DESCRIPTION

Title of Invention

MONOCYCLIC PYRIDINE DERIVATIVE

Technical Field

[0001] The present invention relates to a monocyclic pyridine derivative having an FGFR inhibitory action or a pharmaceutically acceptable salt thereof, and a medical use thereof.

[0002] All references cited herein are hereby incorporated by reference in their entireties.

Background Art

[0003] An FGF (fibroblast growth factor) is known as a growth factor for controlling a variety of physiological functions such as cell growth, cell migration, cellular infiltration, cell survival, differential induction, wound healing and angiogenesis.

The FGF controls the various physiological functions via FGF receptors (FGFRs: FGFR1, FGFR2, FGFR3 and FGFR4), that is, receptor tyrosine kinases. Each FGFR includes three types of domains of an extracellular domain, a transmembrane domain and an intracellular tyrosine kinase domain. When an FGF binds to the extracellular domain of an FGFR, a dimer of the receptor is formed. Thereafter, the intracellular tyrosine kinase is activated, and then, an intracellular signal is transmitted mainly via a MAPK (mitogen-activated protein kinase)/ERK (extracellular signal-regulated kinase) pathway or a PI3K (phosphatidylinositol 3-kinase)/Akt pathway.

[0004] Meanwhile, it has been reported that various cancers such as breast cancer, bladder cancer, EMS (8p11 myeloproliferative syndrome), stomach cancer, endometrial cancer and prostatic cancer are caused as a result of induction of FGF/FGFR signal abnormality accompanying FGF production enhancement, FGFR gene amplification, FGFR overexpression, FGFR fusion protein production, FGFR mutation and the like (Non Patent Literature 1). Furthermore, the following have been reported as cancers accompanied by the FGF/FGFR signal abnormality: Non-small-cell lung carcinoma, small-cell lung carcinoma, ovarian cancer, sarcoma, colon cancer, melanoma, glioblastoma, astrocytoma, and head and neck cancer (Non Patent Literatures 2 and 3), thyroid cancer (Non Patent Literature 4), pancreatic cancer (Non Patent Literatures 5 and 6), liver cancer (Non Patent Literature 7), skin cancer (Non Patent Literature 8), kidney cancer (Non Patent Literature 9), and lung squamous cell carcinoma (Non Patent Literatures 10, 11, and 12).

[0005] Besides, the FGF/FGFR signal is one of main angiogenic signals in endothelial cells along with a VEGF (vascular endothelial growth factor)/KDR (kinase-insert

domain-containing receptor) signal, and is reported to be involved in the interaction between cancer stromal cells (fibroblasts) and cancer cells (Non Patent Literature 1).

Accordingly, an FGFR inhibitor targeting an FGF/FGFR signal is expected to work as an antitumor drug, against cancers accompanied by the FGF/FGFR signal abnormality, based on its inhibitory action against the signal abnormality and its inhibitory action against the angiogenic signal. Recently, a selective FGFR inhibitor regarded to be insusceptible to be affected by a confronting effect of another signal, such as a selective FGFR inhibitor against FGFR1, FGFR2 or FGFR3, which is obviously different in the structure from a compound of the present invention, has been reported. In the development as an antitumor drug for humans, however, the selective FGFR inhibitor falls behind an antitumor drug simultaneously targeting both the FGF/FGFR signal and the VEGF/KDR signal, and has not been put on the market yet (Non Patent Literatures 13 and 14; Patent Literatures 1 and 2). Patent Literature 3 discloses pyrimidine derivatives but does not disclose an inhibitory action against the signal abnormality of the FGF/FGFR signal. Patent Literature 4 discloses pyridine derivatives or pyrimidine derivatives that inhibit angiogenesis induced by the VEGF and the FGF. None of these literatures, however, discloses the compounds of the present invention.

Citation List

Patent Literature

[0006]

[Patent Literature 1] International Publication No. WO 2008/075068

[Patent Literature 2] International Publication No. WO 2006/000420

[Patent Literature 3] International Publication No. WO 2002/032872

[Patent Literature 4] International Publication No. WO 2004/020434

Non Patent Literature

[0007]

[Non Patent Literature 1] Nicholas et al., "Fibroblast growth factor signalling: from development to cancer", Nature Reviews Cancer. 2010; 10: 116-129

[Non Patent Literature 2] Joergen WESCHE et al., Fibroblast growth factors and their receptors in cancer, Biochem J. 2011: 437; 199-213

[Non Patent Literature 3] Gennaro Daniele et al., FGF Receptor Inhibitors: Role in Cancer Therapy, Curr Oncol Rep. 2012; 14:111-119

[Non Patent Literature 4] Rosanne St. Bernard et al., Fibroblast Growth Factor Receptors as

Molecular Targets in Thyroid Carcinoma, Endocrinology. 2005; 146: 1145-1153

[Non Patent Literature 5] Toshiyuki Ishiwata et al., Enhanced Expression of Fibroblast Growth Factor Receptor 2 IIIc Promotes Human Pancreatic Cancer Cell Proliferation, Am J Pathol. 2012; 180: 1928-1941

[Non Patent Literature 6] G Chen et al., Inhibition of endogenous SPARC enhances pancreatic cancer cell growth: modulation by FGFR1-III isoform expression, Br J Cancer. 2010; 102: 188-195

[Non Patent Literature 7] Dorothy M. French et al., Targeting FGFR4 Inhibits Hepatocellular Carcinoma in Preclinical Mouse Models, PLoS One. 2012; 7: e36713

[Non Patent Literature 8] Armelle Logie et al., Activating mutations of the tyrosine kinase receptor FGFR3 are associated with benign skin tumors in mice and humans, Hum Mol Genet 2005; 14: 1153-1160

[Non Patent Literature 9] Tsimafeyeu I et al., Overexpression of fibroblast growth factor receptors FGFR1 and FGFR2 in renal cell carcinoma, Scand J Urol Nephrol 2011; 45: 190-195

[Non Patent Literature 10] Jonathan Weiss et al., Frequent and Focal FGFR1 Amplification Associates with Therapeutically Tractable FGFR1 Dependency in Squamous Cell Lung Cancer, Sci Transl Med. 2010; 2: issue 62 62-93

[Non Patent Literature 11] Hidefumi Sasaki et al., Increased FGFR1 copy number in lung squamous cell carcinomas, Mol Med Report. 2012; 5: 725-728

[Non Patent Literature 12] The Cancer Genome Atlas Research Network, Comprehensive genomic characterization of squamous cell lung cancers, Nature 2012; 489: 519-525

[Non Patent Literature 13] Paul R Gavine et al., AZD4547: An Orally Bioavailable, Potent, and Selective Inhibitor of the Fibroblast Growth Factor Receptor Tyrosine Kinase Family, Cancer Res. 2012; 72: 2045-2056

[Non Patent Literature 14] Vito Guagnano et al., Discovery of 3-(2,6-Dichloro-3,5-dimethoxy-phenyl)-1-{6-[4-(4-ethyl-piperazin-1-yl)-phenylamino]-pyrimidin-4-yl}-1-methyl-urea (NVP-BGJ398), A Potent and Selective Inhibitor of the Fibroblast Growth Factor Receptor Family of Receptor Tyrosine Kinase, J Med Chem. 2011; 54: 7066-7083

Summary of Invention

Technical Problem

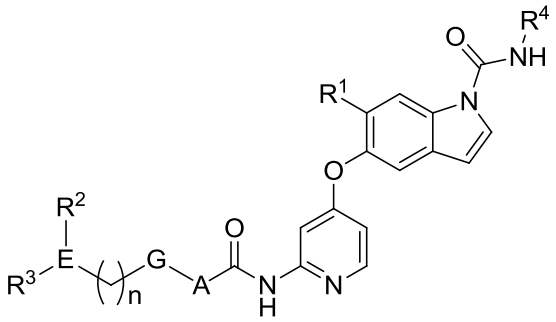
[0008] Under these circumstances, an object of the present invention is to provide a novel

compound having an FGFR inhibitory action or a pharmaceutically acceptable salt thereof, and a pharmaceutical composition containing the same.

Solution to Problem

[0009] The present inventors have made earnest studies in consideration of the aforementioned circumstances, and as a result, have succeeded in synthesizing a novel monocyclic pyridine derivative represented by the following formula (IA) (hereinafter referred to as the compound (IA) of the present invention), and have found that such a compound has an FGFR1 inhibitory action and an FGFR2 inhibitory action, and thus, have accomplished the present invention. Furthermore, the present inventors have found that the compound (IA) of the present invention has an action to selectively inhibit an FGF/FGFR signal against a VEGF/KDR signal, particularly, a selective FGFR1, FGFR2 or FGFR3 inhibitory action.

[Chemical Formula 1]

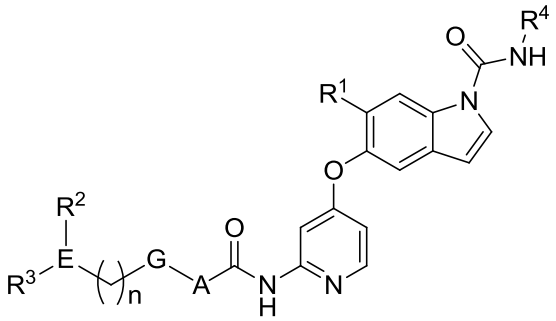


(IA)

[0010] Specifically, the present invention provides the following [1] to [26].

[1] A compound represented by the following formula (IA) or a pharmaceutically acceptable salt thereof:

[Chemical Formula 2]



(IA)

wherein

n represents 0 to 2;

A represents a C_{6-10} arylene group or a C_{3-5} heteroarylene group;

G represents a single bond, an oxygen atom or $–CH_2–$;

E represents a C_{3-5} nitrogen-containing non-aromatic heterocycle;

R^1 represents a cyano group, a mono-C_{1-6} alkylamino group, a di-C_{1-6} alkylamino group, a C_{2-6} alkyl group optionally substituted by 1 to 3 halogen atoms, a C_{1-6} alkoxy group optionally substituted by 1 to 3 halogen atoms or one hydroxyl group, a C_{1-6} alkoxy C_{1-6} alkyl group optionally substituted by 1 to 3 halogen atoms, or a C_{1-6} alkoxy C_{1-6} alkoxy group optionally substituted by 1 to 3 halogen atoms;

R^2 represents a hydrogen atom, a halogen atom, a hydroxyl group, a C_{2-6} acyl group optionally substituted by one substituent selected from a group S described below, a C_{1-6} alkyl group optionally substituted by 1 to 3 halogen atoms, a hydroxy C_{1-6} alkyl group optionally substituted by 1 to 3 halogen atoms, or a C_{3-5} nitrogen-containing non-aromatic heterocyclic group;

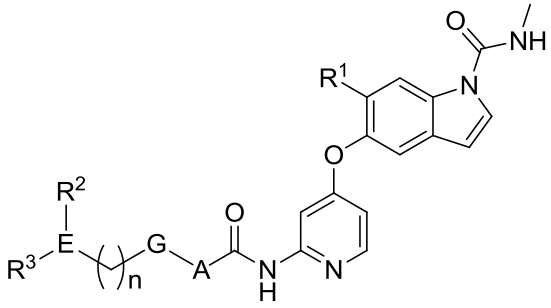
R^3 represents a hydrogen atom, an oxo group, a C_{1-6} alkyl group optionally substituted by 1 to 3 halogen atoms, or a C_{1-6} alkoxy group optionally substituted by 1 to 3 halogen atoms;

R^4 represents a C_{1-6} alkyl group, with the proviso that when E represents an azetidine ring and R^2 or R^3 is present on a nitrogen atom on the azetidine ring, the R^2 or R^3 does not represent a hydrogen atom; and

the group S represents a group consisting of a hydroxyl group, a mono-C_{1-6} alkylamino group, a di-C_{1-6} alkylamino group, a C_{1-6} alkoxy group and a C_{3-5} nitrogen-containing non-aromatic heterocyclic group.

[2] The compound or the pharmaceutically acceptable salt thereof according to [1], represented by the following formula (IB):

[Chemical Formula 3]



(IB)

wherein

n represents 0 to 2;

A represents a C_{6-10} arylene group or a C_{3-5} heteroarylene group;

G represents a single bond, an oxygen atom or $–CH_2–$;

E represents a C_{3-5} nitrogen-containing non-aromatic heterocycle;

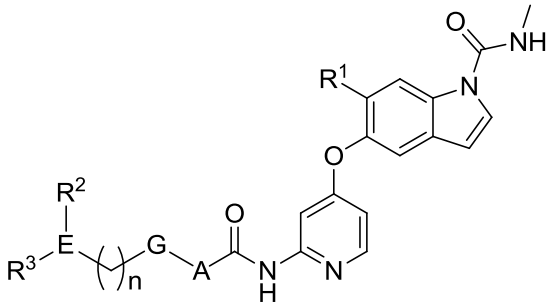
R^1 represents a C_{1-6} alkoxy group optionally substituted by 1 to 3 halogen atoms or one hydroxyl group, or a C_{1-6} alkoxy C_{1-6} alkoxy group optionally substituted by 1 to 3 halogen atoms;

R^2 represents a hydrogen atom, a halogen atom, a hydroxyl group, a C_{1-6} alkyl group optionally substituted by 1 to 3 halogen atoms, a hydroxy C_{1-6} alkyl group optionally substituted by 1 to 3 halogen atoms, or a C_{3-5} nitrogen-containing non-aromatic heterocyclic group; and

R^3 represents a hydrogen atom, an oxo group, a C_{1-6} alkyl group optionally substituted by 1 to 3 halogen atoms, or a C_{1-6} alkoxy group optionally substituted by 1 to 3 halogen atoms, with the proviso that when E represents an azetidine ring and R^2 or R^3 is present on a nitrogen atom on the azetidine ring, the R^2 or R^3 does not represent a hydrogen atom.

[3] The compound or the pharmaceutically acceptable salt thereof according to [1], represented by the following formula (IB):

[Chemical Formula 4]



(IB)

wherein

n represents 0 to 2;

A represents a C_{6-10} arylene group or a C_{3-5} heteroarylene group;

G represents a single bond, an oxygen atom or $–CH_2–$;

E represents a C_{3-5} nitrogen-containing non-aromatic heterocycle;

R^1 represents a C_{1-6} alkoxy group optionally substituted by 1 to 3 halogen atoms or a C_{1-6} alkoxy C_{1-6} alkoxy group optionally substituted by 1 to 3 halogen atoms;

R^2 represents a hydrogen atom, a halogen atom, a hydroxyl group, a C_{1-6} alkyl group optionally substituted by 1 to 3 halogen atoms, a hydroxy C_{1-6} alkyl group optionally

substituted by 1 to 3 halogen atoms, or a C_{3-5} nitrogen-containing non-aromatic heterocyclic group; and

R^3 represents a hydrogen atom, a C_{1-6} alkyl group optionally substituted by 1 to 3 halogen atoms, or a C_{1-6} alkoxy group optionally substituted by 1 to 3 halogen atoms, with the proviso that when E represents an azetidine ring and R^2 or R^3 is present on a nitrogen atom on the azetidine ring, the R^2 or R^3 does not represent a hydrogen atom.

[4] The compound or the pharmaceutically acceptable salt thereof according to any one of [1] to [3], wherein A represents a C_{6-10} arylene group.

[5] The compound or the pharmaceutically acceptable salt thereof according to any one of [1] to [4], wherein G represents a single bond or an oxygen atom.

[6] The compound or the pharmaceutically acceptable salt thereof according to any one of [1] to [3], wherein

A represents a phenylene group, a thienylene group, a pyrazolylene group or a pyridylene group; and

E represents an azetidine ring, a pyrrolidine ring, a piperidine ring or a piperazine ring.

[7] The compound or the pharmaceutically acceptable salt thereof according to any one of [1] to [3], wherein

A represents a phenylene group; and

E represents an azetidine ring or a piperidine ring.

[8] The compound or the pharmaceutically acceptable salt thereof according to any one of [1] to [3], wherein

A represents a phenylene group; and

E represents a piperidine ring.

[9] The compound or the pharmaceutically acceptable salt thereof according to any one of [6] to [8], wherein

n represents 0; and

G represents a single bond.

[10] The compound or the pharmaceutically acceptable salt thereof according to any one of [1] to [9], wherein

R^1 represents a C_{1-6} alkoxy group or a C_{1-6} alkoxy C_{1-6} alkoxy group;

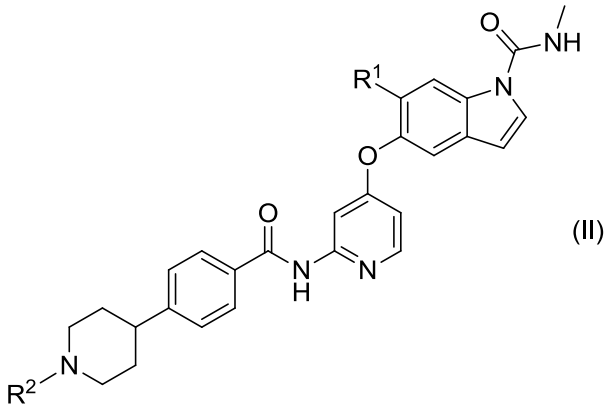
R^2 represents a hydrogen atom, a hydroxyl group, a C_{1-6} alkyl group or a hydroxy C_{1-6} alkyl group; and

R^3 represents a hydrogen atom.

[11] The compound or the pharmaceutically acceptable salt thereof according to any one of [1] to [10], wherein R^1 represents a $C_{1\text{-}6}$ alkoxy $C_{1\text{-}6}$ alkoxy group.

[12] The compound or the pharmaceutically acceptable salt thereof according to any one of [1] to [3], represented by the following formula (II):

[Chemical Formula 5]



(II)

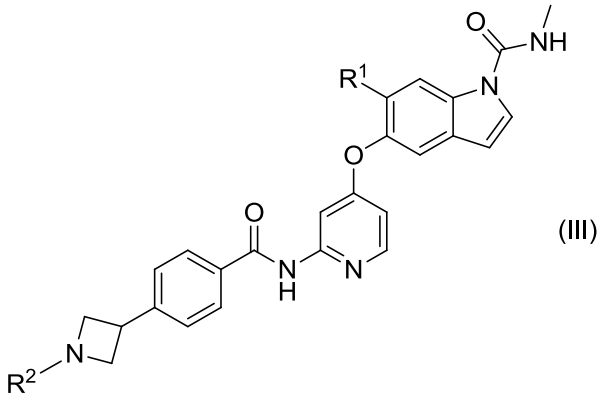
wherein

R^1 represents a $C_{1\text{-}6}$ alkoxy $C_{1\text{-}6}$ alkoxy group; and

R^2 represents a hydrogen atom, a $C_{1\text{-}6}$ alkyl group or a hydroxy $C_{2\text{-}6}$ alkyl group.

[13] The compound or the pharmaceutically acceptable salt thereof according to any one of [1] to [3], represented by the following formula (III):

[Chemical Formula 6]



(III)

wherein

R^1 represents a $C_{1\text{-}6}$ alkoxy $C_{1\text{-}6}$ alkoxy group; and

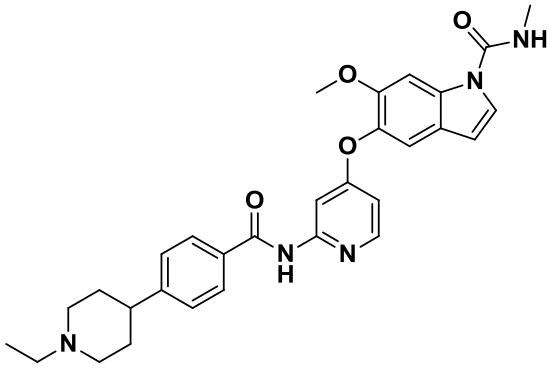
R^2 represents a $C_{1\text{-}6}$ alkyl group or a hydroxy $C_{2\text{-}6}$ alkyl group.

[14]

5-((2-(4-(1-Ethylpiperidin-4-yl)benzamide)pyridin-4-yl)oxy)-6-methoxy-N-methyl

-1H-indole-1-carboxamide represented by the following structural formula, or a pharmaceutically acceptable salt thereof:

[Chemical Formula 7]

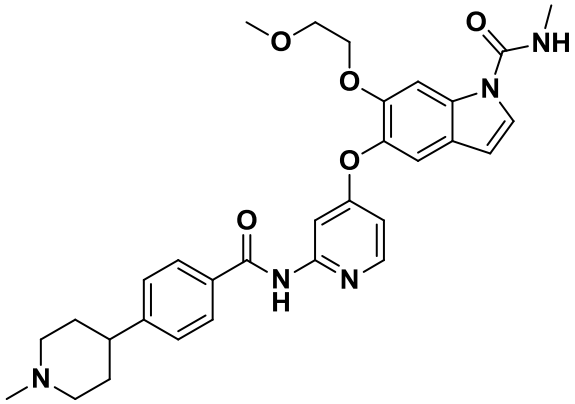


.

[15]

6-(2-Methoxyethoxy)-N-methyl-5-((2-(4-(1-methylpiperidin-4-yl)benzamide)pyridin-4-yl)oxy)-1H-indole-1-carboxamide represented by the following structural formula, or a pharmaceutically acceptable salt thereof:

[Chemical Formula 8]

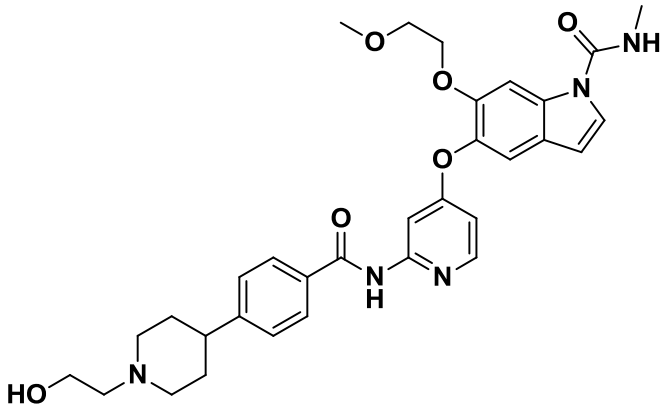


.

[16]

5-((2-(4-(1-(2-Hydroxyethyl)piperidin-4-yl)benzamide)pyridin-4-yl)oxy)-6-(2-methoxyethoxy)-N-methyl-1H-indole-1-carboxamide represented by the following structural formula, or a pharmaceutically acceptable salt thereof:

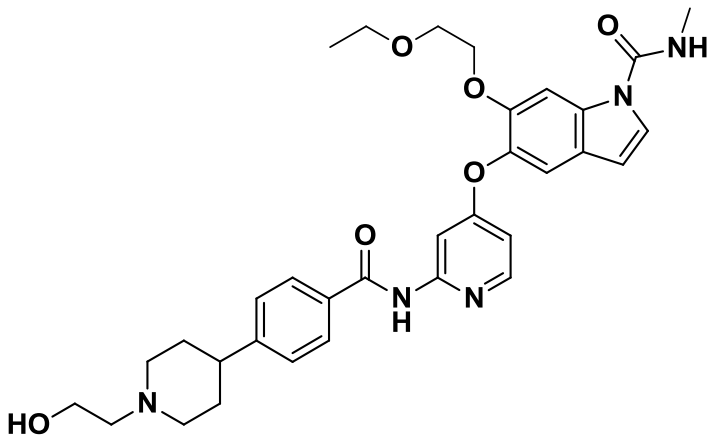
[Chemical Formula 9]



[17]

6-(2-Ethoxyethoxy)-5-((2-(4-(1-(2-hydroxyethyl)piperidin-4-yl)benzamide)pyridin-4-yl)oxy)-N-methyl-1H-indole-1-carboxamide represented by the following structural formula, or a pharmaceutically acceptable salt thereof:

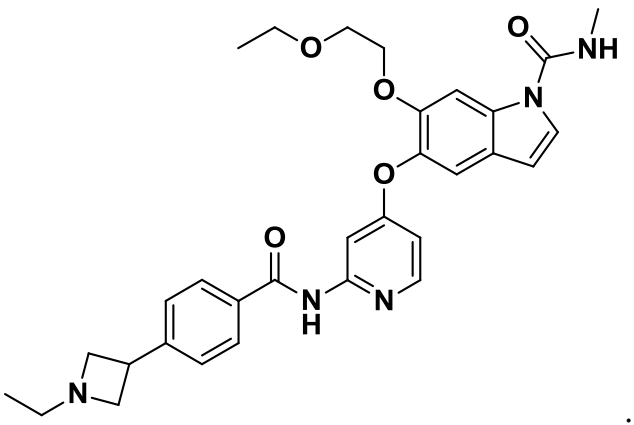
[Chemical Formula 10]



[18]

6-(2-Ethoxyethoxy)-5-((2-(4-(1-ethylazetidin-3-yl)benzamide)pyridin-4-yl)oxy)-N-methyl-1H-indole-1-carboxamide represented by the following structural formula, or a pharmaceutically acceptable salt thereof:

[Chemical Formula 11]



[19] A pharmaceutical composition comprising the compound or the pharmaceutically acceptable salt thereof according to any one of [1] to [18].

[20] A therapeutic agent for stomach cancer, non-small-cell lung carcinoma, bladder cancer or endometrial cancer comprising the compound or the pharmaceutically acceptable salt thereof according to any one of [1] to [18] as an active ingredient.

[21] A method for treating stomach cancer, non-small-cell lung carcinoma, bladder cancer or endometrial cancer comprising administrating a pharmacologically effective dose of the compound or the pharmaceutically acceptable salt thereof according to any one of [1] to [18].

[22] A therapeutic agent for non-small-cell lung carcinoma comprising the compound or the pharmaceutically acceptable salt thereof according to any one of [1] to [18] as an active ingredient.

[23] A therapeutic agent for squamous cell carcinoma comprising the compound or the pharmaceutically acceptable salt thereof according to any one of [1] to [18] as an active ingredient.

[24] An FGFR inhibitor for treating non-small-cell lung carcinoma, comprising the compound or the pharmaceutically acceptable salt thereof according to any one of [1] to [18] as an active ingredient.

[25] The compound or the pharmaceutically acceptable salt thereof according to any one of [1] to [18], for use as a therapeutic agent for stomach cancer, non-small-cell lung carcinoma, bladder cancer or endometrial cancer.

[26] A use of the compound or the pharmaceutically acceptable salt thereof according to any one of [1] to [18], for manufacturing a therapeutic agent for stomach cancer, non-small-cell lung carcinoma, bladder cancer or endometrial cancer.

Advantageous Effects of Invention

[0011] The compound (IA) of the present invention or the pharmaceutically acceptable salt thereof has FGFR1, FGFR2 and FGFR3 inhibitory actions as shown in activity data obtained in pharmacological test examples described later. Furthermore, the compound (IA) of the present invention or the pharmaceutically acceptable salt thereof has a selective FGFR1, FGFR2 or FGFR3 inhibitory action as opposed to a KDR or HUVEC inhibitory action. Accordingly, the compound (IA) of the present invention or a pharmaceutically acceptable salt thereof has a potential use for a therapeutic agent for stomach cancer, non-small-cell lung carcinoma including lung squamous cell carcinoma, bladder cancer or endometrial cancer.

Description of Embodiments

[0012] Now, the present invention is described in details by defining symbols and terms used herein and describing embodiments and the like of the present invention.

[0013] Herein, a structural formula of a compound may represent a given isomer for convenience, but the compound of the present invention includes isomers, such as all geometric isomers structurally formed from the compound, optical isomers based on asymmetric carbon, stereoisomers, rotamers and tautomers, and mixtures of these isomers, and hence is not limited to the formula given for convenience but may be any one of the isomers and mixtures. Accordingly, the compound of the present invention may have asymmetric carbon atom(s) in the molecule, and there may be an optically active substance and a racemate, and the present invention is not limited but includes all of these. It is understood, however, that some isomers, racemates and mixtures of isomers may show stronger activity than the others. Furthermore, there may exist crystal polymorphism, which also does not limit the present invention, and the compound of the present invention may be in any of single crystal forms or a mixture of two or more crystal forms, and the compound of the present invention includes an amorphous form, and embraces an anhydride and a solvate such as a hydrate.

[0014] The present invention includes an isotope-labeled compound of the compound (IA) of the present invention and a pharmaceutically acceptable salt thereof. The isotope-labeled compound is equivalent to the compound represented by formula (IA) except that one or more of atom(s) are replaced by atom(s) having an atomic mass or a mass number different from those usually found in nature. Examples of an isotope that can be incorporated into the compound of the present invention include isotopes of hydrogen, carbon, nitrogen,

oxygen, phosphorus, fluorine, iodine, bromine and chlorine, such as ^{2}H, ^{3}H, ^{11}C, ^{13}C, ^{14}C, ^{18}F, ^{35}S, ^{123}I and ^{125}I.

[0015] The isotope-labeled compound, such as a compound into which a radioactive isotope of, for example, ^{3}H and/or ^{14}C is incorporated, is useful for a tissue distribution assay for a medicine and/or a matrix. The isotopes ^{3}H and ^{14}C are regarded to be useful because these isotopes can be easily prepared and detected. The isotopes ^{11}C and ^{18}F are regarded to be useful in PET (positron emission tomography), the isotope ^{125}I is regarded to be useful in SPECT (single photon emission computed tomography), and can be useful in brain imaging. Replacement by a heavier isotope such as ^{2}H causes, because of its higher metabolic stability, some advantages, in a treatment, of, for example, extension of half-life in vivo or reduction of a necessary dose, and therefore, is regarded useful under given circumstances. The isotope-labeled compound can be similarly prepared by using a readily available isotope-labeled reagent instead of a nonisotope-labeled reagent and by performing processes disclosed in schemes and/or examples described below.

[0016] The compound (IA) of the present invention can be used as a chemical probe for capturing a target protein of a biologically active low molecular weight compound. Specifically, the compound of the present invention can be transformed into an affinity chromatography probe, a photoaffinity probe or the like by introducing a labeling group, a linker or the like into a moiety other than a structural moiety indispensable to activity expression of the compound by a method described in J. Mass Spectrum. Soc. Jpn. Vol. 51, No. 5, 2003, p. 492-498, WO2007/139149 or the like.

[0017] Examples of the labeling group, the linker or the like used in such a chemical probe include groups belonging to the following groups (1) to (5).

(1) Protein labeling groups such as photoaffinity labeling groups (such as a benzoyl group, a benzophenone group, an azide group, a carbonyl azide group, a diaziridine group, an enone group, a diazo group and a nitro group), and chemical affinity groups (such as a ketone group in which an alpha carbon atom is substituted by a halogen atom, a carbamoyl group, an ester group, an alkylthio group, a Michael receptor of α, β-unsaturated ketone, ester or the like, and an oxirane group);

(2) cleavable linkers such as –S–S–, –O–Si–O–, a monosaccharide (such as a glucose group or a galactose group) and a disaccharide (such as lactose), and oligopeptide linkers that can be cleaved by an enzyme reaction;

(3) fishing tag groups such as biotin and a

3-(4,4-difluoro-5,7-dimethyl-4H-3a,4a-diaza-4-bora-s-indacene-3-yl)propionyl group;

(4) radioactive labeling groups such as ^{125}I, ^{32}P, ^{3}H and ^{14}C; fluorescence labeling groups such as fluorescein, rhodamine, dansyl, umbelliferone, 7-nitrofurazanyl, and a 3-(4,4-difluoro-5,7-dimethyl-4H-3a,4a-diaza-4-bora-s-indacene-3-yl)propionyl group; chemiluminescent groups such as luciferin and luminol; and markers capable of detecting heavy metal ions such as lanthanoid metal ions and radium ions; and

(5) groups to be bonded to a solid phase carrier such as glass beads, a glass bed, a microtiter plate, agarose beads, an agarose bed, polystyrene beads, a polystyrene bed, nylon beads and a nylon bed.

[0018] A probe prepared by introducing, into the compound of the present invention, a labeling group or the like selected from the above-described groups (1) to (5) by the method described in any of the aforementioned literatures or the like can be used as a chemical probe for identifying a marker protein useful for research of a novel potential drug target.

[0019] A "halogen atom" used herein means a fluorine atom, a chlorine atom, a bromine atom or an iodine atom.

[0020] A "hetero atom" used herein means a nitrogen atom, a sulfur atom or an oxygen atom.

[0021] A "C_{1-6} alkyl group" used herein means a linear or branched alkyl group having 1 to 6 carbon atoms that is a monovalent group induced by removing one arbitrary hydrogen atom from an aliphatic hydrocarbon having 1 to 6 carbon atoms. Examples of such a group include a methyl group, an ethyl group, a n-propyl group, an isopropyl group, a n-butyl group, an isobutyl group, a sec-butyl group, a tert-butyl group, a n-pentyl group, an isopentyl group, a sec-pentyl group, a neopentyl group, a 1-methylbutyl group, a 2-methylbutyl group, a 1,1-dimethylpropyl group, a 1,2-dimethylpropyl group, a n-hexyl group, an isohexyl group, a 1-methylpentyl group, a 2-methylpentyl group, a 3-methylpentyl group, a 1,1-dimethylbutyl group, a 1,2-dimethylbutyl group, a 2,2-dimethylbutyl group, a 1,3-dimethylbutyl group, a 2,3-dimethylbutyl group, a 3,3-dimethylbutyl group, a 1-ethylbutyl group, a 2-ethylbutyl group, a 1,1,2-trimethylpropyl group, a 1,2,2-trimethylpropyl group, a 1-ethyl-1-methylpropyl group, a 1-ethyl-2-methylpropyl group and the like. More specifically, it is a methyl group, an ethyl group, a n-propyl group, an isopropyl group, a n-butyl group, an isobutyl group, a sec-butyl group, a tert-butyl group or the like, and is preferably a methyl group, an ethyl group or an isopropyl group.

[0022] A "C_{1-6} alkyl group optionally substituted by 1 to 3 halogen atoms" used herein

means the above-described C_{1-6} alkyl group in which arbitrary 1 to 3 hydrogen atoms may be substituted by a halogen atom. The position to be substituted by a halogen atom is not especially limited, and specific examples of such a group include a monofluoromethyl group, a difluoromethyl group, a trifluoromethyl group, a 2-fluoroethyl group, a 2,2-difluoroethyl group, a 2,2,2-trifluoroethyl group, a monochloromethyl group, a dichloromethyl group, a trichloromethyl group, a 2-chloroethyl group, a 2,2-dichloroethyl group, a 2,2,2-trichloroethyl group, a 3-fluoropropyl group and the like. As the halogen atom used for the substitution, specifically, for example, a fluorine atom, a chlorine atom or the like is preferably used, and a fluorine atom is more preferably used.

[0023] A "C_{2-6} alkyl group" used herein means a linear or branched alkyl group having 2 to 6 carbon atoms that is a monovalent group induced by removing one arbitrary hydrogen atom from an aliphatic hydrocarbon having 2 to 6 carbon atoms. Examples of such a group include an ethyl group, a n-propyl group, an isopropyl group, a n-butyl group, an isobutyl group, a sec-butyl group, a tert-butyl group, a n-pentyl group, an isopentyl group, a sec-pentyl group, a neopentyl group, a 1-methylbutyl group, a 2-methylbutyl group, a 1,1-dimethylpropyl group, a 1,2-dimethylpropyl group, a n-hexyl group, an isohexyl group, a 1-methylpentyl group, a 2-methylpentyl group, a 3-methylpentyl group, a 1,1-dimethylbutyl group, a 1,2-dimethylbutyl group, a 2,2-dimethylbutyl group, a 1,3-dimethylbutyl group, a 2,3-dimethylbutyl group, a 3,3-dimethylbutyl group, a 1-ethylbutyl group, a 2-ethylbutyl group, a 1,1,2-trimethylpropyl group, a 1,2,2-trimethylpropyl group, a 1-ethyl-1-methylpropyl group, and a 1-ethyl-2-methylpropyl group. More specifically, it is an ethyl group, a n-propyl group, an isopropyl group, a n-butyl group, an isobutyl group, a sec-butyl group or a tert-butyl group, and is preferably an ethyl group.

[0024] A "C_{2-6} alkyl group optionally substituted by 1 to 3 halogen atoms" used herein means the above-described C_{2-6} alkyl group in which arbitrary 1 to 3 hydrogen atoms may be substituted by a halogen atom. The position to be substituted by a halogen atom is not especially limited, and specific examples of such a group include a 2-fluoroethyl group, a 2,2-difluoroethyl group, a 2,2,2-trifluoroethyl group, a 2-chloroethyl group, a 2,2-dichloroethyl group, a 2,2,2-trichloroethyl group, and a 3-fluoropropyl group. As the halogen atom used for the substitution, specifically, for example, a fluorine atom, a chlorine atom or the like is preferably used, and a fluorine atom is more preferably used.

[0025] A "hydroxy C_{1-6} alkyl group" used herein means the above-described C_{1-6} alkyl group in which one arbitrary hydrogen atom is substituted by a hydroxyl group. The

position to be substituted by a hydroxyl group is not especially limited, and specific examples of such a group include a hydroxymethyl group, a 2-hydroxyethyl group, a 1-hydroxyethyl group, a 3-hydroxypropyl group, a 2-hydroxypropyl group, a 1-hydroxypropyl group, a 2-hydroxy-2,2-dimethylethyl group and the like. It is preferably a 2-hydroxyethyl group, a 2-hydroxypropyl group or a 2-hydroxy-2,2-dimethylethyl group.

[0026] A "hydroxy C_{2-6} alkyl group" used herein means a linear or branched alkyl group having 2 to 6 carbon atoms that is a monovalent group induced by removing one arbitrary hydrogen atom from an aliphatic hydrocarbon having 2 to 6 carbon atoms, in which one arbitrary hydrogen atom is substituted by a hydroxyl group. The position to be substituted by a hydroxyl group is not especially limited, and specific examples of such a group include a 2-hydroxyethyl group, a 1-hydroxyethyl group, a 3-hydroxypropyl group, a 2-hydroxypropyl group, a 1-hydroxypropyl group, a 2-hydroxy-2,2-dimethylethyl group and the like. It is preferably a 2-hydroxyethyl group, a 2-hydroxypropyl group or a 2-hydroxy-2,2-dimethylethyl group.

[0027] A "hydroxy C_{1-6} alkyl group optionally substituted by 1 to 3 halogen atoms" used herein means the above-described hydroxy C_{1-6} alkyl group in which arbitrary 1 to 3 hydrogen atoms may be substituted by a halogen atom. The position to be substituted by a halogen atom is not especially limited. As the halogen atom to be used for the substitution, specifically, for example, a fluorine atom, a chlorine atom or the like is preferably used, and a fluorine atom is more preferably used.

[0028] A "C_{1-6} alkoxy group" used herein means the above defined "C_{1-6} alkyl group" having an oxygen atom bonded to a terminal thereof, and examples of such a group include a methoxy group, an ethoxy group, a n-propoxy group, an isopropoxy group, a n-butoxy group, an isobutoxy group, a sec-butoxy group, a tert-butoxy group, a n-pentyloxy group, an isopentyloxy group, a sec-pentyloxy group, a neopentyloxy group, a 1-methylbutoxy group, a 2-methylbutoxy group, a 1,1-dimethylpropoxy group, a 1,2-dimethylpropoxy group, a n-hexyloxy group, an isohexyloxy group, a 1-methylpentyloxy group, a 2-methylpentyloxy group, a 3-methylpentyloxy group, a 1,1-dimethylbutoxy group, a 1,2-dimethylbutoxy group, a 2,2-dimethylbutoxy group, a 1,3-dimethylbutoxy group, a 2,3-dimethylbutoxy group, a 3,3-dimethylbutoxy group, a 1-ethylbutoxy group, a 2-ethylbutoxy group, a 1,1,2-trimethylpropoxy group, a 1,2,2-trimethylpropoxy group, a 1-ethyl-1-methylpropoxy group, a 1-ethyl-2-methylpropoxy group and the like, and more specifically, it is a methoxy group, an ethoxy group, a n-propoxy group, an isopropoxy group, a n-butoxy group, an

isobutoxy group, a sec-butoxy group, a n-pentyloxy group, an isopentyloxy group, a n-hexyloxy group, an isohexyloxy group or the like, and is preferably a methoxy group, an ethoxy group or an isopropoxy group.

[0029] A "C_{1-6} alkoxy group optionally substituted by 1 to 3 halogen atoms" used herein means the above-described C_{1-6} alkoxy group in which arbitrary 1 to 3 hydrogen atoms are substituted by a halogen atom. The position to be substituted by a halogen atom is not especially limited, and specific examples of such a group include a monofluoromethoxy group, a difluoromethoxy group, a trifluoromethoxy group, a 2-fluoroethoxy group, a 2,2-difluoroethoxy group, a 2,2,2-trifluoroethoxy group, a monochloromethoxy group, a dichloromethoxy group, a trichloromethoxy group, a 2-chloroethoxy group, a 2,2-dichloroethoxy group, a 2,2,2-trichloroethoxy group, a 3-fluoropropoxy group and the like.

[0030] A "C_{1-6} alkoxy group optionally substituted by one hydroxyl group" used herein means the above-described C_{1-6} alkoxy group in which one arbitrary hydrogen atom may be substituted by a hydroxyl group. The position to be substituted by a hydroxyl group is not especially limited, and specific examples of such a group include a 2-hydroxyethoxy group, a 2-hydroxypropoxy group and a 3-hydroxypropoxy group. Preferably, it is a 2-hydroxyethoxy group.

[0031] A "C_{1-6} alkoxy C_{1-6} alkoxy group" used herein means the above defined "C_{1-6} alkoxy group" in which one arbitrary hydrogen atom is substituted by the above defined "C_{1-6} alkoxy group", and specific examples of such a group include a methoxymethoxy group, an ethoxymethoxy group, a n-propoxymethoxy group, a 2-methoxyethoxy group, a 2-ethoxyethoxy group, a 3-methoxypropoxy group and the like. Preferably, it is a 2-methoxyethoxy group, a 2-ethoxyethoxy group or a 3-methoxypropoxy group.

[0032] A "C_{1-6} alkoxy C_{1-6} alkoxy group optionally substituted by 1 to 3 halogen atoms" used herein means the above-described "C_{1-6} alkoxy C_{1-6} alkoxy group" in which arbitrary 1 to 3 hydrogen atoms may be substituted by a halogen atom. The position to be substituted by a halogen atom is not especially limited, and specific examples of such a group include a monofluromethoxymethoxy group, a difluoromethoxymethoxy group, a monofluoroethoxymethoxy group, a difluoroethoxymethoxy group, a monofluoromethoxyethoxy group, a trifluoromethoxyethoxy group, a difluoromethoxyethoxy group, a monofluoroethoxyethoxy group, a difluoroethoxyethoxy group and the like.

[0033] A "C_{1-6} alkoxy C_{1-6} alkyl group" used herein means the above defined "C_{1-6} alkyl group" in which one arbitrary hydrogen atom is substituted by the above defined "C_{1-6} alkoxy group", and specific examples of such a group include a methoxymethyl group, an ethoxymethyl group, a n-propoxymethyl group, a 2-methoxyethyl group, a 2-ethoxyethyl group and a 3-methoxypropyl group. Preferably, it is a methoxymethyl group.

[0034] A "C_{1-6} alkoxy C_{1-6} alkyl group optionally substituted by 1 to 3 halogen atoms" used herein means the above-described C_{1-6} alkoxy C_{1-6} alkyl group in which arbitrary 1 to 3 hydrogen atoms may be substituted by a halogen atom. The position to be substituted by a halogen atom is not especially limited, and specific examples of such a group include a monofluoromethoxymethyl group, a difluoromethoxymethyl group, a monofluoroethoxymethyl group, a difluoroethoxymethyl group, a monofluoromethoxyethyl group, a trifluoromethoxyethyl group, a difluoromethoxyethyl group, a monofluoroethoxyethyl group and a difluoroethoxyethyl group.

[0035] A "mono-C_{1-6} alkylamino group" used herein means an amino group in which one hydrogen atom is substituted by the above defined "C_{1-6} alkyl group", and specific examples of such a group include a methylamino group, an ethylamino group, a n-propylamino group, an isopropylamino group, a n-butylamino group, an isobutylamino group, a sec-butylamino group, a tert-butylamino group, a n-pentylamino group, an isopentylamino group, a sec-pentylamino group, a neopentylamino group, a 1-methylbutylamino group, a 2-methylbutylamino group, a 1,1-dimethylpropylamino group, a 1,2-dimethylpropylamino group, a n-hexylamino group, an isohexylamino group, a 1-methylpentylamino group, a 2-methylpentylamino group, a 3-methylpentylamino group, a 1,1-dimethylbutylamino group, a 1,2-dimethylbutylamino group, a 2,2-dimethylbutylamino group, a 1,3-dimethylbutylamino group, a 2,3-dimethylbutylamino group, a 3,3-dimethylbutylamino group, a 1-ethylbutylamino group, a 2-ethylbutylamino group, a 1,1,2-trimethylpropylamino group, a 1,2,2-trimethylpropylamino group, a 1-ethyl-1-methylpropylamino group and a 1-ethyl-2-methylpropylamino group, and is preferably a methylamino group or the like.

[0036] A "di-C_{1-6} alkylamino group" used herein means an amino group in which two hydrogen atoms are each substituted by the same or different "C_{1-6} alkyl groups" defined above, and specific examples of such a group include a N,N-dimethylamino group, a N,N-diethylamino group, a N,N-di-n-propylamino group, a N,N-di-isopropylamino group, a N,N-di-n-butylamino group, a N,N-di-isobutylamino group, a N,N-di-sec-butylamino group, a N,N-di-tert-butylamino group, a N-ethyl-N-methylamino group, a

N-n-propyl-N-methylamino group, a N-isopropyl-N-methylamino group, a N-n-butyl-N-methylamino group, a N-isobutyl-N-methylamino group, a N-sec-butyl-N-methylamino group and a N-tert-butyl-N-methylamino group, and is preferably a N,N-dimethylamino group or the like.

[0037] A "C_{2-6} acyl group" used herein means a group containing an atomic group obtained by excluding an OH group from a carboxyl group of an aliphatic carboxylic acid having 2 to 6 carbon atoms, and specific examples of such a group include an acetyl group, a propionyl group and a butyloyl group.

[0038] An "oxo group" used herein means a substituent in which an oxygen atom is bonded on a carbon atom or a nitrogen atom, and a specific example of a structure in which an oxygen atom is bonded on a carbon atom includes a carbonyl group, and a specific example of a group in which an oxygen atom is bonded on a nitrogen atom includes N-oxide.

[0039] A "C_{3-5} heteroarylene group" used herein means a bivalent group having 3 to 5 carbon atoms forming a ring that is induced by removing arbitrary 2 hydrogen atoms from a hetero aromatic compound having 1 to 2 hetero atoms as atoms forming the ring, and specific examples of such a group include a furylene group, a thienylene group, a pyrrolylene group, an imidazolylene group, a thiazolylene group, a pyrazolylene group, an oxazolylene group, an isooxazolylene group, an isothiazolylene group, a furazanylene group, a pyridylene group, a pyrazinylene group, a pyridazinylene group, a pyrimidinylene group and the like, and it is preferably a pyridylene group, a pyrazolylene group or a thienylene group.

[0040] A "C_{3-5} nitrogen-containing non-aromatic heterocyclic group" used herein means a monovalent non-aromatic cyclic group having 3 to 5 carbon atoms forming a ring and having 1 to 2 nitrogen atoms among atoms forming the ring, and specific examples of such a group include an azetidinyl group, a pyrrolidinyl group, a pyrazolidinyl group, an imidazolidinyl group, a piperidinyl group, a piperazinyl group, an isooxazolidinyl group, an isothiazolidinyl group, a morpholinyl group, a thiomorpholinyl group and the like.

[0041] A "C_{3-5} nitrogen-containing non-aromatic heterocycle" used herein means a non-aromatic ring having 3 to 5 carbon atoms forming the ring and having 1 to 2 nitrogen atoms among atoms forming the ring, and specific examples of such a group include an azetidine ring, a pyrrolidine ring, a pyrazolidine ring, an imidazolidine ring, a piperidine ring, a piperazine ring, an isooxazolidine ring, an isothiazolidine ring, a morpholine ring, a thiomorpholine ring and the like.

[0042] A "C_{6-10} arylene group" used herein means a bivalent group induced by removing arbitrary two hydrogen atoms from an aromatic hydrocarbon having 6 to 10 carbon atoms, and specific examples of such a group include a phenylene group, a naphthylene group, an indenylene group, an azulenylene group, a heptalenylene group and the like, and it is preferably a phenylene group.

[0043] In formula used herein, n represents 0 to 2. Preferably, n is 0 or 1, and more preferably, n is 0.

[0044] In formula used herein, A represents a C_{6-10} arylene group or a C_{3-5} heteroarylene group, preferably a phenylene group, a thienylene group, a pyridylene group or a pyrazolylene group, and more preferably, a phenylene group.

[0045] In formula used herein, G represents a single bond, an oxygen atom or $-CH_2-$, preferably a single bond or an oxygen atom, and more preferably a single bond.

[0046] In formula used herein, E represents the C_{3-5} nitrogen-containing non-aromatic heterocycle described above, and specifically, for example, an azetidine ring, a pyrrolidine ring, a piperidine ring or a piperazine ring, preferably an azetidine ring or a piperidine ring, and more preferably a piperidine ring.

[0047] In formula used herein, R^1 represents a cyano group, a mono-C_{1-6} alkylamino group, a di-C_{1-6} alkylamino group, a C_{2-6} alkyl group optionally substituted by 1 to 3 halogen atoms, a C_{1-6} alkoxy group optionally substituted by 1 to 3 halogen atoms or one hydroxyl group, a C_{1-6} alkoxy C_{1-6} alkyl group optionally substituted by 1 to 3 halogen atoms, or a C_{1-6} alkoxy C_{1-6} alkoxy C_{1-6} alkoxy group optionally substituted by 1 to 3 halogen atoms. Preferably, it is a C_{1-6} alkoxy group or a C_{1-6} alkoxy C_{1-6} alkoxy group. Specific examples of such a group include a cyano group, a methylamino group, a N,N-dimethylamino group, an ethyl group, a n-propyl group, an isopropyl group, a methoxy group, an ethoxy group, a n-propoxy group, an isopropoxy group, a n-butoxy group, an isobutoxy group, a sec-butoxy group, a n-pentyloxy group, an isopentyloxy group, a n-hexyloxy group, an isohexyloxy group, a monofluoromethoxy group, a difluoromethoxy group, a trifluoromethoxy group, a 2-fluoroethoxy group, a 2,2-difluoroethoxy group, a 3-fluoropropoxy group, a 2-hydroxyethoxy group, a methoxymethyl group, an ethoxymethyl group, a n-propoxymethyl group, an ethoxymethoxy group, a n-propoxymethoxy group, a 2-methoxyethoxy group, a 2-ethoxyethoxy group, a 3-methoxypropoxy group, a monofluoromethoxymethoxy group, a difluoromethoxymethoxy group, a monofluoroethoxymethoxy group, a difluoroethoxymethoxy group, a

monofluoromethoxyethoxy group, a difluoromethoxyethoxy group, a trifluoromethoxyethoxy group, a monofluoroethoxyethoxy group and a difluoroethoxyethoxy group. Preferable examples include a cyano group, a N,N-dimethylamino group, an ethyl group, a methoxy group, an ethoxy group, an isopropoxy group, a 3-fluoropropoxy group, a 2-hydroxyethoxy group, a methoxymethyl group, a 2-methoxyethoxy group, a 2-ethoxyethoxy group and a 3-methoxypropoxy group, among which a methoxy group, a 2-methoxyethoxy group, a 2-ethoxyethoxy group and the like are preferred, and a 2-methoxyethoxy group and a 2-ethoxyethoxy group are more preferred.

[0048] In formula used herein, R^2 represents a hydrogen atom, a halogen atom, a hydroxyl group, a C_{2-6} acyl group optionally substituted by one substituent selected from the group S, a C_{1-6} alkyl group optionally substituted by 1 to 3 halogen atoms, a hydroxy C_{1-6} alkyl group optionally substituted by 1 to 3 halogen atoms, or a C_{3-5} nitrogen-containing non-aromatic heterocyclic group. Here, the group S represents a group consisting of a hydroxyl group, a mono-C_{1-6} alkylamino group, a di-C_{1-6} alkylamino group, a C_{1-6} alkoxy group and a C_{3-5} nitrogen-containing non-aromatic heterocyclic group. Preferably, it is a hydrogen atom, a halogen atom, a hydroxyl group, a C_{1-6} alkyl group or a hydroxy C_{1-6} alkyl group, and more preferably, it is a hydrogen atom, a hydroxyl group, a C_{1-6} alkyl group or a hydroxy C_{1-6} alkyl group. Specific examples of R^2 include a hydrogen atom, a fluorine atom, a chlorine atom, a bromine atom, an iodine atom, a hydroxyl group, a methyl group, an ethyl group, a n-propyl group, an isopropyl group, a n-butyl group, an isobutyl group, a sec-butyl group, a tert-butyl group, a monofluoromethyl group, a difluoromethyl group, a trifluoromethyl group, a 2-fluoroethyl group, a 2,2-difluoroethyl group, a 2,2,2-trifluoroethyl group, a monochloromethyl group, a dichloromethyl group, a trichloromethyl group, a 2-chloroethyl group, a 2,2-dichloroethyl group, a 2,2,2-trichloroethyl group, a 3-fluoropropyl group, a hydroxymethyl group, a 2-hydroxyethyl group, a 1-hydroxyethyl group, a 3-hydroxypropyl group, a 2-hydroxypropyl group, a 1-hydroxypropyl group, a 2-hydroxy-2,2-dimethylethyl group, an azetidinyl group, a pyrrolidinyl group, a piperidinyl group and a piperazinyl group. Preferably, it is a hydrogen atom, a fluorine atom, a hydroxyl group, a methyl group, an ethyl group, a n-propyl group, an isopropyl group, a hydroxymethyl group, a 2-hydroxyethyl group, a 1-hydroxyethyl group, a 3-hydroxypropyl group, a 2-hydroxypropyl group, a 1-hydroxypropyl group, a 2-hydroxy-2,2-dimethylethyl group, an azetidinyl group, a pyrrolidinyl group or a piperidinyl group, and more preferably, it is a methyl group, an ethyl

group or a 2-hydroxyethyl group.

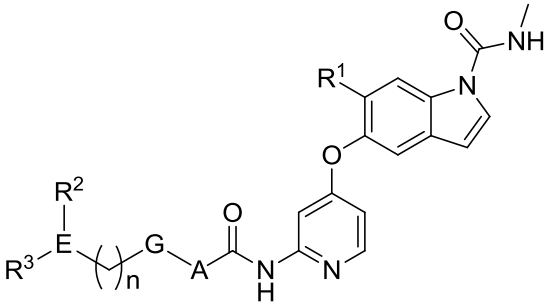
[0049] In formula used herein, R^3 represents a hydrogen atom, an oxo group, a C_{1-6} alkyl group optionally substituted by 1 to 3 halogen atoms, or a C_{1-6} alkoxy group optionally substituted by 1 to 3 halogen atoms. Preferably, it is a hydrogen atom, a C_{1-6} alkyl group or a C_{1-6} alkoxy group. Specifically, it is preferably a hydrogen atom, a methyl group or an ethyl group, and more preferably a hydrogen atom.

[0050] In formula used herein, R^4 represents a C_{1-6} alkyl group. Preferably, it is a methyl group.

[0051] However, if E represents an azetidine ring and R^2 or R^3 is present on a nitrogen atom of the azetidine ring, this R^2 or R^3 does not represent a hydrogen atom. Besides, each of R^2 and R^3 is an atom or a group substituted in an arbitrary position on E, namely, in an arbitrary position on the C_{3-5} nitrogen-containing non-aromatic heterocycle.

[0052] In the following formula (IB),

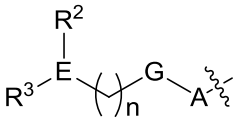
[Chemical Formula 12]



(IB)

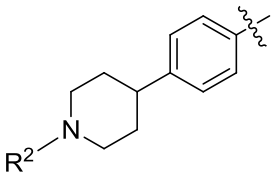
a partial structure represented by the following formula (IV) is preferably a partial structure represented by the following formula (V) or (VI), and more preferably a partial structure presented by formula (V).

[Chemical Formula 13]



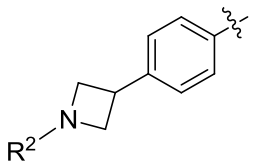
(IV)

[Chemical Formula 14]



(V)

[Chemical Formula 15]



(VI)

[0053] In formula (V), R^2 represents a hydrogen atom, a C_{1-6} alkyl group or a hydroxy C_{2-6} alkyl group, and specific examples include a hydrogen atom, a methyl group, an ethyl group, a propyl group, an isopropyl group, a 2-hydroxyethyl group, a 3-hydroxypropyl group, a 2-hydroxypropyl group, a 2-hydroxy-2,2-dimethylethyl group and the like. It is preferably a methyl group, an ethyl group, a 2-hydroxyethyl group, a 2-hydroxypropyl group or a 2-hydroxy-2,2-dimethylethyl group.

[0054] In formula (VI), R^2 represents a C_{1-6} alkyl group or a hydroxy C_{2-6} alkyl group, and specific examples include a methyl group, an ethyl group, a propyl group, an isopropyl group, a 2-hydroxyethyl group, a 3-hydroxypropyl group, a 2-hydroxypropyl group, a 2-hydroxy-2,2-dimethylethyl group and the like. It is preferably a methyl group, an ethyl group, a 2-hydroxyethyl group, a 2-hydroxypropyl group or a 2-hydroxy-2,2-dimethylethyl group.

[0055] A compound of the present invention is preferably any one of the following compounds or the like or pharmaceutically acceptable salts thereof:

5-((2-(4-(1-Ethylpiperidin-4-yl)benzamide)pyridin-4-yl)oxy)-6-methoxy-N-methyl-1H-indole-1-carboxamide;

6-(2-Methoxyethoxy)-N-methyl-5-((2-(4-(1-methylpiperidin-4-yl)benzamide)pyridin-4-yl)oxy)-1H-indole-1-carboxamide;

5-((2-(4-(1-(2-Hydroxyethyl)piperidin-4-yl)benzamide)pyridin-4-yl)oxy)-6-(2-methoxyethoxy)-N-methyl-1H-indole-1-carboxamide;

6-(2-Ethoxyethoxy)-5-((2-(4-(1-(2-hydroxyethyl)piperidin-4-yl)benzamide)pyridin-4-yl)oxy)-N-methyl-1H-indole-1-carboxamide;

6-(2-Ethoxyethoxy)-5-((2-(4-(1-ethylazetidin-3-yl)benzamide)pyridin-4-yl)oxy)-N-methyl-1H-indole-1-carboxamide.

[0056] Examples of a "salt" used herein include salts with inorganic acids, salts with organic acids, and salts with acidic amino acids, and in particular, pharmaceutically acceptable salts are preferred. Besides, a salt of the compound of the present invention embraces an anhydride of a pharmaceutically acceptable salt thereof and a solvate, such as a hydrate, of the pharmaceutically acceptable salt.

[0057] Preferable examples of a salt with an inorganic acid include salts with hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid and the like, and preferable examples of a salt with an organic acid include salts with acetic acid, succinic acid, fumaric acid, maleic acid, tartaric acid, citric acid, lactic acid, stearic acid, benzoic acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid and the like.

[0058] Preferable examples of a salt with an acidic amino acid include salts with aspartic acid and glutamic acid and the like.

[0059] The compound (IA) of the present invention or the pharmaceutically acceptable salt thereof can be formulated by a general method, and the dosage form can be, for example, an oral formulation (such as a tablet, a granule, a powder, a capsule, a syrup or the like), an injection formulation (for intravenous administration, intramuscular administration, subcutaneous administration, intraperitoneal administration or the like), or an external formulation (such as a transdermal absorbable drug (including an ointment, a patch and the like), an eye dropper, nasal drops, a suppository or the like).

[0060] For producing an oral solid formulation, a vehicle, a binder, a disintegrator, a lubricant, a colorant and the like can be added, if necessary, to the compound (IA) of the present invention or the pharmaceutically acceptable salt thereof, and the resulting mixture can be prepared by a conventional method into tablets, granulates, powders, or capsules. Furthermore, the tablets, granulates, powders, capsules or the like can be coated with a film if necessary.

Examples of the vehicle include lactose, corn starch, crystalline cellulose and the like, examples of the binder include hydroxypropyl cellulose, hydroxypropyl methyl cellulose and the like, examples of the disintegrator include calcium carboxymethylcellulose, sodium croscarmellose and the like, examples of the lubricant include magnesium stearate, calcium stearate and the like, an example of the colorant includes titanium oxide and the like, and examples of a film-coating agent include hydroxypropyl cellulose, hydroxypropyl methyl cellulose, methyl cellulose and the like, but these components are not limited to the aforementioned examples.

The solid formulation such as a tablet, a capsule, a granule or a powder may contain the compound (IA) of the present invention or the pharmaceutically acceptable salt thereof in a content of generally 0.001 to 99.5% by weight, and specifically 0.001 to 90% by weight.

[0061] For producing an injection formulation (for intravenous administration,

intramuscular administration, subcutaneous administration, intraperitoneal administration or the like), a pH adjuster, a buffer, a suspending agent, a solubilizing agent, an antioxidant, a preservative (an antiseptic agent), a tonicity adjusting agent and the like are added, if necessary, to the compound (IA) of the present invention or the pharmaceutically acceptable salt thereof, and the resulting mixture can be prepared into an injection formulation by a conventional method. Furthermore, the resultant can be freeze-dried to be used as a lyophilized product to be dissolved before use.

Examples of the pH adjuster and the buffer include organic acids or inorganic acids and/or pharmaceutically acceptable salts thereof, examples of the suspending agent include methyl cellulose, Polysorbate 80 , sodium carboxymethylcellulose and the like, examples of the solubilizing agent include Polysorbate 80, polyoxyethylene sorbitan monolaurate and the like, an example of the antioxidant includes α-tocopherol and the like, examples of the preservative include methyl paraoxybenzoate, ethyl paraoxybenzoate and the like, and examples of the tonicity adjusting agent include grape sugar, sodium chloride, mannitol and the like, but these components are not limited to the aforementioned examples.

Such an injection formulation may contain the compound (IA) of the present invention or the pharmaceutically acceptable salt thereof in a content of generally 0.000001 to 99.5% by weight, and specifically 0.00001 to 90% by weight.

[0062] For producing an external formulation, a base material is added to the compound (IA) of the present invention or the pharmaceutically acceptable salt thereof, and if necessary, for example, a preservative, a stabilizer, a pH adjuster, an antioxidant, a colorant and the like described above are further added thereto, and the resulting mixture is prepared by a conventional method into, for example, a transdermal absorbable drug (such as an ointment or a patch), an eye dropper, nasal drops, a suppository or the like.

As the base material to be used, various materials usually used for, for example, medicines, quasi-drugs and cosmetics can be used. Specific examples of the material include animal and vegetable oils, mineral oils, ester oils, waxes, emulsifiers, higher alcohols, fatty acids, silicone oils, surfactants, phospholipids, alcohols, polyhydric alcohols, water soluble polymers, clay minerals, purified water and the like.

Such an external formulation can contain the compound (IA) of the present invention or the pharmaceutically acceptable salt thereof in a content of generally 0.000001 to 99.5% by weight, and specifically 0.00001 to 90% by weight.

[0063] A dose of the compound (IA) of the present invention or the pharmaceutically

acceptable salt thereof depends upon the level of symptom severity, the patient's age, sex and weight, the administration form and the kind of salt, a specific kind of disease and the like, and is not especially limited unless it exceeds the maximum dose of the medicine that can be given without causing an unacceptable adverse reaction, and in an adult patient, it is administered, once or dividedly several times per day, at a dose for oral administration of generally approximately 30 μg to 10g, specifically 100 μg to 5 g and more specifically 100 μg to 1 g, or a dose for injection administration of generally approximately 30 μg to 1 g, specifically 100 μg to 500 mg, and more specifically 100 μg to 300 mg.

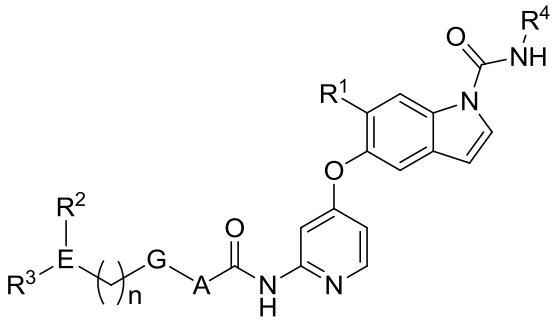
[0064] [General synthesis method]

A production method for the compound (IA) of the present invention will now be described. The compound (IA) of the present invention can be synthesized by using general organic synthesizing means, and some examples of the compound (IA) of the present invention, for example, compounds (1-1), (1-2), (1-3), (1-4), (1-5), (1-6), (1-7), (1-8), (1-9) and (1-10) can be synthesized by methods described in [Production Method 1] or the like described below. If a protective group is used in production methods described herein, known protective groups, for example, as those described in Green's PROTECTIVE GROUP IN ORGANIC CHEMISTRY, fourth edition, JOHN WILEY & SONS, INC. are appropriately selected and introduced, and deprotection can be appropriately performed by a known method.

[0065] [Production Method 1]

Representative production method for compound (IA) of the present invention

[Chemical Formula 16]



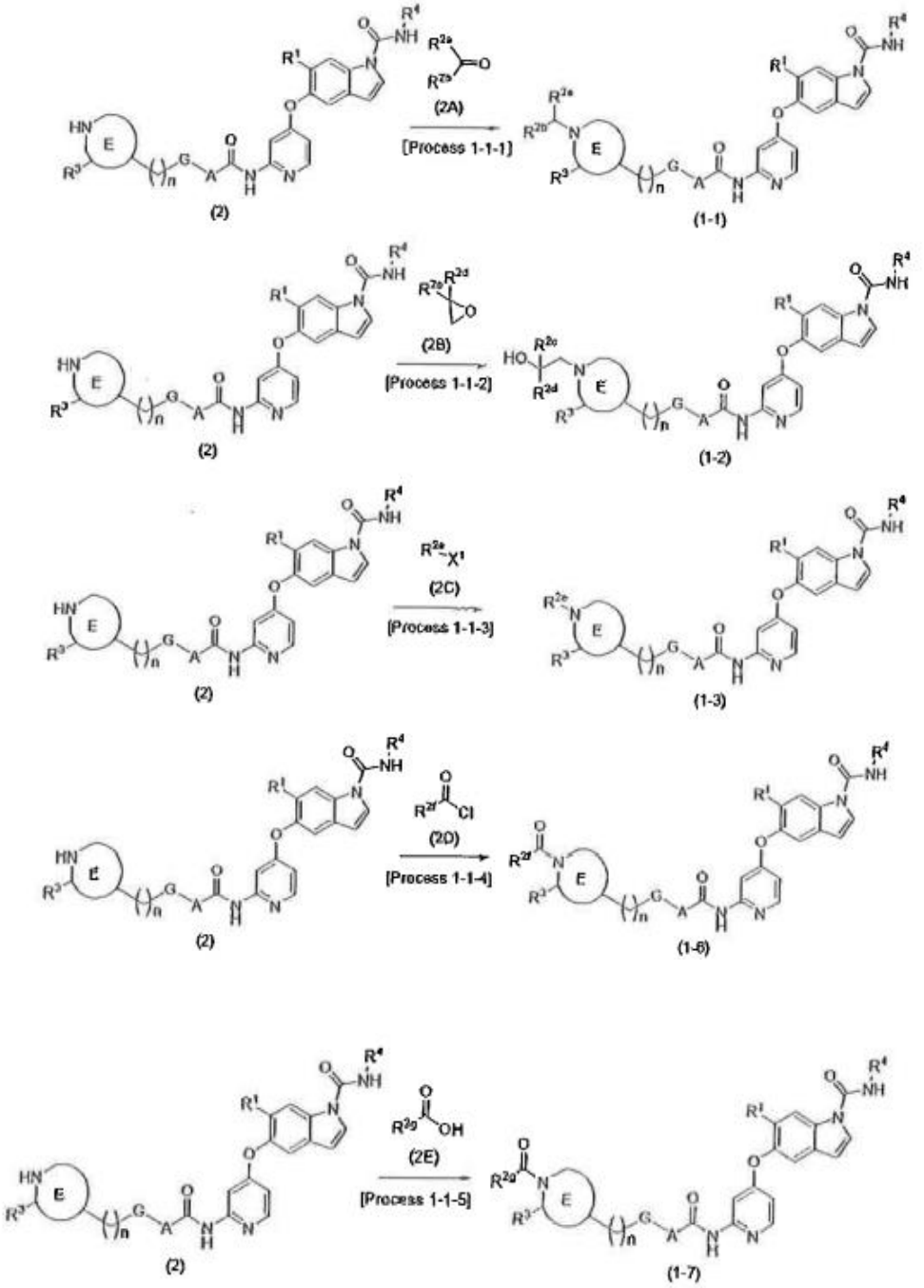
(IA)

wherein R^1, R^2, R^3, A, E, G and n represent the same as defined above.

[0066] [Production Method 1-1]

Production method for compound (1-1), (1-2), (1-3), (1-6) or (1-7)

[Chemical Formula 17]



In the above formula, R^1, R^3 (an oxo group is excluded.), R^4, A, E, G and n represent the same as defined above; R^{2a} and R^{2b} each represent a hydrogen atom, a C_{1-5} alkyl group optionally substituted by 1 to 3 halogen atoms, or a hydroxy C_{1-5} alkyl group optionally substituted by 1 to 3 halogen atoms; R^{2c} and R^{2d} each represent a hydrogen atom or a C_{1-4} alkyl group optionally substituted by 1 to 3 halogen atoms; R^{2e} represents a C_{1-6} alkyl group

optionally substituted by 1 to 3 halogen atoms, or a hydroxy C_{1-6} alkyl group optionally substituted by 1 to 3 halogen atoms, if R^{2e} has a hydroxyl group, the hydroxyl group may be protected by a known suitable protective group; X^1 represents a halogen atom such as a chlorine atom, a bromine atom, or an iodine atom, or a leaving group of sulfonate such as methanesulfonate or p-toluenesulfonate; R^{2f} represents a C_{1-5} alkyl group optionally substituted by a C_{1-6} alkoxy group; R^{2g} represents a hydroxy group, a mono-C_{1-6} alkylamino group or a C_{1-5} alkyl group optionally substituted by a di-C_{1-6} alkylamino group, if R^{2g} has a hydroxyl group or a mono-C_{1-6} alkylamino group, the hydroxyl group or the mono-C_{1-6} alkylamino group may be protected by a known suitable protective group.

[0067] A compound (2) can be also produced by a method described in a production example in any of examples described below, [Production Method 2] or the like.

Compounds (2A), (2B), (2C), (2D) and (2E) can be commercially available products, or can be produced from commercially available products by known methods. Alternatively, these compounds can be produced by methods described in production examples in any of the examples described below or the like. The compound (2A) can be in any form ranging a dimer to a multimer.

[0068] [Process 1-1-1]

In this process, the compound (2) and the compound (2A) are reacted with each other in the presence of a reducing agent to give a compound (1-1). A solvent used in this reaction is not especially limited as long as it dissolves a starting material to some extent and does not inhibit the reaction, and for example, an ether solvent such as tetrahydrofuran, an alcohol solvent such as ethanol, a nitrile solvent such as acetonitrile, carboxylic acid solvent such as acetic acid, an aromatic hydrocarbon solvent such as benzene or toluene, an amide solvent such as N,N-dimethylformamide or N-methylpyrrolidinone, a halogenated hydrocarbon solvent such as dichloromethane or chloroform, water, or a mixed solvent of these can be used. As the reducing agent used in this reaction, a metal hydrogen complex compound such as sodium borohydride, sodium cyanoborohydride or sodium triacetoxyborohydride, or substituted borane such as diborane or a pyridine-borane complex can be used. Besides, a catalytic reduction catalyst such as palladium-carbon can be used under a hydrogen atmosphere. The compound (2A) can be used in an amount of 1 to 10 equivalents to the compound (2), and is preferably used in an amount of 1 to 2 equivalents. The reducing agent can be used in an amount of 1 equivalent or more to the compound (2), and is preferably used in an amount of 1 to 5 equivalents. In this reaction, an acid such as

acetic acid can be added in an amount of 0 to 10 equivalents. The reaction temperature is from –20°C to reflux temperature, and the reaction time is from 10 minutes to 24 hours.

[0069] [Process 1-1-2]

In this process, the compound (2) and the compound (2B) are reacted with each other to give a compound (1-2). A solvent used in this reaction is not especially limited as long as it dissolves a starting material to some extent and does not inhibit the reaction, and for example, an ether solvent such as tetrahydrofuran, an alcohol solvent such as ethanol, an amide solvent such as N,N-dimethylformamide or N-methylpyrrolidinone, a nitrile solvent such as acetonitrile, an aromatic hydrocarbon solvent such as toluene, a halogenated hydrocarbon solvent such as dichloromethane or chloroform, or a mixed solvent of these can be used. In this reaction, alkyl amine such as triethyl amine, aromatic amine such as pyridine, or an inorganic base such as potassium carbonate can be used as a base. The compound (2B) can be used in an amount of 1 equivalent or more to the compound (2), and is preferably used in an amount of 1 to 10 equivalents. The base can be used in an amount of 0 to 10 equivalents to the compound (2). The reaction temperature is from 0°C to 200°C, and the reaction time is from 10 minutes to 24 hours.

[0070] [Process 1-1-3]

In this process, the compound (2) and the compound (2C) are reacted with each other to give a compound (1-3). A solvent used in this reaction is not especially limited as long as it dissolves a starting material to some extent and does not inhibit the reaction, and for example, an ether solvent such as tetrahydrofuran, a nitrile solvent such as acetonitrile, an aromatic hydrocarbon solvent such as toluene, a halogenated hydrocarbon solvent such as dichloromethane or chloroform, an amide solvent such as N,N-dimethylformamide or N-methylpyrrolidinone, dimethylsulfoxide, or a mixed solvent of these can be used. In this reaction, alkyl amine such as triethyl amine, aromatic amine such as pyridine, or an inorganic base such as sodium hydrogen carbonate, potassium carbonate or cesium carbonate can be used as a base. The compound (2C) can be used in an amount of 1 equivalent or more to the compound (2), and is preferably used in an amount of 1 to 3 equivalents. The base can be used in an amount of 1 to 10 equivalents to the compound (2). The reaction temperature is from 0°C to reflux temperature, and the reaction time is from 10 minutes to 24 hours. If the hydroxyl group of R^{2e} is protected, it can be deprotected by a known method.

[0071] [Process 1-1-4]

In this process, the compound (2) and the compound (2D) are reacted with each

other to give the compound (1-6). A solvent used in this reaction is not especially limited as long as it dissolves a starting material to some extent and does not inhibit the reaction, and for example, an ester solvent such as ethyl acetate, an ether solvent such as tetrahydrofuran, a nitrile solvent such as acetonitrile, an aromatic hydrocarbon solvent such as toluene, a halogenated hydrocarbon solvent such as dichloromethane or chloroform, an amide solvent such as N,N-dimethylformamide or N-methylpyrrolidinone, or a mixed solvent of these can be used. In this reaction, alkyl amine such as triethylamine, aromatic amine such as pyridine, or an inorganic base such as sodium hydrogen carbonate, potassium carbonate or cesium carbonate can be used as a base. The compound (2D) can be used in an amount of 1 equivalent or more to the compound (2), and is preferably used in an amount of 1 to 3 equivalents. The base can be used in an amount of 1 to 10 equivalents to the compound (2). The reaction temperature is from 0°C to reflux temperature, and the reaction time is from 10 minutes to 24 hours.

[0072] [Process 1-1-5]

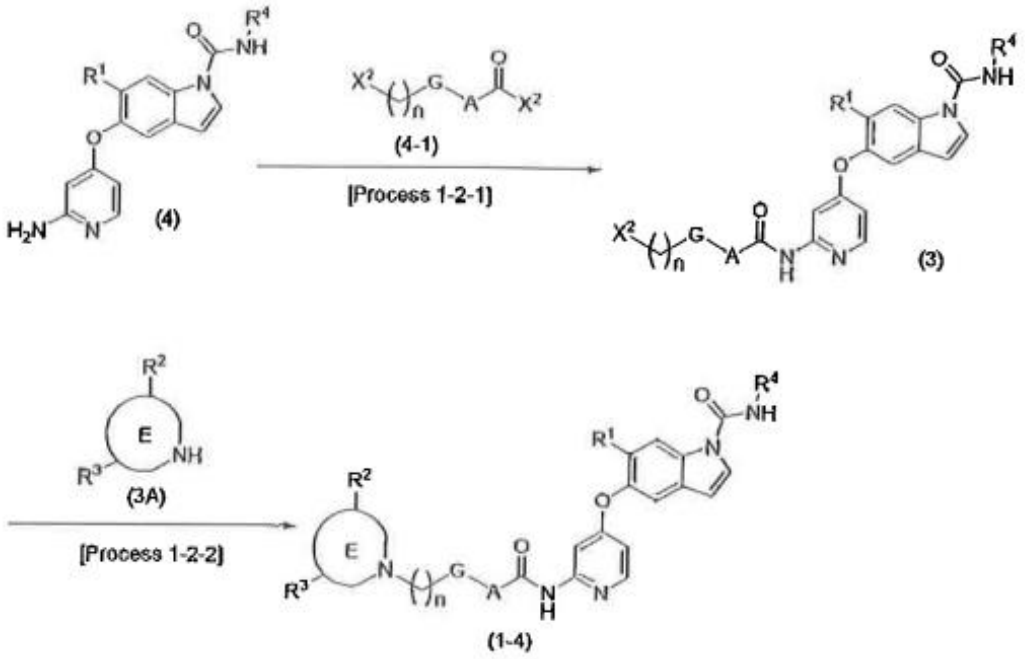
In this process, the compound (2) and the compound (2E) are reacted with each other by using a condensation agent to give the compound (1-7). A solvent used in this reaction is not especially limited as long as it dissolves a starting material to some extent and does not inhibit the reaction, and for example, an ether solvent such as tetrahydrofuran, an ester solvent such as ethyl acetate, a nitrile solvent such as acetonitrile, an aromatic hydrocarbon solvent such as toluene, a halogenated hydrocarbon solvent such as dichloromethane or chloroform, an amide solvent such as N,N-dimethylformamide or N-methylpyrrolidinone, dimethylsulfoxide, or a mixed solvent of these can be used. In this reaction, a condensation agent such as O-(7-azabenzotriazole-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate or 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride can be used. Furthermore, 1-hydroxybenzotriazole or the like can be used as an additive. In this reaction, alkyl amine such as triethyl amine or N,N-diisopropylethylamine, aromatic amine such as 4-dimethylaminopyridine, or an inorganic base such as potassium carbonate or cesium carbonate can be used as a base, or a combination of these bases can be used. The compound (2E) can be used in an amount of 1 equivalent or more to the compound (2), and is preferably used in an amount of 1 to 3 equivalents. The condensation agent can be used in an amount of the same equivalents as the compound (2E), and the base can be used in an amount of 1 to 10 equivalents to the compound (2). The reaction temperature is from 0°C

to reflux temperature, and the reaction time is from 10 minutes to 24 hours. If R^{2g} is protected by a hydroxyl group or a mono-C_{1-6} alkylamino group, it can be deprotected by a known method.

[0073] [Production Method 1-2]

Production method for compound (1-4)

[Chemical Formula 18]



In the above formula, R^1, R^2, R^3, R^4, A, E, G and n represent the same as defined above; and X^2 represents a halogen atom such as a chorine atom or a bromine atom, or a leaving group of sulfonate such as methanesulfonate or a p-toluenesulfonate.

Compounds (3) and (4) can be also produced by methods described in [Production Method 3], production examples of any of the examples described below or the like.

Compounds (3A) and (4-1) can be commercially available products, or can be produced from commercially available products by known methods. Alternatively, these compounds can be produced by methods described in [Production Method 6], production examples of any of the examples described below or the like.

[0074] [Process 1-2-1]

In this process, the compound (4) and the compound (4-1) are reacted with each other to give the compound (3). A solvent used in this reaction is not especially limited as long as it dissolves a starting material to some extent and does not inhibit the reaction, and for example, an ether solvent such as tetrahydrofuran, an ester solvent such as ethyl acetate, a

nitrile solvent such as acetonitrile, an aromatic hydrocarbon solvent such as toluene, a halogenated hydrocarbon solvent such as dichloromethane or chloroform, an amide solvent such as N,N-dimethylformamide or N-methylpyrrolidinone, or a mixed solvent of these can be used. In this reaction, alkyl amine such as triethyl amine or N,N-diisopropylethylamine, aromatic amine such as 4-dimethylaminopyridine, or an inorganic base such as potassium carbonate or cesium carbonate can be used as a base, or a combination of these bases can be used. The compound (4-1) can be used in an amount of 1 equivalent or more to the compound (4), and is preferably used in an amount of 2 to 3 equivalents. The base can be used in an amount of 1 to 10 equivalents to the compound (4). The reaction temperature is from 0°C to reflux temperature, and the reaction time is from 10 minutes to 24 hours. In this process, a diacyl form resulting from a reaction of 2 equivalents of the compound (4-1) may be produced, but this can be directly used in the following reaction.

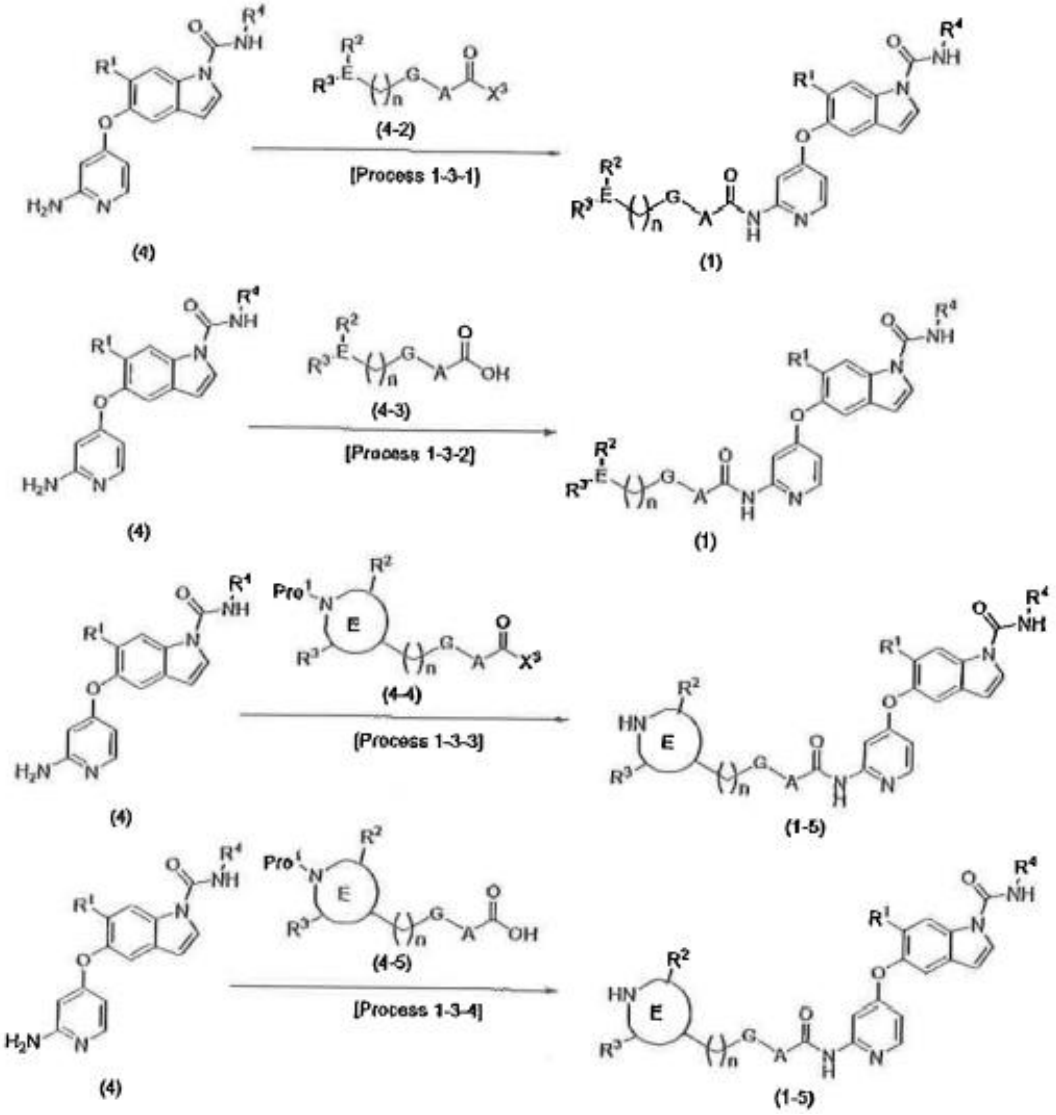
[0075] [Process 1-2-2]

In this process, the compound (3) and the compound (3A) are reacted with each other to give a compound (1-4). A solvent used in this reaction is not especially limited as long as it dissolves a starting material to some extent and does not inhibit the reaction, and for example, an ether solvent such as tetrahydrofuran, an aromatic hydrocarbon solvent such as toluene, a halogenated hydrocarbon solvent such as dichloromethane or chloroform, an amide solvent such as N,N-dimethylformamide or N-methylpyrrolidinone, dimethylsulfoxide, or a mixed solvent of these can be used. In this reaction, alkyl amine such as triethyl amine or N,N-diisopropylethylamine, or an inorganic base such as potassium carbonate or cesium carbonate can be used as a base. The compound (3A) can be used in an amount of 1 equivalent or more to the compound (3), and is preferably used in an amount of 1 to 10 equivalents. The base can be used in an amount of 1 to 10 equivalents to the compound (3). The reaction temperature is from 0°C to reflux temperature, and the reaction time is from 10 minutes to 24 hours.

[0076] [Production Method 1-3]

Production method for compound (1) or (1-5)

[Chemical Formula 19]



In the above formula, R^1, R^2, R^3, R^4, A, E, G and n represent the same as defined above; X^3 represents a halogen atom such as a chlorine atom or a bromine atom; and Pro^1 represents a known protective group for a nitrogen atom such as a tert-butoxycarbonyl group.

The compound (4) can be produced by a method described in a production example of any of the examples described below, [Production Method 3] or the like.

Compounds (4-2), (4-3), (4-4) and (4-5) can be commercially available products, or can be produced from commercially available products by known methods. These compounds can be also produced by methods described in [Production Method 5], production examples of any of the examples described below or the like.

[0077] [Process 1-3-1 or 1-3-3]

In this process, the compound (4) and the compound (4-2) or (4-4) are reacted with each other to give the compound (1) or (1-5) respectively. A solvent used in this reaction is not especially limited as long as it dissolves a starting material to some extent and does not inhibit the reaction, and for example, an ether solvent such as tetrahydrofuran, an ester solvent such as ethyl acetate, a nitrile solvent such as acetonitrile, an aromatic hydrocarbon solvent such as toluene, a halogenated hydrocarbon solvent such as dichloromethane or chloroform, an amide solvent such as N,N-dimethylformamide or N-methylpyrrolidinone, or a mixed solvent of these can be used. In this reaction, alkyl amine such as triethyl amine or N,N-diisopropylethylamine, aromatic amine such as 4-dimethylaminopyridine, or an inorganic base such as potassium carbonate or cesium carbonate can be used as a base, or a combination of these bases can be used. The compound (4-2) or (4-4) can be used in an amount of 1 equivalent or more to the compound (4), and is preferably used in an amount of 2 to 3 equivalents. The base can be used in an amount of 1 to 10 equivalents to the compound (4). The reaction temperature is from 0°C to reflux temperature, and the reaction time is from 10 minutes to 24 hours. In this process, a diacyl form resulting from a reaction of 2 equivalents of the compound (4-2) or (4-4) may be produced. In this case, the diacyl form can be changed into a desired monoacyl form by a treatment with ammonia or primary or secondary alkyl amine such as methyl amine or piperidine.

In process 1-3-3, a protective group for a nitrogen atom can be subsequently removed by a known method. If Pro^1 is, for example, a tert-butoxycarbonyl group, the deprotection can be performed by using a solvent not inhibiting the reaction, for example, a halogenated hydrocarbon solvent such as dichloromethane, an ester solvent such as ethyl acetate, an alcohol solvent such as methanol, or a mixed solvent of these, and by using an acid such as trifluoroacetic acid or hydrochloric acid.

[0078] [Process 1-3-2 or 1-3-4]

In this process, the compound (4) and the compound (4-3) or (4-5) are reacted with each other by using a condensation agent to give the compound (1) or (1-5). A solvent used in this reaction is not especially limited as long as it dissolves a starting material to some extent and does not inhibit the reaction, and for example, an ether solvent such as tetrahydrofuran, an ester solvent such as ethyl acetate, a nitrile solvent such as acetonitrile, an aromatic hydrocarbon solvent such as toluene, a halogenated hydrocarbon solvent such as dichloromethane or chloroform, an amide solvent such as N,N-dimethylformamide or

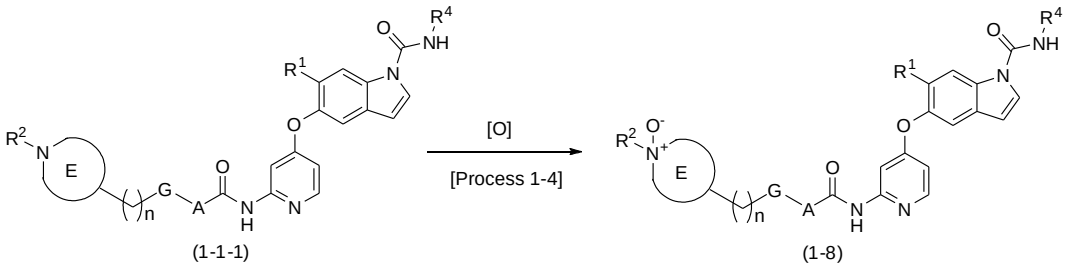
N-methylpyrrolidinone, dimethylsulfoxide, or a mixed solvent of these can be used. In this reaction, a condensation agent such as O-(7-azabenzotriazole-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate or 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride can be used. Furthermore, 1-hydroxybenzotriazole or the like can be used as an additive. In this reaction, alkyl amine such as triethyl amine or N,N-diisopropylethylamine, aromatic amine such as 4-dimethylaminopyridine, or an inorganic base such as potassium carbonate or cesium carbonate can be used as a base, or a combination of these bases can be used. The compound (4-3) or (4-5) can be used in an amount of 1 equivalent or more to the compound (4), and is preferably used in an amount of 2 to 3 equivalents. The condensation agent can be used in an amount of the same equivalents as the compound (4-3) or (4-5), and the base can be used in an amount of 1 to 10 equivalents to the compound (4). The reaction temperature is from 0°C to reflux temperature, and the reaction time is from 10 minutes to 24 hours. In this process, a diacyl form resulting from a reaction of 2 equivalents of the compound (4-3) or (4-5) may be produced. In this case, the diacyl form can be changed into a desired monoacyl form by a treatment with ammonia or primary or secondary alkyl amine such as methyl amine or piperidine. If R^2 is protected by a known protective group, the protective group is deprotected by a known method.

In process 1-3-4, a protective group for a nitrogen atom can be subsequently removed by a known method. If Pro^1 is, for example, a tert-butoxycarbonyl group, the deprotection can be performed by using a solvent not inhibiting the reaction, for example, a halogenated hydrocarbon solvent such as dichloromethane, an ester solvent such as ethyl acetate, an alcohol solvent such as methanol, or a mixed solvent of these, and by using an acid such as trifluoroacetic acid or hydrochloric acid.

[0079] [Production Method 1-4]

Production method for compound (1-8)

[Chemical Formula 20]



In the above formula, R^1, R^2, R^4, A, E, G and n represent the same as defined above.

A compound (1-1-1) can be also produced by a method described in a production example in any of examples described below, [Production Method 1-1] or the like.

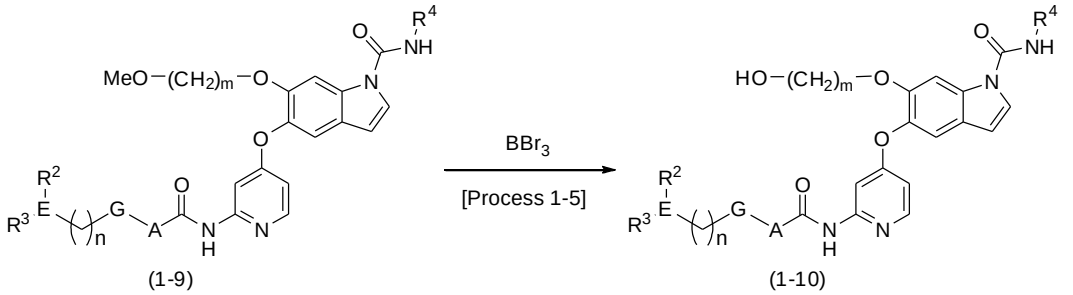
[0080] [Process 1-4]

In this process, the compound (1-1-1) and an oxidizing agent are reacted with each other to give the compound (1-8). A solvent used in this reaction is not especially limited as long as it dissolves a starting material to some extent and does not inhibit the reaction, and for example, a halogenated hydrocarbon solvent such as dichloromethane or chloroform, an alcohol solvent such as methanol or t-butanol, an organic acid such as acetic acid, or a mixed solvent of these can be used. In this reaction, hydrogen peroxide water, an organic peroxide, or an organic peroxy acid such as 3-chloroperoxybenzoic acid can be used as the oxidizing agent. The oxidizing agent can be used in an amount of 0.5 to 10 equivalents to the compound (1-1-1). The reaction temperature is from 0°C to reflux temperature, and the reaction time is from 10 minutes to 24 hours.

[0081] [Production Method 1-5]

Production method for compound (1-10)

[Chemical Formula 21]



In the above formula, R^2, R^4, A, E, G and n represent the same as defined above; and m represents an integer of 2 to 6.

The compound (1-9) can be also produced by a method described in a production example in any of examples described below, [Production Method 1-1], [Production Method 1-2], [Production Method 1-3] or the like.

[0082] [Process 1-5]

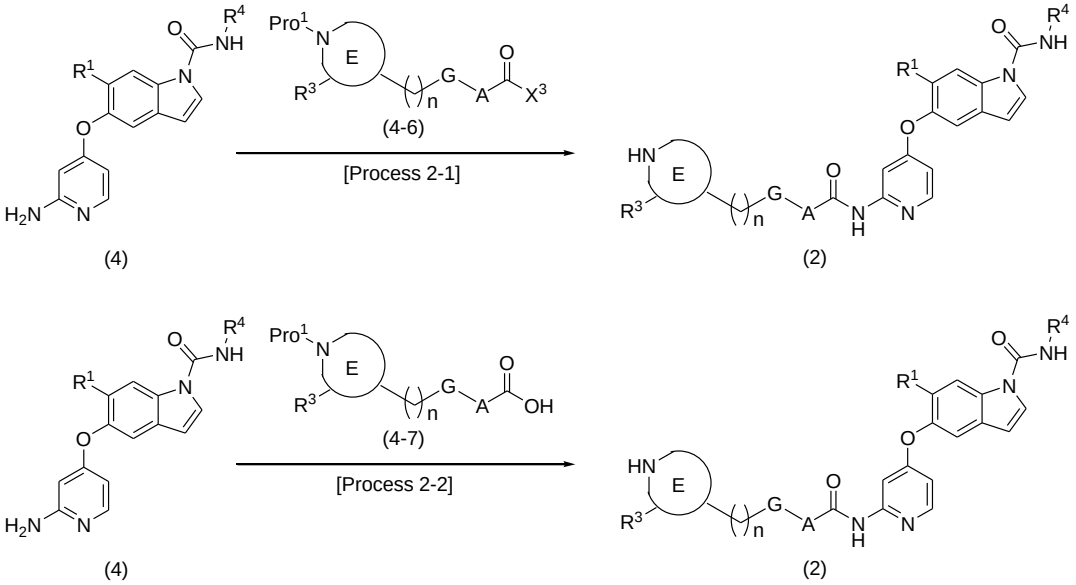
In this process, the compound (1-9) and boron tribromide are reacted with each other to give the compound (1-10). A solvent used in this reaction is not especially limited as long as it dissolves a starting material to some extent and does not inhibit the reaction, and

for example, a halogenated hydrocarbon solvent such as dichloromethane or chloroform can be used. The boron tribromide used in this reaction can be used in an amount of 1 to 10 equivalents to the compound (1-9). The reaction temperature is from –20°C to reflux temperature, and the reaction time is from 10 minutes to 24 hours.

[0083] [Production Method 2]

Production method for compound (2)

[Chemical Formula 22]



In the above formula, R^1, R^3, R^4, A, E, G and n represent the same as defined above; X^3 represents a halogen atom such as a chlorine atom or a bromine atom; and Pro^1 represents a known protective group for a nitrogen atom such as a tert-butoxycarbonyl group.

Compounds (4-6) and (4-7) can be commercially available products, or can be produced from commercially available products by known methods. These compounds can be also produced by methods described in production examples of any of the examples described below or the like. Compound (4-6) can be also produced by methods described in [Production Method 5] or the like.

[0084] [Process 2-1]

In this process, the compound (4) and the compound (4-6) are reacted with each other to give the compound (2). A solvent used in this reaction is not especially limited as long as it dissolves a starting material to some extent and does not inhibit the reaction, and for example, an ether solvent such as tetrahydrofuran, an ester solvent such as ethyl acetate, a nitrile solvent such as acetonitrile, an aromatic hydrocarbon solvent such as toluene, a

halogenated hydrocarbon solvent such as dichloromethane or chloroform, an amide solvent such as N,N-dimethylformamide or N-methylpyrrolidinone, or a mixed solvent of these can be used. In this reaction, alkyl amine such as triethyl amine or N,N-diisopropylethylamine, aromatic amine such as 4-dimethylaminopyridine, or an inorganic base such as potassium carbonate or cesium carbonate can be used as a base, or a combination of these bases can be used. The compound (4-6) can be used in an amount of 1 equivalent or more to the compound (4), and is preferably used in an amount of 2 to 3 equivalents. The base can be used in an amount of 1 to 10 equivalents to the compound (4). The reaction temperature is from 0°C to reflux temperature, and the reaction time is from 10 minutes to 24 hours. In this process, a diacyl form resulting from a reaction of 2 equivalents of the compound (4-6) may be produced. In this case, the diacyl form can be changed into a desired monoacyl form by a treatment with ammonia or primary or secondary alkyl amine such as methyl amine or piperidine. A protective group for a nitrogen atom can be subsequently removed by a known method. If Pro^1 is, for example, a tert-butoxycarbonyl group, the deprotection can be performed by using a solvent not inhibiting the reaction, for example, a halogenated hydrocarbon solvent such as dichloromethane, an ester solvent such as ethyl acetate, an alcohol solvent such as methanol, or a mixed solvent of these, and by using an acid such as trifluoroacetic acid or hydrochloric acid.

[0085] [Process 2-2]

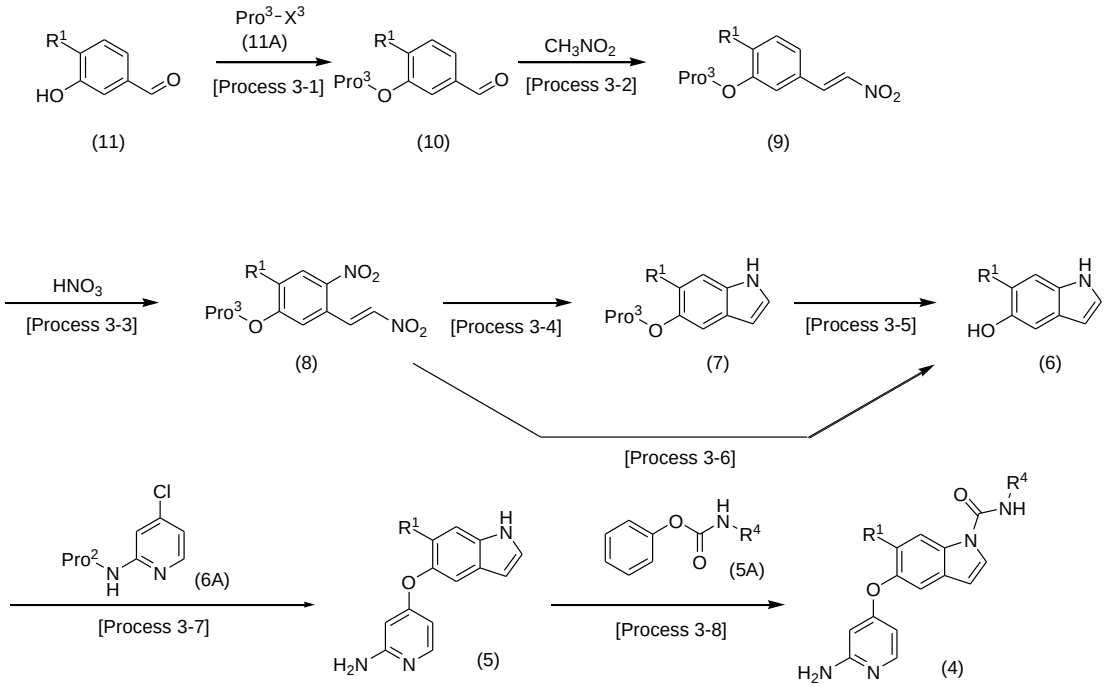
In this process, the compound (4) and the compound (4-7) are reacted with each other to give the compound (2). A solvent used in this reaction is not especially limited as long as it dissolves a starting material to some extent and does not inhibit the reaction, and for example, an ether solvent such as tetrahydrofuran, an ester solvent such as ethyl acetate, a nitrile solvent such as acetonitrile, an aromatic hydrocarbon solvent such as toluene, a halogenated hydrocarbon solvent such as dichloromethane or chloroform, an amide solvent such as N,N-dimethylformamide or N-methylpyrrolidinone, dimethylsulfoxide, or a mixed solvent of these can be used. In this reaction, a condensation agent such as O-(7-azabenzotriazole-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate or 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride can be used. Furthermore, 1-hydroxybenzotriazole or the like can be used as an additive. In this reaction, alkyl amine such as triethyl amine or N,N-diisopropylethylamine, aromatic amine such as 4-dimethylaminopyridine, or an inorganic base such as potassium carbonate or cesium carbonate can be used as a base, or a combination of these bases can be used. The

compound (4-7) can be used in an amount of 1 equivalent or more to the compound (4), and is preferably used in an amount of 2 to 3 equivalents. The base can be used in an amount of 1 to 10 equivalents to the compound (4). The reaction temperature is from 0°C to reflux temperature, and the reaction time is from 10 minutes to 24 hours. In this process, a diacyl form resulting from a reaction of 2 equivalents of the compound (4-7) may be produced. In this case, the diacyl form can be changed into a desired monoacyl form by a treatment with ammonia or primary or secondary alkyl amine such as methyl amine or piperidine. A protective group for a nitrogen atom can be subsequently removed by a known method. If Pro^1 is, for example, a tert-butoxycarbonyl group, the deprotection can be performed by using a solvent not inhibiting the reaction, for example, a halogenated hydrocarbon solvent such as dichloromethane, an ester solvent such as ethyl acetate, an alcohol solvent such as methanol, or a mixed solvent of these, and by using an acid such as trifluoroacetic acid or hydrochloric acid.

[0086] [Production Method 3]

Production method for compound (4)

[Chemical Formula 23]



In the above formula, R^1, R^4 represents the same as defined above; Pro^2 represents a protective group for a nitrogen atom, such as an acetyl group; Pro^3 represents a protective group for a phenolic oxygen atom, such as a benzyl group; and X^3 represents a halogen atom

such as a chlorine atom or a bromine atom.

Compounds (7), (8), (9), (10) and (11) can be commercially available products, or can be produced from commercially available products by known methods. These compounds can be also produced by methods described in production examples of any of the examples described below. Compounds (5) and (6) can be also produced by methods described in production examples of any of the examples described below or the like.

Compounds (5A), (6A) and (11A) can be commercially available products, or can be produced from commercially available products by known methods. Alternatively, these compounds can be produced by methods described in production examples of any of the examples described below or the like.

[0087] [Process 3-1]

In this process, the compound (11) and the compound (11A) are reacted with each other to give the compound (10). A solvent used in this reaction is not especially limited as long as it dissolves a starting material to some extent and does not inhibit the reaction, and for example, an ether solvent such as tetrahydrofuran, an alcohol solvent such as ethanol, a nitrile solvent such as acetonitrile, a ketone solvent such as acetone, a halogenated hydrocarbon solvent such as dichloromethane, an amide solvent such as N,N-dimethylformamide or N-methylpyrrolidinone, dimethylsulfoxide, or a mixed solvent of these can be used. In this reaction, the compound (11A) is used in an amount of 1 to 5 equivalents to the compound (11), and 1 to 5 equivalents of a base, such as sodium hydrogen carbonate, potassium carbonate, sodium methoxide, sodium hydride or diisopropylethylamine can be added. Besides, sodium iodide or potassium iodide can be added as an additive. The reaction temperature is from −20°C to reflux temperature, and the reaction time is from 10 minutes to 24 hours.

[0088] [Process 3-2]

In this process, the compound (10) and nitromethane are reacted with each other to give the compound (9). A solvent used in this reaction is not especially limited as long as it dissolves a starting material to some extent and does not inhibit the reaction, and for example, an alcohol solvent such as methanol, an organic acid solvent such as acetic acid, or a mixed solvent of these can be used. In this reaction, nitromethane is used in an amount of 1 to 10 equivalents, and 0.1 to 10 equivalents of ammonium acetate, ethylenediamine-N,N'-diacetic acid or the like can be added as an additive. The reaction temperature is from 0°C to reflux temperature, and the reaction time is from 10 minutes to 100 hours.

[0089] [Process 3-3]

In this process, the compound (9) is nitrated to give the compound (8). A solvent used in this reaction is not especially limited as long as it dissolves a starting material to some extent and does not inhibit the reaction, and for example, a halogenated hydrocarbon solvent such as dichloromethane, an organic acid solvent such as acetic acid, sulfuric acid, or a mixed solvent of these can be used. In this reaction, fuming nitric acid, concentrated nitric acid or nitric acid is used, and acetic anhydride or the like can be added as an additive. The nitric acid or the like used in this reaction may be in an amount of 1 to 100 equivalents to the compound (9). The reaction temperature is from −20°C to reflux temperature, and the reaction time is from 10 minutes to 100 hours.

[0090] [Process 3-4]

In this process, the compound (8) is cyclized to give the compound (7). A solvent used in this reaction is not especially limited as long as it dissolves a starting material to some extent and does not inhibit the reaction, and for example, an ether solvent such as tetrahydrofuran, an alcohol solvent such as ethanol, an aromatic hydrocarbon solvent such as benzene or toluene, a hydrocarbon solvent such as cyclohexane, water, or a mixed solvent of these can be used. In this reaction, a heavy metal such as iron or zinc is used, and an acid such as acetic acid, a salt such as ammonium chloride, a base such as sodium hydroxide, an inorganic compound such as silica gel or a mixture of these can be added as an additive. The heavy metal such as iron used in this reaction may be in an amount of 5 to 20 equivalents to the compound (8). The reaction temperature is from 0°C to reflux temperature, and the reaction time is from 10 minutes to 24 hours.

[0091] [Process 3-5]

In this process, Pro^3 of the compound (7) is deprotected to give the compound (6). Pro^3 can be deprotected by a known method, and if Pro^3 is benzyl, a solvent used in this reaction is not especially limited as long as it dissolves a starting material to some extent and does not inhibit the reaction, and for example, an ether solvent such as tetrahydrofuran, an alcohol solvent such as ethanol, an aromatic hydrocarbon solvent such as benzene or toluene, acetic acid, water, or a mixed solvent of these can be used. This reaction can be performed under a hydrogen atmosphere with a catalytic reduction catalyst such as palladium-carbon used as a catalyst. The pressure of the hydrogen can be from normal pressure to 20 atm, and the catalyst can be used in an amount of 0.001 to 1 equivalent to the compound (7). Besides, an acid such as hydrochloric acid can be added. The reaction temperature is from

0°C to reflux temperature, and the reaction time is from 10 minutes to 24 hours.

[0092] [Process 3-6]

In this process, the compound (8) is cyclized to give the compound (6). A solvent used in this reaction is not especially limited as long as it dissolves a starting material to some extent and does not inhibit the reaction, and for example, an ether solvent such as tetrahydrofuran, an alcohol solvent such as methanol, an aromatic hydrocarbon solvent such as benzene or toluene, acetic acid, water, or a mixed solvent of these can be used. This reaction can be performed under a hydrogen atmosphere with a catalytic reduction catalyst such as palladium-carbon used as a catalyst. The pressure of the hydrogen can be from normal pressure to 20 atm, and the catalyst can be used in an amount of 0.001 to 1 equivalent to the compound (8). An acid such as hydrochloric acid can be added as an additive. The reaction temperature is from 0°C to reflux temperature, and the reaction time is from 10 minutes to 24 hours.

[0093] [Process 3-7]

In this process, the compound (6) and the compound (6A) are reacted with each other to give the compound (5). A solvent used in this reaction is not especially limited as long as it dissolves a starting material to some extent and does not inhibit the reaction, and for example, an amide solvent such as N,N-dimethylformamide or N-methylpyrrolidinone, dimethylsulfoxide, or a mixed solvent of these can be used. In this reaction, a base such as potassium carbonate, cesium carbonate or potassium tert-butoxide can be used as a base. The base can be used in an amount of 1 to 10 equivalents to the compound (6), and is preferably used in an amount of 1 to 2 equivalents. The reaction temperature is from 0°C to reflux temperature, and the reaction time is from 10 minutes to 24 hours. Pro^2 can be deprotected by a known method, and if Pro^2 is an acetyl group, it can be deprotected by using a solvent not inhibiting the reaction, such as an alcohol solvent like methanol, and by using a base such as potassium carbonate, sodium hydroxide or sodium methoxide, or it can be deprotected by using a solvent not inhibiting the reaction, such as an ether solvent like 1,4-dioxane, and by using an acid such as hydrochloric acid. Alternatively, this process can be performed by using a compound not protected by Pro^2 as the compound (6A).

[0094] [Process 3-8]

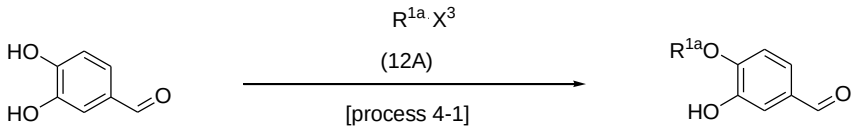
In this process, the compound (5) and the compound (5A) are reacted with each other to give the compound (4). A solvent used in this reaction is not especially limited as long as it dissolves a starting material to some extent and does not inhibit the reaction, and for

example, an ether solvent such as tetrahydrofuran, an amide solvent such as N,N-dimethylformamide or N-methylpyrrolidinone, dimethylsulfoxide, or a mixed solvent of these can be used. In this reaction, a base such as sodium hydroxide or potassium tert-butoxide can be used as a base. The compound (5A) can be used in an amount of 1 equivalent or more to the compound (5), and is preferably used in an amount of 1 to 2 equivalents. The base can be used in an amount of 1 to 2 equivalents to the compound (5). The reaction temperature is from –20°C to reflux temperature, and the reaction time is from 10 minutes to 24 hours.

[0095] [Production Method 4]

Production method for compound (11-1)

[Chemical Formula 24]



(12) (11-1)

In the above formula, R^{1a} represents a C_{1-6} alkyl group optionally substituted by 1 to 3 halogen atoms, or a C_{1-6} alkoxy C_{1-6} alkyl group optionally substituted by 1 to 3 halogen atoms; and X^3 represents a leaving group of a halogen atom such as a bromine atom or an iodine atom.

A compound (12) can be a commercially available product, or can be produced from a commercially available product by a known method.

A compound (12A) can be a commercially available product, or can be produced from a commercially available product by a known method.

[0096] [Process 4-1]

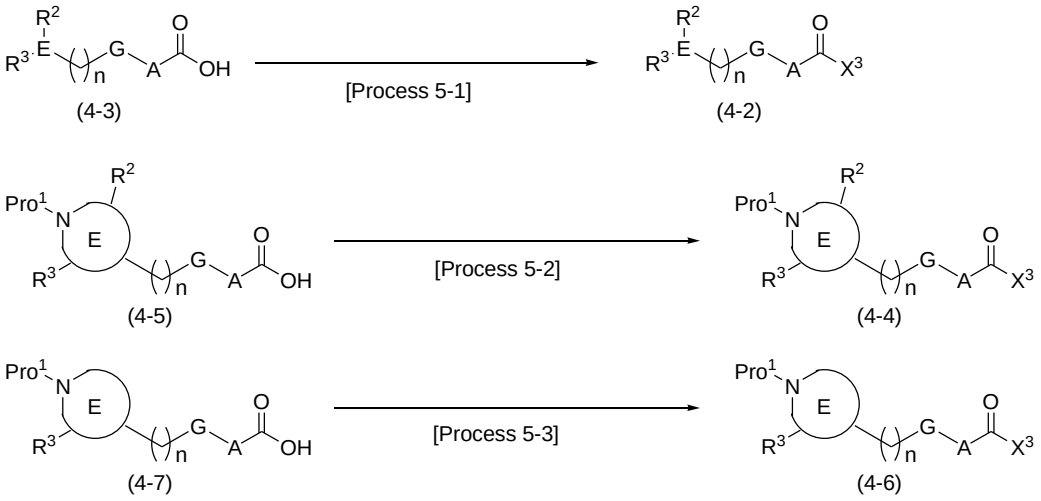
In this process, the compound (12) and the compound (12A) are reacted with each other to give a compound (11-1). A solvent used in this reaction is not especially limited as long as it dissolves a starting material to some extent and does not inhibit the reaction, and for example, an ether solvent such as tetrahydrofuran, an alcohol solvent such as ethanol, a nitrile solvent such as acetonitrile, an amide solvent such as N,N-dimethylformamide or N-methylpyrrolidinone, dimethylsulfoxide, or a mixed solvent of these can be used. In this reaction, the compound (12A) is used in an amount of 0.5 to 1.5 equivalents to the compound (12), and 0.5 to 1.5 equivalents of a base such as sodium hydrogen carbonate, potassium carbonate, sodium methoxide or sodium hydride can be added as an additive.

The reaction temperature is from 0°C to reflux temperature, and the reaction time is from 10 minutes to 100 hours.

[0097] [Production Method 5]

Production method for compound (4-2), (4-4) or (4-6)

[Chemical Formula 25]



In the above formula, R^2, R^3, A, E, G and n represent the same as defined above; X^3 represents a halogen atom such as a chlorine atom or a bromine atom; and Pro^1 represents a known protective group for a nitrogen atom such as a tert-butoxycarbonyl group.

Compounds (4-3), (4-5) and (4-7) can be commercially available products, or can be produced from commercially available products by known methods. Alternatively, these compounds can be also produced by methods described in production examples in any of the examples described below or a method described in [Production Method 7], [Production Method 9] or the like.

[0098] [Process 5-1, 5-2 or 5-3]

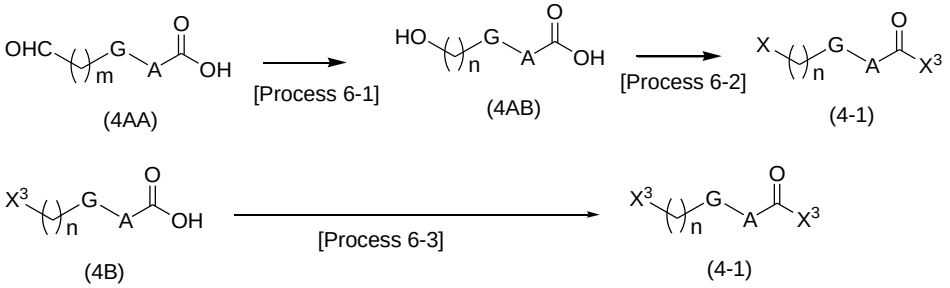
In this process, the compound (4-3), (4-5) or (4-7) is reacted to give the compound (4-2), (4-4) or (4-6) respectively. A solvent used in this reaction is not especially limited as long as it dissolves a starting material to some extent and does not inhibit the reaction, and for example, a halogenated hydrocarbon solvent such as dichloromethane, an ether solvent such as tetrahydrofuran, a nitrile solvent such as acetonitrile, or a mixed solvent of these can be used. In this reaction, an acid halide such as oxalyl chloride or an inorganic halogen compound such as thionyl chloride is used in an amount of 1 to 10 equivalents to the compound (4-3), (4-5) or (4-7), and 1 to 10 equivalents of a base such as benzotriazole can be added as an additive. Furthermore, a catalytic amount of N,N-dimethylformamide,

N-methylpyrrolidinone or the like can be added. The reaction temperature is from –20°C to reflux temperature, and the reaction time is from 10 minutes to 24 hours.

[0099] [Production Method 6]

Production method for compound (4-1)

[Chemical Formula 26]



In the above formula, A, G and n represent the same as defined above; m represents 0 or 1; and X^3 represents a halogen atom such as a chlorine atom or a bromine atom.

Compounds (4AA), (4AB) and (4B) can be commercially available products, or can be produced from commercially available products by known methods. Alternatively, these compounds can be produced by methods described in production examples in any of the examples described below or the like.

[0100] [Process 6-1]

In this process, the compound (4AA) is reacted to give the compound (4AB). A solvent used in this reaction is not especially limited as long as it dissolves a starting material to some extent and does not inhibit the reaction, and for example, an ether solvent such as tetrahydrofuran, an alcohol solvent such as ethanol, or a mixed solvent of these can be used. In this reaction, a reducing reagent such as sodium borohydride can be used in an amount of 1 to 10 equivalents to the compound (4AA). The reaction temperature is from –20°C to reflux temperature, and the reaction time is from 10 minutes to 24 hours.

[0101] [Process 6-2 or 6-3]

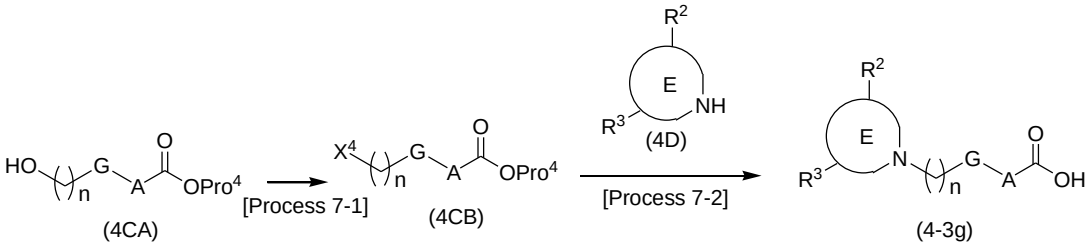
In this process, the compound (4AB) or (4B) is reacted to give the compound (4-1). A solvent used in this reaction is not especially limited as long as it dissolves a starting material to some extent and does not inhibit the reaction, and for example, a halogenated hydrocarbon solvent such as dichloromethane, an ether solvent such as tetrahydrofuran, a nitrile solvent such as acetonitrile, or a mixed solvent of these can be used. In this reaction, an acid halide such as oxalyl chloride or an inorganic halogen compound such as thionyl chloride can be used in an amount of 1 to 10 equivalents to the compound (4AB) or (4B),

and a catalytic amount of N,N-dimethylformamide, N-methylpyrrolidinone or the like can be added as an additive. The reaction temperature is from 0°C to reflux temperature, and the reaction time is from 10 minutes to 24 hours.

[0102] [Production Method 7]

Production method for compound (4-3g)

[Chemical Formula 27]



In the above formula, R^2, R^3, A, E, G and n represent the same as defined above; X^4 represents a halogen atom such as a chlorine atom, a bromine atom or an iodine atom, or a leaving group of sulfonate such as methanesulfonate, p-toluenesulfonate or trifluoromethanesulfonate; and Pro^4 represents a known protective group for carboxylic acid such as an ethyl group.

A compound (4CB) can be a commercially available product, or can be produced from a commercially available product by a known method. Alternatively, it can be produced by a method described in a production example in any of the examples described below or the like.

A compound (4CA) or (4D) can be a commercially available product, or can be produced from a commercially available product by a known method.

[0103] [Process 7-1]

In this process, the compound (4CA) is reacted with a halogenating reagent to give the compound (4CB) or reacted with a sulfonating reagent to give the compound (4CB). A solvent used in this reaction is not especially limited as long as it dissolves a starting material to some extent and does not inhibit the reaction, and for example, an ether solvent such as tetrahydrofuran, a nitrile solvent such as acetonitrile, a halogenated hydrocarbon solvent such as dichloromethane, an amide solvent such as N,N-dimethylformamide or N-methylpyrrolidinone, water, or a mixed solvent of these can be used. In the halogenation reaction, an excessive amount of hydrohalic acid such as hydrochloric acid or hydrobromic acid can be used. In this case, an inorganic chloride such as zinc chloride or lithium bromide, a phase transfer catalyst or the like can be used. Besides, this reaction can be

performed by using, as the halogenating reagent, a halogenated phosphorus compound such as phosphorus trichloride. In this case, N,N-dimethylformamide can be acted to be used as an iminium salt. Alternatively, a combination of an organic phosphorus compound, such as triphenylphosphine, and a carbon tetrahalide can be used as the halogenating reagent. Alternatively, a halogenating reagent such as thionyl chloride can be used. In this case, a base such as pyridine can be used as an additive. The halogenating reagent can be used in an amount of 1 to 10 equivalents. In the sulfonation reaction, a sulfonating reagent such as p-toluenesulfonylchloride can be used in an amount of 1 to 10 equivalents, and a base such as triethylamine or pyridine can be used in an amount of 1 to 10 equivalents as an additive. The reaction temperature is from 0°C to reflux temperature, and the reaction time is from 10 minutes to 24 hours.

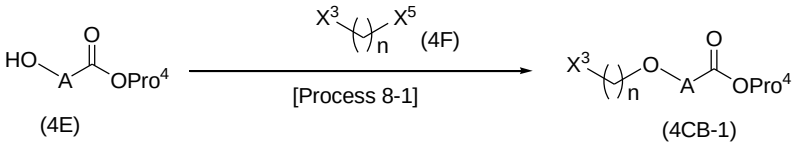
[0104] [Process 7-2]

In this process, the compound (4CB) is reacted with the compound (4D) to give the compound (4-3g). A solvent used in this reaction is not especially limited as long as it dissolves a starting material to some extent and does not inhibit the reaction, and for example, an ether solvent such as tetrahydrofuran, an amide solvent such as N,N-dimethylformamide or N-methylpyrrolidinone, dimethylsulfoxide, or a mixed solvent of these can be used. In this reaction, an organic base such as triethylamine or an inorganic base such as cesium carbonate can be used for condensation. The compound (4D) is used in an amount of 1 to 10 equivalents to the compound (4-CB), and the base can be added in an amount of 0 to 10 equivalents. The reaction temperature is from 0°C to reflux temperature, and the reaction time is from 10 minutes to 24 hours. Pro^4 can be deprotected by a known deprotection method for carboxylic acid.

[0105] [Production Method 8]

Production method for compound (4CB-1)

[Chemical Formula 28]



In the above formula, A and n represent the same as defined above; X^3 represents a halogen atom such as a chorine atom or a bromine atom; X^5 represents a halogen atom such as a bromine atom or an iodine atom; and Pro^4 represents a known protective group for carboxylic acid such as an ethyl group.

Compounds (4E) and (4F) can be commercially available products, or can be produced from commercially available products by known methods.

[0106] [Process 8-1]

In this process, the compound (4E) is reacted with the compound (4F) to give the compound (4CB-1). A solvent used in this reaction is not especially limited as long as it dissolves a starting material to some extent and does not inhibit the reaction, and for example, an ether solvent such as tetrahydrofuran, an amide solvent such as N,N-dimethylformamide or N-methylpyrrolidinone, dimethylsulfoxide, or a mixed solvent of these can be used. In this reaction, an organic base such as triethylamine or an inorganic base such as potassium carbonate can be used for condensation. The compound (4F) is used in an amount of 1 to 10 equivalents to the compound (4E), and the base can be added in an amount of 1 to 10 equivalents. The reaction temperature is from 0°C to reflux temperature, and the reaction time is from 10 minutes to 24 hours. Pro^4 can be also deprotected by a known deprotection method for carboxylic acid.

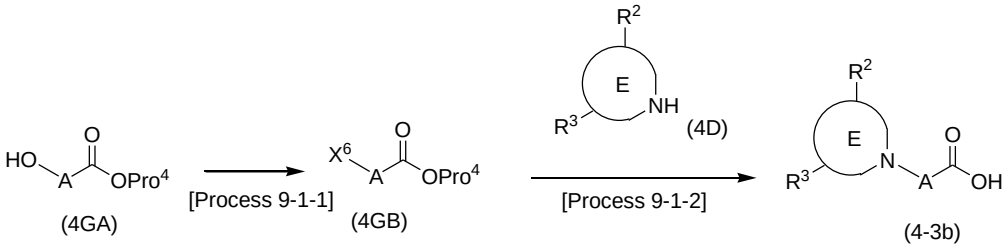
[0107] [Production Method 9]

Production method for compound (4-3b), (4-5a), (4-5b), (4-5c), (4-5d), (4-5e) or (4-5f)

[0108] [Production Method 9-1]

Production method for compound (4-3b)

[Chemical Formula 29]



In the above formula, R^2, R^3, A and E represent the same as defined above; X^6 represents a halogen atom such as a chlorine atom, a bromine atom or an iodine atom, or a leaving group of sulfonate such as trifluoromethanesulfonate; and Pro^4 represents a known protective group for carboxylic acid such as an ethyl group.

Compounds (4GA) and (4GB) can be commercially available products, or can be produced from commercially available products by known methods. Alternatively, the compound (4GB) can be produced by a method described in a production example in any of the examples described below or the like.

[0109] [Process 9-1-1]

In this process, the compound (4GA) is reacted with a halogenating reagent to give the compound (4GB) or reacted with a sulfonating reagent to give the compound (4GB). A solvent used in this reaction is not especially limited as long as it dissolves a starting material to some extent and does not inhibit the reaction, and for example, an ether solvent such as tetrahydrofuran, a halogenated hydrocarbon solvent such as dichloromethane, an amide solvent such as N,N-dimethylformamide or N-methylpyrrolidinone, a nitrile solvent such as acetonitrile, or a mixed solvent of these can be used. In the halogenation reaction, a phosphorus halide such as phosphorus pentabromide or a halogenating reagent such as triphenylphosphinedibromide can be used in an amount of 1 to 5 equivalents. In the sulfonation reaction, a sulfonating reagent such as trifluoromethanesulfonic anhydride can be used in an amount of 1 to 5 equivalents, and a base such as triethylamine or pyridine can be used, as an additive, in an amount of 1 to 10 equivalents. The reaction temperature is from –20°C to reflux temperature, and the reaction time is from 10 minutes to 24 hours.

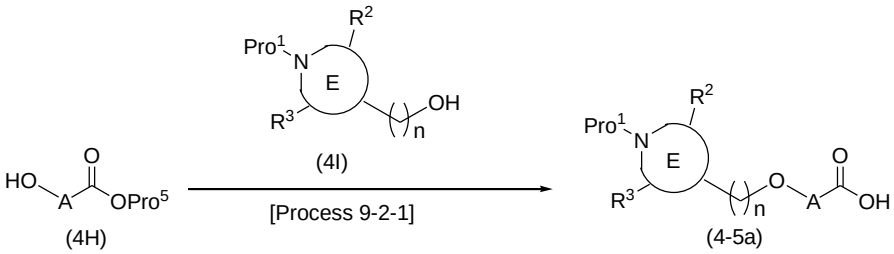
[0110] [Process 9-1-2]

In this process, the compound (4GB) is reacted with the compound (4D) to give a compound (4-3b). A solvent used in this reaction is not especially limited as long as it dissolves a starting material to some extent and does not inhibit the reaction, and for example, an ether solvent such as tetrahydrofuran, an amide solvent such as N,N-dimethylformamide or N-methylpyrrolidinone, dimethylsulfoxide, or a mixed solvent of these can be used. In this reaction, an organic base such as triethylamine or an inorganic base such as cesium carbonate can be used for condensation. The compound (4D) can be used in an amount of 1 to 10 equivalents to the compound (4GB), and the base can be added in an amount of 0 to 10 equivalents. The reaction temperature is from 0°C to reflux temperature, and the reaction time is from 10 minutes to 24 hours. Furthermore, in this reaction, a heavy metal such as copper can be added, and an organometallic catalyst containing palladium and an organophosphorus ligand can be also added. Pro^4 can be deprotected by a known deprotection method for carboxylic acid.

[0111] [Production method 9-2]

Production method for compound (4-5a)

[Chemical Formula 30]



In the above formula, R^2, R^3, A, E and n represent the same as defined above; Pro^1 represents a known protective group for a nitrogen atom such as a tert-butoxycarbonyl group; and Pro^5 represents a known protective group for carboxylic acid such as an ethyl group or a benzyl group.

Compounds (4H) and (4I) can be commercially available products, or can be produced from commercially available products by known methods.

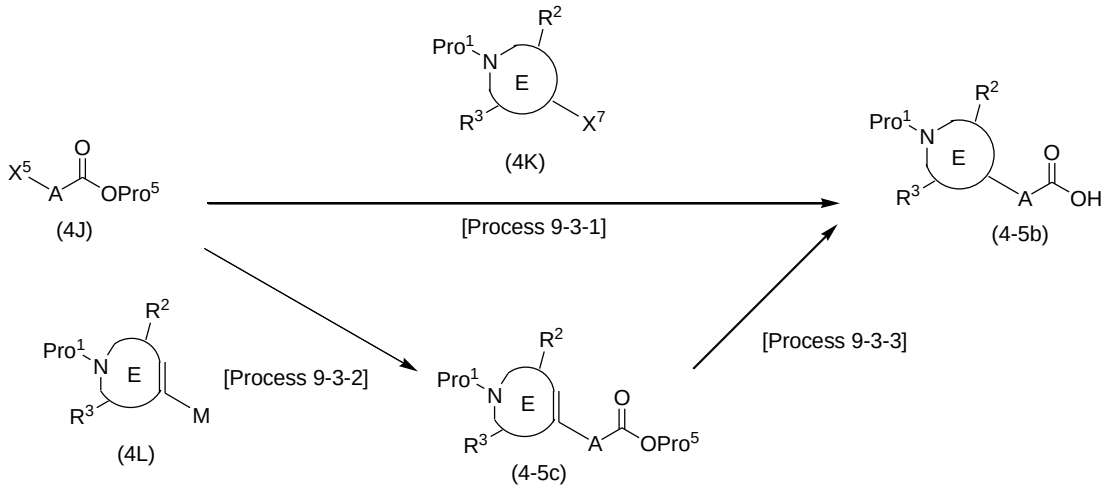
[0112] [Process 9-2-1]

In this process, the compound (4H) and the compound (4I) are reacted with each other to give a compound (4-5a). A solvent used in this reaction is not especially limited as long as it dissolves a starting material to some extent and does not inhibit the reaction, and for example, an ether solvent such as tetrahydrofuran, an aromatic hydrocarbon solvent such as toluene, a halogenated hydrocarbon solvent such as dichloromethane, an ester solvent such as ethyl acetate, or a mixed solvent of these can be used. In this reaction, the compound (4H) can be used in an amount of 0.5 to 2 equivalents to the compound (4I). In this reaction, azodicarboxylate such as diisopropyl azodicarboxylate, and triphenylphosphine can be used in an amount of 1 to 5 equivalents respectively to the compounds (4H) and (4I). The reaction temperature is from –20°C to reflux temperature, and the reaction time is from 10 minutes to 24 hours. Pro^5 can be deprotected by a known deprotection method for carboxylic acid.

[0113] [Production Method 9-3]

Production method for compound (4-5b) or (4-5c)

[Chemical Formula 31]



In the above formula, R^2, R^3, A and E represent the same as defined above; X^5 represents a halogen atom such as a bromine atom or an iodine atom; X^7 represents a halogen atom such as a bromine atom or an iodine atom, or a leaving group of sulfonate such as methanesulfonate or trifluoromethanesulfonate; M represents a leaving group of borate ester or the like; Pro^1 represents a known protective group for a nitrogen atom such as a tert-butoxycarbonyl group; and Pro^5 represents a known protective group for carboxylic acid such as an ethyl group or a benzyl group, and carboxylic acid may be or may not be protected in this reaction.

Compounds (4J), (4K) and (4L) can be commercially available products, or can be produced from commercially available products by known methods.

[0114] [Process 9-3-1]

In this process, the compound (4J) and the compound (4K) are reacted with each other to give a compound (4-5b). A solvent used in this reaction is not especially limited as long as it dissolves a starting material to some extent and does not inhibit the reaction, and for example, an ether solvent such as tetrahydrofuran, an aromatic hydrocarbon solvent such as toluene, an amide solvent such as N,N-dimethylformamide or N-methylpyrrolidinone, or a mixed solvent of these can be used. In this reaction, the compound (4K) can be used in an amount of 0.5 to 2 equivalents to the compound (4J). In this reaction, a palladium complex compound containing an organic phosphorus compound as a ligand can be used as a catalyst. The catalyst can be prepared within the reaction system. In this reaction, a zinc powder can be used in an amount of 0.5 to 2 equivalents to the compound (4J). Besides, a copper halide, a dihalogenated alkyl compound, a halogenated organic silicon compound or the like can be added as an additive. The reaction temperature is from 0°C to reflux temperature,

and the reaction time is from 10 minutes to 24 hours. Pro^5 can be deprotected by a known deprotection method for carboxylic acid.

[0115] [Process 9-3-2]

In this process, the compound (4J) and the compound (4L) are reacted with each other to give a compound (4-5c). A solvent used in this reaction is not especially limited as long as it dissolves a starting material to some extent and does not inhibit the reaction, and for example, an ether solvent such as 1,4-dioxane, an aromatic hydrocarbon solvent such as toluene, an alcohol solvent such as ethanol, an amide solvent such as N,N-dimethylformamide or N-methylpyrrolidinone, or a mixed solvent of these can be used. In this reaction, the compound (4L) can be used in an amount of 0.5 to 2 equivalents to the compound (4J). In this reaction, a palladium complex compound containing an organic phosphorus compound as a ligand can be used as a catalyst. The catalyst can be prepared within the reaction system. In this reaction, a base such as sodium carbonate can be used in an amount of 1 to 10 equivalents to the compound (4J). The reaction temperature is from 0°C to reflux temperature, and the reaction time is from 10 minutes to 24 hours.

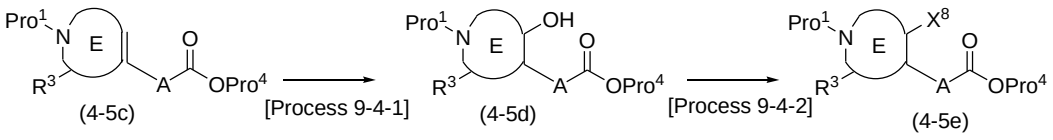
[0116] [Process 9-3-3]

In this process, the compound (4-5c) is reduced and deprotected to give the compound (4-5b). A solvent used in this reaction is not especially limited as long as it dissolves a starting material to some extent and does not inhibit the reaction, and for example, an ether solvent such as tetrahydrofuran, an ester solvent such as ethyl acetate, an alcohol solvent such as ethanol, an amide solvent such as N,N-dimethylformamide or N-methylpyrrolidinone, or a mixed solvent of these can be used. In this reaction, a catalytic reduction catalyst such as palladium-carbon can be used in an amount of 0.001 to 1 equivalent to the compound (4-5c). Besides, the reaction can be performed in a hydrogen atmosphere at a pressure ranging from normal pressure to 20 atm. The reaction temperature is from 0°C to reflux temperature, and the reaction time is from 10 minutes to 24 hours. Pro^5 can be deprotected by a known deprotection method for carboxylic acid.

[0117] [Production Method 9-4]

Production method for compound (4-5d) or (4-5e)

[Chemical Formula 32]



In the above formula, R^3, A and E represent the same as defined above; X^8 represents a halogen atom such as a fluorine atom; Pro^1 represents a known protective group for a nitrogen atom such as a tert-butoxycarbonyl group; and Pro^4 represents a known protective group for carboxylic acid such as an ethyl group, and in this reaction, carboxylic acid may be or may not be protected.

The compound (4-5c) can be a commercially available product, or can be produced from a commercially available product by a known method. Alternatively, it can be produced by a method described in a production example in any of the examples described below or the like.

[0118] [Process 9-4-1]

In this process, the compound (4-5c) is reacted to give a compound (4-5d). A solvent used in this reaction is not especially limited as long as it dissolves a starting material to some extent and does not inhibit the reaction, and for example, an ether solvent such as tetrahydrofuran can be used. In this reaction, a borane complex compound such as a borane-methyl sulfide complex can be used in an amount of 1 to 2 equivalents to the compound (4-5c). The reaction temperature is from –20°C to reflux temperature, and the reaction time is from 10 minutes to 24 hours. Subsequently, by using a sodium hydroxide aqueous solution in an amount of 1 to 10 equivalents and a hydrogen peroxide solution in an amount of 1 to 10 equivalents, a hydroxyl group can be obtained. The reaction temperature is from 0°C to reflux temperature, and the reaction time is from 10 minutes to 24 hours.

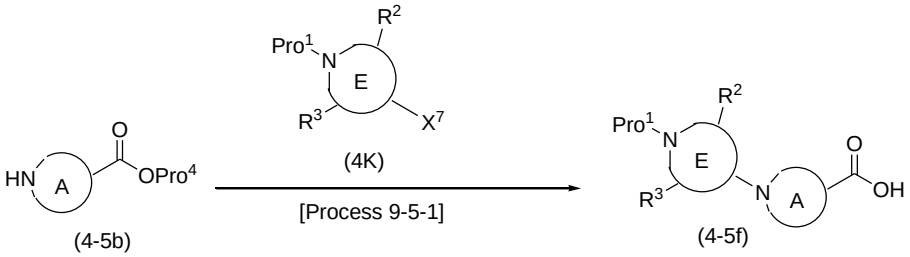
[0119] [Process 9-4-2]

In this process, the hydroxyl group of the compound (4-5d) is substituted by halogen to give a compound (4-5e). A solvent used in this reaction is not especially limited as long as it dissolves a starting material to some extent and does not inhibit the reaction, and for example, a halogenated hydrocarbon solvent such as a dichloromethane, an ether solvent such as tetrahydrofuran, an ester solvent such as ethyl acetate, an amide solvent such as N,N-dimethylformamide or N-methylpyrrolidinone, or a mixed solvent of these can be used. In this reaction, a halogenating reagent such as [bis-(2-methoxyethyl)-amino]sulfur trifluoride can be used in an amount of 1 to 10 equivalents to the compound (4-5d). The reaction temperature is from 0°C to reflux temperature, and the reaction time is from 10 minutes to 24 hours. Pro^4 can be deprotected by a known deprotection method for carboxylic acid.

[0120] [Production Method 9-5]

Production method for compound (4-5f)

[Chemical Formula 33]



In the above formula, R^2, R^3, A and E represent the same as defined above; X^7 represents a halogen atom such as a bromine atom or an iodine atom, or a leaving group of sulfonate such as methanesulfonate or trifluoromethanesulfonate; Pro^1 represents a known protective group for a nitrogen atom such as a tert-butoxycarbonyl group; and Pro^4 represents a known protective group for carboxylic acid such as an ethyl group, and in this reaction, carboxylic acid may be or may not be protected.

The compounds (4-5b) and (4K) can be commercially available products, or can be produced from commercially available products by known methods. Alternatively, these compounds can be produced by methods described in production examples in any of the examples described below or the like.

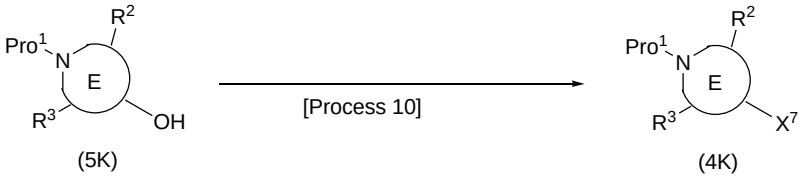
[0121] [Process 9-5-1]

In this process, the compound (4-5b) and the compound (4K) are reacted with each other to give a compound (4-5f). A solvent used in this reaction is not especially limited as long as it dissolves a starting material to some extent and does not inhibit the reaction, and for example, an ether solvent such as tetrahydrofuran, an amide solvent such as N,N-dimethylformamide or N-methylpyrrolidinone, or a mixed solvent of these can be used. In this reaction, the compound (4K) can be used in an amount of 0.5 to 2 equivalents to the compound (4-5b). Besides, a base such as a sodium hydride or potassium tert-butoxide can be used in an amount of 1 to 5 equivalents to the compound (4-5b). The reaction temperature is from −20°C to reflux temperature, and the reaction time is from 10 minutes to 24 hours. Pro^4 can be deprotected by a known deprotection method for carboxylic acid.

[0122] [Production Method 10]

Production method for compound (4K)

[Chemical Formula 34]



(5K) (4K)

In the above formula, R^2, R^3 and E represent the same as defined above; X^7 represents a halogen atom such as a bromine atom or an iodine atom, or a leaving group of sulfonate such as methanesulfonate or trifluoromethanesulfonate; and Pro^1 represents a known protective group for a nitrogen atom such as a tert-butoxycarbonyl group.

A compound (5K) can be a commercially available product, or can be produced from a commercially available product by a known method.

[0123] [Process 10]

In this process, the compound (5K) is reacted with a halogenating reagent to give the compound (4K), or reacted with a sulfonating reagent to give the compound (4K). A solvent used in this reaction is not especially limited as long as it dissolves a starting material to some extent and does not inhibit the reaction, and for example, an ether solvent such as tetrahydrofuran, a halogenated hydrocarbon solvent such as dichloromethane, an amide solvent such as N,N-dimethylformamide or N-methylpyrrolidinone, a nitrile solvent such as acetonitrile, or a mixed solvent of these can be used. In the halogenation reaction, a phosphorus halide such as phosphorus pentabromide or a halogenating reagent such as triphenylphosphinedibromide can be used in an amount of 1 to 5 equivalents. In the sulfonation reaction, a sulfonating reagent such as methanesulfonyl chloride or trifluoromethanesulfonic anhydride can be used in an amount of 1 to 5 equivalents, and a base such as triethylamine or pyridine can be used, as an additive, in an amount of 1 to 10 equivalents. The reaction temperature is from –20°C to reflux temperature, and the reaction time is from 10 minutes to 24 hours.

Example

[0124] Compounds according to the present invention can be produced by methods described in Production Examples and Examples described below, for example. However, these methods are mere examples, and therefore the compounds according to the present invention are not limited to those produced by specific examples described below in any cases.

[0125] In Production Examples and Examples, Silica gel 60 (Kanto Chemicals) or Presep Silica Gel (WAKO) was used as a purification silica gel used for silica gel column

chromatography unless otherwise stated. In addition, NH silica gel (Fuji Silysia Chemical LTD.) or Hi-Flash Column Amino (YAMAZENE CORPORATION) was used as a purification silica gel used for NH silica gel column chromatography, and TLC Plates NH (20 cm × 20 cm, Fuji Silysia Chemical LTD.) was used as a thin-layer plate used for NH silica gel TLC (Thin Layer Chromatography).

[0126] Varian Mercury 400, Varian Mercury Plus 400, Varian INOVA 500 or Avance 600 MHz spectrometer (Bruker) was used for the measurement of proton nuclear magnetic resonance spectra, and the proton nuclear magnetic resonance spectra were measured at 400 MHz unless otherwise stated. Chemical shifts of proton nuclear magnetic resonance spectra are recorded in the unit of δ (ppm) with respect to tetramethylsilane and coupling constants are recorded in the unit of Hertz (Hz). Abbreviations for splitting patterns are as follows: s: singlet; d: doublet; t: triplet; q: quartet; quin: quintet; spt: septet; m: multiplet; and brs: broad singlet.

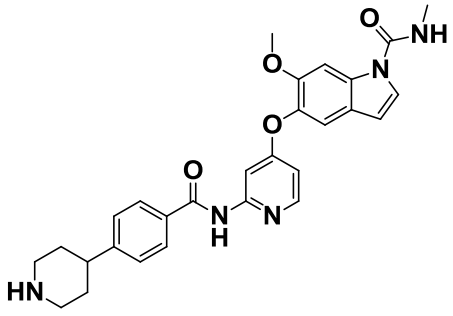
[0127] Waters Micromass ZQ 2000, Waters SQ Detector 2, or Thermo Fisher Scientific LCQ was used for the measurement of mass spectra. For the ionization method, an electrospray ionization (ESI) method was used for the measurement.

[0128] In Production Examples and Examples, commercially available products were appropriately used as commercially available compounds. In the description below, the term "BOC" refers to tert-butoxycarbonyl and the term "T" refers to Tert.

[0129] [Example 1]

6-Methoxy-N-methyl-5-((2-(4-(piperidin-4-yl)benzamide)pyridin-4-yl)oxy)-1H-indole-1-carboxamide

[Chemical Formula 35]



tert-Butyl 4-(4-((4-((6-methoxy-1-(methylcarbamoyl)-1H-indol-5-yl)oxy)pyridin-2-yl)carbamoyl)phenyl)piperidine-1-carboxylate described in Production Example 1-8 (3.42 g, 5.70 mmol) was

dissolved in dichloromethane (45 mL), and trifluoroacetic acid (15 mL) was added at 0°C. The mixture was stirred at room temperature for 60 minutes and then concentrated under vacuum, and then the residue was dissolved in dichloromethane-triethylamine, and the resultant was purified with NH silica gel column chromatography (ethyl acetate:methanol = 97:3 - 4:1). The target fraction was concentrated under vacuum and then the precipitate was collected by filteration and washed with diethyl ether and ethyl acetate to obtain the title compound (2.61 g, 92%).

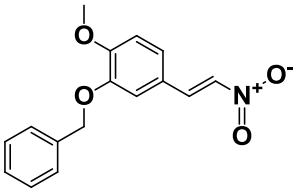
^{1}H-NMR Spectrum ($CDCl_3$) δ (ppm): 1.55-1.70 (2H, m), 1.78-1.88 (2H, m), 2.62-2.80 (3H, m), 3.06 (3H, d, J = 4.8 Hz), 3.15-3.24 (2H, m), 3.86 (3H, s), 5.52-5.61 (1H, m), 6.54 (1H, d, J = 3.3 Hz), 6.60 (1H, dd, J = 5.7, 2.4 Hz), 7.23 (1H, d, J = 3.7 Hz), 7.28-7.35 (3H, m), 7.80 (2H, d, J = 8.4 Hz), 7.91 (1H, d, J = 2.2 Hz), 8.03 (1H, s), 8.10 (1H, d, J = 5.9 Hz), 8.53 (1H, brs).

[0130] The starting material tert-butyl 4-(4-((4-(((6-methoxy-1-(methylcarbamoyl)-1H-indol-5-yl)oxy)pyridin-2-yl)carbamoyl)phenyl)piperidine-1-carboxylate was synthesized by the following method.

[0131] [Production Example 1-1]

(E)-2-(Benzyloxy)-1-methoxy-4-(2-nitrovinyl)benzene

[Chemical Formula 36]



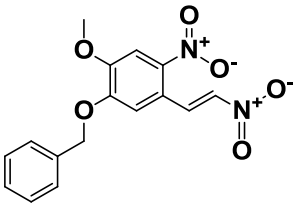
Commercially available 3-benzyloxy-4-methoxybenzaldehyde (30 g, 124 mmol) was dissolved in acetic acid (100 mL), then ammonium acetate (10.8 g, 140 mmol) and nitromethane (16.8 mL, 310 mmol) were added under nitrogen atmosphere at room temperature, and the mixture was heated and stirred at 130°C for 2 hours and 20 minutes. The mixture was cooled to room temperature, then the precipitate was collected by filteration and washed with ethanol to obtain the title compound (28.5 g, 81%).

^{1}H-NMR Spectrum ($CDCl_3$) δ (ppm): 3.95 (3H, s), 5.18 (2H, s), 6.93 (1H, d, J = 8.1 Hz), 7.03 (1H, d, J = 2.2 Hz), 7.17 (1H, dd, J = 8.4, 2.2 Hz), 7.30-7.47 (6H, m), 7.91 (1H, d, J = 13.5 Hz).

[0132] [Production Example 1-2]

(E)-1-(Benzyloxy)-2-methoxy-4-nitro-5-(2-nitrovinyl)benzene

[Chemical Formula 37]



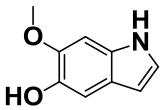
69% Nitric acid (10 mL, 155 mmol) was added to a mixture of (E)-2-(benzyloxy)-1-methoxy-4-(2-nitrovinyl)benzene described in Production Example 1-1 (10 g, 35.1 mmol) and acetic acid (70 mL) under nitrogen atmosphere at 25°C, and the mixture was stirred at 40°C for 3 hours. The reaction mixture was poured onto ice and the precipitate was collected by filteration and then washed with ethanol to obtain the title compound (10.5 g, 91%).

^{1}H-NMR Spectrum ($CDCl_3$) δ (ppm): 4.02 (3H, s), 5.28 (2H, s), 6.93 (1H, s), 7.22 (1H, d, J = 13.5 Hz), 7.35-7.48 (5H, m), 7.75 (1H, s), 8.58 (1H, d, J = 13.2 Hz).

[0133] [Production Example 1-3]

6-Methoxy-1H-indol-5-ol

[Chemical Formula 38]



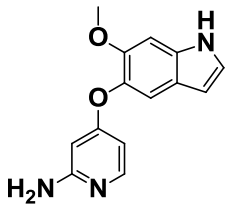
(E)-1-(Benzyloxy)-2-methoxy-4-nitro-5-(2-nitrovinyl)benzene described in Production Example 1-2 (9.4 g, 28.5 mmol) was suspended in methanol (300 mL), then 10% palladium-carbon (water content, 50%) (3.09 g) was added, and the mixture was stirred under hydrogen atmosphere for 3 hours. The catalyst was filtered off with celite and washed with methanol. The filtrate was concentrated under vacuum and the resultant was purified with silica gel column chromatography (n-heptane:ethyl acetate = 3:1 - 3:7). The target fraction was concentrated under vacuum to obtain the title compound (2.12 g, 46%).

^{1}H-NMR Spectrum ($CDCl_3$) δ (ppm): 3.92 (3H, s), 5.45 (1H, s), 6.39-6.44 (1H, m), 6.88 (1H, s), 7.08 (1H, t, J = 2.9 Hz), 7.14 (1H, s), 7.95 (1H, brs).

[0134] [Production Example 1-4]

4-((6-Methoxy-1H-indol-5-yl)oxy)pyridin-2-amine

[Chemical Formula 39]



6-Methoxy-1H-indol-5-ol described in Production Example 1-3 (2.86 g, 17.6 mmol), N-(4-chloropyridin-2-yl)acetamide described in Production Example 1-5 (8.98 g, 52.7 mmol), and potassium tert-butoxide (3.94 g, 35.1 mmol) were dissolved in dimethylsulfoxide (45 mL) under nitrogen atmosphere and the mixture was heated and stirred at 160°C for 12.5 hours. The reaction liquid was cooled to room temperature, and water and ethyl acetate were added for partition. The aqueous layer was extracted with ethyl acetate twice, and the combined organic layer was washed with water twice and then with a saturated saline solution. The organic layer was dried over anhydrous magnesium sulfate. The drying agent was filtered off, then the filtrate was concentrated under vacuum, and the resultant was purified with NH silica gel column chromatography (n-heptane:ethyl acetate = 1:1 - 0:1 - ethyl acetate:methanol = 99:1 - 9:1). The mixture fraction was concentrated under vacuum, the resultant was purified with NH silica gel column chromatography (n-heptane:ethyl acetate = 1:1 - 0:1 - ethyl acetate:methanol = 99:1 - 9:1), and then the target fraction was concentrated under vacuum to obtain a crude product (3.88 g).

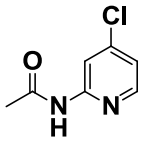
The crude product (3.88 g) was dissolved in methanol (75 mL), 28% sodium methoxide (14 mL, 68.6 mmol) was added under nitrogen atmosphere at room temperature, and then the mixture was heated and stirred at 70°C for 5.5 hours. The reaction mixture was cooled to room temperature and then water and ethyl acetate were added for partition. The aqueous layer was extracted with ethyl acetate once and the combined organic layer was washed with a saturated saline solution. The organic layer was dried over anhydrous magnesium sulfate. The drying agent was filtered off, the filtrate was concentrated under vacuum, and then the resultant was purified with NH silica gel column chromatography (n-heptane:ethyl acetate = 1:3 - 0:1 - ethyl acetate:methanol = 99:1 - 19:1). The target fraction was concentrated under vacuum to obtain the title compound (1.97 g, 44%).

^{1}H-NMR Spectrum ($CDCl_3$) δ (ppm): 3.82 (3H, s), 4.29 (2H, brs), 5.89-5.92 (1H, m), 6.30 (1H, dd, J = 5.9, 2.2 Hz), 6.49 (1H, ddd, J = 3.2, 2.2, 0.9 Hz), 7.01 (1H, s), 7.17 (1H, dd, J = 3.1, 2.4 Hz), 7.33 (1H, s), 7.89 (1H, d, J = 6.0 Hz), 8.19 (1H, brs).

[0135] [Production Example 1-5]

N-(4-Chloropyridin-2-yl)acetamide

[Chemical Formula 40]



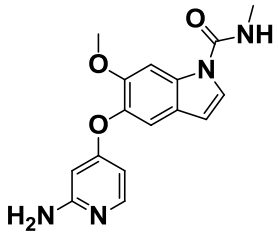
Commercially available 2-amino-4-chloropyridine (50 g, 389 mmol) was dissolved in acetic anhydride (500 mL), triethylamine (271 mL, 1.94 mol) was added at 20°C, and the mixture was stirred at 60°C for 12 hours. The mixture was cooled to room temperature and then the solvent was evaporated. The residue was purified with silica gel column chromatography (n-heptane:ethyl acetate = 4:1 - 1:1) and then the target fraction was concentrated under vacuum to obtain the title compound (66 g, 99%).

^{1}H-NMR Spectrum ($CDCl_3$) δ (ppm): 2.21 (3H, s), 7.05 (1H, dd, J = 5.4, 1.9 Hz), 8.15 (1H, d, J = 5.4 Hz), 8.30 (2H, brs).

[0136] [Production Example 1-6]

5-((2-Aminopyridin-4-yl)oxy)-6-methoxy-N-methyl-1H-indole-1-carboxamide

[Chemical Formula 41]



4-((6-Methoxy-1H-indol-5-yl)oxy)pyridin-2-amine described in Production Example 1-4 (1.7 g, 6.66 mmol) was dissolved in N,N-dimethylformamide (25 mL), 50 - 72% oily sodium hydride (424 mg) was added under nitrogen atmosphere at 0°C, and then the mixture was stirred at room temperature for 45 minutes. The mixture was cooled to 0°C again, phenyl methylcarbamate described in Production Example 1-7 (1.64 g, 10.8 mmol) was added, and the resultant was stirred at room temperature for 3 hours. A saturated aqueous ammonium chloride solution, water, and ethyl acetate were added to the reaction mixture for partition. The aqueous layer was extracted with ethyl acetate once and the combined organic layer was washed with water and a saturated saline solution. The organic layer was dried over anhydrous magnesium sulfate. The drying agent was filtered off, then the filtrate was concentrated under vacuum, and then the resultant was purified with

NH silica gel column chromatography (n-heptane:ethyl acetate = 1:3 - 0:1 - ethyl acetate:methanol = 99:1 - 19:1). The target fraction was concentrated under vacuum and then the precipitate was collected by filteration and washed with ethyl acetate to obtain the title compound (1.37 g, 66%). The mixture fraction was concentrated under vacuum and purified with NH silica gel column chromatography (n-heptane: ethyl acetate = 3:7 - 0:1 - ethyl acetate:methanol = 99:1 - 19:1). The target fraction was concentrated under vacuum, and then the precipitate was collected by filteration and washed with ethyl acetate twice to obtain the title compound (387 mg, 19%).

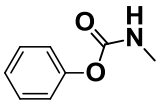
^{1}H-NMR Spectrum ($CDCl_3$) δ (ppm): 3.07 (3H, d, J = 4.6 Hz), 3.86 (3H, s), 4.31 (2H, brs), 5.44-5.56 (1H, m), 5.89 (1H, d, J = 2.2 Hz), 6.27 (1H, dd, J = 5.9, 2.2 Hz), 6.55 (1H, d, J = 3.7 Hz), 7.23 (1H, d, J = 3.7 Hz), 7.25-7.28 (1H, m), 7.89 (1H, d, J = 5.9 Hz), 8.01 (1H, brs).

[0137] The reagent phenyl methylcarbamate was synthesized by the following method.

[0138] [Production Example 1-7]

Phenyl methylcarbamate

[Chemical Formula 42]



A mixture of commercially available methylamine hydrochloride (50 g, 0.74 mol), pyridine (124 mL, 1.53 mol), and N,N-dimethylformamide (500 mL) was stirred at 5°C, and commercially available phenyl chlorocarbonate (94 mL, 0.75 mol) was added dropwise over 2 hours. After the dripping was complete, the mixture was stirred under nitrogen atmosphere at room temperature for 16 hours. The reaction mixture was added to ice water (2 L) and extracted with ethyl acetate (1.5 L) twice. The organic layer was washed with water (1 L) and a saturated saline solution (300 mL). The organic layer was dried over anhydrous magnesium sulfate and then the solvent was evaporated. n-Heptane and ethyl acetate were added to the concentrated residue and the precipitate was collected by filteration and washed with n-heptane and tert-butyl methyl ether to obtain the title compound (74.2 g, 66%).

^{1}H-NMR Spectrum ($CDCl_3$) δ (ppm): 2.90 (3H, d, J = 4.9 Hz), 4.95 (1H, brs), 7.08-7.16 (2H, m), 7.16-7.24 (1H, m), 7.31-7.41 (2H, m)

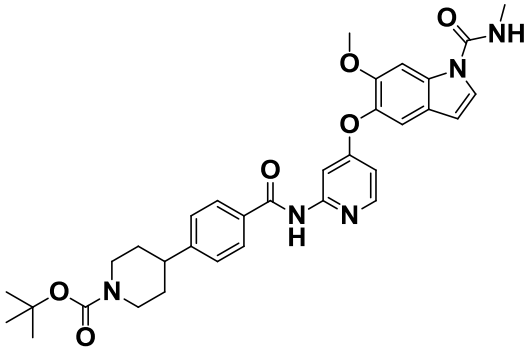
[0139] [Production Example 1-8]

tert-Butyl

4-(4-((4-((6-methoxy-1-(methylcarbamoyl)-1H-indol-5-yl)oxy)pyridin-2-yl)carbamoyl)phen

yl)piperidine-1-carboxylate

[Chemical Formula 43]



Benzotriazole (2.32 g, 19.5 mmol) was dissolved in dichloromethane (100 mL), thionyl chloride (1.4 mL, 19.2 mmol) was added under nitrogen atmosphere at room temperature, and the mixture was stirred for 5 minutes. 4-(1-(tert-Butoxycarbonyl)piperidin-4-yl)benzoic acid described in Production Example 1-12 (5.4 g, 17.7 mmol) was added to the reaction mixture at room temperature, and the mixture was stirred for 25 minutes. The reaction mixture was filtered through a glass filter entirely covered with anhydrous sodium sulfate and then the anhydrous sodium sulfate was washed with dichloromethane, then the filtrate was added to a mixture of 5-((2-aminopyridin-4-yl)oxy)-6-methoxy-N-methyl-1H-indole-1-carboxamide described in Production Example 1-6 (2.5 g, 8.01 mmol), triethylamine (11 mL, 79.4 mmol), and 4-dimethylaminopyridine (101 mg, 0.827 mmol) in tetrahydrofuran (80 mL) at 0°C. The resultant was stirred at room temperature for 5 hours and then the reaction mixture was concentrated under vacuum. Water and ethyl acetate were added to the residue for partition, and the organic layer was washed with a saturated saline solution, and then dried over anhydrous magnesium sulfate and filtered. The filtrate was concentrated under vacuum, the residue was dissolved in tetrahydrofuran, an excessive quantity of 9.8 M methylamine methanol solution was added at room temperature, and the mixture was stirred for 50 minutes. The reaction mixture was concentrated under vacuum, the residue was dissolved in dichloromethane, and the resultant was purified with NH silica gel column chromatography (n-heptane:ethyl acetate = 1:1 - 1:3 - 0:1). The target fraction was concentrated under vacuum and the precipitate was collected by filteration and washed with diethyl ether and ethyl acetate to obtain the title compound (3.15 g, 66%). The filtrate was combined with the mixture fraction and the resultant was concentrated under vacuum and dissolved in dichloromethane, and the resultant was purified with NH silica gel column

chromatography (n-heptane:ethyl acetate = 1:1 - 1:3 - 0:1). The target fraction was concentrated under vacuum and the precipitate was collected by filteration and washed with diethyl ether and ethyl acetate to obtain the title compound (264 mg, 5.5%).

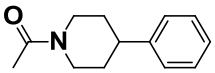
^{1}H-NMR Spectrum ($CDCl_3$) δ (ppm): 1.48 (9H, s), 1.55-1.69 (2H, m), 1.77-1.87 (2H, m), 2.64-2.89 (3H, m), 3.02-3.07 (3H, m), 3.86 (3H, s), 4.26 (2H, brs), 5.62 (1H, brs), 6.50-6.55 (1H, m), 6.61 (1H, dd, J = 5.9, 2.2 Hz), 7.22 (1H, d, J = 3.7 Hz), 7.27-7.33 (3H, m), 7.80 (2H, d, J = 8.4 Hz), 7.90 (1H, d, J = 2.2 Hz), 8.04 (1H, s), 8.09 (1H, d, J = 5.9 Hz), 8.54 (1H, brs).

[0140] 4-(1-(tert-Butoxycarbonyl)piperidin-4-yl)benzoic acid was synthesized by the following method.

[0141] [Production Example 1-9]

1-(4-Phenylpiperidin-1-yl)ethanone

[Chemical Formula 44]



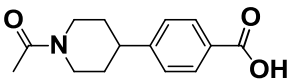
A mixture of commercially available 4-phenylpiperidine (10 g, 62 mmol), pyridine (5.7 mL, 70.5 mmol), and tetrahydrofuran (80 mL) was stirred at 0°C and a mixture of acetyl chloride (5 mL, 70.3 mmol) and tetrahydrofuran (20 mL) was dripped over 10 minutes. The mixture was stirred under nitrogen atmosphere at 25°C for 14 hours. Ethyl acetate (100 mL) and water (100 mL) were added to the reaction liquid for separation. The aqueous layer was extracted with ethyl acetate (100 mL), then the organic layers were combined, and the resultant was washed with a saturated aqueous sodium bicarbonate solution (100 mL), water (100 mL), and then a saturated saline solution (50 mL). The organic layer was dried over anhydrous magnesium sulfate and then the solvent was evaporated to obtain the title compound (12.3 g, 98%).

^{1}H-NMR Spectrum ($CDCl_3$) δ (ppm): 1.52-1.78 (2H, m), 1.81-1.99 (2H, m), 2.14 (3H, s), 2.63 (1H, td, J = 12.9, 2.7 Hz), 2.74 (1H, tt, J = 12.1, 3.7 Hz), 3.17 (1H, td, J = 13.2, 2.6 Hz), 3.84-4.02 (1H, m), 4.69-4.89 (1H, m), 7.08-7.43 (5H, m).

[0142] [Production Example 1-10]

4-(1-Acetylpiperidin-4-yl)benzoic acid

[Chemical Formula 45]



A mixture of aluminum chloride(III) (26 g, 195 mmol) and dichloromethane (200

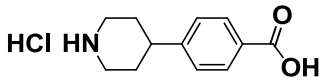
mL) was stirred at 0°C, and oxalyl chloride (20 mL, 228 mmol) was dripped over 10 minutes. Then a mixture of 1-(4-phenylpiperidin-1-yl)ethanone described in Production Example 1-9 (12.3 g, 60.5 mmol) and dichloromethane (50 mL) was dripped over 30 minutes. The mixture was stirred under nitrogen atmosphere at 25°C for 14 hours. The reaction liquid was poured onto ice and ethyl acetate (1 L) and water (1 L) were added for separation. The aqueous layer was extracted with ethyl acetate (1 L) twice, then the organic layer was washed with water (1 L) twice and then with a saturated saline solution (500 mL). The organic layer was dried over anhydrous magnesium sulfate and then the solvent was evaporated. Ethyl acetate was added to the concentrated residue and the product was collected by filteration and washed with ethyl acetate to obtain the title compound (9.09 g, 61%).

^{1}H-NMR Spectrum ($CDCl_3$) δ (ppm): 1.49-1.82 (2H, m), 1.92 (2H, t, J = 13.2 Hz), 2.15 (3H, s), 2.65 (1H, t, J = 11.7 Hz), 2.75-2.94 (1H, m), 3.08-3.30 (1H, m), 3.97 (1H, d, J = 13.2 Hz), 4.82 (1H, d, J = 12.8 Hz), 7.30 (2H, d, J = 8.4 Hz), 8.05 (2H, d, J = 8.1 Hz).

[0143] [Production Example 1-11]

4-(Piperidin-4-yl)benzoic acid hydrochloride

[Chemical Formula 46]



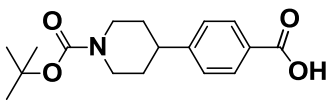
A mixture of 4-(1-acetylpiperidin-4-yl)benzoic acid described in Production Example 1-10 (4.50 g, 18.2 mmol) and 5 M hydrochloric acid (50 mL, 250 mmol) was stirred under nitrogen atmosphere at 140°C for 18 hours. The mixture was cooled to room temperature and then the product was collected by filteration and washed with water to obtain the title compound (3.77 g, 86%).

^{1}H-NMR Spectrum (DMSO-d_6) δ (ppm): 1.60-2.15 (4H, m), 2.76-3.16 (3H, m), 3.27-3.45 (2H, m), 7.36 (2H, d, J = 8.1 Hz), 7.92 (2H, d, J = 8.1 Hz), 8.65-9.04 (2H, m), 12.89 (1H, brs).

[0144] [Production Example 1-12]

4-(1-(tert-Butoxycarbonyl)piperidin-4-yl)benzoic acid

[Chemical Formula 47]



A mixture of 4-(piperidin-4-yl)benzoic acid hydrochloride described in Production Example 1-11 (2.00 g, 8.27 mmol), a 1 M sodium hydroxide solution (25 mL, 25 mmol),

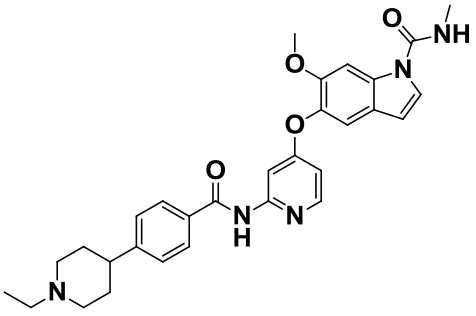
and acetone (50 mL) was stirred at 25°C, and a solution of di-tert-butyl dicarbonate (1.9 g, 8.71 mmol) in acetone (25 mL) was added dropwise over 10 minutes. The mixture was stirred under nitrogen atmosphere at 25°C for 18 hours. 1 M hydrochloric acid (17 mL) was added under cooling at 0°C. The mixture was extracted with ethyl acetate (100 mL) twice. The organic layer was washed with a saturated saline solution (50 mL). The organic layer was dried over anhydrous magnesium sulfate and then concentrated under vacuum. n-Heptane and tert-butyl methyl ether were added to the concentrated residue and the product was collected by filteration and washed with n-heptane to obtain the title compound (2.30 g, 91%).

^{1}H-NMR Spectrum ($CDCl_3$) δ (ppm): 1.49 (9H, s), 1.57-1.76 (2H, m), 1.84 (2H, d, J = 13.5 Hz), 2.62-2.97 (3H, m), 4.27 (2H, brs), 7.28-7.36 (2H, m), 7.98-8.10 (2H, m).

[0145] [Example 2]

5-((2-(4-(1-Ethylpiperidin-4-yl)benzamide)pyridin-4-yl)oxy)-6-methoxy-N-methyl-1H-indole-1-carboxamide

[Chemical Formula 48]



Acetaldehyde (0.677 mL, 12.1 mmol) and sodium triacetoxyborohydride (2.57 g, 12.1 mmol) were added to a mixture of 6-methoxy-N-methyl-5-((2-(4-(piperidin-4-yl) benzamide)pyridin-4-yl)oxy)-1H-indole-1-carboxamide described in Example 1 (3.03 g, 6.06 mmol) and tetrahydrofuran (80 mL), and the mixture was stirred at room temperature for 3 hours. Ethyl acetate, a saturated aqueous sodium bicarbonate solution, and water were added to the reaction mixture for partition. The organic layer was washed with a saturated saline solution, and then dried over anhydrous sodium sulfate and filtered. The solvent was evaporated, the resultant residue was dissolved in dichloromethane, and the resultant was purified with NH silica gel column chromatography (n-heptane:ethyl acetate = 1:4 - 0:1 - ethyl acetate:methanol = 99:1 - 9:1). The target fraction was concentrated under vacuum and the residue was collected by filteration and washed with n-heptane and diethyl ether to

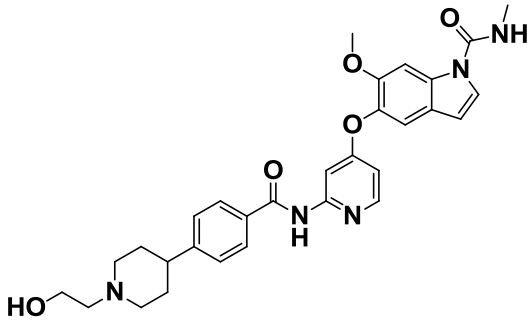
obtain the title compound (2.61 g, 82%).

^{1}H-NMR Spectrum ($CDCl_3$) δ (ppm): 1.12 (3H, t, J = 7.1 Hz), 1.77-1.90 (4H, m), 1.98-2.07 (2H, m), 2.45 (2H, q, J = 7.1 Hz), 2.52-2.62 (1H, m), 3.05-3.12 (5H, m), 3.83 (3H, s), 5.50-5.58 (1H, m), 6.55 (1H, d, J = 3.7 Hz), 6.60 (1H, dd, J = 5.9, 2.4 Hz), 7.23 (1H, d, J = 3.7 Hz), 7.30-7.35 (3H, m), 7.79 (2H, d, J = 8.2 Hz), 7.91 (1H, d, J = 2.4 Hz), 8.03 (1H, s), 8.10 (1H, d, J = 5.7 Hz), 8.50 (1H, brs).

[0146] [Example 3]

5-((2-(4-(1-(2-Hydroxyethyl)piperidin-4-yl)benzamide)pyridin-4-yl)oxy)-6-methoxy-N-methyl-1H-indole-1-carboxamide

[Chemical Formula 49]



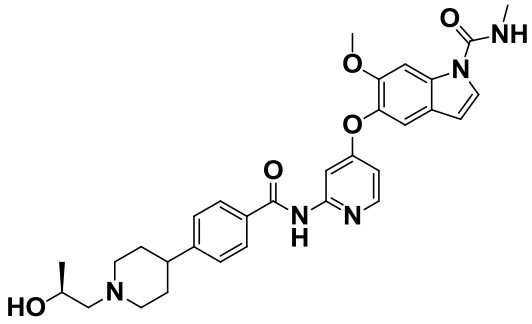
Commercially available 2-hydroxyacetaldehyde (110 mg, 1.83 mmol), sodium triacetoxyborohydride (382 mg, 1.80 mmol), and acetic acid (103 μL, 1.80 mmol) were added to a mixture of 6-methoxy-N-methyl-5-((2-(4-(piperidin-4-yl)benzamide)pyridin-4-yl)oxy)-1H-indole-1-carboxamide described in Example 1 (300 mg, 0.601 mmol) and tetrahydrofuran (15 mL) under nitrogen atmosphere, and the mixture was stirred at room temperature for 15 hours. A saturated aqueous sodium bicarbonate solution and ethyl acetate were added to the reaction mixture for partition. The organic layer was washed with a saturated saline solution, and then dried over anhydrous sodium sulfate and filtered. The solvent was evaporated, the resultant residue was dissolved in dichloromethane, and the resultant was purified with NH silica gel column chromatography (ethyl acetate:methanol = 99:1 - 4:1). The target fraction and the mixture fraction were concentrated under vacuum, then the residue of the mixture fraction was purified with NH silica gel column chromatography (ethyl acetate:methanol = 97:3 - 19:1 - 23:2). The combined target fraction was concentrated under vacuum and the precipitate was collected by filteration and washed with diethyl ether and ethyl acetate to obtain the title compound (209 mg, 64%).

^{1}H-NMR Spectrum ($CDCl_3$) δ (ppm): 1.70-1.90 (4H, m), 2.14-2.25 (2H, m), 2.53-2.65 (3H, m), 2.97-3.09 (2H, m), 3.06 (3H, d, J = 4.4 Hz), 3.63 (2H, t, J = 5.3 Hz), 3.86 (3H, s), 5.51-5.60 (1H, m), 6.54 (1H, d, J = 3.7 Hz), 6.61 (1H, dd, J = 5.7, 2.4 Hz), 7.23 (1H, d, J = 3.7 Hz), 7.29-7.35 (3H, m), 7.80 (2H, d, J = 8.4 Hz), 7.91 (1H, d, J = 2.6 Hz), 8.04 (1H, s), 8.10 (1H, d, J = 5.9 Hz), 8.51 (1H, brs).

[0147] [Example 4]

(S)-5-((2-(4-(1-(2-Hydroxypropyl)piperidin-4-yl)benzamide)pyridin-4-yl)oxy)-6-methoxy-N-methyl-1H-indole-1-carboxamide

[Chemical Formula 50]



Commercially available (S)-(-)-propylene oxide (233 mg, 4.00 mmol) was added to a mixture of 6-methoxy-N-methyl-5-((2-(4-(piperidin-4-yl)benzamide)pyridin-4-yl)oxy)-1H-indole-1-carboxamide described in Example 1 (400 mg, 0.801 mmol) and ethanol (10 mL), and the mixture was heated and stirred with a sealed tube at 60°C for 1 hour. The mixture was cooled to room temperature and then tetrahydrofuran (5.0 mL) was added, and the mixture was heated and stirred at 70°C for 2 hours. The reaction mixture was concentrated under vacuum, the resultant residue was dissolved in dichloromethane, and the resultant was purified with NH silica gel column chromatography (n-heptane:ethyl acetate = 1:4 - 0:1 - ethyl acetate:methanol = 99:1 - 19:1). The target fraction was concentrated under vacuum and the precipitate was collected by filteration and washed with diethyl ether and ethyl acetate to obtain the title compound (347 mg, 78%).

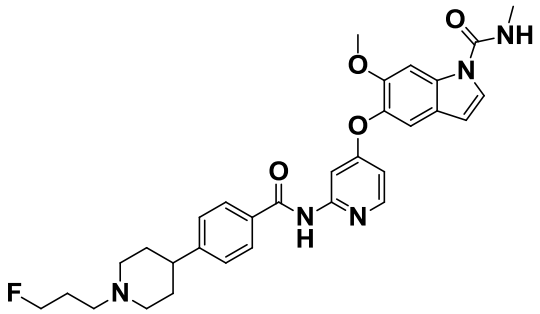
^{1}H-NMR Spectrum ($CDCl_3$) δ (ppm): 1.14 (3H, d, J = 6.2 Hz), 1.66-1.89 (4H, m), 1.98-2.09 (1H, m), 2.21-2.45 (3H, m), 2.52-2.64 (1H, m), 2.88-2.96 (1H, m), 3.06 (3H, d, J = 4.8 Hz), 3.10-3.17 (1H, m), 3.57 (1H, brs), 3.80-3.92 (1H, m), 3.86 (3H, s), 5.52-5.59 (1H, m), 6.54 (1H, d, J = 3.7 Hz), 6.60 (1H, dd, J = 5.9, 2.6 Hz), 7.23 (1H, d, J = 3.7 Hz), 7.29-7.35 (3H, m), 7.78-7.83 (2H, m), 7.91 (1H, d, J = 2.6 Hz), 8.03 (1H, s), 8.10 (1H, d, J = 5.9 Hz), 8.53 (1H,

brs).

[0148] [Example 5]

5-((2-(4-(1-(3-Fluoropropyl)piperidin-4-yl)benzamide)pyridin-4-yl)oxy)-6-methoxy-N-methyl-1H-indole-1-carboxamide

[Chemical Formula 51]



Triethylamine (11.8 μL, 0.085 mmol) and 3-fluoropropyl 4-methylbenzenesulfonate described in Production Example 5-1 (16.1 mg, 0.069 mmol) were added to a mixture of 6-methoxy-N-methyl-5-((2-(4-(piperidin-4-yl)benzamide)pyridin-4-yl)oxy)-1H-indole-1-carboxamide described in Example 1 (14.1 mg, 0.028 mmol) and N,N-dimethylformamide (0.5 mL), and the mixture was heated and stirred at 50°C for 1 hour and then stirred at room temperature for 13 hours. Triethylamine (11.8 μL, 0.085 mmol) and 3-fluoropropyl 4-methylbenzenesulfonate (16.1 mg, 0.069 mmol) were added to the reaction mixture, and the mixture was heated and stirred at 50°C for 3 hours. The resultant was cooled to room temperature and then water and ethyl acetate were added for partition. The organic layer was washed with a saturated saline solution, and then dried over anhydrous sodium sulfate and filtered. The solvent was evaporated, the resultant residue was dissolved in dichloromethane, and the resultant was purified with NH silica gel column chromatography (n-heptane:ethyl acetate = 2:3 - 0:1 - ethyl acetate:methanol = 99:1 - 19:1 - 9:1). The target fraction was concentrated under vacuum and the precipitate was collected by filteration and washed with diethyl ether to obtain the title compound (10.2 mg, 65%).

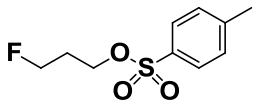
^{1}H-NMR Spectrum ($CDCl_3$) δ (ppm): 1.72-2.00 (6H, m), 2.02-2.13 (2H, m), 2.47-2.62 (3H, m), 3.01-3.09 (2H, m), 3.06 (3H, d, J = 4.8 Hz), 3.86 (3H, s), 4.47 (1H, t, J = 6.0 Hz), 4.59 (1H, t, J = 6.0 Hz), 5.48-5.58 (1H, m), 6.55 (1H, d, J = 3.7 Hz), 6.60 (1H, dd, J = 5.7, 2.4 Hz), 7.23 (1H, d, J = 3.7 Hz), 7.30-7.34 (3H, m), 7.77-7.82 (2H, m), 7.91 (1H, d, J = 2.6 Hz), 8.03 (1H, s), 8.10 (1H, d, J = 6.2 Hz), 8.50 (1H, brs).

[0149] The reagent 3-fluoropropyl 4-methylbenzenesulfonate was synthesized by the following method.

[0150] [Production Example 5-1]

3-Fluoropropyl 4-methylbenzenesulfonate

[Chemical Formula 52]



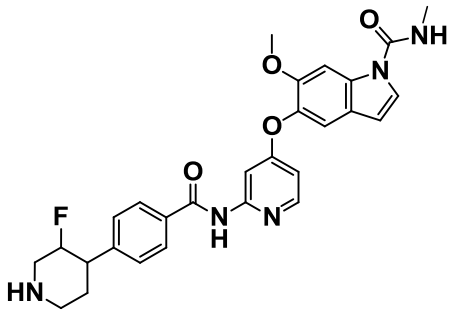
Triethylamine (11 mL, 79.4 mmol), 4-dimethylaminopyridine (390 mg, 3.19 mmol), and p-toluenesulfonyl chloride (13.4 g, 70.4 mmol) were added to a mixture of commercially available 3-fluoropropan-1-ol (5.0 g, 64 mmol) and tetrahydrofuran (120 mL) under nitrogen atmosphere at 0°C, and the mixture was stirred at room temperature for 90 hours. Water and ethyl acetate were added to the reaction mixture for partition. The organic layer was washed with water and a saturated saline solution, dried over anhydrous magnesium sulfate, and filtered. The solvent was evaporated, the resultant residue was dissolved in dichloromethane and n-heptane, and the resultant was purified with silica gel column chromatography (n-heptane:ethyl acetate = 10:1 - 2:1) to obtain the title compound (12.7 g, 85%).

^{1}H-NMR Spectrum ($CDCl_3$) δ (ppm): 1.97-2.15 (2H, m), 2.46 (3H, s), 4.16 (2H, t, J = 6.2 Hz), 4.49 (2H, dt, J = 46.8, 5.6 Hz), 7.36 (2H, dd, J = 8.4, 0.6 Hz), 7.75-7.85 (2H, m).

[0151] [Example 6]

5-((2-(4-(3-Fluoropiperidin-4-yl)benzamide)pyridin-4-yl)oxy)-6-methoxy-N-methyl-1H-indole-1-carboxamide

[Chemical Formula 53]



tert-Butyl

3-fluoro-4-(4-((4-((6-methoxy-1-(methylcarbamoyl)-1H-indol-5-yl)oxy)pyridin-2-yl)carbam

oyl)phenyl)piperidine-1-carboxylate described in Production Example 6-5 (29.1 mg, 0.047 mmol) was dissolved in dichloromethane (4 mL), trifluoroacetic acid (0.8 mL, 10.4 mmol) was added at room temperature, and then the mixture was stirred for 30 minutes. The solvent was evaporated, the resultant residue was dissolved in dichloromethane (4 mL), and triethylamine was added to neutralize the excessive trifluoroacetic acid. The solvent was evaporated and the resultant residue was purified with NH silica gel column chromatography (n-heptane:ethyl acetate = 1:4 - 0:1 - ethyl acetate:methanol = 97:3 - 19:1) to obtain the title compound (16.8 mg, 69%).

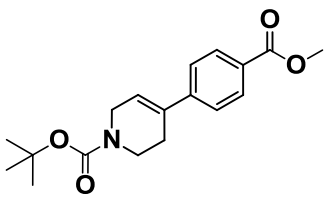
^{1}H-NMR Spectrum (500MHz, $CDCl_3$) δ (ppm): 1.71-1.80 (2H, m), 1.89-1.97 (1H, m), 2.63-2.70 (1H, m), 2.70-2.76 (1H, m), 2.79-2.89 (1H, m), 3.05 (3H, d, J = 4.9 Hz), 3.09 (1H, d, J = 11.2 Hz), 3.48 (1H, dt, J = 11.3, 4.1 Hz), 3.87 (3H, s), 4.58 (1H, dtd, J = 50.0, 9.9, 4.6 Hz), 5.58 (1H, q, J = 4.7 Hz), 6.54 (1H, d, J = 3.4 Hz), 6.61 (1H, dd, J = 5.6, 2.2 Hz), 7.22 (1H, d, J = 3.9 Hz), 7.32 (1H, s), 7.38 (2H, d, J = 8.3 Hz), 7.84 (2H, d, J = 8.3 Hz), 7.91 (1H, d, J = 2.4 Hz), 8.04 (1H, s), 8.10 (1H, d, J = 5.9 Hz), 8.57 (1H, s).

[0152] The starting material tert-butyl 3-fluoro-4-(4-((4-((6-methoxy-1-(methylcarbamoyl)-1H-indol-5-yl)oxy)pyridin-2-yl)carbamoyl)phenyl)piperidine-1-carboxylate was synthesized by the following method.

[0153] [Production Example 6-1]

tert-Butyl 4-(4-(methoxycarbonyl)phenyl)-5,6-dihydropyridine-1(2H)-carboxylate

[Chemical Formula 54]



Toluene (20 mL), ethanol (6 mL), and water (2 mL) were added to commercially available 1-N-BOC-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-3,6-dihydro-2H-pyridine (1.00 g, 3.23 mmol), methyl 4-bromobenzoate (695 mg, 3.23 mmol), 2-dicyclohexylphosphino-2',6'-dimethoxy biphenyl (266 mg, 0.65 mmol), palladium(II) acetate (73 mg, 0.32 mmol), and tripotassium phosphate (2.06 g, 9.70 mmol) under nitrogen atmosphere, and the mixture was stirred at 90°C for 5 hours. The reaction mixture was cooled to room temperature and a saturated aqueous sodium bicarbonate solution and ethyl acetate were added for partition. The aqueous layer was extracted with ethyl acetate three

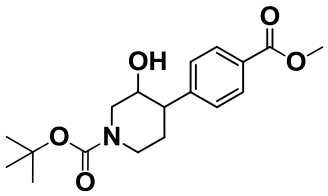
times and then the organic layer was dried over anhydrous sodium sulfate and filtered. The solvent was evaporated and the resultant residue was purified with silica gel column chromatography (n-heptane:ethyl acetate = 19:1 - 13:7) to obtain the title compound (0.99 g, 96%).

^{1}H-NMR Spectrum (500MHz, $CDCl_3$) δ (ppm): 1.49 (9H, s), 2.55 (2H, brs), 3.65 (2H, t, J = 5.9 Hz), 3.92 (3H, s), 4.10 (2H, brs), 6.16 (1H, brs), 7.43 (2H, d, J = 8.3 Hz), 8.00 (2H, d, J = 8.8 Hz).

[0154] [Production Example 6-2]

tert-Butyl 3-hydroxy-4-(4-(methoxycarbonyl)phenyl)piperidine-1-carboxylate

[Chemical Formula 55]



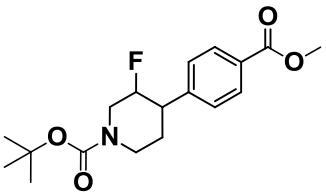
tert-Butyl 4-(4-(methoxycarbonyl)phenyl)-5,6-dihydropyridine-1(2H)-carboxylate described in Production Example 6-1 (776 mg, 2.45 mmol) was dissolved in tetrahydrofuran (10 mL), a solution of borane-methyl sulfide complex (0.269 mL, 2.69 mmol) in tetrahydrofuran (10 mL) was added at room temperature over 3 minutes, and the mixture was stirred for 13 hours. The reaction liquid was cooled to 0°C and a 1 M sodium hydroxide solution (6.12 mL, 6.12 mmol) was added over 1 minute. 30% Hydrogen peroxide water (0.625 mL, 6.12 mmol) was added, and the mixture was stirred at room temperature for 45 minutes. A saturated aqueous sodium thiosulfate solution (20 mL), water, and ethyl acetate were serially added to the reaction mixture. The aqueous layer was extracted with ethyl acetate three times and then the organic layers were combined, dried over anhydrous magnesium sulfate, and filtered. The solvent was evaporated and the resultant residue was purified with silica gel column chromatography (n-heptane:ethyl acetate = 4:1 - 1:4) to obtain the title compound (518 mg, 63%).

^{1}H-NMR Spectrum (500MHz, $CDCl_3$) δ (ppm): 1.49 (9H, s), 1.59 (1H, d, J = 2.9 Hz), 1.69-1.88 (2H, m), 2.57-2.71 (2H, m), 2.77 (1H, brs), 3.67-3.82 (1H, m), 3.91 (3H, s), 4.22 (1H, brs), 4.42 (1H, brs), 7.34 (2H, d, J = 8.3 Hz), 8.02 (2H, d, J = 8.3 Hz).

[0155] [Production Example 6-3]

tert-Butyl 3-fluoro-4-(4-(methoxycarbonyl)phenyl)piperidine-1-carboxylate

[Chemical Formula 56]



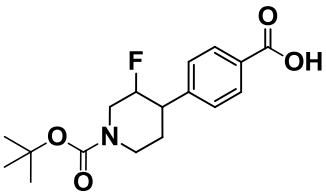
tert-Butyl 3-hydroxy-4-(4-(methoxycarbonyl)phenyl)piperidine-1-carboxylate described in Production Example 6-2 (518 mg, 1.54 mmol) was dissolved in dichloromethane (15 mL), [bis-(2-methoxyethyl)amino]sulfur trifluoride (0.313 mL, 1.70 mmol) was added at -78°C over 3 minutes, and the mixture was stirred for 1 hour while warming to room temperature. A saturated aqueous sodium bicarbonate solution and ethyl acetate were serially added to the reaction mixture. The aqueous layer was extracted with ethyl acetate three times and then the organic layers were combined, dried over anhydrous sodium sulfate, and filtered. The solvent was evaporated and the resultant residue was purified with silica gel column chromatography (n-heptane:ethyl acetate = 19:1 - 3:2) to obtain the title compound (402 mg, 77%).

^{1}H-NMR Spectrum (500MHz, $CDCl_3$) δ (ppm): 1.49 (9H, s), 1.64-1.81 (1H, m), 1.86-2.01 (1H, m), 2.72-2.94 (3H, m), 3.91 (3H, s), 4.19 (1H, brs), 4.44-4.66 (2H, m), 7.33 (2H, d, J = 8.3 Hz), 8.02 (2H, d, J = 8.3 Hz).

[0156] [Production Example 6-4]

4-(1-(tert-Butoxycarbonyl)-3-fluoropiperidin-4-yl)benzoic acid

[Chemical Formula 57]



tert-Butyl 3-fluoro-4-(4-(methoxycarbonyl)phenyl)piperidine-1-carboxylate described in Production Example 6-3 (402 mg, 1.19 mmol) was dissolved in tetrahydrofuran (18 mL), methanol (6 mL), and water (4 mL), then a 2 M aqueous lithium hydroxide solution (4.17 mL, 8.34 mmol) was added at room temperature, and then the mixture was stirred for 3 hours. Tetrahydrofuran and methanol were evaporated under vacuum and 1 M hydrochloric acid was added to the residual solution for neutralization. The aqueous layer was extracted with ethyl acetate four times, and the organic layers were combined, dried over anhydrous sodium sulfate, and filtered. The solvent was evaporated and the resultant residue was purified with silica gel column chromatography (n-heptane:ethyl acetate = 4:1 -

1:4) to obtain the title compound (347 mg, 90%).

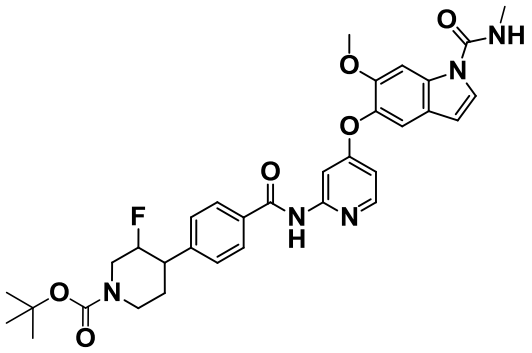
^{1}H-NMR Spectrum (500MHz, $CDCl_3$) δ (ppm): 1.50 (9H, s), 1.77 (1H, qd, J = 13.0, 3.9 Hz), 1.92 (1H, d, J = 14.1 Hz), 2.72-2.95 (3H, m), 4.21 (1H, brs), 4.46-4.67 (2H, m), 7.37 (2H, d, J = 8.3 Hz), 8.09 (2H, d, J = 8.3 Hz).

[0157] [Production Example 6-5]

tert-Butyl

3-fluoro-4-(4-((4-((6-methoxy-1-(methylcarbamoyl)-1H-indol-5-yl)oxy)pyridin-2-yl)carbamoyl)phenyl)piperidine-1-carboxylate

[Chemical Formula 58]



Thionyl chloride (30 μL, 0.319 mmol) was added to a mixture of benzotriazole (49.3 mg, 0.414 mmol) and dichloromethane (4 mL) under nitrogen atmosphere, and the mixture was stirred at room temperature for 5 minutes. 4-(1-(tert-Butoxycarbonyl)-3-fluoropiperidin-4-yl)benzoic acid described in Production Example 6-4 (103 mg, 0.319 mmol) was added, and the mixture was stirred at room temperature for 30 minutes. The reaction liquid was filtered through anhydrous sodium sulfate and the anhydrous sodium sulfate was washed with dichloromethane (4 mL) to obtain a dichloromethane solution of the crude product.

A dichloromethane solution of the above-described crude product (4 mL, 0.16 mmol) was added to a mixture of 5-((2-aminopyridin-4-yl)oxy)-6-methoxy-N-methyl-1H-indole-1-carboxamide described in Production Example 1-6 (25.0 mg, 0.080 mmol), triethylamine (56 μL, 0.40 mmol), 4-dimethylaminopyridine (1.0 mg, 0.008 mmol), and dichloromethane (1 mL) at 0°C, then the mixture was stirred at 0°C for 10 minutes and then at room temperature for 3 hours. A 40% aqueous methylamine solution (138 μL, 1.60 mmol) was added, and the mixture was further stirred at room temperature for 2 hours. A saturated aqueous sodium bicarbonate solution and ethyl acetate were added to the reaction mixture for partition. The aqueous

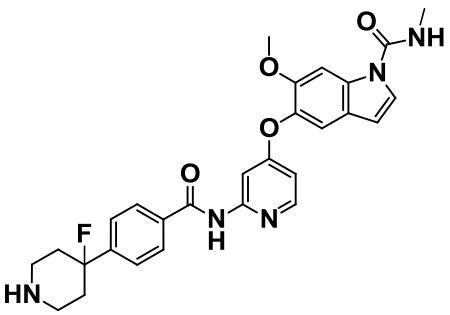
layer was extracted with ethyl acetate three times and then the organic layers were combined, dried over anhydrous sodium sulfate, and filtered. The solvent was evaporated and the resultant residue was purified with NH silica gel column chromatography (n-heptane:ethyl acetate = 1:1 - 0:1) to obtain the title compound (29.1 mg, 59%).

^{1}H-NMR Spectrum (500MHz, $CDCl_3$) δ (ppm): 1.49 (9H, s), 1.65-1.82 (1H, m), 1.91 (1H, brs), 2.69-2.93 (3H, m), 3.04 (3H, d, J = 4.9 Hz), 3.86 (3H, s), 4.18 (1H, brs), 4.42-4.66 (2H, m), 5.65 (1H, q, J = 4.4 Hz), 6.53 (1H, d, J = 3.4 Hz), 6.62 (1H, dd, J = 5.9, 2.4 Hz), 7.23 (1H, d, J = 3.9 Hz), 7.31 (1H, s), 7.36 (2H, d, J = 8.3 Hz), 7.84 (2H, d, J = 8.3 Hz), 7.91 (1H, d, J = 2.0 Hz), 8.05 (1H, s), 8.09 (1H, d, J = 5.9 Hz), 8.63 (1H, s).

[0158] [Example 7]

5-((2-(4-(4-Fluoropiperidin-4-yl)benzamide)pyridin-4-yl)oxy)-6-methoxy-N-methyl-1H-indole-1-carboxamide

[Chemical Formula 59]



Benzotriazole (33.2 mg, 0.278 mmol) was dissolved in dichloromethane (10 mL) under nitrogen atmosphere, then thionyl chloride (20 μL, 0.278 mmol) was added, and the mixture was stirred at 20°C for 5 minutes. 4-(1-tert-Butoxycarbonyl)-4-fluoropiperidin-4-yl)benzoic acid described in Production Example 7-4 (60 mg, 0.186 mmol) was added to the reaction mixture, and the mixture was stirred at 20°C for 2 hours. The reaction mixture was filtered and dichloromethane was evaporated under vacuum until the amount thereof became as small as about 5 ml. 5-((2-Aminopyridin-4-yl)oxy)-6-methoxy-N-methyl-1H-indole-1-carboxamide described in Production Example 1-6 (25 mg, 0.08 mmol), triethylamine (55 μL, 0.40 mmol), and 4-dimethylaminopyridine (1.96 mg, 0.016 mmol) were serially added to the resultant reaction mixture, and the mixture was stirred at room temperature for 2 hours. A 2 M methylamine tetrahydrofuran solution (120 μL, 0.24 mmol) was added to the reaction mixture, then the mixture was stirred at room temperature for 1 hour, and then ethyl acetate

and a saturated aqueous sodium bicarbonate solution were added for partition. The organic layer was dried over anhydrous sodium sulfate and filtered. The solvent was evaporated under vacuum and the resultant residue was dissolved in dichloromethane (5 mL), then trifluoroacetic acid (1 mL) was added at 0°C, and then the mixture was stirred at room temperature for 1 hour. The solvent was evaporated under vacuum, an azeotropic mixture of the resultant residue with toluene was formed, and then the mixture was dried under vacuum. The resultant residue was dissolved in a mixed solvent of dichloromethane and triethylamine, and the resultant was purified with NH silica gel column chromatography (ethyl acetate:methanol = 1:0 - 17:3). The target fraction was concentrated under vacuum to obtain the title compound (11.8 mg, 29%).

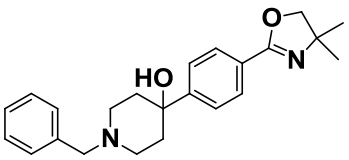
^{1}H-NMR Spectrum ($CDCl_3$) δ (ppm): 1.73-2.01 (4H, m), 2.91- 3.23 (7H, m), 3.86 (3H, s), 5.76-5.91 (1H, m), 6.44-6.52 (1H, m), 6.64 (1H, dd, J = 5.9, 2.2 Hz), 7.22 (1H, d, J = 3.7 Hz), 7.31 (1H, s), 7.48 (2H, d, J = 8.4 Hz) 7.81-7.97 (3H, m), 8.02-8.14 (2H, m), 8.74 (1H, brs).

[0159] The starting material 4-(1-tert-butoxycarbonyl)-4-fluoropiperidin-4-yl)benzoic acid was synthesized by the following method.

[0160] [Production Example 7-1]

1-Benzyl-4-(4-(4,4-dimethyl-4,5-dihydrooxazol-2-yl)phenyl)piperidin-4-ol

[Chemical Formula 60]



Magnesium (3.10 g, 127 mmol), iodine (135 mg, 0.531 mmol), and 2-(4-bromophenyl)-4,5-dihydro-4,4-dimethyloxazole (27 g, 106 mmol) were added to tetrahydrofuran (120 mL), and the mixture was heated under reflux for 1 hour. This reaction mixture was cooled to room temperature, then 1-benzyl-4-piperidone (21.7 mL, 117 mmol) was added, and the mixture was heated under reflux for 3 hours. The reaction mixture was cooled to room temperature and then a saturated aqueous ammonium chloride solution and ethyl acetate were added for partition. The aqueous layer was extracted with ethyl acetate, and then the organic layers were combined and washed serially with water and a saturated saline solution. The organic layer was dried over anhydrous magnesium sulfate and filtered. The solvent was evaporated under vacuum and the resultant residue was purified with silica gel column chromatography (n-heptane:ethyl acetate = 3:1 - 1:1). The

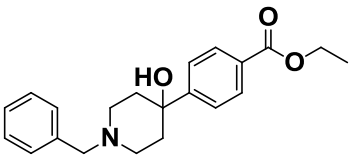
target fraction was concentrated under vacuum to obtain the title compound (13.4 g, 35%).

^{1}H-NMR Spectrum ($CDCl_3$) δ (ppm): 1.37 (6H, s), 1.67-1.76 (2H, m), 2.16 (2H, td, J = 13.1, 4.5 Hz), 2.47 (2H, td, J = 12.0, 2.5 Hz), 2.79 (2H, d, J = 11.4 Hz), 3.58 (2H, s), 4.09 (2H, s), 7.23-7.40 (5H, m), 7.55 (2H, d, J = 8.8 Hz), 7.91 (2H, d, J = 8.6 Hz).

[0161] [Production Example 7-2]

Ethyl 4-(1-benzyl-4-hydroxypiperidin-4-yl)benzoate

[Chemical Formula 61]



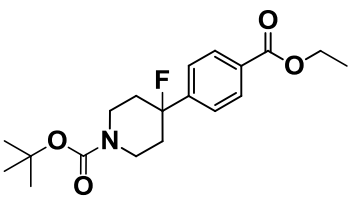
1-Benzyl-4-(4-(4,4-dimethyl-4,5-dihydrooxazol-2-yl)phenyl)piperidin-4-ol described in Production Example 7-1 (13.4 g, 36.8 mmol) was dissolved in ethanol (300 mL), then sulfuric acid was added, and the mixture was stirred at 90°C for 12 hours. The reaction mixture was cooled to room temperature and then the solvent was evaporated under vacuum. The resultant residue was dissolved in dichloromethane, the resultant was washed with a saturated aqueous sodium bicarbonate solution, and then the organic layer was dried over anhydrous sodium sulfate and filtered. The solvent was evaporated under vacuum and the resultant residue was purified with NH silica gel column chromatography (n-heptane:ethyl acetate = 4:1 - 1:1). The target fraction was concentrated under vacuum to obtain the title compound (7.23 g, 58%).

^{1}H-NMR Spectrum ($CDCl_3$) δ (ppm): 1.39 (3H, t, J = 7.1 Hz), 1.59-1.85 (2H, m), 2.17 (2H, td, J = 13.1, 4.5 Hz), 2.47 (2H, td, J = 12.0, 2.5 Hz), 2.72-2.93 (2H, m), 3.59 (2H, s), 4.37 (2H, q, J = 7.0 Hz), 7.14-7.44 (5H, m), 7.59 (2H, d, J = 8.4 Hz), 8.02 (2H, d, J = 8.4 Hz).

[0162] [Production Example 7-3]

tert-Butyl 4-(4-(ethoxycarbonyl)phenyl)-4-fluoropiperidine-1-carboxylate

[Chemical Formula 62]



Ethyl 4-(1-benzyl-4-hydroxypiperidin-4-yl)benzoate described in Production Example 7-2 (6.23 g, 18.4 mmol) was dissolved in dichloromethane (200 mL) under

nitrogen atmosphere, then diethylaminosulfur trifluoride (2.89 mL, 22.0 mmol) was added at -78°C, and the mixture was stirred at room temperature for 3 hours. Dichloromethane was added to the reaction mixture, and the mixture was washed with water and then dried over anhydrous magnesium sulfate and filtered. The solvent was evaporated under vacuum to obtain a crude product A (6.13 g).

The crude product A (6.13 g) was dissolved in dichloromethane (100 mL) under nitrogen atmosphere, then 1-chloroethyl chloroformate (2.13 mL, 19.8 mmol) was added, and the mixture was stirred at 20°C for 2 hours. The reaction mixture was concentrated under vacuum, then the resultant residue was dissolved in methanol (100 mL), and the resultant was heated under reflux for 30 minutes. The reaction mixture was concentrated under vacuum, then diethyl ether was added to the resultant residue, the precipitate was collected by filteration, and then the resultant was washed with diethyl ether to obtain a crude product B (4.72 g).

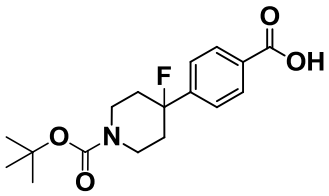
The crude product B (4.72 g) was dissolved in dichloromethane (50 mL), then triethylamine (5.24 mL, 37.6 mmol) and di-tert-butyl dicarbonate (4.92 g, 22.5 mmol) were added, and the mixture was stirred at room temperature for 1 hour. Water and ethyl acetate were added to the reaction mixture for partition. The aqueous layer was extracted with ethyl acetate again, and then the organic layers were combined and washed with water and then with a saturated saline solution. The organic layer was dried over anhydrous magnesium sulfate and filtered. The solvent was evaporated under vacuum and the resultant residue was purified with silica gel column chromatography (n-heptane:ethyl acetate = 9:1 - 1:1). The target fraction was concentrated under vacuum to obtain the title compound (3.74 g, 58%).

^{1}H-NMR Spectrum ($CDCl_3$) δ (ppm): 1.24-1.34 (1H, m), 1.40 (3H, t, J = 7.1 Hz), 1.50 (9H, s), 1.86-2.14 (2H, m), 2.54 (1H, brs), 3.18 (1H, brs), 3.65 (1H, t, J = 5.7 Hz), 4.00-4.26 (2H, m), 4.38 (2H, qd, J = 7.1, 3.1 Hz), 7.43 (2H, dd, J = 8.6, 1.3 Hz), 8.03 (2H, dd, J = 18.1, 8.6 Hz).

[0163] [Production Example 7-4]

4-(1-tert-Butoxycarbonyl)-4-fluoropiperidin-4-yl)benzoic acid

[Chemical Formula 63]



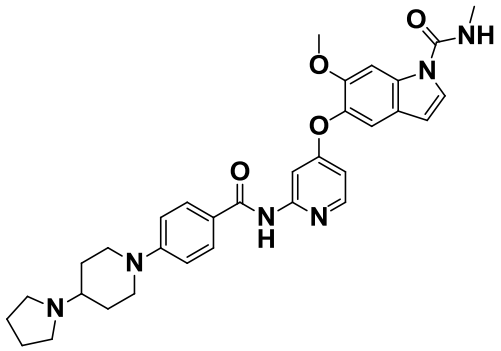
tert-Butyl 4-(4-(ethoxycarbonyl)phenyl)-4-fluoropiperidine-1-carboxylate described in Production Example 7-3 (3.74 g, 10.6 mmol) was dissolved in a mixed solvent of tetrahydrofuran (10 mL) and methanol (5 mL), then a 1 M sodium hydroxide solution (42.6 mL) was added, and the mixture was stirred at 50°C for 4 hours. 1 M Hydrochloric acid was added to the reaction mixture, the precipitate was collected by filteration and washed with water, and then the resultant was dried by through-flow drying to obtain the title compound (1.33 g, 39%).

^{1}H-NMR Spectrum (DMSO-d_6) δ (ppm): 1.43 (9H, s), 1.83-2.15 (4H, m), 3.06 (2H, brs), 3.99 (2H, d, J = 10.3 Hz), 7.50 (2H, d, J = 8.4 Hz), 7.92 (2H, d, J = 8.4 Hz).

[0164] [Example 8]

6-Methoxy-N-methyl-5-((2-(4-(4-(pyrrolidin-1-yl)piperidin-1-yl)benzamide)pyridin-4-yl)oxy)-1H-indole-1-carboxamide

[Chemical Formula 64]



Oxalyl chloride (27 μL, 0.321 mmol) and N,N-dimethylformamide (1.24 μL, 0.016 mmol) were added to a solution of 4-(4-(pyrrolidin-1-yl)piperidin-1-yl)benzoic acid described in Production Example 8-2 (44 mg, 0.16 mmol) in dichloromethane (2 mL) at room temperature. The reaction liquid mixture was stirred at room temperature for 1 hour. The reaction liquid mixture was concentrated and triethylamine (112 μL, 0.80 mmol), 5-((2-aminopyridin-4-yl)oxy)-6-methoxy-N-methyl-1H-indole-1-carboxamide described in Production Example 1-6 (50 mg, 0.16 mmol), and 4-dimethylaminopyridine (3.91 mg, 0.032 mmol) were serially added to a solution of the residue in dichloromethane (2 mL) at room temperature. The reaction liquid mixture was stirred at room temperature. A saturated

aqueous sodium bicarbonate solution was added to the reaction liquid and then ethyl acetate was added for dilution. The aqueous layer was extracted with ethyl acetate, then the combined organic layer was dried over anhydrous sodium sulfate. The drying agent was separated by filtration and then the filtrate was concentrated under vacuum. The residue was purified with NH silica gel column chromatography (n-heptane:ethyl acetate = 1:1 - 0:1) to obtain the title compound (3.6 mg, 4.0%).

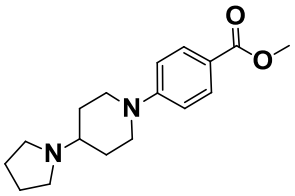
^{1}H-NMR Spectrum ($CDCl_3$) δ (ppm): 1.18-1.38 (2H, m), 1.84 (4H, brs), 1.95-2.11 (2H, m), 2.24-2.38 (1H, m), 2.70 (4H, brs), 2.82-2.96 (2H, m), 3.06 (3H, d, J = 4.8 Hz), 3.80-3.91 (5H, m), 5.52-5.68 (1H, m), 6.54 (1H, d, J = 3.3 Hz), 6.61 (1H, dd, J = 5.9, 2.2 Hz), 6.89 (2H, d, J = 8.8 Hz), 7.23 (1H, d, J = 3.7 Hz), 7.32 (1H, s), 7.75 (2H, d, J = 8.8 Hz), 7.90 (1H, d, J = 2.2 Hz), 8.02 (1H, s), 8.09 (1H, d, J = 5.9 Hz), 8.56 (1H, brs).

[0165] The starting material 4-(4-(pyrrolidin-1-yl)piperidin-1-yl)benzoic acid was synthesized by the following method.

[0166] [Production Example 8-1]

Methyl 4-(4-(pyrrolidin-1-yl)piperidin-1-yl)benzoate

[Chemical Formula 65]



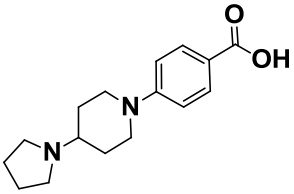
Commercially available methyl 4-fluorobenzoate (1.5 g, 9.73 mmol) was added to a solution of commercially available 4-(1-pyrrolidinyl)piperidine (3.0 g, 19.5 mmol) in dimethylsulfoxide (15 mL) at room temperature and then the mixture was stirred under nitrogen atmosphere and under irradiation with microwave at 150°C for 4 hours. The reaction liquid was allowed to stand to cool to room temperature and then diluted with water and ethyl acetate. The organic layer was washed with water and then dried by a conventional method. The drying agent was separated by filtration and then the filtrate was concentrated under vacuum. The residue was purified with NH silica gel column chromatography (n-heptane:ethyl acetate = 1:1) to obtain the title compound (2.06 g, 73%).

^{1}H-NMR Spectrum ($CDCl_3$) δ (ppm): 1.54-1.70 (2H, m), 1.74-1.88 (4H, m), 1.93-2.06 (2H, m), 2.12-2.26 (1H, m), 2.53-2.65 (4H, m), 2.90 (2H, td, J = 12.4, 2.6 Hz), 3.74-3.97 (5H, m), 6.86 (2H, d, J = 9.2 Hz), 7.89 (2H, d, J = 9.2 Hz).

[0167] [Production Example 8-2]

4-(4-(Pyrrolidin-1-yl)piperidin-1-yl)benzoic acid

[Chemical Formula 66]



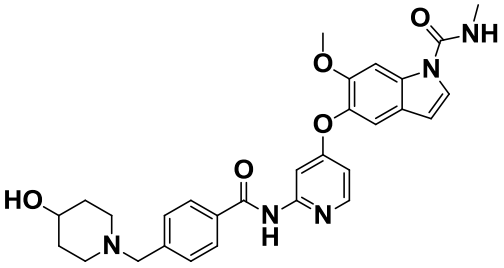
A 5 M sodium hydroxide solution (15 mL, 75.0 mmol) was added to a solution of methyl 4-(4-(pyrrolidin-1-yl)piperidin-1-yl)benzoate described in Production Example 8-1 (2.06 g, 7.14 mmol) in tetrahydrofuran (10 mL) and methanol (10 mL). The reaction liquid was stirred at 50°C for 4 hours. The reaction liquid was cooled to 0°C and then 5 M hydrochloric acid was dripped until pH reached 1. The liquid mixture was diluted with ethyl acetate. The organic layer was washed with a saturated saline solution and then dried over anhydrous sodium sulfate. The drying agent was separated by filtration and then the filtrate was concentrated under vacuum to obtain the title compound (1.61 g, 82%).

ESI-MS(m/z):297[M+H]$^+$.

[0168] [Example 9]

5-((2-(4-((4-Hydroxypiperidin-1-yl)methyl)benzamide)pyridin-4-yl)oxy)-6-methoxy-N-methyl-1H-indole-1-carboxamide

[Chemical Formula 67]



Triethylamine (1.6 mL, 11.5 mmol) and commercially available 4-(chloromethyl)benzoyl chloride (1.37 g, 7.25 mmol) were added to a mixture of 5-((2-aminopyridin-4-yl)oxy)-6-methoxy-N-methyl-1H-indole-1-carboxamide described in Production Example 1-6 (905 mg, 2.90 mmol) and tetrahydrofuran (28 mL) under nitrogen atmosphere at 0°C. The mixture was stirred at room temperature for 100 minutes, then triethylamine (1.6 mL, 11.5 mmol) and 4-(chloromethyl)benzoyl chloride (0.90 g, 4.76 mmol) were added to the reaction mixture at 0°C, and then the resultant was stirred at room temperature for 1.5 hours. Water, tetrahydrofuran, and ethyl acetate were added to the

reaction mixture for partition. The organic layer was washed with a saturated saline solution and then dried over anhydrous magnesium sulfate. The resultant was filtered with NH silica gel (ethyl acetate) and then concentrated under vacuum to obtain a crude product.

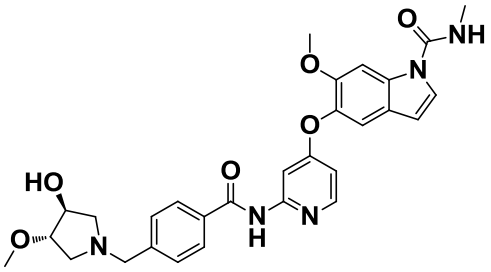
The crude product was dissolved in N,N-dimethylformamide (15 mL), commercially available 4-hydroxypiperidine (1.48 g, 14.6 mmol) was added under nitrogen atmosphere at room temperature, and the mixture was stirred for 16 hours. Water and ethyl acetate were added to the reaction mixture for partition and the aqueous layer was extracted with ethyl acetate. The combined organic layer was washed with water and a saturated saline solution, dried over anhydrous magnesium sulfate, and filtered. The solvent was evaporated, the resultant residue was dissolved in dichloromethane, and the resultant was purified with NH silica gel column chromatography (ethyl acetate:methanol = 1:0 - 9:1 - 17:3 - 4:1). The target product was collected by filteration and washed with ethyl acetate to obtain the title compound (1.30 g, 84%).

^{1}H-NMR Spectrum (DMSO-d_6) δ (ppm): 1.32-1.44 (2H, m), 1.64-1.74 (2H, m), 1.97-2.09 (2H, m), 2.59-2.69 (2H, m), 2.86 (3H, d, J = 4.2 Hz), 3.39-3.50 (3H, m), 3.76 (3H, s), 4.54 (1H, d, J = 4.2 Hz), 6.63 (1H, d, J = 3.7 Hz), 6.65 (1H, dd, J = 5.7, 2.2 Hz), 7.37 (2H, d, J = 8.1 Hz), 7.44 (1H, s), 7.66 (1H, d, J = 2.4 Hz), 7.78 (1H, d, J = 3.7 Hz), 7.92 (2H, d, J = 8.2 Hz), 8.10 (1H, s), 8.15-8.22 (2H, m), 10.68 (1H, s).

[0169] [Example 10]

5-((2-(4-(((3S,4S)-3-Hydroxy-4-methoxypyrrolidin-1-yl)methyl)benzamide)pyridin-4-yl)oxy)-6-methoxy-N-methyl-1H-indole-1-carboxamide

[Chemical Formula 68]



The crude product described in Example 9 (20.2 mg, 0.033 mmol) was dissolved in N,N-dimethylformamide (0.5 mL), then (3S,4S)-4-methoxypyrrolidin-3-ol (55.9 mg, 0.477 mmol) (described in EP 1375465) was added under nitrogen atmosphere at room temperature, and then the mixture was stirred for 200 minutes. Water and ethyl acetate were added to the reaction mixture for partition, and the organic layer was washed with a

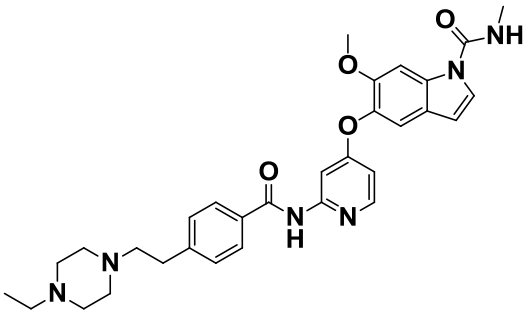
saturated saline solution and then dried over anhydrous sodium sulfate. The drying agent was filtered off, the solvent was evaporated, the resultant residue was dissolved in dichloromethane, and the resultant was purified with NH silica gel column chromatography (ethyl acetate:methanol = 1:0 - 19:1 - 9:1). The residue was washed with diethyl ether to obtain the title compound (13.8 mg, 77%).

^{1}H-NMR Spectrum ($CDCl_3$) δ (ppm): 2.32 (1H, dd, J = 10.1, 4.2 Hz), 2.61-2.68 (1H, m), 2.70-2.77 (1H, m), 3.03-3.16 (4H, m), 3.36 (3H, s), 3.62-3.76 (4H, m), 3.87 (3H, s), 4.12-4.19 (1H, m), 5.42-5.51 (1H, m), 6.56 (1H, d, J = 3.7 Hz), 6.59-6.62 (1H, m), 7.23 (1H, d, J = 3.7 Hz), 7.32 (1H, s), 7.42 (2H, d, J = 8.4 Hz), 7.81 (2H, d, J = 8.1 Hz), 7.91 (1H, d, J = 2.2 Hz), 8.03 (1H, s), 8.11 (1H, d, J = 5.9 Hz), 8.48 (1H, brs).

[0170] [Example 11]

5-((2-(4-(2-(4-Ethylpiperazin-1-yl)ethyl)benzamide)pyridin-4-yl)oxy)-6-methoxy-N-methyl-1H-indole-1-carboxamide

[Chemical Formula 69]



Thionyl chloride (0.116 mL, 1.60 mmol) was added to a mixture of commercially available 4-(2-chloroethyl)benzoic acid (88 mg, 0.479 mmol) and 1,2-dichloroethane (1.0 mL) under nitrogen atmosphere at room temperature, and the mixture was heated under reflux at 90°C for 1.5 hours. The mixture was cooled to room temperature, then the solvent was evaporated, and the resultant was dissolved in tetrahydrofuran (1.0 mL), and thus an acid chloride solution was prepared. Triethylamine (0.443 mL, 3.20 mmol) was added to a mixture of 5-((2-aminopyridin-4-yl)oxy)-6-methoxy-N-methyl-1H-indole-1-carboxamide described in Production Example 1-6 (49.9 mg, 0.160 mmol) and N,N-dimethylformamide (0.5 mL) under nitrogen atmosphere at room temperature, and the mixture was cooled to 0°C. A previously prepared tetrahydrofuran solution of acid chloride was added at the same temperature, and the mixture was stirred at room temperature for 2.5 hours. Water and ethyl acetate were added to the reaction mixture for partition, then the organic layer was

washed with a saturated saline solution and dried over anhydrous sodium sulfate. The solvent was evaporated, and the resultant residue was dissolved in dichloromethane, the resultant was purified with NH silica gel column chromatography (n-heptane:ethyl acetate = 3:1 - 0:1), and then the target fraction was concentrated under vacuum to obtain a crude product (48.9 mg).

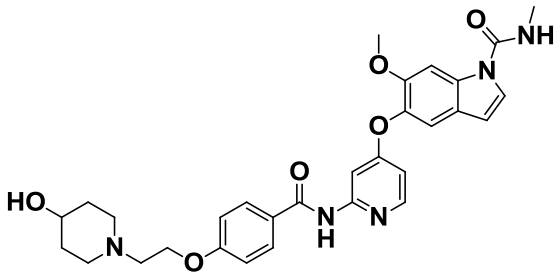
The crude product (48.9 mg) was dissolved in N,N-dimethylformamide (0.25 mL), then commercially available N-ethylpiperazine (129 μL, 1.02 mmol) and N,N-diisopropylethylamine (26.6 μL, 0.153 mmol) were added under nitrogen atmosphere at room temperature, and the mixture was heated and stirred at 60°C for 16 hours. The mixture was cooled to room temperature, then water and ethyl acetate were added to the reaction mixture for partition, and then the organic layer was washed with a saturated saline solution, dried over anhydrous sodium sulfate, and filtered. The solvent was evaporated, the resultant residue was dissolved in dichloromethane, and the resultant was purified with NH silica gel column chromatography (n-heptane:ethyl acetate = 1:1 - 0:1 - ethyl acetate:methanol = 99:1 - 19:1). The mixture fraction was concentrated under vacuum and the residue was purified with NH silica gel TLC (ethyl acetate) to obtain the title compound (7.03 mg, 16%).

^{1}H-NMR Spectrum ($CDCl_3$) δ (ppm): 1.10 (3H, t, J = 7.3 Hz), 2.44 (2H, q, J = 7.0 Hz), 2.35-2.70 (10H, m), 2.81-2.90 (2H, m), 3.07 (3H, d, J = 4.8 Hz), 3.86 (3H, s), 5.43-5.51 (1H, m), 6.56 (1H, d, J = 3.7 Hz), 6.60 (1H, dd, J = 5.9, 2.6 Hz), 7.23 (1H, d, J = 3.7 Hz), 7.28-7.33 (3H, m), 7.78 (2H, d, J = 8.4 Hz), 7.91 (1H, d, J = 2.2 Hz), 8.03 (1H, s), 8.10 (1H, d, J = 5.9 Hz), 8.46 (1H, brs).

[0171] [Example 12]

5-((2-(4-(2-(4-Hydroxypiperidin-1-yl)ethoxy)benzamide)pyridin-4-yl)oxy)-6-methoxy-N-methyl-1H-indole-1-carboxamide

[Chemical Formula 70]



Oxalyl chloride (44 μL, 0.513 mmol) and a catalytic quantity of

N,N-dimethylformamide were added to a mixture of 4-(2-chloroethoxy)benzoic acid described in Production Example 12-1 (51.2 mg, 0.255 mmol) and dichloromethane (2.0 mL) under nitrogen atmosphere at room temperature, and the mixture was stirred for 45 minutes. Oxalyl chloride (44 μL, 0.513 mmol) was added to the reaction mixture at room temperature, and the mixture was stirred for 30 minutes. The solvent was evaporated and the resultant was dissolved in tetrahydrofuran (0.5 mL), and thus an acid chloride solution was prepared. Triethylamine (89 μL, 0.64 mmol) was added to a mixture of 5-((2-aminopyridin-4-yl)oxy)-6-methoxy-N-methyl-1H-indole-1-carboxamide described in Production Example 1-6 (40 mg, 0.128 mmol) and N,N-dimethylformamide (0.5 mL) under nitrogen atmosphere at room temperature. The previously prepared tetrahydrofuran solution of acid chloride was added at the same temperature, and the mixture was stirred at room temperature for 80 minutes. A saturated aqueous sodium bicarbonate solution and ethyl acetate were added to the reaction mixture for partition and the organic layer was dried over anhydrous sodium sulfate. The resultant was filtered with NH silica gel (ethyl acetate) and then concentrated under vacuum to obtain a crude product (80.6 mg).

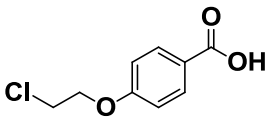
The crude product (80.6 mg) was dissolved in N,N-dimethylformamide (0.7 mL), commercially available 4-hydroxypiperidine (93 mg, 0.919 mmol) was added under nitrogen atmosphere at room temperature, and the mixture was heated and stirred at 80°C for 12 hours. The mixture was cooled to room temperature, water and ethyl acetate were added to the reaction mixture for partition, and the aqueous layer was extracted with ethyl acetate once. The combined organic layer was washed with water and a saturated saline solution, then dried over anhydrous sodium sulfate, and then filtered. The solvent was evaporated and the resultant residue was purified with NH silica gel TLC (ethyl acetate:methanol = 9:1). The resultant residue was purified with NH silica gel TLC (ethyl acetate) to obtain the title compound (10.8 mg, 30%).

^{1}H-NMR Spectrum ($CDCl_3$) δ (ppm): 1.55-1.67 (2H, m), 1.86-1.97 (2H, m), 2.31 (2H, t, J = 9.5 Hz), 2.78-2.92 (4H, m), 3.06 (3H, d, J = 4.4 Hz), 3.67-3.77 (1H, m), 3.86 (3H, s), 4.14 (2H, t, J = 5.7 Hz), 5.50-5.59 (1H, m), 6.54 (1H, d, J = 3.3 Hz), 6.60 (1H, dd, J = 5.7, 2.4 Hz), 6.95 (2H, d, J = 8.8 Hz), 7.22 (1H, d, J = 3.7 Hz), 7.32 (1H, s), 7.81 (2H, d, J = 8.8 Hz), 7.88 (1H, d, J = 1.8 Hz), 8.03 (1H, s), 8.09 (1H, d, J = 5.9 Hz), 8.47 (1H, brs).

[0172] The reagent 4-(2-chloroethoxy)benzoic acid was synthesized by the following method.

[0173] [Production Example 12-1] 4-(2-Chloroethoxy)benzoic acid

[Chemical Formula 71]



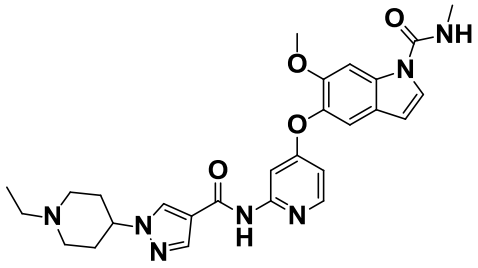
Potassium carbonate (7.27 g, 52.6 mmol) and commercially available 1-chloro-2-iodoethane (3.6 mL, 39.5 mmol) were added to a liquid mixture of commercially available methyl p-hydroxybenzoate (2.0 g, 13.1 mmol) and N,N-dimethylformamide (50 mL) under nitrogen atmosphere at room temperature, and the mixture was heated and stirred at 60°C for 12 hours. The mixture was cooled to room temperature and then a saturated aqueous ammonium chloride solution, water, and diethyl ether were added to the reaction mixture for partition. The organic layer was washed with water and a saturated saline solution, then dried over anhydrous magnesium sulfate, and then filtered and concentrated under vacuum. Tetrahydrofuran (25 mL), methanol (10 mL), and a 2 M sodium hydroxide solution (10 mL) were added to the residue at room temperature, and the mixture was heated and stirred at 80°C for 4 hours. The reaction mixture was cooled to 0°C, acidified with 5 M hydrochloric acid, and then the mixture was diluted with ethyl acetate for partition. The aqueous layer was extracted with ethyl acetate, the combined organic layer was washed with water and a saturated saline solution, then dried over anhydrous magnesium sulfate, and filtered. The solvent was evaporated, the precipitate was separated by filtration with a liquid mixture of ethyl acetate and tetrahydrofuran, the resultant was washed, and the filtrate was concentrated under vacuum. The residue was purified with silica gel column chromatography (n-heptane:ethyl acetate = 3:1 - 2:1 - 1:1) and the target fraction was concentrated under vacuum to obtain the title compound (278 mg, 11%).

^{1}H-NMR Spectrum (DMSO-d_6) δ (ppm): 3.92-3.98 (2H, m), 4.26-4.35 (2H, m), 6.96-7.06 (2H, m), 7.82-7.91 (2H, m), 12.68 (1H, brs).

[0174] [Example 13]

5-((2-(1-(1-Ethylpiperidin-4-yl)-1H-pyrazole-4-carboxamide)pyridin-4-yl)oxy)-6-methoxy-N-methyl-1H-indole-1-carboxamide

[Chemical Formula 72]



Acetaldehyde (8.9 mg, 0.202 mmol) and sodium triacetoxyborohydride (43.9 mg, 0.207 mmol) were added to a mixture of 6-methoxy-N-methyl-5-((2-(1-(piperidin-4-yl)-1H-pyrazole-4-carboxamide)pyridin-4-yl)oxy)-1H-indole-1-carboxamide described in Production Example 13-4 (20.3 mg, 0.041 mmol) and tetrahydrofuran (1.0 mL) at room temperature, and the mixture was stirred for 2.5 hours. A saturated aqueous sodium bicarbonate solution and ethyl acetate were added to the reaction mixture for partition. The organic layer was washed with a saturated saline solution, dried over anhydrous sodium sulfate, and filtered. The solvent was evaporated and the resultant residue was purified with NH silica gel TLC (ethyl acetate). The product was washed with diethyl ether to obtain the title compound (9.3 mg, 43%).

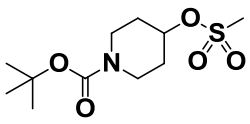
^{1}H-NMR Spectrum ($CDCl_3$) δ (ppm): 1.11 (3H, t, J = 7.1 Hz), 1.94-2.24 (6H, m), 2.46 (2H, q, J = 7.4 Hz), 3.03-3.11 (5H, m), 3.86 (3H, s), 4.09-4.19 (1H, m), 5.49-5.56 (1H, m), 6.54 (1H, d, J = 2.9 Hz), 6.60 (1H, dd, J = 5.9, 2.4 Hz), 7.22 (1H, d, J = 3.7 Hz), 7.31 (1H, s), 7.81 (1H, d, J = 2.0 Hz), 7.85 (1H, d, J = 0.7 Hz), 7.96 (1H, s), 8.02 (1H, s), 8.08 (1H, d, J = 5.9 Hz), 8.17 (1H, brs).

[0175] The starting material 6-methoxy-N-methyl-5-((2-(1-(piperidin-4-yl)-1H-pyrazole-4-carboxamide)pyridin-4-yl)oxy)-1H-indole-1-carboxamide was synthesized by the following method.

[0176] [Production Example 13-1]

tert-Butyl 4-((methylsulfonyl)oxy)piperidine -1-carboxylate

[Chemical Formula 73]



Commercially available methanesulfonyl chloride (6.35 mL, 82.0 mmol) and triethylamine (26.0 mL, 186 mmol) were added to a mixture of commercially available tert-butyl 4-hydroxy-1-piperidine carboxylate (15 g, 74.5 mmol) and tetrahydrofuran (200

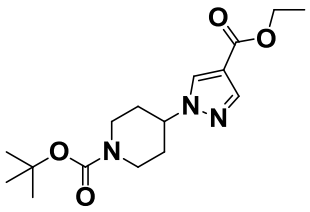
mL) at 0°C, and the mixture was stirred for 30 minutes. Water and ethyl acetate were added to the reaction mixture for partition. The organic layer was dried and filtered by conventional methods. The solvent was evaporated, and the residue was collected by filteration and washed with n-heptane to obtain the title compound (19.8 g, 95%).

^{1}H-NMR Spectrum ($CDCl_3$) δ (ppm): 1.46 (9H, s), 1.72-1.88 (2H, m), 1.90-2.04 (2H, m), 3.03 (3H, s), 3.24-3.36 (2H, m), 3.64-3.77 (2H, m), 4.80-4.94 (1H, m).

[0177] [Production Example 13-2]

tert-Butyl 4-(4-(ethoxycarbonyl)-1H-pyrazol-1-yl)piperidine-1-carboxylate

[Chemical Formula 74]



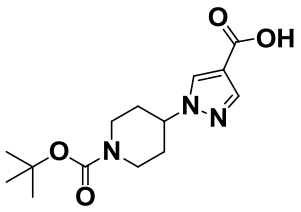
tert-Butyl 4-((methylsulfonyl)oxy)piperidine-1-carboxylate described in Production Example 13-1 (2.7 g, 9.67 mmol) and commercially available ethyl 4-pyrazole carboxylate (1.49 g, 10.6 mmol) were dissolved in N,N-dimethylformamide (30 mL), 50 - 72% oily sodium hydride (570 mg) was added at 0°C, and the mixture was heated and stirred at 60°C for 11 hours. The reaction mixture was cooled to room temperature and water and ethyl acetate were added for partition. The organic layer was washed with water twice and then dried over anhydrous sodium sulfate and filtered. The solvent was evaporated, the resultant residue was dissolved in dichloromethane, the resultant was purified with silica gel column chromatography (n-heptane:ethyl acetate = 4:1 - 1:1 - 1:3 - 0:1), and the target fraction was concentrated under vacuum to obtain the title compound (2.11 g, 68%).

^{1}H-NMR Spectrum ($CDCl_3$) δ (ppm): 1.34 (3H, t, J = 7.1 Hz), 1.47 (9H, s), 1.82-1.96 (2H, m), 2.10-2.18 (2H, m), 2.82-2.96 (2H, m), 4.19-4.34 (3H, m), 4.29 (2H, q, J = 7.1 Hz), 7.91 (1H, s), 7.92 (1H, s).

[0178] [Production Example 13-3]

1-(1-(tert-Butoxycarbonyl)piperidin-4-yl)-1H-pyrazole-4-carboxylic acid

[Chemical Formula 75]



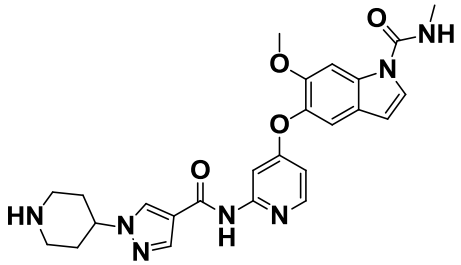
tert-Butyl 4-(4-(ethoxycarbonyl)-1H-pyrazol-1-yl)piperidine-1-carboxylate described in Production Example 13-2 (2.11 g, 6.53 mmol) was dissolved in methanol (60 mL), then potassium hydroxide (1.46 g, 26.1 mmol) dissolved in water (16 mL) was added, and then the mixture was stirred for 27 hours. The reaction mixture was concentrated under vacuum and diethyl ether was added for partition. Ethyl acetate was added to the aqueous layer for dilution, then a 5% aqueous potassium hydrogensulfate solution was added for acidification, and the mixture was extracted with ethyl acetate twice. The combined organic layer was dried over anhydrous magnesium sulfate and filtered. The solvent was evaporated to obtain the title compound (1.58 g, 82%).

^{1}H-NMR Spectrum ($CDCl_3$) δ (ppm): 1.48 (9H, s), 1.84-1.98 (2H, m), 2.11-2.20 (2H, m), 2.81-2.97 (2H, m), 4.18-4.36 (3H, m), 7.97 (1H, s), 7.98 (1H, s).

[0179] [Production Example 13-4]

6-Methoxy-N-methyl-5-((2-(1-(piperidin-4-yl)-1H-pyrazole-4-carboxamide)pyridin-4-yl)oxy)-1H-indole-1-carboxamide

[Chemical Formula 76]



Benzotriazole (97 mg, 0.813 mmol) was dissolved in dichloromethane (4.0 mL), and thionyl chloride (59 μL, 0.813 mmol) was added at room temperature and the mixture was stirred for 5 minutes under nitrogen atmosphere. 1-(1-(tert-Butoxycarbonyl)piperidin-4-yl)-1H-pyrazole-4-carboxylic acid described in Production Example 13-3 (200 mg, 0.677 mmol) was added to the reaction mixture at room temperature, and the mixture was stirred for 25 minutes. The reaction mixture was filtered through a glass filter entirely covered with anhydrous sodium sulfate and then the anhydrous

sodium sulfate was washed with dichloromethane, the filtrate was added to a mixture of 5-((2-aminopyridin-4-yl)oxy)-6-methoxy-N-methyl-1H-indole-1-carboxamide described in Production Example 1-6 (102 mg, 0.327 mmol), triethylamine (0.453 mL, 3.27 mmol), and 4-dimethylaminopyridine (3.99 mg, 0.033 mmol) in tetrahydrofuran (5.0 mL) at 0°C. The mixture was stirred at room temperature for 2 hours, then water and ethyl acetate were added to the reaction mixture for partition, then the organic layer was washed with a saturated saline solution and then dried over anhydrous sodium sulfate. The drying agent was filtered off and the filtrate was concentrated under vacuum. The residue was dissolved in tetrahydrofuran, an excessive quantity of 9.8 M methylamine methanol solution was added at room temperature, and the mixture was stirred for 4 hours. The reaction mixture was concentrated under vacuum and the residue was dissolved in dichloromethane, and the resultant was purified with NH silica gel column chromatography (n-heptane:ethyl acetate = 1:1 - 1:9 - 0:1). The target fraction was concentrated under vacuum to obtain a crude product (170 mg).

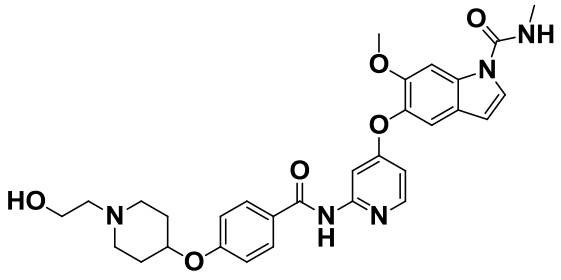
The crude product (170 mg) was dissolved in dichloromethane (1.8 mL) and trifluoroacetic acid (0.5 mL) was added at 0°C. The mixture was stirred at room temperature for 80 minutes, then was concentrated under vacuum, and the residue was dissolved in dichloromethane-triethylamine, then the resultant was purified with NH silica gel column chromatography (ethyl acetate:methanol = 49:1 - 4:1), then the target fraction was concentrated under vacuum to obtain the title compound (81.2 mg, 51%).

^{1}H-NMR Spectrum ($CDCl_3$) δ (ppm): 1.78-1.91 (2H, m), 2.11-2.19 (2H, m), 2.75 (2H, td, J = 12.3, 2.3 Hz), 3.05 (3H, d, J = 4.6 Hz), 3.19-3.27 (2H, m), 3.85 (3H, s), 4.16-4.26 (1H, m), 5.53-5.63 (1H, m), 6.53 (1H, d, J = 3.5 Hz), 6.60 (1H, dd, J = 5.8, 2.5 Hz), 7.22 (1H, d, J = 3.8 Hz), 7.30 (1H, s), 7.81 (1H, d, J = 2.4 Hz), 7.86 (1H, s), 7.96 (1H, s), 8.03 (1H, s), 8.08 (1H, d, J = 5.9 Hz), 8.22 (1H, brs).

[0180] [Example 14]

5-((2-(4-((1-(2-Hydroxyethyl)piperidin-4-yl)oxy)benzamide)pyridin-4-yl)oxy)-6-methoxy-N-methyl-1H-indole-1-carboxamide

[Chemical Formula 77]



Benzotriazole (34.1 mg, 0.286 mmol) was dissolved in dichloromethane (1.5 mL), then thionyl chloride (20 μL, 0.274 mmol) was added under nitrogen atmosphere at room temperature, and then the mixture was stirred for 5 minutes. 4-((1-(tert-Butoxycarbonyl)piperidin-4-yl)oxy)benzoic acid described in Production Example 14-1 (79.3 mg, 0.247 mmol) was added to the reaction mixture at room temperature, and the mixture was stirred for 25 minutes. The reaction mixture was filtered through a glass filter entirely covered with anhydrous sodium sulfate and then the anhydrous sodium sulfate was washed with dichloromethane, then the filtrate was added to a mixture of 5-((2-aminopyridin-4-yl)oxy)-6-methoxy-N-methyl-1H-indole-1-carboxamide described in Production Example 1-6 (35.6 mg, 0.114 mmol), triethylamine (0.158 mL, 1.14 mmol), and 4-dimethylaminopyridine (1.39 mg, 0.011 mmol), in tetrahydrofuran (1.1 mL) at 0°C. The reaction mixture was stirred at room temperature for 1.5 hours, then water and ethyl acetate were added to the reaction mixture for partition, and then the organic layer was washed with a saturated saline solution and dried over anhydrous sodium sulfate. The drying agent was filtered off, the filtrate was concentrated under vacuum, the residue was dissolved in tetrahydrofuran, an excessive quantity of 9.8 M methylamine methanol solution was added at room temperature, and the mixture was stirred for 2 hours. The reaction mixture was concentrated under vacuum, the residue was dissolved in dichloromethane, and the resultant was purified with NH silica gel column chromatography (n-heptane:ethyl acetate = 1:1 - 1:3 - 0:1). The target fraction was concentrated under vacuum to obtain a crude product A (41.1 mg).

The crude product A (41.1 mg) was dissolved in dichloromethane (0.6 mL) and trifluoroacetic acid (0.2 mL) was added at 0°C. The mixture was stirred at room temperature for 75 minutes and the resultant was concentrated under vacuum, the residue was dissolved in dichloromethane-triethylamine and then the resultant was purified with NH silica gel column chromatography (ethyl acetate:methanol = 49:1 - 4:1), and then the target fraction was concentrated under vacuum to obtain a crude product B (34 mg).

Sodium triacetoxyborohydride (17.5 mg, 0.082 mmol) and commercially available 2-hydroxyacetaldehyde (4.95 mg, 0.082 mmol) were added to a mixture of the crude product B (8.5 mg, 0.016 mmol) and tetrahydrofuran (0.5 mL) at room temperature, and the mixture was stirred for 2 hours. A saturated aqueous sodium bicarbonate solution and ethyl acetate were added to the reaction mixture for partition. The organic layer was washed with a saturated saline solution, and then dried over anhydrous sodium sulfate and filtered. The solvent was evaporated and the resultant residue was purified with NH silica gel TLC (ethyl acetate). The residue was washed with diethyl ether to obtain the title compound (6.4 mg, 40%).

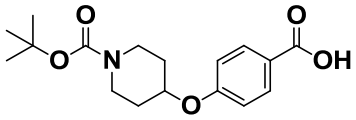
^{1}H-NMR Spectrum ($CDCl_3$) δ (ppm): 1.78-1.90 (2H, m), 1.95-2.06 (2H, m), 2.35-2.47 (2H, m), 2.57 (2H, t, J = 5.6 Hz), 2.72-2.83 (2H, m), 3.07 (3H, d, J = 4.4 Hz), 3.62 (2H, t, J = 5.3 Hz), 3.86 (3H, s), 4.38-4.48 (1H, m), 5.45-5.54 (1H, m), 6.55 (1H, d, J = 3.7 Hz), 6.59 (1H, dd, J = 5.7, 2.4 Hz), 6.94 (2H, d, J = 8.8 Hz), 7.23 (1H, d, J = 3.7 Hz), 7.32 (1H, s), 7.81 (2H, d, J = 8.8 Hz), 7.89 (1H, d, J = 2.6 Hz), 8.03 (1H, s), 8.09 (1H, d, J = 5.5 Hz), 8.45 (1H, brs).

[0181] The starting material 4-((1-(tert-butoxycarbonyl)piperidin-4-yl)oxy)benzoic acid was synthesized by the following method.

[0182] [Production Example 14-1]

4-((1-(tert-Butoxycarbonyl)piperidin-4-yl)oxy)benzoic acid

[Chemical Formula 78]



Diisopropyl azodicarboxylate (9.65 mL, 1.9 M, 18.3 mmol) was added to a mixture of commercially available benzyl 4-hydroxy benzoate (3 g, 13.1 mmol), commercially available tert-butyl 4-hydroxypiperidine-1-carboxylate (2.77 g, 13.8 mmol), triphenylphosphine (4.81 g, 18.3 mmol), and tetrahydrofuran (150 mL) at 0°C, and the mixture was stirred at room temperature overnight. Water and ethyl acetate were added to the reaction mixture for partition. The organic layer was washed with a saturated aqueous sodium bicarbonate solution and then with a saturated saline solution, then dried over anhydrous magnesium sulfate and filtered. The solvent was evaporated, the resultant residue was purified with NH silica gel column chromatography (n-heptane:ethyl acetate = 1:1), then the target fraction was concentrated under vacuum to obtain a crude product (3.8 g).

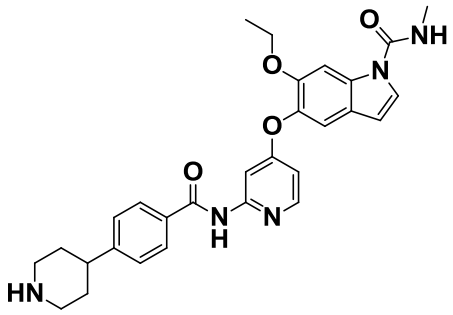
A part of the crude product (500 mg, 1.22 mmol) was dissolved in ethanol (5 mL), a 5 M sodium hydroxide solution (0.729 mL, 3.65 mmol) was added, and the mixture was heated and stirred at 50°C for 7 hours. The reaction mixture was cooled to room temperature, and then 5 M hydrochloric acid and ethyl acetate were added for partition. The organic layer was dried and filtered by conventional methods. The solvent was evaporated and then the resultant was collected by filteration and washed with n-heptane to obtain the title compound (343 mg, 62%).

^{1}H-NMR Spectrum ($CDCl_3$) δ (ppm): 1.47 (9H, s), 1.65-1.84 (2H, m), 1.87-2.07 (2H, m), 3.30-3.51 (2H, m), 3.60-3.80 (2H, m), 4.50-4.66 (1H, m), 6.87-7.03 (2H, m), 7.98-8.14 (2H, m).

[0183] [Example 15]

6-Ethoxy-N-methyl-5-((2-(4-(piperidin-4-yl)benzamide)pyridin-4-yl)oxy)-1H-indole-1-carboxamide

[Chemical Formula 79]



tert-Butyl 4-(4-((4-((6-ethoxy-1-(methylcarbamoyl)-1H-indol-5-yl)oxy)pyridin-2-yl)carbamoyl)phenyl)piperidine-1-carboxylate described in Production Example 15-8 (3.35 g, 5.46 mmol) was dissolved in dichloromethane (45 mL), and trifluoroacetic acid (15 mL) was added at 0°C. The mixture was stirred at room temperature for 110 minutes, then concentrated under vacuum, and the residue was dissolved in dichloromethane-triethylamine, then the resultant was purified with NH silica gel column chromatography (ethyl acetate:methanol = 97:3 - 4:1) to obtain the title compound (2.41 g, 86%).

^{1}H-NMR Spectrum ($CDCl_3$) δ (ppm): 1.25 (3H, t, J = 7.0 Hz), 1.50-1.70 (2H, m), 1.79-1.88 (2H, m), 2.63-2.80 (3H, m), 3.06 (3H, d, J = 4.8 Hz), 3.16-3.24 (2H, m), 4.11 (2H, q, J = 7.0 Hz), 5.46-5.54 (1H, m), 6.55 (1H, d, J = 3.3 Hz), 6.60 (1H, dd, J = 5.9, 2.6 Hz), 7.23 (1H, d, J = 3.7 Hz), 7.29-7.34 (3H, m), 7.78-7.83 (2H, m), 7.92 (1H, d, J = 2.2 Hz), 8.00 (1H, s),

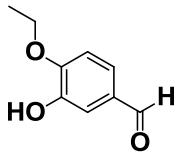
8.08-8.11 (1H, m), 8.50 (1H, brs).

[0184] The starting material tert-butyl 4-(4-((4-((6-ethoxy-1-(methylcarbamoyl)-1H-indol-5-yl)oxy)pyridin-2-yl)carbamoyl)phenyl)piperidine-1-carboxylate was synthesized by the following method.

[0185] [Production Example 15-1]

4-Ethoxy-3-hydroxybenzaldehyde

[Chemical Formula 80]



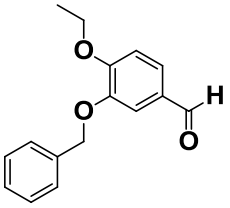
Commercially available 3,4-dihydroxy benzaldehyde (35.8 g, 259 mmol) and potassium carbonate (37.6 g, 272 mmol) were dissolved in N,N-dimethylformamide (150 mL), then commercially available iodoethane (22 mL, 275 mmol) was added under nitrogen atmosphere at 0°C, and then the mixture was stirred for 2 days. The solvent was evaporated under vacuum, the resultant was cooled to 0°C, and then 5 M hydrochloric acid, ethyl acetate, and water were added for partition. The aqueous layer was extracted with ethyl acetate, the combined organic layer was washed with water twice and then with a saturated saline solution, and the mixture was dried over anhydrous magnesium sulfate and then filtered. The solvent was evaporated, then dichloromethane was added, and then the precipitate was collected by filteration to obtain the title compound (25.8 g, 60%). The filtrate was purified with silica gel column chromatography (n-heptane:ethyl acetate = 9:1 - 4:1 - 1:1). The target fraction was concentrated under vacuum, then diethyl ether and dichloromethane were added to the residue, and the precipitate was collected by filteration to obtain the title compound (3.45 g, 8.0%).

^{1}H-NMR Spectrum ($CDCl_3$) δ (ppm): 1.50 (3H, t, J = 7.1 Hz), 4.22 (2H, q, J = 7.0 Hz), 5.75 (1H, s), 6.95 (1H, d, J = 8.1 Hz), 7.39-7.45 (2H, m), 9.84 (1H, s).

[0186] [Production Example 15-2]

3-(Benzyloxy)-4-ethoxybenzaldehyde

[Chemical Formula 81]



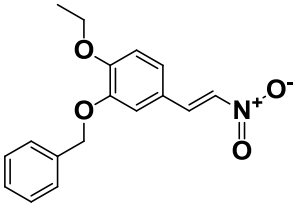
Potassium carbonate (19.8 g, 143 mmol) and benzyl chloride (16.5 mL, 143 mmol) were added to a suspension of 4-ethoxy-3-hydroxybenzaldehyde described in Production Example 15-1 (20 g, 120 mmol) in ethanol (200 mL) under nitrogen atmosphere at room temperature, and the mixture was heated and stirred at 90°C for 2.5 hours. The mixture was cooled to 0°C, and 2 M hydrochloric acid, ethyl acetate, and water were added for partition. The organic layer was washed with a saturated saline solution, dried over anhydrous magnesium sulfate, and filtered. The solvent was evaporated and the resultant residue was purified with silica gel column chromatography (n-heptane:ethyl acetate = 9:1 - 4:1 - 3:1). The target fraction was concentrated under vacuum to obtain the title compound (28.5 g, 92%).

^{1}H-NMR Spectrum ($CDCl_3$) δ (ppm): 1.51 (3H, t, J = 7.0 Hz), 4.20 (2H, q, J = 7.0 Hz), 5.19 (2H, s), 6.98 (1H, d, J = 8.8 Hz), 7.29-7.34 (1H, m), 7.35-7.41 (2H, m), 7.43-7.49 (4H, m), 9.81 (1H, s).

[0187] [Production Example 15-3]

(E)-2-(Benzyloxy)-1-ethoxy-4-(2-nitrovinyl)benzene

[Chemical Formula 82]



3-(Benzyloxy)-4-ethoxy benzaldehyde described in Production Example 15-2 (14.5 g, 56.4 mmol) was dissolved in acetic acid (45 mL), then ammonium acetate (5.22 g, 67.7 mmol) and nitromethane (7.5 mL, 138 mmol) were added under nitrogen atmosphere at room temperature, and the mixture was heated and stirred at 130°C for 2.5 hours. The mixture was cooled to room temperature and the precipitate was collected by filteration and washed with ethanol to quantitatively obtain the title compound.

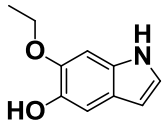
^{1}H-NMR Spectrum ($CDCl_3$) δ (ppm): 1.50 (3H, t, J = 7.0 Hz), 4.17 (2H, q, J = 7.2 Hz), 5.17

(2H, s), 6.92 (1H, d, J = 8.4 Hz), 7.04 (1H, d, J = 2.2 Hz), 7.16 (1H, dd, J = 8.6, 2.0 Hz), 7.29-7.51 (6H, m), 7.90 (1H, d, J = 13.5 Hz).

[0188] [Production Example 15-4]

6-Ethoxy-1H-indol-5-ol

[Chemical Formula 83]



Fuming nitric acid (13 mL, 289 mmol) was slowly added to a mixture of (E)-2-(benzyloxy)-1-ethoxy-4-(2-nitrovinyl)benzene described in Production Example 15-3 (16.9 g, 56.6 mmol) and acetic acid (160 mL) at room temperature, and the mixture was stirred for 6 hours. The reaction mixture was poured onto ice, then the precipitate was collected by filteration and then washed with a liquid mixture of acetic acid and ethanol to obtain a crude product (19.5 g).

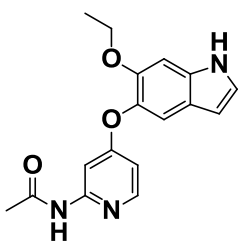
The crude product (19.5 g) was suspended in methanol (500 mL), then 10% palladium-carbon (water content, 50%) (6.85 g) was added, and the mixture was stirred under hydrogen atmosphere for 17 hours. The catalyst was filtered off with celite, and the resultant was washed with methanol. The filtrate was concentrated under vacuum and the resultant was dissolved in tetrahydrofuran and adsorbed by silica gel. The adsorbed silica gel was concentrated under vacuum and the resultant was purified with silica gel column chromatography (n-heptane:ethyl acetate = 9:1 - 13:7). The target fraction was concentrated under vacuum, and the residue was collected by filteration and washed with diethyl ether to obtain the title compound (3.78 g, 38%).

^{1}H-NMR Spectrum ($CDCl_3$) δ (ppm): 1.48 (3H, t, J = 6.9 Hz), 4.13 (2H, q, J = 6.8Hz), 5.50 (1H, s), 6.39-6.43 (1H, m), 6.87 (1H, s), 7.05-7.09 (1H, m), 7.13 (1H, s), 7.91 (1H, brs).

[0189] [Production Example 15-5]

N-(4-((6-Ethoxy-1H-indol-5-yl)oxy)pyridin-2-yl) acetamide

[Chemical Formula 84]



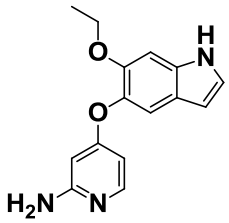
6-Ethoxy-1H-indol-5-ol described in Production Example 15-4 (7.0 g, 39.5 mmol) was dissolved in dimethylsulfoxide (40 mL) under nitrogen atmosphere, then N-(4-chloropyridin-2-yl)acetamide described in Production Example 1-5 (8.09 g, 47.4 mmol) and potassium tert-butoxide (4.88 g, 43.5 mmol) were added at room temperature, and the mixture was heated and stirred at 160°C for 4 hours. The reaction liquid was cooled to room temperature and water and ethyl acetate were added for partition. The aqueous layer was extracted with ethyl acetate and the combined organic layer was washed with water twice and then with a saturated saline solution. The organic layer was dried over anhydrous magnesium sulfate and then filtered, and the filtrate was concentrated under vacuum. The residue was dissolved in dichloromethane, and the resultant was purified with silica gel column chromatography (n-heptane:ethyl acetate = 3:1 - 2:1 - 3:2 - 1:3 - 1:4 - 0:1), and then the target fraction was concentrated under vacuum to obtain the title compound (7.16 g, 58%).

^{1}H-NMR Spectrum ($CDCl_3$) δ (ppm): 1.23 (3H, t, J = 7.0 Hz), 2.14 (3H, s), 4.02 (2H, q, J = 7.0 Hz), 6.46-6.49 (1H, m), 6.54 (1H, dd, J = 5.9, 2.2 Hz), 7.01 (1H, s), 7.13-7.16 (1H, m), 7.35 (1H, s), 7.74 (1H, brs), 7.87 (1H, brs), 8.02 (1H, d, J = 5.9 Hz), 8.10 (1H, brs).

[0190] [Production Example 15-6]

4-((6-Ethoxy-1H-indol-5-yl)oxy)pyridin-2-amine

[Chemical Formula 85]



N-(4-((6-ethoxy-1H-indol-5-yl)oxy)pyridin-2-yl)acetamide described in Production Example 15-5 (7.16 g, 23.0 mmol) was dissolved in methanol (50 mL), a 2 M sodium hydroxide solution (50 mL) was added under nitrogen atmosphere at room temperature, and the mixture was heated and stirred at 75°C for 2.5 hours. The reaction mixture was cooled to room temperature and then water and ethyl acetate were added for partition. The aqueous layer was extracted with ethyl acetate and the combined organic layer was washed with a saturated saline solution. The organic layer was dried over anhydrous magnesium sulfate, then the resultant was filtered and concentrated under vacuum. A liquid mixture of diethyl ether and ethyl acetate was added to the residue, and the mixture

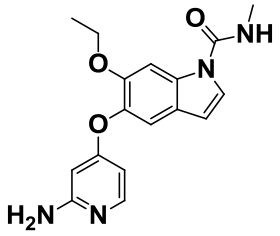
was collected by filteration and washed to obtain the title compound (5.35 g, 86%).

^{1}H-NMR Spectrum ($CDCl_3$) δ (ppm): 1.28 (3H, t, J = 7.0 Hz), 4.02 (2H, q, J = 7.0 Hz), 4.28 (2H, brs), 5.91 (1H, d, J = 2.2 Hz), 6.29 (1H, dd, J = 5.9, 2.2 Hz), 6.46-6.50 (1H, m), 7.00 (1H, s), 7.15-7.18 (1H, m), 7.33 (1H, s), 7.88 (1H, d, J = 5.9 Hz), 8.13 (1H, brs).

[0191] [Production Example 15-7]

5-((2-Aminopyridin-4-yl)oxy)-6-ethoxy-N-methyl-1H-indole-1-carboxamide

[Chemical Formula 86]



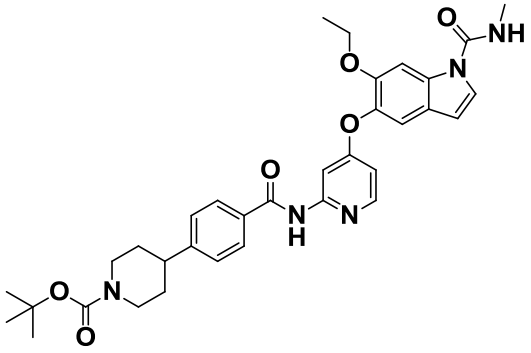
4-((6-Ethoxy-1H-indol-5-yl)oxy)pyridin-2-amine described in Production Example 15-6 (6.44 g, 23.9 mmol) was dissolved in N,N-dimethylformamide (80 mL), 50 - 72% oily sodium hydride (1.41 g) was added under nitrogen atmosphere at 0°C, and the mixture was stirred at room temperature for 40 minutes. The mixture was cooled to 0°C again, phenyl methylcarbamate described in Production Example 1-7 (5.78 g, 38.3 mmol) was added, and the mixture was stirred at room temperature for 3 hours. A saturated aqueous ammonium chloride solution, water, and ethyl acetate were added to the reaction mixture for partition. The aqueous layer was extracted with ethyl acetate and the combined organic layer was washed with water twice and then with a saturated saline solution. The organic layer was dried over anhydrous magnesium sulfate and then filtered, then the filtrate was concentrated under vacuum. A liquid mixture of diethyl ether and ethyl acetate was added to the residue, then the precipitate was collected by filteration and the resultant was washed with ethyl acetate again to obtain the title compound (4.24 g, 54%). The filtrate was purified with NH silica gel column chromatography (ethyl acetate:methanol = 1:0 - 9:1), the target fraction was concentrated under vacuum, and then the residue was collected by filteration and washed with a liquid mixture of diethyl ether and ethyl acetate to obtain the title compound (1.58 g, 20%).

^{1}H-NMR Spectrum ($CDCl_3$) δ (ppm): 1.29 (3H, t, J = 7.0 Hz), 3.07 (3H, d, J = 4.8 Hz), 4.09 (2H, q, J = 7.0 Hz), 4.29 (2H, brs), 5.42-5.51 (1H, m), 5.90 (1H, d, J = 2.2 Hz), 6.27 (1H, dd, J = 6.2, 2.2 Hz), 6.55 (1H, dd, J = 3.7, 0.7 Hz), 7.23 (1H, d, J = 3.7 Hz), 7.27 (1H, s), 7.89 (1H, d, J = 5.9 Hz), 7.98 (1H, s).

[0192] [Production Example 15-8]

tert-Butyl 4-(4-((4-((6-ethoxy-1-(methylcarbamoyl)-1H-indol-5-yl)oxy)pyridin-2-yl)carbamoyl)phenyl)piperidine-1-carboxylate

[Chemical Formula 87]



Benzotriazole (1.92 g, 16.1 mmol) was dissolved in dichloromethane (80 mL), thionyl chloride (1.15 mL, 15.8 mmol) was added under nitrogen atmosphere at room temperature, and the mixture was stirred for 5 minutes. 4-(1-(tert-Butoxycarbonyl)piperidin-4-yl)benzoic acid described in Production Example 1-12 (4.1 g, 13.4 mmol) was added to the reaction mixture at room temperature, and the mixture was stirred for 25 minutes. The reaction mixture was filtered through a glass filter entirely covered with anhydrous sodium sulfate and then the anhydrous sodium sulfate was washed with dichloromethane, the filtrate was added to a mixture of 5-((2-aminopyridin-4-yl)oxy)-6-ethoxy-N-methyl-1H-indole-1-carboxamide described in Production Example 15-7 (2 g, 6.13 mmol), triethylamine (8.5 mL, 61.3 mmol), and 4-dimethylaminopyridine (75 mg, 0.613 mmol) in tetrahydrofuran (40 mL) at 0°C. The mixture was stirred at room temperature for 14 hours, then water and ethyl acetate were added to the reaction mixture for partition. The organic layer was washed with a saturated saline solution, then the resultant was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under vacuum, the residue was dissolved in tetrahydrofuran, an excessive quantity of 9.8 M methylamine methanol solution was added at room temperature, and the mixture was stirred for 5 hours. The reaction mixture was concentrated under vacuum, dichloromethane was added to the residue, and diethyl ether and ethyl acetate were further added, and then the product was collected by filteration and washed to obtain the title compound (3.08 g, 82%). The filtrate was concentrated under vacuum and the resultant was dissolved in dichloromethane and purified with NH silica gel column chromatography

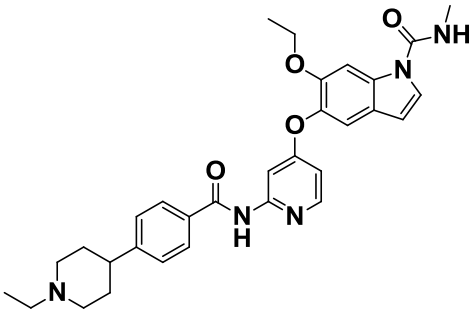
(n-heptane:ethyl acetate = 1:1 - 1:9). The target fraction was concentrated under vacuum to obtain the title compound (273 mg, 7.3%).

^{1}H-NMR Spectrum ($CDCl_3$) δ (ppm): 1.25 (3H, t, J = 7.0 Hz), 1.48 (9H, s), 1.50-1.70 (2H, m), 1.78-1.87 (2H, m), 2.64-2.87 (3H, m), 3.07 (3H, d, J = 4.8 Hz), 4.11 (2H, q, J = 7.0 Hz), 4.16-4.33 (2H, m), 5.45-5.52 (1H, m), 6.55 (1H, d, J = 3.6 Hz), 6.60 (1H, dd, J = 5.9, 2.3 Hz), 7.23 (1H, d, J = 3.7 Hz), 7.28-7.33 (3H, m), 7.79-7.83 (2H, m), 7.92 (1H, d, J = 2.2 Hz), 8.00 (1H, s), 8.09 (1H, d, J = 5.9 Hz), 8.51 (1H, brs).

[0193] [Example 16]

6-Ethoxy-5-((2-(4-(1-ethylpiperidin-4-yl)benzamide)pyridin-4-yl)oxy)-N-methyl-1H-indole-1-carboxamide

[Chemical Formula 88]



Sodium triacetoxyborohydride (1.36 g, 6.43 mmol) was added to a mixture of 6-ethoxy-N-methyl-5-((2-(4-(piperidin-4-yl)benzamide)pyridin-4-yl)oxy)-1H-indole-1-carboxamide described in Example 15 (2.2 g, 4.28 mmol) and tetrahydrofuran (33 mL) at room temperature, then a tetrahydrofuran solution (11 mL) of commercially available acetaldehyde (283 mg, 6.43 mmol) was added, and then the mixture was stirred at room temperature for 1.5 hours. Ethyl acetate and a saturated aqueous sodium bicarbonate solution were added to the reaction mixture for partition. The organic layer was washed with a saturated saline solution, and then dried over anhydrous sodium sulfate and filtered. The solvent was evaporated, and the residue thus obtained was combined with the residue obtained from the similar starting material 6-ethoxy-N-methyl-5-((2-(4-(piperidin-4-yl)benzamide)pyridin-4-yl)oxy)-1H-indole-1-carboxamide (200 mg, 0.389 mmol) by the similar method. Ethyl acetate was added to the combined residue and the product was collected by filteration to obtain the title compound (2.20 g, 87%).

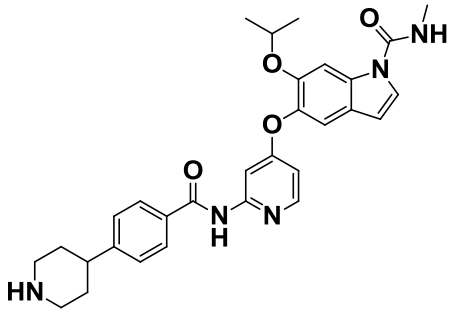
^{1}H-NMR Spectrum ($CDCl_3$) δ (ppm): 1.15 (3H, t, J = 7.2 Hz), 1.25 (3H, t, J = 7.0 Hz),

1.82-1.92 (4H, m), 2.01-2.13 (2H, m), 2.43-2.62 (3H, m), 3.04 (3H, d, J = 4.6 Hz), 3.08-3.17 (2H, m), 4.10 (2H, q, J = 6.8 Hz), 5.55-5.62 (1H, m), 6.53 (1H, d, J = 3.7 Hz), 6.60 (1H, dd, J = 5.7, 2.2 Hz), 7.23 (1H, d, J = 3.7 Hz), 7.30-7.35 (3H, m), 7.79 (2H, d, J = 8.2 Hz), 7.91 (1H, d, J = 2.2 Hz), 8.00 (1H, s), 8.09 (1H, d, J = 5.7 Hz), 8.53 (1H, brs).

[0194] [Example 17]

6-Isopropoxy-N-methyl-5-((2-(4-(piperidin-4-yl)benzamide)pyridin-4-yl)oxy)-1H-indole-1-carboxamide

[Chemical Formula 89]



Benzotriazole (88.7 mg, 0.745 mmol) was dissolved in dichloromethane (4.0 mL), thionyl chloride (52 μL, 0.707 mmol) was added under nitrogen atmosphere at room temperature, and the mixture was stirred for 5 minutes. 4-(1-(tert-Butoxycarbonyl)piperidin-4-yl)benzoic acid described in Production Example 1-12 (180 mg, 0.589 mmol) was added to the reaction mixture at room temperature, and the mixture was stirred for 55 minutes. The reaction mixture was filtered through a glass filter entirely covered with anhydrous sodium sulfate and then the anhydrous sodium sulfate was washed with dichloromethane, the filtrate was added to a mixture of 5-((2-aminopyridin-4-yl)oxy)-6-isopropoxy-N-methyl-1H-indole-1-carboxamide described in Production Example 17-7 (77 mg, 0.226 mmol), triethylamine (0.314 mL, 2.26 mmol), and 4-dimethylaminopyridine (2.76 mg, 0.023 mmol) in tetrahydrofuran (2.0 mL), dichloromethane (5.0 mL), and N,N-dimethylformamide (0.2 mL) at 0°C. The mixture was stirred at room temperature for 140 minutes, and then water and ethyl acetate were added to the reaction mixture for partition. The organic layer was washed with water and a saturated saline solution, dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated under vacuum, the residue was dissolved in tetrahydrofuran, an excessive quantity of methylamine tetrahydrofuran solution was added at room temperature, and the mixture was stirred for 30 minutes. The reaction mixture was concentrated under vacuum,

the residue was dissolved in dichloromethane, and the resultant was purified with NH silica gel column chromatography (n-heptane:ethyl acetate = 1:1 - 1:3 - 0:1), and the target fraction was concentrated under vacuum to obtain a crude product (111 mg).

The crude product (111 mg) was dissolved in dichloromethane (1.8 mL), and trifluoroacetic acid (0.65 mL) was added at 0°C. The mixture was stirred for 90 minutes at room temperature and then concentrated under vacuum, the residue was dissolved in dichloromethane-triethylamine, and then the resultant was purified with NH silica gel column chromatography (ethyl acetate:methanol = 1:0 - 17:3 - 4:1) to obtain the title compound (85.4 mg, 92%).

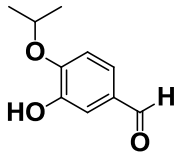
^{1}H-NMR Spectrum ($CDCl_3$) δ (ppm): 1.22 (6H, d, J = 6.0 Hz), 1.55-1.71 (2H, m), 1.79-1.88 (2H, m), 2.62-2.80 (3H, m), 3.05 (3H, d, J = 4.8 Hz), 3.15-3.25(2H, m), 4.52-4.64 (1H, m), 5.49-5.57 (1H, m), 6.54 (1H, d, J = 3.7 Hz), 6.58 (1H, dd, J = 5.7, 2.4 Hz), 7.24 (1H, d, J = 3.8 Hz), 7.29-7.35 (3H, m), 7.80 (2H, d, J = 8.2 Hz), 7.93 (1H, d, J = 2.4 Hz), 8.01 (1H, s), 8.08 (1H, d, J = 5.9 Hz), 8.51 (1H, brs).

[0195] The starting material 5-((2-aminopyridin-4-yl)oxy)-6-isopropoxy-N-methyl-1H-indole-1-carboxamide was synthesized by the following method.

[0196] [Production Example 17-1]

3-Hydroxy-4-isopropoxy benzaldehyde

[Chemical Formula 90]



Commercially available 3,4-dihydroxybenzaldehyde (5 g, 36.2 mmol) and potassium carbonate (5.15 g, 37.3 mmol) were dissolved in N,N-dimethylformamide (20 mL), then 2-bromopropane (3.5 mL, 37.3 mmol) was added under nitrogen atmosphere at room temperature, and the mixture was heated and stirred at 40°C for 2.5 hours. The reaction mixture was cooled to 0°C, and then 2 M hydrochloric acid, ethyl acetate, and water were added for partition. The aqueous layer was extracted with ethyl acetate, the combined organic layer was washed with water and a saturated saline solution, and the resultant was dried over anhydrous magnesium sulfate and then filtered. The solvent was evaporated, dichloromethane was added to the residue, the precipitate was separated by filtration, and the

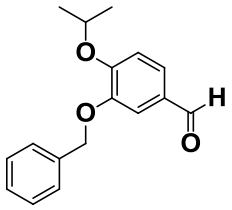
filtrate was concentrated under vacuum. The residue was purified with silica gel column chromatography (n-heptane:ethyl acetate = 19:1 - 13:7) and then the target fraction was concentrated under vacuum to obtain the title compound (1.84 g, 28%).

^{1}H-NMR Spectrum ($CDCl_3$) δ (ppm): 1.42 (6H, d, J = 5.9 Hz), 4.73 (1H, spt, J = 6.1 Hz), 5.78 (1H, s), 6.95 (1H, d, J = 8.1 Hz), 7.41 (1H, dd, J = 8.2, 2.0 Hz), 7.44 (1H, d, J = 1.8 Hz), 9.83 (1H, s).

[0197] [Production Example 17-2]

3-(Benzyloxy)-4-isopropoxybenzaldehyde

[Chemical Formula 91]



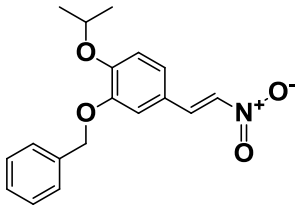
Potassium carbonate (1.83 g, 13.2 mmol) and benzyl chloride (1.55 mL, 13.5 mmol) were added to a suspension of 3-hydroxy-4-isopropoxybenzaldehyde described in Production Example 17-1 (1.84 g, 10.2 mmol) in ethanol (20 mL) under nitrogen atmosphere at room temperature, and the mixture was heated and stirred at 90°C for 2 hours. The mixture was cooled to 0°C and then 2 M hydrochloric acid, ethyl acetate, and water were added for partition. The organic layer was washed with a saturated saline solution, and the resultant was dried over anhydrous sodium sulfate, and then filtered. The solvent was evaporated, the resultant residue was dissolved in dichloromethane, and the resultant was purified with silica gel column chromatography (n-heptane:ethyl acetate = 19:1 - 3:1). The target fraction was concentrated under vacuum to obtain the title compound (2.59 g, 94%).

^{1}H-NMR Spectrum ($CDCl_3$) δ (ppm): 1.42 (6H, d, J = 6.0 Hz), 4.69 (1H, spt, J = 6.1 Hz), 5.18 (2H, s), 7.00 (1H, d, J = 8.1 Hz), 7.29-7.41 (3H, m), 7.43-7.48 (4H, m), 9.81 (1H, s).

[0198] [Production Example 17-3]

(E)-2-(Benzyloxy)-1-isopropoxy-4-(2-nitrovinyl) benzene

[Chemical Formula 92]



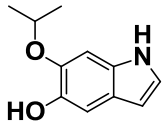
3-(Benzyloxy)-4-isopropoxybenzaldehyde described in Production Example 17-2 (2.59 g, 9.59 mmol) was dissolved in acetic acid (7.5 mL), then ammonium acetate (887 mg, 11.5 mmol) and nitromethane (1.25 mL, 23.1 mmol) were added under nitrogen atmosphere at room temperature, and the mixture was heated and stirred at 130°C for 2 hours. The mixture was cooled to room temperature, and the precipitate was collected by filteration and washed with ethanol to obtain the title compound (2.20 g, 73%).

^{1}H-NMR Spectrum ($CDCl_3$) δ (ppm): 1.41 (6H, d, J = 6.2 Hz), 4.55-4.71 (1H, m), 5.15 (2H, s), 6.94 (1H, d, J = 8.4 Hz), 7.05 (1H, d, J = 1.8 Hz), 7.15 (1H, dd, J = 8.4, 1.8 Hz), 7.29-7.48 (6H, m), 7.90 (1H, d, J = 13.5 Hz).

[0199] [Production Example 17-4]

6-Isopropoxy-1H-indol-5-ol

[Chemical Formula 93]



Fuming nitric acid (1.5 mL, 33.3 mmol) was slowly added to a mixture of (E)-2-(benzyloxy)-1-isopropoxy-4-(2-nitrovinyl)benzene described in Production Example 17-3 (2.20 g, 7.02 mmol) and acetic acid (20 mL) at room temperature, and the mixture was stirred for 7.5 hours. The reaction mixture was poured onto ice, the precipitate was collected by filteration, and then the resultant was washed with a liquid mixture of acetic acid and ethanol to obtain a crude product (2.28 g).

The crude product (2.28 g) was suspended in methanol (60 mL), 10% palladium-carbon (water content, 50%) (677 mg) was added, and the mixture was stirred under hydrogen atmosphere for 14.5 hours. The catalyst was filtered off with celite, and the resultant was washed with methanol. The filtrate was concentrated under vacuum and purified with silica gel column chromatography (n-heptane:ethyl acetate = 9:1 - 3:2). The target fraction was concentrated under vacuum to obtain the title compound (475 mg, 35%).

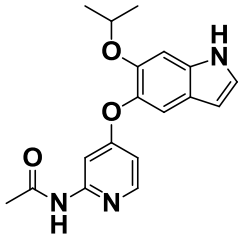
^{1}H-NMR Spectrum ($CDCl_3$) δ (ppm): 1.40 (6H, d, J = 6.2 Hz), 4.57 (1H, spt, J = 6.1 Hz),

5.55 (1H, s), 6.38-6.44 (1H, m), 6.90 (1H, s), 7.08 (1H, t, J = 2.7 Hz), 7.13 (1H, s), 7.90 (1H, brs).

[0200] [Production Example 17-5]

N-(4-((6-Isopropoxy-1H-indol-5-yl)oxy)pyridin-2-yl)acetamide

[Chemical Formula 94]



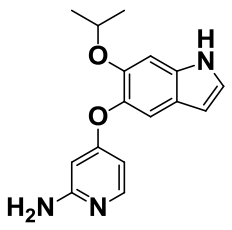
6-Isopropoxy-1H-indol-5-ol described in Production Example 17-4 (165 mg, 0.863 mmol) and N-(4-chloropyridin-2-yl)acetamide described in Production Example 1-5 (442 mg, 2.59 mmol) were dissolved in dimethylsulfoxide (2.0 mL) under nitrogen atmosphere, then potassium tert-butoxide (194 mg, 1.73 mmol) was added at room temperature, and the mixture was heated and stirred at 160°C for 3 hours. The reaction liquid was cooled to room temperature and water and ethyl acetate were added for partition. The aqueous layer was extracted with ethyl acetate and the combined organic layer was washed with water and a saturated saline solution. The organic layer was dried over anhydrous magnesium sulfate and then filtered, then the filtrate was concentrated under vacuum. The residue was dissolved in dichloromethane, the resultant was purified with NH silica gel column chromatography (n-heptane:ethyl acetate = 3:2 - 1:3), and then the target fraction was concentrated under vacuum to obtain the title compound (116 mg, 41%).

^{1}H-NMR Spectrum ($CDCl_3$) δ (ppm): 1.21 (6H, d, J = 6.2 Hz), 2.14 (3H, s), 4.34-4.48 (1H, m), 6.45-6.53 (2H, m), 7.03 (1H, s), 7.16 (1H, t, J = 2.7 Hz), 7.35 (1H, s), 7.77 (1H, brs), 7.85-8.05 (2H, m), 8.10 (1H, brs).

[0201] [Production Example 17-6]

4-((6-Isopropoxy-1H-indol-5-yl)oxy)pyridin-2-amine

[Chemical Formula 95]



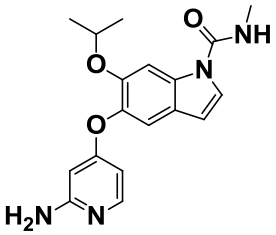
N-(4-((6-isopropoxy-1H-indol-5-yl)oxy)pyridin-2-yl)acetamide described in Production Example 17-5 (116 mg, 0.357 mmol) was dissolved in methanol (2.5 mL), 28% sodium methoxide (0.728 mL) was added under nitrogen atmosphere at room temperature, and the mixture was heated and stirred at 70°C for 3 hours. The reaction mixture was cooled to room temperature and then water and ethyl acetate were added for partition. The organic layer was washed with a saturated saline solution and then dried over anhydrous sodium sulfate. The drying agent was filtered off and the resultant was concentrated under vacuum. The residue was dissolved in dichloromethane and the resultant was purified with silica gel column chromatography (n-heptane:ethyl acetate = 3:7 - 0:1 - ethyl acetate:methanol = 99:1 - 9:1), then the target fraction was concentrated under vacuum to obtain the title compound (66.3 mg, 66%).

^{1}H-NMR Spectrum ($CDCl_3$) δ (ppm): 1.22 (6H, d, J = 5.9 Hz), 4.28 (2H, brs), 4.36-4.47 (1H, m), 5.89 (1H, d, J = 2.2 Hz), 6.29 (1H, dd, J = 5.9, 2.2 Hz), 6.46-6.51 (1H, m), 7.04 (1H, s), 7.18 (1H, t, J = 2.9 Hz), 7.34 (1H, s), 7.88 (1H, d, J = 5.9 Hz), 8.12 (1H, brs).

[0202] [Production Example 17-7]

5-((2-Aminopyridin-4-yl)oxy)-6-isopropoxy-N-methyl-1H-indole-1-carboxamide

[Chemical Formula 96]



4-((6-Isopropoxy-1H-indol-5-yl)oxy)pyridin-2-amine described in Production Example 17-6 (65.6 mg, 0.232 mmol) was dissolved in N,N-dimethylformamide (1.5 mL), 50 - 72% oily sodium hydride (16.7 mg) was added under nitrogen atmosphere at 0°C, and the mixture was stirred at room temperature for 50 minutes. The mixture was cooled to 0°C again, phenyl methylcarbamate described in Production Example 1-7 (69.2 mg, 0.458 mmol) was added, and the mixture was stirred at room temperature for 3 hours. A saturated aqueous ammonium chloride solution, water, and ethyl acetate were added to the reaction mixture for partition. The aqueous layer was extracted with ethyl acetate and the combined organic layer was washed with water and then with a saturated saline solution. The organic layer was dried over anhydrous magnesium sulfate and then filtered, then the filtrate was concentrated under vacuum. The residue was dissolved in dichloromethane and the

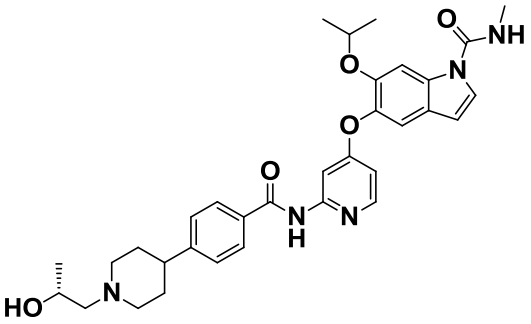
resultant was purified with NH silica gel column chromatography (n-heptane:ethyl acetate = 3:7 - 0:1 - ethyl acetate:methanol = 99:1 - 19:1), then the target fraction was concentrated under vacuum to obtain the title compound (77.0 mg, 98%).

^{1}H-NMR Spectrum ($CDCl_3$) δ (ppm): 1.24 (6H, d, J = 6.0 Hz), 3.06 (3H, d, J = 4.8 Hz), 4.32 (2H, brs), 4.56 (1H, spt, J = 6.1 Hz), 5.50-5.61 (1H, m), 5.89 (1H, d, J = 2.2 Hz), 6.27 (1H, dd, J = 5.9, 2.2 Hz), 6.55 (1H, dd, J = 3.6, 0.6 Hz), 7.24-7.28 (2H, m), 7.88 (1H, d, J = 5.9 Hz), 8.00 (1H, s).

[0203] [Example 18]

(R)-5-((2-(4-(1-(2-Hydroxypropyl)piperidin-4-yl)benzamide)pyridin-4-yl)oxy)-6-isopropoxy-N-methyl-1H-indole-1-carboxamide

[Chemical Formula 97]



Commercially available (R)-(+)-propylene oxide (20.5 mg, 0.353 mmol) was added to a mixture of 6-isopropoxy-N-methyl-5-((2-(4-(piperidin-4-yl)benzamide)pyridin-4-yl) oxy)-1H-indole-1-carboxamide described in Example 17 (12.7 mg, 0.024 mmol) and ethanol (0.5 mL), and the mixture was heated and stirred with a sealed tube at 80°C for 3 hours and 40 minutes. The mixture was cooled to room temperature, then the reaction mixture was concentrated under vacuum, the resultant residue was dissolved in dichloromethane, and the resultant was purified with NH silica gel column chromatography (n-heptane:ethyl acetate = 1:4 - 0:1 - ethyl acetate:methanol = 99:1 - 19:1). The target fraction was concentrated under vacuum, and the precipitate was collected by filteration and washed with diethyl ether to obtain the title compound (8.28 mg, 59%).

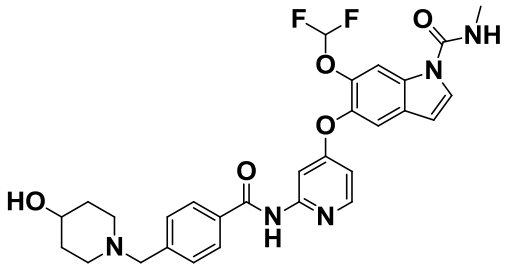
^{1}H-NMR Spectrum ($CDCl_3$) δ (ppm): 1.15 (3H, d, J = 6.2 Hz), 1.22 (6H, d, J = 6.2 Hz), 1.70-1.90 (3H, m), 2.00-2.09 (1H, m), 2.21-2.46 (3H, m), 2.53-2.64 (1H, m), 2.92 (1H, d, J = 11.0 Hz), 3.07 (3H, d, J = 4.8 Hz), 3.14 (1H, d, J = 11.3 Hz), 3.80-3.91 (1H, m), 4.53-4.64 (1H, m), 5.44-5.52 (1H, m), 6.55 (1H, d, J = 3.3 Hz), 6.58 (1H, dd, J = 5.7, 2.4 Hz), 7.25 (1H,

d, J = 3.7 Hz), 7.30-7.36 (3H, m), 7.81 (2H, d, J = 8.4 Hz), 7.93 (1H, d, J = 2.2 Hz), 8.01 (1H, s), 8.09 (1H, d, J = 5.9 Hz), 8.49 (1H, s).

[0204] [Example 19]

6-(Difluoromethoxy)-5-((2-(4-((4-hydroxypiperidin-1-yl)methyl)benzamide)pyridin-4-yl)oxy)-N-methyl-1H-indole-1-carboxamide

[Chemical Formula 98]



Triethylamine (17 μL, 0.123 mmol) and commercially available 4-(chloromethyl)benzoyl chloride (11.5 mg, 0.061 mmol) were added to a mixture of 5-((2-aminopyridin-4-yl)oxy)-6-(difluoromethoxy)-N-methyl-1H-indole-1-carboxamide described in Production Example 19-7 (4.3 mg, 0.012 mmol) and tetrahydrofuran (0.5 mL) under nitrogen atmosphere at room temperature. The mixture was stirred at room temperature for 2.5 hours and water and ethyl acetate were added to the reaction mixture for partition. The organic layer was washed with a saturated saline solution and then dried over anhydrous sodium sulfate and the resultant was filtered with NH silica gel (ethyl acetate) and concentrated under vacuum to obtain a crude product (6.18 mg).

The crude product (6.18 mg) was dissolved in N,N-dimethylformamide (0.5 mL), commercially available 4-hydroxypiperidine (17.7 mg, 0.175 mmol) was added under nitrogen atmosphere at room temperature, and the mixture was stirred for 14 hours. Water and ethyl acetate were added to the reaction mixture for partition, and the organic layer was washed with a saturated saline solution, dried over anhydrous sodium sulfate, and filtered. The solvent was evaporated and the resultant residue was purified with NH silica gel TLC (ethyl acetate) to obtain the title compound (6.0 mg, 86%).

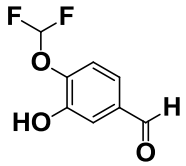
^{1}H-NMR Spectrum ($CDCl_3$) δ (ppm): 1.50-1.66 (2H, m), 1.83-1.94 (2H, m), 2.16 (2H, t, J = 9.7 Hz), 2.67-2.78 (2H, m), 3.08 (3H, d, J = 4.4 Hz), 3.54 (2H, s), 3.62-3.77 (2H, m), 5.46-5.57 (1H, m), 6.53 (1H, t, J = 73.9 Hz), 6.61 (1H, d, J = 3.7 Hz), 6.64 (1H, dd, J = 5.7, 2.4 Hz), 7.38-7.46 (4H, m), 7.80 (2H, d, J = 8.1 Hz), 7.91 (1H, d, J = 2.2 Hz), 8.15 (1H, d, J = 5.9 Hz), 8.24 (1H, s), 8.53 (1H, brs).

[0205] The starting material 5-((2-aminopyridin-4-yl)oxy)-6-(difluoromethoxy)-N-methyl-1H-indole-1-carboxamide was synthesized by the following method.

[0206] [Production Example 19-1]

4-(Difluoromethoxy)-3-hydroxybenzaldehyde

[Chemical Formula 99]



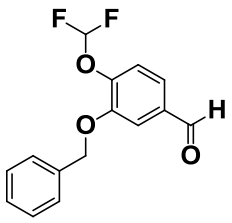
Commercially available 3,4-dihydroxybenzaldehyde (5 g, 36.2 mmol) and commercially available sodium chlorodifluoroacetate (5.57 g, 36.5 mmol) were dissolved in N,N-dimethylformamide (45 mL) and water (905 μL), and then sodium hydroxide (1.48 g, 37.0 mmol) was added at room temperature, and the mixture was heated and stirred at 120°C for 2 hours. The solvent was evaporated under vacuum, the residue was cooled to 0°C, and 5 M hydrochloric acid and diethyl ether were added for partition. The organic layer was washed with water and a saturated saline solution, and then the solvent was evaporated. The residue was dissolved in dichloromethane and the resultant was purified with silica gel column chromatography (n-heptane:ethyl acetate = 9:1 - 7:3), and then the target fraction was concentrated under vacuum to obtain the title compound (2.66 g, 39%).

^{1}H-NMR Spectrum ($CDCl_3$) δ (ppm): 5.69-5.74 (1H, m), 6.65 (1H, t, J = 72.5 Hz), 7.23-7.31 (1H, m), 7.46 (1H, dd, J = 8.4, 1.8 Hz), 7.54 (1H, d, J = 1.8 Hz), 9.92 (1H, s).

[0207] [Production Example 19-2]

3-(Benzyloxy)-4-(difluoromethoxy)benzaldehyde

[Chemical Formula 100]



Potassium carbonate (3.91 g, 28.3 mmol) and benzyl bromide (2.5 mL, 21.1 mmol) were added to a solution of 4-(difluoromethoxy)-3-hydroxybenzaldehyde described in Production Example 19-1 (2.66 g, 14.2 mmol) in acetonitrile (50 mL) at room temperature,

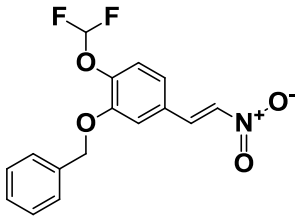
and the mixture was stirred at room temperature for 3 hours. The reaction mixture was filtered and then the solvent was evaporated. The resultant residue was purified with silica gel column chromatography (n-heptane:ethyl acetate = 9:1 - 3:2). The target fraction was concentrated under vacuum and then the title compound was quantitatively obtained.

^{1}H-NMR Spectrum ($CDCl_3$) δ (ppm): 5.21 (2H, s), 6.68 (1H, t, J = 74.3 Hz), 7.31-7.51 (7H, m), 7.57 (1H, d, J = 1.8 Hz), 9.92 (1H, s).

[0208] [Production Example 19-3]

(E)-2-(Benzyloxy)-1-(difluoromethoxy)-4-(2-nitrovinyl)benzene

[Chemical Formula 101]



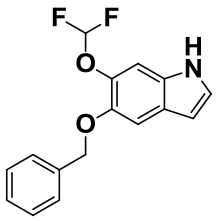
3-(Benzyloxy)-4-(difluoromethoxy)benzaldehyde described in Production Example 19-2 (3.94 g, 14.2 mmol) was dissolved in acetic acid (11 mL), then ammonium acetate (1.27 g, 16.4 mmol) and nitromethane (1.9 mL, 35.1 mmol) were added under nitrogen atmosphere at room temperature, and the mixture was heated and stirred at 130°C for 2 hours. The mixture was cooled to room temperature and then heated and stirred at 130°C again for 1 hour. The precipitate was collected by filteration and washed with a liquid mixture of acetic acid and ethanol to obtain the title compound (2.36 g, 52%). The filtrate was dissolved in dichloromethane and the resultant was purified with silica gel column chromatography (n-heptane:ethyl acetate = 19:1 - 4:1), and then the target fraction was concentrated under vacuum. The precipitate was washed with ethanol to obtain the title compound (406 mg, 8.9%).

^{1}H-NMR Spectrum ($CDCl_3$) δ (ppm): 5.18 (2H, s), 6.65 (1H, t, J = 74.3 Hz), 7.12-7.19 (2H, m), 7.21-7.29 (1H, m), 7.32-7.45 (5H, m), 7.48 (1H, d, J = 13.9 Hz), 7.92 (1H, d, J = 13.9 Hz).

[0209] [Production Example 19-4]

5-(Benzyloxy)-6-(difluoromethoxy)-1H-indole

[Chemical Formula 102]



Fuming nitric acid (6.0 mL, 133 mmol) was slowly added to a mixture of (E)-2-(benzyloxy)-1-(difluoromethoxy)-4-(2-nitrovinyl)benzene described in Production Example 19-3 (2.77 g, 8.61 mmol) and acetic acid (36 mL) in an ice bath, and the mixture was stirred for 7.5 hours. A part of the reaction mixture was heated and stirred at 50°C for 30 minutes, then at 70°C for 40 minutes, and then at 75°C for 165 minutes. A part of the reaction mixture was poured onto ice and the resultant was diluted with ethyl acetate for partition. The organic layer was washed with water and a saturated saline solution and dried over anhydrous magnesium sulfate, and then the solvent was evaporated. The residue was dissolved in dichloromethane and the resultant was purified with silica gel column chromatography (n-heptane:ethyl acetate = 17:3 - 3:1), then the target fraction was concentrated under vacuum, and then the residue was collected by filteration and washed with diethyl ether to obtain a crude product A (23.6 mg). The remaining reaction mixture was heated and stirred at 65°C for 3 hours, then the resultant was poured onto ice, and then the precipitate was collected by filteration and washed with a liquid mixture of acetic acid and ethanol to obtain a crude product B (603 mg). Ethyl acetate was added to the filtrate for partition. The organic layer was washed with water and a saturated saline solution, dried over anhydrous magnesium sulfate, and filtered, and then the solvent was evaporated. The residue was dissolved in dichloromethane and the resultant was purified with silica gel column chromatography (n-heptane:ethyl acetate = 9:1 - 3:1), then the target fraction was concentrated under vacuum, diethyl ether was added to the residue, and the precipitate was collected by filteration to obtain a crude product C (73.3 mg).

The crude products A, B, and C (550 mg) were suspended in ethanol (5.5 mL), acetic acid (5.5 mL), and water (676 μL), then iron powder (419 mg, 7.51 mmol) was added under nitrogen atmosphere, and the mixture was heated and stirred at 70°C for 1 hour. The reaction mixture was cooled to room temperature and ethyl acetate and an aqueous sodium disulfite solution were added for partition. The organic layer was washed with water and a saturated saline solution, dried over anhydrous magnesium sulfate, and filtered, and then the solvent was evaporated. The residue was dissolved in dichloromethane and the resultant

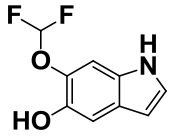
was purified with NH silica gel column chromatography (n-heptane:ethyl acetate = 9:1 - 3:2), and then the target fraction was concentrated under vacuum to obtain the title compound (245 mg, 13%).

^{1}H-NMR Spectrum ($CDCl_3$) δ (ppm): 5.15 (2H, s), 6.45-6.49 (1H, m), 6.58 (1H, t, J = 76.0 Hz), 7.19-7.22 (1H, m), 7.23 (1H, s), 7.24-7.27(1H, m), 7.29-7.43 (3H, m), 7.44-7.50 (2H, m), 8.12 (1H, brs).

[0210] [Production Example 19-5]

6-(Difluoromethoxy)-1H-indol-5-ol

[Chemical Formula 103]



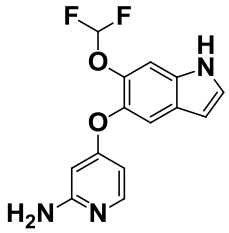
5-(Benzyloxy)-6-(difluoromethoxy)-1H-indole described in Production Example 19-4 (245 mg, 0.847 mmol) was dissolved in ethanol (8.0 mL), then 10% palladium-carbon (water content, 50%) (90 mg) was added at room temperature, and the mixture was stirred under hydrogen atmosphere for 75 minutes. The reaction mixture was diluted with ethyl acetate and the catalyst was filtered off with celite. The filtrate was concentrated under vacuum and then filtered with silica gel (ethyl acetate). The target fraction was concentrated under vacuum to quantitatively obtain the title compound.

^{1}H-NMR Spectrum ($CDCl_3$) δ (ppm): 5.15 (1H, s), 6.41-6.49 (1H, m), 6.53 (1H, t, J = 74.1 Hz), 7.15-7.24 (3H, m), 8.06 (1H, brs).

[0211] [Production Example 19-6]

4-((6-(Difluoromethoxy)-1H-indol-5-yl)oxy)pyridin -2-amine

[Chemical Formula 104]



6-(Difluoromethoxy)-1H-indol-5-ol described in Production Example 19-5 (35.1 mg, 0.176 mmol), N-(4-chloropyridin-2-yl)acetamide described in Production Example 1-5 (89.0 mg, 0.522 mmol), and potassium tert-butoxide (44.0 mg, 0.392 mmol) were dissolved in dimethylsulfoxide (500 μL) under nitrogen atmosphere, and the mixture was heated and

stirred at 160°C for 80 minutes. The reaction liquid was cooled to room temperature and water and ethyl acetate were added for partition. The organic layer was washed with a saturated saline solution, dried over anhydrous sodium sulfate, and then filtered, and then the filtrate was concentrated under vacuum. The residue was dissolved in dichloromethane and the resultant was purified with NH silica gel column chromatography (n-heptane:ethyl acetate = 1:1 - 0:1 - ethyl acetate:methanol = 99:1 - 9:1), then the target fraction was concentrated under vacuum to obtain a crude product (12.5 mg).

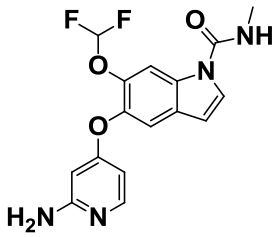
The crude product (12.5 mg) was dissolved in methanol (500 μL), 28% sodium methoxide (39 μL, 0.382 mmol) was added under nitrogen atmosphere at room temperature, and the mixture was heated and stirred at 65°C for 1 hour. The mixture was cooled to room temperature, 28% sodium methoxide (39 μL, 0.382 mmol) was added, and the mixture was heated and stirred at 65°C for 2.5 hours. Water and ethyl acetate were added to the reaction mixture for partition. The organic layer was washed with a saturated saline solution and then dried over anhydrous sodium sulfate. The drying agent was filtered off and the resultant was concentrated under vacuum. The residue was dissolved in dichloromethane and the resultant was purified with NH silica gel column chromatography (n-heptane:ethyl acetate = 1:1 - 0:1 - ethyl acetate:methanol = 97:3 - 9:1), and then the target fraction was concentrated under vacuum to obtain the title compound (4.4 mg, 8.6%).

^{1}H-NMR Spectrum ($CDCl_3$) δ (ppm): 4.48 (2H, brs), 5.91 (1H, d, J = 1.8 Hz), 6.28 (1H, dd, J = 5.9, 1.8 Hz), 6.45 (1H, t, J = 74.5 Hz), 6.52-6.58 (1H, m), 7.30 (1H, t, J = 2.9 Hz), 7.36 (1H, s), 7.41 (1H, s), 7.90 (1H, d, J = 5.9 Hz), 8.35 (1H, brs).

[0212] [Production Example 19-7]

5-((2-Aminopyridin-4-yl)oxy)-6-(difluoromethoxy)-N-methyl-1H-indole-1-carboxamide

[Chemical Formula 105]



4-((6-(Difluoromethoxy)-1H-indol-5-yl)oxy)pyridin-2-amine described in Production Example 19-6 (4.4 mg, 0.015 mmol) was dissolved in N,N-dimethylformamide (500 μL), then 50 - 72% oily sodium hydride (4.1 mg) was added under nitrogen atmosphere at 0°C, and the mixture was stirred at room temperature for 30 minutes. The mixture was

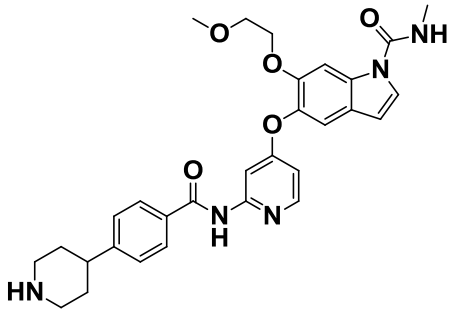
cooled to 0°C again and phenyl methylcarbamate described in Production Example 1-7 (16.4 mg, 0.108 mmol) was added, and the mixture was stirred at room temperature for 50 minutes. Water and ethyl acetate were added to the reaction mixture for partition. The organic layer was washed with a saturated saline solution, then dried over anhydrous sodium sulfate and filtered, and then the filtrate was concentrated under vacuum. The residue was dissolved in dichloromethane and the resultant was purified with NH silica gel column chromatography (n-heptane:ethyl acetate = 1:1 - 0:1 - ethyl acetate:methanol = 99:1 - 9:1), and then the target fraction was concentrated under vacuum to obtain the title compound (4.3 mg, 82%).

^{1}H-NMR Spectrum ($CDCl_3$) δ (ppm): 3.08 (3H, d, J = 4.8 Hz), 4.44 (2H, brs), 5.49 (1H, brs), 5.91 (1H, d, J = 1.8 Hz), 6.26 (1H, dd, J = 6.2, 2.2 Hz), 6.50 (1H, t, J = 74.0 Hz), 6.61 (1H, d, J = 3.7 Hz), 7.35 (1H, s), 7.41 (1H, d, J = 3.7 Hz), 7.92 (1H, d, J = 5.9 Hz), 8.23 (1H, s).

[0213] [Example 20]

6-(2-Methoxyethoxy)-N-methyl-5-((2-(4-(piperidin-4-yl)benzamide)pyridin-4-yl)oxy)-1H-indole-1-carboxamide

[Chemical Formula 106]



Benzotriazole (609 mg, 5.11 mmol) was dissolved in dichloromethane (25 mL), thionyl chloride (373 μL, 5.11 mmol) was added under nitrogen atmosphere at room temperature, and the mixture was stirred for 5 minutes. 4-(1-(tert-Butoxycarbonyl)piperidin-4-yl)benzoic acid described in Production Example 1-12 (1.3 g, 4.26 mmol) was added to the reaction mixture at room temperature, and the mixture was stirred for 30 minutes. The reaction mixture was filtered through a glass filter entirely covered with anhydrous sodium sulfate and the anhydrous sodium sulfate was washed with dichloromethane, the filtrate was added to a mixture of 5-((2-aminopyridin-4-yl)oxy)-6-(2-methoxyethoxy)-N-methyl-1H-indole-1-carboxamide described in Production Example 20-7 (0.95 g, 2.67 mmol), triethylamine (1.86 mL, 13.3 mmol), and 4-dimethylaminopyridine (16 mg, 0.133 mmol) in N,N-dimethylformamide (3

mL) and dichloromethane (20 mL) at 0°C over 5 minutes, and the mixture was rinsed with dichloromethane (10 mL) and then stirred at the same temperature for 5 minutes. The mixture was stirred at room temperature for 2 hours, then a 40% aqueous methylamine solution (2.3 mL, 26.7 mmol) was added, and then the mixture was stirred at room temperature for 1.5 hours. A saturated aqueous sodium bicarbonate solution was added to the reaction mixture for partition and the aqueous layer was extracted with ethyl acetate three times. The combined organic layer was dried over anhydrous sodium sulfate. The drying agent was filtered off, then the filtrate was concentrated under vacuum and the resultant was purified with silica gel column chromatography (n-heptane:ethyl acetate = 1:1 - 0:1 - ethyl acetate:methanol = 49:1 - 23:2) to obtain a crude product (1.11 g).

The crude product (1.11 g) was dissolved in dichloromethane (50 mL) and trifluoroacetic acid (5.0 mL) was added at room temperature. The mixture was stirred at room temperature for 30 minutes, then the resultant was concentrated under vacuum, and then the residue was dissolved in dichloromethane and triethylamine and the resultant was concentrated under vacuum. The residue was purified with NH silica gel column chromatography (ethyl acetate:methanol = 1:0 - 22:3) to obtain the title compound (829 mg, 57%).

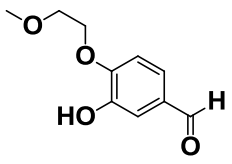
^{1}H-NMR Spectrum (500MHz, $CDCl_3$) δ (ppm): 1.59-1.69 (2H, m), 1.83 (2H, d, J = 14.1 Hz), 2.68 (1H, tt, J = 12.0, 3.6 Hz), 2.75 (2H, td, J = 12.2, 2.4 Hz), 3.04 (3H, d, J = 4.9 Hz), 3.17-3.23 (2H, m), 3.26 (3H, s), 3.55-3.61 (2H, m), 4.15-4.21 (2H, m), 5.57-5.65 (1H, m), 6.53 (1H, d, J = 3.4 Hz), 6.62 (1H, dd, J = 5.8, 2.4 Hz), 7.25 (1H, d, J = 3.9 Hz), 7.30-7.34 (3H, m), 7.77-7.82 (2H, m), 7.91 (1H, d, J = 2.4 Hz), 8.02 (1H, s), 8.10 (1H, d, J = 5.9 Hz), 8.50 (1H, brs).

[0214] The starting material 5-((2-aminopyridin-4-yl)oxy)-6-(2-methoxyethoxy)-N-methyl-1H-indole-1-carboxamide was synthesized by the following method.

[0215] [Production Example 20-1]

3-Hydroxy-4-(2-methoxyethoxy)benzaldehyde

[Chemical Formula 107]



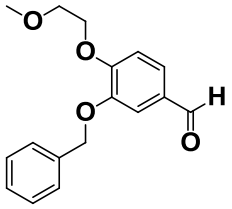
Commercially available 3,4-dihydroxybenzaldehyde (39.3 g, 285 mmol) and sodium carbonate (45.2 g, 427 mmol) were dissolved in N,N-dimethylformamide (400 mL), then commercially available 2-bromoethyl methyl ether (26.7 mL, 285 mmol) was added under nitrogen atmosphere at room temperature, and the mixture was stirred for 5 days. The mixture was cooled to 0°C and then 2 M hydrochloric acid, ethyl acetate, and water were added for partition. The aqueous layer was extracted with ethyl acetate, then the combined organic layer was washed with a saturated saline solution and dried over anhydrous magnesium sulfate, and then filtered. The solvent was evaporated, dichloromethane was added, the precipitate was separated by filtration, and then the resultant filtrate was purified with silica gel column chromatography (n-heptane:ethyl acetate = 17:3 - 1:1). The target fraction was concentrated under vacuum to obtain the title compound (12.9 g, 23%).

^{1}H-NMR Spectrum ($CDCl_3$) δ (ppm): 3.47 (3H, s), 3.76-3.80 (2H, m), 4.25-4.29 (2H, m), 6.40 (1H, brs), 7.01 (1H, d, J = 8.4 Hz), 7.41 (1H, dd, J = 8.2, 2.0 Hz), 7.45 (1H, d, J = 1.8 Hz), 9.85 (1H, s).

[0216] [Production Example 20-2]

3-(Benzyloxy)-4-(2-methoxyethoxy)benzaldehyde

[Chemical Formula 108]



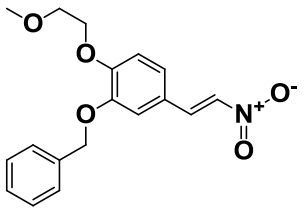
Potassium carbonate (11.8 g, 85.7 mmol) and benzyl chloride (10 mL, 86.9 mmol) were added to a liquid mixture of 3-hydroxy-4-(2-methoxyethoxy)benzaldehyde described in Production Example 20-1 (12.9 g, 65.9 mmol) in ethanol (130 mL) under nitrogen atmosphere at room temperature, and the mixture was heated and stirred at 90°C for 2 hours. The mixture was cooled to 0°C and then 2 M hydrochloric acid, ethyl acetate, and water were added for partition. The organic layer was washed with a saturated saline solution, dried over anhydrous magnesium sulfate, and then filtered. The solvent was evaporated and the resultant residue was purified with silica gel column chromatography (n-heptane:ethyl acetate = 9:1 - 1:1). The target fraction was concentrated under vacuum to obtain the title compound (17.6 g, 93%).

^{1}H-NMR Spectrum ($CDCl_3$) δ (ppm): 3.46 (3H, s), 3.79-3.85 (2H, m), 4.24-4.30 (2H, m), 5.18 (2H, s), 7.03 (1H, d, J = 8.1 Hz), 7.29-7.35 (1H, m), 7.35-7.41 (2H, m), 7.43-7.50 (4H, m), 9.82 (1H, s).

[0217] [Production Example 20-3]

(E)-2-(Benzyloxy)-1-(2-methoxyethoxy)-4-(2-nitrovinyl)benzene

[Chemical Formula 109]



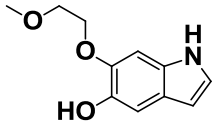
3-(Benzyloxy)-4-(2-methoxyethoxy)benzaldehyde described in Production Example 20-2 (17.6 g, 61.5 mmol) was dissolved in acetic acid (49.3 mL), then ammonium acetate (5.69 g, 73.8 mmol) and nitromethane (8.32 mL, 154 mmol) were added under nitrogen atmosphere at room temperature, and the mixture was heated and stirred at 130°C for 2 hours. The mixture was cooled to room temperature and then the precipitate was collected by filteration and washed with ethanol to quantitatively obtain the title compound.

^{1}H-NMR Spectrum ($CDCl_3$) δ (ppm): 3.46 (3H, s), 3.78-3.84 (2H, m), 4.21-4.27 (2H, m), 5.16 (2H, s), 6.97 (1H, d, J = 8.4 Hz), 7.06 (1H, d, J = 1.8 Hz), 7.16 (1H, dd, J = 8.4, 2.2 Hz), 7.30-7.48 (6H, m), 7.91 (1H, d, J = 13.5 Hz).

[0218] [Production Example 20-4]

6-(2-Methoxyethoxy)-1H-indol-5-ol

[Chemical Formula 110]



69% Nitric acid (15 mL, 233 mmol) was added to a mixture of (E)-2-(benzyloxy)-1-(2-methoxyethoxy)-4-(2-nitrovinyl)benzene described in Production Example 20-3 (20.2 g, 61.5 mmol) and acetic acid (120 mL) at 25°C, and the mixture was stirred at room temperature for 6 hours. The reaction mixture was poured onto ice, and the precipitate was collected by filteration and then washed with water to obtain a crude product (23.0 g).

The crude product (23.0 g) was suspended in methanol (500 mL), then 10%

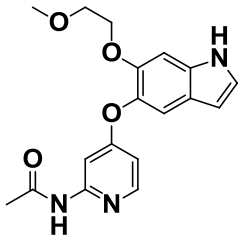
palladium-carbon (water content, 50%) (8 g) was added at room temperature, and the mixture was stirred under hydrogen atmosphere for 6 hours. The catalyst was filtered off with celite, the filtrate was concentrated under vacuum, and the resultant was purified with silica gel column chromatography (n-heptane:ethyl acetate = 2:1 - 1:1). The target fraction was concentrated under vacuum to obtain the title compound (3.94 g, 31%).

^{1}H-NMR Spectrum ($CDCl_3$) δ (ppm): 3.48 (3H, s), 3.69-3.78 (2H, m), 4.16-4.23 (2H, m), 6.24 (1H, s), 6.41 (1H, ddd, J = 3.1, 2.1, 0.8 Hz), 6.97 (1H, s), 7.10 (1H, dd, J = 3.2, 2.5 Hz), 7.15 (1H, s), 7.94 (1H, brs).

[0219] [Production Example 20-5]

N-(4-((6-(2-Methoxyethoxy)-1H-indol-5-yl)oxy)pyridin-2-yl)acetamide

[Chemical Formula 111]



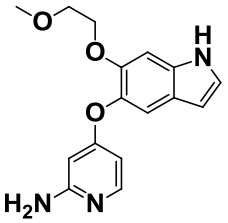
6-(2-Methoxyethoxy)-1H-indol-5-ol described in Production Example 20-4 (3.94 g, 19.0 mmol) and N-(4-chloropyridin-2-yl)acetamide described in Production Example 1-5 (3.25 g, 19.0 mmol) were dissolved in dimethylsulfoxide (25 mL), then 97% potassium tert-butoxide (2.20 g, 19.0 mmol) was added at room temperature, and the mixture was heated and stirred at 150°C for 13 hours. Water and ethyl acetate were added to the reaction liquid at room temperature for partition. The aqueous layer was extracted with ethyl acetate three times and the combined organic layer was washed with water. The organic layer was dried over anhydrous sodium sulfate. The drying agent was filtered off and the filtrate was concentrated under vacuum, and then the resultant was purified with NH silica gel column chromatography (n-heptane:ethyl acetate = 2:3 - 0:1 - ethyl acetate:methanol = 49:1 - 9:1). The target fraction was concentrated under vacuum to obtain the title compound (3.45 g, 53%).

^{1}H-NMR Spectrum (500MHz, $CDCl_3$) δ (ppm): 2.13 (3H, s), 3.27 (3H, s), 3.54-3.58 (2H, m), 4.07-4.11 (2H, m), 6.46-6.50 (1H, m), 6.54 (1H, dd, J = 5.8, 1.9 Hz), 7.05 (1H, s), 7.14-7.17 (1H, m), 7.36 (1H, s), 7.75 (1H, brs), 8.02 (1H, d, J = 5.8 Hz), 8.10 (1H, brs), 8.19 (1H, brs).

[0220] [Production Example 20-6]

4-((6-(2-Methoxyethoxy)-1H-indol-5-yl)oxy) pyridin-2-amine

[Chemical Formula 112]



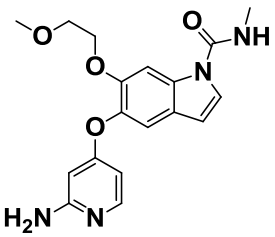
N-(4-((6-(2-methoxyethoxy)-1H-indol-5-yl)oxy)pyridin-2-yl)acetamide described in Production Example 20-5 (3.45 g, 10.1 mmol) was dissolved in methanol (50 mL), a 2 M sodium hydroxide solution (50 mL) was added at room temperature, and the mixture was heated and stirred at 70°C for 3 hours. Water and ethyl acetate were added to the reaction mixture for partition. The aqueous layer was extracted with ethyl acetate three times and the combined organic layer was dried over anhydrous sodium sulfate. The drying agent was filtered off and the filtrate was concentrated under vacuum and the resultant was purified with NH silica gel column chromatography (n-heptane:ethyl acetate = 3:7 - 0:1 - ethyl acetate:methanol = 49:1 - 24:1). The target fraction and the mixture fraction were concentrated under vacuum separately from each other, the mixture fraction was purified again with silica gel column chromatography (ethyl acetate:methanol = 1:0 - 9:1), and then the resultant was combined with the above-described target fraction to obtain the title compound (2.60 g, 86%).

^{1}H-NMR Spectrum (500MHz, $CDCl_3$) δ (ppm): 3.31 (3H, s), 3.58-3.63 (2H, m), 4.08-4.11 (2H, m), 4.28 (2H, brs), 5.90 (1H, d, J = 2.4 Hz), 6.29 (1H, dd, J = 6.1, 2.2 Hz), 6.44-6.52 (1H, m), 7.06 (1H, s), 7.15-7.20 (1H, m), 7.34 (1H, s), 7.88 (1H, d, J = 5.8 Hz), 8.22 (1H, brs).

[0221] [Production Example 20-7]

5-((2-Aminopyridin-4-yl)oxy)-6-(2-methoxyethoxy)-N-methyl-1H-indole-1-carboxamide

[Chemical Formula 113]



4-((6-(2-Methoxyethoxy)-1H-indol-5-yl)oxy)pyridin-2-amine described in Production Example 20-6 (2.60 g, 8.67 mmol) was dissolved in N,N-dimethylformamide

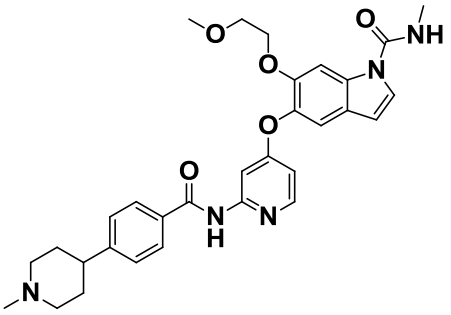
(50 mL), then 50 - 72% oily sodium hydride (499 mg) was added under nitrogen atmosphere at room temperature. Phenyl methylcarbamate described in Production Example 1-7 (1.97 g, 13.0 mmol) was added, and the mixture was stirred at room temperature for 1 hour. The reaction mixture was cooled to 0°C and ethyl acetate and water were added for partition. The aqueous layer was extracted with ethyl acetate twice, sodium chloride was added to the aqueous layer, and the resultant was extracted with ethyl acetate three times. The combined organic layer was dried over anhydrous sodium sulfate. The drying agent was filtered off and the filtrate was concentrated under vacuum, and then the resultant was purified with NH silica gel column chromatography (n-heptane:ethyl acetate = 1:4 - 0:1 - ethyl acetate:methanol = 49:1 - 24:1). The target fraction was concentrated under vacuum, and ethyl acetate was added and the precipitate was collected by filteration and washed to obtain the title compound (2.23 g, 72%).

^{1}H-NMR Spectrum (500MHz, $CDCl_3$) δ (ppm): 3.06 (3H, d, J = 4.9 Hz), 3.29 (3H, s), 3.59-3.63 (2H, m), 4.14-4.17 (2H, m), 4.30 (2H, brs), 5.52-5.59 (1H, m), 5.89 (1H, d, J = 2.4 Hz), 6.27 (1H, dd, J = 5.8, 1.9 Hz), 6.55 (1H, d, J = 3.9 Hz), 7.27-7.29 (2H, m), 7.89 (1H, d, J = 5.9 Hz), 7.99 (1H, s).

[0222] [Example 21]

6-(2-Methoxyethoxy)-N-methyl-5-((2-(4-(1-methylpiperidin-4-yl)benzamide)pyridin-4-yl)oxy)-1H-indole-1-carboxamide

[Chemical Formula 114]



A 35% aqueous formaldehyde solution (186 μL, 2.36 mmol) and sodium triacetoxyborohydride (200 mg, 0.946 mmol) were added to a mixture of 6-(2-methoxyethoxy)-N-methyl-5-((2-(4-(piperidin-4-yl)benzamide)pyridin-4-yl)oxy)-1H-indole-1-carboxamide described in Example 20 (257 mg, 0.473 mmol) and tetrahydrofuran (30 mL) at room temperature, and the mixture was stirred at room temperature for 3 minutes. Acetic acid (54 μL, 0.946 mmol) was added to the reaction mixture, and the mixture was

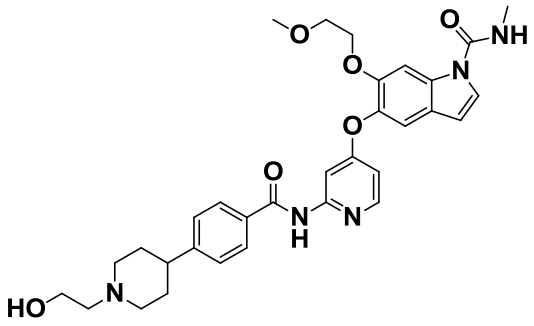
stirred at room temperature for 3 hours. A saturated aqueous sodium bicarbonate solution and ethyl acetate were added to the reaction mixture for partition. The aqueous layer was extracted with ethyl acetate three times, and the combined organic layer was dried over anhydrous sodium sulfate and filtered. The solvent was evaporated and the resultant residue was purified with NH silica gel column chromatography (ethyl acetate:methanol = 1:0 - 23:2). The target fraction was concentrated under vacuum to quantitatively obtain the title compound.

^{1}H-NMR Spectrum (500MHz, $CDCl_3$) δ (ppm): 1.75-1.88 (4H, m), 2.02-2.11 (2H, m), 2.33 (3H, s), 2.49-2.59 (1H, m), 2.99 (2H, d, J = 11.2 Hz), 3.05 (3H, d, J = 4.9 Hz), 3.26 (3H, s), 3.56-3.60 (2H, m), 4.15-4.21 (2H, m), 5.52-5.58 (1H, m), 6.54 (1H, d, J = 3.9 Hz), 6.61 (1H, dd, J = 5.8, 2.4 Hz), 7.25-7.27 (1H, m), 7.30-7.34 (3H, m), 7.79 (2H, d, J = 8.3 Hz), 7.91 (1H, d, J = 2.4 Hz), 8.01 (1H, s), 8.09 (1H, d, J = 5.8 Hz), 8.48 (1H, brs).

[0223] [Example 22]

5-((2-(4-(1-(2-Hydroxyethyl)piperidin-4-yl)benzamide)pyridin-4-yl) oxy)-6-(2-methoxyethoxy)-N-methyl-1H-indole-1-carboxamide

[Chemical Formula 115]



Sodium triacetoxyborohydride (286 mg, 1.35 mmol) and commercially available 2-hydroxyacetaldehyde (86.1 mg, 1.43 mmol) were added to a mixture of 6-(2-methoxyethoxy)-N-methyl-5-((2-(4-(piperidin-4-yl)benzamide)pyridin-4-yl)oxy)-1H-indole-1-carboxamide described in Example 20 (250 mg, 0.46 mmol) and tetrahydrofuran (10 mL) at room temperature, and the mixture was stirred at room temperature for 3 hours and 45 minutes. A saturated aqueous sodium bicarbonate solution and ethyl acetate were added to the reaction mixture for partition. The aqueous layer was extracted with ethyl acetate, and the combined organic layer was washed with a saturated saline solution, then dried over anhydrous sodium sulfate, and then filtered. The solvent was evaporated and the resultant residue was purified with NH silica gel column chromatography (ethyl acetate:methanol =

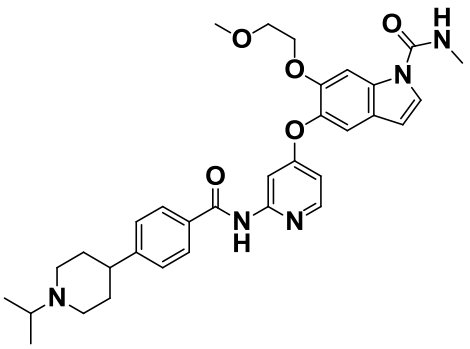
1:0 - 97:3 - 9:1). The target fraction was concentrated under vacuum, then the precipitate was collected by filteration and washed with a liquid mixture of diethyl ether and n-hexane to obtain the title compound (236 mg, 87%).

^{1}H-NMR Spectrum ($CDCl_3$) δ (ppm): 1.70-1.92 (4H, m), 2.14-2.25 (2H, m), 2.53-2.64 (3H, m), 3.01-3.08 (5H, m), 3.26 (3H, s), 3.56-3.60 (2H, m), 3.63 (2H, t, J = 5.4 Hz), 4.15-4.20 (2H, m), 5.50-5.59 (1H, m), 6.54 (1H, d, J = 3.7 Hz), 6.61 (1H, dd, J = 5.7, 2.4 Hz), 7.24-7.28 (1H, m), 7.30-7.35 (3H, m), 7.80 (2H, d, J = 8.4 Hz), 7.91 (1H, d, J = 2.2 Hz), 8.01 (1H, s), 8.09 (1H, d, J = 5.9 Hz), 8.50 (1H, brs).

[0224] [Example 23]

5-((2-(4-(1-Isopropylpiperidin-4-yl)benzamide)pyridin-4-yl)oxy)-6-(2-methoxyethoxy)-N-methyl-1H-indole-1-carboxamide

[Chemical Formula 116]



Acetone (54 μL, 0.736 mmol), sodium triacetoxyborohydride (62.4 mg, 0.294 mmol), and acetic acid (17 μL, 0.294 mmol) were added to a solution of 6-(2-methoxyethoxy)-N-methyl-5-((2-(4-(piperidin-4-yl)benzamide)pyridin-4-yl)oxy)-1H-indole-1-carboxamide described in Example 20 (20 mg, 0.037 mmol) in tetrahydrofuran (3 mL) at room temperature. The reaction liquid was stirred at the same temperature overnight. A saturated aqueous sodium bicarbonate solution and ethyl acetate were added to the reaction liquid at room temperature for partition. The organic layer was washed with a saturated saline solution and then dried over anhydrous sodium sulfate. The drying agent was separated by filtration and then the resultant was concentrated under vacuum. The residue was purified with NH silica gel column chromatography (ethyl acetate) to obtain the title compound (6.6 mg, 31%).

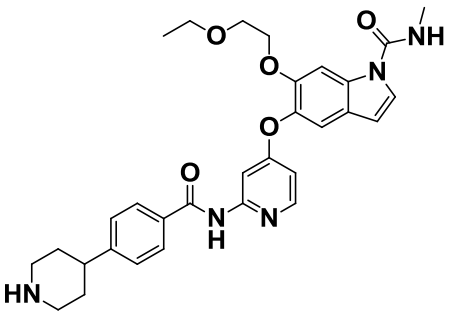
^{1}H-NMR Spectrum (DMSO-d_6) δ (ppm): 0.99 (6H, d, J = 6.6 Hz), 1.54-1.68 (2H, m), 1.70-1.81 (2H, m), 2.16-2.26 (2H, m), 2.44-2.57 (1H, m), 2.66-2.76 (1H, m), 2.82-2.91 (5H, m), 3.12 (3H, s), 3.45-3.52 (2H, m), 4.05-4.13 (2H, m), 6.63 (1H, d, J = 3.7 Hz), 6.67 (1H, dd,

J = 5.7, 2.4 Hz), 7.33 (2H, d, J = 8.4 Hz), 7.45 (1H, s), 7.69 (1H, d, J = 2.6 Hz), 7.78 (1H, d, J = 4.0 Hz), 7.89 (2H, d, J = 8.4 Hz), 8.08 (1H, s), 8.14-8.21 (2H, m), 10.64 (1H, s).

[0225] [Example 24]

6-(2-Ethoxyethoxy)-N-methyl-5-((2-(4-(piperidin-4-yl)benzamide)pyridin-4-yl)oxy)-1H-indole-1-carboxamide

[Chemical Formula 117]



Trifluoroacetic acid (1.79 mL, 23.2 mmol) was added to a solution of tert-butyl 4-(4-((4-((6-(2-ethoxyethoxy)-1-(methylcarbamoyl)-1H-indol-5-yl)oxy)pyridin-2-yl)carbamoyl)phenyl)piperidine-1-carboxylate described in Production Example 24-9 (382 mg, 0.581 mmol) in dichloromethane (10 mL) at room temperature. The reaction liquid was stirred at the same temperature for 1 hour. The reaction liquid was concentrated under vacuum, and trifluoroacetic acid was removed. The residue was diluted with dichloromethane and then triethylamine was added to neutralize the trifluoroacetic acid. The solution was concentrated under vacuum and then the residue was purified with NH silica gel column chromatography (ethyl acetate:methanol = 49:1 - 17:3) to obtain the title compound (276 mg, 85%).

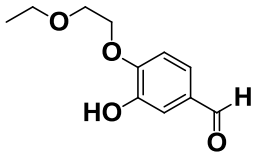
^{1}H-NMR Spectrum (DMSO-d_6) δ (ppm): 0.94 (3H, t, J = 7.0 Hz), 1.44-1.57 (2H, m), 1.63-1.72 (2H, m), 2.47-2.69 (3H, m), 2.85 (3H, d, J = 4.4 Hz), 2.97-3.05 (2H, m), 3.29 (2H, q, J = 7.0 Hz), 3.47-3.58 (2H, m), 4.04-4.13 (2H, m), 6.57-6.73 (2H, m), 7.31 (2H, d, J = 8.1 Hz), 7.45 (1H, s), 7.70 (1H, d, J = 2.2 Hz), 7.78 (1H, d, J = 3.7 Hz), 7.90 (2H, d, J = 8.8 Hz), 8.08 (1H, s), 8.13-8.24 (2H, m), 10.64(1H, s).

[0226] The starting material tert-butyl 4-(4-((4-((6-(2-ethoxyethoxy)-1-(methylcarbamoyl)-1H-indol-5-yl)oxy)pyridin-2-yl)carbamoyl)phenyl)piperidine-1-carboxylate was synthesized by the following method.

[0227] [Production Example 24-1]

4-(2-Ethoxyethoxy)-3-hydroxybenzaldehyde

[Chemical Formula 118]



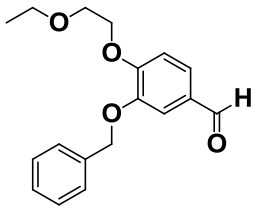
Commercially available 2-bromoethyl ethyl ether (33.8 g, 221 mmol) was added to a solution of commercially available 3,4-dihydroxybenzaldehyde (30.5 g, 221 mmol) and sodium carbonate (35.1 g, 331 mmol) in N,N-dimethylformamide (310 mL) under nitrogen atmosphere at room temperature. The liquid mixture was stirred at room temperature for 5 days. The reaction liquid was cooled to 0°C and diluted with 2 M hydrochloric acid, ethyl acetate, and water. The aqueous layer was extracted with ethyl acetate. The combined organic layer was washed serially with water and a saturated saline solution and then dried over anhydrous magnesium sulfate. The drying agent was separated by filtration and then the filtrate was concentrated under vacuum. The insoluble matters were separated by filtration with dichloromethane and the raw material was removed. The filtrate was purified with silica gel column chromatography (n-heptane:ethyl acetate = 17:3 - 1:1) to obtain the title compound (13.2 g, 28%).

^{1}H-NMR Spectrum ($CDCl_3$) δ (ppm): 1.27 (3H, t, J = 7.0 Hz), 3.63 (2H, q, J = 7.0 Hz), 3.80-3.85 (2H, m), 4.24-4.30 (2H, m), 6.65 (1H, s), 7.02 (1H, d, J = 8.4 Hz), 7.38-7.42 (1H, m), 7.45 (1H, d, J = 2.2 Hz), 9.85 (1H, s).

[0228] [Production Example 24-2]

3-(Benzyloxy)-4-(2-ethoxyethoxy)benzaldehyde

[Chemical Formula 119]



Potassium carbonate (11.3 g, 81.5 mmol) and benzyl chloride (9.5 mL, 82.6 mmol) were added to a solution of 4-(2-ethoxyethoxy)-3-hydroxybenzaldehyde described in Production Example 24-1 (13.2 g, 62.7 mmol) in ethanol (130 mL) under nitrogen atmosphere at room temperature. The liquid mixture was stirred under a thermal condition of 90°C for 2 hours. The reaction liquid was cooled to 0°C and then diluted with 2 M

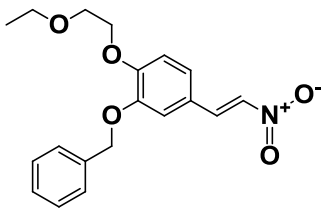
hydrochloric acid, ethyl acetate, and water. The organic layer was washed with a saturated saline solution and then dried over anhydrous magnesium sulfate. The drying agent was separated by filtration and the filtrate was concentrated under vacuum. The resultant residue was dissolved in dichloromethane and the resultant was purified with silica gel column chromatography (n-heptane:ethyl acetate = 9:1 - 1:1) to obtain the title compound (13.5 g, 72%).

^{1}H-NMR Spectrum ($CDCl_3$) δ (ppm): 1.22 (3H, t, J = 7.0 Hz), 3.63 (2H, q, J = 7.0 Hz), 3.82-3.90 (2H, m), 4.23-4.30 (2H, m), 5.18 (2H, s), 7.03 (1H, d, J = 7.7 Hz), 7.28-7.34 (1H, m), 7.35-7.42 (2H, m), 7.43-7.50 (4H, m), 9.82 (1H, s).

[0229] [Production Example 24-3]

(E)-2-(Benzyloxy)-1-(2-ethoxyethoxy)-4-(2-nitrovinyl) benzene

[Chemical Formula 120]



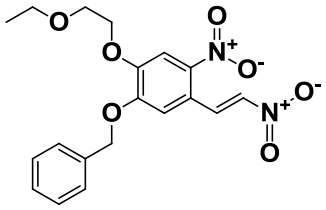
Ammonium acetate (4.16 g, 53.9 mmol) and nitromethane (6.1 mL, 113 mmol) were added to a solution of 3-(benzyloxy)-4-(2-ethoxyethoxy)benzaldehyde described in Production Example 24-2 (13.5 g, 45.0 mmol) in acetic acid (36 mL) under nitrogen atmosphere at room temperature. The liquid mixture was heated and stirred under reflux at 130°C for 2 hours. The reaction liquid was allowed to stand to cool to room temperature. The precipitate was collected by filteration and washed with ethanol to quantitatively obtain the title compound.

^{1}H-NMR Spectrum ($CDCl_3$) δ (ppm): 1.22 (3H, t, J = 7.1 Hz), 3.62 (2H, q, J = 7.0 Hz), 3.82-3.88 (2H, m), 4.21-4.26 (2H, m), 5.16 (2H, s), 6.97 (1H, d, J = 8.3 Hz), 7.06 (1H, d, J = 2.2 Hz), 7.16 (1H, dd, J = 8.3, 2.1 Hz), 7.29-7.50 (6H, m), 7.91 (1H, d, J = 13.6 Hz).

[0230] [Production Example 24-4]

(E)-1-(Benzyloxy)-2-(2-ethoxyethoxy)-4-nitro -5-(2-nitrovinyl)benzene

[Chemical Formula 121]

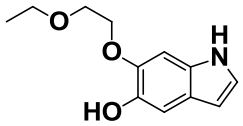


Nitric acid (11 mL, 69%, 171 mmol) was added to a solution of (E)-2-(benzyloxy)-1-(2-ethoxyethoxy)-4-(2-nitrovinyl)benzene described in Production Example 24-3 (15.4 g, 44.9 mmol) and acetic acid (100 mL) at 25°C, and the mixture was stirred for 6 hours. The reaction liquid was poured onto ice. The suspension was subjected to suction filtration and the product was washed with water to quantitatively obtain the title compound.

^{1}H-NMR Spectrum ($CDCl_3$) δ (ppm): 1.23 (3H, t, J = 7.0 Hz), 3.62 (2H, q, J = 6.9 Hz), 3.84-3.90 (2H, m), 4.29-4.34 (2H, m), 5.27 (2H, s), 6.93 (1H, s), 7.23 (1H, d, J = 13.6 Hz), 7.35-7.50 (5H, m), 7.84 (1H, s), 8.57 (1H, d, J = 13.5 Hz).

[0231] [Production Example 24-5] 6-(2-Ethoxyethoxy)-1H-indol-5-ol

[Chemical Formula 122]



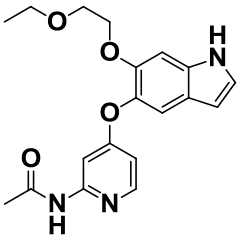
10% Palladium-carbon (water content, 50%) (6 g) was added to a solution of (E)-1-(benzyloxy)-2-(2-ethoxyethoxy)-4-nitro-5-(2-nitrovinyl)benzene described in Production Example 24-4 (17.5 g, 44.9 mmol) in methanol (180 mL) at room temperature. The reaction liquid was stirred under hydrogen atmosphere at room temperature. After 6 hours, the catalyst was filtered off with celite. The filtrate was concentrated under vacuum and then the residue was purified with silica gel column chromatography (n-heptane:ethyl acetate = 2:1 - 1:1) to obtain the title compound (3.28 g, 33%).

^{1}H-NMR Spectrum ($CDCl_3$) δ (ppm): 1.29 (3H, t, J = 7.0 Hz), 3.63 (2H, q, J = 7.0 Hz), 3.73-3.80 (2H, m), 4.16-4.24 (2H, m), 6.41 (1H, td, J = 2.1, 1.1 Hz), 6.46 (1H, s), 6.99 (1H, s), 7.10 (1H, dd, J = 3.1, 2.4 Hz), 7.15 (1H, s), 7.93 (1H, brs).

[0232] [Production Example 24-6]

N-(4-((6-(2-Ethoxyethoxy)-1H-indol-5-yl)oxy) pyridin-2-yl)acetamide

[Chemical Formula 123]



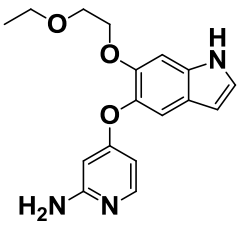
Dimethylsulfoxide (20 mL) was added to a mixture of 6-(2-ethoxyethoxy)-1H-indol-5-ol described in Production Example 24-5 (3.28 g, 14.8 mmol), N-(4-chloropyridin-2-yl)acetamide described in Production Example 1-5 (2.78 g, 16.3 mmol), and potassium tert-butoxide (1.83 g, 16.3 mmol) under nitrogen atmosphere at room temperature. The liquid mixture was stirred at 150°C overnight. The reaction liquid was allowed to stand to cool to room temperature and then diluted with water and ethyl acetate. The organic layer was washed with a saturated saline solution and dried over anhydrous sodium sulfate, and then the drying agent was separated by filtration. The filtrate was concentrated under vacuum. The residue was purified with silica gel column chromatography (n-heptane:ethyl acetate = 1:1 - 0:1 - ethyl acetate:methanol = 99:1 - 19:1) to obtain the title compound (2.5 g, 48%).

^{1}H-NMR Spectrum ($CDCl_3$) δ (ppm): 1.09 (3H, t, J = 7.0 Hz), 2.14 (3H, s), 3.41 (2H, q, J = 7.0 Hz), 3.56-3.66 (2H, m), 4.05-4.13 (2H, m), 6.44-6.50 (1H, m), 6.53 (1H, dd, J = 5.9, 2.6 Hz), 7.05 (1H, d, J = 0.7 Hz), 7.16 (1H, dd, J = 3.3, 2.6 Hz), 7.36 (1H, s), 7.75 (1H, brs), 8.01 (1H, d, J = 5.9 Hz), 8.11 (1H, brs), 8.19 (1H, brs).

[0233] [Production Example 24-7]

4-((6-(2-Ethoxyethoxy)-1H-indol-5-yl)oxy)pyridin -2-amine

[Chemical Formula 124]



A 2 M sodium hydroxide solution (20 mL) was added to a solution of N-(4-((6-(2-ethoxyethoxy)-1H-indol-5-yl)oxy)pyridin-2-yl)acetamide described in Production Example 24-6 (2.5 g, 7.04 mmol) in methanol (20 mL) under nitrogen atmosphere at room temperature, and the mixture was heated and stirred under reflux at 75°C for 2 hours. The reaction liquid was allowed to stand to cool to room temperature and then

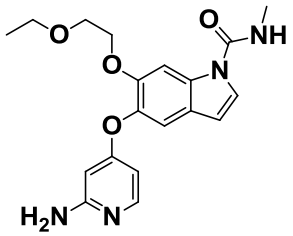
diluted with ethyl acetate and water. The organic layer was washed with a saturated saline solution and then dried over anhydrous sodium sulfate. The drying agent was separated by filtration and then the filtrate was concentrated under vacuum. The resultant residue was purified with silica gel column chromatography (n-heptane:ethyl acetate = 1:9 - 0:1 - ethyl acetate:methanol = 49:1 - 24:1) to obtain the title compound (1.92 g, 87%).

^{1}H-NMR Spectrum ($CDCl_3$) δ (ppm): 1.12 (3H, t, J = 7.0 Hz), 3.45 (2H, q, J = 7.2 Hz), 3.60-3.72 (2H, m), 4.03-4.13 (2H, m), 4.29 (2H, s), 5.89 (1H, d, J = 1.8 Hz), 6.29 (1H, dd, J = 6.2, 2.2 Hz), 6.44-6.54 (1H, m), 7.05 (1H, s), 7.18 (1H, dd, J = 3.1, 2.4 Hz), 7.34 (1H, s), 7.88 (1H, d, J = 5.9 Hz), 8.25 (1H, brs).

[0234] [Production Example 24-8]

5-((2-Aminopyridin-4-yl)oxy)-6-(2-ethoxyethoxy)-N-methyl-1H-indole-1-carboxamide

[Chemical Formula 125]



50 - 72% Oily sodium hydride (265 mg) was added to a solution of 4-((6-(2-ethoxyethoxy)-1H-indol-5-yl)oxy)pyridin-2-amine described in Production Example 24-7 (1.92 g, 6.13 mmol) in N,N-dimethylformamide (20 mL) under nitrogen atmosphere at 0°C. The reaction liquid was stirred at the same temperature for 10 minutes. Phenyl methylcarbamate described in Production Example 1-7 (1.20 g, 7.97 mmol) was added to the reaction liquid, and then the mixture was warmed to room temperature and stirred for 1 hour. Water and ethyl acetate were added to the reaction liquid. The organic layer was washed serially with water and a saturated saline solution and then dried over anhydrous sodium sulfate. The drying agent was separated by filtration and then the filtrate was concentrated under vacuum. The residue was purified with NH silica gel column chromatography (the solution: n-heptane:ethyl acetate = 9:1 - 0:1) to obtain the title compound (1.97 g, 87%).

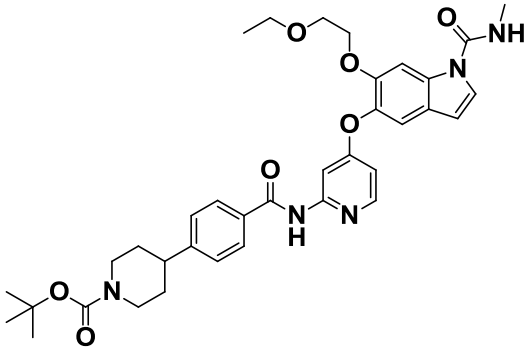
^{1}H-NMR Spectrum (DMSO-d_6) δ (ppm): 1.01 (3H, t, J = 7.0 Hz), 2.84 (3H, d, J = 4.4 Hz), 3.37 (2H, q, J = 7.1 Hz), 3.54-3.59 (2H, m), 4.02-4.10 (2H, m), 5.69 (1H, d, J = 2.2 Hz), 5.77 (2H, s), 6.09 (1H, dd, J = 5.9, 2.2 Hz), 6.60 (1H, d, J = 3.3 Hz), 7.35 (1H, s), 7.71-7.77 (2H, m), 8.04 (1H, s), 8.09-8.17 (1H, m).

[0235] [Production Example 24-9]

tert-Butyl

4-(4-((4-((6-(2-ethoxyethoxy)-1-(methylcarbamoyl)-1H-indol-5-yl)oxy)pyridin-2-yl)carbamoyl)phenyl)piperidine-1-carboxylate

[Chemical Formula 126]



Thionyl chloride (370 μL, 5.06 mmol) was added to a solution of benzotriazole (603 mg, 5.06 mmol) in dichloromethane (20 mL) under nitrogen atmosphere at room temperature. The mixture was stirred at room temperature for 5 minutes, then 4-(1-(tert-butoxycarbonyl)piperidin-4-yl)benzoic acid described in Production Example 1-12 (1.03 g, 3.38 mmol) was added, and the mixture was stirred for 1 hour. The reaction liquid was filtered through anhydrous sodium sulfate on the glass filter, and the anhydrous sodium sulfate was washed with dichloromethane. Triethylamine (1.87 mL, 13.5 mmol), 4-dimethylaminopyridine (16.5 mg, 0.135 mmol), and a solution of 5-((2-aminopyridin-4-yl)oxy)-6-(2-ethoxyethoxy)-N-methyl-1H-indole-1-carboxamide described in Production Example 24-8 (500 mg, 1.35 mmol) in tetrahydrofuran (5 mL) were serially added to the resultant filtrate under nitrogen atmosphere at 0°C, and the mixture was stirred at room temperature for 4 hours. An excessive quantity of methylamine was added to the reaction liquid and then the resultant was diluted with ethyl acetate and water for partition. The organic layer was washed with a saturated saline solution and then dried over anhydrous sodium sulfate, and the drying agent was separated by filtration. The filtrate was concentrated under vacuum. The resultant residue was purified with NH silica gel column chromatography (n-heptane:ethyl acetate = 2:3 - 0:1) to obtain the title compound (383 mg, 43%).

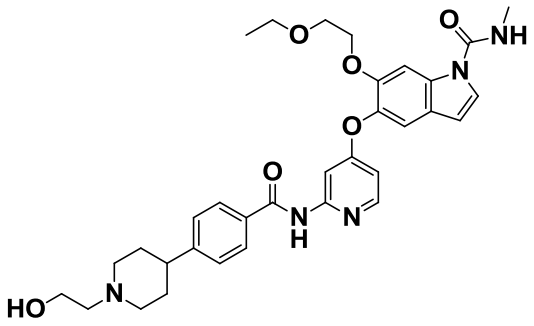
^{1}H-NMR Spectrum (DMSO-d_6) δ (ppm): 0.94 (3H, t, J = 7.1 Hz), 1.42 (9H, s), 1.43-1.60 (2H, m), 1.69-1.84 (2H, m), 2.75 (3H, brs), 2.85 (3H, d, J = 4.4 Hz), 3.29 (2H, q, J = 7.0 Hz), 3.47-3.58 (2H, m), 3.98-4.16 (4H, m), 6.56-6.71 (2H, m), 7.34 (2H, d, J = 8.4 Hz), 7.45 (1H,

s), 7.70 (1H, d, J = 2.6 Hz), 7.78 (1H, d, J = 3.7 Hz), 7.90 (2H, d, J = 8.4 Hz), 8.08 (1H, s), 8.12-8.24 (2H, m), 10.66 (1H, s).

[0236] [Example 25]

6-(2-Ethoxyethoxy)-5-((2-(4-(1-(2-hydroxyethyl)piperidin-4-yl)benzamide)pyridin-4-yl)oxy)-N-methyl-1H-indole-1-carboxamide

[Chemical Formula 127]



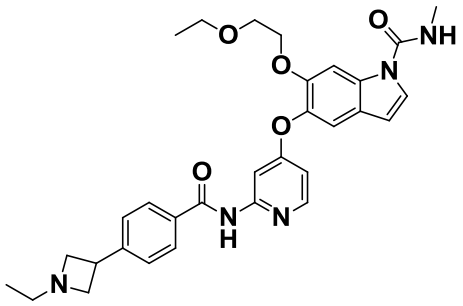
Commercially available 2-hydroxyacetaldehyde (48.5 mg, 0.807 mmol), sodium triacetoxyborohydride (91 mg, 0.43 mmol), and acetic acid (25 μL, 0.43 mmol) were added to a suspension of 6-(2-ethoxyethoxy)-N-methyl-5-((2-(4-(piperidin-4-yl)benzamide)pyridin-4-yl)oxy)-1H-indole-1-carboxamide described in Example 24 (30 mg, 0.054 mmol) in tetrahydrofuran (3 mL) at room temperature. The reaction liquid was stirred at room temperature for 2 hours. A saturated aqueous sodium bicarbonate solution was added to the reaction liquid at room temperature, and the mixture was diluted with ethyl acetate. The organic layer was washed with a saturated saline solution, dried over anhydrous sodium sulfate, and the solvent was concentrated under vacuum. The resultant residue was purified with NH silica gel column chromatography (ethyl acetate) to obtain the title compound (20.1 mg, 62%).

^{1}H-NMR Spectrum ($CDCl_3$) δ (ppm): 1.07 (3H, t, J = 7.0 Hz), 1.67-1.99 (4H, m), 2.20 (2H, td, J = 11.7, 2.6 Hz), 2.53-2.66 (3H, m), 2.98-3.11 (5H, m), 3.40 (2H, q, J = 7.0 Hz), 3.59-3.69 (4H, m), 4.16-4.20 (2H, m), 5.02 (1H, s), 5.69-5.80 (1H, m), 6.51 (1H, d, J = 3.7 Hz), 6.62 (1H, dd, J = 5.7, 2.4 Hz), 7.25 (1H, d, J = 3.7 Hz), 7.28-7.36 (3H, m), 7.76-7.83 (2H, m), 7.91 (1H, d, J = 2.6 Hz), 8.02 (1H, s), 8.09 (1H, d, J = 5.9 Hz), 8.62 (1H, s).

[0237] [Example 26]

6-(2-Ethoxyethoxy)-5-((2-(4-(1-ethylazetidin-3-yl)benzamide)pyridin-4-yl)oxy)-N-methyl-1H-indole-1-carboxamide

[Chemical Formula 128]



Sodium triacetoxyborohydride (172 mg, 0.812 mmol) and acetaldehyde (51.2 mg, 1.16 mmol) were added to a mixture of 5-((2-(4-(azetidin-3-yl)benzamide)pyridin-4-yl)oxy)-6-(2-ethoxyethoxy)-N-methyl-1H-indole-1-carboxamide described in Production Example 26-6 (215 mg, 0.406 mmol) and tetrahydrofuran (4.0 mL) at room temperature, and the mixture was stirred at room temperature for 1.5 hours. A saturated aqueous sodium bicarbonate solution and ethyl acetate were added to the reaction mixture for partition. The organic layer was washed with a saturated saline solution, then dried over anhydrous sodium sulfate, and filtered. The solvent was evaporated, the resultant residue was dissolved in dichloromethane, and the resultant was purified with NH silica gel column chromatography (n-heptane:ethyl acetate = 2:3 - 0:1 - ethyl acetate:methanol = 99:1 - 19:1). The target fraction was concentrated under vacuum, then the residue was collected by filteration and washed with diethyl ether to obtain the title compound (180 mg, 79%).

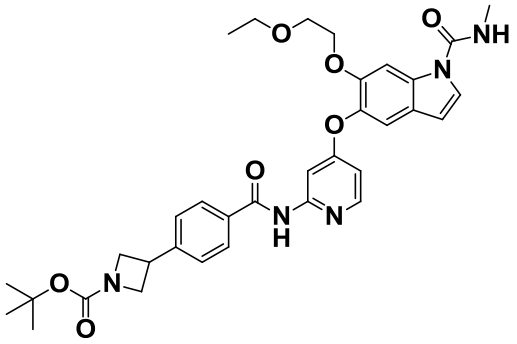
^{1}H-NMR Spectrum ($CDCl_3$) δ (ppm): 1.00 (3H, t, J = 7.1 Hz), 1.07 (3H, t, J = 7.0 Hz), 2.51 (2H, q, J = 7.1 Hz), 3.06 (3H, d, J = 4.8 Hz), 3.09-3.16 (2H, m), 3.40 (2H, q, J = 7.1 Hz), 3.60-3.65 (2H, m), 3.71-3.80 (3H, m), 4.15-4.20 (2H, m), 5.47-5.57 (1H, m), 6.54 (1H, d, J = 3.7 Hz), 6.61 (1H, dd, J = 5.7, 2.4 Hz), 7.24-7.27 (1H, m), 7.34 (1H, s), 7.36-7.40 (2H, m), 7.77-7.83 (2H, m), 7.91 (1H, d, J = 2.2 Hz), 8.01 (1H, s), 8.10 (1H, d, J = 5.9 Hz), 8.47 (1H, brs).

[0238] The starting material 5-((2-(4-(azetidin-3-yl)benzamide)pyridin-4-yl)oxy)-6-(2-ethoxyethoxy)-N-methyl-1H-indole-1-carboxamide was synthesized by the following method.

[0239] [Production Example 26-1]

tert-Butyl 3-(4-((4-((6-(2-ethoxyethoxy)-1-(methylcarbamoyl)-1H-indol-5-yl)oxy)pyridin-2-yl)carbamoyl)phenyl)azetidine-1-carboxylate

[Chemical Formula 129]



Benzotriazole (335 mg, 2.81 mmol) was dissolved in dichloromethane (20 mL), and thionyl chloride (200 μL, 2.74 mmol) was added under nitrogen atmosphere at room temperature, and the mixture was stirred for 5 minutes. 4-(1-(tert-Butoxycarbonyl)azetidin-3-yl)benzoic acid described in Production Example 26-5 (650 mg, 2.34 mmol) was added to the reaction mixture at room temperature, and the mixture was stirred for 25 minutes. The reaction mixture was filtered through a glass filter entirely covered with anhydrous sodium sulfate and then the anhydrous sodium sulfate was washed with dichloromethane, and then the filtrate was added to a mixture of 5-((2-aminopyridin-4-yl)oxy)-6-(2-ethoxyethoxy)-N-methyl-1H-indole-1-carboxamide described in Production Example 24-8 (300 mg, 0.810 mmol), triethylamine (1.3 mL, 9.38 mmol), and 4-dimethylaminopyridine (9.9 mg, 0.081 mmol) in tetrahydrofuran (16 mL) at 0°C. The mixture was stirred at room temperature for 3 hours, then water and ethyl acetate were added to the reaction mixture for partition, and the organic layer was washed with a saturated saline solution and then dried over anhydrous magnesium sulfate. The drying agent was filtered off, then the filtrate was concentrated under vacuum, the residue was dissolved in tetrahydrofuran, an excessive quantity of 9.8 M methylamine methanol solution was added at room temperature, and the mixture was stirred for 75 minutes. The reaction mixture was concentrated under vacuum, the residue was dissolved in dichloromethane, and the resultant was purified with NH silica gel column chromatography (n-heptane:ethyl acetate = 1:1 - 1:3 - 0:1 - ethyl acetate:methanol = 9:1). The mixture fraction was concentrated under vacuum, the residue was dissolved in dichloromethane, and the resultant was purified with NH silica gel column chromatography (n-heptane:ethyl acetate = 2:3 - 1:3 - 0:1 - ethyl acetate:methanol = 9:1). The target fraction was concentrated under vacuum to obtain the title compound (279 mg, 76%).

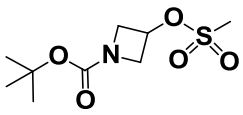
^{1}H-NMR Spectrum ($CDCl_3$) δ (ppm): 1.07 (3H, t, J = 7.0 Hz), 1.47 (9H, s), 2.81 (3H, d, J = 4.8 Hz), 3.40 (2H, q, J = 6.8 Hz), 3.60-3.65 (2H, m), 3.73-3.83 (1H, m), 3.93-4.01 (2H, m),

4.15-4.20 (2H, m), 4.35 (2H, t, J = 8.6 Hz), 5.44-5.54 (1H, m), 6.56 (1H, d, J = 3.7 Hz), 6.61 (1H, dd, J = 5.9, 1.8 Hz), 7.23-7.29 (1H, m), 7.34 (1H, s), 7.42 (2H, d, J = 8.4 Hz), 7.85 (2H, d, J = 8.4 Hz), 7.91 (1H, d, J = 2.2 Hz), 8.01 (1H, s), 8.09 (1H, d, J = 5.9 Hz), 8.55 (1H, brs).

[0240] [Production Example 26-2]

tert-Butyl 3-((methylsulfonyl)oxy)azetidine -1-carboxylate

[Chemical Formula 130]



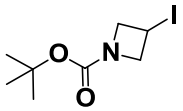
Methanesulfonyl chloride (2.57 mL, 33.3 mmol) and triethylamine (11.6 mL, 83.1 mmol) were added to a solution of commercially available N-BOC-3-hydroxy azetidine (4.8 g, 27.7 mmol) in tetrahydrofuran (100 mL) under nitrogen atmosphere at room temperature. The reaction liquid was stirred at room temperature for 2 hours. A saturated aqueous sodium bicarbonate solution was added to the reaction liquid at room temperature, and the mixture was diluted with ethyl acetate. The organic layer was washed with a saturated saline solution and then dried over anhydrous sodium sulfate. The drying agent was separated by filtration and then the filtrate was concentrated under vacuum. The residue was purified with silica gel column chromatography (n-heptane:ethyl acetate = 9:1 - 1:1) to quantitatively obtain the title compound.

^{1}H-NMR Spectrum ($CDCl_3$) δ (ppm): 1.45 (9H, s), 3.07 (3H, s), 4.03-4.18 (2H, m), 4.22-4.36 (2H, m), 5.12-5.27 (1H, m).

[0241] [Production Example 26-3]

tert-Butyl 3-iodoazetidine-1-carboxylate

[Chemical Formula 131]



Potassium iodide (51.0 g, 307 mmol) was added to a solution of tert-butyl 3-((methylsulfonyl)oxy)azetidine-1-carboxylate described in Production Example 26-2 (7.72 g, 30.7 mmol) in dimethylsulfoxide (80 mL) under nitrogen atmosphere at room temperature, and the mixture was stirred at 140°C for 2 hours. The reaction liquid was diluted with diethyl ether and water. The aqueous layer was extracted with diethyl ether. The combined organic layer was washed serially with an aqueous sodium pyrosulfite solution

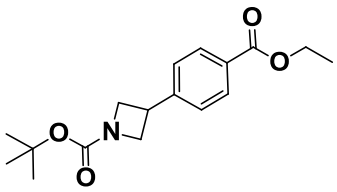
and a saturated saline solution and then dried over anhydrous sodium sulfate. The drying agent was separated by filtration and then the resultant was concentrated under vacuum. The residue was purified with silica gel column chromatography (n-heptane:ethyl acetate = 9:1 - 1:1) to obtain the title compound (5.91 g, 68%).

^{1}H-NMR Spectrum ($CDCl_3$) δ (ppm): 1.44 (9H, s), 4.25-4.33 (2H, m), 4.42-4.51 (1H, m), 4.61-4.69 (2H, m).

[0242] [Production Example 26-4]

tert-Butyl 3-(4-(ethoxycarbonyl)phenyl)azetidine -1-carboxylate

[Chemical Formula 132]



1,2-Dibromoethane (0.286 mL, 3.32 mmol) was added to a suspension of zinc powder (2.12 g, 32.4 mmol) in tetrahydrofuran (10 mL) under nitrogen atmosphere at room temperature. The liquid mixture was stirred at 65°C for 10 minutes. The reaction liquid was allowed to stand to cool to room temperature, then chlorotrimethylsilane (0.400 mL, 3.13 mmol) was added, and the mixture was stirred at room temperature for 30 minutes. A solution of tert-butyl 3-iodoazetidine-1-carboxylate described in Production Example 26-3 (5.91 g, 20.9 mmol) in tetrahydrofuran (10 mL) was added to the reaction liquid over 5 minutes, and the mixture was stirred at room temperature for 40 minutes (a solution A). A solution of tris(dibenzylideneacetone)dipalladium(0) (382 mg, 0.418 mmol) and tri-2-furylphosphine (402 mg, 1.73 mmol) in tetrahydrofuran (10 mL) was stirred under nitrogen atmosphere at room temperature for 15 minutes, and then the previously prepared solution A was added at room temperature. Subsequently, a solution of ethyl 4-iodobenzoate (6.92 g, 25.1 mmol) in tetrahydrofuran (18.5 mL) was added under nitrogen atmosphere at room temperature. The reaction liquid was stirred at 65°C overnight. The reaction liquid was allowed to stand to cool to room temperature, then was filtered with celite, and the resultant was washed with ethyl acetate. The filtrate was washed serially with a saturated aqueous sodium bicarbonate solution and a saturated saline solution and then dried over anhydrous sodium sulfate. The drying agent was separated by filtration and then the filtrate was concentrated under vacuum. The residue was dissolved in dichloromethane, then the resultant was purified with silica gel column chromatography (n-heptane:ethyl

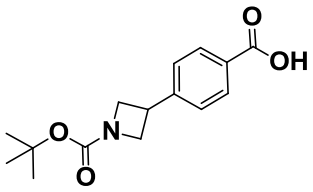
acetate = 9:1 - 4:1) to obtain the title compound (4.35 g, 68%).

^{1}H-NMR Spectrum ($CDCl_3$) δ (ppm): 1.40 (3H, t, J = 8.0 Hz), 1.47 (9H, s), 3.71-3.84 (1H, m), 3.95-4.02 (2H, m), 4.32-4.44 (4H, m), 7.34-7.42 (2H, m), 7.98-8.07 (2H, m).

[0243] [Production Example 26-5]

4-(1-(tert-Butoxycarbonyl)azetidin-3-yl)benzoic acid

[Chemical Formula 133]



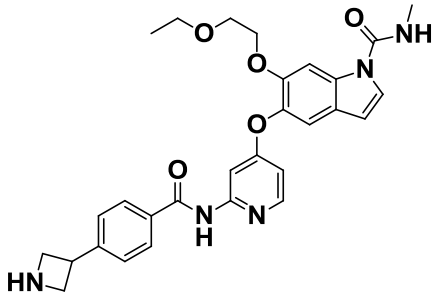
A 2 M sodium hydroxide solution (28.5 mL, 57.0 mmol) was added to a solution of tert-butyl 3-(4-(ethoxycarbonyl)phenyl)azetidine-1-carboxylate described in Production Example 26-4 (4.35 g, 14.2 mmol) in tetrahydrofuran (32 mL) and methanol (7 mL) at 25°C. The reaction liquid was stirred at 60°C for 1 hour. 2 M hydrochloric acid (28.5 mL) was added to the reaction liquid, and the mixture was diluted with ethyl acetate. The organic layer was washed with a saturated saline solution and then dried over anhydrous sodium sulfate. The drying agent was separated by filtration and then the filtrate was concentrated under vacuum. The residue was purified with silica gel column chromatography (n-heptane:ethyl acetate = 9:1 - 1:1) to obtain the title compound (3.4 g, 86%).

^{1}H-NMR Spectrum ($CDCl_3$) δ (ppm): 1.48 (9H, s), 3.71-3.88 (1H, m), 3.96-4.04 (2H, m), 4.37 (2H, t, J = 8.6 Hz), 7.42 (2H, d, J = 8.4 Hz), 8.09 (2H, d, J = 8.3 Hz).

[0244] [Production Example 26-6]

5-((2-(4-(Azetidin-3-yl)benzamide)pyridin-4-yl)oxy)-6-(2-ethoxyethoxy)-N-methyl-1H-indole-1-carboxamide

[Chemical Formula 134]



tert-Butyl

3-(4-((4-(((6-(2-ethoxyethoxy)-1-(methylcarbamoyl)-1H-indol-5-yl)oxy)pyridin-2-yl)carbam

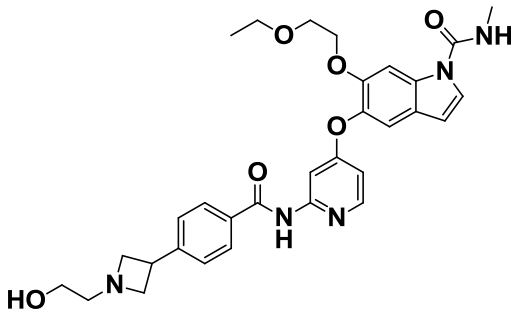
oyl)phenyl)azetidine-1-carboxylate described in Production Example 26-1 (279 mg, 0.443 mmol) was dissolved in dichloromethane (8.0 mL), and trifluoroacetic acid (1.6 mL) was added at 0°C. The mixture was stirred at room temperature for 40 minutes and then concentrated under vacuum, the residue was dissolved in dichloromethane and triethylamine, and the resultant was purified with NH silica gel column chromatography (ethyl acetate:methanol = 97:3 - 4:1) to obtain the title compound (215 mg, 92%).

^{1}H-NMR Spectrum ($CDCl_3$) δ (ppm): 1.07 (3H, t, J = 7.0 Hz), 3.05 (3H, d, J = 4.8 Hz), 3.40 (2H, q, J = 7.0 Hz), 3.61-3.65 (2H, m), 3.81 (2H, t, J = 7.0 Hz), 3.93-4.09 (3H, m), 4.15-4.20 (2H, m), 5.51-5.63 (1H, m), 6.53 (1H, d, J = 3.7 Hz), 6.61 (1H, dd, J = 5.9, 2.2 Hz), 7.24-7.28 (1H, m), 7.33 (1H, s), 7.40 (2H, d, J = 8.1 Hz), 7.82 (2H, d, J = 8.1 Hz), 7.91 (1H, d, J = 2.2 Hz), 8.01 (1H, s), 8.09 (1H, d, J = 5.5 Hz), 8.52 (1H, brs).

[0245] [Example 27]

6-(2-Ethoxyethoxy)-5-((2-(4-(1-(2-hydroxyethyl)azetidin-3-yl)benzamide)pyridin-4-yl)oxy)-N-methyl-1H-indole-1-carboxamide

[Chemical Formula 135]



Commercially available 2-hydroxyacetaldehyde (45.9 mg, 0.765 mmol), sodium triacetoxyborohydride (86 mg, 0.408 mmol), and acetic acid (23 μL, 0.408 mmol) were added to a solution of 5-((2-(4-(azetidin-3-yl)benzamide)pyridin-4-yl)oxy)-6-(2-ethoxyethoxy)-N-methyl-1H-indole-1-carboxamide described in Production Example 26-6 (27 mg, 0.051 mmol) in tetrahydrofuran (2 mL) at room temperature, and the mixture was stirred at the same temperature for 2 hours. A saturated aqueous sodium bicarbonate solution was added to the reaction liquid at room temperature, and the mixture was diluted with ethyl acetate. The organic layer was washed with a saturated saline solution and then dried over anhydrous sodium sulfate. The drying agent was separated by filtration and the filtrate was concentrated under vacuum. The residue was purified with NH silica gel column

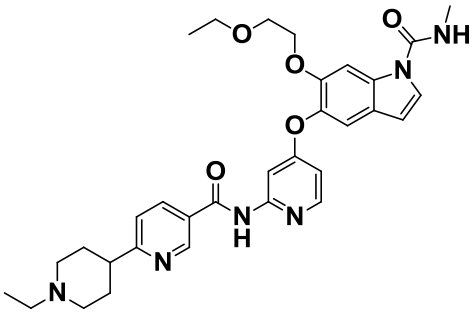
chromatography (ethyl acetate) to obtain the title compound (20.0 mg, 68%).

^{1}H-NMR Spectrum ($CDCl_3$) δ (ppm): 1.08 (3H, t, J = 7.0 Hz), 2.68-2.76 (2H, m), 3.06 (3H, d, J = 4.8 Hz), 3.27-3.34 (2H, m), 3.40 (2H, q, J = 7.0 Hz), 3.55-3.67 (4H, m), 3.71-3.94 (3H, m), 4.15-4.22 (2H, m), 5.53-5.65 (1H, m), 6.55 (1H, d, J = 3.7 Hz), 6.62 (1H, dd, J = 5.9, 2.2 Hz), 7.23-7.29 (1H, m), 7.34 (1H, s), 7.38 (2H, d, J = 8.4 Hz), 7.83 (2H, d, J = 8.1 Hz), 7.91 (1H, d, J = 2.6 Hz), 8.01 (1H, s), 8.09 (1H, d, J = 5.9 Hz), 8.63 (1H, brs).

[0246] [Example 28]

6-(2-Ethoxyethoxy)-5-((2-(6-(1-ethylpiperidin-4-yl)nicotinamide)pyridin-4-yl)oxy)-N-methyl-1H-indole-1-carboxamide

[Chemical Formula 136]



Acetaldehyde (38 μL, 0.671 mmol), acetic acid (20 μL, 0.358 mmol), and sodium triacetoxyborohydride (76 mg, 0.358 mmol) were added to a solution of 6-(2-ethoxyethoxy)-N-methyl-5-((2-(6-(piperidin-4-yl)nicotinamide)pyridin-4-yl)oxy)-1H-indole-1-carboxamide described in Production Example 28-5 (25 mg, 0.045 mmol) in tetrahydrofuran (3 mL) at room temperature, and the mixture was stirred for 1 hour. A saturated aqueous sodium bicarbonate solution was added to the reaction liquid at room temperature, and the mixture was diluted with ethyl acetate. The organic layer was washed with a saturated saline solution and then dried over anhydrous sodium sulfate. The drying agent was separated by filtration and then the filtrate was concentrated under vacuum. The residue was purified with NH silica gel column chromatography (ethyl acetate) to obtain the title compound (13.6 mg, 52%).

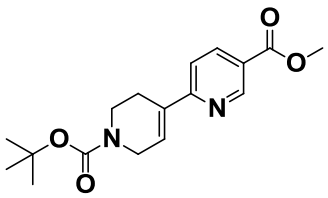
^{1}H-NMR Spectrum ($CDCl_3$) δ (ppm): 1.07 (3H, t, J = 7.0 Hz), 1.13 (3H, t, J = 7.1 Hz), 1.78-1.93 (2H, m), 1.94-2.15 (4H, m), 2.46 (2H, q, J = 7.3 Hz), 2.74-2.86 (1H, m), 3.00-3.17(5H, m), 3.40 (2H, q, J = 7.1 Hz), 3.63 (2H, t, J = 4.8 Hz), 4.18 (2H, t, J = 4.8 Hz), 5.45-5.57 (1H, m), 6.56 (1H, d, J = 3.3 Hz), 6.61 (1H, dd, J = 5.9, 1.5 Hz), 7.20-7.39 (3H, m), 7.84-7.92 (1H, m), 8.02 (1H, s), 8.05-8.15 (2H, m), 8.49 (1H, s), 8.93-9.07 (1H, m).

[0247] The starting material 6-(2-ethoxyethoxy)-N-methyl-5-((2-(6-(piperidin-4-yl)nicotinamide)pyridin-4-yl)oxy)-1H-indole-1-carboxamide was synthesized by the following method.

[0248] [Production Example 28-1]

1'-tert-Butyl 5-methyl 5',6'-dihydro-[2,4'-bipyridine]-1',5(2'H)-dicarboxylate

[Chemical Formula 137]



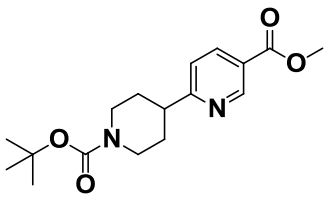
N,N-dimethylformamide (100 mL) was added to commercially available 1-N-BOC-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-3,6-dihydro-2H-pyridine (4.68 g, 15.1 mmol), commercially available methyl 6-chloronicotinate (2.81 g, 16.4 mmol), 1,1'-bis(diphenylphosphino)ferrocenedichloropalladium(II) (1.17 g, 1.60 mmol), and potassium carbonate (7.02 g, 50.8 mmol). The reaction liquid was stirred under nitrogen atmosphere at 100°C for 2 hours. The reaction liquid was allowed to stand to cool to room temperature and then diluted with ethyl acetate and water. The aqueous layer was extracted with ethyl acetate. The combined organic layer was washed serially with a dilute aqueous ammonia solution and a saturated saline solution, and then dried over anhydrous sodium sulfate. The drying agent was separated by filtration and then the filtrate was concentrated under vacuum. The residue was purified with silica gel column chromatography (n-heptane:ethyl acetate = 9:1 - 1:1) to obtain the title compound (1.07 g, 22%).

^{1}H-NMR Spectrum ($CDCl_3$) δ (ppm): 1.49 (9H, s), 2.59-2.73 (2H, m), 3.66 (2H, t, J = 5.5 Hz), 3.95 (3H, s), 4.17 (2H, d, J = 2.9 Hz), 6.79 (1H, dt, J = 3.4, 1.8 Hz), 7.44 (1H, d, J = 8.4 Hz), 8.25 (1H, dd, J = 8.4, 2.2 Hz), 9.15 (1H, dd, J = 2.2, 0.7 Hz).

[0249] [Production Example 28-2]

Methyl 6-(1-(tert-butoxycarbonyl)piperidin-4-yl) nicotinate

[Chemical Formula 138]



10% Palladium-carbon (water content, 50%) (213 mg) was added to a solution of

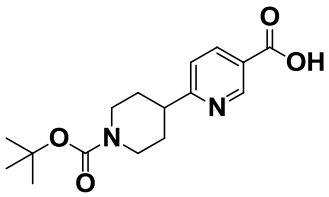
1'-tert-butyl 5-methyl 5',6'-dihydro-[2,4'-bipyridine]-1',5(2'H)-dicarboxylate described in Production Example 28-1 (1.06 g, 3.33 mmol) in ethanol (71 mL) and tetrahydrofuran (12 mL), and the mixture was stirred under hydrogen atmosphere at room temperature for 2 hours. The mixture was filtered, then the filtrate was concentrated under vacuum, and the residue was purified with NH silica gel column chromatography (n-heptane:ethyl acetate = 9:1 - 1:1) to quantitatively obtain the title compound.

^{1}H-NMR Spectrum ($CDCl_3$) δ (ppm): 1.48 (9H, s), 1.73 (2H, qd, J = 12.6, 4.4 Hz), 1.88-1.97 (2H, m), 2.76-2.98 (3H, m), 3.94 (3H, s), 4.27 (2H, brs), 7.22-7.26 (1H, m), 8.23 (1H, dd, J = 8.4, 2.2 Hz), 9.09-9.18 (1H, m).

[0250] [Production Example 28-3]

6-(1-(tert-Butoxycarbonyl)piperidin-4-yl)nicotinic acid

[Chemical Formula 139]



A 2 M sodium hydroxide solution (20 mL) was added to a solution of methyl 6-(1-(tert-butoxycarbonyl)piperidin-4-yl)nicotinate described in Production Example 28-2 (1.07 g, 3.32 mmol) in ethanol (5 mL), and the mixture was stirred for 1 hour. 2 M hydrochloric acid was added to the reaction liquid at 0°C. The aqueous layer was extracted with ethyl acetate. The combined organic layer was washed with a saturated saline solution and then dried over anhydrous sodium sulfate. The drying agent was separated by filtration and then the filtrate was concentrated under vacuum to obtain the title compound (534 mg, 52%).

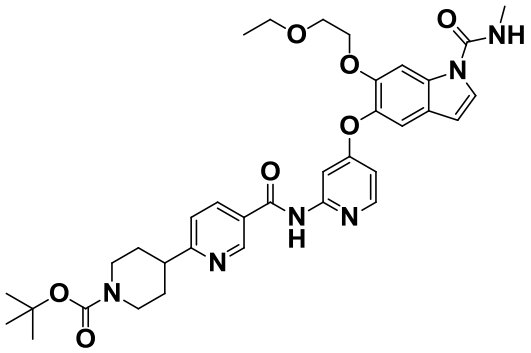
^{1}H-NMR Spectrum (DMSO-d_6) δ (ppm): 1.42 (9H, s), 1.58 (2H, qd, J = 12.6, 4.4 Hz), 1.77-1.89 (2H, m), 2.67-3.04 (3H, m), 3.95-4.17 (2H, m), 7.40 (1H, d, J = 7.7 Hz), 8.16 (1H, dd, J = 8.1, 2.2 Hz), 8.97 (1H, dd, J = 2.2, 0.7 Hz).

[0251] [Production Example 28-4]

tert-Butyl

4-(5-((4-((6-(2-ethoxyethoxy)-1-(methylcarbamoyl)-1H-indol-5-yl)oxy)pyridin-2-yl)carbamoyl)pyridin-2-yl)piperidine-1-carboxylate

[Chemical Formula 140]



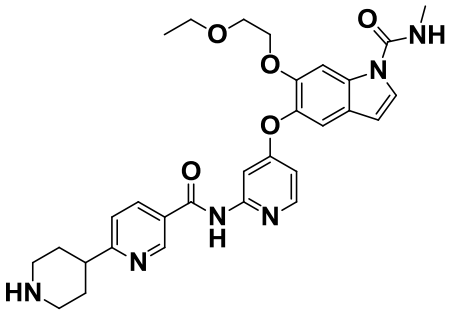
Oxalyl chloride (74 μL, 0.864 mmol) and one drop of N,N-dimethylformamide were added to a solution of 6-(1-(tert-butoxycarbonyl)piperidin-4-yl)nicotinic acid described in Production Example 28-3 (80 mg, 0.216 mmol) in dichloromethane (2 mL) at 0°C, and the mixture was stirred for 30 minutes. The reaction liquid was concentrated under vacuum. The residue was dissolved in tetrahydrofuran (2 mL), then triethylamine (301 μL, 2.16 mmol) and 5-((2-aminopyridin-4-yl)oxy)-6-(2-ethoxyethoxy)-N-methyl-1H-indole-1-carboxamide described in Production Example 24-8 (80 mg, 0.216 mmol) were added, and the mixture was stirred for 5 hours. An excessive quantity of methylamine was added to the reaction liquid, and then the mixture was diluted with water and ethyl acetate for partition. The organic layer was washed with a saturated saline solution and then dried over anhydrous sodium sulfate. The drying agent was separated by filtration and then the filtrate was concentrated under vacuum. The residue was purified with NH silica gel column chromatography (n-heptane:ethyl acetate = 1:1) to obtain the title compound (80 mg, 56%).

^{1}H-NMR Spectrum ($CDCl_3$) δ (ppm): 1.04 (3H, t, J = 7.0 Hz), 1.45 (9H, s), 1.68 (2H, qd, J = 12.6, 4.4 Hz), 1.83-1.93 (2H, m), 2.69-2.92 (3H, m), 2.96 (3H, d, J = 4.8 Hz), 3.37 (2H, q, J = 7.0 Hz), 3.56-3.63 (2H, m), 4.11-4.15 (2H, m), 4.21 (2H, brs), 6.10-6.20 (1H, m), 6.44 (1H, d, J = 3.7 Hz), 6.58 (1H, dd, J = 5.7, 2.4 Hz), 7.21 (1H, d, J = 7.7 Hz), 7.24-7.31 (2H, m), 7.86 (1H, d, J = 2.2 Hz), 7.95 (1H, d, J = 5.9 Hz), 8.02 (1H, s), 8.07 (1H, dd, J = 8.2, 2.4 Hz), 8.96-9.02 (1H, m), 9.20 (1H, brs).

[0252] [Production Example 28-5]

6-(2-Ethoxyethoxy)-N-methyl-5-((2-(6-(piperidin-4-yl)nicotinamide)pyridin-4-yl)oxy)-1H-indole-1-carboxamide

[Chemical Formula 141]



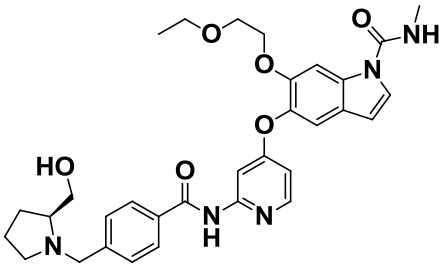
Trifluoroacetic acid (374 μL, 4.86 mmol) was added to a solution of tert-butyl 4-(5-((4-((6-(2-ethoxyethoxy)-1-(methylcarbamoyl)-1H-indol-5-yl)oxy)pyridin-2-yl)carbamoyl)pyridin-2-yl)piperidine-1-carboxylate described in Production Example 28-4 (80 mg, 0.121 mmol) in dichloromethane (3 mL) at room temperature, and the mixture was stirred for 1.5 hours. The reaction liquid was concentrated under vacuum. The residue was dissolved in dichloromethane and then triethylamine was added to neutralize the trifluoroacetic acid. The solution was concentrated under vacuum and then the residue was purified with NH silica gel column chromatography (ethyl acetate:methanol = 49:1 - 17:3) to obtain the title compound (51.3 mg, 76%).

^{1}H-NMR Spectrum ($CDCl_3$) δ (ppm): 1.07 (3H, t, J = 7.1 Hz), 1.72 (2H, qd, J = 12.4, 4.0 Hz), 1.87-1.97 (2H, m), 2.76 (2H, td, J = 12.3, 2.6 Hz), 2.84-2.95 (1H, m), 2.99 (3H, d, J = 4.4 Hz), 3.16-3.28 (2H, m), 3.40 (2H, q, J = 7.1 Hz), 3.59-3.68 (2H, m), 4.14-4.20 (2H, m), 6.04-6.17 (1H, m), 6.48 (1H, d, J = 3.7 Hz), 6.62 (1H, dd, J = 5.7, 2.4 Hz), 7.23-7.29 (2H, m), 7.31 (1H, s), 7.88 (1H, d, J = 2.2 Hz), 7.98-8.05 (2H, m), 8.10 (1H, dd, J = 8.2, 2.4 Hz), 9.02 (1H, dd, J = 2.6, 0.7 Hz).

[0253] [Example 29]

(S)-6-(2-Ethoxyethoxy)-5-((2-(4-((2-hydroxymethyl)pyrrolidin-1-yl)methyl)benzamide)pyridin-4-yl)oxy)-N-methyl-1H-indole-1-carboxamide

[Chemical Formula 142]



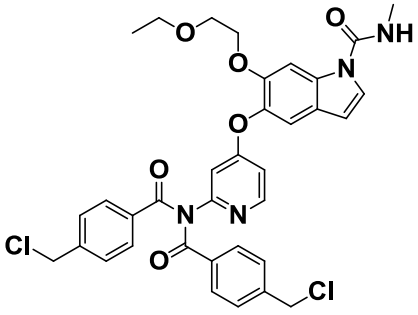
Commercially available L-prolinol (31.3 mg, 0.309 mmol) was added to a mixture

of
5-((2-(4-(chloromethyl)-N-(4-(chloromethyl)benzoyl)benzamide)pyridin-4-yl)oxy)-6-(2-ethoxyethoxy)-N-methyl-1H-indole-1-carboxamide described in Production Example 29-1 (19.6 mg, 0.029 mmol) and N,N-dimethylformamide (500 μL) at room temperature, and the mixture was stirred under nitrogen atmosphere for 17.5 hours. Water and ethyl acetate were added to the reaction mixture for partition. The organic layer was washed with a saturated saline solution, and then dried over anhydrous sodium sulfate and filtered. The solvent was evaporated, the resultant residue was purified with NH silica gel TLC (ethyl acetate), and the product was collected by filteration and washed with diethyl ether to obtain the title compound (13.3 mg, 78%).

^{1}H-NMR Spectrum ($CDCl_3$) δ (ppm): 1.08 (3H, t, J = 7.1 Hz), 1.65-1.99 (5H, m), 2.23-2.32 (1H, m), 2.71-2.79 (1H, m), 2.92-2.99 (1H, m), 3.06 (3H, d, J = 4.8 Hz), 3.37-3.48 (4H, m), 3.61-3.69 (3H, m), 4.03 (1H, d, J = 13.5 Hz), 4.16-4.20 (2H, m), 5.48-5.56 (1H, m), 6.55 (1H, d, J = 3.7 Hz), 6.61 (1H, dd, J = 5.9, 2.6 Hz), 7.24-7.28 (1H, m), 7.34 (1H, s), 7.41 (2H, d, J = 8.4 Hz), 7.79-7.84 (2H, m), 7.91 (1H, d, J = 2.2 Hz), 8.01 (1H, s), 8.10 (1H, d, J = 5.5 Hz), 8.50 (1H, brs).

[0254] The starting material 5-((2-(4-(chloromethyl)-N-(4-(chloromethyl)benzoyl)benzamide)pyridin-4-yl)oxy)-6-(2-ethoxyethoxy)-N-methyl-1H-indole-1-carboxamide was synthesized by the following method.

[0255] [Production Example 29-1]
5-((2-(4-(Chloromethyl)-N-(4-(chloromethyl)benzoyl)benzamide)pyridin-4-yl)oxy)-6-(2-ethoxyethoxy)-N-methyl-1H-indole-1-carboxamide
[Chemical Formula 143]



Triethylamine (300 μL, 2.16 mmol) and commercially available 4-(chloromethyl)benzoyl chloride (221 mg, 1.17 mmol) were added to a mixture of 5-((2-aminopyridin-4-yl)oxy)-6-(2-ethoxyethoxy)-N-methyl-1H-indole-1-carboxamide

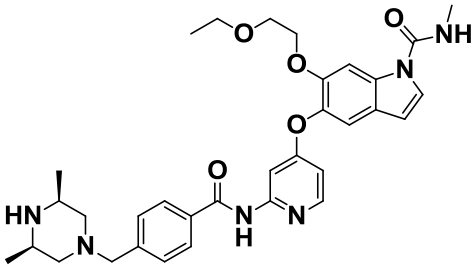
described in Production Example 24-8 (107 mg, 0.289 mmol) and tetrahydrofuran (8.0 mL) under nitrogen atmosphere at 0°C. The mixture was stirred at room temperature for 1 hour and then water and ethyl acetate were added to the reaction mixture for partition. The organic layer was washed with a saturated saline solution, then dried over anhydrous sodium sulfate, and then filtered with NH silica gel. The filtrate was concentrated under vacuum to quantitatively obtain the title compound.

^{1}H-NMR Spectrum ($CDCl_3$) δ (ppm): 1.11 (3H, t, J = 7.0 Hz), 3.06 (3H, d, J = 4.8 Hz), 3.43 (2H, q, J = 7.0 Hz), 3.56-3.60 (2H, m), 4.08-4.12 (2H, m), 4.56 (4H, s), 5.41-5.49 (1H, m), 6.55 (1H, d, J = 3.7 Hz), 6.67 (1H, d, J = 2.2 Hz), 6.71 (1H, dd, J = 5.9, 2.2 Hz), 7.24 (1H, s), 7.25-7.28 (1H, m), 7.34-7.39 (4H, m), 7.69-7.75 (4H, m), 7.98 (1H, s), 8.17 (1H, d, J = 5.9 Hz).

[0256] [Example 30]

5-((2-(4-(((3S,5R)-3,5-Dimethylpiperazin-1-yl)methyl)benzamide)pyridin-4-yl)oxy)-6-(2-ethoxyethoxy)-N-methyl-1H-indole-1-carboxamide

[Chemical Formula 144]



Commercially available cis-2,6-dimethylpiperazine (32.5 mg, 0.285 mmol) was added to a mixture of 5-((2-(4-(chloromethyl)-N-(4-(chloromethyl)benzoyl) benzamide)pyridin-4-yl)oxy)-6-(2-ethoxyethoxy)-N-methyl-1H-indole-1-carboxamide described in Production Example 29-1 (21.1 mg, 0.031 mmol) and N,N-dimethylformamide (500 μL) at room temperature, and the mixture was stirred under nitrogen atmosphere for 13 hours and 20 minutes. Water and ethyl acetate were added to the reaction mixture for partition. The organic layer was washed with a saturated saline solution, and then dried over anhydrous sodium sulfate and filtered. The solvent was evaporated and the resultant residue was purified with NH silica gel TLC (ethyl acetate), then the product was collected by filteration and washed with diethyl ether to obtain the title compound (14.4 mg, 77%).

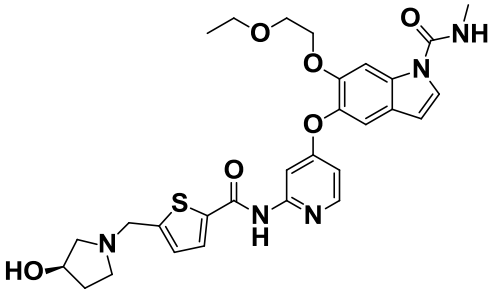
^{1}H-NMR Spectrum ($CDCl_3$) δ (ppm): 1.02 (6H, d, J = 6.2 Hz), 1.07 (3H, t, J = 7.0 Hz), 1.63 (2H, t, J = 10.6 Hz), 2.69-2.76 (2H, m), 2.89-2.99 (2H, m), 3.07 (3H, d, J = 4.8 Hz), 3.40 (2H,

q, J = 7.0 Hz), 3.52 (2H, s), 3.61-3.65 (2H, m), 4.16-4.20 (2H, m), 5.45-5.52 (1H, m), 6.55 (1H, d, J = 3.7 Hz), 6.60 (1H, dd, J = 5.9, 2.2 Hz), 7.25-7.27 (1H, m), 7.34 (1H, s), 7.43 (2H, d, J = 8.1 Hz), 7.79-7.83 (2H, m), 7.92 (1H, d, J = 2.2 Hz), 8.01 (1H, s), 8.10 (1H, d, J = 5.9 Hz), 8.47 (1H, brs).

[0257] [Example 31]

(R)-6-(2-Ethoxyethoxy)-5-((2-(5-((3-hydroxypyrrolidin-1-yl)methyl)thiophene-2-carboxamide)pyridin-4-yl)oxy)-N-methyl-1H-indole-1-carboxamide

[Chemical Formula 145]



Thionyl chloride (2.8 mL, 38.4 mmol) and N,N-dimethylformamide (5.87 μL, 0.076 mmol) were added to 5-(hydroxymethyl)thiophene-2-carboxylic acid described in Production Example 31-1 (120 mg, 0.759 mmol), and the mixture was heated and stirred at 90°C for 2 hours. The reaction mixture was evaporated under vacuum to obtain a crude product A (148 mg).

Triethylamine (191 μL, 1.38 mmol) and a tetrahydrofuran solution (1.0 mL) of a part of the crude product A (74.0 mg, 0.379 mmol) were added to a mixture of 5-((2-aminopyridin-4-yl)oxy)-6-(2-ethoxyethoxy)-N-methyl-1H-indole-1-carboxamide described in Production Example 24-8 (51.1 mg, 0.138 mmol) and tetrahydrofuran (1.4 mL) under nitrogen atmosphere at 0°C. The mixture was stirred at room temperature for 170 minutes and then water and ethyl acetate were added to the reaction mixture for partition. The organic layer was washed with a saturated saline solution, then dried over anhydrous sodium sulfate and filtered with NH silica gel, and then the resultant was concentrated under vacuum to obtain a crude product B (86.7 mg).

A part of the crude product B (17.3 mg) was dissolved in N,N-dimethylformamide (1.0 mL), commercially available (R)-3-hydroxy pyrrolidine (24.4 mg, 0.28 mmol) was added under nitrogen atmosphere at room temperature, and the mixture was stirred for 17 hours. Water and ethyl acetate were added to the reaction mixture for partition, and the organic layer was washed with a saturated saline solution, dried over anhydrous sodium

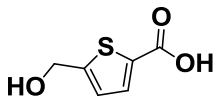
sulfate, and filtered. The solvent was evaporated and the resultant residue was purified with NH silica gel TLC (ethyl acetate), then the product was collected by filteration and washed with n-hexane to obtain the title compound (9.0 mg, 56%).

^{1}H-NMR Spectrum ($CDCl_3$) δ (ppm): 1.07 (3H, t, J = 6.8 Hz), 1.71-1.81 (1H, m), 2.13-2.24(1H, m), 2.34-2.43 (1H, m), 2.57-2.64 (1H, m), 2.69-2.76 (1H, m), 2.87-2.97 (1H, m), 3.06 (3H, d, J = 4.8 Hz), 3.39 (2H, q, J = 7.3 Hz), 3.59-3.64 (2H, m), 3.84 (2H, s), 4.14-4.19 (2H, m), 4.31-4.37 (1H, m), 5.48-5.55 (1H, m), 6.54 (1H, d, J = 3.7 Hz), 6.61 (1H, dd, J = 5.9, 2.4 Hz), 6.91 (1H, d, J = 3.5 Hz), 7.24-7.28 (1H, m), 7.32 (1H, s), 7.47 (1H, d, J = 3.9 Hz), 7.78-7.82 (1H, m), 7.99 (1H, s), 8.08 (1H, d, J = 5.7 Hz), 8.34 (1H, brs).

[0258] [Production Example 31-1]

5-(Hydroxymethyl)thiophene-2-carboxylic acid

[Chemical Formula 146]



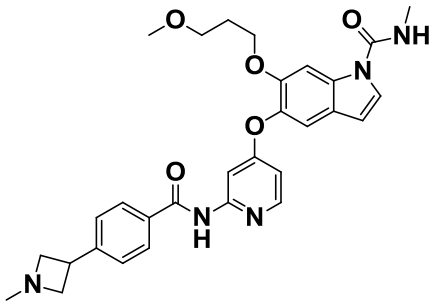
Sodium borohydride (218 mg, 5.76 mmol) was added to a solution of commercially available 5-formyl-2-thiophenecarboxylic acid (599 mg, 3.84 mmol) in methanol (19 mL), and the mixture was stirred under nitrogen atmosphere at room temperature for 4 hours and 30 minutes. Acetone was added to the reaction mixture, and the mixture was concentrated under vacuum. 2 M hydrochloric acid and ethyl acetate were added to the residue for partition, and the aqueous layer was extracted with ethyl acetate. The combined organic layer was washed with water, dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated under vacuum and the precipitate was washed with diethyl ether and n-hexane to obtain the title compound (529 mg, 87%).

^{1}H-NMR Spectrum (DMSO-d_6) δ (ppm): 4.61-4.74 (2H, m), 5.65-72 (1H, m), 6.97-7.7.03 (1H, m), 7.55-7.62 (1H, m), 12.92 (1H, brs).

[0259] [Example 32]

6-(3-Methoxypropoxy)-N-methyl-5-((2-(4-(1-methylazetidin-3-yl)benzamide)pyridin-4-yl)oxy)-1H-indole-1-carboxamide

[Chemical Formula 147]



Formaldehyde (12 μL, 0.425 mmol), acetic acid (13 μL, 0.227 mmol), and sodium triacetoxyborohydride (48.0 mg, 0.227 mmol) were added to a solution of 5-((2-(4-(azetidin-3-yl)benzamide)pyridin-4-yl)oxy)-6-(3-methoxypropoxy)-N-methyl-1H-indole-1-carboxamide described in Production Example 32-10 (15 mg, 0.028 mmol) in tetrahydrofuran (2 mL) at room temperature. The reaction liquid was stirred at room temperature for 1 hour. A saturated aqueous sodium bicarbonate solution and ethyl acetate were added to the reaction liquid at room temperature. The organic layer was washed with a saturated saline solution and then dried over anhydrous sodium sulfate. The drying agent was separated by filtration and the filtrate was concentrated under vacuum. The residue was purified with NH silica gel column chromatography (ethyl acetate) to obtain the title compound (8.8 mg, 57%).

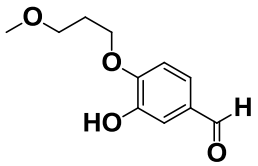
^{1}H-NMR Spectrum (DMSO-d_6) δ (ppm): 1.76 (2H, t, J = 6.4 Hz), 2.25 (3H, s), 2.85 (3H, d, J = 4.4 Hz), 3.02-3.13 (7H, m), 3.54-3.65 (3H, m), 3.99 (2H, t, J = 6.2 Hz), 6.64 (1H, d, J = 3.3 Hz), 6.69 (1H, dd, J = 5.9, 2.6 Hz), 7.42 (2H, d, J = 8.4 Hz), 7.46 (1H, s), 7.69 (1H, d, J = 2.6 Hz), 7.77 (1H, d, J = 3.7 Hz), 7.92 (2H, d, J = 8.4 Hz), 8.06 (1H, s), 8.14-8.19 (1H, m), 8.21 (1H, d, J = 5.9 Hz), 10.70 (1H, s).

[0260] The starting material 5-((2-(4-(azetidin-3-yl)benzamide)pyridin-4-yl)oxy)-6-(3-methoxypropoxy)-N-methyl-1H-indole-1-carboxamide was synthesized by the following method.

[0261] [Production Example 32-1]

3-Hydroxy-4-(3-methoxypropoxy)benzaldehyde

[Chemical Formula 148]



Commercially available 1-bromo-3-methoxypropane (24.0 g, 157 mmol) was

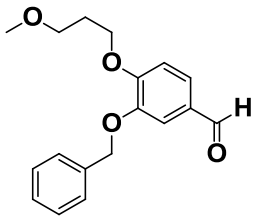
added to a solution of commercially available 3,4-dihydroxybenzaldehyde (21.7 g, 157 mmol) and sodium carbonate (25.0 g, 236 mmol) in N,N-dimethylformamide (50 mL) under nitrogen atmosphere at room temperature. The reaction liquid was stirred at room temperature for 3 days and 4 hours. 2 M hydrochloric acid, ethyl acetate, and water were added to the reaction liquid at 0°C. The aqueous layer was extracted with ethyl acetate. The combined organic layer was washed serially with water and a saturated saline solution and then dried over anhydrous sodium sulfate. The drying agent was separated by filtration and the filtrate was concentrated under vacuum. The insoluble matters were separated by filtration with dichloromethane and the filtrate was concentrated under vacuum. The residue was purified with silica gel column chromatography (n-heptane:ethyl acetate = 17:3 - 1:1) to obtain the title compound (17.2 g, 52%).

^{1}H-NMR Spectrum ($CDCl_3$) δ (ppm): 2.07-2.18 (2H, m), 3.38 (3H, s), 3.59 (2H, t, J = 5.9 Hz), 4.26 (2H, t, J = 6.2 Hz), 6.21 (1H, s), 7.00 (1H, d, J = 8.1 Hz), 7.35-7.48 (2H, m), 9.85 (1H, s).

[0262] [Production Example 32-2]

3-(Benzyloxy)-4-(3-methoxypropoxy)benzaldehyde

[Chemical Formula 149]



Potassium carbonate (14.7 g, 106 mmol) and benzyl chloride (12.2 mL, 106 mmol) were added to a solution of 3-hydroxy-4-(3-methoxypropoxy)benzaldehyde described in Production Example 32-1 (17.2 g, 81.7 mmol) in ethanol (200 mL) under nitrogen atmosphere at room temperature, and the mixture was stirred under a thermal condition of 90°C for 2 hours. The reaction liquid was cooled to 0°C, and the mixture was diluted with 2 M hydrochloric acid, ethyl acetate, and water. The organic layer was washed with a saturated saline solution and then dried over anhydrous magnesium sulfate. The drying agent was separated by filtration and then the filtrate was concentrated under vacuum. The residue was purified with silica gel column chromatography (n-heptane:ethyl acetate = 4:1 - 3:7) to obtain the title compound (19.8 g, 81%).

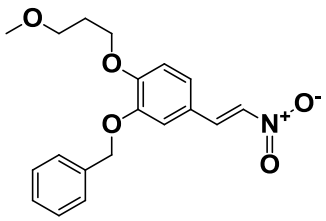
^{1}H-NMR Spectrum ($CDCl_3$) δ (ppm): 2.10-2.20 (2H, m), 3.35 (3H, d, J = 0.7 Hz), 3.59 (2H,

t, J = 6.0 Hz), 4.21 (2H, t, J = 6.4 Hz), 5.18 (2H, s), 6.95-7.09 (1H, m), 7.28-7.50 (7H, m), 9.76-9.87 (1H, m).

[0263] [Production Example 32-3]

(E)-2-(Benzyloxy)-1-(3-methoxypropoxy) -4-(2-nitrovinyl)benzene

[Chemical Formula 150]



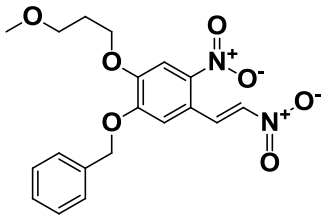
Ammonium acetate (6.10 g, 79.1 mmol) and nitromethane (8.93 mL, 165 mmol) were added to a solution of 3-(benzyloxy)-4-(3-methoxypropoxy)benzaldehyde described in Production Example 32-2 (19.8 g, 65.9 mmol) in acetic acid (52.8 mL) under nitrogen atmosphere at room temperature. The liquid mixture was stirred under a thermal condition of 130°C for 2 hours. The reaction liquid was allowed to stand to cool to room temperature, then the precipitate was collected by filteration and washed with ethanol to quantitatively obtain the title compound.

^{1}H-NMR Spectrum ($CDCl_3$) δ (ppm): 2.07-2.17 (2H, m), 3.35 (3H, s), 3.59 (2H, t, J = 6.0 Hz), 4.19 (2H, t, J = 6.4 Hz), 5.16 (2H, s), 6.96 (1H, d, J = 8.4 Hz), 7.05 (1H, d, J = 1.8 Hz), 7.16 (1H, dd, J = 8.4, 1.8 Hz), 7.29-7.47 (6H, m), 7.91 (1H, d, J = 13.5 Hz).

[0264] [Production Example 32-4]

(E)-1-(Benzyloxy)-2-(3-methoxypropoxy)-4-nitro-5-(2-nitrovinyl)benzene

[Chemical Formula 151]



69% Nitric acid (16 mL, 249 mmol) was added to a liquid mixture of (E)-2-(benzyloxy)-1-(3-methoxypropoxy)-4-(2-nitrovinyl)benzene described in Production Example 32-3 (22.6 g, 65.9 mmol) in acetic acid (150 mL) at room temperature. The liquid mixture was stirred at room temperature for 6 hours. The reaction liquid was transferred into an ice bath, then the precipitate was collected by filteration and washed with water to

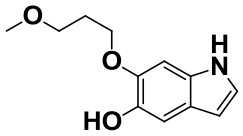
quantitatively obtain the title compound.

^{1}H-NMR Spectrum ($CDCl_3$) δ (ppm): 2.10-2.13 (2H, m), 3.36 (3H, s), 3.59 (2H,t, J = 5.9 Hz), 4.25 (2H, t, J = 6.4 Hz), 5.27 (2H, s), 6.93 (1H, s), 7.24 (1H, d, J = 13.6 Hz), 7.34-7.46 (5H, m), 7.78 (1H, s), 8.52-8.62 (1H, m).

[0265] [Production Example 32-5]

6-(3-Methoxypropoxy)-1H-indol-5-ol

[Chemical Formula 152]



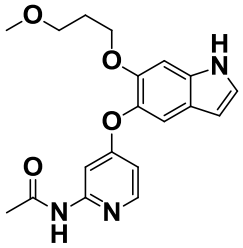
10% Palladium-carbon (water content, 50%) (8 g) was added to a solution of (E)-1-(benzyloxy)-2-(3-methoxypropoxy)-4-nitro-5-(2-nitrovinyl)benzene described in Production Example 32-4 (19.6 g, 50.5 mmol) in methanol (300 mL) at room temperature. The liquid mixture was stirred under hydrogen atmosphere at room temperature for 6 hours. The reaction liquid was filtered through celite and then the filtrate was concentrated under vacuum. The residue was purified with silica gel column chromatography (n-heptane:ethyl acetate = 2:1 - 1:1) to obtain the title compound (3.81 g, 34%).

^{1}H-NMR Spectrum ($CDCl_3$) δ (ppm): 2.05-2.13 (2H, m), 3.40 (3H, s), 3.61 (2H,t, J = 6.0 Hz), 4.16 (2H, t, J = 6.0 Hz), 5.97-6.05 (1H, m), 6.36-6.46 (1H, m), 6.92 (1H, s), 7.08 (1H, t, J = 2.8 Hz), 7.14 (1H, s), 7.26 (1H, s), 7.82-8.06 (1H, m).

[0266] [Production Example 32-6]

N-(4-((6-(3-Methoxypropoxy)-1H-indol-5-yl)oxy)pyridin-2-yl)acetamide

[Chemical Formula 153]



Dimethylsulfoxide (25 mL) was added to a mixture of 6-(3-methoxypropoxy)-1H-indol-5-ol described in Production Example 32-5 (3.81 g, 17.2 mmol), N-(4-chloropyridin-2-yl)acetamide described in Production Example 1-5 (3.23 g, 18.9 mmol), and potassium tert-butoxide (2.12 g, 18.9 mmol) under nitrogen atmosphere at room temperature. The liquid mixture was stirred at 150°C for 14 hours. The reaction

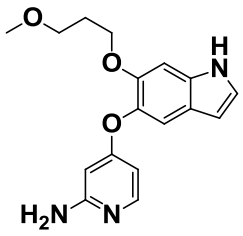
liquid was cooled to room temperature, and then ethyl acetate and water were added. The organic layer was washed with a saturated saline solution and then dried over anhydrous sodium sulfate. The drying agent was separated by filtration and then the filtrate was concentrated under vacuum. The residue was purified with silica gel column chromatography (n-heptane:ethyl acetate = 1:1 - 0:1 - ethyl acetate:methanol = 49:1) to obtain the title compound (2.83 g, 46%).

^{1}H-NMR Spectrum ($CDCl_3$) δ (ppm): 1.85-1.91 (2H, m), 2.13 (3H, s), 3.20 (3H, s), 3.24 (2H, t, J = 6.2 Hz), 4.02 (2H, t, J = 6.2 Hz), 6.44-6.49 (1H, m), 6.51-6.56 (1H, m), 6.95-7.02 (1H, m), 7.10-7.18 (1H, m), 7.31-7.38 (1H, m), 7.71-7.82 (1H, m), 7.97-8.06 (1H, m), 8.20-8.30 (1H, m), 8.36-8.52 (1H, m).

[0267] [Production Example 32-7]

4-((6-(3-Methoxypropoxy)-1H-indol-5-yl)oxy) pyridin-2-amine

[Chemical Formula 154]



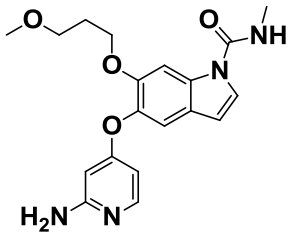
A 2 M sodium hydroxide solution (30 mL) was added to a solution of N-(4-((6-(3-methoxypropoxy)-1H-indol-5-yl)oxy)pyridin-2-yl)acetamide described in Production Example 32-6 (2.8 g, 7.88 mmol) in methanol (30 mL) under nitrogen atmosphere at room temperature. The liquid mixture was stirred under reflux under a thermal condition of 75°C for 2 hours. The reaction liquid was allowed to stand to cool to room temperature, and then ethyl acetate and water were added. The organic layer was washed with a saturated saline solution and then dried over anhydrous sodium sulfate. The drying agent was separated by filtration and then the filtrate was concentrated under vacuum. The residue was purified with silica gel column chromatography (n-heptane:ethyl acetate = 1:9 - 0:1 - ethyl acetate:methanol = 49:1) to obtain the title compound (2.24 g, 91%).

^{1}H-NMR Spectrum ($CDCl_3$) δ (ppm): 1.75-1.92 (2H, m), 3.23 (3H, s), 3.28 (2H,t, J = 6.0 Hz), 4.03 (2H, t, J = 6.0 Hz), 4.30 (2H, s), 5.89 (1H, d, J = 2.2 Hz), 6.29 (1H, dd, J = 5.9, 2.2 Hz), 6.46-6.53 (1H, m), 7.01 (1H, s), 7.16 (1H, dd, J = 3.3, 2.6 Hz), 7.35 (1H, s), 7.88 (1H, d, J = 5.9 Hz), 8.14-8.26 (1H, m).

[0268] [Production Example 32-8]

5-((2-Aminopyridin-4-yl)oxy)-6-(3-methoxypropoxy)-N-methyl-1H-indole-1-carboxamide

[Chemical Formula 155]



50 - 72% Oily sodium hydride (308 mg) was added to a solution of 4-((6-(3-methoxypropoxy)-1H-indol-5-yl)oxy)pyridin-2-amine described in Production Example 32-7 (2.23 g, 7.12 mmol) in N,N-dimethylformamide (30 mL) under nitrogen atmosphere at 0°C. The reaction liquid was stirred for 10 minutes, then phenyl methylcarbamate described in Production Example 1-7 (1.40 g, 9.25 mmol) was added, and the resultant was further stirred at the same temperature for 30 minutes. Water and ethyl acetate were added to the reaction liquid. The organic layer was washed serially with water and a saturated saline solution and then dried over anhydrous sodium sulfate. The drying agent was separated by filtration and then the filtrate was concentrated under vacuum. The residue was purified with NH silica gel column chromatography (n-heptane:ethyl acetate = 9:1 - 0:1) to obtain the title compound (2.44 g, 93%).

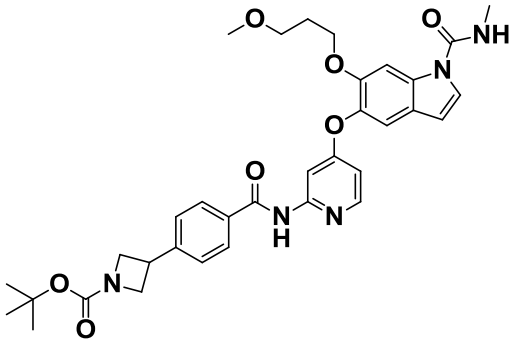
^{1}H-NMR Spectrum (DMSO-d_6) δ (ppm): 1.73-1.86 (2H, m), 2.81-2.87 (3H, m), 3.12 (3H, d, J = 1.8 Hz), 3.16-3.24 (2H, m), 3.98 (2H, t, J = 5.7 Hz), 5.62-5.71 (1H, m), 5.78 (2H, s), 6.06-6.15 (1H, m), 6.61 (1H, dd, J = 3.5, 1.7 Hz), 7.36 (1H, d, J = 1.8 Hz), 7.71-7.78 (2H, m), 7.98-8.04 (1H, m), 8.10-8.22 (1H, m).

[0269] [Production Example 32-9]

tert-Butyl

3-(4-((4-((6-(3-methoxypropoxy)-1-(methylcarbamoyl)-1H-indol-5-yl)oxy)pyridin-2-yl)carbamoyl)phenyl)azetidine-1-carboxylate

[Chemical Formula 156]



Thionyl chloride (118 μL, 1.62 mmol) was added to a solution of benzotriazole (193 mg, 1.62 mmol) in dichloromethane (5 mL) under nitrogen atmosphere at room temperature, and the mixture was stirred for 5 minutes. 4-(1-(tert-Butoxycarbonyl)azetidin-3-yl)benzoic acid described in Production Example 26-5 (300 mg, 1.08 mmol) was added to the reaction liquid, and the mixture was further stirred for 1 hour. The reaction liquid was filtered through anhydrous sodium sulfate on the glass filter, and the anhydrous sodium sulfate was washed with dichloromethane. A solution of triethylamine (748 μL, 5.40 mmol), 4-dimethylaminopyridine (6.60 mg, 0.054 mmol), and 5-((2-aminopyridin-4-yl)oxy)-6-(3-methoxypropoxy)-N-methyl-1H-indole-1-carboxamide described in Production Example 32-8 (200 mg, 0.54 mmol) in tetrahydrofuran (10 mL) was added to the resultant dichloromethane solution under nitrogen atmosphere at 0°C, and the mixture was stirred for 4 hours and 20 minutes. The reaction liquid was diluted with ethyl acetate and water. The organic layer was washed with a saturated saline solution and then dried over anhydrous sodium sulfate. The drying agent was separated by filtration and then the filtrate was concentrated under vacuum. Tetrahydrofuran and an excessive quantity of methylamine tetrahydrofuran solution were added to the residue, and the mixture was stirred at room temperature. The liquid mixture was concentrated under vacuum. The residue was purified with silica gel column chromatography (n-heptane:ethyl acetate = 2:3 - 0:1) to obtain the title compound (146 mg, 43%).

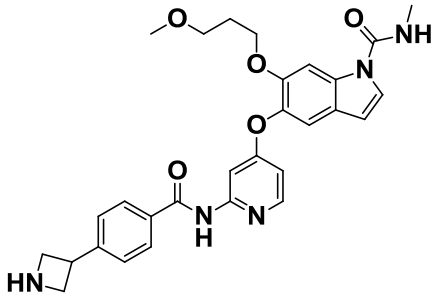
^{1}H-NMR Spectrum ($CDCl_3$) δ (ppm): 1.43-1.51 (9H, m), 1.80-1.95 (2H, m), 2.95 (3H, d, J = 4.8 Hz), 3.17 (3H, s), 3.20-3.27 (2H, m), 3.69-3.82 (1H, m), 3.95 (2H, dd, J = 8.6, 6.0 Hz), 4.05-4.17 (2H, m), 4.33 (2H, t, J = 8.6 Hz), 6.13-6.25 (1H, m), 6.44 (1H, d, J = 3.7 Hz), 6.63 (1H, dd, J = 5.7, 2.4 Hz), 6.97 (1H, s), 7.24 (2H, d, J = 3.7 Hz), 7.38 (2H, d, J = 8.4 Hz), 7.83 (2H, d, J = 8.4 Hz), 7.88 (1H, d, J = 2.6 Hz), 8.01-8.09 (2H, m), 8.79-9.00 (1H, m).

[0270] [Production Example 32-10]

5-((2-(4-(Azetidin-3-yl)benzamide)pyridin-4-yl)oxy)-6-(3-methoxypropoxy)-N-methyl-1H-i

ndole-1-carboxamide

[Chemical Formula 157]



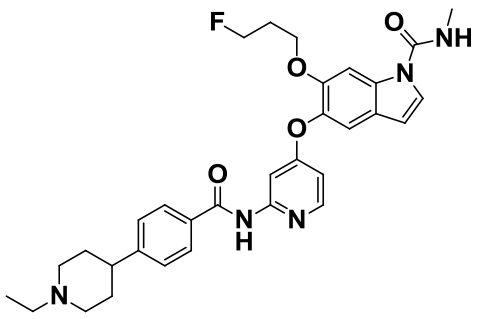
Trifluoroacetic acid (713 μL, 9.25 mmol) was added to a solution of tert-butyl 3-(4-((4-((6-(3-methoxypropoxy)-1-(methylcarbamoyl)-1H-indol-5-yl)oxy)pyridin-2-yl)carbamoyl)phenyl)azetidine-1-carboxylate described in Production Example 32-9 (146 mg, 0.231 mmol) in dichloromethane (5 mL) at room temperature. The reaction liquid was stirred for 1.5 hours, and then the resultant was concentrated under vacuum. The residue was dissolved in dichloromethane and triethylamine to neutralize the trifluoroacetic acid, and then the resultant was concentrated under vacuum. The residue was purified with NH silica gel column chromatography (ethyl acetate:methanol = 49:1 - 17:3) to obtain the title compound (96.2 mg, 79%).

^{1}H-NMR Spectrum ($CDCl_3$) δ (ppm): 1.82-1.95 (2H, m), 3.06 (3H, d, J = 4.8 Hz), 3.19 (3H, s), 3.24 (2H, t, J = 6.4 Hz), 3.79-4.00 (5H, m), 4.11 (2H, t, J = 6.0 Hz), 5.56-5.64 (1H, m), 6.55 (1H, d, J = 3.7 Hz), 6.61 (1H, dd, J = 5.9, 2.2 Hz), 7.21-7.29 (1H, m), 7.34 (1H, s), 7.41 (2H, d, J = 8.4 Hz), 7.84 (2H, d, J = 8.4 Hz), 7.92 (1H, d, J = 2.2 Hz), 8.00 (1H, s), 8.10 (1H, d, J = 5.9 Hz), 8.56-8.68 (1H, m).

[0271] [Example 33]

5-((2-(4-(1-Ethylpiperidin-4-yl)benzamide)pyridin-4-yl)oxy)-6-(3-fluoropropoxy)-N-methyl-1H-indole-1-carboxamide

[Chemical Formula 158]



Benzotriazole (37.8 mg, 0.317 mmol) was dissolved in dichloromethane (2.0 mL), thionyl chloride (24 μL, 0.322 mmol) was added under nitrogen atmosphere at room temperature, and the mixture was stirred for 5 minutes. 4-(1-(tert-Butoxycarbonyl) piperidin-4-yl)benzoic acid described in Production Example 1-12 (82 mg, 0.269 mmol) was added to the reaction mixture at room temperature, and the mixture was stirred for 20 minutes. The reaction mixture was filtered through a glass filter entirely covered with anhydrous sodium sulfate and then the anhydrous sodium sulfate was washed with dichloromethane, the filtrate was added to a mixture of 5-((2-aminopyridin-4-yl)oxy)-6-(3-fluoropropoxy)-N-methyl-1H-indole -1-carboxamide described in Production Example 33-6 (34.4 mg, 0.096 mmol), triethylamine (133 μL, 0.960 mmol), and 4-dimethylaminopyridine (1.17 mg, 0.0096 mmol) in tetrahydrofuran (1.5 mL) at 0°C, and the mixture was stirred at room temperature for 320 minutes. Water and ethyl acetate were added to the reaction mixture for partition, then the organic layer was washed with a saturated saline solution and dried over anhydrous sodium sulfate. The resultant was purified with NH silica gel column chromatography, then the filtrate was concentrated under vacuum. The residue was dissolved in tetrahydrofuran, an excessive quantity of 9.8 M methylamine methanol solution was added at room temperature, and the mixture was stirred for 50 minutes. The reaction mixture was concentrated under vacuum, the residue was dissolved in dichloromethane, and the resultant was purified with NH silica gel column chromatography (n-heptane:ethyl acetate = 1:1 - 3:7 - 0:1). The target fraction was concentrated under vacuum to obtain a crude product A (46.3 mg).

The crude product A (46.3 mg) was dissolved in dichloromethane (1.25 mL), and trifluoroacetic acid (250 μL) was added at 0°C. The mixture was stirred at room temperature for 20 minutes and then concentrated under vacuum, then the residue was dissolved in dichloromethane-triethylamine, and the resultant was purified with NH silica gel column chromatography (ethyl acetate:methanol = 97:3 - 4:1). The target fraction was concentrated under vacuum to obtain a crude product B (35.8 mg).

Sodium triacetoxyborohydride (10.4 mg, 0.049 mmol) and acetaldehyde (2.17 mg, 0.049 mmol) were added to a mixture of a part of crude product B (9.0 mg, 0.016 mmol) and tetrahydrofuran (500 μL) at room temperature, and the mixture was stirred at room temperature for 140 minutes. A saturated aqueous sodium bicarbonate solution and ethyl acetate were added to the reaction mixture for partition. The organic layer was washed with a saturated saline solution, and then dried over anhydrous sodium sulfate and filtered. The

solvent was evaporated and the resultant residue was purified with NH silica gel TLC (ethyl acetate). The resultant solid was washed with diethyl ether to obtain the title compound (6.7 mg, 49%).

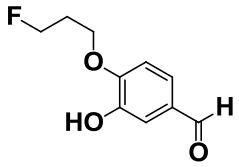
^{1}H-NMR Spectrum ($CDCl_3$) δ (ppm): 1.14 (3H, t, J = 7.1 Hz), 1.76-1.91 (4H, m), 1.93-2.12 (4H, m), 2.41-2.64 (3H, m), 3.03-3.17 (5H, m), 4.16 (2H, t, J = 6.0 Hz), 4.24 (1H, t, J = 5.9 Hz), 4.36 (1H, t, J = 5.7 Hz), 5.46-5.57 (1H, m), 6.55 (1H, d, J = 3.3 Hz), 6.58 (1H, dd, J = 5.9, 2.2 Hz), 7.24 (1H, d, J = 3.7 Hz), 7.31-7.36 (3H, m), 7.80 (2H, d, J = 8.1 Hz), 7.90 (1H, d, J = 2.2 Hz), 8.02 (1H, s), 8.10 (1H, d, J = 5.9 Hz), 8.49 (1H, brs).

[0272] The starting material 5-((2-aminopyridin-4-yl)oxy)-6-(3-fluoropropoxy)-N-methyl-1H-indole-1-carboxamide was synthesized by the following method.

[0273] [Production Example 33-1]

4-(3-Fluoropropoxy)-3-hydroxybenzaldehyde

[Chemical Formula 159]



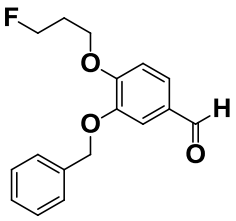
Commercially available 3,4-dihydroxybenzaldehyde (6.5 g, 47.1 mmol) and potassium carbonate (6.83 g, 49.4 mmol) were suspended in N,N-dimethylformamide (30 mL), then 3-fluoropropyl 4-methylbenzenesulfonate described in Production Example 4-1 (11.3 g, 48.4 mmol) was added under nitrogen atmosphere at room temperature, and the mixture was stirred for 37 hours. The mixture was cooled to 0°C and then 2 M hydrochloric acid, ethyl acetate, and water were added for partition. The organic layer was washed with water and a saturated saline solution, dried over anhydrous magnesium sulfate, and then filtered. The solvent was evaporated and the resultant residue was purified with silica gel column chromatography (n-heptane:ethyl acetate = 4:1 - 2:1 - 1:1). The target fraction was concentrated under vacuum to obtain the title compound (4.62 g, 50%).

^{1}H-NMR Spectrum ($CDCl_3$) δ (ppm): 2.23 (1H, quin, J = 5.9 Hz), 2.30 (1H, quin, J = 5.8 Hz), 4.31 (2H, t, J = 6.2 Hz), 4.60 (1H, t, J = 5.6 Hz), 4.72 (1H, t, J = 5.6 Hz), 5.70 (1H, s), 6.99 (1H, d, J = 8.2 Hz), 7.41-7.47 (2H, m), 9.85 (1H, s).

[0274] [Production Example 33-2]

3-(Benzyloxy)-4-(3-fluoropropoxy)benzaldehyde

[Chemical Formula 160]



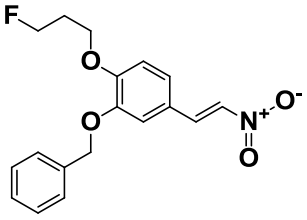
Potassium carbonate (3.87 g, 28.0 mmol) and benzyl chloride (3.2 mL, 27.8 mmol) were added to a suspension of 4-(3-fluoropropoxy)-3-hydroxybenzaldehyde described in Production Example 33-1 (4.62 g, 23.3 mmol) in ethanol (46 mL) under nitrogen atmosphere at room temperature, and the mixture was stirred at 90°C for 1.5 hours. The reaction mixture was cooled to 0°C, then 2 M hydrochloric acid, ethyl acetate, and water were added for partition. The organic layer was washed with a saturated saline solution, dried over anhydrous magnesium sulfate, and then filtered. The solvent was evaporated and the resultant residue was purified with silica gel column chromatography (n-heptane:ethyl acetate = 9:1 - 3:2 - 1:1). The target fraction was concentrated under vacuum to obtain the title compound (6.14 g, 91%).

^{1}H-NMR Spectrum ($CDCl_3$) δ (ppm): 2.22 (1H, quin, J = 5.9 Hz), 2.29 (1H, quin, J = 5.9 Hz), 4.25 (2H, t, J = 6.2 Hz), 4.62 (1H, t, J = 5.7 Hz), 4.74 (1H, t, J = 5.7 Hz), 5.18 (2H, s), 7.02 (1H, d, J = 8.1 Hz), 7.29-7.50 (7H, m), 9.83 (1H, s).

[0275] [Production Example 33-3]

(E)-2-(Benzyloxy)-1-(3-fluoropropoxy)-4-(2-nitrovinyl) benzene

[Chemical Formula 161]



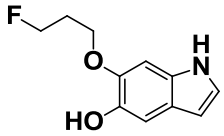
3-(Benzyloxy)-4-(3-fluoropropoxy)benzaldehyde described in Production Example 33-2 (6.14 g, 21.3 mmol) was dissolved in acetic acid (17.0 mL), then ammonium acetate (1.97 g, 25.6 mmol) and nitromethane (2.8 mL, 51.7 mmol) were added under nitrogen atmosphere at room temperature, and the mixture was heated and stirred at 130°C for 2 hours. The mixture was cooled to room temperature, then the precipitate was collected by filteration and washed with a small quantity of ethanol to quantitatively obtain

the title compound.

^{1}H-NMR Spectrum ($CDCl_3$) δ (ppm): 2.21 (1H, quin, J = 6.0 Hz), 2.28 (1H, quin, J = 5.9 Hz), 4.22 (2H, t, J = 6.0 Hz), 4.62 (1H, t, J = 5.7 Hz), 4.73 (1H, t, J = 5.7 Hz), 5.15 (2H, s), 6.95 (1H, d, J = 8.4 Hz), 7.06 (1H, d, J = 1.8 Hz), 7.17 (1H, dd, J = 8.2, 2.0 Hz), 7.29-7.49 (6H, m), 7.91 (1H, d, J = 13.5 Hz).

[0276] [Production Example 33-4] 6-(3-Fluoropropoxy)-1H-indol-5-ol

[Chemical Formula 162]



Fuming nitric acid (4.80 mL, 107 mmol) was added to a mixture of (E)-2-(benzyloxy)-1-(3-fluoropropoxy)-4-(2-nitrovinyl)benzene described in Production Example 33-3 (7.06 g, 21.3 mmol) and acetic acid (61 mL) in an ice bath, and the mixture was stirred at room temperature for 2.5 hours. The reaction mixture was poured onto ice, the precipitate was collected by filteration, and then the resultant was washed with a liquid mixture of a small quantity of acetic acid and ethanol to obtain a crude product (8.02 g).

The crude product (8.02 g) was suspended in methanol (150 mL), then 10% palladium-carbon (water content, 50%) (2.27 g) was added, and the mixture was stirred under hydrogen atmosphere for 6 hours. The inside of the reaction system was substituted with nitrogen, then the mixture was diluted with methanol. The catalyst was filtered off with celite, then the filtrate was concentrated under vacuum, and the resultant was purified with silica gel column chromatography (n-heptane:ethyl acetate = 9:1 - 1:1). The target fraction was concentrated under vacuum to obtain the title compound (1.47 g, 33%).

^{1}H-NMR Spectrum ($CDCl_3$) δ (ppm): 2.22 (1H, quin, J = 5.9 Hz), 2.29 (1H, quin, J = 5.9 Hz), 4.23 (2H, t, J = 6.0 Hz), 4.62 (1H, t, J = 5.7 Hz), 4.74 (1H, t, J = 5.7 Hz), 5.42 (1H, s), 6.42 (1H, ddd, J = 3.1, 2.2, 0.9 Hz), 6.91 (1H, s), 7.09 (1H, dd, J = 3.1, 2.4 Hz), 7.15 (1H, s), 7.94 (1H, brs).

[0277] [Production Example 33-5]

4-((6-(3-Fluoropropoxy)-1H-indol-5-yl)oxy)pyridin -2-amine

[Chemical Formula 163]

6-(3-Fluoropropoxy)-1H-indol-5-ol described in Production Example 33-4 (1.47 g, 7.04 mmol), N-(4-chloropyridin-2-yl)acetamide described in Production Example 1-5 (1.32 g, 7.74 mmol), and potassium tert-butoxide (864 mg, 7.70 mmol) were dissolved in dimethylsulfoxide (7.0 mL), and the mixture was heated and stirred under nitrogen atmosphere at 160°C for 4.5 hours. The reaction liquid was cooled to room temperature, and then water and ethyl acetate were added for partition. The aqueous layer was extracted with ethyl acetate again, then the combined organic layer was washed with water and a saturated saline solution and then dried over anhydrous magnesium sulfate. The drying agent was filtered off, the filtrate was concentrated under vacuum, and the resultant was purified with NH silica gel column chromatography (n-heptane:ethyl acetate = 4:1 - 1:1 - 0:1 - ethyl acetate:methanol = 99:1 - 9:1). The target fraction was concentrated under vacuum to obtain a crude product (177 mg).

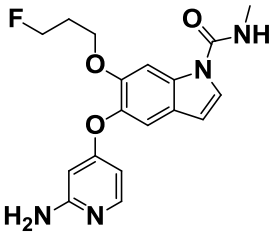
The resultant crude product (177 mg) was dissolved in methanol (2.5 mL), a 2 M sodium hydroxide solution (2.5 mL) was added under nitrogen atmosphere at room temperature, and the mixture was heated and stirred at 70°C for 2 hours. The reaction mixture was cooled to room temperature and then water and ethyl acetate were added for partition. The organic layer was washed with a saturated saline solution and dried over anhydrous sodium sulfate. The drying agent was filtered off, then the filtrate was concentrated under vacuum, and the resultant was purified with silica gel column chromatography (n-heptane:ethyl acetate = 2:3 - 1:4 - 0:1 - ethyl acetate:methanol = 19:1). The target fraction was concentrated under vacuum to obtain the title compound (49.4 mg, 2.3%).

^{1}H-NMR Spectrum ($CDCl_3$) δ (ppm): 1.95-2.11 (2H, m), 4.07 (2H, t, J = 5.9 Hz), 4.28-4.47 (4H, m), 5.88 (1H, d, J = 2.2 Hz), 6.28 (1H, dd, J = 5.9, 2.2 Hz), 6.48-6.52 (1H, m), 7.02 (1H, s), 7.16-7.20 (1H, m), 7.35 (1H, s), 7.88 (1H, d, J = 5.9 Hz), 8.25 (1H, brs).

[0278] [Production Example 33-6]

5-((2-Aminopyridin-4-yl)oxy)-6-(3-fluoropropoxy)-N-methyl-1H-indole-1-carboxamide

[Chemical Formula 164]

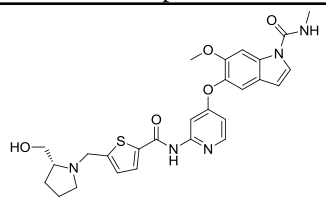
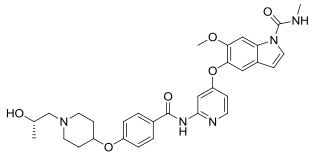
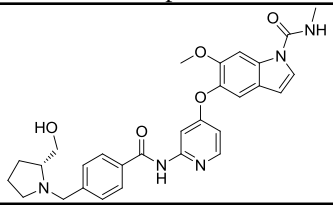
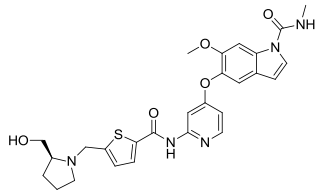
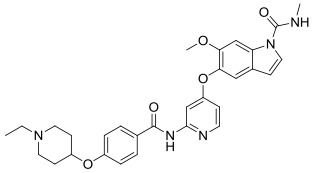
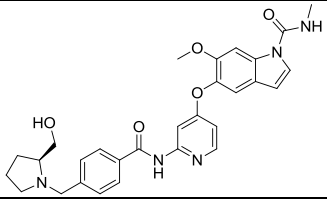
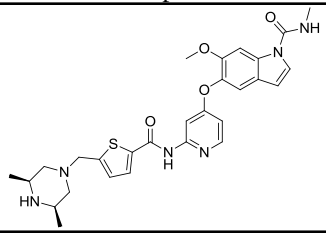
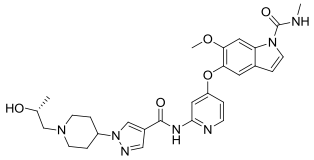
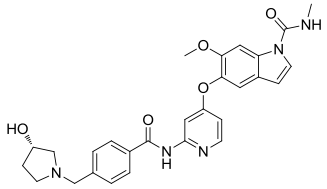
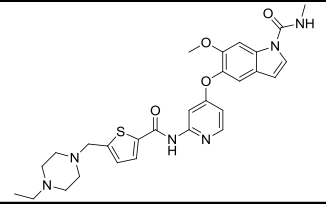
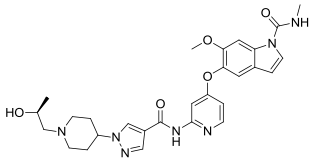
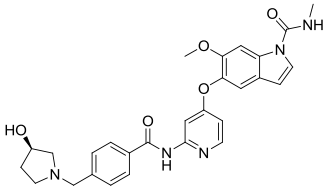
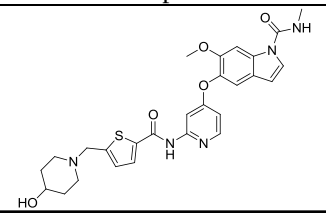
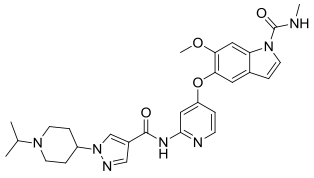
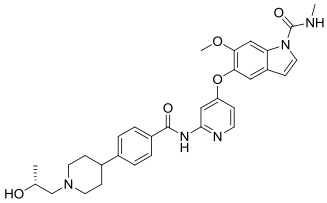


4-((6-(3-Fluoropropoxy)-1H-indol-5-yl)oxy)pyridin-2-amine described in Production Example 33-5 (49.4 mg, 0.164 mmol) was dissolved in N,N-dimethylformamide (1.6 mL), 50 - 72% oily sodium hydride (14.9 mg) was added under nitrogen atmosphere at 0°C, and the mixture was stirred at room temperature for 15 minutes. The mixture was cooled to 0°C again, phenyl methylcarbamate described in Production Example 1-7 (62.0 mg, 0.41 mmol) was added, and the mixture was stirred at room temperature for 3.5 hours. A saturated aqueous ammonium chloride solution, water, and ethyl acetate were added to the reaction mixture for partition. The organic layer was washed with a saturated saline solution and then dried over anhydrous sodium sulfate. The drying agent was filtered off, the filtrate was concentrated under vacuum, and the resultant was purified with NH silica gel column chromatography (n-heptane:ethyl acetate = 1:4 - 0:1 - ethyl acetate:methanol = 99:1 - 9:1). The target fraction was concentrated under vacuum to obtain the title compound (34.4 mg, 59%).

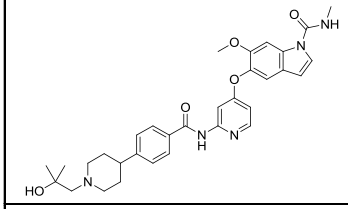
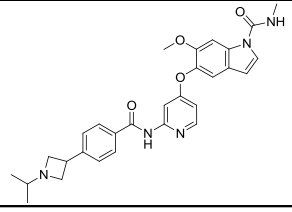
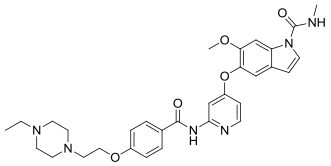
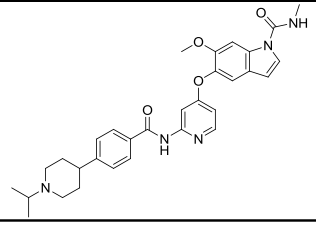
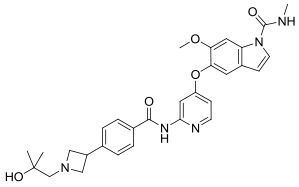
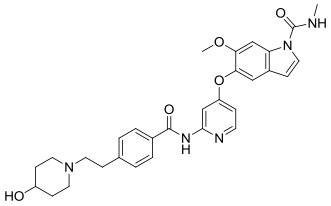
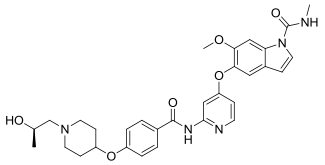
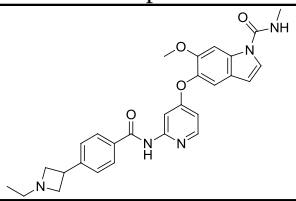
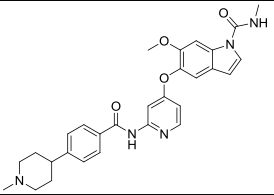
^{1}H-NMR Spectrum ($CDCl_3$) δ (ppm): 1.95-2.11 (2H, m), 3.07 (3H, dd, J = 4.7, 1.2), 4.12-4.17 (2H, m), 4.29 (1H, t, J = 5.8 Hz), 4.38-4.52 (3H, m), 5.50 (1H, brs), 5.87 (1H, d, J = 2.0 Hz), 6.26 (1H, dd, J = 6.0, 2.1 Hz), 6.56 (1H, d, J = 3.7 Hz), 7.23-7.27 (1H, m), 7.29 (1H, s), 7.87 (1H, d, J = 6.0 Hz), 8.00 (1H, s).

[0279] According to Examples 1 to 33, the example compounds illustrated in Tables 1 and 2 were synthesized from 5-((2-aminopyridin-4-yl)oxy)-6-methoxy-N-methyl-1H-indole-1-carboxamide described in Production Example 1-6.

[0280] [Table 1]

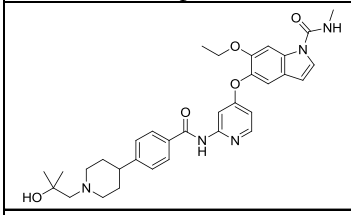
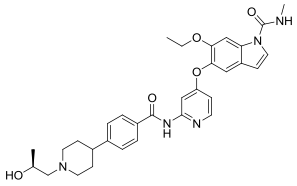
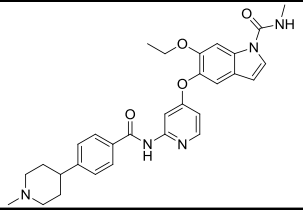
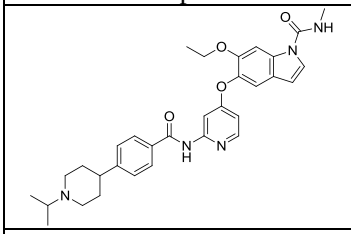
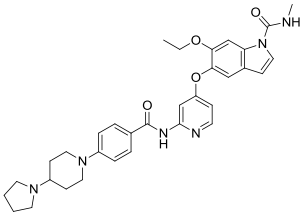
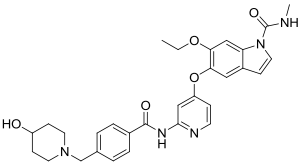
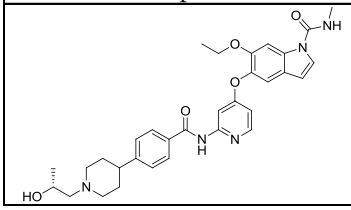
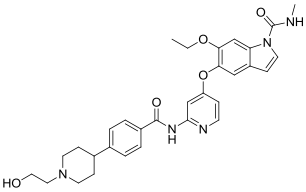
Example 34	Example 42	Example 50
		
Example 35	Example 43	Example 51
		
Example 36	Example 44	Example 52
		
Example 37	Example 45	Example 53
		
Example 38	Example 46	Example 54
		

[0281] [Table 2]

Example 39	Example 47	Example 55
		
Example 40	Example 48	Example 56
		
Example 41	Example 49	Example 57
		

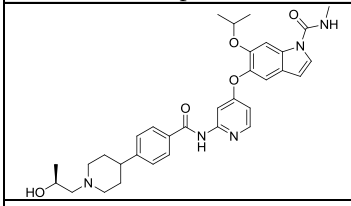
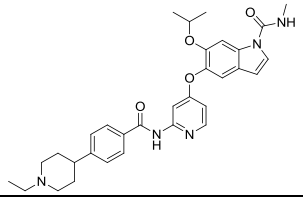
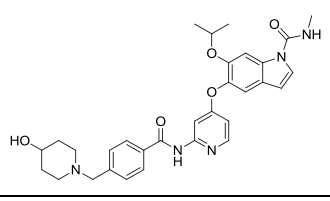
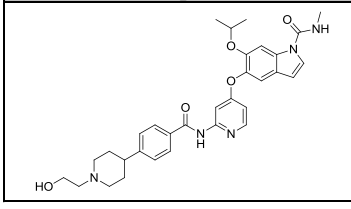
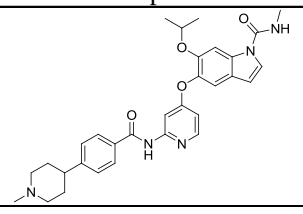
[0282] According to Examples 1 to 33, the example compounds illustrated in Table 3 were synthesized from 5-((2-aminopyridin-4-yl)oxy)-6-ethoxy-N-methyl-1H-indole-1-carboxamide described in Production Example 15-7.

[0283] [Table 3]

Example 58	Example 61	Example 64
		
Example 59	Example 62	Example 65
		
Example 60	Example 63	
		

[0284] According to Examples 1 to 33, the example compounds illustrated in Table 4 were synthesized from 5-((2-aminopyridin-4-yl)oxy)-6-isopropoxy-N-methyl-1H-indole-1-carboxamide described in Production Example 17-7.

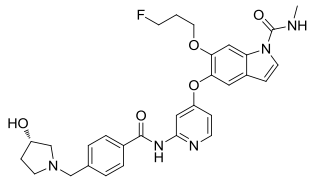
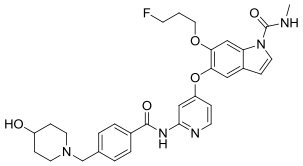
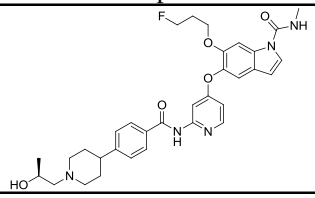
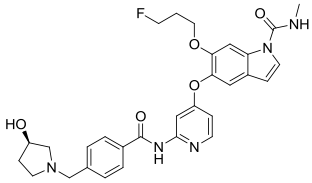
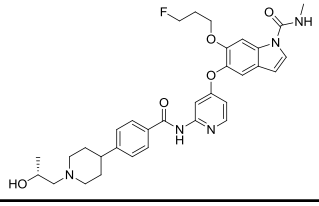
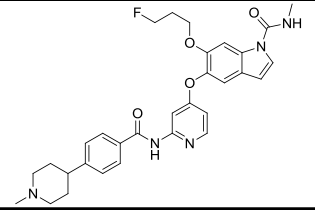
[0285] [Table 4]

Example 66	Example 68	Example 70
		
Example 67	Example 69	
		

[0286] According to Examples 1 to 33, the example compounds illustrated in Table 5 were synthesized from 5-((2-aminopyridin-4-yl)oxy)-6-(3-fluoropropoxy)-N-methyl-1H-indole-1-carboxamide

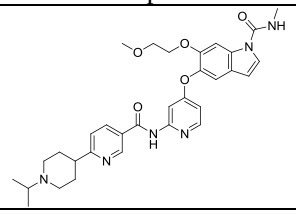
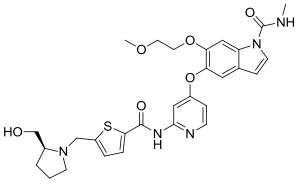
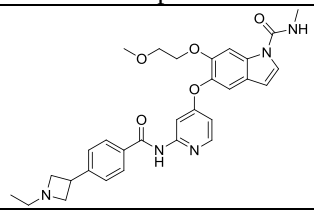
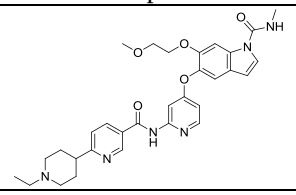
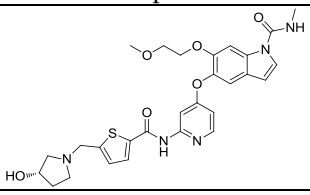
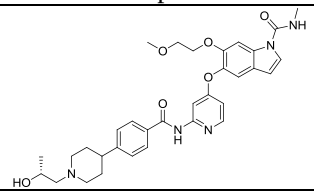
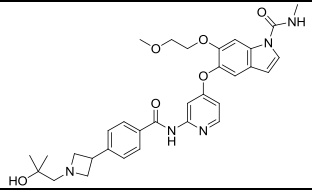
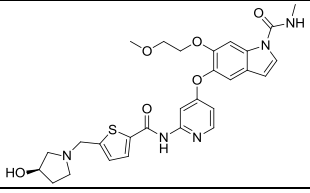
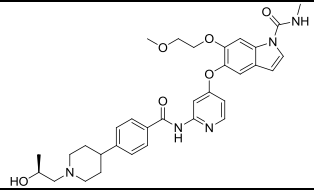
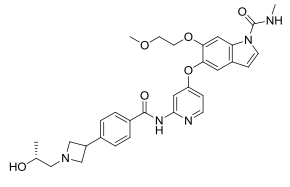
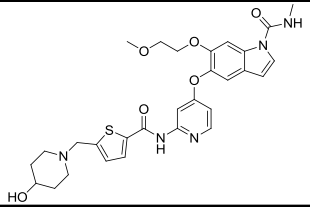
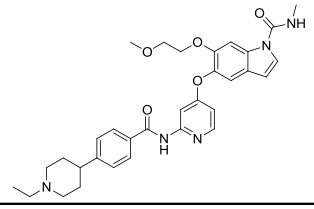
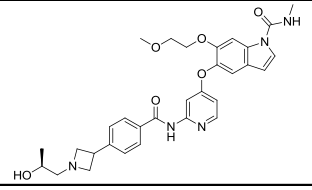
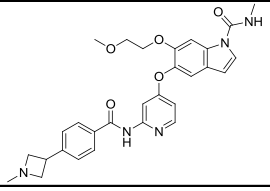
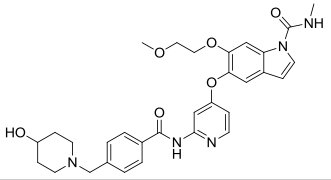
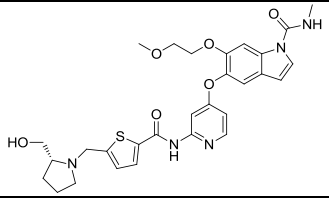
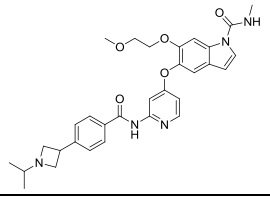
described in Production Example 33-6.

[0287] [Table 5]

Example 71	Example 73	Example 75
		
Example 72	Example 74	Example 76
		

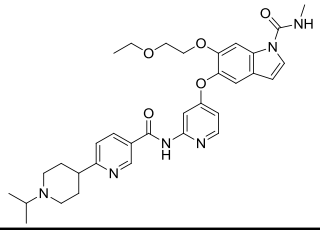
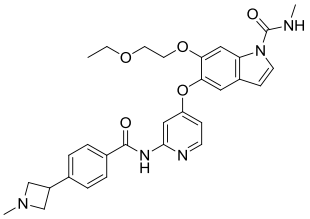
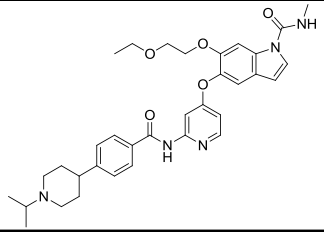
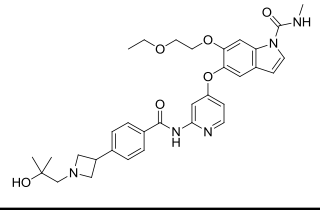
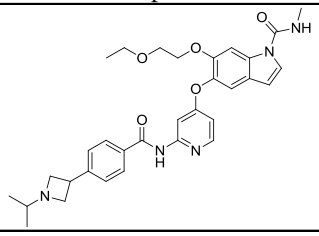
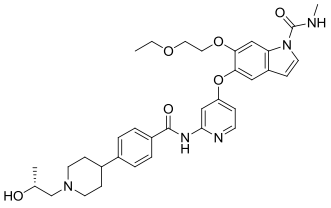
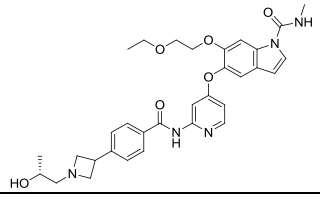
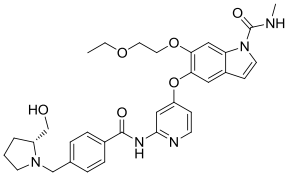
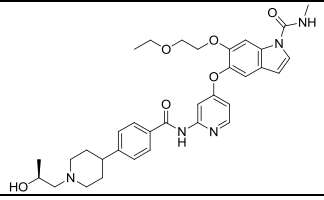
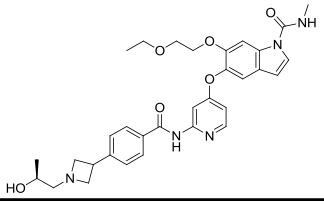
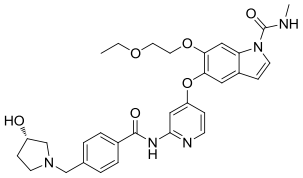
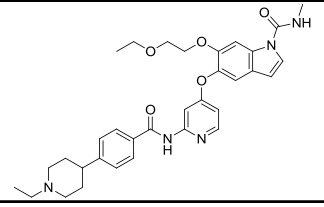
[0288] According to Examples 1 to 33, the example compounds illustrated in Table 6 were synthesized from 5-((2-aminopyridin-4-yl)oxy)-6-(2-methoxyethoxy)-N-methyl-1H-indole-1-carboxamide described in Production Example 20-7.

[0289] [Table 6]

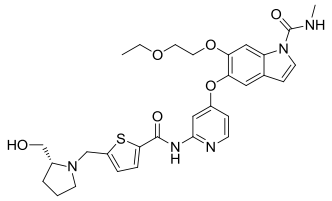
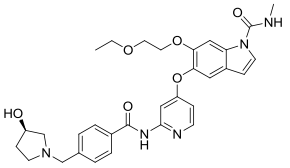
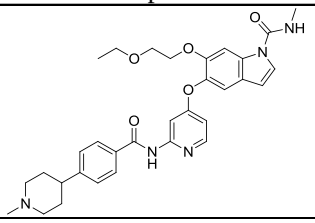
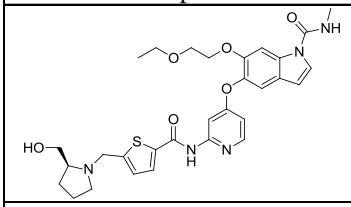
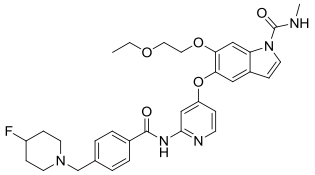
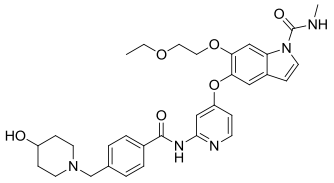
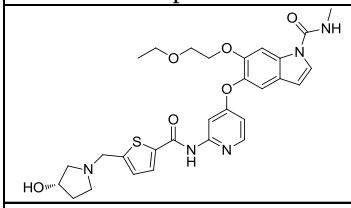
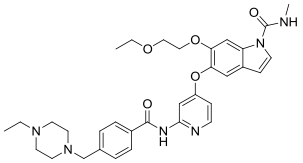
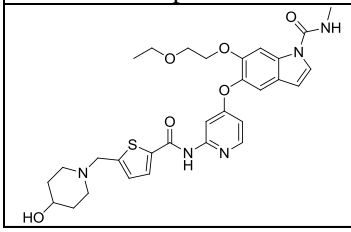
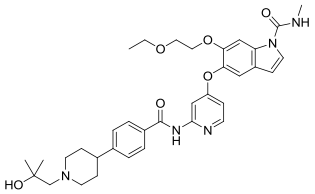
Example 77	Example 83	Example 89
		
Example 78	Example 84	Example 90
		
Example 79	Example 85	Example 91
		
Example 80	Example 86	Example 92
		
Example 81	Example 87	Example 93
		
Example 82	Example 88	
		

[0290] According to Examples 1 to 33, the example compounds illustrated in Tables 7 and 8 were synthesized from 5-((2-aminopyridin-4-yl)oxy)-6-(2-ethoxyethoxy)-N-methyl-1H-indole-1-carboxamide described in Production Example 24-8.

[0291] [Table 7]

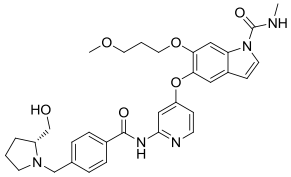
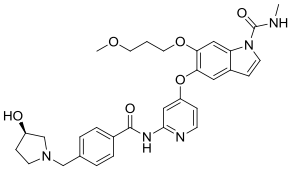
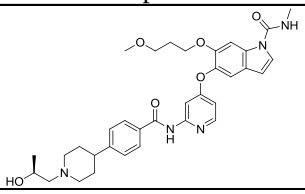
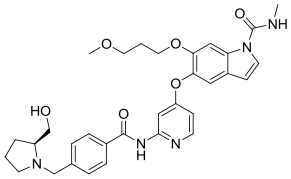
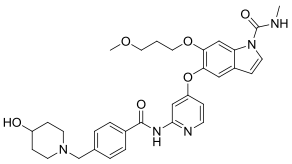
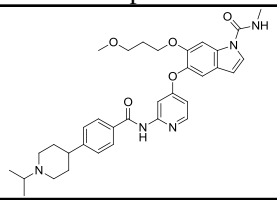
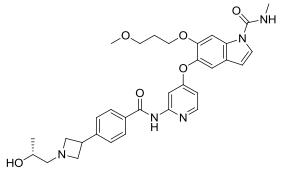
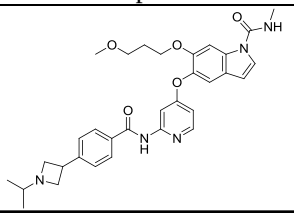
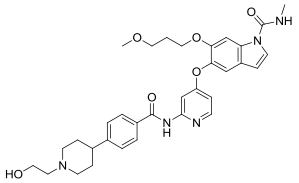
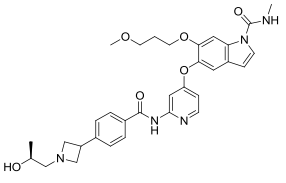
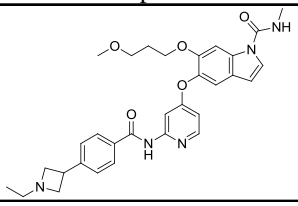
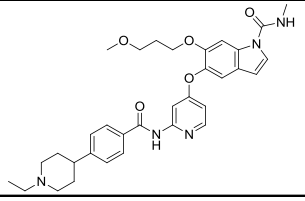
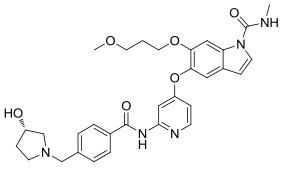
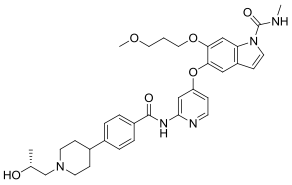
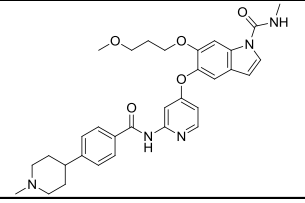
Example 94	Example 102	Example 110
		
Example 95	Example 103	Example 111
		
Example 96	Example 104	Example 112
		
Example 97	Example 105	Example 113
		

[0292] [Table 8]

Example 98	Example 106	Example 114
		
Example 99	Example 107	Example 115
		
Example 100	Example 108	
		
Example 101	Example 109	
		

[0293] According to Examples 1 to 33, the example compounds illustrated in Table 9 were synthesized from 5-((2-aminopyridin-4-yl)oxy)-6-(3-methoxypropoxy)-N-methyl-1H-indole-1-carboxamide described in Production Example 32-8.

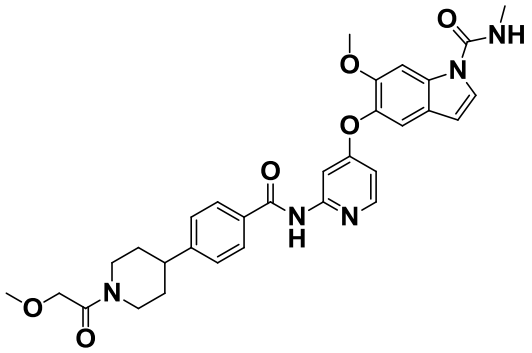
[0294] [Table 9]

Example 116	Example 121	Example 126
		
Example 117	Example 122	Example 127
		
Example 118	Example 123	Example 128
		
Example 119	Example 124	Example 129
		
Example 120	Example 125	Example 130
		

[0295] [Example 131]

6-Methoxy-5-((2-(4-(1-(2-methoxyacetyl)piperidin-4-yl)benzamide)pyridin-4-yl)oxy)-N-methyl-1H-indole-1-carboxamide

[Chemical Formula 165]

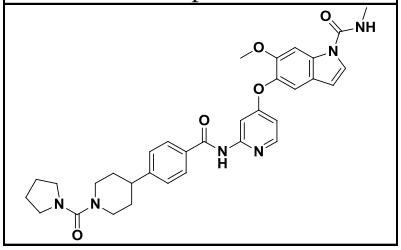


Triethylamine (33 μL, 0.237 mmol) and methoxyacetyl chloride (12.5 mg, 0.115 mmol) were added to a mixture of 6-methoxy-N-methyl-5-((2-(4-(piperidin-4-yl)benzamide)pyridin-4-yl)oxy)-1H-indole-1-car boxamide described in Example 1 (13.4 mg, 0.027 mmol) and tetrahydrofuran (1.0 mL), and the mixture was stirred at room temperature for 3.5 hours. Water and ethyl acetate were added to the reaction mixture for partition. The organic layer was washed with a saturated saline solution, and then dried over anhydrous sodium sulfate and filtered. The solvent was evaporated, and the resultant residue was dissolved in dichloromethane, and the resultant was purified with NH silica gel column chromatography (ethyl acetate:methanol = 1:0 - 9:1). The target fraction was concentrated under vacuum, and the solid was washed with diethyl ether to obtain the title compound (10.2 mg, 67%).

^{1}H-NMR Spectrum ($CDCl_3$) δ (ppm): 1.50-1.73 (2H, m), 1.87-1.98 (2H, m), 2.62-2.75 (1H, m), 2.76-2.89 (1H, m), 3.02-3.19 (4H, m), 3.45 (3H, s), 3.86 (3H, s), 3.97-4.03 (1H, m), 4.06-4.21 (2H, m), 4.71-4.81 (1H, m), 5.47-5.55 (1H, m), 6.55 (1H, d, J=3.7 Hz), 6.60 (1H, dd, J=5.8, 2.3 Hz), 7.23 (1H, d, J=3.8 Hz), 7.27-7.34 (3H, m), 7.81 (2H, d, J=8.4 Hz), 7.91 (1H, d, J=2.4 Hz), 8.03 (1H, s), 8.10 (1H, d, J=5.7 Hz), 8.49 (1H, brs).

[0296] According to Example 131, the example compound illustrated in Table 10 was synthesized from 6-methoxy-N-methyl-5-((2-(4-(piperidin-4-yl)benzamide)pyridin-4-yl)oxy)-1H-indole-1-car boxamide described in Example 1.

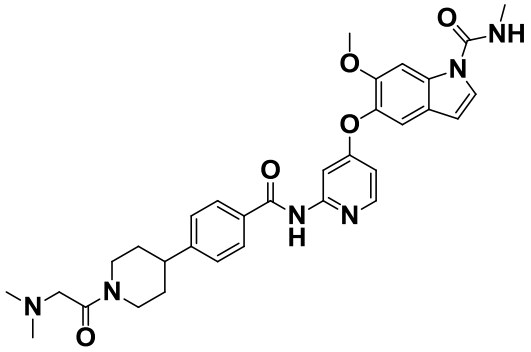
[0297] [Table 10]

Example 132


[0298] [Example 133]

5-((2-(4-(1-(2-(Dimethylamino)acetyl)piperidin-4-yl)benzamide)pyridin-4-yl)oxy)-6-methoxy-N-methyl-1H-indole-1-carboxamide

[Chemical Formula 166]



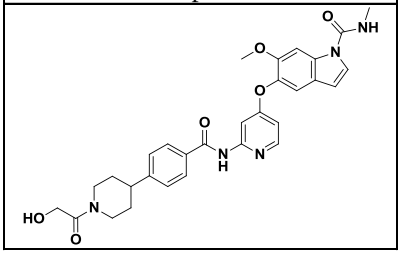
N,N-dimethylformamide (0.5 mL) and N,N-diisopropylethylamine (24 μL, 0.137 mmol) were added to a mixture of 6-methoxy-N-methyl-5-((2-(4-(piperidin-4-yl)benzamide)pyridin-4-yl)oxy)-1H-indole-1-carboxamide described in Example 1 (13.7 mg, 0.027 mmol), O-(7-azabenzotriazole-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (16.3 mg, 0.043 mmol) and N,N-dimethylglycine (5.5 mg, 0.053 mmol), and the mixture was stirred at room temperature for 2 hours. Water and ethyl acetate were added to the reaction mixture for partition. The organic layer was washed with a saturated saline solution, and then dried over anhydrous sodium sulfate and filtered. The solvent was evaporated, and the resultant residue was dissolved in dichloromethane, and the resultant was purified with NH silica gel column chromatography (ethyl acetate:methanol = 1:0 - 9:1). The target fraction was concentrated under vacuum, and the solid was washed with diethyl ether to obtain the title compound (13.7 mg, 85%).

^{1}H-NMR Spectrum ($CDCl_3$) δ (ppm): 1.49-1.74 (2H, m), 1.85-1.97 (2H, m), 2.32 (6H, s), 2.60-2.71 (1H, m), 2.76-2.87 (1H, m), 3.04-3.26 (6H, m), 3.87 (3H, s), 4.20-4.32 (1H, m),

4.71-4.83 (1H, m), 5.45-5.54 (1H, m), 6.54-6.57 (1H, m), 6.60 (1H, dd, J=5.8, 2.3 Hz), 7.24 (1H, d, J=3.7 Hz), 7.28-7.34 (3H, m), 7.82 (2H, d, J=8.6 Hz), 7.92 (1H, d, J=2.4 Hz), 8.04 (1H, s), 8.10 (1H, d, J=5.7 Hz), 8.49 (1H, brs).

[0299] According to Example 133, the example compound illustrated in Table 11 was synthesized from 6-methoxy-N-methyl-5-((2-(4-(piperidin-4-yl)benzamide)pyridin-4-yl)oxy)-1H-indole-1-carboxamide described in Example 1.

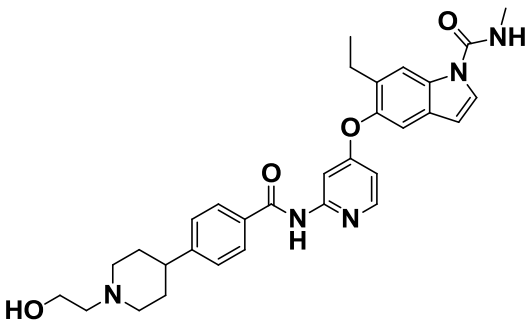
[0300] [Table 11]

Example 134


[0301] [Example 135]

6-Ethyl-5-((2-(4-(1-(2-hydroxyethyl)piperidin-4-yl)benzamide)pyridin-4-yl)oxy)-N-methyl-1H-indole-1-carboxamide

[Chemical Formula 167]



2-Hydroxyacetaldehyde (9.41 mg, 0.157 mmol), sodium triacetoxyborohydride (33.2 mg, 0.157 mmol) and acetic acid (8.97 μL, 0.157 mmol) were added to a mixture of 6-ethyl-N-methyl-5-((2-(4-(piperidin-4-yl)benzamide)pyridin-4-yl)oxy)-1H-indole-1-carboxamide (15.6 mg, 0.031 mmol) and tetrahydrofuran (1.0 mL), and the mixture was stirred at room temperature for 15 hours and 50 minutes. A saturated aqueous sodium bicarbonate solution and ethyl acetate were added to the reaction mixture for partition. The organic layer was washed with a saturated saline solution, and then dried over anhydrous sodium

sulfate and filtered. The solvent was evaporated, and the resultant residue was dissolved in dichloromethane, and the resultant was purified with NH silica gel column chromatography (ethyl acetate:methanol = 1:0 - 9:1 - 17:3). The target fraction was concentrated under vacuum to obtain the title compound (13.2 mg, 78%).

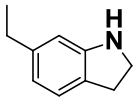
^{1}H-NMR Spectrum ($CDCl_3$) δ (ppm): 1.24 (3H, t, J=7.5 Hz), 1.71-1.92 (5H, m), 2.16-2.26 (2H, m), 2.55-2.72 (5H, m), 3.01-3.13 (5H, m), 3.64 (2H, t, J=5.3 Hz), 5.46-5.53 (1H, m), 6.52 (1H, dd, J=5.9, 2.2 Hz), 6.56 (1H, d, J=3.7 Hz), 7.24-7.29 (1H, m), 7.34 (2H, d, J=8.4 Hz), 7.37 (1H, d, J=3.7 Hz), 7.82 (2H, d, J=8.1 Hz), 7.98 (1H, d, J=2.2 Hz), 8.10 (1H, d, J=5.9 Hz), 8.12 (1H, s), 8.49 (1H, brs).

[0302] The starting material 6-ethyl-N-methyl-5-((2-(4-(piperidin-4-yl)benzamide)pyridin-4-yl)oxy)-1H-indole-1-carbox amide was synthesized by the following method.

[0303] [Production Example 135-1]

6-Ethylindoline

[Chemical Formula 168]



Commercially available 3-ethylaniline (10.1 g, 83.3 mmol) was dissolved in ethanol (40 mL), then sodium hydrogen carbonate (7.00 g, 83.3 mmol) and bromoacetaldehyde diethyl acetal (8.44 mL, 54.8 mmol) were added, and the mixture was heated and stirred at 80°C for 80 hours. Water was added to the reaction mixture for partition. The aqueous layer was extracted with ethyl acetate three times and then the combined organic layer was washed with a saturated saline solution. The organic layer was dried over anhydrous magnesium sulfate, filtered and then concentrated under vacuum. The resultant residue was purified with silica gel column chromatography (n-heptane:ethyl acetate = 2:1). The target fraction was concentrated under vacuum to obtain a crude product A (11 g).

A part of the resultant crude product A (10 g) was dissolved in trifluoroacetic acid (45 mL), anhydrous trifluoroacetic acid (45 mL) was added at 4°C, and the mixture was stirred for 30 minutes. Trifluoroacetic acid (60 mL) was added to the reaction mixture, and the mixture was stirred at 75°C for 2.5 hours. After concentration under vacuum, the aqueous layer was extracted with ethyl acetate three times, and then the combined organic layer was washed with a saturated saline solution. The organic layer was dried over

anhydrous magnesium sulfate, filtered and then concentrated under vacuum. The resultant residue was purified with NH silica gel column chromatography (n-heptane:ethyl acetate = 3:1). The target fraction was concentrated under vacuum to obtain a crude product B (3 g).

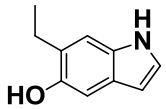
A part of the resultant crude product B (1.5 g) was dissolved in acetic acid (50 mL), sodium cyanoborohydride (1.30 g, 20.7 mmol) was added at 0°C, and the mixture was stirred at room temperature for 1 hour. A saturated aqueous sodium bicarbonate solution was added to the reaction mixture for partition. The aqueous layer was extracted with ethyl acetate three times, and then the combined organic layer was washed with a saturated saline solution. The organic layer was dried over anhydrous magnesium sulfate, filtered and then concentrated under vacuum. The resultant residue was purified with silica gel column chromatography (n-heptane:ethyl acetate = 3:1). The target fraction was concentrated under vacuum to obtain the title compound (560 mg, 15%).

^{1}H-NMR Spectrum ($CDCl_3$) δ (ppm): 1.20 (3H, t, J=7.6 Hz), 2.55 (2H, q, J=7.7 Hz), 2.99 (2H, t, J=8.4 Hz), 3.54 (2H, t, J=8.3 Hz), 3.72 (1H, brs), 6.43-6.61 (2H, m), 6.93-7.07 (1H, m).

[0304] [Production Example 135-2]

6-Ethyl-1H-indol-5-ol

[Chemical Formula 169]

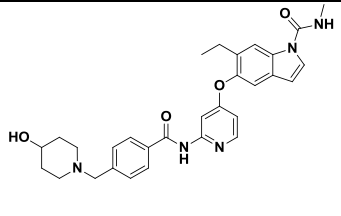
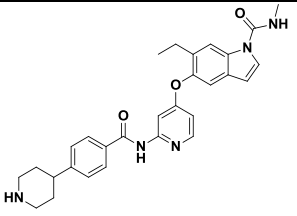
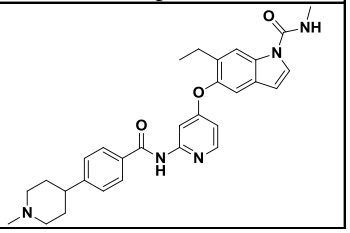


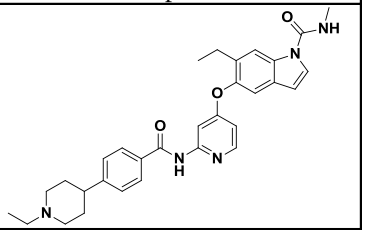
Potassium nitrosodisulfonate (6.82 g, 25.4 mmol) was dissolved in a 0.1 M potassium phosphate buffer (450 mL), then 6-ethylindoline described in Production Example 135-1 (1.7 g, 11.5 mmol) dissolved in acetone (150 mL) was added, and the mixture was stirred at room temperature for 12 hours. 2 M Sodium hydroxide was added to the reaction mixture for partition. The aqueous layer was extracted with ethyl acetate three times, and then the combined organic layer was washed with a saturated saline solution. The organic layer was dried over anhydrous magnesium sulfate, filtered and then concentrated under vacuum. The resultant residue was purified with silica gel column chromatography (n-heptane:ethyl acetate = 1:1). The target fraction was concentrated under vacuum to obtain the title compound (560 mg, 30%).

^{1}H-NMR Spectrum ($CDCl_3$) δ (ppm): 1.29 (3H, t, J=7.5 Hz), 2.74 (2H, q, J=7.5 Hz), 4.50 (1H, s), 6.34-6.43 (1H, m), 6.99 (1H, s), 7.07-7.18 (2H, m), 7.95 (1H, brs).

[0305] According to Examples 1 to 33, the example compounds illustrated in Table 12 containing the starting material of Example 135, 6-ethyl-N-methyl-5-((2-(4-(piperidin-4-yl)benzamide)pyridin-4-yl)oxy)-1H-indole-1-carbox amide were synthesized from 6-ethyl-1H-indol-5-ol described in Production Example 135-2 and N-(4-chloropyridin-2-yl)acetamide described in Production Example 1-5.

[0306] [Table 12]

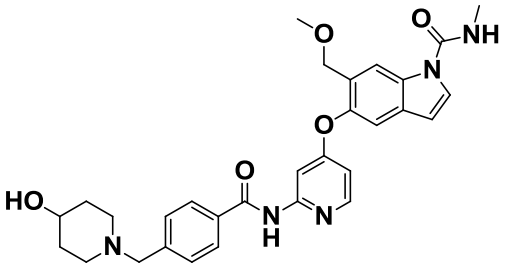
Example 136	Example 137	Example 138
		

Example 139


[0307] [Example 140]

5-((2-(4-((4-Hydroxypiperidin-1-yl)methyl)benzamide)pyridin-4-yl)oxy)-6-(methoxymethyl)-N-methyl-1H-indole-1-carboxamide

[Chemical Formula 170]



Triethylamine (20 μL, 0.144 mmol) and commercially available 4-(chloromethyl)benzoyl chloride (16.6 mg, 0.088 mmol) were added to a mixture of 5-((2-aminopyridin-4-yl)oxy)-6-(methoxymethyl)-N-methyl-1H-indole-1-carboxamide (5.5 mg, 0.017 mmol) and tetrahydrofuran (450 μL) at room temperature under nitrogen atmosphere, and the mixture was stirred for 70 minutes. Tetrahydrofuran, water and ethyl acetate were added to the reaction mixture for partition. The organic layer was washed with

a saturated saline solution, and then dried over anhydrous sodium sulfate, and filtered with NH silica gel, and the resultant was concentrated under vacuum to obtain a crude product.

The resultant crude product was dissolved in N,N-dimethylformamide (500 μL), 4-hydroxypiperidine (16.5 mg, 0.163 mmol) was added at room temperature under nitrogen atmosphere, and the mixture was stirred for 12 hours and 50 minutes. Ethyl acetate and water were added to the reaction mixture for partition. The organic layer was washed with a saturated saline solution, dried over anhydrous sodium sulfate, filtered, and then concentrated under vacuum. The residue was dissolved in dichloromethane, and the resultant was purified with NH silica gel TLC (ethyl acetate) to obtain the title compound (7.6 mg, 83%).

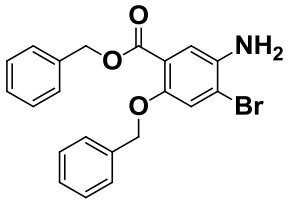
^{1}H-NMR Spectrum ($CDCl_3$) δ (ppm): 1.38-1.67 (2H, m), 1.83-1.95 (2H, m), 2.10-2.25 (2H, m), 2.68-2.79 (2H, m), 3.10 (3H, d, J=4.8 Hz), 3.37 (3H, s), 3.56 (2H, brs), 3.62-3.77 (2H, m), 4.52 (2H, s), 5.60-5.69 (1H, m), 6.55 (1H, dd, J=5.9, 2.2 Hz), 6.58 (1H, dd, J=3.7, 0.7 Hz), 7.30 (1H, s), 7.44 (2H, d, J=8.1 Hz), 7.50 (1H, d, J=3.7 Hz), 7.82 (2H, d, J=8.1 Hz), 7.97 (1H, d, J=2.2 Hz), 8.09 (1H, d, J=5.5 Hz), 8.21 (1H, s), 8.60 (1H, brs).

[0308] The starting material 5-((2-aminopyridin-4-yl)oxy)-6-(methoxymethyl)-N-methyl-1H-indole-1-carboxamide was synthesized by the following method.

[0309] [Production Example 140-1]

Benzyl 5-amino-2-(benzyloxy)-4-bromobenzoate

[Chemical Formula 171]



Benzyl 5-amino-2-(benzyloxy)benzoate (5 g, 15.0 mmol) obtained by benzylating and reducing commercially available 5-aminosalicylic acid by a conventional method was dissolved in dichloromethane (100 mL) and methanol (50 mL), then tetra-N-butylammonium tribromide (7.25 g, 15.0 mmol) was added at room temperature under nitrogen atmosphere, and the mixture was stirred for 4 hours. An aqueous sodium hydrogen sulfite solution and ethyl acetate were added to the reaction mixture for partition. The organic layer was washed with a saturated saline solution, dried over anhydrous magnesium sulfate, and then filtered. The filtrate was concentrated under vacuum, and the

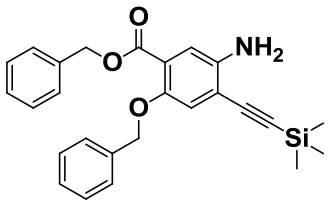
resultant residue was purified with silica gel column chromatography (n-heptane:ethyl acetate = 9:1 - 4:1 - 3:2). The target fraction was concentrated under vacuum to obtain the title compound (3.58 g, 58%).

^{1}H-NMR Spectrum ($CDCl_3$) δ (ppm): 3.88 (2H, s), 5.04 (2H, s), 5.31 (2H, s), 7.15 (1H, s), 7.27-7.43 (11H, m).

[0310] [Production Example 140-2]

Benzyl 5-amino-2-(benzyloxy)-4-((trimethylsilyl)ethynyl)benzoate

[Chemical Formula 172]



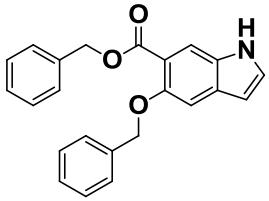
Benzyl 5-amino-2-(benzyloxy)-4-bromobenzoate described in Production Example 140-1 (3.58 g, 8.68 mmol) was dissolved in tetrahydrofuran (20 mL) and triethylamine (40 mL), then trimethylsilylacetylene (2.5 mL, 17.7 mmol), bis(triphenylphosphine)palladium(II) chloride (304 mg, 0.434 mmol) and copper iodide(I) (165 mg, 0.868 mmol) were added at room temperature under nitrogen atmosphere, and the mixture was stirred at 70°C for 6 hours. Water and ethyl acetate were added to the reaction mixture for partition. The organic layer was washed with a saturated saline solution, dried over anhydrous sodium sulfate, and then filtered. The filtrate was concentrated under vacuum, and the resultant residue was dissolved in dichloromethane and the resultant was purified with silica gel column chromatography (n-heptane:ethyl acetate = 19:1 - 4:1 - 7:3). The target fraction was concentrated under vacuum to obtain the title compound (2.75 g, 74%).

^{1}H-NMR Spectrum ($CDCl_3$) δ (ppm): 0.25-0.35 (9H, m), 4.03 (2H, s), 5.03 (2H, s), 5.31 (2H, s), 7.00 (1H, s), 7.20 (1H, s), 7.28-7.47 (10H, m).

[0311] [Production Example 140-3]

Benzyl 5-(benzyloxy)-1H-indole-6-carboxylate

[Chemical Formula 173]



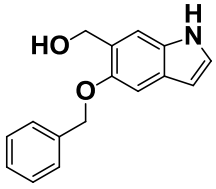
Benzyl 5-amino-2-(benzyloxy)-4-((trimethylsilyl)ethynyl)benzoate described in Production Example 140-2 (2.75 g, 6.40 mmol) was dissolved in N,N-dimethylformamide (30 mL), then copper iodide(I) (610 mg, 3.20 mmol) was added at room temperature under nitrogen atmosphere, and the mixture was heated and stirred at 100°C for 3 hours. Ethyl acetate was added to the reaction mixture and the resultant mixture was filtered with celite. The filtrate was concentrated under vacuum, and the resultant residue was dissolved in dichloromethane and the resultant was purified with silica gel column chromatography (n-heptane:ethyl acetate = 17:3 - 3:2). The target fraction was concentrated under vacuum to obtain the title compound (1.83 g, 80%).

^{1}H-NMR Spectrum ($CDCl_3$) δ (ppm): 5.18 (2H, s), 5.37 (2H, s), 6.44-6.50 (1H, m), 7.22 (1H, s), 7.27-7.38 (7H, m), 7.40-7.46 (2H, m), 7.47-7.53 (2H, m), 7.99 (1H, d, J=0.7 Hz), 8.25 (1H, brs).

[0312] [Production Example 140-4]

(5-(Benzyloxy)-1H-indole-6-yl)methanol

[Chemical Formula 174]



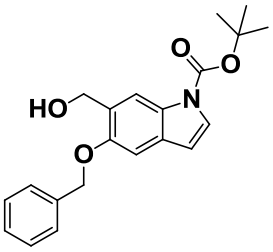
Lithium aluminum hydride (239 mg, 6.30 mmol) was suspended in tetrahydrofuran (22 mL), then a solution of benzyl 5-(benzyloxy)-1H-indole-6-carboxylate described in Production Example 140-3 (1.5 g, 4.20 mmol) dissolved in tetrahydrofuran (11 mL) was added at 0°C under nitrogen atmosphere, and the mixture was stirred at room temperature for 3 hours. Water (0.24 mL), a 5 M aqueous sodium hydroxide solution (0.24 mL) and water (0.72 mL) were added to the reaction mixture, and the mixture was stirred at room temperature for 30 minutes. The suspension was filtered with celite, and washed with tetrahydrofuran. The filtrate was concentrated under vacuum, and the resultant residue was dissolved in dichloromethane and the resultant was purified with silica gel column chromatography (n-heptane:ethyl acetate = 4:1 - 1:1 - 1:3). The target fraction was concentrated under vacuum to quantitatively obtain the title compound.

^{1}H-NMR Spectrum ($CDCl_3$) δ (ppm): 2.95 (1H, t, J=6.4 Hz), 4.81 (2H, d, J=6.6 Hz), 5.17 (2H, s), 6.46-6.50 (1H, m), 7.16-7.21 (2H, m), 7.30-7.43 (4H, m), 7.44-7.50 (2H, m), 8.11 (1H, brs).

[0313] [Production Example 140-5]

tert-Butyl 5-(benzyloxy)-6-(hydroxymethyl)-1H-indole-1-carboxylate

[Chemical Formula 175]



tert-Butyl dimethylchlorosilane (280 mg, 1.86 mmol) was added to a solution of (5-(benzyloxy)-1H-indole-6-yl)methanol described in Production Example 140-4 (392 mg, 1.55 mmol) and imidazole (158 mg, 2.32 mmol) in N,N-dimethylformamide (3.8 mL) at room temperature under nitrogen atmosphere, and the mixture was stirred for 70 minutes. Ethyl acetate and water were added to the reaction mixture for partition. The organic layer was washed with water and a saturated saline solution, dried over anhydrous sodium sulfate, and then filtered. The filtrate was concentrated under vacuum to obtain a crude product A.

The resultant crude product A was dissolved in dichloromethane (6.0 mL), di-tert-butyl dicarbonate (538 mg, 2.47 mmol) and 4-dimethylaminopyridine (18.9 mg, 0.155 mmol) were added at room temperature under nitrogen atmosphere, and the mixture was stirred for 1.5 hours. Ethyl acetate and water were added to the reaction mixture for partition. The organic layer was washed with a saturated saline solution, dried over anhydrous sodium sulfate, and then filtered. The filtrate was concentrated under vacuum to obtain a crude product B.

The resultant crude product B was dissolved in tetrahydrofuran (6.0 mL), then 1 M tetrabutylammonium fluoride (3.0 mL, 3.00 mmol) was added at room temperature under nitrogen atmosphere, and the mixture was stirred for 6 hours. Ethyl acetate and water were added to the reaction mixture for partition. The organic layer was washed with a saturated saline solution, dried over anhydrous sodium sulfate, and then filtered. The filtrate was concentrated under vacuum, and the resultant residue was dissolved in dichloromethane and the resultant was purified with silica gel column chromatography (n-heptane:ethyl acetate = 9:1 - 1:1). The target fraction was concentrated under vacuum to quantitatively obtain the title compound.

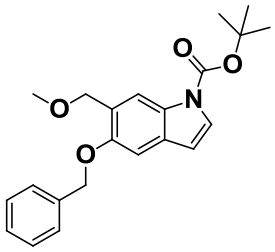
^{1}H-NMR Spectrum ($CDCl_3$) δ (ppm): 1.66 (9H, s), 2.42 (1H, t, J=6.6 Hz), 4.82 (2H, d, J=6.6 Hz), 5.17 (2H, s), 6.49 (1H, dd, J=3.7, 0.7 Hz), 7.09 (1H, s), 7.30-7.49 (5H, m), 7.56 (1H, d,

J=3.7 Hz), 8.09 (1H, brs).

[0314] [Production Example 140-6]

tert-Butyl 5-(benzyloxy)-6-(methoxymethyl)-1H-indole-1-carboxylate

[Chemical Formula 176]



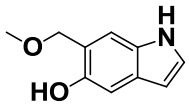
Methyl iodide (290 μL, 4.66 mmol) and 50 - 72% oily sodium hydride (122 mg) were added to a solution of tert-butyl 5-(benzyloxy)-6-(hydroxymethyl)-1H-indole-1-carboxylate described in Production Example 140-5 (547 mg, 1.55 mmol) in N,N-dimethylformamide (10 mL) at room temperature under nitrogen atmosphere, and the mixture was stirred for 3 hours and 15 minutes. The reaction mixture was quenched with water, and then diluted with ethyl acetate for partition. The organic layer was washed with water twice, dried over anhydrous sodium sulfate, and then filtered. The filtrate was concentrated under vacuum, and the resultant residue was dissolved in dichloromethane and the resultant was purified with silica gel column chromatography (n-heptane:ethyl acetate = 19:1 - 4:1). The target fraction was concentrated under vacuum to obtain the title compound (487 mg, 86%).

^{1}H-NMR Spectrum ($CDCl_3$) δ (ppm): 1.67(9H, s), 3.45 (3H, s), 4.65 (2H, s), 5.14 (2H, s), 6.47 (1H, d, J=3.7 Hz), 7.06 (1H, s), 7.29-7.50 (5H, m), 7.55 (1H, d, J=3.7 Hz), 8.17 (1H, brs).

[0315] [Production Example 140-7]

6-(Methoxymethyl)-1H-indol-5-ol

[Chemical Formula 177]



28% Sodium methoxide (4.0 mL, 19.6 mmol) was added to a solution of tert-butyl 5-(benzyloxy)-6-(methoxymethyl)-1H-indole-1-carboxylate described in Production Example 140-6 (427 mg, 1.16 mmol) in methanol (4.0 mL) at room temperature under nitrogen atmosphere, and the mixture was stirred for 2.5 hours. Water and ethyl acetate

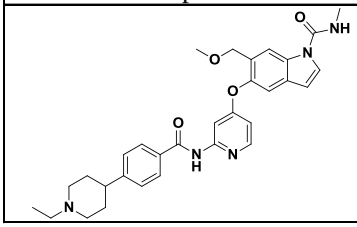
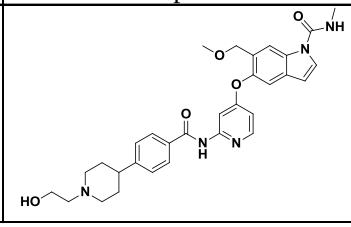
were added to the reaction mixture for partition. The organic layer was washed with a saturated saline solution, dried over anhydrous sodium sulfate, and then filtered. The filtrate was concentrated under vacuum to obtain a crude product (301 mg).

The resultant crude product (301 mg) was dissolved in methanol (11 mL), 10% palladium-carbon (water content, 50%) (12.0 mg) was added at room temperature, and the mixture was stirred for 3 hours under hydrogen atmosphere. The mixture was diluted with methanol, and the catalyst was filtered off with celite. The filtrate was concentrated under vacuum and the resultant was purified with silica gel column chromatography (n-heptane:ethyl acetate = 4:1 - 2:3). The target fraction was concentrated under vacuum to obtain the title compound (156 mg, 76%).

^{1}H-NMR Spectrum ($CDCl_3$) δ (ppm): 3.43 (3H, s), 4.73 (2H, s), 6.43-6.47 (1H, m), 6.91 (1H, s), 7.10 (1H, s), 7.13 (1H, s), 7.17 (1H, t, J=2.7 Hz), 8.00 (1H, brs).

[0316] According to Examples 1 to 33, the example compounds illustrated in Table 13 containing the starting material of Example 140, 5-((2-aminopyridin-4-yl)oxy)-6-(methoxymethyl)-N-methyl-1H-indole-1-carboxamide were synthesized from 6-(methoxymethyl)-1H-indol-5-ol described in Production Example 140-7 and N-(4-chloropyridin-2-yl)acetamide described in Production Example 1-5.

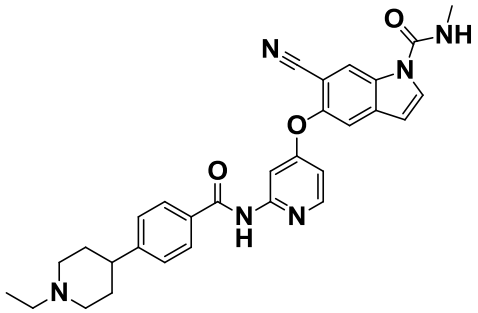
[0317] [Table 13]

Example 141	Example 142
	

[0318] [Example 143]

6-Cyano-5-((2-(4-(1-ethylpiperidin-4-yl)benzamide)pyridin-4-yl)oxy)-N-methyl-1H-indole-1-carboxamide

[Chemical Formula 178]



Sodium triacetoxyborohydride (10.7 mg, 0.05 mmol) and acetaldehyde (5.6 mg, 0.127 mmol) were added to a mixture of 6-cyano-N-methyl-5-((2-(4-(piperidin-4-yl)benzamide)pyridin-4-yl)oxy)-1H-indole-1-carboxamide (3.9 mg, 7.89 mmol) and tetrahydrofuran (1.0 mL) at room temperature under nitrogen atmosphere, and the mixture was stirred for 1 hour. A saturated aqueous sodium bicarbonate solution and ethyl acetate were added to the reaction mixture for partition. The organic layer was washed with a saturated saline solution, and then dried over anhydrous sodium sulfate and filtered. The solvent was evaporated, and the resultant residue was dissolved in dichloromethane, and the resultant was purified with NH silica gel TLC (chloroform:methanol = 49:1) to obtain the title compound (2.54 mg, 62%).

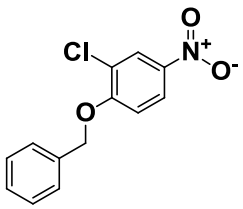
^{1}H-NMR Spectrum ($CDCl_3$) δ (ppm): 1.16 (3H, t, J=7.3 Hz), 1.81-1.96 (4H, m), 2.06-2.20 (2H, m), 2.47-2.65 (3H, m), 3.01-3.08 (3H, m), 3.16 (2H, d, J=11.7 Hz), 5.82 (1H, brs), 6.59-6.65 (1H, m), 6.76 (1H, dd, J=5.7, 2.4 Hz), 7.33 (2H, d, J=8.4 Hz), 7.41 (1H, s), 7.57 (1H, d, J=3.7 Hz), 7.78 (2H, d, J=8.1 Hz), 7.93 (1H, s), 8.20 (1H, d, J=5.5 Hz), 8.60-8.68 (2H, m).

[0319] The starting material 6-cyano-N-methyl-5-((2-(4-(piperidin-4-yl)benzamide)pyridin-4-yl)oxy)-1H-indole-1-carboxamide was synthesized by the following method.

[0320] [Production Example 143-1]

1-(Benzyloxy)-2-chloro-4-nitrobenzene

[Chemical Formula 179]



Commercially available 2-chloro-4-nitrophenol (10 g, 57.6 mmol) and benzyl

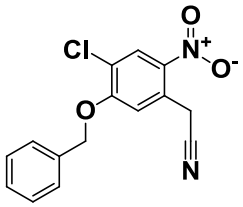
bromide (7.6 mL, 63.9 mmol) were dissolved in N,N-dimethylformamide (100 mL), potassium carbonate (9.56 g, 69.1 mmol) was added, and the mixture was stirred at room temperature for 3.5 hours. Water was added to the reaction mixture, and the mixture was stirred at room temperature for 10 minutes. The deposited solid was filtered out, washed with tert-butyl methyl ether, and dried by through-flow drying to quantitatively obtain the title compound.

^{1}H-NMR Spectrum ($CDCl_3$) δ (ppm): 5.28 (2H, s), 7.03 (1H, d, J=9.2 Hz), 7.33-7.48 (5H, m), 8.12 (1H, dd, J=9.2, 2.9 Hz), 8.32 (1H, d, J=2.6 Hz).

[0321] [Production Example 143-2]

2-(5-(Benzyloxy)-4-chloro-2-nitrophenyl)acetonitrile

[Chemical Formula 180]



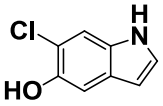
1-(Benzyloxy)-2-chloro-4-nitrobenzene described in Production Example 143-1 (5 g, 19.0 mmol) and 4-chlorophenoxyacetonitrile (3.50 g, 20.9 mmol) were dissolved in N,N-dimethylformamide (35 mL), and then potassium tert-butoxide (2 g, 17.8 mmol) was added at -30 to -40°C under nitrogen atmosphere. Potassium tert-butoxide (2.32 g, 20.7 mmol) was added at the same temperature. The mixture was stirred at the same temperature for 45 minutes, and then 1 M hydrochloric acid was added. After performing extraction with ethyl acetate, the organic layer was washed with water twice and with a saturated saline solution, and then dried over anhydrous magnesium sulfate. After performing filtration, the filtrate was concentrated under vacuum, the resultant residue was dissolved in dichloromethane, and the resultant was purified with silica gel column chromatography (n-heptane:ethyl acetate = 9:1 - 3:1 - 1:1). The mixture fraction was concentrated under vacuum, the resultant residue was dissolved in dichloromethane, and the resultant was purified with silica gel column chromatography (n-heptane:ethyl acetate = 9:1 - 4:1 - 13:7). The resultant solid was washed with diethyl ether to obtain the title compound (1.04 g, 18%).

^{1}H-NMR Spectrum ($CDCl_3$) δ (ppm): 4.24 (2H, s), 5.33 (2H, s), 7.29 (1H, s), 7.34-7.52 (5H, m), 8.34 (1H, s).

[0322] [Production Example 143-3]

6-Chloro-1H-indol-5-ol

[Chemical Formula 181]



2-(5-(Benzyloxy)-4-chloro-2-nitrophenyl)acetonitrile described in Production Example 143-2 (1.04 g, 3.45 mmol) was suspended in ethanol (40 mL), 5% rhodium-carbon (355 mg) was added at room temperature, and the mixture was stirred for 39 hours and 20 minutes under hydrogen atmosphere. Methanol was added to the reaction mixture, and the resultant mixture was filtered with celite. The filtrate was concentrated under vacuum, and the resultant solid was filtered out and washed with ethyl acetate. The filtrate was concentrated, the residue was purified with silica gel column chromatography (n-heptane:ethyl acetate = 9:1 - 3:2), and the target fraction was concentrated under vacuum to obtain a crude product.

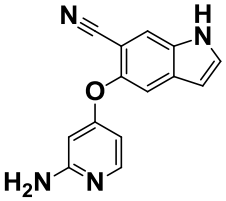
The resultant crude product was dissolved in ethanol (20 mL), 10% palladium-carbon (water content, 50%) (367 mg) was added at room temperature, and the mixture was stirred for 50 minutes under hydrogen atmosphere. Methanol was added to the reaction mixture, and the resultant mixture was filtered with celite. The filtrate was concentrated under vacuum, and the resultant solid was filtered out and washed with dichloromethane. The filtrate was concentrated, the residue was purified with silica gel column chromatography (n-heptane:ethyl acetate = 3:1 - 3:2), and the target fraction was concentrated under vacuum to obtain the title compound (193 mg, 33%).

^{1}H-NMR Spectrum ($CDCl_3$) δ (ppm): 5.25 (1H, s), 6.41-6.47 (1H, m), 7.19 (1H, t, J=2.7 Hz), 7.24 (1H, s), 7.37 (1H, s), 8.02 (1H, brs).

[0323] [Production Example 143-4]

5-((2-Aminopyridin-4-yl)oxy)-1H-indole-6-carbonitrile

[Chemical Formula 182]



6-Chloro-1H-indol-5-ol described in Production Example 143-3 (137 mg, 0.817 mmol) was dissolved in dimethyl sulfoxide (1.0 mL), N-(4-chloropyridin-2-yl)acetamide

described in Production Example 1-5 (181 mg, 1.06 mmol) and potassium tert-butoxide (110 mg, 0.981 mmol) were added at room temperature under nitrogen atmosphere, and the mixture was heated and stirred at 150°C for 6.5 hours. Water and ethyl acetate were added to the reaction mixture for partition. The organic layer was washed with water and a saturated saline solution, dried over anhydrous sodium sulfate, and then filtered. The filtrate was concentrated under vacuum, and the resultant residue was dissolved in dichloromethane, and the resultant was purified with NH silica gel column chromatography (n-heptane:ethyl acetate = 1:1 - 1:3 - 0:1). The target fraction was concentrated under vacuum to obtain a crude product A (96.6 mg).

A part of the resultant crude product A (57.4 mg) was dissolved in methanol (2 mL), a 2 M sodium hydroxide solution (2 mL) was added at room temperature under nitrogen atmosphere, and the mixture was heated and stirred at 65°C for 2 hours. Water and ethyl acetate were added to the reaction mixture for partition. The organic layer was washed with a saturated saline solution, dried over anhydrous sodium sulfate, and then filtered. The filtrate was concentrated under vacuum, and the resultant residue was dissolved in dichloromethane, and the resultant was purified with silica gel column chromatography (n-heptane:ethyl acetate = 1:1 - 0:1). The target fraction was concentrated under vacuum to obtain a crude product B (34.7 mg).

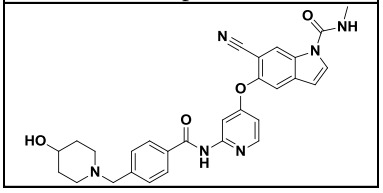
A part of the resultant crude product B (10.4 mg), bis(tri-t-butylphosphine)palladium(0) (8.19 mg, 0.016 mmol) and zinc cyanide (9.4 mg, 0.08 mmol) were dissolved in N,N-dimethylacetamide (500 μL), and the mixture was heated and stirred under nitrogen atmosphere and under irradiation with microwave at 150°C for 1 hour. Ethyl acetate and water were added to the reaction mixture for partition. The organic layer was washed with a saturated saline solution, dried over anhydrous sodium sulfate, and then filtered. The filtrate was concentrated under vacuum, and the resultant residue was dissolved in dichloromethane and the resultant was purified with silica gel TLC (n-heptane:ethyl acetate = 1:3) to obtain the title compound (5.0 mg, 14%).

^{1}H-NMR Spectrum ($CDCl_3$) δ (ppm): 4.57 (2H, brs), 5.97 (1H, d, J=2.2 Hz), 6.31 (1H, dd, J=6.2, 2.2 Hz), 6.56-6.63 (1H, m), 7.41 (1H, s), 7.48 (1H, t, J=3.0 Hz), 7.77 (1H, s), 7.92 (1H, d, J=5.9 Hz), 8.98 (1H, brs).

[0324] According to Examples 1 to 33, the example compound illustrated in Table 14 containing the starting material of Example 143, 6-cyano-N-methyl-5-((2-(4-(piperidin-4-yl)benzamide)pyridin-4-yl)oxy)-1H-indole-1-carbo

xamide was synthesized from 5-((2-aminopyridin-4-yl)oxy)-1H-indole-6-carbonitrile described in Production Example 143-5.

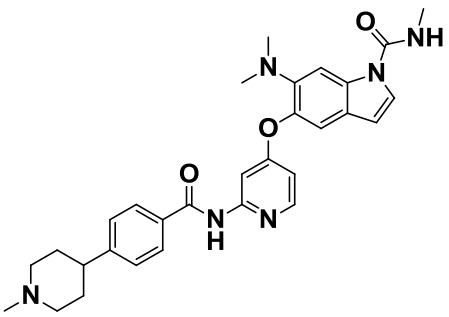
[0325] [Table 14]

Example 144


[0326] [Example 145]

6-(Dimethylamino)-N-methyl-5-((2-(4-(1-methylpiperidin-4-yl)benzamide)pyridin-4-yl)oxy)-1H-indole-1-carboxamide

[Chemical Formula 183]



A 36.5% aqueous formaldehyde solution (7.95 μL, 0.105 mmol), sodium triacetoxyborohydride (14 mg, 0.066 mmol) and acetic acid (3.02 μL, 0.053 mmol) were added to a mixture of 6-(dimethylamino)-N-methyl-5-((2-(4-(piperidin-4-yl)benzamide)pyridin-4-yl)oxy)-1H-indole-1-carboxamide (5.4 mg, 10.5 μmol) and tetrahydrofuran (300 μL) at room temperature, and the mixture was stirred for 2 hours. A saturated aqueous sodium bicarbonate solution and ethyl acetate were added to the reaction mixture for partition. The organic layer was washed with a saturated saline solution, then dried over anhydrous sodium sulfate, and filtered. The solvent was evaporated, and the resultant residue was dissolved in chloroform and the resultant was purified with NH silica gel TLC (ethyl acetate). The resultant solid was washed with diethyl ether to obtain the title compound (3.31 mg, 60%).

^{1}H-NMR Spectrum ($CDCl_3$) δ (ppm): 1.77-1.88 (4H, m), 2.01-2.11 (2H, m), 2.33 (3H, s), 2.48-2.60 (1H, m), 2.79 (6H, s), 2.95-3.03 (2H, m), 3.07 (3H, d, J=4.8 Hz), 5.48 (1H, brs), 6.47 (1H, dd, J=5.9, 2.6 Hz), 6.52 (1H, d, J=3.7 Hz), 7.22-7.25 (2H, m), 7.33 (2H, d, J=8.4

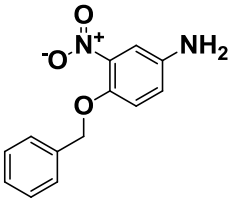
Hz), 7.78-7.84 (2H, m), 7.96 (1H, s), 7.99 (1H, d, J=2.2 Hz), 8.06 (1H, d, J=5.9 Hz), 8.49 (1H, brs).

[0327] The starting material 6-(dimethylamino)-N-methyl-5-((2-(4-(piperidin-4-yl)benzamide)pyridin-4-yl)oxy)-1H-indole-1-carboxamide was synthesized by the following method.

[0328] [Production Example 145-1]

4-(Benzyloxy)-3-nitroaniline

[Chemical Formula 184]



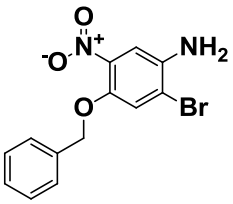
Commercially available 4-amino-2-nitrophenol (5 g, 32.4 mmol) and triphenylphosphine (10.2 g, 38.9 mmol) were dissolved in dichloromethane (200 mL), benzyl alcohol (4.0 mL, 38.7 mmol) was added at 0°C, then a solution of diisopropyl azodicarboxylate (7.87 g, 38.9 mmol) in dichloromethane (50 mL) was added, and the mixture was stirred at room temperature for 21.5 hours. The reaction mixture was concentrated under vacuum, and the residue was dissolved in dichloromethane, and the resultant was purified with NH silica gel column chromatography (n-heptane:ethyl acetate = 4:1 - 2:3), and the target fraction was concentrated under vacuum to obtain the title compound (7.26 g, 92%).

^{1}H-NMR Spectrum (DMSO-d_6) δ (ppm): 5.09 (2H, s), 5.25 (2H, s), 6.81 (1H, dd, J=9.0, 2.7 Hz), 7.01 (1H, d, J=2.9 Hz), 7.13 (1H, d, J=9.2 Hz), 7.25-7.44 (5H, m).

[0329] [Production Example 145-2]

4-(Benzyloxy)-2-bromo-5-nitroaniline

[Chemical Formula 185]



4-(Benzyloxy)-3-nitroaniline described in Production Example 145-1 (2.9 g, 11.9 mmol) was dissolved in dichloromethane (80 mL) and methanol (40 mL), then tetra-N-butylammonium tribromide (5.73 g, 11.9 mmol) was added at room temperature

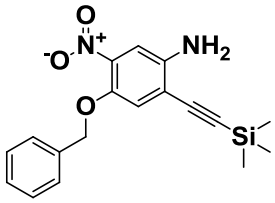
under nitrogen atmosphere, and the mixture was stirred for 50 minutes. The reaction mixture was diluted with an aqueous sodium hydrogen sulfite solution and dichloromethane. The organic layer was washed with a saturated saline solution, and dried over anhydrous magnesium sulfate. After performing filtration, the filtrate was concentrated under vacuum, and the resultant residue was dissolved in dichloromethane, and the resultant was purified with silica gel column chromatography (n-heptane:ethyl acetate = 9:1 - 3:2). The target fraction was concentrated under vacuum to obtain the title compound (2.59 g, 67%) in a purity of 84%.

^{1}H-NMR Spectrum ($CDCl_3$) δ (ppm): 4.06 (2H, brs), 5.12 (2H, s), 7.25 (1H, s), 7.31 (1H, s), 7.32-7.47 (5H, m).

[0330] [Production Example 145-3]

4-(Benzyloxy)-5-nitro-2-((trimethylsilyl)ethynyl)aniline

[Chemical Formula 186]

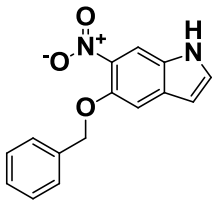


4-(Benzyloxy)-2-bromo-5-nitroaniline described in Production Example 145-2 (2.59 g, 8.01 mmol) was dissolved in tetrahydrofuran (20 mL) and triethylamine (40 mL), then trimethylsilylacetylene (2.26 mL, 16.0 mmol), bis(triphenylphosphine)palladium(II) chloride (291 mg, 0.415 mmol) and copper iodide(I) (164 mg, 0.861 mmol) were added at room temperature, and the mixture was heated and stirred at 60°C under nitrogen atmosphere. Water and ethyl acetate were added to the reaction mixture for partition. The organic layer was washed with a saturated saline solution, and then dried over anhydrous sodium sulfate and filtered. The solvent was evaporated, and the resultant residue was dissolved in dichloromethane, and the resultant was purified with silica gel column chromatography (n-heptane:ethyl acetate = 9:1 - 3:1). The target fraction was concentrated under vacuum to obtain the title compound (2.19 g, 80%).

^{1}H-NMR Spectrum ($CDCl_3$) δ (ppm): 0.28 (9H, s), 4.19 (2H, brs), 5.11 (2H, s), 7.09 (1H, s), 7.21 (1H, s), 7.29-7.48 (5H, m).

[0331] [Production Example 145-4] 5-(Benzyloxy)-6-nitro-1H-indole

[Chemical Formula 187]



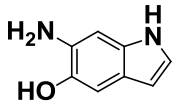
4-(Benzyloxy)-5-nitro-2-(trimethylsilyl)ethynyl)aniline described in Production Example 145-3 (2.19 g, 6.44 mmol) was dissolved in N,N-dimethylformamide (20 mL), copper iodide(I) (1.23 g, 6.44 mmol) was added at room temperature, and the mixture was heated and stirred at 100°C. Water and ethyl acetate were added to the reaction mixture for partition. The aqueous layer was extracted with ethyl acetate, and the combined organic layer was washed with water and a saturated saline solution, then dried over anhydrous magnesium sulfate, and filtered. The solvent was evaporated, and the resultant residue was dissolved in dichloromethane, and the resultant was purified with silica gel column chromatography (n-heptane:ethyl acetate = 4:1 - 7:3 - 3:2). The target fraction was concentrated under vacuum to obtain the title compound (1.23 g, 71%).

^{1}H-NMR Spectrum ($CDCl_3$) δ (ppm): 5.24 (2H, s), 6.49-6.56 (1H, m), 7.27-7.46 (5H, m), 7.49-7.57 (2H, m), 8.06 (1H, d, J=1.1 Hz), 8.39 (1H, brs).

[0332] [Production Example 145-5]

6-Amino-1H-indol-5-ol

[Chemical Formula 188]



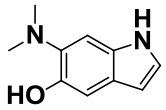
5-(Benzyloxy)-6-nitro-1H-indole described in Production Example 145-4 (400 mg, 1.49 mmol) was suspended in methanol (10 mL) and tetrahydrofuran (5 mL), 10% palladium-carbon (water content, 50%) (159 mg) was added at room temperature, and the mixture was stirred for 50 minutes under hydrogen atmosphere. Methanol was added to the reaction mixture, and the resultant mixture was filtered with celite. The filtrate was concentrated under vacuum, and then the resultant solid was washed with diethyl ether and ethyl acetate to obtain the title compound (168 mg, 76%).

^{1}H-NMR Spectrum (DMSO-d_6) δ (ppm): 4.31 (2H, brs), 6.05 (1H, t, J=2.0 Hz), 6.59 (1H, s), 6.74 (1H, s), 6.88 (1H, t, J=2.8 Hz), 8.48 (1H, brs), 10.25 (1H, brs).

[0333] [Production Example 145-6]

6-(Dimethylamino)-1H-indol-5-ol

[Chemical Formula 189]

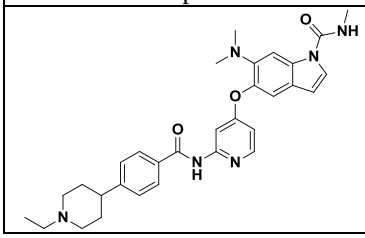
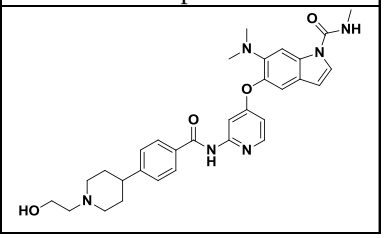


6-Amino-1H-indol-5-ol described in Production Example 145-5 (80 mg, 0.54 mmol) was dissolved in tetrahydrofuran (5.4 mL), a 36.5% aqueous formaldehyde solution (122 μL, 1.62 mmol), sodium triacetoxyborohydride (343 mg, 1.62 mmol) and acetic acid (93 μL, 1.62 mmol) were added at room temperature, and the mixture was stirred for 2 hours. Water and ethyl acetate were added to the reaction mixture for partition. The aqueous layer was extracted with ethyl acetate, and the combined organic layer was washed with a saturated saline solution, then dried over anhydrous magnesium sulfate, and filtered. The solvent was evaporated, and the resultant residue was dissolved in dichloromethane, and the resultant was purified with NH silica gel column chromatography (n-heptane:ethyl acetate = 7:3 - 1:4). The target fraction was concentrated under vacuum to obtain the title compound (62.0 mg, 65%).

^{1}H-NMR Spectrum ($CDCl_3$) δ(ppm): 2.70 (6H, s), 6.42 (1H, ddd, J=3.0, 2.1, 1.1 Hz), 7.11-7.15 (2H, m), 7.21 (1H, s), 7.94 (1H, brs).

[0334] According to Examples 1 to 33, the example compounds illustrated in Table 15 containing the starting material of Example 145, 6-(dimethylamino)-N-methyl-5-((2-(4-(piperidin-4-yl)benzamide)pyridin-4-yl)oxy)-1H-indole-1-carboxamide were synthesized from 6-(dimethylamino)-1H-indol-5-ol described in Production Example 145-6 and N-(4-chloropyridin-2-yl)acetamide described in Production Example 1-5.

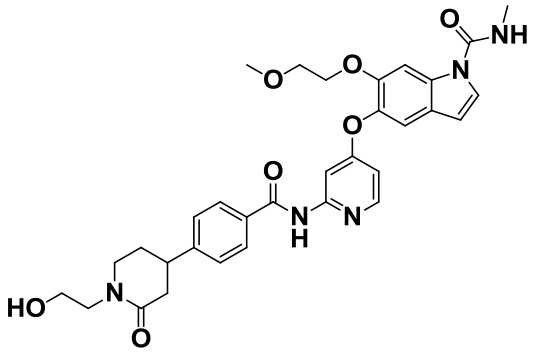
[0335] [Table 15]

Example 146	Example 147
	

[0336] [Example 148]

5-((2-(4-(1-(2-Hydroxyethyl)-2-oxopiperidin-4-yl)benzamide)pyridin-4-yl)oxy)-6-(2-methoxyethoxy)-N-methyl-1H-indole-1-carboxamide

[Chemical Formula 190]



5-((2-Aminopyridin-4-yl)oxy)-6-(2-methoxyethoxy)-N-methyl-1H-indole-1-carboxamide described in Production Example 20-7 (460 mg, 1.29 mmol), 4-(1-(2-((tert-butyldimethylsilyl)oxy)ethyl)-2-oxopiperidin-4-yl)benzoic acid described in Production Example 148-4 (585 mg, 1.55 mmol) and 4-dimethylaminopyridine (315 mg, 2.58 mmol) were dissolved in 1,2-dimethoxyethane (6 mL), triethylamine (360 μL, 2.58 mmol) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (495 mg, 2.58 mmol) were added, and the mixture was stirred at room temperature for 1 hour and then at 55°C for 2 hours. 2 M Hydrochloric acid (5 mL, 10.0 mmol) was added to the reaction mixture, and the mixture was stirred for 3 hours. Ethyl acetate was added to the reaction mixture, the resultant was neutralized with a 2 M sodium hydroxide solution, and then extracted with ethyl acetate. The organic layer was washed with a saturated saline solution, and then the organic layer was dried over anhydrous magnesium sulfate, and filtered. The solvent was evaporated, and the resultant residue was purified with NH silica gel column chromatography (n-heptane:ethyl acetate = 1:1 - 0:1 - ethyl acetate:methanol= 24:1 - 9:1). The target fraction was concentrated under vacuum, then a solid was deposited by using dichloromethane and tert-butyl methyl ether, and the solid was filtered out to obtain the title compound (632 mg, 81%).

^{1}H-NMR Spectrum ($CDCl_3$) δ (ppm): 1.98-2.10 (1H, m), 2.11-2.22 (1H, m), 2.54 (1H, dd, J=17.6, 11.0 Hz), 2.71-2.81 (1H, m), 3.06 (3H, d, J=4.4 Hz), 3.15-3.23 (2H, m), 3.26 (3H, s), 3.39-3.48 (1H, m), 3.49-3.61 (4H, m), 3.63-3.71 (1H, m), 3.84 (2H, d, J=4.8 Hz), 4.08-4.26 (2H, m), 5.60 (1H, brs), 6.55 (1H, d, J=3.3 Hz), 6.62 (1H, dd, J=5.7, 2.4 Hz), 7.26-7.35 (4H, m), 7.85 (2H, d, J=8.4 Hz), 7.91 (1H, d, J=2.2 Hz), 8.02 (1H, s), 8.09 (1H, d, J=5.9 Hz), 8.56 (1H, brs).

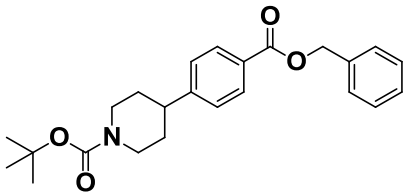
[0337] The starting material 4-(1-(2-((tert-butyldimethylsilyl)oxy)ethyl)-2-oxopiperidin-4-yl)benzoic acid was

synthesized by the following method.

[0338] [Production Example 148-1]

tert-Butyl 4-(4-(benzyloxy)carbonyl)phenyl)piperidin-1-carboxylate

[Chemical Formula 191]



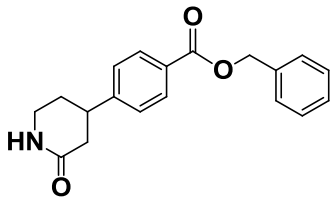
4-(1-(tert-Butoxycarbonyl)piperidin-4-yl)benzoic acid described in Production Example 1-12 (3.0 g, 9.82 mmol) was dissolved in N,N-dimethylformamide (15 mL), then potassium carbonate (1.63 g, 11.8 mmol) and benzyl bromide (1.29 mL, 10.8 mmol) were added, and the mixture was stirred at room temperature for 24 hours. Water and ethyl acetate were added to the reaction mixture for partition. The aqueous layer was extracted with ethyl acetate, and the combined organic layer was washed with a saturated saline solution. The organic layer was dried over anhydrous magnesium sulfate, and filtered. The solvent was evaporated, and the resultant residue was purified with silica gel column chromatography (n-heptane:ethyl acetate = 2:1). The target fraction was concentrated under vacuum to obtain the title compound (3.83 g, 99%).

^{1}H-NMR Spectrum ($CDCl_3$) δ (ppm): 1.48 (9H, s), 1.58-1.70 (2H, m), 1.82 (2H, d, J=12.4 Hz), 2.56-2.96 (3H, m), 4.17-4.39 (2H, m), 5.36 (2H, s), 7.25-7.29 (3H, m), 7.31-7.50 (4H, m), 8.02 (2H, d, J=8.4 Hz).

[0339] [Production Example 148-2]

Benzyl 4-(2-oxopiperidin-4-yl)benzoate

[Chemical Formula 192]



tert-Butyl 4-(4-((benzyloxy)carbonyl)phenyl)piperidin-1-carboxylate described in Production Example 148-1 (3.83 g, 9.68 mmol) was dissolved in ethyl acetate (90 mL), then a ruthenium oxide(IV) hydrate (44.0 mg, 0.29 mmol) dissolved in water (270 mL) and sodium periodate (8.29 g, 38.7 mmol) were added at room temperature, and the mixture was stirred at room temperature for 18 hours. Ethyl acetate was added to the reaction mixture

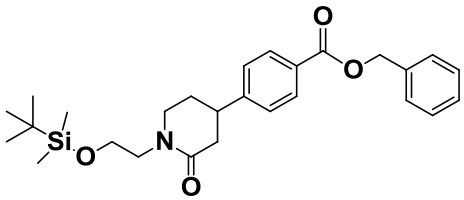
for partition, and then the organic layer was washed with a saturate saline solution. The organic layer was dried over anhydrous magnesium sulfate, and filtered. The solvent was evaporated, the resultant residue was dissolved in dichloromethane (30 mL), then trifluoroacetic acid (15 mL, 202 mmol) was added, and the mixture was stirred at room temperature for 1 hour. The resultant was concentrated under vacuum, and a saturated aqueous sodium carbonate solution was added to the residue. Ethyl acetate was added for partition, and then the organic layer was washed with a saturated saline solution. The organic layer was dried over anhydrous magnesium sulfate, and filtered. The solvent was evaporated, and the residue was washed with diethyl ether to obtain the title compound (2.03 g, 68%).

^{1}H-NMR Spectrum ($CDCl_3$) δ (ppm): 1.88-2.05 (1H, m), 2.06-2.17 (1H, m), 2.41-2.58 (1H, m), 2.64-2.78 (1H, m), 3.10-3.26 (1H, m), 3.33-3.52 (2H, m), 5.37 (2H, s), 5.71-5.83 (1H, m), 7.27-7.50 (7H, m), 8.01-8.10 (2H, m).

[0340] [Production Example 148-3]

Benzyl 4-(1-(2-((tert-butyldimethylsilyl)oxy)ethyl)-2-oxopiperidin-4-yl)benzoate

[Chemical Formula 193]



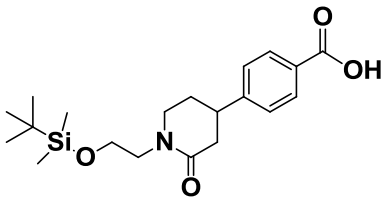
Benzyl 4-(2-oxopiperidin-4-yl)benzoate described in Production Example 148-2 (1.3 g, 4.20 mmol) was dissolved in dimethyl sulfoxide (20 mL), then 50 - 72% oily sodium hydride (218 mg) was added at room temperature under nitrogen atmosphere, and the mixture was stirred at room temperature for 1 hour. Subsequently, tert-butyl(2-iodoethoxy)dimethylsilane (1.92 g, 6.27 mmol) dissolved in dimethyl sulfoxide (10 mL) was added, and the mixture was stirred at room temperature for 20 hours. A saturated aqueous ammonium chloride solution and ethyl acetate were added to the reaction mixture at 0°C for partition. The aqueous layer was extracted with ethyl acetate, and the combined organic layer was washed with a saturated saline solution. The organic layer was dried over anhydrous magnesium sulfate, and filtered. The solvent was evaporated, and the resultant residue was purified with silica gel column chromatography (n-heptane:ethyl acetate = 10:1 - 1:2). The target fraction was concentrated under vacuum to obtain the title compound (920 mg, 47%).

^{1}H-NMR Spectrum ($CDCl_3$) δ (ppm): 0.06 (6H, d, J=1.8 Hz), 0.89 (9H, s), 1.87-2.03 (1H, m), 2.07-2.18 (1H, m), 2.50 (1H, dd, J=17.4, 11.2 Hz), 2.63-2.81 (1H, m), 3.09-3.20 (1H, m), 3.46-3.59 (4H, m), 3.82 (2H, t, J=5.3 Hz), 5.36 (2H, s), 7.27-7.50 (7H, m), 8.01-8.08 (2H, m).

[0341] [Production Example 148-4]

4-(1-(2-((tert-Butyldimethylsilyl)oxy)ethyl)-2-oxopiperidin-4-yl)benzoic acid

[Chemical Formula 194]

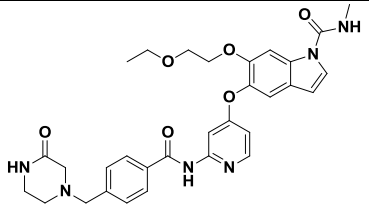


Benzyl 4-(1-(2-((tert-butyldimethylsilyl)oxy)ethyl)-2-oxopiperidin-4-yl)benzoate described in Production Example 148-3 (920 mg, 1.97 mmol) was dissolved in methanol (20 mL), then 10% palladium-carbon (water content, 50%) (209 mg) was added, and the mixture was stirred under hydrogen atmosphere for 3 hours. The inside of the reaction system was substituted with nitrogen, then the catalyst was filtered off with celite, and the resultant was washed with methanol. The filtrate was concentrated under vacuum, and the resultant was purified with silica gel column chromatography (n-heptane:ethyl acetate = 2:1 - 0:1). The target fraction was concentrated under vacuum to obtain the title compound (592 mg, 80%).

^{1}H-NMR Spectrum ($CDCl_3$) δ (ppm): 0.07 (6H, d, J=1.5 Hz), 0.90 (9H, s), 1.96-2.02 (1H, m), 2.10-2.16 (1H, m), 2.52 (1H, dd, J=17.6, 11.0 Hz), 2.72-2.80 (1H, m), 3.10-3.24 (1H, m), 3.47-3.60 (4H, m), 3.83 (2H, t, J=5.5 Hz), 7.31 (2H, d, J=8.1 Hz), 8.06 (2H, d, J=8.4 Hz).

[0342] According to Examples 1 to 33, the example compound illustrated in Table 16 was synthesized from 5-((2-aminopyridin-4-yl)oxy)-6-(2-ethoxyethoxy)-N-methyl-1H-indole-1-carboxamide described in Production Example 24-8.

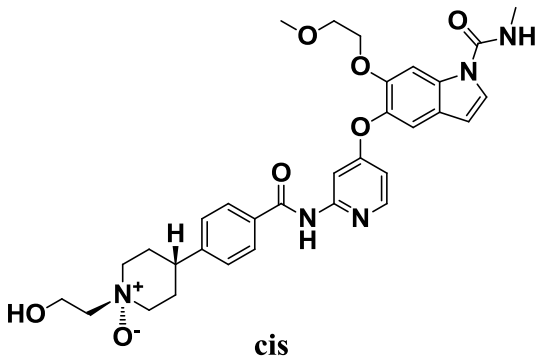
[0343] [Table 16]

Example 149


[0344] [Example 150]

5-((2-(((4-(cis-1-(2-Hydroxyethyl)-1-oxidepiperidin-4-yl)phenyl)carbonyl)amino)pyridin-4-yl)oxy)-6-(2-methoxyethoxy)-N-methyl-1H-indole-1-carboxamide

[Chemical Formula 195]



cis

3-Chloroperoxybenzoic acid (229 mg, 0.864 mmol) (purity: 65%) was added to a mixture of 5-((2-(4-(1-(2-hydroxyethyl)piperidin-4-yl)benzamide)pyridin-4-yl)oxy)-6-(2-methoxyethoxy)-N-methyl-1H-indole-1-carboxamide described in Example 22 (508 mg, 0.864 mmol) and dichloromethane (25 mL) under nitrogen atmosphere, and the mixture was stirred at room temperature for 30 minutes. Ethyl acetate and a 10% aqueous sodium sulfite solution were added to the reaction mixture for partition. The aqueous layer was saturated with sodium chloride, and extracted by using a mixed solvent of ethyl acetate, tetrahydrofuran and methanol. The combined organic layer was dried over anhydrous sodium sulfate, and filtered. The solvent was evaporated, and the resultant residue was dissolved in methanol and dichloromethane, and the resultant was purified with NH silica gel column chromatography (chloroform:methanol = 49:1 - 4:1). The target fraction was concentrated under vacuum, and then the deposited solid was dissolved in ethyl acetate, tetrahydrofuran and methanol. The deposited solid was filtered out and washed with ethyl acetate to obtain

a filtrate. The filtrate was concentrated under vacuum (168 mg), suspended in tetrahydrofuran, ethyl acetate and isopropanol, and the resultant was stirred at 60°C for 20 minutes. The resultant was cooled to room temperature, and the deposited solid was filtered out and washed with ethyl acetate to obtain a filtrate. The filtrate was concentrated under vacuum (62.4 mg), and a part of the filtrate (10.4 mg) was purified with ODS column chromatography (0.5% trifluoroacetic acid/water:acetonitrile = 37:13) to separate it to a cis-form (retention time = 73 - 75 min) and a trans-form (retention time = 65 - 67 min). Buffers were added to these, and after extraction with butanol, the solvents were concentrated under vacuum, and the resultants were purified with ODS column chromatography (methanol:water = 1:9, acetonitrile:water = 1:9, successively eluted with acetonitrile and methanol) to obtain the cis-form of the title compound (1.1 mg) as a high polar component and a low polar component of Example 151.

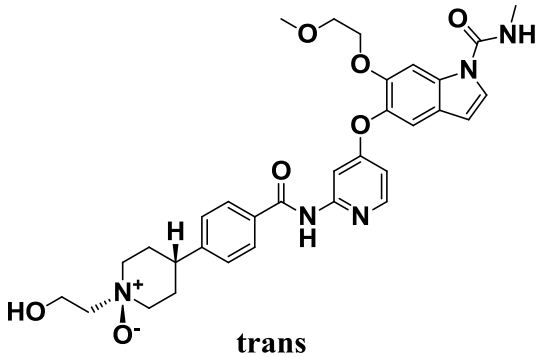
cis-form

^{1}H-NMR Spectrum (600MHz, DMSO-d_6) δ (ppm): 1.68 (2H, d, J=13.0 Hz), 2.32-2.63 (2H, m), 2.72-2.81 (1H, m), 2.85 (3H, d, J=4.2 Hz), 3.06-3.56 (11H, m), 3.86-3.97 (2H, m), 4.03-4.14 (2H, m), 6.63 (1H, d, J=3.5 Hz), 6.67 (1H, dd, J=5.7, 2.4 Hz), 7.37 (2H, d, J=8.2 Hz), 7.45 (1H, s), 7.64-7.72 (1H, m), 7.75-7.82 (1H, m), 7.93 (2H, d, J=8.2 Hz), 8.08 (1H, s), 8.11-8.24 (2H, m), 10.65 (1H, s).

[0345] [Example 151]

5-((2-(((4-(trans-1-(2-Hydroxyethyl)-1-oxidepiperidin-4-yl)phenyl)carbonyl)amino)pyridin-4-yl)oxy)-6-(2-methoxyethoxy)-N-methyl-1H-indole-1-carboxamide

[Chemical Formula 196]



trans

The trans-form (1.3 mg) was obtained as the low polar component of Example 150.

trans-form

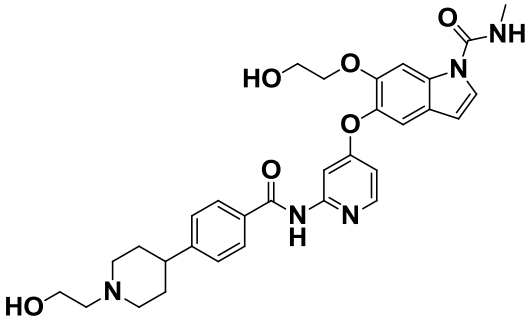
^{1}H-NMR Spectrum (600MHz, DMSO-d_6) δ (ppm): 1.85-2.03 (4H, m), 2.85 (3H, d, J=4.2

Hz), 2.90-3.02 (1H, m), 3.05-3.63 (11H, m), 3.72-3.91 (2H, m), 3.99-4.18 (2H, m), 6.63 (1H, d, J=3.5 Hz), 6.68 (1H, dd, J=5.8, 2.1 Hz), 7.34-7.53 (3H, m), 7.68 (1H, d, J=2.1 Hz), 7.78 (1H, d, J=3.5 Hz), 7.92 (2H, d, J=8.2 Hz), 8.08 (1H, s), 8.12-8.25 (2H, m), 10.65 (1H, s).

[0346] [Example 152]

6-(2-Hydroxyethoxy)-5-((2-(4-(1-(2-hydroxyethyl)piperidin-4-yl)benzamide)pyridin-4-yl)oxy)-N-methyl-1H-indole-1-carboxamide

[Chemical Formula 197]



Boron tribromide (2.55 mL, 2.55 mmol) was added to a mixture of 5-((2-(4-(1-(2-hydroxyethyl)piperidin-4-yl)benzamide)pyridin-4-yl)oxy)-6-(2-methoxyethoxy)-N-methyl-1H-indole-1-carboxamide described in Example 22 (500 mg, 0.851 mmol) and dichloromethane (5 mL) at 0°C under nitrogen atmosphere, and the mixture was stirred at room temperature for 4 hours. The reaction mixture was cooled to 0°C, and then methanol and a saturated aqueous sodium bicarbonate solution were added for partition. The aqueous layer was extracted with dichloromethane, then the organic layers were combined, and the resultant was washed with a saturated saline solution. The organic layer was dried over anhydrous sodium sulfate, and filtered. The solvent was evaporated, and the resultant residue was purified with NH silica gel column chromatography (ethyl acetate:methanol = 1:0 - 5:1). The target fraction was concentrated under vacuum, and the resultant solid was washed with dichloromethane to obtain the title compound (97 mg, 20%).

^{1}H-NMR Spectrum (DMSO-d_6) δ (ppm): 1.58-1.79 (4H, m), 2.00-2.11 (2H, m), 2.41 (2H, t, J=6.4 Hz), 2.52-2.59 (1H, m), 2.85 (3H, d, J=4.4 Hz), 2.97 (2H, d, J=11.7 Hz), 3.46-3.58 (4H, m), 3.96-4.01 (2H, m), 4.37 (1H, t, J=5.3 Hz), 4.72 (1H, t, J=5.5 Hz), 6.63 (1H, d, J=3.5 Hz), 6.66 (1H, m), 7.33 (2H, m), 7.43 (1H, s), 7.70 (1H, d, J=2.2 Hz), 7.78 (1H, d, J=3.7 Hz), 7.85-7.96 (2H, m), 8.10 (1H, s), 8.13-8.26 (2H, m), 10.65 (1H, brs).

[0347] The mass spectra (ESI-MS (m/z)) of the compounds of Examples 34 to 130, Example 132, Example 134, Examples 136 to 139, Example 141, Example 142, Example

144, Example 146, Example 147 and Example 149 are illustrated in Tables 17 and 18.

[0348] [Table 17]

Example No.	ESI-MS (m/z)	Example No.	ESI-MS (m/z)	Example No.	ESI-MS (m/z)
Example 34	536[M+H]$^+$	Example 70	558[M+H]$^+$	Example 106	574[M+H]$^+$
Example 35	536[M+H]$^+$	Example 71	562[M+H]$^+$	Example 107	590[M+H]$^+$
Example 36	549[M+H]$^+$	Example 72	562[M+H]$^+$	Example 108	601[M+H]$^+$
Example 37	549[M+H]$^+$	Example 73	576[M+H]$^+$	Example 109	630[M+H]$^+$
Example 38	536[M+H]$^+$	Example 74	604[M+H]$^+$	Example 110	600[M+H]$^+$
Example 39	572[M+H]$^+$	Example 75	604[M+H]$^+$	Example 111	616[M+H]$^+$
Example 40	542[M+H]$^+$	Example 76	560[M+H]$^+$	Example 112	616[M+H]$^+$
Example 41	574[M+H]$^+$	Example 77	587[M+H]$^+$	Example 113	586[M+H]$^+$
Example 42	574[M+H]$^+$	Example 78	573[M+H]$^+$	Example 114	572[M+H]$^+$
Example 43	544[M+H]$^+$	Example 79	588[M+H]$^+$	Example 115	588[M+H]$^+$
Example 44	548[M+H]$^+$	Example 80	574[M+H]$^+$	Example 116	588[M+H]$^+$
Example 45	548[M+H]$^+$	Example 81	574[M+H]$^+$	Example 117	588[M+H]$^+$
Example 46	532[M+H]$^+$	Example 82	580[M+H]$^+$	Example 118	588[M+H]$^+$
Example 47	514[M+H]$^+$	Example 83	580[M+H]$^+$	Example 119	588[M+H]$^+$
Example 48	544[M+H]$^+$	Example 84	566[M+H]$^+$	Example 120	574[M+H]$^+$
Example 49	500[M+H]$^+$	Example 85	566[M+H]$^+$	Example 121	574[M+H]$^+$
Example 50	530[M+H]$^+$	Example 86	580[M+H]$^+$	Example 122	588[M+H]$^+$
Example 51	530[M+H]$^+$	Example 87	530[M+H]$^+$	Example 123	572[M+H]$^+$
Example 52	516[M+H]$^+$	Example 88	558[M+H]$^+$	Example 124	558[M+H]$^+$
Example 53	516[M+H]$^+$	Example 89	544[M+H]$^+$	Example 125	616[M+H]$^+$
Example 54	558[M+H]$^+$	Example 90	602[M+H]$^+$	Example 126	616[M+H]$^+$
Example 55	573[M+H]$^+$	Example 91	602[M+H]$^+$	Example 127	600[M+H]$^+$
Example 56	544[M+H]$^+$	Example 92	572[M+H]$^+$	Example 128	602[M+H]$^+$
Example 57	514[M+H]$^+$	Example 93	574[M+H]$^+$	Example 129	586[M+H]$^+$
Example 58	586[M+H]$^+$	Example 94	601[M+H]$^+$	Example 130	572[M+H]$^+$
Example 59	556[M+H]$^+$	Example 95	602[M+H]$^+$	Example 132	597[M+H]$^+$
Example 60	572[M+H]$^+$	Example 96	588[M+H]$^+$	Example 134	558[M+H]$^+$
Example 61	572[M+H]$^+$	Example 97	588[M+H]$^+$	Example 136	528[M+H]$^+$
Example 62	583[M+H]$^+$	Example 98	594[M+H]$^+$	Example 137	498[M+H]$^+$
Example 63	558[M+H]$^+$	Example 99	594[M+H]$^+$	Example 138	512[M+H]$^+$
Example 64	528[M+H]$^+$	Example 100	580[M+H]$^+$	Example 139	526[M+H]$^+$
Example 65	544[M+H]$^+$	Example 101	594[M+H]$^+$	Example 141	542[M+H]$^+$
Example 66	586[M+H]$^+$	Example 102	544[M+H]$^+$	Example 142	558[M+H]$^+$

[0349] [Table 18]

Example No.	ESI-MS (m/z)	Example No.	ESI-MS (m/z)	Example No.	ESI-MS (m/z)
Example 67	572[M+H]$^+$	Example 103	572[M+H]$^+$	Example 144	525[M+H]$^+$
Example 68	556[M+H]$^+$	Example 104	588[M+H]$^+$	Example 146	541[M+H]$^+$
Example 69	542[M+H]$^+$	Example 105	574[M+H]$^+$	Example 147	557[M+H]$^+$
				Example 149	587[M+H]$^+$

[0350] [Pharmacological Test Examples]

1. FGFR1 kinase assay

In this assay, the inhibitory activity of a test substance against the tyrosine kinase activity of FGFR1 protein is measured.

[0351] To each well of a flat bottom 96 well white plate (Sumitomo Bakelite Co., Ltd., MS-8496W), 10 μl of a solution of FGFR1 protein (Carna Biosciences, Inc., 08-133) diluted to 1 μg/mL with an assay buffer (20 mM HEPES-NaOH, 0.01% Triton X-100, 2 mM DTT, and 5 mM $MgCl_2$), 10 μL of an assay buffer solution containing CSK-tide substrate (Ana Spec Inc., 63843) in a final concentration of 1000 nM and ATP (Promega Corporation, V9102) in a final concentration of 58.3 μM, and 5 μl of a test substance diluted with the assay buffer were added, and the reaction was performed at room temperature for 1 hour. For measuring kinase activity, ADP-Glo (TM) Kinase Assay (Promega Corporation, V9102) was used. After the reaction, 25 μL of ADP-Glo reagent was added to each well of the plate, and the reaction was performed at room temperature for 40 minutes, the kinase reaction was stopped, and the remaining ATP was depleted. The kinase detection reagent was further added, and the reaction was performed at room temperature for 40 minutes, so as to cause conversion from ADP to ATP, a luciferase/luciferin coupling reaction and a luminous reaction by ATP. The amount of luminescence in each well was measured by Envision (TM) (PerkinElmer Co., Ltd.) for evaluating the enzyme activity. Assuming that the amount of luminescence attained by adding the kinase protein without adding the test substance was 100% and that the amount of luminescence attained by adding neither the test substance nor the kinase protein was 0%, a luminescence amount ratio attained in the presence of the test substance was obtained. On the basis of this luminescence amount ratio, the concentration of the test substance necessary for inhibiting the kinase activity by 50% (i.e., an IC_{50} value) was calculated, and IC_{50} values of respective test substances thus calculated are shown in Tables 19, 20 and 21.

[0352] <Data of FGFR1 cell-free kinase inhibitory action>

[Table 19]

Example No.	FGFR1 (IC_{50} (nM))	Example No.	FGFR1 (IC_{50} (nM))
Example 1	9.8	Example 66	10.3
Example 2	10.1	Example 67	11.2
Example 3	7.9	Example 68	11.7
Example 4	7.2	Example 69	12.4
Example 5	12.0	Example 70	32.0
Example 6	11.0	Example 71	18.4
Example 7	11.6	Example 72	22.5
Example 8	13.2	Example 73	24.2
Example 9	30.0	Example 74	8.5
Example 10	37.7	Example 75	8.0
Example 11	18.0	Example 76	10.4
Example 12	19.9	Example 77	19.1
Example 13	31.2	Example 78	20.2
Example 14	10.9	Example 79	8.5
Example 15	12.5	Example 80	8.5
Example 16	11.5	Example 81	7.0
Example 17	14.6	Example 82	6.4
Example 18	12.7	Example 83	10.2
Example 19	13.5	Example 84	8.6
Example 20	5.6	Example 85	6.7
Example 21	5.7	Example 86	6.5
Example 22	5.8	Example 87	7.1
Example 23	5.3	Example 88	6.7
Example 24	4.4	Example 89	5.7
Example 25	5.2	Example 90	7.0
Example 26	6.3	Example 91	5.0
Example 27	8.0	Example 92	5.4
Example 28	11.2	Example 93	14.9
Example 29	10.0	Example 94	10.6
Example 30	14.5	Example 95	5.7
Example 31	6.5	Example 96	11.0
Example 32	10.9	Example 97	7.2
Example 33	8.5	Example 98	6.6

[0353] [Table 20]

Example No.	FGFR1 (IC_{50} (nM))	Example No.	FGFR1 (IC_{50} (nM))
Example 34	12.3	Example 99	5.1
Example 35	10.8	Example 100	5.4
Example 36	11.2	Example 101	5.6
Example 37	10.9	Example 102	6.5
Example 38	10.5	Example 103	5.0
Example 39	7.9	Example 104	12.1
Example 40	8.9	Example 105	8.6
Example 41	10.6	Example 106	8.9
Example 42	13.0	Example 107	16.1
Example 43	12.5	Example 108	11.5
Example 44	22.8	Example 109	3.9
Example 45	26.5	Example 110	5.4
Example 46	24.1	Example 111	4.2
Example 47	12.8	Example 112	3.4
Example 48	12.1	Example 113	4.2
Example 49	11.7	Example 114	3.7
Example 50	32.3	Example 115	10.3
Example 51	18.3	Example 116	22.3
Example 52	23.7	Example 117	10.7
Example 53	23.4	Example 118	7.0
Example 54	5.5	Example 119	11.5
Example 55	34.1	Example 120	16.6
Example 56	24.2	Example 121	16.1
Example 57	10.0	Example 122	17.9
Example 58	9.8	Example 123	8.9
Example 59	8.7	Example 124	8.5
Example 60	9.6	Example 125	5.2
Example 61	8.9	Example 126	6.4
Example 62	18.8	Example 127	7.1
Example 63	10.0	Example 128	6.1
Example 64	11.8	Example 129	7.0
Example 65	33.8	Example 130	6.2

[0354] [Table 21]

Example No.	FGFR1 (IC_{50}(nM))	Example No.	FGFR1 (IC_{50}(nM))
Example 131	18.1	Example 142	12.1
Example 132	44.5	Example 143	19.2
Example 133	9.0	Example 144	47.7
Example 134	12.0	Example 145	45.6
Example 135	12.3	Example 146	42.9
Example 136	34.2	Example 147	48.3
Example 137	17.5	Example 148	13.2
Example 138	10.9	Example 149	20.5
Example 139	15.7	Example 150	10.7
Example 141	49.1	Example 151	8.0
		Example 152	11.0

[0355] 2. FGFR2 kinase assay

In this assay, the inhibitory activity of a test substance against the tyrosine kinase activity of FGFR2 protein is measured.

[0356] To each well of a flat bottom 96 well white plate (Sumitomo Bakelite Co., Ltd., MS-8496W), 10 μl of a solution of FGFR2 protein (Carna Biosciences, Inc., 08-134) diluted to 1 μg/mL with an assay buffer (20 mM HEPES-NaOH, 0.01% Triton X-100, 2 mM DTT, and 5 mM $MgCl_2$), 10 μL of an assay buffer solution containing CSK-tide substrate (Ana Spec Inc., 63843) in a final concentration of 1000 nM and ATP (Promega Corporation, V9102) in a final concentration of 35 μM, and 5 μl of a test substance diluted with the assay buffer were added, and the reaction was performed at room temperature for 1 hour. For measuring kinase activity, ADP-Glo (TM) Kinase Assay (Promega Corporation, V9102) was used. After the reaction, 25 μL of ADP-Glo reagent was added to each well of the plate, and the reaction was performed at room temperature for 40 minutes, the kinase reaction was stopped, and the remaining ATP was depleted. The kinase detection reagent was further added, and the reaction was performed at room temperature for 40 minutes, so as to cause conversion from ADP to ATP, a luciferase/luciferin coupling reaction and a luminous reaction by ATP. The amount of luminescence in each well was measured by Envision (TM) (PerkinElmer Co., Ltd.) for evaluating the enzyme activity. Assuming that the amount of luminescence attained by adding the kinase protein without adding the test substance was 100% and that the amount of luminescence attained by adding neither the test substance nor the kinase protein was 0%, a luminescence amount ratio attained in the presence of the test substance was obtained. On the basis of this luminescence amount ratio, the concentration

of the test substance necessary for inhibiting the kinase activity by 50% (i.e., an IC_{50} value) was calculated, and IC_{50} values of respective test substances thus calculated are shown in Table 22.

[0357] <Data of FGFR2 cell-free kinase inhibitory action>

[Table 22]

Example No.	FGFR2 (IC_{50} (nM))
Example 2	6.4
Example 21	5.1
Example 22	4.5

[0358] 3. FGFR3 kinase assay

In this assay, the inhibitory activity of a test substance against the tyrosine kinase activity of FGFR3 protein is measured.

[0359] To each well of a flat bottom 96 well white plate (Sumitomo Bakelite Co., Ltd., MS-8496W), 10 μl of a solution of FGFR3 protein (Carna Biosciences, Inc., 08-135) diluted to 1 μg/mL with an assay buffer (20 mM HEPES-NaOH, 0.01% Triton X-100, 2 mM DTT, and 5 mM $MgCl_2$), 10 μL of an assay buffer solution containing CSK-tide substrate (Ana Spec Inc., 63843) in a final concentration of 1000 nM and ATP (Promega Corporation, V9102) in a final concentration of 16.7 μM, and 5 μl of a test substance diluted with the assay buffer were added, and the reaction was performed at room temperature for 2 hours. For measuring kinase activity, ADP-Glo (TM) Kinase Assay (Promega Corporation, V9102) was used. After the reaction, 25 μL of ADP-Glo reagent was added to each well of the plate, and the reaction was performed at room temperature for 40 minutes, the kinase reaction was stopped, and the remaining ATP was depleted. The kinase detection reagent was further added, and the reaction was performed at room temperature for 40 minutes, so as to cause conversion from ADP to ATP, a luciferase/luciferin coupling reaction and a luminous reaction by ATP. The amount of luminescence in each well was measured by Envision (TM) (PerkinElmer Co., Ltd.) for evaluating the enzyme activity. Assuming that the amount of luminescence attained by adding the kinase protein without adding the test substance was 100% and that the amount of luminescence attained by adding neither the test substance nor the kinase protein was 0%, a luminescence amount ratio attained in the presence of the test substance was obtained. On the basis of this luminescence amount ratio, the concentration of the test substance necessary for inhibiting the kinase activity by 50% (i.e.,

an IC_{50} value) was calculated, and IC_{50} values of respective test substances thus calculated are shown in Table 23.

[0360] <Data of FGFR3 cell-free kinase inhibitory action>

[Table 23]

Example No.	FGFR3 (IC_{50} (nM))
Example 2	7.9
Example 21	6.0
Example 22	5.4

[0361] 4. FGFR4 kinase assay

In this assay, the inhibitory activity of a test substance against the tyrosine kinase activity of FGFR4 protein is measured.

[0362] To each well of a flat bottom 96 well white plate (Sumitomo Bakelite Co., Ltd., MS-8496W), 10 μl of a solution of FGFR4 protein (Carna Biosciences, Inc., 08-136) diluted to 1 μg/mL with an assay buffer (20 mM HEPES-NaOH, 0.01% Triton X-100, 2 mM DTT, 5 mM $MgCl_2$ and 2 mM $MnCl_2$), 10 μL of an assay buffer solution containing CSK-tide substrate (Ana Spec Inc., 63843) in a final concentration of 1000 nM and ATP (Promega Corporation, V9102) in a final concentration of 75 μM, and 5 μl of a test substance diluted with the assay buffer were added, and the reaction was performed at room temperature for 2 hours. For measuring kinase activity, ADP-Glo (TM) Kinase Assay (Promega Corporation, V9102) was used. After the reaction, 25 μL of ADP-Glo reagent was added to each well of the plate, and the reaction was performed at room temperature for 40 minutes, the kinase reaction was stopped, and the remaining ATP was depleted. The kinase detection reagent was further added, and the reaction was performed at room temperature for 40 minutes, so as to cause conversion from ADP to ATP, a luciferase/luciferin coupling reaction and a luminous reaction by ATP. The amount of luminescence in each well was measured by Envision (TM) (PerkinElmer Co., Ltd.) for evaluating the enzyme activity. Assuming that the amount of luminescence attained by adding the kinase protein without adding the test substance was 100% and that the amount of luminescence attained by adding neither the test substance nor the kinase protein was 0%, a luminescence amount ratio attained in the presence of the test substance was obtained. On the basis of this luminescence amount ratio, the concentration of the test substance necessary for inhibiting the kinase activity by 50% (i.e., an IC_{50} value) was calculated, and IC_{50} values of respective test substances thus calculated

are shown in Table 24.

[0363] <Data of FGFR4 cell-free kinase inhibitory action>

[Table 24]

Example No.	FGFR4 (IC_{50} (nM))
Example 2	651.1
Example 21	683.3
Example 22	644.5

[0364] 5. SNU-16 growth inhibition assay

In this assay, the growth inhibitory activity of a test substance in a human stomach cancer cell line having FGFR2 gene amplification is measured.

[0365] It has been reported that a human stomach cancer cell line SNU-16 (ATCC Number CRL-5974) has FGFR2 gene amplification (Cancer Res. 2008. 68: 2340-2348). SNU-16 cells were maintenance-cultured in a 5% CO_2 incubator (37°C) by using an RPMI-1640 (Wako Pure Chemical Industries, Ltd., 187-02021) medium containing 10% FBS and penicillin/streptomycin (Wako Pure Chemical Industries, Ltd., 168-23191). To each well of a 96 well plate (Becton, Dickinson and Company, 35-3075), 150 μL of a SNU-16 cell suspension adjusted to a concentration of 1 x 10^4 cells/mL by using an RPMI-1640 medium containing 10% FBS was added, and the resultant was cultured overnight in a 5% CO_2 incubator (37°C). On the next day, 50 μL of a test substance diluted with an RPMI-1640 medium containing 10% FBS was added to each well, and the resultant was cultured for 3 days in a 5% CO_2 incubator (37°C). Ten μL of Cell Counting Kit-8 (Dojindo Laboratories, CK04) was added to each well, and the resultant was cultured for 1 to 2 hours in a 5% CO_2 incubator (37°C) to cause a color reaction. ENVISION (TM) (PerkinElmer Co., Ltd.) was used for measuring absorbance at 450 nm. Assuming that the absorbance attained without adding the test substance was 100% and that the absorbance attained in a well containing no cells was 0%, an absorbance ratio attained in the presence of the test substance was obtained. The concentration of the test substance necessary for inhibiting the cell growth by 50% (i.e., an IC_{50} value) was calculated, and IC_{50} values of respective test substances thus calculated are shown in Tables 25, 26 and 27.

[0366] <Data of evaluation of SNU-16 growth inhibitory action>

[Table 25]

Example No.	SNU-16 (IC_{50} (nM))	Example No.	SNU-16 (IC_{50} (nM))
Example 1	7.5	Example 66	16.1
Example 2	6.2	Example 67	17.6
Example 3	7.7	Example 68	20.0
Example 4	6.9	Example 69	17.5
Example 5	13.4	Example 70	22.4
Example 6	9.1	Example 71	17.0
Example 7	9.6	Example 72	17.1
Example 8	15.4	Example 73	17.4
Example 9	24.0	Example 74	8.4
Example 10	28.7	Example 75	7.3
Example 11	14.5	Example 76	7.5
Example 12	13.0	Example 77	9.6
Example 13	10.9	Example 78	6.2
Example 14	9.5	Example 79	4.6
Example 15	9.7	Example 80	3.8
Example 16	12.2	Example 81	3.8
Example 17	17.7	Example 82	6.2
Example 18	13.9	Example 83	10.2
Example 19	14.1	Example 84	6.2
Example 20	7.5	Example 85	6.9
Example 21	4.2	Example 86	6.2
Example 22	3.0	Example 87	3.9
Example 23	6.5	Example 88	6.9
Example 24	6.2	Example 89	6.5
Example 25	3.8	Example 90	6.1
Example 26	5.6	Example 91	5.3
Example 27	6.2	Example 92	5.8
Example 28	7.3	Example 93	17.6
Example 29	8.8	Example 94	7.9
Example 30	14.5	Example 95	5.1
Example 31	4.7	Example 96	6.4
Example 32	6.8	Example 97	3.6
Example 33	8.1	Example 98	6.3

[0367] [Table 26]

Example No.	SNU-16 (IC_{50} (nM))	Example No.	SNU-16 (IC_{50} (nM))
Example 34	14.0	Example 99	6.3
Example 35	9.8	Example 100	5.8
Example 36	11.0	Example 101	6.8
Example 37	9.4	Example 102	3.7
Example 38	8.0	Example 103	5.4
Example 39	7.8	Example 104	13.7
Example 40	8.3	Example 105	7.8
Example 41	9.3	Example 106	9.0
Example 42	14.1	Example 107	22.0
Example 43	11.8	Example 108	14.7
Example 44	16.3	Example 109	6.7
Example 45	15.5	Example 110	5.8
Example 46	17.4	Example 111	5.1
Example 47	13.1	Example 112	3.8
Example 48	11.7	Example 113	5.7
Example 49	9.6	Example 114	4.7
Example 50	16.6	Example 115	11.4
Example 51	12.5	Example 116	22.6
Example 52	14.4	Example 117	16.6
Example 53	14.5	Example 118	8.6
Example 54	6.4	Example 119	11.9
Example 55	20.8	Example 120	16.7
Example 56	15.0	Example 121	14.9
Example 57	7.6	Example 122	11.3
Example 58	10.0	Example 123	8.5
Example 59	14.5	Example 124	8.9
Example 60	14.7	Example 125	7.2
Example 61	10.7	Example 126	6.6
Example 62	27.4	Example 127	7.1
Example 63	9.6	Example 128	6.4
Example 64	10.3	Example 129	7.7
Example 65	23.6	Example 130	6.8

[0368] [Table 27]

Example No.	SNU-16 (IC_{50}(nM))	Example No.	SNU-16 (IC_{50}(nM))
Example 131	17.9	Example 142	9.6
Example 132	48.6	Example 143	17.1
Example 133	7.1	Example 144	45.6
Example 134	16.2	Example 145	34.3
Example 135	17.9	Example 146	42.0
Example 136	44.8	Example 147	37.6
Example 137	18.7	Example 148	8.6
Example 138	17.2	Example 149	18.4
Example 139	18.2	Example 150	33.0
Example 141	24.8	Example 151	48.0
		Example 152	5.9

[0369] 6. HUVEC growth inhibition assay

In this assay, the inhibitory activity of a test substance against the growth of vascular endothelial cells induced by VEGF is measured.

[0370] Normal human umbilical vein endothelial cells (HUVEC) were isolated by a reported method (Shin Seikagaku Jikken Koza "Saibo Baiyo Gijutsu" (New Lectures on Biochemical Experiments "Cell Culture Techniques" (in Japanese), p. 197-202). The cells were cultured to be confluent by using an EGM-2 medium (LONZA Inc., CC-3162) in a 5% CO_2 incubator (37°C). To each well of a 96 well plate (Becton, Dickinson and Company, 35-3075), 100 μl of a HUVEC cell suspension, which had been adjusted to a concentration of 1.5 x 10^4 cells/mL by using an EGM-2 medium containing 2% fetal bovine serum (FBS: Cell Culture Technologies, CC3008-504), was added, and the resultant was cultured overnight in a 5% CO_2 incubator (37°C). On the next day, a test substance diluted with an EGM-2 medium containing 2% FBS, and 50 μL of VEGF (R & D Systems, 293-VE-010), which had been adjusted to a final concentration of 10 ng/mL by using an EGM-2 medium containing 2% FBS, were added to each well, and the resultant was cultured for 3 days in a 5% CO_2 incubator (37°C). Twenty μL of Cell Counting Kit-8 (Dojindo Laboratories, CK04) was added to each well, and the resultant was cultured for 3 to 4 hours in a 5% CO_2 incubator (37°C) to cause a color reaction. ENVISION (TM) (PerkinElmer Co., Ltd.) was used for measuring absorbance at 450 nm. Assuming that the absorbance attained without adding the test substance but with VEGF added was 100% and that the absorbance attained with neither the test substance nor VEGF added was 0%, an absorbance ratio attained in the presence of the test substance was obtained. On the basis of the absorbance ratio, the

concentration of the test substance necessary for inhibiting the HUVEC growth by 50% in the presence of VEGF (i.e., an IC_{50} value) was calculated, and IC_{50} values of respective test substances thus calculated are shown in Tables 28, 29 and 30.

[0371] <Data of evaluation of HUVEC growth inhibitory action>

[Table 28]

Example No.	HUVEC (IC_{50} (nM))	Example No.	HUVEC (IC_{50} (nM))
Example 1	98.7	Example 66	203.4
Example 2	130.5	Example 67	223.3
Example 3	95.0	Example 68	255.6
Example 4	93.0	Example 69	214.2
Example 5	386.7	Example 70	609.9
Example 6	180.1	Example 71	647.8
Example 7	205.3	Example 72	681.4
Example 8	139.9	Example 73	702.8
Example 9	645.8	Example 74	198.0
Example 10	350.2	Example 75	211.1
Example 11	131.5	Example 76	247.5
Example 12	141.2	Example 77	1029.4
Example 13	396.5	Example 78	835.4
Example 14	169.0	Example 79	88.5
Example 15	168.3	Example 80	181.5
Example 16	165.3	Example 81	126.2
Example 17	292.8	Example 82	263.7
Example 18	179.7	Example 83	309.5
Example 19	151.1	Example 84	255.3
Example 20	459.3	Example 85	235.3
Example 21	225.0	Example 86	250.3
Example 22	189.5	Example 87	259.4
Example 23	300.4	Example 88	357.8
Example 24	237.2	Example 89	416.2
Example 25	191.0	Example 90	203.1
Example 26	258.1	Example 91	191.1
Example 27	217.8	Example 92	182.2
Example 28	663.7	Example 93	886.9
Example 29	600.1	Example 94	606.8
Example 30	565.5	Example 95	116.4
Example 31	186.3	Example 96	179.2
Example 32	203.3	Example 97	158.7
Example 33	273.6	Example 98	228.3

[0372] [Table 29]

Example No.	HUVEC (IC_{50} (nM))	Example No.	HUVEC (IC_{50} (nM))
Example 34	194.8	Example 99	224.4
Example 35	139.1	Example 100	207.1
Example 36	135.7	Example 101	181.6
Example 37	79.1	Example 102	226.4
Example 38	137.3	Example 103	295.5
Example 39	124.1	Example 104	599.6
Example 40	162.3	Example 105	687.3
Example 41	178.8	Example 106	726.4
Example 42	183.9	Example 107	906.7
Example 43	165.6	Example 108	362.8
Example 44	392.4	Example 109	186.5
Example 45	379.4	Example 110	233.7
Example 46	402.3	Example 111	195.0
Example 47	174.0	Example 112	201.7
Example 48	77.8	Example 113	195.9
Example 49	162.8	Example 114	201.4
Example 50	393.6	Example 115	615.6
Example 51	410.1	Example 116	520.1
Example 52	388.3	Example 117	534.0
Example 53	400.6	Example 118	183.4
Example 54	86.7	Example 119	241.7
Example 55	201.4	Example 120	457.1
Example 56	96.8	Example 121	517.9
Example 57	126.9	Example 122	494.3
Example 58	251.6	Example 123	156.1
Example 59	252.7	Example 124	196.7
Example 60	178.1	Example 125	202.8
Example 61	181.9	Example 126	197.1
Example 62	222.9	Example 127	226.2
Example 63	170.4	Example 128	216.7
Example 64	175.4	Example 129	248.5
Example 65	575.0	Example 130	253.8

[0373] [Table 30]

Example No.	HUVEC (IC_{50}(nM))	Example No.	HUVEC (IC_{50}(nM))
Example 131	162.7	Example 142	96.4
Example 132	221.8	Example 143	336.3
Example 133	121.5	Example 144	855.5
Example 134	165.8	Example 145	719.8
Example 135	82.3	Example 146	657.1
Example 136	190.3	Example 147	828.7
Example 137	114.2	Example 148	203.4
Example 138	81.7	Example 149	882.9
Example 139	115.8	Example 150	1201.7
Example 141	383.2	Example 151	1438.2
		Example 152	126.2

[0374] 7. NCI-H1581 growth inhibition assay

In this assay, the growth inhibitory activity of a test substance in a human lung cancer cell line having FGFR1 gene amplification is measured.

[0375] It has been reported that a human lung cancer cell line of NCI-H1581 (ATCC Number CRL-5878) has FGFR1 gene amplification (PLoS One, 2011; 6: e20351, Sci Transl Med 2010; 2: 62ra93). NCI-H1581 cells were maintenance-cultured in a 5% CO_2 incubator (37°C) by using an RPMI-1640 medium containing 10% FBS and penicillin/streptomycin. To each well of a 96 well plate (Becton, Dickinson and Company, 35-3075), 150 μL of a NCI-H1581 cell suspension adjusted to a concentration of 1.3×10^4 cells/mL by using an RPMI-1640 medium containing 10% FBS was added, and the resultant was cultured overnight in a 5% CO_2 incubator (37°C). On the next day, 50 μl of a test substance diluted with an RPMI-1640 medium containing 10% FBS was added to each well, and the resultant was cultured for 3 days in a 5% CO_2 incubator (37°C). Ten μL of Cell Counting Kit-8 (Dojindo Laboratories, CK04) was added to each well, and the resultant was cultured for 2 to 3 hours in a 5% CO_2 incubator (37°C) to cause a color reaction. ENVISION (TM) (PerkinElmer Co., Ltd.) was used for measuring absorbance at 450 nm. Assuming that the absorbance attained without adding the test substance was 100% and that the absorbance attained in a well containing no cells was 0%, an absorbance ratio attained in the presence of the test substance was obtained. The concentration of each test substance necessary for inhibiting the cell growth by 50% (i.e., an IC_{50} value) was calculated, and IC_{50} values of respective test substances thus calculated are shown in Table 31.

[0376] <Data of evaluation of NCI-H1581 growth inhibitory action>

[Table 31]

	NCI-H1581 (IC_{50} (nM))
Example 2	8.5
Example 3	7.6
Example 4	9.4
Example 9	18.1
Example 16	18.4
Example 21	4.5
Example 22	4.4

[0377] 8. Antitumor effect in mouse model having SNU-16 subcutaneously implanted

Cells of a human stomach cancer cell line SNU-16, which had been cultured in an RPMI-1640 medium containing 10% FBS and penicillin/streptomycin, were prepared in a concentration of 1 x 10^8 cells/mL by using Hanks' Balanced Salt Solution (GIBCO #24020), and the resultant was mixed with MATRIGEL (BD Biosciences, Cat# 354234) in a ratio of 1:1 to prepare a cell suspension in a concentration of 5 x 10^7 cells/ml. The suspension was implanted in a volume of 100 μL into a subcutaneous part of a right flank of each of nude mice (BALB/cAJcl-nu/nu, female, Clea Japan Inc.) of 6 to 7 weeks old. Seven days after the implantation, the shortest diameter and the longest diameter of a tumor thus caused in each mouse were measured by using an electronic digital caliper (Digimatic TM caliper, Mitutoyo Corporation), so as to calculate the volume of the tumor in accordance with the following calculation formula:

Tumor volume (mm^3) = Longest diameter (mm) × Shortest diameter (mm) × Shortest diameter (mm) / 2

On the basis of the volumes of tumors obtained on the first day of administration, the mice were grouped such that averages of the tumor volumes were substantially equal among the groups. Each test substance was dissolved in DMSO, Tween 80 was added thereto to prepare a solution in a 10-fold concentration and the thus prepared solution was frozen for storage. Immediately before the administration, a 5% glucose solution was added thereto to obtain a final administration solution (in which a ratio in % among DMSO, Tween 80 and the 5% glucose solution was 3.5:6.5:90). Each evaluation sample was orally administered at a dose of 20 mL/kg once a day continuously for 11 days, and in a control group, an administration solvent was orally administered under the same conditions. Incidentally, the experiment was conducted on groups each consisting of 5 mice.

With respect to each of the control group and test substance administration groups, a ratio of the weight measured on the final day to the weight measured on the first day (relative body weight: RBW) was calculated. If a ratio of the RBW of the test substance administration group/the RBW of the control group is 0.9 or more, the corresponding test substance administration group was determined as a safely administrable group. In the test substance administration group thus determined as safely administrable, a ratio of the tumor volume attained after the administration of the test substance to the tumor volume of the control group obtained on the final day (T/C) (%) was calculated, and such ratios of respective test substances thus calculated are shown in Table 32.

[0378] <Data of evaluation of antitumor effect in model having SNU-16 subcutaneously implanted>

[Table 32]

Example No.	Dose (mg/kg)	T/C (%)
Example 2	6.25	51
	12.5	28
	25	18
Example 3	6.25	45
	12.5	27
	25	19
Example 4	6.25	40
	12.5	27
	25	15
Example 9	25	55
	50	39
	100	30
Example 16	6.25	39
	12.5	21
	25	15
Example 21	6.25	49
	12.5	26
	25	16
	50	7
Example 22	6.25	49
	12.5	26
	25	17
	50	18
Example 25	6.25	31
	12.5	23
	25	14
	50	12
Example 26	6.25	45
	12.5	36
	25	22
	50	27

[0379] 9. Antitumor effect in mouse model having NCI-H1581 subcutaneously implanted

Cells of a human lung cancer cell line NCI-H1581 (ATCC number CRL-5878), which had been cultured in an RPMI-1640 medium containing 10% FBS, penicillin and streptomycin, were prepared as a cell suspension in a concentration of 1×10^8 cells/mL by using Hanks' Balanced Salt Solution (GIBCO #24020). Furthermore, the resultant suspension was mixed with MATRIGEL in a ratio of 1:1 to prepare a cell suspension in a concentration of 5×10^7 cells/mL. The cell suspension was implanted in a volume of 100 μL into a subcutaneous part of a right flank of each of nude mice (BALB/cAJcl-nu/nu,

female, Clea Japan Inc.) of 6 to 7 weeks old. Ten to 11 days after the implantation, the shortest diameter and the longest diameter of a tumor thus caused in each mouse were measured by using an electronic digital caliper (Digimatic TM caliper, Mitutoyo Corporation), so as to calculate the volume of the tumor in accordance with the following calculation formula:

Tumor volume (mm^3) = Longest diameter (mm) × Shortest diameter (mm) × Shortest diameter (mm) / 2

On the basis of the volumes of tumors obtained on the first day of administration, the nude mice were grouped such that averages of the tumor volumes were substantially equal among the groups. Each test substance was dissolved in DMSO, Tween 80 was added thereto to prepare a storage solution in a 10-fold concentration of an evaluation sample, and the thus prepared solution was frozen for storage until use. Immediately before the administration, the storage solution was diluted with a 5% glucose solution to obtain an evaluation sample (in which a ratio in % among DMSO, Tween 80 and the 5% glucose solution was 3.5:6.5:90). In a test substance administration group, the evaluation sample was orally administered at a dose of 0.4 mL per 20 g of the weight once a day continuously for 11 days, and in a control group, an administration solvent was orally administered under the same conditions. Incidentally, the experiment was conducted on groups each consisting of 5 mice.

With respect to each of the control group and test substance administration groups, a ratio of the weight measured on the final day to the weight measured on the first day (relative body weight: RBW) was calculated. If a ratio of the RBW of the test substance administration group/the RBW of the control group is 0.9 or more, the corresponding test substance administration group was determined as a safely administrable group. In the test substance administration group thus determined as safely administrable, a ratio of the tumor volume attained after the administration of the test substance to the tumor volume of the control group obtained on the final day (T/C) (%) was calculated, and such ratios of respective test substances thus calculated are shown in Table 33.

[0380] <Data of evaluation of antitumor effect in model having NCI-H1581 subcutaneously implanted>

[Table 33]

Example No.	Dose (mg/kg)	T/C (%)
Example 2	6.25	36
	12.5	19
	25	11
Example 16	6.25	50
	12.5	25
	25	15
Example 21	6.25	36
	12.5	18
	25	10
	50	6
Example 22	6.25	46
	12.5	21
	25	13
	50	8

[0381] 10. AN3CA growth inhibition assay

In this assay, the growth inhibitory activity of a test substance in a human endometrial cancer cell line expressing N549K-variant FGFR2 is measured.

[0382] It has been reported that a human endometrial cancer cell line AN3CA (ATCC Number HTB-111) expresses N549K-variant FGFR2 (Proc Natl Acad Sci USA, 2008, 105:8713-8717). AN3CA cells were maintenance-cultured in a 5% CO_2 incubator (37°C) by using an RPMI-1640 (Wako Pure Chemical Industries, Ltd., 187-02021) medium containing 10% FBS, penicillin and streptomycin (Wako Pure Chemical Industries, Ltd., 168-23191). To each well of a 96 well plate (Becton, Dickinson and Company, 35-3075), 150 μL of an AN3CA cell suspension adjusted to a concentration of 1.3×10^4 cells/mL by using an RPMI-1640 medium containing 10% FBS, penicillin and streptomycin was added, and the cells were cultured overnight in a 5% CO_2 incubator (37°C). On the next day, 50 μL of a test substance diluted with an RPMI-1640 medium containing 10% FBS, penicillin and streptomycin was added to each well, and the resultant was cultured for 3 days in a 5% CO_2 incubator (37°C). Ten μL of Cell Counting Kit-8 (Dojindo Laboratories, CK04) was added to each well, and the resultant was cultured for 1 to 2 hours in a 5% CO_2 incubator (37°C) to cause a color reaction. ENVISION (TM) (PerkinElmer Co., Ltd.) was used for measuring absorbance at 450 nm. Assuming that the absorbance attained in a well containing the cells but not containing the test substance was 100% and that the absorbance attained in a well containing no cells was 0%, an absorbance ratio attained in the presence of the test substance was obtained. The concentration of the test substance necessary for

inhibiting the cell growth by 50% (i.e., an IC_{50} value) was calculated, and IC_{50} values of respective test substances thus calculated are shown in Table 34.

[0383] <Data of evaluation of AN3CA growth inhibitory action>

[Table 34]

Example No.	AN3CA (IC_{50}(nM))
Example 2	25.1
Example 21	24.6
Example 22	11.0

[0384] 11. MFE296 growth inhibition assay

In this assay, the growth inhibitory activity of a test substance in a human endometrial cancer cell line expressing N549K-variant FGFR2 is measured.

[0385] It has been reported that a human endometrial cancer cell line MFE296 (DSMZ Number ACC-419) expresses N549K-variant FGFR2 (Proc Natl Acad Sci USA, 2008, 105:8713-8717). MFE296 cells were maintenance-cultured in a 5% CO_2 incubator (37°C) by using an RPMI-1640 (Wako Pure Chemical Industries, Ltd., 187-02021) medium containing 10% FBS, penicillin and streptomycin (Wako Pure Chemical Industries, Ltd., 168-23191). To each well of a 96 well plate (Becton, Dickinson and Company, 35-3075), 150 μL of an MFE296 cell suspension adjusted to a concentration of 1.3×10^4 cells/mL by using an RPMI-1640 medium containing 10% FBS, penicillin and streptomycin was added, and the cells were cultured overnight in a 5% CO_2 incubator (37°C). On the next day, 50 μL of a test substance diluted with an RPMI-1640 medium containing 10% FBS, penicillin and streptomycin was added to each well, and the resultant was cultured for 3 days in a 5% CO_2 incubator (37°C). Ten μL of Cell Counting Kit-8 (Dojindo Laboratories, CK04) was added to each well, and the resultant was cultured for 1 to 2 hours in a 5% CO_2 incubator (37°C) to cause a color reaction. ENVISION (TM) (PerkinElmer Co., Ltd.) was used for measuring absorbance at 450 nm. Assuming that the absorbance attained in a well containing the cells but not containing the test substance was 100% and that the absorbance attained in a well containing no cells was 0%, an absorbance ratio attained in the presence of the test substance was obtained. The concentration of the test substance necessary for inhibiting the cell growth by 50% (i.e., an IC_{50} value) was calculated, and IC_{50} values of respective test substances thus calculated are shown in Table 35.

[0386] <Data of evaluation of MFE296 growth inhibitory action>

[Table 35]

Example No.	MFE296 (IC_{50}(nM))
Example 2	10.4
Example 21	8.8
Example 22	12.2

[0387] 12. MFE280 growth inhibition assay

In this assay, the growth inhibitory activity of a test substance in a human endometrial cancer cell line expressing S252W-variant FGFR2 is measured.

[0388] It has been reported that a human endometrial cancer cell line MFE280 (DMSZ Number ACC-410) expresses S252W-variant FGFR2 (Proc Natl Acad Sci USA, 2008, 105:8713-8717). MFE280 cells were maintenance-cultured in a 5% CO_2 incubator (37°C) by using an RPMI-1640 (Wako Pure Chemical Industries, Ltd., 187-02021) medium containing 10% FBS, penicillin and streptomycin (Wako Pure Chemical Industries, Ltd., 168-23191). To each well of a 96 well plate (Becton, Dickinson and Company, 35-3075), 150 μL of an MFE280 cell suspension adjusted to a concentration of 3.3 x 10^4 cells/mL by using an RPMI-1640 medium containing 10% FBS, penicillin and streptomycin was added, and the cells were cultured overnight in a 5% CO_2 incubator (37°C). On the next day, 50 μL of a test substance diluted with an RPMI-1640 medium containing 10% FBS, penicillin and streptomycin was added to each well, and the resultant was cultured for 3 days in a 5% CO_2 incubator (37°C). Ten μL of Cell Counting Kit-8 (Dojindo Laboratories, CK04) was added to each well, and the resultant was cultured for 1 to 2 hours in a 5% CO_2 incubator (37°C) to cause a color reaction. ENVISION (TM) (PerkinElmer Co., Ltd.) was used for measuring absorbance at 450 nm. Assuming that the absorbance attained in a well containing the cells but not containing the test substance was 100% and that the absorbance attained in a well containing no cells was 0%, an absorbance ratio attained in the presence of the test substance was obtained. The concentration of the test substance necessary for inhibiting the cell growth by 50% (i.e., an IC_{50} value) was calculated, and IC_{50} values of respective test substances thus calculated are shown in Table 36.

[0389] <Data of evaluation of MFE280 growth inhibitory action>

[Table 36]

Example No.	MFE280 (IC_{50}(nM))
Example 2	44.1
Example 21	27.6
Example 22	17.1

[0390] 13. Antitumor effect in mouse model having AN3CA subcutaneously implanted

Cells of a human endometrial cancer cell line AN3CA (ATCC Number HTB-111), which had been cultured in an RPMI-1640 medium containing 10% FBS, penicillin and streptomycin, were prepared as a cell suspension in a concentration of 1 x 10^8 cells/mL by using Hanks' Balanced Salt Solution (GIBCO #24020). The resultant cell suspension was mixed with MATRIGEL (BD Biosciences, Cat# 354234) in a ratio of 1:1 to prepare a cell suspension in a concentration of 5 x 10^7 cells/ml. The cell suspension was implanted in a volume of 100 μL into a subcutaneous part of a right flank of each of nude mice (BALB/cAJcl-nu/nu, female, Clea Japan Inc.) of 7 weeks old. Eleven days after the implantation, the shortest diameter and the longest diameter of a tumor thus caused in each mouse were measured by using an electronic digital caliper (Digimatic TM caliper, Mitutoyo Corporation), so as to calculate the volume of the tumor in accordance with the following calculation formula:

Tumor volume (mm^3) = Longest diameter (mm) × Shortest diameter (mm) × Shortest diameter (mm) / 2

On the basis of the volumes of tumors obtained on the first day of administration, the nude mice were grouped such that averages of the tumor volumes were substantially equal among the groups. Each test substance was dissolved in DMSO, Tween 80 was added thereto to prepare a storage solution in a 10-fold concentration of an evaluation sample, and the thus prepared solution was frozen for storage until use. Immediately before the administration, the storage solution was diluted with a 5% glucose solution to obtain an evaluation sample (in which a ratio in % among DMSO, Tween 80 and the 5% glucose solution was 3.5:6.5:90). In a test substance administration group, the evaluation sample was orally administered at a dose of 0.4 mL per 20 g of the weight once a day continuously for 14 days, and in a control group, an administration solvent was orally administered under the same conditions. Incidentally, the experiment was conducted on groups each consisting of 5 mice.

With respect to each of the control group and test substance administration groups,

a ratio of the weight measured on the final day to the weight measured on the first day (relative body weight: RBW) was calculated. If a ratio of the RBW of the test substance administration group/the RBW of the control group is 0.9 or more, the corresponding test substance administration group was determined as a safely administrable group. In the test substance administration group thus determined as safely administrable, a ratio of the tumor volume attained after the administration of the test substance to the tumor volume of the control group obtained on the final day (T/C) (%) was calculated, and such ratios of respective test substances thus calculated are shown in Table 37.

[0391] <Data of evaluation of antitumor effect in mouse model having AN3CA subcutaneously implanted>

[Table 37]

Example No.	Dose (mg/kg)	T/C(%)
Example 22	6.25	29
	12.5	11
	25	4
	50	2

[0392] 14. Antitumor effect in mouse model having MFE296 subcutaneously implanted

Cells of a human endometrial cancer cell line MFE296 (DSMZ Number ACC-419), which had been cultured in an RPMI-1640 medium containing 10% FBS, penicillin and streptomycin, were prepared as a cell suspension in a concentration of 1×10^8 cells/mL by using Hanks' Balanced Salt Solution (GIBCO #24020). The resultant cell suspension was mixed with MATRIGEL (BD Biosciences, Cat# 354234) in a ratio of 1:1 to prepare a cell suspension in a concentration of 5×10^7 cells/ml. The cell suspension was implanted in a volume of 100 μL into a subcutaneous part of a right flank of each of nude mice (BALB/cAJcl-nu/nu, female, Clea Japan Inc.) of 7 weeks old. Twelve days after the implantation, the shortest diameter and the longest diameter of a tumor thus caused in each mouse were measured by using an electronic digital caliper (Digimatic TM caliper, Mitutoyo Corporation), so as to calculate the volume of the tumor in accordance with the following calculation formula:

Tumor volume (mm^3) = Longest diameter (mm) × Shortest diameter (mm) × Shortest diameter (mm) / 2

On the basis of the volumes of tumors obtained on the first day of administration, the nude mice were grouped such that averages of the tumor volumes were substantially

equal among the groups. Each test substance was dissolved in DMSO, Tween 80 was added thereto to prepare a storage solution in a 10-fold concentration of an evaluation sample, and the thus prepared solution was frozen for storage until use. Immediately before the administration, the storage solution was diluted with a 5% glucose solution to obtain an evaluation sample (in which a ratio in % among DMSO, Tween 80 and the 5% glucose solution was 3.5:6.5:90). In a test substance administration group, the evaluation sample was orally administered at a dose of 0.4 mL per 20 g of the weight once a day continuously for 14 days, and in a control group, an administration solvent was orally administered under the same conditions. Incidentally, the experiment was conducted on groups each consisting of 5 mice.

With respect to each of the control group and test substance administration groups, a ratio of the weight measured on the final day to the weight measured on the first day (relative body weight: RBW) was calculated. If a ratio of the RBW of the test substance administration group/the RBW of the control group is 0.9 or more, the corresponding test substance administration group was determined as a safely administrable group. In the test substance administration group thus determined as safely administrable, a ratio of the tumor volume attained after the administration of the test substance to the tumor volume of the control group obtained on the final day (T/C) (%) was calculated, and such ratios of respective test substances thus calculated are shown in Table 38.

[0393] <Data of evaluation of antitumor effect in mouse model having MFE296 subcutaneously implanted>

[Table 38]

Example No.	Dose (mg/kg)	T/C(%)
Example 22	6.25	91
	12.5	85
	25	60
	50	54

[0394] 15. Antitumor effect in mouse model having MFE280 subcutaneously implanted

Cells of a human endometrial cancer cell line MFE280 (DMSZ Number ACC-410), which had been cultured in an RPMI-1640 medium containing 10% FBS, penicillin and streptomycin, were prepared as a cell suspension in a concentration of 4.7 x 10^7 cells/mL by using Hanks' Balanced Salt Solution (GIBCO #24020). The resultant cell suspension was mixed with MATRIGEL (BD Biosciences, Cat# 354234) in a ratio of 1:1 to

prepare a cell suspension in a concentration of 2.4 x 10^7 cells/ml. The cell suspension was implanted in a volume of 100 μL into a subcutaneous part of a right flank of each of nude mice (BALB/cAJcl-nu/nu, female, Clea Japan Inc.) of 7 weeks old. Thirty-five days after the implantation, the shortest diameter and the longest diameter of a tumor thus caused in each mouse were measured by using an electronic digital caliper (Digimatic TM caliper, Mitutoyo Corporation), so as to calculate the volume of the tumor in accordance with the following calculation formula:

Tumor volume (mm^3) = Longest diameter (mm) × Shortest diameter (mm) × Shortest diameter (mm) / 2

On the basis of the volumes of tumors obtained on the first day of administration, the nude mice were grouped such that averages of the tumor volumes were substantially equal among the groups. Each test substance was dissolved in DMSO, Tween 80 was added thereto to prepare a storage solution in a 10-fold concentration of an evaluation sample, and the thus prepared solution was frozen for storage until use. Immediately before the administration, the storage solution was diluted with a 5% glucose solution to obtain an evaluation sample (in which a ratio in % among DMSO, Tween 80 and the 5% glucose solution was 3.5:6.5:90). In a test substance administration group, the evaluation sample was orally administered at a dose of 0.4 mL per 20 g of the weight once a day continuously for 14 days, and in a control group, an administration solvent was orally administered under the same conditions. Incidentally, the experiment was conducted on groups each consisting of 5 mice.

With respect to each of the control group and test substance administration groups, a ratio of the weight measured on the final day to the weight measured on the first day (relative body weight: RBW) was calculated. If a ratio of the RBW of the test substance administration group/the RBW of the control group is 0.9 or more, the corresponding test substance administration group was determined as a safely administrable group. In the test substance administration group thus determined as safely administrable, a ratio of the tumor volume attained after the administration of the test substance to the tumor volume of the control group obtained on the final day (T/C) (%) was calculated, and such ratios of respective test substances thus calculated are shown in Table 39.

[0395] <Data of evaluation of antitumor effect in mouse model having MFE280 subcutaneously implanted>

[Table 39]

Example No.	Dose (mg/kg)	T/C(%)
Example 22	6.25	72
	12.5	57
	25	31
	50	11

[0396] 16. RT112/84 growth inhibition assay

In this assay, the growth inhibitory activity of a test substance in a human bladder cancer cell line expressing FGFR3-TACC3 fusion protein is measured.

[0397] Cells of a human bladder cancer cell line RT112/84 (ECACC Number EC85061106-F0) were maintenance-cultured in a 5% CO_2 incubator (37°C) by using an RPMI-1640 (Wako Pure Chemical Industries, Ltd., 187-02021) medium containing 10% FBS, penicillin and streptomycin (Wako Pure Chemical Industries, Ltd., 168-23191). To each well of a 96 well plate (Becton, Dickinson and Company, 35-3075), 150 μL of an RT112/84 cell suspension adjusted to a concentration of 1.3 x 10^4 cells/mL by using an RPMI-1640 medium containing 10% FBS, penicillin and streptomycin was added, and the cells were cultured overnight in a 5% CO_2 incubator (37°C). On the next day, 50 μL of a test substance solution diluted with an RPMI-1640 medium containing 10% FBS, penicillin and streptomycin was added to each well, and the resultant was cultured for 3 days in a 5% CO_2 incubator (37°C). Thereafter, 10 μL of Cell Counting Kit-8 (Dojindo Laboratories, CK04) was added to each well, and the resultant was cultured for 1 to 2 hours in a 5% CO_2 incubator (37°C) to cause a color reaction. ENVISION (TM) (PerkinElmer Co., Ltd.) was used for measuring absorbance at 450 nm. Assuming that the absorbance attained in a well of a cell suspension containing the cells but not containing the test substance was 100% and that the absorbance attained in a well containing no cells was 0%, an absorbance ratio attained in the presence of the test substance was obtained. The concentration of the test substance necessary for inhibiting the cell growth by 50% (i.e., an IC_{50} value) was calculated, and IC_{50} values of respective test substances thus calculated are shown in Table 40.

[0398] <Data of evaluation of RT112/84 growth inhibitory action>

[Table 40]

Example No.	RT112/84 (IC_{50}(nM))
Example 2	42.3
Example 21	19.4
Example 22	19.0

[0399] 17. SW780 growth inhibition assay

In this assay, the growth inhibitory activity of a test substance in a human bladder cancer cell line expressing FGFR3-BAIAP2L1 fusion protein is measured.

[0400] It has been reported that a human bladder cancer cell line SW780 (ATCC Number CRL-2169) expresses FGFR3-BAIAP2L1 fusion protein (Hum Mol Genet. 2013, 22:795-803). SW780 cells were maintenance-cultured in a 5% CO_2 incubator (37°C) by using an RPMI-1640 (Wako Pure Chemical Industries, Ltd., 187-02021) medium containing 10% FBS, penicillin and streptomycin (Wako Pure Chemical Industries, Ltd., 168-23191). To each well of a 96 well plate (Becton, Dickinson and Company, 35-3075), 150 μL of a SW780 cell suspension adjusted to a concentration of 2.6 x 10^4 cells/mL by using an RPMI-1640 medium containing 1% FBS, penicillin and streptomycin was added, and the cells were cultured overnight in a 5% CO_2 incubator (37°C). On the next day, 50 μL of a test substance diluted with an RPMI-1640 medium containing 1% FBS, penicillin and streptomycin was added to each well, and the resultant was cultured for 3 days in a 5% CO_2 incubator (37°C). Ten μL of Cell Counting Kit-8 (Dojindo Laboratories, CK04) was added to each well, and the resultant was cultured for 1 to 2 hours in a 5% CO_2 incubator (37°C) to cause a color reaction. ENVISION (TM) (PerkinElmer Co., Ltd.) was used for measuring absorbance at 450 nm. Assuming that the absorbance attained in a well containing the cells but not containing the test substance was 100% and that the absorbance attained in a well containing no cells was 0%, an absorbance ratio attained in the presence of the test substance was obtained. The concentration of the test substance necessary for inhibiting the cell growth by 50% (i.e., an IC_{50} value) was calculated, and IC_{50} values of respective test substances thus calculated are shown in Table 41.

[0401] <Data of evaluation of SW780 growth inhibitory action>

[Table 41]

Example No.	SW780 (IC_{50}(nM))
Example 22	20.3

[0402] 18. RT4 growth inhibition assay

In this assay, the growth inhibitory activity of a test substance in a human bladder cancer cell line expressing FGFR3-TACC3 fusion protein is measured.

[0403] It has been reported that a human bladder cancer cell line RT4 (ATCC Number HTB-2) expresses FGFR3-TACC3 fusion protein (Hum Mol Genet. 2013, 22:795-803). RT4 cells were maintenance-cultured in a 5% CO_2 incubator (37°C) by using an RPMI-1640 (Wako Pure Chemical Industries, Ltd., 187-02021) medium containing 10% FBS, penicillin and streptomycin (Wako Pure Chemical Industries, Ltd., 168-23191). To each well of a 96 well plate (Becton, Dickinson and Company, 35-3075), 150 μL of an RT4 cell suspension adjusted to a concentration of 2.6 x 10^4 cells/mL by using an RPMI-1640 medium containing 10% FBS, penicillin and streptomycin was added, and the cells were cultured overnight in a 5% CO_2 incubator (37°C). On the next day, 50 μL of a test substance diluted with an RPMI-1640 medium containing 10% FBS, penicillin and streptomycin was added to each well, and the resultant was cultured for 3 days in a 5% CO_2 incubator (37°C). Ten μL of Cell Counting Kit-8 (Dojindo Laboratories, CK04) was added to each well, and the resultant was cultured for 1 to 2 hours in a 5% CO_2 incubator (37°C) to cause a color reaction. ENVISION (TM) (PerkinElmer Co., Ltd.) was used for measuring absorbance at 450 nm. Assuming that the absorbance attained in a well containing the cells but not containing the test substance was 100% and that the absorbance attained in a well containing no cells was 0%, an absorbance ratio attained in the presence of the test substance was obtained. The concentration of the test substance necessary for inhibiting the cell growth by 50% (i.e., an IC_{50} value) was calculated, and IC_{50} values of respective test substances thus calculated are shown in Table 42.

[0404] <Data of evaluation of RT4 growth inhibitory action>

[Table 42]

Example No.	RT4 (IC_{50}(nM))
Example 22	16.4

[0405] 19. Antitumor effect in mouse model having RT112/84 subcutaneously implanted

Cells of a human cancer cell line RT112/84 (ECACC Number EC85061106-F0), which had been cultured in an RPMI-1640 medium containing 10% FBS, penicillin and streptomycin, were prepared as a cell suspension in a concentration of 1 x 10^8 cells/mL by

using Hanks' Balanced Salt Solution (GIBCO #24020). The resultant suspension was mixed with MATRIGEL (BD Biosciences, Cat# 354234) in a ratio of 1:1 to prepare a cell suspension in a concentration of 5 x 10^7 cells/ml. The cell suspension was implanted in a volume of 100 μL into a subcutaneous part of a right flank of each of nude mice (BALB/cAJcl-nu/nu, female, Clea Japan Inc.) of 7 weeks old. Ten days after the implantation, the shortest diameter and the longest diameter of a tumor thus caused in each mouse were measured by using an electronic digital caliper (Digimatic TM caliper, Mitutoyo Corporation), so as to calculate the volume of the tumor in accordance with the following calculation formula:

Tumor volume (mm^3) = Longest diameter (mm) × Shortest diameter (mm) × Shortest diameter (mm) / 2

On the basis of the volumes of tumors obtained on the first day of administration, the nude mice were grouped such that averages of the tumor volumes were substantially equal among the groups. Each test substance was dissolved in DMSO, Tween 80 was added thereto to prepare a storage solution in a 10-fold concentration of an evaluation sample, and the thus prepared solution was frozen for storage until use. Immediately before the administration, the storage solution was diluted with a 5% glucose solution to obtain an evaluation sample (in which a ratio in % among DMSO, Tween 80 and the 5% glucose solution was 3.5:6.5:90). In a test substance administration group, the evaluation sample was orally administered at a dose of 0.4 mL per 20 g of the weight once a day continuously for 14 days, and in a control group, an administration solvent was orally administered under the same conditions. Incidentally, the experiment was conducted on groups each consisting of 5 mice.

With respect to each of the control group and test substance administration groups, a ratio of the weight measured on the final day to the weight measured on the first day (relative body weight: RBW) was calculated. If a ratio of the RBW of the test substance administration group/the RBW of the control group is 0.9 or more, the corresponding test substance administration group was determined as a safely administrable group. In the test substance administration group thus determined as safely administrable, a ratio of the tumor volume attained after the administration of the test substance to the tumor volume of the control group obtained on the final day (T/C) (%) was calculated, and such ratios of respective test substances thus calculated are shown in Table 43.

[0406] <Data of evaluation of antitumor effect in mouse model having RT112/84

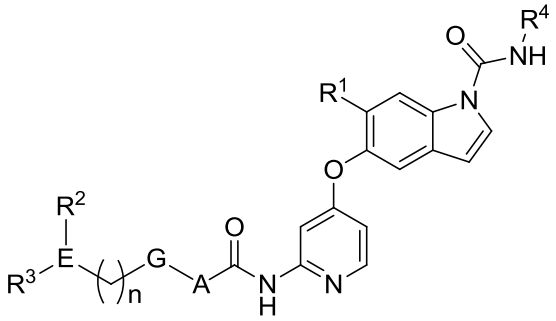
subcutaneously implanted>

[Table 43]

Example No.	Dose (mg/kg)	T/C(%)
Example 22	25	62
	50	33

CLAIMS

1. A compound represented by the following formula (IA) or a pharmaceutically acceptable salt thereof:



(IA)

wherein

n represents 0 to 2;

A represents a C_{6-10} arylene group;

G represents a single bond, an oxygen atom or $–CH_2–$;

E represents a C_{3-5} nitrogen-containing non-aromatic heterocycle;

R^1 represents a cyano group, a mono-C_{1-6} alkylamino group, a di-C_{1-6} alkylamino group, a C_{2-6} alkyl group optionally substituted by 1 to 3 halogen atoms, a C_{1-6} alkoxy group optionally substituted by 1 to 3 halogen atoms or one hydroxyl group, a C_{1-6} alkoxy C_{1-6} alkyl group optionally substituted by 1 to 3 halogen atoms, or a C_{1-6} alkoxy C_{1-6} alkoxy group optionally substituted by 1 to 3 halogen atoms;

R^2 represents a hydrogen atom, a halogen atom, a hydroxyl group, a C_{2-6} acyl group optionally substituted by one substituent selected from a group S described below, a C_{1-6} alkyl group optionally substituted by 1 to 3 halogen atoms, a hydroxy C_{1-6} alkyl group optionally substituted by 1 to 3 halogen atoms, or a C_{3-5} nitrogen-containing non-aromatic heterocyclic group;

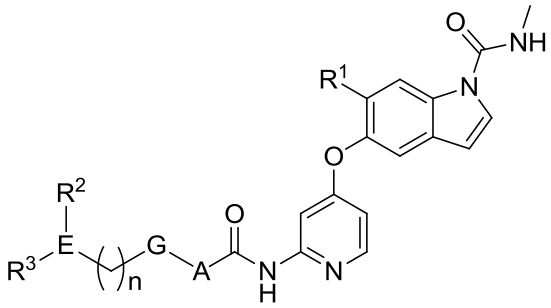
R^3 represents a hydrogen atom, an oxo group, a C_{1-6} alkyl group optionally substituted by 1 to 3 halogen atoms, or a C_{1-6} alkoxy group optionally substituted by 1 to 3 halogen atoms;

R^4 represents a C_{1-6} alkyl group, with the proviso that when E represents an azetidine ring and R^2 or R^3 is present on a nitrogen atom on the azetidine ring, the R^2 or R^3 does not represent a hydrogen atom; and

the group S represents a group consisting of a hydroxyl group, a mono-C_{1-6} alkylamino group, a di-C_{1-6} alkylamino group, a C_{1-6} alkoxy group and a C_{3-5}

nitrogen-containing non-aromatic heterocyclic group.

2. The compound or the pharmaceutically acceptable salt thereof according to claim 1, represented by the following formula (IB):



(IB)

wherein

n represents 0 to 2;

A represents a C_{6-10} arylene group;

G represents a single bond, an oxygen atom or $–CH_2–$;

E represents a C_{3-5} nitrogen-containing non-aromatic heterocycle;

R^1 represents a C_{1-6} alkoxy group optionally substituted by 1 to 3 halogen atoms or one hydroxyl group, or a C_{1-6} alkoxy C_{1-6} alkoxy group optionally substituted by 1 to 3 halogen atoms;

R^2 represents a hydrogen atom, a halogen atom, a hydroxyl group, a C_{1-6} alkyl group optionally substituted by 1 to 3 halogen atoms, a hydroxy C_{1-6} alkyl group optionally substituted by 1 to 3 halogen atoms, or a C_{3-5} nitrogen-containing non-aromatic heterocyclic group; and

R^3 represents a hydrogen atom, an oxo group, a C_{1-6} alkyl group optionally substituted by 1 to 3 halogen atoms, or a C_{1-6} alkoxy group optionally substituted by 1 to 3 halogen atoms, with the proviso that when E represents an azetidine ring and R^2 or R^3 is present on a nitrogen atom on the azetidine ring, the R^2 or R^3 does not represent a hydrogen atom.

3. The compound or the pharmaceutically acceptable salt thereof according to claim 1 or 2, wherein G represents a single bond or an oxygen atom.

4. The compound or the pharmaceutically acceptable salt thereof according to claim 1 or 2, wherein

A represents a phenylene group; and

E represents an azetidine ring, a pyrrolidine ring, a piperidine ring or a piperazine ring.

5. The compound or the pharmaceutically acceptable salt thereof according to claim 1 or 2, wherein

A represents a phenylene group; and

E represents an azetidine ring or a piperidine ring.

6. The compound or the pharmaceutically acceptable salt thereof according to claim 1 or 2, wherein

A represents a phenylene group; and

E represents a piperidine ring.

7. The compound or the pharmaceutically acceptable salt thereof according to any one of claims 4 to 6, wherein

n represents 0; and

G represents a single bond.

8. The compound or the pharmaceutically acceptable salt thereof according to any one of claims1 to 7, wherein

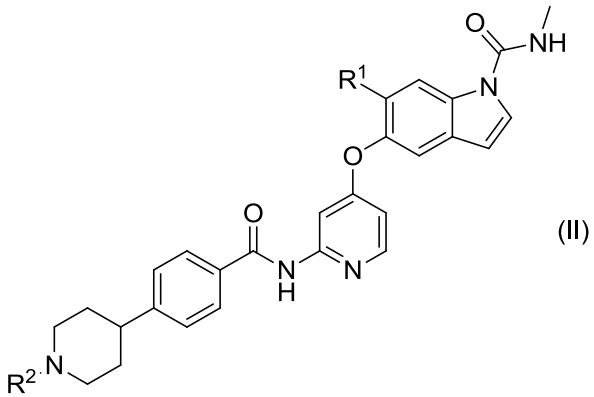
R^1 represents a C_{1-6} alkoxy group or a C_{1-6} alkoxy C_{1-6} alkoxy group;

R^2 represents a hydrogen atom, a hydroxyl group, a C_{1-6} alkyl group or a hydroxy C_{1-6} alkyl group; and

R^3 represents a hydrogen atom.

9. The compound or the pharmaceutically acceptable salt thereof according to any one of claims 1 to 8, wherein R^1 represents a C_{1-6} alkoxy C_{1-6} alkoxy group.

10. The compound or the pharmaceutically acceptable salt thereof according to claim 1 or 2, represented by the following formula (II):



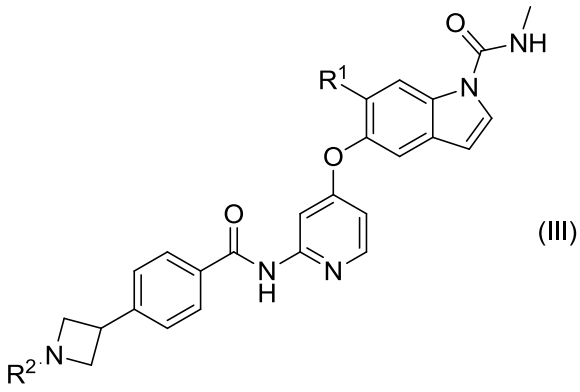
(II)

wherein

R^1 represents a C_{1-6} alkoxy C_{1-6} alkoxy group; and

R^2 represents a hydrogen atom, a C_{1-6} alkyl group or a hydroxy C_{2-6} alkyl group.

11. The compound or the pharmaceutically acceptable salt thereof according to claim 1 or 2, represented by the following formula (III):



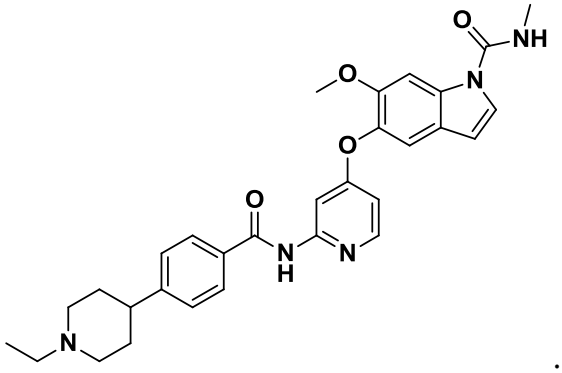
(III)

wherein

R^1 represents a C_{1-6} alkoxy C_{1-6} alkoxy group; and

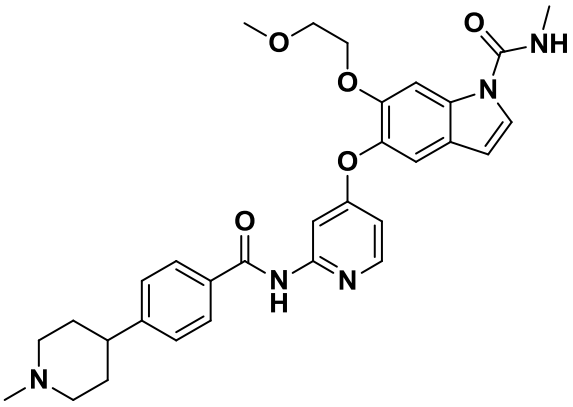
R^2 represents a C_{1-6} alkyl group or a hydroxy C_{2-6} alkyl group.

12. 5-((2-(4-(1-Ethylpiperidin-4-yl)benzamide)pyridin-4-yl)oxy)-6-methoxy-N-methyl-1H-indole-1-carboxamide represented by the following structural formula, or a pharmaceutically acceptable salt thereof:



.

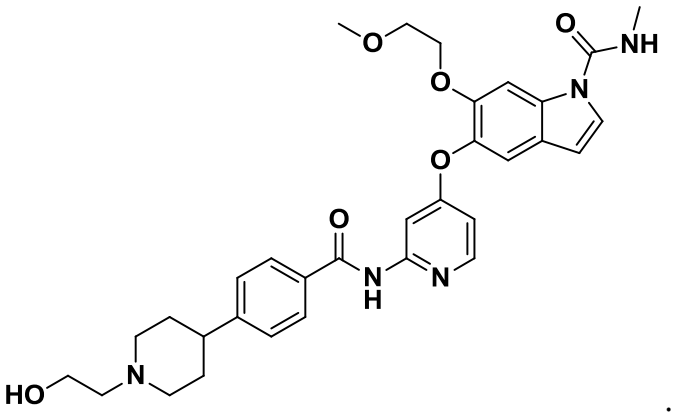
13. 6-(2-Methoxyethoxy)-N-methyl-5-((2-(4-(1-methylpiperidin-4-yl)benzamide)pyridin-4-yl)oxy)-1H-indole-1-carboxamide represented by the following structural formula, or a pharmaceutically acceptable salt thereof:



.

14.

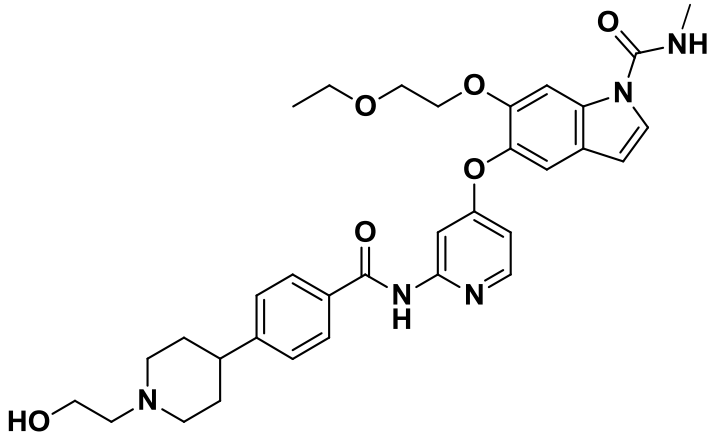
5-((2-(4-(1-(2-Hydroxyethyl)piperidin-4-yl)benzamide)pyridin-4-yl)oxy)-6-(2-methoxyethoxy)-N-methyl-1H-indole-1-carboxamide represented by the following structural formula, or a pharmaceutically acceptable salt thereof:



.

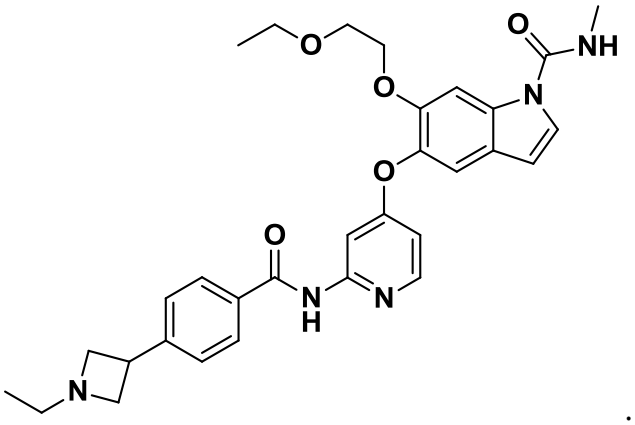
15.

6-(2-Ethoxyethoxy)-5-((2-(4-(1-(2-hydroxyethyl)piperidin-4-yl)benzamide)pyridin-4-yl)oxy)-N-methyl-1H-indole-1-carboxamide represented by the following structural formula, or a pharmaceutically acceptable salt thereof:



16.

6-(2-Ethoxyethoxy)-5-((2-(4-(1-ethylazetidin-3-yl)benzamide)pyridin-4-yl)oxy)-N-methyl-1H-indole-1-carboxamide represented by the following structural formula, or a pharmaceutically acceptable salt thereof:



17. A pharmaceutical composition comprising the compound or the pharmaceutically acceptable salt thereof according to any one of claims 1 to 16.

18. A therapeutic agent for stomach cancer, non-small-cell lung carcinoma, bladder cancer or endometrial cancer comprising the compound or the pharmaceutically acceptable salt thereof according to any one of claims 1 to 16 as an active ingredient.

19. A therapeutic agent for non-small-cell lung carcinoma comprising the compound or the pharmaceutically acceptable salt thereof according to any one of claims 1 to 16 as an active ingredient.

20. A therapeutic agent for squamous cell carcinoma comprising the compound or the pharmaceutically acceptable salt thereof according to any one of claims 1 to 16 as an active ingredient.

21. An FGFR inhibitor for treating non-small-cell lung carcinoma, comprising the compound or the pharmaceutically acceptable salt thereof according to any one of claims 1 to 16 as an active ingredient.

22. The compound or the pharmaceutically acceptable salt thereof according to any one of claims 1 to 16, for use as a therapeutic agent for stomach cancer, non-small-cell lung carcinoma, bladder cancer or endometrial cancer.

23. A use of the compound or the pharmaceutically acceptable salt thereof according to any one of claims 1 to 16, for manufacturing a therapeutic agent for stomach cancer, non-small-cell lung carcinoma, bladder cancer or endometrial cancer.