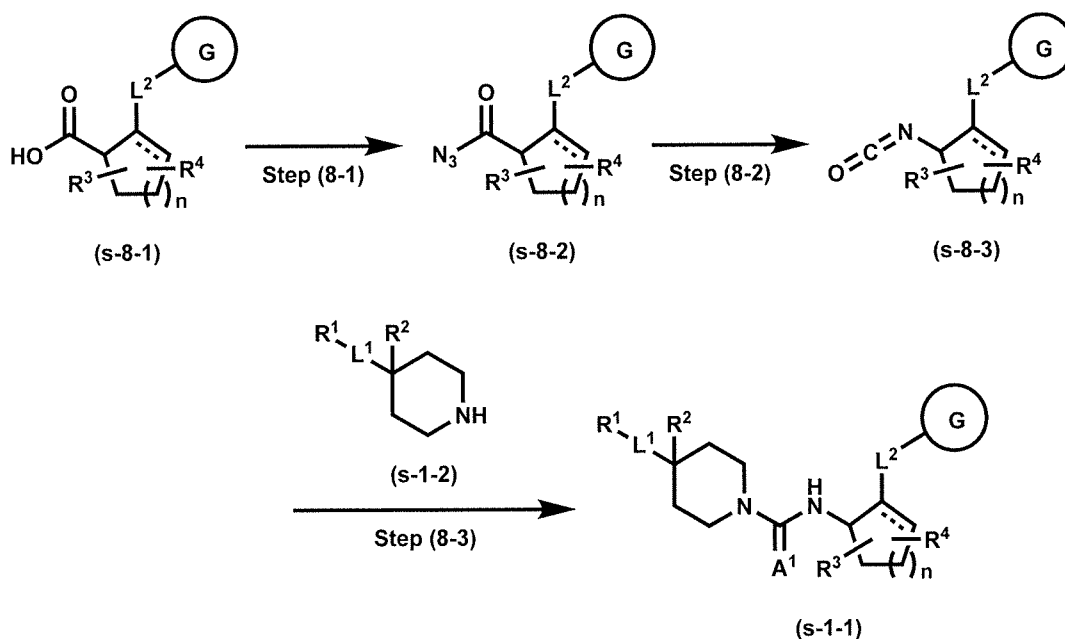
Step (7-6) :

Compound (s-7-1) can be prepared in a similar aziridine-ring-open reaction to Step (2-3) with compound (s-7-4) and compound (s-2-3).

[0166]

Preparation Process 8:

The compound of formula (s-1-1) can be also prepared from compound (s-8-1) via Step (8-1) - Step (8-3).



wherein $R^1 - R^4$, L^1 , L^2 , n , Ring G , A^1 , and the bond accompanied with broken line are as defined in Item 1.

[0167]

Step (8-1) :

Compound (s-8-2) can be prepared by reacting compound

(s-8-1) in a suitable inert solvent under a conventional condition of acyl azide formulation. The present reaction condition includes, for example, using diphenylphosphoryl azide, or converting the carboxylic acid to its acid halide and then azidating the acid halide with a metallic azide. The inert solvent includes an ether solvent such as diethyl ether, diisopropyl ether, tetrahydrofuran, and 1,4-dioxane; an aromatic hydrocarbon solvent such as benzene, toluene, and xylene, an ester solvent such as ethyl acetate and methyl acetate; an aprotic polar solvent such as N,N-dimethylformamide, N,N-dimethylacetamide, N-methyl-2-pyrrolidinone, 1,3-dimethyl-2-imidazolidinone, and dimethyl sulfoxide. The reaction time is generally about 1 hour to 24 hours, and the reaction temperature is -20°C to boiling point of a solvent used herein.

[0168]

Step (8-2):

Compound (s-8-3) can be prepared by reacting compound (s-8-2) in a suitable inert solvent under a condition of Curtius rearrangement reaction. Compound (s-8-2) used herein may be the un-isolated product from the prior step.

[0169]

Step (8-3):

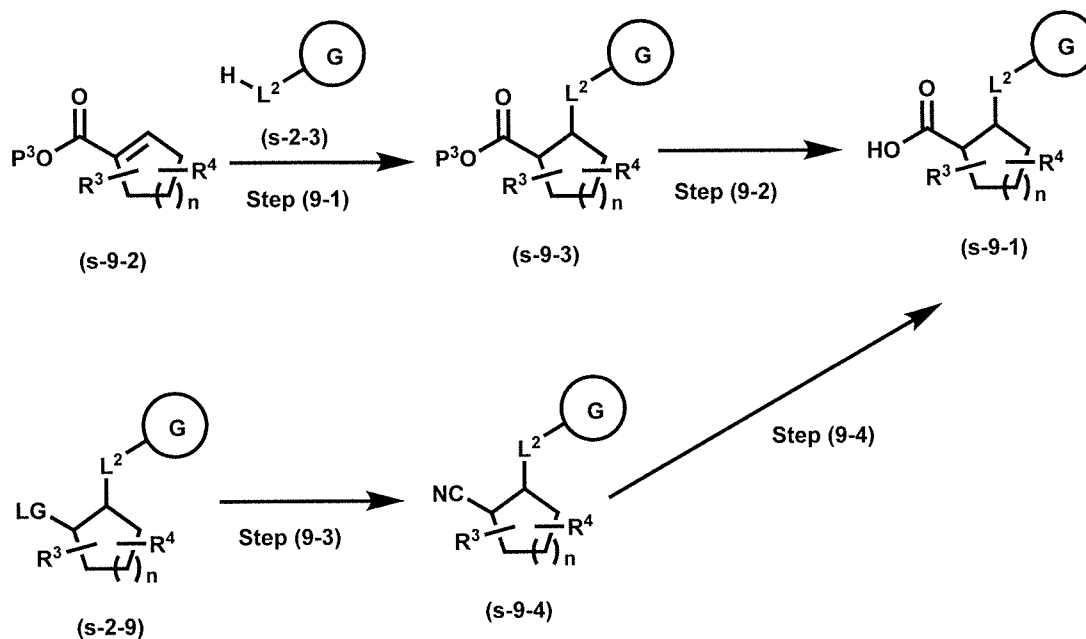
Compound (s-1-1) can be prepared by reacting compound (s-8-3) and compound (s-1-2) in a suitable inert solvent

under a conventional condition of addition reaction.
Compound (s-8-3) used herein may be the un-isolated product
from the prior step.

[0170]

5 Preparation Process 9:

In compounds according to formula (s-8-1), the compound
of formula (s-9-1) which has no unsaturated bond in the ring
can be prepared, for example, by the following process.



10 wherein R^3 , R^4 , L^2 , n , and Ring G are as defined in Item 1;
and P^3 is a suitable protecting group or C_{1-3} alkyl, said
definitions are used below unless otherwise indicated.

[0171]

Compound (s-9-1) can be prepared from compound (s-9-2)
15 via Step (9-1) and Step (9-2).

[0172]

Step (9-1):

Compound (s-9-3) can be prepared in a similar manner to Step (2-1) with compound (s-9-2) and compound (s-2-3).

[0173]

5 Step (9-2):

Compound (s-9-1) can be prepared by subjecting compound (s-9-3) to a general condition of hydrolysis or deprotection.

[0174]

10 Compound (s-9-1) can be prepared from compound (s-2-9) via Step (9-3) and Step (9-4).

[0175]

Step (9-3):

Compound (s-9-4) can be prepared in a similar manner to Step (2-7) with compound (s-2-9) and a metallic cyanide.

15 [0176]

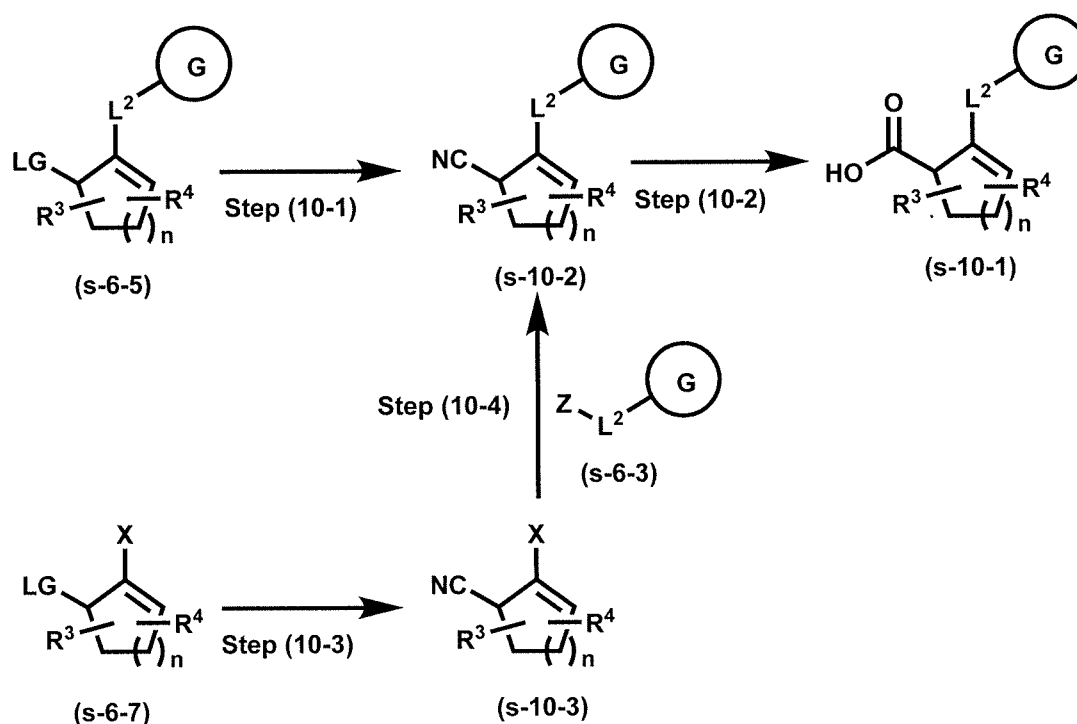
Step (9-4):

Compound (s-9-1) can be prepared by reacting compound (s-9-4) in a suitable inert solvent under a general condition of hydrolysis.

20 [0177]

Preparation Process 10:

In compounds according to formula (s-8-1), the compound of formula (s-10-1) which has an unsaturated bond in the ring can be prepared, for example, by the following process.



wherein R^3 , R^4 , L^2 , n , and Ring G are as defined in Item 1; Z is boronic acid, boronate ester, BF_3K , BF_3Na , trialkyl tin, zinc halide, or hydrogen atom; and X is halogen.

5 [0178]

Compound (s-10-1) can be prepared from compound (s-10-2) via Step (10-2). And, compound (s-10-2) can be prepared from compound (s-6-5) via Step (10-1), or from compound (s-6-7) via Step (10-3) and Step (10-4).

10 [0179]

Step (10-1):

Compound (s-10-2) can be prepared in a similar manner to Step (2-7) with compound (s-6-5) and a metallic cyanide.

[0180]

15 Step (10-2):

Compound (s-10-1) can be prepared by reacting compound (s-10-2) in a suitable inert solvent under a general condition of hydrolysis.

[0181]

5 Step (10-3):

Compound (s-10-3) can be prepared in a similar manner to Step (10-1) with compound (s-6-7) and a metallic cyanide.

[0182]

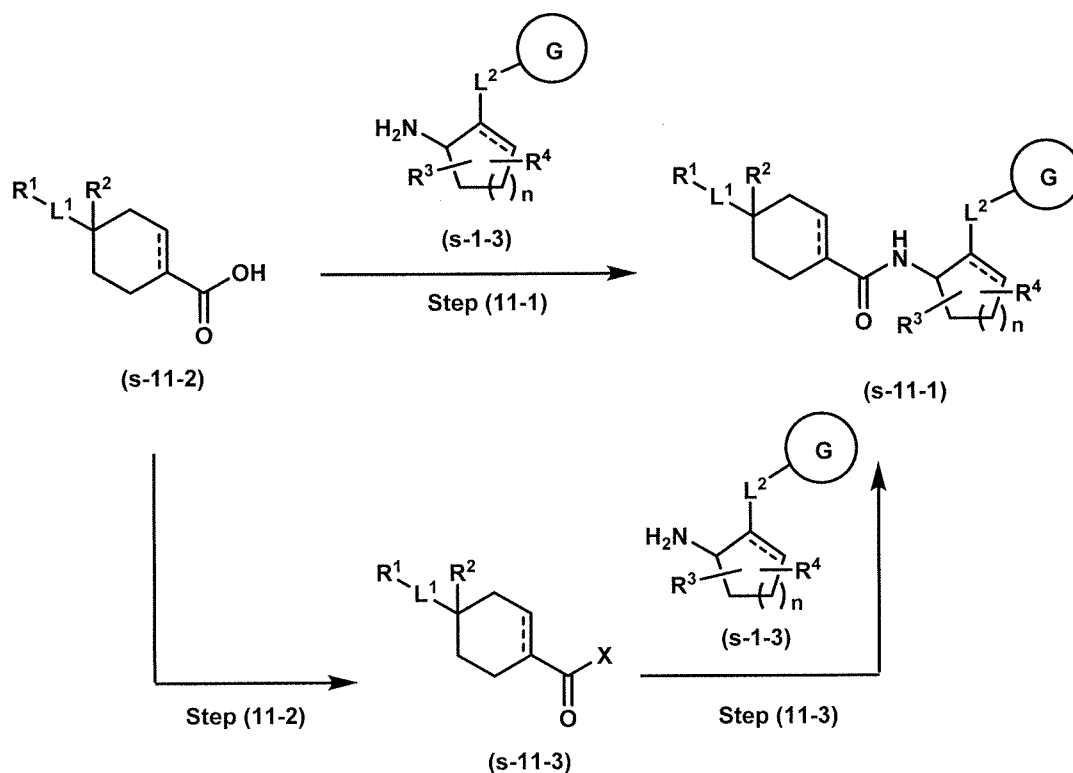
Step (10-4):

10 Compound (s-10-2) can be prepared in a similar manner to Step (6-1) with compound (s-10-3) and compound (s-6-3).

[0183]

Preparation Process 11:

15 In compounds according to formula (1) or a pharmaceutically acceptable salt thereof, the compound of formula (s-11-1) which is a compound of formula (1) wherein A³ is carbon atom or a pharmaceutically acceptable salt thereof can be prepared, for example, by the following process.



wherein $R^1 - R^4$, L^1 , L^2 , n , Ring G, and the bond accompanied with broken line are as defined in Item 1.

[0184]

5 Step (11-1):

Compound (s-11-1) can be prepared by reacting compound (s-11-2) and compound (s-1-3) in a suitable inert solvent under a conventional condition of amide-bond formulation reaction. The present reaction condition includes, for example, using a condensation agent and a base, and the condensation agent used herein includes, for example, a carbodiimide such as dicyclohexylcarbodiimide, 1,1'-carbonyldiimidazole, diphenylphosphoryl azide (DPPA), diethylphosphoryl cyanide (DEPC), dicyclohexylcarbodiimide

(DCC), carbonyldiimidazole (CDI), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDC·HCl), O-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrahydroborate (TBTU), O-(benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (HBTU), and O-(7-azabenzotriazol-1-yl)-N,N,N',N',-tetramethyluronium hexafluorophosphate (HATU). The base used herein includes an organic base such as triethylamine, diisopropylethylamine, tributylamine, DBU, pyridine, and dimethylaminopyridine. The inert solvent includes a halogenated hydrocarbon solvent such as dichloromethane and chloroform; an ether solvent such as diethyl ether, diisopropyl ether, tetrahydrofuran, and 1,4-dioxane; an aromatic hydrocarbon solvent such as benzene, toluene, and xylene; an ester solvent such as ethyl acetate and methyl acetate; an aprotic polar solvent such as N,N-dimethylformamide, N,N-dimethylacetamide, N-methyl-2-pyrrolidinone, 1,3-dimethyl-2-imidazolidinone, and dimethyl sulfoxide. The reaction time is generally about 1 hour to 24 hours, and the reaction temperature is -20°C to boiling point of a solvent used herein.

[0185]

Compound (s-11-1) can be also prepared from compound (s-11-2) via Step (11-2) and Step (11-3).

[0186]

Step (11-2):

Compound (s-11-3) can be prepared by reacting compound (s-11-2) in a suitable inert solvent under a conventional condition of acid halide formulation reaction. The present
5 reaction condition includes, for example, using a halogenating agent, and the halogenating agent used herein includes, for example, thionyl chloride, oxalyl chloride, phosphoryl chloride, sulfuryl chloride, phosphorus trichloride, phosphorus tribromide, and phosphorus
10 pentachloride. The inert solvent includes a halogenated hydrocarbon solvent such as dichloromethane and chloroform; an ether solvent such as diethyl ether, diisopropyl ether, tetrahydrofuran, and 1,4-dioxane; an aromatic hydrocarbon solvent such as benzene, toluene, and xylene; and an ester
15 solvent such as ethyl acetate and methyl acetate. The reaction time is generally about 1 hour to 24 hours, and the reaction temperature is -20°C to boiling point of a solvent used herein.

[0187]

20 Step (11-3):

Compound (s-11-1) can be prepared by reacting compound (s-11-3) and compound (s-1-3) in a suitable inert solvent in the presence of a base. The base used herein includes an organic base such as triethylamine, diisopropylethylamine,
25 tributylamine, DBU, pyridine, and dimethylaminopyridine; and

an inorganic base such as sodium hydrogen carbonate, sodium carbonate, and potassium carbonate. The inert solvent includes a halogenated hydrocarbon solvent such as dichloromethane and chloroform; an ether solvent such as diethyl ether, diisopropyl ether, tetrahydrofuran, and 1,4-dioxane; an aromatic hydrocarbon solvent such as benzene, toluene, and xylene; and an ester solvent such as ethyl acetate and methyl acetate. The reaction time is generally about 1 hour to 24 hours, and the reaction temperature is -

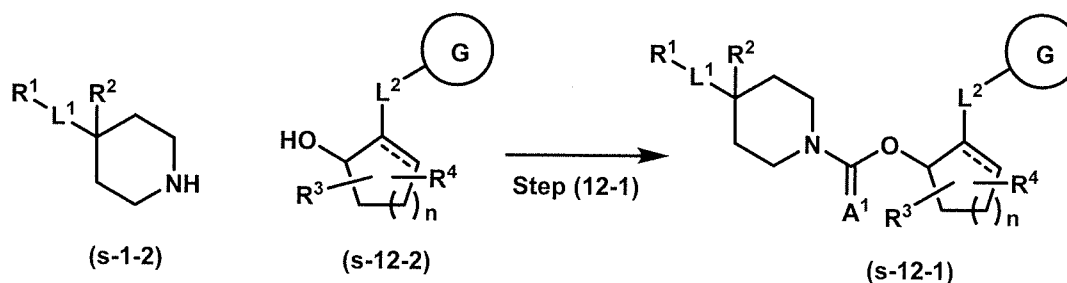
10 20°C to boiling point of a solvent used herein.

[0188]

Preparation Process 12:

In compounds according to formula (1) or a pharmaceutically acceptable salt thereof, the compound of formula (s-12-1) which is a compound of formula (1) wherein A² is oxygen atom or a pharmaceutically acceptable salt thereof can be prepared, for example, by the following process.

15



20 wherein R¹ - R⁴, L¹, L², n, Ring G, A¹, and the bond accompanied with broken line are as defined in Item 1.

[0189]

Step (12-1):

Compound (s-12-1) can be prepared by reacting compound (s-1-2) and compound (s-12-2) in a suitable inert solvent under a conventional condition of carbamate formulation reaction. The present reaction condition includes, for example, using triphosgene, 4-nitrophenyl chloroformate, or thiophosgene. A base is used in the present reaction, and the base used herein includes triethylamine and diisopropylethylamine. The inert solvent includes a halogenated carbon solvent such as chloroform and dichloromethane; a ether solvent such as diethyl ether, THF, and 1,4-dioxane; an aromatic hydrocarbon solvent such as benzene, toluene, and xylene; and an ester solvent such as ethyl acetate and methyl acetate. The reaction time is generally about 1 hour to 24 hours, and the reaction temperature is -20°C to boiling point of a solvent used herein.

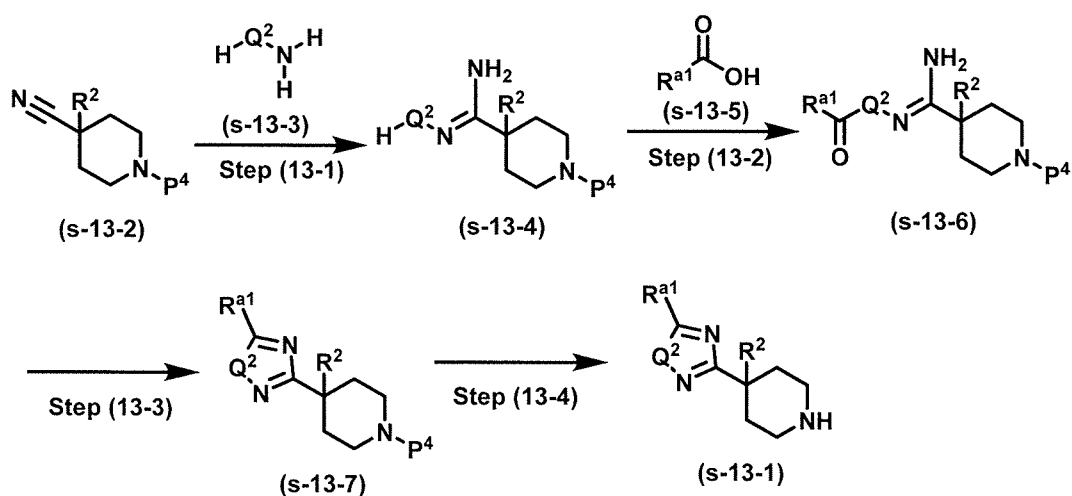
[0190]

Compound (s-12-2) which has no unsaturated bond in the ring is prepared in the Preparation Process of compound (s-2-8). And, compound (s-12-2) which has a unsaturated bond in the ring is prepared in the Preparation Process of compound (s-6-4).

[0191]

Preparation Process 13:

In compounds according to formula (s-1-2), the compound of formula (s-13-1) can be prepared, for example, by the following process.



wherein R² is as defined in Item 1, R^{a1} and Q² are as defined in Item 4; and P⁴ is a suitable protecting group, said definitions are used below unless otherwise indicated.

10 [0192]

Step (13-1):

Compound (s-13-4) can be prepared by reacting compound (s-13-2) and compound (s-13-3) in a suitable inert solvent under a conventional condition of addition reaction. The inert solvent includes a halogenated carbon solvent such as chloroform and dichloromethane; a ether solvent such as diethyl ether, THF, and 1,4-dioxane; an aromatic hydrocarbon solvent such as benzene, toluene, and xylene; an alcohol

solvent such as methanol and ethanol; and water. The reaction time is generally about 1 hour to 24 hours, and the reaction temperature is -20°C to boiling point of a solvent used herein.

5 [0193]

Step (13-2):

Compound (s-13-6) can be prepared by reacting compound (s-13-4) and compound (s-13-5) in a suitable inert solvent under a conventional condition of condensation reaction. The present reaction condition includes, for example, using HATU, DCC, or CDI. A base is used in the present reaction, and the base used herein includes triethylamine and diisopropylethylamine. The inert solvent includes a halogenated carbon solvent such as chloroform and dichloromethane; a ether solvent such as diethyl ether, THF, and 1,4-dioxane; an aromatic hydrocarbon solvent such as benzene, toluene, and xylene; and an ester solvent such as ethyl acetate and methyl acetate. The reaction time is generally about 1 hour to 24 hours, and the reaction temperature is -20°C to boiling point of a solvent used herein.

[0194]

Step (13-3):

Compound (s-13-7) can be prepared by reacting compound (s-13-6) in a suitable inert solvent under a conventional

condition of dehydration reaction. In the present reaction, a base such as triethylamine and DBU may be used as appropriate. The inert solvent includes a halogenated carbon solvent such as chloroform and dichloromethane; a ether solvent such as diethyl ether, THF, and 1,4-dioxane; an aromatic hydrocarbon solvent such as benzene, toluene, and xylene; and an ester solvent such as ethyl acetate and methyl acetate. The reaction time is generally about 1 hour to 24 hours, and the reaction temperature is -20°C to boiling point of a solvent used herein.

[0195]

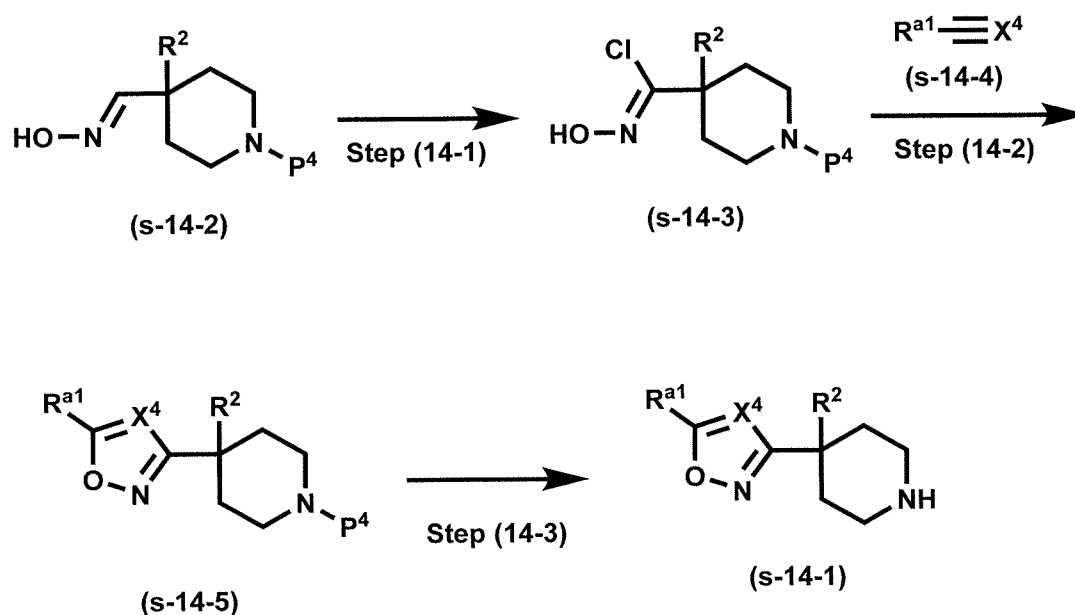
Step (13-4):

Compound (s-13-1) can be prepared by deprotecting compound (s-13-7) in a known manner (for example, a manner described in Protective Groups in Organic Synthesis 3rd Edition (John Wiley & Sons, Inc.), Comprehensive Organic Transformation, edited by R. C. Larock, VCH publisher Inc., 1989, etc.) or a similar manner thereto.

[0196]

Preparation Process 14:

In compounds according to formula (s-1-2), the compound of formula (s-14-1) which is a compound of formula (s-1-2) wherein L¹ is single bond and R¹ is optionally-substituted 5-membered aromatic heterocyclyl group can be also prepared, for example, by the following process.



wherein R^2 is as defined in Item 1, X^4 and R^{a1} are as defined in Item 4.

[0197]

- 5 Compound (s-14-1) can be prepared from compound (s-14-2) via Step (14-1) - Step (14-3).

[0198]

Step (14-1):

Compound (s-14-3) can be prepared by reacting compound (s-14-2) in a suitable inert solvent under a conventional condition of chlorination reaction. The present reaction condition includes, for example, using chlorine, N-succinimide, and trimethylbenzylammonium tetrachloroiodate. The inert solvent includes a halogenated carbon solvent such as chloroform and dichloromethane; a ether solvent such as diethyl ether, THF, and 1,4-dioxane; an aromatic hydrocarbon solvent such as benzene, toluene, and xylene; an aprotic

10

15

polar solvent such as N,N-dimethylformamide, N,N-dimethylacetamide, N-methyl-2-pyrrolidinone, 1,3-dimethyl-2-imidazolidinone and dimethyl sulfoxide; water; and a mixture thereof. The reaction time is generally about 1
5 hour to 24 hours, and the reaction temperature is -20°C to boiling point of a solvent used herein.

[0199]

Step (14-2):

Compound (s-14-5) can be prepared by reacting compound
10 (s-14-3) and compound (s-14-4) in a suitable inert solvent under a conventional condition of 1,3-dipolar cycloaddition reaction. The present reaction condition includes, for example, using a base, and the base used herein includes an inorganic base such as potassium carbonate, cesium
15 carbonate, sodium carbonate, sodium hydrogen carbonate, sodium methoxide, sodium t-butoxide, sodium hydroxide, potassium hydroxide, and potassium fluoride; and an organic base such as triethylamine, diisopropylethylamine, tributylamine, DBN, DABCO, DBU, pyridine,
20 dimethylaminopyridine, picoline, and NMM. The inert solvent includes a halogenated carbon solvent such as chloroform and dichloromethane; a ether solvent such as diethyl ether, THF, and 1,4-dioxane; an aromatic hydrocarbon solvent such as benzene, toluene, and xylene; and an ester solvent such as
25 ethyl acetate and methyl acetate. The reaction time is

generally about 1 hour to 24 hours, and the reaction temperature is -20°C to boiling point of a solvent used herein.

[0200]

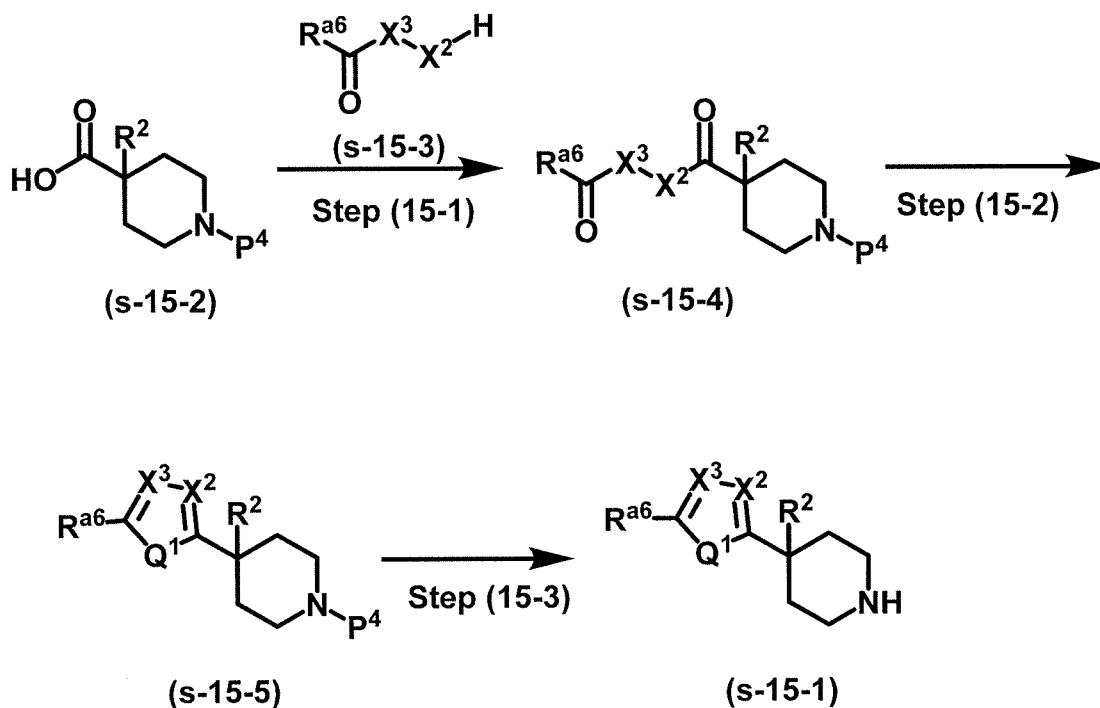
5 Step (14-3):

Compound (s-14-1) can be prepared in a similar manner to Step (13-4) with compound (s-14-5).

[0201]

Preparation Process 15:

10 In compounds according to formula (s-1-2), the compound of formula (s-15-1) can be prepared, for example, by the following process.



wherein R^2 is as defined in Item 1, $\text{X}^1 - \text{X}^3$, Q^1 and Ra^6 are as defined in Item 4.

15

[0202]

Step (15-1):

Compound (s-15-4) can be prepared by reacting compound (s-15-2) and compound (s-15-3) in a suitable inert solvent
5 under a condensation reaction like Step (13-2).

[0203]

Step (15-2):

Compound (s-15-5) can be prepared by reacting compound (s-15-4) in a suitable inert solvent under a conventional
10 condition of dehydration reaction, or a cyclization condition after the treatment with Lawesson's reagent or the like.

[0204]

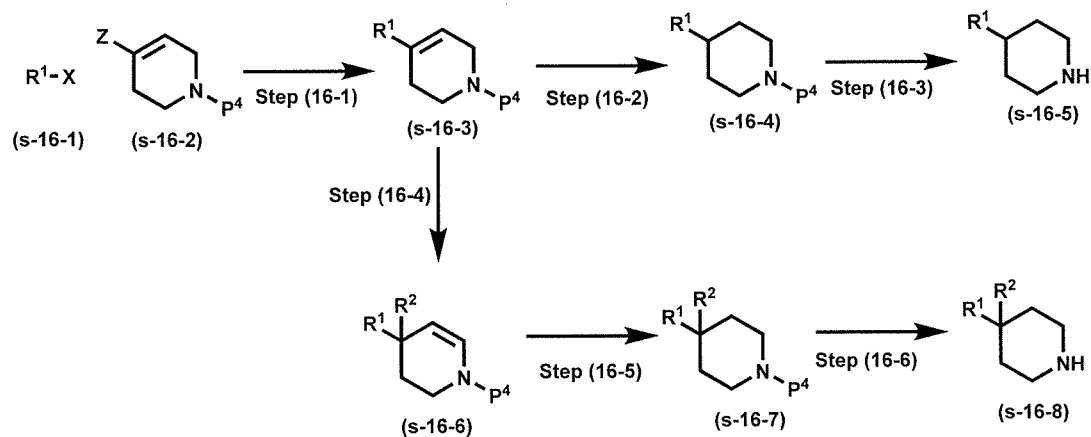
Step (15-3):

15 Compound (s-15-1) can be prepared in a similar manner to Step (13-4) with compound (s-15-5).

[0205]

Preparation Process 16:

In compounds according to formula (s-1-2), the compound
20 of formula (s-16-5) or the compound of formula (s-16-8) which is a compound of formula (s-1-2) wherein L¹ is single bond and R¹ is optionally-substituted C₆₋₁₀ aromatic carbocyclyl group or optionally-substituted 5- to 10-membered aromatic heterocyclyl group can be prepared, for example, by the
25 following process.



wherein R^1 and R^2 are as defined in Item 1; Z is exemplified in the following Step (16-1); and X is halogen.

[0206]

- 5 Compound (s-16-5) can be prepared from compound (s-16-1) via Step (16-1) - Step (16-3).

[0207]

Step (16-1):

- 10 Compound (s-16-3) can be prepared by coupling compound (s-16-1) with organic boron compound (for example, Z is $B(OH)_2$ and the like), organic zinc compound (for example, Z is $ZnCl$ and the like), alkenyl compound, alkynyl compound, hydroxy compound (for example, Z is OH and the like), amine compound (for example, Z is NH_2 and the like), or metallic cyanide (for example, Z is $CuCN$ and the like), in the presence of a base and metallic catalyst. The base used herein includes an inorganic base such as potassium carbonate, cesium carbonate, sodium carbonate, sodium hydrogen carbonate, sodium methoxide, sodium t-butoxide,
- 15

sodium hydroxide, potassium hydroxide, and potassium fluoride; and an organic base such as triethylamine, diisopropylethylamine, tributylamine, DBN, DABCO, DBU, pyridine, dimethylaminopyridine, picoline, and NMM.

5 Sometimes, a base is not used depending on the coupling type.

The metallic catalyst used herein includes, for example,

bis(tri-tert-butylphosphine)palladium, bis(tri-o-

tolylphosphine)dichloropalladium, bis(tri-o-

tolylphosphine)palladium,

10 tetrakis(triphenylphosphine)palladium,

dichlorobis(acetonitrile)palladium, bis(tri-o-

tolylphosphine)dichloropalladium, [1,1'-

bis(diphenylphosphino)ferrocene]dichloropalladium, and

PEPPSITM·IPr((1,3-bis(2,6-diisopropylphenyl)imidazolidene)

15 (3-chloropyridyl)palladium(II)dichloride). Palladium

acetate or palladium chloride may be used herein, and a

ligand described in Palladium reagents and catalysts, John

Wiley & Sons Inc. (2004) or a similar ligand may be also

used in place of the acetate in palladium acetate or the

20 chloride in palladium chloride. The solvent used herein

includes, for example, an ether solvent such as diethyl

ether, diisopropyl ether, tetrahydrofuran, methyl

cyclopentyl ether, anisole, and 1,4-dioxane; an aromatic

hydrocarbon solvent such as benzene, toluene, chlorobenzene,

25 and xylene; an ester solvent such as ethyl acetate and methyl

acetate; an aprotic polar solvent such as N,N-dimethylformamide, N,N-dimethylacetamide, N-methyl-2-pyrrolidinone, 1,3-dimethyl-2-imidazolidinone, and dimethyl sulfoxide; water; and a mixture thereof. The reaction
5 temperature should be determined depending on the starting compound to be used, which is generally about 0°C to about 250°C, preferably about 20°C to about 200°C. The reaction time is generally 30 minutes to 48 hours, preferably 1 to 24 hours.

10 [0208]

Step (16-2):

Compound (s-16-4) can be prepared by reacting compound (s-16-3) in a suitable inert solvent under a conventional condition of alkene-reduction reaction, and under hydrogen
15 atmosphere if necessary. The present reaction condition includes, for example, using a reducing agent such as palladium carbon, palladium(II) hydroxide, platinum on carbon, platinum(IV) oxide, Raney nickel, ruthenium carbon, and tris(triphenylphosphine)rhodium(I) chloride. The inert
20 solvent includes a halogenated carbon solvent such as chloroform and dichloromethane; a ether solvent such as diethyl ether, THF, and 1,4-dioxane; an aromatic hydrocarbon solvent such as benzene, toluene, and xylene; an alcohol solvent such as methanol and ethanol; and an ester solvent
25 such as ethyl acetate and methyl acetate. The reaction time

is generally about 1 hour to 24 hours, and the reaction temperature is -20°C to boiling point of a solvent used herein.

[0209]

5 Step (16-3):

Compound (s-16-5) can be prepared in a similar manner to Step (13-4) with compound (s-16-4).

[0210]

10 Compound (s-16-8) can be prepared from compound (s-16-1) via Step (16-1), and Step (16-4) - Step (16-6).

[0211]

Step (16-4):

15 Compound (s-16-6) can be prepared by reacting compound (s-16-3), an alkylating agent $\text{R}^2\text{-X}$, and a base in a suitable inert solvent under a condition of alkylation reaction. The base used herein includes LDA, LHMDs, and n-butyllithium. The inert solvent includes an ether solvent such as diethyl ether, THF, and 1,4-dioxane; and an aromatic hydrocarbon solvent such as benzene, toluene, and xylene. The reaction
20 time is generally about 1 hour to 24 hours, and the reaction temperature is -20°C to boiling point of a solvent used herein.

[0212]

Step (16-5):

25 Compound (s-16-7) can be prepared by reacting compound

(s-16-6) in a suitable inert solvent in a similar manner to Step (16-2) wherein the reducing agent may include sodium borohydride, sodium cyanoborohydride, and sodium triacetoxyborohydride.

5 [0213]

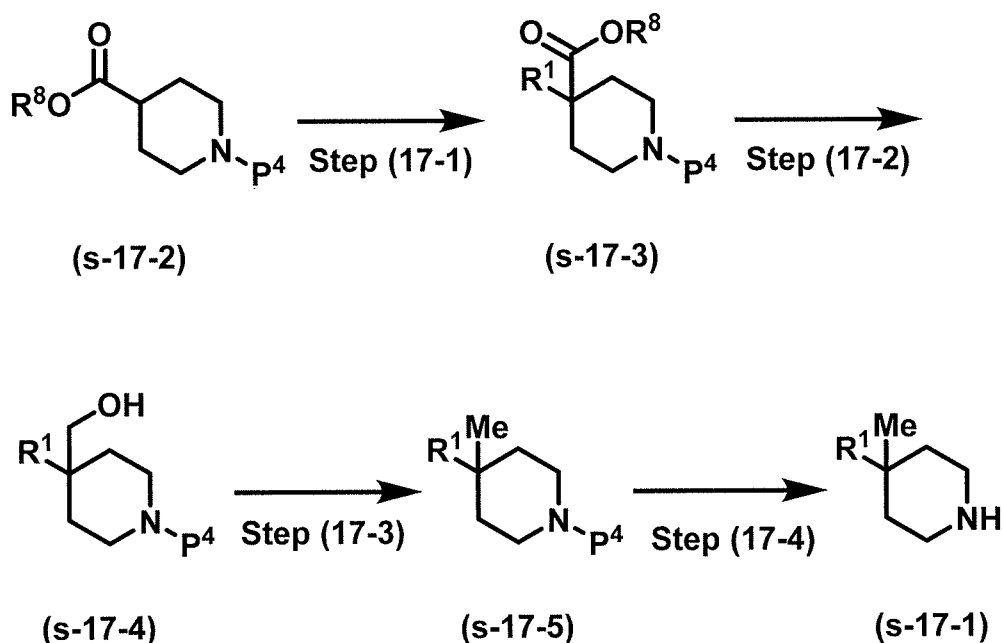
Step (16-6):

Compound (s-16-8) can be prepared in a similar manner to Step (13-4) with compound (s-16-7).

[0214]

10 Preparation Process 17:

In compounds according to formula (s-1-2), the compound of formula (s-17-1) can be prepared, for example, by the following process.



15 wherein R^1 is as defined in Item 1, and R^8 is C_{1-3} alkyl.

[0215]

Step (17-1):

Compound (s-17-3) can be prepared by reacting compound (s-17-2) and an alkylating agent R^1-X wherein X is halogen in a suitable inert solvent under a condition of alkylation reaction like Step (16-4).

[0216]

Step (17-2):

Compound (s-17-4) can be prepared by reacting compound (s-17-3) in a suitable inert solvent under a conventional condition of reduction reaction. The present reaction condition includes, for example, using LAH or DIBAL. The inert solvent includes a halogenated carbon solvent such as chloroform and dichloromethane; a ether solvent such as diethyl ether, THF, and 1,4-dioxane; and an aromatic hydrocarbon solvent such as benzene, toluene, and xylene. The reaction time is generally about 1 hour to 24 hours, and the reaction temperature is -20°C to boiling point of a solvent used herein.

[0217]

Step (17-3):

Compound (s-17-5) can be prepared by reacting compound (s-17-4) in a suitable inert solvent under a condition of Barton-McCombie deoxygenation.

[0218]

Step (17-4):

Compound (s-17-1) can be prepared in a similar manner to Step (13-4) with compound (s-17-5).

EXAMPLES

5 [0219]

The present invention is explained in more detail in the following by referring to Reference examples, Examples, and Tests; however, the technical scope of the present invention should not be limited thereto. It should be understood that the names of compounds used in the following Reference examples and Examples do not necessarily follow the IUPAC nomenclature.

[0220]

15 In the present specification, the abbreviations shown below may be used.

CDCl₃: deuteriochloroform

DMSO-d₆: deuterodimethylsulfoxide

Rt: retention time

min: minute

20 HATU: O-(7-aza-1H-benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate

DCC: N,N'-dicyclohexylcarbodiimide

CDI: carbonyldiimidazole

THF: tetrahydrofuran

25 TFA: trifluoroacetic acid

DMF: N,N-dimethylformamide

DMSO: dimethyl sulfoxide

CPME: cyclopentyl methyl ether

Boc: *tert*-butoxycarbonyl

5 Ns: 2-nitrobenzenesulfonyl

Tf: trifluoromethanesulfonyl

DBU: diazabicycloundecene

DBN: 1,5-diazabicyclo[4.3.0]non-5-ene

LDA: lithium diisopropylamide

10 LHMDs: lithium bis(trimethylsilyl)amide

mCPBA: meta-chloroperoxybenzoic acid

DABCO: 1,4-diazabicyclo[2.2.2]octane

NMM: N-methylmorpholine

LAH: lithium aluminium hydride

15 DIBAL: diisobutylaluminium hydride

Abs: Absolute Configuration; each chemical structure of compounds described along with Abs mark surrounded with a square frame is shown in absolute configuration with a wedged bond. However, not all compounds without Abs mark are shown in non-absolute configuration, *i.e.*, the configuration should be properly judged based on the disclosure about the subject compound in the present description and its context, and a skilled person's technical knowledge, with or without Abs mark.

25 [0221]

In the column chromatography and amino chromatography used in Reference examples and Examples, silica gel column and amino column made by YAMAZEN CORPORATION were used. The TLC (silica gel plate) used in the TLC purification was
5 Silica gel 60F254 (Merck), and the TLC (NH silica gel plate) used therein was TLC plate NH (FujiSilysia).

[0222]

In Reference examples and Examples, the reactors shown below were used. The physicochemical data described in
10 Reference examples and Examples were obtained with the apparatuses below.

Microwave reactor: Biotage AB Initiator

¹H-NMR: JEOL JNM-AL400; JEOL JNM-ECS400; Bruker AVANCE 400
Spectrometer

15 [0223]

The symbols used in NMR are defined as follows, s: singlet, d: doublet, dd: doublet of doublet, ddd: doublet of doublet of doublet, dddd: doublet of doublet of doublet of doublet, t: triplet, td: triplet of doublet, q: quartet, m:
20 multiplet, br: broad singlet or multiplet, and J: coupling constant.

[0224]

The LC/MS data of each compound in Examples and Reference examples were obtained with any one of the
25 apparatuses below.

Method A

Detection apparatus: ACQUITY™ SQ detector (Waters Corporation)

HPLC: ACQUITY™ UPLC SYSTEM

5 Column: Waters ACQUITY™ UPLC BEH C18 (1.7 μ m, 2.1 mm $\times$ 30 mm)

Method B

Detection apparatus: Shimadzu LCMS-2020

Column: Phenomenex Kinetex (C18, 1.7 μ m, 2.1 mm $\times$ 50 mm)

10 Method C

Detection apparatus: ACQUITY™ SQ detector (Waters Corporation)

HPLC: ACQUITY™ UPLC SYSTEM

15 Column: Waters ACQUITY™ UPLC BEH C18 (1.7 μ m, 2.1 mm $\times$ 30 mm)

[0225]

High-performance liquid chromatograph mass spectrometer; the measurement conditions of LC/MS are as follows, wherein the observed [MS (m/z)] is denoted by [M+H]⁺ and the retention time is denoted by Rt (min). Each measured MS value shown in the working examples is accompanied by any one of A - D which were measurement methods used in the actual measurements.

20

Method A

25 Solvent: A; 0.06 % formic acid/H₂O, B; 0.06 % formic

acid/acetonitrile

Gradient condition: 0.0-1.3 min (linear gradient from B 2 % to B 96 %)

Flow rate: 0.8 mL/min; Detective UV: 220 nm and 254 nm;

5 Temperature: 40°C

Hereinafter, the LC-MS data shown below were measured by Method A, unless otherwise indicated.

Method B

Solvent: A; 0.05 % TFA/H₂O, B; acetonitrile

10 Gradient condition: 0.0-1.7 min (linear gradient from B 10 % to B 99 %)

Flow rate: 0.5 mL/min; Detective UV: 220 nm; Temperature: 40°C

Method C

15 Solvent: A; 0.05 % formic acid/H₂O, B; acetonitrile

Gradient condition: 0.0-1.3 min (linear gradient from B 10 % to B 95 %) 1.3-1.5 min (B 10 %)

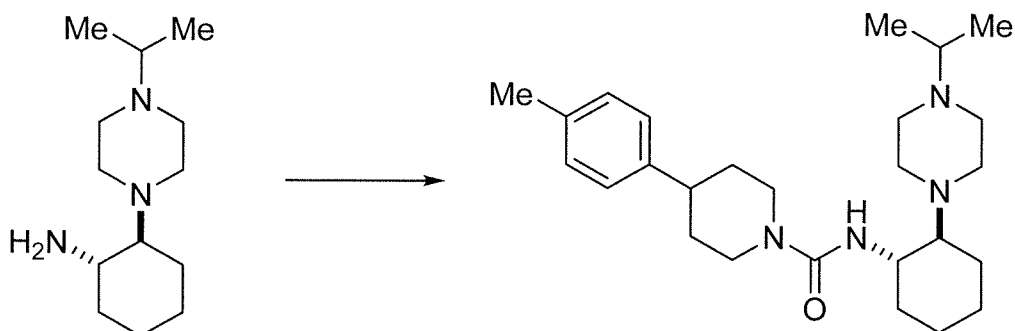
Flow rate: 0.8 mL/min; Detective UV: 220 nm and 254 nm;

Temperature: 40°C

20 [0226]

Example 1:

rac-4-(4-Methylphenyl)-N-{(1S,2S)-2-[4-(propan-2-yl)piperazin-1-yl]cyclohexyl}piperidine-1-carboxamide



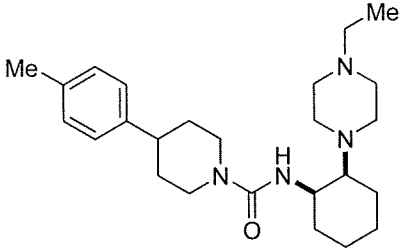
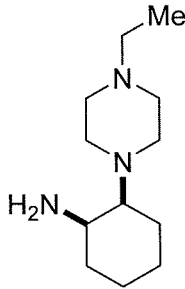
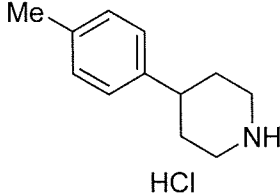
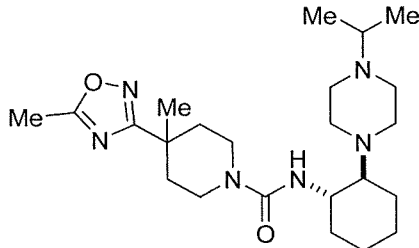
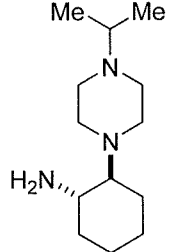
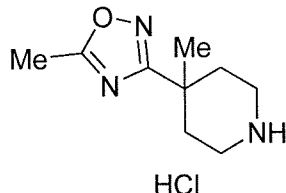
To a mixture of Reference example 1 (211 mg) (Material A), triethylamine (0.391 mL), and chloroform (3 mL) was added 4-nitrophenyl chloroformate (208 mg) at 0°C, and the mixture was stirred at the same temperature for 40 minutes. To the reaction mixture was added 4-(4-methylphenyl)piperidine hydrochloride (238 mg) (Material B) at 0°C, and the mixture was stirred at room temperature for one hour. Water was added to the reaction mixture, and the mixture was extracted with chloroform. The organic layer was dried over anhydrous sodium sulfate, concentrated *in vacuo*, and then the obtained residue was purified by amino silica gel column chromatography (eluate: hexane/ethyl acetate) to give the title compound (346 mg).

¹H-NMR (CDCl₃) δ: 1.02 (6H, d, J = 6.7 Hz), 1.04-1.11 (1H, m), 1.12-1.40 (3H, m), 1.58-1.71 (3H, m), 1.76-1.93 (4H, m), 2.27 (1H, dd, J = 10.4, 3.6 Hz), 2.32 (3H, s), 2.35-2.54 (6H, m), 2.54-2.65 (3H, m), 2.65-2.75 (2H, m), 2.78-2.91 (2H, m), 3.25-3.33 (1H, m), 4.08-4.19 (2H, m), 5.76 (1H, s), 7.09 (2H, d, J = 8.8 Hz), 7.12 (2H, d, J = 8.8 Hz).

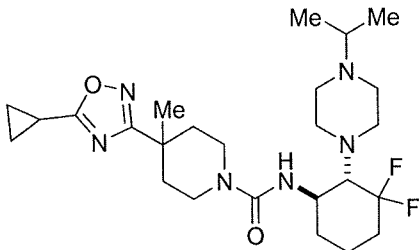
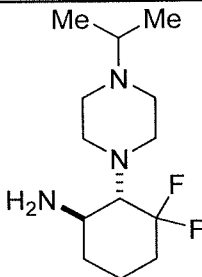
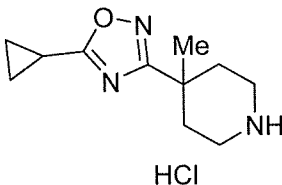
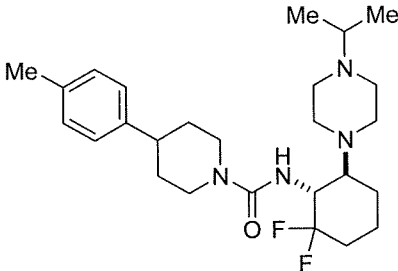
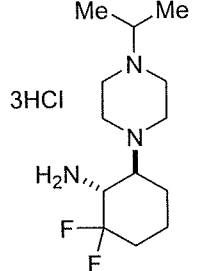
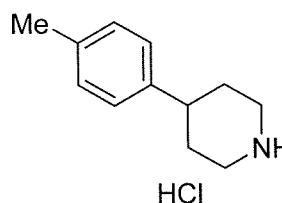
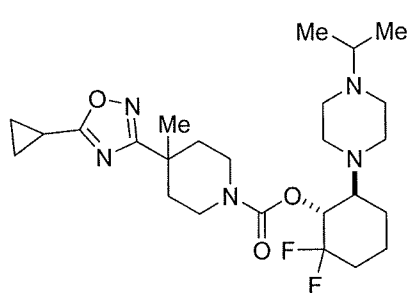
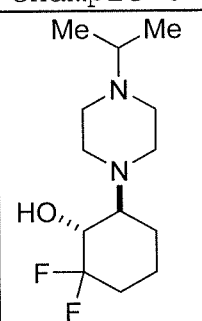
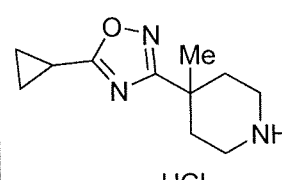
[0227]

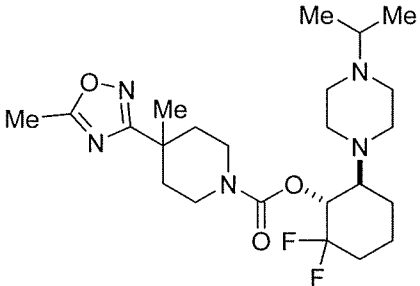
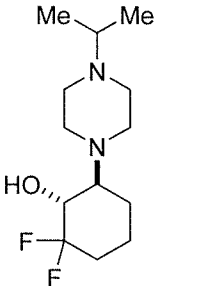
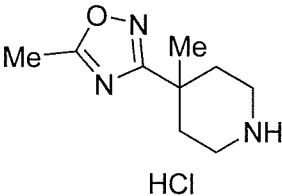
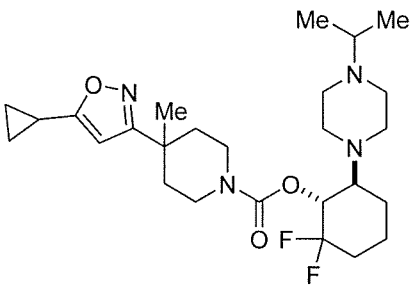
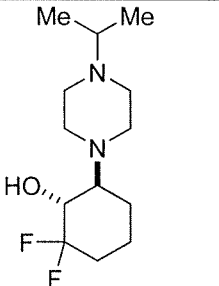
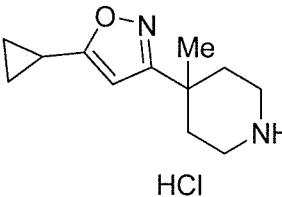
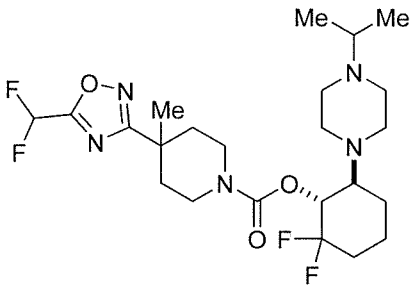
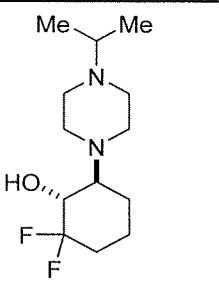
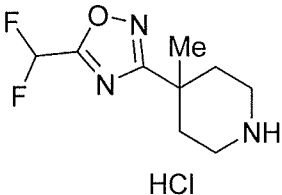
Examples 2 to 16:

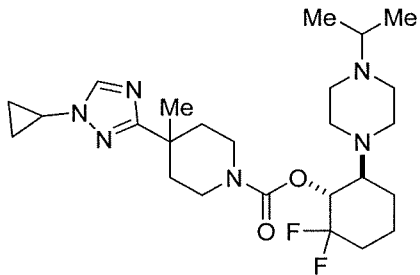
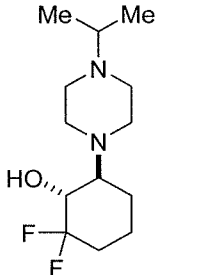
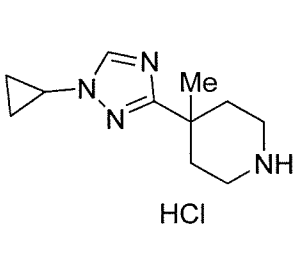
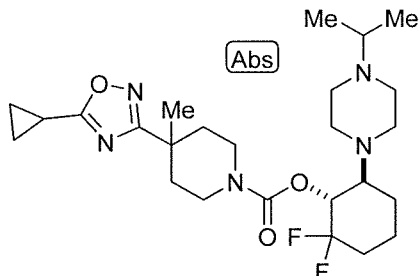
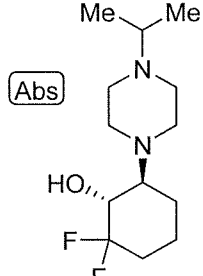
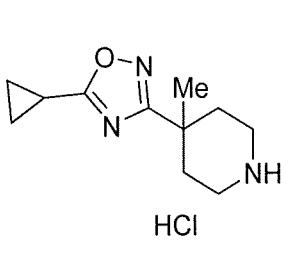
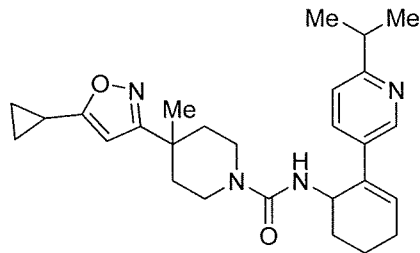
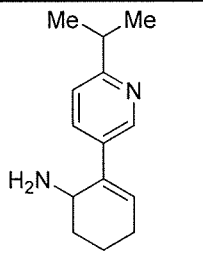
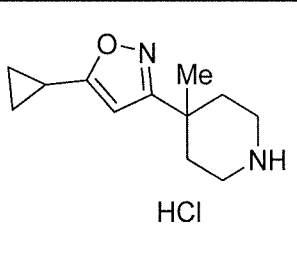
The compounds of Examples 2 to 16 shown in the table below were prepared in the same manner as Example 1, by using commercial compounds or Reference example compounds which correspond to Material A and Material B described in Example 1.

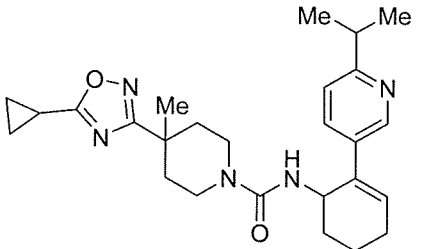
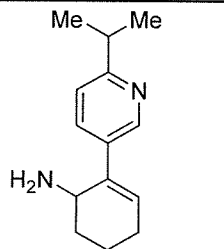
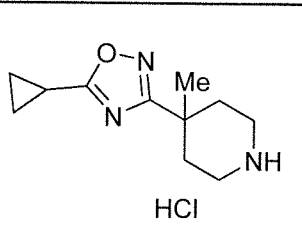
Example	Structure	Material A	Material B
	Spectral data		
2		Reference example 3	Commercial product
			
	¹ H-NMR (CDCl ₃) δ: 1.07 (3H, t, J = 7.3 Hz), 1.12-1.35 (6H, m), 1.36-1.45 (2H, m), 1.56-1.69 (2H, m), 1.80-1.88 (2H, m), 1.89-1.96 (1H, m), 2.12-2.20 (1H, m), 2.30-2.58 (11H, m), 2.59-2.70 (2H, m), 2.80-2.91 (2H, m), 3.98-4.04 (1H, m), 4.07-4.15 (2H, m), 5.16 (1H, s), 7.10 (2H, d, J = 8.5 Hz), 7.13 (2H, d, J = 8.5 Hz).		
3		Reference example 1	Commercial product
			
	¹ H-NMR (CDCl ₃) δ: 1.03 (6H, d, J = 6.1 Hz), 1.14-1.28 (3H, m), 1.32 (3H, s), 1.58-1.68 (3H, m), 1.76-1.82 (1H, m), 1.83-1.91 (1H, m), 2.19-2.30 (3H, m), 2.34-2.53 (6H, m), 2.53-2.62 (6H, m), 2.62-2.71 (2H, m), 3.07 (2H, ddd, J = 13.2, 10.4, 2.8 Hz), 3.20-3.31 (1H, m), 3.63-3.74 (2H, m), 5.70 (1H, s).		

4		Reference example 4	Commercial product
	¹ H-NMR (CDCl ₃) δ: 1.01 (6H, d, J = 6.1 Hz), 1.15-1.35 (4H, m), 1.42-1.58 (2H, m), 1.58-1.71 (2H, m), 1.81-1.90 (2H, m), 1.91-2.01 (1H, m), 2.32 (3H, s), 2.38-2.63 (8H, m), 2.63-2.71 (3H, m), 2.72-2.95 (3H, m), 3.35 (3H, s), 3.50-3.57 (1H, m), 4.01-4.06 (1H, m), 4.06-4.23 (2H, m), 5.53 (1H, d, J = 3.7 Hz), 7.09 (2H, d, J = 8.2 Hz), 7.12 (2H, d, J = 8.2 Hz).		
5		Reference example 5	Commercial product
	¹ H-NMR (CDCl ₃) δ: 1.06 (6H, d, J = 6.1 Hz), 1.35-1.48 (1H, m), 1.48-1.73 (5H, m), 1.78-1.91 (2H, m), 2.12-2.25 (1H, m), 2.32 (3H, s), 2.39-2.79 (12H, m), 2.79-2.93 (2H, m), 3.96-4.12 (3H, m), 4.63 (1H, s), 7.09 (2H, d, J = 7.9 Hz), 7.12 (2H, d, J = 7.9 Hz).		
6		Reference example 5	Reference example 20
	¹ H-NMR (CDCl ₃) δ: 0.92-0.99 (2H, m), 0.99-1.09 (8H, m), 1.26 (3H, s), 1.35-1.45 (1H, m), 1.46-1.76 (6H, m), 1.80-1.90 (1H, m), 1.94-2.10 (3H, m), 2.10-2.21 (1H, m), 2.37-2.84 (9H, m), 3.08-3.17 (2H, m), 3.52-3.64 (2H, m), 3.98-4.08 (1H, m), 4.61 (1H, s), 5.77 (1H, s).		

7		Reference example 7	Reference example 8
			
	¹ H-NMR (CDCl ₃) δ: 0.80-0.91 (1H, m), 1.02 (3H, d, J = 6.0 Hz), 1.03 (3H, d, J = 6.0 Hz), 1.18-1.23 (4H, m), 1.24-1.28 (2H, m), 1.31 (3H, s), 1.53-1.70 (2H, m), 1.92-2.28 (5H, m), 2.28-2.69 (7H, m), 2.73-2.81 (2H, m), 3.02-3.14 (4H, m), 3.52-3.63 (1H, m), 3.63-3.75 (2H, m), 5.52 (1H, s).		
8		Reference example 14	Commercial product
			
	¹ H-NMR (CDCl ₃) δ: 0.96-1.52 (11H, m), 1.70-1.93 (3H, m), 1.94-2.08 (2H, m), 2.13-2.26 (1H, m), 2.32 (3H, s), 2.42-3.27 (12H, m), 4.02-4.26 (3H, m), 4.61 (1H, d, J = 6.7 Hz), 7.08 (2H, d, J = 8.5 Hz), 7.12 (2H, d, J = 8.5 Hz).		
9		Reference example 6	Reference example 8
			
	¹ H-NMR (CDCl ₃) δ: 1.46-1.63 (6H, m), 1.12-1.24 (4H, m), 1.24-1.39 (5H, m), 1.39-1.50 (1H, m), 1.51-1.71 (3H, m), 1.86-1.96 (1H, m), 2.07-2.29 (4H, m), 2.31-2.59 (6H, m), 2.59-2.74 (2H, m), 2.74-2.89 (2H, m), 2.93-3.17 (1H, m), 3.18-3.41 (1H, m), 3.62-3.83 (1H, m).		

	m), 3.83-4.00 (1H, m), 4.82-5.00 (1H, m).		
10		Reference example 6	Commercial product
			 HCl
	¹ H-NMR (CDCl ₃) δ: 0.88-1.10 (6H, m), 1.23-1.39 (1H, m), 1.33 (3H, s), 1.40-1.51 (1H, m), 1.53-2.99 (2H, m), 1.73-1.83 (1H, m), 1.83-1.96 (1H, m), 2.06-2.31 (3H, m), 2.31-2.60 (9H, m), 2.60-2.86 (3H, m), 2.90-3.16 (1H, m), 3.16-3.42 (1H, m), 3.63-3.86 (1H, m), 3.86-4.03 (1H, m), 4.83-5.00 (1H, m).		
11		Reference example 6	Reference example 20
			 HCl
	¹ H-NMR (CDCl ₃) δ: 0.90-1.10 (10H, m), 1.15-1.37 (5H, m), 1.37-1.50 (1H, m), 1.53-1.81 (4H, m), 1.83-1.95 (1H, m), 1.95-2.24 (4H, m), 2.24-2.71 (7H, m), 2.71-2.87 (2H, m), 3.01-3.49 (2H, m), 3.60-3.81 (1H, m), 3.81-3.97 (1H, m), 4.83-5.00 (1H, m), 5.77 (1H, s).		
12		Reference example 6	Reference example 10
			 HCl
	¹ H-NMR (CDCl ₃) δ: 0.82-1.12 (6H, m), 1.23-1.50 (5H, m), 1.56-1.83 (4H, m), 1.85-1.97 (1H, m), 2.10-2.33 (3H, m), 2.33-2.73 (8H, m), 2.73-2.88 (2H, m), 2.95-3.22 (1H, m), 3.21-3.48 (1H, m), 3.65-3.84 (1H, m),		

	3.86-4.04 (1H, m), 4.85-5.00 (1H, m), 6.79 (1H, t, J = 52.3 Hz).		
13		Reference example 6	Reference example 27
			 HCl
	¹ H-NMR (CDCl ₃) δ: 0.83-1.15 (10H, m), 1.18-1.34 (1H, m), 1.29 (3H, s), 1.34-1.50 (1H, m), 1.52-1.72 (3H, m), 1.72-1.82 (1H, m), 1.83-1.97 (1H, m), 2.08-2.21 (1H, m), 2.21-2.60 (8H, m), 2.60-2.73 (2H, m), 2.73-2.89 (2H, m), 2.91-3.11 (1H, m), 3.14-3.37 (1H, m), 3.42-3.59 (1H, m), 3.59-3.83 (1H, m), 3.83-4.03 (1H, m), 4.79-5.02 (1H, m), 8.00 (1H, s).		
14		Reference example 42	Reference example 8
			 HCl
	¹ H-NMR (CDCl ₃) δ: 1.46-1.63 (6H, m), 1.12-1.24 (4H, m), 1.24-1.39 (5H, m), 1.39-1.50 (1H, m), 1.51-1.71 (3H, m), 1.86-1.96 (1H, m), 2.07-2.29 (4H, m), 2.31-2.59 (6H, m), 2.59-2.74 (2H, m), 2.74-2.89 (2H, m), 2.93-3.17 (1H, m), 3.18-3.41 (1H, m), 3.62-3.83 (1H, m), 3.83-4.00 (1H, m), 4.82-5.00 (1H, m).		
15		Reference example 44	Reference example 20
			 HCl
	¹ H-NMR (CDCl ₃) δ: 0.89-0.98 (2H, m), 0.98-1.06 (2H, m), 1.18 (3H, s), 1.28 (6H, d, J = 7.3 Hz), 1.32-1.41		

	(1H, m), 1.41-1.54 (1H, m), 1.54-1.79 (2H, m), 1.79-2.05 (5H, m), 2.12-2.32 (2H, m), 2.91-3.09 (3H, m), 3.35-3.44 (1H, m), 3.50-3.59 (1H, m), 4.37 (1H, d, J = 7.9 Hz), 4.90-4.97 (1H, m), 5.72 (1H, s), 6.26 (1H, dd, J = 3.7, 3.7 Hz), 7.10 (1H, d, J = 8.3 Hz), 7.61 (1H, dd, J = 8.3, 2.0 Hz), 8.55 (1H, d, J = 2.0 Hz).		
16		Reference example 44	Reference example 8
			
	¹ H-NMR (CDCl ₃) δ: 1.15-1.20 (4H, m), 1.23 (3H, s), 1.24-1.32 (1H, m), 1.28 (6H, d, J = 6.7 Hz), 1.37 (1H, ddd, J = 14.1, 10.3, 3.6 Hz), 1.50 (1H, ddd, J = 14.1, 10.3, 3.8 Hz), 1.69-1.79 (1H, m), 1.79-1.97 (2H, m), 2.02-2.18 (3H, m), 2.18-2.34 (2H, m), 2.84-3.09 (3H, m), 3.39-3.48 (1H, m), 3.53-3.61 (1H, m), 4.36 (1H, d, J = 7.9 Hz), 4.91-4.98 (1H, m), 6.27 (1H, dd, J = 4.0, 4.0 Hz), 7.10 (1H, d, J = 8.2 Hz), 7.61 (1H, dd, J = 8.2, 2.1 Hz), 8.56 (1H, d, J = 2.1 Hz).		

[0228]

The chemical names of Example 2 to Example 16 are listed below.

Example 2: *rac*-N-[(1R,2S)-2-(4-ethylpiperazin-1-yl)cyclohexyl]-4-(4-methylphenyl)piperidine-1-carboxamide

Example 3: *rac*-4-methyl-4-(5-methyl-1,2,4-oxadiazol-3-yl)-N-[(1S,2S)-2-[4-(propan-2-yl)piperazin-1-yl]cyclohexyl]piperidine-1-carboxamide

Example 4: *rac*-N-[(1R,2S,6S)-2-methoxy-6-[4-(propan-2-yl)piperazin-1-yl]cyclohexyl]-4-(4-methylphenyl)piperidine-1-carboxamide

Example 5: *rac*-4-(4-methylphenyl)-N-{(1*S*,2*S*)-2-[4-(propan-2-yl)piperazin-1-yl]cyclopentyl}piperidine-1-carboxamide

Example 6: *rac*-4-(5-cyclopropyl-1,2-oxazol-3-yl)-4-methyl-N-{(1*S*,2*S*)-2-[4-(propan-2-yl)piperazin-1-yl]cyclopentyl}piperidine-1-carboxamide

Example 7: *rac*-4-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)-N-{(1*R*,2*S*)-3,3-difluoro-2-[4-(propan-2-yl)piperazin-1-yl]cyclohexyl}-4-methylpiperidine-1-carboxamide

Example 8: *rac*-N-{(1*R*,6*S*)-2,2-difluoro-6-[4-(propan-2-yl)piperazin-1-yl]cyclohexyl}-4-(4-methylphenyl)piperidine-1-carboxamide

Example 9: *rac*-(1*R*,6*S*)-2,2-difluoro-6-[4-(propan-2-yl)piperazin-1-yl]cyclohexyl 4-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)-4-methylpiperidine-1-carboxylate

Example 10: *rac*-(1*R*,6*S*)-2,2-difluoro-6-[4-(propan-2-yl)piperazin-1-yl]cyclohexyl 4-methyl-4-(5-methyl-1,2,4-oxadiazol-3-yl)piperidine-1-carboxylate

Example 11: *rac*-(1*R*,6*S*)-2,2-difluoro-6-[4-(propan-2-yl)piperazin-1-yl]cyclohexyl 4-(5-cyclopropyl-1,2-oxazol-3-yl)-4-methylpiperidine-1-carboxylate

Example 12: *rac*-(1*R*,6*S*)-2,2-difluoro-6-[4-(propan-2-yl)piperazin-1-yl]cyclohexyl 4-[5-(difluoromethyl)-1,2,4-oxadiazol-3-yl]-4-methylpiperidine-1-carboxylate

Example 13: *rac*-(1*R*,6*S*)-2,2-difluoro-6-[4-(propan-2-

yl)piperazin-1-yl]cyclohexyl 4-(1-cyclopropyl-1H-1,2,4-triazol-3-yl)-4-methylpiperidine-1-carboxylate

Example 14: (1R,6S)-2,2-difluoro-6-[4-(propan-2-yl)piperazin-1-yl]cyclohexyl 4-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)-4-methylpiperidine-1-carboxylate

Example 15: *rac*-4-(5-cyclopropyl-1,2-oxazol-3-yl)-4-methyl-N-{2-[6-(propan-2-yl)pyridin-3-yl]cyclohex-2-en-1-yl}piperidine-1-carboxamide

Example 16: *rac*-4-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)-4-methyl-N-{2-[6-(propan-2-yl)pyridin-3-yl]cyclohex-2-en-1-yl}piperidine-1-carboxamide

[0229]

Example 17:

rac-N-[(1S,2S)-2-(4-Ethylpiperazin-1-yl)cyclohexyl]-4-(4-methylphenyl)piperidine-1-carboxamide



To a mixture of Reference example 2 (73.7 mg), sodium acetate (18.9 mg), acetaldehyde (0.054 ml), and dichloromethane (2 mL) was added sodium triacetoxyborohydride (122 mg) at 0°C, and the mixture was warmed to room temperature and stirred for 1.5 hours. Water was added to the reaction mixture at 0°C, and the mixture

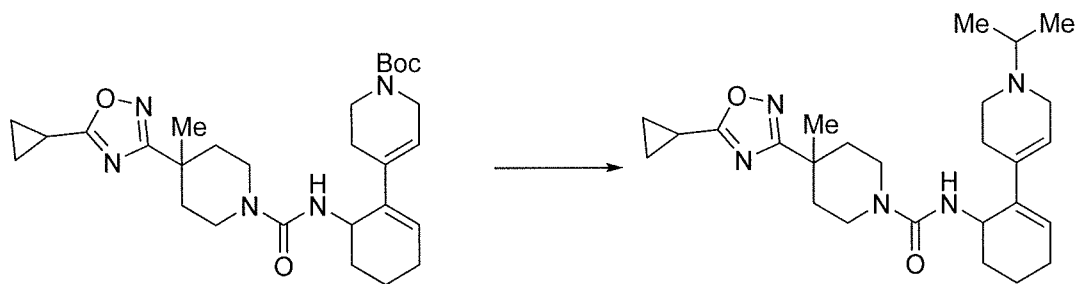
was extracted with chloroform. The organic layer was dried over anhydrous sodium sulfate, concentrated *in vacuo*, and then the obtained residue was purified by amino silica gel column chromatography (eluate: hexane/ethyl acetate) to give the title compound (24 mg).

$^1\text{H-NMR}$ (CDCl_3) δ : 1.02-1.12 (1H, m), 1.07 (3H, t, $J = 7.3$ Hz), 1.14-1.41 (3H, m), 1.57-1.71 (3H, m), 1.75-1.96 (5H, m), 2.16-2.78 (15H, m), 2.78-2.90 (2H, m), 3.24-3.39 (1H, m), 4.05-4.18 (2H, m), 5.72 (1H, s), 7.09 (2H, d, $J = 7.9$ Hz), 7.12 (2H, d, $J = 7.9$ Hz).

[0230]

Example 18:

rac-4-(5-Cyclopropyl-1,2,4-oxadiazol-3-yl)-4-methyl-N-{2-[1-(propan-2-yl)-1,2,3,6-tetrahydropyridin-4-yl]cyclohex-2-en-1-yl}piperidine-1-carboxamide



To a solution of Reference example 13 (13.5 mg) in chloroform (2 mL) was added hydrogen chloride/acetic acid solution (4 M, 0.198 mL), and the mixture was stirred at room temperature. After the reaction was terminated as judged by the consumption of the starting material, the

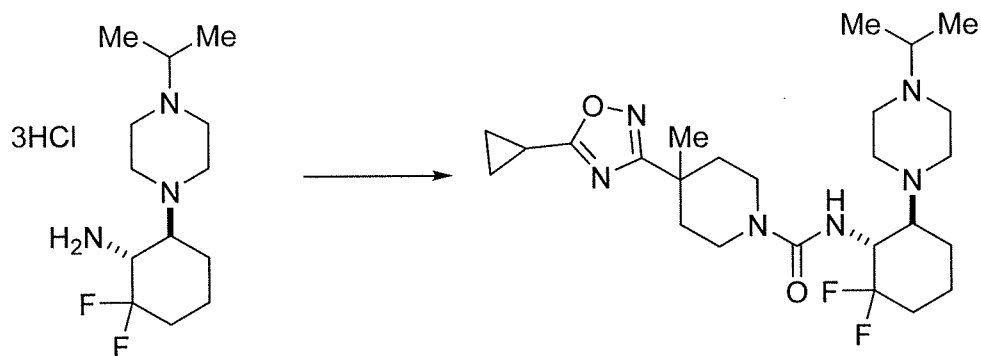
reaction mixture was concentrated *in vacuo*. To the obtained residue were added sodium acetate (8.66 mg), acetone (0.058 mL), and chloroform (2 mL). To the mixture was added sodium triacetoxymethylborohydride (33.6 mg) at 0°C, and the mixture was warmed to room temperature and stirred. After the reaction was completed, water was added to the reaction mixture under ice temperature, and the mixture was extracted with chloroform. The organic layer was dried over anhydrous sodium sulfate, concentrated *in vacuo*, and then the obtained residue was purified by amino silica gel column chromatography (eluate: hexane/ethyl acetate) to give the title compound (10 mg).

¹H-NMR (CDCl₃) δ: 1.07 (6H, d, J = 6.1 Hz), 1.17-1.22 (4H, m), 1.23-1.32 (2H, m), 1.29 (3H, s), 1.43-1.66 (3H, m), 1.91-1.98 (1H, m), 2.08-2.26 (6H, m), 2.26-2.41 (1H, m), 2.50 (1H, ddd, J = 11.2, 7.2, 4.8 Hz), 2.63-2.76 (2H, m), 2.97-3.13 (3H, m), 3.13-3.23 (1H, m), 3.52-3.63 (2H, m), 4.43 (1H, d, J = 7.3 Hz), 4.63-4.69 (1H, m), 5.78-5.84 (1H, m), 5.85-5.91 (1H, m).

[0231]

Example 19:

rac-4-(5-Cyclopropyl-1,2,4-oxadiazol-3-yl)-N-{(1R,6S)-2,2-difluoro-6-[4-(propan-2-yl)piperazin-1-yl]cyclohexyl}-4-methylpiperidine-1-carboxamide



To a mixture of Reference example 14 (84.6 mg) (Material A), triethylamine (0.318 mL), and chloroform (2 mL) was added triphosgene (27.1 mg) at 0°C, and the mixture was stirred at
 5 the same temperature for 40 minutes. To the reaction mixture was added Reference example 8 (66.7 mg) (Material B) at 0°C, and the mixture was stirred at room temperature for one hour. Water was added to the reaction mixture, and the mixture was extracted with chloroform. The organic layer was dried over
 10 anhydrous sodium sulfate, concentrated *in vacuo*, and then the obtained residue was purified by silica gel column chromatography (eluate: chloroform/methanol) to give the title compound (99.1 mg).

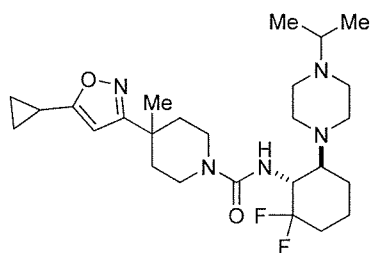
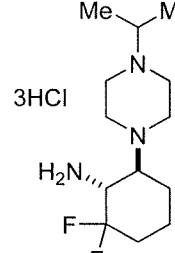
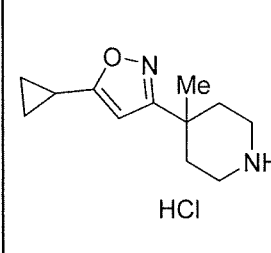
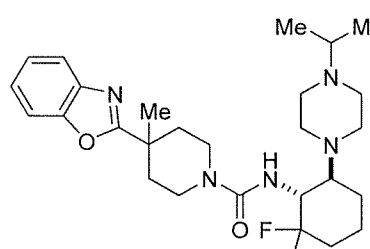
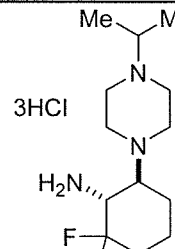
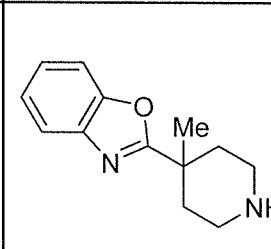
¹H-NMR (CDCl₃) δ: 1.00 (3H, d, J = 6.0 Hz), 1.01 (3H, d, J =
 15 6.0 Hz), 1.17-1.22 (4H, m), 1.23-1.30 (1H, m), 1.30-1.48 (2H, m), 1.31 (3H, s), 1.57-1.70 (2H, m), 1.75-1.84 (1H, m), 1.89-1.97 (1H, m), 2.10-2.27 (4H, m), 2.32-2.53 (7H, m), 2.53-2.64 (1H, m), 2.68-2.78 (2H, m), 3.08 (1H, ddd, J = 13.6, 10.7, 3.1 Hz), 3.16 (1H, ddd, J = 13.6, 10.7, 3.1 Hz),
 20 3.66 (1H, ddd, J = 13.6, 4.7, 4.1 Hz), 3.77 (1H, ddd, J =

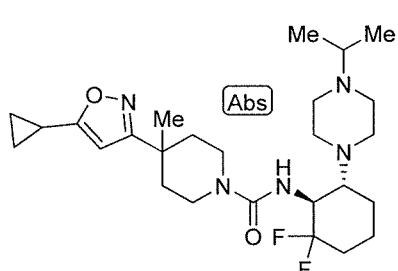
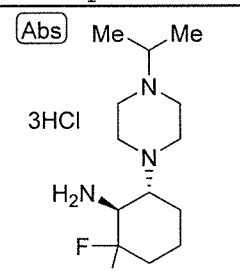
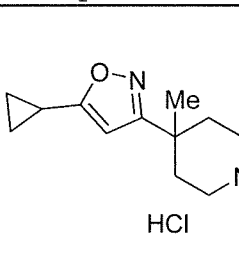
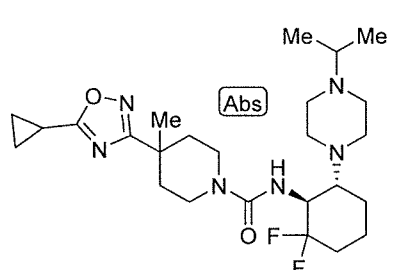
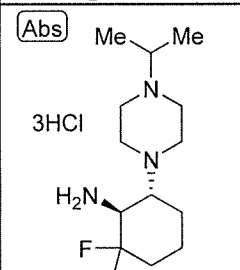
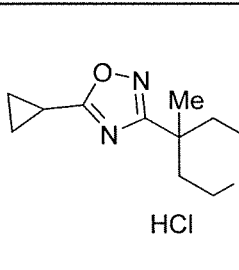
13.6, 4.7, 4.1 Hz), 4.10-4.21 (1H, m), 4.54 (1H, d, $J = 7.3$ Hz).

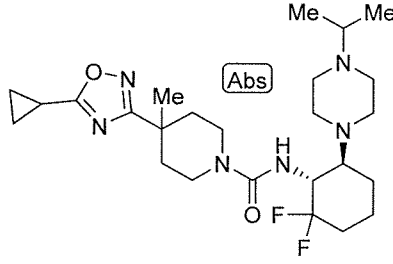
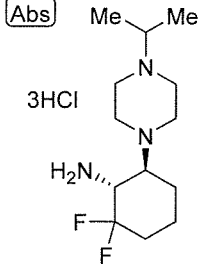
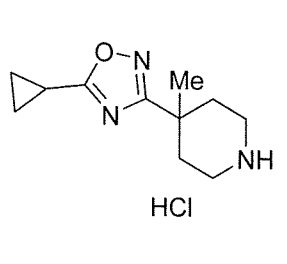
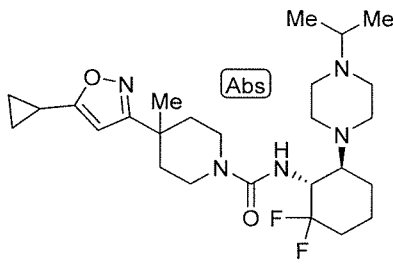
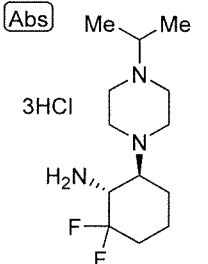
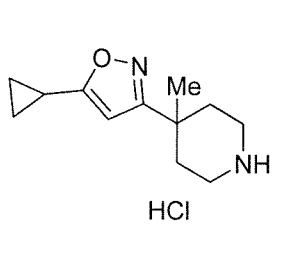
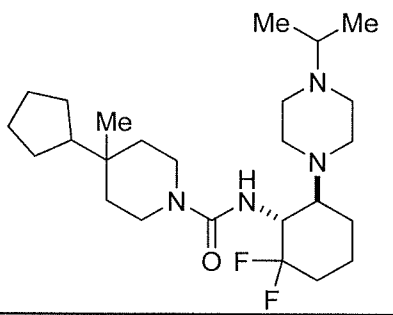
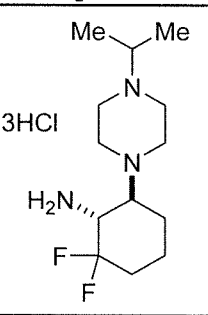
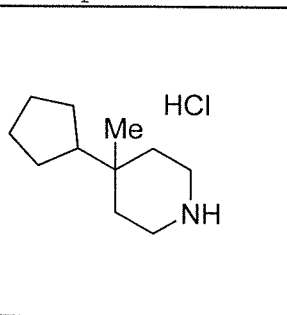
[0232]

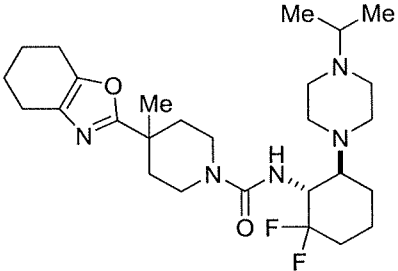
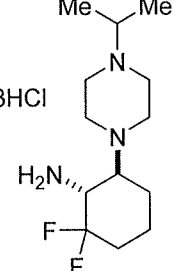
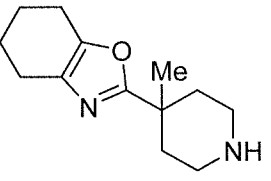
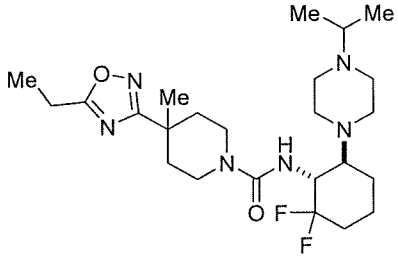
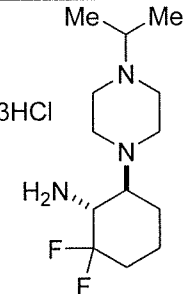
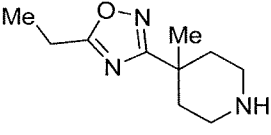
Examples 20 to 76:

5 The compounds of Examples 20 to 76 shown in the table below were prepared in the same manner as Example 19, by using commercial compounds or Reference example compounds which correspond to Material A and Material B described in Example 19.

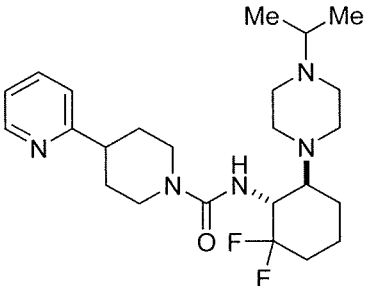
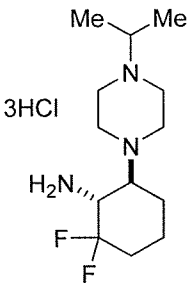
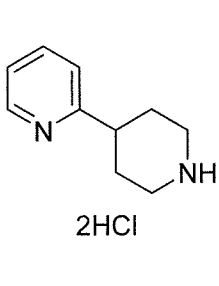
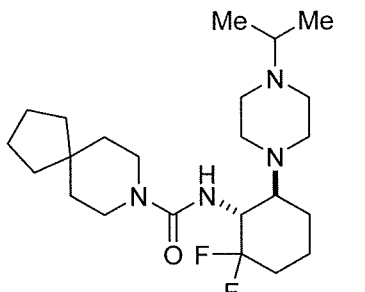
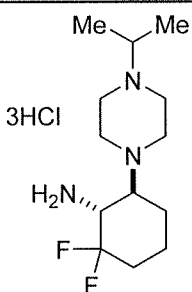
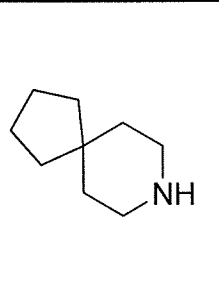
Example	Structure	Material A	Material B
	Spectral data		
20		Reference example 14	Reference example 20
		 3HCl	 HCl
	¹ H-NMR (CDCl ₃) δ : 0.92-1.19 (10H, m), 1.27 (3H, s), 1.30-1.74 (3H, m), 1.75-1.88 (3H, m), 1.89-1.97 (1H, m), 1.97-2.04 (1H, m), 2.05-2.27 (3H, m), 2.32-2.67 (8H, m), 2.69-2.81 (2H, m), 3.12-3.29 (2H, m), 3.57-3.68 (1H, m), 3.68-3.80 (1H, m), 4.08-4.25 (1H, m), 4.54 (1H, d, J = 7.3 Hz), 5.77 (1H, s).		
21		Reference example 14	Reference example 21
		 3HCl	
	¹ H-NMR (CDCl ₃) δ : 0.93 (6H, d, J = 6.1 Hz), 1.22-		

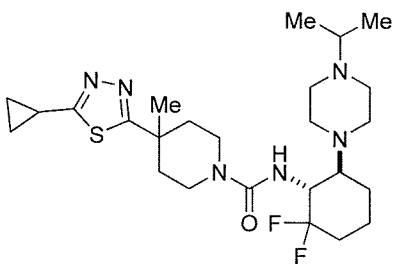
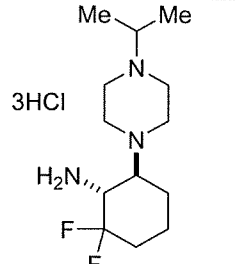
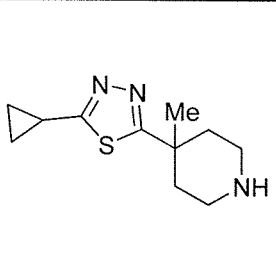
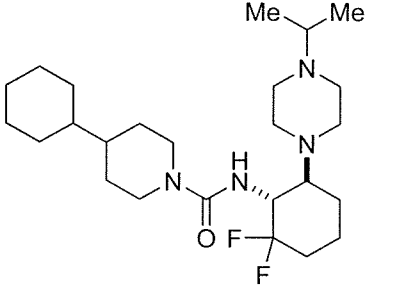
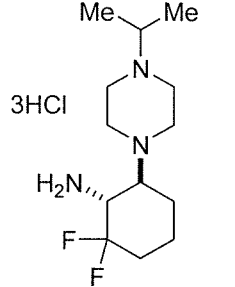
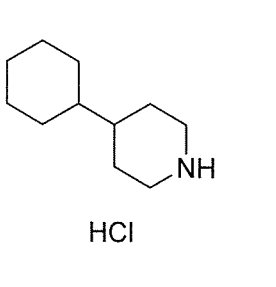
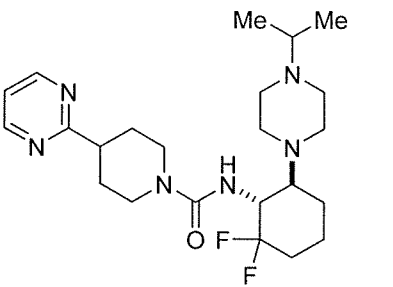
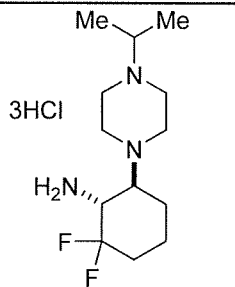
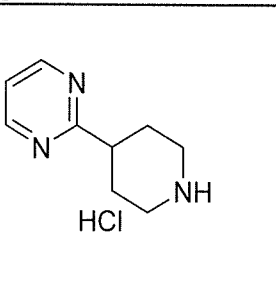
	1.43 (2H, m), 1.45 (3H, s), 1.63-1.86 (4H, m), 1.89-1.97 (1H, m), 2.11-2.22 (1H, m), 2.28-2.54 (10H, m), 2.68-2.78 (2H, m), 3.11-3.26 (2H, m), 3.76 (1H, ddd, J = 13.5, 4.1, 4.0 Hz), 3.84 (1H, ddd, J = 13.5, 4.1, 4.0 Hz), 4.09-4.22 (1H, m), 4.56 (1H, d, J = 7.3 Hz), 7.29-7.35 (2H, m), 7.47-7.53 (1H, m), 7.67-7.72 (1H, m).		
22		Reference example 15'	Reference example 20
			
	¹ H-NMR (CDCl ₃) δ: 0.92-0.98 (2H, m), 1.00-1.08 (2H, m), 1.13 (6H, d, J = 6.0 Hz), 1.28 (3H, s), 1.28-1.47 (3H, m), 1.47-1.88 (5H, m), 1.90-2.25 (5H, m), 2.25-3.07 (8H, m), 3.13-3.03 (2H, m), 3.58-3.74 (2H, m), 4.07-4.23 (1H, m), 4.54 (1H, d, J = 8.0 Hz), 5.78 (1H, s).		
23		Reference example 15'	Reference example 8
			
	¹ H-NMR (CDCl ₃) δ: 0.97-1.16 (6H, m), 1.16-1.26 (4H, m), 1.26-1.44 (3H, m), 1.31 (3H, s), 1.47-1.75 (5H, m), 1.75-1.88 (2H, m), 1.88-2.03 (1H, m), 2.09-2.28 (4H, m), 2.28-3.01 (6H, m), 3.01-3.26 (2H, m), 3.58-3.84 (2H, m), 4.06-4.26 (1H, m), 4.54 (1H, d, J = 8.0 Hz).		
24		Reference example 15	Reference example 8

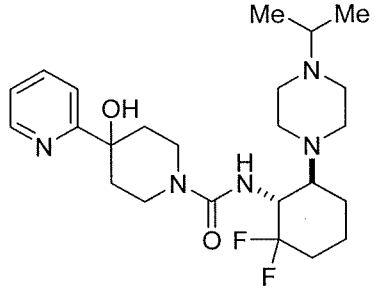
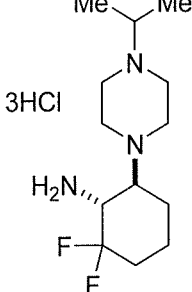
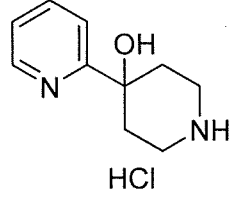
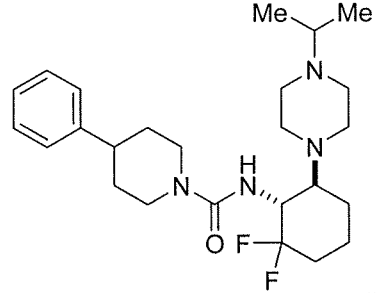
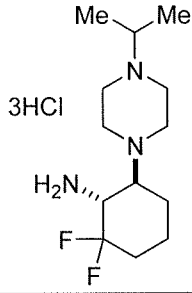
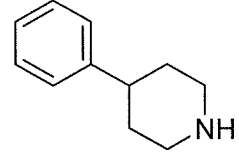
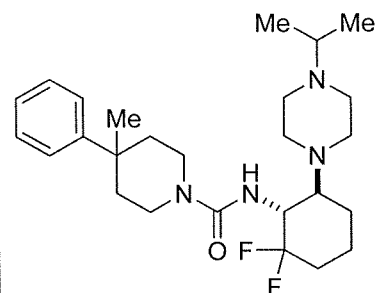
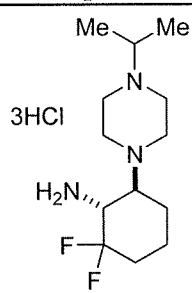
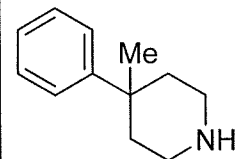
			
	¹ H-NMR (CDCl ₃) δ: 1.00 (3H, d, J = 6.0 Hz), 1.01 (3H, d, J = 6.0 Hz), 1.17-1.22 (4H, m), 1.23-1.30 (1H, m), 1.30-1.48 (2H, m), 1.31 (3H, s), 1.57-1.70 (2H, m), 1.75-1.84 (1H, m), 1.89-1.97 (1H, m), 2.10-2.27 (4H, m), 2.32-2.53 (7H, m), 2.53-2.64 (1H, m), 2.68-2.78 (2H, m), 3.08 (1H, ddd, J = 13.6, 10.7, 3.1 Hz), 3.16 (1H, ddd, J = 13.6, 10.7, 3.1 Hz), 3.66 (1H, ddd, J = 13.6, 4.7, 4.1 Hz), 3.77 (1H, ddd, J = 13.6, 4.7, 4.1 Hz), 4.10-4.21 (1H, m), 4.54 (1H, d, J = 7.3 Hz).		
25		Reference example 15	Reference example 20
			
	¹ H-NMR (CDCl ₃) δ: 0.92-1.19 (10H, m), 1.27 (3H, s), 1.30-1.74 (3H, m), 1.75-1.88 (3H, m), 1.89-1.97 (1H, m), 1.97-2.04 (1H, m), 2.05-2.27 (3H, m), 2.32-2.67 (8H, m), 2.69-2.81 (2H, m), 3.12-3.29 (2H, m), 3.57-3.68 (1H, m), 3.68-3.80 (1H, m), 4.08-4.25 (1H, m), 4.54 (1H, d, J = 7.3 Hz), 5.77 (1H, s).		
26		Reference example 14	Reference example 22
			
	¹ H-NMR (CDCl ₃) δ: 0.84-0.91 (4H, m), 1.02 (6H, d, J = 6.7 Hz), 1.20-1.31 (3H, m), 1.31-1.41 (2H, m), 1.45 (3H, s), 1.46-1.59 (3H, m), 1.66-1.85 (3H, m),		

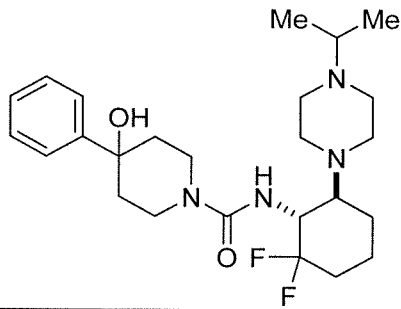
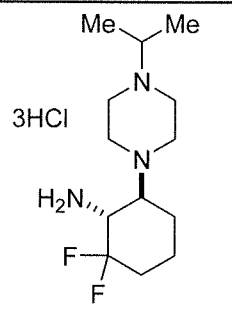
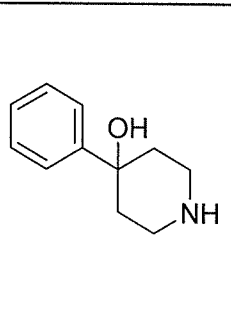
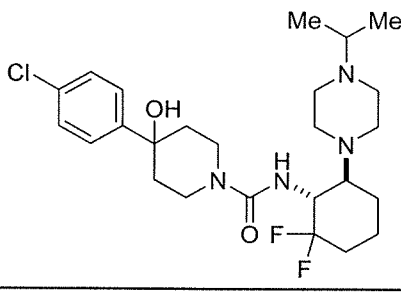
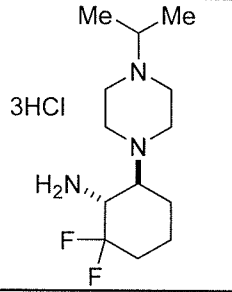
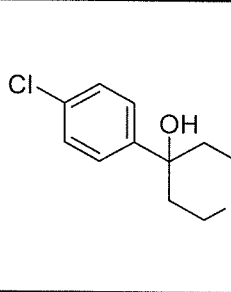
	1.89-1.97 (1H, m), 2.10-2.22 (1H, m), 2.35-2.55 (7H, m), 2.55-2.66 (1H, m), 2.67-2.79 (2H, m), 2.98-3.13 (2H, m), 3.18 (1H, ddd, J = 13.8, 10.5, 3.6 Hz), 3.59 (1H, ddd, J = 13.8, 4.6, 3.6 Hz), 3.63-3.79 (2H, m), 4.10-4.22 (1H, m), 4.53 (1H, d, J = 7.9 Hz).		
27		Reference example 14	Reference example 19
			
	¹ H-NMR (CDCl ₃) δ: 1.00 (6H, d, J = 6.8 Hz), 1.28-1.46 (2H, m), 1.32 (3H, s), 1.57-1.66 (2H, m), 1.74-1.88 (6H, m), 1.89-1.97 (1H, m), 2.10-2.21 (1H, m), 2.22-2.31 (2H, m), 2.35-2.54 (9H, m), 2.54-2.63 (3H, m), 2.69-2.78 (2H, m), 3.09 (1H, ddd, J = 13.8, 10.5, 2.9 Hz), 3.17 (1H, ddd, J = 13.8, 10.5, 2.9 Hz), 3.65 (1H, ddd, J = 13.8, 4.1, 4.1 Hz), 3.79 (1H, ddd, J = 13.8, 4.1, 4.1 Hz), 4.08-4.22 (1H, m), 4.53 (1H, d, J = 7.9 Hz).		
28		Reference example 14	Reference example 9
			
	¹ H-NMR (CDCl ₃) δ: 1.00 (3H, d, J = 6.0 Hz), 1.00 (3H, d, J = 6.0 Hz), 1.20-1.43 (3H, m), 1.33 (3H, s), 1.39 (3H, t, J = 7.7 Hz), 1.61-1.74 (2H, m), 1.75-1.86 (1H, m), 1.89-1.98 (1H, m), 2.10-2.21 (1H, m), 2.21-2.30 (2H, m), 2.34-2.54 (7H, m), 2.54-2.64 (1H, m), 2.70-2.78 (2H, m), 2.89 (2H, q, J = 7.7 Hz), 3.09 (1H, ddd, J = 13.8, 10.7, 3.1 Hz), 3.17 (1H, ddd, J = 13.8, 10.7, 3.1 Hz), 3.66 (1H, ddd, J = 13.6, 4.4, 4.4 Hz), 3.79 (1H, ddd, J = 13.6, 4.4, 4.4 Hz), 4.08-4.22 (1H, m), 4.53 (1H, d, J = 7.9 Hz).		

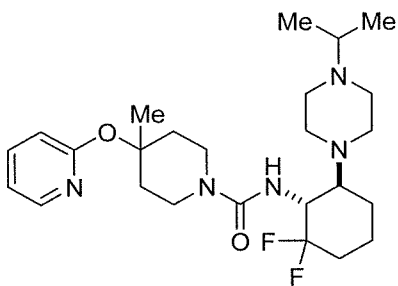
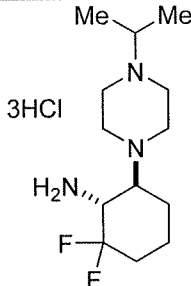
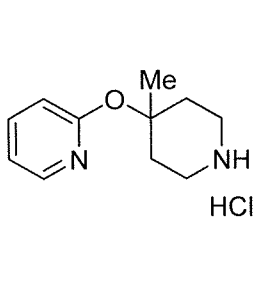
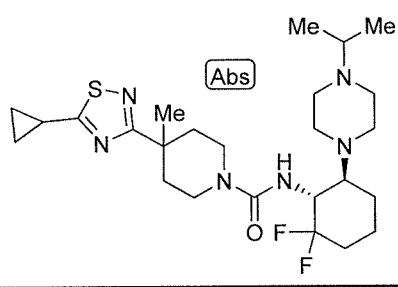
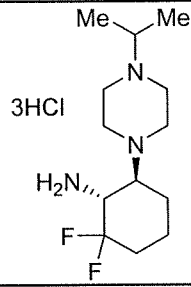
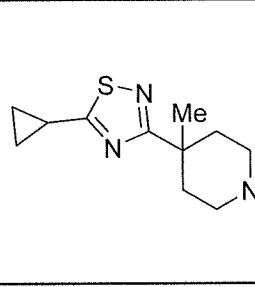
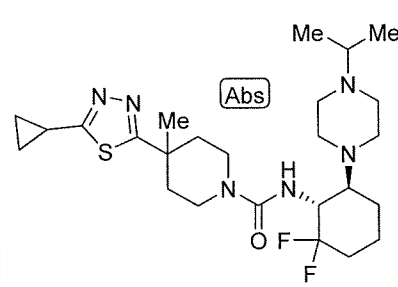
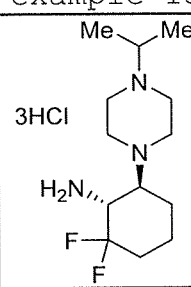
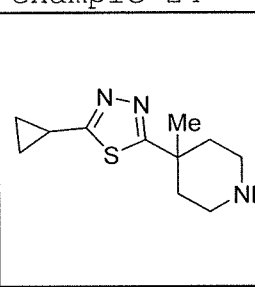
29		Reference example 14	Reference example 27
¹ H-NMR (CDCl ₃) δ: 0.94-1.15 (10H, m), 1.16-1.47 (3H, m), 1.29 (3H, s), 1.52-1.87 (5H, m), 1.87-1.99 (1H, m), 2.10-2.22 (1H, m), 2.23-2.36 (2H, m), 2.37-2.92 (8H, m), 2.97-3.08 (1H, m), 3.08-3.19 (1H, m), 3.43-3.65 (2H, m), 3.72-3.84 (1H, m), 4.07-4.23 (1H, m), 4.52 (1H, d, J = 7.9 Hz), 8.00 (1H, s).			
30		Reference example 14	Reference example 23
¹ H-NMR (CDCl ₃) δ: 1.03 (6H, d, J = 6.1 Hz), 1.10-1.21 (1H, m), 1.22--1.51 (9H, m), 1.54-1.86 (5H, m), 1.61 (3H, s), 1.89-1.98 (1H, m), 2.08-2.23 (3H, m), 2.32-2.55 (7H, m), 2.55-2.65 (1H, m), 2.68-2.79 (2H, m), 3.01-3.19 (2H, m), 3.66 (1H, ddd, J = 13.6, 4.4, 3.2 Hz), 3.78 (1H, ddd, J = 13.6, 4.4, 3.2 Hz), 4.09-4.23 (1H, m), 4.52 (1H, d, J = 7.3 Hz).			
31		Reference example 14	Reference example 28
¹ H-NMR (CDCl ₃) δ: 1.00 (3H, d, J = 6.1 Hz), 1.01 (3H, d, J = 6.1 Hz), 1.11-1.18 (2H, m), 1.22-1.35 (4H, m), 1.30 (3H, s), 1.35-1.47 (1H, m), 1.62-1.75 (2H, m), 1.75-1.85 (1H, m), 1.88-1.97 (1H, m), 2.10-2.22			

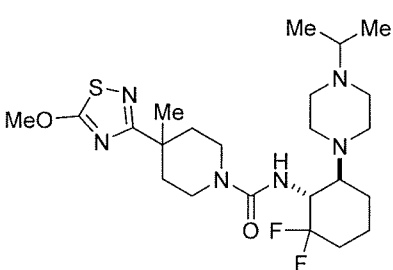
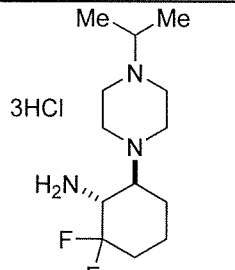
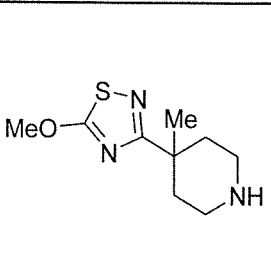
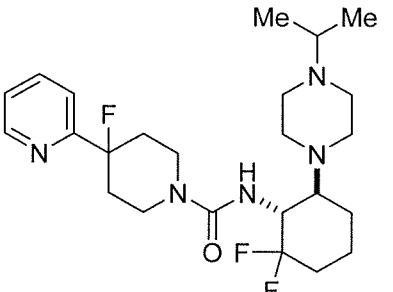
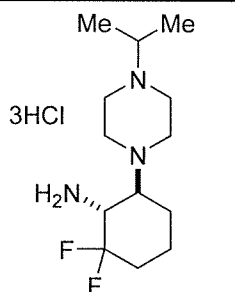
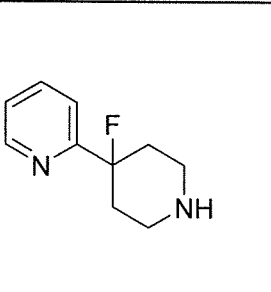
	(1H, m), 2.31-2.62 (11H, m), 2.67-2.78 (2H, m), 3.01 (1H, ddd, J = 13.8, 10.7, 3.1 Hz), 3.10 (1H, ddd, J = 13.8, 10.7, 3.1 Hz), 3.65 (1H, ddd, J = 14.0, 4.3, 4.3 Hz), 3.79 (1H, ddd, J = 14.0, 4.3, 4.3 Hz), 4.08-4.22 (1H, m), 4.53 (1H, d, J = 7.3 Hz).		
32		Reference example 14	Commercial product
			
	¹ H-NMR (CDCl ₃) δ: 1.01 (6H, d, J = 6.8 Hz), 1.21-1.49 (2H, m), 1.62-1.88 (4H, m), 1.89-2.06 (3H, m), 2.10-2.23 (1H, m), 2.34-2.66 (8H, m), 2.70-2.83 (2H, m), 2.85-3.07 (3H, m), 4.05-4.30 (3H, m), 4.60 (1H, d, J = 8.0 Hz), 7.10-7.18 (2H, m), 7.62 (1H, ddd, J = 8.0, 8.0, 1.6 Hz), 8.52 (1H, dd, J = 4.8, 1.6 Hz).		
33		Reference example 14	Commercial product
			
	¹ H-NMR (CDCl ₃) δ: 1.03 (6H, d, J = 6.4 Hz), 1.20-1.53 (10H, m), 1.54-1.66 (4H, m), 1.66-1.86 (3H, m), 1.88-1.98 (1H, m), 2.08-2.24 (1H, m), 2.26-2.56 (6H, m), 2.56-2.69 (1H, m), 2.69-2.82 (2H, m), 3.20-3.51 (4H, m), 4.06-4.25 (1H, m), 4.52 (1H, d, J = 8.0 Hz).		
34		Reference example 14	Reference example 24

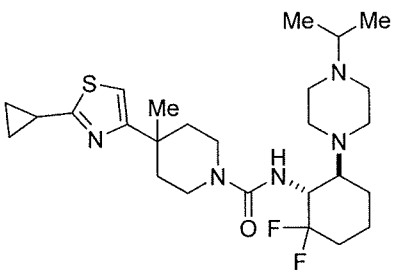
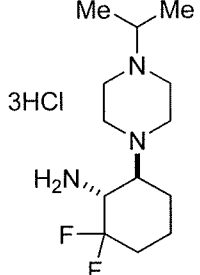
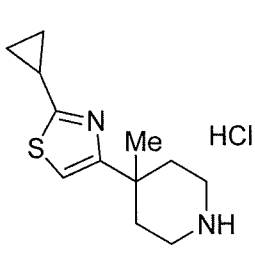
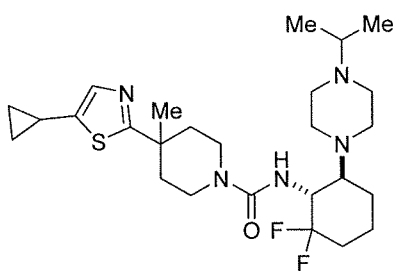
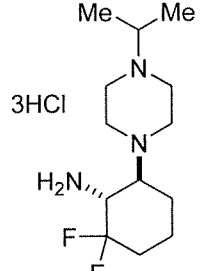
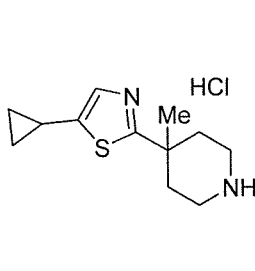
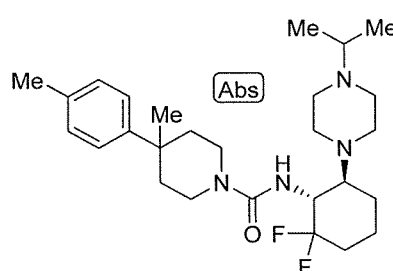
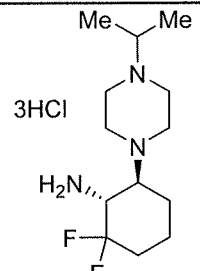
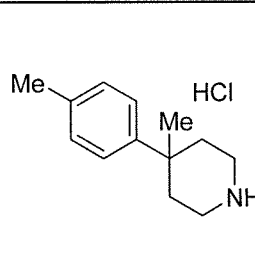
			
	¹ H-NMR (CDCl ₃) δ: 1.01-1.23 (10H, m), 1.23-1.46 (4H, m), 1.43 (3H, s), 1.60-1.74 (1H, m), 1.74-1.87 (3H, m), 1.92-2.03 (1H, m), 2.11-2.29 (3H, m), 2.31-2.40 (1H, m), 2.40-3.14 (8H, m), 3.26-3.38 (2H, m), 3.58-3.71 (2H, m), 4.08-4.23 (1H, m), 4.52 (1H, d, J = 7.9 Hz).		
35		Reference example 14	Commercial product
			 HCl
	¹ H-NMR (CDCl ₃) δ: 0.82-1.07 (3H, m), 1.03 (6H, d, J = 6.8 Hz), 1.07-1.49 (11H, m), 1.49-1.86 (6H, m), 1.89-1.99 (1H, m), 2.09-2.25 (1H, m), 2.34-2.56 (7H, m), 2.56-2.67 (1H, m), 2.67-2.87 (4H, m), 3.89-3.99 (1H, m), 4.05-4.27 (2H, m), 4.49 (1H, d, J = 8.0 Hz).		
36		Reference example 14	Commercial product
			 HCl
	¹ H-NMR (CDCl ₃) δ: 0.99 (6H, d, J = 6.4 Hz), 1.21-1.49 (2H, m), 1.61-2.00 (5H, m), 2.01-2.12 (2H, m), 2.12-2.24 (1H, m), 2.29-2.64 (8H, m), 2.68-2.81 (2H, m), 2.87-3.00 (1H, m), 3.00-3.14 (2H, m), 3.97-4.09 (1H, m), 4.09-4.29 (2H, m), 4.58 (1H, d, J = 8.0 Hz), 7.13 (1H, t, J = 4.8 Hz), 8.67 (2H, d, J = 4.8 Hz).		

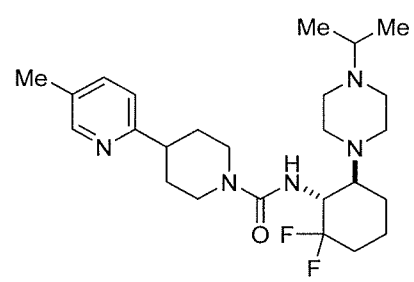
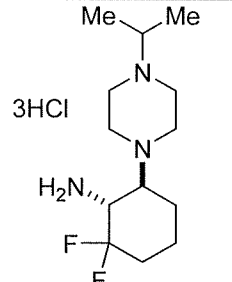
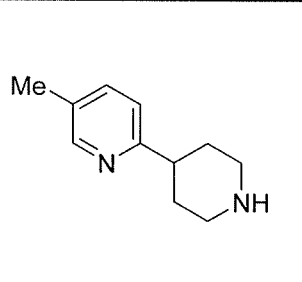
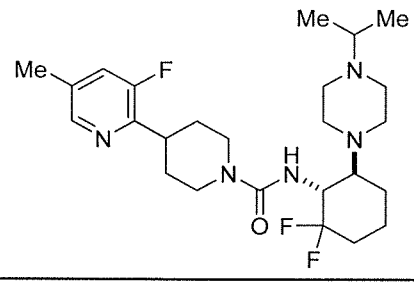
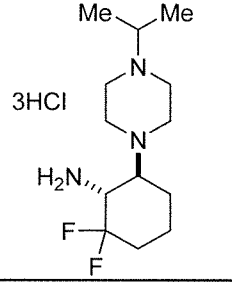
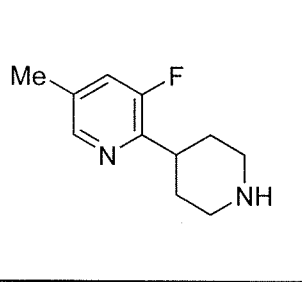
37		Reference example 14	Commercial product
			
¹ H-NMR (CDCl ₃) δ: 1.03 (6H, d, J = 6.4 Hz), 1.22-1.51 (2H, m), 1.59-1.90 (4H, m), 1.90-2.07 (3H, m), 2.10-2.24 (1H, m), 2.34-2.65 (8H, m), 2.69-2.82 (2H, m), 3.33-3.50 (2H, m), 3.92-4.10 (2H, m), 4.13-4.28 (1H, m), 4.64 (1H, d, J = 8.0 Hz), 5.30 (1H, bs), 7.23 (1H, ddd, J = 8.0, 8.0, 1.6 Hz), 7.32 (1H, dd, J = 8.0, 1.6 Hz), 7.71 (1H, ddd, J = 8.0, 8.0, 1.6 Hz), 8.51-8.55 (1H, m).			
38		Reference example 14	Commercial product
			
¹ H-NMR (CDCl ₃) δ: 1.02 (6H, d, J = 6.4 Hz), 1.22-1.50 (2H, m), 1.61-1.77 (3H, m), 1.77-2.00 (4H, m), 2.11-2.24 (1H, m), 2.31-2.64 (8H, m), 2.65-2.82 (3H, m), 2.83-3.04 (2H, m), 4.02-4.13 (1H, m), 4.13-4.33 (2H, m), 4.60 (1H, d, J = 8.0 Hz), 7.17-7.24 (3H, m), 7.27-7.34 (2H, m).			
39		Reference example 14	Commercial product
			
¹ H-NMR (CDCl ₃) δ: 0.95 (6H, d, J = 6.4 Hz), 1.18-			

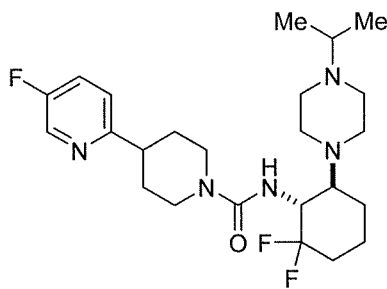
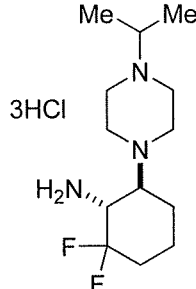
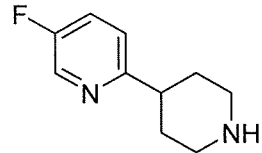
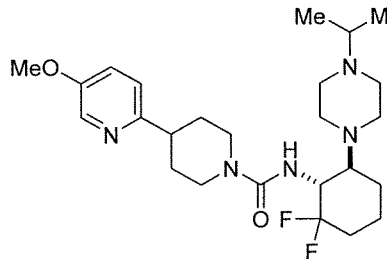
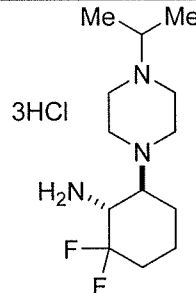
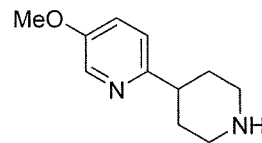
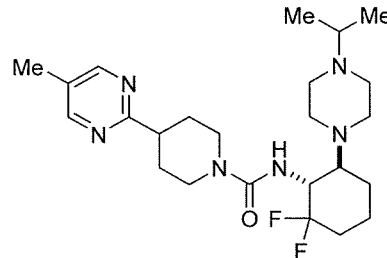
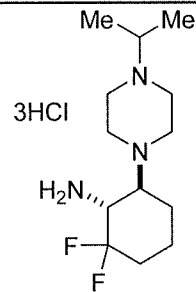
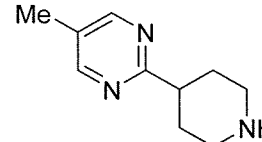
	1.48 (4H, m), 1.60-1.86 (5H, m), 1.87-1.98 (1H, m), 2.07-2.23 (3H, m), 2.25-2.55 (8H, m), 2.66-2.78 (2H, m), 3.28-3.62 (4H, m), 4.07-4.24 (1H, m), 4.54 (1H, d, $J = 8.0$ Hz), 7.16-7.24 (1H, m), 7.28-7.38 (4H, m).		
40		Reference example 14	Commercial product
			
	¹ H-NMR (CDCl ₃) δ : 0.99 (6H, d, $J = 6.4$ Hz), 1.22-1.49 (2H, m), 1.56-1.88 (5H, m), 1.89-2.00 (1H, m), 2.01-2.24 (3H, m), 2.29-2.61 (8H, m), 2.68-2.81 (2H, m), 3.30-3.47 (2H, m), 3.85-4.05 (2H, m), 4.11-4.27 (1H, m), 4.62 (1H, d, $J = 8.0$ Hz), 7.25-7.31 (1H, m), 7.36 (2H, t, $J = 8.0$ Hz), 7.48 (2H, d, $J = 8.0$ Hz).		
41		Reference example 14	Commercial product
			
	¹ H-NMR (CDCl ₃) δ : 0.99 (6H, d, $J = 6.0$ Hz), 1.21-1.49 (2H, m), 1.60-1.88 (5H, m), 1.88-1.97 (1H, m), 1.97-2.09 (2H, m), 2.10-2.23 (1H, m), 2.27-2.61 (8H, m), 2.66-2.80 (2H, m), 3.25-3.43 (2H, m), 3.84-4.03 (2H, m), 4.07-4.24 (1H, m), 4.61 (1H, d, $J = 8.0$ Hz), 7.31 (2H, d, $J = 8.8$ Hz), 7.41 (2H, d, $J = 8.8$ Hz).		
42		Reference example 14	Reference example 31

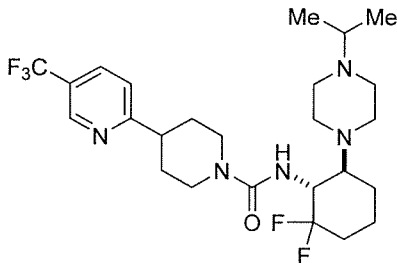
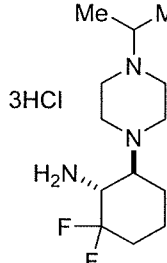
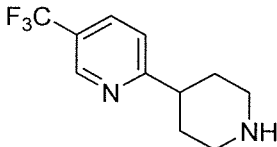
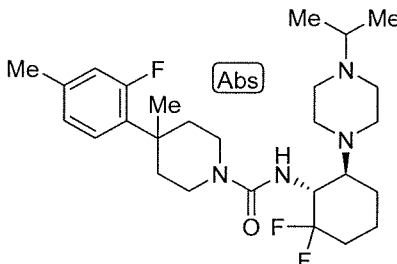
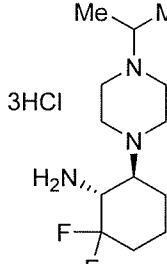
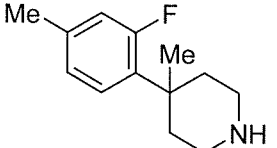
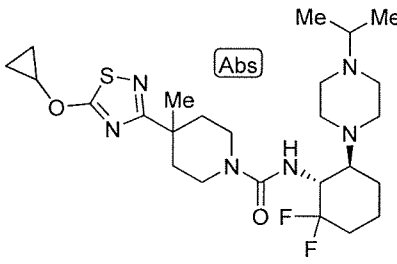
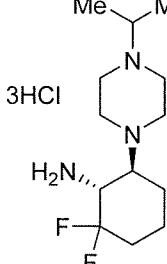
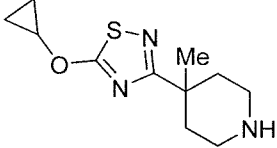
		 3HCl	 HCl
	¹ H-NMR (CDCl ₃) δ: 1.01 (6H, d, J = 6.1 Hz), 1.19-1.47 (3H, m), 1.65 (3H, s), 1.67-1.84 (3H, m), 1.90-1.97 (1H, m), 2.09-2.21 (1H, m), 2.36-2.53 (9H, m), 2.55-2.66 (1H, m), 2.70-2.80 (2H, m), 3.19-3.36 (2H, m), 3.66 (1H, ddd, J = 13.0, 4.1, 3.5 Hz), 3.76 (1H, ddd, J = 13.0, 4.1, 3.5 Hz), 4.11-4.26 (1H, m), 4.52 (1H, d, J = 7.3 Hz), 6.68 (1H, d, J = 8.3 Hz), 6.81 (1H, dd, J = 6.7, 5.5 Hz), 7.49-7.54 (1H, m), 8.10 (1H, dd, J = 5.5, 1.7 Hz).		
43		Reference example 15  3HCl	Reference example 28 
	¹ H-NMR (CDCl ₃) δ: 1.00 (3H, d, J = 6.1 Hz), 1.01 (3H, d, J = 6.1 Hz), 1.11-1.18 (2H, m), 1.22-1.35 (4H, m), 1.30 (3H, s), 1.35-1.47 (1H, m), 1.62-1.75 (2H, m), 1.75-1.85 (1H, m), 1.88-1.97 (1H, m), 2.10-2.22 (1H, m), 2.31-2.62 (11H, m), 2.67-2.78 (2H, m), 3.01 (1H, ddd, J = 13.8, 10.7, 3.1 Hz), 3.10 (1H, ddd, J = 13.8, 10.7, 3.1 Hz), 3.65 (1H, ddd, J = 14.0, 4.3, 4.3 Hz), 3.79 (1H, ddd, J = 14.0, 4.3, 4.3 Hz), 4.08-4.22 (1H, m), 4.53 (1H, d, J = 7.3 Hz).		
44		Reference example 15  3HCl	Reference example 24 

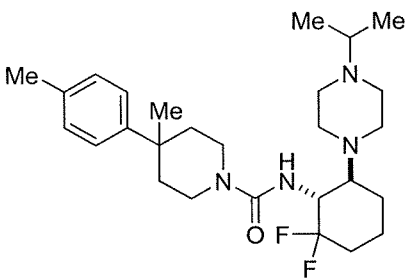
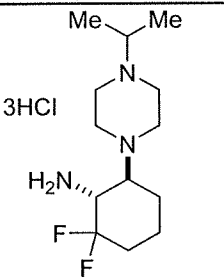
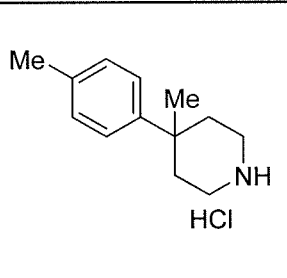
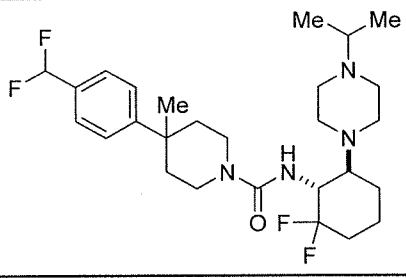
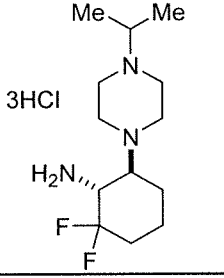
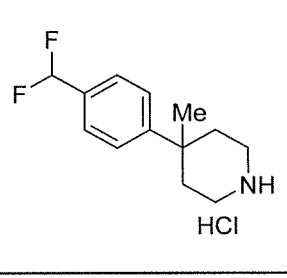
	¹ H-NMR (CDCl ₃) δ: 1.01-1.23 (10H, m), 1.23-1.46 (4H, m), 1.43 (3H, s), 1.60-1.74 (1H, m), 1.74-1.87 (3H, m), 1.92-2.03 (1H, m), 2.11-2.29 (3H, m), 2.31-2.40 (1H, m), 2.40-3.14 (8H, m), 3.26-3.38 (2H, m), 3.58-3.71 (2H, m), 4.08-4.23 (1H, m), 4.52 (1H, d, J = 7.9 Hz).		
45		Reference example 14	Reference example 29
			
	¹ H-NMR (CDCl ₃) δ: 1.04-1.19 (6H, m), 1.21-1.47 (3H, m), 1.31 (3H, s), 1.53-1.87 (3H, m), 1.89-2.01 (1H, m), 2.10-2.23 (1H, m), 2.28-2.40 (2H, m), 2.40-2.74 (7H, m), 2.74-3.03 (3H, m), 3.05-3.22 (2H, m), 3.58-3.77 (2H, m), 4.05-4.22 (1H, m), 4.14 (3H, s), 4.53 (1H, s).		
46		Reference example 14	Commercial product
			
	¹ H-NMR (CDCl ₃) δ: 1.02 (6H, d, J = 6.4 Hz), 1.22-1.49 (2H, m), 1.62-1.88 (2H, m), 1.88-2.01 (3H, m), 2.10-2.23 (1H, m), 2.23-2.66 (10H, m), 2.70-2.83 (2H, m), 3.20-3.43 (2H, m), 3.89-4.01 (1H, m), 4.06-4.27 (2H, m), 4.62 (1H, d, J = 8.0 Hz), 7.20 (1H, ddd, J = 8.0, 4.8, 1.2 Hz), 7.55 (1H, dd, J = 8.0, 1.2 Hz), 7.72 (1H, ddd, J = 8.0, 8.0, 1.2 Hz), 8.51 (1H, d, J = 4.8 Hz).		
47		Reference example 14	Reference example 26

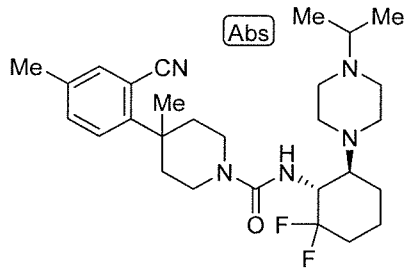
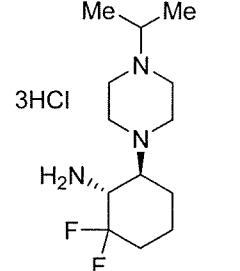
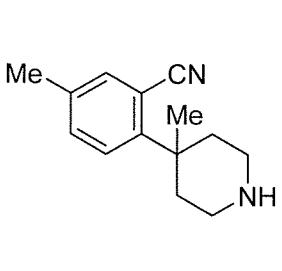
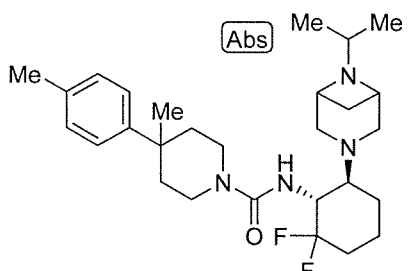
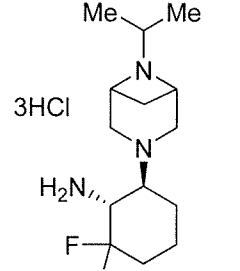
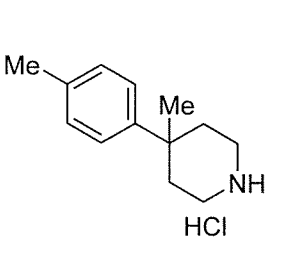
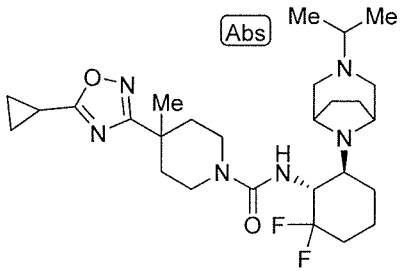
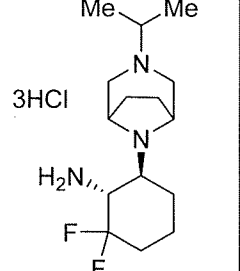
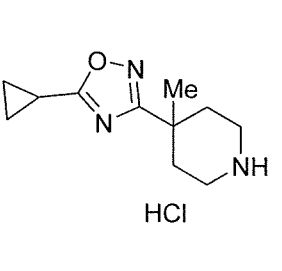
			
	¹ H-NMR (CDCl ₃) δ: 0.96-1.02 (2H, m), 0.99 (6H, d, J = 6.0 Hz), 1.05-1.16 (2H, m), 1.18-1.48 (3H, m), 1.28 (3H, s), 1.62-1.76 (3H, m), 1.89-1.99 (1H, m), 2.08-2.23 (3H, m), 2.24-2.32 (1H, m), 2.32-2.63 (8H, m), 2.68-2.80 (2H, m), 3.24 (1H, ddd, J = 13.1, 9.2, 3.7 Hz), 3.34 (1H, ddd, J = 13.1, 9.2, 3.7 Hz), 3.43-3.52 (1H, m), 3.57-3.67 (1H, m), 4.07-4.22 (1H, m), 4.54 (1H, d, J = 7.3 Hz), 6.63 (1H, s).		
48		Reference example 14	Reference example 25
			
	¹ H-NMR (CDCl ₃) δ: 0.68-0.78 (2H, m), 0.95-1.16 (8H, m), 1.22-1.50 (3H, m), 1.35 (3H, s), 1.62-1.86 (3H, m), 1.88-1.97 (1H, m), 1.97-2.08 (1H, m), 2.10-2.30 (3H, m), 2.32-2.66 (8H, m), 2.68-2.86 (2H, m), 3.23 (1H, ddd, J = 13.6, 9.6, 3.2 Hz), 3.32 (1H, ddd, J = 13.6, 9.6, 3.2 Hz), 3.55-3.66 (1H, m), 3.66-3.76 (1H, m), 4.08-4.23 (1H, m), 4.54 (1H, d, J = 7.3 Hz), 7.32 (1H, s).		
49		Reference example 15	Commercial product
			
	¹ H-NMR (CDCl ₃) δ: 0.95 (6H, d, J = 6.4 Hz), 1.19-1.47 (3H, m), 1.25 (3H, s), 1.61-1.85 (3H, m), 1.88-		

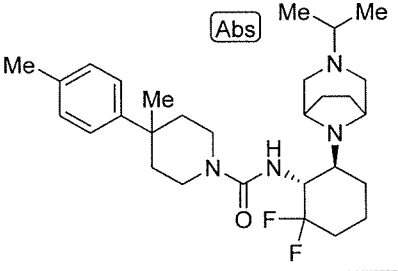
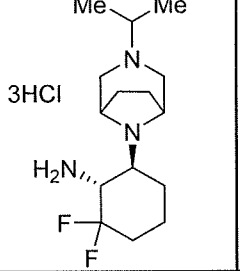
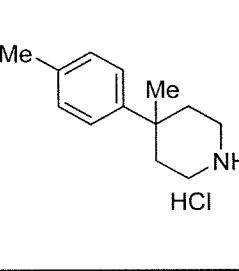
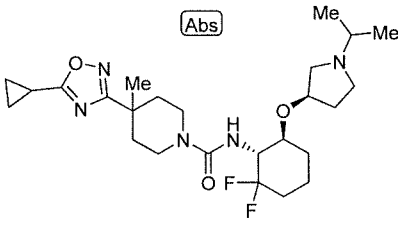
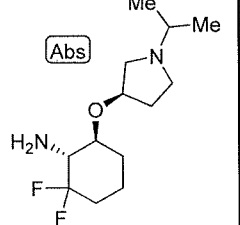
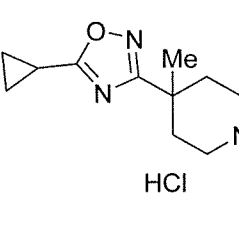
	1.97 (1H, m), 2.06-2.22 (3H, m), 2.28-2.53 (8H, m), 2.32 (3H, s), 2.67-2.76 (2H, m), 3.32 (1H, ddd, J = 11.6, 8.0, 3.6 Hz), 3.40-3.49 (2H, m), 3.56 (1H, ddd, J = 11.6, 8.0, 3.6 Hz), 4.09-4.22 (1H, m), 4.53 (1H, d, J = 7.8 Hz), 7.14 (2H, d, J = 8.2 Hz), 7.22 (2H, d, J = 8.2 Hz).		
50		Reference example 14	Commercial product
			
	¹ H-NMR (CDCl ₃) δ: 0.99 (6H, d, J = 6.0 Hz), 1.21-1.49 (2H, m), 1.62-1.89 (4H, m), 1.89-2.06 (3H, m), 2.09-2.23 (1H, m), 2.30 (3H, s), 2.34-2.63 (8H, m), 2.67-2.80 (2H, m), 2.80-3.06 (3H, m), 4.03-4.29 (3H, m), 4.59 (1H, d, J = 8.0 Hz), 7.04 (1H, d, J = 8.0 Hz), 7.42 (1H, dd, J = 8.0, 2.4 Hz), 8.34 (1H, d, J = 2.4 Hz).		
51		Reference example 14	Reference example 41
			
	¹ H-NMR (CDCl ₃) δ: 1.01 (6H, d, J = 6.8 Hz), 1.21-1.48 (2H, m), 1.61-1.88 (4H, m), 1.88-2.04 (3H, m), 2.09-2.24 (1H, m), 2.31 (3H, s), 2.35-2.66 (8H, m), 2.69-2.81 (2H, m), 2.85-3.09 (2H, m), 3.10-3.23 (1H, m), 4.00-4.10 (1H, m), 4.10-4.33 (2H, m), 4.58 (1H, d, J = 8.0 Hz), 7.14 (1H, d, J = 11.2 Hz), 8.14 (1H, s).		
52		Reference example 14	Commercial product

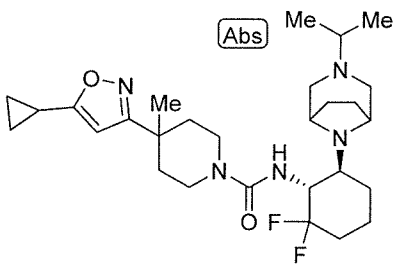
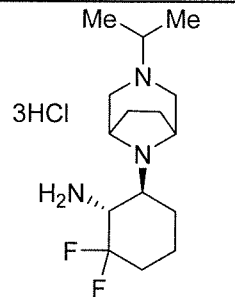
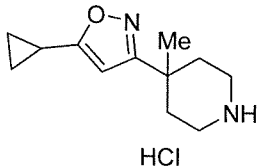
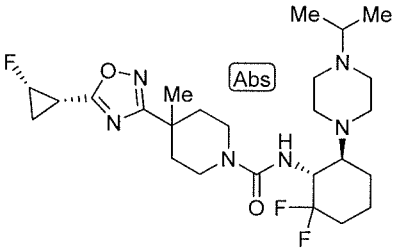
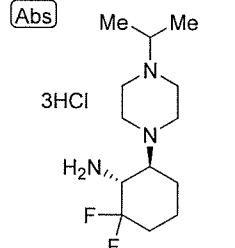
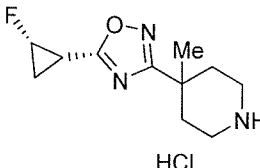
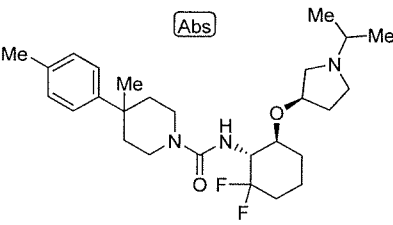
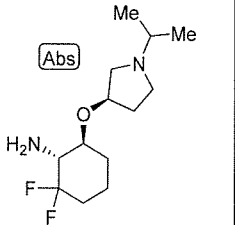
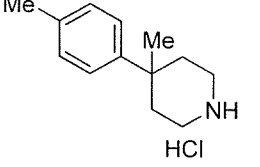
			
	¹ H-NMR (CDCl ₃) δ: 1.00 (6H, d, J = 6.4 Hz), 1.22-1.50 (2H, m), 1.62-1.87 (4H, m), 1.90-2.06 (3H, m), 2.10-2.23 (1H, m), 2.33-2.65 (8H, m), 2.69-2.81 (2H, m), 2.85-3.06 (3H, m), 4.04-4.30 (3H, m), 4.59 (1H, d, J = 8.0 Hz), 7.15 (1H, dd, J = 8.4, 4.4 Hz), 7.33 (1H, ddd, J = 8.4, 8.4, 2.8 Hz), 8.38 (1H, d, J = 2.8 Hz).		
53		Reference example 14	Commercial product
			
	¹ H-NMR (CDCl ₃) δ: 1.00 (6H, d, J = 6.4 Hz), 1.21-1.49 (2H, m), 1.63-1.87 (4H, m), 1.88-2.03 (3H, m), 2.09-2.23 (1H, m), 2.34-2.64 (8H, m), 2.68-2.80 (2H, m), 2.80-3.06 (3H, m), 3.84 (3H, s), 4.03-4.29 (3H, m), 4.59 (1H, d, J = 8.0 Hz), 7.07 (1H, d, J = 8.4 Hz), 7.14 (1H, dd, J = 8.4, 2.8 Hz), 8.22 (1H, d, J = 2.8 Hz).		
54		Reference example 14	Commercial product
			
	¹ H-NMR (CDCl ₃) δ: 0.99 (6H, d, J = 6.4 Hz), 1.21-1.49 (2H, m), 1.60-1.99 (5H, m), 1.99-2.10 (2H, m), 2.10-2.22 (1H, m), 2.27 (3H, s), 2.30-2.63 (8H, m), 2.67-2.81 (2H, m), 2.85-3.11 (2H, m), 3.95-4.08 (1H,		

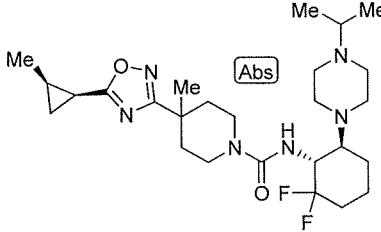
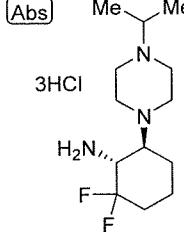
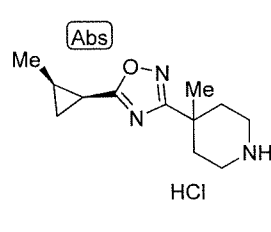
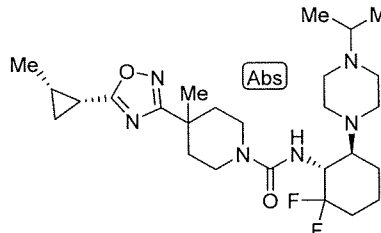
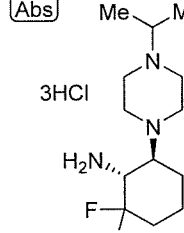
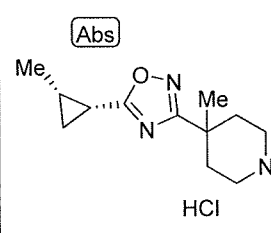
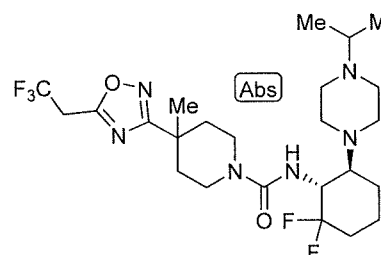
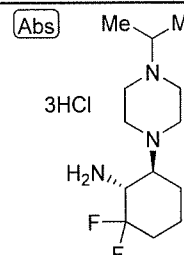
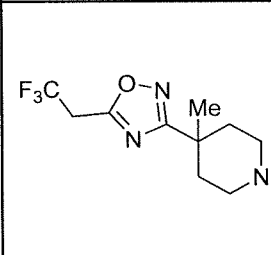
	m), 4.09-4.26 (3H, m), 4.58 (1H, d, J = 8.0 Hz), 8.48 (2H, s).		
55		Reference example 14	Commercial product
			
¹ H-NMR (CDCl ₃) δ: 1.00 (6H, d, J = 6.4 Hz), 1.22-1.50 (2H, m), 1.63-1.90 (4H, m), 1.90-2.06 (3H, m), 2.10-2.25 (1H, m), 2.31-2.65 (8H, m), 2.69-2.81 (2H, m), 2.89-3.08 (3H, m), 4.06-4.32 (3H, m), 4.60 (1H, d, J = 8.0 Hz), 7.29 (1H, d, J = 8.4 Hz), 7.86 (1H, d, J = 8.4, 2.4 Hz), 8.79 (1H, s).			
56		Reference example 15	Reference example 32
			
¹ H-NMR (CDCl ₃) δ: 0.94 (6H, d, J = 6.1 Hz), 1.23-1.47 (3H, m), 1.34 (3H, s), 1.67-1.86 (3H, m), 1.88-1.97 (1H, m), 2.10-2.23 (3H, m), 2.31 (3H, s), 2.31-2.52 (8H, m), 2.67-2.76 (2H, m), 3.36 (1H, ddd, J = 11.6, 8.0, 3.6 Hz), 3.40-3.52 (2H, m), 3.53-3.59 (1H, m), 4.07-4.23 (1H, m), 4.54 (1H, d, J = 7.9 Hz), 6.81-6.91 (2H, m), 7.11 (1H, dd, J = 7.6, 7.6 Hz).			
57		Reference example 15	Reference example 30
			

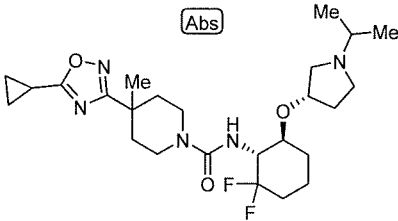
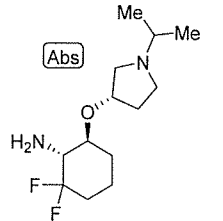
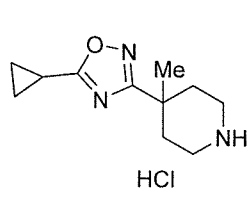
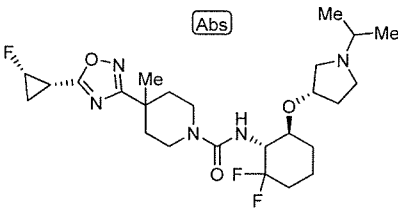
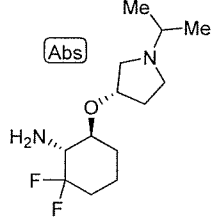
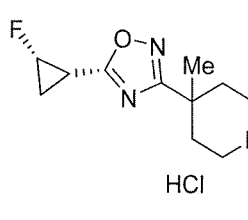
	¹ H-NMR (CDCl ₃) δ: 0.86-0.93 (2H, m), 0.94-1.07 (2H, m), 1.00 (3H, d, J = 6.4 Hz), 1.01 (3H, d, J = 6.4 Hz), 1.20-1.48 (3H, m), 1.30 (3H, s), 1.54-1.85 (3H, m), 1.89-1.97 (1H, m), 2.09-2.22 (1H, m), 2.31-2.54 (9H, m), 2.54-2.64 (1H, m), 2.68-2.79 (2H, m), 3.06 (1H, ddd, J = 13.8, 10.7, 3.1 Hz), 3.16 (1H, ddd, J = 13.8, 10.7, 3.1 Hz), 3.58-3.68 (1H, m), 3.74-3.84 (1H, m), 4.09-4.23 (2H, m), 4.53 (1H, d, J = 7.9 Hz).		
58		Reference example 14	Commercial product
			
	¹ H-NMR (CDCl ₃) δ: 0.95 (6H, d, J = 6.4 Hz), 1.19-1.47 (3H, m), 1.25 (3H, s), 1.61-1.85 (3H, m), 1.88-1.97 (1H, m), 2.06-2.22 (3H, m), 2.28-2.53 (8H, m), 2.32 (3H, s), 2.67-2.76 (2H, m), 3.32 (1H, ddd, J = 11.6, 8.0, 3.6 Hz), 3.40-3.49 (2H, m), 3.56 (1H, ddd, J = 11.6, 8.0, 3.6 Hz), 4.09-4.22 (1H, m), 4.53 (1H, d, J = 7.8 Hz), 7.14 (2H, d, J = 8.2 Hz), 7.22 (2H, d, J = 8.2 Hz).		
59		Reference example 14	Reference example 33
			
	¹ H-NMR (CDCl ₃) δ: 0.92 (3H, d, J = 6.7 Hz), 0.93 (3H, d, J = 6.7 Hz), 1.22-1.46 (3H, m), 1.29 (3H, s), 1.64-1.85 (3H, m), 1.88-1.96 (1H, m), 2.06-2.22 (3H, m), 2.25-2.54 (8H, m), 2.66-2.76 (2H, m), 3.36 (1H, ddd, J = 11.2, 7.6, 3.6 Hz), 3.41-3.59 (3H, m), 4.08-4.22 (1H, m), 4.54 (1H, d, J = 7.9 Hz), 6.63 (1H, t, J = 56.5 Hz), 7.42 (2H, d, J = 8.5 Hz), 7.48 (2H, d, J = 7.9 Hz).		
60		Reference example 15	Reference example 34

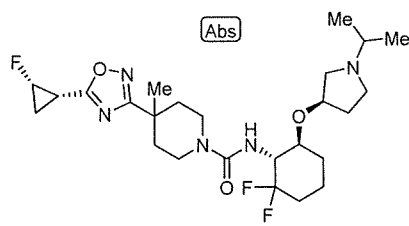
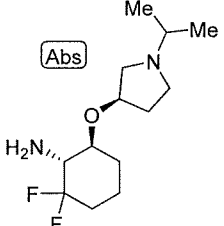
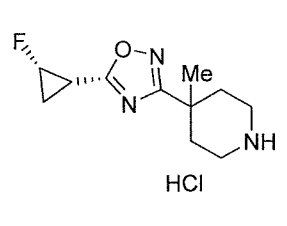
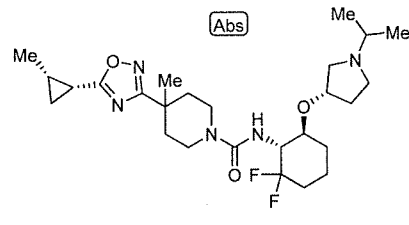
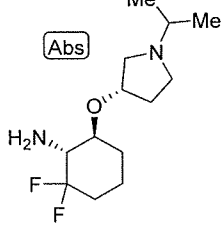
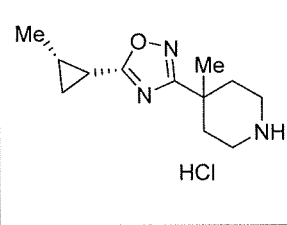
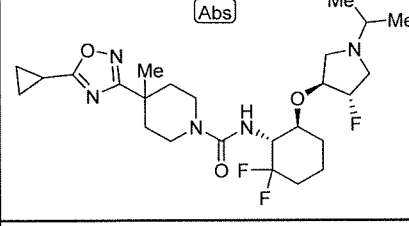
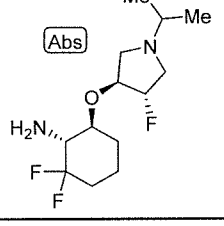
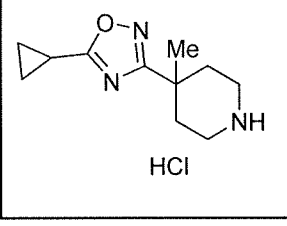
			
	¹ H-NMR (CDCl ₃) δ: 0.95 (6H, d, J = 6.7 Hz), 1.23-1.48 (2H, m), 1.52 (3H, s), 1.59-1.74 (1H, m), 1.74-1.84 (1H, m), 1.89-1.98 (1H, m), 2.00-2.10 (2H, m), 2.10-2.20 (1H, m), 2.21-2.32 (2H, m), 2.32-2.58 (8H, m), 2.35 (3H, s), 2.69-2.80 (2H, m), 3.43 (1H, ddd, J = 13.1, 9.2, 3.7 Hz), 3.48-3.61 (3H, m), 4.09-4.23 (1H, m), 4.52 (1H, d, J = 7.3 Hz), 7.29-7.36 (2H, m), 7.51 (1H, s).		
61		Reference example 16 	Commercial product 
	¹ H-NMR (CDCl ₃) δ: 0.95-1.14 (6H, m), 1.17-1.31 (2H, m), 1.24 (3H, s), 1.33-1.80 (5H, m), 1.80-1.88 (1H, m), 2.05-2.25 (3H, m), 2.32 (3H, s), 2.53-2.63 (1H, m), 2.63-2.73 (1H, m), 2.78-2.88 (1H, m), 2.89-3.14 (2H, m), 3.20-3.34 (3H, m), 3.34-3.54 (3H, m), 3.84-3.98 (2H, m), 4.22-4.37 (1H, m), 4.61 (1H, d, J = 8.5 Hz), 7.15 (2H, d, J = 8.5 Hz), 7.20 (2H, d, J = 8.5 Hz).		
62		Reference example 17 	Reference example 8 
	¹ H-NMR (CDCl ₃) δ: 0.89 (3H, d, J = 6.0 Hz), 0.90 (3H, d, J = 6.0 Hz), 1.15-1.22 (4H, m), 1.22-1.35 (1H,		

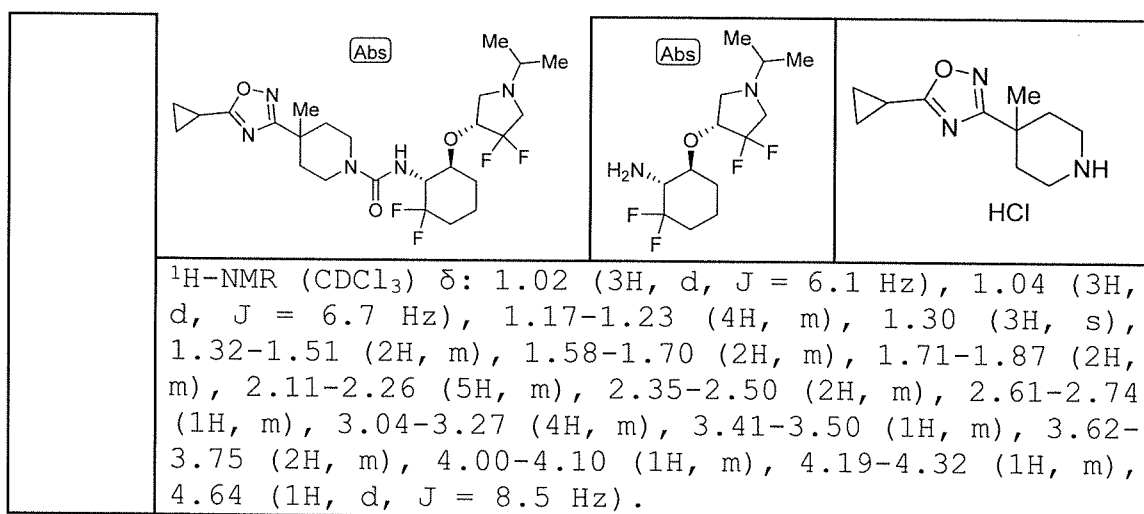
	m), 1.29 (3H, s), 1.35-1.44 (1H, m), 1.44-1.53 (1H, m), 1.61-1.70 (3H, m), 1.70-1.85 (5H, m), 2.04-2.19 (3H, m), 2.20-2.29 (3H, m), 2.41-2.57 (4H, m), 3.03-3.19 (3H, m), 3.19-3.24 (1H, m), 3.68-3.83 (2H, m), 3.94-4.07 (1H, m), 4.72 (1H, d, J = 7.3 Hz).		
63		Reference example 17	Commercial product
			
	¹ H-NMR (CDCl ₃) δ: 0.84 (3H, d, J = 6.8 Hz), 0.85 (3H, d, J = 6.8 Hz), 1.19-1.35 (1H, m), 1.24 (3H, s), 1.35-1.43 (1H, m), 1.43-1.53 (1H, m), 1.59-1.85 (7H, m), 2.02-2.18 (4H, m), 2.21-2.27 (1H, m), 2.32 (3H, s), 2.34-2.59 (5H, m), 3.03-3.09 (1H, m), 3.18-3.25 (1H, m), 3.34-3.45 (2H, m), 3.46-3.59 (2H, m), 3.94-4.08 (1H, m), 4.73 (1H, d, J = 7.3 Hz), 7.13 (2H, d, J = 7.9 Hz), 7.21 (2H, d, J = 7.9 Hz).		
64		Reference example 38	Reference example 8
			
	¹ H-NMR (CDCl ₃) δ: 1.06 (6H, d, J = 6.0 Hz), 1.18-1.24 (4H, m), 1.30 (3H, s), 1.35-1.48 (2H, m), 1.56-1.68 (2H, m), 1.68-1.78 (3H, m), 1.93-2.27 (6H, m), 2.31-2.41 (2H, m), 2.46-2.58 (1H, m), 2.63-2.72 (1H, m), 2.92-3.24 (4H, m), 3.63-3.75 (2H, m), 4.08-4.28 (2H, m), 4.51-4.60 (1H, m).		
65		Reference example 17	Reference example 20

			
	¹ H-NMR (CDCl ₃) δ: 0.88 (3H, d, J = 6.4 Hz), 0.89 (3H, d, J = 6.4 Hz), 0.91-0.99 (2H, m), 0.99-1.07 (2H, m), 1.20-1.35 (1H, m), 1.25 (3H, s), 1.35-1.42 (1H, m), 1.42-1.53 (1H, m), 1.58-1.84 (8H, m), 1.95-2.03 (1H, m), 2.03-2.16 (4H, m), 2.24-2.29 (1H, m), 2.41-2.57 (4H, m), 3.04-3.10 (1H, m), 3.10-3.30 (3H, m), 3.67 (1H, ddd, J = 13.6, 4.5, 4.5 Hz), 3.75 (1H, ddd, J = 13.6, 4.5, 4.5 Hz), 3.93-4.07 (1H, m), 4.72 (1H, d, J = 7.3 Hz), 5.75 (1H, s).		
66			
	¹ H-NMR (DMSO-d ₆) δ: 0.87 (6H, d, J = 6.4 Hz), 1.18-1.36 (2H, m), 1.26 (3H, s), 1.47-1.66 (3H, m), 1.66-1.88 (4H, m), 1.95-2.11 (3H, m), 2.17-2.40 (6H, m), 2.43-2.63 (5H, m), 2.95-3.19 (2H, m), 3.55-3.77 (2H, m), 3.98-4.18 (1H, m), 5.16 (1H, dddd, J = 65.0, 6.0, 6.0, 3.2 Hz), 5.88 (1H, d, J = 8.0 Hz).		
67			
	¹ H-NMR (CDCl ₃) δ: 1.02 (6H, d, J = 7.3 Hz), 1.21-1.30 (1H, m), 1.25 (3H, s), 1.35-1.48 (2H, m), 1.65-1.84 (3H, m), 1.98-2.19 (6H, m), 2.25-2.36 (2H, m), 2.32 (3H, s), 2.48 (1H, dd, J = 16.4, 8.0 Hz), 2.59-2.69 (1H, m), 2.94 (1H, dd, J = 10.1, 6.4 Hz), 3.14-		

	3.23 (1H, m), 3.27-3.42 (2H, m), 3.42-3.56 (2H, m), 4.07-4.28 (2H, m), 4.56 (1H, d, J = 9.2 Hz), 7.14 (2H, d, J = 8.2 Hz), 7.21 (2H, d, J = 8.2 Hz).		
68		Reference example 15 (Abs) 	Reference example 12' (Abs) 
	¹ H-NMR (CDCl ₃) δ: 0.95-1.06 (8H, m), 1.13 (3H, d, J = 6.0 Hz), 1.21-1.57 (7H, m), 1.58-1.73 (2H, m), 1.73-1.87 (1H, m), 1.87-1.98 (1H, m), 2.08-2.30 (4H, m), 2.31-2.66 (8H, m), 2.66-2.83 (2H, m), 3.01-3.19 (2H, m), 3.61-3.72 (1H, m), 3.74-3.85 (1H, m), 4.03-4.24 (1H, m), 4.53 (1H, d, J = 8.0 Hz).		
69		Reference example 15 (Abs) 	Reference example 12 (Abs) 
	¹ H-NMR (CDCl ₃) δ: 0.97-1.06 (8H, m), 1.13 (3H, d, J = 6.4 Hz), 1.22-1.58 (7H, m), 1.58-1.73 (2H, m), 1.73-1.87 (1H, m), 1.89-1.99 (1H, m), 2.08-2.30 (4H, m), 2.31-2.66 (8H, m), 2.66-2.84 (2H, m), 3.00-3.22 (2H, m), 3.61-3.72 (1H, m), 3.74-3.85 (1H, m), 4.03-4.23 (1H, m), 4.53 (1H, d, J = 8.0 Hz).		
70		Reference example 15 (Abs) 	Commercial product 
	¹ H-NMR (CDCl ₃) δ: 0.97-1.04 (6H, m), 1.20-1.48 (7H, m), 1.62-1.87 (3H, m), 1.89-1.98 (1H, m), 2.10-2.21 (1H, m), 2.21-2.31 (2H, m), 2.31-2.54 (6H, m), 2.58 (1H, sept, J = 6.4 Hz), 2.68-2.80 (2H, m), 3.10 (1H,		

	ddd, $J = 12.8, 10.0, 2.4$ Hz), 3.17 (1H, ddd, $J = 13.2, 10.4, 2.8$ Hz), 3.63-3.73 (1H, m) 3.73-3.83 (3H, m), 4.08-4.23 (1H, m), 4.54 (1H, d, $J = 8.0$ Hz).		
71		Reference example 37	Reference example 8
			
	¹ H-NMR (CDCl ₃) δ : 1.05 (3H, d, $J = 6.4$ Hz), 1.06 (3H, d, $J = 6.4$ Hz), 1.17-1.23 (4H, m), 1.30 (3H, s), 1.36-1.47 (2H, m), 1.56-1.81 (5H, m), 1.98 (1H, ddd, $J = 16.0, 13.6, 8.0$ Hz), 2.03-2.26 (5H, m), 2.31-2.42 (2H, m), 2.51 (1H, dd, $J = 16.0, 8.0$ Hz), 2.60-2.67 (1H, m), 2.97 (1H, dd, $J = 10.1, 6.4$ Hz), 3.04-3.23 (3H, m), 3.63-3.75 (2H, m), 4.07-4.27 (2H, m), 4.55 (1H, d, $J = 9.2$ Hz).		
72		Reference example 37	Reference example 11
			
	¹ H-NMR (CDCl ₃) δ : 1.04 (3H, d, $J = 6.0$ Hz), 1.05 (3H, d, $J = 6.0$ Hz), 1.33 (3H, s), 1.35-1.53 (3H, m), 1.57-1.82 (5H, m), 1.90-2.03 (2H, m), 2.03-2.20 (2H, m), 2.21-2.30 (2H, m), 2.30-2.41 (3H, m), 2.50 (1H, dd, $J = 18.4, 8.4$ Hz), 2.64 (1H, ddd, $J = 8.5, 8.4, 4.6$ Hz), 2.98 (1H, dd, $J = 10.1, 6.4$ Hz), 3.03-3.25 (3H, m), 3.65-3.75 (2H, m), 4.06-4.27 (2H, m), 4.55 (1H, d, $J = 9.1$ Hz), 4.91 (1H, dddd, $J = 63.7, 6.4, 6.4, 4.0$ Hz).		
73		Reference example 38	Reference example 11

	  	¹ H-NMR (CDCl ₃) δ: 1.61 (6H, d, J = 6.4 Hz), 1.89 (3H, s), 1.92-2.10 (3H, m), 2.15-2.41 (5H, m), 2.47-2.77 (4H, m), 2.78-2.86 (2H, m), 2.86-2.97 (3H, m), 3.01-3.13 (1H, m), 3.17-3.27 (1H, m), 3.53 (1H, ddd, J = 19.8, 9.9, 6.5 Hz), 3.59-3.81 (3H, m), 4.20-4.34 (2H, m), 4.64-4.86 (2H, m), 5.07-5.17 (1H, m), 5.48 (1H, dddd, J = 63.7, 6.0, 6.0, 3.6 Hz).
74	  	Reference example 37 Reference example 12
75	  	Reference example 39 Reference example 8
76		Reference example 40 Reference example 8



[0233]

The chemical names of Example 20 to Example 76 are listed below.

Example 20: *rac*-4-(5-cyclopropyl-1,2-oxazol-3-yl)-N-
 5 { (1R,6S)-2,2-difluoro-6-[4-(propan-2-yl)piperazin-1-yl]cyclohexyl}-4-methylpiperidine-1-carboxamide

Example 21: *rac*-4-(1,3-benzoxazol-2-yl)-N-{ (1R,6S)-
 2,2-difluoro-6-[4-(propan-2-yl)piperazin-1-yl]cyclohexyl}-
 4-methylpiperidine-1-carboxamide

10 Example 22: 4-(5-cyclopropyl-1,2-oxazol-3-yl)-N-
 { (1S,6R)-2,2-difluoro-6-[4-(propan-2-yl)piperazin-1-yl]cyclohexyl}-4-methylpiperidine-1-carboxamide

Example 23: 4-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)-N-
 { (1S,6R)-2,2-difluoro-6-[4-(propan-2-yl)piperazin-1-yl]cyclohexyl}-4-methylpiperidine-1-carboxamide
 15

Example 24: 4-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)-N-
 { (1R,6S)-2,2-difluoro-6-[4-(propan-2-yl)piperazin-1-

yl]cyclohexyl}-4-methylpiperidine-1-carboxamide

Example 25: 4-(5-cyclopropyl-1,2-oxazol-3-yl)-N-
{(1R,6S)-2,2-difluoro-6-[4-(propan-2-yl)piperazin-1-
yl]cyclohexyl}-4-methylpiperidine-1-carboxamide

5 Example 26: *rac*-4-cyclopentyl-N-[(1R,6S)-2,2-difluoro-
6-[4-(propan-2-yl)piperazin-1-yl]cyclohexyl]-4-
methylpiperidine-1-carboxamide

Example 27: *rac*-N-[(1R,6S)-2,2-difluoro-6-[4-(propan-
2-yl)piperazin-1-yl]cyclohexyl]-4-methyl-4-(4,5,6,7-
10 tetrahydro-1,3-benzoxazol-2-yl)piperidine-1-carboxamide

Example 28: *rac*-N-[(1R,6S)-2,2-difluoro-6-[4-(propan-
2-yl)piperazin-1-yl]cyclohexyl]-4-(5-ethyl-1,2,4-oxadiazol-
3-yl)-4-methylpiperidine-1-carboxamide

Example 29: *rac*-4-(1-cyclopropyl-1H-1,2,4-triazol-3-
15 yl)-N-[(1R,6S)-2,2-difluoro-6-[4-(propan-2-yl)piperazin-1-
yl]cyclohexyl]-4-methylpiperidine-1-carboxamide

Example 30: *rac*-4-(4,4-difluorocyclohexyl)-N-[(1R,6S)-
2,2-difluoro-6-[4-(propan-2-yl)piperazin-1-yl]cyclohexyl]-
4-methylpiperidine-1-carboxamide

20 Example 31: *rac*-4-(5-cyclopropyl-1,2,4-thiadiazol-3-
yl)-N-[(1R,6S)-2,2-difluoro-6-[4-(propan-2-yl)piperazin-1-
yl]cyclohexyl]-4-methylpiperidine-1-carboxamide

Example 32: *rac*-N-[(1R,6S)-2,2-difluoro-6-[4-(propan-
2-yl)piperazin-1-yl]cyclohexyl]-4-(pyridin-2-yl)piperidine-
25 1-carboxamide

Example 33: *rac*-N-((1R,6S)-2,2-difluoro-6-[4-(propan-2-yl)piperazin-1-yl]cyclohexyl)-8-azaspiro[4.5]decane-8-carboxamide

5 Example 34: *rac*-4-(5-cyclopropyl-1,3,4-thiadiazol-2-yl)-N-((1R,6S)-2,2-difluoro-6-[4-(propan-2-yl)piperazin-1-yl]cyclohexyl)-4-methylpiperidine-1-carboxamide

Example 35: *rac*-4-cyclohexyl-N-((1R,6S)-2,2-difluoro-6-[4-(propan-2-yl)piperazin-1-yl]cyclohexyl)piperidine-1-carboxamide

10 Example 36: *rac*-N-((1R,6S)-2,2-difluoro-6-[4-(propan-2-yl)piperazin-1-yl]cyclohexyl)-4-(pyrimidin-2-yl)piperidine-1-carboxamide

Example 37: *rac*-N-((1R,6S)-2,2-difluoro-6-[4-(propan-2-yl)piperazin-1-yl]cyclohexyl)-4-hydroxy-4-(pyridin-2-yl)piperidine-1-carboxamide

15 Example 38: *rac*-N-((1R,6S)-2,2-difluoro-6-[4-(propan-2-yl)piperazin-1-yl]cyclohexyl)-4-phenylpiperidine-1-carboxamide

20 Example 39: *rac*-N-((1R,6S)-2,2-difluoro-6-[4-(propan-2-yl)piperazin-1-yl]cyclohexyl)-4-methyl-4-phenylpiperidine-1-carboxamide

Example 40: *rac*-N-((1R,6S)-2,2-difluoro-6-[4-(propan-2-yl)piperazin-1-yl]cyclohexyl)-4-hydroxy-4-phenylpiperidine-1-carboxamide

25 Example 41: *rac*-4-(4-chlorophenyl)-N-((1R,6S)-2,2-

difluoro-6-[4-(propan-2-yl)piperazin-1-yl]cyclohexyl}-4-hydroxypiperidine-1-carboxamide

Example 42: *rac*-N-{(1R,6S)-2,2-difluoro-6-[4-(propan-2-yl)piperazin-1-yl]cyclohexyl}-4-methyl-4-[(pyridin-2-yl)oxy]piperidine-1-carboxamide

Example 43: 4-(5-cyclopropyl-1,2,4-thiadiazol-3-yl)-N-{(1R,6S)-2,2-difluoro-6-[4-(propan-2-yl)piperazin-1-yl]cyclohexyl}-4-methylpiperidine-1-carboxamide

Example 44: 4-(5-cyclopropyl-1,3,4-thiadiazol-2-yl)-N-{(1R,6S)-2,2-difluoro-6-[4-(propan-2-yl)piperazin-1-yl]cyclohexyl}-4-methylpiperidine-1-carboxamide

Example 45: *rac*-N-{(1R,6S)-2,2-difluoro-6-[4-(propan-2-yl)piperazin-1-yl]cyclohexyl}-4-(5-methoxy-1,2,4-thiadiazol-3-yl)-4-methylpiperidine-1-carboxamide

Example 46: *rac*-N-{(1R,6S)-2,2-difluoro-6-[4-(propan-2-yl)piperazin-1-yl]cyclohexyl}-4-fluoro-4-(pyridin-2-yl)piperidine-1-carboxamide

Example 47: *rac*-4-(2-cyclopropyl-1,3-thiazol-4-yl)-N-{(1R,6S)-2,2-difluoro-6-[4-(propan-2-yl)piperazin-1-yl]cyclohexyl}-4-methylpiperidine-1-carboxamide

Example 48: *rac*-4-(5-cyclopropyl-1,3-thiazol-2-yl)-N-{(1R,6S)-2,2-difluoro-6-[4-(propan-2-yl)piperazin-1-yl]cyclohexyl}-4-methylpiperidine-1-carboxamide

Example 49: N-{(1R,6S)-2,2-difluoro-6-[4-(propan-2-yl)piperazin-1-yl]cyclohexyl}-4-methyl-4-(4-

methylphenyl)piperidine-1-carboxamide

Example 50: *rac*-N-{(1*R*,6*S*)-2,2-difluoro-6-[4-(propan-2-yl)piperazin-1-yl]cyclohexyl}-4-(5-methylpyridin-2-yl)piperidine-1-carboxamide

5 Example 51: *rac*-N-{(1*R*,6*S*)-2,2-difluoro-6-[4-(propan-2-yl)piperazin-1-yl]cyclohexyl}-4-(3-fluoro-5-methylpyridin-2-yl)piperidine-1-carboxamide

Example 52: *rac*-N-{(1*R*,6*S*)-2,2-difluoro-6-[4-(propan-2-yl)piperazin-1-yl]cyclohexyl}-4-(5-fluoropyridin-2-yl)piperidine-1-carboxamide

Example 53: *rac*-N-{(1*R*,6*S*)-2,2-difluoro-6-[4-(propan-2-yl)piperazin-1-yl]cyclohexyl}-4-(5-methoxypyridin-2-yl)piperidine-1-carboxamide

Example 54: *rac*-N-{(1*R*,6*S*)-2,2-difluoro-6-[4-(propan-2-yl)piperazin-1-yl]cyclohexyl}-4-(5-methylpyrimidin-2-yl)piperidine-1-carboxamide

Example 55: *rac*-N-{(1*R*,6*S*)-2,2-difluoro-6-[4-(propan-2-yl)piperazin-1-yl]cyclohexyl}-4-[5-(trifluoromethyl)pyridin-2-yl]piperidine-1-carboxamide

20 Example 56: N-{(1*R*,6*S*)-2,2-difluoro-6-[4-(propan-2-yl)piperazin-1-yl]cyclohexyl}-4-(2-fluoro-4-methylphenyl)-4-methylpiperidine-1-carboxamide

Example 57: 4-[5-(cyclopropyloxy)-1,2,4-thiadiazol-3-yl]-N-{(1*R*,6*S*)-2,2-difluoro-6-[4-(propan-2-yl)piperazin-1-yl]cyclohexyl}-4-methylpiperidine-1-carboxamide

25

Example 58: *rac*-N-((1R,6S)-2,2-difluoro-6-[4-(propan-2-yl)piperazin-1-yl]cyclohexyl)-4-methyl-4-(4-methylphenyl)piperidine-1-carboxamide

Example 59: *rac*-4-[4-(difluoromethyl)phenyl]-N-
5 { (1R,6S)-2,2-difluoro-6-[4-(propan-2-yl)piperazin-1-yl]cyclohexyl}-4-methylpiperidine-1-carboxamide

Example 60: 4-(2-cyano-4-methylphenyl)-N-((1R,6S)-2,2-difluoro-6-[4-(propan-2-yl)piperazin-1-yl]cyclohexyl)-4-methylpiperidine-1-carboxamide

10 Example 61: N-((1R,6S)-2,2-difluoro-6-[6-(propan-2-yl)-3,6-diazabicyclo[3.1.1]heptan-3-yl]cyclohexyl)-4-methyl-4-(4-methylphenyl)piperidine-1-carboxamide

Example 62: 4-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)-N-
15 { (1R,6S)-2,2-difluoro-6-[3-(propan-2-yl)-3,8-diazabicyclo[3.2.1]octan-8-yl]cyclohexyl}-4-methylpiperidine-1-carboxamide

Example 63: N-((1R,6S)-2,2-difluoro-6-[3-(propan-2-yl)-3,8-diazabicyclo[3.2.1]octan-8-yl]cyclohexyl)-4-methyl-4-(4-methylphenyl)piperidine-1-carboxamide

20 Example 64: 4-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)-N-[(1R,6S)-2,2-difluoro-6-[[(3R)-1-(propan-2-yl)pyrrolidin-3-yl]oxy]cyclohexyl]-4-methylpiperidine-1-carboxamide

Example 65: 4-(5-cyclopropyl-1,2-oxazol-3-yl)-N-
25 { (1R,6S)-2,2-difluoro-6-[3-(propan-2-yl)-3,8-diazabicyclo[3.2.1]octan-8-yl]cyclohexyl}-4-

methylpiperidine-1-carboxamide

Example 66: N-[(1R,6S)-2,2-difluoro-6-[4-(propan-2-yl)piperazin-1-yl]cyclohexyl]-4-{5-[(1S,2S)-2-fluorocyclopropyl]-1,2,4-oxadiazol-3-yl}-4-

5 methylpiperidine-1-carboxamide

Example 67: N-[(1R,6S)-2,2-difluoro-6-{[(3R)-1-(propan-2-yl)pyrrolidin-3-yl]oxy}cyclohexyl]-4-methyl-4-(4-methylphenyl)piperidine-1-carboxamide

Example 68: N-[(1R,6S)-2,2-difluoro-6-[4-(propan-2-yl)piperazin-1-yl]cyclohexyl]-4-methyl-4-{5-[(1S,2R)-2-methylcyclopropyl]-1,2,4-oxadiazol-3-yl}piperidine-1-carboxamide

Example 69: N-[(1R,6S)-2,2-difluoro-6-[4-(propan-2-yl)piperazin-1-yl]cyclohexyl]-4-methyl-4-{5-[(1R,2S)-2-methylcyclopropyl]-1,2,4-oxadiazol-3-yl}piperidine-1-carboxamide

Example 70: N-[(1R,6S)-2,2-difluoro-6-[4-(propan-2-yl)piperazin-1-yl]cyclohexyl]-4-methyl-4-[5-(2,2,2-trifluoroethyl)-1,2,4-oxadiazol-3-yl]piperidine-1-carboxamide

Example 71: 4-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)-N-[(1R,6S)-2,2-difluoro-6-{[(3S)-1-(propan-2-yl)pyrrolidin-3-yl]oxy}cyclohexyl]-4-methylpiperidine-1-carboxamide

Example 72: N-[(1R,6S)-2,2-difluoro-6-{[(3S)-1-(propan-2-yl)pyrrolidin-3-yl]oxy}cyclohexyl]-4-{5-[(1S,2S)-

2-fluorocyclopropyl]-1,2,4-oxadiazol-3-yl}-4-methylpiperidine-1-carboxamide

Example 73: N-[(1R,6S)-2,2-difluoro-6-{[(3R)-1-(propan-2-yl)pyrrolidin-3-yl]oxy}cyclohexyl]-4-{5-[(1S,2S)-2-fluorocyclopropyl]-1,2,4-oxadiazol-3-yl}-4-methylpiperidine-1-carboxamide

Example 74: N-[(1R,6S)-2,2-difluoro-6-{[(3S)-1-(propan-2-yl)pyrrolidin-3-yl]oxy}cyclohexyl]-4-methyl-4-{5-[(1R,2S)-2-methylcyclopropyl]-1,2,4-oxadiazol-3-yl}piperidine-1-carboxamide

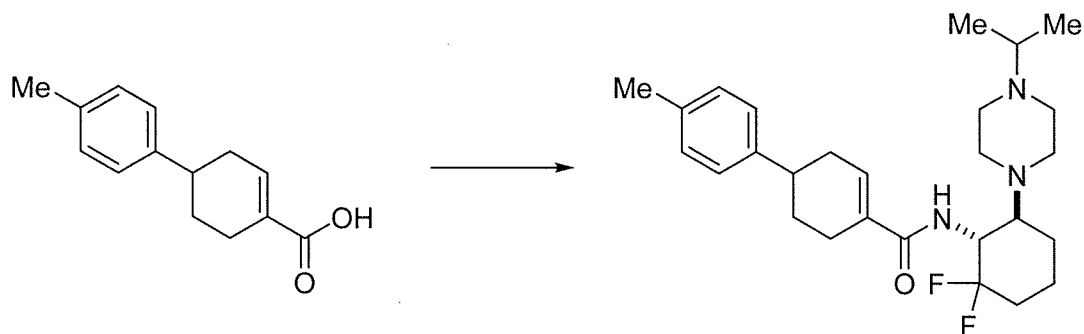
Example 75: 4-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)-N-[(1R,6S)-2,2-difluoro-6-{[(3S,4S)-4-fluoro-1-(propan-2-yl)pyrrolidin-3-yl]oxy}cyclohexyl]-4-methylpiperidine-1-carboxamide

Example 76: 4-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)-N-[(1R,6S)-6-{[(3R)-4,4-difluoro-1-(propan-2-yl)pyrrolidin-3-yl]oxy}-2,2-difluorocyclohexyl]-4-methylpiperidine-1-carboxamide

[0234]

Example 77:

rac-N-{(1R,6S)-2,2-Difluoro-6-[4-(propan-2-yl)piperazin-1-yl]cyclohexyl}-4'-methyl-1,2,3,6-tetrahydro[1,1'-biphenyl]-4-carboxamide



To a solution of 4-(4-methylphenyl)-cyclohex-1-ene-carboxylic acid (64.3 mg) in chloroform (2 mL) were added oxalyl chloride (0.036 mL) and DMF (5 μ L), and the mixture
 5 was stirred at room temperature for 3 hours. Then, the reaction solution was concentrated *in vacuo*, and chloroform (2 mL), triethylamine (0.120 mL), and Reference example 14 (53.3 mg) were added to the reaction residue. The mixture was stirred. After the reaction was completed, water was
 10 added to the reaction mixture, and the mixture was extracted with chloroform. The organic layer was dried over anhydrous sodium sulfate, and concentrated *in vacuo*, and then the obtained residue was purified by amino silica gel column chromatography (eluate: hexane/ethyl acetate) to give the
 15 title compound (55.6 mg).

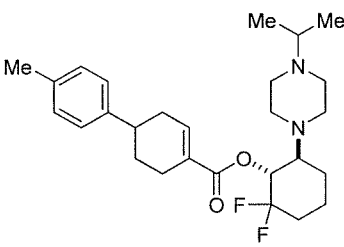
$^1\text{H-NMR}$ (CDCl_3) δ : 1.02 (6H, d, $J = 6.7$ Hz), 1.23-1.50 (2H, m), 1.71-1.91 (4H, m), 1.93-2.11 (2H, m), 2.13-2.68 (14H, m), 2.69-2.89 (4H, m), 4.27-4.44 (1H, m), 5.68-5.77 (1H, m), 6.67-6.77 (1H, m), 7.09-7.20 (4H, m).

20 [0235]

Example 78:

rac-(1*R*,6*S*)-2,2-Difluoro-6-[4-(propan-2-yl)piperazin-1-yl]cyclohexyl 4'-methyl-1,2,3,6-tetrahydro[1,1'-biphenyl]-4-carboxylate

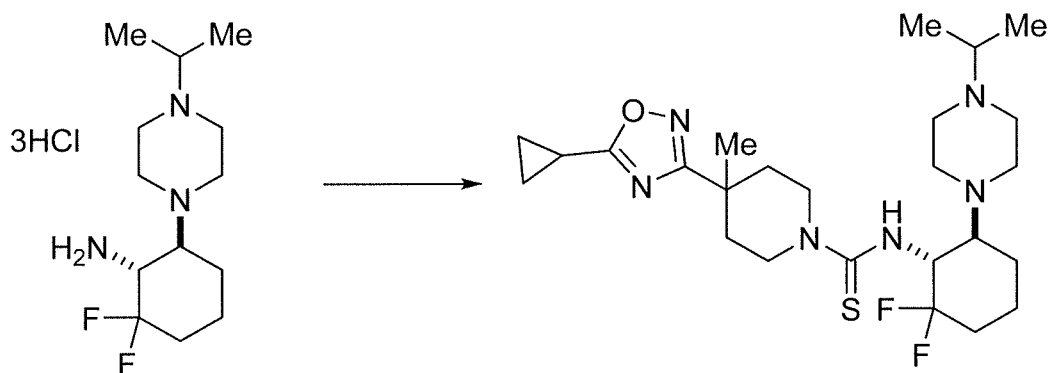
The compound of Example 78 shown in the table below was prepared in the same manner as Example 77, by using Reference example 6 instead of Reference example 14 in Example 77.

Example	Structure	Instrumental analytical data
78		¹ H-NMR (CDCl ₃) δ: 1.02 (3H, d, J = 6.0 Hz), 1.03 (3H, d, J = 6.0 Hz), 1.29-1.53 (2H, m), 1.58-1.85 (4H, m), 1.88-1.97 (1H, m), 1.98-2.08 (1H, m), 2.14-2.25 (1H, m), 2.25-2.53 (11H, m), 2.53-2.66 (2H, m), 2.67-2.83 (4H, m), 5.04-5.16 (1H, m), 7.09-7.16 (5H, m).

[0236]

Example 79:

rac-4-(5-Cyclopropyl-1,2,4-oxadiazol-3-yl)-N-{(1*R*,6*S*)-2,2-difluoro-6-[4-(propan-2-yl)piperazin-1-yl]cyclohexyl}-4-methylpiperidine-1-carbothioamide



To a mixture of Reference example 14 (10.0 mg) (Material A), N,N-diisopropylamine (0.034 mL), and chloroform (0.2 mL)

was added thiophosgene (4.40 mg) at 0°C, and the mixture was stirred at the same temperature for 40 minutes. To the reaction mixture was added Reference example 8 (66.7 mg) (Material B) at 0°C, and the mixture was stirred at room temperature for one hour. The mixture was directly purified by amino silica gel column chromatography (eluate: hexane/ethyl acetate) to give the title compound (9.6 mg).
¹H-NMR (CDCl₃) δ: 1.02 (6H, d, J = 5.6 Hz), 1.14-1.27 (4H, m), 1.27-1.50 (2H, m), 1.50-1.91 (8H, m), 1.91-2.04 (1H, m), 2.08-2.24 (2H, m), 2.24-2.35 (2H, m), 2.35-2.55 (5H, m), 2.55-2.70 (2H, m), 2.79-3.00 (2H, m), 3.33 (1H, t, J = 11.2 Hz), 3.49 (1H, t, J = 11.2 Hz), 4.16 (1H, d, J = 12.8 Hz), 4.49 (1H, d, J = 12.8 Hz), 5.02-5.26 (1H, m), 5.42 (1H, d, J = 8.0 Hz).

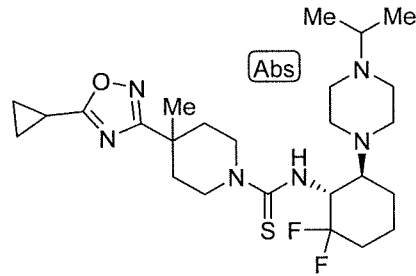
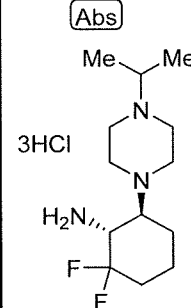
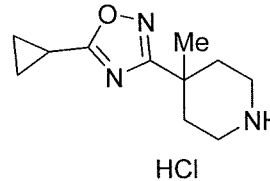
[0237]

Example 80:

4-(5-Cyclopropyl-1,2,4-oxadiazol-3-yl)-N-{(1R,6S)-2,2-difluoro-6-[4-(propan-2-yl)piperazin-1-yl]cyclohexyl}-4-methylpiperidine-1-carbothioamide

The compound of Example 80 shown in the table below was prepared in the same manner as Example 79, by using Reference example 15 corresponding to Material A in Example 79 and Reference example 8 corresponding to Material B in Example 79.

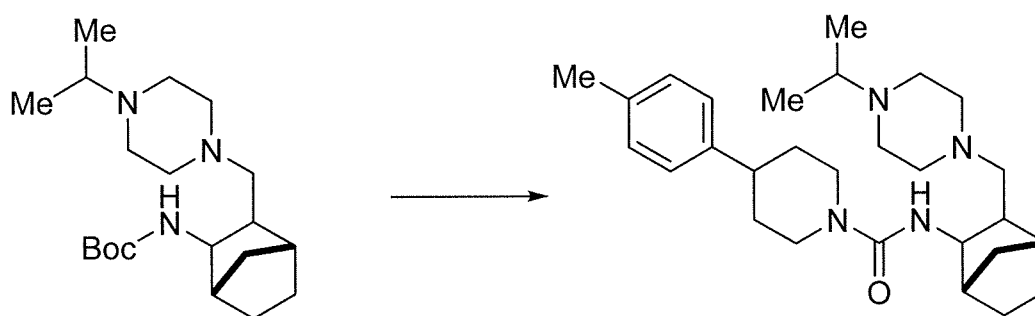
Example	Structure	Material A	Material B
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	Spectral data		
80		Reference example 15	Reference example 8
			
	¹ H-NMR (CDCl ₃) δ: 1.02 (6H, d, J = 5.6 Hz), 1.14-1.27 (4H, m), 1.27-1.50 (2H, m), 1.50-1.91 (8H, m), 1.91-2.04 (1H, m), 2.08-2.24 (2H, m), 2.24-2.35 (2H, m), 2.35-2.55 (5H, m), 2.55-2.70 (2H, m), 2.79-3.00 (2H, m), 3.33 (1H, t, J = 11.2 Hz), 3.49 (1H, t, J = 11.2 Hz), 4.16 (1H, d, J = 12.8 Hz), 4.49 (1H, d, J = 12.8 Hz), 5.02-5.26 (1H, m), 5.42 (1H, d, J = 8.0 Hz).		

[0238]

Example 81:

rac-4-(4-Methylphenyl)-N-[(1*S*,4*R*)-3-{[4-(propan-2-yl)piperazin-1-yl]methyl}bicyclo[2.2.1]heptan-2-yl]piperidine-1-carboxamide



To a solution of Reference example 40 (20 mg) in chloroform (0.5 mL) was added TFA (0.057 mL) at room temperature, and the mixture was stirred at the same temperature for one hour. The reaction solution was

concentrated *in vacuo*, and the obtained residue was purified by amino silica gel column chromatography (eluate: hexane/ethyl acetate). The obtained residue was dissolved in chloroform (0.284 mL). To the solution were added N,N-diisopropylethylamine (36.8 mg) and triphosgene (8.4 mg) at 0°C, and the mixture was stirred at the same temperature for one hour. Then, 4-(4-methylphenyl)piperidine (0.057 mL) was added to the reaction mixture, which was stirred at room temperature for one hour. The reaction mixture was directly purified by amino silica gel column chromatography (eluate: hexane/ethyl acetate) to give the title compound (8 mg).

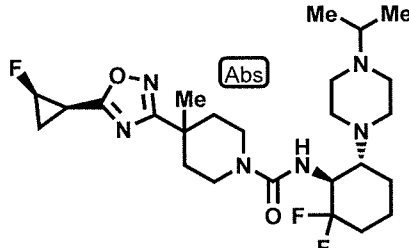
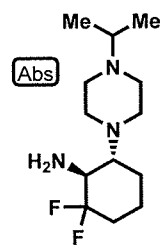
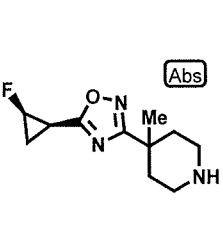
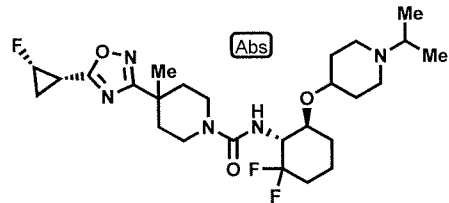
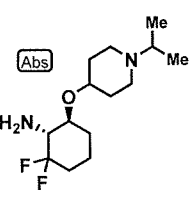
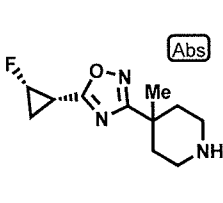
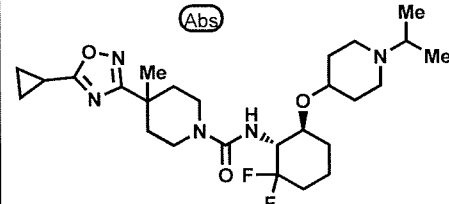
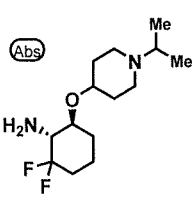
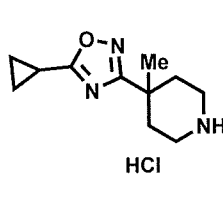
¹H-NMR (CDCl₃) δ: 1.24 (6H, d, J = 7.3 Hz), 1.31-1.49 (7H, m), 1.54-1.67 (4H, m), 1.84 (2H, m), 2.24 (1H, m), 2.32 (3H, s), 2.63 (2H, m), 2.80-2.99 (4H, m), 3.06-3.49 (8H, m), 4.05-4.14 (3H, m), 7.07-7.13 (4H, m).

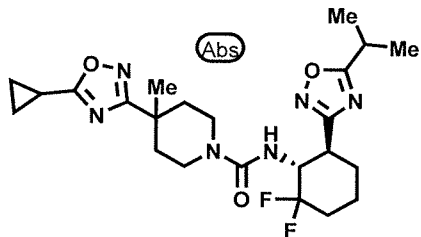
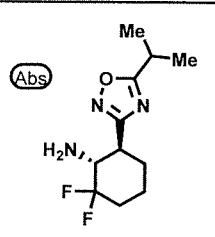
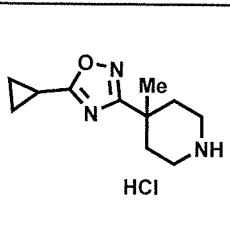
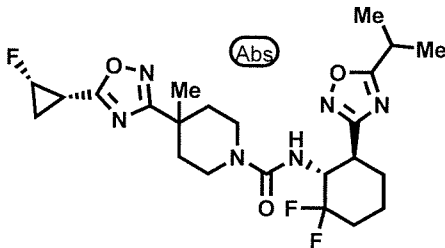
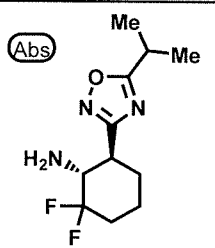
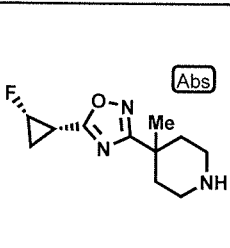
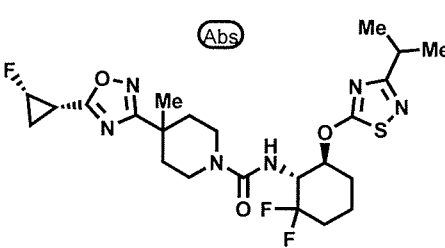
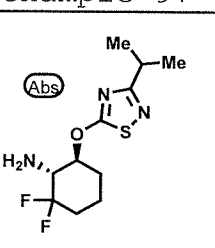
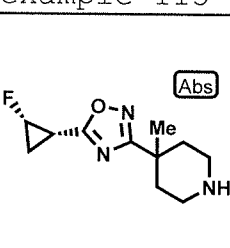
[0239]

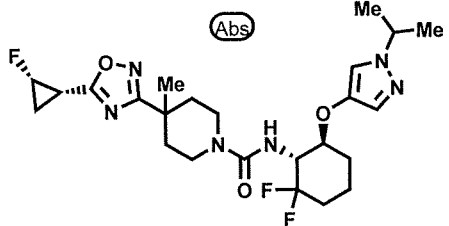
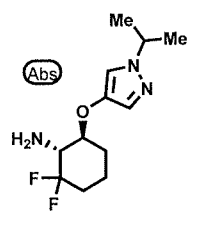
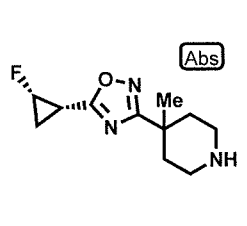
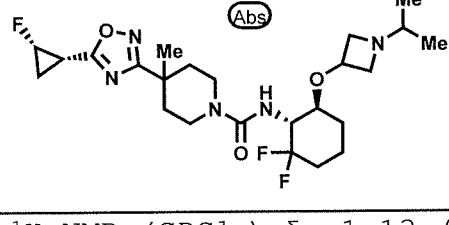
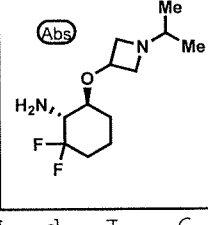
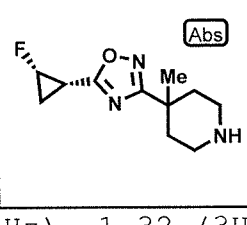
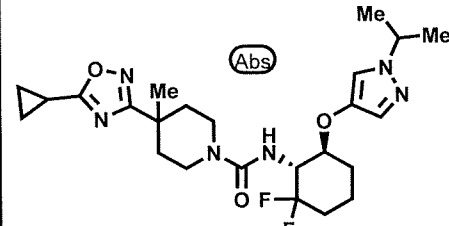
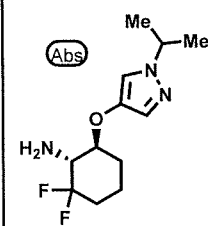
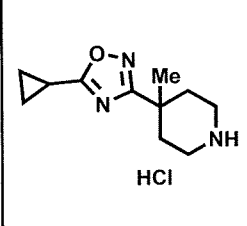
Examples 82 - 156:

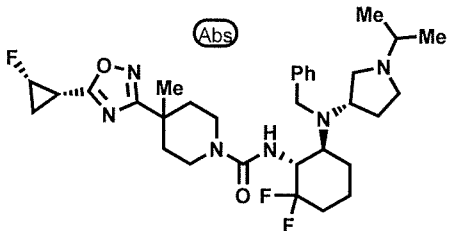
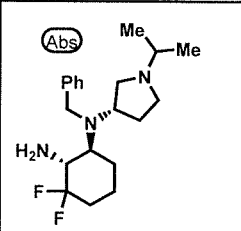
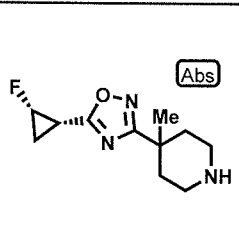
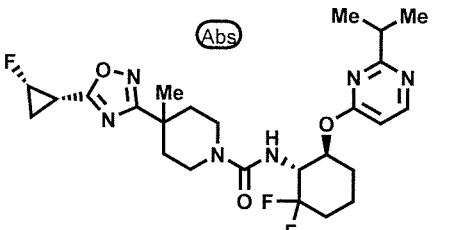
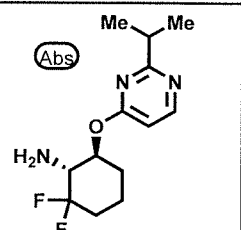
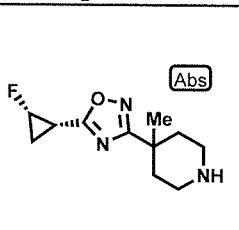
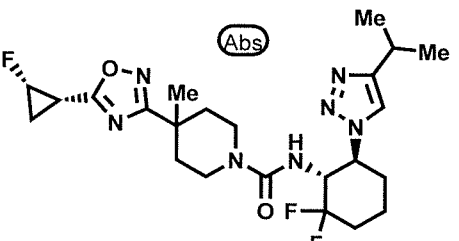
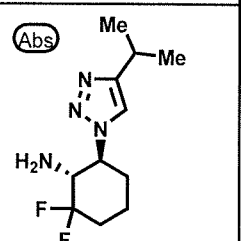
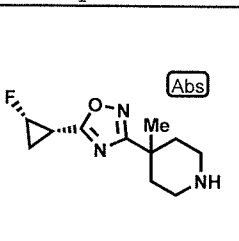
The compounds of Examples 82 to 156 shown in the table below were prepared in the same manner as Example 19, by using commercial compounds or Reference example compounds which correspond to Material A and Material B described in Example 19.

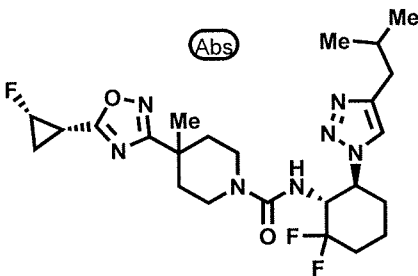
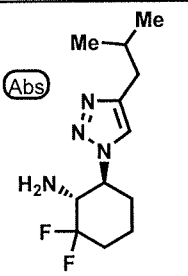
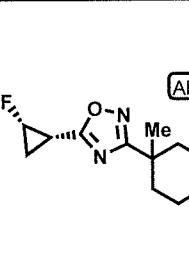
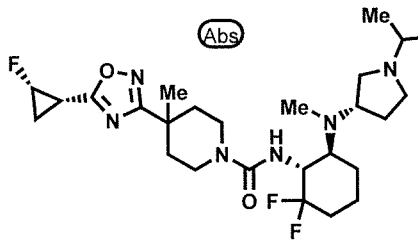
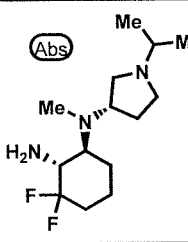
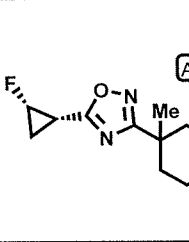
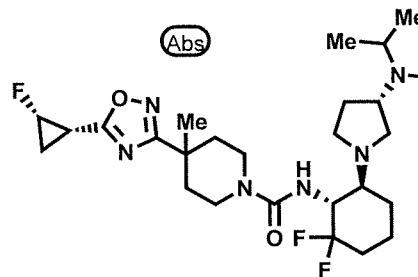
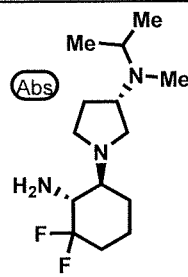
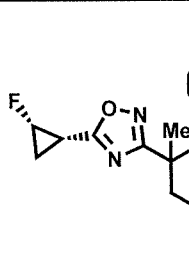
Example	Structure	Material A	Material B
	Spectral data		
82		Reference example 58	Reference example 116

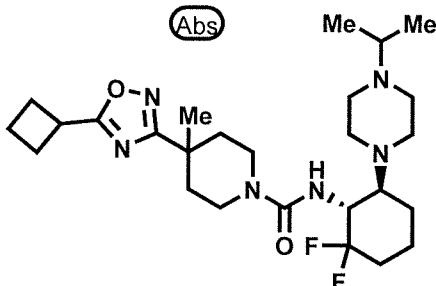
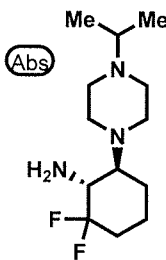
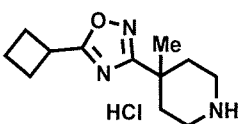
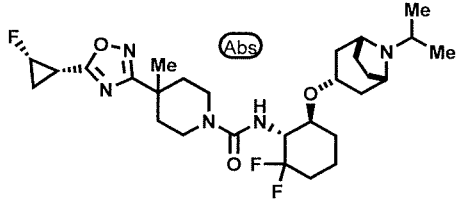
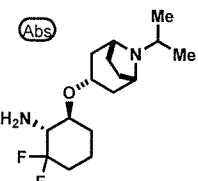
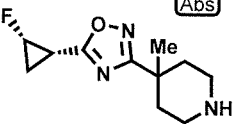
			
	¹ H-NMR (DMSO-d ₆) δ: 0.87 (6H, d, J = 6.4 Hz), 1.18-1.36 (2H, m), 1.26 (3H, s), 1.47-1.66 (3H, m), 1.66-1.88 (4H, m), 1.95-2.11 (3H, m), 2.17-2.40 (6H, m), 2.43-2.63 (5H, m), 2.95-3.19 (2H, m), 3.55-3.77 (2H, m), 3.98-4.18 (1H, m), 5.16 (1H, dddd, J = 65.0, 6.0, 6.0, 3.2 Hz), 5.88 (1H, d, J = 8.0 Hz).		
83		Reference example 96	Reference example 115
			
	¹ H-NMR (CDCl ₃) δ: 1.00 (5H, d, J = 6.4 Hz), 1.13 (1H, d, J = 6.4 Hz), 1.33 (3H, s), 1.38-1.85 (9H, m), 1.90-2.30 (8H, m), 2.32-2.41 (1H, m), 2.60-2.74 (4H, m), 3.03-3.15 (2H, m), 3.17-3.28 (1H, m), 3.33-3.44 (1H, m), 3.65-3.76 (2H, m), 4.13-4.30 (1H, m), 4.51 (1H, d, J = 9.2 Hz), 4.91 (1H, dddd, J = 63.6, 6.0, 6.0, 3.6 Hz).		
84		Reference example 96	Reference example 8
			
	¹ H-NMR (CDCl ₃) δ: 1.00 (6H, dd, J = 6.8, 1.2 Hz), 1.17-1.25 (4H, m), 1.30 (3H, s), 1.38-1.46 (2H, m), 1.50-1.69 (4H, m), 1.69-1.85 (4H, m), 2.00-2.30 (7H, m), 2.60-2.74 (3H, m), 3.03-3.15 (2H, m), 3.17-3.28 (1H, m), 3.33-3.42 (1H, m), 3.64-3.74 (2H, m), 4.13-4.30 (1H, m), 4.50 (1H, d, J = 9.2 Hz).		
85		Reference example 91	Reference example 8

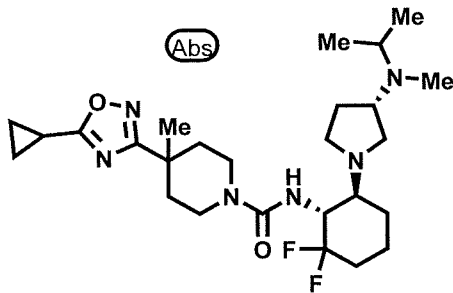
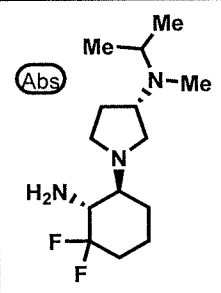
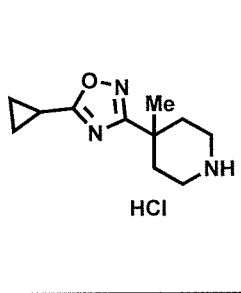
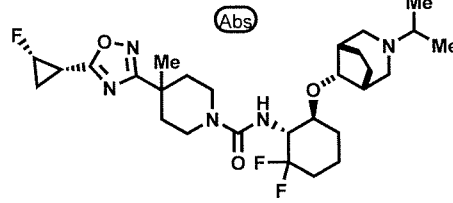
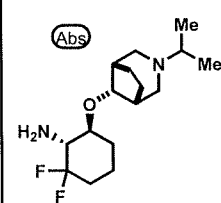
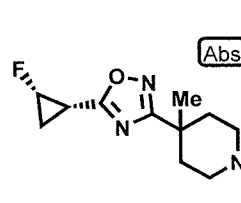
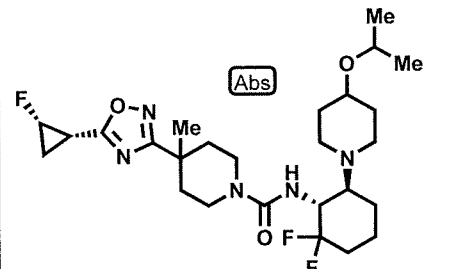
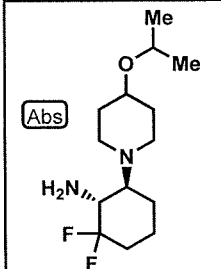
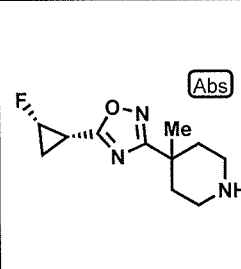
			
	¹ H-NMR (CDCl ₃) δ: 1.16-1.23 (4H, m), 1.27 (3H, s), 1.36 (6H, d, J = 6.8 Hz), 1.44-1.58 (2H, m), 1.58-1.75 (1H, m), 1.80-2.06 (4H, m), 2.09-2.23 (3H, m), 2.23-2.35 (1H, m), 2.88-3.08 (3H, m), 3.11-3.25 (1H, m), 3.48-3.67 (2H, m), 4.41-4.57 (1H, m), 4.57-4.67 (1H, m).		
86		Reference example 91	Reference example 115
			
	¹ H-NMR (CDCl ₃) δ: 1.30 (3H, s), 1.35 (6H, d, J = 6.4 Hz), 1.42-1.62 (3H, m), 1.62-1.75 (1H, m), 1.80-2.07 (5H, m), 2.11-2.22 (2H, m), 2.22-2.41 (2H, m), 2.89-3.08 (3H, m), 3.11-3.24 (1H, m), 3.50-3.66 (2H, m), 4.41-4.56 (1H, m), 4.58-4.67 (1H, m), 4.93 (1H, dddd, J = 63.6, 6.0, 6.0, 3.6 Hz).		
87		Reference example 97	Reference example 115
			
	¹ H-NMR (CDCl ₃) δ: 1.25 (3H, s), 1.26-1.37 (1H, m), 1.30 (3H, d, J = 6.4 Hz), 1.31 (3H, d, J = 6.4 Hz), 1.39-1.74 (4H, m), 1.74-2.01 (3H, m), 2.10-2.19 (2H, m), 2.19-2.30 (1H, m), 2.30-2.39 (2H, m), 2.86 (1H, ddd, J = 14.0, 11.0, 3.1 Hz), 2.96-3.08 (2H, m), 3.41-3.50 (1H, m), 3.63-3.72 (1H, m), 4.46-4.60 (1H, m), 4.78-4.86 (1H, m), 4.41 (1H, dddd, J = 64.0, 6.0, 6.0, 3.6 Hz), 5.06-5.15 (1H, m).		
88		Reference example 98	Reference example 115

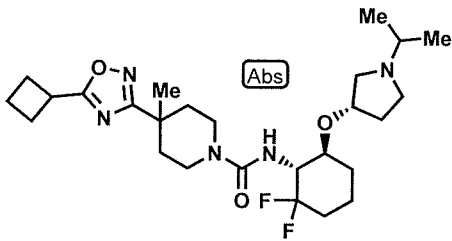
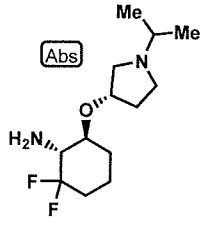
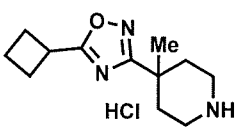
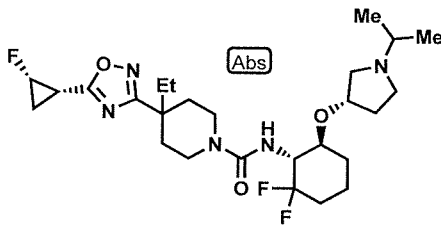
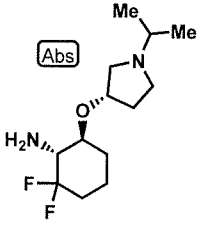
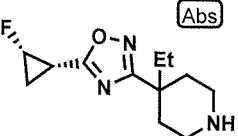
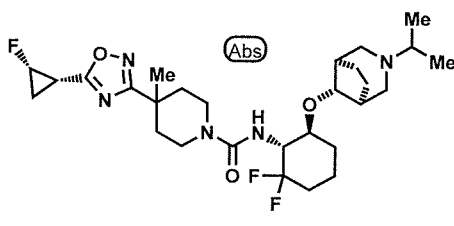
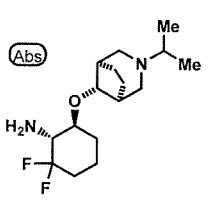
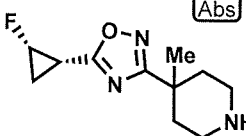
			
	¹ H-NMR (CDCl ₃) δ: 1.30 (3H, s), 1.41-1.89 (14H, m), 1.90-2.02 (1H, m), 2.13-2.30 (4H, m), 2.31-2.41 (1H, m), 2.99-3.13 (2H, m), 3.60-3.78 (2H, m), 4.32-4.50 (2H, m), 4.63 (1H, d, J = 9.2 Hz), 4.91 (1H, dddd, J = 63.6, 6.0, 6.0, 3.6 Hz), 7.17 (1H, s), 7.21 (1H, s).		
89		Reference example 99	Reference example 115
			
	¹ H-NMR (CDCl ₃) δ: 1.13 (6H, d, J = 6.0 Hz), 1.32 (3H, s), 1.42-1.83 (5H, m), 1.87-2.04 (2H, m), 2.06-2.17 (2H, m), 2.18-2.28 (4H, m), 2.31-2.41 (1H, m), 2.60-2.73 (1H, m), 2.88-3.17 (5H, m), 3.30-3.80 (6H, m), 4.80-5.04 (1H, m).		
90		Reference example 98	Reference example 8
			 HCl
	¹ H-NMR (CDCl ₃) δ: 1.17-1.23 (4H, m), 1.27 (3H, s), 1.44 (3H, d, J = 6.7 Hz), 1.45 (3H, d, J = 6.7 Hz), 1.46-1.65 (4H, m), 1.69-1.91 (2H, m), 2.12-2.30 (5H, m), 2.99-3.12 (2H, m), 3.59-3.69 (2H, m), 3.69-3.77 (1H, m), 4.31-4.50 (2H, m), 4.63 (1H, d, J = 9.2 Hz), 7.16 (1H, s), 7.20 (1H, s).		
91		Reference example 89	Reference example 115

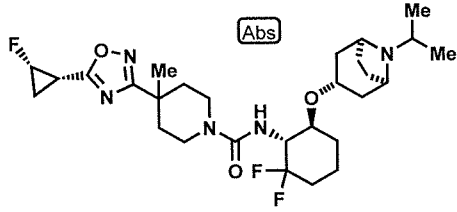
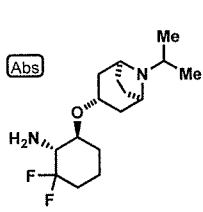
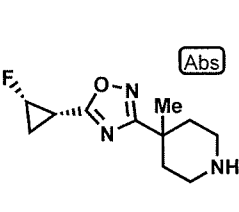
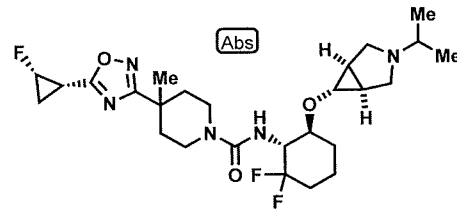
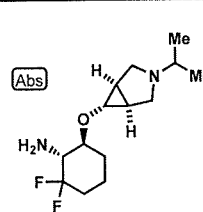
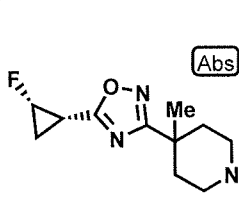
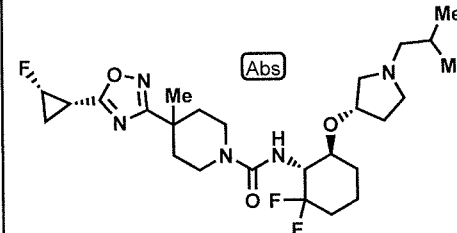
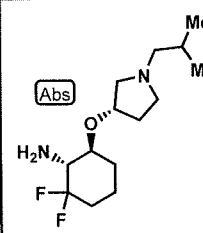
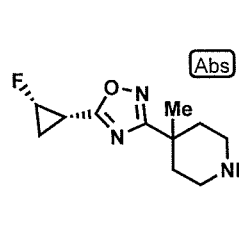
				
	¹ H-NMR (CDCl ₃) δ: 1.09-1.43 (11H, m), 1.43-1.56 (2H, m), 1.56-1.76 (3H, m), 1.76-2.24 (7H, m), 2.24-2.48 (5H, m), 2.48-2.75 (1H, m), 2.75-3.06 (1H, m), 3.06-3.45 (4H, m), 3.45-3.71 (1H, m), 3.71-3.87 (1H, m), 3.87-4.13 (1H, m), 4.13-4.50 (1H, m), 4.94 (1H, dddd, J = 64.4, 6.0, 6.0, 4.0 Hz), 7.13-7.44 (5H, m), 11.97 (1H, brs).			
92		Reference example 119	Reference example 115	
				
	¹ H-NMR (CDCl ₃) δ: 1.18-1.29 (1H, m), 1.22 (3H, s), 1.30 (3H, d, J = 6.4 Hz), 1.31 (3H, d, J = 6.4 Hz), 1.40-1.53 (3H, m), 1.58-1.71 (1H, m), 1.78-2.03 (3H, m), 2.05-2.12 (2H, m), 2.17-2.28 (1H, m), 2.30-2.40 (2H, m), 2.81 (1H, ddd, J = 13.6, 10.8, 2.9 Hz), 2.93-3.06 (2H, m), 3.37-3.47 (1H, m), 3.54-3.61 (1H, m), 4.41-4.54 (1H, m), 4.74 (1H, d, J = 9.2 Hz), 4.91 (1H, dddd, J = 63.6, 6.0, 6.0, 3.6 Hz), 5.40-5.48 (1H, m), 6.53 (1H, d, J = 5.5 Hz), 8.35 (1H, d, J = 5.5 Hz).			
93		Reference example 92	Reference example 115	
				
	¹ H-NMR (CDCl ₃) δ: 1.24-1.30 (9H, m), 1.35-1.53 (3H, m), 1.65-2.04 (6H, m), 2.07-2.20 (2H, m), 2.27-2.40 (2H, m), 2.83 (1H, ddd, J = 14.0, 11.6, 3.2 Hz), 2.95-3.10 (2H, m), 3.40-3.49 (1H, m), 3.57-3.67 (1H, m), 4.60-4.71 (3H, m), 4.90 (1H, dddd, J = 64.0, 6.0,			

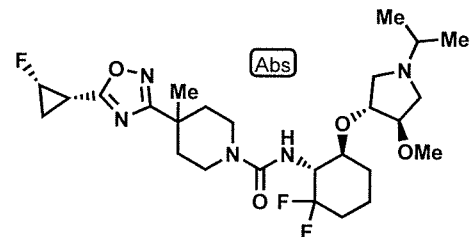
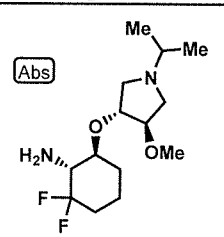
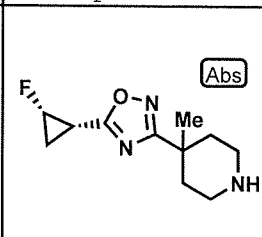
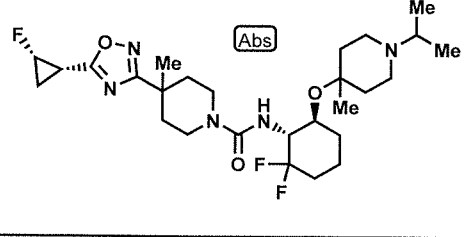
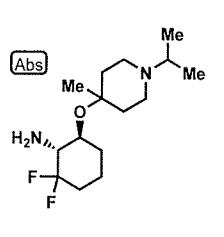
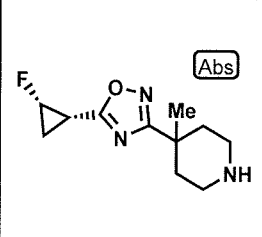
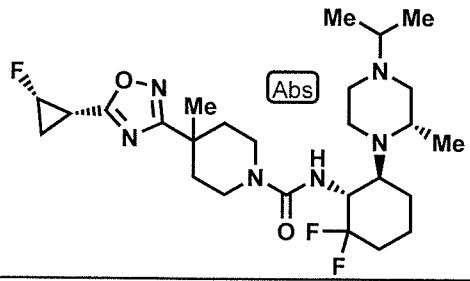
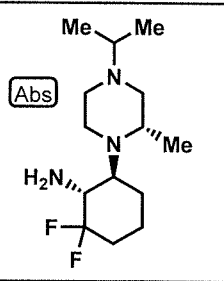
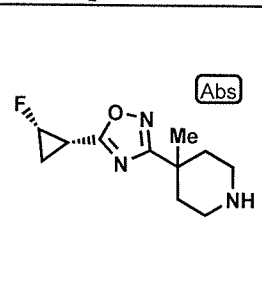
	6.0, 4.0 Hz), 7.42 (1H, s).		
94		Reference example 93 	Reference example 115 
	¹ H-NMR (CDCl ₃) δ: 0.89 (6H, t, J = 6.8 Hz), 1.27 (3H, s), 1.36-1.53 (3H, m), 1.64-2.04 (6H, m), 2.07-2.20 (2H, m), 2.27-2.40 (3H, m), 2.48-2.63 (2H, m), 2.84 (1H, ddd, J = 14.0, 11.2, 3.2 Hz), 2.98 (1H, ddd, J = 14.0, 11.2, 3.2 Hz), 3.40-3.50 (1H, m), 3.54-3.65 (1H, m), 4.60-4.76 (3H, m), 4.90 (1H, dddd, J = 64.0, 6.0, 6.0, 3.6 Hz), 7.43 (1H, s).		
95		Reference example 81 	Reference example 115 
	¹ H-NMR (CDCl ₃) δ: 1.00-1.11 (6H, m), 1.15-1.54 (7H, m), 1.54-1.75 (4H, m), 1.75-2.07 (5H, m), 2.15 (3H, s), 2.20-2.30 (3H, m), 2.30-2.42 (2H, m), 2.42-2.57 (1H, m), 2.59-2.70 (1H, m), 2.73-2.85 (1H, m), 2.90 (1H, t, J = 8.0 Hz), 3.02-3.18 (2H, m), 3.23 (1H, tt, J = 15.2, 7.2 Hz), 3.63-3.79 (2H, m), 4.07-4.22 (1H, m), 4.54 (1H, d, J = 7.6 Hz), 4.91 (1H, dddd, J = 63.6, 6.0, 6.0, 3.6 Hz).		
96		Reference example 59 	Reference example 115 
	¹ H-NMR (CDCl ₃) δ: 0.92-1.02 (6H, m), 1.20-1.54 (6H, m), 1.54-2.03 (8H, m), 2.08 (3H, s), 2.10-2.27 (3H, m), 2.27-2.40 (3H, m), 2.48-2.63 (2H, m), 2.84 (1H, ddd, J = 14.0, 11.2, 3.2 Hz), 2.98 (1H, ddd, J = 14.0, 11.2, 3.2 Hz), 3.40-3.50 (1H, m), 3.54-3.65 (1H, m), 4.60-4.76 (3H, m), 4.90 (1H, dddd, J = 64.0, 6.0, 6.0, 3.6 Hz), 7.43 (1H, s).		

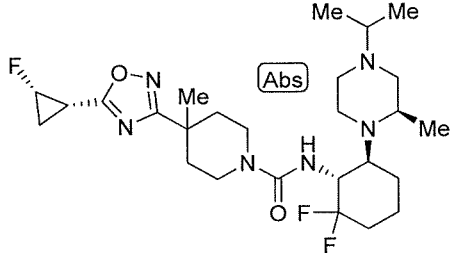
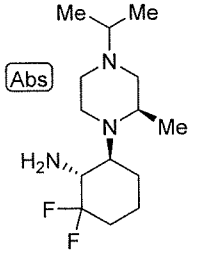
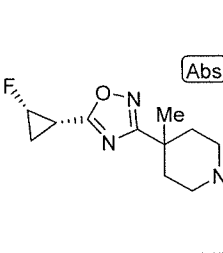
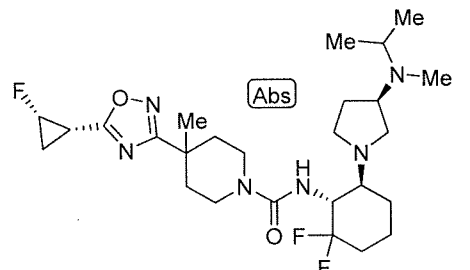
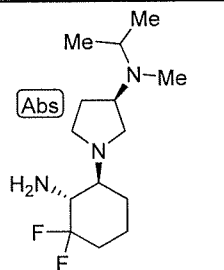
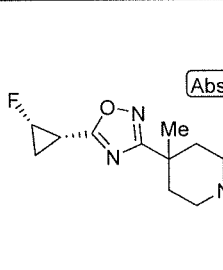
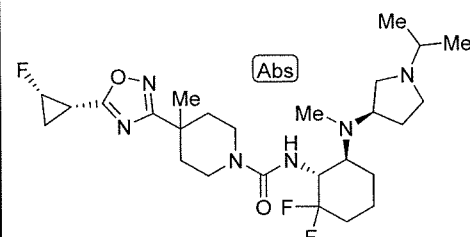
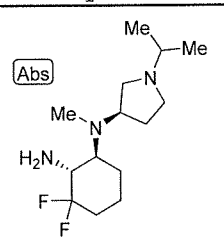
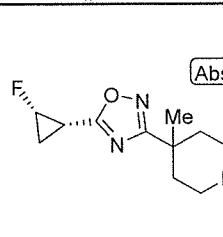
	m), 2.32-2.48 (2H, m), 2.60-2.70 (2H, m), 2.76-3.23 (6H, m), 3.62-3.77 (2H, m), 4.07-4.22 (1H, m), 4.53 (1H, d, J = 8.0 Hz), 4.91 (1H, dddd, J = 64.0 6.4, 6.4, 3.6 Hz).		
97		Reference example 18	Reference example 117
			
	¹ H-NMR (CDCl ₃) δ: 1.00 (6H, d, J = 6.4 Hz), 1.22-1.48 (2H, m), 1.34 (3H, s), 1.49-1.60 (1H, m), 1.61-1.75 (2H, m), 1.75-1.87 (1H, m), 1.87-1.98 (1H, m), 1.98-2.22 (3H, m), 2.22-2.33 (2H, m), 2.33-2.54 (11H, m), 2.54-2.64 (1H, m), 2.68-2.81 (2H, m), 3.14 (2H, dddd, J = 32.4, 14.0, 10.8, 3.2 Hz), 3.62-3.84 (3H, m), 4.16 (1H, dddd, J = 23.6, 11.2, 8.0, 3.6 Hz), 4.54 (1H, d, J = 8.0 Hz).		
98		Reference example 100	Reference example 115
			
	¹ H-NMR (CDCl ₃) δ: 1.00-1.11 (6H, m), 1.33 (3H, s), 1.36-1.84 (13H, m), 1.85-2.07 (4H, m), 2.07-2.20 (1H, m), 2.22-2.31 (2H, m), 2.31-2.41 (1H, m), 2.90 (1H, sep, J = 6.4 Hz), 3.03-3.26 (3H, m), 3.42-3.52 (2H, m), 3.59- 3.78 (3H, m), 4.10-4.24 (1H, m), 4.50 (1H, d, J = 9.2 Hz), 4.91 (1H, dddd, J = 63.6, 6.0, 6.0, 3.6 Hz).		
99		Reference example 59	Reference example 8

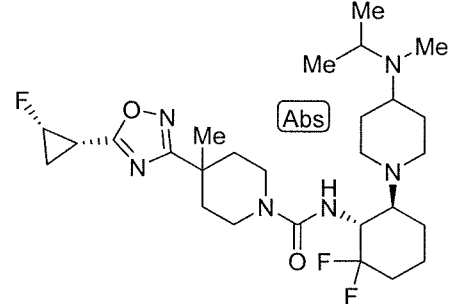
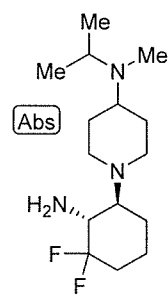
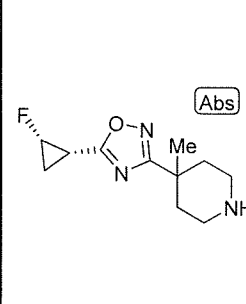
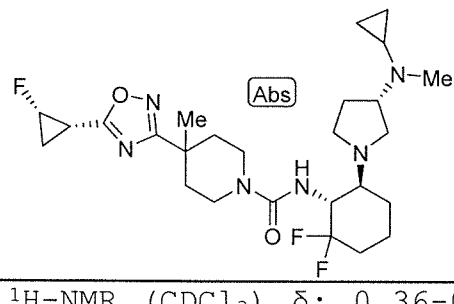
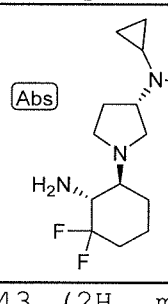
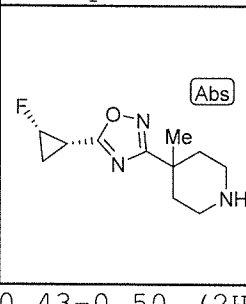
				
	¹ H-NMR (CDCl ₃) δ: 0.92-1.00 (6H, m), 1.13 (2H, d, J = 6.0 Hz), 1.17-1.24 (4H, m), 1.30 (3H, s), 1.32-1.50 (2H, m), 1.56-1.70 (2H, m), 1.70-1.86 (1H, m), 1.86-1.97 (2H, m), 2.08 (3H, s), 2.11-2.26 (4H, m), 2.44 (1H, t, J = 7.6 Hz), 2.60-2.70 (2H, m), 2.76-2.86 (1H, m), 2.86-2.92 (2H, m), 2.92-3.17 (3H, m), 3.60-3.77 (2H, m), 4.07-4.23 (1H, m), 4.53 (1H, d, J = 7.6 Hz).			
100		Reference example 101	Reference example 115	
				
	¹ H-NMR (CDCl ₃) δ: 0.91-0.97 (6H, m), 1.32 (3H, s), 1.37-1.86 (11H, m), 1.90-2.04 (3H, m), 2.07-2.21 (2H, m), 2.21-2.41 (5H, m), 2.49 (1H, sep, J = 6.0 Hz), 2.62 (2H, dd, J = 15.6, 10.8 Hz), 3.02-3.16 (2H, m), 3.21-3.32 (1H, m), 3.59 (1H, t, J = 4.4 Hz), 3.63-3.78 (2H, m), 4.22-4.37 (1H, m), 4.56 (1H, d, J = 8.8 Hz), 4.91 (1H, dddd, J = 63.6, 6.0, 6.0, 4.0 Hz).			
101		Reference example 60	Reference example 115	
				
	¹ H-NMR (CDCl ₃) δ: 1.11 (6H, d, J = 6.4 Hz), 1.20-1.54 (8H, m), 1.60-1.74 (2H, m), 1.74-1.85 (4H, m), 1.85-2.04 (2H, m), 2.09-2.20 (2H, m), 2.21-2.30 (2H, m), 2.32-2.42 (1H, m), 2.46-2.63 (3H, m), 2.76-2.85 (1H, m), 3.01-3.17 (2H, m), 3.28 (1H, sep, J = 4.4 Hz),			

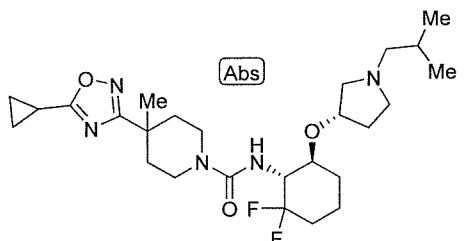
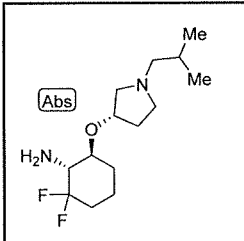
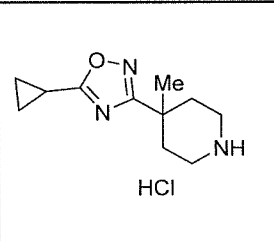
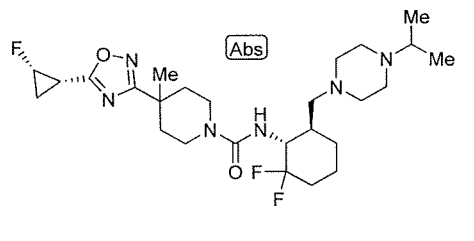
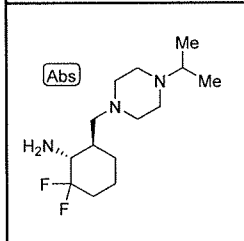
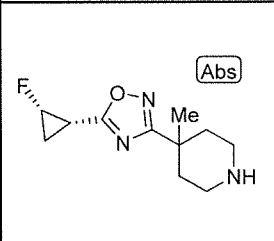
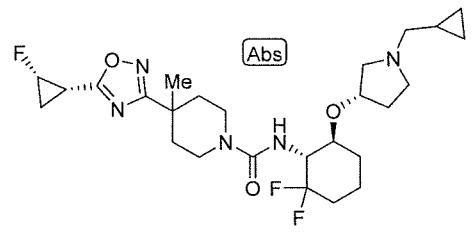
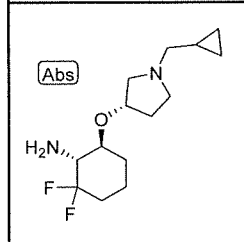
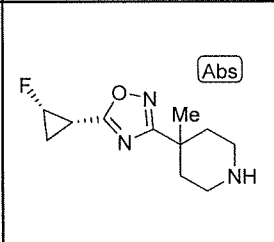
	3.61-3.82 (3H, m), 4.08-4.23 (1H, m), 4.56 (1H, d, J = 7.2 Hz), 4.92 (1H, dddd, J = 64.0, 6.0, 6.0, 3.6 Hz).		
102		Reference example 37	Reference example 117
			
	¹ H-NMR (CDCl ₃) δ: 1.05 (3H, d, J = 6.0 Hz), 1.06 (3H, d, J = 6.0 Hz), 1.33 (3H, s), 1.36-1.51 (2H, m), 1.59-1.86 (5H, m), 1.92-2.12 (5H, m), 2.69 (2H, d, J = 13.2 Hz), 2.31-2.40 (2H, m), 2.40-2.55 (5H, m), 2.61-2.73 (1H, m), 2.95-3.27 (4H, m), 3.62-3.80 (3H, m), 4.06-4.30 (2H, m), 4.54 (1H, d, J = 9.2 Hz).		
103		Reference example 37	Reference example 118
			
	¹ H-NMR (CDCl ₃) δ: 0.71 (3H, t, J = 7.2 Hz), 1.05 (3H, d, J = 6.0 Hz), 1.06 (3H, d, J = 6.0 Hz), 1.32-1.54 (3H, m), 1.54-1.87 (7H, m), 1.91-2.04 (2H, m), 2.04-2.21 (2H, m), 2.30 (2H, d, J = 18.0 Hz), 2.33-2.42 (3H, m), 2.47 (1H, dd, J = 16.4, 8.0 Hz), 2.60-2.76 (1H, m), 2.88-3.11 (3H, m), 3.14-3.26 (1H, m), 3.79 (2H, d, J = 13.6 Hz), 4.06-4.29 (2H, m), 4.53 (1H, d, J = 9.2 Hz), 4.92 (1H, dddd, J = 63.6, 6.0, 6.0, 3.6 Hz).		
104		Reference example 102	Reference example 115
			
	¹ H-NMR (CDCl ₃) δ: 0.95 (6H, d, J = 6.1 Hz), 1.29-1.87 (12H, m), 1.33 (3H, s), 1.90-2.04 (1H, m), 2.04-2.31		

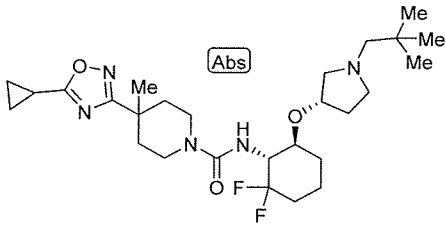
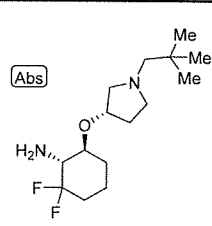
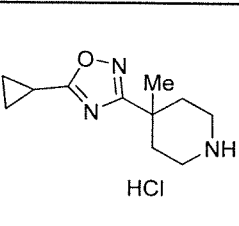
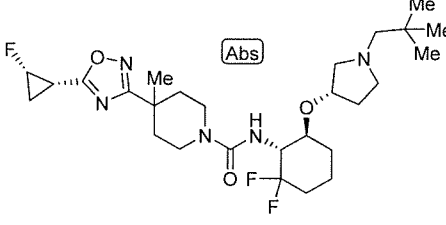
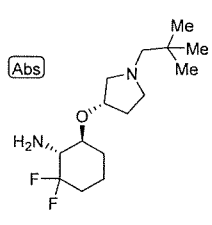
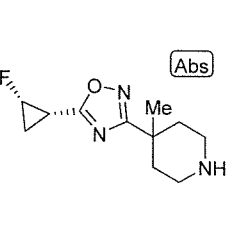
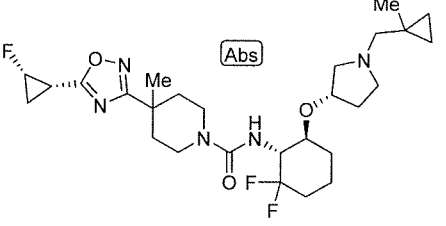
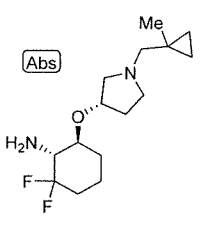
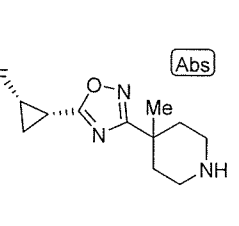
	(8H, m), 2.31-2.43 (1H, m), 2.52-2.67 (2H, m), 3.00-3.31 (3H, m), 3.35-3.43 (1H, m), 3.63-3.79 (2H, m), 4.12-4.29 (1H, m), 4.49 (1H, d, J = 9.2 Hz), 4.80-5.02 (1H, m).		
105		Reference example 103	Reference example 115
			
	¹ H-NMR (CDCl ₃) δ: 1.12 (6H, br s), 1.29-1.42 (2H, m), 1.33 (3H, s), 1.42-1.53 (2H, m), 1.54-1.85 (8H, m), 1.90-2.21 (6H, m), 2.21-2.30 (2H, m), 2.32-2.41 (1H, m), 2.59-2.71 (1H, m), 3.03-3.20 (3H, m), 3.25-3.60 (2H, m), 3.61-3.74 (3H, m), 4.17-4.30 (1H, m), 4.56 (1H, d, J = 9.2 Hz), 4.91 (1H, dddd, J = 63.6, 6.0, 6.0, 3.6 Hz).		
106		Reference example 104	Reference example 115
			
	¹ H-NMR (CDCl ₃) δ: 1.01 (6H, d, J = 5.5 Hz), 1.24-1.84 (8H, m), 1.33 (3H, s), 1.90-2.03 (1H, m), 2.07-2.30 (5H, m), 2.30-2.47 (4H, m), 2.96-3.17 (4H, m), 3.22-3.30 (1H, m), 3.49-3.57 (1H, m), 3.66-3.75 (2H, m), 4.10-4.24 (1H, m), 4.56 (1H, d, J = 8.5 Hz), 4.91 (1H, dddd, J = 63.6, 6.0, 6.0, 3.6 Hz).		
107		Reference example 105	Reference example 115
			
	¹ H-NMR (CDCl ₃) δ: 0.92 (3H, d, J = 4.3 Hz), 0.94 (3H, d, J = 4.3 Hz), 1.34 (3H, s), 1.36-1.54 (3H, m), 1.58-1.84 (7H, m), 1.91-2.21 (4H, m), 2.22-2.46 (6H, m).		

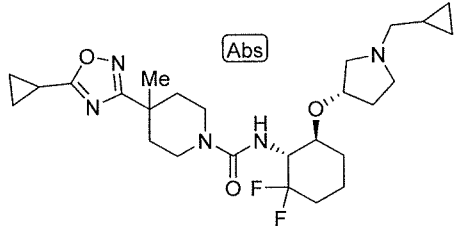
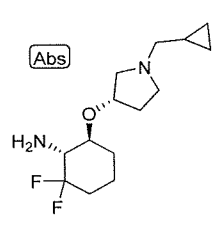
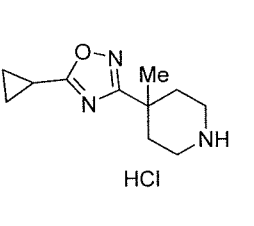
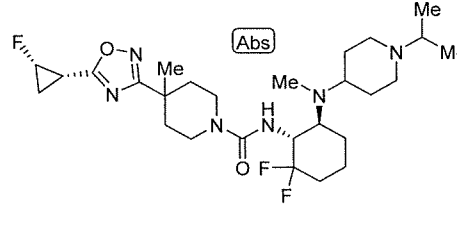
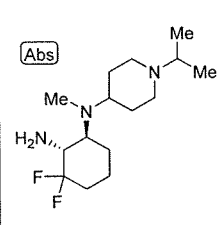
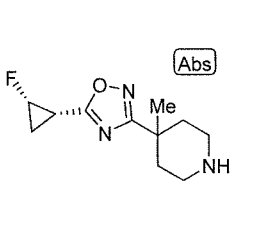
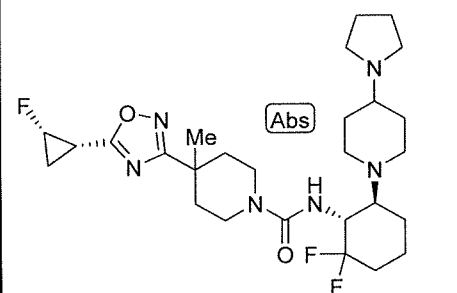
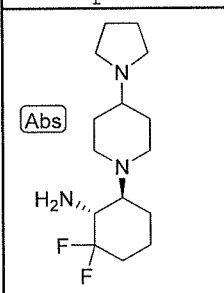
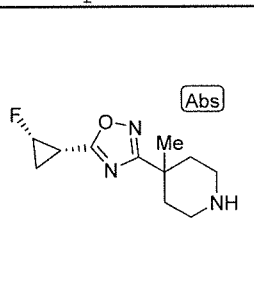
	m), 2.46-2.58 (1H, m), 2.97-3.24 (4H, m), 3.65-3.74 (2H, m), 4.15-4.25 (2H, m), 4.58 (1H, d, J = 9.2 Hz), 4.92 (1H, dddd, J = 63.6, 6.0, 6.0, 3.6 Hz).		
108		Reference example 106	Reference example 115
			
	¹ H-NMR (CDCl ₃) δ: 1.10 (6H, br s), 1.34 (3H, s), 1.39-1.54 (3H, m), 1.54-1.85 (6H, m), 1.91-2.04 (1H, m), 2.04-2.21 (2H, m), 2.21-2.31 (2H, m), 2.32-2.58 (2H, m), 2.62-2.80 (1H, m), 3.05-3.19 (3H, m), 3.24-3.35 (1H, m), 3.29 (3H, s), 3.61-3.79 (3H, m), 3.92-4.01 (1H, m), 4.15-4.30 (1H, m), 4.65 (1H, d, J = 9.2 Hz), 4.92 (1H, dddd, J = 63.6, 6.0, 6.0, 3.6 Hz).		
109		Reference example 107	Reference example 115
			
	¹ H-NMR (CDCl ₃) δ: 0.94-1.29 (8H, m), 1.33 (3H, s), 1.38-1.86 (14H, m), 1.89-2.18 (2H, m), 2.18-2.31 (2H, m), 2.31-2.75 (4H, m), 2.98-3.51 (4H, m), 3.57-3.79 (2H, m), 4.08-4.26 (1H, m), 4.51 (1H, d, J = 8.4 Hz), 4.91 (1H, dddd, J = 63.6, 6.4, 6.4, 4.0 Hz).		
110		Reference example 61	Reference example 115
			
	¹ H-NMR (CDCl ₃) δ: 0.93-1.04 (9H, m), 1.23-1.53 (6H, m), 1.61-1.75 (2H, m), 1.75-1.87 (4H, m), 1.90-2.04 (2H, m), 2.10-2.22 (1H, m), 2.22-2.30 (2H, m), 2.30-2.41 (2H, m), 2.54 (1H, sep, J = 6.4 Hz), 2.62-2.81		

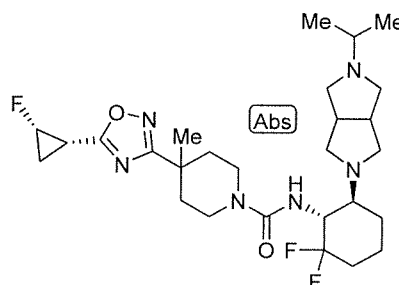
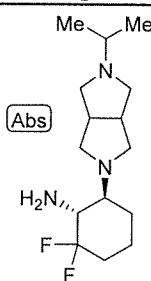
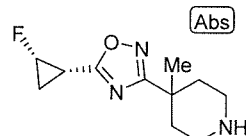
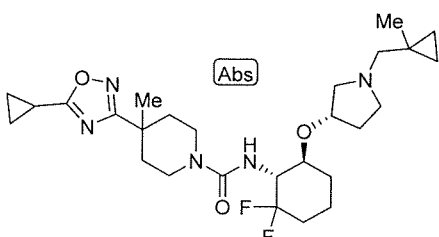
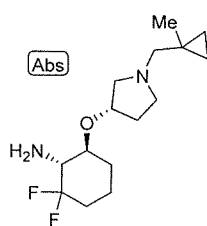
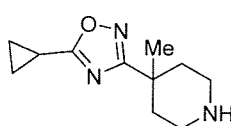
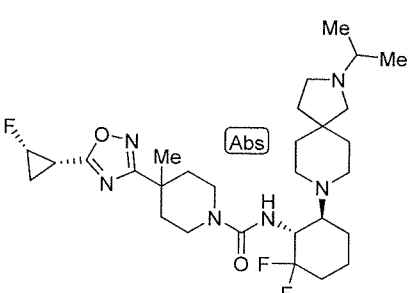
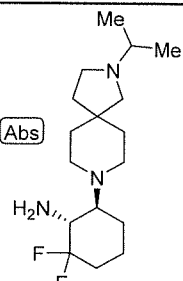
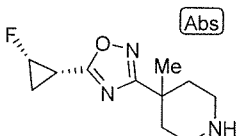
	(4H, m), 2.88 (1H, t, J = 11.0 Hz), 3.02-3.12 (1H, m), 3.12-3.22 (1H, m), 3.62-3.72 (1H, m), 3.74-3.84 (1H, m), 4.10-4.24 (1H, m), 4.48 (1H, d, J = 7.4 Hz), 4.91 (1H, dddd, J =63.6, 6.0, 6.0, 3.6 Hz).		
111		Reference example 62	Reference example 115
			
	¹ H-NMR (CDCl ₃) δ: 0.92-1.00 (6H, m), 1.09 (3H, d, J = 6.0 Hz), 1.33 (3H, s), 1.42-1.54 (3H, m), 1.60-1.89 (5H, m), 1.90-2.22 (3H, m), 2.22-2.42 (4H, m), 2.42-2.67 (4H, m), 2.68-2.79 (2H, m), 2.83-2.94 (1H, m), 3.03-3.18 (2H, m), 3.64-3.77 (2H, m), 4.10-4.27 (1H, m), 4.53 (1H, d, J = 8.4 Hz), 4.91 (1H, dddd, J =64.0, 6.0, 6.0, 3.6 Hz).		
112		Reference example 82	Reference example 115
			
	¹ H-NMR (CDCl ₃) δ: 0.92-1.02 (6H, m), 1.33 (3H, s), 1.35-1.53 (3H, m), 1.54-1.85 (5H, m), 1.86-2.04 (3H, m), 2.08 (3H, s), 2.10-2.20 (1H, m), 2.20-2.28 (2H, m), 2.31-2.42 (1H, m), 2.56-2.68 (2H, m), 2.70-2.80 (3H, m), 2.85-2.97 (1H, m), 3.02-3.16 (3H, m), 3.66-3.77 (2H, m), 4.05-4.20 (1H, m), 4.59 (1H, d, J = 7.2 Hz), 4.92 (1H, dddd, J =64.0, 6.0, 6.0, 4.0 Hz).		
113		Reference example 83	Reference example 115
			

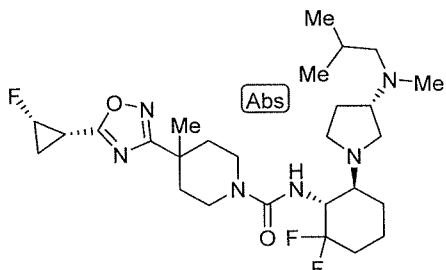
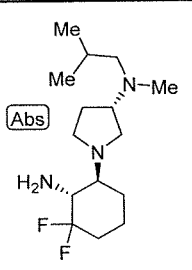
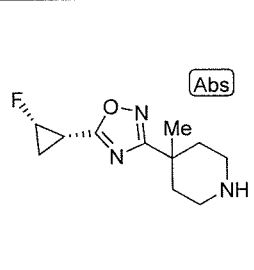
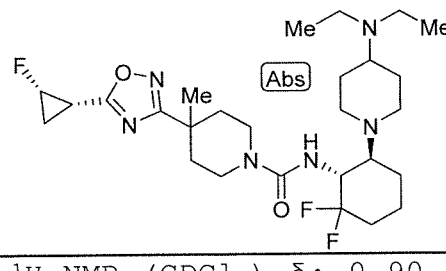
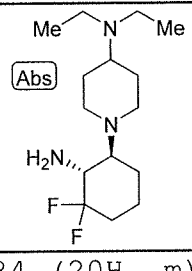
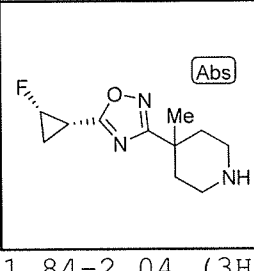
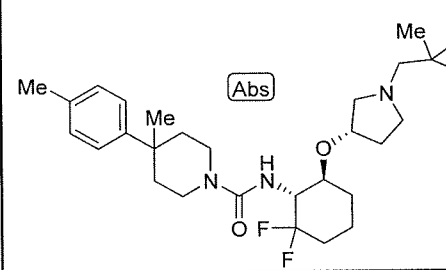
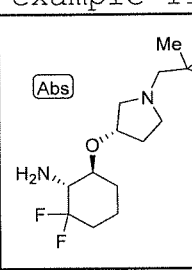
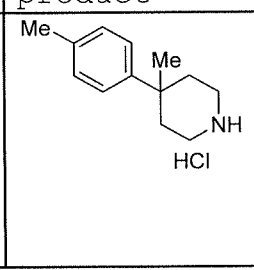
	¹ H-NMR (CDCl ₃) δ: 1.02-1.12 (6H, m), 1.30-1.54 (6H, m), 1.58-1.89 (6H, m), 1.89-2.04 (2H, m), 2.09-2.29 (7H, m), 2.29-2.41 (2H, m), 2.42-2.52 (1H, m), 2.52-2.62 (1H, m), 2.72-2.87 (2H, m), 3.03-3.18 (2H, m), 3.23 (1H, quint, J = 7.6 Hz), 3.63- 3.78 (2H, m), 4.07-4.22 (1H, m), 4.55 (1H, d, J = 7.2 Hz), 4.91 (1H, dddd, J = 64.0, 6.0, 6.0, 3.6 Hz).		
114		Reference example 84	Reference example 115
			
	¹ H-NMR (CDCl ₃) δ: 0.93-1.05 (6H, m), 1.19-1.30 (2H, m), 1.33 (3H, s), 1.37-1.53 (3H, m), 1.60-1.84 (6H, m), 1.85-2.04 (2H, m), 2.05-2.21 (5H, m), 2.21-2.30 (2H, m), 2.30-2.42 (2H, m), 2.46-2.58 (2H, m), 2.61-2.69 (1H, m), 2.76-2.86 (1H, m), 2.91-3.03 (1H, m), 3.03-3.17 (2H, m), 3.68-3.80 (2H, m), 4.07-4.22 (1H, m), 4.55 (1H, d, J = 7.2 Hz), 4.91 (1H, dddd, J = 64.0, 6.0, 6.0, 3.6 Hz).		
115		Reference example 85	Reference example 115
			
	¹ H-NMR (CDCl ₃) δ: 0.36-0.43 (2H, m), 0.43-0.50 (2H, m), 1.33 (3H, s), 1.34-1.53 (3H, m), 1.55-1.77 (5H, m), 1.77-1.86 (1H, m), 1.86-2.04 (3H, m), 2.10-2.30 (6H, m), 2.31-2.42 (1H, m), 2.52-2.73 (3H, m), 2.81 (1H, td, J = 8.4, 4.4 Hz), 2.89 (1H, t, J = 7.6 Hz), 2.98-3.17 (3H, m), 3.62-3.77 (2H, m), 4.09-4.23 (1H, m), 4.54 (1H, d, J = 8.0 Hz), 4.91 (1H, dddd, J = 64.0 6.0, 6.0, 4.0 Hz).		
116		Reference example 105	Reference example 8

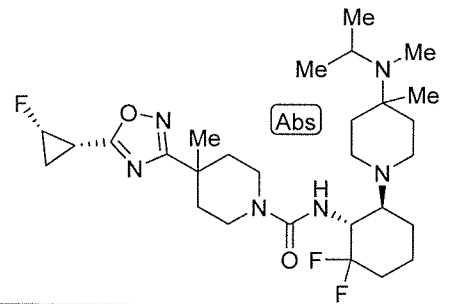
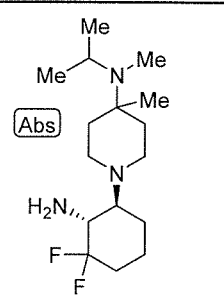
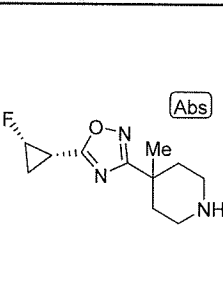
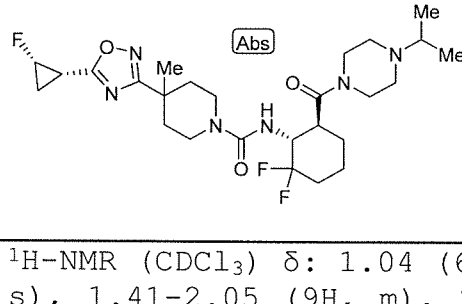
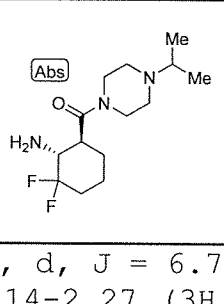
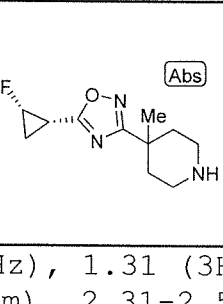
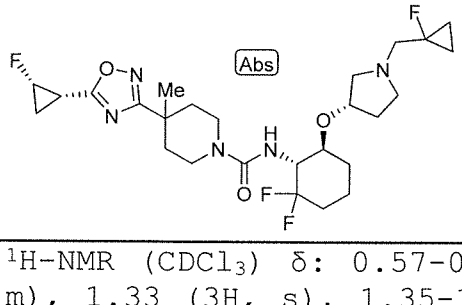
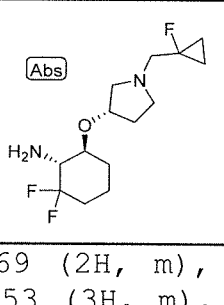
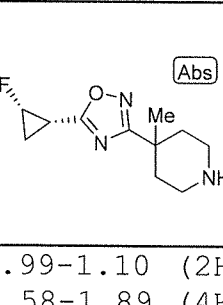
			
	¹ H-NMR (CDCl ₃) δ: 0.89 (3H, d, J = 6.8 Hz), 0.90 (3H, d, J = 6.8 Hz), 1.17-1.24 (4H, m), 1.30 (3H, s), 1.35-1.49 (2H, m), 1.56-1.85 (6H, m), 1.93-2.28 (8H, m), 2.28-2.37 (1H, m), 2.40-2.49 (1H, m), 2.56-2.68 (1H, m), 2.89-2.99 (1H, m), 3.02-3.24 (3H, m), 3.61-3.76 (2H, m), 4.08-4.28 (2H, m), 4.55 (1H, d, J = 9.2 Hz).		
117		Reference example 95	Reference example 115
			
	¹ H-NMR (CDCl ₃) δ: 1.05 (6H, d, J = 6.7 Hz), 1.33 (3H, s), 1.43-1.54 (2H, m), 1.57-1.84 (7H, m), 1.88-2.03 (2H, m), 2.10-2.22 (2H, m), 2.22-2.30 (2H, m), 2.31-2.71 (10H, m), 3.02-3.17 (2H, m), 3.64-3.79 (2H, m), 3.88-4.03 (1H, m), 4.91 (1H, dddd, J = 63.6, 6.0, 6.0, 3.6 Hz), 5.05 (1H, d, J = 7.3 Hz).		
118		Reference example 108	Reference example 115
			
	¹ H-NMR (CDCl ₃) δ: 0.13 (2H, d, J = 4.3 Hz), 0.50 (2H, d, J = 7.3 Hz), 0.84-0.95 (1H, m), 1.33 (3H, s), 1.36-1.54 (3H, m), 1.56-1.87 (7H, m), 1.91-2.21 (4H, m), 2.21-2.30 (2H, m), 2.31-2.46 (3H, m), 2.47-2.60 (1H, m), 2.95-3.27 (4H, m), 3.64-3.74 (2H, m), 4.10-4.25 (2H, m), 4.56 (1H, d, J = 8.5 Hz), 4.92 (1H, dddd, J = 63.6, 6.0, 6.0, 3.6 Hz).		
119		Reference example 109	Reference example 8

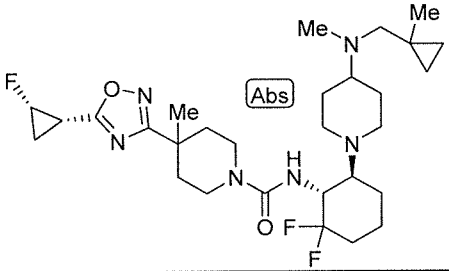
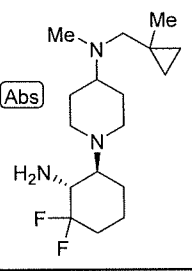
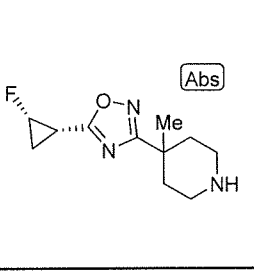
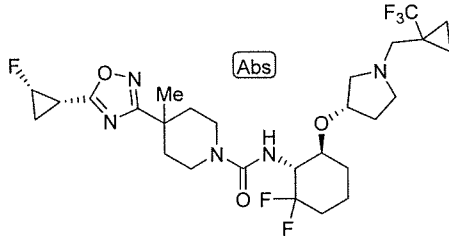
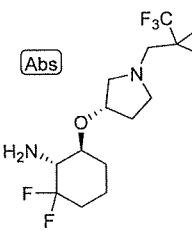
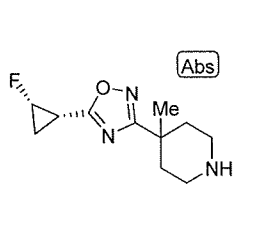
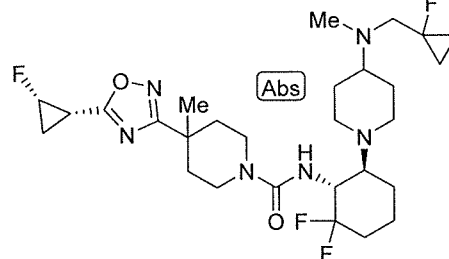
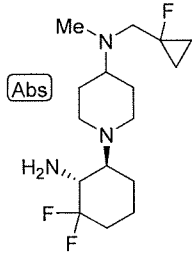
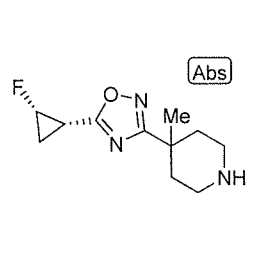
			
	¹ H-NMR (CDCl ₃) δ: 0.86 (9H, s), 1.18-1.24 (4H, m), 1.30 (s, 3H), 1.35-1.50 (2H, m), 1.55-1.72 (3H, m), 1.72-1.86 (2H, m), 1.86-2.00 (1H, m), 2.00-2.29 (7H, m), 2.46 (1H, dd, J = 10.0, 4.0 Hz), 2.53-2.62 (1H, m), 2.62-2.71 (1H, m), 2.98 (1H, dd, J = 10.0, 6.4 Hz), 3.03-3.27 (3H, m), 3.61-3.78 (2H, m), 4.03-4.12 (1H, m), 4.13-4.29 (1H, m), 4.53 (1H, d, J = 9.2 Hz).		
120		Reference example 109	Reference example 115
			
	¹ H-NMR (CDCl ₃) δ: 0.87 (9H, s), 1.33 (3H, s), 1.33-1.54 (3H, m), 1.56-1.85 (6H, m), 1.86-2.31 (7H, m), 2.32-2.42 (1H, m), 2.43-2.52 (1H, m), 2.54-2.75 (2H, m), 2.89-3.26 (4H, m), 3.63-3.80 (2H, m), 4.02-4.12 (1H, m), 4.13-4.29 (1H, m), 4.54 (1H, d, J = 9.2 Hz), 4.92 (1H, dddd, J = 63.6, 6.4, 6.4, 4.0 Hz).		
121		Reference example 110	Reference example 115
			
	¹ H-NMR (CDCl ₃) δ: 0.19-0.38 (4H, m), 1.03-1.17 (3H, m), 1.32-1.54 (4H, m), 1.34 (3H, s), 1.56-1.84 (6H, m), 1.90-2.56 (10H, m), 3.01-3.24 (4H, m), 3.63-3.75 (2H, m), 4.10-4.27 (2H, m), 4.57 (1H, d, J = 9.2 Hz), 4.92 (1H, dddd, J = 63.5, 6.0, 6.0, 3.7 Hz).		
122		Reference example 108	Reference example 8

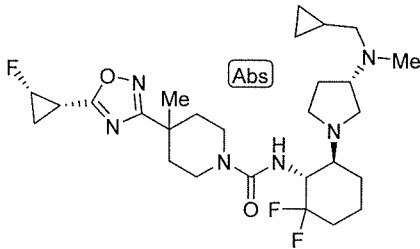
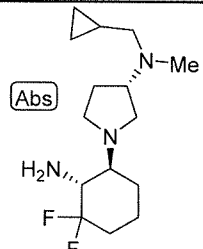
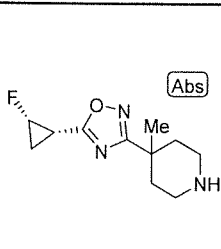
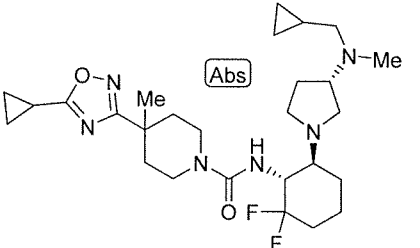
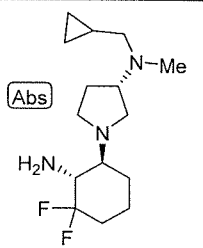
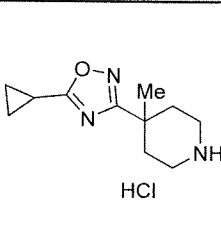
			
	¹ H-NMR (CDCl ₃) δ: 0.06-0.16 (2H, m), 0.44-0.52 (2H, m), 0.81-0.93 (1H, m), 1.09-1.23 (5H, m), 1.30 (3H, s), 1.34-1.49 (2H, m), 1.54-1.85 (4H, m), 1.94-2.26 (6H, m), 2.26-2.42 (3H, m), 2.46-2.54 (1H, m), 2.70-2.79 (1H, m), 3.02-3.26 (4H, m), 3.61-3.74 (2H, m), 4.09-4.27 (2H, m), 4.56 (1H, d, J = 9.2 Hz).		
123		Reference example 63	Reference example 115
			
	¹ H-NMR (CDCl ₃) δ: 0.97-1.09 (6H, m), 1.32 (3H, s), 1.36-1.53 (4H, m), 1.53-1.69 (3H, m), 1.69-1.87 (4H, m), 1.91-2.04 (2H, m), 2.04-2.20 (3H, m), 2.20-2.28 (5H, m), 2.30-2.42 (2H, m), 2.62-2.77 (2H, m), 2.82-2.95 (2H, m), 3.03-3.15 (2H, m), 3.63-3.76 (2H, m), 4.03-4.18 (1H, m), 4.52 (1H, d, J = 7.2 Hz), 4.91 (1H, dddd, J = 63.6, 6.0, 6.0, 3.6 Hz).		
124		Reference example 64	Reference example 115
			
	¹ H-NMR (CDCl ₃) δ: 1.18-1.36 (5H, m), 1.36-1.54 (3H, m), 1.60-2.05 (13H, m), 2.06-2.20 (2H, m), 2.21-2.30 (2H, m), 2.34-2.43 (1H, m), 2.45-2.66 (7H, m), 2.74-2.83 (1H, m), 3.01-3.16 (2H, m), 3.72-3.82 (1H, m), 3.72-3.82 (1H, m), 4.09-4.23 (1H, m), 4.57 (1H, d, J = 7.2 Hz), 4.92 (1H, dddd, J = 64.0, 6.0, 6.0, 3.6 Hz).		

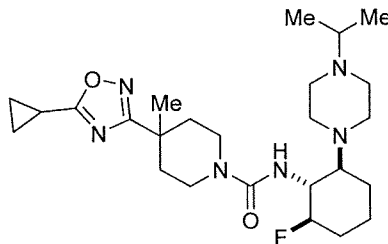
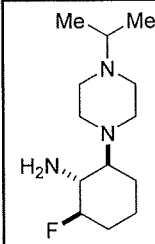
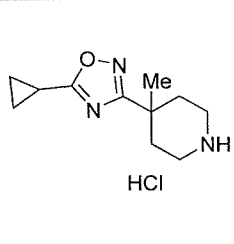
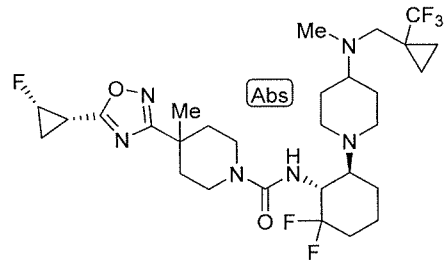
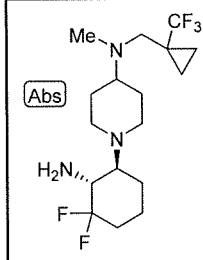
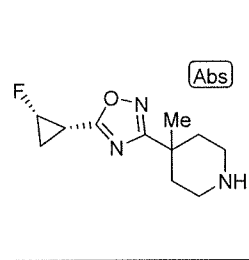
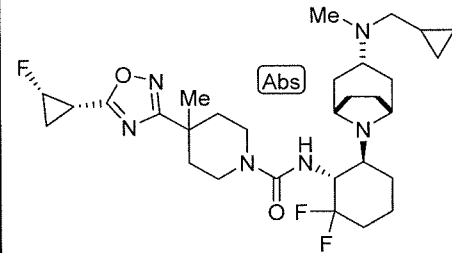
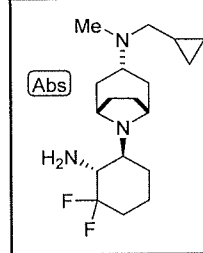
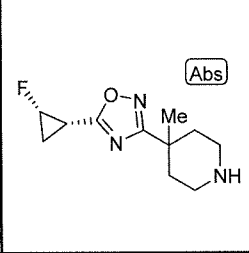
125		Reference example 65	Reference example 115
			
¹ H-NMR (CDCl ₃) δ: 0.97-1.10 (6H, m), 1.21-1.35 (4H, m), 1.35-1.52 (2H, m), 1.62-1.76 (4H, m), 1.76-1.87 (2H, m), 1.87-2.22 (4H, m), 2.22-2.31 (2H, m), 2.31-2.42 (3H, m), 2.48-2.64 (3H, m), 2.64-2.80 (2H, m), 2.98-3.09 (1H, m), 3.09-3.24 (3H, m), 3.58-3.70 (1H, m), 3.76-3.88 (1H, m), 4.07-4.24 (1H, m), 4.52 (1H, d, J = 8.0 Hz), 4.91 (1H, dddd, J = 64.0, 6.0, 6.0, 3.6 Hz).			
126		Reference example 110	Reference example 8
			 HCl
¹ H-NMR (CDCl ₃) δ: 0.22-0.34 (4H, m), 1.04-1.24 (8H, m), 1.31 (3H, s), 1.33-1.49 (2H, m), 1.54-1.84 (6H, m), 1.93-2.55 (9H, m), 3.02-3.24 (4H, m), 3.61-3.74 (2H, m), 4.11-4.27 (2H, m), 4.56 (1H, d, J = 9.2 Hz).			
127		Reference example 66	Reference example 115
			
¹ H-NMR (CDCl ₃) δ: 1.00-1.12 (6H, m), 1.21-1.40 (5H, m), 1.40-1.59 (6H, m), 1.59-1.74 (4H, m), 1.74-1.84 (1H, m), 1.84-2.06 (2H, m), 2.08-2.22 (1H, m), 2.22-2.43 (8H, m), 2.43--2.65 (5H, m), 3.03-3.12 (1H, m), 3.12-3.22 (1H, m), 3.63-3.73 (1H, m), 3.73-3.83 (1H, m), 4.07-4.23 (1H, m), 4.56 (1H, d, J = 8.0 Hz), 4.91			

	(1H, dddd, J = 63.6, 6.0, 6.0, 3.6 Hz).		
128		Reference example 86	Reference example 115
			
	¹ H-NMR (CDCl ₃) δ: 0.86 (6H, d, J = 6.8 Hz), 1.29-1.53 (6H, m), 1.53-1.76 (4H, m), 1.76-2.08 (7H, m), 2.08-2.28 (6H, m), 2.32-2.41 (1H, m), 2.42-2.52 (1H, m), 2.52--2.63 (1H, m), 2.63--2.73 (1H, m), 2.76-2.90 (3H, m), 3.02-3.17 (2H, m), 3.70 (2H, tt, J = 14.8, 4.0 Hz), 4.07-4.22 (1H, m), 4.55 (1H, d, J = 8.0 Hz), 4.91 (1H, dddd, J = 63.6, 6.0, 6.0, 3.6 Hz)		
129		Reference example 67	Reference example 115
			
	¹ H-NMR (CDCl ₃) δ: 0.90-1.84 (20H, m), 1.84-2.04 (3H, m), 2.05-2.31 (5H, m), 2.32-2.43 (1H, m), 2.43-2.77 (6H, m), 2.79-2.95 (1H, m), 3.03-3.19 (2H, m), 3.65-3.81 (2H, m), 4.08-4.24 (1H, m), 4.54 (1H, d, J = 7.9 Hz), 4.93 (1H, dddd, J = 63.6, 6.0, 6.0, 3.6 Hz).		
130		Reference example 110	Commercial product
			
	¹ H-NMR (CDCl ₃) δ: 0.16-0.48 (4H, m), 0.98-1.28 (4H, m), 1.25 (3H, s), 1.30-1.50 (2H, m), 1.50-1.89 (7H, m), 1.95-2.21 (5H, m), 2.22-2.65 (2H, m), 2.33 (3H, s), 3.11-3.24 (1H, m), 3.25-3.41 (2H, m), 3.41-3.67 (3H, m), 4.10-4.27 (2H, m), 4.58 (1H, d, J = 7.9 Hz),		

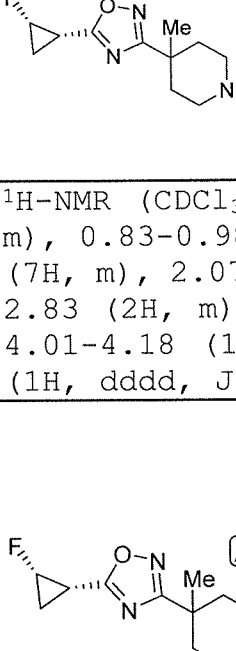
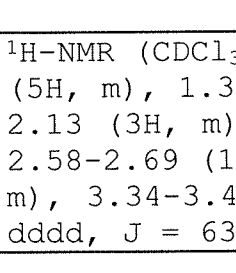
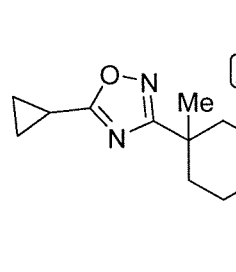
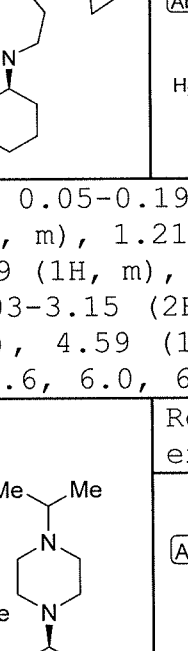
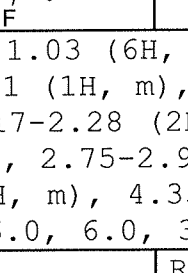
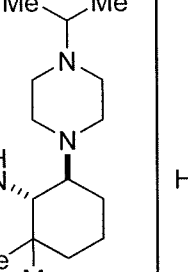
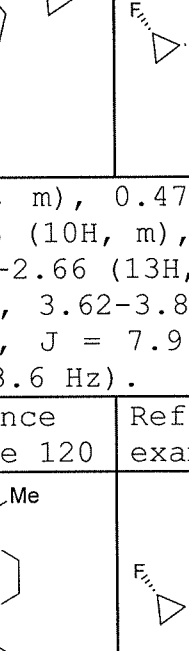
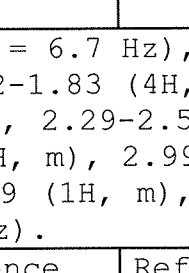
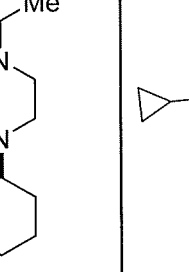
	7.16 (2H, d, $J = 7.9$ Hz), 7.21 (2H, d, $J = 7.9$ Hz).		
131		Reference example 68	Reference example 115
			
	$^1\text{H-NMR}$ (CDCl_3) δ : 0.88 (3H, s), 0.92-0.98 (6H, m), 1.22-1.52 (8H, m), 1.60-1.84 (6H, m), 1.89-2.03 (2H, m), 2.04 (3H, s), 2.09-2.31 (4H, m), 2.31-2.41 (1H, m), 2.41-2.55 (3H, m), 2.70-2.80 (1H, m), 3.00-3.23 (3H, m), 3.64-3.75 (1H, m), 3.75-3.85 (1H, m), 4.06-4.22 (1H, m), 4.58 (1H, d, $J = 7.2$ Hz), 4.91 (1H, dddd, $J = 63.6, 6.0, 6.0, 3.6$ Hz).		
132		Reference example 94	Reference example 115
			
	$^1\text{H-NMR}$ (CDCl_3) δ : 1.04 (6H, d, $J = 6.7$ Hz), 1.31 (3H, s), 1.41-2.05 (9H, m), 2.14-2.27 (3H, m), 2.31-2.59 (5H, m), 2.64-2.77 (1H, m), 2.85-2.96 (1H, m), 2.99-3.10 (2H, m), 3.46-3.74 (6H, m), 4.46-4.53 (1H, m), 4.53-4.68 (1H, m), 4.91 (1H, dddd, $J = 63.6, 6.0, 6.0, 3.6$ Hz).		
133		Reference example 111	Reference example 115
			
	$^1\text{H-NMR}$ (CDCl_3) δ : 0.57-0.69 (2H, m), 0.99-1.10 (2H, m), 1.33 (3H, s), 1.35-1.53 (3H, m), 1.58-1.89 (4H, m), 1.91-2.20 (5H, m), 2.20-2.30 (2H, m), 2.32-2.41 (1H, m), 2.41-2.49 (1H, m), 2.51-2.61 (1H, m), 2.75-		

	2.94 (3H, m), 3.04–3.26 (4H, m), 3.65–3.75 (2H, m), 4.13–4.27 (2H, m), 4.58 (1H, d, J = 9.2 Hz), 4.92 (1H, dddd, J = 63.6, 6.0, 6.0, 3.6 Hz).		
134		Reference example 69	Reference example 115
			
	¹ H-NMR (CDCl ₃) δ: 0.14–0.34 (4H, m), 0.98–1.10 (3H, m), 1.18–1.37 (6H, m), 1.37–1.54 (3H, m), 1.54–1.74 (2H, m), 1.74–1.84 (2H, m), 1.84–2.03 (2H, m), 2.03–2.42 (12H, m), 2.46–2.57 (2H, m), 2.62–2.72 (1H, m), 2.79–2.90 (1H, m), 3.01–3.20 (2H, m), 3.65–3.74 (1H, m), 3.74–3.85 (1H, m), 4.07–4.21 (1H, m), 4.55 (1H, d, J = 7.3 Hz), 4.92 (1H, dddd, J = 63.6, 6.0, 6.0, 3.6 Hz).		
135		Reference example 112	Reference example 115
			
	¹ H-NMR (CDCl ₃) δ: 0.58–0.72 (2H, m), 0.93–1.02 (2H, m), 1.29–1.54 (4H, m), 1.33 (3H, s), 1.55–1.84 (4H, m), 1.90–2.03 (2H, m), 2.03–2.21 (2H, m), 2.21–2.30 (2H, m), 2.30–2.50 (3H, m), 2.55–2.82 (3H, m), 3.00–3.24 (4H, m), 3.65–3.75 (2H, m), 4.08–4.27 (2H, m), 4.56 (1H, d, J = 9.2 Hz), 4.92 (1H, dddd, J = 63.6, 6.0, 6.0, 3.6 Hz).		
136		Reference example 70	Reference example 115
			

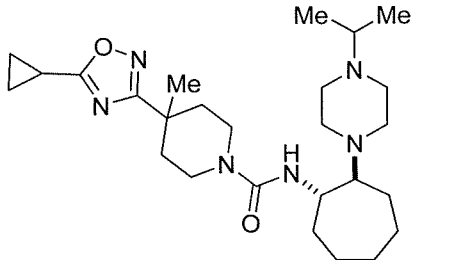
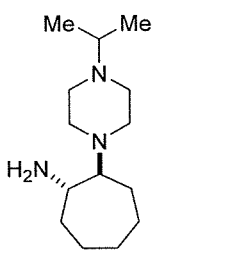
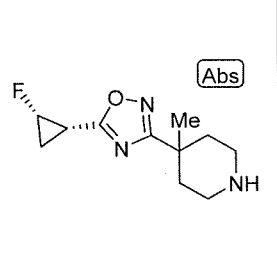
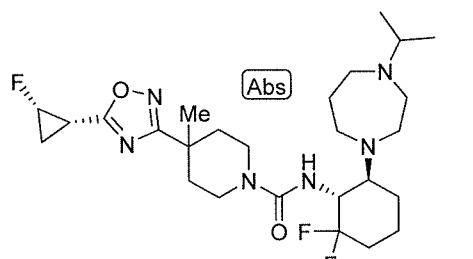
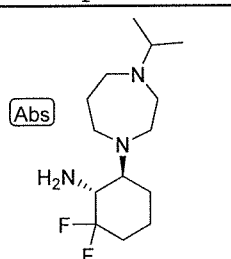
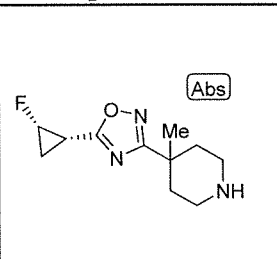
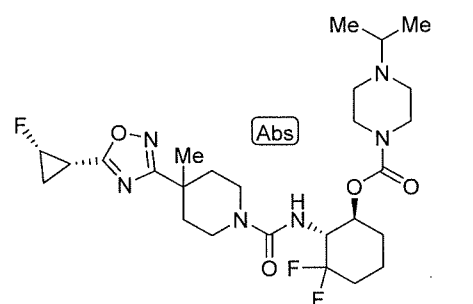
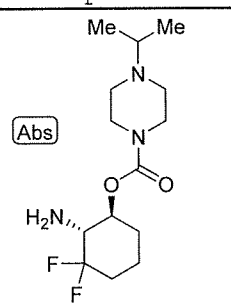
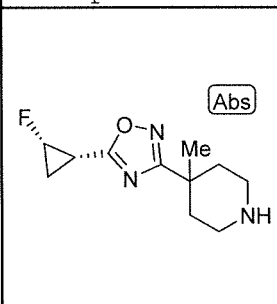
	¹ H-NMR (CDCl ₃) δ: 0.52-0.66 (2H, m), 0.99-1.09 (2H, m), 1.16-1.36 (3H, m), 1.33 (3H, s), 1.36-1.53 (3H, m), 1.53-1.84 (5H, m), 1.84-2.03 (2H, m), 2.04-2.20 (2H, m), 2.21-2.31 (2H, m), 2.31-2.47 (5H, m), 2.47-2.60 (2H, m), 2.63-2.92 (4H, m), 3.04-3.19 (2H, m), 3.68-3.79 (2H, m), 4.08-4.23 (1H, m), 4.49-4.62 (1H, m), 4.92 (1H, dddd, J = 63.6, 6.0, 6.0, 3.6 Hz).		
137		Reference example 87	Reference example 115
			
	¹ H-NMR (CDCl ₃) δ: 0.13-0.33 (2H, m), 0.52-0.74 (2H, m), 0.90-1.14 (1H, m), 1.23-1.38 (5H, m), 1.38-1.55 (2H, m), 1.57-1.69 (2H, m), 1.69-1.87 (2H, m), 1.87-2.05 (4H, m), 2.10-2.27 (4H, m), 2.32-2.41 (2H, m), 2.41-2.62 (4H, m), 2.62-2.73 (2H, m), 2.90-3.04 (2H, m), 3.04-3.17 (2H, m), 3.52-3.75 (2H, m), 4.06-4.23 (1H, m), 4.51-4.64 (1H, m), 4.92 (1H, dddd, J = 64.0, 6.0, 6.0, 3.6 Hz).		
138		Reference example 87	Reference example 8
			 HCl
	¹ H-NMR (CDCl ₃) δ: 0.05-0.24 (2H, m), 0.44-0.63 (2H, m), 0.80-1.00 (1H, m), 1.13 (4H, d, J = 6.0 Hz), 1.17-1.23 (4H, m), 1.24-1.50 (5H, m), 1.54-1.86 (4H, m), 1.86-1.99 (2H, m), 2.11-2.24 (4H, m), 2.24-2.45 (4H, m), 2.52-2.73 (2H, m), 2.82-2.96 (2H, m), 3.00-3.16 (2H, m), 3.58-3.72 (2H, m), 4.06-4.22 (1H, m), 4.55 (1H, d, J = 8.0 Hz).		
139		Reference example 123	Reference example 8

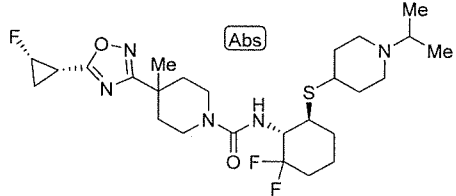
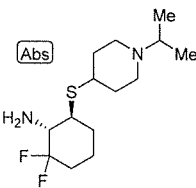
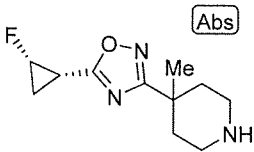
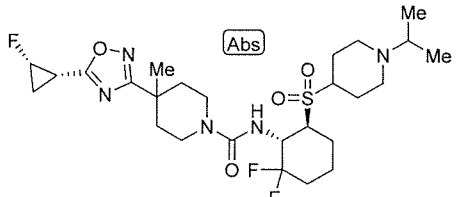
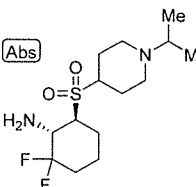
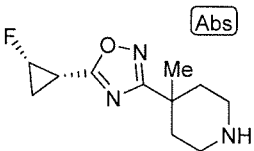
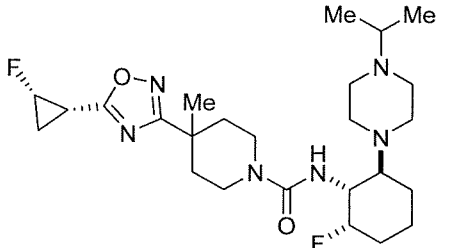
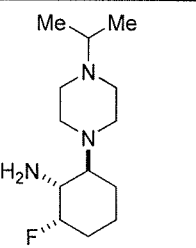
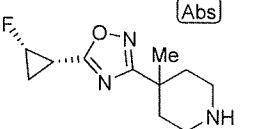
			
	¹ H-NMR (CDCl ₃) δ: 1.01 (6H, d, J = 6.4 Hz), 1.16-1.24 (6H, m), 1.30 (3H, s), 1.54-1.70 (3H, m), 1.81-1.88 (2H, m), 2.09-2.31 (5H, m), 2.34-2.53 (6H, m), 2.53-2.63 (1H, m), 2.67-2.76 (2H, m), 3.04-3.18 (2H, m), 3.62-3.72 (1H, m), 3.72-3.88 (2H, m), 4.19 (1H, dddd, J = 63.6, 6.0, 6.0, 3.6 Hz), 4.68 (1H, d, J = 6.1 Hz) .		
140		Reference example 71	Reference example 115
			
	¹ H-NMR (CDCl ₃) δ: 0.57-0.64 (2H, m), 0.87-0.93 (2H, m), 1.10-1.53 (9H, m), 1.54-1.73 (4H, m), 1.74-1.84 (1H, m), 1.84-1.91 (1H, m), 1.91-2.11 (2H, m), 2.11-2.30 (7H, m), 2.31-2.40 (1H, m), 2.45-2.55 (2H, m), 2.55-2.69 (3H, m), 2.80-2.87 (1H, m), 3.02-3.19 (2H, m), 3.65-3.83 (2H, m), 4.06-4.21 (1H, m), 4.53 (1H, dddd, J = 63.6, 6.0, 6.0, 3.6 Hz), 4.83-5.00 (1H, m) .		
141		Reference example 72	Reference example 115
			
	¹ H-NMR (CDCl ₃) δ: 0.00-0.06 (2H, m), 0.42-0.49 (2H, m), 0.72-0.83 (1H, m), 1.19-1.42 (3H, m), 1.31 (3H, s), 1.42-1.82 (13H, m), 1.89-2.02 (1H, m), 2.05-2.16 (1H, m), 2.16-2.28 (7H, m), 2.30-2.40 (1H, m), 2.51-2.60 (1H, m), 2.72-2.85 (1H, m), 2.99-3.09 (1H, m), 3.09-3.18 (1H, m), 3.20-3.26 (1H, m), 3.36-3.41 (1H, m), 3.65-3.74 (1H, m), 3.77-3.85 (1H, m), 3.97-4.10		

	(1H, m), 4.67 (1H, d, J = 7.3 Hz), 4.90 (1H, dddd, J = 63.6, 6.0, 6.0, 3.6 Hz).		
142		Reference example 73	Reference example 115
	¹ H-NMR (CDCl ₃) δ: 0.01-0.22 (2H, m), 0.39-0.64 (2H, m), 0.77-0.97 (1H, m), 1.13-1.52 (6H, m), 1.52-1.87 (13H, m), 1.89-2.03 (1H, m), 2.03-2.72 (10H, m), 3.01-3.32 (4H, m), 3.33-3.50 (1H, m), 3.60-3.72 (1H, m), 3.74-3.87 (1H, m), 3.95-4.12 (1H, m), 4.65 (1H, d, J = 7.9 Hz), 4.91 (1H, dddd, J = 63.6, 6.0, 6.0, 3.6 Hz).		
143		Reference example 113	Reference example 115
	¹ H-NMR (CDCl ₃) δ: 1.17-1.86 (18H, m), 1.88-2.20 (5H, m), 2.20-2.30 (2H, m), 2.30-2.42 (1H, m), 2.44-3.03 (3H, m), 3.04-3.24 (4H, m), 3.61-3.75 (2H, m), 4.09-4.28 (2H, m), 4.60 (1H, d, J = 9.2 Hz), 4.91 (1H, dddd, J = 63.6, 6.0, 6.0, 3.6 Hz).		
144		Reference example 74	Reference example 115
	¹ H-NMR (CDCl ₃) δ: 0.02-0.10 (2H, m), 0.44-0.52 (2H, m), 0.76-0.87 (1H, m), 1.24-1.52 (10H, m), 1.58-1.87 (5H, m), 1.89-2.01 (2H, m), 2.06-2.16 (1H, m), 2.16-2.30 (8H, m), 2.30-2.40 (1H, m), 2.46-2.79 (6H, m), 3.03-3.19 (2H, m), 3.65-3.78 (2H, m), 4.02-4.16 (1H, m),		

	m), 4.61 (1H, d, J = 7.3 Hz), 4.90 (1H, dddd, J = 63.6, 6.0, 6.0, 3.6 Hz).		
145		Reference example 75	Reference example 115
			
	¹ H-NMR (CDCl ₃) δ: 0.05-0.19 (2H, m), 0.47-0.60 (2H, m), 0.83-0.98 (1H, m), 1.21-1.53 (10H, m), 1.53-2.03 (7H, m), 2.07-2.19 (1H, m), 2.19-2.66 (13H, m), 2.68-2.83 (2H, m), 3.03-3.15 (2H, m), 3.62-3.80 (2H, m), 4.01-4.18 (1H, m), 4.59 (1H, d, J = 7.9 Hz), 4.91 (1H, dddd, J = 63.6, 6.0, 6.0, 3.6 Hz).		
146		Reference example 120	Reference example 115
			
	¹ H-NMR (CDCl ₃) δ: 1.03 (6H, d, J = 6.7 Hz), 1.27-1.39 (5H, m), 1.39-1.51 (1H, m), 1.52-1.83 (4H, m), 1.89-2.13 (3H, m), 2.17-2.28 (2H, m), 2.29-2.58 (7H, m), 2.58-2.69 (1H, m), 2.75-2.99 (7H, m), 2.99-3.09 (1H, m), 3.34-3.46 (2H, m), 4.35-4.49 (1H, m), 4.89 (1H, dddd, J = 63.6, 6.0, 6.0, 3.6 Hz).		
147		Reference example 121	Reference example 8
			
	¹ H-NMR (CD ₃ OD) δ: 0.86 (3H, s), 0.90 (3H, s), 1.01 (3H, d, J = 6.8 Hz), 1.02 (3H, d, J = 6.8 Hz), 1.10-1.33 (6H, m), 1.31 (3H, s), 1.35-1.49 (2H, m), 1.55-		

	1.72 (3H, m), 1.84-1.93 (1H, m), 2.13-2.28 (3H, m), 2.30-2.59 (8H, m), 2.66-2.75 (2H, m), 3.09-3.18 (2H, m), 3.28-3.35 (1H, m), 3.53 (1H, d, J = 11.6 Hz), 3.67-3.79 (2H, m).		
148		Reference example 76 	Reference example 115
	¹ H-NMR (CDCl ₃) δ: 1.15-1.30 (6H, m), 1.33 (3H, s), 1.37-1.57 (3H, m), 1.57-1.85 (6H, m), 1.85-2.03 (3H, m), 2.11-2.30 (3H, m), 2.30-2.61 (4H, m), 3.10-3.22 (2H, m), 3.22-3.42 (1H, m), 3.47-3.68 (4H, m), 3.68-3.77 (1H, m), 3.77-3.84 (1H, m), 4.04-4.25 (1H, m) 4.91 (1H, dddd, J = 63.6, 6.0, 6.0, 3.6 Hz).		
149		Reference example 77 	Reference example 115
	¹ H-NMR (CDCl ₃) δ: 0.02-0.19 (2H, m), 0.44-0.59 (2H, m), 0.75-0.90 (1H, m), 1.12-1.28 (1H, m), 1.32 (3H, s), 1.40-1.55 (2H, m), 1.55-1.70 (3H, m), 1.70-1.82 (2H, m), 1.84-2.04 (4H, m), 2.08-2.29 (8H, m), 2.98-3.20 (4H, m), 3.46-3.56 (2H, m), 3.66-3.76 (2H, m), 4.08-4.23 (1H, m), 4.59-4.73 (1H, m) 4.91 (1H, dddd, J = 64.0, 6.0, 6.0, 4.0 Hz).		
150		Reference example 114 	Reference example 115

	¹ H-NMR (CDCl ₃) δ: 1.32-1.55 (6H, m), 1.35 (3H, s), 1.58-1.86 (6H, m), 1.91-2.11 (3H, m), 2.11-2.21 (1H, m), 2.22-2.31 (2H, m), 2.32-3.05 (6H, m), 3.06-3.24 (3H, m), 3.64-3.76 (2H, m), 4.08-4.28 (2H, m), 4.30-4.35 (2H, m), 4.44-4.51 (2H, m), 4.60 (1H, d, J = 8.5 Hz), 4.93 (1H, dddd, J = 63.6, 6.0, 6.0, 3.6 Hz).		
151		Reference example 122	Reference example 115
			
	¹ H-NMR (CDCl ₃) δ: 1.07 (6H, d, J = 5.5 Hz), 1.14-1.25 (6H, m), 1.31 (3H, s), 1.31-1.43 (2H, m), 1.43-1.79 (4H, m), 1.83-1.93 (1H, m), 2.13-2.26 (4H, m), 2.26-2.82 (12H, m), 3.01-3.16 (2H, m), 3.29-3.42 (1H, m), 3.59-3.76 (2H, m), 5.80-6.06 (1H, brs).		
152		Reference example 78	Reference example 115
			
	¹ H-NMR (CDCl ₃) δ: 0.90-1.12 (6H, m), 1.22-1.53 (7H, m), 1.54-2.05 (7H, m), 2.08-2.20 (1H, m), 2.20-2.29 (2H, m), 2.30-2.40 (1H, m), 2.48-3.04 (10H, m), 3.04-3.17 (2H, m), 3.66-3.80 (2H, m), 4.02-4.17 (1H, m), 4.72 (1H, s), 4.90 (1H, dddd, J = 63.6, 6.0, 6.0, 3.6 Hz).		
153		Reference example 125	Reference example 115
			

	¹ H-NMR (CDCl ₃) δ: 0.89-1.17 (6H, m), 1.33 (3H, s), 1.42-1.69 (6H, m), 1.69-1.89 (2H, m), 1.91-2.04 (1H, m), 2.04-2.14 (1H, m), 2.14-2.82 (8H, m), 2.99-3.13 (2H, m), 3.28-3.77 (6H, m), 4.20-4.35 (1H, m), 4.68-4.80 (1H, m), 4.92 (1H, dddd, J = 63.6, 6.0, 6.0, 3.6 Hz), 4.94 (1H, d, J = 8.5 Hz).		
154		Reference example 88	Reference example 115
			
	¹ H-NMR (CDCl ₃) δ: 1.03-1.21 (6H, m), 1.35 (3H, s), 1.41-1.90 (8H, m), 1.91-2.61 (11H, m), 2.61-2.71 (1H, m), 2.71-3.04 (4H, m), 3.05-3.21 (2H, m), 3.64-3.79 (2H, m), 4.11-4.27 (1H, m), 4.63 (1H, d, J = 9.8 Hz), 4.93 (1H, dddd, J = 63.6, 6.0, 6.0, 3.6 Hz).		
155		Reference example 126	Reference example 115
			
	¹ H-NMR (CDCl ₃) δ: 0.93-1.14 (6H, m), 1.33 (3H, s), 1.43-1.54 (1H, m), 1.54-1.81 (5H, m), 1.82-2.32 (11H, m), 2.32-2.45 (2H, m), 2.71-2.85 (1H, m), 2.96-3.24 (6H, m), 3.66-3.82 (2H, m), 4.67-4.80 (1H, m), 4.92 (1H, dddd, J = 63.6, 6.0, 6.0, 3.6 Hz), 4.93 (1H, d, J = 9.2 Hz).		
156		Reference example 124	Reference example 115
			
	¹ H-NMR (CDCl ₃) δ: 0.98-1.38 (10H, m), 1.40-1.78 (10H, m), 1.89-2.11 (3H, m), 2.16-2.32 (2H, m), 2.32-2.42 (1H, m), 2.43-3.44 (9H, m), 3.54-3.77 (2H, m), 4.89-		

	5.26 (2H, m), 4.93 (1H, dddd, J = 63.6, 6.0, 6.0, 3.6 Hz).
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[0240]

The chemical names of Example 82 to Example 155 are listed below.

Example 82: N-[(1S,6R)-2,2-difluoro-6-[4-(propan-2-yl)piperazin-1-yl]cyclohexyl]-4-{5-[(1R,2R)-2-fluorocyclopropyl]-1,2,4-oxadiazol-3-yl}-4-methylpiperidine-1-carboxamide

Example 83: N-[(1R,6S)-2,2-difluoro-6-{[1-(propan-2-yl)piperidin-4-yl]oxy}cyclohexyl]-4-{5-[(1S,2S)-2-fluorocyclopropyl]-1,2,4-oxadiazol-3-yl}-4-methylpiperidine-1-carboxamide

Example 84: 4-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)-N-[(1R,6S)-2,2-difluoro-6-{[1-(propan-2-yl)piperidin-4-yl]oxy}cyclohexyl]-4-methylpiperidine-1-carboxamide

Example 85: 4-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)-N-[(1R,6S)-2,2-difluoro-6-[5-(propan-2-yl)-1,2,4-oxadiazol-3-yl]cyclohexyl]-4-methylpiperidine-1-carboxamide

Example 86: N-[(1R,6S)-2,2-difluoro-6-[5-(propan-2-yl)-1,2,4-oxadiazol-3-yl]cyclohexyl]-4-{5-[(1S,2S)-2-fluorocyclopropyl]-1,2,4-oxadiazol-3-yl}-4-methylpiperidine-1-carboxamide

Example 87: N-[(1R,6S)-2,2-difluoro-6-{[3-(propan-2-yl)-1,2,4-thiadiazol-5-yl]oxy}cyclohexyl]-4-{5-[(1S,2S)-2-fluorocyclopropyl]-1,2,4-oxadiazol-3-yl}-4-

methylpiperidine-1-carboxamide

Example 88: N-[(1R,6S)-2,2-difluoro-6-{[1-(propan-2-yl)-1H-pyrazol-4-yl]oxy}cyclohexyl]-4-{5-[(1S,2S)-2-fluorocyclopropyl]-1,2,4-oxadiazol-3-yl}-4-

5 methylpiperidine-1-carboxamide

Example 89: N-[(1R,6S)-2,2-difluoro-6-{[1-(propan-2-yl)azetidin-3-yl]oxy}cyclohexyl]-4-{5-[(1S,2S)-2-fluorocyclopropyl]-1,2,4-oxadiazol-3-yl}-4-

methylpiperidine-1-carboxamide

10 Example 90: 4-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)-N-[(1R,6S)-2,2-difluoro-6-{[1-(propan-2-yl)-1H-pyrazol-4-yl]oxy}cyclohexyl]-4-methylpiperidine-1-carboxamide

Example 91: N-[(1R,6S)-6-{benzyl[(3S)-1-(propan-2-yl)pyrrolidin-3-yl]amino}-2,2-difluorocyclohexyl]-4-{5-

15 [(1S,2S)-2-fluorocyclopropyl]-1,2,4-oxadiazol-3-yl}-4-methylpiperidine-1-carboxamide

Example 92: N-[(1R,6S)-2,2-difluoro-6-{[2-(propan-2-yl)pyrimidin-4-yl]oxy}cyclohexyl]-4-{5-[(1S,2S)-2-fluorocyclopropyl]-1,2,4-oxadiazol-3-yl}-4-

20 methylpiperidine-1-carboxamide

Example 93: N-{(1R,6S)-2,2-difluoro-6-[4-(propan-2-yl)-1H-1,2,3-triazol-1-yl]cyclohexyl}-4-{5-[(1S,2S)-2-fluorocyclopropyl]-1,2,4-oxadiazol-3-yl}-4-methylpiperidine-1-carboxamide

25 Example 94: N-{(1R,6S)-2,2-difluoro-6-[4-(2-

methylpropyl)-1H-1,2,3-triazol-1-yl]cyclohexyl}-4-{5-
 [(1S,2S)-2-fluorocyclopropyl]-1,2,4-oxadiazol-3-yl}-4-
 methylpiperidine-1-carboxamide

Example 95: N-[(1R,6S)-2,2-difluoro-6-{methyl[(3S)-1-
 5 (propan-2-yl)pyrrolidin-3-yl]amino}cyclohexyl]-4-{5-
 [(1S,2S)-2-fluorocyclopropyl]-1,2,4-oxadiazol-3-yl}-4-
 methylpiperidine-1-carboxamide

Example 96: N-[(1R,6S)-2,2-difluoro-6-{(3S)-3-
 [methyl(propan-2-yl)amino]pyrrolidin-1-yl}cyclohexyl]-4-{5-
 10 [(1S,2S)-2-fluorocyclopropyl]-1,2,4-oxadiazol-3-yl}-4-
 methylpiperidine-1-carboxamide

Example 97: 4-(5-cyclobutyl-1,2,4-oxadiazol-3-yl)-N-
 {(1R,6S)-2,2-difluoro-6-[4-(propan-2-yl)piperazin-1-
 yl]cyclohexyl}-4-methylpiperidine-1-carboxamide

Example 98: N-[(1R,6S)-2,2-difluoro-6-{[(1R,3S,5S)-8-
 15 (propan-2-yl)-8-azabicyclo[3.2.1]octan-3-
 yl]oxy}cyclohexyl]-4-{5-[(1S,2S)-2-fluorocyclopropyl]-
 1,2,4-oxadiazol-3-yl}-4-methylpiperidine-1-carboxamide

Example 99: 4-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)-N-
 20 [(1R,6S)-2,2-difluoro-6-{(3S)-3-[methyl(propan-2-
 yl)amino]pyrrolidin-1-yl}cyclohexyl]-4-methylpiperidine-1-
 carboxamide

Example 100: N-[(1R,6S)-2,2-difluoro-6-{[(1R,5S,8R)-3-
 (propan-2-yl)-3-azabicyclo[3.2.1]octan-8-
 25 yl]oxy}cyclohexyl]-4-{5-[(1S,2S)-2-fluorocyclopropyl]-

1,2,4-oxadiazol-3-yl}-4-methylpiperidine-1-carboxamide

Example 101: N-[(1R,6S)-2,2-difluoro-6-{4-[(propan-2-yl)oxy]piperidin-1-yl}cyclohexyl]-4-{5-[(1S,2S)-2-fluorocyclopropyl]-1,2,4-oxadiazol-3-yl}-4-methylpiperidine-1-carboxamide

Example 102: 4-(5-cyclobutyl-1,2,4-oxadiazol-3-yl)-N-[(1R,6S)-2,2-difluoro-6-{[(3S)-1-(propan-2-yl)pyrrolidin-3-yl]oxy}cyclohexyl]-4-methylpiperidine-1-carboxamide

Example 103: N-[(1R,6S)-2,2-difluoro-6-{[(3S)-1-(propan-2-yl)pyrrolidin-3-yl]oxy}cyclohexyl]-4-ethyl-4-{5-[(1S,2S)-2-fluorocyclopropyl]-1,2,4-oxadiazol-3-yl}piperidine-1-carboxamide

Example 104: N-[(1R,6S)-2,2-difluoro-6-{[(1R,5S,8S)-3-(propan-2-yl)-3-azabicyclo[3.2.1]octan-8-yl]oxy}cyclohexyl]-4-{5-[(1S,2S)-2-fluorocyclopropyl]-1,2,4-oxadiazol-3-yl}-4-methylpiperidine-1-carboxamide

Example 105: N-[(1R,6S)-2,2-difluoro-6-{[(1R,3R,5S)-8-(propan-2-yl)-8-azabicyclo[3.2.1]octan-3-yl]oxy}cyclohexyl]-4-{5-[(1S,2S)-2-fluorocyclopropyl]-1,2,4-oxadiazol-3-yl}-4-methylpiperidine-1-carboxamide

Example 106: N-[(1R,6S)-2,2-difluoro-6-{[(1R,5S,6S)-3-(propan-2-yl)-3-azabicyclo[3.1.0]hexan-6-yl]oxy}cyclohexyl]-4-{5-[(1S,2S)-2-fluorocyclopropyl]-1,2,4-oxadiazol-3-yl}-4-methylpiperidine-1-carboxamide

Example 107: N-[(1R,6S)-2,2-difluoro-6-{[(3S)-1-(2-

methylpropyl)pyrrolidin-3-yl]oxy}cyclohexyl]-4-{5-[(1S,2S)-2-fluorocyclopropyl]-1,2,4-oxadiazol-3-yl}-4-methylpiperidine-1-carboxamide

Example 108: N-[(1R,6S)-2,2-difluoro-6-{[(3R,4R)-4-methoxy-1-(propan-2-yl)pyrrolidin-3-yl]oxy}cyclohexyl]-4-{5-[(1S,2S)-2-fluorocyclopropyl]-1,2,4-oxadiazol-3-yl}-4-methylpiperidine-1-carboxamide

Example 109: N-[(1R,6S)-2,2-difluoro-6-{[4-methyl-1-(propan-2-yl)piperidin-4-yl]oxy}cyclohexyl]-4-{5-[(1S,2S)-2-fluorocyclopropyl]-1,2,4-oxadiazol-3-yl}-4-methylpiperidine-1-carboxamide

Example 110: N-{(1R,6S)-2,2-difluoro-6-[(2S)-2-methyl-4-(propan-2-yl)piperazin-1-yl]cyclohexyl}-4-{5-[(1S,2S)-2-fluorocyclopropyl]-1,2,4-oxadiazol-3-yl}-4-methylpiperidine-1-carboxamide

Example 111: N-{(1R,6S)-2,2-difluoro-6-[(2R)-2-methyl-4-(propan-2-yl)piperazin-1-yl]cyclohexyl}-4-{5-[(1S,2S)-2-fluorocyclopropyl]-1,2,4-oxadiazol-3-yl}-4-methylpiperidine-1-carboxamide

Example 112: N-[(1R,6S)-2,2-difluoro-6-{(3R)-3-[methyl(propan-2-yl)amino]pyrrolidin-1-yl}cyclohexyl]-4-{5-[(1S,2S)-2-fluorocyclopropyl]-1,2,4-oxadiazol-3-yl}-4-methylpiperidine-1-carboxamide

Example 113: N-[(1R,6S)-2,2-difluoro-6-{methyl[(3R)-1-(propan-2-yl)pyrrolidin-3-yl]amino}cyclohexyl]-4-{5-

[(1S,2S)-2-fluorocyclopropyl]-1,2,4-oxadiazol-3-yl}-4-methylpiperidine-1-carboxamide

Example 114: N-[(1R,6S)-2,2-difluoro-6-{4-[methyl (propan-2-yl) amino]piperidin-1-yl}cyclohexyl]-4-{5-
5 [(1S,2S)-2-fluorocyclopropyl]-1,2,4-oxadiazol-3-yl}-4-methylpiperidine-1-carboxamide

Example 115: N-[(1R,6S)-6-{(3S)-3-[cyclopropyl (methyl) amino]pyrrolidin-1-yl}-2,2-difluorocyclohexyl]-4-{5-[(1S,2S)-2-fluorocyclopropyl]-
10 1,2,4-oxadiazol-3-yl}-4-methylpiperidine-1-carboxamide

Example 116: 4-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)-N-[(1R,6S)-2,2-difluoro-6-{[(3S)-1-(2-methylpropyl)pyrrolidin-3-yl]oxy}cyclohexyl]-4-methylpiperidine-1-carboxamide

Example 117: N-[(1R,6R)-2,2-difluoro-6-{[4-(propan-2-yl)piperazin-1-yl]methyl}cyclohexyl]-4-{5-[(1S,2S)-2-fluorocyclopropyl]-1,2,4-oxadiazol-3-yl}-4-methylpiperidine-1-carboxamide

Example 118: N-[(1R,6S)-6-{[(3S)-1-(cyclopropylmethyl)pyrrolidin-3-yl]oxy}-2,2-difluorocyclohexyl]-4-{5-[(1S,2S)-2-fluorocyclopropyl]-1,2,4-oxadiazol-3-yl}-4-methylpiperidine-1-carboxamide

Example 119: 4-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)-N-[(1R,6S)-6-{[(3S)-1-(2,2-dimethylpropyl)pyrrolidin-3-yl]oxy}-2,2-difluorocyclohexyl]-4-methylpiperidine-1-

carboxamide

Example 120: N-[(1R,6S)-6-{[(3S)-1-(2,2-dimethylpropyl)pyrrolidin-3-yl]oxy}-2,2-difluorocyclohexyl]-4-{5-[(1S,2S)-2-fluorocyclopropyl]-1,2,4-oxadiazol-3-yl}-4-methylpiperidine-1-carboxamide

Example 121: N-[(1R,6S)-2,2-difluoro-6-({(3S)-1-[(1-methylcyclopropyl)methyl]pyrrolidin-3-yl}oxy)cyclohexyl]-4-{5-[(1S,2S)-2-fluorocyclopropyl]-1,2,4-oxadiazol-3-yl}-4-methylpiperidine-1-carboxamide

Example 122: N-[(1R,6S)-6-{[(3S)-1-(cyclopropylmethyl)pyrrolidin-3-yl]oxy}-2,2-difluorocyclohexyl]-4-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)-4-methylpiperidine-1-carboxamide

Example 123: N-[(1R,6S)-2,2-difluoro-6-{methyl[1-(propan-2-yl)piperidin-4-yl]amino}cyclohexyl]-4-{5-[(1S,2S)-2-fluorocyclopropyl]-1,2,4-oxadiazol-3-yl}-4-methylpiperidine-1-carboxamide

Example 124: N-{(1R,6S)-2,2-difluoro-6-[4-(pyrrolidin-1-yl)piperidin-1-yl]cyclohexyl}-4-{5-[(1S,2S)-2-fluorocyclopropyl]-1,2,4-oxadiazol-3-yl}-4-methylpiperidine-1-carboxamide

Example 125: N-{(1R,6S)-2,2-difluoro-6-[5-(propan-2-yl)hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl]cyclohexyl}-4-{5-[(1S,2S)-2-fluorocyclopropyl]-1,2,4-oxadiazol-3-yl}-4-methylpiperidine-1-carboxamide

Example 126: 4-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)-N-
 [(1R,6S)-2,2-difluoro-6-((3S)-1-[(1-
 methylcyclopropyl)methyl]pyrrolidin-3-yl)oxy)cyclohexyl]-4-
 methylpiperidine-1-carboxamide

5 Example 127: N-{(1R,6S)-2,2-difluoro-6-[2-(propan-2-
 yl)-2,8-diazaspiro[4.5]decan-8-yl]cyclohexyl}-4-{5-
 [(1S,2S)-2-fluorocyclopropyl]-1,2,4-oxadiazol-3-yl}-4-
 methylpiperidine-1-carboxamide

10 Example 128: N-[(1R,6S)-2,2-difluoro-6-{(3S)-3-
 [methyl(2-methylpropyl)amino]pyrrolidin-1-yl}cyclohexyl]-4-
 {5-[(1S,2S)-2-fluorocyclopropyl]-1,2,4-oxadiazol-3-yl}-4-
 methylpiperidine-1-carboxamide

15 Example 129: N-{(1R,6S)-6-[4-(diethylamino)piperidin-
 1-yl]-2,2-difluorocyclohexyl}-4-{5-[(1S,2S)-2-
 fluorocyclopropyl]-1,2,4-oxadiazol-3-yl}-4-
 methylpiperidine-1-carboxamide

Example 130: N-[(1R,6S)-2,2-difluoro-6-((3S)-1-[(1-
 methylcyclopropyl)methyl]pyrrolidin-3-yl)oxy)cyclohexyl]-4-
 methyl-4-(4-methylphenyl)piperidine-1-carboxamide

20 Example 131: N-[(1R,6S)-2,2-difluoro-6-{4-methyl-4-
 [methyl(propan-2-yl)amino]piperidin-1-yl}cyclohexyl]-4-{5-
 [(1S,2S)-2-fluorocyclopropyl]-1,2,4-oxadiazol-3-yl}-4-
 methylpiperidine-1-carboxamide

25 Example 132: N-{(1R,6S)-2,2-difluoro-6-[4-(propan-2-
 yl)piperazine-1-carbonyl]cyclohexyl}-4-{5-[(1S,2S)-2-

fluorocyclopropyl]-1,2,4-oxadiazol-3-yl}-4-
methylpiperidine-1-carboxamide

Example 133: N-[(1R,6S)-2,2-difluoro-6-({(3S)-1-[(1-
fluorocyclopropyl)methyl]pyrrolidin-3-yl}oxy)cyclohexyl]-4-
5 {5-[(1S,2S)-2-fluorocyclopropyl]-1,2,4-oxadiazol-3-yl}-4-
methylpiperidine-1-carboxamide

Example 134: N-[(1R,6S)-2,2-difluoro-6-(4-{methyl[(1-
methylcyclopropyl)methyl]amino}piperidin-1-yl)cyclohexyl]-
4-{5-[(1S,2S)-2-fluorocyclopropyl]-1,2,4-oxadiazol-3-yl}-4-
10 methylpiperidine-1-carboxamide

Example 135: N-[(1R,6S)-2,2-difluoro-6-{{(3S)-1-[[1-
(trifluoromethyl)cyclopropyl]methyl}pyrrolidin-3-
yl]oxy}cyclohexyl]-4-{5-[(1S,2S)-2-fluorocyclopropyl]-
1,2,4-oxadiazol-3-yl}-4-methylpiperidine-1-carboxamide

Example 136: N-[(1R,6S)-2,2-difluoro-6-(4-{{(1-
fluorocyclopropyl)methyl}(methyl)amino}piperidin-1-
yl)cyclohexyl]-4-{5-[(1S,2S)-2-fluorocyclopropyl]-1,2,4-
oxadiazol-3-yl}-4-methylpiperidine-1-carboxamide

Example 137: N-[(1R,6S)-6-{(3S)-3-
20 [(cyclopropylmethyl)(methyl)amino]pyrrolidin-1-yl}-2,2-
difluorocyclohexyl]-4-{5-[(1S,2S)-2-fluorocyclopropyl]-
1,2,4-oxadiazol-3-yl}-4-methylpiperidine-1-carboxamide

Example 138: N-[(1R,6S)-6-{(3S)-3-
[(cyclopropylmethyl)(methyl)amino]pyrrolidin-1-yl}-2,2-
25 difluorocyclohexyl]-4-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)-

4-methylpiperidine-1-carboxamide

Example 139: *rac*-4-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)-N-[(1R,2R,6S)-2-fluoro-6-[4-(propan-2-yl)piperazin-1-yl]cyclohexyl]-4-methylpiperidine-1-carboxamide

5 Example 140: N-[(1R,6S)-2,2-difluoro-6-[4-(methyl{[1-(trifluoromethyl)cyclopropyl]methyl}amino)piperidin-1-yl]cyclohexyl]-4-{5-[(1S,2S)-2-fluorocyclopropyl]-1,2,4-oxadiazol-3-yl}-4-methylpiperidine-1-carboxamide

10 Example 141: N-[(1R,6S)-6-{(1R,3R,5S)-3-[(cyclopropylmethyl)(methyl)amino]-8-azabicyclo[3.2.1]octan-8-yl}-2,2-difluorocyclohexyl]-4-{5-[(1S,2S)-2-fluorocyclopropyl]-1,2,4-oxadiazol-3-yl}-4-methylpiperidine-1-carboxamide

15 Example 142: N-[(1R,6S)-6-{(1R,3S,5S)-3-[(cyclopropylmethyl)(methyl)amino]-8-azabicyclo[3.2.1]octan-8-yl}-2,2-difluorocyclohexyl]-4-{5-[(1S,2S)-2-fluorocyclopropyl]-1,2,4-oxadiazol-3-yl}-4-methylpiperidine-1-carboxamide

20 Example 143: N-[(1R,6S)-2,2-difluoro-6-{[(3S)-1-(2-fluoro-2-methylpropyl)pyrrolidin-3-yl]oxy}cyclohexyl]-4-{5-[(1S,2S)-2-fluorocyclopropyl]-1,2,4-oxadiazol-3-yl}-4-methylpiperidine-1-carboxamide

25 Example 144: N-[(1R,6S)-6-{(4S)-4-[(cyclopropylmethyl)(methyl)amino]azepan-1-yl}-2,2-difluorocyclohexyl]-4-{5-[(1S,2S)-2-fluorocyclopropyl]-

1,2,4-oxadiazol-3-yl}-4-methylpiperidine-1-carboxamide

Example 145: N-[(1R,6S)-6-{(4R)-4-[(cyclopropylmethyl)(methyl)amino]azepan-1-yl}-2,2-difluorocyclohexyl]-4-{5-[(1S,2S)-2-fluorocyclopropyl]-

5 1,2,4-oxadiazol-3-yl}-4-methylpiperidine-1-carboxamide

Example 146: N-{(1R,6S)-2,2-difluoro-6-[4-(propan-2-yl)piperazin-1-yl]cyclohexyl}-4-{5-[(1S,2S)-2-fluorocyclopropyl]-1,2,4-oxadiazol-3-yl}-N,4-dimethylpiperidine-1-carboxamide

10 Example 147: 4-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)-N-{(1S,6S)-2,2-dimethyl-6-[4-(propan-2-yl)piperazin-1-yl]cyclohexyl}-4-methylpiperidine-1-carboxamide

Example 148: N-[(1R,6S)-2,2-difluoro-6-{3-[methyl(propan-2-yl)amino]azetidin-1-yl}cyclohexyl]-4-{5-
15 [(1S,2S)-2-fluorocyclopropyl]-1,2,4-oxadiazol-3-yl}-4-methylpiperidine-1-carboxamide

Example 149: N-[(1R,6S)-6-{3-[(cyclopropylmethyl)(methyl)amino]azetidin-1-yl}-2,2-difluorocyclohexyl]-4-{5-[(1S,2S)-2-fluorocyclopropyl]-
20 1,2,4-oxadiazol-3-yl}-4-methylpiperidine-1-carboxamide

Example 150: N-[(1R,6S)-2,2-difluoro-6-({(3S)-1-[(3-methyloxetan-3-yl)methyl]pyrrolidin-3-yl}oxy)cyclohexyl]-4-{5-[(1S,2S)-2-fluorocyclopropyl]-1,2,4-oxadiazol-3-yl}-4-methylpiperidine-1-carboxamide

25 Example 151: *rac*-4-(5-cyclopropyl-1,2,4-oxadiazol-3-

yl)-4-methyl-N-{(1S,2S)-2-[4-(propan-2-yl)piperazin-1-yl]cycloheptyl}piperidine-1-carboxamide

Example 152: N-{(1R,6S)-2,2-difluoro-6-[4-(propan-2-yl)-1,4-diazepan-1-yl]cyclohexyl}-4-{5-[(1S,2S)-2-fluorocyclopropyl]-1,2,4-oxadiazol-3-yl}-4-methylpiperidine-1-carboxamide

Example 153: (1S,2R)-3,3-difluoro-2-[(4-{5-[(1S,2S)-2-fluorocyclopropyl]-1,2,4-oxadiazol-3-yl}-4-methylpiperidine-1-carbonyl)amino]cyclohexyl 4-(propan-2-yl)piperazine-1-carboxylate

Example 154: N-[(1S,6S)-2,2-difluoro-6-{[1-(propan-2-yl)piperidin-4-yl]sulfanyl}cyclohexyl]-4-{5-[(1S,2S)-2-fluorocyclopropyl]-1,2,4-oxadiazol-3-yl}-4-methylpiperidine-1-carboxamide

Example 155: N-{(1S,6S)-2,2-difluoro-6-[1-(propan-2-yl)piperidine-4-sulfonyl]cyclohexyl}-4-{5-[(1S,2S)-2-fluorocyclopropyl]-1,2,4-oxadiazol-3-yl}-4-methylpiperidine-1-carboxamide.

[0241]

The compound of the above Reference example 124 which is a diastereomixture and its intermediates for preparing the compound can be obtained as a sole enantiomer by optical resolution with chiral column chromatography or by crystallization with an acid having a chiral center. In addition, the compound of Reference example 124 can be also

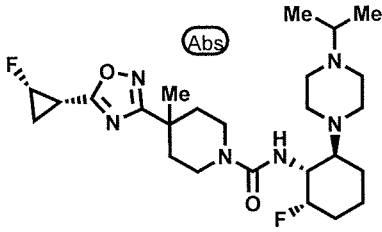
prepared as a sole enantiomer by using optically-active epoxide as a starting material. Thus, when Reference example 124 as a starting Material A is further determined through separation or asymmetric synthesis, the diastereomixture of
 5 Example 156 can be prepared as each diastereomer.

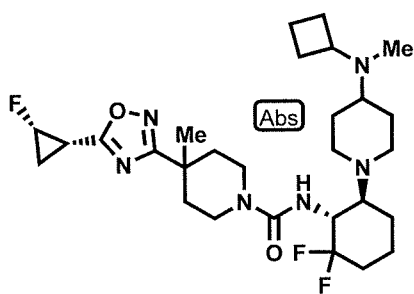
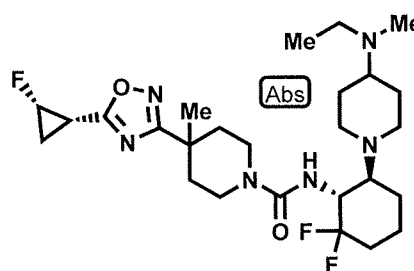
[0242]

In addition, the compound of Example 156 which is a diastereomixture can be obtained as a sole enantiomer by optical resolution with chiral column chromatography or by
 10 crystallization with an acid having a chiral center. Thus, the two diastereomers of Example 156 can be separated as each diastereomer.

[0243]

The compound of Example 156 is a diastereomixture
 15 comprising two different diastereomers. These diastereomers can be separated through its process or by optical resolution with chiral column chromatography. It means that the two different diastereomers were substantially prepared.

No.	Chemical structure of diastereomer	Chemical name
156-A		4-{5-[(1S,2S)-2-fluorocyclopropyl]-1,2,4-oxadiazol-3-yl}-N-[(1R,2S,6S)-2-fluoro-6-[4-(propan-2-yl)piperazin-1-yl]cyclohexyl]-4-methylpiperidine-1-carboxamide

		4.55 (1H, d, J = 7.9 Hz), 4.92 (1H, dddd, J = 63.6, 6.0, 6.0, 3.6 Hz).
159		¹ H-NMR (CDCl ₃) δ: 1.15-1.35 (5H, m), 1.35-1.53 (3H, m), 1.53-1.74 (4H, m), 1.74-2.21 (14H, m), 2.21-2.30 (2H, m), 2.30-2.43 (2H, m), 2.44-2.57 (2H, m), 2.61-2.72 (1H, m), 2.74-2.88 (1H, m), 3.00-3.20 (3H, m), 3.65-3.82 (2H, m), 4.05-4.21 (1H, m), 4.54 (1H, d, J = 8.0 Hz), 4.91 (1H, dddd, J = 64.0, 6.0, 6.0, 3.6 Hz).
160		¹ H-NMR (CDCl ₃) δ: 1.08-1.83 (16H, m), 1.84-2.03 (3H, m), 2.07-2.43 (9H, m), 2.45-2.76 (5H, m), 2.86-2.98 (1H, m), 3.06-3.20 (2H, m), 3.62-3.77 (2H, m), 4.08-4.23 (1H, m), 4.53 (1H, d, J = 7.9 Hz), 4.93 (1H, dddd, J = 63.6, 6.0, 6.0, 3.6 Hz).

[0245]

The chemical names of Example 157 to Example 160 are listed below.

Example 157: N-[(1R,6S)-2,2-difluoro-6-{4-[methyl(2-methylpropyl)amino]piperidin-1-yl}cyclohexyl]-4-{5-[(1S,2S)-2-fluorocyclopropyl]-1,2,4-oxadiazol-3-yl}-4-methylpiperidine-1-carboxamide

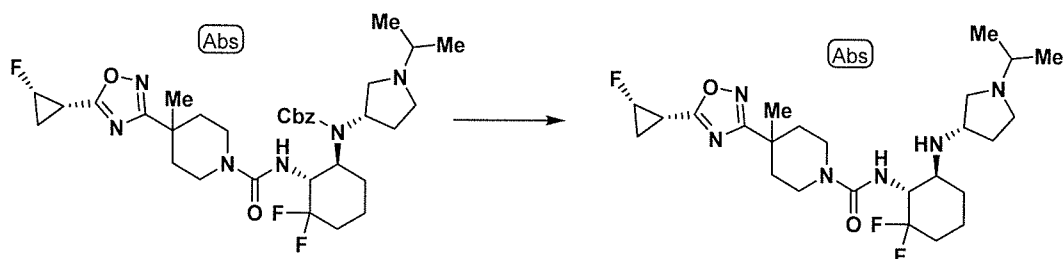
Example 158: N-[(1R,6S)-6-{4-[(cyclopropylmethyl)(methyl)amino]piperidin-1-yl}-2,2-difluorocyclohexyl]-4-{5-[(1S,2S)-2-fluorocyclopropyl]-1,2,4-oxadiazol-3-yl}-4-methylpiperidine-1-carboxamide

Example 159: N-[(1R,6S)-6-{4-[cyclobutyl(methyl)amino]piperidin-1-yl}-2,2-difluorocyclohexyl]-4-{5-[(1S,2S)-2-fluorocyclopropyl]-1,2,4-oxadiazol-3-yl}-4-methylpiperidine-1-carboxamide

5 Example 160: N-[(1R,6S)-6-{4-[ethyl(methyl)amino]piperidin-1-yl}-2,2-difluorocyclohexyl]-4-{5-[(1S,2S)-2-fluorocyclopropyl]-1,2,4-oxadiazol-3-yl}-4-methylpiperidine-1-carboxamide
[0246]

10 Example 161:

N-[(1R,6S)-2,2-Difluoro-6-{[(3S)-1-(propan-2-yl)pyrrolidin-3-yl]amino}cyclohexyl]-4-{5-[(1S,2S)-2-fluorocyclopropyl]-1,2,4-oxadiazol-3-yl}-4-methylpiperidine-1-carboxamide



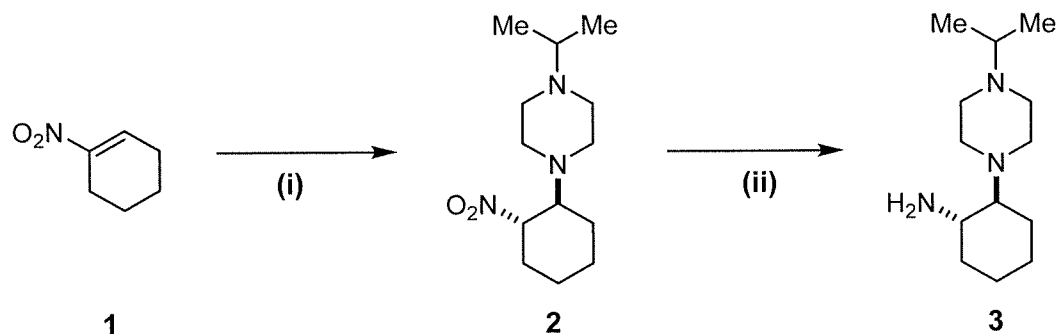
15 To a mixture of Reference example 90 (175 mg) and ethanol (1.3 mL) was added palladium carbon (6.4 mg) at room temperature, and the mixture was stirred under hydrogen atmosphere. After the reaction was terminated as judged by LC-MS, the reaction mixture was filtrated with Celite, and
20 concentrated *in vacuo*. Then, the obtained residue was purified by HPLC (eluate: acetonitrile/water/TFA) to give the title compound (44.1 mg).

$^1\text{H-NMR}$ (CDCl_3) δ : 1.03-1.31 (2H, m), 1.13 (6H, d, $J = 6.0$ Hz), 1.34 (3H, s), 1.38-1.88 (13H, m), 1.91-2.23 (3H, m), 2.27 (2H, d, $J = 13.2$ Hz), 2.33-2.42 (1H, m), 2.42-2.54 (1H, m), 2.95-3.21 (2H, m), 3.32-3.54 (1H, brs), 3.58-3.80 (2H, m), 3.91-4.08 (1H, m), 4.65 (1H, d, $J = 9.2$ Hz), 4.93 (1H, dddd, $J = 63.6, 6.4, 6.4, 4.0$ Hz).

[0247]

Reference example 1:

rac-(1*S*,2*S*)-2-[4-(Propan-2-yl)piperazin-1-yl]cyclohexan-1-amine



[0248]

Step (i):

To a mixture of Compound 1 (1.13 g) and dichloromethane (2 mL) was added 1-isopropylpiperazine (1.14 g) at room temperature, and the mixture was stirred for 17 hours. After the reaction was terminated as judged by the consumption of the starting material, diethyl ether was added to the reaction mixture. The precipitate was removed by filtration, and the filtrate was concentrated *in vacuo* to give a crude product. The obtained crude product was purified by amino

silica gel column chromatography (eluate: hexane/ethyl acetate) to give the title compound 2 (1.82 g).

LCMS: [M+H]⁺/Rt (min): 256/0.48

[0249]

5 Step (ii):

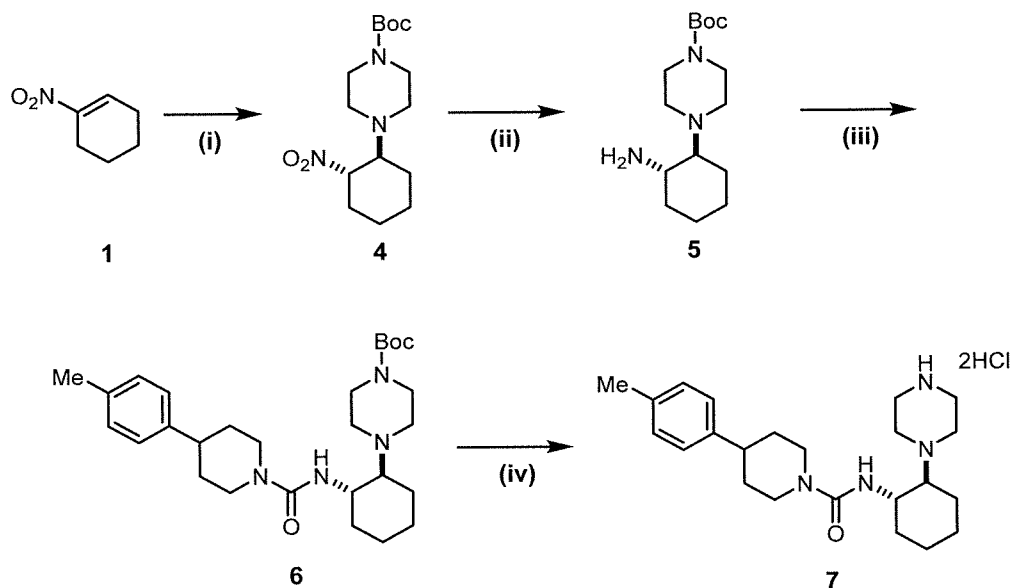
To a mixture of Compound 2 (1.14 g), acetic acid (2.04 mL), and ethanol (15 mL) was added palladium/carbon (0.95 g) at room temperature, and the mixture was stirred under hydrogen atmosphere for 18 hours. After the reaction was
10 terminated as judged by LC-MS, the reaction mixture was filtrated with Celite, and concentrated *in vacuo*. Then, the obtained residue was purified by amino silica gel column chromatography (eluate: chloroform) to give the title compound 3 (0.370 g).

15 LCMS: [M+H]⁺/Rt (min): 226/0.31

[0250]

Reference example 2:

rac-4-(4-Methylphenyl)-N-[(1S,2S)-2-(piperazin-1-yl)cyclohexyl]piperidine-1-carboxamide dihydrochloride



[0251]

Step (i):

The title compound 4 (1.28 g) was prepared in the same manner as Step (i) in Reference example 1 by using Compound 1 (1.17 g) and 1-Boc-piperazine (1.72 g).

[0252]

Step (ii):

To a solution of Compound 4 (593 mg) in ethanol (9 mL) was added palladium hydroxide (266 mg) at room temperature, and the mixture was stirred under hydrogen atmosphere. After the reaction was terminated as judged by LC-MS, the reaction mixture was filtrated with Celite, and the filtrate was concentrated *in vacuo* to give the title compound 5 (560 mg).

[0253]

Step (iii):

To a mixture of Compound 5 (370 mg), triethylamine (0.91

mL), and dichloromethane (5 mL) was added 4-nitrophenyl chloroformate (316 mg) at 0°C, and the mixture was stirred for 2 hours. Then, 4-(4-methylphenyl)piperidine (297 mg) was added to the reaction mixture at 0°C, and the stirring was continued at room temperature. After the reaction was terminated as judged by the consumption of the reaction intermediate, water was added to the reaction mixture, and the mixture was extracted with chloroform. The organic layer was dried over anhydrous sodium sulfate and concentrated *in vacuo*, and then the obtained residue was purified by amino silica gel column chromatography (eluate: hexane/ethyl acetate) to give the title compound 6 (435 mg).

[0254]

Step (iv):

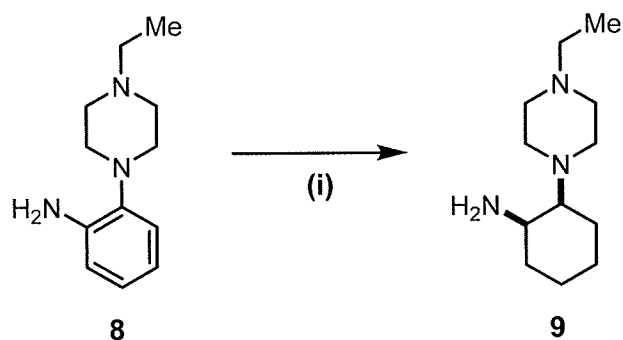
To a mixture of Compound 6 (430 mg) and chloroform (3 mL) was added hydrogen chloride/dioxane solution (4 M, 2.22 mL) at 0°C, and the mixture was stirred for 16 hours. Then, the reaction mixture was concentrated *in vacuo* to give the title compound 7 (310 mg).

LCMS: [M+H]⁺/Rt (min): 385/0.71

[0255]

Reference example 3:

rac-(1R,2S)-2-(4-Ethylpiperazin-1-yl)cyclohexan-1-amine



Step (i):

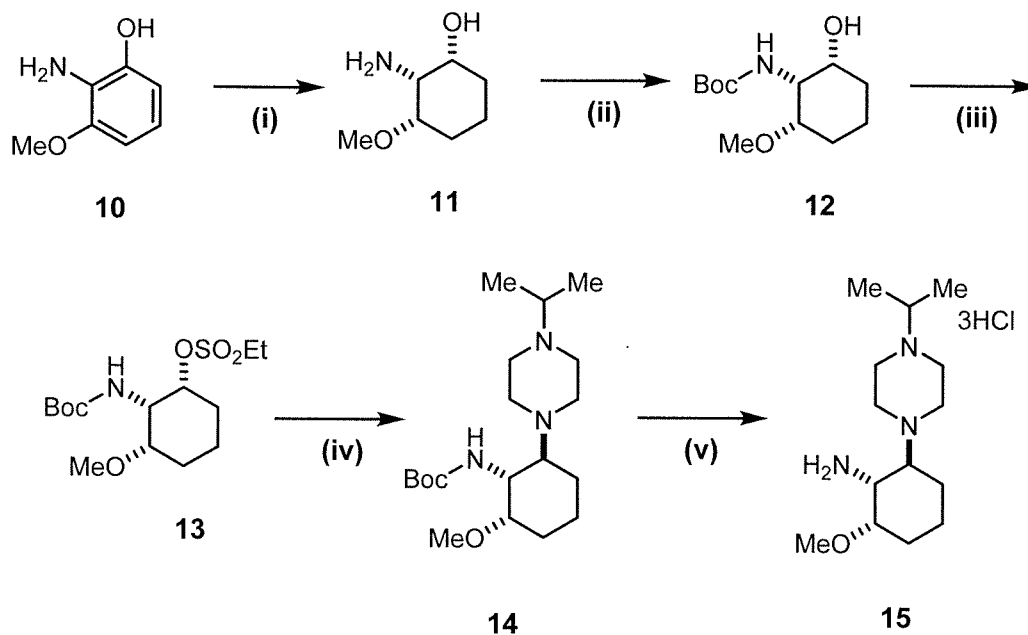
To a mixture of Compound 8 (312 mg) and acetic acid (5 mL) was added platinum(IV) oxide (86 mg), and mixture was stirred at 70°C under hydrogen atmosphere for 6 hour. Then, the reaction mixture was filtrated with Celite, and the filtrate was concentrated *in vacuo* to give a crude product. The obtained crude product was purified by amino silica gel column chromatography (eluate: hexane/ethyl acetate) to give the title compound 9 (9 mg).

LCMS: [M+H]⁺/Rt (min): 212/0.15

[0256]

Reference example 4:

rac-(1R,2S,6S)-2-Methoxy-6-[4-(propan-2-yl)piperazin-1-yl]cyclohexan-1-amine trihydrochloride



[0257]

Step (i):

The title compound 11 (424 mg) was prepared in the same manner as Step (i) in Reference example 3 by using Compound 10 (407 mg).

LCMS: [M+H]⁺/Rt (min): 146/0.15

[0258]

Step (ii):

To a mixture of Compound 11 (424 mg), triethylamine (1.22 mL), and acetonitrile (10 mL) was added Boc₂O (765 mg) at room temperature, and the mixture was stirred at room temperature. After the reaction was terminated as judged by LC-MS, water was added to the reaction mixture and the mixture was extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and concentrated in

vacuo, and then the obtained residue was purified by silica gel column chromatography (eluate: hexane/ethyl acetate) to give the title compound 12 (310 mg).

LCMS: [M+H]⁺/Rt (min): 246/0.78

5 [0259]

Step (iii):

To a mixture of Compound 12 (141 mg), triethylamine (0.160 mL), and THF (3 mL) was added ethanesulfonyl chloride (0.160 mL) under ice temperature, and the mixture was warmed
10 to room temperature and the stirring was continued. After the reaction was terminated as judged by LC-MS, water was added to the reaction mixture, and the mixture was extracted with chloroform. The organic layer was dried over anhydrous sodium sulfate and concentrated *in vacuo*, and then the
15 obtained residue was purified by silica gel column chromatography (eluate: hexane/ethyl acetate) to give the title compound 13 (180 mg).

LCMS: [M+H]⁺/Rt (min): 338/0.86

[0260]

20 Step (iv):

To a mixture of Compound 13 (155 mg), 1-isopropylpiperazine (236 mg), and 1,4-dioxane (4 mL) was added potassium carbonate (76 mg) at room temperature, and the mixture was stirred for 13 hours heating at 150°C with
25 a microwave device. Then, water was added to the reaction

mixture, and the mixture was extracted with chloroform. The organic layer was dried over anhydrous sodium sulfate and concentrated *in vacuo*, and then the obtained residue was purified by amino silica gel column chromatography (eluate:
 5 hexane/ethyl acetate) to give the title compound 14 (17 mg).
 LCMS: [M+H]⁺/Rt (min): 356/0.81

[0261]

Step (v):

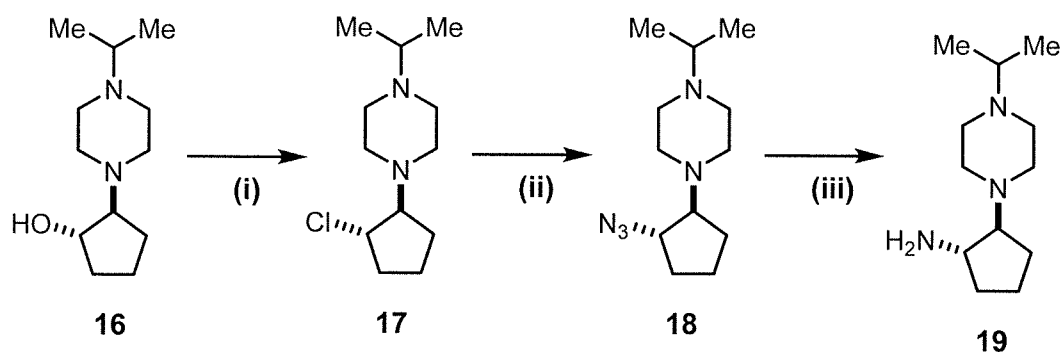
The title compound 15 (16.8 mg) was prepared in the
 10 same manner as Step (iv) in Reference example 2 by using Compound 14 (16.3 mg).

LCMS: [M+H]⁺/Rt (min): 256/0.32

[0262]

Reference example 5:

15 *rac*-(1*S*,2*S*)-2-[4-(Propan-2-yl)piperazin-1-yl]cyclopentane-1-amine



[0263]

Step (i):

20 To a mixture of Compound 16 (315 mg), triethylamine

(0.289 mL), and THF (5 mL) was added ethanesulfonyl chloride (0.15 mL), and the mixture was stirred at room temperature for 15 hours. After the reaction was terminated as judged by the consumption of the starting material, water was added to the reaction mixture, and the mixture was extracted with chloroform. The organic layer was dried over anhydrous sodium sulfate and concentrated *in vacuo*, and then the obtained residue was purified by amino silica gel column chromatography (eluate: ethyl acetate/hexane) to give the title compound 17 (140 mg).

LCMS: [M+H]⁺/Rt (min): 231/0.44

[0264]

Step (ii):

To a mixture of Compound 17 (136 mg) and DMF (4 mL) was added sodium azide (77 mg), and the mixture was stirred at 80°C for 3.5 hours. After the reaction was terminated as judged by the consumption of the starting material, water was added to the reaction mixture, and the mixture was extracted with chloroform. The organic layer was dried over anhydrous sodium sulfate, and concentrated *in vacuo* to give the title compound 18 (137 mg).

LCMS: [M+H]⁺/Rt (min): 238/0.42

[0265]

Step (iii):

To a mixture of Compound 18 (42.4 mg), hydrogen

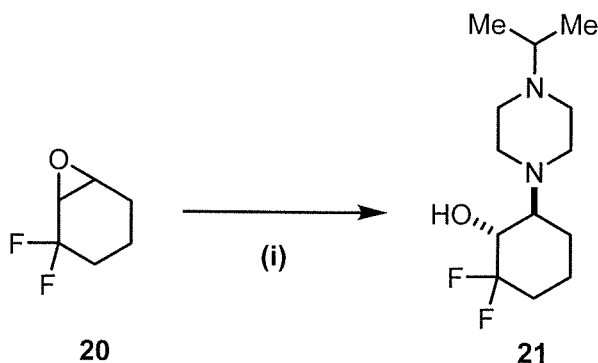
chloride/ethyl acetate solution (4.0 M, 0.711 mL), and ethanol (2.8 mL) was added palladium/carbon (202 mg), and the mixture was stirred under hydrogen atmosphere for 8 hours. After the reaction was terminated as judged by LC-MS, methanol and aqueous sodium bicarbonate were added to the reaction mixture, and the mixture was filtrated with Celite and extracted with chloroform /methanol (6/1). The organic layer was dried over anhydrous sodium sulfate and concentrated *in vacuo*, and then the obtained residue was purified by amino silica gel column chromatography (eluate: chloroform/methanol) to give the title compound 19 (98.7 mg).

LCMS: $[M+H]^+/R_t$ (min): 212/0.15

[0266]

Reference example 6:

rac-(1*R*,6*S*)-2,2-Difluoro-6-[4-(propan-2-yl)piperazin-1-yl]cyclohexan-1-ol



Step (i):

To a mixture of Compound 20 (688 mg) and ethanol (20

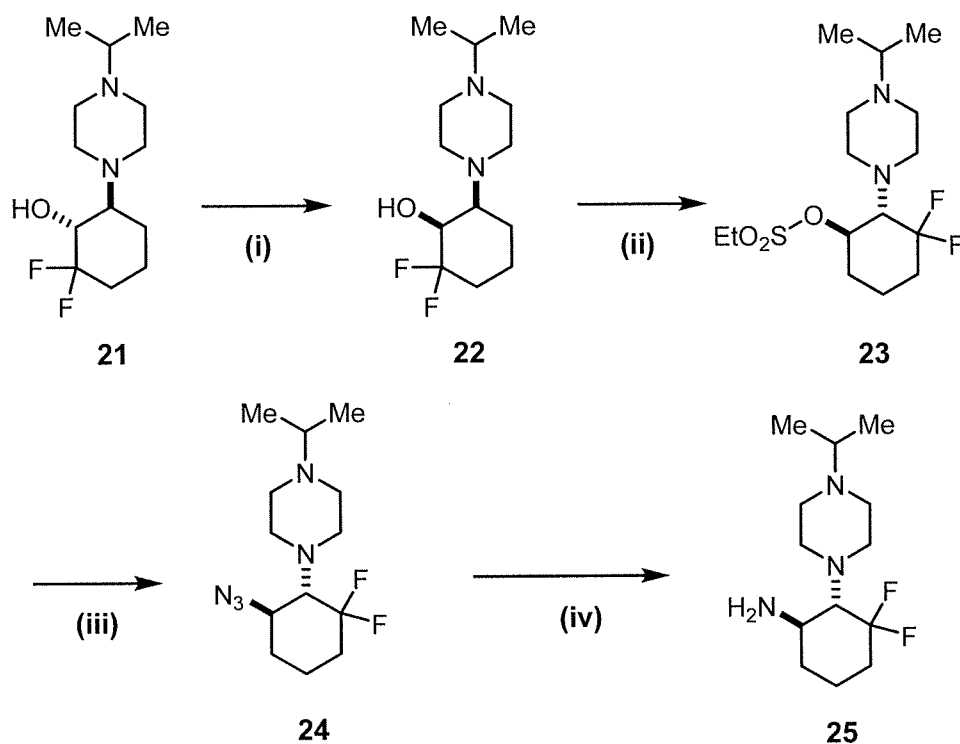
mL) was added 1-isopropylpiperazine (723 mg) at room temperature, and the mixture was stirred for 9 hours heating at 80°C. The reaction mixture was cooled to room temperature, and then concentrated *in vacuo*. And, the
 5 obtained residue was purified by amino silica gel column chromatography (eluate: hexane/ethyl acetate) to give the title compound 21 (830 mg).

LCMS: $[M+H]^+/R_t$ (min): 263/0.35

[0267]

10 Reference example 7:

rac-(1*R*,2*S*)-3,3-Difluoro-2-[4-(propan-2-yl)piperazin-1-yl]cyclohexan-1-amine



[0268]

15 Step (i):

To a mixture of DMSO (0.081 mL) and dichloromethane (2 mL) was added oxalyl chloride (0.075 mL) at -78°C , and the mixture was stirred for 20 minutes. Then, a solution of Compound 21 (150 mL) in dichloromethane (2 mL) was added to the reaction mixture, and the mixture was stirred at -78°C further for 30 minutes. Triethylamine (0.398 mL) was added to the reaction mixture, and the the mixture was warmed to 0°C . Then, the mixture was stirred for 30 minutes, and sodium borohydride was added thereto. The mixture was stirred for 30 minutes. And, water was added to the reaction mixture, and the mixture was extracted with chloroform. The organic layer was dried over anhydrous sodium sulfate, concentrated *in vacuo*, and then the obtained residue was purified by silica gel column chromatography (eluate: chloroform/methanol) to give the title compound 22 (27 mg). LCMS: $[\text{M}+\text{H}]^{+}/\text{Rt}$ (min): 263/0.38

[0269]

Step (ii):

To a mixture of Compound 22 (27 mg), triethylamine (0.029 mL), and THF (2 mL) was added ethanesulfonyl chloride (0.015 mL), and the mixture was stirred at room temperature. After the reaction was terminated as judged by the consumption of the starting material, water was added to the reaction mixture, and the mixture was extracted with chloroform. The organic layer was dried over anhydrous

sodium sulfate and concentrated *in vacuo*, and then the obtained residue was purified by amino silica gel column chromatography (eluate: chloroform/methanol) to give the title compound 23 (23 mg).

5 LCMS: [M+H]⁺/Rt (min): 354/0.65

[0270]

Step (iii):

The title compound 24 (16.0 mg) was prepared in the same manner as Step (ii) in Reference example 5 by using
10 Compound 23 (23.4 mg).

LCMS: [M+H]⁺/Rt (min): 288/0.60

[0271]

Step (iv):

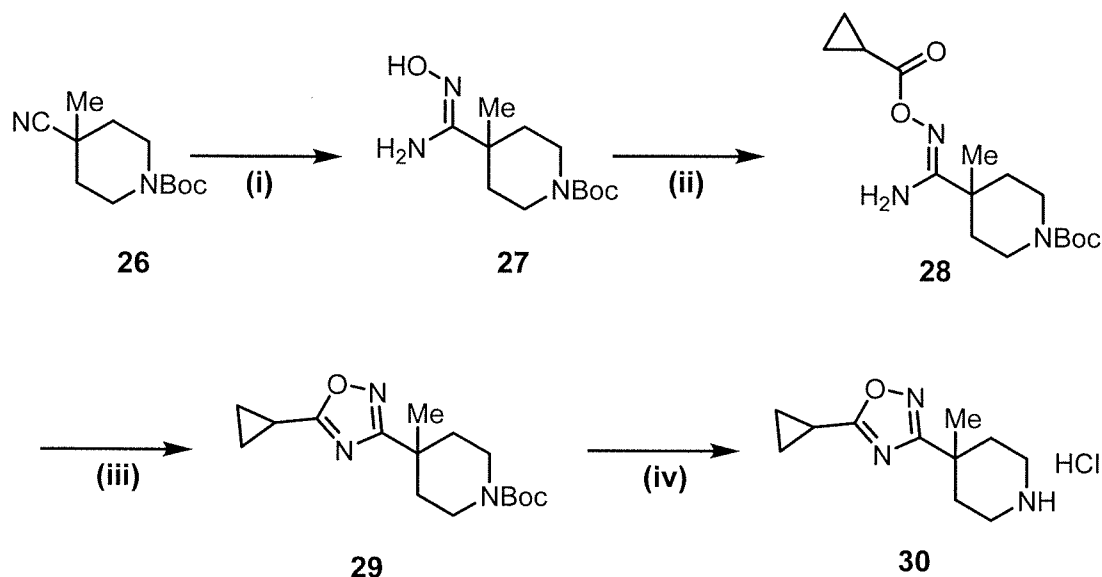
To a mixture of Compound 24 (14 mg), THF (1 mL), and
15 water (1 mL) was added triphenylphosphine (25.6 mg) at room temperature, and the mixture was stirred for 4.5 hours heating at 50°C. Then, the reaction mixture was cooled to room temperature, and aqueous hydrochloric acid was added thereto. The mixture was washed with ethyl acetate, and
20 aqueous sodium bicarbonate was added to the aqueous layer. The obtained mixture was extracted with chloroform/methanol (3/1). The organic layer was dried over anhydrous sodium sulfate, and concentrated *in vacuo* to give the title compound
25 (7.8 mg).

LCMS: [M+H]⁺/Rt (min): 262/0.31

[0272]

Reference example 8:

4-(5-Cyclopropyl-1,2,4-oxadiazol-3-yl)-4-methylpiperidine
monohydrochloride



[0273]

Step (i):

To a solution of Compound 26 (50.0 g) in ethanol (446 mL) was added 50 % aqueous hydroxylamine (132 mL), and the mixture was stirred at 70°C for 8 hours. The reaction mixture was cooled to room temperature, and water (892 mL) was added to the reaction mixture. The mixture was stirred at room temperature for 30 minutes. The precipitated white crystal was collected on a filter, the obtained crystal was suspended in water (344 mL) again, and the suspension was stirred at room temperature for 30 minutes. The precipitated white solid was collected on a filter and dried to give the

10

15

title compound 27 (52.3 g).

LCMS: [M+H]⁺/Rt (min): 258/0.52 (Method C)

[0274]

Step (ii):

5 To a mixture of Compound 27 (52.3 g),
cyclopropanecarboxylic acid (18.4 g), HATU (85 g), and THF
(406 mL) in ice bath was added slowly dropwise triethylamine
(142 mL), and the mixture was stirred at room temperature
for 12 hours. To the reaction mixture was added ethyl
10 acetate (406 mL), and the mixture was washed with water (406
mL) and brine (406 mL). The organic layer was dried over
anhydrous sodium sulfate, concentrated *in vacuo*, and then
the obtained residue was purified by silica gel column
chromatography (eluate: hexane/ethyl acetate) to give the
15 title compound 28 (59.1 g).

LCMS: [M+H]⁺/Rt (min): 326/0.77 (Method C)

[0275]

Step (iii):

20 A mixture of Compound 28 (59.1 g), DBU (54.2 mL), and
toluene (727 mL) was stirred under reflux for one hour. The
reaction mixture was cooled to room temperature, and washed
with water (727 mL). The organic layer was concentrated *in*
vacuo, and then the obtained residue was purified by silica
gel column chromatography (eluate: hexane/ethyl acetate) to
25 give the title compound 29 (54.5 g).

LCMS: [M+H]⁺/Rt (min): 308/1.11

[0276]

Step (iv) :

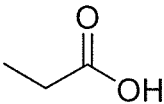
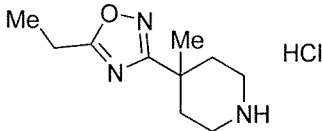
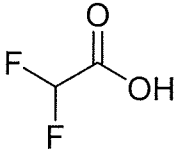
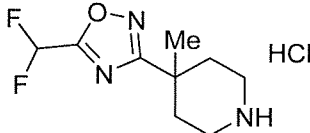
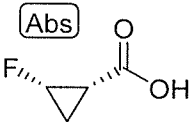
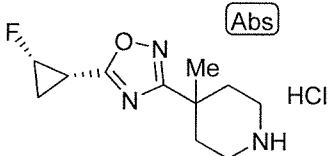
The title compound 30 (35.3 g) was prepared in the same
5 manner as Step (iv) in Reference example 2 by using Compound
29 (54.5 g).

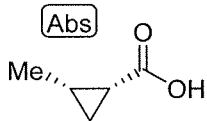
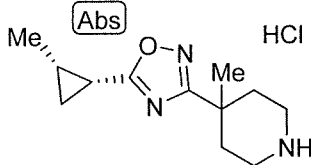
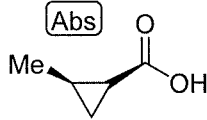
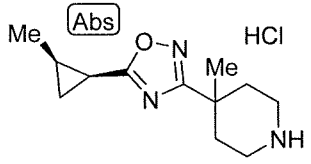
LCMS: [M+H]⁺/Rt (min): 208/0.30 (Method C)

[0277]

Reference examples 9 to 12'

10 The compounds of Reference examples 9 to 12' shown in the table below were prepared according to the process in the above Reference example 8, by using each appropriate strating compound instead of cyclopropanecarboxylic acid at Step (ii) in Reference example 8.

Reference example	Starting compound	Chemical structure	Instrumental analytical data
9			LCMS: [M+H] ⁺ /Rt (min): 196/0.32 (Method C)
10			LCMS: [M+H] ⁺ /Rt (min): 218/0.44
11			LCMS: [M+H] ⁺ /Rt (min): 226/0.29 (Method C)

12			LCMS: [M+H] ⁺ /Rt (min): 222/0.46 (Method C)
12'			LCMS: [M+H] ⁺ /Rt (min): 222/0.46 (Method C)

[0278]

Reference example 9: 4-(5-ethyl-1,2,4-oxadiazol-3-yl)-
4-methylpiperidine monohydrochloride

Reference example 10: 4-[5-(difluoromethyl)-1,2,4-
5 oxadiazol-3-yl]-4-methylpiperidine monohydrochloride

Reference example 11: 4-{5-[(1S,2S)-2-
fluorocyclopropyl]-1,2,4-oxadiazol-3-yl}-4-methylpiperidine
monohydrochloride

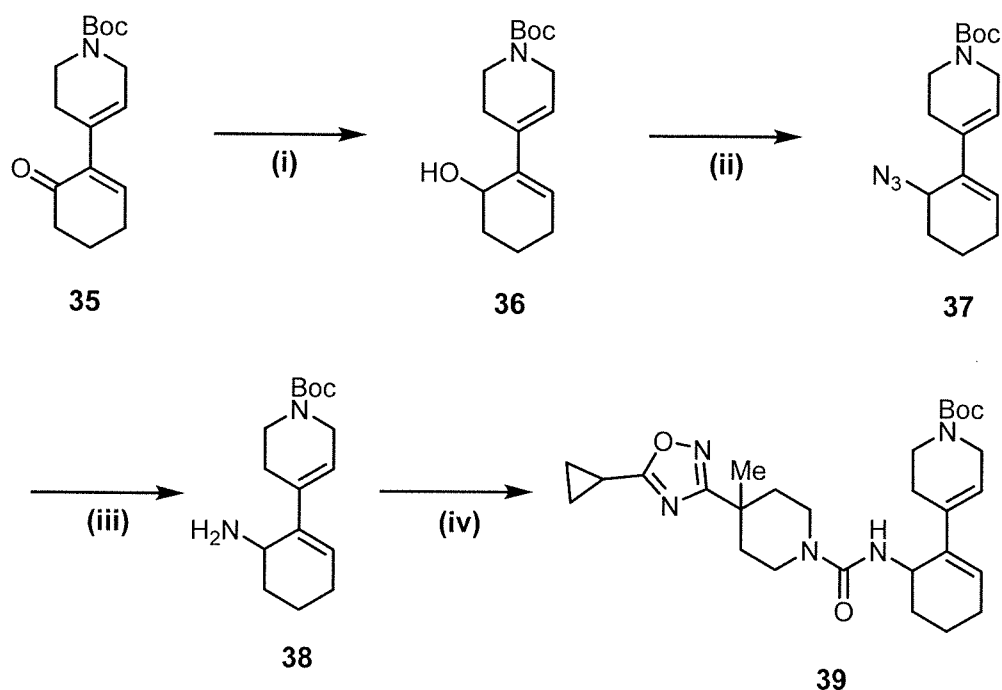
Reference example 12: 4-methyl-4-{5-[(1R,2S)-2-
10 methylcyclopropyl]-1,2,4-oxadiazol-3-yl}piperidine
monohydrochloride

Reference example 12': 4-methyl-4-{5-[(1S,2R)-2-
methylcyclopropyl]-1,2,4-oxadiazol-3-yl}piperidine
monohydrochloride

15 [0279]

Reference example 13:

rac-tert-Butyl 4-(6-{[4-(5-cyclopropyl-1,2,4-oxadiazol-3-
yl)-4-methylpiperidine-1-carbonyl]amino}cyclohex-1-en-1-
yl)-3,6-dihydropyridine-1(2H)-carboxylate



[0280]

Step (i):

To a mixture of Compound 35 (192 mg), cerium(III) chloride heptahydrate (309 mg), and methanol (3 mL) was added sodium borohydride (51.4 mg) under ice temperature, and the mixture was stirred at the same temperature for 3 hours. To the reaction mixture was added aqueous sodium bicarbonate, and the mixture was extracted with chloroform /methanol (6/1). The organic layer was dried over anhydrous sodium sulfate and concentrated *in vacuo*, and then the obtained residue was purified by silica gel column chromatography (eluate: hexane/ethyl acetate) to give the title compound 36 (120 mg).

LCMS: [M+H]⁺/Rt (min): 280/0.97

[0281]

Step (ii):

To a mixture of Compound 36 (115 mg), triethylamine (0.143 mL), and THF (2 mL) was added ethanesulfonyl chloride (0.058 mL) under ice temperature, and the mixture was stirred for 30 minutes. Then, sodium azide (107 mg) was added to the reaction solution. The mixture was warmed to room temperature, and then the mixture was stirred. After the reaction was terminated as judged by the consumption of the reaction intermediate, water was added to the reaction mixture, and the mixture was extracted with chloroform. The organic layer was dried over anhydrous sodium sulfate and concentrated *in vacuo*, and then the obtained residue was purified by silica gel column chromatography (eluate: hexane/ethyl acetate) to give the title compound 37 (80 mg).
LCMS: [M+H]⁺/Rt (min): 305/1.25

[0282]

Step (iii)

The title compound 38 (35 mg) was prepared in the same manner as Step (iv) in Reference example 7 by using Compound 37 (73 mg).

LCMS: [M+H]⁺/Rt (min): 279/0.74

[0283]

Step (iv)

The title compound 39 (14.0 mg) was prepared in the

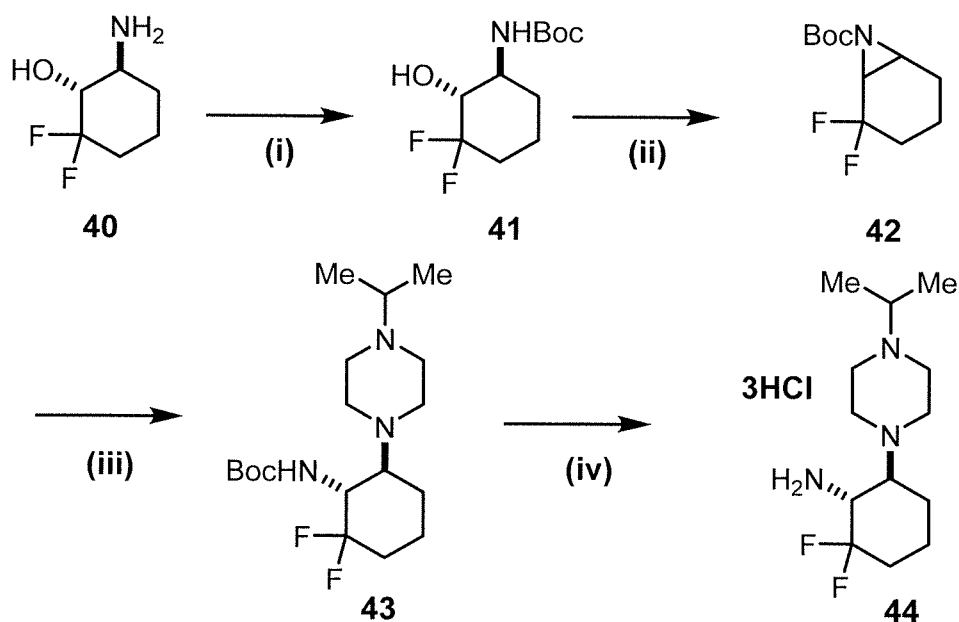
same manner as Step (iii) in Reference example 2 by using Compound 38 (14.4 mg).

LCMS: $[M+H]^+/R_t$ (min): 512/1.14

[0284]

5 Reference example 14:

rac-(1*R*, 6*S*)-2,2-Difluoro-6-[4-(propan-2-yl)piperazin-1-yl]cyclohexan-1-amine trihydrochloride



[0285]

10 Step (i):

The title compound 41 (1.59 g) was prepared in the same manner as Step (ii) in Reference example 4 by using Compound 40 (1.69 g).

LCMS: $[M+H]^+/R_t$ (min): 252/0.73

15 [0286]

Step (ii):

To a mixture of Compound 41 (1.5 g) and THF (30 mL) was added potassium *tert*-butoxide (1.01 g) under ice temperature, and the mixture was stirred at the same temperature for 20 minutes. Then, tosyl chloride (1.37 g) was added to the reaction mixture under ice temperature, and the reaction mixture was stirred further for 2.5 hours. Water was added to the reaction mixture under ice temperature, and the mixture was extracted with chloroform. The organic layer was dried over anhydrous sodium sulfate, and concentrated *in vacuo*. The obtained residue was dissolved in 1,4-dioxane (30 mL), and tosyl chloride (1.37 g) was added to the solution under ice temperature. The solution was heated to 100°C and stirred for 30 minutes. The reaction solution was cooled to room temperature, and aqueous ammonium chloride was added to the reaction solution. The mixture was extracted with chloroform/ethanol (3/1). The organic layer was dried over anhydrous sodium sulfate and concentrated *in vacuo*, and then the obtained residue was purified by silica gel column chromatography (eluate: hexane/ethyl acetate) to give the title compound 42 (1.09 g).

LCMS: [M+H]⁺/Rt (min): 234/1.01

[0287]

Step (iii):

A mixture of Compound 42 (1.09 g), 1-

isopropylpiperazine (0.899 g), and ethanol (10 mL) was stirred for 8 hours heating at 120°C with a microwave device. Then, the reaction solution was concentrated *in vacuo*, and then the obtained residue was purified by amino silica gel column chromatography (eluate: ethyl acetate/hexane) to give
 5 the title compound 43 (1.32 g).

LCMS: [M+H]⁺/Rt (min): 362/0.74

[0288]

Step (iv):

10 The title compound 44 (1.40 g) was prepared in the same manner as Step (iv) in Reference example 2 by using Compound 43 (1.31 g).

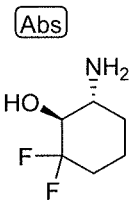
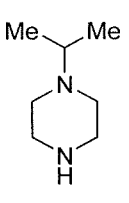
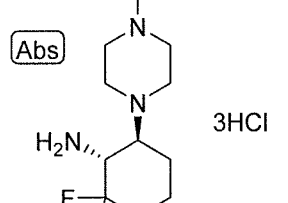
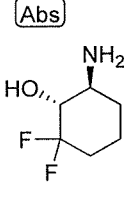
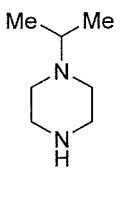
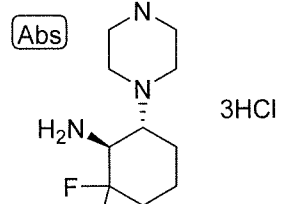
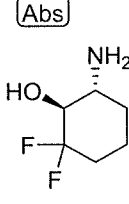
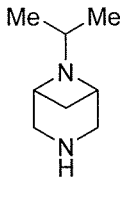
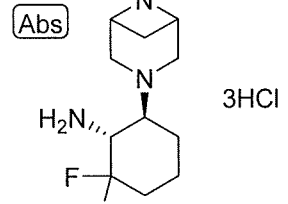
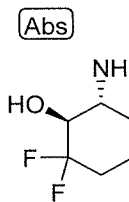
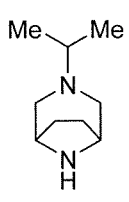
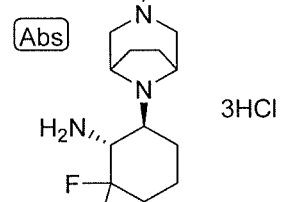
LCMS: [M+H]⁺/Rt (min): 262/0.19

[0289]

15 Reference examples 15 to 17

The compounds of Reference examples 15 to 17 shown in the table below were prepared according to the process in the above Reference example 14, by using an optically active isomer of Compound 40 (as Material A) instead of Compound 40
 20 at Step (i) in Reference example 14 and each appropriate starting compound (as Material B) instead of 1-isopropylpiperazine at Step (iii) in Reference example 14.

Reference example	Material A	Material B	Chemical structure	Instrumental analytical data
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15				LCMS: [M+H] ⁺ /Rt (min): 262/0.19
15'				LCMS: [M+H] ⁺ /Rt (min): 262/0.19 (Method C)
16				LCMS: [M+H] ⁺ /Rt (min): 274/0.242
17				LCMS: [M+H] ⁺ /Rt (min): 288/0.239

[0290]

Reference example 15: (1R,6S)-2,2-difluoro-6-[4-(propan-2-yl)piperazin-1-yl]cyclohexan-1-amine trihydrochloride

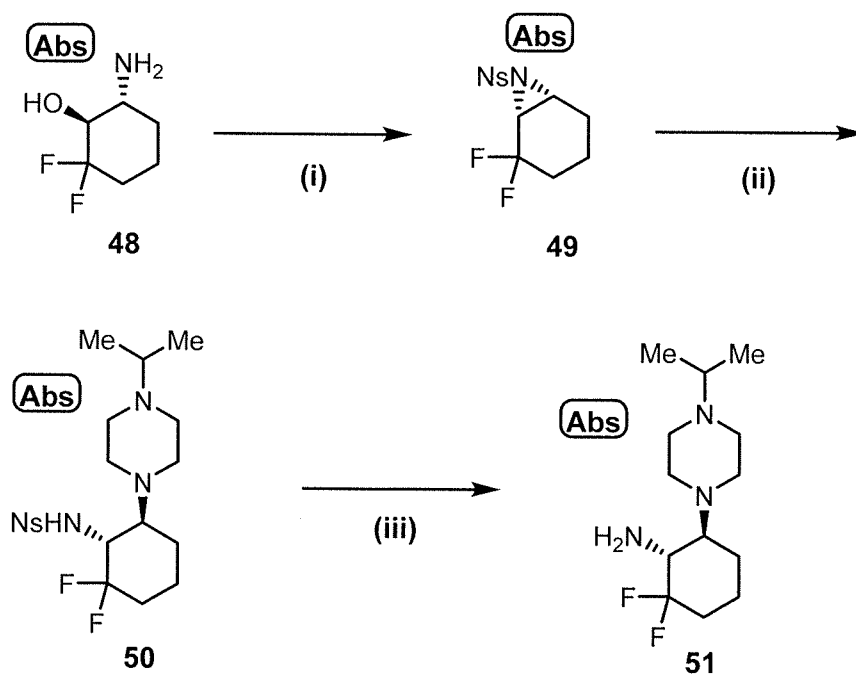
5 Reference example 15': (1S,6R)-2,2-difluoro-6-[4-(propan-2-yl)piperazin-1-yl]cyclohexan-1-amine

Reference example 16: (1R,6S)-2,2-difluoro-6-[6-(propan-2-yl)-3,6-diazabicyclo[3.1.1]heptan-3-yl]cyclohexan-1-amine

Reference example 17: (1R,6S)-2,2-difluoro-6-[3-(propan-2-yl)-3,8-diazabicyclo[3.2.1]octan-8-yl]cyclohexan-1-amine
[0291]

Reference example 18:

(1R,6S)-2,2-Difluoro-6-[4-(propan-2-yl)piperazin-1-yl]cyclohexan-1-amine
10



[0292]

Step (i):

To a mixture of Compound 48 (5.94 g), sodium bicarbonate (13.2 g), and THF (131 mL) was added 2-nitrobenzenesulfonyl chloride (10.5 g) at room temperature, and the mixture was
15

stirred at the same temperature for 16 hours. To the reaction mixture was added aqueous sodium bicarbonate, and the mixture was extracted with chloroform. The organic layer was dried over anhydrous sodium sulfate and concentrated *in vacuo*. The obtained residue was dissolved in THF (131 mL), and triethylamine (11 mL) and methanesulfonyl chloride (3.67 mL) were added to the solution under ice temperature. The mixture was stirred. After the reaction was terminated as judged by the consumption of the starting material, water was added to the reaction mixture, and the mixture was extracted with chloroform. The organic layer was dried over anhydrous sodium sulfate, and concentrated *in vacuo*. The obtained residue was dissolved in acetonitrile (393 mL), and potassium carbonate (16.3 mg) was added to the solution. The mixture was stirred for one hour heating at 80°C. To the reaction mixture was added water, and the mixture was extracted with chloroform. The organic layer was dried over anhydrous sodium sulfate and concentrated *in vacuo*, and then the obtained residue was purified by silica gel column chromatography (eluate: hexane/ethyl acetate) to give the title compound 49 (9.25 g).

LCMS: [M+H]⁺/Rt (min): 319/0.94

[0293]

Step (ii):

A mixture of Compound 49 (7.1 g), 1-isopropylpiperazine

(3.56 mL), and toluene (22.3 mL) was stirred for one hour heating at 110°C. After the reaction was terminated as judged by the consumption of the starting material, the reaction mixture was concentrated *in vacuo*, and the obtained
5 residue was purified by amino silica gel column chromatography (eluate: hexane/ethyl acetate) to give the title compound 50 (9.79 g).

LCMS: [M+H]⁺/Rt (min): 447/0.68

[0294]

10 Step (iii):

To a mixture of benzenethiol (0.530 mL) and toluene (11.2 mL) was added sodium hydride (55 %, 0.215 g) under ice temperature, and the mixture was warmed to room temperature and stirred for 10 minutes. Then, to the reaction mixture
15 was added a solution of Compound 50 (1 g) in toluene (9 mL), and the mixture was stirred heating at 60°C. After the reaction was terminated as judged by the consumption of the starting material, the reaction solution was cooled to 0°C, and 40 % aqueous sodium hydroxide was added to the reaction
20 mixture. The mixture was extracted with toluene. To the organic layer was added 5 M hydrochloric acid under ice temperature, and the aqueous layer was extracted from the mixture. To the obtained aqueous layer was added 40 % aqueous sodium hydroxide, and the obtained mixture was again
25 extracted with toluene. The organic layer was dried over

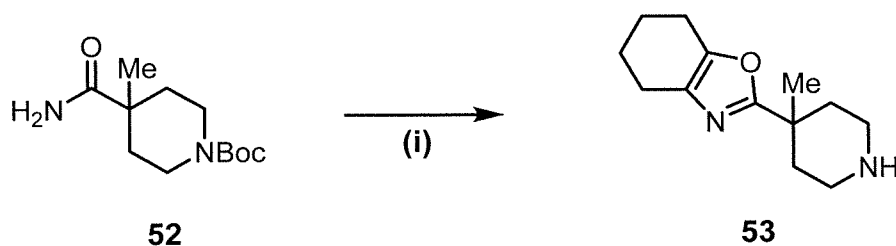
anhydrous sodium sulfate and concentrated *in vacuo*, and then the obtained residue was purified by amino silica gel column chromatography (eluate: hexane/ethyl acetate) to give the title compound 51 (0.47 g).

5 LCMS: $[M+H]^+/\text{Rt}$ (min): 262/0.17

[0295]

Reference example 19:

2-(4-Methylpiperidin-4-yl)-4,5,6,7-tetrahydro-1,3-benzoxazole



10

Step (i):

A mixture of Compound 52 (120 mg), 2-chlorocyclohexanone (68.9 mg), and DMF (1.5 mL) was stirred for 11 hours heating at 130°C with a microwave device. Then, to the reaction solution was added hydrogen chloride/1,4-dioxane solution (0.25 mL), and the mixture was stirred for 6 hours heating at 130°C with a microwave device. The reaction solution was concentrated *in vacuo*, and the obtained residue was dissolved in ethanol. 15 % Aqueous sodium hydroxide (2 mL) was added to the solution, and the mixture was stirred for 3 hours heating at 150°C with a microwave device. To the reaction mixture was added water, and the

15

20

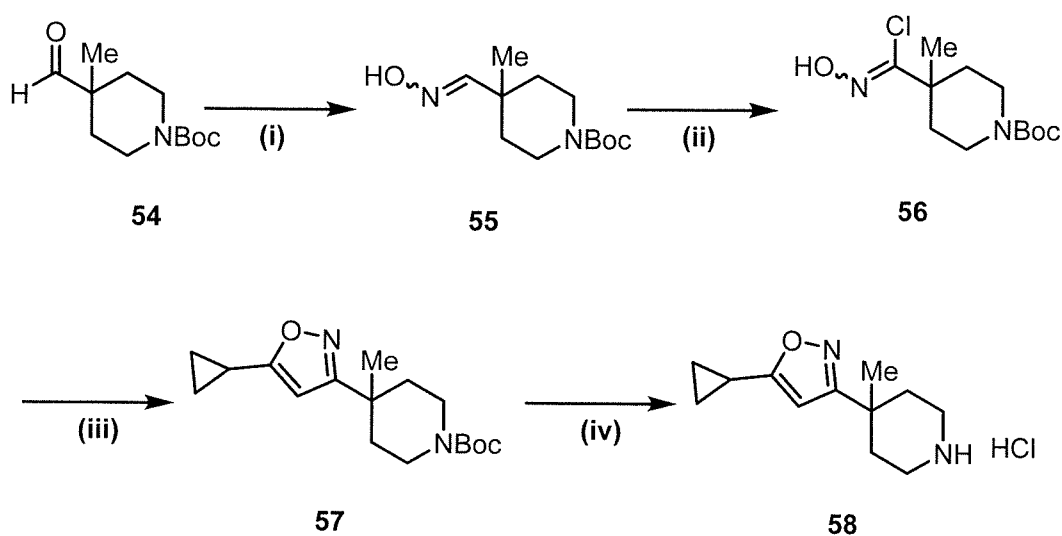
mixture was extracted with chloroform. The organic layer was dried over anhydrous sodium sulfate and concentrated *in vacuo*, and then the obtained residue was purified by amino silica gel column chromatography (eluate: hexane/ethyl acetate) to give the title compound 53 (14 mg).

LCMS: $[M+H]^+/R_t$ (min): 221/0.57

[0296]

Reference example 20:

4-(5-Cyclopropyl-1,2-oxazol-3-yl)-4-methylpiperidine
monohydrochloride



[0297]

Step (i):

To a mixture of Compound 54 (900 mg), sodium acetate (650 mg), and methanol (5 mL) was added hydroxylamine hydrochloride (550 mg), and the mixture was stirred at room temperature for 24 hours. The reaction solution was cooled to 0°C, and water was added thereto. The mixture was

extracted with chloroform, and the organic layer was dried over anhydrous sodium sulfate and concentrated *in vacuo* to give the title compound 55 (1.23 g).

[0298]

5 Step (ii):

To a mixture of Compound 55 (416 mg) and DMF (4 mL) was added N-chlorosuccinimide (252 mg), and the mixture was stirred for 3 hours. The reaction solution was cooled to 0°C, and water (6 mL) was added thereto. The precipitated
10 solid was collected on a filter, and dried to give the title compound 56 (326 mg).

[0299]

Step (iii):

To a mixture of ethynylcyclopropane (117 mg) and toluene
15 (5 mL) were added Compound 56 (326 mg) and sodium bicarbonate (198 mg), and the mixture was stirred at room temperature. After the reaction was terminated as judged by the consumption of the starting material, water was added to the reaction mixture and the mixture was extracted with ethyl
20 acetate. The organic layer was dried over anhydrous sodium sulfate, and concentrated *in vacuo*. Then, the obtained residue was purified by silica gel column chromatography (eluate: hexane/ethyl acetate) to give the title compound 57 (348 mg).

25 LCMS: [M+H]⁺/Rt (min): 307/1.13

[0300]

Step (iv):

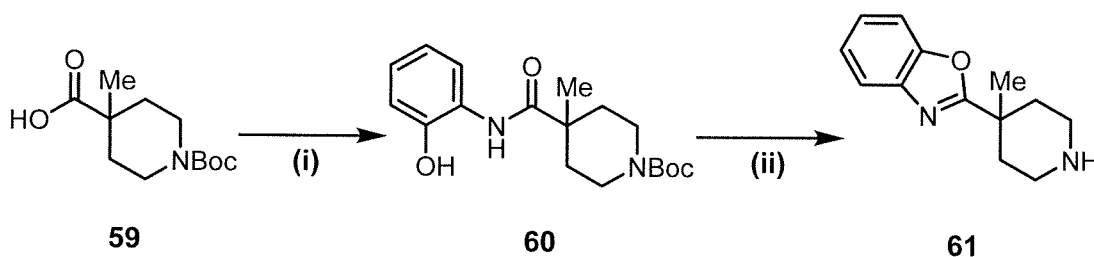
The title compound 58 (307 mg) was prepared in the same manner as Step (iv) in Reference example 2 by using Compound 57 (337 mg).

LCMS: $[M+H]^+/R_t$ (min): 207/0.49

[0301]

Reference example 21

2-(4-Methylpiperidin-4-yl)-1,3-benzoxazole



[0302]

Step (i):

To a solution of Compound 59 (1.46 g) in THF (30 mL) were added isobutyl chloroformate (819 mg) and diisopropylethylamine (3.88 g) under ice temperature, and the mixture was stirred for one hour. 2-Aminophenol (655 mg) was added to the reaction mixture under ice temperature, and the mixture was stirred for 6 hours heating at 70°C. The reaction solution was directly purified by amino silica gel column chromatography (eluate: ethyl acetate/hexane) to give the title compound 60 (710 mg).

LCMS: $[M+H]^+/R_t$ (min): 335/2.28 (Method B)

[0303]

Step (ii):

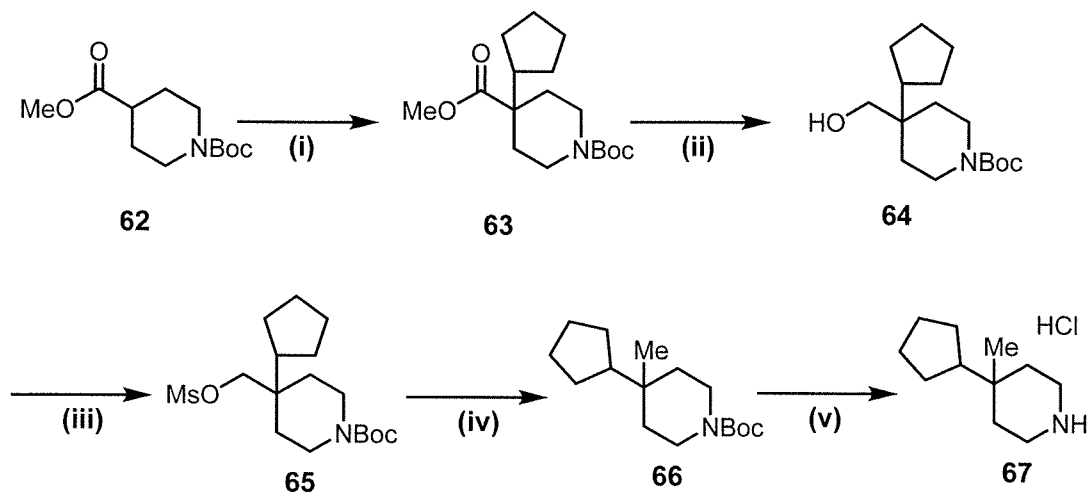
A mixture of Compound 60 (204 mg) and acetic acid (1.10 mL) was stirred for 2 hours heating at 90°C, and concentrated
5 *in vacuo*. The obtained residue was dissolved in chloroform (2 mL), and trifluoromethanesulfonic acid (2.1 mL) was added to the solution. The mixture was stirred at room temperature for one hour. The reaction solution was concentrated *in vacuo*, ethyl acetate and aqueous sodium bicarbonate were
10 added to the residue. The mixture was extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and concentrated *in vacuo*, and then the obtained residue was purified by amino silica gel column chromatography (eluate: ethyl acetate/hexane) to give the
15 title compound 61 (99 mg).

LCMS: [M+H]⁺/Rt (min): 217/1.36 (Method B)

[0304]

Reference example 22

4-Cyclopentyl-4-methylpiperidine monohydrochloride



[0305]

Step (i):

To a mixture of Compound 62 (700 mg) and THF (14 mL) was added lithium diisopropylamide (2 M, 5.18 mL) at -78°C , and the mixture was stirred at the same temperature for 2 hours. To the reaction mixture were added bromocyclopentane (1.23 mL) and potassium iodide (478 mg), and the mixture was warmed to room temperature. The mixture was stirred overnight, and then water was added to the mixture. The mixture was extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and concentrated *in vacuo*, and then the obtained residue was purified by silica gel column chromatography (eluate: ethyl acetate/hexane) to give the title compound 63 (468 mg).

LCMS: $[\text{M}+\text{H}]^{+}/\text{Rt}$ (min): 312/1.26

[0306]

Step (ii):

To a mixture of lithium aluminium hydride (104 mg) and THF (3 mL) were added Compound 63 (371 mg) and THF (6 mL) under ice temperature, and the mixture was stirred for 4 hours. After the reaction was terminated as judged by the consumption of the starting material, water (0.104 mL), 15 % aqueous sodium hydroxide (0.104 mL), and then water (0.312 mL) were added to the reaction mixture at 0°C, and the mixture was stirred. The reaction mixture was filtrated. The filtrate was concentrated *in vacuo*, and then the obtained residue was purified by silica gel column chromatography (eluate: ethyl acetate/hexane) to give the title compound 64 (320 mg).

LCMS: [M+H]⁺/Rt (min): 284/1.06

[0307]

Step (iii):

To a mixture of Compound 64 (314 mg), triethylamine (0.309 mL), and THF (5 mL) was added methanesulfonyl chloride (0.104 mL), and the mixture was stirred at room temperature. After the reaction was terminated as judged by the consumption of the starting material, water was added to the reaction mixture, and the mixture was extracted with chloroform. The organic layer was dried over anhydrous sodium sulfate and concentrated *in vacuo*, and then the obtained residue was purified by silica gel column chromatography (eluate: ethyl acetate/hexane) to give the

title compound 65 (290 mg).

LCMS: [M+H]⁺/Rt (min): 362/1.15

[0308]

Step (iv):

5 To a mixture of Compound 65 (278 mg) and THF (3 mL) was added lithium triethylborohydride (0.99 M, 1.55 mL), and the mixture was stirred at room temperature. Then, the reaction solution was heated to 70°C. After the reaction was terminated as judged by the consumption of the starting
10 material, the reaction solution was cooled to 0°C, and aqueous ammonium chloride was added to the reaction solution. The mixture was extracted with chloroform, and the organic layer was dried over anhydrous sodium sulfate and concentrated *in vacuo*. Then, the obtained residue was
15 purified by silica gel column chromatography (eluate: hexane/ethyl acetate) to give the title compound 66 (100 mg).

LCMS: [M+H]⁺/Rt (min): 268/1.42

[0309]

20 Step (v):

 The title compound 67 (58.5 mg) was prepared in the same manner as Step (iv) in Reference example 2 by using Compound 66 (90 mg).

LCMS: [M+H]⁺/Rt (min): 168/0.62

25 [0310]

Reference example 23:

4-(4,4-Difluorocyclohexyl)-4-methylpiperidine
monohydrochloride

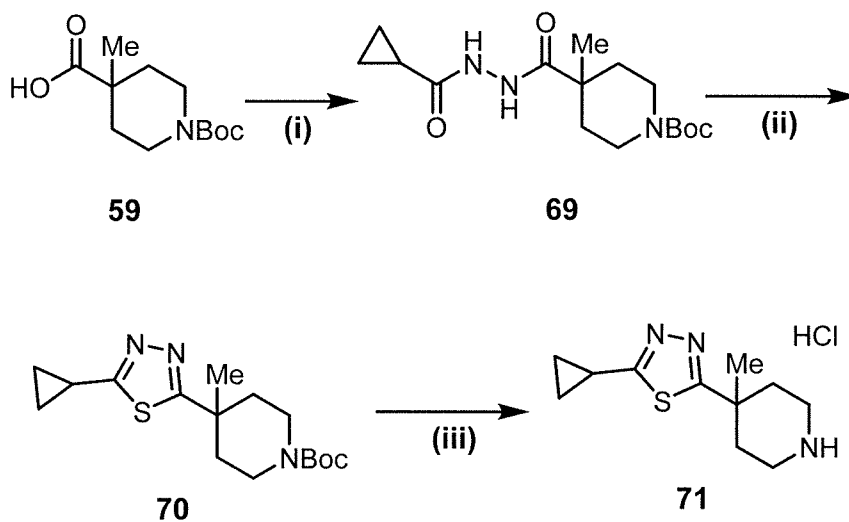
The compound of Reference example 23 shown in the table below was prepared according to the process in the above Reference example 22, by using 1,1-difluoro-4-iodocyclohexane instead of bromocyclopentane at Step (i) in Reference example 22.

Reference example	Chemical structure	Instrumental analytical data
23		LCMS: [M+H] ⁺ /Rt (min): 218/0.57

[0311]

Reference example 24:

4-(5-Cyclopropyl-1,3,4-thiadiazol-2-yl)-4-methylpiperidine
monohydrochloride



[0312]

Step (i):

To a mixture of Compound 59 (399 mg), cyclopropanecarbohydrazide hydrochloride (269 mg), and DMF (5 mL) were added HATU (686 mg) and diisopropylethylamine (1.15 mL), and the mixture was stirred at room temperature for 3 hours. Water was added to the reaction solution, and the mixture was extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and concentrated *in vacuo*, and then the obtained residue was purified by silica gel column chromatography (eluate: hexane/ethyl acetate) to give the title compound 69 (520 mg).

LCMS: [M+H]⁺/Rt (min): 326/0.74

[0313]

Step (ii):

To a mixture of Compound 69 (255 mg) and toluene (6 mL) was added Lawesson's reagent (349 mg), and the mixture was stirred under reflux for one hour. The reaction solution was cooled to 0°C, and aqueous sodium bicarbonate was added to the reaction solution. The mixture was extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and concentrated *in vacuo*, and then the obtained residue was purified by silica gel column chromatography (eluate: hexane/ethyl acetate) and then by amino silica gel column chromatography (eluate: hexane/ethyl

acetate) to give the title compound 70 (102 mg).

LCMS: $[M+H]^+/\text{Rt}$ (min): 324/1.08

[0314]

Step (iii):

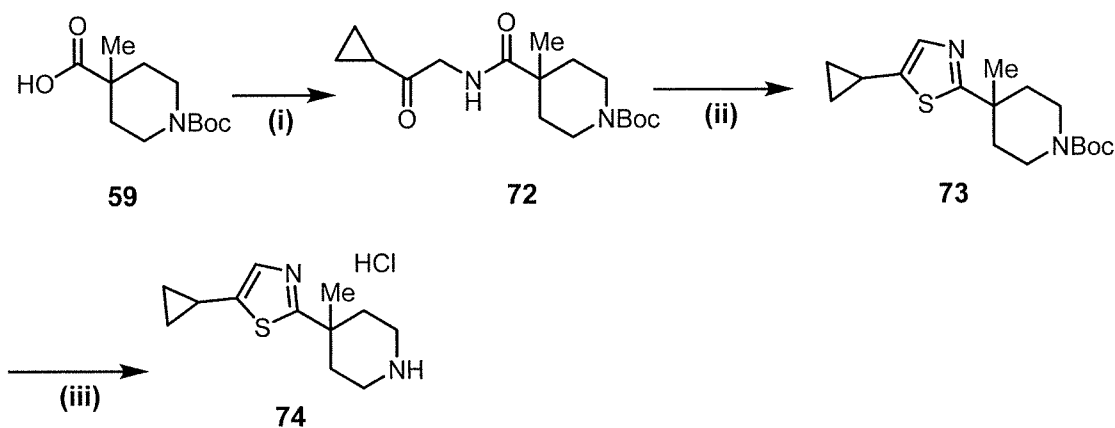
5 The title compound 71 (78 mg) was prepared in the same manner as Step (iv) in Reference example 2 by using Compound 70 (92 mg).

LCMS: $[M+H]^+/\text{Rt}$ (min): 224/0.45

[0315]

10 Reference example 25:

4-(5-Cyclopropyl-1,3-thiazol-2-yl)-4-methylpiperidine monohydrochloride



[0316]

15 Step (i):

The title compound 72 (796 mg) was prepared in the same manner as Step (i) in Reference example 24 by using Compound 59 (718 mg) and 2-amino-1-cyclopropylethan-1-one hydrochloride (400 mg).

LCMS: [M+H]⁺/Rt (min): 325/0.83

[0317]

Step (ii):

To a mixture of Compound 72 (127 mg), pyridine (0.063
5 mL), and toluene (3 mL) was added Lawesson's reagent (205
mg), and the mixture was stirred under reflux for 14 hours.
The reaction solution was cooled to room temperature, and
then aqueous sodium bicarbonate was added to the reaction
solution. The mixture was extracted with ethyl acetate.
10 The organic layer was dried over anhydrous sodium sulfate
and concentrated *in vacuo*, and then the obtained residue was
purified by amino silica gel column chromatography (eluate:
hexane/ethyl acetate) to give the title compound 73 (76.3
mg).

15 LCMS: [M+H]⁺/Rt (min): 323/1.43

[0318]

Step (iii):

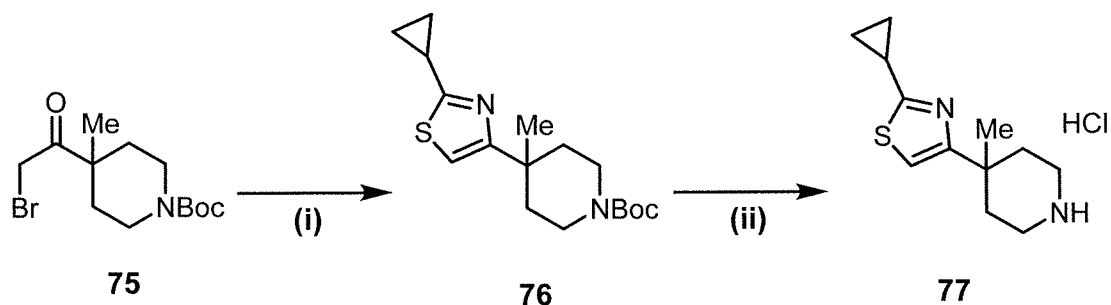
The title compound 74 (66.5 mg) was prepared in the
same manner as Step (iv) in Reference example 2 by using
20 Compound 73 (77 mg).

LCMS: [M+H]⁺/Rt (min): 223/0.67

[0319]

Reference example 26:

4-(2-Cyclopropyl-1,3-thiazol-4-yl)-4-methylpiperidine
25 monohydrochloride



[0320]

Step (i):

A solution of Compound 75 (532 mg) and
 5 cyclopropanecarbothioamide (168 mg) in methanol (6 mL) was
 stirred under reflux for 2.5 hours. The reaction mixture
 was allowed to cool to room temperature, and then saturated
 aqueous sodium bicarbonate was added to the reaction mixture.
 The mixture was extracted with chloroform. The organic layer
 10 was dried over anhydrous sodium sulfate and concentrated *in*
vacuo, and then the obtained residue was purified by silica
 gel column chromatography (eluate: hexane/ethyl acetate) to
 give the title compound 76 (119 mg).

[0321]

15 Step (ii):

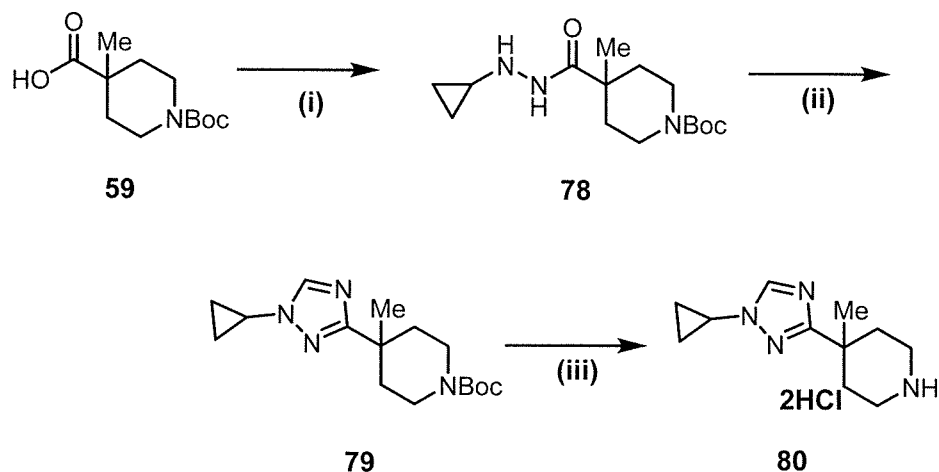
The title compound 77 (137 mg) was prepared in the same
 manner as Step (iv) in Reference example 2 by using Compound
 76 (119 mg).

LCMS: [M+H]⁺/Rt (min): 223/0.572

20 [0322]

Reference example 27:

4-(1-Cyclopropyl-1H-1,2,4-triazol-3-yl)-4-methylpiperidine dihydrochloride



[0323]

5 Step (i):

The title compound 78 (648 mg) was prepared in the same manner as Step (i) in Reference example 24 by using Compound 59 (611 mg) and cyclopropylhydrazine hydrochloride (300 mg).
 LCMS: $[M+H]^+/R_t$ (min): 298/0.80

10 [0324]

Step (ii):

A mixture of Compound 78 (374 mg), ammonium formate (1.43 g), and trimethyl orthoformate (2.78 mL) was stirred heating at 100°C. After the reaction was completed, the reaction solution was concentrated. To the obtained residue was added water, and the mixture was extracted with chloroform. The organic layer was dried over anhydrous sodium sulfate and concentrated *in vacuo*, and then the obtained residue was purified by silica gel column

chromatography (eluate: hexane/ethyl acetate) to give the title compound 79 (163 mg).

LCMS: [M+H]⁺/Rt (min): 307/0.89

[0325]

5 Step (iii):

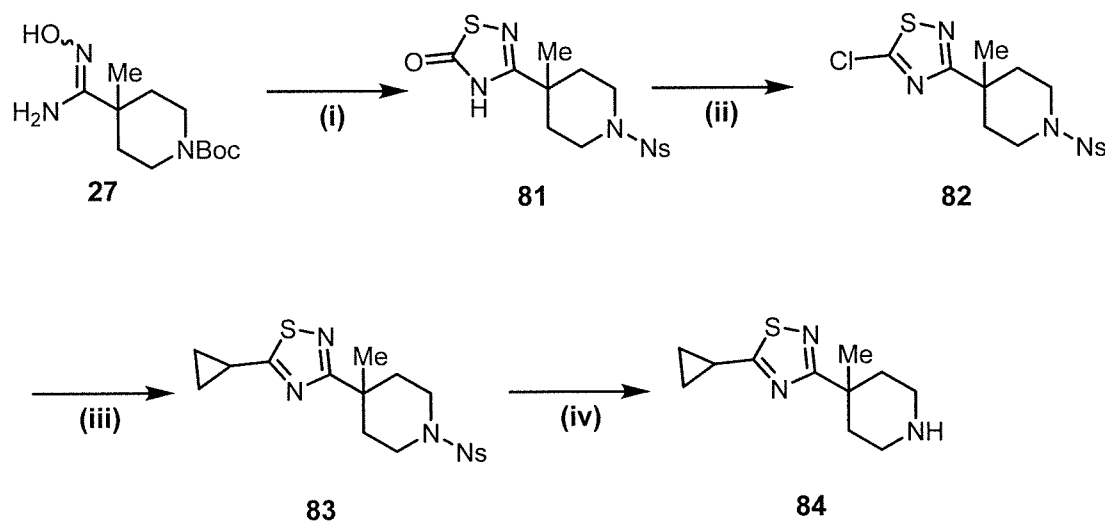
The title compound 80 (142 mg) was prepared in the same manner as Step (iv) in Reference example 2 by using Compound 79 (144 mg).

LCMS: [M+H]⁺/Rt (min): 207/0.39

10 [0326]

Reference example 28:

4-(5-Cyclopropyl-1,2,4-thiadiazol-3-yl)-4-methylpiperidine



[0327]

15 Step (i):

To a solution of Compound 27 (1.04 g) in THF (15 mL) was added thiocarbonylimidazole (0.864 mg) under ice temperature, and the mixture was stirred at room temperature.

After the reaction was terminated as judged by the consumption of the starting material, the reaction solution was cooled to 0°C, and water was added to the reaction solution. The mixture was extracted with ethyl acetate.

5 The organic layer was dried over sodium sulfate, and concentrated *in vacuo*.

The obtained residue was dissolved in THF (15 mL), and boron trifluoride-diethyl ether complex (1.52 mL) was added to the solution at 0°C. The mixture was warmed to room
10 temperature under stirring. After the reaction was completed, aqueous sodium bicarbonate was added to the reaction solution, and the mixture was extracted with chloroform. The organic layer was dried over sodium sulfate and concentrated *in vacuo*, and then the obtained residue was
15 purified by amino silica gel column chromatography (eluate: hexane/ethyl acetate).

To a solution of the purified compound in THF (15 mL) was added hydrogen chloride/dioxane solution (4 M, 5.05 mL) at 0°C, and the mixture was warmed to room temperature and
20 stirred. After the reaction was completed, the reaction solution was concentrated *in vacuo*, and the obtained residue was dissolved in THF (15 mL). To the solution were added triethylamine (3.38 mL) and 2-nitrobenzenesulfonyl chloride (0.985 g), and the mixture was stirred at room temperature.
25 After the reaction was completed, water was added to the

reaction solution, and the mixture was extracted with chloroform. The organic layer was dried over anhydrous sodium sulfate and concentrated *in vacuo*, and then the obtained residue was purified by silica gel column chromatography (eluate: chloroform/methanol) to give the title compound 81 (627 mg).

LCMS: [M+H]⁺/Rt (min): 385/0.93

[0328]

Step (ii):

To a mixture of Compound 81 (590 mg), pyridine (0.248 mL), and toluene (7 mL) was added phosphoryl chloride (0.572 mL), and the mixture was stirred under reflux. After the reaction was completed, the reaction solution was added to aqueous sodium bicarbonate at 0°C, and the mixture was filtrated. The filtrate was extracted with ethyl acetate. The organic layer was dried over sodium sulfate and concentrated *in vacuo*, and then the obtained residue was purified by amino silica gel column chromatography (eluate: hexane/ethyl acetate) to give the title compound 82 (432 mg).

LCMS: [M+H]⁺/Rt (min): 403/1.21

[0329]

Step (iii):

To a mixture of Compound 82 (210 mg), cyclopropylzinc(II) bromide (0.5 M, 3.13 mL), and THF (2 mL)

was added tetrakis(triphenylphosphine)palladium(0) (30.1 mg), and the mixture was stirred at 60°C for 1.5 hours. After the reaction was completed, aqueous sodium bicarbonate was added to the reaction solution, and the mixture was
5 extracted with ethyl acetate. The organic layer was dried over sodium sulfate and concentrated *in vacuo*, and then the obtained residue was purified by amino silica gel column chromatography (eluate: hexane/ethyl acetate) to give the title compound 83 (84 mg).

10 LCMS: [M+H]⁺/Rt (min): 409/1.24

[0330]

Step (iv):

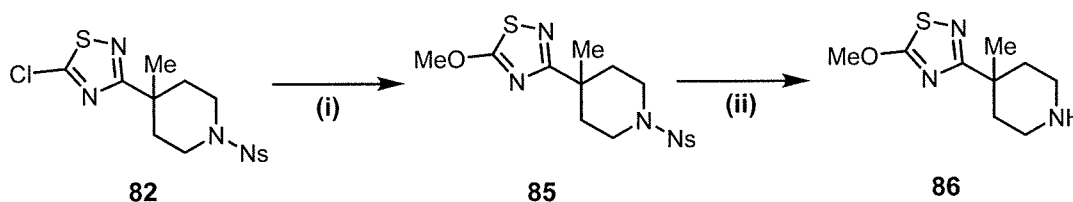
To a mixture of Compound 83 (71.4 mg), 1-dodecanethiol (0.251 mL), and acetonitrile (3 mL) was added potassium
15 carbonate (145 mg), and the mixture was stirred at 80°C. After the reaction was completed, water was added to the reaction solution, and the mixture was extracted with chloroform /methanol (6/1). The organic layer was dried over sodium sulfate and concentrated *in vacuo*, and then the
20 obtained residue was purified by amino silica gel column chromatography (eluate: hexane/ethyl acetate => chloroform/methanol) to give the title compound 84 (38 mg).

LCMS: [M+H]⁺/Rt (min): 224/0.52

[0331]

25 Reference example 29:

4-(5-Methoxy-1,2,4-thiadiazol-3-yl)-4-methylpiperidine



[0332]

Step (i):

5 To a solution of Compound 82 (119 mg) in methanol (2 mL) was added sodium methoxide (28 %, 285 mg), and the mixture was stirred at room temperature. After the reaction was completed, water was added to the reaction solution, and the mixture was extracted with chloroform. The organic layer
10 was concentrated *in vacuo* to give the title compound 85 (97.1 mg).

LCMS: [M+H]⁺/Rt (min): 399/1.18

[0333]

Step (ii):

15 The title compound 86 (14.9 mg) was prepared in the same manner as Step (iv) in Reference example 28 by using Compound 85 (91.6 mg).

LCMS: [M+H]⁺/Rt (min): 214/0.48

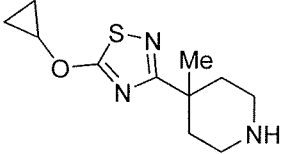
[0334]

20 Reference example 30:

4-[5-(Cyclopropyloxy)-1,2,4-thiadiazol-3-yl]-4-methylpiperidine

The compound of Reference example 30 shown in the table

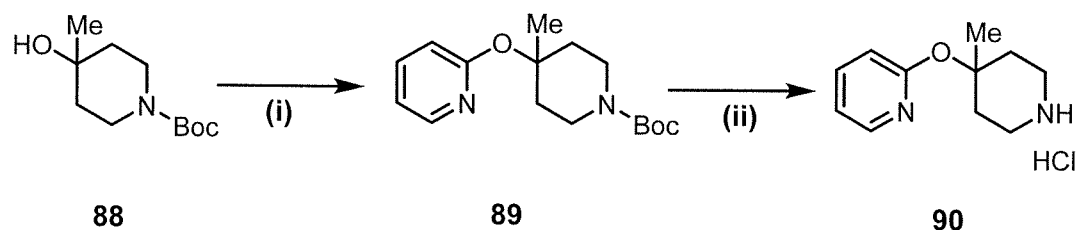
below was prepared according to the process in the above Reference example 29, by using cyclopropyl alcohol and sodium hydride instead of sodium methoxide at Step (i) in Reference example 29.

Reference example	Chemical structure	Instrumental analytical data
30		LCMS: [M+H] ⁺ /Rt (min): 240/0.56

5 [0335]

Reference example 31:

2-[(4-Methylpiperidin-4-yl)oxy]pyridine monohydrochloride



[0336]

10 Step (i):

To a solution of Compound 88 (183 mg) in DMF (2 mL) was added sodium hydride (55 %, 48.2 mg) under ice temperature, and the mixture was stirred for 20 minutes. To the reaction mixture was added 2-fluoropyridine (0.109 mL), and the mixture was stirred at room temperature. After the reaction was completed, the reaction mixture was cooled to 0°C. To the reaction mixture was added water, and the mixture was extracted with chloroform. The organic layer was dried over

15

sodium sulfate and concentrated *in vacuo*, and then the obtained residue was purified by silica gel column chromatography (eluate: hexane/ethyl acetate) to give the title compound 89 (18 mg).

5 LCMS: $[M+H]^+/Rt$ (min): 293/1.29

[0337]

Step (ii):

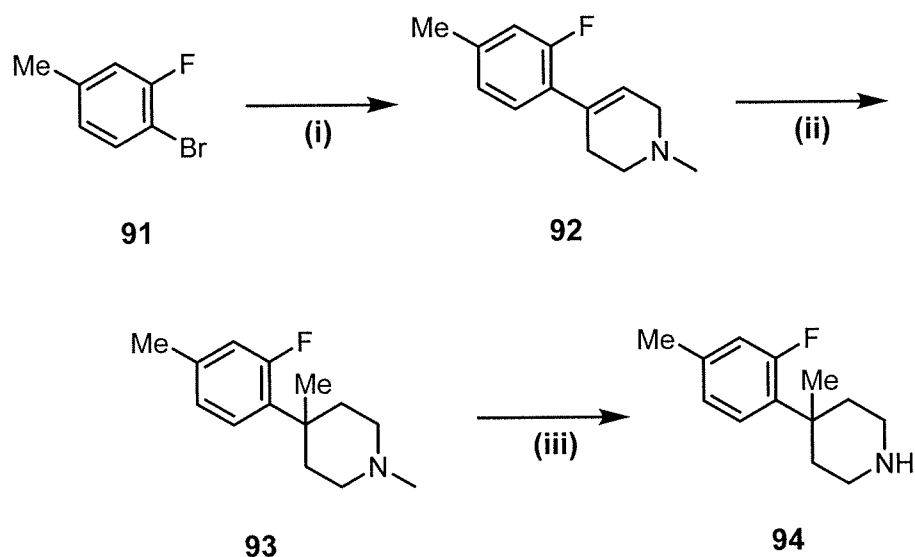
The title compound 90 (13.2 mg) was prepared in the same manner as Step (iv) in Reference example 2 by using
10 Compound 89 (14.7 mg).

LCMS: $[M+H]^+/Rt$ (min): 193/0.48

[0338]

Reference example 32:

4-(2-Fluoro-4-methylphenyl)-4-methylpiperidine



15

[0339]

Step (i):

To a mixture of Compound 91 (211 mg), 1-methyl-1,2,3,6-tetrahydropyridine-4-boronic acid pinacol ester (274 mg), potassium carbonate (386 mg), 1,2-dimethoxymethane (4 mL), and water (1 mL) was added dichloro(1,1'-bis(diphenylphosphino)ferrocene)palladium (45.6 mg) at room temperature, and then the mixture was heated under reflux. After the reaction was completed, water was added to the reaction solution, and the mixture was extracted with chloroform. The organic layer was dried over sodium sulfate and concentrated *in vacuo*, and then the obtained residue was purified by amino silica gel column chromatography (eluate: hexane/ethyl acetate) to give the title compound 92 (32 mg). LCMS: [M+H]⁺/Rt (min): 206/0.51

[0340]

Step (ii):

To a solution of Compound 92 (137 mg) in THF (3 mL) was added n-butyllithium solution (1.57 M, 0.68 mL) at -18°C, and the mixture was further cooled to -50°C. Dimethyl sulfate was added dropwise to the reaction solution, and the mixture was stirred at -50°C for one hour. To the reaction solution was added aqueous ammonia, and the mixture was extracted with ethyl acetate. The organic layer was dried over sodium sulfate, and concentrated *in vacuo* to give a residue.

The obtained residue was dissolved in methanol (3 mL),

and sodium borohydride (80 mg) was added to the solution under ice temperature. After the reaction was completed, aqueous sodium bicarbonate was added to the reaction solution, and the mixture was extracted with chloroform. The organic layer was dried over sodium sulfate and concentrated *in vacuo*, and then the obtained residue was purified by amino silica gel column chromatography (eluate: hexane/ethyl acetate) to give the title compound 93 (32 mg).

LCMS: [M+H]⁺/Rt (min): 222/0.63

[0341]

Step (iii):

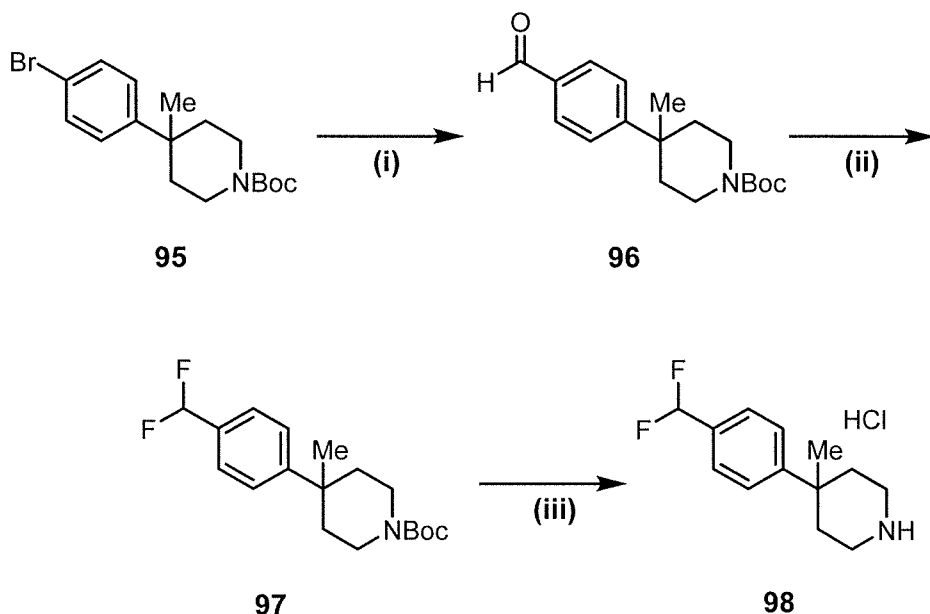
To a solution of Compound 93 (30.4 mg) in 1,2-dichloroethane (3 mL) was added 1-chloroethyl chloroformate (0.045 mL) at room temperature, and the mixture was heated under reflux. The reaction solution was concentrated *in vacuo*, and chloroform and aqueous sodium hydroxide were added to the obtained residue. The mixture was stirred at room temperature, and then extracted with chloroform. The organic layer was dried over sodium sulfate and concentrated *in vacuo*, and then the obtained residue was purified by amino silica gel column chromatography (eluate: chloroform/methanol) to give the title compound 94 (22 mg).

LCMS: [M+H]⁺/Rt (min): 208/0.66

[0342]

Reference example 33:

4-[4-(Difluoromethyl)phenyl]-4-methylpiperidine
monohydrochloride



[0343]

5 Step (i):

To a solution of Compound 95 (490 mg) in THF (6 mL) was added n-butyllithium solution (1.57 M, 1.15 mL) at -78°C , and the mixture was stirred for 30 minutes. To the reaction solution was added DMF (0.535 mL), and the mixture was warmed to 0°C . After the reaction was completed, water was added to the reaction solution, and the mixture was extracted with chloroform. The organic layer was dried over sodium sulfate and concentrated *in vacuo*, and then the obtained residue was purified by silica gel column chromatography (eluate: hexane/ethyl acetate) to give the title compound 96 (256 mg).

LCMS: [M+H]⁺/Rt (min): 304/1.10

[0344]

Step (ii):

To a solution of Compound 96 (157 mg) in dichloromethane
5 (2 mL) was added Deoxo-Fluor(R) (0.285 mL) under ice
temperature, and then the mixture was stirred at room
temperature. After the reaction was completed, the reaction
solution was added to aqueous sodium bicarbonate in ice bath,
and the mixture was extracted with chloroform. The organic
10 layer was dried over sodium sulfate and concentrated *in*
vacuo, and then the obtained residue was purified by amino
silica gel column chromatography (eluate: hexane/ethyl
acetate) to give the title compound 97 (110 mg).

LCMS: [M+H]⁺/Rt (min): 326/1.20

15 [0345]

Step (iii):

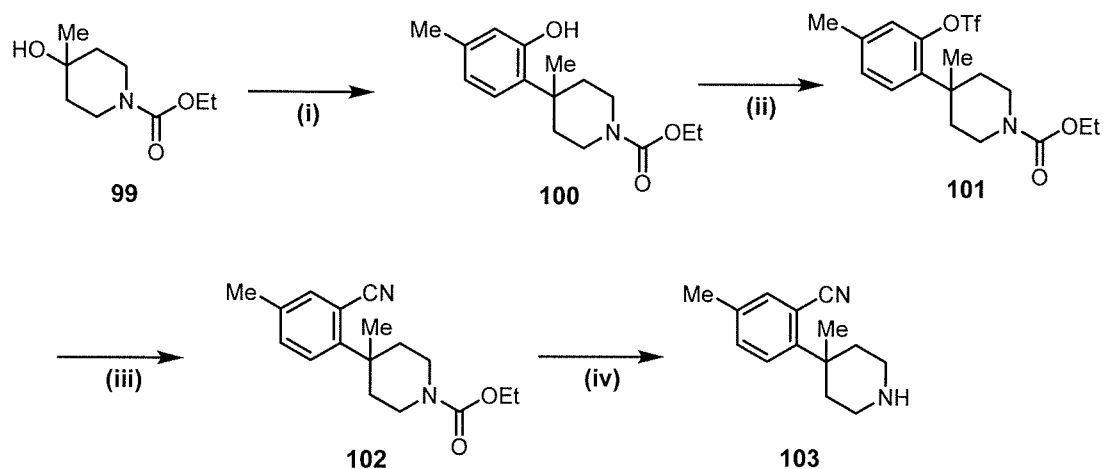
The title compound 98 (84.5 mg) was prepared in the
same manner as Step (iv) in Reference example 2 by using
Compound 97 (104.8 mg).

20 LCMS: [M+H]⁺/Rt (min): 226/0.60

[0346]

Reference example 34:

5-Methyl-2-(4-methylpiperidin-4-yl)benzonitrile



[0347]

Step (i):

To a mixture of Compound 99 (267 mg) and m-cresol (1.20 mL) was added trifluoromethanesulfonic acid (1.01 mL), and the mixture was stirred at room temperature. After the reaction was completed, the reaction solution was added to aqueous sodium bicarbonate at 0°C, and the mixture was extracted with chloroform. The organic layer was dried over sodium sulfate, concentrated *in vacuo*, and then the obtained residue was purified by silica gel column chromatography (eluate: hexane/ethyl acetate) to give the title compound 100 (388 mg).

LCMS: [M+H]⁺/Rt (min): 278/1.01

15 [0348]

Step (ii):

To a mixture of Compound 100 (113 mg), potassium carbonate (169 mg), and THF (4 mL) was added N-phenylbis(trifluoromethanesulfonimide) (175 mg), and the

mixture was stirred heating at 120°C with a microwave device. After the reaction was completed, water was added to the reaction solution, and the mixture was extracted with chloroform. The organic layer was dried over sodium sulfate
5 and concentrated *in vacuo*, and then the obtained residue was purified by silica gel column chromatography (eluate: hexane/ethyl acetate) to give the title compound 101 (138 mg).

LCMS: [M+H]⁺/Rt (min): 410/1.26

10 [0349]

Step (iii):

The title compound 102 (40.8 mg) was prepared in the same manner as Step (iii) in Reference example 28 by using Compound 101 (130 mg) and zinc cyanide (55.8 mg).

15 LCMS: [M+H]⁺/Rt (min): 287/1.07

[0350]

Step (iv):

To a solution of Compound 102 (40 mg) in 2-propanol (3 ml) was added potassium hydroxide (78 mg) at room
20 temperature, and then the mixture was stirred heating at 110°C with a microwave device. After the reaction was completed, water was added to the reaction solution. The mixture was extracted with chloroform/ethanol (4/1). The organic layer was dried over sodium sulfate and concentrated
25 *in vacuo*, and then the obtained residue was purified by amino

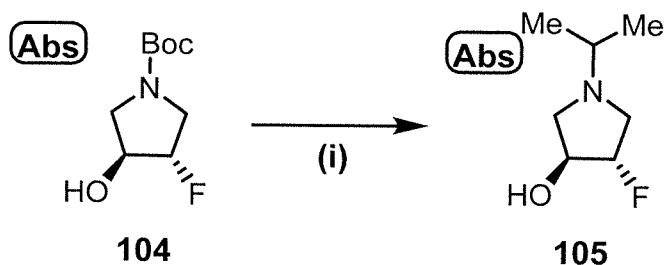
silica gel column chromatography (eluate: chloroform/methanol) to give the title compound 103 (20.6 mg).

LCMS: $[M+H]^+/R_t$ (min): 215/0.57

5 [0351]

Reference example 35:

(3S,4S)-4-Fluoro-1-(propan-2-yl)pyrrolidin-3-ol



Step (i):

10 To a solution of Compound 104 (500 mg) in chloroform (2 mL) was added hydrogen chloride/1,4-dioxane (4 M, 6 mL) at 0°C, and the mixture was warmed to room temperature and stirred. After the reaction was terminated as judged by the consumption of the starting material, the reaction solution

15 was concentrated *in vacuo*. The obtained residue was dissolved in chloroform (2 mL). To the solution were added acetone (1.79 mL), sodium acetate (200 mg), and sodium triacetoxyborohydride (1.03 g) at 0°C, and the mixture was warmed to room temperature and stirred. After the reaction

20 was completed, aqueous sodium bicarbonate was added to the reaction mixture at 0°C, and the mixture was extracted with chloroform/methanol (5/1). The organic layer was dried over

anhydrous sodium sulfate and concentrated *in vacuo*, and then the obtained residue was purified by amino silica gel column chromatography (eluate: hexane/ethyl acetate) to give the title compound 105 (348 mg).

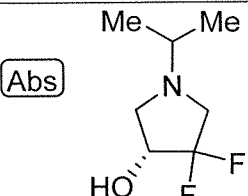
5 LCMS: [M+H]⁺/Rt (min): 148/0.17

[0352]

Reference example 36:

(3R)-4,4-Difluoro-1-(propan-2-yl)pyrrolidin-3-ol

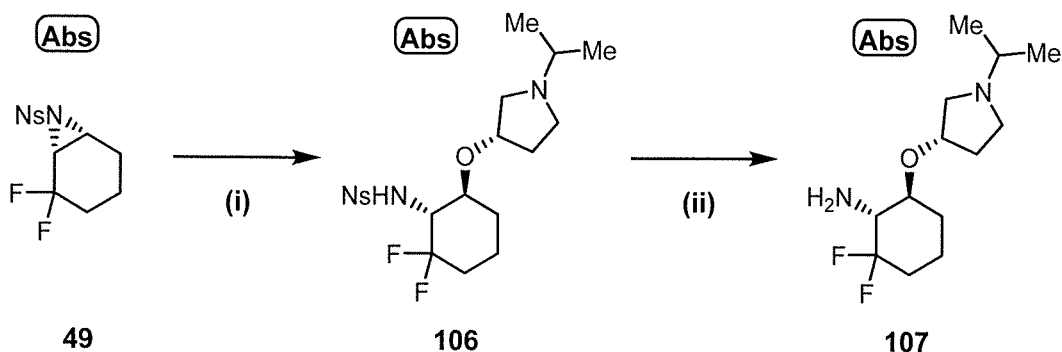
10 The compound of Reference example 36 shown in the table below was prepared according to the process in the above Reference example 35, by using the appropriate starting compound instead of Compound 104 at Step (i) in Reference example 35.

Reference example	Chemical structure	Instrumental analytical data
36		LCMS: [M+H] ⁺ /Rt (min): 166/0.19

[0353]

15 Reference example 37:

(1R,6S)-2,2-Difluoro-6-{[(3S)-1-(propan-2-yl)pyrrolidin-3-yl]oxy}cyclohexan-1-amine



[0354]

Step (i):

A mixture of Compound 49 (1.5 g), (S)-1-isopropylpyrrolidin-3-ol (0.792 mg), and NMP (1 mL) was stirred heating at 150°C. After the reaction was terminated as judged by the consumption of the starting material, the reaction solution was directly purified by silica gel column chromatography (eluate: chloroform/methanol/triethylamine) and then by amino silica gel column chromatography (eluate: hexane/ethyl acetate) to give the title compound 106 (1.03 g).

LCMS: [M+H]⁺/Rt (min): 448/0.78

[0355]

Step (ii):

The title compound 107 (43 mg) was prepared in the same manner as Step (iii) in Reference example 18 by using Compound 106 (100 mg).

LCMS: [M+H]⁺/Rt (min): 263/0.22

[0356]

Reference examples 38 to 40:

The compounds of Reference examples 38 to 40 shown in the table below were prepared according to the process in the above Reference example 37, by using each appropriate starting compound instead of (S)-1-isopropylpyrrolidin-3-ol at Step (i) in Reference example 37.

Reference example	Chemical structure	Instrumental analytical data
38		LCMS: [M+H] ⁺ /Rt (min): 263/0.151
39		LCMS: [M+H] ⁺ /Rt (min): 281/0.18
40		LCMS: [M+H] ⁺ /Rt (min): 299/0.35

[0357]

Reference example 38: (1R,6S)-2,2-difluoro-6-{[(3R)-1-(propan-2-yl)pyrrolidin-3-yl]oxy}cyclohexan-1-amine

Reference example 39: (1R,6S)-2,2-difluoro-6-{[(3S,4S)-4-fluoro-1-(propan-2-yl)pyrrolidin-3-

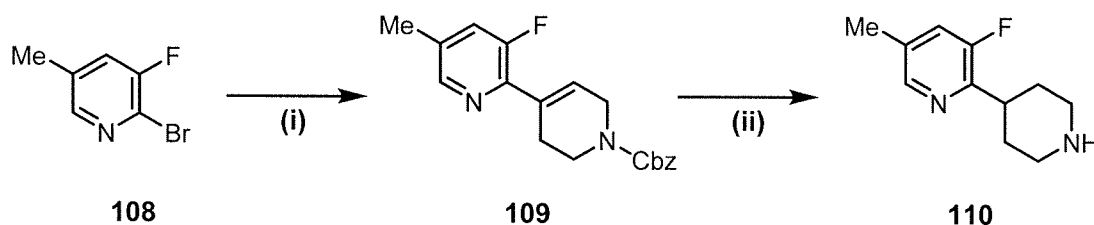
yl]oxy)cyclohexan-1-amine

Reference example 40: (1R,6S)-6-{[(3R)-4,4-difluoro-1-(propan-2-yl)pyrrolidin-3-yl]oxy}-2,2-difluorocyclohexan-1-amine

5 [0358]

Reference example 41:

3-Fluoro-5-methyl-2-(piperidin-4-yl)pyridine



[0359]

10 Step (i):

The title compound 109 (90.5 mg) was prepared in the same manner as Step (i) in Reference example 32 by using Compound 108 (72.4 mg) and 1-carbobenzoyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaboron-2-yl)pyridine.

LCMS: [M+H]⁺/Rt (min): 327/1.04 (Method C)

[0360]

Step (ii):

To a solution of Compound 109 (88.0 mg) in ethyl acetate (1.5 mL) was added palladium/carbon (88.0 mg), and the mixture was stirred under hydrogen atmosphere for 8 hours. The reaction solution was filtrated with Celite, and the

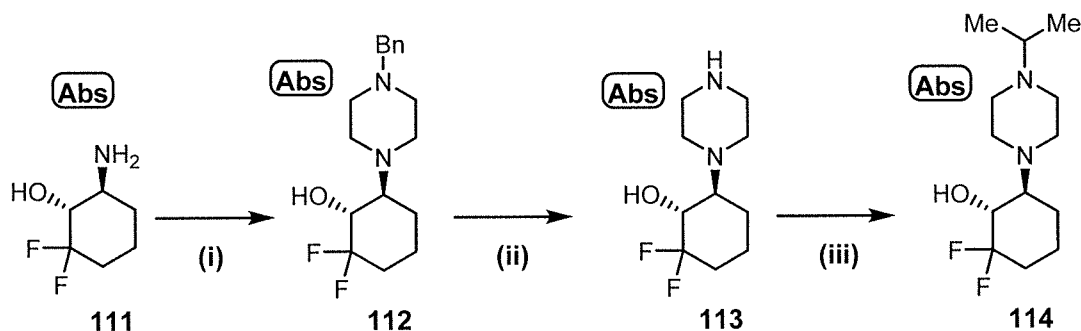
filtrate was concentrated *in vacuo* to give the title compound 110 (22.2 mg).

LCMS: $[M+H]^+/\text{Rt (min)}$: 195/0.35 (Method C)

[0361]

5 Reference example 42:

(1R,6S)-2,2-Difluoro-6-[4-(propan-2-yl)piperazin-1-yl]cyclohexan-1-ol



[0362]

10 Step (i):

To a solution of Compound 111 (300 mg) and sodium bicarbonate (634 mg) in ethanol (10 mL) was added N-benzyl-N,N-bis(2-chloroethyl)amine hydrochloride (586 mg), and the mixture was stirred heating at 120°C with a microwave device. After the reaction was completed, water was added to the reaction solution, and the mixture was extracted with chloroform. The organic layer was dried over sodium sulfate and concentrated *in vacuo*, and then the obtained residue was purified by amino silica gel column chromatography (eluate: hexane/ethyl acetate) to give the title compound 112 (398 mg).

LCMS: [M+H]⁺/Rt (min): 311/0.46

[0363]

Step (ii):

The title compound 113 (289 mg) was prepared in the same manner as Step (ii) in Reference example 2 by using Compound 112 (389 mg).

LCMS: [M+H]⁺/Rt (min): 221/0.16

[0364]

Step (iii):

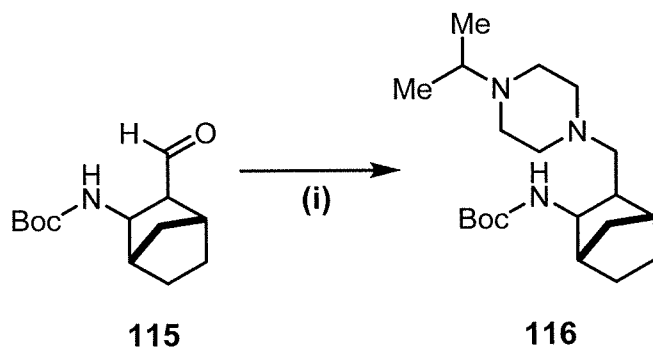
To a mixture of Compound 113 (389 mg), acetone (1.73 mL), and dichloromethane (6 mL) was added sodium triacetoxyborohydride (1.5 g) at 0°C, and the mixture was warmed to room temperature and the stirring was continued for 1.5 hours. To the reaction mixture was added water at 0°C, and the mixture was extracted with chloroform. The organic layer was dried over anhydrous sodium sulfate and concentrated *in vacuo*, and then the obtained residue was purified by amino silica gel column chromatography (eluate: hexane/ethyl acetate) to give the title compound 114 (255 mg).

LCMS: [M+H]⁺/Rt (min): 263/0.36

[0365]

Reference example 43:

tert-Butyl [(1*S*,4*R*)-3-{{4-(propan-2-yl)piperazin-1-yl}methyl}bicyclo[2.2.1]heptan-2-yl]carbamate



Step (i):

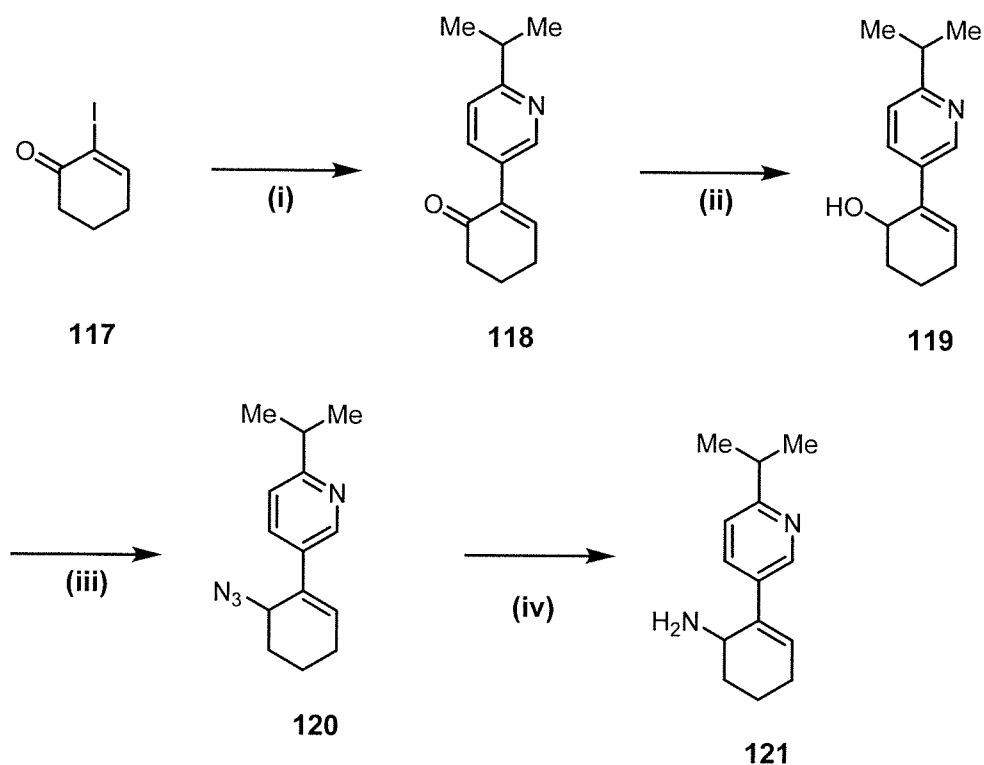
To a mixture of Compound 115 (239 mg), 1-isopropylaziridine (128 mg), acetic acid (0.086 mL), and THF (2.5 mL) was added sodium triacetoxyborohydride (635 mg) at room temperature, and the mixture was stirred at the same temperature for 3 hours. To the reaction mixture was added aqueous sodium bicarbonate at 0°C, and the mixture was extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and concentrated *in vacuo*, and then the obtained residue was purified by amino silica gel column chromatography (eluate: hexane/ethyl acetate) to give the title compound 116 (310 mg).

LCMS: [M+H]⁺/Rt (min): 352/1.35 (Method B)

[0366]

Reference example 44:

rac-2-[6-(Propan-2-yl)pyridin-3-yl]cyclohex-2-en-1-amine



[0367]

Step (i):

To a mixture of Compound 117 (350 mg), 6-isopropylpyridin-3-yl boronate (273 mg), cesium carbonate (1.28 g), 1,4-dioxane (5 mL), and water (1 mL) was added [1,1'-bis(diphenylphosphino)ferrocene]palladium(II) dichloride dichloromethane adduct (129 mg) at room temperature, and the mixture was stirred at 90°C for 3 hours.

To the reaction mixture was added water at 0°C, and the mixture was extracted with chloroform. The organic layer was dried over anhydrous sodium sulfate and concentrated *in vacuo*, and then the obtained residue was purified by silica

gel column chromatography (eluate: hexane/ethyl acetate) to give the title compound 118 (168 mg).

[0368]

Step (ii) to Step (iv):

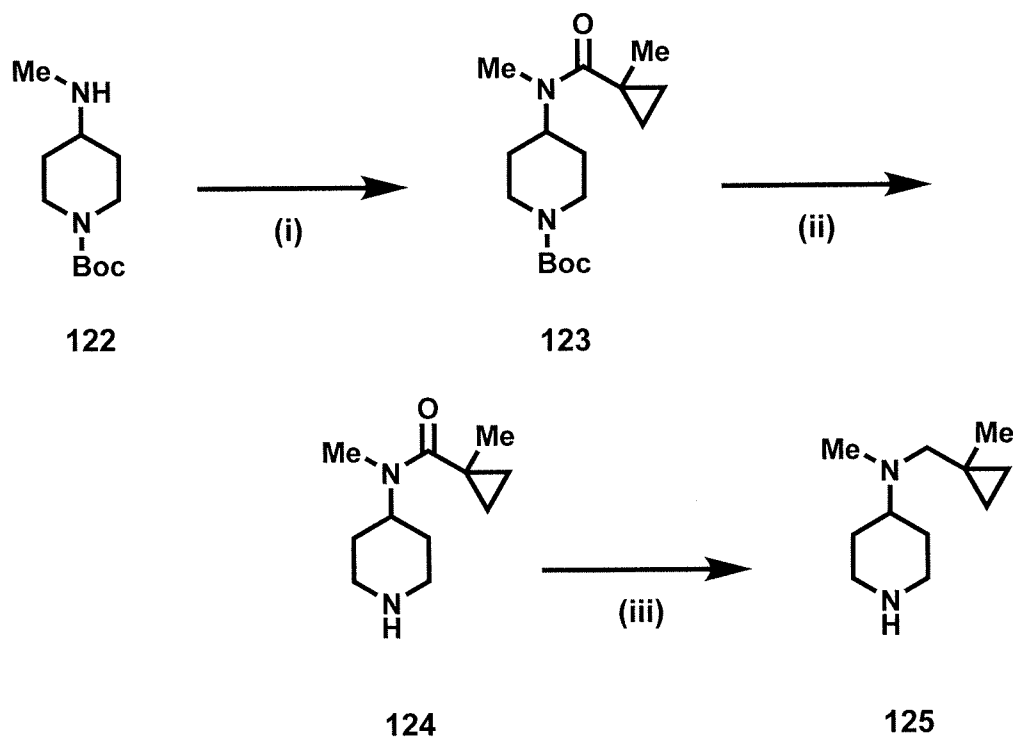
5 The title compound 121 (29.7 mg) was prepared in the same manner as Steps (i) to (iii) in Reference example 13 by using Compound 118 (68.2 mg).

LCMS: $[M+H]^+/\text{Rt (min)}$: 217/0.39

[0369]

10 Reference example 45:

N-Methyl-N-[(1-methylcyclopropyl)methyl]piperidin-4-amine



[0370]

Step (i):

15 To a solution of *tert*-butyl 4-(methylamino)piperidine-

1-carboxylate (584 mg), 1-methylcyclopropane-1-carboxylic acid (300 mg), and triethylamine (0.76 mL) in DMF (4 mL) was added HATU (1.24 g), and the mixture was stirred at room temperature. After the reaction was completed, water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate, concentrated *in vacuo*, and then the obtained residue was purified by silica gel column chromatography (eluate: hexane/ethyl acetate) to give the title compound 123 (926 mg).

[0371]

Step (ii):

To a solution of Compound 123 (806 mg) in chloroform (4.5 mL) was added hydrochloric acid (in CPME, 5 M, 2.7 mL) at 0°C, and the reaction solution was warmed to room temperature and stirred. After the reaction was completed, the reaction mixture was concentrated *in vacuo*, and then the obtained residue was purified by amino silica gel column chromatography (eluate: chloroform/methanol) to give the title compound 124 (477 mg).

[0372]

Step (iii):

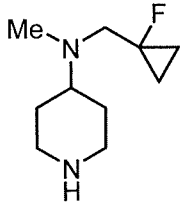
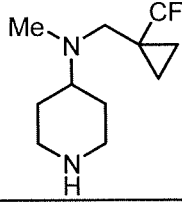
The title compound 125 (203 mg) was prepared in the same manner as Step (ii) in Reference example 22 by using Compound 124 (413 mg).

LCMS: [M+H]⁺/Rt (min):183/0.15

[0373]

Reference examples 46 - 47

The compounds of Reference examples 46 - 47 shown in
 5 the table below was prepared according to the process in the
 above Reference example 45, by using each appropriate
 starting compound instead of 1-methylcyclopropane-1-
 carboxylic acid at Step (i) in Reference example 45.

Reference example	Chemical structure	Instrumental analytical data
46		LCMS: [M+H] ⁺ /Rt (min): 187/0.14
47		LCMS: [M+H] ⁺ /Rt (min): 237/0.19

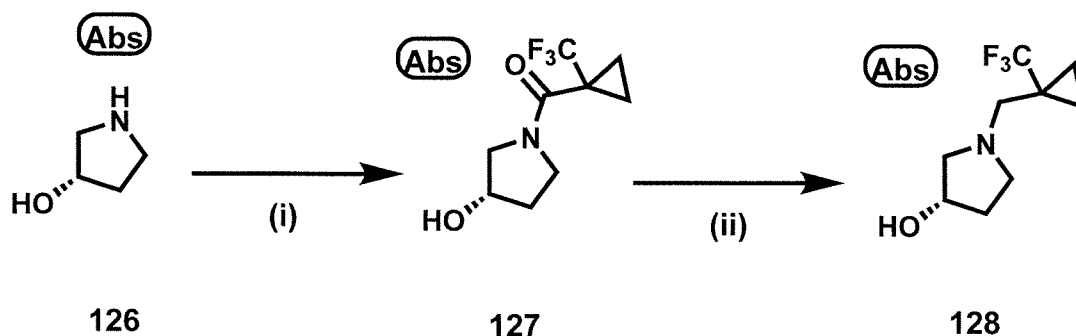
[0374]

10 Reference example 46: N-[(1-fluorocyclopropyl)methyl]-
 N-methylpiperidin-4-amine

Reference example 47: N-methyl-N-{[1-(trifluoromethyl)cyclopropyl]methyl}piperidin-4-amine

[0375]

15 Reference example 48: (3S)-1-{[1-(trifluoromethyl)cyclopropyl]methyl}pyrrolidin-3-ol



[0376]

Step (i):

The title compound 127 (196 mg) was prepared in the same manner as Step (i) in Reference example 45 by using (S)-3-pyrrolidinol (103 mg) and 1-(trifluoromethyl)cyclopropane-1-carboxylic acid (200 mg).

[0377]

Step (ii):

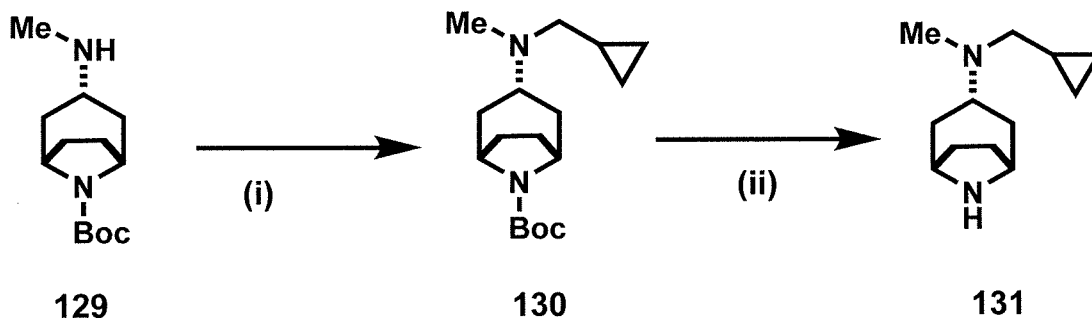
The title compound 128 (87.2 mg) was prepared in the same manner as Step (iii) in Reference example 45 by using Compound 127 (184 mg).

LCMS: [M+H]⁺/Rt (min):210/0.30

[0378]

15 Reference example 49:

(1R,3S,5S)-N-(Cyclopropylmethyl)-N-methyl-8-azabicyclo[3.2.1]octan-3-amine



[0379]

Step (i):

The title compound 130 (178 mg) was prepared in the same manner as Step (iii) in Reference example 42 by using Compound 129 (146 mg) and cyclopropane-carbaldehyde (170 mg).

[0380]

Step (ii):

The title compound 131 (106 mg) was prepared in the same manner as Step (ii) in Reference example 45 by using Compound 130 (166 mg).

LCMS: $[M+H]^+/\text{Rt}$ (min): 195/0.14Reference examples 50 - 52

The compounds of Reference examples 50 - 52 shown in the table below were prepared according to the process in the above Reference example 49, by using each appropriate starting compound instead of Compound 129 at Step (i) in Reference example 49.

Reference example	Chemical structure	Instrumental analytical data
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50		LCMS: [M+H] ⁺ /Rt (min): 195/0.14
51		LCMS: [M+H] ⁺ /Rt (min): 183/0.14
52		LCMS: [M+H] ⁺ /Rt (min): 183/0.14

[0381]

Reference example 50: (1R,3R,5S)-N-(cyclopropylmethyl)-N-methyl-8-azabicyclo[3.2.1]octan-3-amine

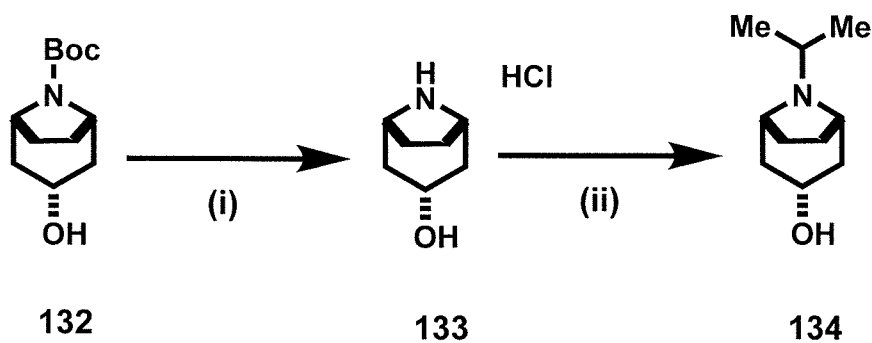
5 Reference example 51: (4S)-N-(cyclopropylmethyl)-N-methylazepan-4-amine

Reference example 52: (4R)-N-(cyclopropylmethyl)-N-methylazepan-4-amine

[0382]

10 Reference example 53:

(1R,3S,5S)-8-(Propan-2-yl)-8-azabicyclo[3.2.1]octan-3-ol



[0383]

Step (i):

The title compound was prepared in the same manner as Step (iv) in Reference example 2 by using Compound 132 (3 g).

Step (ii):

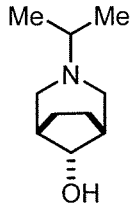
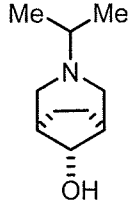
The title compound 134 (1.98 g) was prepared in the same manner as Step (iii) in Reference example 42 by using Compound 133 and acetone (1.3 g).

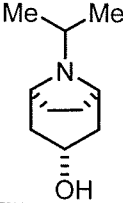
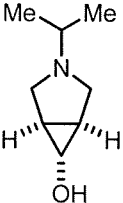
LCMS: $[M+H]^+/Rt$ (min): 170/0.15

[0384]

Reference examples 54 - 57

The compounds of Reference examples 54 - 57 shown in the table below were prepared according to the process in the above Reference example 53, by using each appropriate starting compound instead of Compound 132 at Step (i) in Reference example 53.

Reference example	Chemical structure	Instrumental analytical data
54		LCMS: $[M+H]^+/Rt$ (min): 170/0.25
55		LCMS: $[M+H]^+/Rt$ (min): 170/0.15

56		LCMS: [M+H] ⁺ /Rt (min): 170/0.24
57		LCMS: [M+H] ⁺ /Rt (min): 142/0.15

[0385]

Reference example 54: (1R,5S,8R)-3-(propan-2-yl)-3-azabicyclo[3.2.1]octan-8-ol

Reference example 55: (1R,5S,8S)-3-(propan-2-yl)-3-azabicyclo[3.2.1]octan-8-ol

Reference example 56: (1R,3R,5S)-8-(propan-2-yl)-8-azabicyclo[3.2.1]octan-3-ol

Reference example 57: (1R,5S,6S)-3-(propan-2-yl)-3-azabicyclo[3.1.0]hexan-6-ol

[0386]

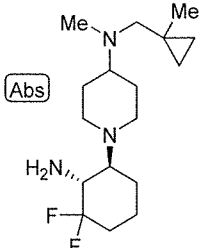
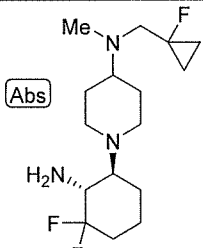
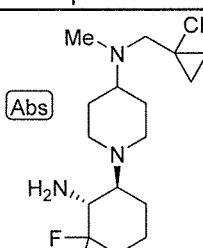
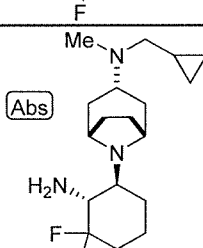
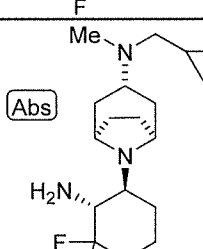
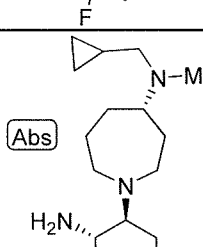
Reference examples 58 - 79

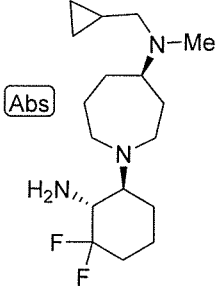
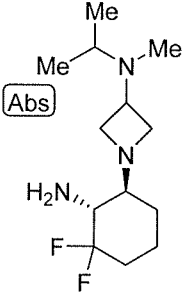
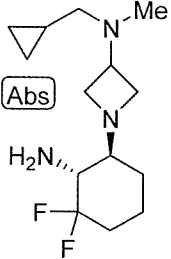
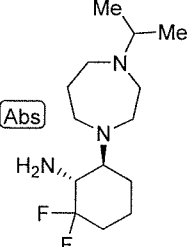
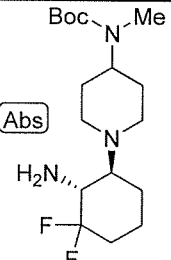
The compounds of Reference examples 58 - 79 shown in the table below were prepared according to the process in the above Reference example 18, by using each appropriate starting compound instead of 1-isopropylpiperazine at Step (ii) in Reference example 18.

Reference example	Chemical structure	Instrumental analytical data
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58	(Abs)	LCMS: [M+H] ⁺ /Rt (min): 262/0.17
59	(Abs)	LCMS: [M+H] ⁺ /Rt (min): 276/0.28
60	(Abs)	LCMS: [M+H] ⁺ /Rt (min): 277/0.55
61	(Abs)	LCMS: [M+H] ⁺ /Rt (min): 276/0.20
62	(Abs)	LCMS: [M+H] ⁺ /Rt (min): 276/0.20
63	(Abs)	LCMS: [M+H] ⁺ /Rt (min): 290/0.24

64	(Abs) <chem>C1CCN1C2CCN(C2)C3CCCC(F)(F)C3N</chem>	LCMS: [M+H] ⁺ /Rt (min): 288/0.31
65	(Abs) <chem>CC1(C)COC1N2CCN(C2)C3CCCC(F)(F)C3N</chem>	LCMS: [M+H] ⁺ /Rt (min): 288/0.32
66	(Abs) <chem>CC1(C)COC1N2CCN(C2)C3CCCC(F)(F)C3N</chem>	LCMS: [M+H] ⁺ /Rt (min): 316/0.35
67	(Abs) <chem>CC1(C)COC1N2CCN(C2)C3CCCC(F)(F)C3N</chem>	LCMS: [M+H] ⁺ /Rt (min): 290/0.38
68	(Abs) <chem>CC1(C)COC1N2CCN(C2)C3CCCC(F)(F)C3N</chem>	LCMS: [M+H] ⁺ /Rt (min): 304/0.32

69	 (Abs)	LCMS: [M+H] ⁺ /Rt (min): 316/0.36
70	 (Abs)	LCMS: [M+H] ⁺ /Rt (min): 320/0.36
71	 (Abs)	LCMS: [M+H] ⁺ /Rt (min): 370/0.48
72	 (Abs)	LCMS: [M+H] ⁺ /Rt (min): 328/0.51
73	 (Abs)	LCMS: [M+H] ⁺ /Rt (min): 328/0.39
74	 (Abs)	LCMS: [M+H] ⁺ /Rt (min): 316/0.49

75		LCMS: [M+H] ⁺ /Rt (min): 316/0.46
76		LCMS: [M+H] ⁺ /Rt (min): 262/0.15
77		LCMS: [M+H] ⁺ /Rt (min): 274/0.15
78		LCMS: [M+H] ⁺ /Rt (min): 276/0.24
79		LCMS: [M+H] ⁺ /Rt (min): 348/0.66

[0387]

Reference example 58: (1S,6R)-2,2-difluoro-6-[4-(propan-2-yl)piperazin-1-yl]cyclohexan-1-amine

Reference example 59: (3S)-1-[(1S,2R)-2-amino-3,3-

difluorocyclohexyl]-N-methyl-N-(propan-2-yl)pyrrolidin-1-amine

Reference example 60: (1R,6S)-2,2-difluoro-6-[4-[(propan-2-yl)oxy]piperidin-1-yl]cyclohexan-1-amine

5 Reference example 61: (1R,6S)-2,2-difluoro-6-[(2S)-2-methyl-4-(propan-2-yl)piperazin-1-yl]cyclohexan-1-amine

Reference example 62: (1R,6S)-2,2-difluoro-6-[(2R)-2-methyl-4-(propan-2-yl)piperazin-1-yl]cyclohexan-1-amine

10 Reference example 63: (1S,2R)-3,3-difluoro-N¹-methyl-N¹-[1-(propan-2-yl)piperidin-4-yl]cyclohexan-1,2-diamine

Reference example 64: (1R,6S)-2,2-difluoro-6-[4-(pyrrolidin-1-yl)piperidin-1-yl]cyclohexan-1-amine

15 Reference example 65: (1R,6S)-2,2-difluoro-6-[5-(propan-2-yl)hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl]cyclohexan-1-amine

Reference example 66: (1R,6S)-2,2-difluoro-6-[2-(propan-2-yl)-2,8-diazaspiro[4.5]decan-8-yl]cyclohexan-1-amine

20 Reference example 67: 1-[(1S,2R)-2-amino-3,3-difluorocyclohexyl]-N,N-diethylpiperidin-4-amine

Reference example 68: 1-[(1S,2R)-2-amino-3,3-difluorocyclohexyl]-N,4-dimethyl-N-(propan-2-yl)piperidin-4-amine

25 Reference example 69: 1-[(1S,2R)-2-amino-3,3-difluorocyclohexyl]-N-methyl-N-[(1-

methylcyclopropyl)methyl]piperidin-4-amine

Reference example 70: 1-[(1S,2R)-2-amino-3,3-difluorocyclohexyl]-N-[(1-fluorocyclopropyl)methyl]-N-methylpiperidin-4-amine

5 Reference example 71: 1-[(1S,2R)-2-amino-3,3-difluorocyclohexyl]-N-methyl-N-{[1-(trifluoromethyl)cyclopropyl)methyl]piperidin-4-amine

Reference example 72: (1R,3R,5S)-8-[(1S,2R)-2-amino-3,3-difluorocyclohexyl]-N-(cyclopropylmethyl)-N-methyl-8-
10 azabicyclo[3.2.1]octan-3-amine

Reference example 73: (1R,3S,5S)-8-[(1S,2R)-2-amino-3,3-difluorocyclohexyl]-N-(cyclopropylmethyl)-N-methyl-8-azabicyclo[3.2.1]octan-3-amine

Reference example 74: (4S)-1-[(1S,2R)-2-amino-3,3-difluorocyclohexyl]-N-(cyclopropylmethyl)-N-methylazepan-4-
15 amine

Reference example 75: (4R)-1-[(1S,2R)-2-amino-3,3-difluorocyclohexyl]-N-(cyclopropylmethyl)-N-methylazepan-4-amine

20 Reference example 76: 1-[(1S,2R)-2-amino-3,3-difluorocyclohexyl]-N-methyl-N-(propan-2-yl)azetidin-3-amine

Reference example 77: 1-[(1S,2R)-2-amino-3,3-difluorocyclohexyl]-N-(cyclopropylmethyl)-N-methylazetidin-
25 3-amine

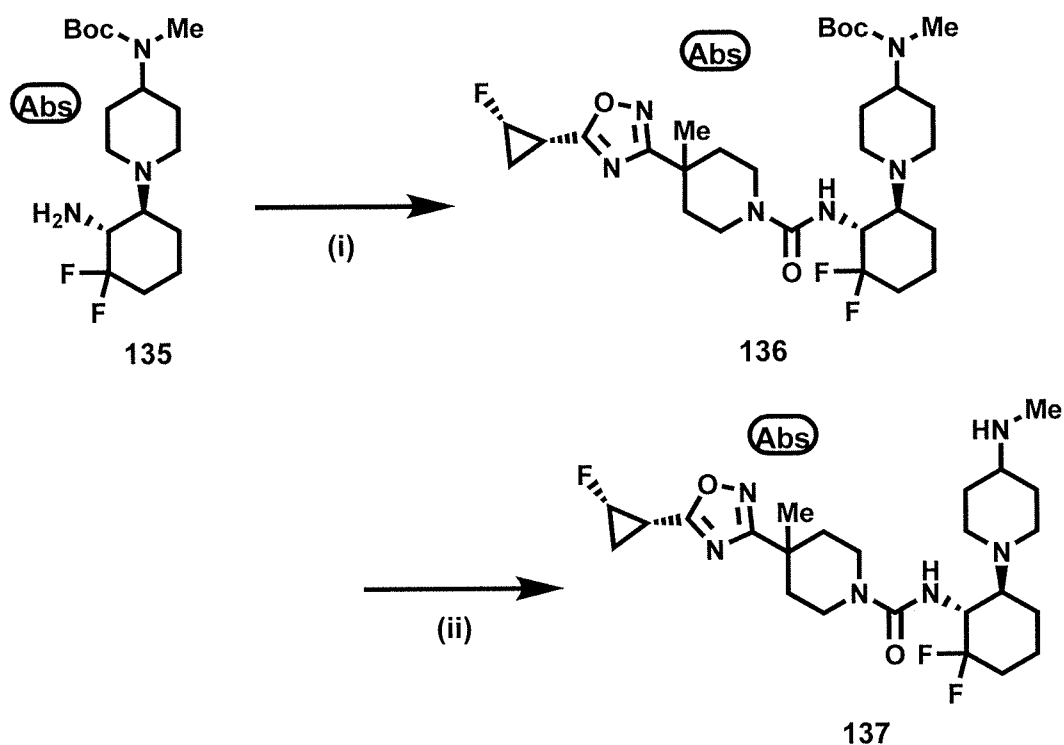
Reference example 78: (1R,6S)-2,2-difluoro-6-[4-(propan-2-yl)-1,4-diazepan-1-yl]cyclohexan-1-amine

Reference example 79: *tert*-butyl {1-[(1S,2R)-2-amino-3,3-difluorocyclohexyl]piperidin-4-yl}methylcarbamate

5 [0388]

Reference example 80:

N-{(1R,6S)-2,2-Difluoro-6-[4-(methylamino)piperidin-1-yl]cyclohexyl}-4-{5-[(1S,2S)-2-fluorocyclopropyl]-1,2,4-oxadiazol-3-yl}-4-methylpiperidine-1-carboxamide



10

[0389]

Step (i):

The title compound 136 (2.92 g) was prepared in the same manner as Example 19 by using the compound of Reference example 79 (2.61 g).

15

[0390]

Step (ii):

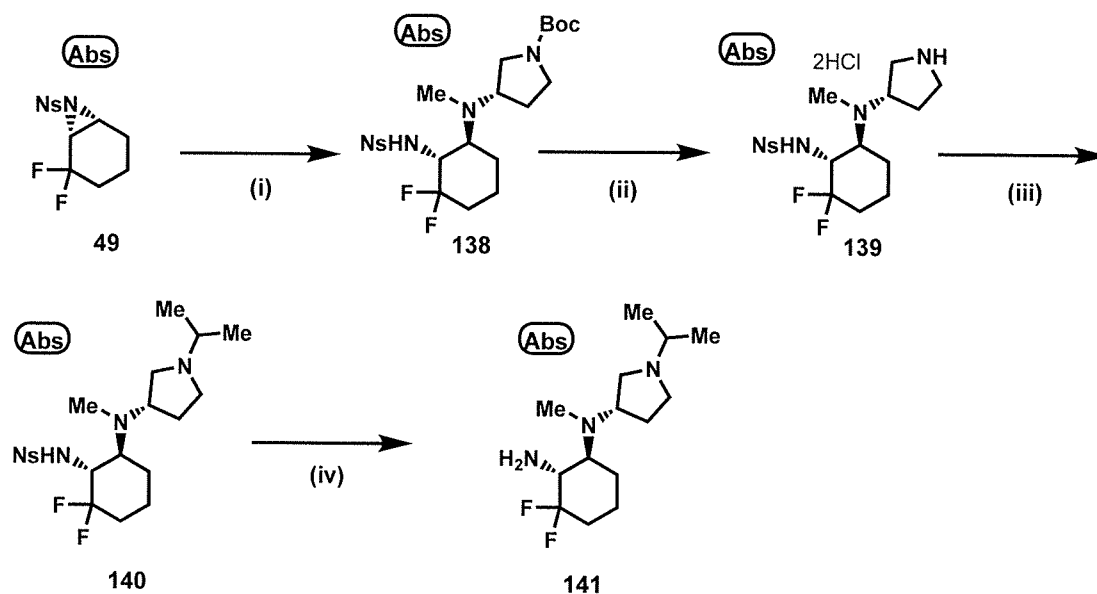
To a solution of Compound 136 (2.92 g) in toluene (24 ml) was added TFA (5.56 g), and the mixture was stirred at room temperature for 3.5 hours. The reaction solution was concentrated *in vacuo*, the obtained residue was dissolved in water, and aqueous sodium bicarbonate was added to the solution. The mixture was extracted with chloroform, and the organic layer was concentrated *in vacuo* to give the title compound 137 (2.38 g).

LCMS: $[M+H]^+/R_t$ (min): 499/0.49 (Method C)

[0391]

Reference example 81:

(1S,2R)-3,3-Difluoro-N¹-methyl-N¹-[(3S)-1-(propan-2-yl)pyrrolidin-3-yl]cyclohexan-1,2-diamine



[0392]

Step (i):

Compound 138 (2.61 g) was prepared in the same manner as Step (ii) in Reference example 18, by using *tert*-butyl (3S)-3-(methylamino)pyrrolidine-1-carboxylate instead of 1-isopropylpiperazine at Step (ii) in Reference example 18.

[0393]

Step (ii):

The title compound 139 (2.59 g) was prepared in the same manner as Step (iv) in Reference example 2 by using Compound 138 (2.61 g).

[0394]

Step (iii):

The title compound 140 (1.97 g) was prepared in the same manner as Step (iii) in Reference example 42 by using Compound 139 (2.59 g) and acetone (3.87 mL).

[0395]

Step (iv):

The title compound 141 (925 mg) was prepared in the same manner as Step (iii) in Reference example 18 by using Compound 140 (1.97 g).

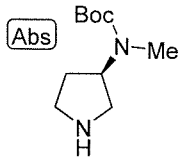
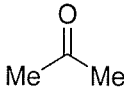
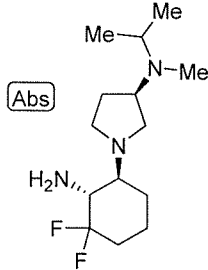
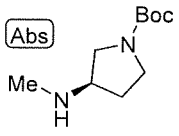
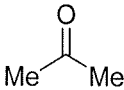
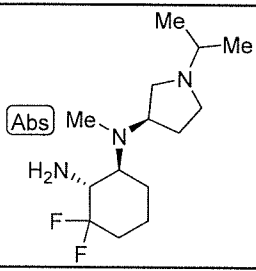
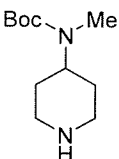
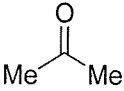
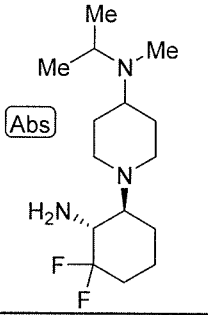
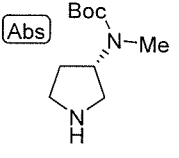
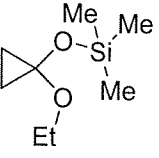
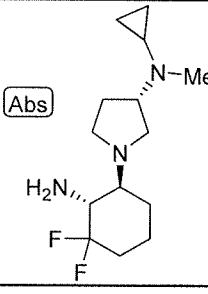
LCMS: [M+H]⁺/Rt (min): 276/0.15

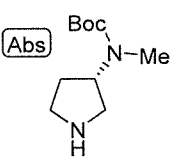
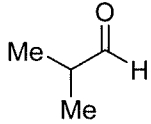
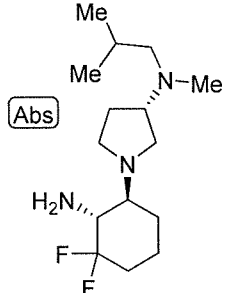
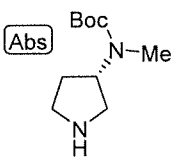
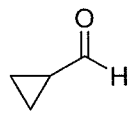
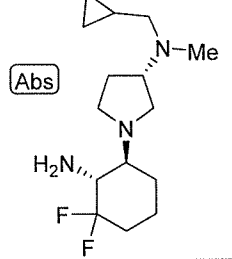
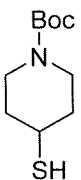
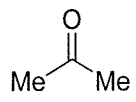
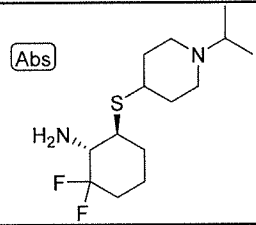
[0396]

Reference examples 82 - 88

The compounds of Reference examples 82 - 88 shown in the table below were prepared in the same manner as Reference

example 81, by using the appropriate strating compound
 (Material A) instead of *tert*-butyl (3*S*)-3-
 (methylamino)pyrrolidine-1-carboxylate at Step (i) in
 Reference example 81, and each appropriate strating compound
 5 (Material B) instead of acetone at Step (iii) in Reference
 example 81.

Reference example	Material A	Material B	Chemical structure	Instrumental analytical data
82				LCMS: [M+H] ⁺ /Rt (min): 276/0.28
83				LCMS: [M+H] ⁺ /Rt (min): 276/0.16
84				LCMS: [M+H] ⁺ /Rt (min): 290/0.34
85				LCMS: [M+H] ⁺ /Rt (min): 274/0.30

86				LCMS: [M+H] ⁺ /Rt (min): 290/0.37
87				LCMS: [M+H] ⁺ /Rt (min): 288/0.36
88				LCMS: [M+H] ⁺ /Rt (min): 293/0.33

[0397]

Reference example 82: (3R)-1-[(1S,2R)-2-amino-3,3-difluorocyclohexyl]-N-methyl-N-(propan-2-yl)pyrrolidin-1-amine

5 Reference example 83: (1S,2R)-3,3-difluoro-N¹-methyl-N¹-[(3R)-1-(propan-2-yl)pyrrolidin-3-yl]cyclohexan-1,2-diamine

Reference example 84: 1-[(1S,2R)-2-amino-3,3-difluorocyclohexyl]-N-methyl-N-(propan-2-yl)piperidin-4-amine

10

Reference example 85: (3S)-1-[(1S,2R)-2-amino-3,3-difluorocyclohexyl]-N-cyclopropyl-N-methylpyrrolidin-1-amine

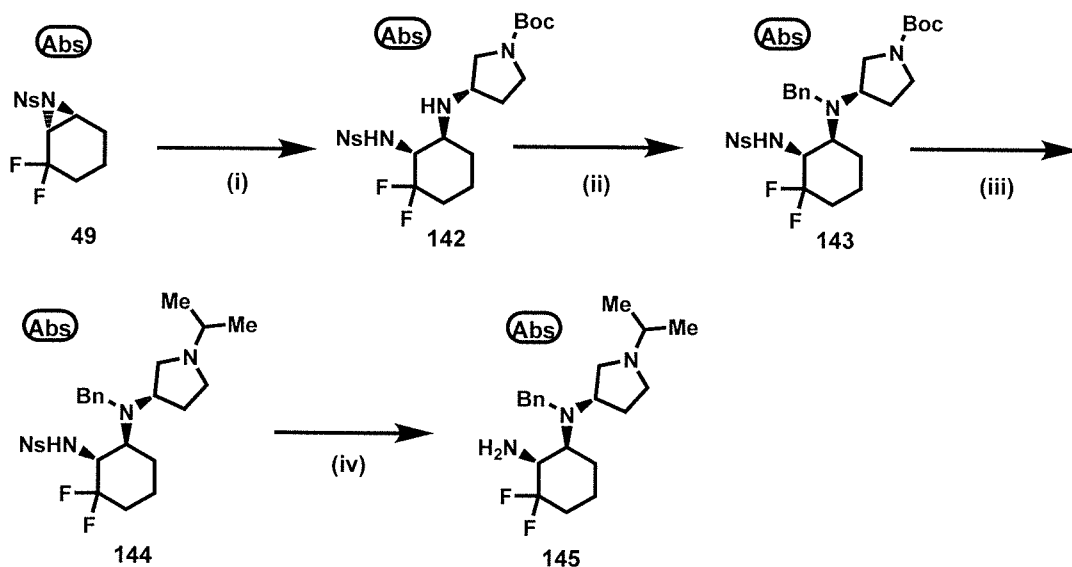
Reference example 86: (3S)-1-[(1S,2R)-2-amino-3,3-difluorocyclohexyl]-N-methyl-N-(2-methylpropyl)pyrrolidin-1-amine

Reference example 87: (3S)-1-[(1S,2R)-2-amino-3,3-difluorocyclohexyl]-N-(cyclopropylmethyl)-N-methylpyrrolidin-1-amine

Reference example 88: (1S,6S)-2,2-difluoro-6-{[1-(propan-2-yl)piperidin-4-yl]sulfanyl}cyclohexan-1-amine
[0398]

10 Reference example 89:

(1S,2R)-N¹-Benzyl-3,3-difluoro-N¹-[(3S)-1-(propan-2-yl)pyrrolidin-3-yl]cyclohexan-1,2-diamine



[0399]

15 Step (i):

Compound 142 (2.19 g) was prepared in the same manner as Step (ii) in Reference example 18, by using *tert*-butyl

(3S)-3-aminopyrrolidine-1-carboxylate instead of 1-isopropylpiperazine at Step (ii) in Reference example 18.

[0400]

Step (ii):

5 The title compound 143 (240 mg) was prepared in the same manner as Step (iii) in Reference example 42 by using Compound 142 (990 mg) and benzaldehyde (312 mg).

[0401]

Step (iii):

10 The title compound 144 (161 mg) was prepared in the same manner as Step (ii) and Step (iii) in Reference example 81 by using Compound 143 (235 mg).

[0402]

Step (iv):

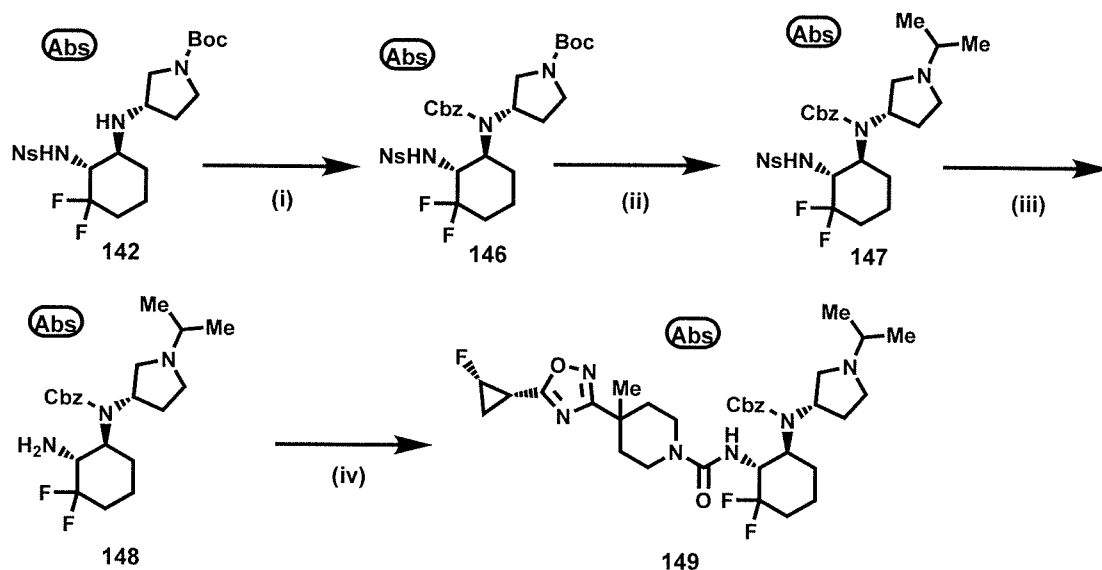
15 The title compound 145 (87.4 mg) was prepared in the same manner as Step (iii) in Reference example 18 by using Compound 144 (158 mg).

LCMS: [M+H]⁺/Rt (min): 352/0.42 (Method C)

[0403]

20 Reference example 90:

Benzyl { (1S,2R)-3,3-difluoro-2-[(4-{5-[(1S,2S)-2-fluorocyclopropyl]-1,2,4-oxadiazol-3-yl}-4-methylpiperidine-1-carbonyl)amino]cyclohexyl}[(3S)-1-(propan-2-yl)pyrrolidin-3-yl]carbamate



[0404]

Step (i):

To a solution of Compound 142 (680 mg) in a mixture of dioxane and water (10 mL/3.3 mL) were added benzyl chloroformate (345 mg) and sodium acetate (116 mg) at 0°C, and the reaction solution was refluxed for 2 hours. After the reaction was completed, the reaction solution was extracted with chloroform. The organic layer was concentrated *in vacuo* to give the title compound 146 (530 mg).

[0405]

Step (ii):

The title compound 147 (256 mg) was prepared in the same manner as Step (ii) and Step (iii) in Reference example 81 by using Compound 146 (530 mg).

[0406]

Step (iii):

The title compound 148 (137 mg) was prepared in the same manner as Step (iii) in Reference example 18 by using Compound 147 (254 mg).

5 [0407]

Step (iv):

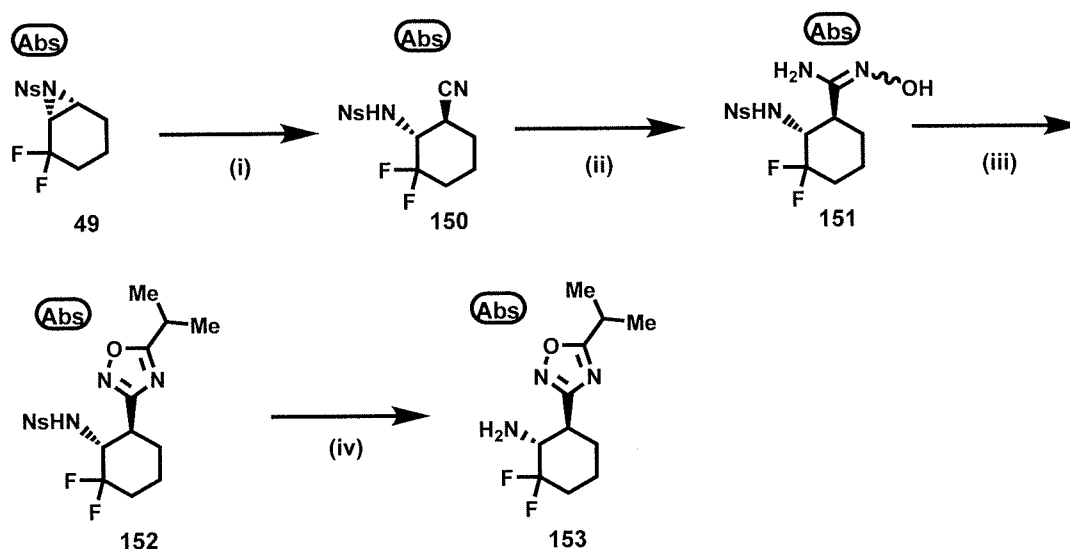
The title compound 149 (175 mg) was prepared in the same manner as Example 19 by using Compound 148 (135 mg).

LCMS: $[M+H]^+/\text{Rt}$ (min): 647/0.79 (Method C)

10 [0408]

Reference example 91:

(1R,6S)-2,2-Difluoro-6-[5-(propan-2-yl)-1,2,4-oxadiazol-3-yl]cyclohexan-1-amine



15 [0409]

Step (i):

To a solution of Compound 49 (2.01 g) in acetonitrile (12.6 ml) were added sodium cyanide (495 mg) and lithium

perchlorate (67 mg), and the reaction solution was refluxed for 3 hours. After the reaction was completed, water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was dried over
5 anhydrous sodium sulfate, concentrated *in vacuo*, and then the obtained residue was purified by silica gel column chromatography (eluate: hexane/ethyl acetate) to give the title compound 150 (2.05 g).

[0410]

10 Step (ii):

The title compound 151 (1.88 g) was prepared in the same manner as Step (i) in Reference example 8 by using Compound 150 (2.04 g).

[0411]

15 Step (iii):

The title compound 152 (89.7 mg) was prepared in the same manner as Step (ii) and Step (iii) in Reference example 8 by using Compound 151 (200 mg) and isobutyric acid (53.6 mg).

20 [0412]

Step (iv):

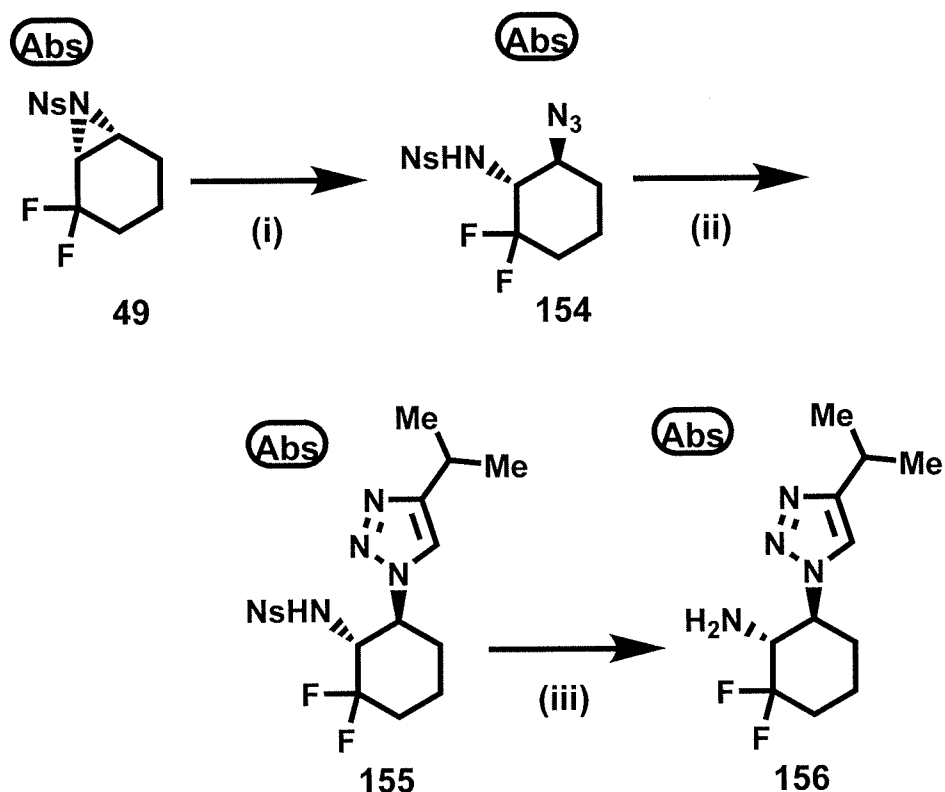
The title compound 153 (41.5 mg) was prepared in the same manner as Step (iii) in Reference example 18 by using Compound 152 (87.7 mg).

25 LCMS: [M+H]⁺/Rt (min): 246/0.37 (Method C)

[0413]

Reference example 92:

(1R,6S)-2,2-Difluoro-6-[4-(propan-2-yl)-1H-1,2,3-triazol-1-yl]cyclohexan-1-amine



5

[0414]

Step (i):

To a solution of Compound 49 (1.6 g) in a mixture of acetonitrile and water (23 mL/2.5 mL) was added sodium azide (490 mg), and the reaction solution was heated at 70°C for 1.5 hours. After the reaction was completed, saturated aqueous sodium bicarbonate was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate,

10

concentrated *in vacuo*, and then the obtained residue was purified by silica gel column chromatography (eluate: hexane/ethyl acetate) to give the title compound 154 (1.78 g).

5 [0415]

Step (ii):

To a solution of Compound 154 (550 mg) in a mixture of methanol and THF (11.4 mL/2.3 mL/4 mL) were added sodium ascorbate (30.2 mg), tris(2-benzimidazolylmethyl)amine (46.5 mg), and 3-methylbut-1-yne (156 mg). A solution of copper sulfate (18.2 mg) in water (3.8 mL) was added to the reaction solution, and the reaction mixture was stirred at room temperature. After the reaction was completed, the reaction mixture was filtrated with Celite, and concentrated *in vacuo*.
10 Then, the obtained residue was purified by silica gel column chromatography (eluate: hexane/ethyl acetate) to give the title compound 155 (353 mg).
15

[0416]

Step (iii):

20 The title compound 156 (168 mg) was prepared in the same manner as Step (iii) in Reference example 18 by using Compound 155 (353 mg).

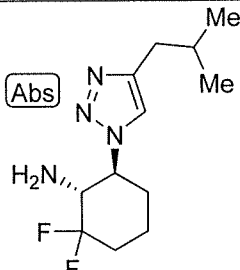
LCMS: [M+H]⁺/Rt (min): 245/0.42

[0417]

25 Reference example 93:

(1R,6S)-2,2-Difluoro-6-[4-(2-methylpropyl)-1H-1,2,3-triazol-1-yl]cyclohexan-1-amine

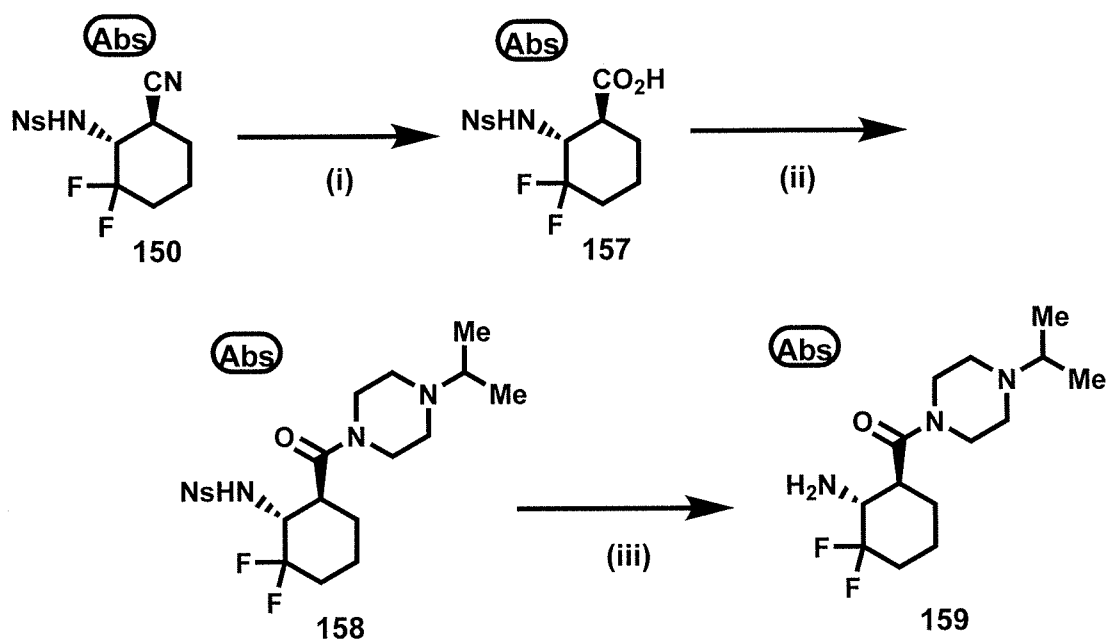
The compound of Reference example 93 shown in the table below was prepared according to the process in the above Reference example 92 by using 4-methylpent-1-yne instead of 3-methylbut-1-yne at Step (ii) in Reference example 92.

Reference example	Chemical structure	Instrumental analytical data
93		LCMS: [M+H] ⁺ /Rt (min):259/0.51

[0418]

Reference example 94:

[(1S,2R)-2-Amino-3,3-difluorocyclohexyl][4-(propan-2-yl)piperazin-1-yl]methanone



[0419]

Step (i):

To a solution of Compound 150 (555 mg) in DMSO (6 mL) was added aqueous hydrochloric acid (9 mL), and the reaction solution was heated at 120°C. After the reaction was completed, water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate, and concentrated *in vacuo* to give the title compound 157 (600 mg).

10 [0420]

Step (ii):

To a solution of Compound 157 (476 mg) in DMF (1.5 mL) were added 1-isopropylpiperazine (234 mg), triethylamine (308 mg), and HATU (753 mg), and the reaction solution was stirred at room temperature. After the reaction was completed, water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate, concentrated *in vacuo*, and then the obtained residue was purified by amino silica gel column chromatography (eluate: chloroform/methanol) to give the title compound 158 (610 mg).

LCMS: [M+H]⁺/Rt (min): 475/0.59

[0421]

25 Step (iii):

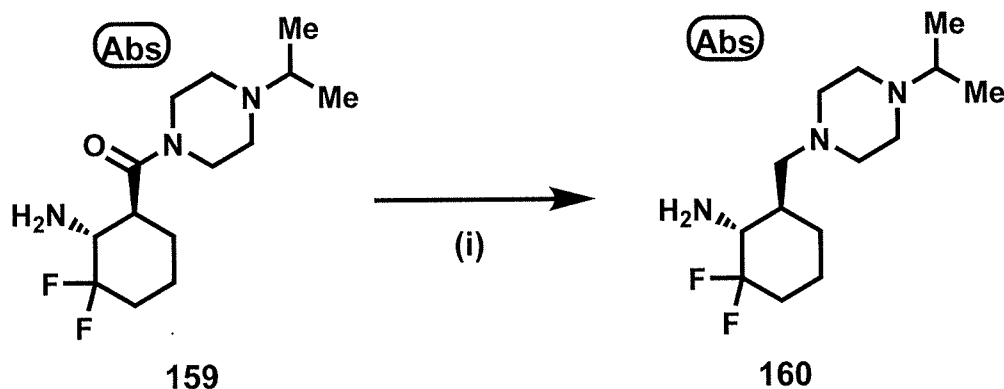
The title compound 159 (180 mg) was prepared in the same manner as Step (iii) in Reference example 18 by using Compound 158 (605 mg).

LCMS: $[M+H]^+/R_t$ (min): 290/0.16

5 [0422]

Reference example 95:

(1R,6R)-2,2-Difluoro-6-{[4-(propan-2-yl)piperazin-1-yl]methyl}cyclohexan-1-amine



10 [0423]

Step (i):

The title compound 160 (112 mg) was prepared in the same manner as Step (ii) in Reference example 22 by using Compound 159 (171 mg).

15 LCMS: $[M+H]^+/R_t$ (min): 276/0.24

[0424]

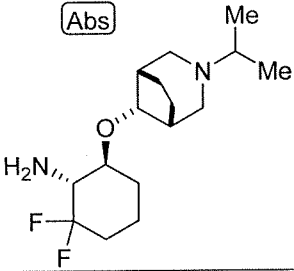
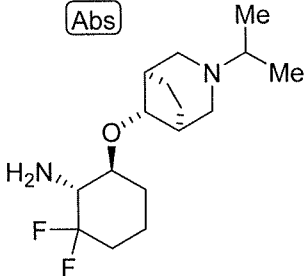
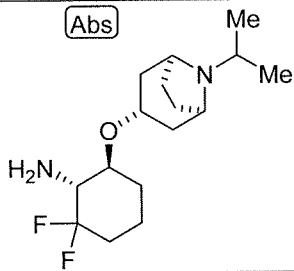
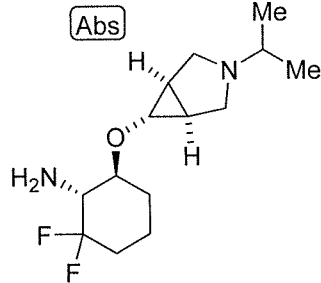
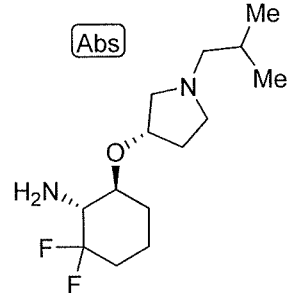
Reference examples 96 - 114:

The compounds of Reference examples shown in the table below were prepared according to the process in the above Reference example 37, by using each appropriate starting

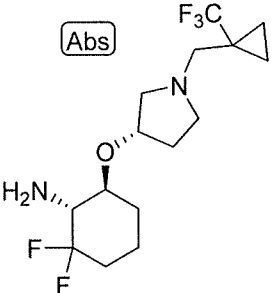
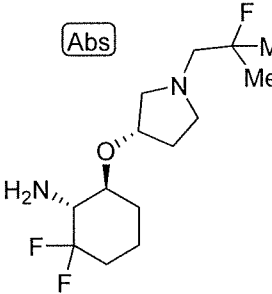
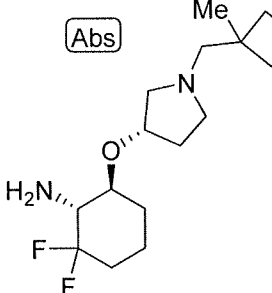
20

compound instead of (S)-1-isopropylpyrrolidin-3-ol at Step (i) in Reference example 37.

Reference example	Chemical structure	Instrumental analytical data
96	(Abs)	LCMS: [M+H] ⁺ /Rt (min): 277/0.30
97	(Abs)	LCMS: [M+H] ⁺ /Rt (min): 278/0.57
98	(Abs)	LCMS: [M+H] ⁺ /Rt (min): 260/0.45
99	(Abs)	LCMS: [M+H] ⁺ /Rt (min): 249/0.16
100	(Abs)	LCMS: [M+H] ⁺ /Rt (min): 303/0.32

101	Abs 	LCMS: [M+H] ⁺ /Rt (min): 303/0.33
102	Abs 	LCMS: [M+H] ⁺ /Rt (min): 303/0.31
103	Abs 	LCMS: [M+H] ⁺ /Rt (min): 303/0.32
104	Abs 	LCMS: [M+H] ⁺ /Rt (min): 275/0.43
105	Abs 	LCMS: [M+H] ⁺ /Rt (min): 277/0.38

106	Abs	LCMS: [M+H] ⁺ /Rt (min): 293/0.36
107	Abs	LCMS: [M+H] ⁺ /Rt (min): 291/0.16 (Method C)
108	Abs	LCMS: [M+H] ⁺ /Rt (min): 275/0.49
109	Abs	LCMS: [M+H] ⁺ /Rt (min): 291/0.20 (Method C)
110	Abs	LCMS: [M+H] ⁺ /Rt (min): 289/0.32
111	Abs	LCMS: [M+H] ⁺ /Rt (min): 293/0.26

112		LCMS: [M+H] ⁺ /Rt (min): 343/0.37
113		LCMS: [M+H] ⁺ /Rt (min): 295/0.37
114		LCMS: [M+H] ⁺ /Rt (min): 305/0.15

[0425]

Reference example 96: (1R,6S)-2,2-difluoro-6-{[1-(propan-2-yl)piperidin-4-yl]oxy}cyclohexan-1-amine

Reference example 97: (1R,6S)-2,2-difluoro-6-{[3-(propan-2-yl)-1,2,4-thiadiazol-5-yl]oxy}cyclohexan-1-amine

Reference example 98: (1R,6S)-2,2-difluoro-6-{[1-(propan-2-yl)-1H-pyrazol-4-yl]oxy}cyclohexan-1-amine

Reference example 99: (1R,6S)-2,2-difluoro-6-{[1-(propan-2-yl)azetidin-3-yl]oxy}cyclohexan-1-amine

Reference example 100: (1R,6S)-2,2-difluoro-6-{[(1R,3S,5S)-8-(propan-2-yl)-8-azabicyclo[3.2.1]octan-3-

yl]oxy}cyclohexan-1-amine

Reference example 101: (1R,6S)-2,2-difluoro-6-
{[(1R,5S,8R)-3-(propan-2-yl)-3-azabicyclo[3.2.1]octan-8-
yl]oxy}cyclohexan-1-amine

5 Reference example 102: (1R,6S)-2,2-difluoro-6-
{[(1R,5S,8S)-3-(propan-2-yl)-3-azabicyclo[3.2.1]octan-8-
yl]oxy}cyclohexan-1-amine

Reference example 103: (1R,6S)-2,2-difluoro-6-
{[(1R,3R,5S)-8-(propan-2-yl)-8-azabicyclo[3.2.1]octan-3-
10 yl]oxy}cyclohexan-1-amine

Reference example 104: (1R,6S)-2,2-difluoro-6-
{[(1R,5S,6S)-3-(propan-2-yl)-3-azabicyclo[3.1.0]hexan-6-
yl]oxy}cyclohexan-1-amine

Reference example 105: (1R,6S)-2,2-difluoro-6-{[(3S)-
15 1-(2-methylpropyl)pyrrolidin-3-yl]oxy}cyclohexan-1-amine

Reference example 106: (1R,6S)-2,2-difluoro-6-
{[(3R,4R)-4-methoxy-1-(propan-2-yl)pyrrolidin-3-
yl]oxy}cyclohexan-1-amine

Reference example 107: (1R,6S)-2,2-difluoro-6-{[4-
20 methyl-1-(propan-2-yl)piperidin-4-yl]oxy}cyclohexan-1-amine

Reference example 108: (1R,6S)-6-{[(3S)-1-
(cyclopropylmethyl)pyrrolidin-3-yl]oxy}-2,2-
difluorocyclohexan-1-amine

Reference example 109: (1R,6S)-6-{[(3S)-1-(2,2-
25 dimethylpropyl)pyrrolidin-3-yl]oxy}-2,2-difluorocyclohexan-

1-amine

Reference example 110: (1R,6S)-2,2-difluoro-6-({(3S)-1-[(1-methylcyclopropyl)methyl]pyrrolidin-3-yl}oxy)cyclohexan-1-amine

5 Reference example 111: (1R,6S)-2,2-difluoro-6-({(3S)-1-[(1-fluorocyclopropyl)methyl]pyrrolidin-3-yl}oxy)cyclohexan-1-amine

Reference example 112: (1R,6S)-2,2-difluoro-6-{[(3S)-1-{[1-(trifluoromethyl)cyclopropyl]methyl}pyrrolidin-3-yl}oxy)cyclohexan-1-amine

10

Reference example 113: (1R,6S)-2,2-difluoro-6-{[(3S)-1-(2-fluoro-2-methylpropyl)pyrrolidin-3-yl}oxy)cyclohexan-1-amine

Reference example 114: (1R,6S)-2,2-difluoro-6-({(3S)-1-[(3-methyloxetan-3-yl)methyl]pyrrolidin-3-yl}oxy)cyclohexan-1-amine

15

[0426]

Reference examples 115 - 118

The compounds of Reference examples 115 - 118 shown in the table below were prepared in the same manner as Reference example 8, by using the appropriate strating compound (Material A) instead of Compound 26 at Step (i) in Reference example 8, and each appropriate strating compound (Material B) instead of cyclopropane-carboxylic acid at Step (iii) in Reference example 8.

20

25

Reference example	Material A	Material B	Chemical structure	Instrumental analytical data
115				LCMS: [M+H] ⁺ /Rt (min): 226/0.29 (Method C)
116				LCMS: [M+H] ⁺ /Rt (min): 226/0.29 (Method C)
117				LCMS: [M+H] ⁺ /Rt (min): 222/0.43 (Method C)
118				LCMS: [M+H] ⁺ /Rt (min): 240/0.39 (Method C)

[0427]

Reference example 115: 4-{5-[(1S,2S)-2-fluorocyclopropyl]-1,2,4-oxadiazol-3-yl}-4-methylpiperidine

Reference example 116: 4-{5-[(1R,2R)-2-fluorocyclopropyl]-1,2,4-oxadiazol-3-yl}-4-methylpiperidine

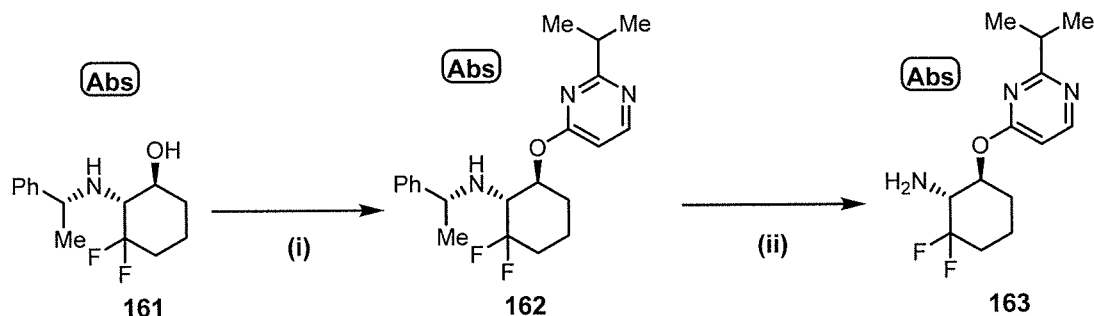
Reference example 117: 4-(5-cyclobutyl-1,2,4-oxadiazol-3-yl)-4-methylpiperidine monohydrochloride

Reference example 118: 4-ethyl-4-{5-[(1S,2S)-2-fluorocyclopropyl]-1,2,4-oxadiazol-3-yl}piperidine

10 [0428]

Reference example 119:

(1R,6S)-2,2-Difluoro-6-{[2-(propan-2-yl)pyrimidin-4-yl]oxy}cyclohexan-1-amine



[0429]

Step (i):

To a solution of Compound 161 (148 mg) known in literature in THF (3 ml) were added sodium hydride (55 %, 30 mg) at 0°C, and then 4-chloro-2-(propan-2-yl)pyrimidine. The reaction solution was warmed to room temperature and stirred. After the reaction was completed, water was added to the reaction mixture, and the mixture was extracted with chloroform. The organic layer was dried over anhydrous sodium sulfate, concentrated *in vacuo*, and then the obtained residue was purified by silica gel column chromatography (eluate: hexane/ethyl acetate) to give the title compound 162 (209 mg).

15 [0430]

Step (ii):

To a solution of Compound 162 (113 mg) in ethyl acetate (2 mL) was added palladium hydroxide (17 mg) at room temperature, and the mixture was stirred under hydrogen atmosphere. After the reaction was terminated as judged by LC-MS, the reaction mixture was filtrated with Celite, and

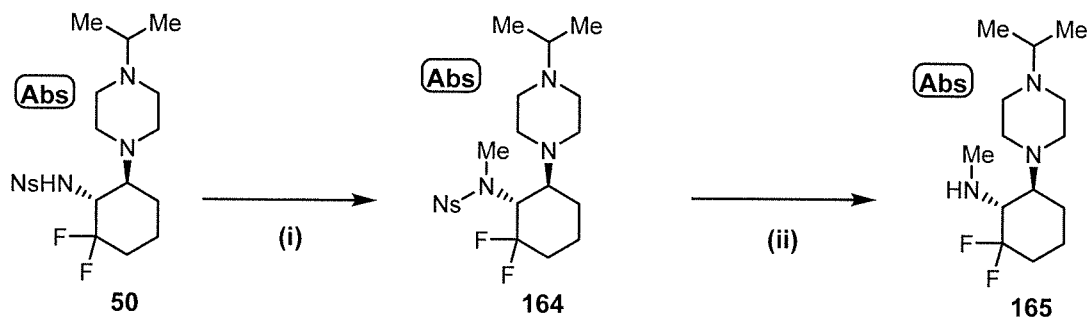
the filtrate was concentrated *in vacuo* to give the title compound 163 (33.5 mg).

LCMS: $[M+H]^+/\text{Rt}$ (min): 272/0.47

[0431]

5 Reference example 120:

(1R,6S)-2,2-Difluoro-N-methyl-6-[4-(propan-2-yl)piperazin-1-yl]cyclohexan-1-amine



[0432]

10 Step (i):

To a solution of Compound 50 (173 mg) in DMF (3 mL) were added cesium carbonate (253 mg) and methyl iodide (72 mg) at 0°C, and then the reaction mixture was warmed to room temperature and stirred. After the reaction was completed, water was added to the reaction mixture, and the mixture was extracted with diethyl ether. The organic layer was dried over anhydrous sodium sulfate, concentrated *in vacuo*, and then the obtained residue was purified by amino silica gel column chromatography (eluate: hexane/ethyl acetate) to give the title compound 164 (159 mg).

[0433]

Step (ii):

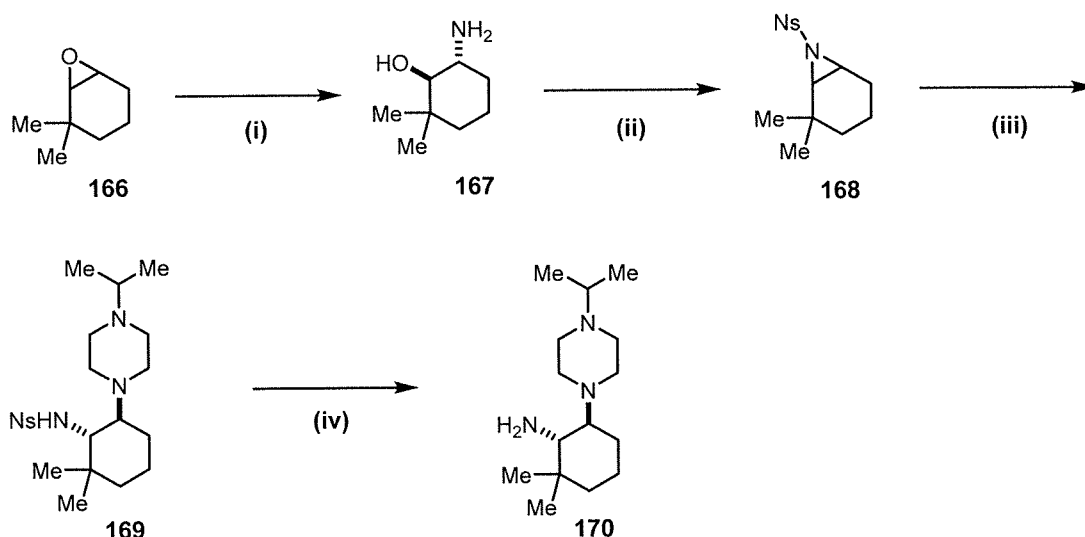
The title compound 165 (71 mg) was prepared in the same manner as Step (iii) in Reference example 18 by using Compound 164 (134 mg).

5 LCMS: $[M+H]^+/Rt$ (min): 276/0.15

[0434]

Reference example 121:

rac-(1*S*,6*S*)-2,2-Dimethyl-6-[4-(propan-2-yl)piperazin-1-yl]cyclohexan-1-amine



10

[0435]

Step (i):

To a solution of Compound 166 (283 mg) in 2-propanol (8 ml) was added aqueous ammonia (6 g), and the reaction mixture was refluxed. After the reaction was terminated as judged by the consumption of the starting material, the reaction solution was concentrated *in vacuo* to be used in the next step.

15

[0436]

Step (ii):

The title compound 168 (64.3 mg) was prepared in the same manner as Step (i) in Reference example 18 by using
5 Compound 167.

[0437]

Step (iii):

The title compound 169 (102 mg) was prepared in the same manner as Step (ii) in Reference example 18 by using
10 Compound 168 (60.8 mg).

[0438]

Step (iv):

The title compound 170 (40.2 mg) was prepared in the same manner as Step (iii) in Reference example 18 by using
15 Compound 169 (102 mg).

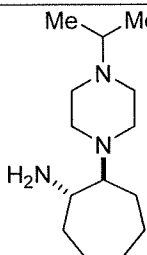
LCMS: [M+H]⁺/Rt (min): 254/0.43

[0439]

Reference example 122:

rac-(1S,2S)-2-[4-(Propan-2-yl)piperazin-1-yl]cycloheptan-1-
20 amine

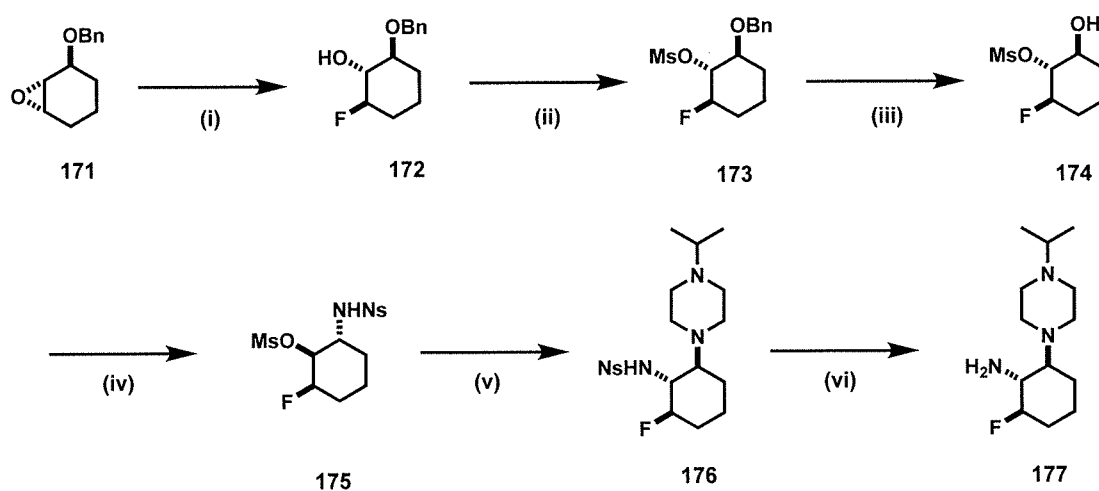
The compounds of Reference examples shown in the table below were prepared according to the process in the above Reference example 120, by using 8-oxabicyclo[5.1.0]octane instead of Compound 166 at Step (i) in Reference example
25 120.

Reference example	Chemical structure	Instrumental analytical data
122		LCMS: [M+H] ⁺ /Rt (min): 240/0.24

[0440]

Reference example 123:

rac-(1R,2R,6S)-2-Fluoro-6-[4-(propan-2-yl)piperazin-1-yl]cyclohexan-1-amine



5

[0441]

Step (i):

A solution of Compound 171 (403 mg) and tetrabutylammonium dihydrogen trifluoride (1.78 g) in toluene (1 mL) was heated at 150°C with a microwave device. After the reaction was completed, water was added to the reaction mixture, and the mixture was extracted with diethyl ether. The organic layer was dried over anhydrous sodium

10

sulfate, concentrated *in vacuo*, and then the obtained residue was purified by amino silica gel column chromatography (eluate: hexane/ethyl acetate) to give the title compound 172 (323 mg).

5 [0442]

Step (ii):

Compound 172 (457 mg) was dissolved in THF (4.1 mL). To the solution were added triethylamine (1.13 mL) and methanesulfonyl chloride (0.318 mL) under ice temperature, and the reaction mixture was stirred. After the reaction was terminated as judged by the consumption of the starting material, water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate, concentrated *in vacuo*, and then the obtained residue was purified by amino silica gel column chromatography (eluate: hexane/ethyl acetate) to give the title compound 173 (578 mg).

10
15

[0443]

Step (iii):

20 To a solution of Compound 173 (571 mg) in ethanol (3.5 mL) was added palladium hydroxide (20 %, 133 mg) at room temperature, and the mixture was stirred under hydrogen atmosphere. After the reaction was completed, the reaction mixture was filtrated with Celite, and the filtrate was
25 concentrated *in vacuo*. The obtained residue was purified by

silica gel column chromatography (eluate: hexane/ethyl acetate) to give the title compound 174 (400 mg).

[0444]

Step (iv):

5 Compound 174 (176 mg) was dissolved in 1,4-dioxane (3.5 mL). To the solution was added DBU (0.25 mL), and the reaction mixture was stirred at 85°C. After the reaction was terminated as judged by the consumption of the starting material, the reaction mixture was subsequently reacted in
10 the same manner as Step (i) in Reference example 121, and methanesulfonylated in the same manner as the present Step (ii). Water was added to the reaction mixture, and the mixture was extracted with chloroform. The organic layer was dried over anhydrous sodium sulfate and concentrated in
15 *vacuo* to give the title compound 175 (86 mg).

[0445]

Step (v):

 The title compound 176 (92.8 mg) was prepared according to the cyclization condition of Step (ii) in Reference
20 example 121 by using Compound 175 (86 mg), followed by the same manner as Step (ii) in Reference example 18.

[0446]

Step (vi):

 The title compound 177 (35.1 mg) was prepared in the
25 same manner as Step (iii) in Reference example 18 by using

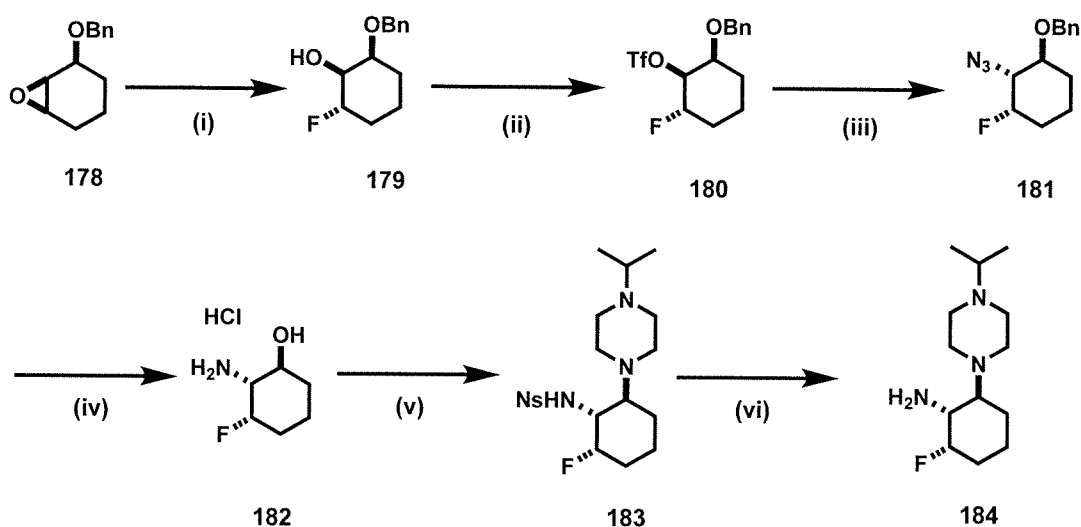
Compound 176 (86.1 mg).

LCMS: $[M+H]^+/R_t$ (min): 244/0.19

[0447]

Reference example 124:

- 5 *rac*-(1R,2S,6S)-2-Fluoro-6-[4-(propan-2-yl)piperazin-1-yl]cyclohexan-1-amine



[0448]

Step (i):

- 10 The title compound 179 (953 mg) was prepared in the same manner as Step (i) in Reference example 123 by using Compound 178 (929 mg).

[0449]

Step (ii):

- 15 Compound 179 (283 mg) was dissolved in chloroform (6 mL). To the solution were added pyridine (0.51 mL) and trifluoromethanesulfonic anhydride (0.256 mL) under ice temperature, and the reaction mixture was stirred. After

the reaction was terminated as judged by the consumption of the starting material, aqueous sodium bicarbonate was added to the reaction mixture, and the mixture was extracted with chloroform. The organic layer was dried over anhydrous sodium sulfate, concentrated *in vacuo*, and then the obtained residue was purified by silica gel column chromatography (eluate: hexane/ethyl acetate) to give the title compound 180 (424 mg).

[0450]

10 Step (iii):

To a solution of Compound 180 (418 mg) in DMF (4 mL) was added sodium azide (229 mg), and the reaction solution was stirred at room temperature. After the reaction was completed, water was added to the reaction mixture, and the mixture was extracted with diethyl ether. The organic layer was dried over anhydrous sodium sulfate, concentrated *in vacuo*, and then the obtained residue was purified by silica gel column chromatography (eluate: hexane/ethyl acetate) to give the title compound 181 (102 mg).

20 [0451]

Step (iv):

To a solution of Compound 181 (102 mg) in ethanol (2 mL) was added palladium hydroxide (20 %, 58 mg) at room temperature, and the mixture was stirred under hydrogen atmosphere. The reaction mixture was filtrated with Celite,

and the filtrate was concentrated *in vacuo*. The obtained residue was dissolved in ethanol (2 mL) again, and aqueous hydrogen chloride (cyclopentylmethyl solution, 5 M, 0.327 mL) and palladium carbon (10 %, 71 mg) were added thereto.

5 The mixture was stirred under hydrogen atmosphere. After the reaction was completed, the reaction mixture was filtrated with Celite, and the filtrate was concentrated *in vacuo* to give the title compound 182 (76.8 mg).

[0452]

10 Step (v):

The title compound 183 (69 mg) was prepared in the same manner as Step (i) and Step (ii) in Reference example 18 by using Compound 182 (103 mg).

[0453]

15 Step (vi):

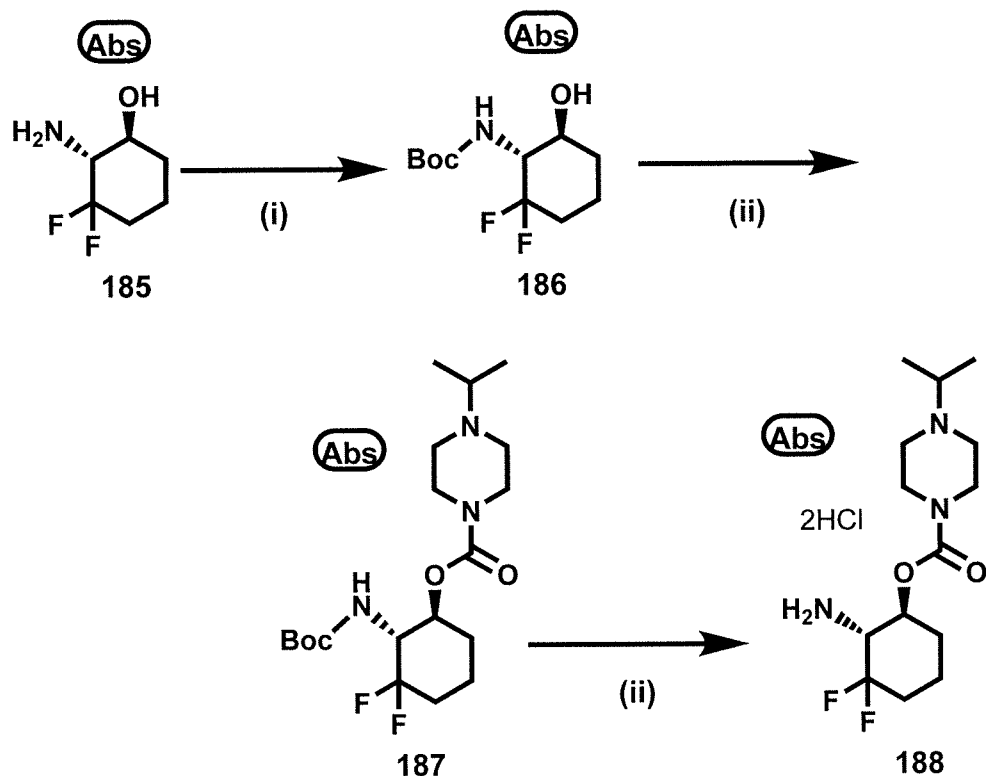
The title compound 184 (34.3 mg) was prepared in the same manner as Step (iii) in Reference example 18 by using Compound 183 (72 mg).

LCMS: [M+H]⁺/Rt (min): 244/0.14

20 [0454]

Reference example 125:

(1S,2R)-2-Amino-3,3-difluorocyclohexyl 4-(propan-2-yl)piperazine-1-carboxylate



[0455]

Step (i):

To a solution of Compound 185 known in literature in
 5 acetonitrile (3 mL) was added Boc₂O (238 mg), and the
 reaction solution was stirred at room temperature. After
 the reaction was completed, the reaction mixture was
 concentrated *in vacuo*, and the obtained residue was purified
 by silica gel column chromatography (eluate: hexane/ethyl
 10 acetate) to give the title compound 186 (216 mg).

[0456]

Step (ii):

The title compound 187 (118 mg) was prepared in the
 same manner as Step (iii) in Reference example 2 by using

Compound 186 (95.7 mg).

[0457]

Step (iii):

The title compound 188 (99.7 mg) was prepared in the same manner as Step (iv) in Reference example 2 by using Compound 187 (118 mg).

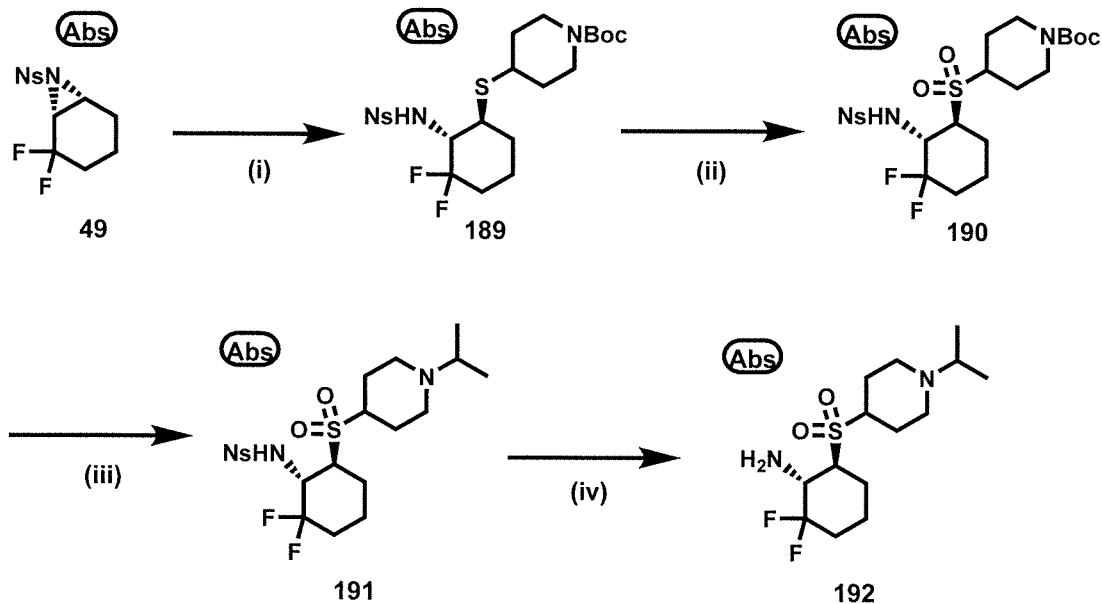
LCMS: $[M+H]^+/R_t$ (min): 306/0.25

[0458]

Reference example 126:

10 N-((1S,6S)-2,2-Difluoro-6-[1-(propan-2-yl)piperidine-4-sulfonyl]cyclohexyl)-4-nitrobenzene-1-sulfonamide

【化1】



[0459]

15 Step (i):

The title compound 189 (402 mg) was prepared in the same manner as Step (ii) in Reference example 18 by using

Compound 49 (399 mg) and *tert*-butyl 4-sulfanylpiperidine-1-carboxylate (300 mg).

[0460]

Step (ii):

5 To a solution of Compound 189 (210 mg) in chloroform (2 mL) was added *m*-CPBA (242 mg), and the reaction solution was stirred at room temperature. After the reaction was completed, aqueous sodium thiosulfate was added to the reaction mixture, and the mixture was extracted with
10 chloroform. The organic layer was dried over anhydrous sodium sulfate, concentrated *in vacuo*, and then the obtained residue was purified by amino silica gel column chromatography (eluate: chloroform/methanol) to give the title compound 190 (250 mg).

15 [0461]

Step (iii):

The title compound 191 (223 mg) was prepared in the same manner as Step (i) and Step (ii) in Reference example 53 by using Compound 190 (250 mg).

20 [0462]

Step (iv):

The title compound 192 (102 mg) was prepared in the same manner as Step (iii) in Reference example 18 by using Compound 191 (223 mg).

25 LCMS: [M+H]⁺/Rt (min): 325/0.21

[0463]

Test 1: Evaluation of agonist activity for orexin receptor type 2

Human orexin receptor type 2 and apoaeguorin were transiently expressed in CHO cells, and the agonist activity was evaluated based on intracellular calcium mobilization with ligand stimulation. The CHO cells-transiently-expressed human orexin receptor type 2 and apoaeguorin were seeded on a 384-well plate by 2,000 cells/well, and then incubated for 16 - 22 hours. After the plate was returned to room temperature, Coelenterazine hcp (final concentration: 1 μ M) was added to the plate, and the plate was allowed to stand at room temperature for 2 hours. And then, Orexin A (PEPTIDE INSTITUTE, INC., Lot. 641114) or each test compound was added to the plate, and the luminescence of the cells was measured with FDSS7000 (Hamamatsu Photonics K.K.), wherein Orexin A and each test compound were dissolved in DMSO (final concentration: 0.1 %), and diluted with a buffer (Hanks, 20 mM HEPES, 0.1 % BSA). The agonist activity (E-max) of each test compound for orexin receptor type 2 was calculated as relative percentage of luminescence for the luminescence (100 %) of Orexin A (100 pM).

[0464]

Result:

The results that each compound obtained in Examples was evaluated about the agonist activity for orexin receptor type 2 showed that the present compounds have agonist activity for orexin receptor type 2. Each agonist activity (E-max) of the example compounds is shown in the table below as relative percentage of luminescence for the luminescence (100 %) of Orexin A (100 pM).

Example	agonist activity (%)	Example	agonist activity (%)	Example	agonist activity (%)
1	137	28	190	56	140
2	58	29	109	57	155
3	67	30	128	58	150
4	62	31	168	59	164
5	103	32	176	60	151
6	43	33	123	61	169
7	75	34	183	62	174
8	207	35	165	63	149
9	207	36	114	64	204
10	213	37	45	65	155
11	211	38	142	66	144
12	178	39	157	67	175
13	56	41	23	68	156
14	178	42	141	69	161
15	62	43	146	70	141
16	39	44	148	71	199
17	72	45	150	72	146
18	73	46	136	73	185
19	167	47	163	74	174
20	160	48	156	75	141
21	153	49	151	76	145
22	163	50	154	77	158
23	104	51	149	78	36

24	210	52	113	79	191
25	165	53	143	80	178
26	198	54	146	81	57
27	162	55	95		

[0465]

Test 2: Evaluation of agonist activity for orexin receptor type 2

5 Human orexin receptor type 2 and apoaeguorin were transiently expressed in CHO cells, and the agonist activity was evaluated based on intracellular calcium mobilization with ligand stimulation. The CHO cells-transiently-expressed human orexin receptor type 2 and apoaeguorin were
10 seeded on a 384-well plate by 2,000 cells/well, and then incubated for 16 - 22 hours. After the plate was returned to room temperature, Coelenterazine hcp (final concentration: 1 μ M) was added to the plate, and the plate was allowed to stand at room temperature for 2 hours. And
15 then, Orexin A (PEPTIDE INSTITUTE, INC., Lot. 671009) or each test compound was added to the plate, and the luminescence of the cells was measured with FDSS7000 (Hamamatsu Photonics K.K.), wherein Orexin A and each test compound were dissolved in DMSO (final concentration: 0.1 %),
20 and diluted with a buffer (Hanks, 20 mM HEPES, 0.1 % BSA). The agonist activity (E-max) of each test compound for orexin receptor type 2 was calculated as relative percentage of

luminescence for the luminescence (100 %) of Orexin A (100 pM) .

[0466]

Result:

5 The results that each compound obtained in Examples was
evaluated about the agonist activity for orexin receptor
type 2 showed that the present compounds have agonist
activity for orexin receptor type 2. Each agonist activity
(E-max) of the example compounds is shown in the table below
10 as relative percentage of luminescence for the luminescence
(100 %) of Orexin A (100 pM) .

Example	agonist activity (%)	Example	agonist activity (%)	Example	agonist activity (%)
82	69	109	359	135	396
83	371	110	380	136	346
84	372	111	382	137	376
85	360	112	376	138	385
86	367	113	374	139	351
87	226	114	438	140	249
88	201	115	403	141	405
89	0	116	488	142	407
90	112	117	465	143	444
91	243	118	524	144	399
92	16	119	378	145	403
93	365	120	387	146	23
94	382	121	379	147	373
95	447	122	369	148	391
96	493	123	366	149	419
97	486	124	391	150	437
98	271	125	402	151	368
99	499	126	394	152	470
100	340	127	367	153	350
101	326	128	402	154	493
102	374	129	435	155	167
103	369	130	450	156	323
104	289	131	461	157	392
105	359	132	166	158	389
106	220	133	506	159	392
107	363	134	456	160	410
108	292			161	374

INDUSTRIAL APPLICABILITY

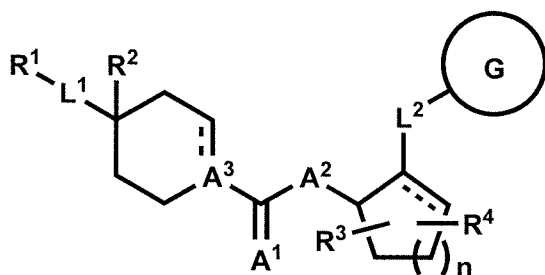
[0467]

The compounds of the present invention exhibit a potent

agonist activity for orexin receptor, thereby they are useful
as a medicament for treating or preventing narcolepsy,
idiopathic hypersomnia, hypersomnia, sleep apnea syndrome,
narcolepsy syndrome involving narcolepsy-like symptom,
5 hypersomnia associated with Parkinson's disease, hypersomnia
associated with dementia with Lewy body, etc.

CLAIMS

1. A compound of formula (1):



(1)

- 5 or a pharmaceutically acceptable salt thereof
wherein

R¹ is optionally-substituted C₆₋₁₀ aromatic carbocyclyl group, optionally-substituted 5- to 10-membered aromatic heterocyclyl group, optionally-substituted C₃₋₆ saturated carbocyclyl group, optionally-substituted 4- to 10-membered saturated heterocyclyl group, or cyano;

L¹ and L² are each independently single bond, methylene (which may be optionally substituted with the same or different one or more C₁₋₄ alky), -NR⁸-, -C(=O)-, -OC(=O)-, -SO-, -SO₂-, -S-, or oxygen atom;

R² is hydrogen atom, hydroxy group, halogen atom, cyano, or optionally-substituted C₁₋₄ alkyl; or

when L¹ is single bond, R¹ and R² may be combined together as a spiro ring to form optionally-substituted C₃₋₆ saturated carbon ring or optionally-substituted 4- to 10-

membered saturated heteroring;

R^3 and R^4 are each independently hydrogen atom, halogen atom, cyano, $-(C=O)NR^5R^6$, carboxy group, $-(C=O)O-R^7$, optionally-substituted C_{1-4} alkyl, or optionally-substituted
 5 C_{1-4} alkoxy, wherein R^3 and R^4 may bind to the same carbon atom if chemically possible; or

when R^3 and R^4 bind to different ring carbon atoms, R^3 and R^4 may be taken together via C_{1-6} alkylene to form a fused ring or a bridged ring;

10 R^5 to R^7 are each independently hydrogen atom, halogen atom, or optionally-substituted C_{1-4} alkyl;

R^8 is each independently hydrogen atom or optionally-substituted C_{1-4} alkyl;

n is an integer of 1, 2, 3, or 4;

15 Ring G is optionally-substituted C_{6-10} aromatic carbocyclyl group, optionally-substituted 5- to 10-membered aromatic heterocyclyl group, optionally-substituted C_{3-6} saturated carbocyclyl group, or optionally-substituted 4- to 10-membered saturated heterocyclyl group;

20 A^1 is oxygen atom or sulfur atom;

A^2 is oxygen atom or $-NR^8-$;

A^3 is $-CH-$, nitrogen atom, or carbon atom; and

the bond accompanied with broken line is each independently single bond or double bond.

2. The compound of claim 1 or a pharmaceutically acceptable salt thereof, wherein

in $R^2 - R^8$, the optional substituent of "optionally-substituted C_{1-4} alkyl" is the same or different one or more substituents selected from the group consisting of halogen atom, hydroxy group, C_{1-4} alkoxy, C_{6-10} aromatic carbocyclyl group, and C_{3-7} cycloalkyl; and the optional substituent of "optionally-substituted C_{1-4} alkoxy" is the same or different one or more substituents selected from the group consisting of halogen atom, hydroxy group, C_{1-4} alkyl, and C_{3-7} cycloalkyl;

in R^1 , the optional substituent of "optionally-substituted C_{6-10} aromatic carbocyclyl group", "optionally-substituted 5- to 10-membered aromatic heterocyclyl group", "optionally-substituted C_{3-6} saturated carbocyclyl group", and "optionally-substituted 4- to 10-membered saturated heterocyclyl group" is each independently at least one substituent selected from the group consisting of hydrogen atom, halogen atom, hydroxy group, C_{6-10} aromatic carbocyclyl group (which may be optionally substituted with the same or different one or more substituents selected from the group consisting of halogen atom, hydroxy group, C_{1-4} alkyl, C_{1-4} alkoxy, and C_{3-7} cycloalkyl), C_{1-4} alkyl (which may be optionally substituted with the same or different one or more substituents selected from the group consisting of

halogen atom, hydroxy group, C₁₋₄ alkoxy, and C₃₋₇ cycloalkyl),
C₃₋₇ cycloalkyl (which may be optionally substituted with the
same or different one or more substituents selected from the
group consisting of halogen atom, hydroxy group, C₁₋₄ alkyl,
5 C₁₋₄ alkoxy, and C₃₋₇ cycloalkyl), C₁₋₆ alkylamino (the alkyl
group of which may be optionally substituted with halogen
atom, hydroxy group, or C₃₋₇ cycloalkyl), C₃₋₇ cycloalkoxy
(which may be optionally substituted with the same or
different one or more substituents selected from the group
10 consisting of halogen atom, hydroxy group, C₁₋₄ alkyl, C₁₋₄
alkoxy, and C₃₋₇ cycloalkyl), cyano, C₁₋₄ alkoxy (which may be
optionally substituted with the same or different one or
more substituents selected from the group consisting of
halogen atom, hydroxy group, C₁₋₄ alkyl optionally-
15 substituted with the same or different one or more halogen
atoms, and C₃₋₇ cycloalkyl), and 5- to 10-membered aromatic
heterocyclyl group (which may be optionally substituted with
the same or different one or more substituents selected from
the group consisting of halogen atom, hydroxy group, C₁₋₄
20 alkyl, C₁₋₄ alkoxy, and C₃₋₇ cycloalkyl); and

in Ring G, the optional substituent of "optionally-
substituted C₆₋₁₀ aromatic carbocyclyl group", "optionally-
substituted 5- to 10-membered aromatic heterocyclyl group",
"optionally-substituted C₃₋₆ saturated carbocyclyl group",
25 and "optionally-substituted 4- to 10-membered saturated

heterocyclyl group" is each independently at least one substituent selected from the group consisting of halogen atom, C₁₋₆ alkyl (which may be optionally substituted with the same or different one or more substituents selected from the group consisting of halogen atom, hydroxy group, C₁₋₄ alkoxy, and C₃₋₇ cycloalkyl), C₆₋₁₀ aromatic carbocyclyl group (which may be optionally substituted with the same or different one or more substituents selected from the group consisting of halogen atom, hydroxy group, C₁₋₄ alkyl, C₁₋₄ alkoxy, and C₃₋₇ cycloalkyl), C₁₋₄ alkoxy (which may be optionally substituted with the same or different one or more substituents selected from the group consisting of halogen atom, hydroxy group, C₁₋₄ alkyl, and C₃₋₇ cycloalkyl), C₁₋₆ alkylamino (the alkyl group of which may be optionally substituted with halogen atom, hydroxy group, or C₃₋₇ cycloalkyl), C₃₋₇ cycloalkyl (which may be optionally substituted with the same or different one or more substituents selected from the group consisting of halogen atom, hydroxy group, C₁₋₄ alkyl, C₁₋₄ alkoxy, and C₃₋₇ cycloalkyl), and C₃₋₇ cycloalkoxy (which may be optionally substituted with the same or different one or more substituents selected from the group consisting of halogen atom, hydroxy group, C₁₋₄ alkyl, C₁₋₄ alkoxy, and C₃₋₇ cycloalkyl); or when there are plural optional substituents, two of them may be taken together via C₁₋₆ alkylene to form

a chemically-possible bicyclic structure selected from a fused ring, a spiro ring, and bridged ring.

3. The compound of claim 1 or 2 or a pharmaceutically acceptable salt thereof, wherein

in $R^2 - R^7$, the optional substituent of "optionally-substituted C_{1-4} alkyl" is the same or different one or more substituents selected from the group consisting of halogen atom and C_{1-4} alkoxy; and the optional substituent of "optionally-substituted C_{1-4} alkoxy" is the same or different one or more substituents selected from the group consisting of halogen atom and C_{1-4} alkyl;

in R^1 , the optional substituent of "optionally-substituted C_{6-10} aromatic carbocyclyl group", "optionally-substituted 5- to 10-membered aromatic heterocyclyl group", "optionally-substituted C_{3-6} saturated carbocyclyl group", and "optionally-substituted 4- to 10-membered saturated heterocyclyl group" is each independently at least one substituent selected from the group consisting of hydrogen atom, halogen atom, hydroxy group, C_{6-10} aromatic carbocyclyl group (which may be optionally substituted with the same or different one or more substituents selected from the group consisting of halogen atom, hydroxy group, C_{1-4} alkyl, C_{1-4} alkoxy, and C_{3-7} cycloalkyl), C_{1-4} alkyl (which may be optionally substituted with the same or different one or

more substituents selected from the group consisting of halogen atom, hydroxy group, C₁₋₄ alkoxy, and C₃₋₇ cycloalkyl), C₃₋₇ cycloalkyl (which may be optionally substituted with the same or different one or more substituents selected from the group consisting of halogen atom, hydroxy group, C₁₋₄ alkyl, C₁₋₄ alkoxy, and C₃₋₇ cycloalkyl), cyano, C₁₋₄ alkoxy (which may be optionally substituted with the same or different one or more substituents selected from the group consisting of halogen atom, hydroxy group, C₁₋₄ alkyl optionally-substituted with the same or different one or more halogen atoms, and C₃₋₇ cycloalkyl), and 5- to 10-membered aromatic heterocyclyl group (which may be optionally substituted with the same or different one or more substituents selected from the group consisting of halogen atom, hydroxy group, C₁₋₄ alkyl, C₁₋₄ alkoxy, and C₃₋₇ cycloalkyl); and

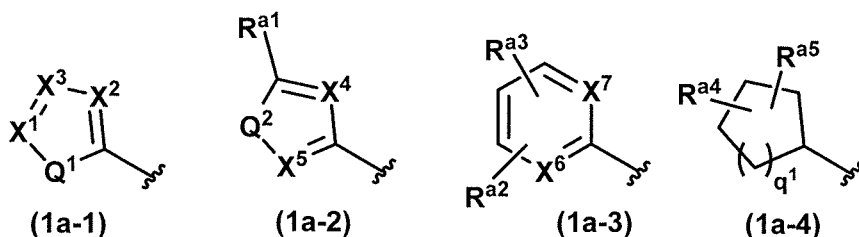
in Ring G, the optional substituent of "optionally-substituted C₆₋₁₀ aromatic carbocyclyl group", "optionally-substituted 5- to 10-membered aromatic heterocyclyl group", "optionally-substituted C₃₋₆ saturated carbocyclyl group", and "optionally-substituted 4- to 10-membered saturated heterocyclyl group" is each independently at least one substituent selected from the group consisting of halogen atom, C₁₋₆ alkyl (which may be optionally substituted with the same or different one or more substituents selected from the group consisting of halogen atom and C₁₋₄ alkoxy), C₆₋₁₀

aromatic carbocyclyl group (which may be optionally substituted with the same or different one or more substituents selected from the group consisting of halogen atom, C₁₋₄ alkyl, and C₁₋₄ alkoxy), C₁₋₄ alkoxy (which may be
5 optionally substituted with the same or different one or more substituents selected from the group consisting of halogen atom and C₁₋₄ alkyl), C₃₋₇ cycloalkyl (which may be optionally substituted with the same or different one or more substituents selected from the group consisting of
10 halogen atom, C₁₋₄ alkyl, and C₁₋₄ alkoxy), C₁₋₆ alkylamino (the alkyl group of which may be optionally substituted with halogen atom, hydroxy group, or C₃₋₇ cycloalkyl), and C₃₋₇ cycloalkoxy (which may be optionally substituted with the same or different one or more substituents selected from the
15 group consisting of halogen atom, C₁₋₄ alkyl, and C₁₋₄ alkoxy); or when there are plural optional substituents, two of them may be taken together via C₁₋₆ alkylene to form a chemically-possible bicyclic structure selected from a fused ring, a spiro ring, and bridged ring.

20

4. The compound of any one of claims 1 to 3 or a pharmaceutically acceptable salt thereof, wherein

R¹ is selected from the following formulae (1a-1) to (1a-4):



wherein

$X^1 - X^7$ are each independently nitrogen atom or CR^{a6} ;

Q^1 and Q^2 are oxygen atom, $-NR^{a7}-$, or sulfur atom;

5 $R^{a1} - R^{a7}$ are each independently (if there are plural CR^{a6} , each R^{a6} is also independently), hydrogen atom, halogen atom, C_{6-10} aromatic carbocyclyl group (which may be optionally substituted with the same or different one or more substituents selected from the group consisting of

10 halogen atom, hydroxy group, C_{1-4} alkyl, and C_{1-4} alkoxy), C_{1-4} alkyl (which may be optionally substituted with the same or different one or more substituents selected from the group consisting of halogen atom, hydroxy group, C_{1-4} alkyl, and C_{1-4} alkoxy), C_{3-7} cycloalkyl (which may be optionally

15 substituted with the same or different one or more substituents selected from the group consisting of halogen atom, hydroxy group, C_{1-4} alkyl, and C_{1-4} alkoxy), cyano, C_{1-4} alkoxy (which may be optionally substituted with the same or different one or more substituents selected from the group

20 consisting of halogen atom, hydroxy group, C_{1-4} alkyl, and C_{1-4} alkoxy), C_{3-7} cycloalkoxy (which may be optionally substituted with the same or different one or more

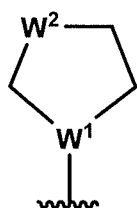
substituents selected from the group consisting of halogen atom, hydroxy group, C₁₋₄ alkyl, and C₁₋₄ alkoxy), or 5- to 10-membered aromatic heterocyclyl group; wherein R^{a4} and R^{a5} may bind to the same carbon atom if chemically possible; and
5 when X¹ and X³ are both CR^{a6}, the two R^{a6} may be taken together with the carbon atoms to which they are each attached to form 6-membered carbon ring that is fused with the 5-membered ring comprising X¹, X², and X³; and

q¹ is an integer of 1 or 2.

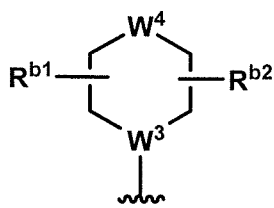
10

5. The compound of any one of claims 1 to 4 or a pharmaceutically acceptable salt thereof, wherein

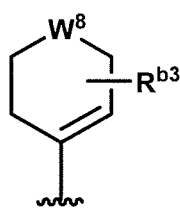
Ring G is selected from the following (1b-1) to (1b-14):



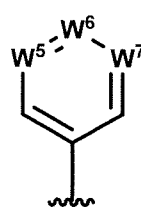
(1b-1)



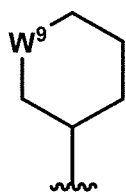
(1b-2)



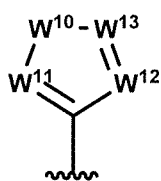
(1b-3)



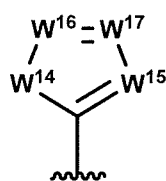
(1b-4)



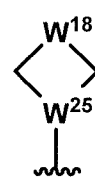
(1b-5)



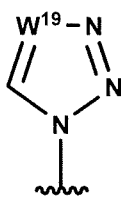
(1b-6)



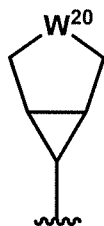
(1b-7)



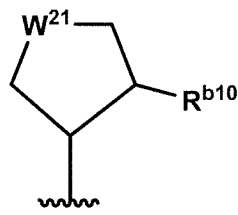
(1b-8)



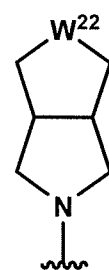
(1b-9)



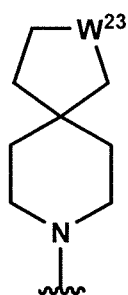
(1b-10)



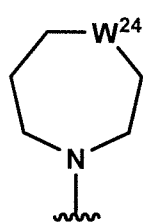
(1b-11)



(1b-12)



(1b-13)



(1b-14)

wherein

W^1 , W^3 , W^5 , W^6 , W^7 , W^{11} , W^{12} , W^{13} , W^{15} , W^{16} , W^{17} , W^{19} , and W^{25} are each independently nitrogen atom or CR^{b4} ;

5 W^2 , W^4 , W^8 , W^9 , W^{10} , W^{14} , W^{18} , W^{20} , W^{21} , W^{22} , W^{23} , and W^{24} are NR^{b5} , oxygen atom, or $CR^{b6}R^{b7}$;

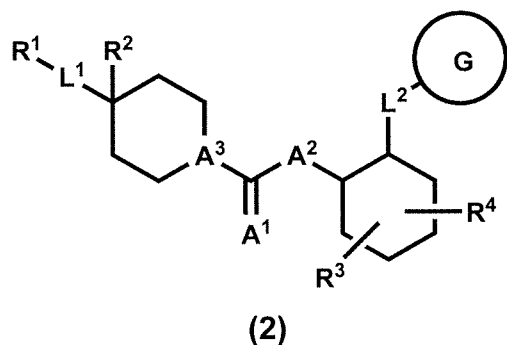
$R^{b1} - R^{b7}$ are each independently (if there are plural CR^{b4} , each R^{b4} is also independently), hydrogen atom, $-N(R^{b8})R^{b9}$, C_{1-6} alkyl (which may be optionally substituted with the same or different one or more substituents selected from the group consisting of halogen atom, C_{3-7} cycloalkyl which may be optionally substituted with the same or different one or more substituents selected from the group consisting of halogen atom and C_{1-4} alkyl (said C_{1-4} alkyl may be substituted with halogen atom), and C_{1-4} alkoxy), C_{6-10} aromatic carbocyclyl group (which may be optionally substituted with the same or different one or more substituents selected from the group consisting of halogen atom, C_{1-4} alkyl, and C_{1-4} alkoxy), 5- to 10-membered aromatic heterocyclyl group (which may be optionally substituted with the same or different one or more substituents selected from the group consisting of halogen atom, C_{1-4} alkyl, and C_{1-4} alkoxy), C_{1-4} alkoxy (which may be optionally substituted with the same or different one or more substituents selected from the group consisting of halogen atom and C_{1-4} alkyl), C_{3-7} cycloalkyl (which may be optionally substituted with the same or different one or more substituents selected from the group consisting of halogen atom, C_{1-4} alkyl, and C_{1-4} alkoxy), or C_{3-7} cycloalkoxy (which may be optionally substituted with the same or different one or more substituents selected from the group consisting of halogen atom, C_{1-4} alkyl, and C_{1-4}

alkoxy); wherein R^{b1} and R^{b2} may bind to the same carbon atom if chemically possible; or R^{b1} and R^{b2} may be taken together via C_{1-6} alkylene to form a chemically-possible bicyclic structure selected from a fused ring, a spiro ring, and
5 bridged ring; and

R^{b8} and R^{b9} are each independently hydrogen atom, C_{1-6} alkyl (which may be optionally substituted with the same or different one or more substituents selected from the group consisting of halogen atom, C_{1-4} alkoxy, C_{3-7} cycloalkyl which
10 may be optionally substituted with the same or different one or more substituents selected from the group consisting of halogen atom and C_{1-4} alkyl (said C_{1-4} alkyl may be substituted with halogen atom), and 5- to 10-membered aromatic heterocyclyl group), C_{1-4} alkoxy (which may be optionally
15 substituted with the same or different one or more substituents selected from the group consisting of halogen atom and C_{1-4} alkyl), 5- to 10-membered aromatic heterocyclyl group (which may be optionally substituted with the same or different one or more substituents selected from the group
20 consisting of halogen atom, C_{1-4} alkyl, and C_{1-4} alkoxy), or C_{3-7} cycloalkyl (which may be optionally substituted with the same or different one or more substituents selected from the group consisting of halogen atom, hydroxy group, C_{1-4} alkyl, and C_{1-4} alkoxy); or R^{b8} and R^{b9} may be taken together with
25 the nitrogen atom to which they are attached to form 3- to

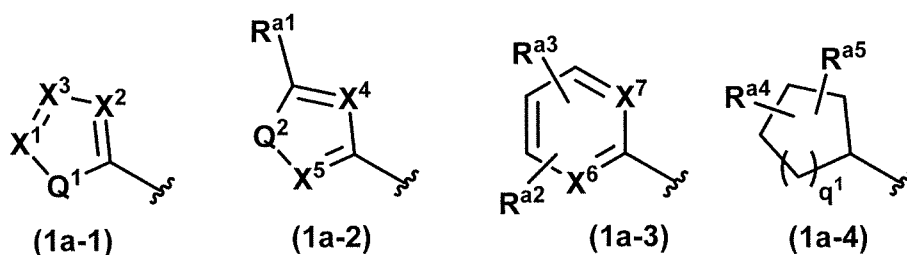
7-membered nitrogen-containing saturated heterocycle.

6. The compound of any one of claims 1 to 5 of formula (2):



or a pharmaceutically acceptable salt thereof, wherein

R¹ is selected from the following formulae (1a-1) to (1a-4):



wherein

X¹ - X⁷ are each independently nitrogen atom or CR^{a6};

Q¹ and Q² are oxygen atom, -NR^{a7}-, or sulfur atom;

R^{a1} - R^{a7} are each independently (if there are plural CR^{a6}, each R^{a6} is also independently), hydrogen atom, halogen atom, C₆₋₁₀ aromatic carbocyclyl group (which may be optionally substituted with the same or different one or more substituents selected from the group consisting of

halogen atom, hydroxy group, C₁₋₄ alkyl, and C₁₋₄ alkoxy), C₁₋₄ alkyl (which may be optionally substituted with the same or different one or more substituents selected from the group consisting of halogen atom, hydroxy group, C₁₋₄ alkyl, and C₁₋₄ alkoxy), C₃₋₆ cycloalkyl (which may be optionally substituted with the same or different one or more substituents selected from the group consisting of halogen atom, hydroxy group, C₁₋₄ alkyl, and C₁₋₄ alkoxy), cyano, C₁₋₄ alkoxy (which may be optionally substituted with the same or different one or more substituents selected from the group consisting of halogen atom, hydroxy group, C₁₋₄ alkyl, and C₁₋₄ alkoxy), C₃₋₇ cycloalkoxy (which may be optionally substituted with the same or different one or more substituents selected from the group consisting of halogen atom, hydroxy group, C₁₋₄ alkyl, and C₁₋₄ alkoxy), or 5- to 10-membered aromatic heterocyclyl group; wherein R^{a4} and R^{a5} may bind to the same carbon atom if chemically possible; and when X¹ and X³ are both CR^{a6}, the two R^{a6} may be taken together with the carbon atoms to which they are each attached to form 6-membered carbon ring that is fused with the 5-membered ring comprising X¹, X², and X³; and

q¹ is an integer of 1 or 2;

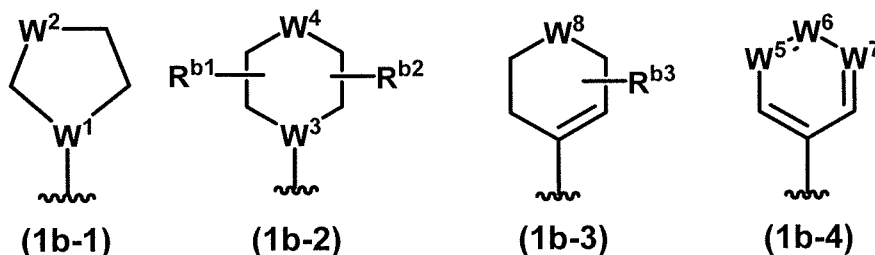
L¹ and L² are each independently single bond, -CH₂-, or oxygen atom;

R² is hydrogen atom, hydroxy group, halogen atom, cyano,

or optionally-substituted C₁₋₄ alkyl;

R³ and R⁴ are each independently hydrogen atom, halogen atom, C₁₋₄ alkyl (which may be optionally substituted with the same or different one or more substituents selected from the group consisting of halogen atom, hydroxy group, C₁₋₄ alkoxy, and C₃₋₇ cycloalkyl), or C₁₋₄ alkoxy (which may be optionally substituted with the same or different one or more substituents selected from the group consisting of halogen atom, hydroxy group, C₁₋₄ alkyl, and C₃₋₇ cycloalkyl); wherein R³ and R⁴ may bind to the same carbon atom if chemically possible; and when R³ and R⁴ bind to different carbon atoms on the ring, R³ and R⁴ may be taken together via C₁₋₆ alkylene to form a fused ring or bridged ring;

Ring G is selected from the following (1b-1) to (1b-4):



wherein

W¹, W³, W⁵, W⁶, and W⁷ are each independently nitrogen atom or CR^{b4};

W², W⁴, and W⁸ are NR^{b5}, oxygen atom or CR^{b6}R^{b7};

R^{b1} - R^{b7} are each independently (if there are plural CR^{b4}, each R^{b4} is also independently), hydrogen atom, C₁₋₆ alkyl (which may be optionally substituted with the same or

different one or more substituents selected from the group consisting of halogen atom and C₁₋₄ alkoxy), C₆₋₁₀ aromatic carbocyclyl group (which may be optionally substituted with the same or different one or more substituents selected from the group consisting of halogen atom, C₁₋₄ alkyl, and C₁₋₄ alkoxy), C₁₋₄ alkoxy (which may be optionally substituted with the same or different one or more substituents selected from the group consisting of halogen atom and C₁₋₄ alkyl), C₃₋₇ cycloalkyl (which may be optionally substituted with the same or different one or more substituents selected from the group consisting of halogen atom, C₁₋₄ alkyl, and C₁₋₄ alkoxy), or C₃₋₇ cycloalkoxy (which may be optionally substituted with the same or different one or more substituents selected from the group consisting of halogen atom, C₁₋₄ alkyl, and C₁₋₄ alkoxy); wherein R^{b1} and R^{b2} may bind to the same carbon atom if chemically possible; or R^{b1} and R^{b2} may be taken together via C₁₋₆ alkylene to form a chemically-possible bicyclic structure selected from a fused ring, a spiro ring, and bridged ring;

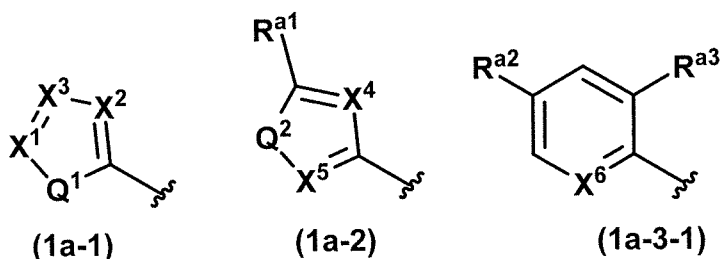
A¹ is oxygen atom or sulfur atom;

A² is oxygen atom or -NH-; and

A³ is -CH-, nitrogen atom, or carbon atom.

7. The compound of claim 6 or a pharmaceutically acceptable salt thereof, wherein

R^1 is selected from the following formulae (1a-1), (1a-2), and (1a-3-1):



wherein

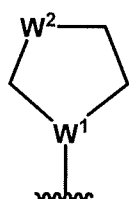
- 5 $X^1 - X^6$ are each independently nitrogen atom or CR^{a6} ;
 Q^1 and Q^2 are oxygen atom, $-NR^{a7}-$, or sulfur atom; and
 $R^{a1} - R^{a3}$, R^{a6} , and R^{a7} are each independently (if there
 are plural CR^{a6} , each R^{a6} is also independently), hydrogen
 atom, halogen atom, C_{6-10} aromatic carbocyclyl group (which
 10 may be optionally substituted with the same or different one
 or more substituents selected from the group consisting of
 halogen atom, hydroxy group, C_{1-4} alkyl, and C_{1-4} alkoxy), C_{1-4}
 alkyl (which may be optionally substituted with the same
 or different one or more substituents selected from the group
 15 consisting of halogen atom, hydroxy group, C_{1-4} alkyl, and
 C_{1-4} alkoxy), C_{3-7} cycloalkyl (which may be optionally
 substituted with the same or different one or more
 substituents selected from the group consisting of halogen
 atom, hydroxy group, C_{1-4} alkyl, and C_{1-4} alkoxy), cyano, C_{1-4}
 20 alkoxy (which may be optionally substituted with the same or
 different one or more substituents selected from the group
 consisting of halogen atom, hydroxy group, C_{1-4} alkyl, and

C₁₋₄ alkoxy), C₃₋₇ cycloalkoxy (which may be optionally substituted with the same or different one or more substituents selected from the group consisting of halogen atom, hydroxy group, C₁₋₄ alkyl, and C₁₋₄ alkoxy), or 5- to 10-membered aromatic heterocyclyl group; wherein when X¹ and X³ are both CR^{a6}, the two R^{a6} may be taken together with the carbon atoms to which they are each attached to form 6-membered carbon ring that is fused with the 5-membered ring comprising X¹, X², and X³.

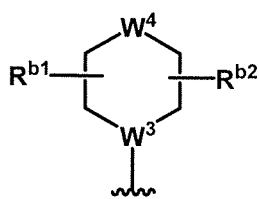
10

8. The compound of claims 6 or 7 or a pharmaceutically acceptable salt thereof, wherein

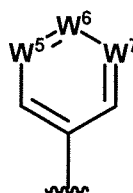
Ring G is selected from the following (1b-1), (1b-2), and (1b-4):



(1b-1)



(1b-2)



(1b-4)

15

wherein

W¹, W³, W⁵, W⁶, and W⁷ are each independently nitrogen atom or CR^{b4};

W² and W⁴ are NR^{b5} or CR^{b6}R^{b7}; and

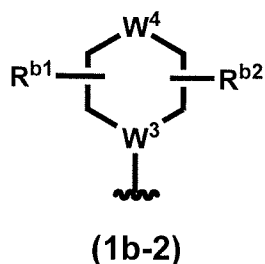
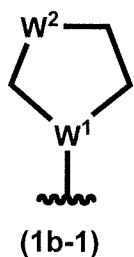
20

R^{b1}, R^{b2}, and R^{b4} - R^{b7} are each independently (if there are plural CR^{b4}, each R^{b4} is also independently), hydrogen atom, C₁₋₆ alkyl (which may be optionally substituted with

the same or different one or more substituents selected from the group consisting of halogen atom and C₁₋₄ alkoxy), C₆₋₁₀ aromatic carbocyclyl group (which may be optionally substituted with the same or different one or more substituents selected from the group consisting of halogen atom, C₁₋₄ alkyl, and C₁₋₄ alkoxy), C₁₋₄ alkoxy (which may be optionally substituted with the same or different one or more substituents selected from the group consisting of halogen atom and C₁₋₄ alkyl), C₃₋₇ cycloalkyl (which may be optionally substituted with the same or different one or more substituents selected from the group consisting of halogen atom, C₁₋₄ alkyl, and C₁₋₄ alkoxy), or C₃₋₇ cycloalkoxy (which may be optionally substituted with the same or different one or more substituents selected from the group consisting of halogen atom, C₁₋₄ alkyl, and C₁₋₄ alkoxy); or R^{b1} and R^{b2} may bind to the same carbon atom if chemically possible; or R^{b1} and R^{b2} may be taken together via C₁₋₆ alkylene to form a bridged bicyclic structure.

9. The compound of any one of claims 6 to 8 or a pharmaceutically acceptable salt thereof, wherein

Ring G is selected from the following (1b-1) and (1b-2):



wherein

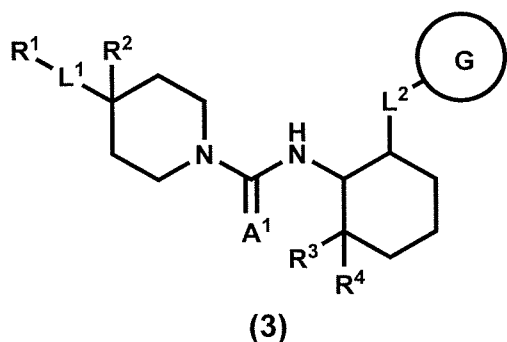
W^1 and W^3 are nitrogen atom or CR^{b4} ;

W^2 and W^4 are NR^{b5} or $CR^{b6}R^{b7}$; and

5 R^{b1} , R^{b2} , and $R^{b4} - R^{b7}$ are each independently hydrogen atom, C_{1-6} alkyl (which may be optionally substituted with the same or different one or more substituents selected from the group consisting of halogen atom and C_{1-4} alkoxy), C_{6-10} aromatic carbocyclyl group (which may be optionally substituted with the same or different one or more substituents selected from the group consisting of halogen atom, C_{1-4} alkyl, and C_{1-4} alkoxy), C_{1-4} alkoxy (which may be optionally substituted with the same or different one or more substituents selected from the group consisting of halogen atom and C_{1-4} alkyl), C_{3-7} cycloalkyl (which may be optionally substituted with the same or different one or more substituents selected from the group consisting of halogen atom, C_{1-4} alkyl, and C_{1-4} alkoxy), or C_{3-7} cycloalkoxy (which may be optionally substituted with the same or different one or more substituents selected from the group consisting of halogen atom, C_{1-4} alkyl, and C_{1-4} alkoxy); wherein R^{b1} and R^{b2} may bind to the same carbon atom if

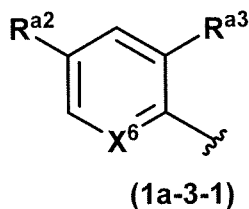
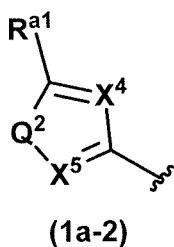
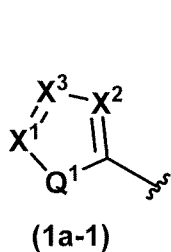
chemically possible; or R^{b1} and R^{b2} may be taken together via C_{1-6} alkylene to form a bridged bicyclic structure.

10. The compound of any one of claims 1 to 9 of formula
5 (3):



or a pharmaceutically acceptable salt thereof, wherein

R^1 is the following formula (1a-1), (1a-2), or (1a-3-1):



wherein

$X^1 - X^6$ are each independently nitrogen atom or CR^{a6} ;

Q^1 and Q^2 are oxygen atom or sulfur atom;

$R^{a1} - R^{a3}$ and R^{a6} are each independently (if there are
15 plural CR^{a6} , each R^{a6} is also independently), hydrogen atom,
halogen atom, C_{1-4} alkyl (which may be optionally substituted
with the same or different one or more substituents selected
from the group consisting of halogen atom, hydroxy group,

and C₁₋₄ alkoxy), C₃₋₇ cycloalkyl (which may be optionally substituted with the same or different one or more substituents selected from the group consisting of halogen atom, hydroxy group, C₁₋₄ alkyl, and C₁₋₄ alkoxy), cyano, or

5 C₁₋₄ alkoxy (which may be optionally substituted with the same or different one or more substituents selected from the group consisting of halogen atom, hydroxy group, C₁₋₄ alkyl, and C₁₋₄ alkoxy); wherein when X¹ and X³ are both CR^{a6}, the two R^{a6} may be taken together with the carbon atoms to which

10 they are each attached to form 6-membered carbon ring that is fused with the 5-membered ring comprising X¹, X², and X³;

L¹ and L² are each independently single bond or oxygen atom;

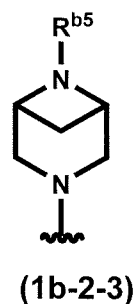
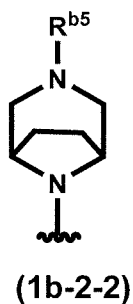
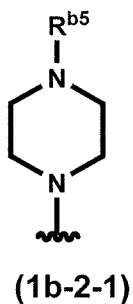
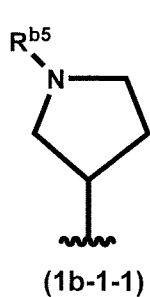
R² is hydrogen atom, halogen atom, or C₁₋₄ alkyl which

15 may be optionally substituted with the same or different one or more substituents selected from the group consisting of halogen atom and hydroxy group;

R³ and R⁴ are each independently halogen atom;

Ring G is the following (1b-1), (1b-2-1), (1b-2-2), or

20 (1b-2-3):



wherein

R^{b5} is hydrogen atom, or C_{1-6} alkyl which may be optionally substituted with the same or different one or more substituents selected from the group consisting of halogen atom and C_{1-4} alkoxy; and

A^1 is oxygen atom or sulfur atom.

11. The compound of any one of claims 4 to 10 or a pharmaceutically acceptable salt thereof, wherein

R^1 is formula (1a-2), and

R^{a1} is hydrogen atom, halogen atom, C_{1-4} alkyl (which may be optionally substituted with the same or different one or more substituents selected from the group consisting of halogen atom and C_{1-4} alkoxy), C_{3-7} cycloalkyl (which may be optionally substituted with the same or different one or more substituents selected from the group consisting of halogen atom, hydroxy group, C_{1-4} alkyl, and C_{1-4} alkoxy), or C_{1-4} alkoxy (which may be optionally substituted with the same or different one or more substituents selected from the group consisting of halogen atom and C_{1-4} alkyl).

12. The compound of claim 10 to 11 or a pharmaceutically acceptable salt thereof, wherein

R^1 is formula (1a-2), and

X^4 and X^5 are both nitrogen atom.

13. The compound of any one of claims 10 to 12 or a pharmaceutically acceptable salt thereof, wherein

Ring G is formula (1b-1-1), and

5 R^{b5} is C_{1-4} alkyl which may be optionally substituted with the same or different one or more halogen atoms.

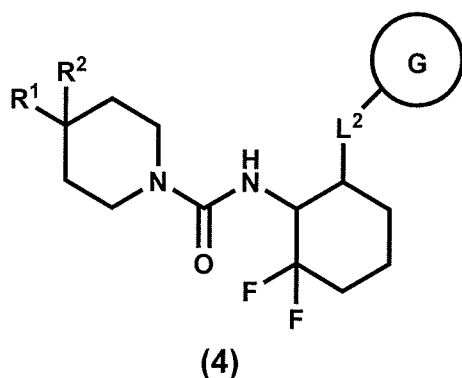
14. The compound of any one of claims 10 to 12 or a pharmaceutically acceptable salt thereof, wherein

10 Ring G is formula (1b-2-1), and

R^{b5} is hydrogen atom, or C_{1-4} alkyl which may be optionally substituted with the same or different one or more substituents selected from the group consisting of halogen atom and C_{1-4} alkoxy.

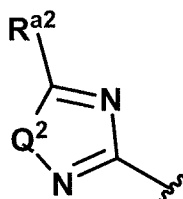
15

15. The compound of any one of claims 1 to 12 of formula (4):



or a pharmaceutically acceptable salt thereof, wherein

20 R^1 is the following (1a-2-1):



(1a-2-1)

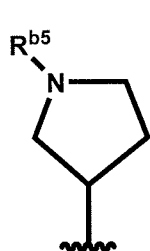
wherein

Q^2 is oxygen atom or sulfur atom;

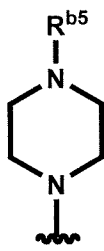
R^{a2} is C_{3-7} cycloalkyl group (which may be optionally substituted with the same or different one or more substituents selected from the group consisting of halogen atom, C_{1-4} alkyl, and C_{1-4} alkoxy) or cycloalkoxy group (which may be optionally substituted with the same or different one or more substituents selected from the group consisting of halogen atom, C_{1-4} alkyl, and C_{1-4} alkoxy);

R^2 is C_{1-4} alkyl;

Ring G is the following (1b-1-1) or (1b-2-1):



(1b-1-1)



(1b-2-1)

wherein

R^{b5} is C_{1-4} alkyl which may be optionally substituted with the same or different one or more substituents selected from the group consisting of halogen atom and C_{1-4} alkoxy; and

L² is single bond or oxygen atom.

16. The compound of claim 15 or a pharmaceutically acceptable salt thereof, wherein

5 R^{a2} is C₃₋₇ cycloalkyl group which may be optionally substituted with the same or different one or more substituents selected from halogen atoms, and

 R² is methyl group.

10 17. The compound of claim 15 or 16 or a pharmaceutically acceptable salt thereof, wherein

 R^{a2} is cyclopropyl group which may be optionally substituted with the same or different one or more substituents selected from halogen atoms, and

15 R² is methyl group.

18. The compound of any one of claims 15 to 17 or a pharmaceutically acceptable salt thereof, wherein

 Ring G is formula (1b-2-1), and

20 R^{b5} is isopropyl group.

19. The compound of any one of claims 15 to 17 or a pharmaceutically acceptable salt thereof, wherein

 Ring G is formula (1b-1-1), and

25 R^{b5} is isobutyl group.

20. The compound of any one of claims 15 to 17 or a pharmaceutically acceptable salt thereof, wherein

Ring G is formula (1b-1-1),

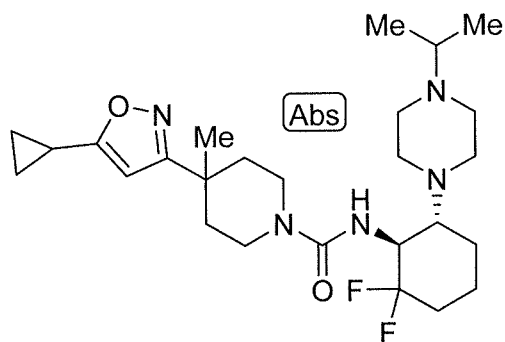
5 R^{b5} is isopropyl group, and

L^2 is oxygen atom.

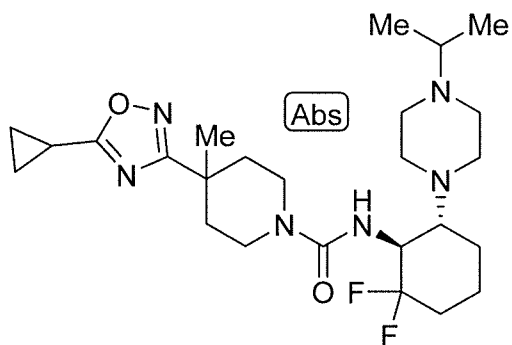
21. The compound of any one of claims 15 to 20 or a pharmaceutically acceptable salt thereof, wherein Q² is oxygen atom.

22. The compound of claim 1 or a pharmaceutically acceptable salt thereof, which is selected from the following compound names or structures:

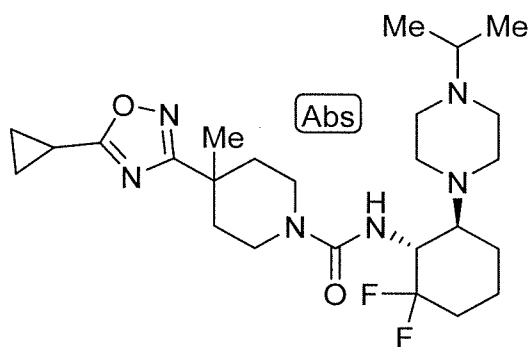
15 4-(5-cyclopropyl-1,2-oxazol-3-yl)-N-{(1S,6R)-2,2-difluoro-6-[4-(propan-2-yl)piperazin-1-yl]cyclohexyl}-4-methylpiperidine-1-carboxamide



4-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)-N-{(1S,6R)-2,2-difluoro-6-[4-(propan-2-yl)piperazin-1-yl]cyclohexyl}-4-methylpiperidine-1-carboxamide

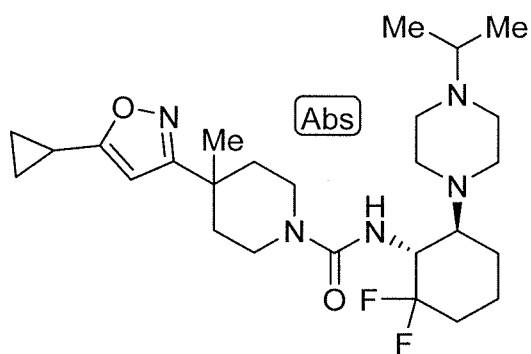


4-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)-N-((1R,6S)-2,2-difluoro-6-[4-(propan-2-yl)piperazin-1-yl]cyclohexyl)-4-methylpiperidine-1-carboxamide



5

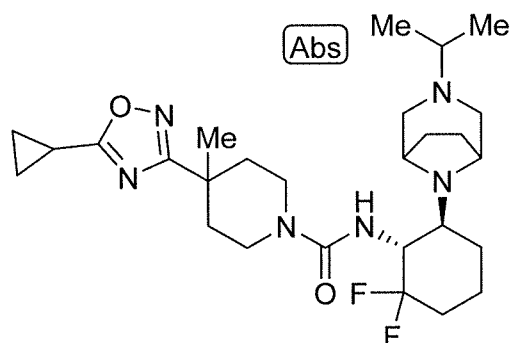
4-(5-cyclopropyl-1,2-oxazol-3-yl)-N-((1R,6S)-2,2-difluoro-6-[4-(propan-2-yl)piperazin-1-yl]cyclohexyl)-4-methylpiperidine-1-carboxamide



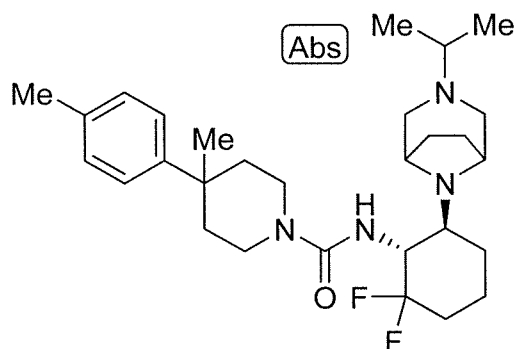
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4-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)-N-((1R,6S)-2,2-

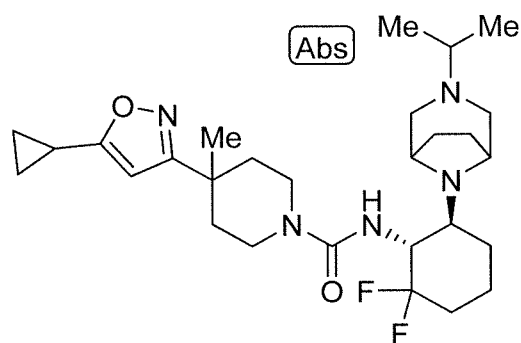
difluoro-6-[3-(propan-2-yl)-3,8-diazabicyclo[3.2.1]octan-8-yl]cyclohexyl}-4-methylpiperidine-1-carboxamide



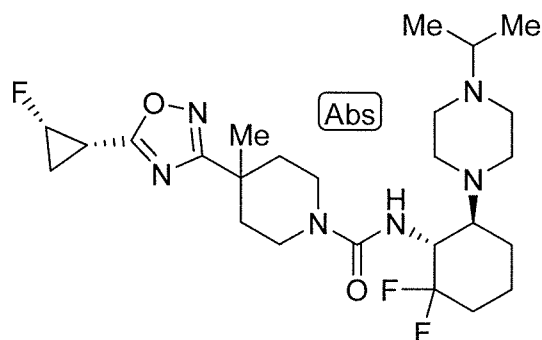
N-{(1R,6S)-2,2-difluoro-6-[3-(propan-2-yl)-3,8-diazabicyclo[3.2.1]octan-8-yl]cyclohexyl}-4-methyl-4-(4-methylphenyl)piperidine-1-carboxamide



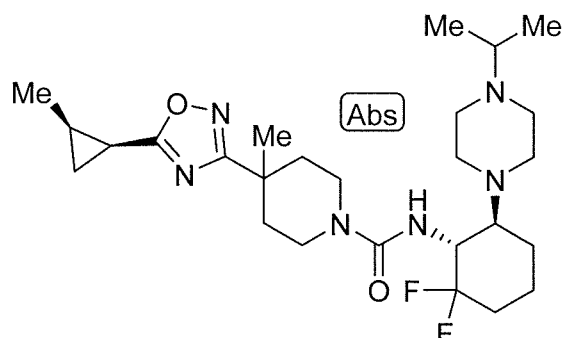
4-(5-cyclopropyl-1,2-oxazol-3-yl)-N-{(1R,6S)-2,2-difluoro-6-[3-(propan-2-yl)-3,8-diazabicyclo[3.2.1]octan-8-yl]cyclohexyl}-4-methylpiperidine-1-carboxamide



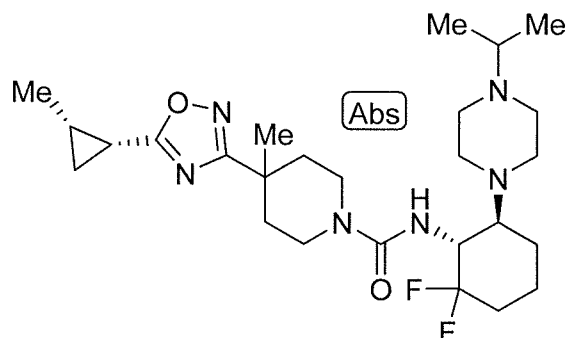
N-[(1R,6S)-2,2-difluoro-6-[4-(propan-2-yl)piperazin-1-yl]cyclohexyl]-4-{5-[(1S,2S)-2-fluorocyclopropyl]-1,2,4-oxadiazol-3-yl}-4-methylpiperidine-1-carboxamide



5 N-[(1R,6S)-2,2-difluoro-6-[4-(propan-2-yl)piperazin-1-yl]cyclohexyl]-4-methyl-4-{5-[(1S,2R)-2-methylcyclopropyl]-1,2,4-oxadiazol-3-yl}piperidine-1-carboxamide

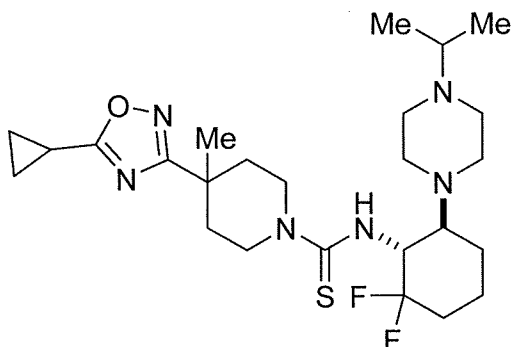


10 N-[(1R,6S)-2,2-difluoro-6-[4-(propan-2-yl)piperazin-1-yl]cyclohexyl]-4-methyl-4-{5-[(1R,2S)-2-methylcyclopropyl]-1,2,4-oxadiazol-3-yl}piperidine-1-carboxamide

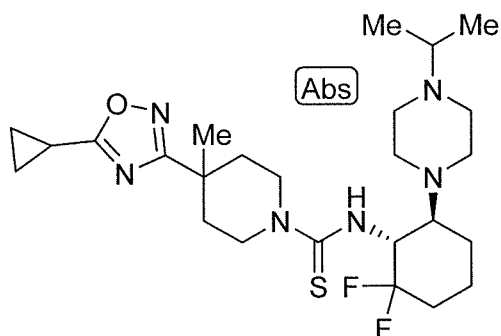


rac-4-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)-N-[(1R,6S)-

2,2-difluoro-6-[4-(propan-2-yl)piperazin-1-yl]cyclohexyl}-
4-methylpiperidine-1-carbothioamide

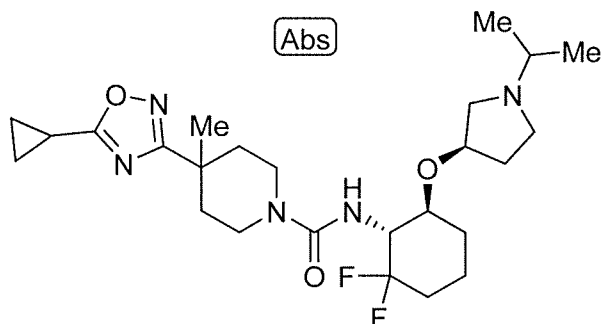


4-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)-N-[(1R,6S)-2,2-
5 difluoro-6-[4-(propan-2-yl)piperazin-1-yl]cyclohexyl]-4-
methylpiperidine-1-carbothioamide.

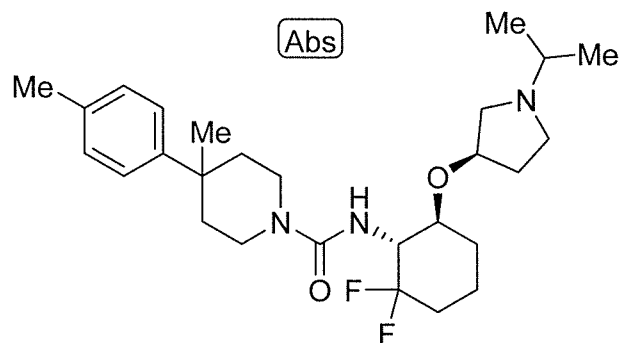


23. The compound of claim 1 or a pharmaceutically acceptable
10 salt thereof, which is selected from the following compound
names or structures:

4-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)-N-[(1R,6S)-2,2-
difluoro-6-[(3R)-1-(propan-2-yl)pyrrolidin-3-
yl]oxy]cyclohexyl]-4-methylpiperidine-1-carboxamide

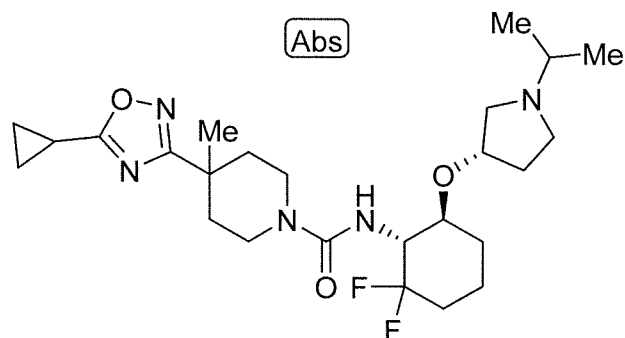


N-[(1R,6S)-2,2-difluoro-6-{[(3R)-1-(propan-2-yl)pyrrolidin-3-yl]oxy}cyclohexyl]-4-methyl-4-(4-methylphenyl)piperidine-1-carboxamide



5

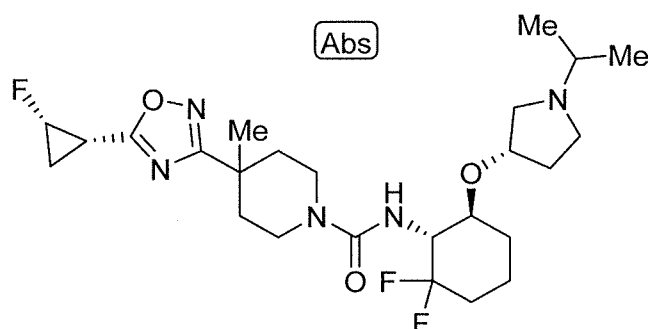
4-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)-N-[(1R,6S)-2,2-difluoro-6-{[(3S)-1-(propan-2-yl)pyrrolidin-3-yl]oxy}cyclohexyl]-4-methylpiperidine-1-carboxamide



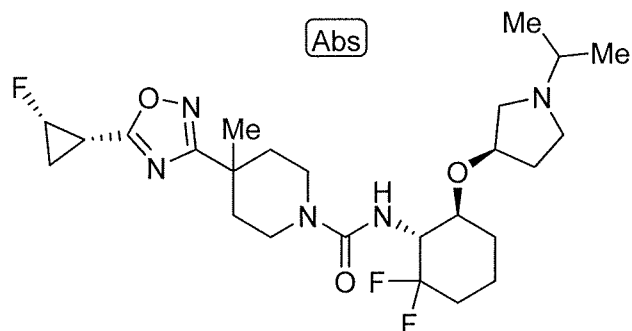
10

N-[(1R,6S)-2,2-difluoro-6-{[(3S)-1-(propan-2-yl)pyrrolidin-3-yl]oxy}cyclohexyl]-4-{5-[(1S,2S)-2-fluorocyclopropyl]-1,2,4-oxadiazol-3-yl}-4-methylpiperidine-1-carboxamide

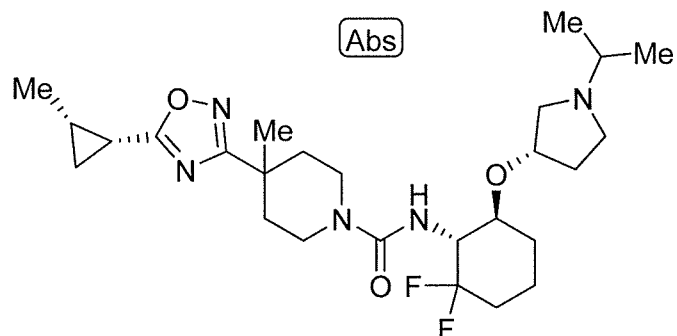
methylpiperidine-1-carboxamide



N-[(1R,6S)-2,2-difluoro-6-{[(3R)-1-(propan-2-yl)pyrrolidin-3-yl]oxy}cyclohexyl]-4-{5-[(1S,2S)-2-fluorocyclopropyl]-1,2,4-oxadiazol-3-yl}-4-methylpiperidine-1-carboxamide

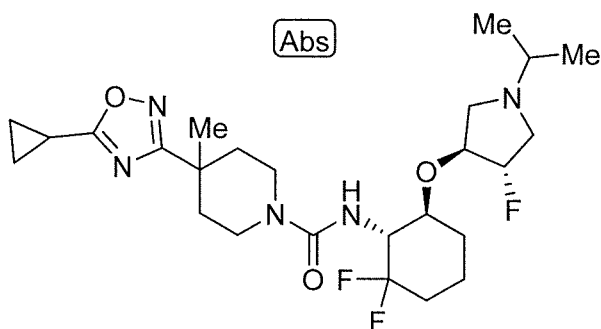


N-[(1R,6S)-2,2-difluoro-6-{[(3S)-1-(propan-2-yl)pyrrolidin-3-yl]oxy}cyclohexyl]-4-methyl-4-{5-[(1R,2S)-2-methylcyclopropyl]-1,2,4-oxadiazol-3-yl}piperidine-1-carboxamide

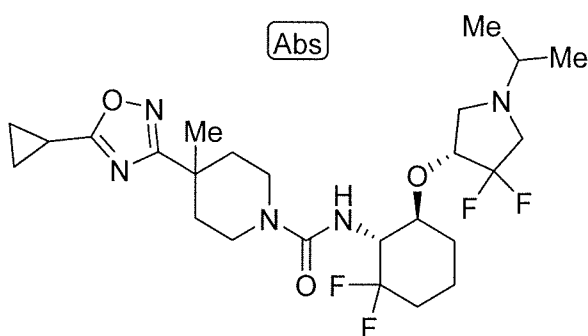


4-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)-N-[(1R,6S)-2,2-

difluoro-6-[[(3S,4S)-4-fluoro-1-(propan-2-yl)pyrrolidin-3-yl]oxy]cyclohexyl]-4-methylpiperidine-1-carboxamide

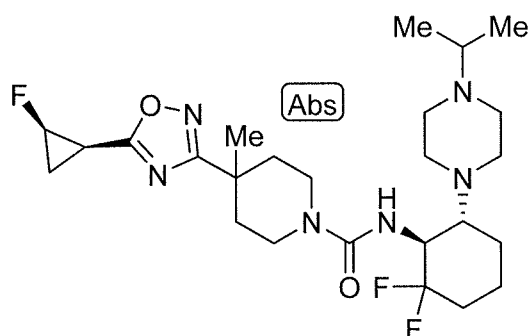


4-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)-N-[(1R,6S)-6-
 5 { [(3R)-4,4-difluoro-1-(propan-2-yl)pyrrolidin-3-yl]oxy}-
 2,2-difluorocyclohexyl]-4-methylpiperidine-1-carboxamide.

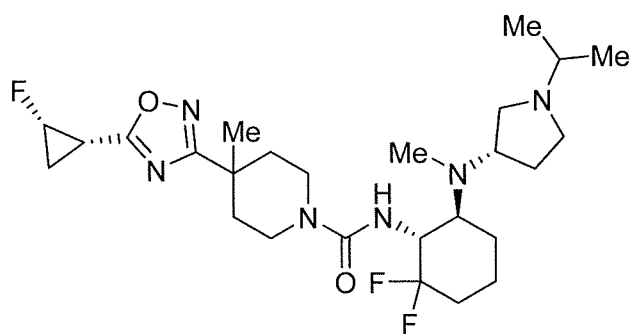


24. The compound of claim 1 or a pharmaceutically acceptable
 10 salt thereof, which is selected from the following compound
 names or structures:

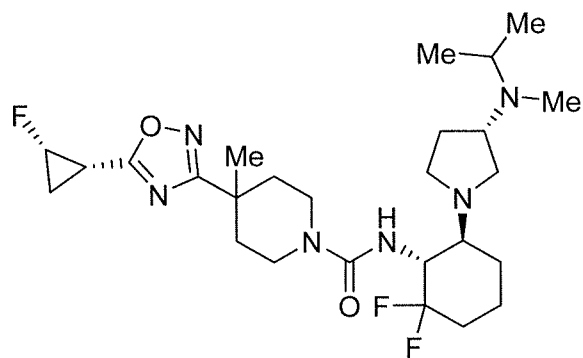
N-[(1S,6R)-2,2-difluoro-6-[4-(propan-2-yl)piperazin-1-yl]cyclohexyl]-4-{5-[(1R,2R)-2-fluorocyclopropyl]-1,2,4-oxadiazol-3-yl}-4-methylpiperidine-1-carboxamide



N-[(1R,6S)-2,2-difluoro-6-{methyl[(3S)-1-(propan-2-yl)pyrrolidin-3-yl]amino}cyclohexyl]-4-{5-[(1S,2S)-2-fluorocyclopropyl]-1,2,4-oxadiazol-3-yl}-4-methylpiperidine-1-carboxamide

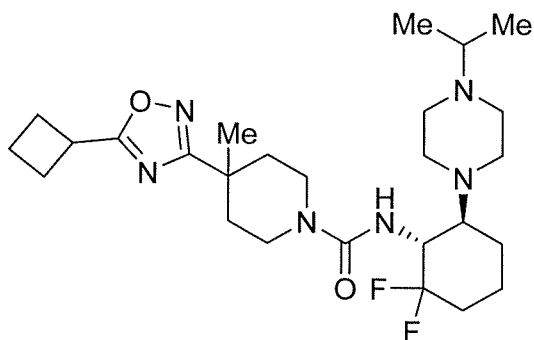


N-[(1R,6S)-2,2-difluoro-6-{(3S)-3-[methyl(propan-2-yl)amino]pyrrolidin-1-yl}cyclohexyl]-4-{5-[(1S,2S)-2-fluorocyclopropyl]-1,2,4-oxadiazol-3-yl}-4-methylpiperidine-1-carboxamide

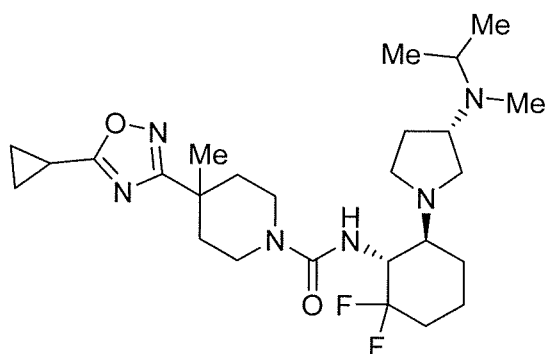


4-(5-cyclobutyl-1,2,4-oxadiazol-3-yl)-N-[(1R,6S)-2,2-

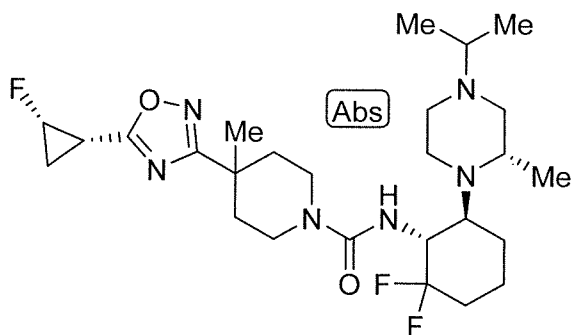
difluoro-6-[4-(propan-2-yl)piperazin-1-yl]cyclohexyl}-4-methylpiperidine-1-carboxamide



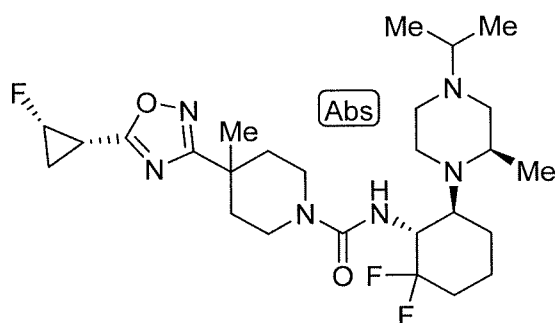
4-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)-N-[(1R,6S)-2,2-difluoro-6-{(3S)-3-[methyl(propan-2-yl)amino]pyrrolidin-1-yl}cyclohexyl]-4-methylpiperidine-1-carboxamide



N-[(1R,6S)-2,2-difluoro-6-{(2S)-2-methyl-4-(propan-2-yl)piperazin-1-yl}cyclohexyl]-4-{5-[(1S,2S)-2-fluorocyclopropyl]-1,2,4-oxadiazol-3-yl}-4-methylpiperidine-1-carboxamide

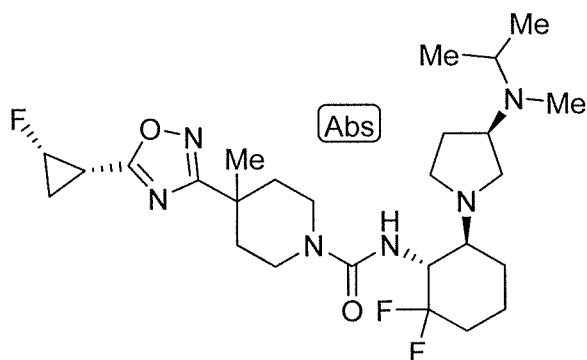


N-[(1R,6S)-2,2-difluoro-6-[(2R)-2-methyl-4-(propan-2-yl)piperazin-1-yl]cyclohexyl]-4-{5-[(1S,2S)-2-fluorocyclopropyl]-1,2,4-oxadiazol-3-yl}-4-methylpiperidine-1-carboxamide



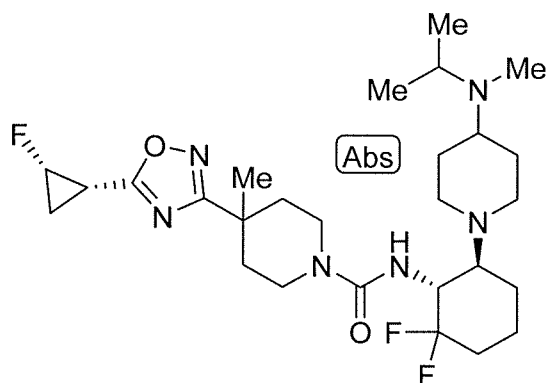
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N-[(1R,6S)-2,2-difluoro-6-{(3R)-3-[methyl (propan-2-yl) amino]pyrrolidin-1-yl}cyclohexyl]-4-{5-[(1S,2S)-2-fluorocyclopropyl]-1,2,4-oxadiazol-3-yl}-4-methylpiperidine-1-carboxamide

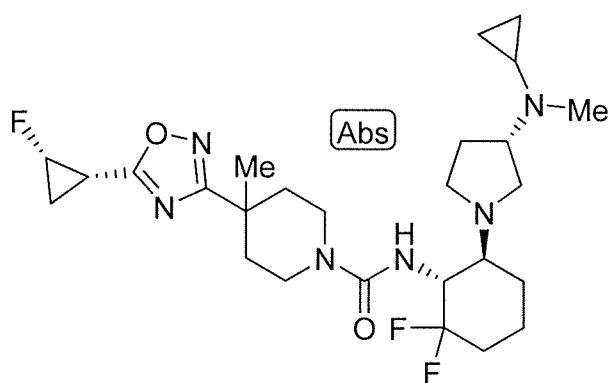


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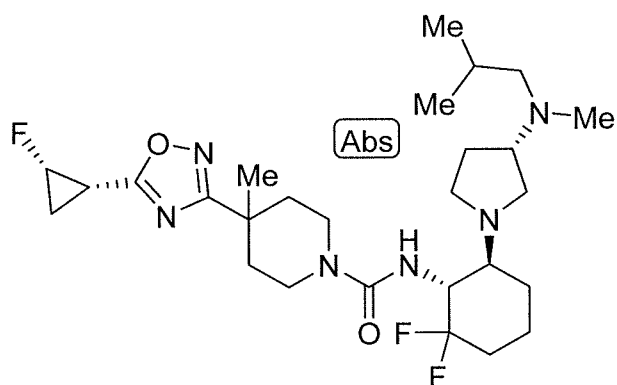
N-[(1R,6S)-2,2-difluoro-6-{4-[methyl (propan-2-yl) amino]piperidin-1-yl}cyclohexyl]-4-{5-[(1S,2S)-2-fluorocyclopropyl]-1,2,4-oxadiazol-3-yl}-4-methylpiperidine-1-carboxamide



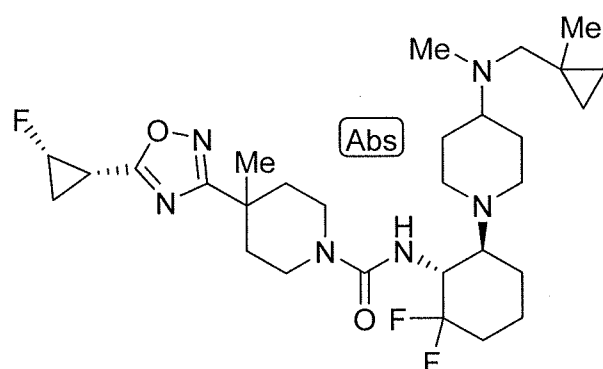
N-[(1R,6S)-6-{(3S)-3-
[cyclopropyl(methyl)amino]pyrrolidin-1-yl}-2,2-
difluorocyclohexyl]-4-{5-[(1S,2S)-2-fluorocyclopropyl]-
5 1,2,4-oxadiazol-3-yl}-4-methylpiperidine-1-carboxamide



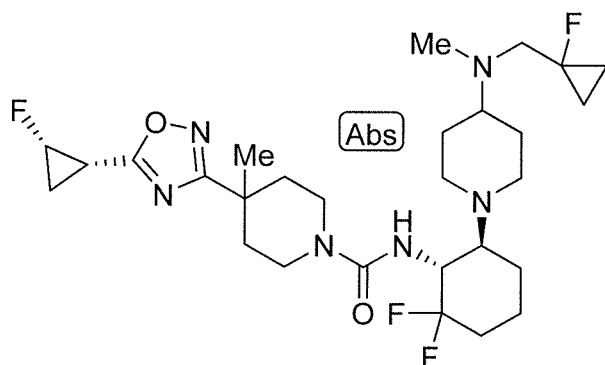
N-[(1R,6S)-2,2-difluoro-6-{(3S)-3-[methyl(2-
methylpropyl)amino]pyrrolidin-1-yl}cyclohexyl]-4-{5-
[(1S,2S)-2-fluorocyclopropyl]-1,2,4-oxadiazol-3-yl}-4-
10 methylpiperidine-1-carboxamide



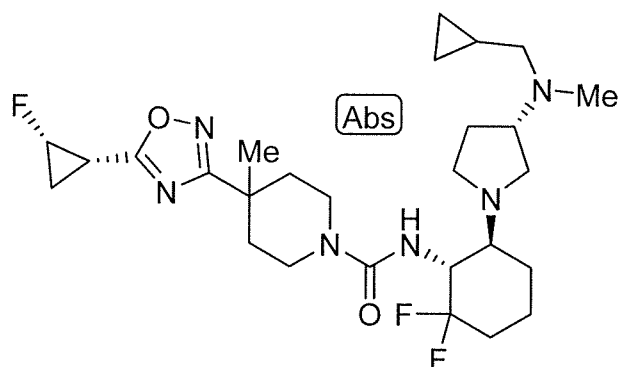
N-[(1R,6S)-2,2-difluoro-6-(4-{methyl[(1-
methylcyclopropyl)methyl]amino}piperidin-1-yl)cyclohexyl]-
4-{5-[(1S,2S)-2-fluorocyclopropyl]-1,2,4-oxadiazol-3-yl}-4-
5 methylpiperidine-1-carboxamide



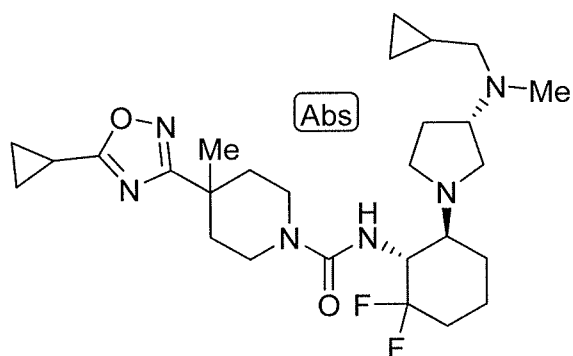
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fluorocyclopropyl)methyl](methyl)amino}piperidin-1-
yl)cyclohexyl]-4-{5-[(1S,2S)-2-fluorocyclopropyl]-1,2,4-
10 oxadiazol-3-yl}-4-methylpiperidine-1-carboxamide



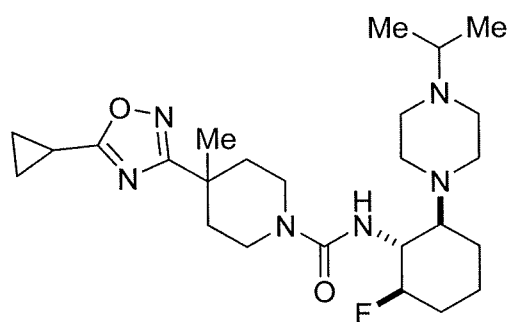
N-[(1R,6S)-6-{(3S)-3-
 [(cyclopropylmethyl)(methyl)amino]pyrrolidin-1-yl}-2,2-
 difluorocyclohexyl]-4-{5-[(1S,2S)-2-fluorocyclopropyl]-
 5 1,2,4-oxadiazol-3-yl}-4-methylpiperidine-1-carboxamide



N-[(1R,6S)-6-{(3S)-3-
 [(cyclopropylmethyl)(methyl)amino]pyrrolidin-1-yl}-2,2-
 difluorocyclohexyl]-4-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)-
 10 4-methylpiperidine-1-carboxamide

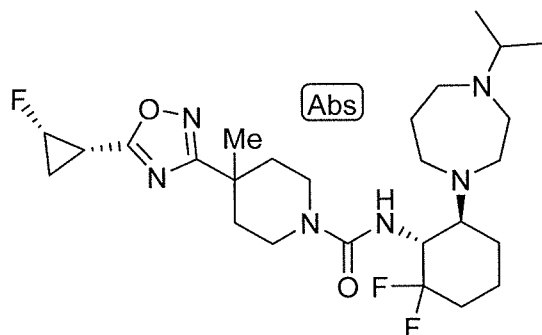


rac-4-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)-N-
 {(1R,2R,6S)-2-fluoro-6-[4-(propan-2-yl)piperazin-1-
 yl]cyclohexyl}-4-methylpiperidine-1-carboxamide



5

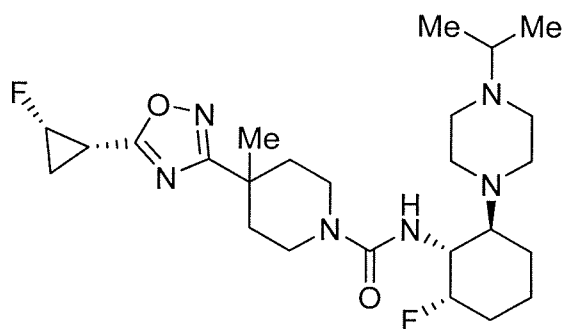
N-{(1R,6S)-2,2-difluoro-6-[4-(propan-2-yl)-1,4-
 diazepan-1-yl]cyclohexyl}-4-{5-[(1S,2S)-2-
 fluorocyclopropyl]-1,2,4-oxadiazol-3-yl}-4-
 methylpiperidine-1-carboxamide



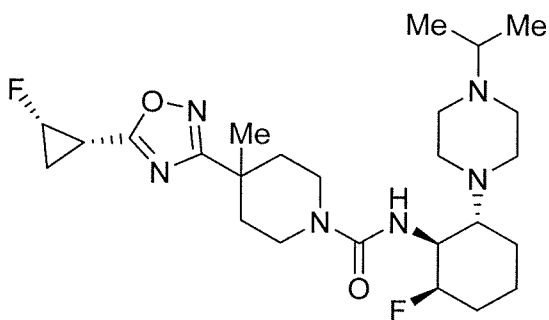
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4-{5-[(1S,2S)-2-fluorocyclopropyl]-1,2,4-oxadiazol-3-
 yl}-N-{(1R,2S,6S)-2-fluoro-6-[4-(propan-2-yl)piperazin-1-

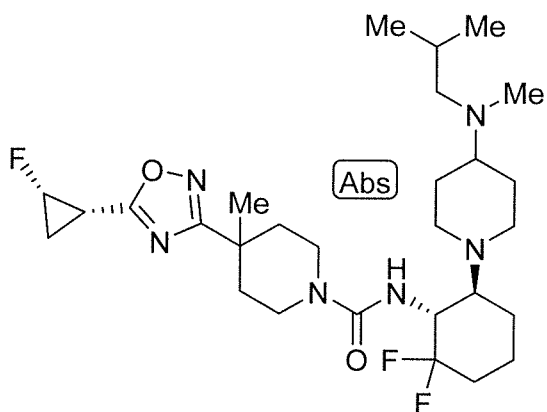
yl]cyclohexyl}-4-methylpiperidine-1-carboxamide



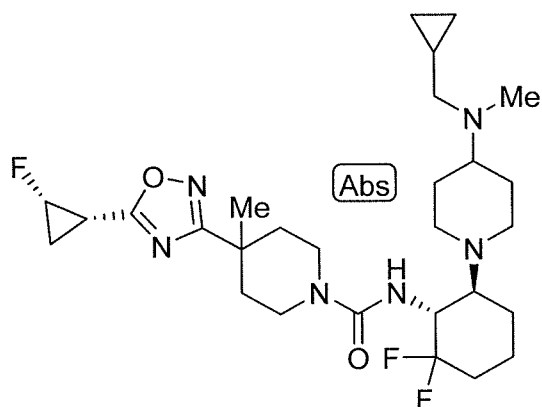
4-{5-[(1S,2S)-2-fluorocyclopropyl]-1,2,4-oxadiazol-3-yl}-N-{(1S,2R,6R)-2-fluoro-6-[4-(propan-2-yl)piperazin-1-yl]cyclohexyl}-4-methylpiperidine-1-carboxamide



N-[(1R,6S)-2,2-difluoro-6-{4-[methyl(2-methylpropyl)amino]piperidin-1-yl}cyclohexyl]-4-{5-[(1S,2S)-2-fluorocyclopropyl]-1,2,4-oxadiazol-3-yl}-4-methylpiperidine-1-carboxamide

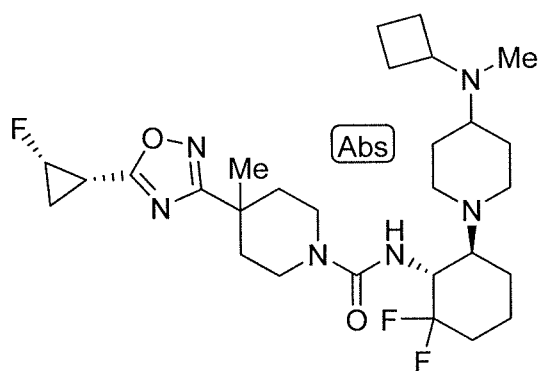


N-[(1R,6S)-6-{4-[(cyclopropylmethyl)(methyl)amino]piperidin-1-yl}-2,2-difluorocyclohexyl]-4-{5-[(1S,2S)-2-fluorocyclopropyl]-1,2,4-oxadiazol-3-yl}-4-methylpiperidine-1-carboxamide



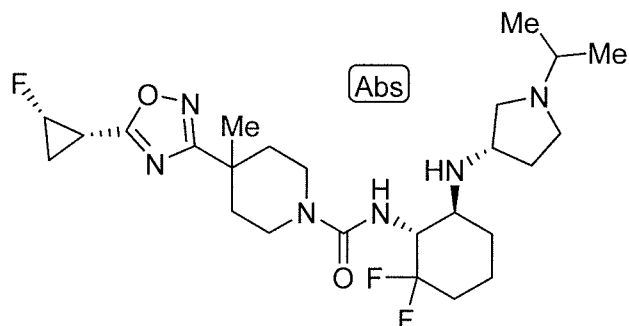
5

N-[(1R,6S)-6-{4-[cyclobutyl(methyl)amino]piperidin-1-yl}-2,2-difluorocyclohexyl]-4-{5-[(1S,2S)-2-fluorocyclopropyl]-1,2,4-oxadiazol-3-yl}-4-methylpiperidine-1-carboxamide



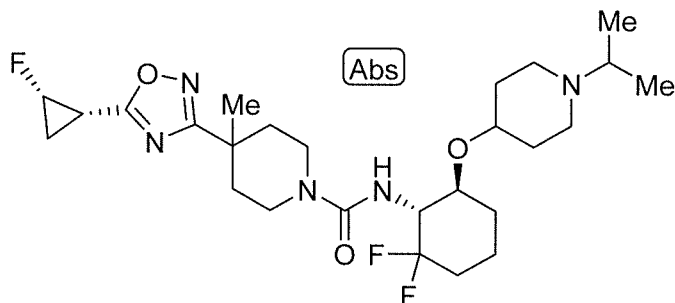
10

N-[(1R,6S)-2,2-difluoro-6-{[(3S)-1-(propan-2-yl)pyrrolidin-3-yl]amino}cyclohexyl]-4-{5-[(1S,2S)-2-fluorocyclopropyl]-1,2,4-oxadiazol-3-yl}-4-methylpiperidine-1-carboxamide

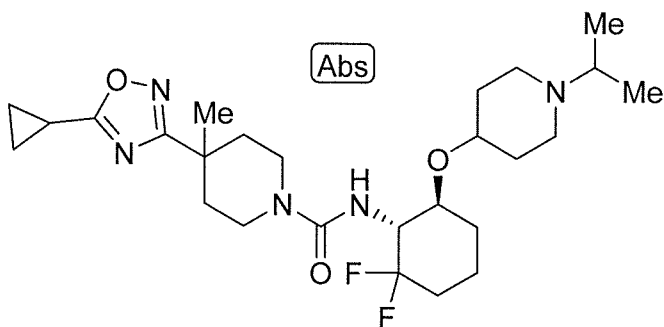


25. The compound of claim 1 or a pharmaceutically acceptable salt thereof, which is selected from the following compound names or structures:

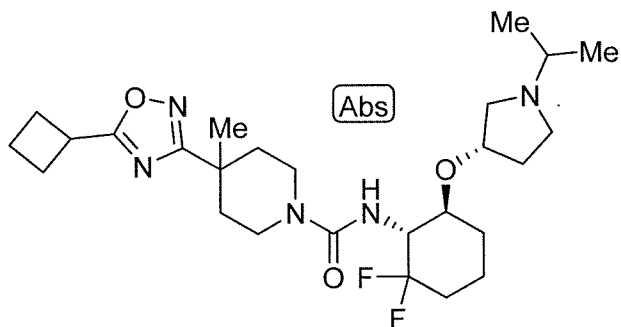
N-[(1R,6S)-2,2-difluoro-6-{[1-(propan-2-yl)piperidin-4-yl]oxy}cyclohexyl]-4-{5-[(1S,2S)-2-fluorocyclopropyl]-1,2,4-oxadiazol-3-yl}-4-methylpiperidine-1-carboxamide



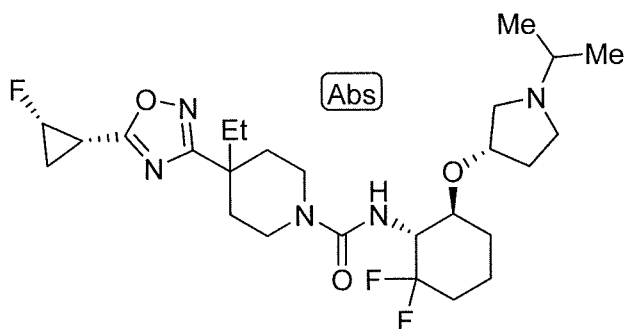
- 10 4-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)-N-[(1R,6S)-2,2-difluoro-6-{[1-(propan-2-yl)piperidin-4-yl]oxy}cyclohexyl]-4-methylpiperidine-1-carboxamide



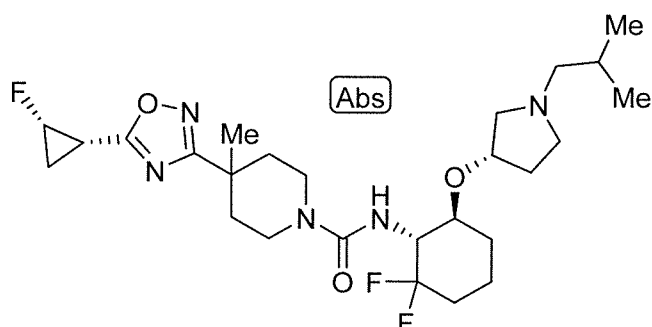
4-(5-cyclobutyl-1,2,4-oxadiazol-3-yl)-N-[(1R,6S)-2,2-difluoro-6-[(3S)-1-(propan-2-yl)pyrrolidin-3-yl]oxy}cyclohexyl]-4-methylpiperidine-1-carboxamide



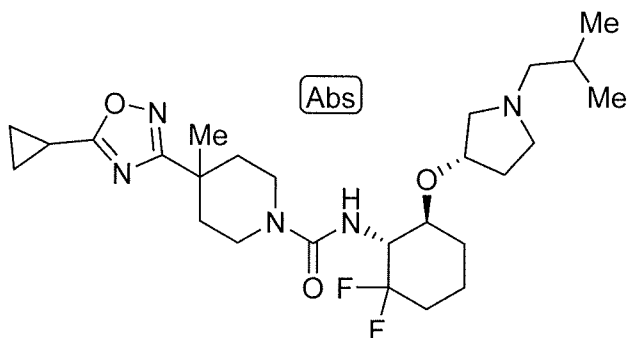
5 N-[(1R,6S)-2,2-difluoro-6-[(3S)-1-(propan-2-yl)pyrrolidin-3-yl]oxy}cyclohexyl]-4-ethyl-4-{5-[(1S,2S)-2-fluorocyclopropyl]-1,2,4-oxadiazol-3-yl}piperidine-1-carboxamide



10 N-[(1R,6S)-2,2-difluoro-6-[(3S)-1-(2-methylpropyl)pyrrolidin-3-yl]oxy}cyclohexyl]-4-{5-[(1S,2S)-2-fluorocyclopropyl]-1,2,4-oxadiazol-3-yl}-4-methylpiperidine-1-carboxamide

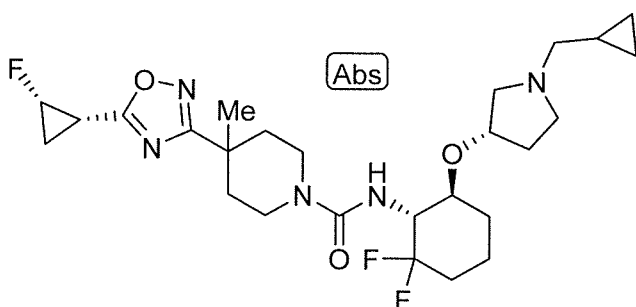


4-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)-N-[(1R,6S)-2,2-difluoro-6-{[(3S)-1-(2-methylpropyl)pyrrolidin-3-yl]oxy}cyclohexyl]-4-methylpiperidine-1-carboxamide



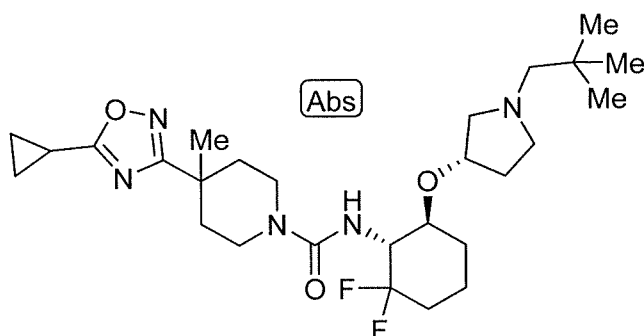
5

N-[(1R,6S)-6-{[(3S)-1-(cyclopropylmethyl)pyrrolidin-3-yl]oxy}-2,2-difluorocyclohexyl]-4-{5-[(1S,2S)-2-fluorocyclopropyl]-1,2,4-oxadiazol-3-yl}-4-methylpiperidine-1-carboxamide

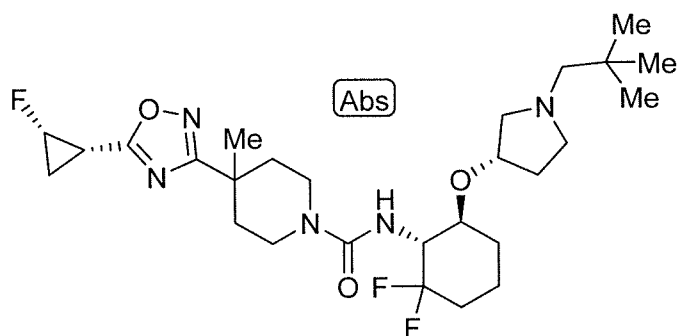


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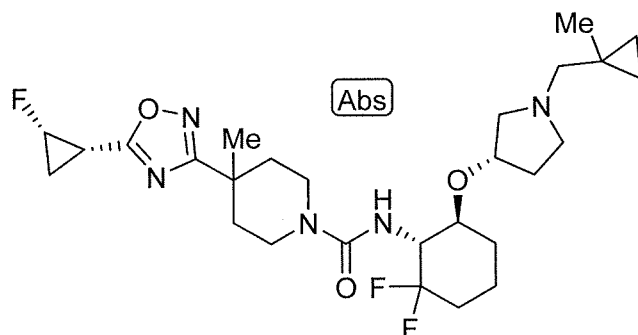
4-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)-N-[(1R,6S)-6-{[(3S)-1-(2,2-dimethylpropyl)pyrrolidin-3-yl]oxy}-2,2-difluorocyclohexyl]-4-methylpiperidine-1-carboxamide



N-[(1R,6S)-6-{{(3S)-1-(2,2-dimethylpropyl)pyrrolidin-3-yl}oxy}-2,2-difluorocyclohexyl]-4-{5-[(1S,2S)-2-fluorocyclopropyl]-1,2,4-oxadiazol-3-yl}-4-methylpiperidine-1-carboxamide

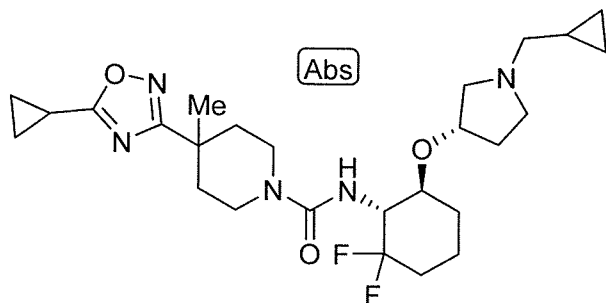


N-[(1R,6S)-2,2-difluoro-6-{{(3S)-1-[(1-methylcyclopropyl)methyl]pyrrolidin-3-yl}oxy}cyclohexyl]-4-{5-[(1S,2S)-2-fluorocyclopropyl]-1,2,4-oxadiazol-3-yl}-4-methylpiperidine-1-carboxamide

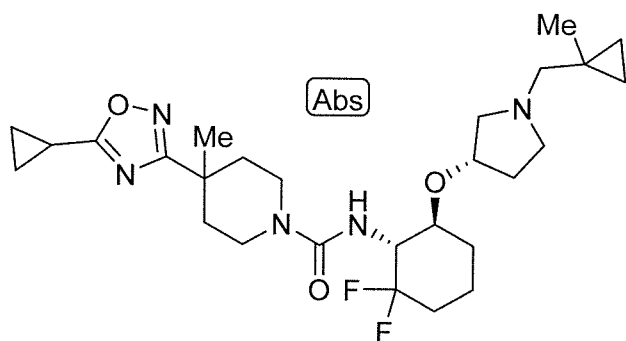


N-[(1R,6S)-6-{{(3S)-1-(cyclopropylmethyl)pyrrolidin-3-yl}oxy}-2,2-difluorocyclohexyl]-4-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)-4-methylpiperidine-1-carboxamide

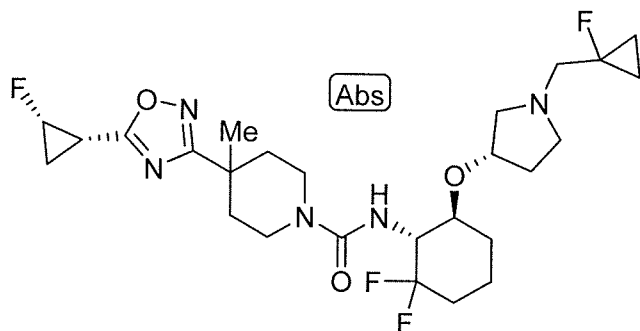
oxadiazol-3-yl)-4-methylpiperidine-1-carboxamide



4-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)-N-[(1R,6S)-2,2-
difluoro-6-((3S)-1-[(1-
5 methylcyclopropyl)methyl]pyrrolidin-3-yl)oxy)cyclohexyl]-4-
methylpiperidine-1-carboxamide

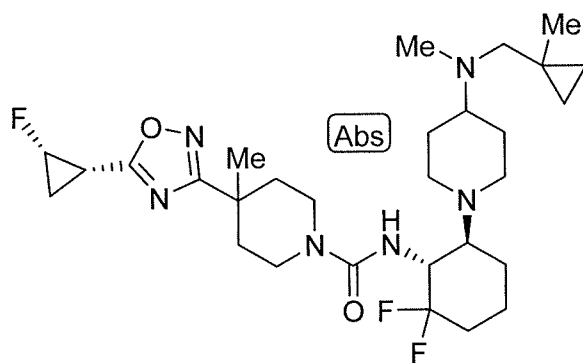


N-[(1R,6S)-2,2-difluoro-6-((3S)-1-[(1-
fluorocyclopropyl)methyl]pyrrolidin-3-yl)oxy)cyclohexyl]-4-
10 {5-[(1S,2S)-2-fluorocyclopropyl]-1,2,4-oxadiazol-3-yl}-4-
methylpiperidine-1-carboxamide

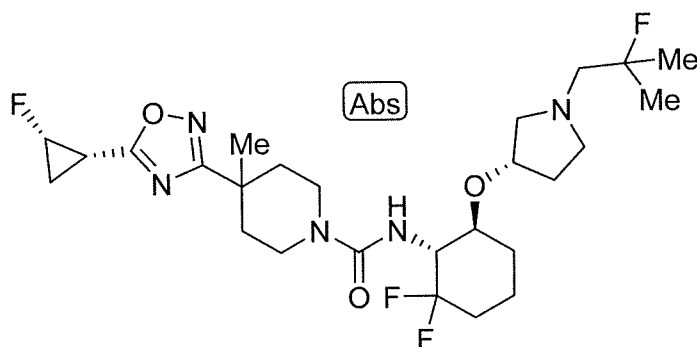


N-[(1R,6S)-2,2-difluoro-6-(4-{methyl[(1-

methylcyclopropyl)methyl]amino}piperidin-1-yl)cyclohexyl]-
4-{5-[(1S,2S)-2-fluorocyclopropyl]-1,2,4-oxadiazol-3-yl}-4-
methylpiperidine-1-carboxamide



- 5 N-[(1R,6S)-2,2-difluoro-6-{[(3S)-1-(2-fluoro-2-methylpropyl)pyrrolidin-3-yl]oxy}cyclohexyl]-4-{5-[(1S,2S)-2-fluorocyclopropyl]-1,2,4-oxadiazol-3-yl}-4-methylpiperidine-1-carboxamide.



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26. A medicament for treating a disease related to orexin receptor, comprising the compound of any one of claims 1 to 25 or a pharmaceutically acceptable salt thereof.

15 27. A medicament for treating narcolepsy, idiopathic

hypersomnia, hypersomnia, sleep apnea syndrome, narcolepsy syndrome involving narcolepsy-like symptom, hypersomnia associated with Parkinson's disease, hypersomnia associated with dementia with Lewy body, hypersomnia syndrome involving daytime hypersomnia (e.g. Kleine-Levin syndrome, major depression accompanied by hypersomnia, dementia with Lewy body, Parkinson's disease, progressive supranuclear palsy, Prader-Willi syndrome, Moebius syndrome, hypoventilation syndrome, Niemann-Pick disease type C, brain contusion, cerebral infarction, brain tumor, muscular dystrophy, multiple sclerosis, acute disseminated encephalomyelitis, Guillain-Barre syndrome, Rasmussen's encephalitis, Wernicke's encephalopathy, limbic encephalitis, Hashimoto encephalopathy), coma, loss of consciousness, obesity (e.g. malignant mast cell, extrinsic obesity, hyperinsular obesity, hyperplasmic obesity, hypophysial obesity, hypoplasmic obesity, hypothyroid obesity, hypothalamic obesity, symptomatic obesity, childhood obesity, upper body obesity, alimentary obesity, gonadal obesity, systemic mastocytosis, primary obesity, central obesity), insulin resistance syndrome, Alzheimer, impaired consciousness such as coma, side effect or complication caused by anesthesia, sleep disturbance, sleep problem, insomnia, intermittent sleep, night myoclonus, REM sleep interruption, jet lag, jet lag syndrome, sleep disorder of shift workers, dyssomnia,

sleep terror, depression, major depression, sleepwalking,
enuresis, sleep disorder, Alzheimer's sundown syndrome,
disease associated with circadian rhythm, fibromyalgia,
condition resulting from decrease in sleeping quality,
5 bulimia, obsessive eating disorder, obesity-related
diseases, hypertension, diabetes, elevated plasma insulin
level/insulin resistance, hyperlipemia, hyperlipidaemia,
endometrial cancer, breast cancer, prostate cancer, colon
cancer, cancer, osteoarthritis, obstructive sleep apnea,
10 cholelithiasis, gallstone, heart disease, abnormal
heartbeat, arrhythmia, myocardial infarction, congestive
heart failure, heart failure, coronary heart disease,
cardiovascular disease, sudden death, polycystic ovary,
craniopharyngioma, Prader-Willi syndrome, Froehlich
15 syndrome, growth hormone deficiency, normal variant short
stature, Turner syndrome, children suffering from acute
lymphoblastic leukemia, syndrome X, reproductive hormone
abnormality, decrease of fecundability, infertility,
hypogonadism in men, sexual/reproductive-function
20 dysfunction such as hirsutism in women, fetal defect
associated with maternity obesity, gastrointestinal motility
disorder such as obesity-related gastroesophageal reflux,
obesity hypoventilation syndrome (Pickwickian syndrome),
respiratory disease such as respiratory distress,
25 inflammation such as vascular systemic inflammation,

arteriosclerosis, hypercholesterolemia, hyperuricemia, low
back pain, gallbladder disease, gout, renal cancer,
secondary risk of obesity such as risk of left ventricle
hypertrophy, migraine, headache, neuropathic pain,
5 Parkinson's disease, psychosis, schizophrenia, facial
flushing, night sweat, disease in genitalium/urinary system,
disease associated with sexual function or fecundability,
dysthymic disorder, bipolar disorder, bipolar I disorder,
bipolar II disorder, cyclothymic disorder, acute stress
10 disorder, agoraphobia, generalized anxiety disorder,
obsessive-compulsive disorder, panic attack, panic disorder,
posttraumatic stress disorder, separation anxiety disorder,
social phobia, anxiety disorder, acute neurological and
psychiatric disorder such as cerebral deficiency developed
15 after heart bypass surgery or heart transplant, stroke,
ischemic stroke, cerebral ischemia, spinal cord trauma, head
injury, periparturient hypoxia, cardiac arrest, hypoglycemic
nerve injury, Huntington's disease, amyotrophic lateral
sclerosis, multiple sclerosis, eye damage, retinopathy,
20 cognitive impairment, muscle spasm, tremor, epilepsy,
disorder associated with muscle spasm, delirium, amnestic
disorder, age-associated cognitive decline, schizoaffective
disorder, paranoia, drug addiction, movement disorder,
chronic fatigue syndrome, fatigue, medication-induced
25 parkinsonian syndrome, Gilles de la Tourette syndrome,

chorea, myoclonus, tic, restless legs syndrome, dystonia, dyskinesia, attention deficit hyperactivity disorder (ADHD), conduct disorder, urinary incontinence, withdrawal symptom, trigeminal neuralgia, hearing loss, tinnitus, nerve injury, retinopathy, macular degeneration, vomiting, cerebral edema, pain, bone pain, arthralgia, toothache, cataplexy, or traumatic brain injury, comprising the compound of any one of claims 1 to 25 or a pharmaceutically acceptable salt thereof.

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28. A medicament for treating narcolepsy, idiopathic hypersomnia, hypersomnia, sleep apnea syndrome, narcolepsy syndrome involving narcolepsy-like symptom, hypersomnia associated with Parkinson's disease, or hypersomnia associated with dementia with Lewy body, comprising the compound of any one of claims 1 to 25 or a pharmaceutically acceptable salt thereof.

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29. A method for treating narcolepsy, idiopathic hypersomnia, hypersomnia, sleep apnea syndrome, narcolepsy syndrome involving narcolepsy-like symptom, hypersomnia associated with Parkinson's disease, or hypersomnia associated with dementia with Lewy body, comprising administering a therapeutically effective amount of the compound of any one of claims 1 to 25 or a pharmaceutically

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acceptable salt thereof to a patient in need thereof.

30. Use of the compound of any one of claims 1 to 25 or a
pharmaceutically acceptable salt thereof, in the manufacture
5 of a medicament for treating narcolepsy, idiopathic
hypersomnia, hypersomnia, sleep apnea syndrome, narcolepsy
syndrome involving narcolepsy-like symptom, hypersomnia
associated with Parkinson's disease, or hypersomnia
associated with dementia with Lewy body.