

TITLE OF INVENTION

NOVEL HETEROCYCLIC COMPOUND, ITS PREPARATION METHOD, AND
PHARMACEUTICAL COMPOSITION COMPRISING THE SAME

TECHNICAL FIELD

5 The present invention relates to a heterocyclic compound having a novel structure that can be used for the prevention or treatment of diseases caused by abnormality in a PRS (prolyl-tRNA synthetase) activity, a method for preparing the same, and a pharmaceutical composition comprising the same.

BACKGROUND OF ART

10 PRS (prolyl-tRNA synthetase) is one of the aminoacyl-tRNA synthetase (ARS) family and serves to activate an amino acid for protein synthesis. That is, ARS performs a translational function to form aminoacyl adenylate (AA-AMP) and then transfer the activated amino acid to the 3-end of the corresponding tRNA. Since ARS plays an important role in the synthesis of protein, ARS inhibitors suppress the growth of all cells. Thus, ARS has been recognized as a promising
15 target for a therapeutic agent for treating diseases that should suppress antibiotics or cell overexpression (Nature, 2013, 494:121-125).

PRS is present in, or functions as, a multi-synthetase complex (MSC) in the form of EPRS (Glutamyl-Prolyl-tRNA Synthetase). In particular, among various MSCs, EPRS functions
20 as a translational silencer that suppresses the production of VEGF A (vascular endothelial growth factor A) which is a key factor in angiogenesis. In addition, it is reported that EPRS is closely related with various solid tumors (Nat. Rev. Cancer, 2011, 11, 708-718).

The only substance, known as the PRS inhibitor, is halofuginone. Halofuginone is a
25 derivative of febrifugine derived from natural products and has anti-malarial effects and various anti-inflammatory effects. It can also be used as an animal feed additive. In addition, it has been reported that halofuginone increases the phosphorylation of GCN2 kinase through PRS inhibition, which induces ATF4 and CHOP expression, and thus promotes cell death (Nat. Chem. Biol. 2012, 8, 311-317). Currently, halofuginone is being clinically studied as anti-cancer agent, an anti-
30 inflammatory agent (J Immunol, 2014, 192(5), 2167-76), therapeutic agents for the treatment of

autoimmune diseases (Arthritis Rheumatol, 2014,66 (5), 1195-207), therapeutic agents for the treatment of fibrosis diseases (World J Gastroenterol, 2014,20 (40), 14778-14786), and the like (Bioorg. Med. Chem. 2014, 22, 1993-2004).

5 However, it has been reported that halofuginone acts on various targets and has a very severe toxicity and further there is a risk of genotoxicity (The EFSA Journal, 2003, 8: 1-45). Therefore, discovering PRS inhibitors having higher safety to the human body among substances capable of inhibiting PRS like halofuginone has a significance in terms of developing an anti-cancer agent of the next generation that can be used as an antifibrosis agent, an anti-inflammatory
10 agent, an autoimmune therapeutic agent alone or in combination with an existing targeted anti-cancer agent.

In this regard, the present inventors have conducted numerous studies to develop a novel compound with reduced toxicity while having a PRS enzyme inhibitory effect, and found that the
15 compound having a novel structure which will be described later selectively inhibits the PRS, thereby completing the present invention. The compounds belonging to the present invention themselves have mainly a PRS enzyme inhibitory activity, but do not exclude a possibility of exhibiting a pharmacological action as an efficacious agent by a special body environment or by products of metabolic process, after absorption into the body.

20 DETAILED DESCRIPTION OF THE INVENTION

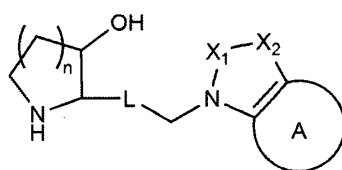
TECHNICAL PROBLEM

It is an object of the present invention to provide a heterocyclic compound having a novel structure that can be used for the prevention or treatment of cancers, inflammatory diseases, autoimmune diseases or fibrosis, a method for preparing the same, and a pharmaceutical
25 composition comprising the same.

TECHNICAL SOLUTION

In order to achieve the above object, the present invention provides a compound represented by the following Chemical Formula 1, or a pharmaceutically acceptable salt thereof:

[Chemical Formula 1]



in Chemical Formula 1,

n is 1, or 2,

L is $-\text{CH}_2\text{CH}_2-$, $-\text{CH}=\text{C}(\text{R}')$ -, or $-\text{C}\equiv\text{C}-$,

5 wherein R' is hydrogen, C_{1-4} alkyl, or halogen,

X_1 is CR_1R_2 , NR_1 , or $-\text{CO}-$,

X_2 is CR_3R_4 , or NR_3 ,

wherein R_1 to R_4 are each independently hydrogen, C_{1-4} alkyl, C_{1-4} hydroxyalkyl, hydroxy, amino, carboxy, $-\text{COO}(\text{C}_{1-4} \text{ alkyl})$, $-\text{CONH}_2$, $-\text{CONH}(\text{C}_{1-4} \text{ alkyl})$, $-\text{CON}(\text{C}_{1-4} \text{ alkyl})_2$, or pyrazolyl unsubstituted or substituted with C_{1-4} haloalkyl; or R_1 and R_3 , together with each other, link X_1 and X_2 via a double bond, and

A is benzene, pyridine, pyrimidine, or pyrimidinedione ring,

wherein A is unsubstituted or substituted with one to three substituents each independently selected from the group consisting of a ring-type substituent selected from the group consisting of furanyl, imidazolyl, isoxazolyl, phenyl, pyrazolyl, pyridinonyl, pyridinyl, pyrrolyl, thiazolyl, and thiophenyl; C_{1-4} alkyl; C_{1-4} alkoxy; C_{1-4} haloalkyl; C_{1-4} haloalkoxy; halogen; di(C_{1-4} alkyl)amino; nitro; $-\text{COO}(\text{C}_{1-4} \text{ alkyl})$; dihydropyranyl; morpholino; piperidinyl; and pyrrolidinyl; and

wherein the ring-type substituent is unsubstituted or substituted with one or two substituents each independently selected from the group consisting of C_{1-5} alkyl, C_{1-4} haloalkyl, C_{3-6} cycloalkyl, monovalent of C_{2-5} alkylene carbonate, $-\text{COO}(\text{C}_{1-4} \text{ alkyl})$, halogen, cyano, thiazolyl, and (1,3-dioxolan-2-yl)methyl.

Preferably, when the ring-type substituent is furanyl, it is unsubstituted or substituted with $-\text{COO}(\text{C}_{1-4} \text{ alkyl})$. When the ring-type substituent is imidazolyl, it is unsubstituted or substituted with C_{1-5} alkyl. When the ring-type substituent is isoxazolyl, it is unsubstituted or substituted with two C_{1-5} alkyls. When the ring-type substituent is phenyl, it is unsubstituted or substituted with halogen, or C_{1-4} haloalkyl. When the ring-type substituent is pyrazolyl, it is unsubstituted or

substituted with C₁₋₅ alkyl, C₁₋₄ haloalkyl, monovalent of C₂₋₅ alkylene carbonate, thiazolyl, and (1,3-dioxolan-2-yl)methyl. When the ring-type substituent is pyridinonyl, it is unsubstituted or substituted with C₁₋₅ alkyl. When the ring-type substituent is pyridinyl, it is unsubstituted or substituted with halogen. When the ring-type substituent is pyrrolyl, it is unsubstituted or substituted with C₁₋₅ alkyl and -COO(C₁₋₄ alkyl). When the ring-type substituent is thiazolyl, it is unsubstituted or substituted with C₁₋₅ alkyl, C₃₋₆ cycloalkyl, cyano, or monovalent of C₂₋₅ alkylene carbonate. When the ring-type substituent is thiophenyl, it is unsubstituted or substituted with one or two substituents each independently selected from the group consisting of C₁₋₅ alkyl, and -COO(C₁₋₄ alkyl).

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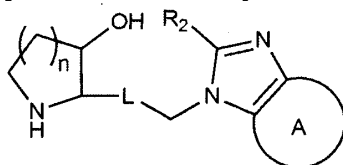
Preferably, A is unsubstituted or substituted with one to three substituents each independently selected from the group consisting of C₁₋₄ alkyl; C₁₋₄ alkoxy; C₁₋₄ haloalkyl; halogen; phenyl unsubstituted or substituted with halogen, or C₁₋₄ haloalkyl; pyrazolyl unsubstituted or substituted with C₁₋₅ alkyl, thiazolyl, or C₁₋₄ haloalkyl; thiophenyl unsubstituted or substituted with C₁₋₅ alkyl, or -COO(C₁₋₄ alkyl); pyrrolyl unsubstituted or substituted with C₁₋₅ alkyl and/or -COO(C₁₋₄ alkyl); di(C₁₋₄ alkyl)amino; morpholino; piperidinyl; furanyl; and pyrrolidinyl.

20

Preferably, L is -CH₂CH₂-, -CH=CH-, -CH=CF-, -CH=C(CH₃)-, or -C≡C-.

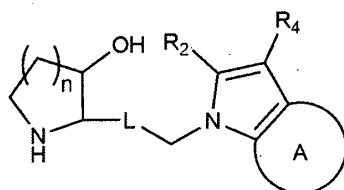
Preferably, according to X₁ and X₂, the compound represented by Chemical Formula 1 is represented by the following Chemical Formulas 1-1 to 1-5:

[Chemical Formula 1-1]

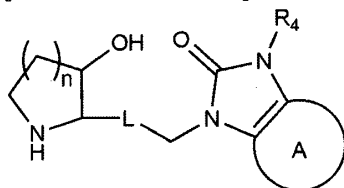


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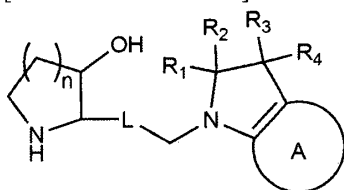
[Chemical Formula 1-2]



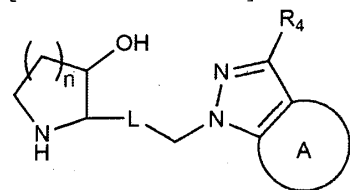
[Chemical Formula 1-3]



[Chemical Formula 1-4]



[Chemical Formula 1-5]



in Chemical Formulas 1-1 to 1-5,
n, L, R₁ to R₄ and A are as previously defined.

10

Preferably, R₁ to R₄ are each independently hydrogen, methyl, hydroxymethyl, hydroxy, amino, carboxy, -COOCH₃, -CONH₂, -CONHCH₃, or -CON(CH₃)₂; or R₁ and R₃, together with each other, link X₁ and X₂ via a double bond.

15

Preferably, A is benzene, pyridine, pyrimidine, or pyrimidinedione ring, wherein A is unsubstituted or substituted with one to three substituents each independently selected from the group consisting of methyl, isobutyl, methoxy, trifluoromethyl, fluoro, chloro, bromo, phenyl, phenyl substituted with fluoro, phenyl substituted with chloro, phenyl substituted with trifluoromethyl, thiophenyl, thiophenyl substituted with methyl, thiophenyl substituted with -

COOCH₃, pyrazolyl substituted with difluoromethyl, pyrazolyl substituted with methyl, pyrazolyl substituted with thiazolyl, pyrrolyl substituted with methyl and -COOCH₂CH₃, furanyl, dimethylamino, diethylamino, methylethylamino, morpholino, piperidinyl, and pyrrolidinyl.

5 Preferably, A is benzene, wherein A is unsubstituted or substituted with one to three substituents each independently selected from the group consisting of C₁₋₄ alkyl; C₁₋₄ alkoxy; halogen; and phenyl unsubstituted or substituted with halogen or C₁₋₄ haloalkyl.

10 Preferably, A is pyridine, wherein A is unsubstituted or substituted with one or two substituents each independently selected from the group consisting of C₁₋₄ alkyl; C₁₋₄ haloalkyl; halogen; and phenyl substituted with halogen.

Preferably, A is pyrimidine, wherein A is substituted with a substituent selected from the group consisting of halogen; di(C₁₋₄ alkyl)amino; morpholino; piperidinyl; and pyrrolidinyl.

15

Preferably, A is pyrimidinedione, wherein A is unsubstituted or substituted with one or two C₁₋₄ alkyl.

Typical examples of the compounds represented by Chemical Formula 1 are as follows:

- 20 1) (2R,3S)-2-(3-(6-chloro-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol,
 2) (2R,3S)-2-(3-(4-bromo-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol,
 3) (2R,3S)-2-(3-(5-bromo-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol,
 4) (2R,3S)-2-(3-(6-bromo-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol,
 5) (2R,3S)-2-(3-(7-bromo-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol,
 25 6) (2R,3S)-2-(3-(4-fluoro-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol,
 7) (2R,3S)-2-(3-(5-fluoro-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol,
 8) (2R,3S)-2-(3-(6-fluoro-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol,
 9) (2R,3S)-2-(3-(7-fluoro-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol,
 10) (2R,3S)-2-(3-(4-chloro-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol,
 30 11) (2R,3S)-2-(3-(5-chloro-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol,

- 12) (2R,3S)-2-(3-(7-chloro-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol,
13) (2R,3S)-2-(3-(6-methyl-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol,
14) (2R,3S)-2-(3-(5-methyl-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol,
15) (2R,3S)-2-(3-(6-(trifluoromethyl)-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-
5 ol,
16) (2R,3S)-2-(3-(7-(trifluoromethyl)-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-
ol,
17) (2R,3S)-2-(3-(7-(trifluoromethoxy)-1H-benzo[d]imidazol-1-yl)propyl)piperidin-
3-ol,
18) (2R,3S)-2-(3-(4-(pyrrolidin-1-yl)-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-
10 ol,
19) (2R,3S)-2-(3-(4-(piperidin-1-yl)-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-
ol,
20) (2R,3S)-2-(3-(4-(3-fluorophenyl)-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-
15 ol,
21) (2R,3S)-2-(3-(4-(3-chlorophenyl)-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-
ol,
22) (2R,3S)-2-(3-(5-(3-fluorophenyl)-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-
ol,
23) (2R,3S)-2-(3-(6-(2-fluorophenyl)-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-
20 ol,
24) (2R,3S)-2-(3-(6-(3-fluorophenyl)-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-
ol,
25) (2R,3S)-2-(3-(6-(4-fluorophenyl)-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-
25 ol,
26) (2R,3S)-2-(3-(7-(2-fluorophenyl)-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-
ol,
27) (2R,3S)-2-(3-(7-(3-fluorophenyl)-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-
ol,
28) (2R,3S)-2-(3-(7-(4-fluorophenyl)-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-
30 ol

- ol,
- 29) (2R,3S)-2-(3-(5-(1H-pyrazol-4-yl)-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol,
- 30) (2R,3S)-2-(3-(6-(1H-pyrazol-4-yl)-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol,
- 5 31) (2R,3S)-2-(3-(7-(1H-pyrazol-4-yl)-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol,
- 32) (2R,3S)-2-(3-(6-chloro-5-fluoro-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol,
- 10 33) (2R,3S)-2-(3-(6-bromo-5-fluoro-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol,
- 34) (2R,3S)-2-(3-(5-chloro-6-fluoro-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol,
- 35) (2R,3S)-2-(3-(5-bromo-6-fluoro-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol,
- 15 36) (2R,3S)-2-(3-(6-bromo-5-chloro-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol,
- 37) (2R,3S)-2-(3-(6-chloro-5-methoxy-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol,
- 20 38) (2R,3S)-2-(3-(6-fluoro-5-methoxy-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol,
- 39) (2R,3S)-2-(3-(5-fluoro-6-methyl-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol,
- 40) (2R,3S)-2-(3-(4,5-dichloro-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol,
- 25 41) (2S,3S)-2-(3-(4,5-dichloro-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol,
- 42) (2S,3R)-2-(3-(4,5-dichloro-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol,
- 43) (2R,3R)-2-(3-(4,5-dichloro-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol,
- 44) (2R,3S)-2-(3-(4-chloro-5-methyl-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol,
- 30 45) (2R,3S)-2-(3-(5-bromo-4-methyl-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-

- ol,
- 46) (2R,3S)-2-(3-(5-chloro-4-methyl-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol,
- 47) (2R,3S)-2-(3-(5-bromo-4-fluoro-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol,
- 5 48) (2R,3S)-2-(3-(6-bromo-7-fluoro-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol,
- 49) (2R,3S)-2-(3-(4,5-difluoro-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol,
- 50) (2R,3S)-2-(3-(6,7-difluoro-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol,
- 10 51) (2R,3S)-2-(3-(4,5-dimethyl-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol,
- 52) (2R,3S)-2-(3-(5,6-difluoro-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol,
- 53) (2R,3S)-2-(3-(5,6-dichloro-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol,
- 54) (2R,3S)-2-(3-(5,6-dibromo-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol,
- 55) (2R,3S)-2-(3-(5,6-dimethyl-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol,
- 15 56) (2R,3S)-2-(3-(6,7-dichloro-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol,
- 57) (2R,3S)-2-(3-(4,6-difluoro-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol,
- 58) (2R,3S)-2-(3-(5,7-difluoro-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol,
- 59) (2R,3S)-2-(3-(4-chloro-5-methoxy-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol,
- 20 60) (2R,3S)-2-(3-(7-chloro-6-methoxy-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol,
- 61) (2R,3S)-2-(3-(6-chloro-4-methyl-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol,
- 62) (2R,3S)-2-(3-(4-chloro-5-fluoro-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol,
- 25 63) (2R,3S)-2-(3-(6-bromo-4-methyl-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol,
- 64) (2R,3S)-2-(3-(5-fluoro-4-methyl-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol,
- 30 65) (2R,3S)-2-(3-(6-fluoro-7-methyl-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-

ol,

66) (2R,3S)-2-(3-(4-chloro-5-(trifluoromethyl)-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol,

67) (2R,3S)-2-(3-(7-chloro-6-(trifluoromethyl)-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol,

68) methyl 7-bromo-1-(3-((2R,3S)-3-hydroxypiperidin-2-yl)propyl)-1H-benzo[d]imidazole-5-carboxylate,

69) (2R,3S)-2-(3-(7-bromo-5-chloro-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol,

70) (2R,3S)-2-(3-(5-bromo-7-chloro-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol,

71) (2R,3S)-2-(3-(7-bromo-5-(trifluoromethyl)-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol,

72) (2R,3S)-2-(3-(6-bromo-4-fluoro-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol,

73) (2R,3S)-2-(3-(5-bromo-7-fluoro-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol,

74) (2R,3S)-2-(3-(7-chloro-4-fluoro-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol,

75) (2R,3S)-2-(3-(5-bromo-4-nitro-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol,

76) (2R,3S)-2-(3-(6-bromo-7-nitro-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol,

77) (2R,3S)-2-(3-(4-chloro-5-nitro-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol,

78) (2R,3S)-2-(3-(7-chloro-5-(trifluoromethyl)-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol,

79) (2R,3S)-2-(3-(5-chloro-7-fluoro-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol,

80) (2R,3S)-2-(3-(5,7-dichloro-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol,

81) (2R,3S)-2-(3-(5-chloro-7-(1H-pyrazol-4-yl)-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol,

82) (2R,3S)-2-(3-(7-(1H-pyrazol-4-yl)-5-(trifluoromethyl)-1H-benzo[d]imidazol-1-

- yl)propyl)piperidin-3-ol,
- 83) (2R,3S)-2-(3-(5-chloro-7-(3-fluorophenyl)-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol,
- 84) (2R,3S)-2-(3-(7-(3-fluorophenyl)-5-(trifluoromethyl)-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol,
- 5 85) (2R,3S)-2-(3-(5-chloro-7-(2-methylthiazol-5-yl)-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol,
- 86) (2R,3S)-2-(3-(5-chloro-7-(pyridin-3-yl)-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol,
- 10 87) (2R,3S)-2-(3-(5-chloro-7-(5-fluoropyridin-3-yl)-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol,
- 88) 5-(5-chloro-1-(3-((2R,3S)-3-hydroxypiperidin-2-yl)propyl)-1H-benzo[d]imidazol-7-yl)-1-methylpyridin-2(1H)-one,
- 89) (2R,3S)-2-(3-(5-chloro-7-(1-(difluoromethyl)-1H-pyrazol-4-yl)-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol,
- 15 90) (2R,3S)-2-(3-(5-chloro-7-(isoxazol-3-yl)-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol,
- 91) (2R,3S)-2-(3-(5-chloro-7-(thiophen-3-yl)-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol,
- 20 92) (2R,3S)-2-(3-(5-chloro-7-(2-methylthiophen-3-yl)-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol,
- 93) (2R,3S)-2-(3-(5-chloro-7-(3,5-dimethylisoxazol-4-yl)-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol,
- 94) (2R,3S)-2-(3-(5-chloro-7-(3,6-dihydro-2H-pyran-4-yl)-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol,
- 25 95) (2R,3S)-2-(3-(7-(1-((1,3-dioxolan-2-yl)methyl)-1H-pyrazol-4-yl)-5-chloro-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol,
- 96) (2R,3S)-2-(3-(5-chloro-7-(1-methyl-1H-imidazol-5-yl)-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol,
- 30 97) (2R,3S)-2-(3-(5-chloro-7-(1-methyl-1H-pyrazol-4-yl)-1H-benzo[d]imidazol-1-

- yl)propyl)piperidin-3-ol,
- 98) (2R,3S)-2-(3-(7-(pyrrolidin-1-yl)-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol,
- 99) (2R,3S)-2-(3-(5-chloro-7-(pyrrolidin-1-yl)-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol,
- 5 100) (2R,3S)-2-(3-(5-chloro-7-(2-cyclopropylthiazol-5-yl)-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol,
- 101) (2R,3S)-2-(3-(5-chloro-7-(1-(thiazol-2-yl)-1H-pyrazol-4-yl)-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol,
- 10 102) (2R,3S)-2-(3-(5-chloro-7-(1-(oxetan-3-yl)-1H-pyrazol-4-yl)-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol,
- 103) (2R,3S)-2-(3-(5-chloro-7-(2-(tetrahydro-2H-pyran-4-yl)thiazol-4-yl)-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol,
- 104) (2R,3S)-2-(3-(5-chloro-7-(furan-3-yl)-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol,
- 15 105) 4-(5-chloro-1-(3-((2R,3S)-3-hydroxypiperidin-2-yl)propyl)-1H-benzo[d]imidazol-7-yl)thiazole-2-carbonitrile,
- 106) (2R,3S)-2-(3-(7-(1-(tert-butyl)-1H-pyrazol-4-yl)-5-chloro-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol,
- 20 107) (2R,3S)-2-(3-(5-chloro-7-(1-isopentyl-1H-pyrazol-4-yl)-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol,
- 108) (2R,3S)-2-(3-(5-chloro-7-(1-isopropyl-1H-pyrazol-4-yl)-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol,
- 109) (2R,3S)-2-(3-(5-chloro-7-(4-methylthiophen-3-yl)-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol,
- 25 110) ethyl 3-(5-chloro-1-(3-((2R,3S)-3-hydroxypiperidin-2-yl)propyl)-1H-benzo[d]imidazol-7-yl)furan-2-carboxylate,
- 111) methyl 4-(5-chloro-1-(3-((2R,3S)-3-hydroxypiperidin-2-yl)propyl)-1H-benzo[d]imidazol-7-yl)thiophene-2-carboxylate,
- 30 112) (2R,3S)-2-(3-(5-chloro-7-(1-(2-fluoroethyl)-1H-pyrazol-4-yl)-1H-

- benzo[d]imidazol-1-yl)propyl)piperidin-3-ol,
- 113) (2R,3S)-2-(3-(7-(1-butyl-1H-pyrazol-4-yl)-5-chloro-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol,
- 114) (2R,3S)-2-(3-(5-chloro-7-(2,5-dimethylthiophen-3-yl)-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol,
- 5 115) (2R,3S)-2-(3-(5-chloro-7-(1-isobutyl-1H-pyrazol-4-yl)-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol,
- 116) ethyl 4-(5-chloro-1-(3-((2R,3S)-3-hydroxypiperidin-2-yl)propyl)-1H-benzo[d]imidazol-7-yl)-1-methyl-1H-pyrrole-2-carboxylate,
- 10 117) (2R,3S)-2-(3-(5-chloro-1H-imidazo[4,5-b]pyridin-1-yl)propyl)piperidin-3-ol,
- 118) (2R,3S)-2-(3-(5-chloro-3H-imidazo[4,5-b]pyridin-3-yl)propyl)piperidin-3-ol,
- 119) (2R,3S)-2-(3-(5-bromo-1H-imidazo[4,5-b]pyridin-1-yl)propyl)piperidin-3-ol,
- 120) (2R,3S)-2-(3-(6-bromo-1H-imidazo[4,5-b]pyridin-1-yl)propyl)piperidin-3-ol,
- 121) (2R,3S)-2-(3-(5-methyl-1H-imidazo[4,5-b]pyridin-1-yl)propyl)piperidin-3-ol,
- 15 122) (2R,3S)-2-(3-(6-chloro-1H-imidazo[4,5-c]pyridin-1-yl)propyl)piperidin-3-ol,
- 123) (2R,3S)-2-(3-(6-chloro-3H-imidazo[4,5-c]pyridin-3-yl)propyl)piperidin-3-ol,
- 124) (2R,3S)-2-(3-(6-bromo-1H-imidazo[4,5-c]pyridin-1-yl)propyl)piperidin-3-ol,
- 125) (2R,3S)-2-(3-(6-bromo-3H-imidazo[4,5-c]pyridin-3-yl)propyl)piperidin-3-ol,
- 126) (2R,3S)-2-(3-(7-chloro-1H-imidazo[4,5-b]pyridin-1-yl)propyl)piperidin-3-ol,
- 20 127) (2R,3S)-2-(3-(5,6-dichloro-1H-imidazo[4,5-b]pyridin-1-yl)propyl)piperidin-3-ol,
- 128) (2R,3S)-2-(3-(7-bromo-1H-imidazo[4,5-c]pyridin-1-yl)propyl)piperidin-3-ol,
- 129) (2R,3S)-2-(3-(5-(trifluoromethyl)-3H-imidazo[4,5-b]pyridin-3-yl)propyl)piperidin-3-ol,
- 130) (2R,3S)-2-(3-(6,7-dichloro-3H-imidazo[4,5-b]pyridin-3-yl)propyl)piperidin-3-ol,
- 25 131) (2R,3S)-2-(3-(6-chloro-7-methyl-3H-imidazo[4,5-b]pyridin-3-yl)propyl)piperidin-3-ol,
- 132) (2R,3S)-2-(3-(6-bromo-7-methyl-3H-imidazo[4,5-b]pyridin-3-yl)propyl)piperidin-3-ol,
- 133) (2R,3S)-2-(3-(6-bromo-7-chloro-3H-imidazo[4,5-b]pyridin-3-yl)propyl)piperidin-3-ol,
- 30

- 134) (2R,3S)-2-(3-(7-chloro-6-(3-chlorophenyl)-3H-imidazo[4,5-b]pyridin-3-yl)propyl)piperidin-3-ol,
- 135) (2R,3S)-2-(3-(2-chloro-7H-purin-7-yl)propyl)piperidin-3-ol,
- 136) (2R,3S)-2-(3-(2-chloro-9H-purin-9-yl)propyl)piperidin-3-ol,
- 5 137) (2R,3S)-2-(3-(6-(dimethylamino)-9H-purin-9-yl)propyl)piperidin-3-ol,
- 138) (2R,3S)-2-(3-(6-(diethylamino)-9H-purin-9-yl)propyl)piperidin-3-ol,
- 139) (2R,3S)-2-(3-(6-(ethyl(methyl)amino)-9H-purin-9-yl)propyl)piperidin-3-ol,
- 140) (2R,3S)-2-(3-(6-morpholino-9H-purin-9-yl)propyl)piperidin-3-ol,
- 141) (2R,3S)-2-(3-(6-(piperidin-1-yl)-9H-purin-9-yl)propyl)piperidin-3-ol,
- 10 142) (2R,3S)-2-(3-(6-(pyrrolidin-1-yl)-9H-purin-9-yl)propyl)piperidin-3-ol,
- 143) 1-(3-((2R,3S)-3-hydroxypiperidin-2-yl)propyl)-1H-benzo[d]imidazol-2-ol,
- 144) 5,6-dichloro-1-(3-((2R,3S)-3-hydroxypiperidin-2-yl)propyl)-1H-benzo[d]imidazol-2-ol,
- 145) (2R,3S)-2-(3-(2-(hydroxymethyl)-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol,
- 15 146) (2R,3S)-2-(3-(2-(hydroxymethyl)-4,5-dimethyl-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol,
- 147) (2R,3S)-2-(3-(5,6-dichloro-2-(hydroxymethyl)-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol,
- 20 148) (2R,3S)-2-(3-(2-amino-5,6-dichloro-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol,
- 149) methyl 7-bromo-1-(3-((2R,3S)-3-hydroxypiperidin-2-yl)propyl)-1H-indole-3-carboxylate,
- 150) methyl 5-bromo-1-(3-((2R,3S)-3-hydroxypiperidin-2-yl)propyl)-1H-indole-3-carboxylate,
- 25 151) methyl 6-bromo-1-(3-((2R,3S)-3-hydroxypiperidin-2-yl)propyl)-1H-indole-3-carboxylate,
- 152) methyl 4-chloro-1-(3-((2R,3S)-3-hydroxypiperidin-2-yl)propyl)-1H-indole-3-carboxylate,
- 30 153) methyl 6-chloro-1-(3-((2R,3S)-3-hydroxypiperidin-2-yl)propyl)-1H-indole-3-

- carboxylate,
- 154) methyl 7-chloro-1-(3-((2R,3S)-3-hydroxypiperidin-2-yl)propyl)-1H-indole-3-carboxylate,
- 155) (2R,3S)-2-(3-(5-chloro-3-cyclopropyl-1H-indazol-1-yl)propyl)piperidin-3-ol,
- 5 156) (2R,3S)-2-(3-(5-chloro-3-(trifluoromethyl)-1H-indazol-1-yl)propyl)piperidin-3-ol,
- 157) (2R,3S)-2-(3-(5-chloro-3-(1-(difluoromethyl)-1H-pyrazol-4-yl)-1H-indazol-1-yl)propyl)piperidin-3-ol,
- 158) (2R,3S)-2-(3-(6-chloro-3-(1-(difluoromethyl)-1H-pyrazol-4-yl)-1H-indazol-1-yl)propyl)piperidin-3-ol,
- 10 159) 1-(3-((2R,3S)-3-hydroxypiperidin-2-yl)propyl)-3-methyl-1H-benzo[d]imidazol-2(3H)-one,
- 160) 5-bromo-1-(3-((2R,3S)-3-hydroxypiperidin-2-yl)propyl)-1H-benzo[d]imidazol-2(3H)-one,
- 15 161) 6-bromo-1-(3-((2R,3S)-3-hydroxypiperidin-2-yl)propyl)-1H-benzo[d]imidazol-2(3H)-one,
- 162) 7-(3-((2R,3S)-3-hydroxypiperidin-2-yl)propyl)-1,3-dimethyl-1H-purine-2,6(3H,7H)-dione,
- 163) 7-(3-((2R,3S)-3-hydroxypiperidin-2-yl)propyl)-3-methyl-1H-purine-2,6(3H,7H)-dione,
- 20 164) 9-(3-((2R,3S)-3-hydroxypiperidin-2-yl)propyl)-1-methyl-1H-purine-2,6(3H,9H)-dione,
- 165) 7-(3-((2R,3S)-3-hydroxypiperidin-2-yl)propyl)-3-isobutyl-1-methyl-1H-purine-2,6(3H,7H)-dione,
- 25 166) (2R,3S)-2-((E)-3-(5,6-dichloro-1H-benzo[d]imidazol-1-yl)prop-1-enyl)piperidin-3-ol,
- 167) (2R,3S)-2-((E)-3-(5-fluoro-4-methyl-1H-benzo[d]imidazol-1-yl)prop-1-enyl)piperidin-3-ol,
- 168) (2R,3S)-2-((E)-3-(5-bromo-4-methyl-1H-benzo[d]imidazol-1-yl)prop-1-enyl)piperidin-3-ol,
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- 169) (2R,3S)-2-((E)-3-(5,6-dimethyl-1H-benzo[d]imidazol-1-yl)prop-1-en-1-yl)piperidin-3-ol,
- 170) (2R,3S)-2-((E)-3-(5,6-dibromo-1H-benzo[d]imidazol-1-yl)prop-1-en-1-yl)piperidin-3-ol,
- 5 171) (2R,3S)-2-((E)-3-(5,6-difluoro-1H-benzo[d]imidazol-1-yl)prop-1-en-1-yl)piperidin-3-ol,
- 172) (2R,3S)-2-((E)-3-(4,5-dimethyl-1H-benzo[d]imidazol-1-yl)prop-1-en-1-yl)piperidin-3-ol,
- 173) (2R,3S)-2-((E)-3-(5-chloro-4-methyl-1H-benzo[d]imidazol-1-yl)prop-1-en-1-yl)piperidin-3-ol,
- 10 174) (2R,3S)-2-((E)-3-(4,5-dichloro-1H-benzo[d]imidazol-1-yl)prop-1-en-1-yl)piperidin-3-ol,
- 175) (2R,3S)-2-((E)-3-(4-chloro-5-methyl-1H-benzo[d]imidazol-1-yl)prop-1-en-1-yl)piperidin-3-ol,
- 15 176) (2R,3S)-2-((E)-3-(5-bromo-4-nitro-1H-benzo[d]imidazol-1-yl)prop-1-en-1-yl)piperidin-3-ol,
- 177) (2R,3S)-2-((E)-3-(6-bromo-7-nitro-1H-benzo[d]imidazol-1-yl)prop-1-en-1-yl)piperidin-3-ol,
- 178) (2R,3S)-2-((E)-3-(4-chloro-5-nitro-1H-benzo[d]imidazol-1-yl)prop-1-en-1-yl)piperidin-3-ol,
- 20 179) (2R,3S)-2-((E)-3-(4,6-difluoro-1H-benzo[d]imidazol-1-yl)prop-1-en-1-yl)piperidin-3-ol,
- 180) (2R,3S)-2-((E)-3-(6-chloro-4-methyl-1H-benzo[d]imidazol-1-yl)prop-1-en-1-yl)piperidin-3-ol,
- 25 181) (2R,3S)-2-((E)-3-(7-chloro-5-(trifluoromethyl)-1H-benzo[d]imidazol-1-yl)prop-1-en-1-yl)piperidin-3-ol,
- 182) (2R,3S)-2-((E)-3-(5,7-dichloro-1H-benzo[d]imidazol-1-yl)prop-1-en-1-yl)piperidin-3-ol,
- 183) (2R,3S)-2-((E)-3-(5-chloro-7-fluoro-1H-benzo[d]imidazol-1-yl)prop-1-en-1-yl)piperidin-3-ol,
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- 184) (2R,3S)-2-((E)-3-(5-bromo-1H-imidazo[4,5-b]pyridin-1-yl)prop-1-enyl)piperidin-3-ol,
- 185) (2R,3S)-2-((E)-3-(7-chloro-6-(3-chlorophenyl)-3H-imidazo[4,5-b]pyridin-3-yl)prop-1-enyl)piperidin-3-ol,
- 5 186) (2R,3S)-2-((E)-3-(6-bromo-7-methyl-3H-imidazo[4,5-b]pyridin-3-yl)prop-1-enyl)piperidin-3-ol,
- 187) (2R,3S)-2-((E)-3-(6-bromo-7-chloro-3H-imidazo[4,5-b]pyridin-3-yl)prop-1-enyl)piperidin-3-ol,
- 188) (2R,3S)-2-((E)-3-(6-chloro-7-methyl-3H-imidazo[4,5-b]pyridin-3-yl)prop-1-enyl)piperidin-3-ol,
- 10 189) (2R,3S)-2-((E)-3-(6,7-dichloro-3H-imidazo[4,5-b]pyridin-3-yl)prop-1-enyl)piperidin-3-ol,
- 190) (2R,3S)-2-((E)-3-(6-(3-chlorophenyl)-1H-benzo[d]imidazol-1-yl)prop-1-enyl)piperidin-3-ol,
- 15 191) (2R,3S)-2-((E)-3-(6-(3-fluorophenyl)-1H-benzo[d]imidazol-1-yl)prop-1-enyl)piperidin-3-ol,
- 192) (2R,3S)-2-((E)-3-(6-(3-(trifluoromethyl)phenyl)-1H-benzo[d]imidazol-1-yl)prop-1-enyl)piperidin-3-ol,
- 193) (2R,3S)-2-((E)-3-(5-bromo-6,7-difluoro-2-methyl-1H-benzo[d]imidazol-1-yl)prop-1-enyl)piperidin-3-ol,
- 20 194) (2R,3S)-2-((E)-3-(indolin-1-yl)prop-1-enyl)piperidin-3-ol,
- 195) (2R,3S)-2-((E)-3-(5-chloroindolin-1-yl)prop-1-enyl)piperidin-3-ol,
- 196) (2R,3S)-2-((E)-3-(1H-pyrrolo[2,3-b]pyridin-1-yl)prop-1-enyl)piperidin-3-ol,
- 197) (2R,3S)-2-((E)-3-(6-chloro-1H-indol-1-yl)prop-1-enyl)piperidin-3-ol,
- 25 198) (2R,3S)-2-((E)-3-(6-chloro-1H-indazol-1-yl)prop-1-enyl)piperidin-3-ol,
- 199) (2R,3S)-2-((E)-3-(4-chloro-7H-pyrrolo[2,3-d]pyrimidin-7-yl)prop-1-enyl)piperidin-3-ol,
- 200) (2R,3S)-2-((E)-3-(5-chloro-1H-pyrazolo[3,4-b]pyridin-1-yl)prop-1-enyl)piperidin-3-ol,
- 30 201) (2R,3S)-2-((E)-3-(3,5-dimethyl-1H-indazol-1-yl)prop-1-enyl)piperidin-3-ol,

- 202) methyl 7-bromo-1-((E)-3-((2R,3S)-3-hydroxypiperidin-2-yl)allyl)-1H-indole-3-carboxylate,
- 203) 7-bromo-1-((E)-3-((2R,3S)-3-hydroxypiperidin-2-yl)allyl)-1H-indole-3-carboxylic acid,
- 5 204) 5-bromo-1-((E)-3-((2R,3S)-3-hydroxypiperidin-2-yl)allyl)-1H-indole-3-carboxylic acid,
- 205) 4-chloro-1-((E)-3-((2R,3S)-3-hydroxypiperidin-2-yl)allyl)-1H-indole-3-carboxylic acid,
- 206) 6-chloro-1-((E)-3-((2R,3S)-3-hydroxypiperidin-2-yl)allyl)-1H-indole-3-
- 10 carboxylic acid,
- 207) 7-chloro-1-((E)-3-((2R,3S)-3-hydroxypiperidin-2-yl)allyl)-1H-indole-3-carboxylic acid,
- 208) 6-fluoro-1-((E)-3-((2R,3S)-3-hydroxypiperidin-2-yl)allyl)-1H-indole-3-carboxylic acid,
- 15 209) 1-((E)-3-((2R,3S)-3-hydroxypiperidin-2-yl)allyl)-1H-indole-3-carboxylic acid,
- 210) methyl 4-chloro-1-((E)-3-((2R,3S)-3-hydroxypiperidin-2-yl)allyl)-1H-indole-3-carboxylate,
- 211) methyl 6-chloro-1-((E)-3-((2R,3S)-3-hydroxypiperidin-2-yl)allyl)-1H-indole-3-carboxylate,
- 20 212) methyl 7-chloro-1-((E)-3-((2R,3S)-3-hydroxypiperidin-2-yl)allyl)-1H-indole-3-carboxylate,
- 213) methyl 5-bromo-1-((E)-3-((2R,3S)-3-hydroxypiperidin-2-yl)allyl)-1H-indole-3-carboxylate,
- 214) methyl 6-bromo-1-((E)-3-((2R,3S)-3-hydroxypiperidin-2-yl)allyl)-1H-indole-3-
- 25 carboxylate,
- 215) 5-bromo-1-((E)-3-((2R,3S)-3-hydroxypiperidin-2-yl)allyl)-N-methyl-1H-indole-3-carboxamide,
- 216) 5-bromo-1-((E)-3-((2R,3S)-3-hydroxypiperidin-2-yl)allyl)-N,N-dimethyl-1H-indole-3-carboxamide,
- 30 217) (2R,3S)-2-((Z)-3-(5-chloro-4-methyl-1H-benzo[d]imidazol-1-yl)-2-fluoroprop-1-

- enyl)piperidin-3-ol,
- 218) (2R,3S)-2-((Z)-3-(5-bromo-4-methyl-1H-benzo[d]imidazol-1-yl)-2-fluoroprop-1-enyl)piperidin-3-ol,
- 219) (2R,3S)-2-((Z)-3-(5,6-dichloro-1H-benzo[d]imidazol-1-yl)-2-fluoroprop-1-enyl)piperidin-3-ol,
- 5 220) (2R,3S)-2-((Z)-3-(5,6-dichloro-2-(hydroxymethyl)-1H-benzo[d]imidazol-1-yl)-2-fluoroprop-1-enyl)piperidin-3-ol,
- 221) (2R,3S)-2-((E)-3-(5-chloro-4-methyl-1H-benzo[d]imidazol-1-yl)-2-methylprop-1-enyl)piperidin-3-ol,
- 10 222) (2R,3S)-2-((E)-3-(5-bromo-4-methyl-1H-benzo[d]imidazol-1-yl)-2-methylprop-1-enyl)piperidin-3-ol,
- 223) (2R,3S)-2-((E)-3-(5,6-dichloro-1H-benzo[d]imidazol-1-yl)-2-methylprop-1-enyl)piperidin-3-ol,
- 224) (2R,3S)-2-((E)-3-(5,6-dichloro-2-(hydroxymethyl)-1H-benzo[d]imidazol-1-yl)-2-methylprop-1-enyl)piperidin-3-ol,
- 15 225) (2R,3S)-2-(3-(5,6-dichloro-1H-benzo[d]imidazol-1-yl)prop-1-ynyl)piperidin-3-ol,
- 226) (2R,3S)-2-(3-(5-bromo-4-methyl-1H-benzo[d]imidazol-1-yl)prop-1-ynyl)piperidin-3-ol,
- 20 227) (2R,3S)-2-(3-(5-chloro-4-methyl-1H-benzo[d]imidazol-1-yl)prop-1-ynyl)piperidin-3-ol,
- 228) (2R,3S)-2-(3-(5,6-dibromo-1H-benzo[d]imidazol-1-yl)prop-1-ynyl)piperidin-3-ol,
- 229) (2R,3S)-2-(3-(5-fluoro-4-methyl-1H-benzo[d]imidazol-1-yl)prop-1-ynyl)piperidin-3-ol, and
- 25 230) (2R,3S)-2-((E)-3-(5,6-dichloro-1H-benzo[d]imidazol-1-yl)prop-1-enyl)pyrrolidin-3-ol.

In addition, the compounds of the present invention may exist in the form of a pharmaceutically acceptable salt. As salt, an acid addition salt formed by a pharmaceutically

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acceptable free acid is useful. As the free acid, an inorganic acid and an organic acid may be used. Examples of the inorganic acid may include hydrochloric acid, bromic acid, sulfuric acid, phosphoric acid, and the like. Examples of the organic acid may include citric acid, acetic acid, lactic acid, maleic acid, gluconic acid, methanesulfonic acid, succinic acid, 4-toluene sulfonic acid,
5 glutamic acid, aspartic acid or the like.

Salts or solvates of the compounds represented by Chemical Formula 1 that are pharmaceutically not acceptable can be used as intermediates in the preparation of the compound represented by Chemical Formula 1, a pharmaceutically acceptable salt or solvate thereof.

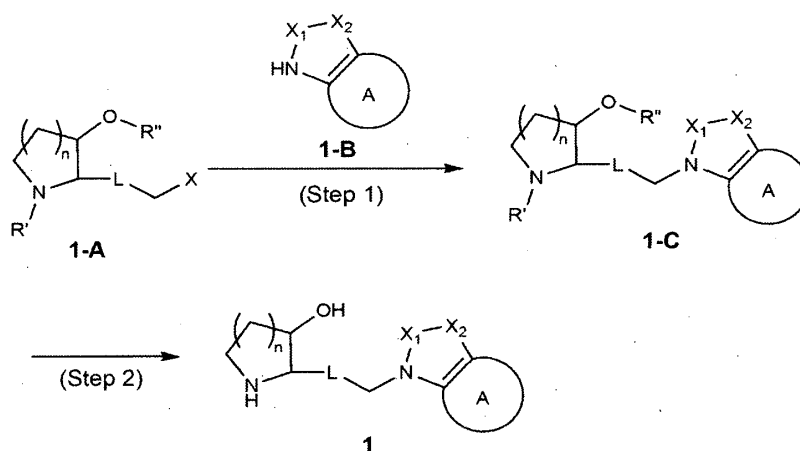
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The compound represented by Chemical Formula 1 according to the present invention includes pharmaceutically acceptable salts thereof as well as both solvates and hydrates which can be prepared therefrom. The salts or solvates of the compound represented by Chemical Formula 1 can be prepared from the compounds represented by Chemical Formula 1 using conventional
15 methods in the technical field to which the present invention pertains.

Further, the compound represented by Chemical Formula 1 according to the present invention can be prepared in crystalline form or non-crystalline form. When the compound represented by Chemical Formula 1 is produced in crystalline form, it may be optionally hydrated
20 or solvated. The present invention may include not only stoichiometric hydrates of the compound represented by Chemical Formula 1 but also compounds containing a various amount of water. The solvates of the compound represented by Chemical Formula 1 according to the present invention include both stoichiometric solvates and non-stoichiometric solvates.

25 The present invention also provides a method for preparing a compound represented by Chemical Formula 1 as shown in the following Reaction Scheme 1:

[Reaction Scheme 1]



(in Reaction Scheme 1, n , L , X_1 , X_2 and A are as previously defined, X is halogen (preferably bromo), and R' and R'' means each independently a protecting group. The protecting group can be *tert*-butyldimethylsilyl, or *tert*-butyloxycarbonyl.)

5

The step 1 is a step of preparing a compound represented by Chemical Formula 1-C by reacting a compound represented by Chemical Formula 1-A with a compound represented by Chemical Formula 1-B in the presence of a base. Conventional inorganic bases and organic bases can be used as the base. Non-limiting examples of the organic bases may include diisopropylethylamine or triethylamine. Non-limiting examples of the inorganic bases may include potassium carbonate, sodium carbonate, sodium hydrogen carbonate, cesium carbonate, or calcium carbonate. Further, the reaction may be carried out in a polar solvent such as methanol, ethanol, butanol, tetrahydrofuran, acetone, toluene, dimethylformamide, dimethylformsulfoxide, chloroform, dioxane, acetonitrile diethyl ether, or dichloromethane at 20°C to 150°C for 10 minutes to 24 hours.

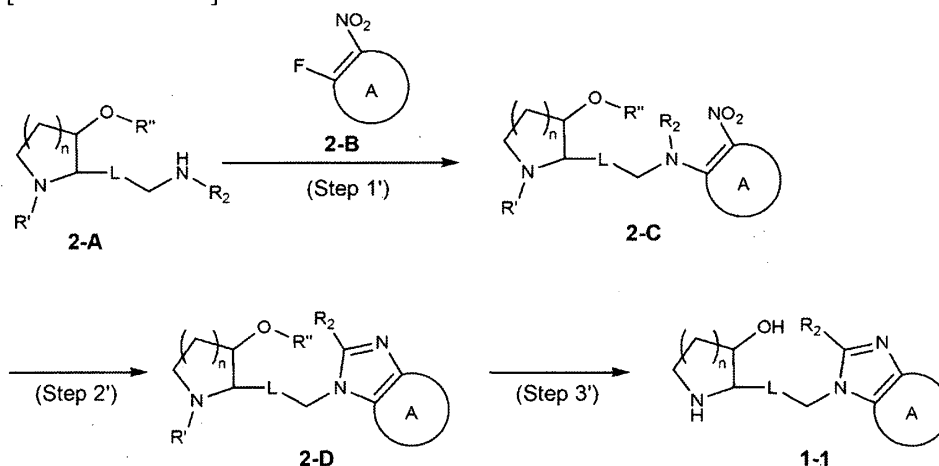
The step 2 is a step of preparing a compound represented by Chemical Formula 1 by reacting a compound represented by Chemical Formula 1-C in the presence of an acid. Non-limiting examples of the acid may include hydrochloric acid, bromic acid, hydrofluoric acid, trifluoroacetic acid or the like. Preferably, the reaction solvent may or may not use a polar organic solvent. Preferably, when using a polar organic solvent, dichloromethane, chloroform, toluene, dimethylformamide, dioxane, tetrahydrofuran or the like may be used, and the reaction can be

carried out at 20°C to 100°C for 10 minutes to 6 hours.

As another example, the compound represented by Chemical Formula 1-1 can be prepared as shown in the following Reaction Scheme 2:

5

[Reaction Scheme 2]



(in Reaction Scheme 2, n , L , R_2 , and A are as previously defined, and R' and R'' means each independently a protecting group. The protecting group can be *tert*-butyldimethylsilyl, or *tert*-butoxycarbonyl.)

10

The step 1' is a step of preparing a compound represented by Chemical Formula 2-C by reacting a compound represented by Chemical Formula 2-A with a compound represented by Chemical Formula 2-B in the presence of a base. Conventional inorganic bases and organic bases can be used as the base. Non-limiting examples of the organic bases may include diisopropylethylamine or triethylamine. Non-limiting examples of the inorganic bases may include potassium carbonate, sodium carbonate, sodium hydrogen carbonate, cesium carbonate, or calcium carbonate. Further, the reaction may be carried out in a polar solvent such as methanol, ethanol, butanol, tetrahydrofuran, acetone, toluene, dimethylformamide, dimethylformsulfoxide, chloroform, dioxane, acetonitrile diethyl ether, or dichloromethane at 20°C to 150°C for 10 minutes to 24 hours.

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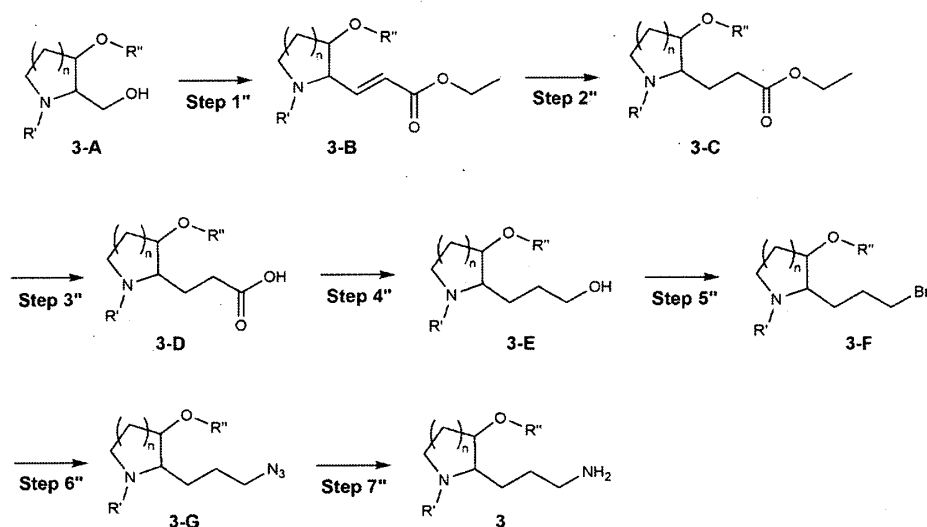
The step 2' is a step of preparing a compound represented by Chemical Formula 2-D by

reacting an amine group and a nitro group of the compound represented by Chemical Formula 2-C to form a ring. The above step is carried out substantially in two stages. First, a compound represented by Chemical Formula 2-C is reacted with hydrogen in the presence of Raney nickel and then reacted with trimethyl orthoformate. The former reaction is carried out in a polar solvent
5 such as methanol, ethanol, butanol, tetrahydrofuran, acetone, toluene, dimethylformamide, dimethylformsulfoxide, chloroform, dioxane, acetonitrile diethyl ether, or dichloromethane at 20°C to 150°C for 10 minutes to 24 hours. The latter reaction is preferably carried out in the presence of para-toluene sulfonic acid, and the reaction may be carried out in a polar solvent such as methanol, ethanol, butanol, tetrahydrofuran, acetone, toluene, dimethylformamide,
10 dimethylformsulfoxide, chloroform, dioxane, acetonitrile diethyl ether, or dichloromethane at 20°C to 150°C for 10 minutes to 24 hours.

The step 3' is a step of preparing a compound represented by Chemical Formula 1-1 by reacting a compound represented by Chemical Formula 2-D in the presence of an acid. The
15 specific reaction conditions of the step 3' can be applied similarly to the reaction conditions of the step 2 of Reaction Scheme 1 described above.

Further, as an example, among the compounds of Chemical Formula 2-A shown in Reaction Scheme 2, a compound where L is ethylene and R₂ is hydrogen (a compound
20 represented by the following Chemical Formula 3) can be prepared by a method as shown in the following Reaction Scheme 3:

[Reaction Scheme 3]



(in Reaction Scheme 3, n is as previously defined, and R' and R'' means each independently a protecting group. The protecting group can be tert-butyldimethylsilyl, or tert-butyloxycarbonyl.)

5

The step 1'' is a step of preparing a compound represented by Chemical Formula 3-B by reacting the compound represented by Chemical Formula 3-A with (carbethoxymethylene) triphenylphosphorane. Preferably, the compound represented by Chemical Formula 3-A is first reacted with oxalyl chloride and then reacted with triphenylphosphorane. The former reaction is preferably carried out in the presence of methylene chloride, N,N -dimethylsulfoxide, and triethylamine. The former reaction may also be carried out at -78°C to 20°C for 10 minutes to 12 hours. Further, in the reaction with triphenylphosphorane, dichloromethane may be used as the solvent, and the reaction can be carried out at 20°C to 150°C for 10 minutes to 24 hours.

The step 2'' is a step of preparing a compound represented by Chemical Formula 3-C by hydrogenating the compound represented by Chemical Formula 3-B. Preferably, the reaction is carried out in the presence of hydrogen and a hydrogenation catalyst (e.g., palladium hydroxide). In addition, tetrahydrofuran can be used as a solvent for the reaction. Further, the reaction can be carried out at 20°C to 150°C for 10 minutes to 24 hours.

20

The step 3'' is a step of preparing a compound represented by Chemical Formula 3-D by

hydrolyzing the compound represented by Chemical Formula 3-C. Preferably, the reaction can be carried out under a basic condition, and sodium hydroxide may be used as the base. In addition, water or methanol may be used as a solvent for the reaction. Further, the reaction can be carried out at 20°C to 150°C for 10 minutes to 24 hours.

5

The step 4'' is a step of preparing a compound represented by Chemical Formula 3-E by subjecting the compound represented by Chemical Formula 3-D to a carbonyl reduction reaction. Preferably, the reaction may be carried out in the presence of lithium aluminum hydride. In addition, tetrahydrofuran can be used as a solvent for the reaction. Further, the reaction can be carried out at -78°C to 20°C for 10 minutes to 12 hours.

10

The step 5'' is a step of preparing a compound represented by Chemical Formula 3-F by brominating the compound represented by Chemical Formula 3-E. Preferably, the reaction is carried out in the presence of triphenylphosphine and tetrabromomethane. In addition, methylene chloride can be used as a solvent for the reaction. Further, the reaction may be carried out at 20°C to 150°C for 10 minutes to 24 hours.

15

The step 6'' is a step of preparing a compound represented by Chemical Formula 3-G by subjecting the compound represented by Chemical Formula 3-F to an azide reaction. Preferably, the reaction is carried out in the presence of sodium azide. In addition, N,N-dimethylformamide can be used as a solvent for the reaction. Further, the reaction may be carried out at 20°C to 150°C for 10 minutes to 24 hours.

20

The step 7'' is a step of preparing a compound represented by Chemical Formula 3 by aminating the compound represented by Chemical Formula 3-G. Preferably, the reaction is carried out in the presence of triphenylphosphine. In addition, tetrahydrofuran can be used as a solvent for the reaction. Further, the reaction can be carried out at 20°C to 150°C for 10 minutes to 24 hours.

25

Further, the present invention provides a pharmaceutical composition for the prevention or treatment of diseases caused by abnormality in a PRS (prolyl-tRNA synthetase) activity,

30

comprising a compound represented by Chemical Formula 1 or a pharmaceutically acceptable salt thereof.

The compound represented by Chemical Formula 1 according to the present invention
5 can inhibit PRS enzymatic activity and thus can be used for the prevention or treatment of diseases caused by abnormality in a PRS (prolyl-tRNA synthetase) activity. Examples of diseases caused by abnormality in the PRS (prolyl-tRNA synthetase) activity may include a cancer, an inflammatory disease, an autoimmune disease and a fibrosis.

10 As shown in Examples which will be described below, the compound represented by Chemical Formula 1 according to the present invention can significantly inhibit PRS enzymatic activity and also inhibit the growth of cancer cells. Thus, this compound may be effectively used for the prevention or treatment of the diseases.

15 The pharmaceutical composition according to the present invention can be formulated in types for oral or parenteral administrations according to a standard pharmaceutical practice. These formulations may contain additives such as pharmaceutically acceptable carrier, adjuvant or diluent in addition to the active ingredient. Suitable carriers may include, for example, physiological saline, polyethylene glycol, ethanol, vegetable oil, and isopropyl myristate, and the
20 diluent may include, for example, lactose, dextrose, sucrose, mannitol, sorbitol, cellulose and/or glycine, but are not limited thereto. Further, the compounds of the present invention can be dissolved in oils, propylene glycol or other solvents which are usually used for the preparation of injectable solutions. In addition, the compounds of the present invention may be formulated as ointments or creams for topical application.

25 A preferred dose of the compound represented by Chemical Formula 1 according to the present invention may be varied depending on the condition and weight of a patient, the severity of a disease, the type of a drug, and the route and duration of administration, but it may be suitably selected by those skilled in the art. In order to achieve the desirable effects, however, the
30 compound represented by Chemical Formula 1 according to the present invention may be

administered daily at a dose of 0.0001 to 100 mg/kg (body weight), and preferably 0.001 to 100 mg/kg (body weight). The administration may be performed once a day or in divided doses each day through an oral or parenteral route.

5 Depending on the method of administration, the pharmaceutical composition according to the present invention may contain the compound represented by Chemical Formula 1 or a pharmaceutically acceptable salt thereof in an amount of 0.001 to 99% by weight, preferably 0.01 to 60% by weight

10 The pharmaceutical composition according to the present invention may be administered to mammals such as a rat, a mouse, a domestic animal, a human or the like, through various routes. The administration may be carried out through all possible methods, for example, oral, rectal, intravenous, intramuscular, subcutaneous, intra-endometrial, intracerebroventricular injection.

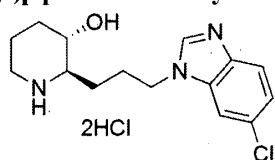
15 **ADVANTAGEOUS EFFECTS**

The compound represented by Chemical Formula 1 according to the present invention can inhibit PRS enzymatic activity and thus may be effectively used for the prevention or treatment of diseases caused by abnormality in a PRS (prolyl-tRNA synthetase) activity, for example, cancers, inflammatory diseases, autoimmune diseases and fibrosis.

20 **DETAILED DESCRIPTION OF THE EMBODIMENTS**

Below, the present invention will be described in more detail by way of examples. However, these examples are provided only for illustration of the present invention, and should not be construed as limiting the scope of the present invention to these examples.

25 **Example 1: Preparation of (2R,3S)-2-(3-(6-chloro-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol dihydrochloride**



Step 1-1: Preparation of tert-butyl (2R,3S)-3-((tert-butyldimethylsilyl)oxy)-2-(E)-3-

ethoxy-3-oxoprop-1-en-1-yl)piperidine-1-carboxylate

Methylene chloride (47 mL, 0.12 M) and oxalyl chloride (1.0 mL, 11.6 mmol) were added to a flask filled with nitrogen and the reaction solution was cooled to -78°C. N,N-dimethylsulfoxide (1.7 mL, 23.2 mmol) was then added at the same temperature and stirred for 30 minutes. Then, tert-butyl (2R,3S)-3-((tert-butyldimethylsilyl)oxy)-2-(hydroxymethyl)piperidine-1-carboxylate (2.0 g, 5.8 mmol) was dissolved in a small amount of methylene chloride and slowly added. After stirring at the same temperature for 1 hour, triethylamine (3.3 mL, 23.2 mmol) was added and the temperature of the reaction solution was raised to room temperature from -78°C. When the reaction was completed, the solvent was removed, and the resulting mixture was diluted with ethyl acetate and washed with saturated sodium chloride solution. The organic layer was collected, dried with magnesium sulfate, filtered and concentrated under reduced pressure, and then dissolved in methylene chloride (47 mL, 0.12 M). (Carbethoxymethylene)triphenylphosphorane (4.0 g, 11.6 mmol) was added thereto at room temperature and stirred for 2 hours. When the reaction was completed, the solvent was removed, and the resulting mixture was diluted with ethyl acetate and washed with saturated sodium chloride solution. The organic layer was collected, dried over magnesium sulfate, filtered and concentrated under reduced pressure, and then purified by column chromatography (hexane: ethyl acetate = 4:1) to give the title compound (2.1 g, 89% yield over two steps).

Step 1-2: Preparation of tert-butyl (2R,3S)-3-((tert-butyldimethylsilyl)oxy)-2-(3-ethoxy-3-oxopropyl)piperidine-1-carboxylate

Tert-butyl (2R,3S)-3-((tert-butyldimethylsilyl)oxy)-2-(E)-3-ethoxy-3-oxoprop-1-en-1-yl)piperidine-1-carboxylate (3.2 g, 7.7 mmol) obtained from Step 1-1 was dissolved in tetrahydrofuran (50 mL, 0.15 M), and then palladium hydroxide (104 mg, 0.77 mmol) was added thereto. After connection a hydrogen balloon, the mixture was stirred at room temperature for 5 hours. When the reaction was completed, the reaction solution was filtered through celite and concentrated under reduced pressure. Subsequent reactions were carried out without purification procedure.

Step 1-3: Preparation of 3-((2R,3S)-1-(tert-butoxycarbonyl)-3-(tert-

butyldimethylsilyl)oxy)piperidin-2-yl)propenoic acid

Tert-butyl (2R,3S)-3-((tert-butyldimethylsilyl)oxy)-2-(3-ethoxy-3-oxopropyl)piperidine-1-carboxylate (3.0 g, 7.2 mmol) obtained from Step 1-2 was dissolved in methanol (20 mL, 0.36 M), and then 2N aqueous sodium hydroxide solution (10 mL) was added thereto and stirred at room temperature for 3 hours. When the reaction was completed, the reaction solution was neutralized with 1N aqueous hydrochloric acid solution, acidified and then diluted with ethyl acetate, and washed with saturated sodium chloride solution. The organic layer was collected, dried over magnesium sulfate, filtered and concentrated under reduced pressure. Subsequent reactions were carried out without purification procedure.

10

Step 1-4: Preparation of tert-butyl (2R,3S)-3-((tert-butyldimethylsilyl)oxy)-2-(3-hydroxypropyl)piperidine-1-carboxylate

3-((2R,3S)-1-(tert-butoxycarbonyl)-3-(tert-butyldimethylsilyl)oxy)piperidin-2-yl)propenoic acid (1.6 g, 4.0 mmol) obtained from Step 1-1 was dissolved in tetrahydrofuran (50 mL, 0.08 M), and the reaction solution was cooled to 0°C. Then, a lithium aluminum hydride solution (1.6 mL, 4.0 mmol) was slowly added thereto, reacted at the same temperature for 30 minutes and then stirred at room temperature for 2 hours. A small amount of water was added to complete the reaction, diluted with ethyl acetate and washed with saturated sodium chloride solution. The organic layer was collected, dried over magnesium sulfate, filtered and concentrated under reduced pressure, and then purified by column chromatography (dichloromethane: methanol = 10:1) to give the title compound (1.3 g, yield: 85%).

20

Step 1-5: Preparation of tert-butyl (2R,3S)-2-(3-bromopropyl)-3-((tert-butyldimethylsilyl)oxy)piperidine-1-carboxylate

Tert-butyl (2R,3S)-3-((tert-butyldimethylsilyl)oxy)-2-(3-hydroxypropyl)piperidine-1-carboxylate (5.1 g, 13.8 mmol) obtained from Step 1-4 was added to methylene chloride (100 mL, 0.14 M). The reaction solution was cooled to 0°C, and then triphenylphosphine (4.3 g, 16.5 mmol) and tetrabromomethane (5.5 g, 16.5 mmol) were sequentially added at the same temperature, followed by stirring at room temperature for 2 hours. When the reaction was completed, the solvent was removed, and the resulting mixture was diluted with ethyl acetate and washed with

30

saturated sodium chloride solution. The organic layer was collected, dried over magnesium sulfate, filtered and then concentrated under reduced pressure, and purified by column chromatography (hexane: ethyl acetate = 5:1) to give the title compound (4.6 g, yield: 76%).

5 Step 1-6: Preparation of tert-butyl (2R,3S)-2-(3-azidopropyl)-3-((tert-butyl dimethylsilyl)oxy)piperidine-1-carboxylate

Tert-butyl (2R,3S)-2-(3-bromopropyl)-3-((tert-butyl dimethylsilyl)oxy)piperidine-1-carboxylate (7.4 g, 17.0 mmol) obtained from Step 1-5 was dissolved in N,N-dimethylformamide (25 mL, 0.67 M). Then, sodium azide (3.3 g, 17.0 mmol) was added thereto and the mixture was
10 stirred at room temperature for 4 hours. When the reaction was completed, the solvent was removed, and the resulting mixture was diluted with ethyl acetate and washed with saturated sodium chloride solution. The organic layer was collected, dried over sodium sulfate, filtered and then concentrated under reduced pressure, and purified by column chromatography (hexane: ethyl acetate = 7:1) to give the title compound (5.8 g, yield 85%).

15

Step 1-7: Preparation of tert-butyl (2R,3S)-2-(3-aminopropyl)-3-((tert-butyl dimethylsilyl)oxy)piperidine-1-carboxylate

Tert-butyl (2R,3S)-2-(3-azidopropyl)-3-((tert-butyl dimethylsilyl)oxy)piperidine-1-carboxylate (5.5 g, 13.8 mmol) obtained from Step 1-6 was dissolved in tetrahydrofuran (24 mL,
20 0.57 M), and then triphenylphosphine (4.3 g, 16.5 mmol) was added thereto and stirred at room temperature for 30 minutes. Then, water (24 mL, 0.57 M) was added thereto and stirred at room temperature for 1 hour. When the reaction was completed, the resulting mixture was diluted with ethyl acetate and washed with saturated sodium chloride solution. The organic layer was collected, dried over sodium sulfate, filtered and then concentrated under reduced pressure, and purified by
25 column chromatography (dichloromethane: methanol= 10:1 + triethylamine 2%) to give the title compound (4.0 g, yield: 78%).

Step 1-8: Preparation of tert-butyl (2R,3S)-3-((tert-butyl dimethylsilyl)oxy)-2-(3-((4-chloro-2-nitrophenyl)amino)propyl)piperidine-1-carboxylate

30 Tert-butyl (2R,3S)-2-(3-aminopropyl)-3-((tert-butyl dimethylsilyl)oxy)piperidine-1-

carboxylate (1.0 g, 2.7 mmol) obtained from Step 1-7 was dissolved in N,N-dimethylformamide (25 mL, 0.67 M). 4-Chloro-2-fluoro-1-nitrobenzene (518 mg, 3.0 mmol) and N,N-diisopropyl ethylamine (0.93 mL, 5.4 mmol) were then added thereto, and the mixture was heated and stirred at 60°C for 2 hours. When the reaction was completed, the resulting mixture was diluted with ethyl acetate and washed with saturated sodium chloride solution. The organic layer was collected, dried over sodium sulfate, filtered and concentrated under reduced pressure, and and purified by column chromatography (hexane: ethyl acetate = 5:1) to give the title compound (1.2 g, yield: 87%).

Step 1-9: Preparation of tert-butyl (2R,3S)-3-((tert-butyldimethylsilyl)oxy)-2-(3-(5-chloro-1H-benzo[d]imidazol-1-yl)propyl)piperidine-1-carboxylate

Tert-butyl (2R,3S)-3-((tert-butyldimethylsilyl)oxy)-2-(3-((4-chloro-2-nitrophenyl)amino)propyl)piperidine-1-carboxylate (2.6 mg, 4.9 mmol) obtained from Step 1-8 was dissolved in methanol (25 mL, 0.2 M), and then an appropriate amount of Rainy nickel was added thereto. After connecting a hydrogen balloon, the mixture was stirred at room temperature for 1 hour. When the reaction was completed, the reaction solution was filtered through celite and concentrated under reduced pressure. Subsequent reactions were carried out without purification procedure. The concentrated compound was dissolved in toluene (30 mL, 0.16 M), and then trimethyl orthoformate (1.6 mL, 14.6 mmol) and paratoluene sulfonic acid (168 mg, 0.98 mmol) was added thereto, followed by heating and stirring at 50°C for 6 hours. When the reaction was completed, the solvent was removed, and the resulting mixture was diluted with ethyl acetate and washed with saturated sodium chloride solution. The organic layer was collected, dried over magnesium sulfate, filtered and concentrated under reduced pressure, and and purified by column chromatography (hexane: ethyl acetate = 1:1) to give the title compound (1.8 g, yield: 74%).

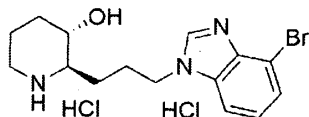
Step 1-10: Preparation of (2R,3S)-2-(3-(6-chloro-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol dihydrochloride

Tert-butyl (2R,3S)-3-((tert-butyldimethylsilyl)oxy)-2-(3-(5-chloro-1H-benzo[d]imidazol-1-yl)propyl)piperidine-1-carboxylate (1.8 g, 3.6 mmol) obtained from Step 1-9 was dissolved in a small amount of tetrahydrofuran. 4N hydrogen chloride dioxane solution (30

mL, 0.12 M) was then added thereto, and the mixture was stirred at room temperature for 12 hours. When the reaction was completed, the reaction solution was concentrated under reduced pressure to remove the solvent, dissolved by addition of a small amount of methanol, and then crystallized with diethyl ether to give the title compound (1.1 g, yield: 81%).

- 5 ¹H-NMR (500 MHz, MeOD) : δ 9.56 (s, 1H), 8.18 (d, 1H), 7.86 (d, 1H), 7.70 (dd, 1H), 4.58 (t, 2H), 3.58 (m, 2H), 2.99 (m, 2H), 2.21 (m, 2H), 2.07 (m, 2H), 1.97 (m, 1H), 1.75 (m, 2H), 1.58 (m, 1H)

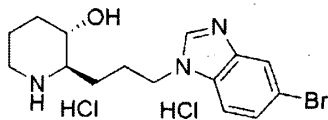
10 **Example 2: Preparation of (2R,3S)-2-(3-(4-bromo-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol dihydrochloride**



The title compound (15 mg, yield: 93%) was obtained in the same manner as in Example 1, with the exception that 1-bromo-3-fluoro-2-nitrobenzene was used instead of 4-chloro-2-fluoro-1-nitrobenzene in Step 1-8 of Example 1.

- 15 ¹H NMR (500MHz, MeOD): 9.63(s, 1H), 8.02(d, 1H), 7.86(d, 1H), 7.59(t, 1H), 4.61(t, 2H), 3.56(m, 2H), 3.46(m, 1H), 3.27(m, 1H), 2.95(m, 2H), 2.20(m, 2H), 2.03(m, 2H), 1.98(m, 1H), 1.78(m, 2H), 1.53(m, 1H)

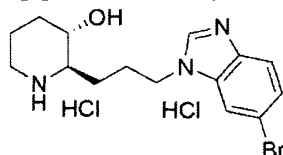
20 **Example 3: Preparation of (2R,3S)-2-(3-(5-bromo-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol dihydrochloride**



The title compound (13 mg, yield: 91%) was obtained in the same manner as in Example 1, with the exception that 4-bromo-1-fluoro-2-nitrobenzene was used instead of 4-chloro-2-fluoro-1-nitrobenzene in Step 1-8 of Example 1.

- 25 ¹H NMR (500MHz, MeOD): δ 9.53(s, 1H), 8.08(d, 1H), 7.98(d, 1H), 7.83(dd, 1H), 4.63(t, 2H), 3.74(t, 1H), 3.67(m, 1H), 3.58(m, 2H), 2.97(m, 2H), 2.30(m, 2H), 2.14(m, 2H), 2.02(m, 1H), 1.78(m, 2H), 1.55(m, 1H)

Example 4: Preparation of (2R,3S)-2-(3-(6-bromo-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol dihydrochloride

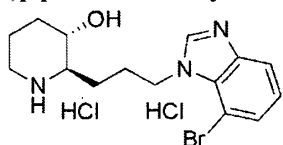


5 The title compound (10 mg, yield: 90%) was obtained in the same manner as in Example 1, with the exception that 4-bromo-2-fluoro-1-nitrobenzene was used instead of 4-chloro-2-fluoro-1-nitrobenzene in Step 1-8 of Example 1.

¹H NMR (500MHz, MeOD): 9.51(s, 1H), 8.32(s, 1H), 7.81(m, 2H), 4.59(t, 2H), 3.58(m, 1H), 2.97(m, 2H), 2.20(m, 2H), 2.12(m, 2H), 2.02(m, 1H), 1.79(m, 2H), 1.59(m, 1H)

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Example 5: Preparation of (2R,3S)-2-(3-(7-bromo-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol dihydrochloride

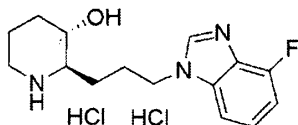


15 The title compound (14 mg, yield: 93%) was obtained in the same manner as in Example 1, with the exception that 1-bromo-2-fluoro-3-nitrobenzene was used instead of 4-chloro-2-fluoro-1-nitrobenzene in Step 1-8 of Example 1.

¹H NMR (500MHz, MeOD): 9.59(s, 1H), 7.89(dd, 2H), 7.56(t, 1H), 3.59(m, 1H), 2.98(m, 2H), 2.30(m, 2H), 2.13(m, 2H), 2.04(m, 1H), 1.79(m, 2H), 1.56(m, 1H)

20

Example 6: Preparation of (2R,3S)-2-(3-(4-fluoro-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol dihydrochloride



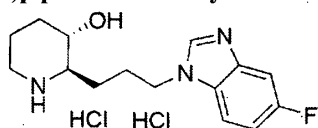
The title compound (13 mg, yield: 92%) was obtained in the same manner as in Example 1, with the exception that 1,3-difluoro-2-nitrobenzene was used instead of 4-chloro-2-fluoro-1-

nitrobenzene in Step 1-8 of Example 1.

¹H NMR (500MHz, MeOD): δ 9.52(s, 1H), 7.82(d, 1H), 7.65(m, 1H), 7.44(m, 1H), 4.61(t, 2H), 3.66(m, 1H), 3.58(m, 1H), 3.27(m, 1H), 2.97(m, 2H), 2.24(m, 2H), 2.08(m, 2H), 2.02(m, 1H), 1.75(m, 2H), 1.54(m, 1H)

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Example 7: Preparation of (2R,3S)-2-(3-(5-fluoro-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol dihydrochloride

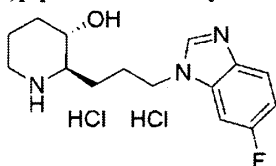


The title compound (11 mg, yield: 90%) was obtained in the same manner as in Example 1, with the exception that 1,4-difluoro-2-nitrobenzene was used instead of 4-chloro-2-fluoro-1-nitrobenzene in Step 1-8 of Example 1.

¹H NMR (500MHz, MeOD): δ 9.56(s, 1H), 8.07(m, 1H), 7.65(d, 1H), 7.50(t, 1H), 4.63(m, 2H), 3.58(m, 1H), 3.00(m, 2H), 2.24(m, 2H), 2.12(m, 2H), 2.02(m, 1H), 1.74(m, 2H), 1.54(m, 1H)

15

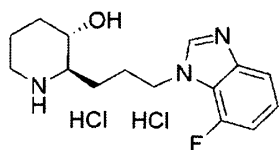
Example 8: Preparation of (2R,3S)-2-(3-(6-fluoro-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol dihydrochloride



The title compound (12 mg, yield: 91%) was obtained in the same manner as in Example 1, with the exception that 2,4-difluoro-1-nitrobenzene was used instead of 4-chloro-2-fluoro-1-nitrobenzene in Step 1-8 of Example 1.

¹H NMR (500MHz, MeOD): δ 9.56(s, 1H), 7.89(m, 2H), 7.48(t, 1H), 4.59(m, 2H), 3.57(m, 1H), 3.03(m, 2H), 2.29(m, 2H), 2.11(m, 2H), 2.03(m, 1H), 1.76(m, 2H), 1.54(m, 1H)

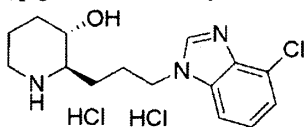
Example 9: Preparation of (2R,3S)-2-(3-(7-fluoro-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol dihydrochloride



The title compound (10 mg, yield: 90%) was obtained in the same manner as in Example 1, with the exception that 1,2-difluoro-3-nitrobenzene was used instead of 4-chloro-2-fluoro-1-nitrobenzene in Step 1-8 of Example 1.

¹H NMR (500MHz, MeOD): δ 9.57(s, 1H), 7.68(m, 1H), 7.63(m, 1H), 7.46(m, 1H), 4.69(t, 2H), 3.58(m, 1H), 3.25(m, 1H), 2.97(m, 2H), 2.30(m, 2H), 2.15(m, 2H), 2.03(m, 1H), 1.75(m, 2H), 1.54(m, 1H)

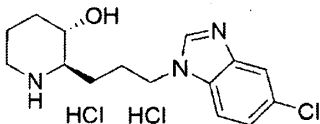
Example 10: Preparation of (2R,3S)-2-(3-(4-chloro-1H-benzod[1,2-b]imidazol-1-yl)propyl)piperidin-3-ol dihydrochloride



The title compound (11 mg, yield: 91%) was obtained in the same manner as in Example 1, with the exception that 1-chloro-3-fluoro-2-nitrobenzene was used instead of 4-chloro-2-fluoro-1-nitrobenzene in Step 1-8 of Example 1.

¹H NMR (500MHz, MeOD): δ 9.55(s, 1H), 7.96(d, 1H), 7.67(d, 1H), 7.63(m, 1H), 4.61(t, 2H), 3.60(m, 1H), 3.34(m, 1H), 3.00(m, 2H), 2.28(m, 2H), 2.14(m, 2H), 2.03(m, 1H), 1.75(m, 2H), 1.54(m, 1H)

Example 11: Preparation of (2R,3S)-2-(3-(5-chloro-1H-benzod[1,2-b]imidazol-1-yl)propyl)piperidin-3-ol dihydrochloride

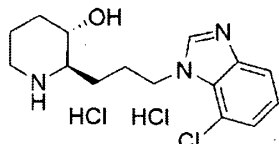


The title compound (8 mg, yield: 87%) was obtained in the same manner as in Example 1, with the exception that 4-chloro-1-fluoro-2-nitrobenzene was used instead of 4-chloro-2-fluoro-1-nitrobenzene in Step 1-8 of Example 1.

¹H NMR (500MHz, MeOD): δ 9.55(s, 1H), 8.03(d, 1H), 7.93(s, 1H), 7.69(d, 1H),

4.61(m, 2H), 3.58(m, 1H), 3.01(m, 2H), 2.29(m, 2H), 2.09(m, 2H), 2.00(m, 1H), 1.74(m, 2H), 1.52(m, 1H)

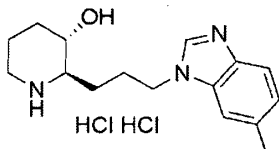
Example 12: Preparation of (2R,3S)-2-(3-(7-chloro-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol dihydrochloride



The title compound (10 mg, yield: 90%) was obtained in the same manner as in Example 1, with the exception that 1-chloro-2-fluoro-3-nitrobenzene was used instead of 4-chloro-2-fluoro-1-nitrobenzene in Step 1-8 of Example 1.

¹H NMR (500MHz, MeOD): δ 9.59(s, 1H), 7.83(d, 1H), 7.66(d, 1H), 7.61(d, 1H), 3.59(m, 1H), 3.00(m, 2H), 2.30(m, 2H), 2.16(m, 2H), 2.03(m, 1H), 1.83(m, 2H), 1.55(m, 1H)

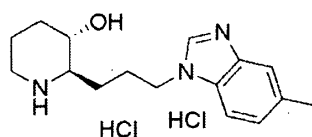
Example 13: Preparation of (2R,3S)-2-(3-(6-methyl-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol dihydrochloride



The title compound (14 mg, yield: 85%) was obtained in the same manner as in Example 1, with the exception that 2-fluoro-4-methyl-1-nitrobenzene was used instead of 4-chloro-2-fluoro-1-nitrobenzene in Step 1-8 of Example 1.

¹H NMR (500MHz, MeOD): δ 9.42(s, 1H), 7.83(s, 1H), 7.73(d, 1H), 7.52(d, 1H), 4.59(m, 2H), 3.57(m, 1H), 2.95(m, 2H), 2.59(s, 3H), 2.24(m, 2H), 2.11(m, 2H), 2.01(m, 1H), 1.74(m, 2H), 1.54(m, 1H)

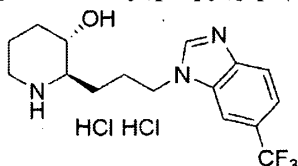
Example 14: Preparation of (2R,3S)-2-(3-(5-methyl-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol dihydrochloride



The title compound (12 mg, yield: 82%) was obtained in the same manner as in Example 1, with the exception that 1-fluoro-4-methyl-2-nitrobenzene was used instead of 4-chloro-2-fluoro-1-nitrobenzene in Step 1-8 of Example 1.

5 ^1H NMR (500MHz, MeOD): δ 9.41(s, 1H), 7.89(d, 1H), 7.65(d, 1H), 7.52(m, 1H), 4.56(m, 2H), 3.36(m, 2H), 2.95(m, 2H), 2.66(s, 3H), 2.24(m, 2H), 2.07(m, 3H), 1.95(m, 2H), 1.72(m, 1H)

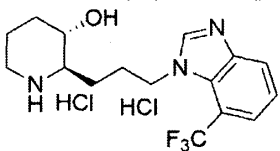
Example 15: Preparation of (2R,3S)-2-(3-(6-(trifluoromethyl)-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol dihydrochloride



The title compound (17 mg, yield: 92%) was obtained in the same manner as in Example 1, with the exception that 2-fluoro-1-nitro-4-(trifluoromethyl)benzene was used instead of 4-chloro-2-fluoro-1-nitrobenzene in Step 1-8 of Example 1.

15 ^1H NMR (500MHz, MeOD): δ 9.62(s, 1H), 8.45(s, 1H), 8.06(d, 1H), 7.95(d, 1H), 4.67(m, 2H), 3.62(m, 1H), 2.98(m, 2H), 2.22(m, 2H), 2.08(m, 2H), 2.01(m, 1H), 1.71(m, 2H), 1.54(m, 1H)

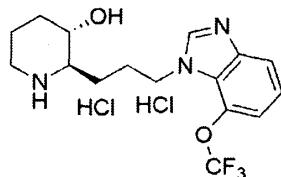
Example 16: Preparation of (2R,3S)-2-(3-(7-(trifluoromethyl)-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol dihydrochloride



The title compound (15 mg, yield: 89%) was obtained in the same manner as in Example 1, with the exception that 2-fluoro-1-nitro-3-(trifluoromethyl)benzene was used instead of 4-chloro-2-fluoro-1-nitrobenzene in Step 1-8 of Example 1.

¹H NMR (500MHz, MeOD): δ 9.32(m, 1H), 8.35(m, 2H), 7.97(m, 1H), 5.02(m, 1H), 4.89(m, 1H), 3.77(m, 1H), 3.59(m, 2H), 3.01(m, 2H), 2.39(m, 4H), 1.78(m, 3H)

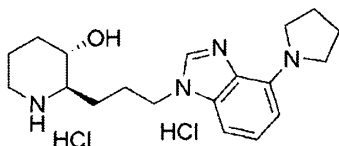
Example 17: Preparation of (2R,3S)-2-(3-(7-(trifluoromethoxy)-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol dihydrochloride



The title compound (14 mg, yield: 87%) was obtained in the same manner as in Example 1, with the exception that 2-fluoro-1-nitro-3-(trifluoromethoxy)benzene was used instead of 4-chloro-2-fluoro-1-nitrobenzene in Step 1-8 of Example 1.

¹H NMR (500MHz, MeOD): δ 9.68(s, 1H), 7.87-7.64(m, 3H), 4.81(m, 3H), 3.59(m, 1H), 2.99(m, 2H), 2.24(m, 2H), 2.08(m, 3H), 1.77(m, 2H), 1.56(m, 1H)

Example 18: Preparation of (2R,3S)-2-(3-(4-(pyrrolidin-1-yl)-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol dihydrochloride



Step 18-1: Preparation of tert-butyl (2R,3S)-2-(3-(4-bromo-1H-benzo[d]imidazol-1-yl)propyl)-3-((tert-butyldimethylsilyl)oxy)piperidine-1-carboxylate

The title compound (1.7 g, yield: 73%) was obtained in the same manner as in Steps 1-1 to 1-9 of Example 1.

Step 18-2: Preparation of tert-butyl (2R,3S)-3-((tert-butyldimethylsilyl)oxy)-2-(3-(4-(pyrrolidin-1-yl)-1H-benzo[d]imidazol-1-yl)propyl)piperidine-1-carboxylate

(2R,3S)-2-(3-(4-bromo-1H-benzo[d]imidazol-1-yl)propyl)-3-((tert-butyldimethylsilyl)oxy)piperidine-1-carboxylate (100 mg, 0.2 mmol) obtained in Step 18-1 was dissolved in N,N-dimethylformamide (2 mL, 0.09 M). Pyrrolidine (14 mg, 0.2 mmol), 2,2'-

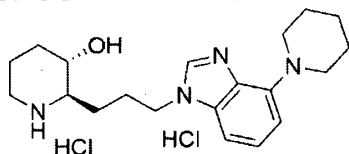
bis(diphenylphosphino)-1,1'-binaphthyl) (25 mg, 0.04 mmol), palladium acetate (II) (5 mg, 0.02 mmol) and cesium carbonate (130 mg, 0.4 mmol) were added thereto, and then stirred in a microwave at 100°C for 30 minutes. When the reaction was completed, it was filtered with celite, diluted with ethyl acetate, and washed with saturated sodium chloride solution. The organic layer
 5 was collected and dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (hexane: ethyl acetate = 1:5) to give the title compound (60 mg, yield: 45%).

Step 18-3: Preparation of (2R,3S)-2-(3-(4-(pyrrolidin-1-yl)-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol dihydrochloride
 10

The title compound (10 mg, yield: 90%) was obtained in the same manner as in Step 1-9 of Example 1.

¹H NMR (500MHz, MeOD): δ 9.32(s, 1H), 7.45(t, 1H), 7.17(d, 1H), 6.76(d, 1H), 4.52(t, 2H), 3.64(m, 3H), 3.57(m, 1H), 3.48(m, 1H), 2.92(m, 2H), 2.27(m, 1H), 2.18(m, 4H), 2.11(m,
 15 2H), 2.02(m, 1H), 1.72(m, 2H), 1.55(m, 1H)

Example 19: Preparation of (2R,3S)-2-(3-(4-(piperidin-1-yl)-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol dihydrochloride

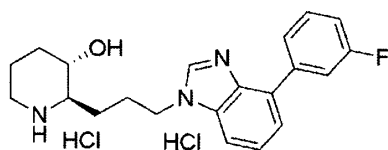


20 The title compound (15 mg, yield: 96%) was obtained in the same manner as in Example 18, with the exception that piperidine was used instead of pyrrolidine in Step 18-2 of Example 18.

¹H NMR (500MHz, MeOD): δ 9.05(s, 1H), 7.69(d, 1H), 7.53(t, 1H), 7.35(d, 1H), 4.52(t, 2H), 3.50(m, 5H), 3.34(m, 1H), 3.26(m, 1H), 2.95(m, 2H), 2.25(m, 2H), 2.09(m, 2H), 2.02(m, 4H), 1.75(m, 4H), 1.53(m, 1H)

25

Example 20: Preparation of (2R,3S)-2-(3-(4-(3-fluorophenyl)-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol dihydrochloride



Step 20-1: tert-butyl (2R,3S)-2-(3-(4-bromo-1H-benzo[d]imidazol-1-yl)propyl)-3-((tert-butyldimethylsilyl)oxy)piperidine-1-carboxylate

The title compound (1.7 g, yield: 73%) was obtained in the same manner as in Steps 1-1 to 1-9 of Example 1.

Step 20-2: tert-butyl (2R,3S)-3-((tert-butyldimethylsilyl)oxy)-2-(3-(4-(3-fluorophenyl)-1H-benzo[d]imidazol-1-yl)propyl)piperidine-1-carboxylate

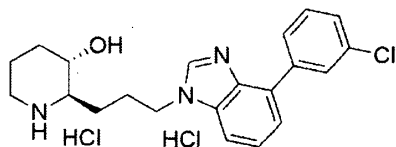
Tert-butyl (2R,3S)-2-(3-(4-bromo-1H-benzo[d]imidazol-1-yl)propyl)-3-((tert-butyldimethylsilyl)oxy)piperidine-1-carboxylate (100 mg, 0.2 mmol) obtained in Step 20-1 was dissolved in N,N-dimethylformamide (2 mL, 0.09 M). (3-fluorophenyl)boronic acid (22 mg, 0.2 mmol), tetrakis(triphenylphosphine)palladium(0) (23 mg, 0.04 mmol), and 2N sodium carbonate (0.3 mL, 0.76 mmol) were added thereto, and stirred in a microwave at 130°C for 45 minutes. When the reaction was completed, it was filtered with celite, diluted with ethyl acetate, and washed with saturated sodium chloride solution. The organic layer was collected and dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (hexane: ethyl acetate = 1:5) to give the title compound (60 mg, yield: 45%).

Step 20-3: Preparation of (2R,3S)-2-(3-(4-(3-fluorophenyl)-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol dihydrochloride

The title compound (19 mg, yield: 91%) was obtained in the same manner as in Step 1-9 of Example 1.

¹H NMR (500MHz, MeOD): δ 9.57(d, 1H), 8.03(d, 1H), 7.77(t, 1H), 7.72(d, 1H), 7.62(m, 1H), 7.49(d, 1H), 7.45(m, 1H), 7.29(t, 1H), 4.66(t, 2H), 3.57(m, 1H), 2.97(m, 2H), 2.25(m, 2H), 2.14(m, 2H), 2.02(m, 1H), 1.75(m, 2H), 1.55(m, 1H)

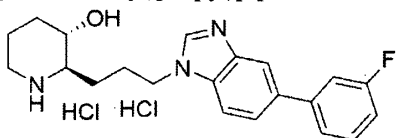
Example 21: Preparation of (2R,3S)-2-(3-(4-(3-chlorophenyl)-1H-

benzo[d]imidazol-1-yl)propyl)piperidin-3-ol dihydrochloride

The title compound (18 mg, yield: 89%) was obtained in the same manner as in Example 20, with the exception that (3-chlorophenyl)boronic acid was used instead of (3-fluorophenyl)boronic acid in Step 20-2 of Example 20.

¹H NMR (500MHz, MeOD): δ 9.63(s, 1H), 8.07(d, 1H), 7.79(t, 1H), 7.71(m, 2H), 7.58(m, 3H), 4.67(t, 2H), 3.60(m, 1H), 2.97(m, 2H), 2.28(m, 2H), 2.10(m, 2H), 2.02(m, 1H), 1.85(m, 2H), 1.55(m, 1H)

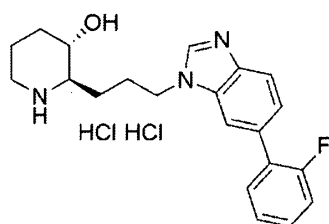
Example 22: Preparation of (2R,3S)-2-(3-(5-(3-fluorophenyl)-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol dihydrochloride



The title compound (7 mg, yield: 26%) was obtained in the same manner as in Example 20, with the exception that tert-butyl (2R,3S)-2-(3-(5-bromo-1H-benzo[d]imidazol-1-yl)propyl)-3-(((tert-butyldimethylsilyl)oxy)piperidine-1-carboxylate was used instead of tert-butyl (2R,3S)-2-(3-(4-bromo-1H-benzo[d]imidazol-1-yl)propyl)-3-(((tert-butyldimethylsilyl)oxy)piperidine-1-carboxylate in Step 20-2 of Example 20.

¹H NMR (500MHz, MeOD): δ 9.56(s, 1H), 8.11(m, 2H), 7.98(m, 1H), 7.54(m, 2H), 7.20(m, 1H), 7.16(m, 1H), 4.67(m, 2H), 3.61(m, 2H), 3.03(m, 2H), 2.30(m, 2H), 2.12(m, 2H), 1.98(m, 1H), 1.78(m, 2H), 1.59(m, 1H)

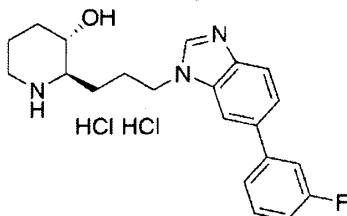
Example 23: Preparation of (2R,3S)-2-(3-(6-(2-fluorophenyl)-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol dihydrochloride



The title compound (13 mg, yield: 34%) was obtained in the same manner as in Example 20, with the exception that tert-butyl (2R,3S)-2-(3-(6-bromo-1H-benzo[d]imidazol-1-yl)propyl)-3-((tert-butyldimethylsilyl)oxy)piperidine-1-carboxylate was used instead of tert-butyl (2R,3S)-2-(3-(4-bromo-1H-benzo[d]imidazol-1-yl)propyl)-3-((tert-butyldimethylsilyl)oxy)piperidine-1-carboxylate, and that (2-fluorophenyl)boronic acid was used instead of (3-fluorophenyl)boronic acid in Step 20-2 of Example 20.

¹H NMR (500MHz, MeOD): δ 7.98(s, 1H), 7.88(m, 1H), 7.71(m, 1H), 7.59(m, 1H), 7.44(m, 1H), 7.32(m, 1H), 7.25(m, 1H), 4.58(m, 2H), 3.55(m, 1H), 2.94(m, 2H), 2.19(m, 2H), 2.06(m, 2H), 2.00(m, 1H), 1.70(m, 2H), 1.53(m, 1H)

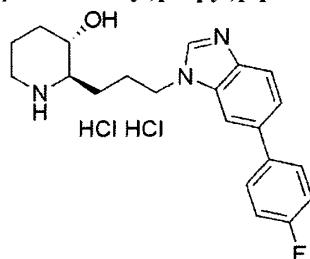
Example 24: Preparation of (2R,3S)-2-(3-(6-(3-fluorophenyl)-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol dihydrochloride



The title compound (11 mg, yield: 30%) was obtained in the same manner as in Example 20, with the exception that tert-butyl (2R,3S)-2-(3-(6-bromo-1H-benzo[d]imidazol-1-yl)propyl)-3-((tert-butyldimethylsilyl)oxy)piperidine-1-carboxylate was used instead of tert-butyl (2R,3S)-2-(3-(4-bromo-1H-benzo[d]imidazol-1-yl)propyl)-3-((tert-butyldimethylsilyl)oxy)piperidine-1-carboxylate in Step 20-2 of Example 20.

¹H NMR (500MHz, MeOD): δ 9.27(s, 1H), 8.18(m, 1H), 7.91(m, 2H), 7.58(m, 1H), 7.52(m, 2H), 7.17(t, 1H), 4.65(m, 2H), 3.57(m, 1H), 2.96(m, 2H), 2.23(m, 2H), 2.08(m, 2H), 2.00(m, 1H), 1.73(m, 2H), 1.57(m, 1H)

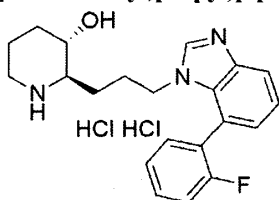
Example 25: Preparation of (2R,3S)-2-(3-(6-(4-fluorophenyl)-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol dihydrochloride



The title compound (8 mg, yield: 28%) was obtained in the same manner as in Example 20, with the exception that tert-butyl (2R,3S)-2-(3-(6-bromo-1H-benzo[d]imidazol-1-yl)propyl)-3-((tert-butyldimethylsilyl)oxy)piperidine-1-carboxylate was used instead of tert-butyl (2R,3S)-2-(3-(4-bromo-1H-benzo[d]imidazol-1-yl)propyl)-3-((tert-butyldimethylsilyl)oxy)piperidine-1-carboxylate, and that (4-fluorophenyl)boronic acid was used instead of (3-fluorophenyl)boronic acid in Step 20-2 of Example 20.

¹H NMR (500MHz, MeOD): δ 7.97(s, 1H), 7.83-7.74(m, 4H), 7.23(m, 2H), 4.55(m, 2H), 3.54(m, 1H), 2.94(m, 2H), 2.20(m, 2H), 2.05(m, 2H), 2.00(m, 1H), 1.69(m, 2H), 1.53(m, 1H)

Example 26: Preparation of (2R,3S)-2-(3-(7-(2-fluorophenyl)-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol dihydrochloride

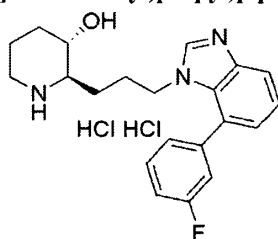


The title compound (11 mg, yield: 30%) was obtained in the same manner as in Example 20, with the exception that tert-butyl (2R,3S)-2-(3-(7-bromo-1H-benzo[d]imidazol-1-yl)propyl)-3-((tert-butyldimethylsilyl)oxy)piperidine-1-carboxylate was used instead of tert-butyl (2R,3S)-2-(3-(4-bromo-1H-benzo[d]imidazol-1-yl)propyl)-3-((tert-butyldimethylsilyl)oxy)piperidine-1-carboxylate, and that (2-fluorophenyl)boronic acid was used instead of (3-fluorophenyl)boronic acid in Step 20-2 of Example 20.

¹H NMR (500MHz, MeOD): δ 9.50(s, 1H), 7.94(d, 1H), 7.75(t, 1H), 7.62(m, 1H),

7.57(m, 1H), 7.53(d, 1H), 7.43(m, 1H), 7.38(t, 1H), 4.27(m, 1H), 4.09(m, 1H), 3.42(m, 1H), 3.16(m, 1H), 2.90(m, 1H), 2.73(m, 1H), 1.97(m, 2H), 1.77-1.62(m, 3H), 1.47(m, 2H), 1.27(m, 1H)

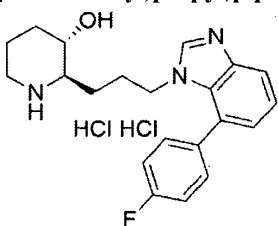
Example 27: Preparation of (2R,3S)-2-(3-(7-(3-fluorophenyl)-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol dihydrochloride



The title compound (7 mg, yield: 28%) was obtained in the same manner as in Example 20, with the exception that tert-butyl (2R,3S)-2-(3-(7-bromo-1H-benzo[d]imidazol-1-yl)propyl)-3-((tert-butyldimethylsilyl)oxy)piperidine-1-carboxylate was used instead of tert-butyl (2R,3S)-2-(3-(4-bromo-1H-benzo[d]imidazol-1-yl)propyl)-3-((tert-butyldimethylsilyl)oxy)piperidine-1-carboxylate in Step 20-2 of Example 20.

¹H NMR (500MHz, MeOD): δ 9.49(s, 1H), 7.91(d, 1H), 7.72(t, 1H), 7.59(m, 1H), 7.50(d, 1H), 7.36(m, 3H), 4.17(m, 2H), 3.37(m, 1H), 3.16(m, 1H), 2.90(m, 1H), 2.73(m, 1H), 1.96(m, 2H), 1.67(m, 3H), 1.50(m, 2H), 1.32(m, 1H)

Example 28: Preparation of (2R,3S)-2-(3-(7-(4-fluorophenyl)-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol dihydrochloride

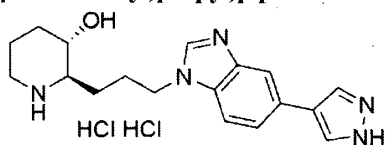


The title compound (13 mg, yield: 32%) was obtained in the same manner as in Example 20, with the exception that tert-butyl (2R,3S)-2-(3-(7-bromo-1H-benzo[d]imidazol-1-yl)propyl)-3-((tert-butyldimethylsilyl)oxy)piperidine-1-carboxylate was used instead of tert-butyl (2R,3S)-2-(3-(4-bromo-1H-benzo[d]imidazol-1-yl)propyl)-3-((tert-butyldimethylsilyl)oxy)piperidine-1-

carboxylate, and that (4-fluorophenyl)boronic acid was used instead of (3-fluorophenyl)boronic acid in Step 20-2 of Example 20.

¹H NMR (500MHz, MeOD): δ 9.48(s, 1H), 7.89(d, 1H), 7.68(t, 1H), 7.54(m, 2H), 7.50(d, 1H), 7.33(t, 2H), 4.14(m, 2H), 3.42(m, 1H), 3.16(m, 1H), 2.90(m, 1H), 2.72(m, 1H),
 5 1.97(m, 2H), 1.72(m, 3H), 1.50(m, 2H), 1.31(m, 1H)

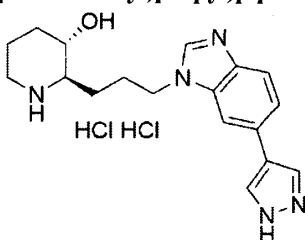
Example 29: Preparation of (2R,3S)-2-(3-(5-(1H-pyrazol-4-yl)-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol dihydrochloride



10 The title compound (7 mg, yield: 19%) was obtained in the same manner as in Example 20, with the exception that tert-butyl (2R,3S)-2-(3-(6-bromo-1H-benzo[d]imidazol-1-yl)propyl)-3-((tert-butyldimethylsilyl)oxy)piperidine-1-carboxylate was used instead of tert-butyl (2R,3S)-2-(3-(4-bromo-1H-benzo[d]imidazol-1-yl)propyl)-3-((tert-butyldimethylsilyl)oxy)piperidine-1-carboxylate, and that (1H-pyrazol-4-yl)boronic acid was used instead of (3-fluorophenyl)boronic
 15 acid in Step 20-2 of Example 20.

¹H NMR (500MHz, MeOD): δ 9.53(s, 1H), 8.32(s, 1H), 8.07(m, 1H), 7.70(m, 2H), 7.58(m, 1H), 4.63(m, 2H), 3.60(m, 1H), 3.00(m, 2H), 2.30(m, 2H), 2.14(m, 2H), 2.05(m, 1H), 1.78(m, 2H), 1.55(m, 1H)

20 **Example 30: Preparation of (2R,3S)-2-(3-(6-(1H-pyrazol-4-yl)-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol dihydrochloride**

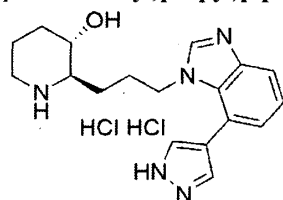


The title compound (6 mg, yield: 15%) was obtained in the same manner as in Example 20, with the exception that tert-butyl (2R,3S)-2-(3-(6-bromo-1H-benzo[d]imidazol-1-yl)propyl)-3-

((tert-butyl dimethylsilyl)oxy)piperidine-1-carboxylate was used instead of tert-butyl (2R,3S)-2-(3-(4-bromo-1H-benzo[d]imidazol-1-yl)propyl)-3-((tert-butyl dimethylsilyl)oxy)piperidine-1-carboxylate, and that (1H-pyrazol-4-yl)boronic acid was used instead of (3-fluorophenyl)boronic acid in Step 20-2 of Example 20.

- 5 ¹H NMR (500MHz, MeOD): δ 9.52(s, 1H), 8.48(s, 1H), 8.03(d, 1H), 7.87(d, 1H), 7.68(m, 1H), 7.58(m, 1H), 4.66(m, 2H), 3.60(m, 1H), 2.97(m, 2H), 2.31(m, 2H), 2.14(m, 2H), 2.00(m, 1H), 1.77(m, 2H), 1.54(m, 1H)

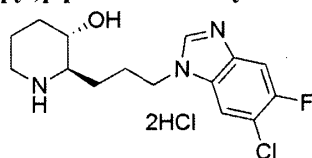
10 **Example 31: Preparation of (2R,3S)-2-(3-(7-(1H-pyrazol-4-yl)-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol dihydrochloride**



- The title compound (5 mg, yield: 12%) was obtained in the same manner as in Example 20, with the exception that tert-butyl (2R,3S)-2-(3-(7-bromo-1H-benzo[d]imidazol-1-yl)propyl)-3-((tert-butyl dimethylsilyl)oxy)piperidine-1-carboxylate was used instead of tert-butyl (2R,3S)-2-(3-(4-bromo-1H-benzo[d]imidazol-1-yl)propyl)-3-((tert-butyl dimethylsilyl)oxy)piperidine-1-carboxylate, and that (1H-pyrazol-4-yl)boronic acid was used instead of (3-fluorophenyl)boronic acid in Step 20-2 of Example 20.

- ¹H NMR (500MHz, MeOD): δ 9.55(s, 1H), 7.99(s, 1H), 7.87(d, 1H), 7.69(t, 1H), 7.51(d, 1H), 4.35(m, 2H), 3.50(m, 2H), 3.21(m, 1H), 2.97(m, 1H), 2.77(m, 1H), 2.01(m, 2H), 1.76(m, 2H), 1.70(m, 2H), 1.55(m, 1H), 1.45(m, 1H)

Example 32: Preparation of (2R,3S)-2-(3-(6-chloro-5-fluoro-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol dihydrochloride



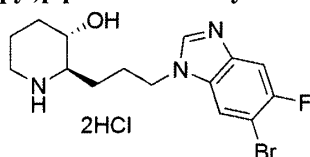
- 25 The title compound (25 mg, yield: 83%) was obtained in the same manner as in Example

1, with the exception that 1-chloro-2,5-difluoro-4-nitrobenzene was used instead of 4-chloro-2-fluoro-1-nitrobenzene in step 1-8 of Example 1.

¹H-NMR (500 MHz, MeOD) : δ 9.55 (s, 1H), 8.33 (d, 1H), 7.82 (d, 1H), 4.58 (td, 2H), 3.59 (m, 2H), 2.98 (m, 2H), 2.23 (m, 2H), 2.08 (m, 2H), 1.98 (m, 1H), 1.77 (m, 2H), 1.76 (m, 1H)

5

Example 33: Preparation of (2R,3S)-2-(3-(6-bromo-5-fluoro-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol dihydrochloride

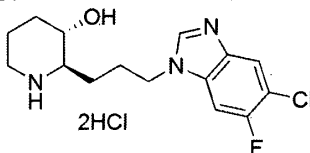


The title compound (15 mg, yield: 81%) was obtained in the same manner as in Example 1, with the exception that 1-bromo-2,5-difluoro-4-nitrobenzene was used instead of 4-chloro-2-fluoro-1-nitrobenzene in step 1-8 of Example 1.

¹H-NMR (500 MHz, MeOD) : δ 9.55 (s, 1H), 8.46 (d, 1H), 7.79 (d, 1H), 4.59 (t, 2H), 3.59 (m, 1H), 2.97 (m, 2H), 2.22 (m, 2H), 2.08 (m, 2H), 1.97 (m, 1H), 1.76 (m, 2H), 1.56 (m, 1H)

15

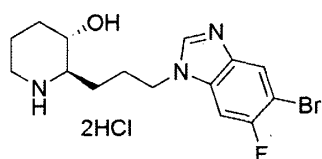
Example 34: Preparation of (2R,3S)-2-(3-(5-chloro-6-fluoro-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol dihydrochloride



The title compound (20 mg, yield: 80%) was obtained in the same manner as in Example 1, with the exception that 1-chloro-2,4-difluoro-5-nitrobenzene was used instead of 4-chloro-2-fluoro-1-nitrobenzene in step 1-8 of Example 1.

¹H-NMR (500 MHz, MeOD) : δ 9.55 (s, 1H), 8.09 (d, 1H), 8.06 (d, 1H), 4.58 (t, 2H), 3.60 (m, 2H), 2.98 (m, 2H), 2.21 (m, 2H), 2.09 (m, 2H), 1.97 (m, 1H), 1.76 (m, 2H), 1.56 (m, 1H)

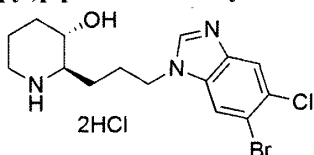
Example 35: Preparation of (2R,3S)-2-(3-(5-bromo-6-fluoro-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol dihydrochloride



The title compound (22 mg, yield: 83%) was obtained in the same manner as in Example 1, with the exception that 1-bromo-2,4-difluoro-5-nitrobenzene was used instead of 4-chloro-2-fluoro-1-nitrobenzene in step 1-8 of Example 1.

¹H-NMR (500 MHz, MeOD) : δ 9.58 (s, 1H), 8.19 (d, 1H), 8.07 (d, 1H), 4.58 (t, 2H), 3.59 (m, 2H), 2.98 (m, 2H), 2.22 (m, 2H), 2.08 (m, 2H), 1.96 (m, 1H), 1.76 (m, 2H), 1.56 (m, 1H)

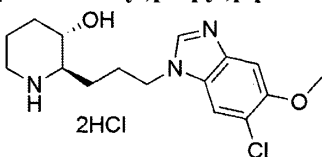
Example 36: Preparation of (2R,3S)-2-(3-(6-bromo-5-chloro-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol dihydrochloride



The title compound (22 mg, yield: 83%) was obtained in the same manner as in Example 1, with the exception that 1-bromo-2-chloro-5-fluoro-4-nitrobenzene was used instead of 4-chloro-2-fluoro-1-nitrobenzene in step 1-8 of Example 1.

¹H-NMR (500 MHz, MeOD) : δ 9.54 (s, 1H), 8.51 (s, 1H), 8.10 (s, 1H), 4.58 (t, 2H), 3.66 (m, 2H), 2.98 (m, 2H), 2.23 (m, 2H), 2.08 (m, 2H), 1.97 (m, 1H), 1.76 (m, 2H), 1.56 (m, 1H)

Example 37: Preparation of (2R,3S)-2-(3-(6-chloro-5-methoxy-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol dihydrochloride

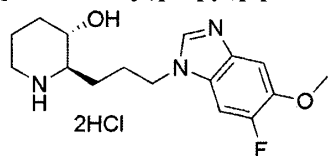


The title compound (18 mg, yield: 81%) was obtained in the same manner as in Example 1, with the exception that 1-chloro-5-fluoro-2-methoxy-4-nitrobenzene was used instead of 4-chloro-2-fluoro-1-nitrobenzene in step 1-8 of Example 1.

¹H-NMR (500 MHz, MeOD) : δ 9.44 (s, 1H), 8.17 (s, 1H), 7.45 (s, 1H), 4.56 (t, 2H), 4.02 (s, 3H), 3.58 (t, 1H), 2.98 (m, 2H), 2.21 (m, 2H), 2.05 (m, 2H), 1.97 (m, 1H), 1.76 (m, 2H),

1.54 (m, 1H)

Example 38: Preparation of (2R,3S)-2-(3-(6-fluoro-5-methoxy-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol dihydrochloride

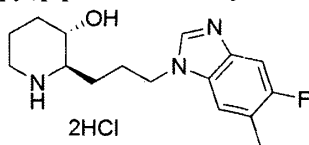


5

The title compound (18 mg, yield: 81%) was obtained in the same manner as in Example 1, with the exception that 1,5-difluoro-2-methoxy-4-nitrobenzene was used instead of 4-chloro-2-fluoro-1-nitrobenzene in step 1-8 of Example 1.

¹H-NMR (500 MHz, MeOD) : δ 9.45 (s, 1H), 7.92 (d, 1H), 7.48 (d, 1H), 4.55 (t, 2H),
 10 4.00 (s, 3H), 3.58 (m, 2H), 2.99 (m, 2H), 2.22 (m, 2H), 2.06 (m, 2H), 1.97 (m, 1H), 1.77 (m, 2H)

Example 39: Preparation of (2R,3S)-2-(3-(5-fluoro-6-methyl-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol dihydrochloride

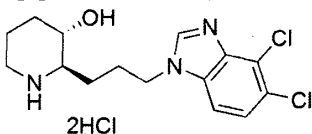


15

The title compound (15 mg, yield: 79%) was obtained in the same manner as in Example 1, with the exception that 1,4-difluoro-2-methyl-5-nitrobenzene was used instead of 4-chloro-2-fluoro-1-nitrobenzene in step 1-8 of Example 1.

¹H-NMR (500 MHz, MeOD) : δ 9.49 (s, 1H), 7.96 (d, 2H), 7.58 (d, 1H), 4.59 (t, 2H),
 3.59 (m, 1H), 3.00 (m, 2H), 2.50 (s, 3H), 2.22 (m, 2H), 2.08 (m, 2H), 1.97 (m, 1H), 1.77 (m, 2H),
 20 1.56 (m, 1H)

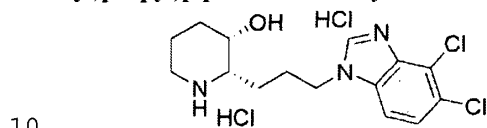
Example 40: Preparation of (2R,3S)-2-(3-(4,5-dichloro-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol dihydrochloride



The title compound (26 mg, yield: 81%) was obtained in the same manner as in Example 1, with the exception that 1,2-dichloro-4-fluoro-3-nitrobenzene was used instead of 4-chloro-2-fluoro-1-nitrobenzene in step 1-8 of Example 1.

¹H-NMR (500 MHz, MeOD): δ 9.67 (s, 1H), 8.02 (d, 1H), 7.82 (d, 1H), 4.62 (m, 2H),
 5 3.60 (m, 1H), 3.28 (m, 1H), 2.99 (m, 2H), 2.25 (m, 2H), 2.08 (m, 2H), 1.99 (m, 1H), 1.78 (m, 2H),
 1.54 (m, 1H)

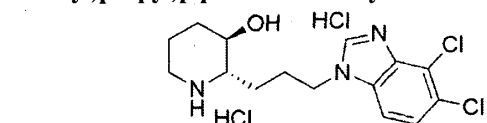
Example 41: Preparation of (2S,3S)-2-(3-(4,5-dichloro-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol dihydrochloride



The title compound (19 mg, yield: 85%) was obtained in the same manner as in Example 1, with the exception that tert-butyl (2S,3S)-3-((tert-butyldimethylsilyl)oxy)-2-(3-hydroxypropyl)piperidine-1-carboxylate was used instead of tert-butyl (2R,3S)-3-((tert-butyldimethylsilyl)oxy)-2-(3-hydroxypropyl)piperidine-1-carboxylate in Step 1-5 of Example 1.

15 ¹H NMR (500MHz, MeOD): δ 9.58(d, 1H), 7.97(d, 1H), 7.81(d, 1H), 4.59(m, 2H),
 4.02(s, 1H), 3.27(s, 1H), 3.20(m, 1H), 3.00(t, 1H), 2.18-2.05(m, 3H), 1.94(m, 1H), 1.87(m, 1H),
 1.72-1.67(m, 3H)

Example 42: Preparation of (2S,3R)-2-(3-(4,5-dichloro-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol dihydrochloride

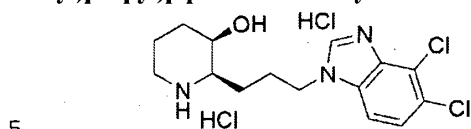


The title compound (33 mg, yield: 84%) was obtained in the same manner as in Example 1, with the exception that tert-butyl (2S,3R)-3-((tert-butyldimethylsilyl)oxy)-2-(3-hydroxypropyl)piperidine-1-carboxylate was used instead of tert-butyl (2R,3S)-3-((tert-butyldimethylsilyl)oxy)-2-(3-hydroxypropyl)piperidine-1-carboxylate in Step 1-5 of Example 1.

25 ¹H NMR (500MHz, MeOD): δ 9.64(d, 1H), 8.00(dd, 1H), 7.82(d, 1H), 4.61(m, 2H),
 3.59(m, 1H), 3.27(s, 1H), 3.02-2.93(m, 2H), 2.29-2.18(m, 2H), 2.07(m, 2H), 1.99(m, 1H), 1.58(m,

2H), 1.51(m, 1H)

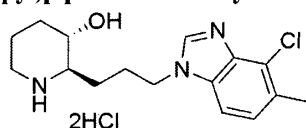
Example 43: Preparation of (2R,3R)-2-(3-(4,5-dichloro-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol dihydrochloride



The title compound (23 mg, yield: 85%) was obtained in the same manner as in Example 1, with the exception that tert-butyl (2R,3R)-3-((tert-butyldimethylsilyl)oxy)-2-(3-hydroxypropyl)piperidine-1-carboxylate was used instead of tert-butyl (2R,3S)-3-((tert-butyldimethylsilyl)oxy)-2-(3-hydroxypropyl)piperidine-1-carboxylate in Step 1-5 of Example 1.

10 ^1H NMR (500MHz, MeOD): δ 9.66(d, 1H), 7.97(d, 1H), 7.83(d, 1H), 4.60(t, 2H), 4.01(s, 1H), 3.27(s, 1H), 3.20(t, 1H), 3.00(t, 1H), 2.20-2.05(m, 3H), 1.94(m, 1H), 1.88(m, 1H), 1.73-1.66(m, 3H)

Example 44: Preparation of (2R,3S)-2-(3-(4-chloro-5-methyl-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol dihydrochloride

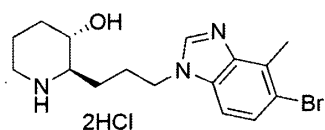


The title compound (25 mg, yield: 80%) was obtained in the same manner as in Example 1, with the exception that 2-chloro-4-fluoro-1-methyl-3-nitrobenzene was used instead of 4-chloro-2-fluoro-1-nitrobenzene in step 1-8 of Example 1.

20 ^1H -NMR (500 MHz, MeOD): δ 9.61 (s, 1H), 7.88 (d, 1H), 7.62 (d, 1H), 4.60 (t, 2H), 3.58 (m, 2H), 2.97 (m, 2H), 2.58 (s, 3H), 2.23 (m, 2H), 2.06 (m, 2H), 1.96 (m, 1H), 1.76 (m, 2H), 1.54 (m, 1H)

Example 45: Preparation of (2R,3S)-2-(3-(5-bromo-4-methyl-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol dihydrochloride

25



Step 45-1: Preparation of tert-butyl(2R,3S)-2-(3-(5-bromo-4-methyl-1H-benzo[d]imidazol-1-yl)propyl)-3-((tert-butyldimethylsilyl)oxy)piperidin-1-carboxylate

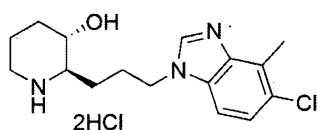
Tert-butyl (2R,3S)-2-(3-bromopropyl)-3-((tert-butyldimethylsilyl)oxy)piperidine-1-carboxylate (40 mg, 0.09 mmol) obtained from Step 1-5 of Example 1 was dissolved in N,N-dimethylformamide (2 mL, 0.05 M). Then, potassium carbonate (25 mg, 0.18 mmol) and 5-bromo-4-methyl-1H-benzo[d]imidazole (18 mg, 0.09 mmol) were added thereto, and the mixture was stirred at room temperature for 4 hours. When the reaction was completed, the solvent was removed, and the resulting mixture was diluted with ethyl acetate and washed with saturated sodium chloride solution. The organic layer was collected, dried over sodium sulfate, filtered and concentrated under reduced pressure, and then purified by column chromatography (hexane: ethyl acetate = 1:1) to give the title compound (43 mg, yield: 85%).

Step 45-2: Preparation of (2R,3S)-2-(3-(5-bromo-4-methyl-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol dihydrochloride

Tert-butyl(2R,3S)-2-(3-(5-bromo-4-methyl-1H-benzo[d]imidazol-1-yl)propyl)-3-((tert-butyldimethylsilyl)oxy)piperidin-1-carboxylate (43 mg, 0.08 mmol) obtained from Step 45-1 was dissolved in a small amount of tetrahydrofuran. Then, 4N hydrogen chloride dioxane solution (2.0 mL, 0.04 M) was added, and the mixture was stirred at room temperature for 12 hours. When the reaction was completed, the reaction solution was concentrated under reduced pressure to remove the solvent, dissolved by addition of a small amount of methanol, and then crystallized with diethyl ether to obtain the title compound (27 mg, yield: 85%).

¹H-NMR (500 MHz, DMSO-d₆) : δ 9.19 (s, 1H), 7.82 (d, 1H), 7.76 (s, 1H), 4.47 (m, 2H), 3.38 (m, 1H), 3.09 (d, 1H), 2.81 (m, 2H), 2.65 (s, 3H), 2.19 (m, 1H), 2.10 (m, 1H), 1.88 (m, 2H), 1.75 (m, 1H), 1.72 (m, 1H), 1.58 (m, 1H), 1.37 (m, 1H)

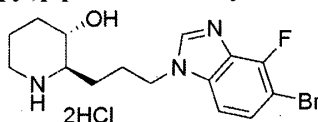
Example 46: Preparation of (2R,3S)-2-(3-(5-chloro-4-methyl-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol dihydrochloride



The title compound (30 mg, yield: 80%) was obtained in the same manner as in Example 45, with the exception that 5-chloro-4-methyl-1H-benzo[d]imidazole was used instead of 5-bromo-4-methyl-1H-benzo[d]imidazole in step 45-1 of Example 45.

¹H-NMR (500 MHz, MeOD): δ 9.53 (s, 1H), 7.83 (d, 1H), 7.69 (d, 1H), 4.58 (t, 2H), 3.58 (m, 1H), 3.28 (m, 1H), 2.96 (m, 2H), 2.70 (s, 3H), 2.22 (m, 2H), 2.05 (m, 2H), 2.00 (m, 1H), 1.75 (m, 2H), 1.55 (m, 1H)

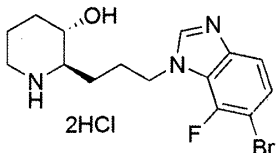
Example 47: Preparation of (2R,3S)-2-(3-(5-bromo-4-fluoro-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol dihydrochloride



The title compound (10 mg, yield: 40%) was obtained in the same manner as in Example 45, with the exception that 5-bromo-4-fluoro-1H-benzo[d]imidazole was used instead of 5-bromo-4-methyl-1H-benzo[d]imidazole in step 45-1 of Example 45.

¹H-NMR (500 MHz, MeOD): δ 9.47 (s, 1H), 7.84 (dd, 1H), 7.79 (d, 1H), 4.60 (m, 2H), 3.59 (m, 1H), 3.27 (m, 1H), 2.99 (m, 2H), 2.20 (m, 2H), 2.07 (m, 2H), 1.98 (m, 1H), 1.75 (m, 2H), 1.56 (m, 1H)

Example 48: Preparation of (2R,3S)-2-(3-(6-bromo-7-fluoro-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol dihydrochloride

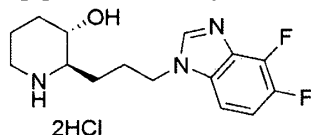


The title compound (11 mg, yield: 43%) was obtained in the same manner as in Example 45, with the exception that 6-bromo-7-fluoro-1H-benzo[d]imidazole was used instead of 5-bromo-4-methyl-1H-benzo[d]imidazole in step 45-1 of Example 45.

¹H-NMR (500 MHz, MeOD): δ 9.53 (s, 1H), 7.85 (dd, 1H), 7.64 (d, 1H), 4.67 (m, 2H),

3.59 (m, 1H), 3.27 (m, 1H), 2.98 (m, 2H), 2.23 (m, 2H), 2.09 (m, 2H), 1.98 (m, 1H), 1.77 (m, 2H), 1.54 (m, 1H)

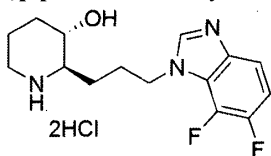
Example 49: Preparation of (2R,3S)-2-(3-(4,5-difluoro-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol dihydrochloride



The title compound (9 mg, yield: 39%) was obtained in the same manner as in Example 45, with the exception that 4,5-difluoro-1H-benzo[d]imidazole was used instead of 5-bromo-4-methyl-1H-benzo[d]imidazole in step 45-1 of Example 45.

¹H-NMR (500 MHz, DMSO-d₆): δ 8.58 (s, 1H), 7.58 (dd, 1H), 7.40 (dd, 1H), 4.33 (m, 2H), 3.38 (m, 1H), 3.09 (d, 1H), 2.98 (m, 2H), 2.10 (m, 1H), 1.96 (m, 1H), 1.87 (m, 2H), 1.77 (m, 1H), 1.65 (m, 1H), 1.54 (m, 1H), 1.36 (m, 1H)

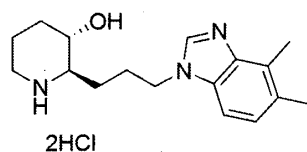
Example 50: Preparation of (2R,3S)-2-(3-(6,7-difluoro-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol dihydrochloride



The title compound (10 mg, yield: 41%) was obtained in the same manner as in Example 45, with the exception that 6,7-difluoro-1H-benzo[d]imidazole was used instead of 5-bromo-4-methyl-1H-benzo[d]imidazole in step 45-1 of Example 45.

¹H-NMR (500 MHz, DMSO-d₆): δ 8.94 (s, 1H), 7.59 (dd, 1H), 7.44 (dd, 1H), 4.44 (m, 2H), 3.41 (m, 1H), 3.09 (d, 1H), 2.78 (m, 2H), 2.13 (m, 1H), 2.03 (m, 1H), 1.89 (m, 2H), 1.76 (d, 1H), 1.66 (m, 1H), 1.57 (m, 1H), 1.35 (m, 1H)

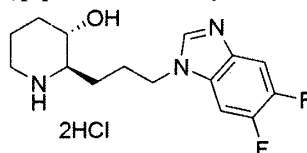
Example 51: Preparation of (2R,3S)-2-(3-(4,5-dimethyl-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol dihydrochloride



The title compound (30 mg, yield: 86%) was obtained in the same manner as in Example 45, with the exception that 4,5-dimethyl-1H-benzo[d]imidazole was used instead of 5-bromo-4-methyl-1H-benzo[d]imidazole in step 45-1 of Example 45.

5 ¹H-NMR (500 MHz, MeOD): δ 9.48 (s, 1H), 7.71 (d, 1H), 7.51 (d, 1H), 4.57 (t, 2H), 3.58 (m, 1H), 3.27 (m, 1H), 2.98 (m, 2H), 2.56 (s, 3H), 2.48 (s, 3H), 2.23 (m, 2H), 2.06 (m, 2H), 1.98 (m, 1H), 1.76 (m, 2H), 1.55 (m, 1H)

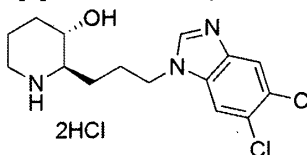
Example 52: Preparation of (2R,3S)-2-(3-(5,6-difluoro-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol dihydrochloride



The title compound (32 mg, yield: 84%) was obtained in the same manner as in Example 45, with the exception that 5,6-difluoro-1H-benzo[d]imidazole was used instead of 5-bromo-4-methyl-1H-benzo[d]imidazole in step 45-1 of Example 45.

15 ¹H-NMR (500 MHz, MeOD): δ 9.58 (s, 1H), 8.17 (dd, 1H), 7.88 (dd, 1H), 4.59 (t, 2H), 3.59 (m, 1H), 3.28 (m, 1H), 2.99 (m, 2H), 2.23 (m, 2H), 2.08 (m, 2H), 1.97 (m, 1H), 1.77 (m, 2H), 1.56 (m, 1H)

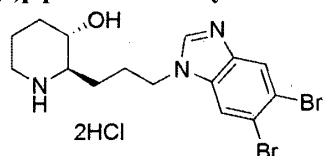
Example 53: Preparation of (2R,3S)-2-(3-(5,6-dichloro-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol dihydrochloride



The title compound (37 mg, yield: 85%) was obtained in the same manner as in Example 45, with the exception that 5,6-dichloro-1H-benzo[d]imidazole was used instead of 5-bromo-4-methyl-1H-benzo[d]imidazole in step 45-1 of Example 45.

¹H-NMR (500 MHz, DMSO-d₆): δ 9.10 (s, 1H), 8.08 (s, 1H), 4.39 (m, 2H), 3.41 (m, 1H), 3.10 (m, 1H), 2.80 (m, 2H), 2.11 (m, 1H), 2.01 (m, 1H), 1.90 (m, 2H), 1.77 (m, 1H), 1.67 (m, 1H), 1.57 (m, 1H), 1.35 (m, 1H).

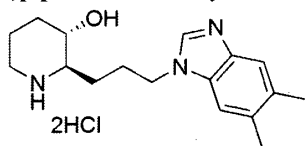
5 **Example 54: Preparation of (2R,3S)-2-(3-(5,6-dibromo-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol dihydrochloride**



The title compound (31 mg, yield: 80%) was obtained in the same manner as in Example 45, with the exception that 5,6-dibromo-1H-benzo[d]imidazole was used instead of 5-bromo-4-methyl-1H-benzo[d]imidazole in step 45-1 of Example 45.

¹H-NMR (500 MHz, DMSO-d₆): δ 8.93 (s, 1H), 8.38 (s, 1H), 8.17 (2, 1H), 4.37 (m, 2H), 3.40 (m, 1H), 3.10 (d, 1H), 2.79 (m, 2H), 2.07 (m, 1H), 1.99 (m, 1H), 1.89 (m, 2H), 1.77 (d, 1H), 1.65 (m, 1H), 1.53 (m, 1H), 1.35 (m, 1H)

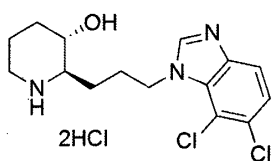
15 **Example 55: Preparation of (2R,3S)-2-(3-(5,6-dimethyl-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol dihydrochloride**



The title compound (36 mg, yield: 85%) was obtained in the same manner as in Example 45, with the exception that 5,6-dimethyl-1H-benzo[d]imidazole was used instead of 5-bromo-4-methyl-1H-benzo[d]imidazole in step 45-1 of Example 45.

¹H-NMR (500 MHz, MeOD): δ 9.38 (s, 1H), 7.80 (s, 1H), 7.62 (s, 1H), 4.59 (m, 2H), 3.59 (m, 1H), 3.27 (m, 1H), 2.99 (m, 2H), 2.51 (s, 3H), 2.49 (s, 3H), 2.24 (m, 2H), 2.08 (m, 2H), 1.97 (m, 1H), 1.77 (m, 2H), 1.56 (m, 1H)

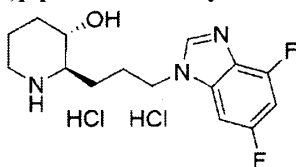
25 **Example 56: Preparation of (2R,3S)-2-(3-(6,7-dichloro-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol dihydrochloride**



The title compound (15 mg, yield: 30%) was obtained in the same manner as in Example 45, with the exception that 6,7-dichloro-1H-benzo[d]imidazole was used instead of 5-bromo-4-methyl-1H-benzo[d]imidazole in step 45-1 of Example 45.

¹H-NMR (500 MHz, MeOD): δ 9.43 (s, 1H), 7.80 (s, 2H), 4.83 (m, 2H), 3.58 (t, 1H), 3.28 (m, 1H), 2.99 (m, 2H), 2.21 (m, 2H), 2.10 (m, 2H), 2.09 (m, 1H), 1.77 (m, 2H), 1.76 (m, 1H)

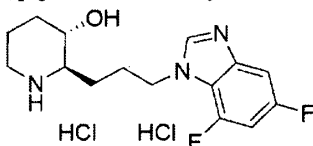
Example 57: Preparation of (2R,3S)-2-(3-(4,6-difluoro-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol dihydrochloride



The title compound (26 mg, yield: 92%) was obtained in the same manner as in Example 45, with the exception that 4,6-difluoro-1H-benzo[d]imidazole was used instead of 5-bromo-4-methyl-1H-benzo[d]imidazole in Step 45-1 of Example 45.

¹H NMR (500MHz, MeOD): δ 9.56(s, 1H), 7.76(d, 1H), 7.39(t, 1H), 4.57(m, 2H), 3.62(m, 1H), 2.99(m, 2H), 2.68(m, 1H), 2.28(m, 2H), 2.12(m, 2H), 2.05(m, 1H), 1.80(m, 2H), 1.55(m, 1H)

Example 58: Preparation of (2R,3S)-2-(3-(5,7-difluoro-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol dihydrochloride

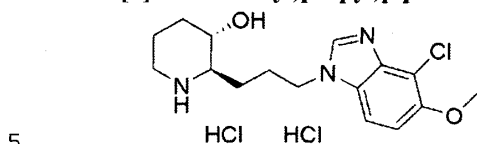


The title compound (25 mg, yield: 90%) was obtained in the same manner as in Example 45, with the exception that 4,6-difluoro-1H-benzo[d]imidazole was used instead of 5-bromo-4-methyl-1H-benzo[d]imidazole in Step 45-1 of Example 45.

¹H NMR (500MHz, MeOD): δ 9.60(d, 1H), 7.51(d, 1H), 7.42(t, 1H), 4.66(m, 2H),

3.58(m, 1H), 2.98(m, 2H), 2.30(m, 2H), 2.12(m, 2H), 2.02(m, 1H), 1.74(m, 2H), 1.54(m, 1H)

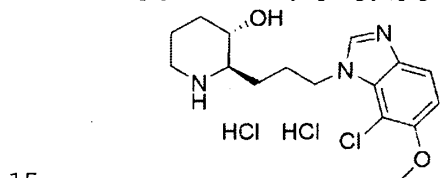
Example 59: Preparation of (2R,3S)-2-(3-(4-chloro-5-methoxy-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol dihydrochloride



The title compound (23 mg, yield: 91%) was obtained in the same manner as in Example 45, with the exception that 4-chloro-5-methoxy-1H-benzo[d]imidazole was used instead of 5-bromo-4-methyl-1H-benzo[d]imidazole in Step 45-1 of Example 45.

¹H NMR (500MHz, MeOD): δ 9.55(s, 1H), 7.97(d, 1H), 7.52(d, 1H), 4.59(t, 2H), 4.04(s, 3H), 3.57(m, 1H), 2.99(m, 2H), 2.31(m, 2H), 2.10(m, 2H), 2.02(m, 1H), 1.79(m, 2H), 1.55(m, 1H)

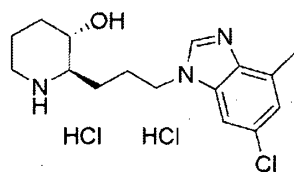
Example 60: Preparation of (2R,3S)-2-(3-(7-chloro-6-methoxy-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol dihydrochloride



The title compound (22 mg, yield: 90%) was obtained in the same manner as in Example 45, with the exception that 4-chloro-5-methoxy-1H-benzo[d]imidazole was used instead of 5-bromo-4-methyl-1H-benzo[d]imidazole in Step 45-1 of Example 45.

¹H NMR (500MHz, MeOD): δ 9.48(s, 1H), 7.79(d, 1H), 7.52(d, 1H), 4.82(m, 2H), 4.03(s, 3H), 3.62(m, 1H), 2.99(m, 2H), 2.30(m, 2H), 2.14(m, 2H), 2.02(m, 1H), 1.80(m, 2H), 1.55(m, 1H)

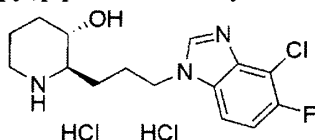
Example 61: Preparation of (2R,3S)-2-(3-(6-chloro-4-methyl-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol dihydrochloride



The title compound (24 mg, yield: 91%) was obtained in the same manner as in Example 45, with the exception that 6-chloro-4-methyl-1H-benzo[d]imidazole was used instead of 5-bromo-4-methyl-1H-benzo[d]imidazole in Step 45-1 of Example 45.

5 ^1H NMR (500MHz, MeOD): δ 9.59(s, 1H), 7.97(s, 1H), 7.52(s, 1H), 4.58(m, 2H), 3.59(m, 1H), 2.97(m, 2H), 2.67(s, 3H), 2.20(m, 2H), 2.10(m, 2H), 2.01(m, 1H), 1.76(m, 2H), 1.55(m, 1H)

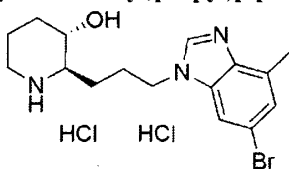
10 **Example 62: Preparation of (2R,3S)-2-(3-(4-chloro-5-fluoro-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol dihydrochloride**



The title compound (19 mg, yield: 89%) was obtained in the same manner as in Example 45, with the exception that 4-chloro-5-fluoro-1H-benzo[d]imidazole was used instead of 5-bromo-4-methyl-1H-benzo[d]imidazole in Step 45-1 of Example 45.

15 ^1H NMR (500MHz, MeOD): δ 9.54(s, 1H), 7.95(d, 1H), 7.50(d, 1H), 4.58(t, 2H), 3.56(m, 1H), 3.42(m, 1H), 2.98(m, 2H), 2.30(m, 2H), 2.08(m, 2H), 2.00(m, 1H), 1.72(m, 2H), 1.52(m, 1H)

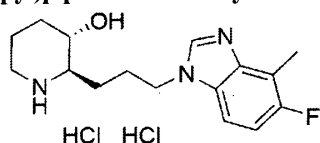
20 **Example 63: Preparation of (2R,3S)-2-(3-(6-bromo-4-methyl-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol dihydrochloride**



The title compound (26 mg, yield: 93%) was obtained in the same manner as in Example 45, with the exception that 6-bromo-4-methyl-1H-benzo[d]imidazole was used instead of 5-bromo-4-methyl-1H-benzo[d]imidazole in Step 45-1 of Example 45.

¹H NMR (500MHz, MeOD): δ 9.58(s, 1H), 8.12(s, 1H), 7.66(s, 1H), 4.57(m, 2H), 3.60(m, 1H), 2.99(m, 2H), 2.65(s, 3H), 2.24(m, 2H), 2.10(m, 2H), 2.02(m, 1H), 1.79(m, 2H), 1.59(m, 1H)

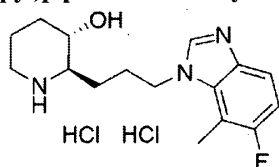
5 **Example 64: Preparation of (2R,3S)-2-(3-(5-fluoro-4-methyl-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol dihydrochloride**



The title compound (22 mg, yield: 90%) was obtained in the same manner as in Example 45, with the exception that 5-fluoro-4-methyl-1H-benzo[d]imidazole was used instead of 5-bromo-4-methyl-1H-benzo[d]imidazole in Step 45-1 of Example 45.

¹H NMR (500MHz, MeOD): δ 9.62(s, 1H), 7.88(dd, 1H), 7.46(t, 1H), 4.61(m, 2H), 3.58(m, 1H), 2.99(m, 2H), 2.59(s, 3H), 2.25(m, 2H), 2.12(m, 2H), 2.01(m, 1H), 1.79(m, 2H), 1.59(m, 1H)

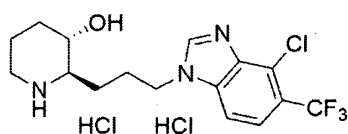
15 **Example 65: Preparation of (2R,3S)-2-(3-(6-fluoro-7-methyl-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol dihydrochloride**



The title compound (20 mg, yield: 88%) was obtained in the same manner as in Example 45, with the exception that 5-fluoro-4-methyl-1H-benzo[d]imidazole was used instead of 5-bromo-4-methyl-1H-benzo[d]imidazole in Step 45-1 of Example 45.

¹H NMR (500MHz, MeOD): δ 9.50(s, 1H), 7.69(dd, 1H), 7.46(t, 1H), 4.76(m, 2H), 3.61(m, 1H), 3.00(m, 2H), 2.77(s, 3H), 2.25(m, 2H), 2.13(m, 2H), 2.02(m, 1H), 1.79(m, 2H), 1.57(m, 1H)

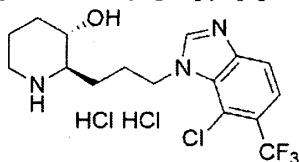
25 **Example 66: Preparation of (2R,3S)-2-(3-(4-chloro-5-(trifluoromethyl)-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol dihydrochloride**



The title compound (27 mg, yield: 95%) was obtained in the same manner as in Example 45, with the exception that 4-chloro-5-(trifluoromethyl)-1H-benzo[d]imidazole was used instead of 5-bromo-4-methyl-1H-benzo[d]imidazole in Step 45-1 of Example 45.

5 ^1H NMR (500MHz, MeOD): δ 9.65(s, 1H), 8.13(d, 1H), 8.01(d, 1H), 4.64(m, 2H), 3.61(m, 2H), 2.98(m, 2H), 2.26(m, 2H), 2.10(m, 2H), 1.98(m, 1H), 1.76(m, 2H), 1.56(m, 1H)

Example 67: Preparation of (2R,3S)-2-(3-(7-chloro-6-(trifluoromethyl)-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol dihydrochloride

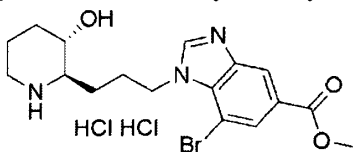


10

The title compound (23 mg, yield: 91%) was obtained in the same manner as in Example 45, with the exception that 4-chloro-5-(trifluoromethyl)-1H-benzo[d]imidazole was used instead of 5-bromo-4-methyl-1H-benzo[d]imidazole in Step 45-1 of Example 45.

15 ^1H NMR (500MHz, MeOD): δ 9.59(s, 1H), 8.01(d, 1H), 7.96(d, 1H), 4.91(m, 2H), 3.61(m, 1H), 2.98(m, 2H), 2.27(m, 2H), 2.10(m, 2H), 2.01(m, 1H), 1.80(m, 2H), 1.56(m, 1H)

Example 68: methyl 7-bromo-1-(3-((2R,3S)-3-hydroxypiperidin-2-yl)propyl)-1H-benzo[d]imidazole-5-carboxylate dihydrochloride

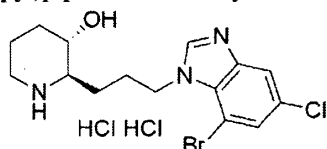


20

The title compound (22 mg, yield: 89%) was obtained in the same manner as in Example 1, with the exception that methyl 3-bromo-4-fluoro-5-nitrobenzoate was used instead of 4-chloro-2-fluoro-1-nitrobenzene in Step 1-8 of Example 1.

^1H NMR (500MHz, MeOD): δ 8.85(s, 1H), 8.38(s, 1H), 8.27(s, 1H), 4.75(m, 2H), 3.96(s, 3H), 3.57(m, 1H), 2.98(m, 2H), 2.25-1.98(m, 5H), 1.72(m, 2H), 1.54(m, 1H)

Example 69: Preparation of (2R,3S)-2-(3-(7-bromo-5-chloro-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol dihydrochloride

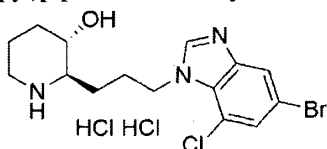


5 The title compound (24 mg, yield: 90%) was obtained in the same manner as in Example 1, with the exception that 1-bromo-5-chloro-2-fluoro-3-nitrobenzene was used instead of 4-chloro-2-fluoro-1-nitrobenzene in Step 1-8 of Example 1.

¹H NMR (500MHz, MeOD): δ 9.28(s, 1H), 7.87(m, 2H), 4.77(m, 2H), 3.59(m, 1H), 2.93(m, 2H), 2.18(m, 2H), 2.08(m, 2H), 2.02(m, 1H), 1.75(m, 2H), 1.55(m, 1H).

10

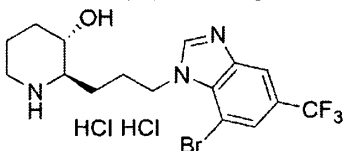
Example 70: Preparation of (2R,3S)-2-(3-(5-bromo-7-chloro-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol dihydrochloride



15 The title compound (23 mg, yield: 89%) was obtained in the same manner as in Example 1, with the exception that 5-bromo-1-chloro-2-fluoro-3-nitrobenzene was used instead of 4-chloro-2-fluoro-1-nitrobenzene in Step 1-8 of Example 1.

¹H NMR (500MHz, MeOD): δ 9.35(s, 1H), 8.00(s, 1H), 7.84(s, 1H), 4.78(m, 2H), 3.58(m, 1H), 2.97(m, 2H), 2.21(m, 2H), 2.08(m, 2H), 1.99(m, 1H), 1.74(m, 2H), 1.53(m, 1H).

20 **Example 71: Preparation of (2R,3S)-2-(3-(7-bromo-5-(trifluoromethyl)-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol dihydrochloride**

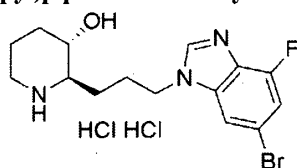


The title compound (19 mg, yield: 89%) was obtained in the same manner as in Example 1, with the exception that 1-bromo-2-fluoro-3-nitro-5-(trifluoromethyl)benzene was used instead

of 4-chloro-2-fluoro-1-nitrobenzene in Step 1-8 of Example 1.

¹H NMR (500MHz, MeOD): δ 9.26(s, 1H), 8.11(s, 1H), 8.02(s, 1H), 3.55(m, 1H), 2.90(m, 2H), 2.18(m, 2H), 2.05(m, 2H), 1.94(m, 1H), 1.71(m, 2H), 1.52(m, 1H)

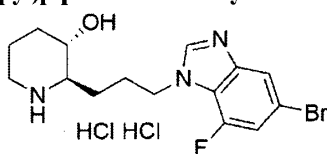
5 **Example 72: Preparation of (2R,3S)-2-(3-(6-bromo-4-fluoro-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol dihydrochloride**



The title compound (23 mg, yield: 90%) was obtained in the same manner as in Example 45, with the exception that 6-bromo-4-fluoro-1H-benzo[d]imidazole was used instead of 5-bromo-4-methyl-1H-benzo[d]imidazole in Step 45-1 of Example 45.

¹H NMR (500MHz, MeOD): δ 9.44(s, 1H), 8.12(s, 1H), 7.65(d, 1H), 4.55(m, 2H), 3.65(m, 1H), 3.57(m, 1H), 2.98(m, 2H), 2.26(m, 2H), 2.10(m, 2H), 1.98(m, 1H), 1.74(m, 2H), 1.54(m, 1H)

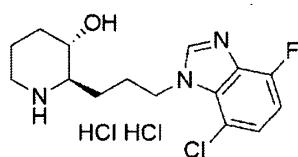
15 **Example 73: Preparation of (2R,3S)-2-(3-(5-bromo-7-fluoro-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol dihydrochloride**



The title compound (24 mg, yield: 92%) was obtained in the same manner as in Example 45, with the exception that 6-bromo-4-fluoro-1H-benzo[d]imidazole was used instead of 5-bromo-4-methyl-1H-benzo[d]imidazole in Step 45-1 of Example 45.

¹H NMR (500MHz, MeOD): δ 9.55(s, 1H), 7.92(s, 1H), 7.69(d, 1H), 4.65(m, 2H), 3.61(m, 1H), 2.96(m, 2H), 2.15(m, 2H), 2.07(m, 2H), 1.98(m, 1H), 1.75(m, 2H), 1.53(m, 1H)

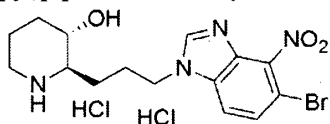
25 **Example 74: Preparation of (2R,3S)-2-(3-(7-chloro-4-fluoro-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol dihydrochloride**



The title compound (9 mg, yield: 45%) was obtained in the same manner as in Example 45, with the exception that 7-chloro-4-fluoro-1H-benzo[d]imidazole was used instead of 5-bromo-4-methyl-1H-benzo[d]imidazole in Step 45-1 of Example 45.

5 ^1H NMR (500MHz, MeOD): δ 9.43(s, 1H), 7.60(dd, 1H), 7.38(t, 1H), 4.82(m, 2H), 3.54(m, 1H), 2.98(m, 2H), 2.24(m, 2H), 2.16(m, 2H), 1.99(m, 1H), 1.72(m, 2H), 1.55(m, 1H)

Example 75: Preparation of (2R,3S)-2-(3-(5-bromo-4-nitro-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol dihydrochloride

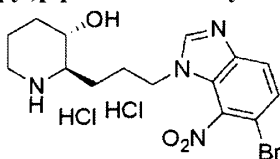


10

The title compound (23 mg, yield: 90%) was obtained in the same manner as in Example 45, with the exception that 5-bromo-4-nitro-1H-benzo[d]imidazole was used instead of 5-bromo-4-methyl-1H-benzo[d]imidazole in Step 45-1 of Example 45.

15 ^1H NMR (500MHz, MeOD): δ 8.81(s, 1H), 7.95(d, 1H), 7.82(d, 1H), 4.51(m, 2H), 3.53(m, 1H), 2.92(m, 2H), 2.10(m, 2H), 2.04(m, 3H), 1.68(m, 2H), 1.57(m, 1H)

Example 76: Preparation of (2R,3S)-2-(3-(6-bromo-7-nitro-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol dihydrochloride

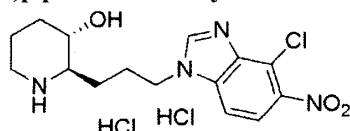


20

The title compound (18 mg, yield: 87%) was obtained in the same manner as in Example 45, with the exception that 5-bromo-4-nitro-1H-benzo[d]imidazole was used instead of 5-bromo-4-methyl-1H-benzo[d]imidazole in Step 45-1 of Example 45.

^1H NMR (500MHz, MeOD): δ 8.51(s, 1H), 7.84(d, 1H), 7.68(d, 1H), 4.24(t, 1H), 3.52(m, 1H), 2.97(m, 2H), 2.00(m, 5H), 1.73(m, 1H), 1.63(m, 1H), 1.53(m, 1H)

Example 77: Preparation of (2R,3S)-2-(3-(4-chloro-5-nitro-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol dihydrochloride

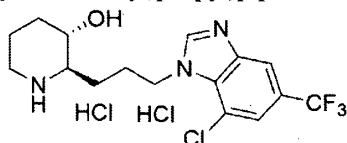


5 The title compound (23 mg, yield: 92%) was obtained in the same manner as in Example 45, with the exception that 4-chloro-5-nitro-1H-benzo[d]imidazole was used instead of 5-bromo-4-methyl-1H-benzo[d]imidazole in Step 45-1 of Example 45.

¹H NMR (500MHz, MeOD): δ 8.76(s, 1H), 8.06(d, 1H), 7.86(d, 1H), 4.51(m, 2H), 3.66(m, 1H), 2.98(m, 2H), 2.08(m, 2H), 1.99(m 3H), 1.74(m, 3H), 1.56(m, 1H)

10

Example 78: Preparation of (2R,3S)-2-(3-(7-chloro-5-(trifluoromethyl)-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol dihydrochloride

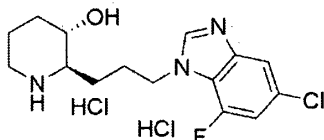


15 The title compound (19 mg, yield: 87%) was obtained in the same manner as in Example 1, with the exception that 1-chloro-2-fluoro-3-nitro-5-(trifluoromethyl)benzene was used instead of 4-chloro-2-fluoro-1-nitrobenzene in Step 1-8 of Example 1.

¹H NMR (500MHz, MeOD): δ 9.32(m, 1H), 8.07(d, 1H), 7.83(d, 1H), 4.78(s, 1H), 3.58(m, 1H), 3.44(m, 1H), 3.00(m, 1H), 2.93(m, 2H), 2.20-2.05(m, 4H), 2.02(m, 1H), 1.97(m, 2H), 1.52(m, 1H)

20

Example 79: Preparation of (2R,3S)-2-(3-(5-chloro-7-fluoro-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol dihydrochloride



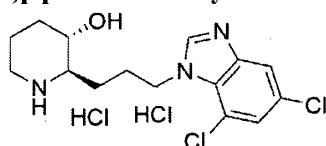
25 The title compound (22 mg, yield: 88%) was obtained in the same manner as in Example 1, with the exception that 5-chloro-1,2-difluoro-3-nitrobenzene was used instead of 4-chloro-2-

fluoro-1-nitrobenzene in Step 1-8 of Example 1.

¹H NMR (500MHz, MeOD): δ 9.39(m, 1H), 7.71(m, 1H), 7.49(m, 1H), 4.59(m, 2H), 3.57(m, 1H), 3.44(m, 1H), 3.29(m, 1H), 2.97(m, 2H), 2.18(m, 2H), 2.07(m, 1H), 1.72(m, 2H), 1.51(m, 1H)

5

Example 80: Preparation of (2R,3S)-2-(3-(5,7-dichloro-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol dihydrochloride

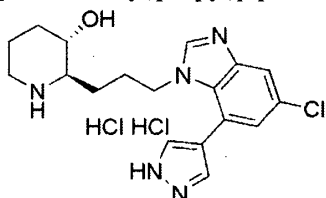


The title compound (7 mg, yield: 31%) was obtained in the same manner as in Example 1, with the exception that 1,5-dichloro-2-fluoro-3-nitrobenzene was used instead of 4-chloro-2-fluoro-1-nitrobenzene in Step 1-8 of Example 1.

¹H NMR (500MHz, MeOD): δ 9.30(s, 1H), 7.84(s, 1H), 7.69(s, 1H), 4.78(m, 2H), 3.69(m, 1H), 3.30(m, 1H), 2.99(m, 2H), 2.25(m, 2H), 2.16(m, 2H), 2.06(m, 1H), 1.78(m, 2H), 1.51(m, 1H)

15

Example 81: Preparation of (2R,3S)-2-(3-(5-chloro-7-(1H-pyrazol-4-yl)-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol dihydrochloride



The title compound (8 mg, yield: 14%) was obtained in the same manner as in Example 20, with the exception that tert-butyl (2R,3S)-2-(3-(7-bromo-5-chloro-1H-benzo[d]imidazol-1-yl)propyl)-3-((tert-butyldimethylsilyl)oxy)piperidine-1-carboxylate was used instead of tert-butyl (2R,3S)-2-(3-(4-bromo-1H-benzo[d]imidazol-1-yl)propyl)-3-((tert-butyldimethylsilyl)oxy)piperidine-1-carboxylate, and that (1H-pyrazol-4-yl)boronic acid was used instead of (3-fluorophenyl)boronic acid in Step 20-2 of Example 20.

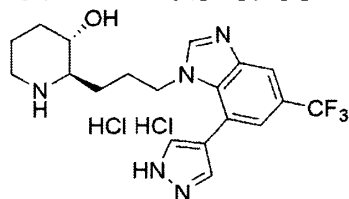
¹H NMR (500MHz, MeOD): δ 9.37(s, 1H), 7.97(s, 2H), 7.88(s, 1H), 7.49(s, 1H),

25

4.28(m, 2H), 3.44(m, 1H), 2.91(m, 1H), 2.75(m, 1H), 1.96(m, 2H), 1.74-1.62(m, 3H), 1.50(m, 1H), 1.36(m, 1H)

Example 82: Preparation of (2R,3S)-2-(3-(7-(1H-pyrazol-4-yl)-5-(trifluoromethyl)-

1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol dihydrochloride

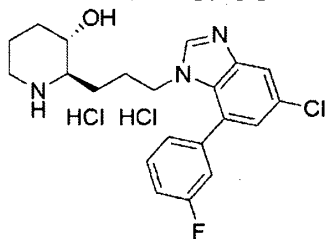


The title compound (9 mg, yield: 15%) was obtained in the same manner as in Example 20, with the exception that tert-butyl (2R,3S)-2-(3-(7-bromo-5-(trifluoromethyl)-1H-benzo[d]imidazol-1-yl)propyl)-3-((tert-butyldimethylsilyl)oxy)piperidine-1-carboxylate was used instead of tert-butyl (2R,3S)-2-(3-(4-bromo-1H-benzo[d]imidazol-1-yl)propyl)-3-((tert-butyldimethylsilyl)oxy)piperidine-1-carboxylate in Step 20-2 of Example 20.

¹H NMR (500MHz, MeOD): δ 9.06(m, 1H), 8.10(s, 1H), 7.97(s, 2H), 7.61(s, 1H), 4.26(m, 2H), 3.44(m, 1H), 3.17(m, 1H), 2.93(m, 1H), 2.76(m, 1H), 1.99(m, 2H), 1.67(m, 3H), 1.53(m, 1H), 1.49(m, 1H)

15

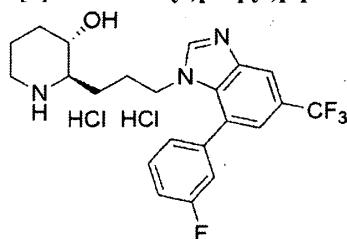
Example 83: Preparation of (2R,3S)-2-(3-(5-chloro-7-(3-fluorophenyl)-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol dihydrochloride



The title compound (13 mg, yield: 22%) was obtained in the same manner as in Example 20, with the exception that tert-butyl (2R,3S)-2-(3-(7-bromo-5-chloro-1H-benzo[d]imidazol-1-yl)propyl)-3-((tert-butyldimethylsilyl)oxy)piperidine-1-carboxylate was used instead of tert-butyl (2R,3S)-2-(3-(4-bromo-1H-benzo[d]imidazol-1-yl)propyl)-3-((tert-butyldimethylsilyl)oxy)piperidine-1-carboxylate in Step 20-2 of Example 20.

¹H NMR (500MHz, MeOD): δ 9.39(s, 1H), 7.95(d, 1H), 7.64(m, 1H), 7.62(m, 1H), 7.39(m, 2H), 7.34(m, 1H), 4.15(m, 1H), 4.05(m, 2H), 3.44(m, 1H), 3.18(m, 1H), 2.91(t, 1H), 2.87(s, 1H), 2.01(m, 2H), 1.96(m, 2H), 1.50(m, 2H), 1.33(m, 1H)

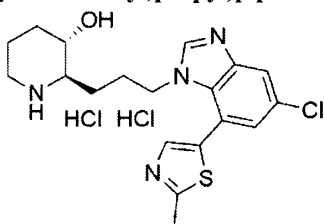
5 **Example 84: Preparation of (2R,3S)-2-(3-(7-(3-fluorophenyl)-5-(trifluoromethyl)-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol dihydrochloride**



The title compound (11 mg, yield: 20%) was obtained in the same manner as in Example 20, with the exception that tert-butyl (2R,3S)-2-(3-(7-bromo-5-(trifluoromethyl)-1H-benzo[d]imidazol-1-yl)propyl)-3-((tert-butyldimethylsilyl)oxy)piperidine-1-carboxylate was used instead of tert-butyl (2R,3S)-2-(3-(4-bromo-1H-benzo[d]imidazol-1-yl)propyl)-3-((tert-butyldimethylsilyl)oxy)piperidine-1-carboxylate in Step 20-2 of Example 20.

¹H NMR (500MHz, MeOD): δ 9.62(s, 1H), 8.24(m, 2H), 7.74(m, 1H), 7.64(m, 1H), 7.42(m, 3H), 4.15(m, 2H), 3.43(m, 1H), 3.21(m, 1H), 2.91(m, 1H), 2.74(m, 1H), 1.97(m, 2H), 1.73(m, 3H), 1.52(m, 2H), 1.33(m, 1H)

20 **Example 85: Preparation of (2R,3S)-2-(3-(5-chloro-7-(2-methylthiazol-5-yl)-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol**

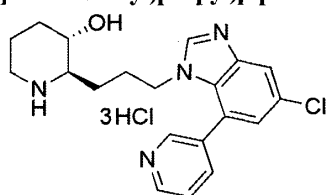


The title compound (6 mg, yield: 12%) was obtained in the same manner as in Example 20, with the exception that tert-butyl (2R,3S)-2-(3-(7-bromo-5-chloro-1H-benzo[d]imidazol-1-yl)propyl)-3-((tert-butyldimethylsilyl)oxy)piperidine-1-carboxylate was used instead of tert-butyl (2R,3S)-2-(3-(4-bromo-1H-benzo[d]imidazol-1-yl)propyl)-3-((tert-

butyldimethylsilyl)oxy)piperidine-1-carboxylate, and that (2-methylthiazol-5-yl)boronic acid was used instead of (3-fluorophenyl)boronic acid in Step 20-2 of Example 20.

¹H NMR (500MHz, MeOD): δ 9.68(s, 1H), 8.06(m, 2H), 7.71(s, 1H), 4.30(t, 2H), 3.52(m, 1H), 3.27(m, 1H), 2.95(m, 1H), 2.84(s, 3H), 2.83(s, 1H), 2.05-1.89(m, 4H), 1.88(m, 2H),
 5 1.74(m, 2H)

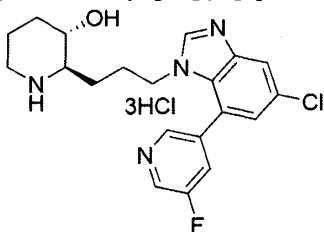
Example 86: Preparation of (2R,3S)-2-(3-(5-chloro-7-(pyridin-3-yl)-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol trihydrochloride



10 The title compound (8 mg, yield: 15%) was obtained in the same manner as in Example 20, with the exception that tert-butyl (2R,3S)-2-(3-(7-bromo-5-chloro-1H-benzo[d]imidazol-1-yl)propyl)-3-((tert-butyldimethylsilyl)oxy)piperidine-1-carboxylate was used instead of tert-butyl (2R,3S)-2-(3-(4-bromo-1H-benzo[d]imidazol-1-yl)propyl)-3-((tert-butyldimethylsilyl)oxy)piperidine-1-carboxylate, and that pyridin-3-ylboronic acid was used
 15 instead of (3-fluorophenyl)boronic acid in Step 20-2 of Example 20.

¹H NMR (500MHz, MeOD): δ 9.55(s, 1H), 9.16(s, 1H), 9.03(s, 1H), 8.74(s, 1H), 8.18(s, 1H), 8.09(s, 1H), 7.68(s, 1H), 4.10(m, 2H), 3.46(m, 1H), 3.24(m, 1H), 2.92(m, 1H), 2.78(m, 1H), 2.03(m, 1H), 1.98(m, 1H), 1.95-1.93(m, 3H), 1.52(m, 1H), 1.44(m, 2H)

20 **Example 87: Preparation of (2R,3S)-2-(3-(5-chloro-7-(5-fluoropyridin-3-yl)-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol trihydrochloride**

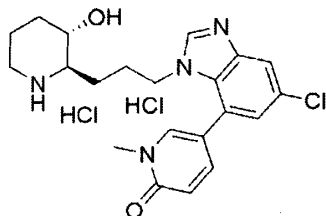


The title compound (9 mg, yield: 16%) was obtained in the same manner as in Example 20, with the exception that tert-butyl (2R,3S)-2-(3-(7-bromo-5-chloro-1H-benzo[d]imidazol-1-

yl)propyl)-3-((tert-butyldimethylsilyl)oxy)piperidine-1-carboxylate was used instead of tert-butyl (2R,3S)-2-(3-(4-bromo-1H-benzo[d]imidazol-1-yl)propyl)-3-((tert-butyldimethylsilyl)oxy)piperidine-1-carboxylate, and that (5-fluoropyridin-3-yl)boronic acid was used instead of (3-fluorophenyl)boronic acid in Step 20-2 of Example 20.

5 ¹H NMR (500MHz, MeOD): δ 9.70(s, 1H), 8.86-8.75(m, 2H), 8.19(m, 1H), 8.07(s, 1H), 7.67(s, 1H), 4.11(m, 2H), 3.47(m, 1H), 3.24(m, 1H), 2.93(td, 1H), 2.77(s, 1H), 2.01-2.00 (m, 2H), 1.93-1.82(m, 3H), 1.73(s, 1H), 1.65(m, 1H)

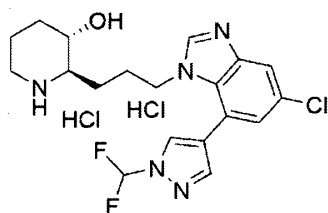
Example 88: 5-(5-chloro-1-(3-((2R,3S)-3-hydroxypiperidin-2-yl)propyl)-1H-benzo[d]imidazol-7-yl)-1-methylpyridin-2(1H)-one dihydrochloride



The title compound (10 mg, yield: 16%) was obtained in the same manner as in Example 20, with the exception that tert-butyl (2R,3S)-2-(3-(7-bromo-5-chloro-1H-benzo[d]imidazol-1-yl)propyl)-3-((tert-butyldimethylsilyl)oxy)piperidine-1-carboxylate was used instead of tert-butyl (2R,3S)-2-(3-(4-bromo-1H-benzo[d]imidazol-1-yl)propyl)-3-((tert-butyldimethylsilyl)oxy)piperidine-1-carboxylate, and that (1-methyl-6-oxo-1,6-dihydropyridin-3-yl)boronic acid was used instead of (3-fluorophenyl)boronic acid in Step 20-2 of Example 20.

¹H NMR (500MHz, MeOD): δ 9.55(m, 1H), 7.98(d, 2H), 7.74(d, 1H), 7.57(s, 1H), 6.71(d, 1H), 4.32(m, 2H), 3.67(s, 3H), 3.44(s, 1H), 3.24(m, 1H), 2.88(t, 1H), 2.80(s, 1H), 2.03-1.89(m, 4H), 1.71(m, 2H), 1.49(m, 2H)

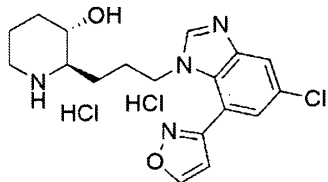
Example 89: Preparation of (2R,3S)-2-(3-(5-chloro-7-(1-(difluoromethyl)-1H-pyrazol-4-yl)-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol dihydrochloride



The title compound (9 mg, yield: 14%) was obtained in the same manner as in Example 20, with the exception that tert-butyl (2R,3S)-2-(3-(7-bromo-5-chloro-1H-benzo[d]imidazol-1-yl)propyl)-3-((tert-butyl(dimethyl)silyl)oxy)piperidine-1-carboxylate was used instead of tert-butyl (2R,3S)-2-(3-(4-bromo-1H-benzo[d]imidazol-1-yl)propyl)-3-((tert-butyl(dimethyl)silyl)oxy)piperidine-1-carboxylate, and that (1-(difluoromethyl)-1H-pyrazol-4-yl)boronic acid was used instead of (3-fluorophenyl)boronic acid in Step 20-2 of Example 20.

¹H NMR (500MHz, MeOD): δ 9.46(s, 1H), 8.50(s, 1H), 8.05(s, 1H), 7.94(s, 1H), 7.56(s, 1H), 4.28(m, 2H), 3.49(m, 1H), 3.24(m, 1H), 2.94(t, 1H), 2.89(m, 1H), 2.01(m, 2H), 1.80(m, 2H), 1.72(m, 2H), 1.64(m, 1H), 1.55(m, 1H)

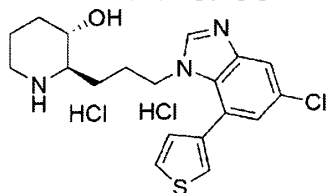
Example 90: Preparation of (2R,3S)-2-(3-(5-chloro-7-(isoxazol-3-yl)-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol dihydrochloride



The title compound (7 mg, yield: 12%) was obtained in the same manner as in Example 20, with the exception that tert-butyl (2R,3S)-2-(3-(7-bromo-5-chloro-1H-benzo[d]imidazol-1-yl)propyl)-3-((tert-butyl(dimethyl)silyl)oxy)piperidine-1-carboxylate was used instead of tert-butyl (2R,3S)-2-(3-(4-bromo-1H-benzo[d]imidazol-1-yl)propyl)-3-((tert-butyl(dimethyl)silyl)oxy)piperidine-1-carboxylate, and that isoxazol-3-ylboronic acid was used instead of (3-fluorophenyl)boronic acid in Step 20-2 of Example 20.

¹H NMR (500MHz, MeOD): δ 9.53(s, 1H), 8.04(m, 2H), 7.92(s, 1H), 7.69(m, 1H), 4.61(m, 2H), 3.61(m, 1H), 3.02(m, 2H), 2.28(m, 2H), 2.04(m, 2H), 1.99(m, 1H), 1.78(m, 2H), 1.52(m, 1H)

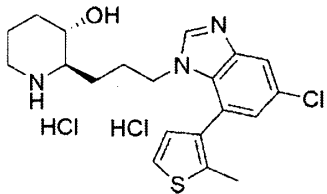
Example 91: Preparation of (2R,3S)-2-(3-(5-chloro-7-(thiophen-3-yl)-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol dihydrochloride



The title compound (24 mg, yield: 31%) was obtained in the same manner as in Example 20, with the exception that tert-butyl (2R,3S)-2-(3-(7-bromo-5-chloro-1H-benzo[d]imidazol-1-yl)propyl)-3-((tert-butyldimethylsilyl)oxy)piperidine-1-carboxylate was used instead of tert-butyl (2R,3S)-2-(3-(4-bromo-1H-benzo[d]imidazol-1-yl)propyl)-3-((tert-butyldimethylsilyl)oxy)piperidine-1-carboxylate, and that thiophen-3-ylboronic acid was used instead of (3-fluorophenyl)boronic acid in Step 20-2 of Example 20.

¹H NMR (500MHz, MeOD): δ 9.52 (s, 1H), 7.93(s, 1H), 7.73(d, 2H), 7.52(s, 1H), 7.36(d, 1H), 4.22(m, 2H), 3.48(m, 1H), 3.23(m, 1H), 2.93(t, 1H), 2.76(m, 1H), 2.02(m, 2H), 1.78-1.63(m, 3H), 1.62(m, 1H), 1.57(m, 1H), 1.55(m, 1H)

Example 92: Preparation of (2R,3S)-2-(3-(5-chloro-7-(2-methylthiophen-3-yl)-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol dihydrochloride

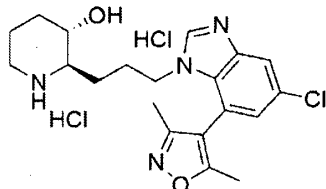


The title compound (20 mg, yield: 25%) was obtained in the same manner as in Example 20, with the exception that tert-butyl (2R,3S)-2-(3-(7-bromo-5-chloro-1H-benzo[d]imidazol-1-yl)propyl)-3-((tert-butyldimethylsilyl)oxy)piperidine-1-carboxylate was used instead of tert-butyl (2R,3S)-2-(3-(4-bromo-1H-benzo[d]imidazol-1-yl)propyl)-3-((tert-butyldimethylsilyl)oxy)piperidine-1-carboxylate, and that (2-methylthiophen-3-yl)boronic acid was used instead of (3-fluorophenyl)boronic acid in Step 20-2 of Example 20.

¹H NMR (500MHz, MeOD): δ 9.56(s, 1H), 7.95(s, 1H), 7.47(d, 2H), 7.15(d, 1H), 4.22(m, 1H), 4.15(m, 1H), 3.50(m, 1H), 3.25(m, 1H), 2.91(t, 1H), 2.81(m, 1H), 2.34(d, 3H),

2.01(m, 2H), 1.99-1.96(m, 3H), 1.79(m, 1H), 1.65(m, 1H), 1.56(m, 1H)

Example 93: Preparation of (2R,3S)-2-(3-(5-chloro-7-(3,5-dimethylisoxazol-4-yl)-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol dihydrochloride



5

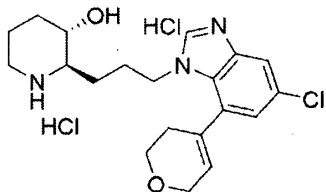
The title compound (19 mg, yield: 24%) was obtained in the same manner as in Example 20, with the exception that tert-butyl (2R,3S)-2-(3-(7-bromo-5-chloro-1H-benzo[d]imidazol-1-yl)propyl)-3-((tert-butyldimethylsilyl)oxy)piperidine-1-carboxylate was used instead of tert-butyl (2R,3S)-2-(3-(4-bromo-1H-benzo[d]imidazol-1-yl)propyl)-3-((tert-butyldimethylsilyl)oxy)piperidine-1-carboxylate, and that (3,5-dimethylisoxazol-4-yl)boronic acid was used instead of (3-fluorophenyl)boronic acid in Step 20-2 of Example 20.

10

¹H NMR (500MHz, MeOD): δ 9.58(s, 1H), 8.04(s, 1H), 7.71(s, 1H), 4.23(m, 2H), 3.61(m, 1H), 3.01(m, 1H), 2.97(m, 1H), 2.39(s, 3H), 2.18(s, 3H), 2.17-2.11(m, 3H), 2.04(m, 2H), 1.86(m, 2H), 1.71(m, 2H)

15

Example 94: Preparation of (2R,3S)-2-(3-(5-chloro-7-(3,6-dihydro-2H-pyran-4-yl)-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol dihydrochloride

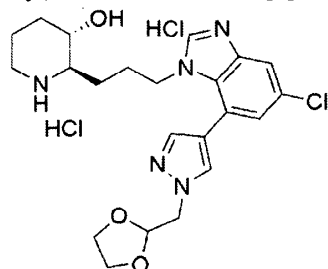


The title compound (22 mg, yield: 27%) was obtained in the same manner as in Example 20, with the exception that tert-butyl (2R,3S)-2-(3-(7-bromo-5-chloro-1H-benzo[d]imidazol-1-yl)propyl)-3-((tert-butyldimethylsilyl)oxy)piperidine-1-carboxylate was used instead of tert-butyl (2R,3S)-2-(3-(4-bromo-1H-benzo[d]imidazol-1-yl)propyl)-3-((tert-butyldimethylsilyl)oxy)piperidine-1-carboxylate, and that (3,6-dihydro-2H-pyran-4-yl)boronic acid was used instead of (3-fluorophenyl)boronic acid in Step 20-2 of Example 20.

20

¹H NMR (500MHz, MeOD): δ 9.60(s, 1H), 7.85(s, 1H), 7.51(s, 1H), 6.08(s, 1H), 4.60(t, 2H), 4.39(s, 2H), 4.03(t, 2H), 3.61(m, 1H), 2.99(m, 2H), 2.58(s, 2H), 2.12-1.96(m, 5H), 1.72(m, 2H), 1.51(m, 1H)

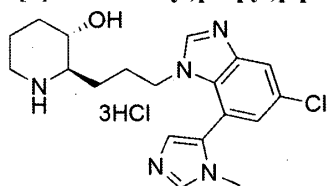
Example 95: Preparation of (2R,3S)-2-(3-(7-(1-((1,3-dioxolan-2-yl)methyl)-1H-pyrazol-4-yl)-5-chloro-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol dihydrochloride



The title compound (17 mg, yield: 22%) was obtained in the same manner as in Example 20, with the exception that tert-butyl (2R,3S)-2-(3-(7-bromo-5-chloro-1H-benzo[d]imidazol-1-yl)propyl)-3-((tert-butyldimethylsilyl)oxy)piperidine-1-carboxylate was used instead of tert-butyl (2R,3S)-2-(3-(4-bromo-1H-benzo[d]imidazol-1-yl)propyl)-3-((tert-butyldimethylsilyl)oxy)piperidine-1-carboxylate, and that (1-((1,3-dioxolan-2-yl)methyl)-1H-pyrazol-4-yl)boronic acid was used instead of (3-fluorophenyl)boronic acid in Step 20-2 of Example 20.

¹H NMR (500MHz, MeOD): δ 9.62(s, 1H), 8.07(s, 1H), 7.93(s, 1H), 7.82(s, 1H), 7.53(s, 1H), 4.43(m, 2H), 4.41(m, 2H), 3.97(m, 2H), 3.56(m, 1H), 3.25(m, 1H), 2.96(t, 1H), 2.96(s, 1H), 2.01(m, 1H), 1.82-1.65(m, 5H), 1.56(m, 1H), 1.51(m, 1H)

Example 96: Preparation of (2R,3S)-2-(3-(5-chloro-7-(1-methyl-1H-imidazol-5-yl)-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol trihydrochloride

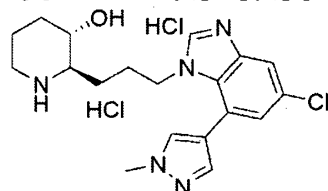


The title compound (20 mg, yield: 29%) was obtained in the same manner as in Example 20, with the exception that tert-butyl (2R,3S)-2-(3-(7-bromo-5-chloro-1H-benzo[d]imidazol-1-yl)propyl)piperidine-1-carboxylate was used instead of tert-butyl (2R,3S)-2-(3-(7-bromo-5-chloro-1H-benzo[d]imidazol-1-yl)propyl)piperidine-1-carboxylate.

yl)propyl)-3-((tert-butyldimethylsilyl)oxy)piperidine-1-carboxylate was used instead of tert-butyl (2R,3S)-2-(3-(4-bromo-1H-benzo[d]imidazol-1-yl)propyl)-3-((tert-butyldimethylsilyl)oxy)piperidine-1-carboxylate, and that (1-methyl-1H-imidazol-5-yl)boronic acid was used instead of (3-fluorophenyl)boronic acid in Step 20-2 of Example 20.

- 5 ¹H NMR (500MHz, MeOD): δ 9.20(s, 1H), 9.12(d, 1H), 8.01(s, 1H), 8.00(s, 1H), 7.68(s, 1H), 4.20(s, 1H), 3.94(s, 1H), 3.78(s, 3H), 3.47(m, 1H), 2.94(t, 1H), 2.89(m, 1H), 2.06(m, 1H), 1.97(m, 1H), 1.85(m, 2H), 1.83-1.74(m, 3H), 1.53(m, 2H)

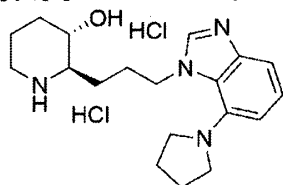
Example 97: Preparation of (2R,3S)-2-(3-(5-chloro-7-(1-methyl-1H-pyrazol-4-yl)-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol dihydrochloride



- The title compound (15 mg, yield: 25%) was obtained in the same manner as in Example 20, with the exception that tert-butyl (2R,3S)-2-(3-(7-bromo-5-chloro-1H-benzo[d]imidazol-1-yl)propyl)-3-((tert-butyldimethylsilyl)oxy)piperidine-1-carboxylate was used instead of tert-butyl (2R,3S)-2-(3-(4-bromo-1H-benzo[d]imidazol-1-yl)propyl)-3-((tert-butyldimethylsilyl)oxy)piperidine-1-carboxylate, and that (1-methyl-1H-pyrazol-4-yl)boronic acid was used instead of (3-fluorophenyl)boronic acid in Step 20-2 of Example 20.

- ¹H NMR (500MHz, MeOD): δ 9.30(s, 1H), 7.97(s, 1H), 7.87(s, 1H), 7.76(s, 1H), 7.45(s, 1H), 4.32(m, 2H), 4.02(s, 3H), 3.24(m, 1H), 2.92(m, 1H), 2.77(m, 1H), 2.00(m, 2H), 1.71(m, 4H), 1.51(m, 1H), 1.40(m, 1H)

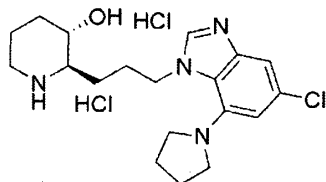
Example 98: Preparation of (2R,3S)-2-(3-(7-(pyrrolidin-1-yl)-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol dihydrochloride



The title compound (12 mg, yield: 20%) was obtained in the same manner as in Example 18, with the exception that tert-butyl (2R,3S)-2-(3-(7-bromo-1H-benzo[d]imidazol-1-yl)propyl)-3-((tert-butyldimethylsilyl)oxy)piperidine-1-carboxylate was used instead of tert-butyl (2R,3S)-2-(3-(4-bromo-1H-benzo[d]imidazol-1-yl)propyl)-3-((tert-butyldimethylsilyl)oxy)piperidine-1-carboxylate in Step 18-2 of Example 18.

¹H NMR (500MHz, MeOD): δ 9.44(s, 1H), 7.55(m, 3H), 4.76(t, 2H), 3.56(m, 1H), 3.20(m, 4H), 2.94(m, 2H), 2.20(m, 2H), 2.07(m, 5H), 2.00(m, 3H), 1.74(m, 2H), 1.53(m, 1H)

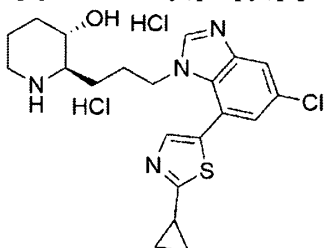
Example 99: Preparation of (2R,3S)-2-(3-(5-chloro-7-(pyrrolidin-1-yl)-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol dihydrochloride



The title compound (13 mg, yield: 21%) was obtained in the same manner as in Example 18, with the exception that tert-butyl (2R,3S)-2-(3-(7-bromo-5-chloro-1H-benzo[d]imidazol-1-yl)propyl)-3-((tert-butyldimethylsilyl)oxy)piperidine-1-carboxylate was used instead of tert-butyl (2R,3S)-2-(3-(4-bromo-1H-benzo[d]imidazol-1-yl)propyl)-3-((tert-butyldimethylsilyl)oxy)piperidine-1-carboxylate in Step 18-2 of Example 18.

¹H NMR (500MHz, MeOD): δ 9.46(s, 1H), 7.58(d, 1H), 7.47(d, 1H), 4.72(m, 2H), 3.53(m, 1H), 3.21(m, 4H), 2.94(m, 2H), 2.20(m, 2H), 2.11(m, 5H), 1.96(m, 2H), 1.77(m, 1H), 1.63(m, 1H), 1.52(m, 1H)

Example 100: Preparation of (2R,3S)-2-(3-(5-chloro-7-(2-cyclopropylthiazol-5-yl)-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol dihydrochloride

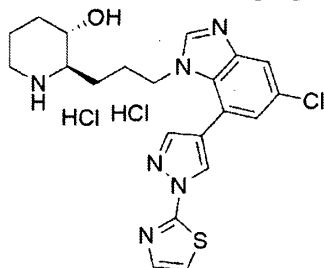


The title compound (12 mg, yield: 25%) was obtained in the same manner as in Example 20, with the exception that tert-butyl (2R,3S)-2-(3-(7-bromo-5-chloro-1H-benzo[d]imidazol-1-yl)propyl)-3-((tert-butyldimethylsilyl)oxy)piperidine-1-carboxylate was used instead of tert-butyl (2R,3S)-2-(3-(4-bromo-1H-benzo[d]imidazol-1-yl)propyl)-3-((tert-butyldimethylsilyl)oxy)piperidine-1-carboxylate, and that (2-cyclopropylthiazol-5-yl)boronic acid was used instead of (3-fluorophenyl)boronic acid in Step 20-2 of Example 20.

¹H NMR (500MHz, MeOD): δ 9.51(s, 1H), 7.97(s, 1H), 7.73(s, 1H), 7.70(s, 1H), 4.63(m, 2H), 3.42(m, 1H), 3.22(m, 1H), 2.93(m, 1H), 2.77(m, 1H), 2.50(m, 1H), 1.95(m, 2H), 1.68(m, 4H), 1.50(m, 2H), 1.23(m, 2H), 1.11(m, 2H)

10

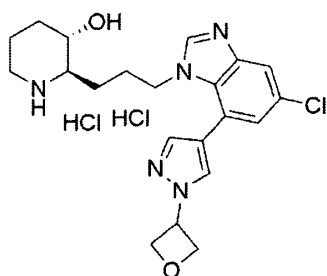
Example 101: Preparation of (2R,3S)-2-(3-(5-chloro-7-(1-(thiazol-2-yl)-1H-pyrazol-4-yl)-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol dihydrochloride



The title compound (17 mg, yield: 30%) was obtained in the same manner as in Example 20, with the exception that tert-butyl (2R,3S)-2-(3-(7-bromo-5-chloro-1H-benzo[d]imidazol-1-yl)propyl)-3-((tert-butyldimethylsilyl)oxy)piperidine-1-carboxylate was used instead of tert-butyl (2R,3S)-2-(3-(4-bromo-1H-benzo[d]imidazol-1-yl)propyl)-3-((tert-butyldimethylsilyl)oxy)piperidine-1-carboxylate, and that (1-(thiazol-2-yl)-1H-pyrazol-4-yl)boronic acid was used instead of (3-fluorophenyl)boronic acid in Step 20-2 of Example 20.

¹H NMR (500MHz, MeOD): δ 9.41(s, 1H), 8.83(s, 1H), 8.10(s, 1H), 7.95(s, 1H), 7.65(s, 1H), 7.61(s, 1H), 7.47(s, 1H), 4.37(m, 2H), 3.44(m, 1H), 3.18(m, 1H), 2.87(m, 1H), 2.78(m, 1H), 1.92(m, 2H), 1.82(m, 2H), 1.65(m, 2H), 1.43(m, 2H)

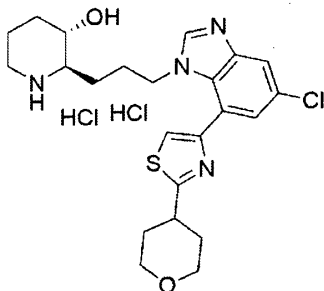
Example 102: Preparation of (2R,3S)-2-(3-(5-chloro-7-(1-(oxetan-3-yl)-1H-pyrazol-4-yl)-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol dihydrochloride



The title compound (12 mg, yield: 23%) was obtained in the same manner as in Example 20, with the exception that tert-butyl (2R,3S)-2-(3-(7-bromo-5-chloro-1H-benzo[d]imidazol-1-yl)propyl)-3-((tert-butyl dimethylsilyl)oxy)piperidine-1-carboxylate was used instead of tert-butyl (2R,3S)-2-(3-(4-bromo-1H-benzo[d]imidazol-1-yl)propyl)-3-((tert-butyl dimethylsilyl)oxy)piperidine-1-carboxylate, and that (1-(oxetan-3-yl)-1H-pyrazol-4-yl)boronic acid was used instead of (3-fluorophenyl)boronic acid in Step 20-2 of Example 20.

¹H NMR (500MHz, MeOD): δ 9.58(s, 1H), 8.15(s, 1H), 7.92(s, 1H), 7.87(s, 1H), 7.54(s, 1H), 4.68(m, 1H), 4.34(m, 2H), 4.03(m, 2H), 3.50(m, 1H), 3.22(m, 1H), 2.92(m, 1H), 2.85(m, 1H), 1.95(m, 2H), 1.78(m, 4H), 1.64(m, 1H), 1.42(m, 1H)

Example 103: Preparation of (2R,3S)-2-(3-(5-chloro-7-(2-(tetrahydro-2H-pyran-4-yl)thiazol-4-yl)-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol dihydrochloride

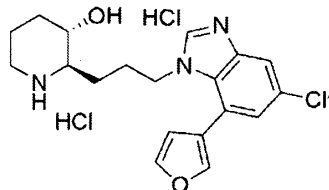


The title compound (10 mg, yield: 18%) was obtained in the same manner as in Example 20, with the exception that tert-butyl (2R,3S)-2-(3-(7-bromo-5-chloro-1H-benzo[d]imidazol-1-yl)propyl)-3-((tert-butyl dimethylsilyl)oxy)piperidine-1-carboxylate was used instead of tert-butyl (2R,3S)-2-(3-(4-bromo-1H-benzo[d]imidazol-1-yl)propyl)-3-((tert-butyl dimethylsilyl)oxy)piperidine-1-carboxylate, and that (2-(tetrahydro-2H-pyran-4-yl)thiazol-5-yl)boronic acid was used instead of (3-fluorophenyl)boronic acid in Step 20-2 of Example 20.

¹H NMR (500MHz, MeOD): δ 9.63(s, 1H), 7.98(s, 1H), 7.73(s, 1H), 7.21(s, 1H),

4.65(m, 2H), 3.84(m, 4H), 3.62(m, 4H), 3.48(m, 1H), 3.25(m, 1H), 2.94(m, 1H), 2.81(m, 1H), 1.99(m, 3H), 1.82(m, 4H), 1.54(m, 2H)

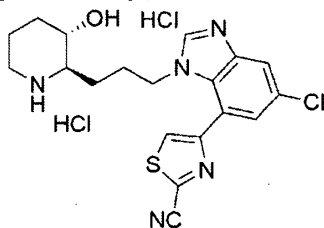
Example 104: Preparation of (2R,3S)-2-(3-(5-chloro-7-(furan-3-yl)-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol dihydrochloride



The title compound (9 mg, yield: 15%) was obtained in the same manner as in Example 20, with the exception that tert-butyl (2R,3S)-2-(3-(7-bromo-5-chloro-1H-benzo[d]imidazol-1-yl)propyl)-3-((tert-butyldimethylsilyl)oxy)piperidine-1-carboxylate was used instead of tert-butyl (2R,3S)-2-(3-(4-bromo-1H-benzo[d]imidazol-1-yl)propyl)-3-((tert-butyldimethylsilyl)oxy)piperidine-1-carboxylate, and that furan-3-ylboronic acid was used instead of (3-fluorophenyl)boronic acid in Step 20-2 of Example 20.

¹H NMR (500MHz, MeOD): δ 9.55(s, 1H), 8.05(d, 1H), 7.93(s, 1H), 7.69(d, 1H), 7.50(m, 1H), 7.32(m, 1H), 4.63(m, 2H), 3.61(m, 1H), 3.02(m, 1H), 2.94(m, 1H), 2.26(m, 2H), 2.09(m, 2H), 2.01(m, 1H), 1.78(m, 2H), 1.53(m, 1H)

Example 105: 4-(5-chloro-1-(3-((2R,3S)-3-hydroxypiperidin-2-yl)propyl)-1H-benzo[d]imidazol-7-yl)thiazole-2-carbonitrile dihydrochloride



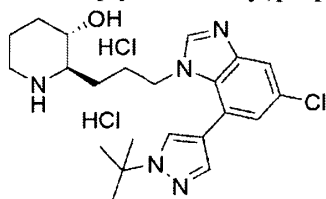
The title compound (14 mg, yield: 20%) was obtained in the same manner as in Example 20, with the exception that tert-butyl (2R,3S)-2-(3-(7-bromo-5-chloro-1H-benzo[d]imidazol-1-yl)propyl)-3-((tert-butyldimethylsilyl)oxy)piperidine-1-carboxylate was used instead of tert-butyl (2R,3S)-2-(3-(4-bromo-1H-benzo[d]imidazol-1-yl)propyl)-3-((tert-butyldimethylsilyl)oxy)piperidine-1-carboxylate, and that (2-cyanothiazol-4-yl)boronic acid was

used instead of (3-fluorophenyl)boronic acid in Step 20-2 of Example 20.

¹H NMR (500MHz, MeOD): δ 9.54(s, 1H), 8.29(s, 1H), 8.02(s, 1H), 7.79(s, 1H), 4.57(m, 2H), 3.42(m, 1H), 3.20(m, 1H), 2.91(m, 1H), 2.76(m, 1H), 1.95(m, 2H), 1.60(m, 4H), 1.52(m, 1H), 1.41(m, 1H)

5

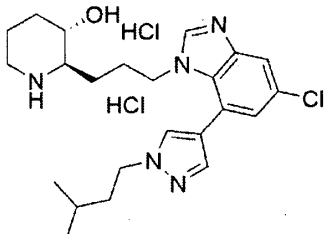
Example 106: Preparation of (2R,3S)-2-(3-(7-(1-(tert-butyl)-1H-pyrazol-4-yl)-5-chloro-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol dihydrochloride



The title compound (10 mg, yield: 18%) was obtained in the same manner as in Example 20, with the exception that tert-butyl (2R,3S)-2-(3-(7-bromo-5-chloro-1H-benzo[d]imidazol-1-yl)propyl)-3-((tert-butyldimethylsilyl)oxy)piperidine-1-carboxylate was used instead of tert-butyl (2R,3S)-2-(3-(4-bromo-1H-benzo[d]imidazol-1-yl)propyl)-3-((tert-butyldimethylsilyl)oxy)piperidine-1-carboxylate, and that (1-(tert-butyl)-1H-pyrazol-4-yl)boronic acid was used instead of (3-fluorophenyl)boronic acid in Step 20-2 of Example 20.

¹H NMR (500MHz, MeOD): δ 9.52(s, 1H), 8.14(s, 1H), 7.89(s, 1H), 7.80(s, 1H), 7.51(s, 1H), 4.36(m, 2H), 3.48(m, 1H), 3.23(m, 1H), 2.95(m, 1H), 2.82(m, 1H), 2.01(m, 2H), 1.81(m, 2H), 1.73(m, 1H), 1.53(m, 1H), 1.43(m, 1H)

Example 107: Preparation of (2R,3S)-2-(3-(5-chloro-7-(1-isopentyl-1H-pyrazol-4-yl)-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol dihydrochloride

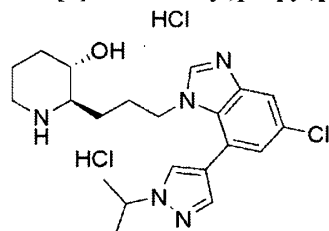


The title compound (17 mg, yield: 25%) was obtained in the same manner as in Example 20, with the exception that tert-butyl (2R,3S)-2-(3-(7-bromo-5-chloro-1H-benzo[d]imidazol-1-

yl)propyl)-3-((tert-butyldimethylsilyl)oxy)piperidine-1-carboxylate was used instead of tert-butyl (2R,3S)-2-(3-(4-bromo-1H-benzo[d]imidazol-1-yl)propyl)-3-((tert-butyldimethylsilyl)oxy)piperidine-1-carboxylate, and that (1-isopentyl-1H-pyrazol-4-yl)boronic acid was used instead of (3-fluorophenyl)boronic acid in Step 20-2 of Example 20.

- 5 ¹H NMR (500MHz, MeOD): δ 9.47(s, 1H), 8.04(s, 1H), 7.89(s, 1H), 7.78(s, 1H), 7.50(s, 1H), 4.32(m, 4H), 3.45(m, 1H), 3.23(m, 1H), 2.95(m, 1H), 2.78(m, 1H), 2.00(m, 2H), 1.87(m, 2H), 1.76(m, 2H), 1.64(m, 4H), 1.54(m, 1H), 1.42(m, 1H), 1.02(s, 6H)

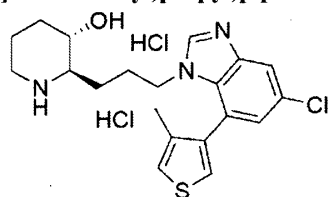
Example 108: Preparation of (2R,3S)-2-(3-(5-chloro-7-(1-isopropyl-1H-pyrazol-4-yl)-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol dihydrochloride



- The title compound (15 mg, yield: 21%) was obtained in the same manner as in Example 20, with the exception that tert-butyl (2R,3S)-2-(3-(7-bromo-5-chloro-1H-benzo[d]imidazol-1-yl)propyl)-3-((tert-butyldimethylsilyl)oxy)piperidine-1-carboxylate was used instead of tert-butyl (2R,3S)-2-(3-(4-bromo-1H-benzo[d]imidazol-1-yl)propyl)-3-((tert-butyldimethylsilyl)oxy)piperidine-1-carboxylate, and that (1-isopropyl-1H-pyrazol-4-yl)boronic acid was used instead of (3-fluorophenyl)boronic acid in Step 20-2 of Example 20.

- ¹H NMR (500MHz, MeOD): δ 9.48(s, 1H), 8.07(s, 1H), 7.90(s, 1H), 7.79(s, 1H), 7.52(s, 1H), 4.70(m, 1H), 4.30(m, 2H), 3.45(m, 1H), 3.24(m, 1H), 2.93(m, 1H), 2.80(m, 1H), 1.99(m, 2H), 1.71(m, 2H), 1.67(m, 2H), 1.59(s, 6H), 1.53(m, 1H), 1.40(m, 1H)

Example 109: Preparation of (2R,3S)-2-(3-(5-chloro-7-(4-methylthiophen-3-yl)-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol dihydrochloride

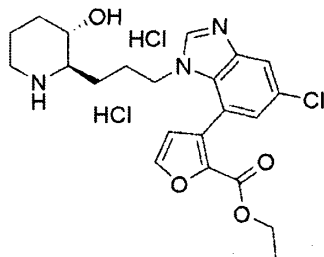


The title compound (20 mg, yield: 31%) was obtained in the same manner as in Example 20, with the exception that tert-butyl (2R,3S)-2-(3-(7-bromo-5-chloro-1H-benzo[d]imidazol-1-yl)propyl)-3-((tert-butyldimethylsilyl)oxy)piperidine-1-carboxylate was used instead of tert-butyl (2R,3S)-2-(3-(4-bromo-1H-benzo[d]imidazol-1-yl)propyl)-3-((tert-butyldimethylsilyl)oxy)piperidine-1-carboxylate, and that (4-methylthiophen-3-yl)boronic acid was used instead of (3-fluorophenyl)boronic acid in Step 20-2 of Example 20.

¹H NMR (500MHz, MeOD): δ 9.53(s, 1H), 7.95(s, 1H), 7.63(s, 1H), 7.48(s, 1H), 7.34(s, 1H), 4.23(m, 1H), 3.96(m, 1H), 3.51(m, 1H), 3.23(m, 1H), 2.96(m, 1H), 2.81(m, 1H), 2.06(d, 3H), 1.99(m, 2H), 1.76(m, 3H), 1.57(m, 2H), 1.42(m, 1H)

10

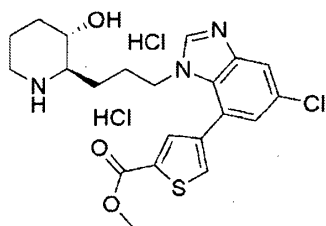
Example 110: ethyl 3-(5-chloro-1-(3-((2R,3S)-3-hydroxypiperidin-2-yl)propyl)-1H-benzo[d]imidazol-7-yl)furan-2-carboxylate dihydrochloride



The title compound (10 mg, yield: 21%) was obtained in the same manner as in Example 20, with the exception that tert-butyl (2R,3S)-2-(3-(7-bromo-5-chloro-1H-benzo[d]imidazol-1-yl)propyl)-3-((tert-butyldimethylsilyl)oxy)piperidine-1-carboxylate was used instead of tert-butyl (2R,3S)-2-(3-(4-bromo-1H-benzo[d]imidazol-1-yl)propyl)-3-((tert-butyldimethylsilyl)oxy)piperidine-1-carboxylate, and that (2-(ethoxycarbonyl)furan-3-yl)boronic acid was used instead of (3-fluorophenyl)boronic acid in Step 20-2 of Example 20.

¹H NMR (500MHz, MeOD): δ 9.53(s, 1H), 8.00(s, 1H), 7.97(s, 1H), 7.55(s, 1H), 6.96(s, 1H), 4.29(m, 1H), 4.15(m, 3H), 3.47(m, 1H), 3.24(m, 2H), 2.94(m, 1H), 2.79(m, 1H), 1.97(m, 3H), 1.84(m, 2H), 1.72(m, 2H), 1.53(m, 2H), 1.08(t, 3H)

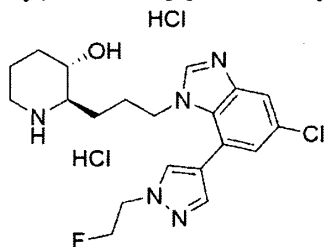
Example 111: methyl 4-(5-chloro-1-(3-((2R,3S)-3-hydroxypiperidin-2-yl)propyl)-1H-benzo[d]imidazol-7-yl)thiophene-2-carboxylate dihydrochloride



The title compound (9 mg, yield: 19%) was obtained in the same manner as in Example 20, with the exception that tert-butyl (2R,3S)-2-(3-(7-bromo-5-chloro-1H-benzo[d]imidazol-1-yl)propyl)-3-((tert-butyldimethylsilyl)oxy)piperidine-1-carboxylate was used instead of tert-butyl
 5 (2R,3S)-2-(3-(4-bromo-1H-benzo[d]imidazol-1-yl)propyl)-3-((tert-butyldimethylsilyl)oxy)piperidine-1-carboxylate, and that (5-(methoxycarbonyl)thiophen-3-yl)boronic acid was used instead of (3-fluorophenyl)boronic acid in Step 20-2 of Example 20.

¹H NMR (500MHz, MeOD): δ 9.54(s, 1H), 8.05(d, 2H), 7.97(s, 1H), 7.57(s, 1H), 4.80(m, 1H), 4.22(m, 2H), 3.93(s, 3H), 3.43(m, 1H), 3.22(m, 2H), 2.93(m, 1H), 2.78(m, 1H),
 10 2.01(m, 2H), 1.78(m, 3H), 1.63(m, 1H), 1.53(m, 1H), 1.41(m, 1H)

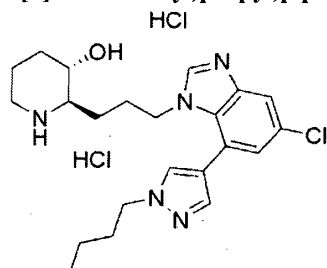
Example 112: Preparation of (2R,3S)-2-(3-(5-chloro-7-(1-(2-fluoroethyl)-1H-pyrazol-4-yl)-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol dihydrochloride



The title compound (15 mg, yield: 29%) was obtained in the same manner as in Example 20, with the exception that tert-butyl (2R,3S)-2-(3-(7-bromo-5-chloro-1H-benzo[d]imidazol-1-yl)propyl)-3-((tert-butyldimethylsilyl)oxy)piperidine-1-carboxylate was used instead of tert-butyl
 15 (2R,3S)-2-(3-(4-bromo-1H-benzo[d]imidazol-1-yl)propyl)-3-((tert-butyldimethylsilyl)oxy)piperidine-1-carboxylate, and that (1-(2-fluoroethyl)-1H-pyrazol-4-yl)boronic acid was used instead of (3-fluorophenyl)boronic acid in Step 20-2 of Example 20.

¹H NMR (500MHz, MeOD): δ 9.53(s, 1H), 8.09(s, 1H), 7.91(s, 1H), 7.85(s, 1H), 7.53(s, 1H), 4.92(m, 1H), 4.64(m, 1H), 4.56(m, 1H), 4.32(m, 2H), 3.49(m, 1H), 3.23(m, 1H), 2.94(m, 1H), 2.80(m, 1H), 1.96(m, 3H), 1.74(m, 4H), 1.54(m, 1H), 1.47(m, 1H)

Example 113: Preparation of (2R,3S)-2-(3-(7-(1-butyl-1H-pyrazol-4-yl)-5-chloro-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol dihydrochloride

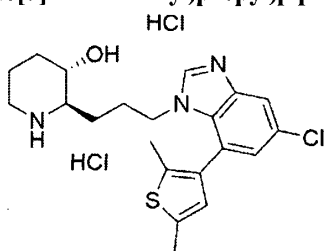


5 The title compound (18 mg, yield: 34%) was obtained in the same manner as in Example 20, with the exception that tert-butyl (2R,3S)-2-(3-(7-bromo-5-chloro-1H-benzo[d]imidazol-1-yl)propyl)-3-((tert-butyldimethylsilyl)oxy)piperidine-1-carboxylate was used instead of tert-butyl (2R,3S)-2-(3-(4-bromo-1H-benzo[d]imidazol-1-yl)propyl)-3-((tert-

10 butyldimethylsilyl)oxy)piperidine-1-carboxylate, and that (1-butyl-1H-pyrazol-4-yl)boronic acid was used instead of (3-fluorophenyl)boronic acid in Step 20-2 of Example 20.

¹H NMR (500MHz, MeOD): δ 9.43(s, 1H), 8.02(s, 1H), 7.89(s, 1H), 7.79(s, 1H), 7.50(s, 1H), 4.30(m, 3H), 3.45(m, 1H), 3.36(m, 1H), 3.22(m, 1H), 2.95(m, 1H), 2.78(m, 1H), 2.01(m, 4H), 1.75(m, 4H), 1.54(m, 1H), 1.42(m, 3H), 1.01(m, 3H)

15 **Example 114: Preparation of (2R,3S)-2-(3-(5-chloro-7-(2,5-dimethylthiophen-3-yl)-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol dihydrochloride**



The title compound (12 mg, yield: 20%) was obtained in the same manner as in Example 20, with the exception that tert-butyl (2R,3S)-2-(3-(7-bromo-5-chloro-1H-benzo[d]imidazol-1-yl)propyl)-3-((tert-butyldimethylsilyl)oxy)piperidine-1-carboxylate was used instead of tert-butyl (2R,3S)-2-(3-(4-bromo-1H-benzo[d]imidazol-1-yl)propyl)-3-((tert-

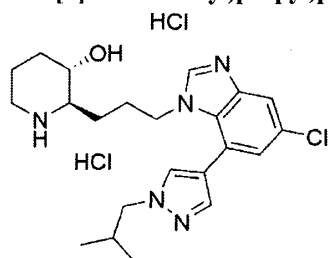
20 butyldimethylsilyl)oxy)piperidine-1-carboxylate, and that (2,5-dimethylthiophen-3-yl)boronic

acid was used instead of (3-fluorophenyl)boronic acid in Step 20-2 of Example 20.

¹H NMR (500MHz, MeOD): δ 9.54(m, 1H), 7.92(s, 1H), 7.44(s, 1H), 6.80(s, 1H), 4.25(m, 1H), 4.09(m, 1H), 3.48(m, 1H), 3.25(m, 2H), 2.95(m, 1H), 2.80(m, 1H), 2.51(s, 3H), 2.24(d, 3H), 1.99(m, 3H), 1.80(m, 2H), 1.66(m, 3H), 1.56(m, 1H), 1.47(m, 1H)

5

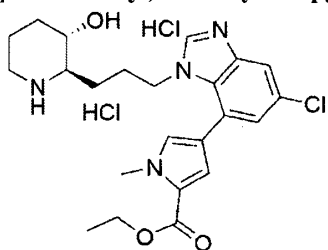
Example 115: Preparation of (2R,3S)-2-(3-(5-chloro-7-(1-isobutyl-1H-pyrazol-4-yl)-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol dihydrochloride



The title compound (18 mg, yield: 27%) was obtained in the same manner as in Example 20, with the exception that tert-butyl (2R,3S)-2-(3-(7-bromo-5-chloro-1H-benzo[d]imidazol-1-yl)propyl)-3-((tert-butyldimethylsilyl)oxy)piperidine-1-carboxylate was used instead of tert-butyl (2R,3S)-2-(3-(4-bromo-1H-benzo[d]imidazol-1-yl)propyl)-3-((tert-butyldimethylsilyl)oxy)piperidine-1-carboxylate, and that (1-isobutyl-1H-pyrazol-4-yl)boronic acid was used instead of (3-fluorophenyl)boronic acid in Step 20-2 of Example 20.

¹H NMR (500MHz, MeOD): δ 9.53(s, 1H), 8.03(s, 1H), 7.90(s, 1H), 7.80(s, 1H), 7.50(s, 1H), 4.33(m, 2H), 4.10(m, 2H), 3.48(m, 1H), 3.23(m, 1H), 2.92(m, 1H), 2.81(m, 1H), 2.30(m, 1H), 1.99(m, 2H), 1.81(m, 2H), 1.74(m, 2H), 1.54(m, 1H), 1.44(m, 1H), 0.99(d, 6H)

Example 116: ethyl 4-(5-chloro-1-(3-((2R,3S)-3-hydroxypiperidin-2-yl)propyl)-1H-benzo[d]imidazol-7-yl)-1-methyl-1H-pyrrole-2-carboxylate dihydrochloride



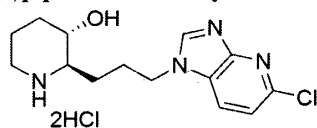
The title compound (18 mg, yield: 31%) was obtained in the same manner as in Example

20, with the exception that tert-butyl (2R,3S)-2-(3-(7-bromo-5-chloro-1H-benzo[d]imidazol-1-yl)propyl)-3-((tert-butyldimethylsilyl)oxy)piperidine-1-carboxylate was used instead of tert-butyl (2R,3S)-2-(3-(4-bromo-1H-benzo[d]imidazol-1-yl)propyl)-3-((tert-butyldimethylsilyl)oxy)piperidine-1-carboxylate, and that (5-(ethoxycarbonyl)-1-methyl-1H-pyrrol-3-yl)boronic acid was used instead of (3-fluorophenyl)boronic acid in Step 20-2 of Example 20.

¹H NMR (500MHz, MeOD): δ 9.50(s, 1H), 7.87(s, 1H), 7.49(s, 1H), 7.31(s, 1H), 7.15(s, 1H), 4.41(m, 2H), 4.32(m, 2H), 4.04(s, 3H), 3.42(m, 1H), 3.21(m, 1H), 2.92(m, 1H), 2.76(m, 1H), 1.96(m, 2H), 1.88-1.62(m, 5H), 1.52(m, 2H), 1.40(m, 3H)

10

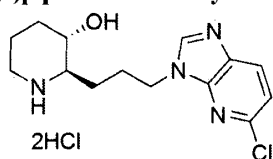
Example 117: Preparation of (2R,3S)-2-(3-(5-chloro-1H-imidazo[4,5-b]pyridin-1-yl)propyl)piperidin-3-ol dihydrochloride



The title compound (17 mg, yield: 35%) was obtained in the same manner as in Example 45, with the exception that 5-chloro-1H-imidazo[4,5-b]pyridine was used instead of 5-bromo-4-methyl-1H-benzo[d]imidazole in step 45-1 of Example 45.

¹H-NMR (500 MHz, MeOD): δ 9.48 (s, 1H), 8.29 (d, 1H), 7.68 (d, 1H), 4.58 (t, 2H), 3.66 (m, 2H), 3.00 (m, 2H), 2.20 (m, 2H), 2.07 (m, 2H), 1.98 (m, 1H), 1.74 (m, 2H), 1.56 (m, 1H)

Example 118: Preparation of (2R,3S)-2-(3-(5-chloro-3H-imidazo[4,5-b]pyridin-3-yl)propyl)piperidin-3-ol dihydrochloride

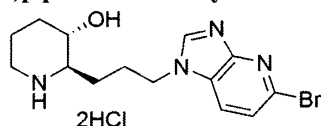


The title compound (15 mg, yield: 40%) was obtained in the same manner as in Example 45, with the exception that 5-chloro-3H-imidazo[4,5-b]pyridine was used instead of 5-bromo-4-methyl-1H-benzo[d]imidazole in step 45-1 of Example 45.

¹H-NMR (500 MHz, MeOD): δ 9.50 (s, 1H), 8.46 (d, 1H), 7.69 (d, 1H), 4.59 (t, 2H),

3.65 (m, 1H), 3.58 (m, 1H), 2.99 (m, 2H), 2.20 (m, 2H), 2.05 (m, 2H), 1.97 (m, 1H), 1.73 (m, 1H), 1.54 (m, 1H)

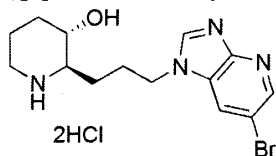
Example 119: Preparation of (2R,3S)-2-(3-(5-bromo-1H-imidazo[4,5-b]pyridin-1-yl)propyl)piperidin-3-ol dihydrochloride



The title compound (30 mg, yield: 80%) was obtained in the same manner as in Example 45, with the exception that 5-bromo-1H-imidazo[4,5-b]pyridine was used instead of 5-bromo-4-methyl-1H-benzo[d]imidazole in step 45-1 of Example 45.

¹H-NMR (500 MHz, MeOD): δ 9.54 (s, 1H), 8.20 (d, 1H), 7.84 (d, 1H), 4.59 (t, 2H), 3.58 (m, 2H), 2.99 (m, 2H), 2.24 (m, 2H), 2.07 (m, 2H), 1.98 (m, 1H), 1.74 (m, 2H), 1.56 (m, 1H)

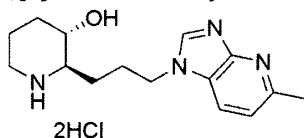
Example 120: Preparation of (2R,3S)-2-(3-(6-bromo-1H-imidazo[4,5-b]pyridin-1-yl)propyl)piperidin-3-ol dihydrochloride



The title compound (33 mg, yield: 82%) was obtained in the same manner as in Example 45, with the exception that 6-bromo-1H-imidazo[4,5-b]pyridine was used instead of 5-bromo-4-methyl-1H-benzo[d]imidazole in step 45-1 of Example 45.

¹H-NMR (500 MHz, MeOD): δ 9.50 (s, 1H), 8.78 (d, 1H), 8.53 (d, 1H), 4.60 (t, 2H), 3.56 (t, 1H), 2.98 (m, 2H), 2.26 (m, 2H), 2.21 (m, 2H), 1.97 (m, 1H), 1.74 (m, 2H), 1.55 (m, 1H)

Example 121: Preparation of (2R,3S)-2-(3-(5-methyl-1H-imidazo[4,5-b]pyridin-1-yl)propyl)piperidin-3-ol dihydrochloride

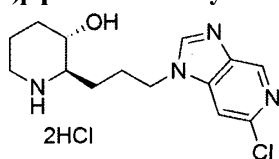


The title compound (19 mg, yield: 49%) was obtained in the same manner as in Example

45, with the exception that 5-methyl-1H-imidazo[4,5-b]pyridine was used instead of 5-bromo-4-methyl-1H-benzo[d]imidazole in step 45-1 of Example 45.

¹H-NMR (500 MHz, MeOD): δ 9.55 (s, 1H), 8.18 (d, 1H), 7.58 (d, 1H), 4.63 (t, 2H), 3.58 (m, 2H), 3.00 (m, 2H), 2.74 (s, 3H), 2.24 (m, 2H), 2.06 (m, 2H), 1.98 (m, 1H), 1.74 (m, 2H),
 5 1.56 (m, 2H), 1.56 (m, 1H)

Example 122: Preparation of (2R,3S)-2-(3-(6-chloro-1H-imidazo[4,5-c]pyridin-1-yl)propyl)piperidin-3-ol dihydrochloride

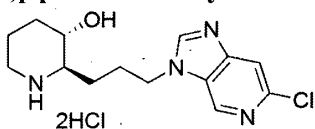


10 The title compound (15 mg, yield: 40%) was obtained in the same manner as in Example 45, with the exception that 6-chloro-1H-imidazo[4,5-c]pyridine was used instead of 5-bromo-4-methyl-1H-benzo[d]imidazole in step 45-1 of Example 45.

¹H-NMR (500 MHz, MeOD): δ 9.30 (s, 1H), 9.09 (s, 1H), 7.91 (s, 1H), 4.62 (t, 2H), 3.60 (m, 2H), 2.99 (m, 2H), 2.22 (m, 2H), 2.06 (m, 2H), 1.98 (m, 1H), 1.73 (m, 2H), 1.56 (m, 1H)

15

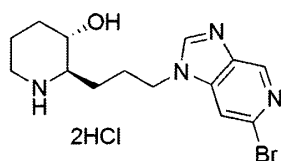
Example 123: Preparation of (2R,3S)-2-(3-(6-chloro-3H-imidazo[4,5-c]pyridin-3-yl)propyl)piperidin-3-ol dihydrochloride



20 The title compound (18 mg, yield: 37%) was obtained in the same manner as in Example 45, with the exception that 6-chloro-3H-imidazo[4,5-c]pyridine was used instead of 5-bromo-4-methyl-1H-benzo[d]imidazole in step 45-1 of Example 45.

¹H-NMR (500 MHz, MeOD): δ 9.21 (s, 1H), 8.97 (s, 1H), 8.18 (s, 1H), 4.52 (t, 2H), 3.58 (m, 1H), 2.98 (m, 2H), 2.19 (m, 2H), 2.05 (m, 2H), 1.97 (m, 1H), 1.73 (m, 2H), 1.56 (m, 1H)

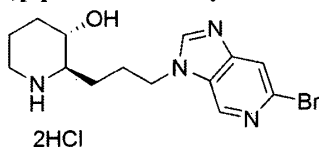
25 **Example 124: Preparation of (2R,3S)-2-(3-(6-bromo-1H-imidazo[4,5-c]pyridin-1-yl)propyl)piperidin-3-ol dihydrochloride**



The title compound (18 mg, yield: 35%) was obtained in the same manner as in Example 45, with the exception that 6-bromo-3H-imidazo[4,5-c]pyridine was used instead of 5-bromo-4-methyl-1H-benzo[d]imidazole in step 45-1 of Example 45.

5 $^1\text{H-NMR}$ (500 MHz, MeOD): δ 9.43 (s, 1H), 9.16 (s, 1H), 8.12 (s, 1H), 4.64 (t, 2H), 3.65 (m, 2H), 3.01 (m, 2H), 2.26 (m, 2H), 2.07 (m, 2H), 1.97 (m, 1H), 1.75 (m, 2H), 1.56 (m, 1H)

Example 125: Preparation of (2R,3S)-2-(3-(6-bromo-3H-imidazo[4,5-c]pyridin-3-yl)propyl)piperidin-3-ol dihydrochloride

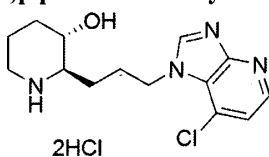


10

The title compound (20 mg, yield: 40%) was obtained in the same manner as in Example 45, with the exception that 6-bromo-3H-imidazo[4,5-c]pyridine was used instead of 5-bromo-4-methyl-1H-benzo[d]imidazole in step 45-1 of Example 45.

15 $^1\text{H-NMR}$ (500 MHz, MeOD): δ 9.18 (s, 1H), 9.01 (s, 1H), 8.38 (s, 1H), 4.53 (t, 2H), 3.58 (m, 2H), 2.97 (m, 2H), 2.19 (m, 2H), 2.05 (m, 2H), 1.97 (m, 1H), 1.74 (m, 2H), 1.56 (m, 1H)

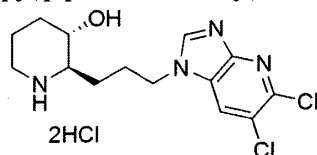
Example 126: Preparation of (2R,3S)-2-(3-(7-chloro-1H-imidazo[4,5-b]pyridin-1-yl)propyl)piperidin-3-ol dihydrochloride



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The title compound (25 mg, yield: 32%) was obtained in the same manner as in Example 45, with the exception that 7-chloro-1H-imidazo[4,5-b]pyridine was used instead of 5-bromo-4-methyl-1H-benzo[d]imidazole in step 45-1 of Example 45.

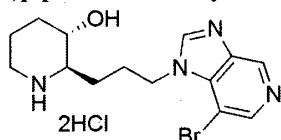
Example 127: Preparation of (2R,3S)-2-(3-(5,6-dichloro-1H-imidazo[4,5-b]pyridin-

1-yl)propyl)piperidin-3-ol dihydrochloride

The title compound (35 mg, yield: 48%) was obtained in the same manner as in Example 45, with the exception that 5,6-dichloro-1H-imidazo[4,5-b]pyridine was used instead of 5-bromo-4-methyl-1H-benzo[d]imidazole in step 45-1 of Example 45.

¹H-NMR (500 MHz, MeOD): δ 9.10 (s, 1H), 8.45 (s, 1H), 4.50 (t, 2H), 3.56 (m, 1H), 2.98 (m, 2H), 2.21 (m, 2H), 2.03 (m, 3H), 1.69 (m, 2H), 1.53 (m, 1H)

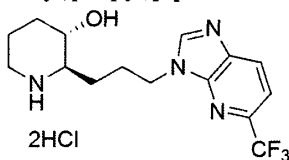
Example 128: Preparation of (2R,3S)-2-(3-(7-bromo-1H-imidazo[4,5-c]pyridin-1-yl)propyl)piperidin-3-ol dihydrochloride



The title compound (18 mg, yield: 35%) was obtained in the same manner as in Example 45, with the exception that 7-bromo-1H-imidazo[4,5-c]pyridine was used instead of 5-bromo-4-methyl-1H-benzo[d]imidazole in step 45-1 of Example 45.

¹H-NMR (500 MHz, MeOD): δ 9.66 (s, 1H), 9.07 (s, 1H), 8.89 (s, 1H), 4.62 (t, 2H), 3.58 (m, 2H), 2.99 (m, 2H), 2.21 (m, 2H), 2.00 (m, 3H), 1.74 (m, 2H), 1.55 (m, 1H)

Example 129: Preparation of (2R,3S)-2-(3-(5-(trifluoromethyl)-3H-imidazo[4,5-b]pyridin-3-yl)propyl)piperidin-3-ol dihydrochloride

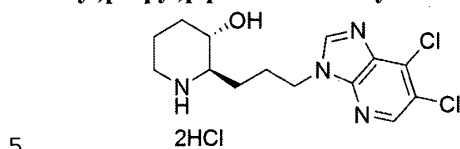


The title compound (20 mg, yield: 45%) was obtained in the same manner as in Example 45, with the exception that 5-(trifluoromethyl)-3H-imidazo[4,5-b]pyridine was used instead of 5-bromo-4-methyl-1H-benzo[d]imidazole in step 45-1 of Example 45.

¹H-NMR (500 MHz, MeOD): δ 9.71 (s, 1H), 8.53 (d, 1H), 8.08 (d, 1H), 4.67 (t, 2H),

3.59 (m, 1H), 2.95 (m, 2H), 2.28 (m, 2H), 2.07 (m, 2H), 1.98 (m, 1H), 1.75 (m, 2H), 1.55 (m, 1H)

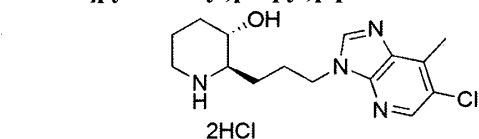
Example 130: Preparation of (2R,3S)-2-(3-(6,7-dichloro-3H-imidazo[4,5-b]pyridin-3-yl)propyl)piperidin-3-ol dihydrochloride



The title compound (25 mg, yield: 80%) was obtained in the same manner as in Example 45, with the exception that 6,7-dichloro-3H-imidazo[4,5-b]pyridine was used instead of 5-bromo-4-methyl-1H-benzo[d]imidazole in step 45-1 of Example 45.

¹H-NMR (500 MHz, MeOD): δ 8.62 (s, 1H), 8.51 (s, 1H), 4.43 (m, 2H), 3.51 (m, 1H),
10 3.22 (m, 1H), 2.91 (m, 2H), 2.08 (m, 2H), 1.96 (m, 3H), 1.55 (m, 3H)

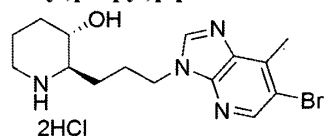
Example 131: Preparation of (2R,3S)-2-(3-(6-chloro-7-methyl-3H-imidazo[4,5-b]pyridin-3-yl)propyl)piperidin-3-ol dihydrochloride



The title compound (31 mg, yield: 84%) was obtained in the same manner as in Example 45, with the exception that 6-chloro-7-methyl-3H-imidazo[4,5-b]pyridine was used instead of 5-bromo-4-methyl-1H-benzo[d]imidazole in step 45-1 of Example 45.

¹H-NMR (500 MHz, MeOD): δ 9.68 (s, 1H), 8.67 (s, 1H), 4.62 (t, 2H), 3.57 (m, 2H),
20 2.97 (m, 2H), 2.74 (s, 3H), 2.25 (m, 2H), 2.06 (m, 2H), 1.97 (m, 1H), 1.75 (m, 2H), 1.53 (m, 1H)

Example 132: Preparation of (2R,3S)-2-(3-(6-bromo-7-methyl-3H-imidazo[4,5-b]pyridin-3-yl)propyl)piperidin-3-ol dihydrochloride



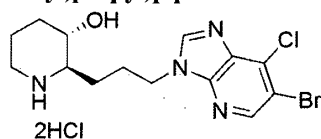
The title compound (35 mg, yield: 85%) was obtained in the same manner as in Example 45, with the exception that 6-bromo-7-methyl-3H-imidazo[4,5-b]pyridine was used instead of 5-

25

bromo-4-methyl-1H-benzo[d]imidazole in step 45-1 of Example 45.

¹H-NMR (500 MHz, MeOD): δ 9.74 (s, 1H), 8.80 (d, 1H), 4.63 (t, 2H), 3.57 (m, 1H), 2.96 (m, 2H), 2.76 (s, 3H), 2.28 (m, 2H), 2.06 (m, 2H), 1.97 (m, 1H), 1.74 (m, 2H), 1.55 (m, 1H)

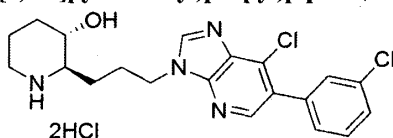
Example 133: Preparation of (2R,3S)-2-(3-(6-bromo-7-chloro-3H-imidazo[4,5-b]pyridin-3-yl)propyl)piperidin-3-ol dihydrochloride



The title compound (30 mg, yield: 78%) was obtained in the same manner as in Example 45, with the exception that 6-bromo-7-chloro-3H-imidazo[4,5-b]pyridine was used instead of 5-bromo-4-methyl-1H-benzo[d]imidazole in step 45-1 of Example 45.

¹H-NMR (500 MHz, MeOD): δ 9.24 (s, 1H), 8.77 (s, 1H), 4.55 (t, 2H), 3.55 (m, 1H), 3.26 (m, 1H), 2.97 (m, 2H), 2.23 (m, 2H), 2.03 (m, 3H), 1.70 (m, 2H), 1.54 (m, 1H)

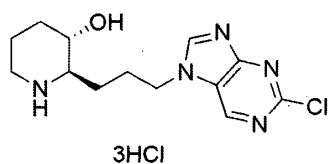
Example 134: Preparation of (2R,3S)-2-(3-(7-chloro-6-(3-chlorophenyl)-3H-imidazo[4,5-b]pyridin-3-yl)propyl)piperidin-3-ol dihydrochloride



The title compound (28 mg, yield: 70%) was obtained in the same manner as in Example 45, with the exception that 7-chloro-6-(3-chlorophenyl)-3H-imidazo[4,5-b]pyridine was used instead of 5-bromo-4-methyl-1H-benzo[d]imidazole in step 45-1 of Example 45.

¹H-NMR (500 MHz, MeOD): δ 9.69 (s, 1H), 8.67 (s, 1H), 7.55 (m, 4H), 4.66 (t, 2H), 3.59 (m, 1H), 3.02 (m, 2H), 2.33 (m, 2H), 2.07 (m, 2H), 1.97 (m, 1H), 1.56 (m, 2H), 1.55 (m, 1H)

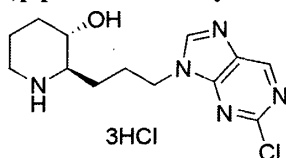
Example 135: Preparation of (2R,3S)-2-(3-(2-chloro-7H-purin-7-yl)propyl)piperidin-3-ol trihydrochloride



The title compound (15 mg, yield: 35%) was obtained in the same manner as in Example 45, with the exception that 2-chloro-7H-purine was used instead of 5-bromo-4-methyl-1H-benzo[d]imidazole in step 45-1 of Example 45.

5 ¹H-NMR (500 MHz, MeOD): δ 9.05 (s, 1H), 8.81 (s, 1H), 4.44 (t, 2H), 3.55 (m, 1H), 3.28 (m, 1H), 2.98 (m, 2H), 2.19 (m, 2H), 2.03 (m, 3H), 1.70 (m, 2H), 1.55 (m, 1H)

Example 136: Preparation of (2R,3S)-2-(3-(2-chloro-9H-purin-9-yl)propyl)piperidin-3-ol trihydrochloride

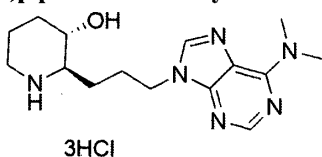


10

The title compound (12 mg, yield: 30%) was obtained in the same manner as in Example 45, with the exception that 2-chloro-9H-purine was used instead of 5-bromo-4-methyl-1H-benzo[d]imidazole in step 45-1 of Example 45.

15 ¹H-NMR (500 MHz, MeOD): δ 9.19 (s, 1H), 8.87 (s, 1H), 4.52 (m, 2H), 3.55 (m, 1H), 3.25 (m, 1H), 2.97 (m, 2H), 2.16 (m, 2H), 2.00 (m, 3H), 1.65 (m, 2H), 1.55 (m, 1H)

Example 137: Preparation of (2R,3S)-2-(3-(6-(dimethylamino)-9H-purin-9-yl)propyl)piperidin-3-ol trihydrochloride



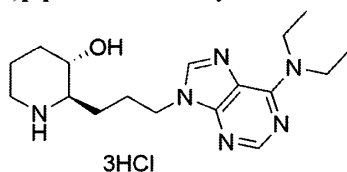
20

The title compound (25 mg, yield: 75%) was obtained in the same manner as in Example 45, with the exception that N,N-dimethyl-9H-purin-6-amine was used instead of 5-bromo-4-methyl-1H-benzo[d]imidazole in step 45-1 of Example 45.

¹H-NMR (500 MHz, MeOD): δ 8.38 (s, 1H), 8.37 (s, 1H), 4.41 (t, 2H), 3.98 (br, 2H), 3.56 (t, 1H), 3.42 (br, 3H), 3.26 (m, 1H), 2.97 (m, 2H), 2.19 (m, 5H), 1.78 (m, 1H), 1.67 (m, 1H),

1.53 (m, 1H)

Example 138: Preparation of (2R,3S)-2-(3-(6-(diethylamino)-9H-purin-9-yl)propyl)piperidin-3-ol trihydrochloride

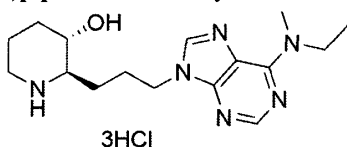


5

The title compound (27 mg, yield: 77%) was obtained in the same manner as in Example 45, with the exception that N,N-diethylamino-9H-purin-6-amine was used instead of 5-bromo-4-methyl-1H-benzo[d]imidazole in step 45-1 of Example 45.

¹H-NMR (500 MHz, MeOD): δ 8.34 (s, 1H), 8.32 (d, 1H), 4.38 (m, 2H), 3.66 (br, 4H),
 10 3.55 (m, 1H), 3.27 (m, 1H), 2.96 (m, 2H), 2.14-2.00 (m, 6H), 1.68 (m, 1H), 1.53 (m, 1H), 1.38 (br, 6H)

Example 139: Preparation of (2R,3S)-2-(3-(6-(ethyl(methyl)amino)-9H-purin-9-yl)propyl)piperidin-3-ol trihydrochloride

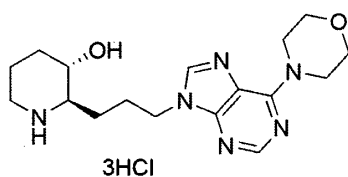


15

The title compound (28 mg, yield: 78%) was obtained in the same manner as in Example 45, with the exception that N-ethyl-N-methyl-9H-purin-6-amine was used instead of 5-bromo-4-methyl-1H-benzo[d]imidazole in step 45-1 of Example 45.

¹H-NMR (500 MHz, MeOD): δ 8.39 (s, 1H), 8.38 (s, 1H), 4.51 (br, 2H), 4.41 (t, 2H),
 20 3.56 (m, 1H), 3.41 (m, 1H), 3.27 (m, 3H), 2.96 (m, 2H), 2.19-1.99 (m, 5H), 1.75 (m, 1H), 1.68 (m, 1H), 1.53 (t, 3H)

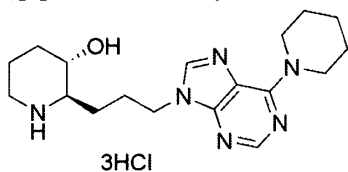
Example 140: Preparation of (2R,3S)-2-(3-(6-morpholino-9H-purin-9-yl)propyl)piperidin-3-ol trihydrochloride



The title compound (27 mg, yield: 80%) was obtained in the same manner as in Example 45, with the exception that 4-(9H-purin-6-yl)morpholine was used instead of 5-bromo-4-methyl-1H-benzo[d]imidazole in step 45-1 of Example 45.

¹H-NMR (500 MHz, MeOD): δ 8.35 (s, 1H), 8.33 (d, 1H), 4.39 (m, 2H), 3.66 (s, 6H), 3.54 (m, 1H), 3.25 (m, 1H), 2.96 (m, 2H), 2.14-1.98 (m, 5H), 1.84 (s, 6H), 1.72 (m, 2H), 1.53 (m, 1H)

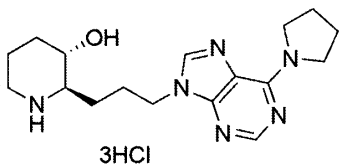
Example 141: Preparation of (2R,3S)-2-(3-(6-(piperidin-1-yl)-9H-purin-9-yl)propyl)piperidin-3-ol trihydrochloride



The title compound (30 mg, yield: 81%) was obtained in the same manner as in Example 45, with the exception that 6-(piperidin-1-yl)-9H-purine was used instead of 5-bromo-4-methyl-1H-benzo[d]imidazole in step 45-1 of Example 45.

¹H-NMR (500 MHz, MeOD): δ 8.43 (s, 1H), 8.36 (s, 1H), 4.40 (m, 4H), 3.91 (m, 4H), 3.66 (s, 6H), 3.27 (m, 1H), 2.96 (m, 2H), 2.03 (m, 5H), 1.69 (m, 2H), 1.53 (m, 1H)

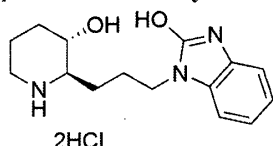
Example 142: Preparation of (2R,3S)-2-(3-(6-(pyrrolidin-1-yl)-9H-purin-9-yl)propyl)piperidin-3-ol trihydrochloride



The title compound (29 mg, yield: 80%) was obtained in the same manner as in Example 45, with the exception that 6-(pyrrolidin-1-yl)-9H-purine was used instead of 5-bromo-4-methyl-1H-benzo[d]imidazole in step 45-1 of Example 45.

¹H-NMR (500 MHz, MeOD): δ 8.33 (br, 2H), 4.37 (m, 4H), 3.75 (br, 2H), 3.66 (m, 1H), 2.96 (m, 2H), 2.17 (br, 6H), 2.00 (m, 4H), 1.73 (m, 2H), 1.53 (m, 1H)

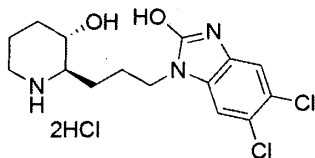
Example 143: Preparation of 1-(3-((2R,3S)-3-hydroxypiperidin-2-yl)propyl)-1H-benzo[d]imidazol-2-ol dihydrochloride



The title compound (25 mg, yield: 79%) was obtained in the same manner as in Example 45, with the exception that 1H-benzo[d]imidazol-2-ol was used instead of 5-bromo-4-methyl-1H-benzo[d]imidazole in step 45-1 of Example 45.

¹H-NMR (500 MHz, MeOD): δ 7.16 (d, 1H), 7.10 (m, 3H), 3.96 (m, 2H), 3.53 (m, 1H), 3.20 (m, 1H), 2.91 (m, 2H), 2.00 (m, 5H), 1.62 (m, 2H), 1.51 (m, 1H)

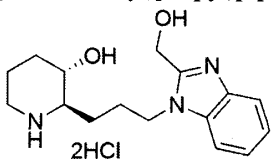
Example 144: Preparation of 5,6-dichloro-1-(3-((2R,3S)-3-hydroxypiperidin-2-yl)propyl)-1H-benzo[d]imidazol-2-ol dihydrochloride



The title compound (27 mg, yield: 84%) was obtained in the same manner as in Example 45, with the exception that 5,6-dichloro-1H-benzo[d]imidazol-2-ol was used instead of 5-bromo-4-methyl-1H-benzo[d]imidazole in step 45-1 of Example 45.

¹H-NMR (500 MHz, MeOD): δ 7.38 (s, 1H), 7.21 (s, 1H), 3.92 (m, 2H), 3.48 (m, 2H), 3.20 (m, 3H), 2.89 (m, 3H), 2.04-1.92 (m, 7H), 1.67 (m, 5H)

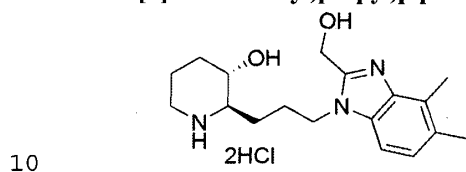
Example 145: Preparation of (2R,3S)-2-(3-(2-(hydroxymethyl)-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol dihydrochloride



The title compound (25 mg, yield: 80%) was obtained in the same manner as in Example 45, with the exception that (1H-benzo[d]imidazol-2-yl)methanol was used instead of 5-bromo-4-methyl-1H-benzo[d]imidazole in step 45-1 of Example 45.

¹H-NMR (500 MHz, MeOD): δ 7.99 (d, 1H), 7.81 (d, 1H), 7.64 (m, 2H), 5.20 (s, 2H),
 5 4.51 (m, 2H), 3.59 (m, 1H), 3.27 (m, 1H), 2.97 (m, 2H), 2.20 (m, 1H), 2.08 (m, 3H), 1.96 (m, 1H),
 1.87 (m, 2H), 1.55 (m, 1H)

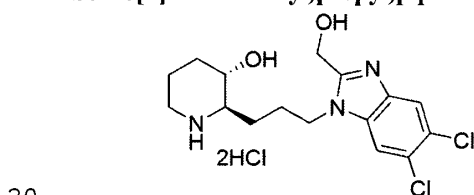
Example 146: Preparation of (2R,3S)-2-(3-(2-(hydroxymethyl)-4,5-dimethyl-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol dihydrochloride



The title compound (31 mg, yield: 83%) was obtained in the same manner as in Example 45, with the exception that (4,5-dimethyl-1H-benzo[d]imidazol-2-yl)methanol was used instead of 5-bromo-4-methyl-1H-benzo[d]imidazole in step 45-1 of Example 45.

¹H-NMR (500 MHz, MeOD): δ 7.67 (d, 1H), 7.47 (d, 1H), 5.14 (s, 2H), 4.53 (m, 2H),
 15 3.59 (m, 1H), 3.28 (m, 1H), 2.97 (m, 2H), 2.57 (s, 3H), 2.47 (s, 3H), 2.20 (m, 1H), 2.10 (m, 3H),
 1.97 (m, 1H), 1.76 (m, 2H), 1.54 (m, 1H)

Example 147: Preparation of (2R,3S)-2-(3-(5,6-dichloro-2-(hydroxymethyl)-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol dihydrochloride

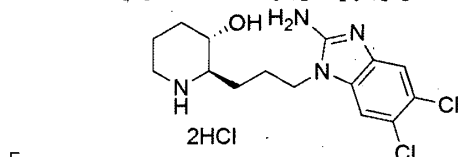


The title compound (28 mg, yield: 79%) was obtained in the same manner as in Example 45, with the exception that (5,6-dichloro-1H-benzo[d]imidazol-2-yl)methanol was used instead of 5-bromo-4-methyl-1H-benzo[d]imidazole in step 45-1 of Example 45.

¹H-NMR (500 MHz, DMSO-d₆): δ 8.37 (s, 1H), 7.99 (s, 1H), 4.99 (s, 2H), 4.40 (m, 2H),
 25 3.41 (m, 1H), 3.09 (d, 1H), 2.78 (m, 2H), 2.08 (m, 1H), 1.98 (m, 2H), 1.89 (m, 1H), 1.77 (m, 1H),

1.64 (m, 2H), 1.35 (m, 1H)

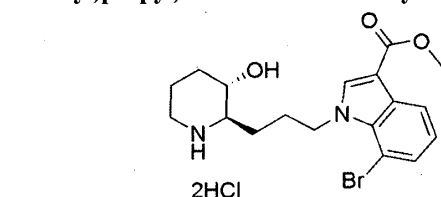
Example 148: Preparation of (2R,3S)-2-(3-(2-amino-5,6-dichloro-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol dihydrochloride



The title compound (25 mg, yield: 81%) was obtained in the same manner as in Example 45, with the exception that 5,6-dichloro-1H-benzo[d]imidazol-2-amine was used instead of 5-bromo-4-methyl-1H-benzo[d]imidazole in step 45-1 of Example 45.

¹H-NMR (500 MHz, MeOD): δ 7.84 (s, 1H), 7.57 (s, 1H), 4.20 (t, 2H), 3.58 (m, 1H),
10 2.97 (m, 1H), 2.98 (m, 2H), 2.07-1.95 (m, 5H), 1.77 (m, 2H), 1.54 (m, 1H)

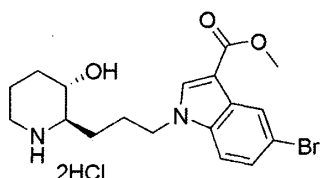
Example 149: Preparation of methyl 7-bromo-1-(3-((2R,3S)-3-hydroxypiperidin-2-yl)propyl)-1H-indole-3-carboxylate dihydrochloride



The title compound (30 mg, yield: 75%) was obtained in the same manner as in Example 45, with the exception that methyl 7-bromo-1H-indole-3-carboxylate was used instead of 5-bromo-4-methyl-1H-benzo[d]imidazole in step 45-1 of Example 45.

¹H-NMR (500 MHz, MeOD): δ 8.13 (d, 1H), 8.05 (s, 1H), 7.45 (d, 1H), 7.09 (t, 1H),
4.69 (m, 2H), 3.88 (s, 3H), 3.48 (m, 1H), 3.16 (m, 1H), 2.88 (m, 2H), 2.00 (m, 5H), 1.64 (m, 2H),
20 1.52 (m, 1H)

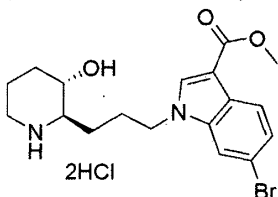
Example 150: Preparation of methyl 5-bromo-1-(3-((2R,3S)-3-hydroxypiperidin-2-yl)propyl)-1H-indole-3-carboxylate dihydrochloride



The title compound (29 mg, yield: 73%) was obtained in the same manner as in Example 45, with the exception that methyl 5-bromo-1H-indole-3-carboxylate was used instead of 5-bromo-4-methyl-1H-benzo[d]imidazole in step 45-1 of Example 45.

¹H-NMR (500 MHz, MeOD): δ 8.20 (s, 1H), 8.05 (s, 1H), 7.49 (d, 1H), 7.38 (d, 1H), 4.33 (m, 2H), 3.88 (s, 3H), 3.50 (m, 1H), 3.20 (d, 1H), 2.90 (m, 2H), 1.99 (m, 5H), 1.65 (m, 1H), 1.52 (m, 2H)

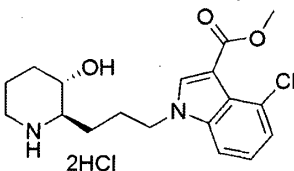
Example 151: Preparation of methyl 6-bromo-1-((2R,3S)-3-hydroxypiperidin-2-yl)propyl-1H-indole-3-carboxylate dihydrochloride



The title compound (25 mg, yield: 77%) was obtained in the same manner as in Example 45, with the exception that methyl 6-bromo-1H-indole-3-carboxylate was used instead of 5-bromo-4-methyl-1H-benzo[d]imidazole in step 45-1 of Example 45.

¹H-NMR (500 MHz, MeOD): δ 8.03 (s, 1H), 7.97 (d, 1H), 7.78 (s, 1H), 7.34 (d, 1H), 4.30 (m, 2H), 3.87 (s, 3H), 3.50 (m, 1H), 3.20 (d, 1H), 2.91 (m, 2H), 1.97 (m, 5H), 1.67 (m, 1H), 1.53 (m, 2H)

Example 152: Preparation of methyl 4-chloro-1-((2R,3S)-3-hydroxypiperidin-2-yl)propyl-1H-indole-3-carboxylate dihydrochloride



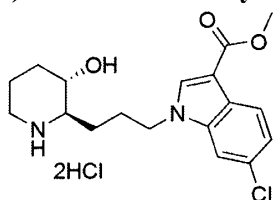
The title compound (27 mg, yield: 70%) was obtained in the same manner as in Example

45, with the exception that methyl 4-chloro-1H-indole-3-carboxylate was used instead of 5-bromo-4-methyl-1H-benzo[d]imidazole in step 45-1 of Example 45.

¹H-NMR (500 MHz, MeOD): δ 8.07 (s, 1H), 7.51 (d, 1H), 7.24 (s, 1H), 7.23 (s, 1H), 4.33 (m, 2H), 3.84 (s, 3H), 3.20 (m, 1H), 2.91 (m, 2H), 2.00 (m, 5H), 1.67 (m, 1H), 1.52 (m, 2H)

5

Example 153: Preparation of methyl 6-chloro-1-(3-((2R,3S)-3-hydroxypiperidin-2-yl)propyl)-1H-indole-3-carboxylate dihydrochloride

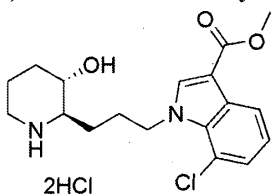


The title compound (21 mg, yield: 73%) was obtained in the same manner as in Example 45, with the exception that methyl 6-chloro-1H-indole-3-carboxylate was used instead of 5-bromo-4-methyl-1H-benzo[d]imidazole in step 45-1 of Example 45.

¹H-NMR (500 MHz, MeOD): δ 8.04 (s, 1H), 8.02 (d, 1H), 7.62 (s, 1H), 7.21 (d, 1H), 4.31 (m, 2H), 3.87 (s, 3H), 3.50 (m, 1H), 3.19 (d, 1H), 2.91 (m, 2H), 1.97 (m, 5H), 1.65 (m, 1H), 1.53 (m, 2H)

15

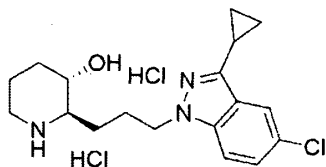
Example 154: Preparation of methyl 7-chloro-1-(3-((2R,3S)-3-hydroxypiperidin-2-yl)propyl)-1H-indole-3-carboxylate dihydrochloride



The title compound (19 mg, yield: 77%) was obtained in the same manner as in Example 45, with the exception that methyl 7-chloro-1H-indole-3-carboxylate was used instead of 5-bromo-4-methyl-1H-benzo[d]imidazole in step 45-1 of Example 45.

¹H-NMR (500 MHz, MeOD): δ 8.07 (d, 1H), 8.04 (s, 1H), 7.25 (d, 1H), 7.17 (t, 1H), 4.66 (m, 2H), 3.88 (s, 3H), 3.51 (m, 1H), 3.20 (d, 1H), 2.91 (m, 2H), 3.11 (m, 1H), 2.08 (m, 4H), 1.69 (m, 2H), 1.55 (m, 1H)

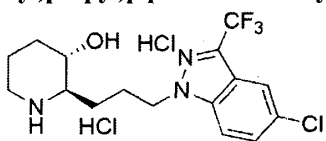
Example 155: Preparation of (2R,3S)-2-(3-(5-chloro-3-cyclopropyl-1H-indazol-1-yl)propyl)piperidin-3-ol dihydrochloride



5 The title compound (20 mg, yield: 65%) was obtained in the same manner as in Example 45, with the exception that 5-chloro-3-cyclopropyl-1H-indazole was used instead of 5-bromo-4-methyl-1H-benzo[d]imidazole in Step 45-1 of Example 45.

¹H NMR (500MHz, MeOD): δ 7.93(s, 1H), 7.47(s, 2H), 4.35(m, 2H), 3.51(m, 1H), 3.20(m, 1H), 2.92(m, 2H), 2.22(m, 1H), 2.10-1.91(m, 4H), 1.68(m, 1H), 1.51(m, 2H), 1.04(m, 2H), 0.97(m, 2H)

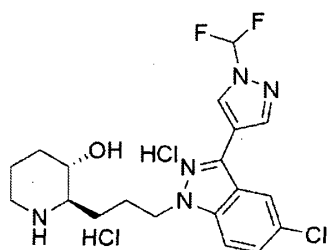
Example 156: Preparation of (2R,3S)-2-(3-(5-chloro-3-(trifluoromethyl)-1H-indazol-1-yl)propyl)piperidin-3-ol dihydrochloride



15 The title compound (17 mg, yield: 31%) was obtained in the same manner as in Example 45, with the exception that 5-chloro-3-(trifluoromethyl)-1H-indazole was used instead of 5-bromo-4-methyl-1H-benzo[d]imidazole in Step 45-1 of Example 45.

¹H NMR (500MHz, MeOD): δ 7.96(s, 1H), 7.72(d, 1H), 7.65(d, 1H), 4.57(m, 2H), 3.52(m, 1H), 3.22(m, 1H), 2.92(m, 2H), 2.20(m, 1H), 2.12(m, 1H), 2.00(m, 3H), 1.68(m, 1H), 1.62(m, 1H), 1.50(m, 1H)

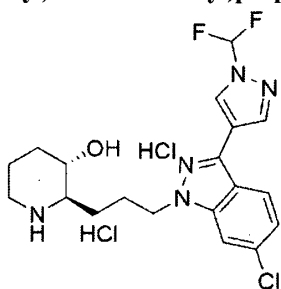
Example 157: Preparation of (2R,3S)-2-(3-(5-chloro-3-(1-(difluoromethyl)-1H-pyrazol-4-yl)-1H-indazol-1-yl)propyl)piperidin-3-ol dihydrochloride



The title compound (16 mg, yield: 29%) was obtained in the same manner as in Example 45, with the exception that 5-chloro-3-(1-(difluoromethyl)-1H-pyrazol-4-yl)-1H-indazole was used instead of 5-bromo-4-methyl-1H-benzo[d]imidazole in Step 45-1 of Example 45.

¹H NMR (500MHz, MeOD): δ 8.69(s, 1H), 8.27(s, 1H), 8.03(s, 1H), 7.65(d, 1H), 7.44(d, 1H), 4.52(m, 2H), 3.50(m, 1H), 3.16(m, 1H), 2.90(m, 2H), 2.21(m, 1H), 2.12(m, 1H), 2.07(m, 3H), 1.66(m, 2H), 1.50(m, 1H)

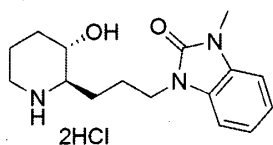
Example 158: Preparation of (2R,3S)-2-(3-(6-chloro-3-(1-(difluoromethyl)-1H-pyrazol-4-yl)-1H-indazol-1-yl)propyl)piperidin-3-ol dihydrochloride



The title compound (17 mg, yield: 30%) was obtained in the same manner as in Example 45, with the exception that 6-chloro-3-(1-(difluoromethyl)-1H-pyrazol-4-yl)-1H-indazole was used instead of 5-bromo-4-methyl-1H-benzo[d]imidazole in Step 45-1 of Example 45.

¹H NMR (500MHz, MeOD): δ 8.66(s, 1H), 8.27(s, 1H), 7.99(d, 1H), 7.70(s, 1H), 7.23(d, 1H), 4.51(m, 2H), 3.50(m, 1H), 3.21(m, 1H), 2.92(m, 2H), 2.18(m, 1H), 2.10(m, 1H), 2.07(m, 3H), 1.66(m, 2H), 1.55(m, 1H)

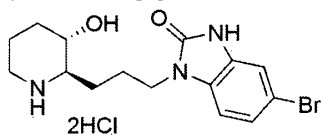
Example 159: Preparation of 1-(3-((2R,3S)-3-hydroxypiperidin-2-yl)propyl)-3-methyl-1H-benzo[d]imidazol-2(3H)-one dihydrochloride



The title compound (18 mg, yield: 69%) was obtained in the same manner as in Example 45, with the exception that 1-methyl-1,3-dihydro-2H-benzo[d]imidazol-2-one was used instead of 5-bromo-4-methyl-1H-benzo[d]imidazole in step 45-1 of Example 45.

5 $^1\text{H-NMR}$ (500 MHz, MeOD): δ 7.16 (m, 4H), 3.99 (m, 2H), 3.66 (s, 2H), 3.53 (m, 2H), 3.43 (s, 3H), 2.94 (m, 2H), 2.00 (m, 4H), 1.88 (m, 1H), 1.62 (m, 2H), 1.52 (m, 1H)

Example 160: Preparation of 5-bromo-1-(3-((2R,3S)-3-hydroxypiperidin-2-yl)propyl)-1H-benzo[d]imidazol-2(3H)-one dihydrochloride

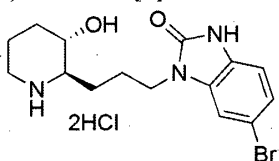


10

The title compound (15 mg, yield: 42%) was obtained in the same manner as in Example 45, with the exception that 5-bromo-1,3-dihydro-2H-benzo[d]imidazol-2-one was used instead of 5-bromo-4-methyl-1H-benzo[d]imidazole in step 45-1 of Example 45.

15 $^1\text{H-NMR}$ (500 MHz, MeOD): δ 7.37 (s, 1H), 7.21 (d, 1H), 6.99 (d, 1H), 3.94 (m, 2H), 3.54 (m, 1H), 3.23 (m, 1H), 2.94 (m, 2H), 2.05-1.87 (m, 5H), 1.65 (m, 2H), 1.53 (m, 1H)

Example 161: Preparation of 6-bromo-1-(3-((2R,3S)-3-hydroxypiperidin-2-yl)propyl)-1H-benzo[d]imidazol-2(3H)-one dihydrochloride

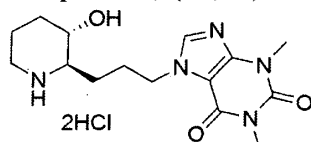


20

The title compound (14 mg, yield: 40%) was obtained in the same manner as in Example 45, with the exception that 5-bromo-1,3-dihydro-2H-benzo[d]imidazol-2-one was used instead of 5-bromo-4-methyl-1H-benzo[d]imidazole in step 45-1 of Example 45.

$^1\text{H-NMR}$ (500 MHz, MeOD): δ 7.23 (d, 1H), 7.22 (s, 1H), 7.09 (d, 1H), 3.95 (m, 2H), 3.53 (m, 1H), 3.23 (m, 1H), 2.94 (m, 2H), 2.02-1.87 (m, 5H), 1.66 (m, 2H), 1.53 (m, 1H)

Example 162: Preparation of 7-(3-((2R,3S)-3-hydroxypiperidin-2-yl)propyl)-1,3-dimethyl-1H-purine-2,6(3H,7H)-dione dihydrochloride

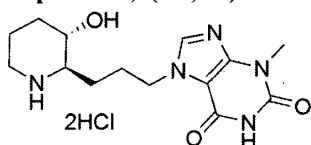


5 The title compound (21 mg, yield: 75%) was obtained in the same manner as in Example 45, with the exception that 1,3-dimethyl-3,7-dihydro-1H-purine-2,6-dione was used instead of 5-bromo-4-methyl-1H-benzo[d]imidazole in step 45-1 of Example 45.

¹H-NMR (500 MHz, MeOD): δ 8.15 (s, 1H), 4.40 (br, 2H), 3.57 (m, 1H), 3.34 (s, 6H), 3.26 (m, 1H), 2.98 (m, 2H), 2.00 (m, 5H), 1.72 (m, 2H), 1.55 (m, 1H)

10

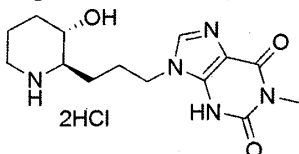
Example 163: Preparation of 7-(3-((2R,3S)-3-hydroxypiperidin-2-yl)propyl)-3-methyl-1H-purine-2,6(3H,7H)-dione dihydrochloride



15 The title compound (21 mg, yield: 72%) was obtained in the same manner as in Example 45, with the exception that 3-methyl-3,7-dihydro-1H-purine-2,6-dione was used instead of 5-bromo-4-methyl-1H-benzo[d]imidazole in step 45-1 of Example 45.

¹H-NMR (500 MHz, MeOD): δ 7.95 (s, 1H), 4.34 (m, 2H), 3.48 (m, 3H), 3.22 (m, 1H), 2.89 (m, 2H), 1.95 (m, 5H), 1.68 (m, 1H), 1.52 (m, 2H)

20 **Example 164: Preparation of 9-(3-((2R,3S)-3-hydroxypiperidin-2-yl)propyl)-1-methyl-1H-purine-2,6(3H,9H)-dione dihydrochloride**

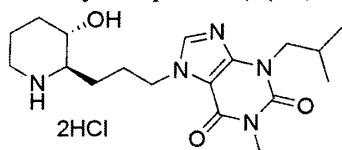


The title compound (25 mg, yield: 70%) was obtained in the same manner as in Example 45, with the exception that 1-methyl-3,9-dihydro-1H-purine-2,6-dione was used instead of 5-

bromo-4-methyl-1H-benzo[d]imidazole in step 45-1 of Example 45.

¹H-NMR (500 MHz, MeOD): δ 7.89 (s, 1H), 4.36 (m, 2H), 3.66 (m, 1H), 3.23 (m, 1H), 2.98 (m, 2H), 1.99 (m, 5H), 1.69 (m, 1H), 1.56 (m, 2H)

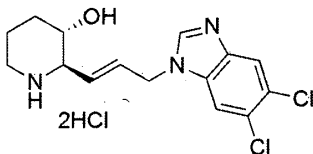
Example 165: Preparation of 7-(3-((2R,3S)-3-hydroxypiperidin-2-yl)propyl)-3-isobutyl-1-methyl-1H-purine-2,6(3H,7H)-dione dihydrochloride



The title compound (25 mg, yield: 70%) was obtained in the same manner as in Example 45, with the exception that 3-isobutyl-1-methyl-3,7-dihydro-1H-purine-2,6-dione was used instead of 5-bromo-4-methyl-1H-benzo[d]imidazole in step 45-1 of Example 45.

¹H-NMR (500 MHz, MeOD): δ 7.95 (s, 1H), 4.38 (m, 2H), 3.90 (m, 3H), 3.54 (m, 1H), 3.36 (m, 4H), 3.28 (m, 1H), 2.99 (m, 2H), 2.26 (m, 1H), 2.04 (m, 5H), 1.69 (m, 1H), 1.63 (m, 1H), 1.54 (m, 1H), 0.94 (m, 8H)

Example 166: Preparation of (2R,3S)-2-((E)-3-(5,6-dichloro-1H-benzo[d]imidazol-1-yl)prop-1-en-1-yl)piperidin-3-ol dihydrochloride



Step 166-1: Preparation of tert-butyl (2R,3S)-3-((tert-butyldimethylsilyl)oxy)-2-((E)-3-ethoxy-3-oxoprop-1-en-1-yl)piperidine-1-carboxylate

Methylene chloride (47 mL, 0.12 M) and oxalyl chloride (1.0 mL, 11.6 mmol) were added to a flask filled with nitrogen and the reaction solution was cooled to -78°C. Dimethylsulfoxide (1.7 mL, 23.2 mmol) was then added at the same temperature and stirred for 30 minutes. Then, tert-butyl (2R,3S)-3-((tert-butyldimethylsilyl)oxy)-2-(hydroxymethyl)piperidine-1-carboxylate (2.0 g, 5.8 mmol) was dissolved in a small amount of methylene chloride and slowly added. After stirring at the same temperature for 1 hour, triethylamine (3.3 mL, 23.2 mmol) was added and the temperature of the reaction solution was

raised to room temperature from -78°C. When the reaction was completed, the solvent was removed, and the resulting mixture was diluted with ethyl acetate and washed with saturated sodium chloride solution. The organic layer was collected, dried with magnesium sulfate, filtered and concentrated under reduced pressure, and then dissolved in methylene chloride (47 mL, 0.12 M). Then, (carbethoxymethylene)triphenylphosphorane (4.0 g, 11.6 mmol) was added thereto and stirred for 2 hours. When the reaction was completed, the solvent was removed, and the resulting mixture was diluted with ethyl acetate and washed with saturated sodium chloride solution. The organic layer was collected, dried over magnesium sulfate, filtered and then concentrated under reduced pressure, and purified by column chromatography (hexane: ethyl acetate = 4: 1) to give the title compound (2.1 g, yield: 89%).

Step 166-2: Preparation of (E)-3-((2R,3S)-1-(tert-butoxycarbonyl)-3-((tert-butyldimethylsilyl)oxy)piperidin-2-yl)acrylic acid

Tert-butyl (2R,3S)-3-((tert-butyldimethylsilyl)oxy)-2-((E)-3-ethoxy-3-oxoprop-1-en-1-yl)piperidine-1-carboxylate (3.0 g, 7.2 mmol) obtained from Step 166-1 was dissolved in methanol (20 mL, 0.36 mmol). Then, 2N sodium hydroxide aqueous solution (10 mL) was added thereto and stirred at room temperature for 3 hours. When the reaction was completed, the reaction solution was neutralized with 1N aqueous hydrochloric acid solution, acidified, diluted with ethyl acetate and then washed with saturated sodium chloride solution. The organic layer was collected, dried over magnesium sulfate, filtered and concentrated under reduced pressure. Subsequent reactions were carried out without purification procedure.

Step 166-3: Preparation of tert-butyl (2R,3S)-3-((tert-butyldimethylsilyl)oxy)-2-((E)-3-hydroxyprop-en-1-yl) piperidine-1-carboxylate

(E)-3-((2R,3S)-1-(tert-butoxycarbonyl)-3-((tert-butyldimethylsilyl)oxy)piperidin-2-yl)acrylic acid (1.6 g, 4.0 mmol) obtained from Step 166-2 was dissolved in tetrahydrofuran (50 mL, 0.08 M), and the reaction solution was cooled to 0°C. Then, a lithium aluminum hydride solution (1.6 mL, 4.0 mmol) was slowly added thereto, reacted at the same temperature for 30 minutes and then stirred at room temperature for 2 hours. A small amount of water was added to complete the reaction, diluted with ethyl acetate and washed with saturated sodium chloride

solution. The organic layer was collected, dried over magnesium sulfate, filtered and concentrated under reduced pressure, and then purified by column chromatography (dichloromethane: methanol = 10:1) to give the title compound (1.3 g, yield: 85%).

5 Step 166-4: Preparation of tert-butyl (2R,3S)-2-((E)-3-bromoprop-1-en-1-yl)-3-((tert-butyl)dimethylsilyl)oxy)piperidine-1-carboxylate

 Tert-butyl (2R,3S)-3-((tert-butyl)dimethylsilyl)oxy)-2-((E)-3-hydroxyprop-en-1-yl)piperidine-1-carboxylate (100 mg, 0.27 mmol) obtained from Step 166-3 was added to methylene chloride (10 mL, 0.03 M). The reaction solution was cooled to 0°C, and then
10 triphenylphosphine (106 g, 0.40 mmol) and tetrabromomethane (134 mg, 0.40 mmol) were sequentially added at the same temperature, followed by stirring at room temperature for 2 hours. When the reaction was completed, the solvent was removed, and the resulting mixture was diluted with ethyl acetate and washed with saturated sodium chloride solution. The organic layer was collected, dried over magnesium sulfate, filtered and concentrated under reduced pressure, and
15 then purified by column chromatography (hexane: ethyl acetate = 5:1) to give the title compound (89 mg, yield: 76%).

 Step 166-5: Preparation of tert-butyl (2R,3S)-3-((tert-butyl)dimethylsilyl)oxy)-2-((E)-3-(5,6-dichloro-1H-benzo[d]imidazol-1-yl)prop-1-en-1-yl)piperidine-1-carboxylate

20 Tert-butyl (2R,3S)-2-((E)-3-bromoprop-1-en-1-yl)-3-((tert-butyl)dimethylsilyl)oxy)piperidine-1-carboxylate (83 mg, 0.19 mmol) obtained from Step 166-4 was dissolved in N,N-dimethylformamide (3 mL, 0.06 M). Potassium carbonate (53 mg, 0.38 mmol) and 5,6-dichloro-1H-benzo[d]imidazole (35 mg, 0.19 mmol) were added thereto and the mixture was stirred at room temperature for 4 hours. When the reaction was completed, the
25 solvent was removed, and the resulting mixture was diluted with ethyl acetate and washed with saturated sodium chloride solution. The organic layer was collected, dried over sodium sulfate, filtered and concentrated under reduced pressure, and then purified by column chromatography (hexane: ethyl acetate = 1:2) to give the title compound (88 g, yield: 85%).

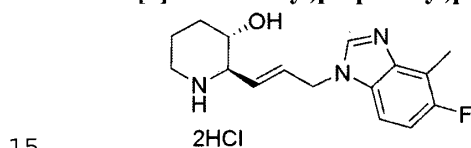
30 Step 166-6: Preparation of (2R,3S)-2-((E)-3-(5,6-dichloro-1H-benzo[d]imidazol-

yl)prop-1-en-1-yl)piperidin-3-ol dihydrochloride

Tert-butyl (2R,3S)-3-((tert-butyldimethylsilyl)oxy)-2-((E)-3-(5,6-dichloro-1H-benzo[d]imidazol-1-yl)prop-1-en-1-yl)piperidine-1-carboxylate (85 mg, 0.16 mmol) obtained from Step 166-5 was dissolved in a small amount of tetrahydrofuran. Then, 4N hydrogen chloride dioxane solution (5 mL, 0.03 M) was added thereto and stirred at room temperature for 12 hours. When the reaction was completed, the reaction solution was concentrated under reduced pressure to remove the solvent, dissolved by addition of a small amount of methanol and then crystallized with diethyl ether to obtain the title compound (51 mg, yield: 81%).

¹H-NMR (500 MHz, DMSO-d₆) : δ 8.86 (s, 1H), 8.12 (s, 1H), 8.04 (s, 1H), 6.11 (dt, 1H), 5.85 (d, 1H), 5.03 (d, 2H), 3.54 (m, 1H), 3.40 (m, 1H), 3.13 (d, 1H), 2.79 (m, 1H), 1.94 (m, 1H), 1.79 (d, 1H), 1.68 (m, 1H), 1.41 (m, 1H)

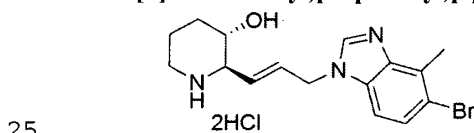
Example 167: Preparation of (2R,3S)-2-((E)-3-(5-fluoro-4-methyl-1H-benzo[d]imidazol-1-yl)prop-1-enyl)piperidin-3-ol dihydrochloride



The title compound (24 mg, yield: 80%) was obtained in the same manner as in Example 166, with the exception that 5-fluoro-4-methyl-1H-benzo[d]imidazole was used instead of 5,6-dichloro-1H-benzo[d]imidazole in Step 166-5 of Example 166.

¹H-NMR (500 MHz, MeOD): δ 9.45 (d, 1H), 7.73 (m, 1H), 7.42 (m, 1H), 6.25 (m, 1H), 5.98 (m, 1H), 5.23 (s, 2H), 3.55 (m, 2H), 2.96 (m, 1H), 2.56 (s, 3H), 2.00 (m, 3H), 1.74 (m, 1H), 1.56 (m, 1H)

Example 168: Preparation of (2R,3S)-2-((E)-3-(5-bromo-4-methyl-1H-benzo[d]imidazol-1-yl)prop-1-enyl)piperidin-3-ol dihydrochloride



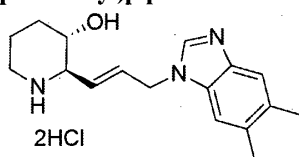
The title compound (30 mg, yield: 85%) was obtained in the same manner as in Example 166, with the exception that 5-bromo-4-methyl-1H-benzo[d]imidazole was used instead of 5,6-

dichloro-1H-benzo[d]imidazole in Step 166-5 of Example 166.

¹H-NMR (500 MHz, MeOD): δ 9.38 (d, 1H), 7.68 (m, 1H), 7.37 (m, 1H), 6.15 (m, 1H), 5.88 (m, 1H), 5.00 (s, 2H), 3.34 (m, 2H), 2.78 (m, 1H), 2.54 (s, 3H), 1.97 (m, 3H), 1.68 (m, 1H), 1.48 (m, 1H)

5

Example 169: Preparation of (2R,3S)-2-((E)-3-(5,6-dimethyl-1H-benzo[d]imidazol-1-yl)prop-1-en-1-yl)piperidin-3-ol dihydrochloride

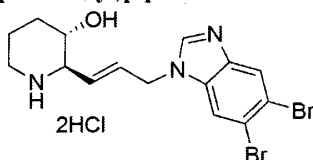


The title compound (30 mg, yield: 85%) was obtained in the same manner as in Example 166, with the exception that 5,6-dimethyl-1H-benzo[d]imidazole was used instead of 5,6-dichloro-1H-benzo[d]imidazole in Step 166-5 of Example 166.

¹H-NMR (500 MHz, MeOD): δ 7.64 (m, 1H), 7.61 (s, 1H), 6.25 (m, 1H), 5.91 (m, 1H), 5.20 (s, 2H), 3.56 (m, 2H), 2.95 (m, 1H), 2.46 (m, 1H), 2.45 (s, 6H), 2.09 (m, 1H), 2.00 (m, 2H), 1.72 (m, 1H), 1.56 (m, 1H)

15

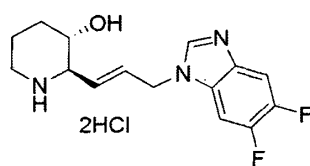
Example 170: Preparation of (2R,3S)-2-((E)-3-(5,6-dibromo-1H-benzo[d]imidazol-1-yl)prop-1-en-1-yl)piperidin-3-ol dihydrochloride



The title compound (24 mg, yield: 80%) was obtained in the same manner as in Example 166, with the exception that 5,6-dibromo-1H-benzo[d]imidazole was used instead of 5,6-dichloro-1H-benzo[d]imidazole in Step 166-5 of Example 166.

¹H-NMR (500 MHz, MeOD): δ 9.21 (m, 1H), 8.30 (m, 1H), 8.21 (m, 1H), 6.22 (m, 1H), 5.92 (m, 1H), 5.16 (m, 2H), 3.56 (m, 2H), 2.95 (m, 1H), 1.99 (m, 3H), 1.72 (m, 1H), 1.56 (m, 1H)

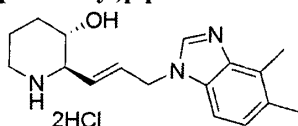
Example 171: Preparation of (2R,3S)-2-((E)-3-(5,6-difluoro-1H-benzo[d]imidazol-1-yl)prop-1-en-1-yl)piperidin-3-ol dihydrochloride



The title compound (20 mg, yield: 86%) was obtained in the same manner as in Example 166, with the exception that 5,6-difluoro-1H-benzo[d]imidazole was used instead of 5,6-dichloro-1H-benzo[d]imidazole in Step 166-5 of Example 166.

5 $^1\text{H-NMR}$ (500 MHz, MeOD): δ 7.76 (m, 1H), 6.22 (m, 1H), 5.88 (m, 1H), 5.12 (m, 2H), 3.57 (m, 3H), 2.92 (m, 1H), 2.20 (m, 4H), 1.72 (m, 1H), 1.56 (m, 1H)

Example 172: Preparation of (2R,3S)-2-((E)-3-(4,5-dimethyl-1H-benzo[d]imidazol-1-yl)prop-1-en-1-yl)piperidin-3-ol dihydrochloride

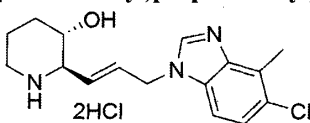


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The title compound (19 mg, yield: 81%) was obtained in the same manner as in Example 166, with the exception that 4,5-dimethyl-1H-benzo[d]imidazole was used instead of 5,6-dichloro-1H-benzo[d]imidazole in Step 166-5 of Example 166.

15 $^1\text{H-NMR}$ (500 MHz, MeOD): δ 9.42 (m, 1H), 7.62 (m, 1H), 7.47 (m, 1H), 6.25 (m, 1H), 5.94 (m, 1H), 5.21 (m, 2H), 3.55 (m, 2H), 3.34 (m, 1H), 2.95 (m, 1H), 1.99 (m, 2H), 1.74 (m, 1H), 1.53 (m, 1H)

Example 173: Preparation of (2R,3S)-2-((E)-3-(5-chloro-4-methyl-1H-benzo[d]imidazol-1-yl)prop-1-en-1-yl)piperidin-3-ol hydrochloride



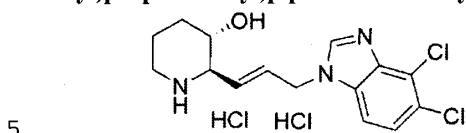
20

The title compound (25 mg, yield: 82%) was obtained in the same manner as in Example 166, with the exception that 5-chloro-4-methyl-1H-benzo[d]imidazole was used instead of 5,6-dichloro-1H-benzo[d]imidazole in Step 166-5 of Example 166.

25 $^1\text{H-NMR}$ (500 MHz, MeOD): δ 9.50 (s, 1H), 7.76 (d, 1H), 7.67 (d, 1H), 5.98 (m, 1H), 5.23 (m, 2H), 3.63 (m, 1H), 3.55 (m, 1H), 2.96 (m, 1H), 2.66 (s, 3H), 2.09 (m, 1H), 2.00 (m, 1H),

1.74 (m, 1H), 1.53 (m, 1H)

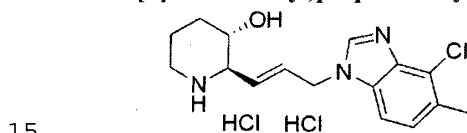
Example 174: Preparation of (2R,3S)-2-((E)-3-(4,5-dichloro-1H-benzo[d]imidazol-1-yl)prop-1-en-1-yl)piperidin-3-ol dihydrochloride



The title compound (20 mg, yield: 89%) was obtained in the same manner as in Example 166, with the exception that 4,5-dichloro-1H-benzo[d]imidazole was used instead of 5,6-dichloro-1H-benzo[d]imidazole in Step 166-5 of Example 166.

¹H NMR (500MHz, MeOD): δ 9.58(s, 1H), 7.91(d, 1H), 7.79(d, 1H), 6.30(m, 1H),
 10 6.03(m, 1H), 5.25(d, 2H), 3.69(m, 1H), 3.58(m, 1H), 3.01(m, 1H), 2.11(m, 1H), 2.03(m, 1H),
 1.80(m, 1H), 1.55(m, 1H)

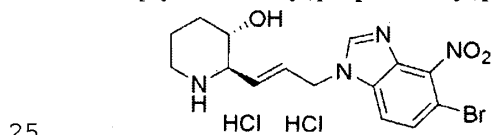
Example 175: Preparation of (2R,3S)-2-((E)-3-(4-chloro-5-methyl-1H-benzo[d]imidazol-1-yl)prop-1-en-1-yl)piperidin-3-ol dihydrochloride



The title compound (23 mg, yield: 91%) was obtained in the same manner as in Example 166, with the exception that 4-chloro-5-methyl-1H-benzo[d]imidazole was used instead of 5,6-dichloro-1H-benzo[d]imidazole in Step 166-5 of Example 166.

¹H NMR (500MHz, MeOD): δ 9.52(s, 1H), 7.88(d, 1H), 7.70(d, 1H), 6.25(m, 1H),
 20 6.01(m, 1H), 5.20(d, 2H), 3.62(m, 1H), 3.49(m, 1H), 3.00(m, 1H), 2.65(s, 3H), 2.05(m, 1H),
 2.00(m, 1H), 1.74(m, 1H), 1.51(m, 1H)

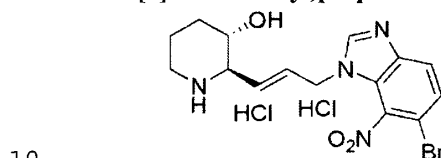
Example 176: Preparation of (2R,3S)-2-((E)-3-(5-bromo-4-nitro-1H-benzo[d]imidazol-1-yl)prop-1-en-1-yl)piperidin-3-ol dihydrochloride



The title compound (9 mg, yield: 45%) was obtained in the same manner as in Example 166, with the exception that 5-bromo-4-nitro-1H-benzo[d]imidazole was used instead of 5,6-dichloro-1H-benzo[d]imidazole in Step 166-5 of Example 166.

¹H NMR (500MHz, MeOD): δ 8.94(s, 1H), 7.93(d, 1H), 7.83(d, 1H), 6.27(m, 1H),
 5.84(m, 1H), 5.20(m, 2H), 3.62(m, 2H), 3.58(m, 1H), 2.99(m, 1H), 2.11(m, 1H), 2.08(m, 1H),
 1.98(m, 1H), 1.59(m, 1H)

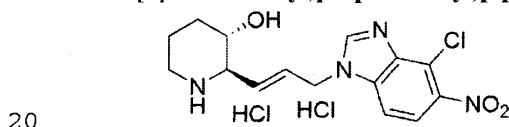
Example 177: Preparation of (2R,3S)-2-((E)-3-(6-bromo-7-nitro-1H-benzo[d]imidazol-1-yl)prop-1-en-1-yl)piperidin-3-ol dihydrochloride



The title compound (10 mg, yield: 51%) was obtained in the same manner as in Example 166, with the exception that 5-bromo-4-nitro-1H-benzo[d]imidazole was used instead of 5,6-dichloro-1H-benzo[d]imidazole in Step 166-5 of Example 166.

¹H NMR (500MHz, MeOD): δ 8.45(s, 1H), 7.85(d, 1H), 7.69(d, 1H), 6.11(m, 1H),
 15 5.59(m, 1H), 4.28(m, 2H), 3.62(m, 2H), 2.96(m, 1H), 2.24(m, 1H), 1.72(m, 2H), 1.58(m, 1H),
 1.53(m, 1H)

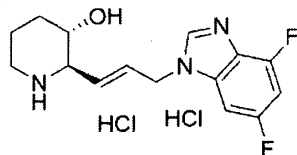
Example 178: Preparation of (2R,3S)-2-((E)-3-(4-chloro-5-nitro-1H-benzo[d]imidazol-1-yl)prop-1-en-1-yl)piperidin-3-ol dihydrochloride



The title compound (11 mg, yield: 52%) was obtained in the same manner as in Example 166, with the exception that 4-chloro-5-nitro-1H-benzo[d]imidazole was used instead of 5,6-dichloro-1H-benzo[d]imidazole in Step 166-5 of Example 166.

¹H NMR (500MHz, MeOD): δ 9.06(s, 1H), 8.04(m, 1H), 7.92(m, 1H), 7.87(m, 1H),
 25 6.26(m, 1H), 5.86(m, 1H), 5.26(m, 2H), 3.60(m, 2H), 2.96(m, 2H), 2.07(m, 1H), 1.99(m, 2H),
 1.77(m, 1H), 1.51(m, 1H)

Example 179: Preparation of (2R,3S)-2-((E)-3-(4,6-difluoro-1H-benzo[d]imidazol-1-yl)prop-1-en-1-yl)piperidin-3-ol dihydrochloride

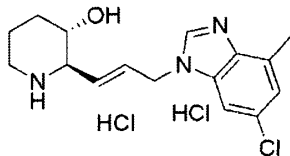


The title compound (15 mg, yield: 62%) was obtained in the same manner as in Example 166, with the exception that 4,6-difluoro-1H-benzo[d]imidazole was used instead of 5,6-dichloro-1H-benzo[d]imidazole in Step 166-5 of Example 166.

¹H NMR (500MHz, MeOD): δ 9.22(m, 1H), 7.58(m, 1H), 7.32(m, 1H), 6.38(m, 1H), 5.99(m, 1H), 5.27(d, 1H), 3.65(m, 2H), 2.99(t, 1H), 2.19(m, 1H), 2.08(m, 2H), 1.87(m, 2H), 1.65(m, 1H)

10

Example 180: Preparation of (2R,3S)-2-((E)-3-(6-chloro-4-methyl-1H-benzo[d]imidazol-1-yl)prop-1-en-1-yl)piperidin-3-ol dihydrochloride

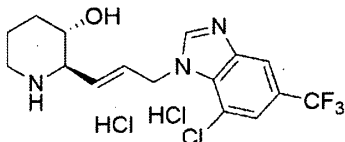


The title compound (14 mg, yield: 58%) was obtained in the same manner as in Example 166, with the exception that 6-chloro-4-methyl-1H-benzo[d]imidazole was used instead of 5,6-dichloro-1H-benzo[d]imidazole in Step 166-5 of Example 166.

¹H NMR (500MHz, MeOD): δ 9.53(m, 1H), 7.85(m, 1H), 7.50(m, 1H), 6.31(m, 1H), 6.01(m, 1H), 5.41(m, 1H), 3.66(m, 1H), 3.00(m, 2H), 2.64(s, 3H), 2.08(m, 3H), 1.73(m, 1H)

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Example 181: Preparation of (2R,3S)-2-((E)-3-(7-chloro-5-(trifluoromethyl)-1H-benzo[d]imidazol-1-yl)prop-1-en-1-yl)piperidin-3-ol dihydrochloride



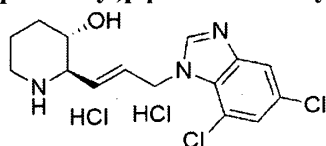
The title compound (19 mg, yield: 75%) was obtained in the same manner as in Example 166, with the exception that 7-chloro-5-(trifluoromethyl)-1H-benzo[d]imidazole was used instead

of 5,6-dichloro-1H-benzo[d]imidazole in Step 166-5 of Example 166.

¹H NMR (500MHz, MeOD): δ 9.51(m, 1H), 8.20(m, 1H), 7.99(m, 1H), 6.37(m, 1H), 5.89(m, 1H), 5.47(m, 2H), 3.59(m, 2H), 2.93(m, 1H), 2.08(m, 2H), 2.06(m, 1H), 1.75(m, 1H), 1.58(m, 1H), 1.51(m, 1H)

5

Example 182: Preparation of (2R,3S)-2-((E)-3-(5,7-dichloro-1H-benzo[d]imidazol-1-yl)prop-1-en-1-yl)piperidin-3-ol dihydrochloride

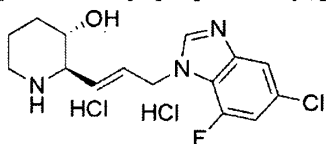


The title compound (22 mg, yield: 85%) was obtained in the same manner as in Example 166, with the exception that 5,7-dichloro-1H-benzo[d]imidazole was used instead of 5,6-dichloro-1H-benzo[d]imidazole in Step 166-5 of Example 166.

¹H NMR (500MHz, MeOD): δ 9.04(s, 1H), 7.81(s, 1H), 7.61(s, 1H), 6.36(m, 1H), 5.74(m, 1H), 5.42(m, 1H), 3.63-3.53(m, 2H), 2.99(m, 1H), 2.09(m, 1H), 2.01(m, 1H), 1.76(m, 1H), 1.59(m, 1H), 1.51(m, 1H)

15

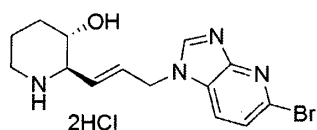
Example 183: Preparation of (2R,3S)-2-((E)-3-(5-chloro-7-fluoro-1H-benzo[d]imidazol-1-yl)prop-1-en-1-yl)piperidin-3-ol dihydrochloride



The title compound (18 mg, yield: 72%) was obtained in the same manner as in Example 166, with the exception that 5-chloro-7-fluoro-1H-benzo[d]imidazole was used instead of 5,6-dichloro-1H-benzo[d]imidazole in Step 166-5 of Example 166.

¹H NMR (500MHz, MeOD): δ 9.56(s, 1H), 7.75(m, 1H), 7.47(m, 1H), 6.33(m, 1H), 6.02(m, 1H), 5.28(m, 2H), 3.66(m, 2H), 2.99(m, 1H), 2.11(m, 2H), 1.78(m, 2H), 1.55(m, 1H)

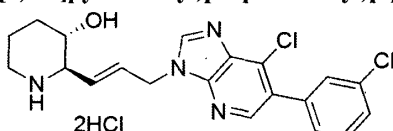
Example 184: Preparation of (2R,3S)-2-((E)-3-(5-bromo-1H-imidazo[4,5-b]pyridin-1-yl)prop-1-en-1-yl)piperidin-3-ol dihydrochloride



The title compound (18 mg, yield: 40%) was obtained in the same manner as in Example 166, with the exception that 5-bromo-1H-imidazo[4,5-b]pyridine was used instead of 5,6-dichloro-1H-benzo[d]imidazole in Step 166-5 of Example 166.

¹H-NMR (500 MHz, MeOD): δ 8.37 (s, 1H), 7.94 (m, 1H), 7.46 (m, 1H), 6.24 (m, 1H), 5.70 (m, 1H), 5.08 (m, 2H), 3.49 (m, 2H), 3.24 (m, 1H), 2.91 (m, 1H), 1.97 (m, 2H), 1.68 (m, 1H), 1.51 (m, 1H)

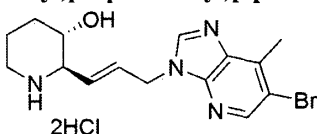
Example 185: Preparation of (2R,3S)-2-((E)-3-(7-chloro-6-(3-chlorophenyl)-3H-imidazo[4,5-b]pyridin-3-yl)prop-1-en-1-yl)piperidin-3-ol dihydrochloride



The title compound (20 mg, yield: 41%) was obtained in the same manner as in Example 166, with the exception that 7-chloro-6-(3-chlorophenyl)-3H-imidazo[4,5-b]pyridine was used instead of 5,6-dichloro-1H-benzo[d]imidazole in Step 166-5 of Example 166.

¹H-NMR (500 MHz, MeOD): δ 8.52 (s, 1H), 8.38 (s, 1H), 7.42 (m, 4H), 6.26 (m, 1H), 5.68 (m, 1H), 5.12 (m, 2H), 3.51 (m, 2H), 3.34 (m, 1H), 2.92 (m, 1H), 1.99 (m, 2H), 1.53 (m, 2H)

Example 186: Preparation of (2R,3S)-2-((E)-3-(6-bromo-7-methyl-3H-imidazo[4,5-b]pyridin-3-yl)prop-1-en-1-yl)piperidin-3-ol dihydrochloride

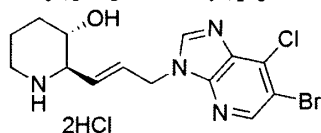


The title compound (18 mg, yield: 40%) was obtained in the same manner as in Example 166, with the exception that 6-bromo-7-methyl-3H-imidazo[4,5-b]pyridine was used instead of 5,6-dichloro-1H-benzo[d]imidazole in Step 166-5 of Example 166.

¹H-NMR (500 MHz, MeOD): δ 8.39 (s, 1H), 8.34 (s, 1H), 6.24 (m, 1H), 5.70 (m, 1H), 5.08 (m, 2H), 3.49 (m, 2H), 3.24 (m, 1H), 2.91 (m, 1H), 2.23 (s, 3H), 1.97 (m, 2H), 1.68 (m, 1H),

1.51 (m, 1H)

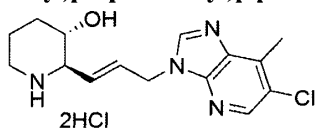
Example 187: Preparation of (2R,3S)-2-((E)-3-(6-bromo-7-chloro-3H-imidazo[4,5-b]pyridin-3-yl)prop-1-en-1-yl)piperidin-3-ol dihydrochloride



The title compound (25 mg, yield: 45%) was obtained in the same manner as in Example 166, with the exception that 6-bromo-7-chloro-3H-imidazo[4,5-b]pyridine was used instead of 5,6-dichloro-1H-benzo[d]imidazole in Step 166-5 of Example 166.

¹H-NMR (500 MHz, MeOD): δ 8.58 (m, 2H), 6.24 (m, 1H), 5.70 (m, 1H), 5.08 (m, 2H), 3.49 (m, 2H), 3.24 (m, 1H), 2.91 (m, 1H), 1.97 (m, 2H), 1.68 (m, 1H), 1.51 (m, 1H)

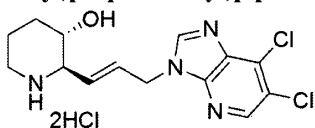
Example 188: Preparation of (2R,3S)-2-((E)-3-(6-chloro-7-methyl-3H-imidazo[4,5-b]pyridin-3-yl)prop-1-en-1-yl)piperidin-3-ol dihydrochloride



The title compound (32 mg, yield: 84%) was obtained in the same manner as in Example 166, with the exception that 6-chloro-7-methyl-3H-imidazo[4,5-b]pyridine was used instead of 5,6-dichloro-1H-benzo[d]imidazole in Step 166-5 of Example 166.

¹H-NMR (500 MHz, MeOD): δ 8.37 (s, 1H), 8.31 (s, 1H), 6.22 (m, 1H), 5.68 (m, 1H), 5.06 (m, 2H), 3.38 (m, 2H), 3.20 (m, 1H), 2.84 (m, 1H), 2.20 (s, 3H), 1.87 (m, 2H), 1.54 (m, 1H), 1.48 (m, 1H)

Example 189: Preparation of (2R,3S)-2-((E)-3-(6,7-dichloro-3H-imidazo[4,5-b]pyridin-3-yl)prop-1-en-1-yl)piperidin-3-ol dihydrochloride

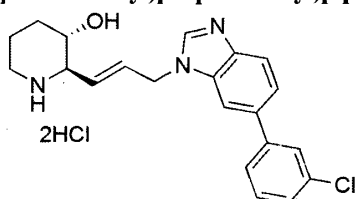


The title compound (25 mg, yield: 60%) was obtained in the same manner as in Example

166, with the exception that 6,7-dichloro-3H-imidazo[4,5-b]pyridine was used instead of 5,6-dichloro-1H-benzo[d]imidazole in Step 166-5 of Example 166.

¹H-NMR (500 MHz, DMSO-d₆): δ 8.68 (s, 1H), 8.57 (s, 1H), 6.15 (dd, 1H), 5.76 (dd, 1H), 4.98 (d, 2H), 3.52 (m, 1H), 3.40 (m, 1H), 3.09 (d, 1H), 2.78 (dd, 1H), 1.92 (m, 1H), 1.77 (m, 1H), 1.68 (m, 1H), 1.37 (m, 1H)

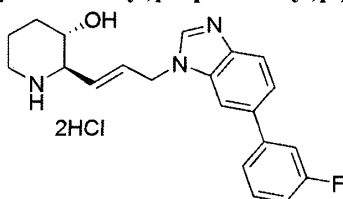
Example 190: Preparation of (2R,3S)-2-((E)-3-(6-(3-chlorophenyl)-1H-benzo[d]imidazol-1-yl)prop-1-en-1-yl)piperidin-3-ol dihydrochloride



The title compound (18 mg, yield: 40%) was obtained in the same manner as in Example 166, with the exception that 6-(3-chlorophenyl)-1H-benzo[d]imidazole was used instead of 5,6-dichloro-1H-benzo[d]imidazole in Step 166-5 of Example 166.

¹H-NMR (500 MHz, MeOD): δ 9.53 (s, 1H), 8.18 (s, 1H), 7.96 (s, 2H), 7.80 (s, 1H), 6.69 (d, 1H), 7.50 (t, 1H), 7.45 (d, 1H), 6.34 (dd, 1H), 6.00 (dd, 1H), 5.32 (d, 2H), 3.64 (m, 2H), 2.97 (m, 1H), 2.10 (m, 1H), 1.98 (m, 1H), 1.75 (m, 1H), 1.56 (m, 1H), 1.30 (m, 1H)

Example 191: Preparation of (2R,3S)-2-((E)-3-(6-(3-fluorophenyl)-1H-benzo[d]imidazol-1-yl)prop-1-en-1-yl)piperidin-3-ol dihydrochloride

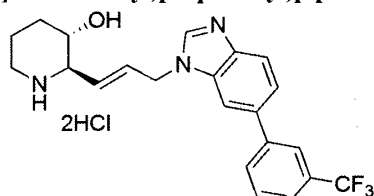


The title compound (15 mg, yield: 42%) was obtained in the same manner as in Example 166, with the exception that 6-(3-fluorophenyl)-1H-benzo[d]imidazole was used instead of 5,6-dichloro-1H-benzo[d]imidazole in Step 166-5 of Example 166.

¹H-NMR (500 MHz, MeOD): δ 9.35 (s, 1H), 8.23 (d, 1H), 7.93 (s, 2H), 7.57 (d, 1H), 7.52 (d, 2H), 7.17 (t, 1H), 6.32 (d, 1H), 5.94 (m, 1H), 5.31 (m, 2H), 3.56 (m, 3H), 2.97 (m, 1H),

2.10 (m, 1H), 2.01 (m, 1H), 1.72 (m, 1H), 1.55 (m, 1H)

Example 192: Preparation of (2R,3S)-2-((E)-3-(6-(3-(trifluoromethyl)phenyl)-1H-benzo[d]imidazol-1-yl)prop-1-en-1-yl)piperidin-3-ol dihydrochloride

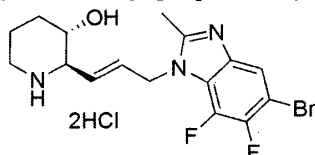


5

The title compound (15 mg, yield: 40%) was obtained in the same manner as in Example 166, with the exception that 6-(3-(trifluoromethyl)phenyl)-1H-benzo[d]imidazole was used instead of 5,6-dichloro-1H-benzo[d]imidazole in Step 166-5 of Example 166.

¹H-NMR (500 MHz, MeOD): δ 9.48 (s, 1H), 8.21 (s, 1H), 8.03 (m, 2H), 8.01 (s, 2H),
 10 7.73 (m, 2H), 6.34 (td, 1H), 5.99 (dd, 1H), 5.34 (m, 2H), 3.60 (td, 2H), 2.95 (m, 1H), 2.10 (d, 1H),
 2.01 (d, 1H), 1.74 (m, 1H), 1.55 (m, 1H), 1.31 (m, 1H)

Example 193: Preparation of (2R,3S)-2-((E)-3-(5-bromo-6,7-difluoro-2-methyl-1H-benzo[d]imidazol-1-yl)prop-1-en-1-yl)piperidin-3-ol dihydrochloride

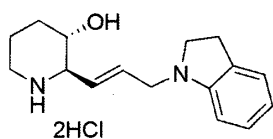


15

The title compound (12 mg, yield: 40%) was obtained in the same manner as in Example 166, with the exception that 5-bromo-6,7-difluoro-2-methyl-1H-benzo[d]imidazole was used instead of 5,6-dichloro-1H-benzo[d]imidazole in Step 166-5 of Example 166.

¹H-NMR (500 MHz, MeOD): δ 8.37 (s, 1H), 8.31 (s, 1H), 6.22 (m, 1H), 5.68 (m, 1H),
 20 5.06 (m, 2H), 3.38 (m, 2H), 3.20 (m, 1H), 2.84 (m, 1H), 2.20 (s, 3H), 1.87 (m, 2H), 1.54 (m, 1H),
 1.48 (m, 1H)

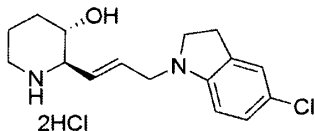
Example 194: Preparation of (2R,3S)-2-((E)-3-(indolin-1-yl)prop-1-en-1-yl)piperidin-3-ol dihydrochloride



The title compound (25 mg, yield: 80%) was obtained in the same manner as in Example 166, with the exception that indoline was used instead of 5,6-dichloro-1H-benzo[d]imidazole in Step 166-5 of Example 166.

5 $^1\text{H-NMR}$ (500 MHz, MeOD): δ 7.29 (m, 4H), 6.89 (s, 2H), 4.14 (m, 2H), 3.82 (m, 2H), 3.56 (m, 2H), 3.25 (m, 5H), 2.95 (m, 1H), 1.99 (m, 2H), 1.74 (m 1H), 1.56 (m, 1H)

Example 195: Preparation of (2R,3S)-2-((E)-3-(5-chloroindolin-1-yl)prop-1-en-1-yl)piperidin-3-ol dihydrochloride

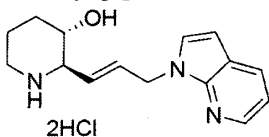


10

The title compound (27 mg, yield: 82%) was obtained in the same manner as in Example 166, with the exception that 5-chloroindoline was used instead of 5,6-dichloro-1H-benzo[d]imidazole in Step 166-5 of Example 166.

15 $^1\text{H-NMR}$ (500 MHz, MeOD): δ 7.10 (s, 1H), 6.89 (m, 2H), 6.04 (s, 2H), 4.12 (m, 2H), 3.74 (m, 2H), 3.42 (m, 2H), 3.20 (m, 5H), 2.84 (m, 1H), 1.97 (m, 2H), 1.68 (m, 1H), 1.52 (m, 1H)

Example 196: Preparation of (2R,3S)-2-((E)-3-(1H-pyrrolo[2,3-b]pyridin-1-yl)prop-1-en-1-yl)piperidin-3-ol dihydrochloride

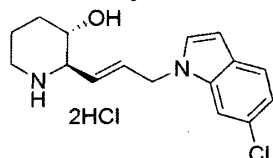


20

The title compound (30 mg, yield: 80%) was obtained in the same manner as in Example 166, with the exception that 1H-pyrrolo[2,3-b]pyridine was used instead of 5,6-dichloro-1H-benzo[d]imidazole in Step 166-5 of Example 166.

25 $^1\text{H-NMR}$ (500 MHz, MeOD): δ 8.21 (d, 1H), 7.98 (m, 1H), 7.37 (m, 1H), 7.09 (m, 1H), 6.51 (m, 1H), 6.20 (m, 1H), 5.90 (m, 1H), 4.87 (m, 2H), 3.61 (m, 1H), 3.52 (m, 1H), 3.27 (m, 1H), 2.95 (m, 1H), 2.00 (m, 2H), 1.71 (m, 1H), 1.56 (m, 1H)

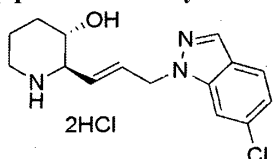
Example 197: Preparation of (2R,3S)-2-((E)-3-(6-chloro-1H-indol-1-yl)prop-1-en-1-yl)piperidin-3-ol dihydrochloride



5 The title compound (37 mg, yield: 83%) was obtained in the same manner as in Example 166, with the exception that 6-chloro-1H-indole was used instead of 5,6-dichloro-1H-benzo[d]imidazole in Step 166-5 of Example 166.

¹H-NMR (500 MHz, MeOD): δ 7.36 (m, 3H), 7.08 (d, 1H), 6.90 (m, 1H), 6.13 (m, 1H), 5.38 (m, 1H), 4.87 (m, 2H), 3.44 (m, 2H), 3.15 (m, 1H), 2.88 (m, 1H), 1.94 (m, 2H), 1.65 (m, 1H),
10 1.48 (m, 1H)

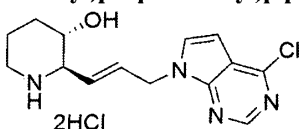
Example 198: Preparation of (2R,3S)-2-((E)-3-(6-chloro-1H-indazol-1-yl)prop-1-en-1-yl)piperidin-3-ol dihydrochloride



15 The title compound (25 mg, yield: 79%) was obtained in the same manner as in Example 166, with the exception that 6-chloro-1H-indazole was used instead of 5,6-dichloro-1H-benzo[d]imidazole in Step 166-5 of Example 166.

¹H-NMR (500 MHz, MeOD): δ 8.02 (s, 1H), 7.71 (m, 1H), 7.63 (s, 1H), 7.12 (m, 1H), 6.20 (m, 1H), 5.62 (m, 1H), 5.21 (m, 2H), 3.54 (m, 1H), 3.46 (m, 1H), 3.22 (m, 1H), 2.90 (m, 1H),
20 2.05 (m, 1H), 1.96 (m, 1H), 1.65 (m, 1H), 1.50 (m, 1H)

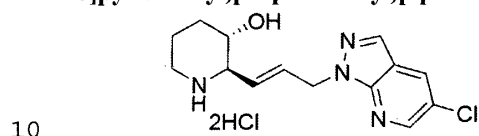
Example 199: Preparation of (2R,3S)-2-((E)-3-(4-chloro-7H-pyrrolo[2,3-d]pyrimidin-7-yl)prop-1-en-1-yl)piperidin-3-ol dihydrochloride,



The title compound (27 mg, yield: 85%) was obtained in the same manner as in Example 166, with the exception that 4-chloro-7H-pyrrolo[2,3-d]pyrimidine was used instead of 5,6-dichloro-1H-benzo[d]imidazole in Step 166-5 of Example 166.

¹H-NMR (500 MHz, MeOD): δ 8.53 (s, 1H), 7.60 (s, 1H), 6.69 (m, 1H), 6.18 (m, 1H),
 5 5.53 (m, 1H), 5.04 (m, 2H), 3.46 (m, 2H), 3.21 (m, 1H), 2.90 (m, 1H), 1.96 (m, 2H), 1.56 (m, 1H),
 1.50 (m, 1H)

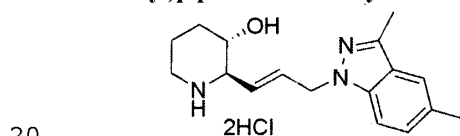
Example 200: Preparation of (2R,3S)-2-((E)-3-(5-chloro-1H-pyrazolo[3,4-b]pyridin-1-yl)prop-1-en-1-yl)piperidin-3-ol dihydrochloride



The title compound (25 mg, yield: 81%) was obtained in the same manner as in Example 166, with the exception that chloro-1H-pyrazolo[3,4-b]pyridine was used instead of 5,6-dichloro-1H-benzo[d]imidazole in Step 166-5 of Example 166.

¹H-NMR (500 MHz, MeOD): δ 8.52 (m, 1H), 8.26 (m, 1H), 8.13 (s, 1H), 6.20 (m, 1H),
 15 5.62 (m, 1H), 5.21 (m, 2H), 3.54 (m, 1H), 3.46 (m, 1H), 3.22 (m, 1H), 2.90 (m, 1H), 2.05 (m, 1H),
 1.96 (m, 1H), 1.65 (m, 1H), 1.50 (m, 1H)

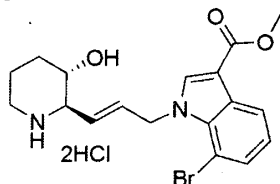
Example 201: Preparation of (2R,3S)-2-((E)-3-(3,5-dimethyl-1H-indazol-1-yl)prop-1-en-1-yl)piperidin-3-ol dihydrochloride



The title compound (28 mg, yield: 79%) was obtained in the same manner as in Example 166, with the exception that 3,5-dimethyl-1H-indazole was used instead of 5,6-dichloro-1H-benzo[d]imidazole in Step 166-5 of Example 166.

¹H-NMR (500 MHz, MeOD): δ 7.74 (s, 1H), 7.50 (m, 1H), 7.37 (m, 1H), 6.13 (m, 1H),
 25 5.49 (m, 1H), 5.02 (m, 2H), 3.50 (m, 1H), 3.44 (m, 1H), 3.32 (s, 3H), 3.21 (m, 1H), 2.90 (m, 1H),
 2.51 (s, 3H), 2.04 (m, 1H), 1.95 (m, 1H), 1.56 (m, 1H), 1.49 (m, 1H)

Example 202: Preparation of methyl 7-bromo-1-((E)-3-((2R,3S)-3-hydroxypiperidin-2-yl)allyl)-1H-indole-3-carboxylate dihydrochloride

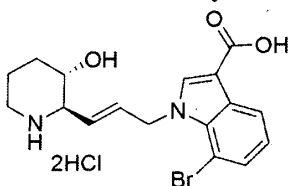


The title compound (30 mg, yield: 82%) was obtained in the same manner as in Example 166, with the exception that methyl 7-bromo-1H-indole-3-carboxylate was used instead of 5,6-dichloro-1H-benzo[d]imidazole in Step 166-5 of Example 166.

¹H-NMR (500 MHz, MeOD): δ 8.14 (m, 1H), 8.04 (s, 1H), 7.44 (m, 1H), 7.09 (m, 1H), 6.26 (m, 1H), 5.43 (m, 1H), 5.31 (m, 1H), 3.50 (m, 2H), 3.15 (m, 1H), 2.88 (m, 1H), 1.94 (m, 2H), 1.62 (m, 1H), 1.50 (m, 1H)

10

Example 203: Preparation of 7-bromo-1-((E)-3-((2R,3S)-3-hydroxypiperidin-2-yl)allyl)-1H-indole-3-carboxylic acid dihydrochloride

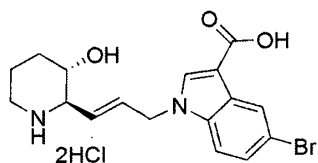


The title compound (28 mg, yield: 80%) was obtained in the same manner as in Example 166, with the exception that 7-bromo-1H-indole-3-carboxylic acid was used instead of 5,6-dichloro-1H-benzo[d]imidazole in Step 166-5 of Example 166.

¹H-NMR (500 MHz, MeOD): δ 8.02 (m, 2H), 7.39 (d, 1H), 7.09 (m, 1H), 6.21 (m, 1H), 5.91 (m, 1H), 4.83 (m, 2H), 3.62 (m, 1H), 3.51 (m, 1H), 3.26 (m, 1H), 2.94 (m, 1H), 1.98 (m, 2H), 1.71 (m, 1H), 1.52 (m, 1H)

20

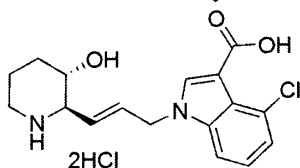
Example 204: Preparation of 5-bromo-1-((E)-3-((2R,3S)-3-hydroxypiperidin-2-yl)allyl)-1H-indole-3-carboxylic acid dihydrochloride



The title compound (35 mg, yield: 82%) was obtained in the same manner as in Example 166, with the exception that 5-bromo-1H-indole-3-carboxylic acid was used instead of 5,6-dichloro-1H-benzo[d]imidazole in Step 166-5 of Example 166.

- 5 $^1\text{H-NMR}$ (500 MHz, MeOD): δ 8.18 (s, 1H), 8.01 (m, 1H), 7.31 (m, 2H), 6.21 (m, 1H), 5.90 (m, 1H), 4.89 (m, 2H), 3.61 (m, 1H), 3.53 (m, 1H), 3.23 (m, 1H), 2.95 (m, 1H), 1.99 (m, 2H), 1.68 (m, 1H), 1.53 (m, 1H)

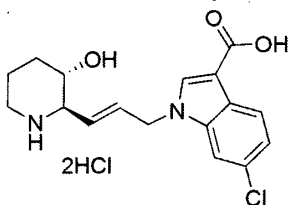
10 **Example 205: Preparation of 4-chloro-1-((E)-3-((2R,3S)-3-hydroxypiperidin-2-yl)allyl)-1H-indole-3-carboxylic acid dihydrochloride**



The title compound (31 mg, yield: 83%) was obtained in the same manner as in Example 166, with the exception that 4-chloro-1H-indole-3-carboxylic acid was used instead of 5,6-dichloro-1H-benzo[d]imidazole in Step 166-5 of Example 166.

- 15 $^1\text{H-NMR}$ (500 MHz, MeOD): δ 8.06 (s, 1H), 7.41 (d, 1H), 7.15 (m, 2H), 6.20 (m, 1H), 5.90 (m, 1H), 4.87 (m, 2H), 3.61 (m, 1H), 3.52 (m, 1H), 3.27 (m, 1H), 2.95 (m, 1H), 2.00 (m, 2H), 1.71 (m, 1H), 1.56 (m, 1H)

20 **Example 206: Preparation of 6-chloro-1-((E)-3-((2R,3S)-3-hydroxypiperidin-2-yl)allyl)-1H-indole-3-carboxylic acid dihydrochloride**

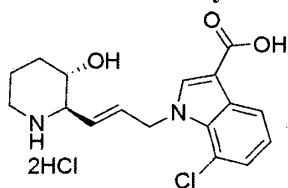


The title compound (27 mg, yield: 79%) was obtained in the same manner as in Example

166, with the exception that 6-chloro-1H-indole-3-carboxylic acid was used instead of 5,6-dichloro-1H-benzo[d]imidazole in Step 166-5 of Example 166.

¹H-NMR (500 MHz, MeOD): δ 8.01 (d, 1H), 7.46 (m, 1H), 7.17 (d, 1H), 6.22 (m, 1H), 5.91 (m, 1H), 4.88 (m, 2H), 4.36 (m, 1H), 3.61 (m, 1H), 3.27 (m, 1H), 2.94 (m, 1H), 2.05 (m, 2H),
5 1.72 (m, 1H), 1.56 (m, 1H)

Example 207: Preparation of 7-chloro-1-((E)-3-((2R,3S)-3-hydroxypiperidin-2-yl)allyl)-1H-indole-3-carboxylic acid dihydrochloride

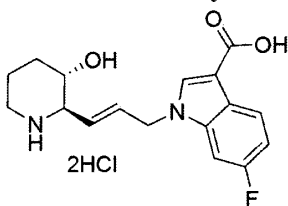


10 The title compound (25 mg, yield: 77%) was obtained in the same manner as in Example 166, with the exception that 7-chloro-1H-indole-3-carboxylic acid was used instead of 5,6-dichloro-1H-benzo[d]imidazole in Step 166-5 of Example 166.

¹H-NMR (500 MHz, MeOD): δ 8.00 (m, 2H), 7.16 (m, 2H), 6.22 (m, 1H), 5.91 (m, 1H), 4.90 (m, 2H), 3.53 (m, 2H), 2.96 (m, 1H), 1.99 (m, 2H), 1.71 (m, 1H), 1.55 (m, 1H)

15

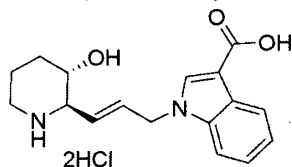
Example 208: Preparation of 6-fluoro-1-((E)-3-((2R,3S)-3-hydroxypiperidin-2-yl)allyl)-1H-indole-3-carboxylic acid dihydrochloride



20 The title compound (24 mg, yield: 81%) was obtained in the same manner as in Example 166, with the exception that 6-fluoro-1H-indole-3-carboxylic acid was used instead of 5,6-dichloro-1H-benzo[d]imidazole in Step 166-5 of Example 166.

¹H-NMR (500 MHz, MeOD): δ 7.99 (m, 2H), 7.15 (m, 1H), 6.95 (m, 1H), 6.21 (m, 1H), 5.90 (m, 1H), 4.87 (m, 2H), 3.60 (m, 1H), 3.51 (m, 1H), 3.26 (m, 1H), 2.94 (m, 1H), 2.01 (m, 2H), 1.71 (m, 1H), 1.56 (m, 1H)

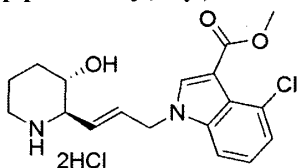
Example 209: Preparation of 1-((E)-3-((2R,3S)-3-hydroxypiperidin-2-yl)allyl)-1H-indole-3-carboxylic acid dihydrochloride



5 The title compound (20 mg, yield: 78%) was obtained in the same manner as in Example 166, with the exception that 1H-indole-3-carboxylic acid was used instead of 5,6-dichloro-1H-benzo[d]imidazole in Step 166-5 of Example 166.

¹H-NMR (500 MHz, MeOD): δ 8.05 (d, 1H), 7.99 (d, 1H), 7.45 (d, 1H), 7.16 (m, 2H), 6.22 (m, 1H), 5.91 (m, 1H), 4.83 (m, 2H), 4.37 (m, 1H), 3.61 (m, 1H), 3.52 (m, 1H), 2.94 (m, 1H),
10 2.00 (m, 2H), 1.69 (m, 1H), 1.53 (m, 1H)

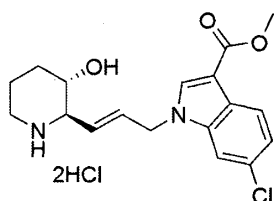
Example 210: Preparation of methyl 4-chloro-1-((E)-3-((2R,3S)-3-hydroxypiperidin-2-yl)allyl)-1H-indole-3-carboxylate dihydrochloride



15 The title compound (18 mg, yield: 82%) was obtained in the same manner as in Example 166, with the exception that methyl 4-chloro-1H-indole-3-carboxylate was used instead of 5,6-dichloro-1H-benzo[d]imidazole in Step 166-5 of Example 166.

¹H-NMR (500 MHz, MeOD): δ 8.05 (s, 1H), 7.44 (d, 1H), 7.20 (m, 2H), 6.17 (m, 1H), 5.42 (m, 1H), 4.98 (m, 2H), 3.84 (s, 3H), 3.45 (m, 2H), 3.18 (m, 1H), 2.89 (m, 1H), 1.94 (m, 2H),
20 1.64 (m, 1H), 1.50 (m, 1H)

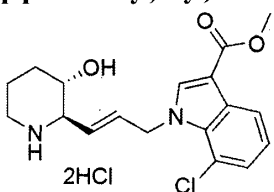
Example 211: Preparation of methyl 6-chloro-1-((E)-3-((2R,3S)-3-hydroxypiperidin-2-yl)allyl)-1H-indole-3-carboxylate dihydrochloride



The title compound (28 mg, yield: 80%) was obtained in the same manner as in Example 166, with the exception that methyl 6-chloro-1H-indole-3-carboxylate was used instead of 5,6-dichloro-1H-benzo[d]imidazole in Step 166-5 of Example 166.

¹H-NMR (500 MHz, MeOD): δ 8.02 (m, 2H), 7.56 (s, 1H), 7.22 (t, 1H), 6.17 (m, 1H), 5.45 (m, 1H), 4.96 (m, 2H), 3.87 (s, 3H), 3.46 (m, 2H), 3.20 (m, 1H), 2.89 (m, 1H), 1.95 (m, 2H), 1.65 (m, 1H), 1.51 (m, 1H)

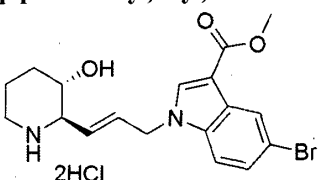
Example 212: Preparation of methyl 7-chloro-1-((E)-3-((2R,3S)-3-hydroxypiperidin-2-yl)allyl)-1H-indole-3-carboxylate dihydrochloride



The title compound (28 mg, yield: 84%) was obtained in the same manner as in Example 166, with the exception that methyl 7-chloro-1H-indole-3-carboxylate was used instead of 5,6-dichloro-1H-benzo[d]imidazole in Step 166-5 of Example 166.

¹H-NMR (500 MHz, MeOD): δ 8.08 (d, 1H), 8.03 (s, 1H), 7.25 (d, 1H), 7.16 (m, 1H), 6.26 (m, 1H), 5.28 (m, 2H), 3.89 (s, 3H), 3.65 (s, 1H), 3.46 (m, 2H), 3.16 (m, 1H), 2.90 (m, 1H), 1.95 (m, 2H), 1.60 (m, 1H), 1.50 (m, 1H)

Example 213: Preparation of methyl 5-bromo-1-((E)-3-((2R,3S)-3-hydroxypiperidin-2-yl)allyl)-1H-indole-3-carboxylate dihydrochloride

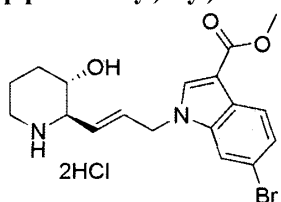


The title compound (30 mg, yield: 85%) was obtained in the same manner as in Example

166, with the exception that methyl 5-bromo-1H-indole-3-carboxylate was used instead of 5,6-dichloro-1H-benzo[d]imidazole in Step 166-5 of Example 166.

¹H-NMR (500 MHz, MeOD): δ 8.19 (d, 1H), 8.04 (d, 1H), 7.36 (m, 2H), 6.17 (m, 1H), 5.46 (m, 1H), 4.97 (m, 2H), 3.90 (s, 3H), 3.43 (m, 2H), 3.20 (m, 1H), 2.88 (m, 1H), 1.97 (m, 2H),
5 1.66 (m, 1H), 1.51 (m, 1H)

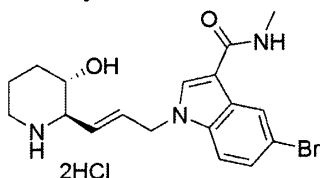
Example 214: Preparation of methyl 6-bromo-1-((E)-3-((2R,3S)-3-hydroxypiperidin-2-yl)allyl)-1H-indole-3-carboxylate dihydrochloride



10 The title compound (31 mg, yield: 83%) was obtained in the same manner as in Example 166, with the exception that methyl 6-bromo-1H-indole-3-carboxylate was used instead of 5,6-dichloro-1H-benzo[d]imidazole in Step 166-5 of Example 166.

¹H-NMR (500 MHz, MeOD): δ 7.96 (m, 2H), 7.71 (s, 1H), 7.33 (m, 1H), 6.17 (m, 1H), 5.44 (m, 1H), 4.96 (m, 2H), 3.87 (s, 3H), 3.47 (m, 2H), 3.19 (m, 1H), 2.89 (m, 1H), 1.97 (m, 2H),
15 1.65 (m, 1H), 1.51 (m, 1H)

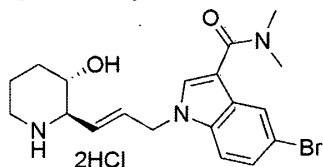
Example 215: Preparation of 5-bromo-1-((E)-3-((2R,3S)-3-hydroxypiperidin-2-yl)allyl)-N-methyl-1H-indole-3-carboxamide dihydrochloride



20 The title compound (21 mg, yield: 86%) was obtained in the same manner as in Example 166, with the exception that 5-bromo-N-methyl-1H-indole-3-carboxamide was used instead of 5,6-dichloro-1H-benzo[d]imidazole in Step 166-5 of Example 166.

¹H-NMR (500 MHz, MeOD): δ 8.25 (m, 1H), 7.84 (s, 1H), 7.34 (m, 2H), 6.16 (m, 1H), 5.38 (m, 1H), 4.89 (m, 2H), 3.44 (m, 2H), 3.16 (m, 1H), 2.86 (m, 4H), 1.94 (m, 2H), 1.63 (m, 1H),
25 1.48 (m, 1H)

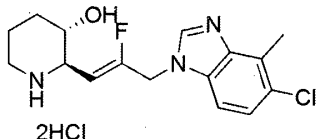
Example 216: Preparation of 5-bromo-1-((E)-3-((2R,3S)-3-hydroxypiperidin-2-yl)allyl)-N,N-dimethyl-1H-indole-3-carboxamide dihydrochloride



5 The title compound (21 mg, yield: 86%) was obtained in the same manner as in Example 166, with the exception that 5-bromo-N,N-dimethyl-1H-indole-3-carboxylamide was used instead of 5,6-dichloro-1H-benzo[d]imidazole in Step 166-5 of Example 166.

¹H-NMR (500 MHz, MeOD): δ 7.95 (s, 1H), 7.71 (s, 1H), 7.41 (d, 1H), 7.34 (m, 1H), 6.14 (m, 1H), 5.39 (m, 1H), 4.96 (m, 2H), 3.45 (m, 2H), 3.16 (m, 7H), 2.89 (m, 1H), 1.97 (m, 2H),
10 1.65 (m, 1H), 1.50 (m, 1H)

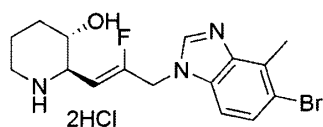
Example 217: Preparation of (2R,3S)-2-((Z)-3-(5-chloro-4-methyl-1H-benzo[d]imidazol-1-yl)-2-fluoroprop-1-enyl)piperidin-3-ol dihydrochloride



15 The title compound (25 mg, yield: 80%) was obtained in the same manner as in Example 166, with the exception that triethyl 2-fluoro-2-phosphonoacetate was used instead of (carbethoxymethylene)triphenylphosphorane in Step 166-1 of Example 166, and 5-chloro-4-methyl-1H-benzo[d]imidazole was used instead of 5,6-dichloro-1H-benzo[d]imidazole in Step 166-5 of Example 166.

20 ¹H-NMR (500 MHz, MeOD): δ 8.30 (s, 1H), 7.52 (d, 1H), 7.32 (d, 1H), 5.36 (m, 1H), 5.25 (m, 1H), 5.19 (m, 1H), 3.36 (t, 1H), 3.31 (m, 1H), 3.10 (d, 1H), 2.79 (m, 1H), 2.61 (s, 3H), 2.15 (m, 1H), 1.87 (m, 1H), 1.68 (m, 1H), 1.56 (m, 1H)

Example 218: Preparation of (2R,3S)-2-((Z)-3-(5-bromo-4-methyl-1H-benzo[d]imidazol-1-yl)-2-fluoroprop-1-en-1-yl)piperidin-3-ol dihydrochloride

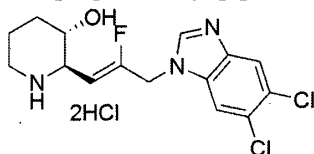


The title compound (27 mg, yield: 81%) was obtained in the same manner as in Example 166, with the exception that triethyl 2-fluoro-2-phosphonoacetate was used instead of (carbethoxymethylene)triphenylphosphorane in Step 166-1 of Example 166, and 5-bromo-4-methyl-1H-benzo[d]imidazole was used instead of 5,6-dichloro-1H-benzo[d]imidazole in Step 166-5 of Example 166.

¹H-NMR (500 MHz, MeOD): δ 8.29 (s, 1H), 7.46 (s, 2H), 5.35 (m, 1H), 5.25 (m, 1H), 5.21 (m, 1H), 3.54 (t, 1H), 3.41 (m, 1H), 3.12 (d, 1H), 2.77 (m, 1H), 2.63 (s, 3H), 2.15 (m, 1H), 1.87 (m, 1H), 1.68 (m, 1H), 1.56 (m, 1H)

10

Example 219: Preparation of (2R,3S)-2-((Z)-3-(5,6-dichloro-1H-benzo[d]imidazol-1-yl)-2-fluoroprop-1-en-1-yl)piperidin-3-ol dihydrochloride

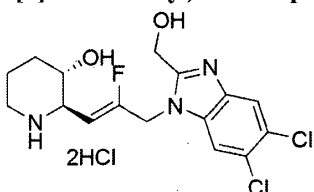


The title compound (35 mg, yield: 84%) was obtained in the same manner as in Example 166, with the exception that triethyl 2-fluoro-2-phosphonoacetate was used instead of (carbethoxymethylene)triphenylphosphorane in Step 166-1 of Example 166.

¹H-NMR (500 MHz, MeOD): δ 8.38 (s, 1H), 8.00 (s, 1H), 7.80 (s, 1H), 5.26 (m, 3H), 3.59 (t, 1H), 3.42 (m, 1H), 3.14 (d, 1H), 2.83 (t, 1H), 2.14 (m, 1H), 1.89 (d, 1H), 1.69 (m, 1H), 1.58 (m, 1H)

20

Example 220: Preparation of (2R,3S)-2-((Z)-3-(5,6-dichloro-2-(hydroxymethyl)-1H-benzo[d]imidazol-1-yl)-2-fluoroprop-1-en-1-yl)piperidin-3-ol dihydrochloride

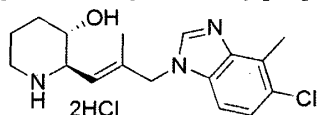


The title compound (30 mg, yield: 79%) was obtained in the same manner as in Example

166, with the exception that triethyl 2-fluoro-2-phosphonoacetate was used instead of (carbethoxymethylene)triphenylphosphorane in Step 166-1 of Example 166, and (5,6-dichloro-1H-benzo[d]imidazol-2-yl)methanol was used instead of 5,6-dichloro-1H-benzo[d]imidazole in Step 166-5 of Example 166.

5 ¹H-NMR (500 MHz, MeOD): δ 8.01 (s, 1H), 7.71 (s, 1H), 5.41 (m, 3H), 4.85 (m, 2H), 3.80 (m, 1H), 3.57 (m, 2H), 3.26 (s, 1H), 2.96 (t, 1H), 2.18 (m, 1H), 1.98 (m, 1H), 1.73 (m, 1H), 1.63 (m, 1H)

Example 221: Preparation of (2R,3S)-2-((E)-3-(5-chloro-4-methyl-1H-benzo[d]imidazol-1-yl)-2-methylprop-1-en-1-yl)piperidin-3-ol dihydrochloride

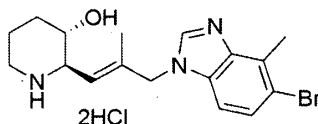


The title compound (27 mg, yield: 81%) was obtained in the same manner as in Example 166, with the exception that (1-ethoxycarbonylethylidene diene)triphenylphosphorane was used instead of (carbethoxymethylene)triphenylphosphorane in Step 166-1 of Example 166, and 5-chloro-4-methyl-1H-benzo[d]imidazole was used instead of 5,6-dichloro-1H-benzo[d]imidazole in Step 166-5 of Example 166.

¹H-NMR (500 MHz, MeOD): δ 8.21 (s, 1H), 7.39 (d, 1H), 7.31 (d, 1H), 5.13 (d, 1H), 4.93 (m, 2H), 3.62 (t, 1H), 3.39 (m, 1H), 3.15 (m, 1H), 2.87 (m, 1H), 2.62 (s, 3H), 2.06 (m, 1H), 1.93 (m, 1H), 1.78 (s, 3H), 1.62 (m, 1H), 1.57 (m, 1H)

20

Example 222: Preparation of (2R,3S)-2-((E)-3-(5-bromo-4-methyl-1H-benzo[d]imidazol-1-yl)-2-methylprop-1-en-1-yl)piperidin-3-ol dihydrochloride



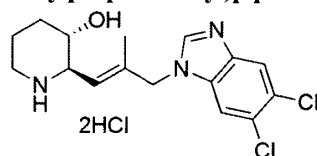
The title compound (34 mg, yield: 80%) was obtained in the same manner as in Example 166, with the exception that (1-ethoxycarbonylethylidene diene)triphenylphosphorane was used instead of (carbethoxymethylene)triphenylphosphorane in Step 166-1 of Example 166, and 5-bromo-4-methyl-1H-benzo[d]imidazole was used instead of 5,6-dichloro-1H-benzo[d]imidazole

in Step 166-5 of Example 166.

¹H-NMR (500 MHz, MeOD): δ 8.20 (s, 1H), 7.47 (d, 1H), 7.35 (d, 1H), 5.12 (d, 1H), 4.93 (m, 2H), 3.62 (t, 1H), 3.40 (m, 1H), 3.15 (m, 1H), 2.86 (m, 1H), 2.64 (s, 3H), 2.06 (m, 1H), 1.92 (m, 1H), 1.78 (s, 3H), 1.66 (m, 1H), 1.56 (m, 1H)

5

Example 223: Preparation of (2R,3S)-2-((E)-3-(5,6-dichloro-1H-benzo[d]imidazol-1-yl)-2-methylprop-1-en-1-yl)piperidin-3-ol dihydrochloride

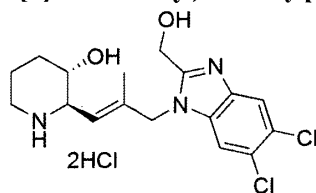


The title compound (28 mg, yield: 78%) was obtained in the same manner as in Example 166, with the exception that (1-ethoxycarbonylethylidene)triphenylphosphorane was used instead of (carbethoxymethylene)triphenylphosphorane in Step 166-1 of Example 166.

¹H-NMR (500 MHz, MeOD): δ 8.28 (s, 1H), 7.83 (s, 2H), 5.18 (d, 1H), 4.91 (m, 2H), 3.48 (t, 1H), 3.07 (d, 1H), 2.76 (t, 1H), 2.07 (m, 1H), 1.86 (m, 1H), 1.76 (s, 3H), 1.62 (m, 1H), 1.46 (m, 1H)

15

Example 224: Preparation of (2R,3S)-2-((E)-3-(5,6-dichloro-2-(hydroxymethyl)-1H-benzo[d]imidazol-1-yl)-2-methylprop-1-en-1-yl)piperidin-3-ol dihydrochloride



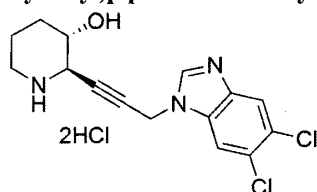
The title compound (31 mg, yield: 78%) was obtained in the same manner as in Example 166, with the exception that (1-ethoxycarbonylethylidene)triphenylphosphorane was used instead of (carbethoxymethylene)triphenylphosphorane in Step 166-1 of Example 166, and 5,6-dichloro-1H-benzo[d]imidazol-2-yl)methanol was used instead of 5,6-dichloro-1H-benzo[d]imidazole in Step 166-5 of Example 166.

¹H-NMR (500 MHz, MeOD): δ 7.79 (s, 2H), 5.03 (m, 2H), 4.89 (m, 3H), 3.70 (t, 1H), 3.40 (m, 1H), 3.14 (m, 1H), 2.92 (m, 1H), 2.03 (m, 1H), 1.94 (m, 1H), 1.84 (s, 3H), 1.65 (m, 1H),

25

1.55 (m, 1H)

Example 225: Preparation of (2R,3S)-2-(3-(5,6-dichloro-1H-benzo[d]imidazol-1-yl)prop-1-yn-1-yl)piperidin-3-ol dihydrochloride



5

Step 225-1: Preparation of tert-butyl (2R,3S)-3-((tert-butyldimethylsilyl)oxy)-2-(E)-3-ethoxy-3-oxoprop-1-en-1-yl)piperidine-1-carboxylate

Methylene chloride (47 mL, 0.12 M) and oxalyl chloride (1.0 mL, 11.6 mmol) were added to a flask filled with nitrogen and the reaction solution was cooled to -78°C . Dimethylsulfoxide (1.7 mL, 23.2 mmol) was then added at the same temperature and stirred for 30 minutes. Then, tert-butyl (2R,3S)-3-((tert-butyldimethylsilyl)oxy)-2-(hydroxymethyl)piperidine-1-carboxylate (2.0 g, 5.8 mmol) was dissolved in a small amount of methylene chloride and slowly added. After stirring at the same temperature for 1 hour, triethylamine (3.3 mL, 23.2 mmol) was added and the temperature of the reaction solution was raised to room temperature from -78°C . When the reaction was completed, the solvent was removed, and the resulting mixture was diluted with ethyl acetate and washed with saturated sodium chloride solution. The organic layer was collected and dried with magnesium sulfate, filtered and concentrated under reduced pressure, and then dissolved in methylene chloride (47 mL, 0.12 M), and (carbethoxymethylene)triphenylphosphorane (4.0 g, 11.6 mmol) was added thereto at room temperature and stirred for 2 hours. When the reaction was completed, the solvent was removed, and the resulting mixture was diluted with ethyl acetate and washed with saturated sodium chloride solution. The organic layer was collected, dried over magnesium sulfate, filtered and concentrated under reduced pressure, and purified by column chromatography (hexane: ethyl acetate = 4:1) to give the title compound (2.1 g, 89% yield over two steps).

25

Step 225-2: Preparation of tert-butyl (2R,3S)-3-((tert-butyldimethylsilyl)oxy)-2-(3-ethoxy-3-oxoprop-1-yn-1-yl)piperidine-1-carboxylate

Tert-butyl (2R,3S)-3-((tert-butyldimethylsilyl)oxy)-2-(E)-3-ethoxy-3-oxoprop-1-en-1-yl)piperidine-1-carboxylate (3.2 g, 7.7 mmol) obtained from Step 225-1 was dissolved in methanol (50 mL, 0.15 M), and a lindlar catalyst (82 mg, 0.77 mmol) was added thereto. After connecting a hydrogen balloon, the mixture was stirred at room temperature for 5 hours. When the reaction was completed, the reaction solution was filtered through celite and concentrated under reduced pressure. Subsequent reactions were carried out without purification procedure.

Step 225-3: Preparation of 3-((2R,3S)-1-(tert-butoxycarbonyl)-3-(tert-butyldimethylsilyl)oxy)piperidin-2-yl)propenoic acid

Tert-butyl (2R,3S)-3-((tert-butyldimethylsilyl)oxy)-2-(3-ethoxy-3-oxoprop-1-yn-1-yl)piperidine-1-carboxylate (3.0 g, 7.2 mmol) obtained from Step 225-2 was dissolved in methanol (20 mL, 0.36 M), and then 2N aqueous sodium hydroxide solution (10 mL) was added thereto and stirred at room temperature for 3 hours. When the reaction was completed, the reaction solution was neutralized with 1N aqueous hydrochloric acid solution, acidified, diluted with ethyl acetate and then washed with saturated sodium chloride solution. The organic layer was collected, dried over magnesium sulfate, filtered and concentrated under reduced pressure. Subsequent reactions were carried out without purification procedure.

Step 225-4: Preparation of tert-butyl (2R,3S)-3-((tert-butyldimethylsilyl)oxy)-2-(3-hydroxyprop-1-yn-1-yl)piperidine-1-carboxylate

3-((2R,3S)-1-(tert-butoxycarbonyl)-3-(tert-butyldimethylsilyl)oxy)piperidin-2-yl)propenoic acid (1.6 g, 4.0 mmol) obtained from Step 225-3 was dissolved in tetrahydrofuran (50 mL, 0.08 M), and the reaction solution was cooled to 0°C. Then, a lithium aluminum hydride solution (1.6 mL, 4.0 mmol) was slowly added thereto, reacted at the same temperature for 30 minutes and then stirred at room temperature for 2 hours. A small amount of water was added to complete the reaction, diluted with ethyl acetate and washed with saturated sodium chloride solution. The organic layer was collected, dried over magnesium sulfate, filtered and concentrated under reduced pressure, and then purified by column chromatography (dichloromethane: methanol = 10:1) to give the title compound (1.3 g, yield: 85%).

30

Step 225-5: Preparation of tert-butyl (2R,3S)-2-(3-bromoprop-1-yn-1-yl)-3-((tert-butyltrimethylsilyl)oxy)piperidine-1-carboxylate

Tert-butyl (2R,3S)-3-((tert-butyltrimethylsilyl)oxy)-2-(3-hydroxyprop-1-yn-1-yl)piperidine-1-carboxylate (100 mg, 0.27 mmol) obtained from Step 225-4 was added to
5 methylene chloride (100 mL, 0.03 M). The reaction solution was cooled to 0°C, and then triphenylphosphine (107 g, 0.41 mmol) and tetrabromomethane (135 g, 0.41 mmol) were sequentially added at the same temperature, followed by stirring at room temperature for 2 hours. When the reaction was completed, the solvent was removed, and the resulting mixture was diluted with ethyl acetate and washed with saturated sodium chloride solution. The organic layer was
10 collected and dried over magnesium sulfate, filtered and concentrated under reduced pressure, and then purified by column chromatography (hexane: ethyl acetate = 5:1) to give the title compound (89 g, yield: 76%).

Step 225-6: Preparation of tert-butyl (2R,3S)-3-((tert-butyltrimethylsilyl)oxy)-2-(3-(5,6-dichloro-1H-benzo[d]imidazol-1-yl)prop-1-yn-1-yl)piperidine-1-carboxylate

Tert-butyl (2R,3S)-2-(3-bromoprop-1-yn-1-yl)-3-((tert-butyltrimethylsilyl)oxy)piperidine-1-carboxylate (200 mg, 0.46 mmol) obtained from Step 225-5 was dissolved in N,N-dimethylformamide (5 mL, 0.69 M). Then, potassium carbonate (127 mg, 0.92 mmol) and 5,6-dichloro-1H-benzo[d]imidazole (86 mg, 0.46 mmol) were added thereto, and
20 the mixture was stirred at room temperature for 4 hours. When the reaction was completed, the solvent was removed, and the resulting mixture was diluted with ethyl acetate and washed with saturated sodium chloride solution. The organic layer was collected, dried over sodium sulfate, filtered and concentrated under reduced pressure, and then purified by column chromatography (hexane: ethyl acetate = 1:2) to give the title compound (293 mg, yield 85%).

25

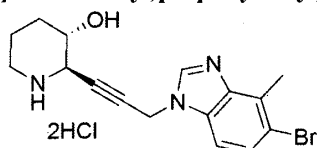
Step 225-7: Preparation of (2R,3S)-2-(3-(5,6-dichloro-1H-benzo[d]imidazol-1-yl)prop-1-yn-1-yl)piperidin-3-ol dihydrochloride

Tert-butyl (2R,3S)-3-((tert-butyltrimethylsilyl)oxy)-2-(3-(5,6-dichloro-1H-benzo[d]imidazol-1-yl)prop-1-yn-1-yl)piperidine-1-carboxylate (293 mg, 0.54 mmol) obtained
30 from Step 225-6 was dissolved in a small amount of tetrahydrofuran and 4N hydrogen chloride

dioxane solution (5 mL, 0.10 M) was added thereto, and the mixture was heated and stirred at room temperature for 12 hours. When the reaction was completed, the reaction solution was concentrated under reduced pressure to remove the solvent, dissolved by addition of a small amount of methanol and then crystallized with diethyl ether to give the title compound (176 mg, yield: 82%).

¹H-NMR (500 MHz, MeOD): δ 8.44 (br, 1H), 7.99 (s, 1H), 7.88 (s, 1H), 5.34 (s, 2H), 4.11 (m, 1H), 3.90 (m, 1H), 3.22 (m, 1H), 3.04 (m, 1H), 1.99 (m, 2H), 1.65 (m, 2H)

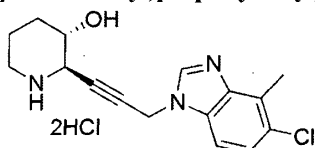
Example 226: Preparation of (2R,3S)-2-(3-(5-bromo-4-methyl-1H-benzo[d]imidazol-1-yl)prop-1-yn-1-yl)piperidin-3-ol dihydrochloride



The title compound (42 mg, yield: 85%) was obtained in the same manner as in Example 225, with the exception that 5-bromo-4-methyl-1H-benzo[d]imidazole was used instead of 5,6-dichloro-1H-benzo[d]imidazole in Step 225-6 of Example 225.

¹H-NMR (500 MHz, MeOD): δ 9.61 (m, 1H), 7.86 (m, 1H), 7.78 (m, 1H), 5.57 (d, 2H), 4.86 (m, 1H), 4.16 (m, 1H), 3.97 (m, 1H), 3.06 (m, 1H), 2.72 (s, 3H), 2.02 (m, 2H), 1.65 (m, 2H)

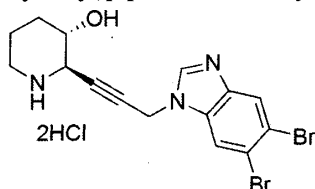
Example 227: Preparation of (2R,3S)-2-(3-(5-chloro-4-methyl-1H-benzo[d]imidazol-1-yl)prop-1-yn-1-yl)piperidin-3-ol dihydrochloride



The title compound (35 mg, yield: 81%) was obtained in the same manner as in Example 225, with the exception that 5-chloro-4-methyl-1H-benzo[d]imidazole was used instead of 5,6-dichloro-1H-benzo[d]imidazole in Step 225-6 of Example 225.

¹H-NMR (500 MHz, MeOD): δ 9.65 (s, 1H), 7.86 (d, 1H), 7.71 (d, 1H), 5.57 (s, 2H), 4.82 (m, 1H), 4.16 (m, 1H), 3.95 (m, 1H), 3.05 (m, 1H), 2.17 (s, 3H), 2.00 (m, 2H), 1.63 (m, 2H)

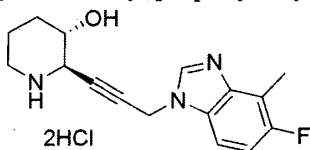
Example 228: Preparation of (2R,3S)-2-(3-(5,6-dibromo-1H-benzo[d]imidazol-1-yl)prop-1-yn-1-yl)piperidin-3-ol dihydrochloride



The title compound (30 mg, yield: 80%) was obtained in the same manner as in Example 225, with the exception that 5,6-dibromo-1H-benzo[d]imidazole was used instead of 5,6-dichloro-1H-benzo[d]imidazole in Step 225-6 of Example 225.

¹H-NMR (500 MHz, MeOD): δ 9.18 (br, 1H), 8.39 (s, 1H), 8.20 (m, 1H), 5.47 (s, 2H), 4.88 (m, 1H), 4.16 (m, 1H), 3.94 (m, 1H), 3.06 (m, 1H), 1.99 (m, 2H), 1.68 (m, 2H)

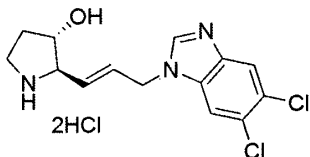
Example 229: Preparation of (2R,3S)-2-(3-(5-fluoro-4-methyl-1H-benzo[d]imidazol-1-yl)prop-1-yn-1-yl)piperidin-3-ol dihydrochloride



The title compound (28 mg, yield: 75%) was obtained in the same manner as in Example 225, with the exception that 5-fluoro-4-methyl-1H-benzo[d]imidazole was used instead of 5,6-dichloro-1H-benzo[d]imidazole in Step 225-6 of Example 225.

¹H-NMR (500 MHz, MeOD): δ 8.44 (br, 1H), 7.99 (s, 1H), 7.88 (s, 1H), 5.34 (s, 2H), 4.11 (m, 1H), 3.90 (m, 1H), 3.22 (m, 1H), 3.04 (m, 1H), 1.99 (m, 2H), 1.65 (m, 2H)

Example 230: Preparation of (2R,3S)-2-((E)-3-(5,6-dichloro-1H-benzo[d]imidazol-1-yl)prop-1-en-1-yl)pyrrolidin-3-ol dihydrochloride



Step 230-1: Preparation of (2R,3S)-1-(tert-butoxycarbonyl)-3-((tert-butyltrimethylsilyl)oxy)pyrrolidine-2-carboxylic acid

(2R,3S)-1-(tert-butoxycarbonyl)-3-hydroxypyrrolidine-2-carboxylic acid (10.7 g, 46.2 mmol) was dissolved in N,N-dimethylformamide (100 mL, 0.46 M). Then, the reaction solution was cooled to 0°C, and tert-butyldimethylsilyl chloride (20.9 g, 138.6 mmol) and triethylamine (32.2 mL, 231.0 mmol) were added thereto. The reaction solution was stirred at room temperature
5 for 12 hours. When the reaction was completed, the solvent was removed, and the resulting mixture was diluted with ethyl acetate and washed with saturated sodium chloride solution. The organic layer was collected, dried over magnesium sulfate, filtered and concentrated under reduced pressure, and then purified by column chromatography (dichloromethane: methanol = 7:1) to give the title compound (14.4 g, yield: 90%).

10

Step 230-2: Preparation of tert-butyl (2R,3S)-3-((tert-butyldimethylsilyl)oxy)-2-(hydroxymethyl)pyrrolidine-1-carboxylate

(2R,3S)-1-(tert-butoxycarbonyl)-3-((tert-butyldimethylsilyl)oxy)pyrrolidine-2-carboxylic acid (2.0 g, 4.3 mmol) obtained from Step 230-1 was dissolved in tetrahydrofuran (50 mL, 0.09
15 M). Then, the reaction solution was cooled to 0°C and a borane solution (5.2 mL, 4.7 mmol) was added thereto. The reaction solution was stirred at the same temperature for 1 hour and then stirred at room temperature for 2 hours. A small amount of methanol was added to complete the reaction. After removing the solvent, the reaction solution was diluted with ethyl acetate and washed with saturated sodium chloride solution. The organic layer was collected and the resulting mixture was
20 dried over magnesium sulfate, filtered and concentrated under reduced pressure, and then purified by column chromatography (hexane: ethyl acetate = 3:1) to give the title compound (1.1 g, yield 80%).

Step 230-3: Preparation of tert-butyl (2R,3S)-3-((tert-butyldimethylsilyl)oxy)-2-((E)-3-ethoxy-3-oxoprop-1-en-1-yl)pyrrolidine-1-carboxylate
25

Methylene chloride (61 mL, 0.12 M) and oxalyl chloride (0.76 mL, 8.7 mmol) were added to a flask filled with nitrogen and the reaction solution was cooled to -78°C. N,N-dimethylsulfoxide (1.2 mL, 17.4 mmol) was then added at the same temperature and stirred for 30 minutes. Then, tert-butyl (2R,3S)-3-((tert-butyldimethylsilyl)oxy)-2-(hydroxymethyl)pyrrolidine-
30 1-carboxylate (1.4 g, 4.3 mmol) obtained from Step 230-2 was dissolved in a small amount of

methylene chloride and slowly added. After stirring at the same temperature for 1 hour, triethylamine (2.4 mL, 17.4 mmol) was added and the temperature of the reaction solution was raised to room temperature from -78°C. When the reaction was completed, the solvent was removed, and the resulting mixture was diluted with ethyl acetate and washed with saturated sodium chloride solution. The organic layer was collected, dried with magnesium sulfate, filtered and concentrated under reduced pressure, and then dissolved in methylene chloride (20 mL, 0.22 M), and (carbethoxymethylene)triphenylphosphorane (3.0 g, 8.7 mmol) was added thereto at room temperature and stirred for 2 hours. When the reaction was completed, the solvent was removed, and the resulting mixture was diluted with ethyl acetate and washed with saturated sodium chloride solution. The organic layer was collected, dried over magnesium sulfate, filtered and concentrated under reduced pressure, and then purified by column chromatography (hexane: ethyl acetate = 4:1) to give the title compound (1.5 g, yield: 87%).

Step 230-4: Preparation of (E)-3-((2R,3S)-1-(tert-butoxycarbonyl)-3-((tert-butyltrimethylsilyl)oxy)pyrrolidin-2-yl)acrylic acid

Tert-butyl (2R,3S)-3-((tert-butyltrimethylsilyl)oxy)-2-((E)-3-ethoxy-3-oxoprop-1-en-1-yl)pyrrolidine-1-carboxylate (1.5 g, 3.8 mmol) obtained from Step 230-3 was dissolved in ethanol (27 mL, 0.14 M), and then 2N aqueous sodium hydroxide solution (8 mL) was added thereto and stirred at room temperature for 3 hours. When the reaction was completed, the reaction solution was neutralized with 1N aqueous hydrochloric acid solution, acidified and then diluted with ethyl acetate, and washed with saturated sodium chloride solution. The organic layer was collected, dried over magnesium sulfate, filtered and concentrated under reduced pressure. Subsequent reactions were carried out without purification procedure.

Step 230-5: Preparation of tert-butyl (2R,3S)-3-((tert-butyltrimethylsilyl)oxy)-2-((E)-3-hydroxyprop-1-en-1-yl)pyrrolidine-1-carboxylate

(E)-3-((2R,3S)-1-(tert-butoxycarbonyl)-3-((tert-butyltrimethylsilyl)oxy)pyrrolidin-2-yl)acrylic acid (400 mg, 1.1 mmol) obtained from Step 230-4 was dissolved in tetrahydrofuran (10 mL, 0.1 M), and the reaction solution was cooled to 0°C. Then, a lithium aluminum hydride solution (0.43 mL, 1.1 mmol) was slowly added thereto, reacted at the same temperature for 30

minutes and then stirred at room temperature for 2 hours. A small amount of water was added to complete the reaction, diluted with ethyl acetate and washed with saturated sodium chloride solution. The organic layer was collected, dried over magnesium sulfate, filtered and concentrated under reduced pressure, and then purified by column chromatography (dichloromethane: methanol = 10:1) to give the title compound (328 g, yield: 85%).

Step 230-6: Preparation of tert-butyl (2R,3S)-3-((tert-butyl(dimethylsilyl)oxy)-2-((E)-3-(5,6-dichloro-1H-benzo[d]imidazol-1-yl)prop-1-en-1-yl)pyrrolidine-1-carboxylate

Tert-butyl (2R,3S)-3-((tert-butyl(dimethylsilyl)oxy)-2-((E)-3-hydroxyprop-1-en-1-yl)pyrrolidin-1-carboxylate (177 mg, 0.49 mmol) obtained from Step 230-5 was added to methylene chloride (5 mL, 0.1 M). The reaction solution was cooled to 0°C, and then a 50% aqueous solution of potassium hydroxide (0.05 mL, 0.49 mmol) and para-toluenesulfonyl chloride (104 mg, 0.55 mmol) were sequentially added at the same temperature, followed by stirring at room temperature for 2 hours. When the reaction was completed, the solvent was removed, and the resulting mixture was diluted with ethyl acetate and washed with saturated sodium chloride solution. The organic layer was collected and dried over magnesium sulfate, filtered and then concentrated under reduced pressure, and dissolved in N,N-dimethylformamide (3 mL, 0.16 M). Then, potassium carbonate (53 mg, 0.38 mmol) and 5,6-dichloro-1H-benzo[d]imidazole (92 mg, 0.49 mmol) were added thereto and stirred at room temperature for 4 hours. When the reaction was completed, the solvent was removed, and the resulting mixture was diluted with ethyl acetate and washed with saturated sodium chloride solution. The organic layer was collected, dried over sodium sulfate, filtered and concentrated under reduced pressure, and then purified by column chromatography (hexane: ethyl acetate = 1:1) to give the title compound (155 mg, yield: 60%).

Step 230-7: Preparation of (2R,3S)-2-((E)-3-(5,6-dichloro-1H-benzo[d]imidazol-1-yl)prop-1-en-1-yl)pyrrolidin-3-ol dihydrochloride

Tert-butyl (2R,3S)-3-((tert-butyl(dimethylsilyl)oxy)-2-((E)-3-(5,6-dichloro-1H-benzo[d]imidazol-1-yl)prop-1-en-1-yl)pyrrolidine-1-carboxylate (43 mg, 0.08 mmol) obtained from Step 230-6 was dissolved in a small amount of tetrahydrofuran and then a 4N hydrogen chloride dioxane solution (2 mL, 0.04M) was added thereto and the mixture was stirred at room

temperature for 12 hours. When the reaction was completed, the reaction solution was concentrated under reduced pressure to remove the solvent, dissolved by addition of a small amount of methanol, and then crystallized with diethyl ether to give the title compound (25 mg, yield 79%).

5 ¹H-NMR (500 MHz, DMSO-d₆): δ 8.80 (s, 1H), 8.11 (s, 1H), 8.04 (s, 1H), 6.12 (m, 1H), 5.78 (m, 1H), 5.02 (d, 2H), 4.05 (m, 1H), 3.81 (m, 1H), 3.22 (m, 2H), 2.10 (m, 1H), 1.79 (m, 1H)

Experimental Example: PRS enzyme activity inhibition experiment

In order to confirm the biological activities of the compounds prepared in
10 Examples, %inhibition or IC₅₀ values of PRS enzyme (phosphoribosylpyrophosphate synthetase enzyme) activities were calculated.

Specifically, the portion corresponding to PRS in cDNA of EPRS was subcloned, and the obtained high-purity PRS protein was purified and used in the experiment. The compounds (1
15 μM) prepared in Examples were added into the reaction buffer (20 mM KPO₄ (pH 7.4), 6 mM MgAc, 5 mM ATP, 400 mg/mL tRNA, 0.5 mM DTT, 20 mCi[³H]proline (1 mCi/mL)) and allowed to react at 37°C for 5 to 10 minutes. The reaction was terminated with 3M paper that was in advance dried by addition of 5% TCA. The radioactivity was measured using a liquid scintillation counter.

20

% Inhibition and IC₅₀ values of the respective compounds were calculated and analyzed using Microsoft Excel or Sigma Plot 8.0. The results are shown in Tables 1 to 3 below. In Tables 1 to 3, the results are divided into A, B and C according to the range of IC₅₀. The case where the derived IC₅₀ is 100 nM or less is represented by "A", the case where the IC₅₀ is 100 to 500nM is
25 represented by "B", and the case where the IC₅₀ is 500 nM or higher is represented by "C".

[Table 1]

Example No.	PRS IC ₅₀	Example No.	PRS IC ₅₀	Example No.	PRS IC ₅₀	Example No.	PRS IC ₅₀
1	B	21	C	41	C	61	A
2	B	22	C	42	C	62	B
3	C	23	B	43	A	63	A
4	B	24	A	44	B	64	A
5	B	25	C	45	B	65	B
6	C	26	C	46	A	66	C

7	B	27	B	47	B	67	A
8	C	28	B	48	B	68	C
9	C	29	C	49	B	69	A
10	B	30	B	50	B	70	A
11	B	31	B	51	C	71	B
12	B	32	B	52	B	72	B
13	C	33	B	53	B	73	B
14	C	34	B	54	C	74	B
15	B	35	B	55	C	75	C
16	B	36	B	56	B	76	C
17	C	37	B	57	C	77	B
18	C	38	C	58	A	78	B
19	C	39	B	59	B	79	A
20	C	40	A	60	B	80	A

[Table 2]

Example No.	PRS IC ₅₀	Example No.	PRS IC ₅₀	Example No.	PRS IC ₅₀	Example No.	PRS IC ₅₀
81	C	101	A	121	B	141	C
82	C	102	B	122	B	142	C
83	A	103	C	123	C	143	C
84	C	104	A	124	C	144	C
85	B	105	C	125	C	145	C
86	B	106	B	126	B	146	C
87	B	107	B	127	B	147	C
88	C	108	B	128	C	148	B
89	A	109	A	129	C	149	B
90	B	110	C	130	B	150	C
91	A	111	A	131	B	151	B
92	B	112	B	132	B	152	C
93	C	113	B	133	C	153	B
94	B	114	B	134	C	154	B
95	B	115	B	135	C	155	C
96	C	116	A	136	C	156	C
97	A	117	B	137	C	157	C
98	B	118	C	138	C	158	C
99	A	119	C	139	C	159	C
100	B	120	C	140	C	160	C

[Table 3]

Example No.	PRS IC ₅₀	Example No.	PRS IC ₅₀	Example No.	PRS IC ₅₀	Example No.	PRS IC ₅₀
161	C	181	B	201	C	221	C
162	C	182	A	202	B	222	C
163	C	183	B	203	C	223	C
164	C	184	C	204	C	224	C
165	C	185	C	205	C	225	C
166	B	186	B	206	C	226	C
167	B	187	A	207	C	227	C
168	B	188	C	208	C	228	C
169	C	189	B	209	C	229	C

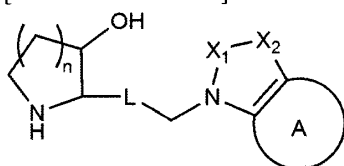
170	B	190	B	210	C	230	C
171	C	191	B	211	C		
172	C	192	B	212	C		
173	B	193	C	213	C		
174	A	194	C	214	B		
175	B	195	C	215	C		
176	C	196	C	216	C		
177	C	197	C	217	C		
178	B	198	C	218	C		
179	B	199	C	219	C		
180	B	200	C	220	C		

WHAT IS CLAIMED IS:

[Claim 1]

A compound represented by the following Chemical Formula 1, or a pharmaceutically acceptable salt thereof:

[Chemical Formula 1]



in Chemical Formula 1,

n is 1, or 2,

L is $-\text{CH}_2\text{CH}_2-$, $-\text{CH}=\text{C}(\text{R}')$, or $-\text{C}\equiv\text{C}-$,

wherein R' is hydrogen, C_{1-4} alkyl, or halogen,

X_1 is CR_1R_2 , NR_1 , or $-\text{CO}-$,

X_2 is CR_3R_4 , or NR_3 ,

wherein R_1 to R_4 are each independently hydrogen, C_{1-4} alkyl, C_{1-4} hydroxyalkyl, hydroxy, amino, carboxy, $-\text{COO}(\text{C}_{1-4} \text{ alkyl})$, $-\text{CONH}_2$, $-\text{CONH}(\text{C}_{1-4} \text{ alkyl})$, $-\text{CON}(\text{C}_{1-4} \text{ alkyl})_2$, or pyrazolyl unsubstituted or substituted with C_{1-4} haloalkyl; or R_1 and R_3 , together with each other, links X_1 and X_2 via a double bond, and

A is benzene, pyridine, pyrimidine, or pyrimidinedione ring,

wherein A is unsubstituted or substituted with one to three substituents each independently selected from the group consisting of a ring-type substituent selected from the group consisting of furanyl, imidazolyl, isoxazolyl, phenyl, pyrazolyl, pyridinonyl, pyridinyl, pyrrolyl, thiazolyl, and thiophenyl; C_{1-4} alkyl; C_{1-4} alkoxy; C_{1-4} haloalkyl; C_{1-4} haloalkoxy; halogen; $\text{di}(\text{C}_{1-4} \text{ alkyl})\text{amino}$; nitro; $-\text{COO}(\text{C}_{1-4} \text{ alkyl})$; dihydropyranyl; morpholino; piperidinyl; and pyrrolidinyl; and

wherein the ring-type substituent is unsubstituted or substituted with one or two substituents each independently selected from the group consisting of C_{1-5} alkyl, C_{1-4} haloalkyl, C_{3-6} cycloalkyl, monovalent of C_{2-5} alkylene carbonate, $-\text{COO}(\text{C}_{1-4} \text{ alkyl})$, halogen, cyano, thiazolyl, and (1,3-dioxolan-2-yl)methyl.

[Claim 2]

The compound or a pharmaceutically acceptable salt thereof according to claim 1,

wherein, A is unsubstituted or substituted with one to three substituents each
 5 independently selected from the group consisting of C₁₋₄ alkyl; C₁₋₄ alkoxy; C₁₋₄ haloalkyl;
 halogen; phenyl unsubstituted or substituted with halogen, or C₁₋₄ haloalkyl; pyrazolyl
 unsubstituted or substituted with C₁₋₅ alkyl, thiazolyl, or C₁₋₄ haloalkyl; thiophenyl unsubstituted or
 substituted with C₁₋₅ alkyl, or -COO(C₁₋₄ alkyl); pyrrolyl unsubstituted or substituted with C₁₋₅
 alkyl and/or -COO(C₁₋₄ alkyl); di(C₁₋₄ alkyl)amino; morpholino; piperidiny; furanyl; and
 10 pyrrolidinyl.

[Claim 3]

The compound or a pharmaceutically acceptable salt thereof according to claim 1,

wherein L is -CH₂CH₂-, -CH=CH-, -CH=CF-, -CH=C(CH₃)-, or -C≡C-.

15

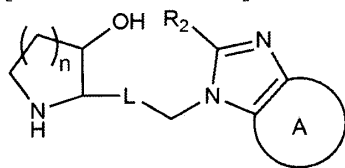
[Claim 4]

The compound or a pharmaceutically acceptable salt thereof according to claim 1,

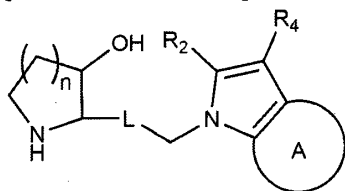
wherein the compound represented by Chemical Formula 1 is represented by the
 following Chemical Formulas 1-1 to 1-5:

20

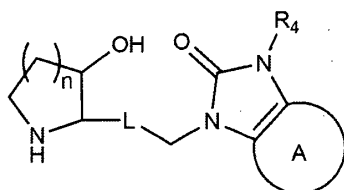
[Chemical Formula 1-1]



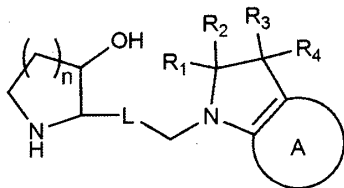
[Chemical Formula 1-2]



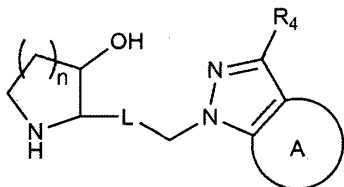
[Chemical Formula 1-3]



[Chemical Formula 1-4]



[Chemical Formula 1-5]



5

in Chemical Formulas 1-1 to 1-5,
n, L, R₁ to R₄ and A are as defined in claim 1.

[Claim 5]

- 10 The compound or a pharmaceutically acceptable salt thereof according to claim 1,
wherein R₁ to R₄ are each independently hydrogen, methyl, hydroxymethyl, hydroxy,
amino, carboxy, -COOCH₃, -CONH₂, -CONHCH₃, or -CON(CH₃)₂; or R₁ and R₃, together with
each other, link X₁ and X₂ via a double bond.

15 [Claim 6]

The compound or a pharmaceutically acceptable salt thereof according to claim 1,
wherein A is benzene, pyridine, pyrimidine, or pyrimidinedione ring, and

- A is unsubstituted or substituted with one to three substituents each independently
selected from the group consisting of methyl, isobutyl, methoxy, trifluoromethyl, fluoro, chloro,
20 bromo, phenyl, phenyl substituted with fluoro, phenyl substituted with chloro, phenyl substituted
with trifluoromethyl, thiophenyl, thiophenyl substituted with methyl, thiophenyl substituted with -
COOCH₃, pyrazolyl substituted with difluoromethyl, pyrazolyl substituted with methyl, pyrazolyl

substituted with thiazolyl, pyrrolyl substituted with methyl and -COOCH₂CH₃, furanyl, dimethylamino, diethylamino, methylethylamino, morpholino, piperidinyl, and pyrrolidinyl.

[Claim 7]

5 The compound or a pharmaceutically acceptable salt thereof according to claim 1,
 wherein A is benzene, and

 A is unsubstituted or substituted with one to three substituents each independently
selected from the group consisting of C₁₋₄ alkyl; C₁₋₄ alkoxy; halogen; and phenyl unsubstituted or
substituted with halogen or C₁₋₄ haloalkyl.

10

[Claim 8]

 The compound or a pharmaceutically acceptable salt thereof according to claim 1,
 wherein A is pyridine, and

 A is unsubstituted or substituted with one or two substituents each independently
15 selected from the group consisting of C₁₋₄ alkyl; C₁₋₄ alkoxy; halogen; and phenyl substituted with
halogen.

[Claim 9]

 The compound or a pharmaceutically acceptable salt thereof according to claim 1,
20 wherein A is pyrimidine, and

 A is substituted with a substituent selected from the group consisting of halogen;
di(C₁₋₄ alkyl)amino; morpholino; piperidinyl; and pyrrolidinyl.

[Claim 10]

25 The compound or a pharmaceutically acceptable salt thereof according to claim 1,
 wherein A is pyrimidinedione, and

 A is unsubstituted or substituted with one or two C₁₋₄ alkyl.

[Claim 11]

30 The compound or a pharmaceutically acceptable salt thereof according to claim 1,

wherein the compound represented by Chemical Formula 1 is selected from the group consisting of:

- 1) (2R,3S)-2-(3-(6-chloro-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol,
- 2) (2R,3S)-2-(3-(4-bromo-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol,
- 5 3) (2R,3S)-2-(3-(5-bromo-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol,
- 4) (2R,3S)-2-(3-(6-bromo-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol,
- 5) (2R,3S)-2-(3-(7-bromo-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol,
- 6) (2R,3S)-2-(3-(4-fluoro-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol,
- 7) (2R,3S)-2-(3-(5-fluoro-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol,
- 10 8) (2R,3S)-2-(3-(6-fluoro-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol,
- 9) (2R,3S)-2-(3-(7-fluoro-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol,
- 10) (2R,3S)-2-(3-(4-chloro-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol,
- 11) (2R,3S)-2-(3-(5-chloro-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol,
- 12) (2R,3S)-2-(3-(7-chloro-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol,
- 15 13) (2R,3S)-2-(3-(6-methyl-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol,
- 14) (2R,3S)-2-(3-(5-methyl-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol,
- 15) (2R,3S)-2-(3-(6-(trifluoromethyl)-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol,
- 16) (2R,3S)-2-(3-(7-(trifluoromethyl)-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol,
- 20 17) (2R,3S)-2-(3-(7-(trifluoromethoxy)-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol,
- 18) (2R,3S)-2-(3-(4-(pyrrolidin-1-yl)-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol,
- 25 19) (2R,3S)-2-(3-(4-(piperidin-1-yl)-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol,
- 20) (2R,3S)-2-(3-(4-(3-fluorophenyl)-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol,
- 21) (2R,3S)-2-(3-(4-(3-chlorophenyl)-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol,
- 30

- 22) (2R,3S)-2-(3-(5-(3-fluorophenyl)-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol,
- 23) (2R,3S)-2-(3-(6-(2-fluorophenyl)-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol,
- 5 24) (2R,3S)-2-(3-(6-(3-fluorophenyl)-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol,
- 25) (2R,3S)-2-(3-(6-(4-fluorophenyl)-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol,
- 26) (2R,3S)-2-(3-(7-(2-fluorophenyl)-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol,
- 10 27) (2R,3S)-2-(3-(7-(3-fluorophenyl)-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol,
- 28) (2R,3S)-2-(3-(7-(4-fluorophenyl)-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol,
- 15 29) (2R,3S)-2-(3-(5-(1H-pyrazol-4-yl)-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol,
- 30) (2R,3S)-2-(3-(6-(1H-pyrazol-4-yl)-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol,
- 31) (2R,3S)-2-(3-(7-(1H-pyrazol-4-yl)-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol,
- 20 32) (2R,3S)-2-(3-(6-chloro-5-fluoro-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol,
- 33) (2R,3S)-2-(3-(6-bromo-5-fluoro-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol,
- 25 34) (2R,3S)-2-(3-(5-chloro-6-fluoro-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol,
- 35) (2R,3S)-2-(3-(5-bromo-6-fluoro-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol,
- 36) (2R,3S)-2-(3-(6-bromo-5-chloro-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol,
- 30

- 37) (2R,3S)-2-(3-(6-chloro-5-methoxy-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol,
38) (2R,3S)-2-(3-(6-fluoro-5-methoxy-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol,
5 39) (2R,3S)-2-(3-(5-fluoro-6-methyl-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol,
40) (2R,3S)-2-(3-(4,5-dichloro-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol,
41) (2S,3S)-2-(3-(4,5-dichloro-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol,
42) (2S,3R)-2-(3-(4,5-dichloro-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol,
10 43) (2R,3R)-2-(3-(4,5-dichloro-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol,
44) (2R,3S)-2-(3-(4-chloro-5-methyl-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol,
45) (2R,3S)-2-(3-(5-bromo-4-methyl-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol,
15 46) (2R,3S)-2-(3-(5-chloro-4-methyl-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol,
47) (2R,3S)-2-(3-(5-bromo-4-fluoro-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol,
48) (2R,3S)-2-(3-(6-bromo-7-fluoro-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol,
20 49) (2R,3S)-2-(3-(4,5-difluoro-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol,
50) (2R,3S)-2-(3-(6,7-difluoro-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol,
51) (2R,3S)-2-(3-(4,5-dimethyl-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol,
52) (2R,3S)-2-(3-(5,6-difluoro-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol,
25 53) (2R,3S)-2-(3-(5,6-dichloro-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol,
54) (2R,3S)-2-(3-(5,6-dibromo-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol,
55) (2R,3S)-2-(3-(5,6-dimethyl-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol,
56) (2R,3S)-2-(3-(6,7-dichloro-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol,
57) (2R,3S)-2-(3-(4,6-difluoro-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol,
30 58) (2R,3S)-2-(3-(5,7-difluoro-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol,

- 59) (2R,3S)-2-(3-(4-chloro-5-methoxy-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol,
- 60) (2R,3S)-2-(3-(7-chloro-6-methoxy-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol,
- 5 61) (2R,3S)-2-(3-(6-chloro-4-methyl-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol,
- 62) (2R,3S)-2-(3-(4-chloro-5-fluoro-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol,
- 63) (2R,3S)-2-(3-(6-bromo-4-methyl-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol,
- 10 64) (2R,3S)-2-(3-(5-fluoro-4-methyl-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol,
- 65) (2R,3S)-2-(3-(6-fluoro-7-methyl-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol,
- 15 66) (2R,3S)-2-(3-(4-chloro-5-(trifluoromethyl)-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol,
- 67) (2R,3S)-2-(3-(7-chloro-6-(trifluoromethyl)-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol,
- 68) methyl 7-bromo-1-(3-((2R,3S)-3-hydroxypiperidin-2-yl)propyl)-1H-benzo[d]imidazole-5-carboxylate,
- 20 69) (2R,3S)-2-(3-(7-bromo-5-chloro-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol,
- 70) (2R,3S)-2-(3-(5-bromo-7-chloro-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol,
- 25 71) (2R,3S)-2-(3-(7-bromo-5-(trifluoromethyl)-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol,
- 72) (2R,3S)-2-(3-(6-bromo-4-fluoro-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol,
- 73) (2R,3S)-2-(3-(5-bromo-7-fluoro-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol,
- 30 ol,

- 74) (2R,3S)-2-(3-(7-chloro-4-fluoro-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol,
- 75) (2R,3S)-2-(3-(5-bromo-4-nitro-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol,
- 76) (2R,3S)-2-(3-(6-bromo-7-nitro-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol,
- 5 77) (2R,3S)-2-(3-(4-chloro-5-nitro-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol,
- 78) (2R,3S)-2-(3-(7-chloro-5-(trifluoromethyl)-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol,
- 79) (2R,3S)-2-(3-(5-chloro-7-fluoro-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol,
- 10 80) (2R,3S)-2-(3-(5,7-dichloro-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol,
- 81) (2R,3S)-2-(3-(5-chloro-7-(1H-pyrazol-4-yl)-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol,
- 82) (2R,3S)-2-(3-(7-(1H-pyrazol-4-yl)-5-(trifluoromethyl)-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol,
- 15 83) (2R,3S)-2-(3-(5-chloro-7-(3-fluorophenyl)-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol,
- 84) (2R,3S)-2-(3-(7-(3-fluorophenyl)-5-(trifluoromethyl)-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol,
- 85) (2R,3S)-2-(3-(5-chloro-7-(2-methylthiazol-5-yl)-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol,
- 20 86) (2R,3S)-2-(3-(5-chloro-7-(pyridin-3-yl)-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol,
- 87) (2R,3S)-2-(3-(5-chloro-7-(5-fluoropyridin-3-yl)-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol,
- 25 88) 5-(5-chloro-1-(3-((2R,3S)-3-hydroxypiperidin-2-yl)propyl)-1H-benzo[d]imidazol-7-yl)-1-methylpyridin-2(1H)-one,
- 89) (2R,3S)-2-(3-(5-chloro-7-(1-(difluoromethyl)-1H-pyrazol-4-yl)-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol,
- 90) (2R,3S)-2-(3-(5-chloro-7-(isoxazol-3-yl)-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol,
- 30

- 91) (2R,3S)-2-(3-(5-chloro-7-(thiophen-3-yl)-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol,
- 92) (2R,3S)-2-(3-(5-chloro-7-(2-methylthiophen-3-yl)-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol,
- 5 93) (2R,3S)-2-(3-(5-chloro-7-(3,5-dimethylisoxazol-4-yl)-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol,
- 94) (2R,3S)-2-(3-(5-chloro-7-(3,6-dihydro-2H-pyran-4-yl)-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol,
- 95) (2R,3S)-2-(3-(7-(1-((1,3-dioxolan-2-yl)methyl)-1H-pyrazol-4-yl)-5-chloro-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol,
- 10 96) (2R,3S)-2-(3-(5-chloro-7-(1-methyl-1H-imidazol-5-yl)-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol,
- 97) (2R,3S)-2-(3-(5-chloro-7-(1-methyl-1H-pyrazol-4-yl)-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol,
- 15 98) (2R,3S)-2-(3-(7-(pyrrolidin-1-yl)-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol,
- 99) (2R,3S)-2-(3-(5-chloro-7-(pyrrolidin-1-yl)-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol,
- 100) (2R,3S)-2-(3-(5-chloro-7-(2-cyclopropylthiazol-5-yl)-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol,
- 20 101) (2R,3S)-2-(3-(5-chloro-7-(1-(thiazol-2-yl)-1H-pyrazol-4-yl)-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol,
- 102) (2R,3S)-2-(3-(5-chloro-7-(1-(oxetan-3-yl)-1H-pyrazol-4-yl)-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol,
- 25 103) (2R,3S)-2-(3-(5-chloro-7-(2-(tetrahydro-2H-pyran-4-yl)thiazol-4-yl)-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol,
- 104) (2R,3S)-2-(3-(5-chloro-7-(furan-3-yl)-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol,
- 105) 4-(5-chloro-1-(3-((2R,3S)-3-hydroxypiperidin-2-yl)propyl)-1H-benzo[d]imidazol-7-yl)thiazole-2-carbonitrile,
- 30

- 106) (2R,3S)-2-(3-(7-(1-(tert-butyl)-1H-pyrazol-4-yl)-5-chloro-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol,
- 107) (2R,3S)-2-(3-(5-chloro-7-(1-isopentyl-1H-pyrazol-4-yl)-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol,
- 5 108) (2R,3S)-2-(3-(5-chloro-7-(1-isopropyl-1H-pyrazol-4-yl)-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol,
- 109) (2R,3S)-2-(3-(5-chloro-7-(4-methylthiophen-3-yl)-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol,
- 110) ethyl 3-(5-chloro-1-(3-((2R,3S)-3-hydroxypiperidin-2-yl)propyl)-1H-benzo[d]imidazol-7-yl)furan-2-carboxylate,
- 10 111) methyl 4-(5-chloro-1-(3-((2R,3S)-3-hydroxypiperidin-2-yl)propyl)-1H-benzo[d]imidazol-7-yl)thiophene-2-carboxylate,
- 112) (2R,3S)-2-(3-(5-chloro-7-(1-(2-fluoroethyl)-1H-pyrazol-4-yl)-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol,
- 15 113) (2R,3S)-2-(3-(7-(1-butyl-1H-pyrazol-4-yl)-5-chloro-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol,
- 114) (2R,3S)-2-(3-(5-chloro-7-(2,5-dimethylthiophen-3-yl)-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol,
- 115) (2R,3S)-2-(3-(5-chloro-7-(1-isobutyl-1H-pyrazol-4-yl)-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol,
- 20 116) ethyl 4-(5-chloro-1-(3-((2R,3S)-3-hydroxypiperidin-2-yl)propyl)-1H-benzo[d]imidazol-7-yl)-1-methyl-1H-pyrrole-2-carboxylate,
- 117) (2R,3S)-2-(3-(5-chloro-1H-imidazo[4,5-b]pyridin-1-yl)propyl)piperidin-3-ol,
- 118) (2R,3S)-2-(3-(5-chloro-3H-imidazo[4,5-b]pyridin-3-yl)propyl)piperidin-3-ol,
- 25 119) (2R,3S)-2-(3-(5-bromo-1H-imidazo[4,5-b]pyridin-1-yl)propyl)piperidin-3-ol,
- 120) (2R,3S)-2-(3-(6-bromo-1H-imidazo[4,5-b]pyridin-1-yl)propyl)piperidin-3-ol,
- 121) (2R,3S)-2-(3-(5-methyl-1H-imidazo[4,5-b]pyridin-1-yl)propyl)piperidin-3-ol,
- 122) (2R,3S)-2-(3-(6-chloro-1H-imidazo[4,5-c]pyridin-1-yl)propyl)piperidin-3-ol,
- 123) (2R,3S)-2-(3-(6-chloro-3H-imidazo[4,5-c]pyridin-3-yl)propyl)piperidin-3-ol,
- 30 124) (2R,3S)-2-(3-(6-bromo-1H-imidazo[4,5-c]pyridin-1-yl)propyl)piperidin-3-ol,

- 125) (2R,3S)-2-(3-(6-bromo-3H-imidazo[4,5-c]pyridin-3-yl)propyl)piperidin-3-ol,
126) (2R,3S)-2-(3-(7-chloro-1H-imidazo[4,5-b]pyridin-1-yl)propyl)piperidin-3-ol,
127) (2R,3S)-2-(3-(5,6-dichloro-1H-imidazo[4,5-b]pyridin-1-yl)propyl)piperidin-3-ol,
128) (2R,3S)-2-(3-(7-bromo-1H-imidazo[4,5-c]pyridin-1-yl)propyl)piperidin-3-ol,
5 129) (2R,3S)-2-(3-(5-(trifluoromethyl)-3H-imidazo[4,5-b]pyridin-3-yl)propyl)piperidin-3-ol,
130) (2R,3S)-2-(3-(6,7-dichloro-3H-imidazo[4,5-b]pyridin-3-yl)propyl)piperidin-3-ol,
131) (2R,3S)-2-(3-(6-chloro-7-methyl-3H-imidazo[4,5-b]pyridin-3-yl)propyl)piperidin-3-ol,
10 132) (2R,3S)-2-(3-(6-bromo-7-methyl-3H-imidazo[4,5-b]pyridin-3-yl)propyl)piperidin-3-ol,
133) (2R,3S)-2-(3-(6-bromo-7-chloro-3H-imidazo[4,5-b]pyridin-3-yl)propyl)piperidin-3-ol,
134) (2R,3S)-2-(3-(7-chloro-6-(3-chlorophenyl)-3H-imidazo[4,5-b]pyridin-3-yl)propyl)piperidin-3-ol,
15 135) (2R,3S)-2-(3-(2-chloro-7H-purin-7-yl)propyl)piperidin-3-ol,
136) (2R,3S)-2-(3-(2-chloro-9H-purin-9-yl)propyl)piperidin-3-ol,
137) (2R,3S)-2-(3-(6-(dimethylamino)-9H-purin-9-yl)propyl)piperidin-3-ol,
138) (2R,3S)-2-(3-(6-(diethylamino)-9H-purin-9-yl)propyl)piperidin-3-ol,
20 139) (2R,3S)-2-(3-(6-(ethyl(methyl)amino)-9H-purin-9-yl)propyl)piperidin-3-ol,
140) (2R,3S)-2-(3-(6-morpholino-9H-purin-9-yl)propyl)piperidin-3-ol,
141) (2R,3S)-2-(3-(6-(piperidin-1-yl)-9H-purin-9-yl)propyl)piperidin-3-ol,
142) (2R,3S)-2-(3-(6-(pyrrolidin-1-yl)-9H-purin-9-yl)propyl)piperidin-3-ol,
143) 1-(3-((2R,3S)-3-hydroxypiperidin-2-yl)propyl)-1H-benzo[d]imidazol-2-ol,
25 144) 5,6-dichloro-1-(3-((2R,3S)-3-hydroxypiperidin-2-yl)propyl)-1H-benzo[d]imidazol-2-ol,
145) (2R,3S)-2-(3-(2-(hydroxymethyl)-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol,
146) (2R,3S)-2-(3-(2-(hydroxymethyl)-4,5-dimethyl-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol,
30

- 147) (2R,3S)-2-(3-(5,6-dichloro-2-(hydroxymethyl)-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol,
- 148) (2R,3S)-2-(3-(2-amino-5,6-dichloro-1H-benzo[d]imidazol-1-yl)propyl)piperidin-3-ol,
- 5 149) methyl 7-bromo-1-(3-((2R,3S)-3-hydroxypiperidin-2-yl)propyl)-1H-indole-3-carboxylate,
- 150) methyl 5-bromo-1-(3-((2R,3S)-3-hydroxypiperidin-2-yl)propyl)-1H-indole-3-carboxylate,
- 151) methyl 6-bromo-1-(3-((2R,3S)-3-hydroxypiperidin-2-yl)propyl)-1H-indole-3-
10 carboxylate,
- 152) methyl 4-chloro-1-(3-((2R,3S)-3-hydroxypiperidin-2-yl)propyl)-1H-indole-3-carboxylate,
- 153) methyl 6-chloro-1-(3-((2R,3S)-3-hydroxypiperidin-2-yl)propyl)-1H-indole-3-carboxylate,
- 15 154) methyl 7-chloro-1-(3-((2R,3S)-3-hydroxypiperidin-2-yl)propyl)-1H-indole-3-carboxylate,
- 155) (2R,3S)-2-(3-(5-chloro-3-cyclopropyl-1H-indazol-1-yl)propyl)piperidin-3-ol,
- 156) (2R,3S)-2-(3-(5-chloro-3-(trifluoromethyl)-1H-indazol-1-yl)propyl)piperidin-3-ol,
- 20 157) (2R,3S)-2-(3-(5-chloro-3-(1-(difluoromethyl)-1H-pyrazol-4-yl)-1H-indazol-1-yl)propyl)piperidin-3-ol,
- 158) (2R,3S)-2-(3-(6-chloro-3-(1-(difluoromethyl)-1H-pyrazol-4-yl)-1H-indazol-1-yl)propyl)piperidin-3-ol,
- 159) 1-(3-((2R,3S)-3-hydroxypiperidin-2-yl)propyl)-3-methyl-1H-benzo[d]imidazol-
25 2(3H)-one,
- 160) 5-bromo-1-(3-((2R,3S)-3-hydroxypiperidin-2-yl)propyl)-1H-benzo[d]imidazol-2(3H)-one,
- 161) 6-bromo-1-(3-((2R,3S)-3-hydroxypiperidin-2-yl)propyl)-1H-benzo[d]imidazol-2(3H)-one,
- 30 162) 7-(3-((2R,3S)-3-hydroxypiperidin-2-yl)propyl)-1,3-dimethyl-1H-purine-

- 2,6(3H,7H)-dione,
- 163) 7-(3-((2R,3S)-3-hydroxypiperidin-2-yl)propyl)-3-methyl-1H-purine-2,6(3H,7H)-dione,
- 164) 9-(3-((2R,3S)-3-hydroxypiperidin-2-yl)propyl)-1-methyl-1H-purine-2,6(3H,9H)-dione,
- 5 165) 7-(3-((2R,3S)-3-hydroxypiperidin-2-yl)propyl)-3-isobutyl-1-methyl-1H-purine-2,6(3H,7H)-dione,
- 166) (2R,3S)-2-((E)-3-(5,6-dichloro-1H-benzo[d]imidazol-1-yl)prop-1-en-1-yl)piperidin-3-ol,
- 10 167) (2R,3S)-2-((E)-3-(5-fluoro-4-methyl-1H-benzo[d]imidazol-1-yl)prop-1-en-1-yl)piperidin-3-ol,
- 168) (2R,3S)-2-((E)-3-(5-bromo-4-methyl-1H-benzo[d]imidazol-1-yl)prop-1-en-1-yl)piperidin-3-ol,
- 169) (2R,3S)-2-((E)-3-(5,6-dimethyl-1H-benzo[d]imidazol-1-yl)prop-1-en-1-yl)piperidin-3-ol,
- 15 170) (2R,3S)-2-((E)-3-(5,6-dibromo-1H-benzo[d]imidazol-1-yl)prop-1-en-1-yl)piperidin-3-ol,
- 171) (2R,3S)-2-((E)-3-(5,6-difluoro-1H-benzo[d]imidazol-1-yl)prop-1-en-1-yl)piperidin-3-ol,
- 20 172) (2R,3S)-2-((E)-3-(4,5-dimethyl-1H-benzo[d]imidazol-1-yl)prop-1-en-1-yl)piperidin-3-ol,
- 173) (2R,3S)-2-((E)-3-(5-chloro-4-methyl-1H-benzo[d]imidazol-1-yl)prop-1-en-1-yl)piperidin-3-ol,
- 174) (2R,3S)-2-((E)-3-(4,5-dichloro-1H-benzo[d]imidazol-1-yl)prop-1-en-1-yl)piperidin-3-ol,
- 25 175) (2R,3S)-2-((E)-3-(4-chloro-5-methyl-1H-benzo[d]imidazol-1-yl)prop-1-en-1-yl)piperidin-3-ol,
- 176) (2R,3S)-2-((E)-3-(5-bromo-4-nitro-1H-benzo[d]imidazol-1-yl)prop-1-en-1-yl)piperidin-3-ol,
- 30 177) (2R,3S)-2-((E)-3-(6-bromo-7-nitro-1H-benzo[d]imidazol-1-yl)prop-1-en-1-yl)piperidin-3-ol,

- yl)piperidin-3-ol,
- 178) (2R,3S)-2-((E)-3-(4-chloro-5-nitro-1H-benzo[d]imidazol-1-yl)prop-1-en-1-yl)piperidin-3-ol,
- 179) (2R,3S)-2-((E)-3-(4,6-difluoro-1H-benzo[d]imidazol-1-yl)prop-1-en-1-yl)piperidin-3-ol,
- 5 180) (2R,3S)-2-((E)-3-(6-chloro-4-methyl-1H-benzo[d]imidazol-1-yl)prop-1-en-1-yl)piperidin-3-ol,
- 181) (2R,3S)-2-((E)-3-(7-chloro-5-(trifluoromethyl)-1H-benzo[d]imidazol-1-yl)prop-1-en-1-yl)piperidin-3-ol,
- 10 182) (2R,3S)-2-((E)-3-(5,7-dichloro-1H-benzo[d]imidazol-1-yl)prop-1-en-1-yl)piperidin-3-ol,
- 183) (2R,3S)-2-((E)-3-(5-chloro-7-fluoro-1H-benzo[d]imidazol-1-yl)prop-1-en-1-yl)piperidin-3-ol,
- 184) (2R,3S)-2-((E)-3-(5-bromo-1H-imidazo[4,5-b]pyridin-1-yl)prop-1-en-1-yl)piperidin-3-ol,
- 15 185) (2R,3S)-2-((E)-3-(7-chloro-6-(3-chlorophenyl)-3H-imidazo[4,5-b]pyridin-3-yl)prop-1-en-1-yl)piperidin-3-ol,
- 186) (2R,3S)-2-((E)-3-(6-bromo-7-methyl-3H-imidazo[4,5-b]pyridin-3-yl)prop-1-en-1-yl)piperidin-3-ol,
- 20 187) (2R,3S)-2-((E)-3-(6-bromo-7-chloro-3H-imidazo[4,5-b]pyridin-3-yl)prop-1-en-1-yl)piperidin-3-ol,
- 188) (2R,3S)-2-((E)-3-(6-chloro-7-methyl-3H-imidazo[4,5-b]pyridin-3-yl)prop-1-en-1-yl)piperidin-3-ol,
- 189) (2R,3S)-2-((E)-3-(6,7-dichloro-3H-imidazo[4,5-b]pyridin-3-yl)prop-1-en-1-yl)piperidin-3-ol,
- 25 190) (2R,3S)-2-((E)-3-(6-(3-chlorophenyl)-1H-benzo[d]imidazol-1-yl)prop-1-en-1-yl)piperidin-3-ol,
- 191) (2R,3S)-2-((E)-3-(6-(3-fluorophenyl)-1H-benzo[d]imidazol-1-yl)prop-1-en-1-yl)piperidin-3-ol,
- 30 192) (2R,3S)-2-((E)-3-(6-(3-(trifluoromethyl)phenyl)-1H-benzo[d]imidazol-1-yl)prop-

- 1-enyl)piperidin-3-ol,
- 193) (2R,3S)-2-((E)-3-(5-bromo-6,7-difluoro-2-methyl-1H-benzo[d]imidazol-1-yl)prop-1-enyl)piperidin-3-ol,
- 194) (2R,3S)-2-((E)-3-(indolin-1-yl)prop-1-enyl)piperidin-3-ol,
- 5 195) (2R,3S)-2-((E)-3-(5-chloroindolin-1-yl)prop-1-enyl)piperidin-3-ol,
- 196) (2R,3S)-2-((E)-3-(1H-pyrrolo[2,3-b]pyridin-1-yl)prop-1-enyl)piperidin-3-ol,
- 197) (2R,3S)-2-((E)-3-(6-chloro-1H-indol-1-yl)prop-1-enyl)piperidin-3-ol,
- 198) (2R,3S)-2-((E)-3-(6-chloro-1H-indazol-1-yl)prop-1-enyl)piperidin-3-ol,
- 199) (2R,3S)-2-((E)-3-(4-chloro-7H-pyrrolo[2,3-d]pyrimidin-7-yl)prop-1-
- 10 enyl)piperidin-3-ol,
- 200) (2R,3S)-2-((E)-3-(5-chloro-1H-pyrazolo[3,4-b]pyridin-1-yl)prop-1-enyl)piperidin-3-ol,
- 201) (2R,3S)-2-((E)-3-(3,5-dimethyl-1H-indazol-1-yl)prop-1-enyl)piperidin-3-ol,
- 202) methyl 7-bromo-1-((E)-3-((2R,3S)-3-hydroxypiperidin-2-yl)allyl)-1H-indole-3-
- 15 carboxylate,
- 203) 7-bromo-1-((E)-3-((2R,3S)-3-hydroxypiperidin-2-yl)allyl)-1H-indole-3-carboxylic acid,
- 204) 5-bromo-1-((E)-3-((2R,3S)-3-hydroxypiperidin-2-yl)allyl)-1H-indole-3-carboxylic acid,
- 20 205) 4-chloro-1-((E)-3-((2R,3S)-3-hydroxypiperidin-2-yl)allyl)-1H-indole-3-carboxylic acid,
- 206) 6-chloro-1-((E)-3-((2R,3S)-3-hydroxypiperidin-2-yl)allyl)-1H-indole-3-carboxylic acid,
- 207) 7-chloro-1-((E)-3-((2R,3S)-3-hydroxypiperidin-2-yl)allyl)-1H-indole-3-
- 25 carboxylic acid,
- 208) 6-fluoro-1-((E)-3-((2R,3S)-3-hydroxypiperidin-2-yl)allyl)-1H-indole-3-carboxylic acid,
- 209) 1-((E)-3-((2R,3S)-3-hydroxypiperidin-2-yl)allyl)-1H-indole-3-carboxylic acid,
- 210) methyl 4-chloro-1-((E)-3-((2R,3S)-3-hydroxypiperidin-2-yl)allyl)-1H-indole-3-
- 30 carboxylate,

- 211) methyl 6-chloro-1-((E)-3-((2R,3S)-3-hydroxypiperidin-2-yl)allyl)-1H-indole-3-carboxylate,
- 212) methyl 7-chloro-1-((E)-3-((2R,3S)-3-hydroxypiperidin-2-yl)allyl)-1H-indole-3-carboxylate,
- 5 213) methyl 5-bromo-1-((E)-3-((2R,3S)-3-hydroxypiperidin-2-yl)allyl)-1H-indole-3-carboxylate,
- 214) methyl 6-bromo-1-((E)-3-((2R,3S)-3-hydroxypiperidin-2-yl)allyl)-1H-indole-3-carboxylate,
- 215) 5-bromo-1-((E)-3-((2R,3S)-3-hydroxypiperidin-2-yl)allyl)-N-methyl-1H-indole-3-carboxamide,
- 10 216) 5-bromo-1-((E)-3-((2R,3S)-3-hydroxypiperidin-2-yl)allyl)-N,N-dimethyl-1H-indole-3-carboxamide,
- 217) (2R,3S)-2-((Z)-3-(5-chloro-4-methyl-1H-benzo[d]imidazol-1-yl)-2-fluoroprop-1-enyl)piperidin-3-ol,
- 15 218) (2R,3S)-2-((Z)-3-(5-bromo-4-methyl-1H-benzo[d]imidazol-1-yl)-2-fluoroprop-1-enyl)piperidin-3-ol,
- 219) (2R,3S)-2-((Z)-3-(5,6-dichloro-1H-benzo[d]imidazol-1-yl)-2-fluoroprop-1-enyl)piperidin-3-ol,
- 220) (2R,3S)-2-((Z)-3-(5,6-dichloro-2-(hydroxymethyl)-1H-benzo[d]imidazol-1-yl)-2-fluoroprop-1-enyl)piperidin-3-ol,
- 20 221) (2R,3S)-2-((E)-3-(5-chloro-4-methyl-1H-benzo[d]imidazol-1-yl)-2-methylprop-1-enyl)piperidin-3-ol,
- 222) (2R,3S)-2-((E)-3-(5-bromo-4-methyl-1H-benzo[d]imidazol-1-yl)-2-methylprop-1-enyl)piperidin-3-ol,
- 25 223) (2R,3S)-2-((E)-3-(5,6-dichloro-1H-benzo[d]imidazol-1-yl)-2-methylprop-1-enyl)piperidin-3-ol,
- 224) (2R,3S)-2-((E)-3-(5,6-dichloro-2-(hydroxymethyl)-1H-benzo[d]imidazol-1-yl)-2-methylprop-1-enyl)piperidin-3-ol,
- 225) (2R,3S)-2-(3-(5,6-dichloro-1H-benzo[d]imidazol-1-yl)prop-1-ynyl)piperidin-3-ol,
- 30 ol,

226) (2R,3S)-2-(3-(5-bromo-4-methyl-1H-benzo[d]imidazol-1-yl)prop-1-ynyl)piperidin-3-ol,

227) (2R,3S)-2-(3-(5-chloro-4-methyl-1H-benzo[d]imidazol-1-yl)prop-1-ynyl)piperidin-3-ol,

5 228) (2R,3S)-2-(3-(5,6-dibromo-1H-benzo[d]imidazol-1-yl)prop-1-ynyl)piperidin-3-ol,

229) (2R,3S)-2-(3-(5-fluoro-4-methyl-1H-benzo[d]imidazol-1-yl)prop-1-ynyl)piperidin-3-ol, and

230) (2R,3S)-2-((E)-3-(5,6-dichloro-1H-benzo[d]imidazol-1-yl)prop-1-enyl)pyrrolidin-3-ol.

[Claim 12]

A pharmaceutical composition for the prevention or treatment of cancers, inflammatory diseases, autoimmune diseases or fibrosis, comprising the compound according to any one of
15 claims 1 to 11 or a pharmaceutically acceptable salt thereof.

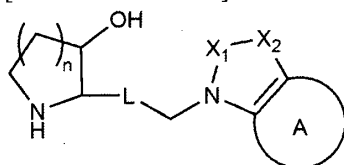
[Claim 13]

A method for preparing a compound represented by the following Chemical Formula 1 comprising the steps of:

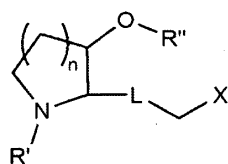
20 reacting a compound represented by the following Chemical Formula 1-A with a compound represented by the following Chemical Formula 1-B in the presence of a base to prepare a compound represented by the following Chemical Formula 1-C; and

reacting a compound represented by the Chemical Formula 1-C in the presence of an acid to prepare a compound represented by the following Chemical Formula 1:

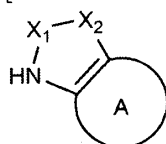
25 [Chemical Formula 1]



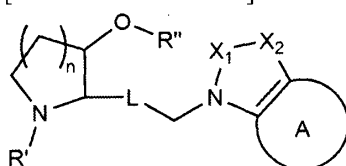
[Chemical Formula 1-A]



[Chemical Formula 1-B]



[Chemical Formula 1-C]



5

in Chemical Formulas 1, 1-A, 1-B, and 1-C,

n , L , X_1 , X_2 and A are as defined in claim 1,

X is halogen, and

R' and R'' are each independently a protecting group.

10

[Claim 14]

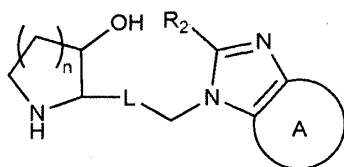
A method for preparing a compound represented by the following Chemical Formula 1-1 comprising the steps of:

15 reacting a compound represented by the following Chemical Formula 2-A with a compound represented by the following Chemical Formula 2-B in the presence of a base to prepare a compound represented by the following Chemical Formula 2-C;

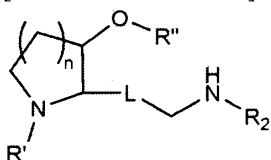
reacting an amine group and a nitro group of the compound represented by the Chemical Formula 2-C to form a ring, thereby preparing a compound represented by the following Chemical Formula 2-D; and

20 reacting a compound represented by the Chemical Formula 2-D in the presence of an acid to prepare a compound represented by the following Chemical Formula 1-1:

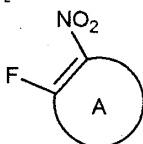
[Chemical Formula 1-1]



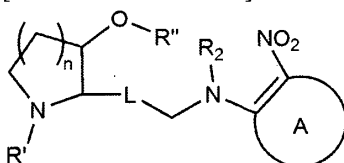
[Chemical Formula 2-A]



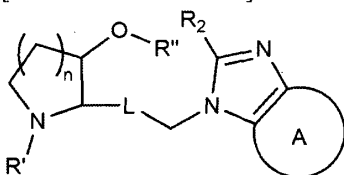
[Chemical Formula 2-B]



[Chemical Formula 2-C]



[Chemical Formula 2-D]



in Chemical Formulas 1-1, 2-A, 2-B, 2-C, and 2-D,
 n , L , R_2 and A are as defined in claim 1, and
 R' and R'' are each independently a protecting group.

[Claim 15]

A method for preparing a compound represented by the following Chemical Formula 3 comprising the steps of:

reacting the compound represented by the following Chemical Formula 3-A with (carbethoxymethylene)triphenylphosphorane to prepare a compound represented by the following Chemical Formula 3-B;

hydrogenating the compound represented by the following Chemical Formula 3-B to prepare a compound represented by the following Chemical Formula 3-C;

hydrolyzing the compound represented by the Chemical Formula 3-C to prepare a compound represented by the following Chemical Formula 3-D;

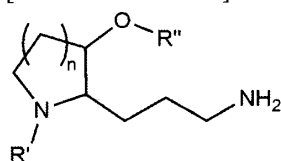
5 subjecting the compound represented by the Chemical Formula 3-D to a carbonyl reduction reaction to prepare a compound represented by the following Chemical Formula 3-E;

 brominating the compound represented by the Chemical Formula 3-E to prepare a compound represented by the following Chemical Formula 3-F;

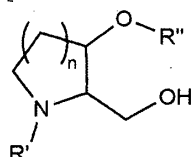
 subjecting the compound represented by the Chemical Formula 3-F to an azide reaction
10 to prepare a compound represented by the following Chemical Formula 3-G; and

 aminating the compound represented by the Chemical Formula 3-G to prepare a compound represented by the following Chemical Formula 3.

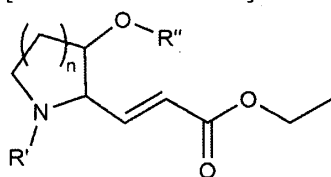
[Chemical Formula 3]



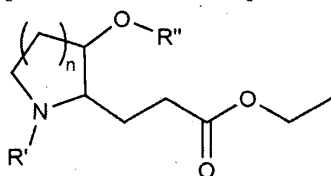
15 [Chemical Formula 3-A]



[Chemical Formula 3-B]

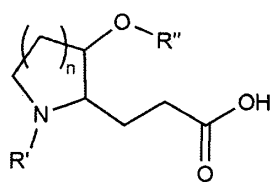


[Chemical Formula 3-C]

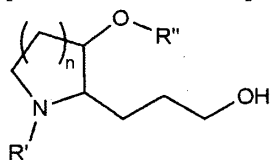


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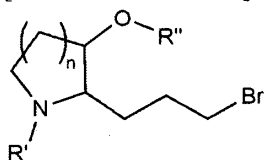
[Chemical Formula 3-D]



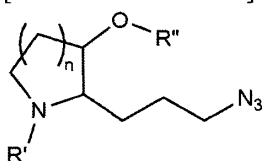
[Chemical Formula 3-E]



[Chemical Formula 3-F]



[Chemical Formula 3-G]



in Chemical Formulas 3, 3-A, 3-B, 3-C, 3-D, 3-E, 3-F, and 3-G,
n is as defined in claim 1, and

R' and R'' are each independently a protecting group.