

PYRIDONE DERIVATIVES

BACKGROUND OF THE INVENTION

Field of the Invention

The present invention relates to pyridone derivatives or salts thereof, or crystals thereof, which have Axl inhibitory activity.

Description of the Related Art

Axl is a receptor tyrosine kinase of the Tyro3-Axl-Mer (TAM) receptor tyrosine kinase family, which has the growth arrest-specific gene 6 (Gas6) protein as a ligand, and has initially been identified as a transforming gene in chronic myelogenous leukemia (Non Patent Document 1).

The Gas6/Axl signaling pathway has been reported to modulate various cellular responses such as cell survival, cell division, autophagy, cell migration, angiogenesis, platelet aggregation and NK cell differentiation (Non Patent Document 2), and also has often been reported to be overexpressed in cancer tissues such as tissues of primary colon cancer (Non Patent Document 3), gastric cancer (Non Patent Document 4), esophageal cancer (Non Patent Document 5), melanoma (Non Patent Document 6), ovarian cancer (Non Patent Document 7), renal cancer (Non Patent Document 8), endometrial cancer (Non Patent Document 9) and thyroid cancer (Non Patent Document 10). It has also been demonstrated that the presence of Axl is

greatly related to the lymph node status and the stage in lung cancer and the ER expression in breast cancer (Non Patent Document 11).

It has further been demonstrated that Axl has a role in immunity (Non Patent Document 12), platelet function (Non Patent Document 13), spermatogenesis (Non Patent Document 14), vascular calcification (Non Patent Document 15), thrombin-induced vascular smooth muscle cell (VSMC) growth (Non Patent Document 16), and various renal diseases such as acute and chronic glomerulonephritis, diabetic nephropathy and chronic allograft rejection (Non Patent Document 17). Axl inhibitors are expected to be useful not only for the treatment of cancer (including solid tumors such as carcinoma and sarcoma, leukemia, and lymphoid malignancy) but also for the treatment of many diseases such as vascular diseases (including, but not limited to, thrombosis, atherosclerosis and restenosis), renal diseases (including, but not limited to, acute and chronic glomerulonephritis, diabetic nephropathy, and transplant rejection), and diseases with significant chaotic angiogenesis (including, but not limited to, diabetic retinopathy, retinopathy, psoriasis, rheumatoid arthritis, atheroma, Kaposi's sarcoma and hemangioma).

Compounds reported to inhibit Axl include compounds having a sulfonamide structure (Patent Document 3), compounds having a pyrrolopyrimidine structure (Patent Document 4, Patent Document 5), compounds having pyridine

and pyrazine structures (Patent Document 6), compounds having a pyrazine structure (Patent Document 7), compounds having a pyrazinylbenzimidazole structure (Patent Document 8), compounds having an indolinone structure (Patent Document 9), compounds having triazolopyridine and triazolopyrimidine structures (Patent Document 10), compounds having an imidazole structure (Patent Document 11), compounds having a triazole structure (Patent Document 12, Patent Document 13, Patent Document 14, Patent Document 15, Patent Document 16, Patent Document 17, Patent Document 20, Patent Document 24, Patent Document 25, Patent Document 26, Patent Document 27, Patent Document 28), compounds having a pyrimidinediamine structure (Patent Document 18), compounds having a pyrimidine structure (Patent Document 19, Non Patent Document 18, Non Patent Document 22), compounds having a quinolinyloxyphenylsulfonamide structure (Patent Document 21), compounds having a quinoline structure (Patent Document 22, Patent Document 30, Non Patent Document 21), compounds having a pyridine structure (Patent Document 23, Non Patent Document 19), compounds having a urea structure (Patent Document 29), compounds having a 2,4-disubstituted arylamide structure (Non Patent Document 20), compounds having a secosteroid structure (Non Patent Document 23), compounds having a bicyclic pyrimidine structure (Patent Document 31, Patent

Document 32) and compounds having aminopyrazine and aminopyridine structures (Patent Document 33).

Prior art documents

Patent documents

Patent document 1: WO 2008/025820

Patent document 2: WO 2008/074997

Patent document 3: WO 2008/128072

Patent document 4: US Patent Application Publication No.
20100204221

Patent document 5: WO 2010/090764

Patent document 6: WO 2009/053737

Patent document 7: WO 2009/007390

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Patent document 10: WO 2009/047514

Patent document 11: WO 2009/058801

Patent document 12: WO 2008/083367

Patent document 13: WO 2008/083353

Patent document 14: WO 2010/005879

Patent document 15: WO 2008/083357

Patent document 16: WO 2008/083356

Patent document 17: WO 2008/083354

Patent document 18: WO 2008/045978

Patent document 19: WO 2007/070872

Patent document 20: WO 2007/030680

Patent document 21: WO 2011/045084

Patent document 22: WO 2009/127417

Patent document 23: WO 2007/066187

Patent document 24: WO 2009/054864

Patent document 25: WO 2010/005876

Patent document 26: WO 2009/054864

Patent document 27: US Patent Application Publication No.
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Patent document 28: US Patent Application Publication No.
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Patent document 29: WO 2009/138799

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Patent document 31: US Patent Application Publication No.
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Patent document 32: US Patent Application Publication No.
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Patent document 33: WO 2012/121939

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Non Patent Document 2: Rachel MA Linger et al., Expert
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Non Patent Document 4: Sawabu et al., Mol. Carcinog.,
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Non Patent Document 5: Nemoto et al., Pathobiology, 1997,
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Non Patent Document 10: Ito et al., Thyroid, 1999, 9, 563

Non Patent Document 11: Berclaz et al., Ann. Oncol., 2001,
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Non Patent Document 12: Lu et al., Science, 2001, 293,
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Non Patent Document 13: Angelillo-Scherrer et al., Nat.
Med., 2001, 7, 215

Non Patent Document 14: Lu et al., Nature, 1999, 398, 723

Non Patent Document 15: Son et al., Eur. J. Pharmacol.,
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Non Patent Document 16: Nakano et al., J. Biol. Chem.,
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Non Patent Document 17: Yanagita et al., J. Clin. Invest.,
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Non Patent Document 18: Alexis Mollard et al., Med. Chem.
Lett., 2011, 2, 907

Non Patent Document 19: Gretchen M. Schroeder et al., J. Med. Chem., 2009, 52, 1251

Non Patent Document 20: Carl R. Illig et al., Bioorg. Med. Chem. Lett., 2008, 18, 1642

Non Patent Document 21: Yi-Xiang Zhang et al., Cancer Res., 2008, 68, 1905

Non Patent Document 22: D Mahadevan et al., Oncogene, 2007, 26, 3909

Non Patent Document 23: Daowan Lai et al., Bioorg. Med. Chem., 2011, 19, 6873

SUMMARY OF THE INVENTION

Problems to be solved by the invention

The present invention provides novel Axl-inhibiting compounds or salts thereof, or crystals thereof. The present invention also provides a therapeutic agent for a disease caused by Axl hyperfunction, a disease associated with Axl hyperfunction and/or a disease accompanied by Axl hyperfunction, e.g., an anticancer agent, comprising such Axl-inhibiting compounds or salts thereof, or crystals thereof.

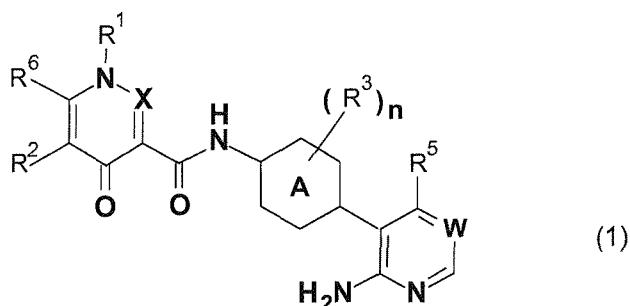
Means of solving the problems

As a result of extensive studies, the present inventors have found that a compound having a structure represented by the following general formula (1) or a salt thereof, or a crystal thereof, has high Axl

inhibitory activity. This finding has led to the completion of the present invention.

Specifically, the present invention relates to the following [1] to [59].

[1] A compound represented by the general formula (1):



[wherein in the formula (1),

A represents a phenylene group or a six-membered heteroarylene group, where the amino group bonded to A and the nitrogen-containing heterocycle are para-positioned relative to each other,

R¹ represents a C₁-C₆ alkyl group which may have one or more substituents selected from Group 1, an aryl group which may have one or more substituents selected from Group 2, a heteroaryl group which may have one or more substituents selected from Group 2, or a hydrogen atom, R² represents a C₁-C₆ alkyl group which may have one or more substituents selected from Group 1, a C₁-C₆ alkoxy group which may have one or more substituents selected from a halogen atom and a hydroxyl group, -CONR^AR^B (where R^A and R^B each independently represents a C₁-C₆ alkyl group which may have one or more substituents selected

from a halogen atom, a C₁-C₆ alkoxy group and a hydroxyl group, or a hydrogen atom, or R^A and R^B together with the nitrogen atom to which they are bonded may form a three- to seven-membered heterocycloalkyl group which may have one or more substituents selected from a halogen atom, a C₁-C₆ alkyl group, a C₁-C₆ alkoxy group and a hydroxyl group), a cycloalkyl group which may have one or more substituents selected from Group 2, a phenyl group which may have one or more substituents selected from Group 2, a heteroaryl group which may have one or more substituents selected from Group 2, or a hydrogen atom, R³ is a substituent on A (where n represents an integer from 0 to 4, and each R³ may be identical to or different from each other when n is two or more), and represents a C₁-C₆ alkyl group which may have one or more substituents selected from Group 1, a C₁-C₆ alkoxy group which may have one or more substituents selected from a halogen atom and a hydroxyl group, a C₁-C₆ alkylthio group which may have one or more substituents selected from a halogen atom and a hydroxyl group, a halogen atom, or a hydroxyl group,

R⁵ represents a C₁-C₆ alkyl group which may have one or more substituents selected from Group 1, -OR^C (where R^C represents a C₁-C₆ alkyl group which may have one or more substituents selected from a C₁-C₆ alkoxy group, a halogen atom and a hydroxyl group, a three- to seven-membered heterocycloalkyl group which may have one or

more substituents selected from a halogen atom, a C₁-C₆ alkyl group and a hydroxyl group, or a hydrogen atom), a C₁-C₆ alkylthio group which may have one or more substituents selected from a halogen atom and a hydroxyl group, or a hydrogen atom,

R⁶ represents a hydrogen atom, or a C₁-C₆ alkyl group which may have one or more substituents selected from Group 1,

W represents C-R⁴ or a nitrogen atom (where R⁴ represents a C₁-C₆ alkyl group which may have one or more substituents selected from Group 1, a C₁-C₆ alkoxy group which may have one or more substituents selected from a C₁-C₆ alkoxy group, a heterocycloalkyl group, a halogen atom and a hydroxyl group, a cycloalkyl group which may have one or more substituents selected from Group 3, a cycloalkenyl group which may have one or more substituents selected from Group 3, a heterocycloalkyl group which may have one or more substituents selected from Group 3, a heterocycloalkenyl group which may have one or more substituents selected from Group 3, an aryl group which may have one or more substituents selected from Group 3, a heteroaryl group which may have one or more substituents selected from Group 3, a halogen atom, or a hydrogen atom), and

X represents CH or a nitrogen atom]

or a salt thereof.

Group 1:

a halogen atom,
-NR^AR^B and -CONR^AR^B (where R^A and R^B each independently represents a C₁-C₆ alkyl group which may have one or more substituents selected from a halogen atom, a C₁-C₆ alkoxy group and a hydroxyl group, or a hydrogen atom, or R^A and R^B together with the nitrogen atom to which they are bonded may form a three- to seven-membered heterocycloalkyl group which may have one or more substituents selected from a halogen atom, a C₁-C₆ alkyl group, a C₁-C₆ alkoxy group and a hydroxyl group),
-OR^C (where R^C represents a C₁-C₆ alkyl group which may have one or more substituents selected from a C₁-C₆ alkoxy group, a halogen atom and a hydroxyl group, a three- to seven-membered heterocycloalkyl group which may have one or more substituents selected from a halogen atom, a C₁-C₆ alkyl group and a hydroxyl group, or a hydrogen atom),
an aryl group which may have one or more substituents selected from a C₁-C₆ alkyl group which may have one or more substituents selected from a halogen atom and a hydroxyl group, a C₁-C₆ alkoxy group, an oxo group and a halogen atom,
a heteroaryl group which may have one or more substituents selected from a C₁-C₆ alkyl group which may have one or more substituents selected from a halogen atom and a hydroxyl group, a C₁-C₆ alkoxy group, an oxo group, a hydroxyl group and a halogen atom,

a three- to seven-membered cycloalkyl group which may have one or more substituents selected from a C₁-C₆ alkyl group which may have one or more substituents selected from a halogen atom and a hydroxyl group, a C₁-C₆ alkoxy group, an oxo group, a hydroxyl group and a halogen atom, and

a three- to seven-membered heterocycloalkyl group which may have one or more substituents selected from a C₁-C₆ alkyl group which may have one or more substituents selected from a halogen atom and a hydroxyl group, a C₁-C₆ alkoxy group, an oxo group, a hydroxyl group and a halogen atom

Group 2: a C₁-C₆ alkyl group which may have one or more substituents selected from a halogen atom and a hydroxyl group, a C₁-C₆ alkoxy group, an oxo group, a hydroxyl group and a halogen atom

Group 3: a C₁-C₆ alkyl group which may have one or more substituents selected from Group 1, a C₁-C₆ acyl group, a C₁-C₆ alkylthio group which may have one or more substituents selected from a halogen atom and a hydroxyl group,

-CONR^AR^B (where R^A and R^B each independently represents a C₁-C₆ alkyl group which may have one or more substituents selected from a halogen atom, a C₁-C₆ alkoxy group and a hydroxyl group, or a hydrogen atom, or R^A and R^B together with the nitrogen atom to which they are bonded may form a three- to seven-membered heterocycloalkyl group which

may have one or more substituents selected from a halogen atom, a C₁-C₆ alkyl group, a C₁-C₆ alkoxy group and a hydroxyl group),

-OR^c (where R^c represents a C₁-C₆ alkyl group which may have one or more substituents selected from a C₁-C₆ alkoxy group, a halogen atom, a three- to seven-membered heterocycloalkyl group and a hydroxyl group, a three- to seven-membered heterocycloalkyl group which may have one or more substituents selected from a halogen atom, a C₁-C₆ alkyl group and a hydroxyl group, or a hydrogen atom), and

a heterocycloalkyl group which may have one or more substituents selected from Group 2

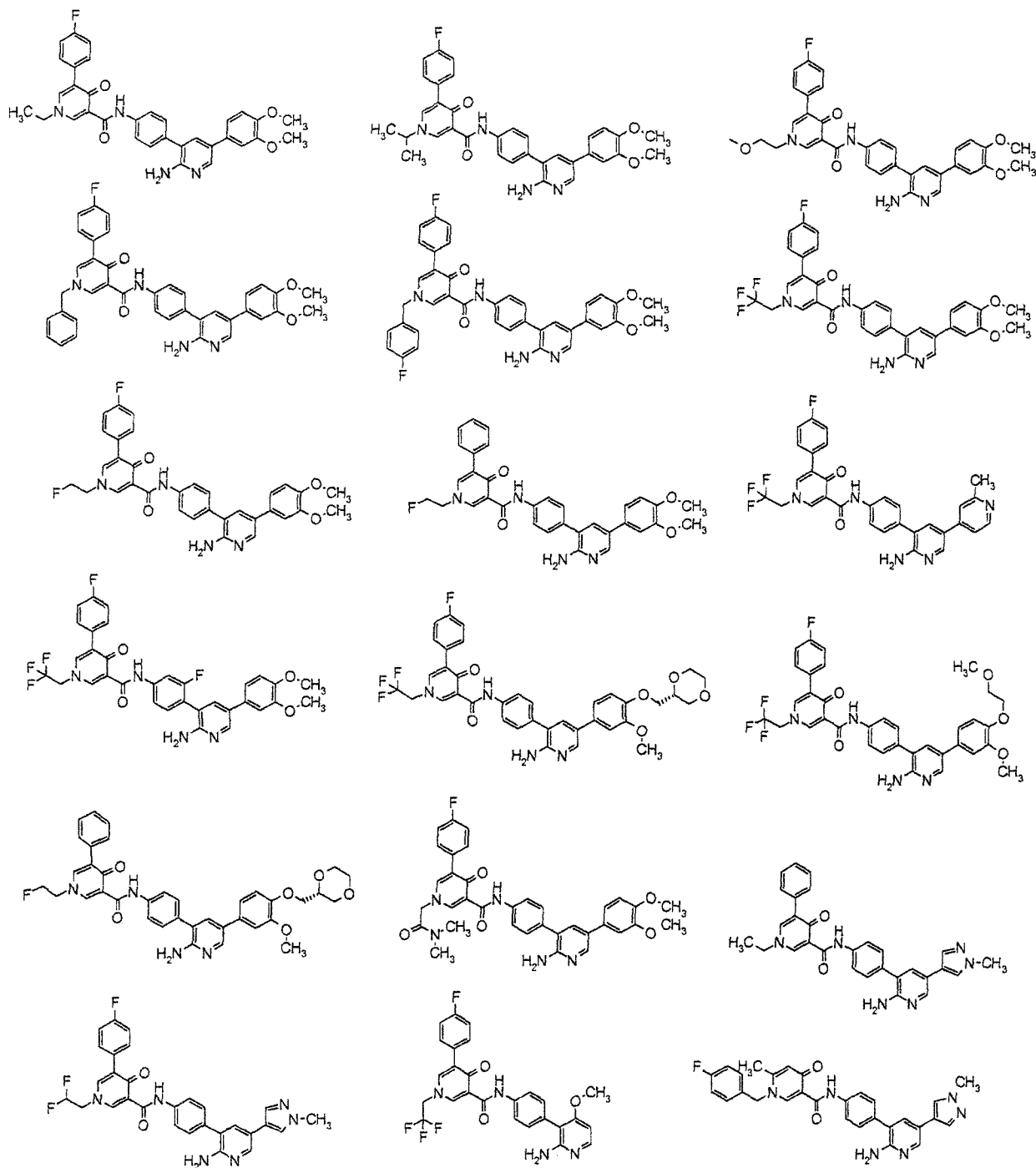
[2] A compound or salt thereof according to [1], wherein A is a phenylene group.

[3] A compound or salt thereof according to [1] or [2], wherein W is C-R⁴.

[4] A compound or salt thereof according to any one of [1] to [3], wherein n is 0.

[5] A compound or salt thereof according to any one of [1] to [4], wherein R⁵ is a hydrogen atom.

[6] Any one compound selected from the following group, or a salt thereof.



[7] N-{4-[2-Amino-5-(3,4-dimethoxyphenyl)pyridin-3-yl]phenyl}-5-(4-fluorophenyl)-4-oxo-1-(2,2,2-trifluoroethyl)-1,4-dihydropyridine-3-carboxamide or a salt thereof.

[8] N-{4-[2-Amino-5-(3,4-dimethoxyphenyl)pyridin-3-yl]phenyl}-5-(4-fluorophenyl)-4-oxo-1-(2,2,2-trifluoroethyl)-1,4-dihydropyridine-3-carboxamide hydrochloride.

[9] A crystal of N-{4-[2-amino-5-(3,4-dimethoxyphenyl)pyridin-3-yl]phenyl}-5-(4-fluorophenyl)-4-oxo-1-(2,2,2-trifluoroethyl)-1,4-dihydropyridine-3-carboxamide hydrochloride.

[10] A crystal according to [9], which has an X-ray diffraction pattern shown in FIG. 1 in a powder X-ray diffraction diagram obtained by irradiation with copper K α radiation (wavelength $\lambda = 1.54 \text{ \AA}$).

[11] A crystal according to [9], which has an X-ray diffraction pattern shown in FIG. 2 in a powder X-ray diffraction diagram obtained by irradiation with copper K α radiation (wavelength $\lambda = 1.54 \text{ \AA}$).

[12] A crystal according to [9], which has an X-ray diffraction pattern shown in FIG. 3 in a powder X-ray diffraction diagram obtained by irradiation with copper K α radiation (wavelength $\lambda = 1.54 \text{ \AA}$).

[13] A crystal according to [9], which has an X-ray diffraction pattern shown in FIG. 4 in a powder X-ray diffraction diagram obtained by irradiation with copper K α radiation (wavelength $\lambda = 1.54 \text{ \AA}$).

[14] A crystal according to [9], which has an X-ray diffraction pattern shown in FIG. 5 in a powder X-ray

diffraction diagram obtained by irradiation with copper $K\alpha$ radiation (wavelength $\lambda = 1.54 \text{ \AA}$).

[15] A crystal according to [9], which has an X-ray diffraction pattern shown in FIG. 6 in a powder X-ray diffraction diagram obtained by irradiation with copper $K\alpha$ radiation (wavelength $\lambda = 1.54 \text{ \AA}$).

[16] A crystal according to [9], which has an X-ray diffraction pattern shown in FIG. 7 in a powder X-ray diffraction diagram obtained by irradiation with copper $K\alpha$ radiation (wavelength $\lambda = 1.54 \text{ \AA}$).

[17] A crystal according to [9], which has an X-ray diffraction pattern shown in FIG. 8 in a powder X-ray diffraction diagram obtained by irradiation with copper $K\alpha$ radiation (wavelength $\lambda = 1.54 \text{ \AA}$).

[18] A crystal according to [9], which has an X-ray diffraction pattern shown in FIG. 9 in a powder X-ray diffraction diagram obtained by irradiation with copper $K\alpha$ radiation (wavelength $\lambda = 1.54 \text{ \AA}$).

[19] A crystal according to [9], which has an X-ray diffraction pattern shown in FIG. 10 in a powder X-ray diffraction diagram obtained by irradiation with copper $K\alpha$ radiation (wavelength $\lambda = 1.54 \text{ \AA}$).

[20] A crystal according to [9], which has an X-ray diffraction pattern shown in FIG. 11 in a powder X-ray diffraction diagram obtained by irradiation with copper $K\alpha$ radiation (wavelength $\lambda = 1.54 \text{ \AA}$).

[21] A crystal according to [9], which has an X-ray diffraction pattern shown in FIG. 12 in a powder X-ray diffraction diagram obtained by irradiation with copper $K\alpha$ radiation (wavelength $\lambda = 1.54 \text{ \AA}$).

[22] A crystal according to [9], which has an X-ray diffraction pattern shown in FIG. 13 in a powder X-ray diffraction diagram obtained by irradiation with copper $K\alpha$ radiation (wavelength $\lambda = 1.54 \text{ \AA}$).

[23] A crystal according to [9], which has an X-ray diffraction pattern shown in FIG. 14 in a powder X-ray diffraction diagram obtained by irradiation with copper $K\alpha$ radiation (wavelength $\lambda = 1.54 \text{ \AA}$).

[24] A crystal according to [9], which has an X-ray diffraction pattern shown in FIG. 15 in a powder X-ray diffraction diagram obtained by irradiation with copper $K\alpha$ radiation (wavelength $\lambda = 1.54 \text{ \AA}$).

[25] A crystal according to [9], which has an X-ray diffraction pattern shown in FIG. 16 in a powder X-ray diffraction diagram obtained by irradiation with copper $K\alpha$ radiation (wavelength $\lambda = 1.54 \text{ \AA}$).

[26] A crystal according to [9], which has characteristic peaks at diffraction angles 2θ of 7.44, 10.00, 13.48, 14.86, 16.10, 19.30, 20.30, 22.62, 23.02, 23.70, 24.54, 25.92 and 28.46 in a powder X-ray diffraction diagram obtained by irradiation with copper $K\alpha$ radiation (wavelength $\lambda = 1.54 \text{ \AA}$).

[27] A crystal according to [9], which has characteristic peaks at diffraction angles 2θ of 4.32, 9.10, 15.52, 18.32, 18.54, 19.22, 20.54, 20.70, 23.54, 24.14, 25.34 and 27.02 in a powder X-ray diffraction diagram obtained by irradiation with copper $K\alpha$ radiation (wavelength $\lambda = 1.54 \text{ \AA}$).

[28] A crystal according to [9], which has characteristic peaks at diffraction angles 2θ of 13.86, 15.04, 19.76, 20.58, 22.26, 22.58, 23.82, 24.10, 24.36 and 24.88 in a powder X-ray diffraction diagram obtained by irradiation with copper $K\alpha$ radiation (wavelength $\lambda = 1.54 \text{ \AA}$).

[29] A crystal according to [9], which has characteristic peaks at diffraction angles 2θ of 5.34, 7.22, 8.20, 11.68, 14.54, 15.74, 17.54, 23.24, 23.72, 25.12 and 26.16 in a powder X-ray diffraction diagram obtained by irradiation with copper $K\alpha$ radiation (wavelength $\lambda = 1.54 \text{ \AA}$).

[30] A crystal according to [9], which has characteristic peaks at diffraction angles 2θ of 11.02, 11.86, 15.56, 18.20, 22.12, 24.70, 25.80, 26.04, 26.26 and 28.62 in a powder X-ray diffraction diagram obtained by irradiation with copper $K\alpha$ radiation (wavelength $\lambda = 1.54 \text{ \AA}$).

[31] A crystal according to [9], which has characteristic peaks at diffraction angles 2θ of 3.58, 4.56, 6.60, 6.72, 7.20, 9.62, 10.28, 13.06 and 24.52 in a powder X-ray diffraction diagram obtained by irradiation with copper $K\alpha$ radiation (wavelength $\lambda = 1.54 \text{ \AA}$).

[32] A crystal according to [9], which has characteristic peaks at diffraction angles 2θ of 7.78, 8.14, 8.88, 12.54, 15.68, 16.36, 18.76, 19.34, 20.08, 22.36, 24.66, 25.74, 26.70 and 28.02 in a powder X-ray diffraction diagram obtained by irradiation with copper $K\alpha$ radiation (wavelength $\lambda = 1.54 \text{ \AA}$).

[33] A crystal according to [9], which has characteristic peaks at diffraction angles 2θ of 5.78, 8.90, 13.66, 14.42, 16.84, 17.56, 19.26, 20.74, 22.42, 24.66, 25.12, 25.60 and 26.96 in a powder X-ray diffraction diagram obtained by irradiation with copper $K\alpha$ radiation (wavelength $\lambda = 1.54 \text{ \AA}$).

[34] A crystal according to [9], which has characteristic peaks at diffraction angles 2θ of 11.12, 14.82, 18.86, 20.32, 20.66, 21.64, 22.36, 22.68, 23.00, 24.10, 25.26 and 27.00 in a powder X-ray diffraction diagram obtained by irradiation with copper $K\alpha$ radiation (wavelength $\lambda = 1.54 \text{ \AA}$).

[35] A crystal according to [9], which has characteristic peaks at diffraction angles 2θ of 7.80, 12.18, 12.78, 16.20, 16.82, 19.20, 19.66, 20.20, 21.20, 24.52, 25.68 and 26.78 in a powder X-ray diffraction diagram obtained by irradiation with copper $K\alpha$ radiation (wavelength $\lambda = 1.54 \text{ \AA}$).

[36] A crystal according to [9], which has characteristic peaks at diffraction angles 2θ of 2.80, 6.86, 7.88, 11.60, 13.68, 14.86, 17.40, 22.40, 23.78 and 25.74 in a powder

X-ray diffraction diagram obtained by irradiation with copper K α radiation (wavelength $\lambda = 1.54 \text{ \AA}$).

[37] A crystal according to [9], which has characteristic peaks at diffraction angles 2θ of 5.32, 7.98, 10.68, 11.70, 14.84, 16.02, 19.78, 21.76, 23.08, 25.30 and 25.68 in a powder X-ray diffraction diagram obtained by irradiation with copper K α radiation (wavelength $\lambda = 1.54 \text{ \AA}$).

[38] A crystal according to [9], which has characteristic peaks at diffraction angles 2θ of 8.10, 10.60, 12.06, 14.16, 14.58, 15.60, 18.16, 20.72, 20.94, 22.86, 23.90, 24.32 and 27.14 in a powder X-ray diffraction diagram obtained by irradiation with copper K α radiation (wavelength $\lambda = 1.54 \text{ \AA}$).

[39] A crystal according to [9], which has characteristic peaks at diffraction angles 2θ of 3.60, 6.22, 9.56, 10.42, 14.04, 14.66, 15.30, 16.40, 19.52, 22.12 and 26.42 in a powder X-ray diffraction diagram obtained by irradiation with copper K α radiation (wavelength $\lambda = 1.54 \text{ \AA}$).

[40] A crystal according to [9], which has characteristic peaks at diffraction angles 2θ of 5.46, 7.98, 9.54, 11.00, 14.00, 15.36, 16.56, 22.00, 23.54, 24.00 and 26.56 in a powder X-ray diffraction diagram obtained by irradiation with copper K α radiation (wavelength $\lambda = 1.54 \text{ \AA}$).

[41] A crystal according to [9], which has characteristic peaks at diffraction angles 2θ of 5.64, 6.92, 8.06, 11.32, 14.40, 16.18, 17.04, 21.84, 22.50, 23.82 and 24.28 in a

powder X-ray diffraction diagram obtained by irradiation with copper K α radiation (wavelength $\lambda = 1.54 \text{ \AA}$).

[42] An Axl inhibitor comprising a compound or salt thereof according to any one of [1] to [6], or a crystal thereof.

[43] A medicine comprising a compound or salt thereof according to any one of [1] to [6], or a crystal thereof as an active ingredient.

[44] A medicine for treating a disease caused by Axl kinase hyperfunction, a disease associated with Axl kinase hyperfunction and/or a disease accompanied by Axl kinase hyperfunction, comprising a compound or salt thereof according to any one of [1] to [6], or a crystal thereof as an active ingredient.

[45] A medicine for treating hyperproliferative disease, comprising a compound or salt thereof according to any one of [1] to [6], or a crystal thereof as an active ingredient.

[46] A medicine for treating cancer, comprising a compound or salt thereof according to any one of [1] to [6], or a crystal thereof as an active ingredient.

[47] A medicine for preventing cancer metastasis, comprising a compound or salt thereof according to any one of [1] to [6], or a crystal thereof as an active ingredient.

[48] A medicine for overcoming drug resistance, comprising a compound or salt thereof according to any

one of [1] to [6], or a crystal thereof as an active ingredient.

[49] A medicine according to [46] or [47], wherein the cancer is selected from breast cancer, colon cancer, prostate cancer, lung cancer, gastric cancer, ovarian cancer, endometrial cancer, renal cancer, hepatocellular carcinoma, thyroid cancer, uterine cancer, esophageal cancer, squamous cell carcinoma, leukemia, osteosarcoma, melanoma, glioblastoma, neuroblastoma and pancreatic cancer.

[50] A pharmaceutical composition comprising a compound or salt thereof according to any one of [1] to [6], or a crystal thereof, and a pharmaceutically acceptable carrier.

[51] A method for treating a disease caused by Axl kinase hyperfunction, a disease associated with Axl kinase hyperfunction and/or a disease accompanied by Axl kinase hyperfunction, comprising using a compound or salt thereof according to any one of [1] to [6], or a crystal thereof.

[52] A method for treating hyperproliferative disease, comprising using a compound or salt thereof according to any one of [1] to [6], or a crystal thereof.

[53] A method for treating cancer, comprising using a compound or salt thereof according to any one of [1] to [6], or a crystal thereof.

[54] A method for preventing cancer metastasis, comprising using a compound or salt thereof according to any one of [1] to [6], or a crystal thereof.

[55] A method for overcoming drug resistance, comprising using a compound or salt thereof according to any one of [1] to [6], or a crystal thereof.

[56] A method according to [53] or [54], wherein the cancer is selected from breast cancer, colon cancer, prostate cancer, lung cancer, gastric cancer, ovarian cancer, endometrial cancer, renal cancer, hepatocellular carcinoma, thyroid cancer, uterine cancer, esophageal cancer, squamous cell carcinoma, leukemia, osteosarcoma, melanoma, glioblastoma and neuroblastoma.

[57] Use of a compound or salt thereof according to any one of [1] to [6], or a crystal thereof for manufacturing a medicine.

[58] Use of a compound or salt thereof according to any one of [1] to [6], or a crystal thereof for treating cancer.

[59] Use of a compound or salt thereof according to any one of [1] to [6], or a crystal thereof for preventing cancer metastasis.

Advantageous effect of the invention

The present invention provides novel pyridone derivatives represented by the above formula (1) having Axl inhibitory activity. Such novel compounds are useful

as therapeutic agents for diseases caused by Axl hyperfunction, diseases associated with Axl hyperfunction and/or diseases accompanied by Axl hyperfunction, e.g., anticancer agents.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is a powder X-ray diffraction diagram of the crystals obtained in Example 90, where the vertical axis represents diffraction intensity in counts per seconds (cps), and the horizontal axis represents values of diffraction angles 2θ ;

FIG. 2 is a powder X-ray diffraction diagram of the crystals obtained in Example 91, where the vertical axis represents diffraction intensity in counts per seconds (cps), and the horizontal axis represents values of diffraction angles 2θ ;

FIG. 3 is a powder X-ray diffraction diagram of the crystals obtained in Example 92, where the vertical axis represents diffraction intensity in counts per seconds (cps), and the horizontal axis represents values of diffraction angles 2θ ;

FIG. 4 is a powder X-ray diffraction diagram of the crystals obtained in Example 93, where the vertical axis represents diffraction intensity in counts per seconds (cps), and the horizontal axis represents values of diffraction angles 2θ ;

FIG. 5 is a powder X-ray diffraction diagram of the crystals obtained in Example 94, where the vertical axis represents diffraction intensity in counts per seconds (cps), and the horizontal axis represents values of diffraction angles 2θ ;

FIG. 6 is a powder X-ray diffraction diagram of the crystals obtained in Example 95, where the vertical axis represents diffraction intensity in counts per seconds (cps), and the horizontal axis represents values of diffraction angles 2θ ;

FIG. 7 is a powder X-ray diffraction diagram of the crystals obtained in Example 96, where the vertical axis represents diffraction intensity in counts per seconds (cps), and the horizontal axis represents values of diffraction angles 2θ ;

FIG. 8 is a powder X-ray diffraction diagram of the crystals obtained in Example 97, where the vertical axis represents diffraction intensity in counts per seconds (cps), and the horizontal axis represents values of diffraction angles 2θ ;

FIG. 9 is a powder X-ray diffraction diagram of the crystals obtained in Example 98, where the vertical axis represents diffraction intensity in counts per seconds (cps), and the horizontal axis represents values of diffraction angles 2θ ;

FIG. 10 is a powder X-ray diffraction diagram of the crystals obtained in Example 99, where the vertical axis

represents diffraction intensity in counts per seconds (cps), and the horizontal axis represents values of diffraction angles 2θ ;

FIG. 11 is a powder X-ray diffraction diagram of the crystals obtained in Example 100, where the vertical axis represents diffraction intensity in counts per seconds (cps), and the horizontal axis represents values of diffraction angles 2θ ;

FIG. 12 is a powder X-ray diffraction diagram of the crystals obtained in Example 101, where the vertical axis represents diffraction intensity in counts per seconds (cps), and the horizontal axis represents values of diffraction angles 2θ ;

FIG. 13 is a powder X-ray diffraction diagram of the crystals obtained in Example 102, where the vertical axis represents diffraction intensity in counts per seconds (cps), and the horizontal axis represents values of diffraction angles 2θ ;

FIG. 14 is a powder X-ray diffraction diagram of the crystals obtained in Example 103, where the vertical axis represents diffraction intensity in counts per seconds (cps), and the horizontal axis represents values of diffraction angles 2θ ;

FIG. 15 is a powder X-ray diffraction diagram of the crystals obtained in Example 104, where the vertical axis represents diffraction intensity in counts per seconds

(cps), and the horizontal axis represents values of diffraction angles 2θ ; and

FIG. 16 is a powder X-ray diffraction diagram of the crystals obtained in Example 105, where the vertical axis represents diffraction intensity in counts per seconds (cps), and the horizontal axis represents values of diffraction angles 2θ .

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

In the present invention, Axl refers to a protein encoded by an Axl gene. "Axl" includes Axl proteins encoded by full-length Axl genes or Axl proteins encoded by Axl gene mutants (including deletion mutants, substitution mutants or addition mutants). In the present invention, "Axl" refers to homologs derived from various animal species.

In the present invention, the "Axl inhibitor" refers to an agent inhibiting functions of Axl as a tyrosine kinase.

In the present invention, the terms "tumor" and "cancer" are used interchangeably. In the present invention, tumor, malignant tumor, cancer, malignant neoplasm, carcinoma, sarcoma and the like may be collectively referred to as "tumor" or "cancer."

In the present invention,

A " C_1 - C_6 alkyl group" refers to a linear or branched alkyl group having 1 to 6 carbon atoms. Examples of a

"C₁-C₆ alkyl group" include a methyl group, an ethyl group, a propyl group, an isopropyl group, a butyl group and a tert-butyl group.

A "C₁-C₆ alkoxy group" refers to an alkoxy group having a linear or branched alkyl group having 1 to 6 carbon atoms. Examples of a "C₁-C₆ alkoxy group" include a methoxy group, an ethoxy group, a propoxy group, an isopropoxy group and a butoxy group.

Examples of a "halogen atom" include a fluorine atom, a chlorine atom, a bromine atom and an iodine atom.

An "oxo group" refers to a group represented by "=O" unless otherwise stated.

A "cycloalkyl group" refers to a cyclic alkyl group having 3 to 8 carbon atoms unless otherwise stated. Examples of this group include a cyclopropyl group, a cyclobutyl group, a cyclopentyl group and a cyclohexyl group.

A "heterocycloalkyl group" refers to a monovalent saturated heterocyclic group and includes a saturated heterocyclic group having a nitrogen atom in the ring and a saturated heterocyclic group having an oxygen atom in the ring. Examples of this group include monovalent groups derived from pyrrolidine, imidazoline, piperidine, piperazine, azetidine, morpholine, dioxane, oxetane, tetrahydropyran and quinuclidine.

A "cycloalkenyl group" includes the above "cycloalkyl group" having one or more unsaturated bonds

such as double bonds. Examples of this group include a cyclopentenyl group and a cyclohexenyl group.

A "heterocycloalkenyl group" includes the above "heterocycloalkyl group" having one or more unsaturated bonds such as double bonds. Examples of this group include a tetrahydropyridinyl group and a dihydropyranyl group.

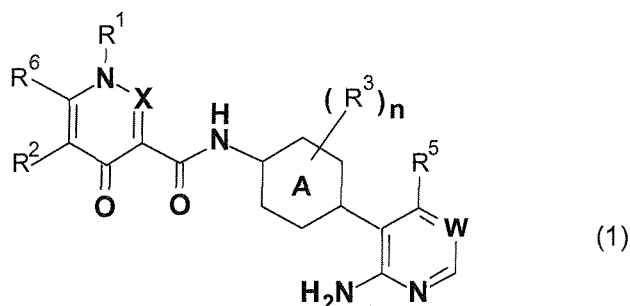
An "aryl group" refers to a monovalent substituent derived from an aromatic hydrocarbon. Examples of an aryl group include a phenyl group, an indenyl group, a naphthyl group, a fluorenyl group, an anthranyl group and a phenanthrenyl group.

A "heteroaryl group" refers to a monovalent aromatic heterocyclic group. Examples of this group include a pyrrolyl group, a pyrazolyl group, a triazolyl group, an oxazolyl group, an oxadiazolyl group, a thiophenyl group, a thiazolyl group, a thiadiazolyl group, a pyridinyl group, a pyrimidinyl group, a pyridazinyl group, a pyrazinyl group, a benzimidazolyl group, a benzotriazolyl group, a benzofuranyl group, a benzothiophenyl group, a quinolyl group, a carbazolyl group and a dibenzofuranyl group.

A "heteroarylene group" refers to a divalent aromatic heterocyclic group. Examples of the group include divalent groups derived from pyridine, pyrimidine, pyrazine, pyridazine and triazine.

Each substituent in formula (1) will be described below.

In the following general formula (1):



A represents a phenylene group or a six-membered heteroarylene group. The amino group bonded to the ring A and the nitrogen-containing heterocycle are para-positioned relative to each other.

When A is a heteroarylene group, A is preferably a group containing a nitrogen atom, and it is particularly preferred that it is a group derived from pyridine. The position of an atom other than carbon in the ring A is not particularly limited.

A is more preferably a phenylene group.

R¹ represents a C₁-C₆ alkyl group which may have one or more substituents selected from the above Group 1, an aryl group which may have one or more substituents selected from the above Group 2, a heteroaryl group which may have one or more substituents selected from the above Group 2, or a hydrogen atom.

Here, when R¹ is a "C₁-C₆ alkyl group which may have one or more substituents selected from the above Group

1," the C₁-C₆ alkyl group is preferably a methyl group, an ethyl group, a propyl group, an isopropyl group, a butyl group or an isobutyl group.

A halogen atom as a substituent for the C₁-C₆ alkyl group is preferably a fluorine atom, a chlorine atom or a bromine atom. The C₁-C₆ alkyl group may be substituted with a plurality of identical or different halogen atoms, and the number of substitutions is preferably 1 to 3 if it is substituted with a halogen atom(s).

-NR^AR^B and -CONR^AR^B as substituents for the C₁-C₆ alkyl group (where R^A and R^B each independently represents a C₁-C₆ alkyl group which may have one or more substituents selected from a halogen atom, a C₁-C₆ alkoxy group and a hydroxyl group, or a hydrogen atom, or R^A and R^B together with the nitrogen atom to which they are bonded may form a three- to seven-membered heterocycloalkyl group which may have one or more substituents selected from a halogen atom, a C₁-C₆ alkyl group, a C₁-C₆ alkoxy group and a hydroxyl group) are preferably an amino group which may be substituted with a C₁-C₆ alkyl group which may have one or more substituents selected from a halogen atom, a C₁-C₆ alkoxy group and a hydroxyl group, or a carbamoyl group which may be substituted with a C₁-C₆ alkyl group which may have one or more substituents selected from a halogen atom, a C₁-C₆ alkoxy group and a hydroxyl group, more preferably an amino group which may be substituted with a C₁-C₆ alkyl

group(s), or a carbamoyl group which may be substituted with a C₁-C₆ alkyl group(s), still more preferably an amino group which may be substituted with a C₁-C₃ alkyl group(s), or a carbamoyl group which may be substituted with a C₁-C₃ alkyl group(s), and particularly preferably an amino group, a carbamoyl group, a monomethylamino group, a dimethylamino group, a monomethylcarbamoyl group, a dimethylcarbamoyl group, a monoethylamino group, a diethylamino group, a methylethylamino group, a monoethylcarbamoyl group, a diethylcarbamoyl group or a methylethylcarbamoyl group.

In -OR^c as a substituent for the C₁-C₆ alkyl group (where R^c represents a C₁-C₆ alkyl group which may have one or more substituents selected from a C₁-C₆ alkoxy group, a halogen atom and a hydroxyl group, a three- to seven-membered heterocycloalkyl group which may have one or more substituents selected from a halogen atom, a C₁-C₆ alkyl group and a hydroxyl group, or a hydrogen atom), R^c is preferably a C₁-C₆ alkyl group, a three- to seven-membered heterocycloalkyl group or a hydrogen atom, and R^c is more preferably a C₁-C₃ alkyl group, a tetrahydropyranyl group or a hydrogen atom.

The "aryl group which may have one or more substituents selected from a C₁-C₆ alkyl group which may have one or more substituents selected from a halogen atom and a hydroxyl group, a C₁-C₆ alkoxy group, an oxo group and a halogen atom" as a substituent for the C₁-C₆

alkyl group is preferably a phenyl group which may have one or more substituents selected from a C₁-C₆ alkyl group which may have one or more substituents selected from a halogen atom and a hydroxyl group, a C₁-C₆ alkoxy group, an oxo group and a halogen atom, more preferably a phenyl group which may have one or more substituents selected from a C₁-C₆ alkyl group which may have 1 to 3 substituents selected from 1 to 3 halogen atoms and hydroxyl groups, a C₁-C₃ alkoxy group, an oxo group and 1 to 3 halogen atoms, and still more preferably a phenyl group unsubstituted or substituted with 1 to 3 halogen atoms or a C₁-C₃ alkoxy group.

The "heteroaryl group" in the "heteroaryl group which may have one or more substituents selected from a C₁-C₆ alkyl group which may have one or more substituents selected from a halogen atom and a hydroxyl group, a C₁-C₆ alkoxy group, an oxo group, a hydroxyl group and a halogen atom" as a substituent for the C₁-C₆ alkyl group is preferably a heteroaryl group containing a nitrogen atom. The "heteroaryl group which may have one or more substituents selected from a C₁-C₆ alkyl group which may have one or more substituents selected from a halogen atom and a hydroxyl group, a C₁-C₆ alkoxy group, an oxo group, a hydroxyl group and a halogen atom" is preferably a pyridinyl group which may have one or more substituents selected from a C₁-C₆ alkyl group which may have one or more substituents selected from a halogen atom and a

hydroxyl group, a C₁-C₆ alkoxy group, an oxo group, a hydroxyl group and a halogen atom, a pyrimidinyl group which may have one or more substituents selected from a C₁-C₆ alkyl group which may have one or more substituents selected from a halogen atom and a hydroxyl group, a C₁-C₆ alkoxy group, an oxo group, a hydroxyl group and a halogen atom, a pyrazinyl group which may have one or more substituents selected from a C₁-C₆ alkyl group which may have one or more substituents selected from a halogen atom and a hydroxyl group, a C₁-C₆ alkoxy group, an oxo group, a hydroxyl group and a halogen atom, a pyridazinyl group which may have one or more substituents selected from a C₁-C₆ alkyl group which may have one or more substituents selected from a halogen atom and a hydroxyl group, a C₁-C₆ alkoxy group, an oxo group, a hydroxyl group and a halogen atom, or a thiophenyl group which may have one or more substituents selected from a C₁-C₆ alkyl group which may have one or more substituents selected from a halogen atom and a hydroxyl group, a C₁-C₆ alkoxy group, an oxo group, a hydroxyl group and a halogen atom, and particularly preferably a pyridinyl group which may have one or more substituents selected from a C₁-C₆ alkyl group which may have one or more substituents selected from a halogen atom and a hydroxyl group, a C₁-C₆ alkoxy group, an oxo group, a hydroxyl group and a halogen atom. The position at which each heteroaryl group is bonded to the C₁-C₆ alkyl group is not limited, but the pyridinyl

group is preferably bonded at the 2-position, the pyrimidinyl group is preferably bonded at the 2-position, the pyrazinyl group is preferably bonded at the 2-position, the pyridazinyl group is preferably bonded at the 3-position, and the thiophenyl group is preferably bonded at the 2-position. The "heteroaryl group which may have one or more substituents selected from a C₁-C₆ alkyl group which may have one or more substituents selected from a halogen atom and a hydroxyl group, a C₁-C₆ alkoxy group, an oxo group, a hydroxyl group and a halogen atom" as a substituent for the C₁-C₆ alkyl group is particularly preferably an unsubstituted pyridinyl group, a pyridinyl group substituted with a C₁-C₃ alkoxy group, or a pyridinyl group substituted with a halogen atom.

The "three- to seven-membered cycloalkyl group which may have one or more substituents selected from a C₁-C₆ alkyl group which may have one or more substituents selected from a halogen atom and a hydroxyl group, a C₁-C₆ alkoxy group, an oxo group, a hydroxyl group and a halogen atom" as a substituent for the C₁-C₆ alkyl group is preferably an unsubstituted three- to seven-membered cycloalkyl group or a three- to seven-membered cycloalkyl group substituted with a plurality of halogen atoms, and more preferably an unsubstituted three- to seven-membered cycloalkyl group.

The "three- to seven-membered heterocycloalkyl group which may have one or more substituents selected from a C₁-C₆ alkyl group which may have one or more substituents selected from a halogen atom and a hydroxyl group, a C₁-C₆ alkoxy group, an oxo group, a hydroxyl group and a halogen atom" as a substituent for the C₁-C₆ alkyl group is preferably a three- to seven-membered heterocycloalkyl group unsubstituted or substituted with a C₁-C₆ alkyl group or an oxo group. Here, the "three- to seven-membered heterocycloalkyl group" is preferably a tetrahydropyranyl group, a tetrahydrofuranyl group, a pyrrolidinyl group, an imidazolidinyl group, a pyrazolidinyl group, a piperidino group, a morpholino group, a dioxanyl group or an oxetanyl group, and more preferably a pyrrolidinyl group, a tetrahydropyranyl group or a dioxanyl group. The position at which each heterocycloalkyl group is bonded to the C₁-C₆ alkyl group is not limited, but the dioxanyl group is preferably bonded at the 2-position, the tetrahydrofuranyl group is preferably bonded at the 2-position, and the pyrrolidinyl group is preferably bonded at the 2-position.

When R¹ is an "aryl group which may have one or more substituents selected from the above Group 2," the "aryl group" is preferably a phenyl group. The substituent for the phenyl group is preferably a C₁-C₆ alkyl group which may have 1 to 3 substituents selected from a fluorine atom, a chlorine atom and a hydroxyl group, a C₁-C₆

alkoxy group, a hydroxyl group, a fluorine atom or a chlorine atom. When R^1 is a "heteroaryl group which may have one or more substituents selected from the above Group 2," the "heteroaryl group" is preferably a heteroaryl group containing a nitrogen atom, more preferably a pyridinyl group, a pyrimidinyl group, a pyridazinyl group or a pyrazinyl group, and particularly preferably a pyridinyl group. The substituent for the heteroaryl group is preferably a C_1 - C_6 alkyl group which may have 1 to 3 substituents selected from a fluorine atom, a chlorine atom and a hydroxyl group, a C_1 - C_6 alkoxy group, a hydroxyl group, a fluorine atom or a chlorine atom.

R^1 is particularly preferably a C_1 - C_6 alkyl group substituted with 1 to 3 halogen atoms, a methoxyethyl group, an ethoxyethyl group, a benzyl group, or a benzyl group having a benzene ring substituted with 1 to 3 halogen atoms. Here, the halogen atom is preferably a fluorine atom.

R^2 represents a C_1 - C_6 alkyl group which may have one or more substituents selected from the above Group 1, a C_1 - C_6 alkoxy group which may have one or more substituents selected from a halogen atom and a hydroxyl group, $-\text{CONR}^A\text{R}^B$ (where R^A and R^B each independently represents a C_1 - C_6 alkyl group which may have one or more substituents selected from a halogen atom, a C_1 - C_6 alkoxy group and a hydroxyl group, or a hydrogen atom, or R^A and

R^B together with the nitrogen atom to which they are bonded may form a three- to seven-membered heterocycloalkyl group which may have one or more substituents selected from a halogen atom, a C_1-C_6 alkyl group, a C_1-C_6 alkoxy group and a hydroxyl group), a cycloalkyl group which may have one or more substituents selected from the above Group 2, a phenyl group which may have one or more substituents selected from the above Group 2, a heteroaryl group which may have one or more substituents selected from the above Group 2, or a hydrogen atom.

When R^2 is a " C_1-C_6 alkyl group which may have one or more substituents selected from the above Group 1," preferred examples thereof are the same as those of the " C_1-C_6 alkyl group which may have one or more substituents selected from the above Group 1" in the above R^1 . When R^2 is a " C_1-C_6 alkyl group which may have one or more substituents selected from the above Group 1," it is more preferably an unsubstituted C_1-C_6 alkyl group.

When R^2 is a " C_1-C_6 alkoxy group which may have one or more substituents selected from a halogen atom and a hydroxyl group," it is preferably an unsubstituted C_1-C_6 alkoxy group, and more preferably a methoxy group or an ethoxy group.

When R^2 is " $-\text{CONR}^A\text{R}^B$ " (where R^A and R^B each independently represents a C_1-C_6 alkyl group which may

have one or more substituents selected from a halogen atom, a C₁-C₆ alkoxy group and a hydroxyl group, or a hydrogen atom, or R^A and R^B together with the nitrogen atom to which they are bonded may form a three- to seven-membered heterocycloalkyl group which may have one or more substituents selected from a halogen atom, a C₁-C₆ alkyl group, a C₁-C₆ alkoxy group and a hydroxyl group), "it is preferred that R^A and R^B be each independently an unsubstituted C₁-C₆ alkyl group or a hydrogen atom, or R^A and R^B together with the nitrogen atom to which they are bonded form a three- to six-membered heterocycloalkyl group which may have one or more substituents selected from a halogen atom, a C₁-C₆ alkyl group, a C₁-C₆ alkoxy group and a hydroxyl group. Here, the "three- to six-membered heterocycloalkyl group" is preferably a pyrrolidinyl group, a morpholino group or an azetidiny group.

When R² is a "cycloalkyl group which may have one or more substituents selected from the above Group 2," the "cycloalkyl group" is preferably a cyclopropyl group or a cyclohexyl group. Here, R² is preferably an unsubstituted cyclohexyl group.

When R² is a "phenyl group which may have one or more substituents selected from the above Group 2," the substituents for the phenyl group are preferably 1 to 3 groups selected from a C₁-C₆ alkyl group, a fluorine atom, a chlorine atom and a bromine atom.

When R^2 is a "heteroaryl group which may have one or more substituents selected from the above Group 2," the "heteroaryl group" is preferably a pyridinyl group, a pyrimidinyl group, a pyrazinyl group, a pyridazinyl group, a thiophenyl group, a furanyl group or an oxadiazolyl group, and more preferably a pyridinyl group, a thiophenyl group or an oxadiazolyl group. The substituents for the heteroaryl group are preferably 1 to 3 groups selected from a C_1 - C_6 alkyl group, a fluorine atom, a chlorine atom and a bromine atom.

R^2 is preferably a phenyl group substituted with 1 to 3 groups selected from a C_1 - C_6 alkyl group substituted with 1 to 3 halogen atoms, and a halogen atom, an unsubstituted phenyl group, a hydrogen atom, a methyl group or a methoxy group. It is more preferably an unsubstituted phenyl group or a phenyl group substituted with 1 to 3 fluorine atoms.

R^3 is a substituent on A (where n represents an integer from 0 to 4, and each R^3 may be identical to or different from each other when n is two or more), and represents a C_1 - C_6 alkyl group which may have one or more substituents selected from Group 1, a C_1 - C_6 alkoxy group which may have one or more substituents selected from a halogen atom and a hydroxyl group, a C_1 - C_6 alkylthio group which may have one or more substituents selected from a halogen atom and a hydroxyl group, a halogen atom, or a hydroxyl group.

When R^3 is a "C₁-C₆ alkyl group which may have one or more substituents selected from the above Group 1," preferred examples thereof are the same as those of the "C₁-C₆ alkyl group which may have one or more substituents selected from the above Group 1" in the above R¹. When R^3 is a "C₁-C₆ alkyl group which may have one or more substituents selected from the above Group 1," it is preferably a C₁-C₆ alkyl group which may be substituted with 1 to 3 fluorine atoms, chlorine atoms, bromine atoms or hydroxyl groups, and more preferably an unsubstituted C₁-C₆ alkyl group.

When R^3 is a "C₁-C₆ alkoxy group which may have one or more substituents selected from a halogen atom and a hydroxyl group," it is preferably a C₁-C₃ alkoxy group which may be substituted with 1 to 3 fluorine atoms, chlorine atoms, bromine atoms or hydroxyl groups, and more preferably an unsubstituted C₁-C₃ alkoxy group.

When R^3 is a "C₁-C₆ alkylthio group which may have one or more substituents selected from a halogen atom and a hydroxyl group," it is preferably a C₁-C₃ alkylthio group which may be substituted with 1 to 3 fluorine atoms, chlorine atoms, bromine atoms or hydroxyl groups, and more preferably an unsubstituted C₁-C₃ alkylthio group.

When R^3 is a "halogen atom," it is preferably a fluorine atom, a chlorine atom or a bromine atom.

In R^3 , n is preferably 0 to 3, n is more preferably 0 or 1, and n is still more preferably 0. When n is 1 to

3, R^3 is still more preferably a fluorine atom, a chlorine atom, a bromine atom, a C_1-C_6 alkyl group or a C_1-C_6 alkoxy group.

R^5 represents a C_1-C_6 alkyl group which may have one or more substituents selected from Group 1, $-OR^C$ (where R^C represents a C_1-C_6 alkyl group which may have one or more substituents selected from a C_1-C_6 alkoxy group, a halogen atom and a hydroxyl group, a three- to seven-membered heterocycloalkyl group which may have one or more substituents selected from a halogen atom, a C_1-C_6 alkyl group and a hydroxyl group, or a hydrogen atom), a C_1-C_6 alkylthio group which may have one or more substituents selected from a halogen atom and a hydroxyl group, or a hydrogen atom.

When R^5 is a " C_1-C_6 alkyl group which may have one or more substituents selected from the above Group 1," preferred examples thereof are the same as those of the " C_1-C_6 alkyl group which may have one or more substituents selected from the above Group 1" in the above R^1 . It is preferably an unsubstituted C_1-C_6 alkyl group or a C_1-C_6 alkyl group substituted with 1 to 3 halogen atoms, and more preferably an unsubstituted C_1-C_6 alkyl group.

When R^5 is $-OR^C$ (where R^C represents a C_1-C_6 alkyl group which may have one or more substituents selected from a C_1-C_6 alkoxy group, a halogen atom and a hydroxyl group, a three- to seven-membered heterocycloalkyl group

which may have one or more substituents selected from a halogen atom, a C₁-C₆ alkyl group and a hydroxyl group, or a hydrogen atom)," it is preferably a hydrogen atom, an unsubstituted C₁-C₆ alkoxy group or a C₁-C₆ alkoxy group substituted with 1 to 3 halogen atoms, and more preferably an unsubstituted C₁-C₆ alkoxy group.

When R⁵ is a "C₁-C₆ alkylthio group which may have one or more substituents selected from a halogen atom and a hydroxyl group," it is preferably an unsubstituted C₁-C₆ alkylthio group.

R⁵ is preferably a C₁-C₆ alkyl group, a C₁-C₆ alkoxy group or a hydrogen atom, and more preferably a methoxy group, an ethoxy group, a trifluoromethoxy group, a difluoromethoxy group or a hydrogen atom.

R⁶ represents a hydrogen atom, or a C₁-C₆ alkyl group which may have one or more substituents selected from Group 1.

When R⁶ is a "C₁-C₆ alkyl group which may have one or more substituents selected from the above Group 1," preferred examples thereof are the same as those of the "C₁-C₆ alkyl group which may have one or more substituents selected from the above Group 1" in the above R¹. It is preferably an unsubstituted C₁-C₆ alkyl group or a C₁-C₆ alkyl group substituted with 1 to 3 halogen atoms, and more preferably an unsubstituted C₁-C₆ alkyl group.

R^6 is preferably a C_1 - C_6 alkyl group or a hydrogen atom, and more preferably a methyl group, an ethyl group, a propyl group, a butyl group or a hydrogen atom.

W represents $C-R^4$ or a nitrogen atom, where R^4 represents a C_1 - C_6 alkyl group which may have one or more substituents selected from the above Group 1, a C_1 - C_6 alkoxy group which may have one or more substituents selected from a C_1 - C_6 alkoxy group, a heterocycloalkyl group, a halogen atom and a hydroxyl group, a cycloalkyl group which may have one or more substituents selected from the above Group 3, a cycloalkenyl group which may have one or more substituents selected from Group 3, a heterocycloalkyl group which may have one or more substituents selected from Group 3, a heterocycloalkenyl group which may have one or more substituents selected from Group 3, an aryl group which may have one or more substituents selected from Group 3, a heteroaryl group which may have one or more substituents selected from Group 3, a halogen atom, or a hydrogen atom.

When R^4 is a " C_1 - C_6 alkyl group which may have one or more substituents selected from the above Group 1," preferred examples thereof are the same as those of the " C_1 - C_6 alkyl group which may have one or more substituents selected from the above Group 1" in the above R^1 . It is preferably an unsubstituted C_1 - C_6 alkyl group or a C_1 - C_6 alkyl group substituted with 1 to 3

halogen atoms, and more preferably an unsubstituted C₁-C₆ alkyl group.

When R⁴ is a "C₁-C₆ alkoxy group which may have one or more substituents selected from a C₁-C₆ alkoxy group, a heterocycloalkyl group, a halogen atom and a hydroxyl group," it is preferably an unsubstituted C₁-C₆ alkoxy group or a C₁-C₆ alkoxy group substituted with 1 to 3 halogen atoms, and more preferably an unsubstituted C₁-C₆ alkoxy group.

When R⁴ is a "cycloalkyl group which may have one or more substituents selected from the above Group 3," the "cycloalkyl group" is preferably a cyclopropyl group, a cyclobutyl group, a cyclopentyl group or a cyclohexyl group. When R⁴ is a "cycloalkenyl group which may have one or more substituents selected from the above Group 3," the "cycloalkenyl group" is preferably a cyclopentenyl group or a cyclohexenyl group. When R⁴ is a "heterocycloalkyl group which may have one or more substituents selected from the above Group 3," the "heterocycloalkyl group" is preferably an azetidiny group, a pyrrolidinyl group, a piperidinyl group, a piperazinyl group or a morpholinyl group. When R⁴ is a "heterocycloalkenyl group which may have one or more substituents selected from the above Group 3," the "heterocycloalkenyl group" is preferably a tetrahydropyridyl group or a dihydropyranyl group. When R⁴ is an "aryl group which may have one or more

substituents selected from the above Group 3," the aryl group is preferably a phenyl group. When R^4 is a "heteroaryl group which may have one or more substituents selected from the above Group 3," the "heteroaryl group" is preferably a pyridinyl group, a pyrazinyl group, a pyrimidinyl group, a pyrrolyl group, a pyrazolyl group, an imidazolyl group, a thiophenyl group, a thiazolyl group, an isothiazolyl group, a furanyl group, an oxazolyl group or a triazolyl group.

The number of substituents for such a cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, aryl or heteroaryl group is preferably 0 to 3.

When the substituent for such a cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, aryl or heteroaryl group is a " C_1 - C_6 alkyl group which may have one or more substituents selected from the above Group 1," preferred examples thereof are the same as those of the " C_1 - C_6 alkyl group which may have one or more substituents selected from the above Group 1" in the above R^1 . A C_1 - C_6 alkyl group substituted by $-OR^C$ (where R^C represents a C_1 - C_6 alkyl group which may have one or more substituents selected from a C_1 - C_6 alkoxy group, a halogen atom and a hydroxyl group, a three- to seven-membered heterocycloalkyl group which may have one or more substituents selected from a halogen atom, a C_1 - C_6 alkyl group and a hydroxyl group, or a hydrogen atom) or a heterocycloalkyl group which may have a substituent is

more preferable, and a C₁-C₆ alkyl group which may be substituted with an unsubstituted heterocycloalkyl group or a C₁-C₆ alkoxy group, or an unsubstituted C₁-C₆ alkyl group is further preferred.

When the substituent for such a cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, aryl or heteroaryl group is a "C₁-C₆ acyl group," it is preferably an acetyl group. When the substituent is a "C₁-C₆ alkylthio group which may have one or more substituents selected from a halogen atom and a hydroxyl group," it is preferably an unsubstituted C₁-C₆ alkylthio group. When the substituent is "-CONR^AR^B (where R^A and R^B each independently represents a C₁-C₆ alkyl group which may have one or more substituents selected from a halogen atom, a C₁-C₆ alkoxy group and a hydroxyl group, or a hydrogen atom, or R^A and R^B together with the nitrogen atom to which they are bonded may form a three- to seven-membered heterocycloalkyl group which may have one or more substituents selected from a halogen atom, a C₁-C₆ alkyl group, a C₁-C₆ alkoxy group and a hydroxyl group)," it is preferred that R^A and R^B be each independently an unsubstituted C₁-C₆ alkyl group or a hydrogen atom, or R^A and R^B together with the nitrogen atom to which they are bonded form a three- to six-membered heterocycloalkyl group which may have one or more substituents selected from a halogen atom, a C₁-C₆ alkyl group, a C₁-C₆ alkoxy group and a hydroxyl group. Here, the "three- to six-

membered heterocycloalkyl group" is preferably a pyrrolidinyl group, a morpholino group, an azetidiny group or a piperidinyl group.

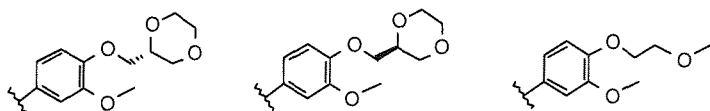
When the substituent for such a cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, aryl or heteroaryl group is "-OR^C (where R^C represents a C₁-C₆ alkyl group which may have one or more substituents selected from a C₁-C₆ alkoxy group, a halogen atom, a three- to seven-membered heterocycloalkyl group and a hydroxyl group, a three- to seven-membered heterocycloalkyl group which may have one or more substituents selected from a halogen atom, a C₁-C₆ alkyl group and a hydroxyl group, or a hydrogen atom)," "R^C" is preferably a C₁-C₆ alkyl group which may have one or more substituents selected from a C₁-C₆ alkoxy group, a halogen atom, a three- to seven-membered heterocycloalkyl group and a hydroxyl group, or a hydrogen atom, and more preferably an unsubstituted C₁-C₆ alkyl group or a C₁-C₆ alkyl group substituted with a C₁-C₆ alkoxy group or a three- to seven-membered heterocycloalkyl group. Here, the three- to seven-membered heterocycloalkyl group is preferably a pyrrolidyl group, an imidazolidinyl group, a pyrazolidinyl group, a piperidinyl group, a piperazinyl group, a tetrahydropyranyl group, a dioxanyl group or a tetrahydrofuranyl group. "R^C" is particularly preferably a methyl group, an ethyl group, a methyl group

substituted with a dioxanyl group, or an ethyl group substituted with a methoxy group.

When the substituent for such a cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, aryl or heteroaryl group is a "heterocycloalkyl group which may have one or more substituents selected from Group 2," it is preferably a heterocycloalkyl group which may be substituted with a C₁-C₆ alkyl group, a C₁-C₆ alkoxy group, an oxo group, a hydroxyl group or a halogen atom, and more preferably a heterocycloalkyl group substituted with a C₁-C₆ alkyl group, a halogen atom or an oxo group, or an unsubstituted heterocycloalkyl group.

When R⁴ is a "halogen atom," it is preferably a fluorine atom, a chlorine atom or a bromine atom.

R⁴ is preferably a phenyl group substituted with 1 to 3 C₁-C₆ alkoxy groups, a five- or six-membered nitrogen-containing heteroaryl group substituted with 1 to 3 C₁-C₆ alkyl groups, or a group represented by any of the following formulae.

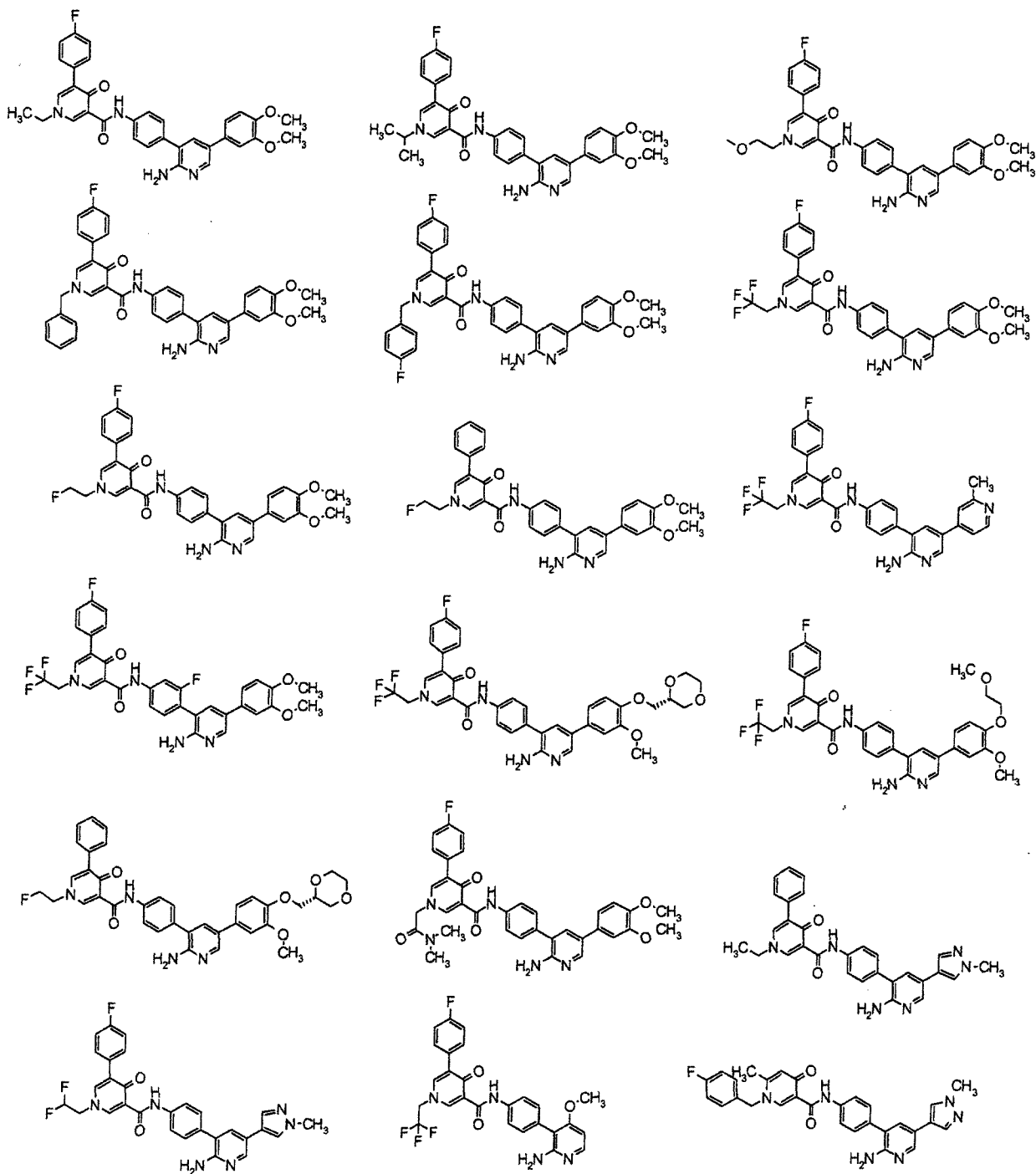


Here, the nitrogen-containing heteroaryl group is preferably a pyridyl group or a pyrazolyl group.

W is preferably C-R⁴.

X represents CH or a nitrogen atom and is preferably CH.

Further, the compound represented by the general formula (1) according to the present invention is preferably one compound selected from the following group.



The compounds represented by the formula (1) according to the present invention may exist as stereoisomers, or optical isomers derived from asymmetric carbon atoms. Such stereoisomers and optical isomers and mixtures thereof are all encompassed by the present invention.

When the compounds represented by the general formula (1) according to the present invention have a basic group such as an amino group, they can be converted to pharmaceutically acceptable salts as desired. Examples of such salts include hydrohalic acid salts such as hydrochlorides and hydroiodides; inorganic acid salts such as nitrates, perchlorates, sulfates and phosphates; lower alkanesulfonates such as methanesulfonates, trifluoromethanesulfonates and ethanesulfonates; arylsulfonates such as benzenesulfonates and p-toluenesulfonates; organic acid salts such as formates, acetates, malates, fumarates, succinates, citrates, tartrates, oxalates and maleates; and amino acid salts such as ornithinates, glutamates and aspartates. Hydrohalic acid salts and organic acid salts are preferred.

When the compounds represented by the general formula (1) according to the present invention have an acidic group such as a carboxy group, base addition salts can generally be formed. Examples of pharmaceutically acceptable salts include alkali metal salts such as

sodium salts, potassium salts and lithium salts; alkaline earth metal salts such as calcium salts and magnesium salts; inorganic salts such as ammonium salts; and organic amine salts such as dibenzylamine salts, morpholine salts, phenylglycine alkyl ester salts, ethylenediamine salts, N-methylglucamine salts, diethylamine salts, triethylamine salts, cyclohexylamine salts, dicyclohexylamine salts, N,N'-dibenzylethylenediamine salts, diethanolamine salts, N-benzyl-N-(2-phenylethoxy)amine salts, piperazine salts, tetramethylammonium salts and tris(hydroxymethyl)aminomethane salts.

The compounds represented by the general formula (1) or salts thereof according to the present invention may also exist as free forms or solvates. They may also exist as solvates due to absorption of moisture in the air, for example. Solvates are not particularly limited if pharmaceutically acceptable, but hydrates (such as monohydrates or dihydrates) and ethanolates are specifically preferred. When nitrogen atoms are present in the inventive compounds represented by the general formula (1), N-oxides may be formed. These solvates and N-oxides are also encompassed within the scope of the present invention.

The compounds represented by the general formula (1) according to the present invention may exist as various isomers including geometric isomers such as cis and trans

isomers, tautomers, or optical isomers such as d- and l-isomers depending on the types and combinations of the substituents. The compounds of the present invention include all of these isomers and stereoisomers, and mixtures of any proportions of these isomers and stereoisomers, unless otherwise specified.

The compounds represented by the general formula (1) according to the present invention may also contain unnatural proportions of atomic isotopes at one or more of the atoms that constitute the compounds. Examples of atomic isotopes include deuterium (^2H), tritium (^3H), iodine-125 (^{125}I) and carbon-14 (^{14}C). These compounds are useful as therapeutic or prophylactic agents, research reagents such as assay reagents, and diagnostic agents such as in vivo diagnostic imaging agents. All isotopic variants of the compounds represented by the general formula (1), whether radioactive or not, are encompassed within the scope of the present invention.

The present invention also encompasses compounds that are converted to the compounds (1) that are active ingredients of the pharmaceutical compositions of the present invention by reactions with an enzyme, gastric acid or the like under physiological conditions in vivo, specifically, "pharmaceutically acceptable prodrug compounds" that are enzymatically oxidized, reduced or hydrolyzed and thus converted to the compounds (1), or

are hydrolyzed by gastric acid or the like and are thus converted to the compounds (1), for example.

Examples of the prodrugs of the compounds (1) in which an amino group is present include compounds in which the amino group is acylated, alkylated or phosphorylated (for example, compounds in which the amino group is eicosanoylated, alanylated, pentylaminocarbonylated, (5-methyl-2-oxo-1,3-dioxolen-4-yl)methoxycarbonylated, tetrahydrofuranylated, pyrrolidylmethylated, pivaloyloxymethylated or tert-butylated). Examples of the prodrugs of the compounds (1) in which a hydroxyl group is present include compounds in which the hydroxyl group is acylated, alkylated, phosphorylated or borated (for example, compounds in which the hydroxyl group is acetylated, palmitoylated, propanoylated, pivaloylated, succinylated, fumarylated, alanylated or dimethylaminomethylcarbonylated). Examples of the prodrugs of the compounds (1) in which a carboxy group is present include compounds in which the carboxy group is esterified or amidated (for example, compounds in which the carboxy group is ethyl esterified, phenyl esterified, carboxymethyl esterified, dimethylaminomethyl esterified, pivaloyloxymethyl esterified, ethoxycarbonyloxyethyl esterified, amidated or methylamidated).

Prodrugs of the compounds of the present invention can be produced from the compounds (1) by known methods.

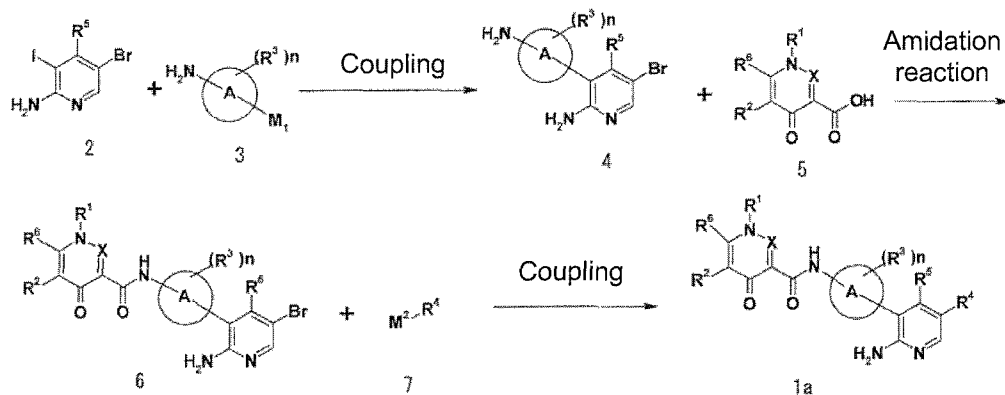
Prodrugs of the compounds of the present invention also include those converted to the compounds (1) under physiological conditions as described in "Iyakuhin No Kaihatsu" [Development of Pharmaceuticals], Vol. 7, Bunshi Sekkei [Molecular Design], Hirokawa Shoten, 1990, pp. 163-198.

Next, representative production processes for the compounds represented by the general formula (1) will be described. The compounds of the present invention can be produced by various production processes. The production processes illustrated below are merely examples, and the present invention should not be construed to be limited thereto. The reactions can be performed with substituents protected by appropriate protecting groups as required, and the type of the protecting group is not particularly limited.

[In the formulae, A, R¹, R², R³, R⁴, R⁵, R⁶, R^A, R^B, W and X are as described above, M¹ to M⁴ each represent a boronic acid or boronate ester, an alkyltin or the like, and L¹ to L³ each represent a halogen atom or the like.]

Compound 1a illustrated below, which is a compound represented by the formula (1), can be produced according to the following reaction scheme, for example.

[Production Process 1]



(1) Conversion of Compound 2 to Compound 4

Compound 2 is converted to Compound 4 by a coupling reaction of Compound 2 with a compound having a partial structure containing A (such as Compound 3) using a known organic chemistry technique.

The reaction is performed by adding to Compound 2 an organic or inorganic base (such as sodium carbonate, potassium carbonate, tripotassium phosphate or diisopropylethylamine), a ligand (such as triphenylphosphine) and a known reaction-promoting additive (such as lithium chloride or copper iodide) as required in the presence of an appropriate organoboronic acid, organotin, organozinc or organomagnesium derivative or the like (such as Compound 3) and an appropriate transition metal catalyst (such as a palladium compound).

The above coupling reaction is performed using an appropriate solvent that does not adversely affect the reaction (such as N,N-dimethylformamide, tetrahydrofuran, toluene, 1,4-dioxane or water) or a mixed solvent thereof

at a reaction temperature of preferably 0°C to 300°C, and more preferably room temperature to 200°C (the optimum temperature is 80°C to 100°C). The above reaction can also be performed by treatment in a sealed tube or under microwave irradiation. The organoboronic acid or the like and the base are preferably used in an amount of one to excess molar equivalents, respectively, and the organoboronic acid or the like is more preferably used in an amount of 1 to 1.5 molar equivalents and the base is more preferably used in an amount of 1 to 5 molar equivalents, based on Compound 2. The reaction time is preferably 1 minute to 60 hours, and more preferably 5 minutes to 24 hours.

(2) Conversion of Compound 4 to Compound 6

Compound 4 is converted to Compound 6 by an amidation reaction of Compound 4 using a known organic chemistry technique. The reaction is performed by reacting with a separately synthesized carboxylic acid Compound 5 in an appropriate solvent that does not adversely affect the reaction (such as benzene, toluene, diethyl ether, dichloromethane, tetrahydrofuran or N,N-dimethylformamide) or a mixed solvent thereof at -30°C to the boiling point of the solvent used for the reaction, and preferably 0°C to 50°C, in the presence of an appropriate condensing agent such as N,N-dicyclohexylcarbodiimide, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide, diethyl cyanophosphate,

(1-cyano-2-ethoxy-2-oxoethylideneaminoxy)dimethylamino-morpholino-carbenium hexafluorophosphate (COMU) or N,N,N',N'-tetramethyl-O-(7-azabenzotriazol-1-yl)uronium hexafluorophosphate (HATU).

The condensing agent may be used in an amount of excess molar equivalents, and preferably 1 to 5 molar equivalents, based on Compound 4. The reaction may also be performed with the addition of a base (such as triethylamine, diisopropylethylamine, N-methylmorpholine or 4-dimethylaminopyridine) as required. The base can be used in a catalytic amount or in an excess amount.

The reaction time is preferably 10 minutes to 72 hours, and more preferably 30 minutes to 24 hours. The reaction is performed using a known reaction promoting additive (such as 1-hydroxybenzotriazole or 1-hydroxy-7-azabenzotriazole) as required. The reaction-promoting additive can be used in a catalytic amount to an excess amount.

The reaction can also be performed by reacting Compound 4 with a carboxylic acid halide derived from the carboxylic acid Compound 5 in an appropriate solvent that does not adversely affect the reaction (such as benzene, toluene, diethyl ether, dichloromethane, tetrahydrofuran or N,N-dimethylformamide) or a mixed solvent thereof at -30°C to the boiling point of the solvent used for the reaction, and preferably 0°C to 100°C, in the presence of an appropriate base (such as triethylamine,

diisopropylethylamine, N-methylmorpholine or 4-dimethylaminopyridine). The base can be used in a catalytic amount or in an excess amount.

The reaction time is preferably 10 minutes to 72 hours, and more preferably 30 minutes to 24 hours.

Alternatively, the reaction can be performed by reacting Compound 4 with the carboxylic acid Compound 5 in an acidic solvent (such as polyphosphoric acid) at 0°C to the boiling point of the solvent used for the reaction, and preferably 10°C to 120°C. The reaction time is preferably 10 minutes to 72 hours, and more preferably 30 minutes to 24 hours.

(3) Conversion of Compound 6 to Compound 1a

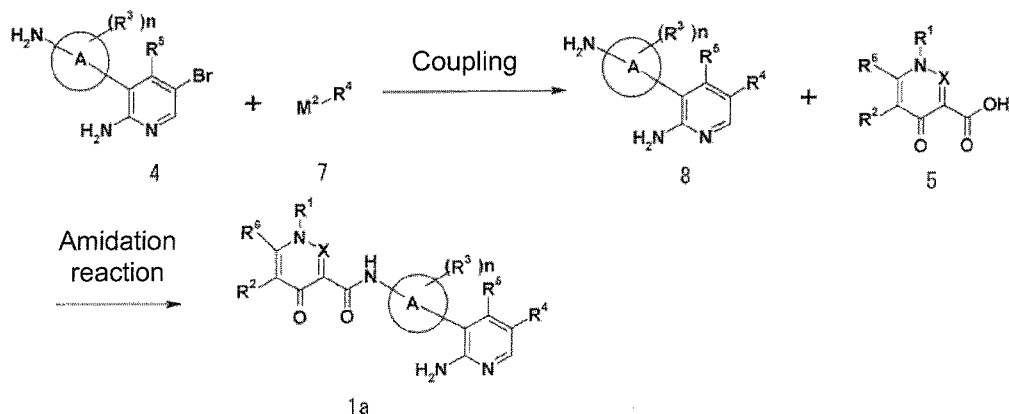
Compound 6 is converted to Compound 1a by a coupling reaction of Compound 6 with a compound having a partial structure containing R⁴ (such as Compound 7) using a known organic chemistry technique. A common coupling reaction similar to the coupling reaction described in (1) can be applied.

For example, the reaction is performed by adding to Compound 6 an organic or inorganic base (such as sodium carbonate, potassium carbonate, tripotassium phosphate or diisopropylethylamine), a ligand (such as triphenylphosphine) and a known reaction-promoting additive (such as lithium chloride or copper iodide) as required in the presence of an appropriate organoboronic acid, organotin, organozinc or organomagnesium derivative

or the like (such as Compound 7) and an appropriate transition metal catalyst (such as a palladium compound).

The above coupling reaction is performed using an appropriate solvent that does not adversely affect the reaction (such as N,N-dimethylformamide, tetrahydrofuran, toluene, 1,4-dioxane or water) or a mixed solvent thereof at a reaction temperature of preferably 0°C to 300°C, and more preferably room temperature to 200°C (the optimum temperature is 80°C to 120°C). The above reaction can also be performed by treatment in a sealed tube or under microwave irradiation. The organoboronic acid or the like and the base may be used in an amount of one to excess molar equivalents, and preferably 1 to 5 molar equivalents, based on Compound 6, respectively. The reaction time is preferably 1 minute to 60 hours, and more preferably 5 minutes to 24 hours.

[Production Process 2]



Compound 1a can also be obtained by performing the amidation reaction (2) and the coupling reaction (3) in the reverse order for Compound 4 of the above Production Process 1.

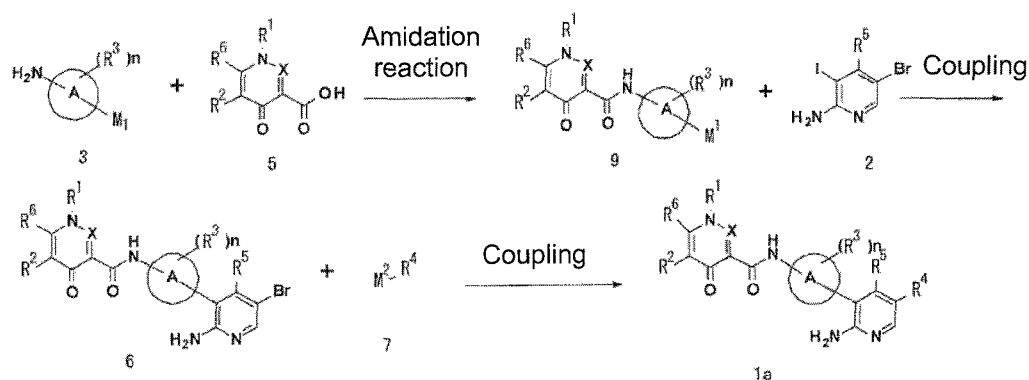
(1) Conversion of Compound 4 to Compound 8

Compound 4 can be converted to Compound 8 by a common coupling reaction similar to the method described in (1) of the above Production Process 1.

(2) Conversion of Compound 8 to Compound 1a

Compounds 8 and 5 can be converted to Compound 1a by a common amidation reaction similar to the method described in the above Production Process 1.

[Production Process 3]



Compound 1a can also be obtained by previously synthesizing Compound 9 having a partial structure containing A and then performing a coupling reaction of Compound 9 with Compound 2.

(1) Conversion of Compound 3 to Compound 9

Compounds 3 and 5 are converted to Compound 9 by an amidation reaction of Compound 3 using a known organic chemistry technique. The details of the reaction are similar to those of the method (2) described in Production Process 1 (a common amidation reaction).

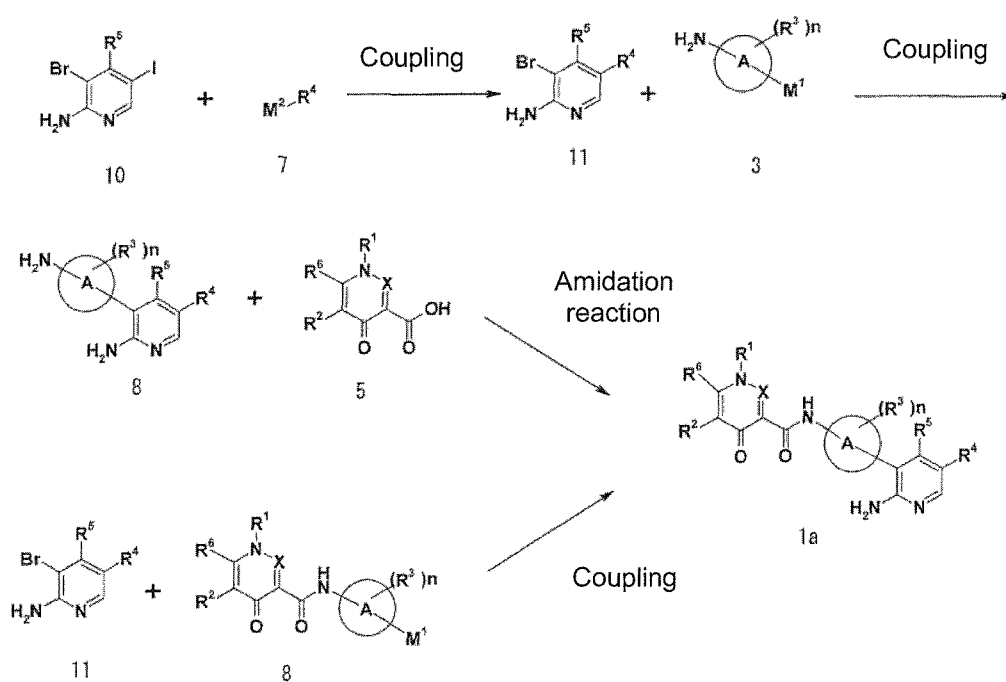
(2) Conversion of Compound 9 to Compound 6

Compounds 2 and 9 are converted to Compound 6 by a coupling reaction of Compound 2 with Compound 9 having a partial structure containing A using a known organic chemistry reaction. The details of the reaction are similar to those of the method (1) described in Production Process 1 (a common coupling reaction).

(3) Conversion of Compound 6 to Compound 1a

The conversion of Compound 6 to Compound 1a is as illustrated in Production Process 1.

[Production Process 4]

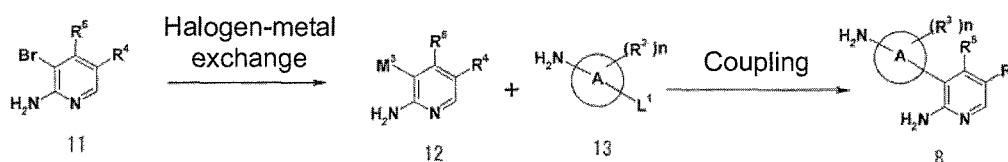


Compound 1a can also be produced using Compound 10.

The details of the reaction are similar to those of Production Processes 1 and 2, and Compounds 3 and 7 can be used in the reverse order in the steps.

Compound 8 of Production Process 4 can also be produced according to the following reaction scheme, for example.

[Production Process 5]



(1) Conversion of Compound 11 to Compound 12

Compound 11 is converted to Compound 12 by subjecting Compound 11 to a halogen-metal exchange reaction using a known organic chemistry technique. The reaction is performed by adding to Compound 11 an organic or inorganic base (such as potassium acetate, sodium carbonate or diisopropylethylamine), a ligand (such as triphenylphosphine) and a known reaction-promoting additive (such as lithium chloride or copper iodide) as required in the presence of an appropriate diboronate ester, alkyltin compound or the like and an appropriate transition metal catalyst (such as a palladium compound), for example.

The above coupling reaction is performed using an appropriate solvent that does not adversely affect the reaction (such as N,N-dimethylformamide, tetrahydrofuran, toluene, 1,4-dioxane or water) or a mixed solvent thereof at a reaction temperature of preferably 0°C to 300°C, and more preferably room temperature to 200°C. The above reaction can also be performed by treatment in a sealed tube or under microwave irradiation. The diboronate ester or the like and the base may be used in an amount of one to excess molar equivalents, and preferably 1 to 5 molar equivalents, based on Compound 11, respectively. The reaction time is preferably 1 minute to 60 hours, and more preferably 5 minutes to 24 hours.

(2) Conversion of Compound 12 to Compound 8

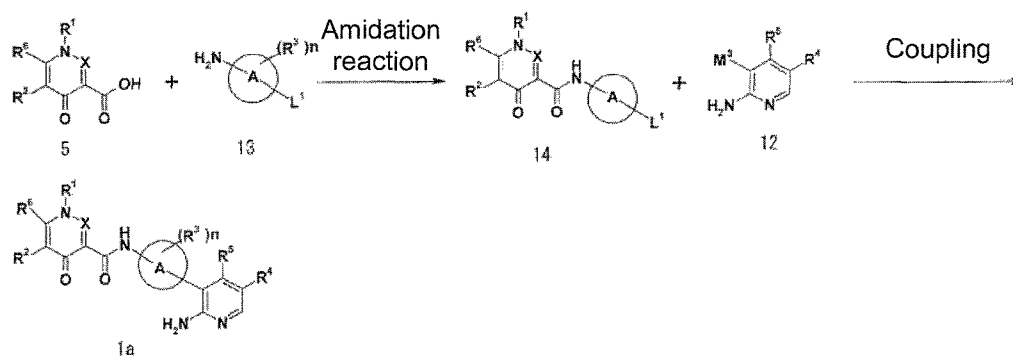
Compound 12 is converted to Compound 8 by a coupling reaction of Compound 12 with Compound 13 using a known organic chemistry technique.

The reaction is performed by adding to Compound 12 an organic or inorganic base (such as sodium carbonate, potassium carbonate, tripotassium phosphate or diisopropylethylamine), a ligand (such as triphenylphosphine) and a known reaction-promoting additive (such as lithium chloride or copper iodide) as required in the presence of Compound 13 and an appropriate transition metal catalyst (such as a palladium compound), for example.

The above coupling reaction is performed using an appropriate solvent that does not adversely affect the reaction (such as N,N-dimethylformamide, tetrahydrofuran, toluene, 1,4-dioxane or water) or a mixed solvent thereof at a reaction temperature of preferably 0°C to 300°C, and more preferably room temperature to 200°C (the optimum temperature is 80°C to 100°C). The above reaction can also be performed by treatment in a sealed tube or under microwave irradiation. Compound 13 and the base may be used in an amount of one to excess molar equivalents, and preferably 1 to 5 molar equivalents, based on Compound 12, respectively. The reaction time is preferably 1 minute to 60 hours, and more preferably 5 minutes to 24 hours.

Compound 1a can also be produced from Compound 14 that can be synthesized from Compounds 5 and 13 and the aforementioned Compound 12.

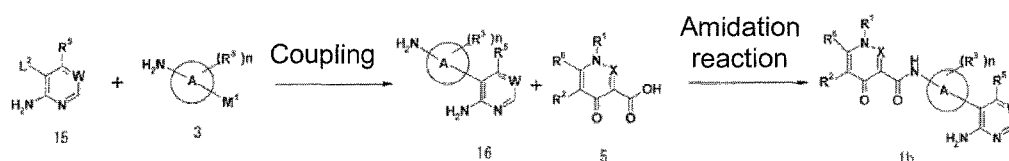
[Production Process 6]



The details of the reaction are similar to those of Production Process 5.

Compound 1b which is a compound represented by the formula (1), where W is N or CH, can be produced according to the following Production Process 7.

[Production Process 7]

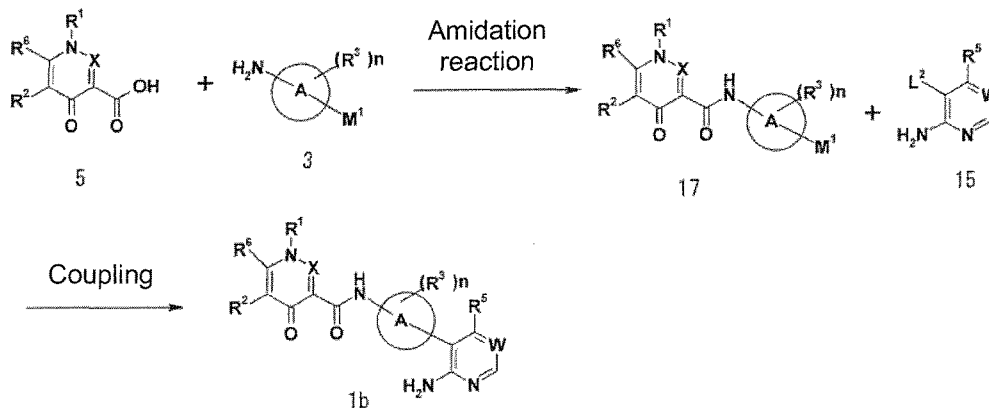


Compound 15 can be converted to Compound 16 by an operation similar to the common coupling reaction described in Production Process 1.

Compound 16 can be converted to Compound 1b by an operation similar to the common amidation reaction described in Production Process 1.

[Production Process 8]

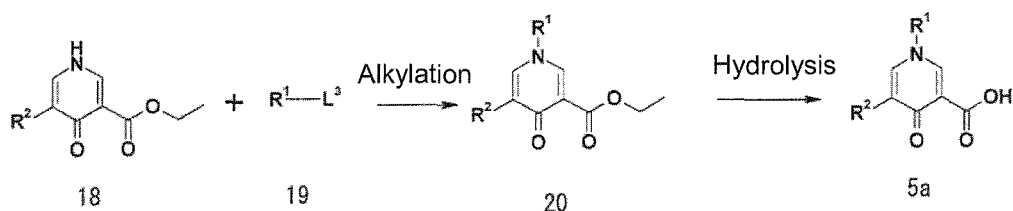
Compound 1b can also be produced as in Production Process 8 where the reactions in Production Process 7 are performed in the reverse order.



The details of the reaction are similar to those of the method described in Production Process 7.

[Production Process 9]

Compound 5a illustrated below, which is a Compound 5, can be produced using Intermediate 18 that is commercially available or can be synthesized by a known method or with reference to an example previously reported in J. Heterocyclic Chem. 1980, 17, 359, Chem. Pharm. Bull. 1995, 43, 450 or the like. Hereinafter, L³ represents a halogen atom, a methanesulfonyloxy group, a trifluoromethanesulfonyloxy group, a p-toluenesulfonyloxy group or the like.



(1) Conversion of Compound 18 to Compound 20

Compound 18 may be converted to Compound 20 by subjecting Compound 18 to an alkylation reaction using a known organic chemistry technique. For example, the reaction is performed by treating Compound 18 with Compound 19 having a partial structure containing R¹ (such as an alkyl halide compound, a methanesulfonyloxyalkyl compound, a trifluoromethanesulfonyloxyalkyl compound or a p-toluenesulfonyloxyalkyl compound) in an appropriate

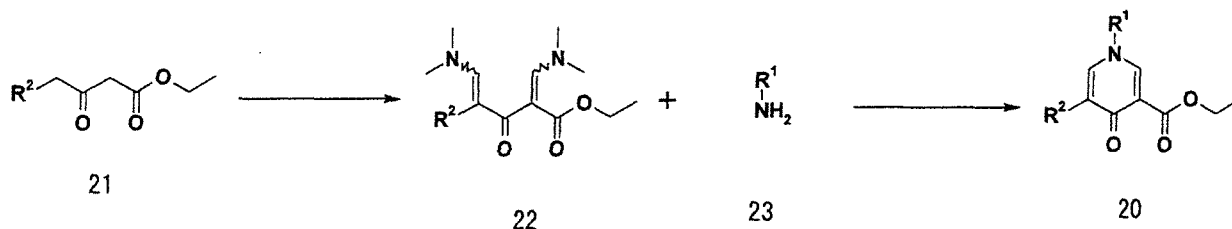
solvent that does not adversely affect the reaction (such as N,N-dimethylformamide, dimethyl sulfoxide or acetonitrile) or a mixed solvent thereof in the presence of an organic or inorganic base (such as potassium carbonate, cesium carbonate, potassium tert-butoxide or triethylamine) at 0°C to 300°C, and preferably 0°C to 100°C. Compound 19 and the base may be used in an amount of one to excess molar equivalents, and preferably 1 to 5 molar equivalents, based on Compound 18, respectively. The reaction time is preferably 1 minute to 72 hours, and more preferably 5 minutes to 24 hours.

(2) Conversion of Compound 20 to Compound 5a

Compound 20 may be converted to Compound 5a by a common hydrolysis reaction. For example, the reaction is performed by treating Compound 20 with an appropriate acid (such as sulfuric acid or hydrochloric acid) or alkali (such as sodium hydroxide or potassium carbonate) in an appropriate solvent that does not adversely affect the reaction (such as ethanol, propanol or water) or a mixed solvent thereof at a reaction temperature of 0°C to 200°C, and preferably 0°C to 100°C. The appropriate acid or alkali is used in an amount of one to excess molar equivalents based on Compound 20. The reaction time is preferably 1 minute to 72 hours, and more preferably 5 minutes to 24 hours.

[Production Process 10]

Compound 20 in Production Process 9 can also be produced from an ester Compound 21 that can be synthesized with reference to J. Org. Chem. 1988, 53, 873 or the like.



(1) Conversion of Compound 21 to Compound 22

Compound 21 is converted to Compound 22 by treating Compound 21 having a partial structure containing R² with N,N-dimethylformamide dimethylacetal without a solvent or in an appropriate solvent that does not adversely affect the reaction (such as toluene, xylene, dichloromethane, ethanol, N,N-dimethylformamide or ethyl acetate) or a mixed solvent thereof at 0°C to 300°C, and preferably 0°C to 130°C. N,N-Dimethylformamide dimethylacetal may be used in an amount of two to excess molar equivalents based on Compound 21. The reaction time is preferably 1 minute to 72 hours, and more preferably 5 minutes to 24 hours.

(2) Conversion of Compound 22 to Compound 20

Compound 22 is converted to Compound 20 by treating Compound 22 with Compound 23 having a partial structure containing R¹ in an appropriate solvent that does not affect the reaction (such as toluene, ethyl acetate,

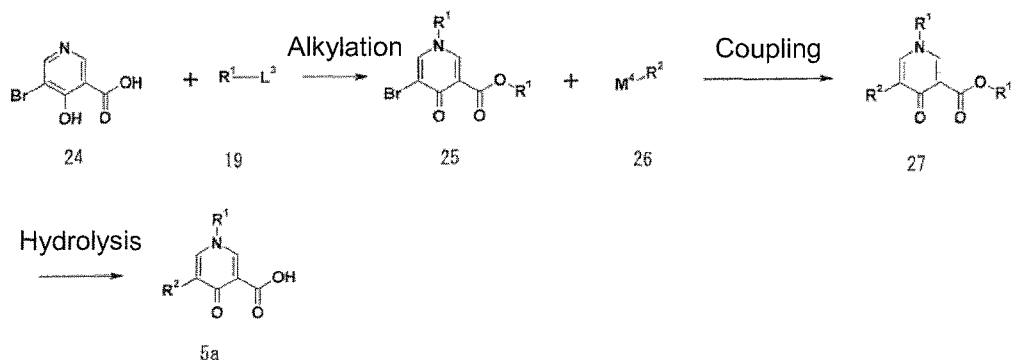
ethanol or 1,4-dioxane) or a mixed solvent thereof at 0°C to 300°C, and preferably 0°C to 130°C. The above reaction is performed by adding an organic or inorganic base (such as potassium carbonate, cesium carbonate, potassium tert-butoxide or triethylamine) or an acid (such as acetic acid, hydrogen chloride, hydrogen bromide or sulfuric acid) as required. Compound 23, base or acid may be used in an amount of one to excess molar equivalents, and preferably 1 to 5 molar equivalents, based on Compound 22. The reaction time is preferably 1 minute to 72 hours, and more preferably 5 minutes to 24 hours.

In Production Process 10, an orthoformate (such as ethyl orthoformate) may also be used in place of N,N-dimethylformamide dimethylacetal.

In Production Process 10, it is also possible to use a salt of Compound 23 having a partial structure containing R¹ with an acid.

[Production Process 11]

Compound 5a can also be produced using Compound 24 known from J. Med. Chem. 2008, 51, 5330.



(1) Conversion of Compound 24 to Compound 25

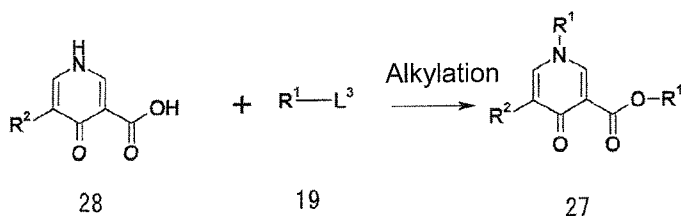
Compound 24 may be converted to Compound 25 by subjecting Compound 24 to an alkylation reaction using a known organic chemistry technique. For example, the reaction is performed by treating Compound 24 with Compound 19 having a partial structure containing R¹ (such as an alkyl halide compound, a methanesulfonyloxyalkyl compound, a trifluoromethanesulfonyloxyalkyl compound or a p-toluenesulfonyloxyalkyl compound) in an appropriate solvent that does not adversely affect the reaction (such as N,N-dimethylformamide, dimethyl sulfoxide, 1,4-dioxane or acetonitrile) or a mixed solvent thereof in the presence of an organic or inorganic base (such as potassium carbonate, cesium carbonate, potassium tert-butoxide or triethylamine) at 0°C to 300°C, and preferably 0°C to 100°C. Compound 19 may be used in an amount of two to excess molar equivalents, and preferably 2 to 10 molar equivalents, based on Compound 24. The reaction time is preferably 1 minute to 72 hours, and more preferably 5 minutes to 24 hours.

(2) Compound 25 may be converted to Compound 27 by subjecting Compound 25 to an operation similar to the common coupling reaction described in Production Process 1.

(3) Compound 27 may be converted to Compound 5a by subjecting Compound 27 to an operation similar to the common hydrolysis reaction described in Production Process 9.

[Production Process 12]

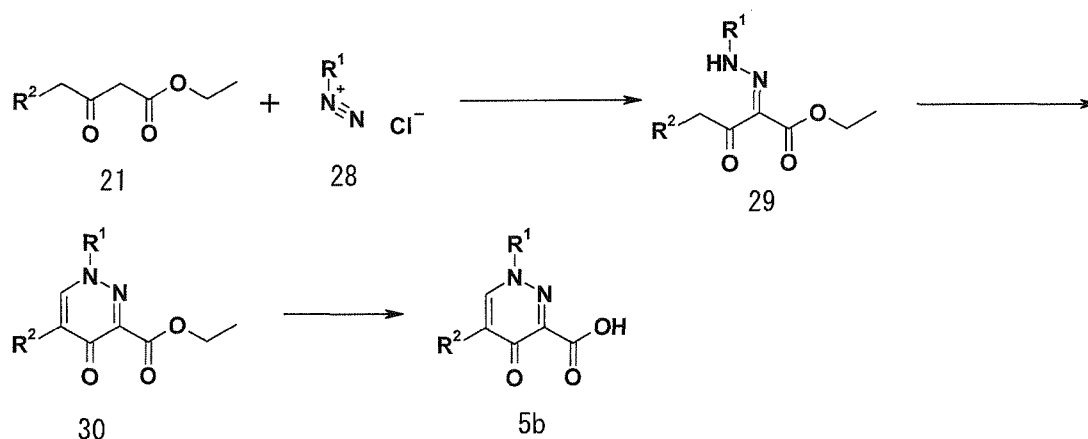
Compound 27 in Production Process 11 can also be produced from a carboxylic acid Compound 28.



Compounds 28 and 19 may be converted to Compound 27 by subjecting Compound 28 to a treatment similar to the alkylation reaction described in Production Process 11-(1).

[Production Process 13]

Compound 5b shown below can be synthesized with reference to the method in Tetrahedron, 1995, 51, 12745.



(1) Conversion of Compound 21 to Compound 29

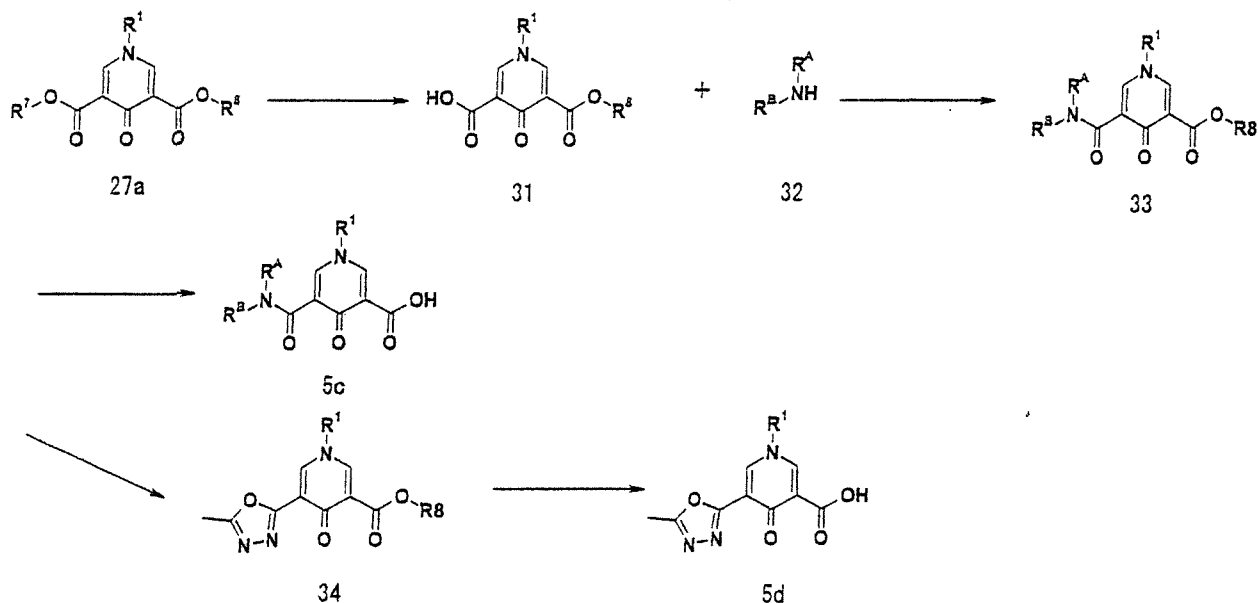
Compound 21 is converted to Compound 29 by treating with a diazo Compound 28 having a partial structure containing R¹ in an appropriate solvent that does not adversely affect the reaction (such as acetone, methanol, ethanol or water) or a mixed solvent thereof in the presence of a base (such as potassium carbonate, sodium acetate or potassium acetate) at 0°C to 300°C, and preferably 0°C to 100°C. Compound 28 may be used in an amount of one to excess molar equivalents, and preferably one molar equivalent, based on Compound 21. The reaction time is preferably 1 minute to 72 hours, and more preferably 5 minutes to 24 hours.

(2) Compound 29 may be converted to Compound 30 by subjecting Compound 29 to an operation similar to the method described in Production Process 10. N,N-Dimethylformamide dimethylacetal may be used in an amount of one to excess molar equivalents based on Compound 29.

(3) Compound 30 may be converted to Compound 5b by subjecting Compound 29 to an operation similar to the common hydrolysis reaction described in Production Process 9.

[Production Process 14]

Compounds 5c and 5d shown below can be synthesized using Compound 27a having a partial structure containing a carboxylate as illustrated below, which is a Compound 27 that can be synthesized according to Production Process 11. Hereinafter, R^7 and R^8 each represent a methyl group, an ethyl group, a tert-butyl group or the like.



(1) Compound 27a may be converted to Compound 31 by subjecting Compound 27a to an operation similar to the hydrolysis reaction described in Production Process 9.

(2) Compound 31 may be converted to Compound 33 by subjecting Compound 31 to an operation similar to the common amidation reaction described in Production Process 1.

(3) Compound 33 can be converted to Compound 34 by subjecting Compound 33 to common reaction conditions for oxadiazole formation with reference to Tetrahedron Letters (2006), 47, 511, for example. The reaction is performed by treating Compound 33 with hexachloroethane and triphenylphosphine in an appropriate solvent that does not adversely affect the reaction (such as dichloromethane, tetrahydrofuran or acetonitrile) or a mixed solvent thereof in the presence of a base (such as diisopropylethylamine or triethylamine) at 0°C to 300°C, and preferably 0°C to 100°C. The base, hexachloroethane and triphenylphosphine may be used in an amount of one to excess molar equivalents, and preferably 1 to 5 molar equivalents, based on Compound 33, respectively. The reaction time is preferably 1 minute to 72 hours, and more preferably 5 minutes to 24 hours.

(4) Compound 33 may be converted to Compound 5c by subjecting Compound 33 to an operation similar to the hydrolysis reaction described in Production Process 9.

(5) Compound 34 can be converted to Compound 5d by an alkali hydrolysis reaction. For example, the reaction is performed by treating Compound 34 with an appropriate alkali (such as sodium hydroxide or potassium carbonate)

in an appropriate solvent that does not adversely affect the reaction (such as ethanol, propanol, tetrahydrofuran or water) or a mixed solvent thereof at a reaction temperature of 0°C to 200°C, and preferably room temperature to 150°C. The appropriate alkali is used in an amount of one to excess molar equivalents based on Compound 34. The reaction time is preferably 1 minute to 72 hours, and more preferably 5 minutes to 24 hours.

Production raw materials 2, 10 and 15 are commercially available or can be synthesized according to a known method.

Production raw material 3 is commercially available or can be synthesized according to a known method such as described in the literature (such as Bioorg. Med. Chem. Lett., 2007, 17, 5406).

Production raw material 7 is commercially available or can be synthesized according to a known method or a method described in Reference Examples.

Production raw materials 18, 28, 21 and 27a are commercially available or can be synthesized according to a known method or a method described in Reference Examples.

Production raw material 19 is commercially available or can be synthesized according to a known method.

As described above, the Gas6/Axl signaling system has been reported to modulate various cellular responses such as cell survival, cell division, autophagy, cell

migration, angiogenesis, platelet aggregation and NK cell differentiation (Rachel MA Linger et al., Expert Opin. Ther. Targets 2010 14, 1073). Therefore, Axl inhibitors are useful for treating diseases caused by Axl kinase hyperfunction, diseases associated with Axl kinase hyperfunction and/or diseases accompanied by Axl kinase hyperfunction.

Diseases caused by Axl kinase hyperfunction, diseases associated with Axl kinase hyperfunction and diseases accompanied by Axl kinase hyperfunction include diseases involving tissues in which Axl genes and/or proteins are overexpressed, and diseases involving tissues in which phosphorylation activity of Axl is increased.

Examples of the above diseases include hyperproliferative diseases. Examples of hyperproliferative diseases include, but are not limited to, endometrial hyperplasia, thrombin-induced vascular smooth muscle cell (VSMC) growth, benign tumor, malignant tumor (cancer), acute and chronic glomerulonephritis, and diabetic nephropathy.

It has further been demonstrated that Axl has a role in immunity (Lu et al., Science, 2001, 293, 306), platelet function (Angelillo-Scherrer et al., Nat. Med., 2001, 7, 215), spermatogenesis (Lu et al., Nature, 1999, 398, 723), vascular calcification (Son et al., Eur. J. Pharmacol., 2007, 556, 1), (Nakano et al, J. Biol. Chem.,

1995, 270, 5702), and various renal diseases such as chronic allograft rejection (Yanagita et al., J. Clin. Invest., 2002, 110, 239). Axl inhibitors are useful for treating many diseases such as vascular diseases (including, but not limited to, thrombosis, atherosclerosis and restenosis) and diseases with significant chaotic angiogenesis (including, but not limited to, diabetic retinopathy, retinopathy, psoriasis, rheumatoid arthritis, atheroma, Kaposi's sarcoma and hemangioma).

The compounds or salts thereof, or crystals thereof, according to the present invention inhibit Axl and are thus useful for treating the above-described diseases.

More preferably, the compounds or salts thereof, or crystals thereof, according to the present invention are useful for treating various cancers. Examples of cancers include, but are not limited to, breast cancer, colon cancer, prostate cancer, lung cancer, gastric cancer, ovarian cancer, cervical cancer, endometrial cancer, uterine body cancer, renal cancer, hepatocellular carcinoma, thyroid cancer, esophageal cancer, squamous cell carcinoma, leukemia, osteosarcoma, melanoma, glioblastoma, neuroblastoma, ovarian cancer, head and neck cancer, testicular tumor, colorectal cancer, blood cancer, retinoblastoma and pancreatic cancer.

Various reports on the relation between cancer and Axl have been made in terms of inhibition of growth,

inhibition of metastasis, migration and invasion, and overcoming of drug resistance.

Axl dominant negative mutants have been reported to inhibit brain tumor growth (Vajkoczy et al., PNAS 2006, 103, 5799). It has been reported that when Axl is expressed or Axl/Gas6 are coexpressed in tissues derived from glioblastoma patients, the tumors grow significantly more rapidly and the lifetime of the patients is short (Hutterer et al., Clin Cancer Res 2008, 14, 130). Axl shRNA has been reported to inhibit proliferation of breast cancer cells (Yi-Xiang et al., Cancer Res 2008, 68, 1905). As is clear from these reports, Axl inhibitors are useful for inhibiting cell proliferation in cancer.

On the other hand, Axl dominant negative mutants have been reported to inhibit cell migration and invasion (Zhang et al., Cancer Res 2008 68, 1905, Vajkoczy et al., PNAS 2006, 103, 5799 and Holland et al., Cancer Res 2005, 65, 9294). Axl shRNA has been reported to inhibit metastasis in vivo (Li et al., Oncogene 2009, 28, 3442). Anti-Axl antibodies and siRNA have been reported to inhibit tumor growth and metastasis in a mouse model (Li et al., Oncogene 2009 28, 3442 and Ye et al., Oncogene 2010, 29, 5254). Axl has been reported to promote cell invasion (Tai et al., Oncogene 2008, 27, 4044). R-428, an Axl inhibitor, has been reported to inhibit a diffusion model of metastatic breast cancer (Holland et al., Cancer Res 2010, 70, 1544). Axl antibodies, Axl

shRNA and NA80x1, an Axl inhibitor, have been reported to inhibit migration and invasion of breast cancer cells (Yi-Xiang et al., Cancer Res 2008, 68 1905).

Additionally, there have been reports on the involvement of Axl in metastasis and malignant progression of prostatic cancer, spleen cancer, metastatic ovarian cancer, thymic carcinoma and the like. As is clear from these reports, Axl inhibitors are useful for suppressing, treating and preventing cancer metastasis, cell migration and cell invasion, for example.

Also, Axl inhibitors have been reported to overcome imatinib resistance in gastric cancer (Mahadevan et al., Oncogene 2007, 26, 3909). It has been demonstrated that Axl is induced in resistance to chemotherapeutic agents such as doxorubicin, VP16 and cisplatin in acute myeloid leukemia (Hong et al., Cancer Letters 2008, 268, 314). It has been reported that Axl is activated in lapatinib resistance in HER-2 positive breast cancer cells (Liu et al., Cancer Res 2009, 69, 6871). Axl has been reported to be involved in the PLX4032 (vemurafenib) resistance mechanism (Johannessen et al., Nature 2010, 468, 968). Additionally, Axl has been reported to be involved in resistance to temozolomide, carboplatin and vincristine (AK Keeating et al., Mol Cancer Ther 2010, 9(5), 1298). As is clear from these reports, Axl inhibitors are useful for overcoming drug resistance such as resistance to various anticancer agents.

Moreover, Axl has been reported to be involved in renal diseases such as fibril formation in the kidney and diabetic nephropathy (National Publication of International Patent Application No. 2005-517412), and Axl inhibitors are obviously useful for treating the above renal diseases as well as fibrillization diseases such as idiopathic pulmonary fibrosis.

Axl inhibitory activity of compounds can be measured by methods including, but not limited to, the methods described in the Test Examples of the present application.

Another embodiment of the present invention is N-{4-[2-amino-5-(3,4-dimethoxyphenyl)pyridin-3-yl]phenyl}-5-(4-fluorophenyl)-4-oxo-1-(2,2,2-trifluoroethyl)-1,4-dihydropyridine-3-carboxamide (hereinafter sometimes described as "compound (1)" in the present specification) or a salt thereof, and preferably N-{4-[2-amino-5-(3,4-dimethoxyphenyl)pyridin-3-yl]phenyl}-5-(4-fluorophenyl)-4-oxo-1-(2,2,2-trifluoroethyl)-1,4-dihydropyridine-3-carboxamide hydrochloride.

Another embodiment of the present invention is crystals of N-{4-[2-amino-5-(3,4-dimethoxyphenyl)pyridin-3-yl]phenyl}-5-(4-fluorophenyl)-4-oxo-1-(2,2,2-trifluoroethyl)-1,4-dihydropyridine-3-carboxamide hydrochloride.

Here, the term crystal refers to a solid whose internal structure is formed by a three-dimensionally regular repetition of constituent atoms (or a group

thereof), and is distinguished from an amorphous solid not having such a regular internal structure.

Further, salts of the compounds (1) include any of those in the Examples. The compounds (1) or salts thereof may exist as free forms or solvates. They may exist as solvates due to absorption of moisture in the air, for example. Solvates are not particularly limited if pharmaceutically acceptable, and specific examples include hydrates (such as monohydrates or dihydrates), ethanolates and 2-propanolates.

Crystals of the same compound having a plurality of different internal structures and physicochemical properties (crystal polymorphs) may be generated depending on the crystallization conditions. The crystals of the present invention may be any of these crystal polymorphs or may be a mixture of two or more crystal polymorphs.

The crystals of the present invention may absorb moisture or adsorb water when left to stand in the air or may be heated to 25 to 150°C under normal atmospheric conditions, for example, to form a hydrate. Further, the crystals of the present invention may also contain a solvent during crystallization in the attached residual solvent or solvate.

In the present specification, the crystals of the present invention may be represented based on powder X-ray diffraction data. Powder X-ray diffraction may be

measured and analyzed by a technique usually used in the art such as a method described in the Examples. Generally, in hydrates and dehydrates, attachment and detachment of water of crystallization may change their lattice constants and thus diffraction angles (2θ) in powder X-ray diffraction. Also, the peak intensity may be changed by the difference in crystal growth surface or the like (crystal habit), for example. Accordingly, when the crystals of the present invention are represented based on powder X-ray diffraction data, crystals whose peak diffraction angles and powder X-ray diffraction patterns in powder X-ray diffraction are identical to those of the crystals of the present invention, as well as hydrates and dehydrates obtained from them, are encompassed within the scope of the present invention.

A preferred form of the crystals of the present invention is crystals having a powder X-ray diffraction pattern shown in FIG. 1 in a powder X-ray diffraction diagram obtained by irradiation with copper $K\alpha$ radiation (wavelength $\lambda = 1.54 \text{ \AA}$). The crystals are also crystals having characteristic peaks at diffraction angles 2θ of 7.44, 10.00, 13.48, 14.86, 16.10, 19.30, 20.30, 22.62, 23.02, 23.70, 24.54, 25.92 and 28.46 in a powder X-ray diffraction diagram obtained by irradiation with copper $K\alpha$ radiation (wavelength $\lambda = 1.54 \text{ \AA}$).

Another preferred form of the crystals of the present invention is crystals having a powder X-ray

diffraction pattern shown in FIG. 2 in a powder X-ray diffraction diagram obtained by irradiation with copper $K\alpha$ radiation (wavelength $\lambda = 1.54 \text{ \AA}$). The crystals are also crystals having characteristic peaks at diffraction angles 2θ of 4.32, 9.10, 15.52, 18.32, 18.54, 19.22, 20.54, 20.70, 23.54, 24.14, 25.34 and 27.02 in a powder X-ray diffraction diagram obtained by irradiation with copper $K\alpha$ radiation (wavelength $\lambda = 1.54 \text{ \AA}$).

Another preferred form of the crystals of the present invention is crystals having a powder X-ray diffraction pattern shown in FIG. 3 in a powder X-ray diffraction diagram obtained by irradiation with copper $K\alpha$ radiation (wavelength $\lambda = 1.54 \text{ \AA}$). The crystals are also crystals having characteristic peaks at diffraction angles 2θ of 13.86, 15.04, 19.76, 20.58, 22.26, 22.58, 23.82, 24.10, 24.36 and 24.88 in a powder X-ray diffraction diagram obtained by irradiation with copper $K\alpha$ radiation (wavelength $\lambda = 1.54 \text{ \AA}$).

Another preferred form of the crystals of the present invention is crystals having a powder X-ray diffraction pattern shown in FIG. 4 in a powder X-ray diffraction diagram obtained by irradiation with copper $K\alpha$ radiation (wavelength $\lambda = 1.54 \text{ \AA}$). The crystals are also crystals having characteristic peaks at diffraction angles 2θ of 5.34, 7.22, 8.20, 11.68, 14.54, 15.74, 17.54, 23.24, 23.72, 25.12 and 26.16 in a powder X-ray

diffraction diagram obtained by irradiation with copper $K\alpha$ radiation (wavelength $\lambda = 1.54 \text{ \AA}$).

Another preferred form of the crystals of the present invention is crystals having a powder X-ray diffraction pattern shown in FIG. 5 in a powder X-ray diffraction diagram obtained by irradiation with copper $K\alpha$ radiation (wavelength $\lambda = 1.54 \text{ \AA}$). The crystals are also crystals having characteristic peaks at diffraction angles 2θ of 11.02, 11.86, 15.56, 18.20, 22.12, 24.70, 25.80, 26.04, 26.26 and 28.62 in a powder X-ray diffraction diagram obtained by irradiation with copper $K\alpha$ radiation (wavelength $\lambda = 1.54 \text{ \AA}$).

Another preferred form of the crystals of the present invention is crystals having a powder X-ray diffraction pattern shown in FIG. 6 in a powder X-ray diffraction diagram obtained by irradiation with copper $K\alpha$ radiation (wavelength $\lambda = 1.54 \text{ \AA}$). The crystals are also crystals having characteristic peaks at diffraction angles 2θ of 3.58, 4.56, 6.60, 6.72, 7.20, 9.62, 10.28, 13.06 and 24.52 in a powder X-ray diffraction diagram obtained by irradiation with copper $K\alpha$ radiation (wavelength $\lambda = 1.54 \text{ \AA}$).

Another preferred form of the crystals of the present invention is crystals having a powder X-ray diffraction pattern shown in FIG. 7 in a powder X-ray diffraction diagram obtained by irradiation with copper $K\alpha$ radiation (wavelength $\lambda = 1.54 \text{ \AA}$). The crystals are

also crystals having characteristic peaks at diffraction angles 2θ of 7.78, 8.14, 8.88, 12.54, 15.68, 16.36, 18.76, 19.34, 20.08, 22.36, 24.66, 25.74, 26.70 and 28.02 in a powder X-ray diffraction diagram obtained by irradiation with copper $K\alpha$ radiation (wavelength $\lambda = 1.54 \text{ \AA}$).

Another preferred form of the crystals of the present invention is crystals having a powder X-ray diffraction pattern shown in FIG. 8 in a powder X-ray diffraction diagram obtained by irradiation with copper $K\alpha$ radiation (wavelength $\lambda = 1.54 \text{ \AA}$). The crystals are also crystals having characteristic peaks at diffraction angles 2θ of 5.78, 8.90, 13.66, 14.42, 16.84, 17.56, 19.26, 20.74, 22.42, 24.66, 25.12, 25.60 and 26.96 in a powder X-ray diffraction diagram obtained by irradiation with copper $K\alpha$ radiation (wavelength $\lambda = 1.54 \text{ \AA}$).

Another preferred form of the crystals of the present invention is crystals having a powder X-ray diffraction pattern shown in FIG. 9 in a powder X-ray diffraction diagram obtained by irradiation with copper $K\alpha$ radiation (wavelength $\lambda = 1.54 \text{ \AA}$). The crystals are also crystals having characteristic peaks at diffraction angles 2θ of 11.12, 14.82, 18.86, 20.32, 20.66, 21.64, 22.36, 22.68, 23.00, 24.10, 25.26 and 27.00 in a powder X-ray diffraction diagram obtained by irradiation with copper $K\alpha$ radiation (wavelength $\lambda = 1.54 \text{ \AA}$).

Another preferred form of the crystals of the present invention is crystals having a powder X-ray

diffraction pattern shown in FIG. 10 in a powder X-ray diffraction diagram obtained by irradiation with copper $K\alpha$ radiation (wavelength $\lambda = 1.54 \text{ \AA}$). The crystals are also crystals having characteristic peaks at diffraction angles 2θ of 7.80, 12.18, 12.78, 16.20, 16.82, 19.20, 19.66, 20.20, 21.20, 24.52, 25.68 and 26.78 in a powder X-ray diffraction diagram obtained by irradiation with copper $K\alpha$ radiation (wavelength $\lambda = 1.54 \text{ \AA}$).

Another preferred form of the crystals of the present invention is crystals having a powder X-ray diffraction pattern shown in FIG. 11 in a powder X-ray diffraction diagram obtained by irradiation with copper $K\alpha$ radiation (wavelength $\lambda = 1.54 \text{ \AA}$). The crystals are also crystals having characteristic peaks at diffraction angles 2θ of 2.80, 6.86, 7.88, 11.60, 13.68, 14.86, 17.40, 22.40, 23.78 and 25.74 in a powder X-ray diffraction diagram obtained by irradiation with copper $K\alpha$ radiation (wavelength $\lambda = 1.54 \text{ \AA}$).

Another preferred form of the crystals of the present invention is crystals having a powder X-ray diffraction pattern shown in FIG. 12 in a powder X-ray diffraction diagram obtained by irradiation with copper $K\alpha$ radiation (wavelength $\lambda = 1.54 \text{ \AA}$). The crystals are also crystals having characteristic peaks at diffraction angles 2θ of 5.32, 7.98, 10.68, 11.70, 14.84, 16.02, 19.78, 21.76, 23.08, 25.30 and 25.68 in a powder X-ray

diffraction diagram obtained by irradiation with copper $K\alpha$ radiation (wavelength $\lambda = 1.54 \text{ \AA}$).

Another preferred form of the crystals of the present invention is crystals having a powder X-ray diffraction pattern shown in FIG. 13 in a powder X-ray diffraction diagram obtained by irradiation with copper $K\alpha$ radiation (wavelength $\lambda = 1.54 \text{ \AA}$). The crystals are also crystals having characteristic peaks at diffraction angles 2θ of 8.10, 10.60, 12.06, 14.16, 14.58, 15.60, 18.16, 20.72, 20.94, 22.86, 23.90, 24.32 and 27.14 in a powder X-ray diffraction diagram obtained by irradiation with copper $K\alpha$ radiation (wavelength $\lambda = 1.54 \text{ \AA}$).

Another preferred form of the crystals of the present invention is crystals having a powder X-ray diffraction pattern shown in FIG. 14 in a powder X-ray diffraction diagram obtained by irradiation with copper $K\alpha$ radiation (wavelength $\lambda = 1.54 \text{ \AA}$). The crystals are also crystals having characteristic peaks at diffraction angles 2θ of 3.60, 6.22, 9.56, 10.42, 14.04, 14.66, 15.30, 16.40, 19.52, 22.12 and 26.42 in a powder X-ray diffraction diagram obtained by irradiation with copper $K\alpha$ radiation (wavelength $\lambda = 1.54 \text{ \AA}$).

Another preferred form of the crystals of the present invention is crystals having a powder X-ray diffraction pattern shown in FIG. 15 in a powder X-ray diffraction diagram obtained by irradiation with copper $K\alpha$ radiation (wavelength $\lambda = 1.54 \text{ \AA}$). The crystals are

also crystals having characteristic peaks at diffraction angles 2θ of 5.46, 7.98, 9.54, 11.00, 14.00, 15.36, 16.56, 22.00, 23.54, 24.00 and 26.56 in a powder X-ray diffraction diagram obtained by irradiation with copper $K\alpha$ radiation (wavelength $\lambda = 1.54 \text{ \AA}$).

Another preferred form of the crystals of the present invention is crystals having a powder X-ray diffraction pattern shown in FIG. 16 in a powder X-ray diffraction diagram obtained by irradiation with copper $K\alpha$ radiation (wavelength $\lambda = 1.54 \text{ \AA}$). The crystals are also crystals having characteristic peaks at diffraction angles 2θ of 5.64, 6.92, 8.06, 11.32, 14.40, 16.18, 17.04, 21.84, 22.50, 23.82 and 24.28 in a powder X-ray diffraction diagram obtained by irradiation with copper $K\alpha$ radiation (wavelength $\lambda = 1.54 \text{ \AA}$).

Another embodiment of the present invention relates to a medicine comprising a crystal of the present invention as an active ingredient.

A medicine comprising a crystal of the present invention as an active ingredient is preferably provided in the form of a pharmaceutical composition comprising a crystal of the present invention and one or more pharmaceutically acceptable carriers. The administration form of the medicine of the present invention is not particularly limited. The medicine can be orally or parenterally administered, but is preferably orally administered.

A pharmaceutical composition of the present invention at least partially comprises a compound (1) or a salt thereof, or a crystal thereof. Crystal forms other than the crystals of the present invention may be present as the compound (1) in the pharmaceutical composition. The content of the crystals of the present invention contained in the pharmaceutical composition may be in the range of 0.01 wt% to 99.9 wt%, such as 0.01 wt% or more, 0.05 wt% or more, 0.1 wt% or more, 0.5 wt% or more, 1 wt% or more, 2 wt% or more, 3 wt% or more, 4 wt% or more, 5 wt% or more, 10 wt% or more, 20 wt% or more, 30 wt% or more, 40 wt% or more, 50 wt% or more, 60 wt% or more, 70 wt% or more, 80 wt% or more, 90 wt% or more, 95 wt% or more, 96 wt% or more, 97 wt% or more, 98 wt% or more, 99 wt% or more, 99.5 wt% or more, 99.6 wt% or more, 99.7 wt% or more, 99.8 wt% or more or 99.9 wt% or more, based on the total compound (1) in the pharmaceutical composition. Whether the crystals of the present invention are contained in the pharmaceutical composition or not can be confirmed by an instrumental analysis method described in the present specification (such as powder X-ray diffractometry, thermal analysis or infrared absorption spectrometry).

Cell proliferation inhibitory activity can be examined using a proliferation inhibition assay usually used by persons skilled in the art. Cell proliferation inhibitory activity can be examined by comparing the

degree of proliferation of cells (such as tumor cells) in the presence or absence of the test compound. The degree of proliferation can be examined using a test system to measure living cells, for example. Examples of the method for measuring living cells include the [³H]-thymidine uptake test, the BrdU method and the MTT assay.

In vivo antitumor activity can be examined using an antitumor assay usually used by persons skilled in the art. For example, in vivo antitumor activity according to the present invention can be confirmed by transplanting various tumor cells into mice or rats; administering a compound or salt thereof, or a crystal thereof, according to the present invention orally or intravenously after engraftment of the transplanted cells has been confirmed; and comparing tumor growth in the drug non-administration group with tumor growth in the compound administration group several days to several weeks after the administration.

Additionally, metastasis suppressing activity, invasion inhibitory activity, migration inhibitory activity and drug resistance overcoming activity can be measured by test methods described in the documents listed above where the relation between Axl and each of the activities has been reported.

The pharmaceutical compositions of the present invention comprise a compound or salt thereof, or a crystal thereof, according to the present invention and a

pharmaceutically acceptable carrier and can be administered as various injections such as intravenous injections, intramuscular injections or subcutaneous injections or by various methods such as oral administration or transdermal administration. The pharmaceutically acceptable carrier refers to a pharmaceutically acceptable material (such as an excipient, a diluent, an additive or a solvent) involved in transport of the compound or salt thereof, or crystal thereof, according to the present invention or a composition comprising a compound or salt thereof, or a crystal thereof, according to the present invention from an organ to another organ.

Formulations (such as oral formulations or injections) can be appropriately selected according to the administration method and prepared by methods usually used for preparing various formulations. Examples of oral formulations include tablets, powders, granules, capsules, pills, troches, solutions, syrups, elixirs, emulsions and oily or aqueous suspensions. They may be orally administered either in free forms or in salt forms. Aqueous formulations can be prepared by forming acid adducts with pharmaceutically acceptable acids or by forming salts of alkali metals such as sodium. In the case of injections, it is possible to use stabilizers, preservatives, solubilizing agents and the like in the formulations. Solutions that may contain these adjuvants

may be stored in containers and then lyophilized, for example, to form solid formulations to be prepared before use. One dose may be stored in one container, or multiple doses may be stored in one container.

Examples of solid formulations include tablets, powders, granules, capsules, pills and troches. These solid formulations may contain pharmaceutically acceptable additives together with the compounds of the present invention. Examples of the additives include fillers, bulking agents, binders, disintegrants, dissolution promoters, wetting agents and lubricants, and they may be selected and mixed as necessary to prepare formulations.

Examples of liquid formulations include solutions, syrups, elixirs, emulsions and suspensions. These liquid formulations may contain pharmaceutically acceptable additives together with the compounds of the present invention. Examples of the additives include suspending agents and emulsifiers, and they may be selected and mixed as necessary to prepare formulations.

The compounds or salts thereof, or crystals thereof, according to the present invention can be used for treating cancer in mammals, in particular, humans. The dose and the dosage interval can be appropriately selected by the judgment of the physician according to the site of the disease and the height, weight, sex or medical history of the patient. When the compound of the

present invention is administered to a human, the dose is in the range of about 0.01 mg/kg weight to about 500 mg/kg weight per day, and preferably about 0.1 mg/kg weight to about 100 mg/kg weight per day. In administration to a human, the dose is preferably administered in either a single dose or two to four separate doses per day, and the administration is preferably repeated at appropriate intervals. The daily dose may exceed the above dose according to the judgment of the physician if necessary.

The compounds or salts thereof, or crystals thereof, according to the present invention may be used in combination with other antitumor agents. Examples include antitumor antibiotics, antitumor plant ingredients, BRM (biological response modifiers), hormones, vitamins, antitumor antibodies, molecular target drugs and other antitumor agents.

More specifically, examples of alkylating agents include alkylating agents such as nitrogen mustard, nitrogen mustard N-oxide and chlorambucil; aziridine alkylating agents such as carboquone and thiotepa; epoxide alkylating agents such as dibromomannitol and dibromodulcitol; nitrosourea alkylating agents such as carmustine, lomustine, semustine, nimustine hydrochloride, streptozocin, chlorozotocin and ranimustine; busulfan, improsulfan tosilate and dacarbazine.

Examples of various antimetabolites include purine antimetabolites such as 6-mercaptopurine, 6-thioguanine and thioinosine; pyrimidine antimetabolites such as fluorouracil, tegafur, tegafur uracil, carmofur, doxifluridine, broxuridine, cytarabine and enocitabine; and antifolates such as methotrexate and trimetrexate.

Examples of antitumor antibiotics include anthracycline antibiotic antitumor agents such as mitomycin C, bleomycin, peplomycin, daunorubicin, aclarubicin, doxorubicin, pirarubicin, THP-adriamycin, 4'-epidoxorubicin and epirubicin; chromomycin A3 and actinomycin D.

Examples of antitumor plant ingredients include vinca alkaloids such as vindesine, vincristine and vinblastine; taxanes such as paclitaxel and docetaxel; and epipodophyllotoxins such as etoposide and teniposide.

Examples of BRM include tumor necrosis factors and indomethacin.

Examples of hormones include hydrocortisone, dexamethasone, methylprednisolone, prednisolone, prasterone, betamethasone, triamcinolone, oxymetholone, nandrolone, metenolone, fosfestrol, ethinyl estradiol, chlormadinone and medroxyprogesterone.

Examples of vitamins include vitamin C and vitamin A.

Antitumor antibodies and molecular target drugs include trastuzumab, rituximab, cetuximab, nimotuzumab, denosumab, bevacizumab, infliximab, imatinib mesylate,

gefitinib, erlotinib, sunitinib, lapatinib, sorafenib, dasatinib, nilotinib and vemurafenib.

Examples of other antitumor agents include cisplatin, carboplatin, oxaliplatin, tamoxifen, camptothecin, ifosfamide, cyclophosphamide, melphalan, L-asparaginase, aceglatone, sizofiran, picibanil, procarbazine, pipobroman, neocarzinostatin, hydroxyurea, ubenimex and krestin.

The present invention also includes a method for preventing and/or treating cancer, comprising administering a compound or salt thereof, or a crystal thereof, according to the present invention.

The present invention further includes use of a compound or salt thereof, or a crystal thereof, according to the present invention for manufacturing the above medicine.

The present invention will be specifically described with reference to Examples illustrated below; however, the present invention is not limited to these Examples and they should not be construed as a limitation in any sense. Reagents, solvents and starting materials not particularly described in the present specification are readily available from commercial sources or known from previous reports.

Examples

Abbreviations

DMF: N,N-Dimethylformamide

THF: Tetrahydrofuran

HATU: N,N,N',N'-Tetramethyl-O-(7-azabenzotriazol-1-yl)uronium hexafluorophosphate

HOAt: 1-Hydroxy-7-azabenzotriazole

DIPEA: N,N-diisopropylethylamine

COMU: (1-Cyano-2-ethoxy-2-oxoethylideneaminoxy)dimethylamino-morpholino-carbenium hexafluorophosphate

TFA: Trifluoroacetic acid

EDC.HCl: 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride

HOBT: 1-Hydroxybenzotriazole

DMAP: 4-Dimethylaminopyridine

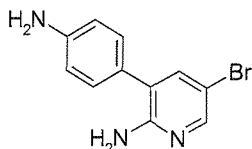
PLC: Preparative thin layer chromatography

HPLC: High performance liquid chromatography

Example 1

N-{4-[2-Amino-5-(3,4-dimethoxyphenyl)pyridin-3-yl]phenyl}-5-(4-fluorophenyl)-4-oxo-1,4-dihydropyridine-3-carboxamide

[Step 1] 3-(4-Aminophenyl)-5-bromopyridin-2-amine



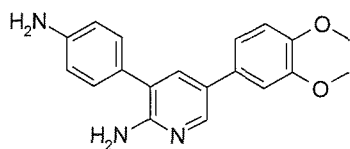
Tetrakis(triphenylphosphine)palladium (1.16 g), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline

(2.48 g) and potassium carbonate (4.15 g) were added to a solution of 5-bromo-3-iodopyridin-2-amine (2.99 g) in 1,4-dioxane (40 ml) and water (10 ml) at room temperature. The reaction mixture was stirred at 100°C overnight. The reaction mixture was concentrated under reduced pressure, and the residue was then purified by silica gel chromatography [chloroform:methanol = 9:1 (v/v)] to give 2.48 g of the title compound as a solid.

¹H-NMR (CDCl₃) δ: 3.80 (2H, br s), 4.58 (2H, br s), 6.76 (2H, dt, J = 8.9, 2.3 Hz), 7.22 (2H, dt, J = 8.9, 2.3 Hz), 7.43 (1H, d, J = 2.3 Hz), 8.05 (1H, d, J = 2.3 Hz).

MS (ESI) m/z: 264 (M+H)+.

[Step 2] 3-(4-Aminophenyl)-5-(3,4-dimethoxyphenyl)pyridin-2-amine



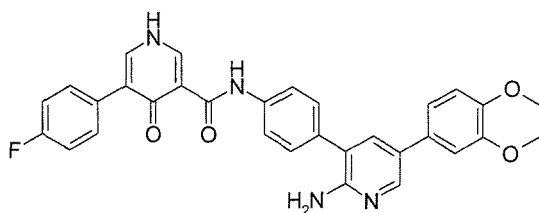
Tetrakis(triphenylphosphine)palladium (1.09 g), 3,4-dimethoxyphenylboronic acid (1.92 g) and potassium carbonate (3.89 g) were added to a solution of the compound obtained in the above Step 1 (2.48 g) in 1,4-dioxane (40 ml) and water (10 ml) at room temperature. The reaction mixture was stirred at 95°C overnight. The reaction mixture was concentrated under reduced pressure, and the residue was then purified by silica gel

chromatography [chloroform:methanol = 9:1 (v/v)] to give 2.48 g of the title compound as a solid.

$^1\text{H-NMR}$ (CDCl_3) δ : 3.80 (2H, br s), 3.91 (3H, s), 3.93 (3H, s), 4.60 (2H, br s), 6.77-6.81 (2H, m), 6.93 (1H, d, J = 8.3 Hz), 7.03 (1H, d, J = 2.3 Hz), 7.08 (1H, dd, J = 8.3, 2.3 Hz), 7.28-7.32 (2H, m), 7.53 (1H, d, J = 2.3 Hz), 8.23 (1H, d, J = 2.3 Hz).

MS (ESI) m/z : 322 ($\text{M}+\text{H}$) $^+$.

[Step 3] N-{4-[2-Amino-5-(3,4-dimethoxyphenyl)pyridin-3-yl]phenyl}-5-(4-fluorophenyl)-4-oxo-1,4-dihydropyridine-3-carboxamide



HOAt (14 mg), HATU (57 mg), DMAP (6 mg) and DIPEA (29 μl) were added to a solution of 5-(4-fluorophenyl)-4-oxo-1,4-dihydropyridine-3-carboxylic acid (23 mg) in DMF (1 ml) at room temperature. The reaction mixture was stirred at room temperature for three hours. The compound obtained in the above Step 2 (32 mg) was added to the reaction mixture at room temperature. The reaction mixture was stirred at room temperature overnight. Water was added to the reaction mixture, and the precipitated solid was collected by filtration, purified by PLC [organic layer of

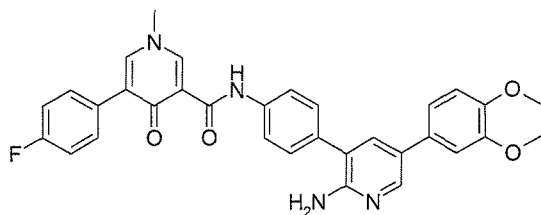
chloroform:methanol:water = 7:3:1 (v/v)] and lyophilized with a dioxane-water mixed solvent to give the title compound (20 mg) as a solid.

$^1\text{H-NMR}$ ($\text{CDCl}_3\text{-CD}_3\text{OD}$) δ : 3.98-3.88 (6H, m), 6.92-7.19 (5H, m), 7.44-7.70 (6H, m), 7.82-7.89 (2H, m), 8.15-8.21 (1H, m), 8.58-8.61 (1H, m).

MS (ESI) m/z : 537 ($\text{M}+\text{H}$) $^+$.

Example 2

N-{4-[2-Amino-5-(3,4-dimethoxyphenyl)pyridin-3-yl]phenyl}-5-(4-fluorophenyl)-1-methyl-4-oxo-1,4-dihydropyridine-3-carboxamide



HOAt (23 mg), HATU (97 mg), DMAP (10 mg) and DIPEA (50 μl) were added to a solution of 5-(4-fluorophenyl)-1-methyl-4-oxo-1,4-dihydropyridine-3-carboxylic acid (46 mg) in DMF (1 ml) at room temperature. The reaction mixture was stirred at room temperature for three hours. The compound obtained in Step 2 of Example 1 (55 mg) was added to the reaction mixture at room temperature. The reaction mixture was stirred at room temperature overnight. Water was added to the reaction mixture, and the precipitated solid was collected by filtration. The resulting solid was purified by PLC [ethyl

acetate:methanol = 20:1 (v/v)] to give 19 mg of the title compound as a solid.

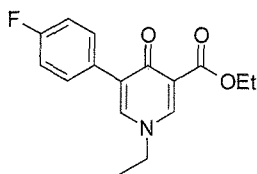
$^1\text{H-NMR}$ (CDCl_3) δ : 3.90 (3H, s), 3.92 (3H, s), 3.94 (3H, s), 4.66 (2H, s), 6.94 (1H, d, $J = 8.3$ Hz), 7.04 (1H, d, $J = 2.3$ Hz), 7.09 (1H, dd, $J = 8.3, 2.3$ Hz), 7.14-7.18 (2H, m), 7.46-7.51 (3H, m), 7.54-7.58 (3H, m), 7.86 (2H, d, $J = 8.7$ Hz), 8.27 (1H, d, $J = 2.3$ Hz), 8.61 (1H, d, $J = 2.3$ Hz).

MS (ESI) m/z : 551 ($\text{M}+\text{H}$) $^+$.

Example 3

N-{4-[2-Amino-5-(3,4-dimethoxyphenyl)pyridin-3-yl]phenyl}-1-ethyl-5-(4-fluorophenyl)-4-oxo-1,4-dihydropyridine-3-carboxamide

[Step 1] Ethyl 1-ethyl-5-(4-fluorophenyl)-4-oxo-1,4-dihydropyridine-3-carboxylate



N,N-Dimethylformamide dimethylacetal (3.9 ml) was added to a solution of ethyl 4-(4-fluorophenyl)-3-oxobutanoate (1310 mg) in n-butyl acetate (15 ml) at room temperature, and the mixture was stirred at 90°C for five hours. The solvent was distilled off under reduced pressure, and ethanol (20 ml) was added, followed by the addition of ethylamine (2 M solution in THF, 4.4 ml).

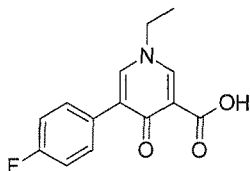
After stirring at 60°C for two hours, ethylamine (2 M solution in THF, 3.0 ml) was added and the mixture was further stirred at 60°C for two hours. The solvent was distilled off under reduced pressure, and the residue was purified by silica gel column chromatography

[chloroform:methanol = 300:1 -> 70:1 (v/v)] to give 985 mg of the title compound as an oily substance.

¹H-NMR (CDCl₃) δ: 1.39 (3H, t, J = 7.1 Hz), 1.53 (3H, t, J = 7.3 Hz), 3.95 (2H, q, J = 7.3 Hz), 4.38 (2H, q, J = 7.1 Hz), 7.04-7.12 (2H, m), 7.37 (1H, d, J = 2.8 Hz), 7.55-7.61 (2H, m), 8.18 (1H, d, J = 2.8 Hz).

MS(ESI) m/z: 290 (M+H)⁺.

[Step 2] 1-Ethyl-5-(4-fluorophenyl)-4-oxo-1,4-dihydropyridine-3-carboxylic acid



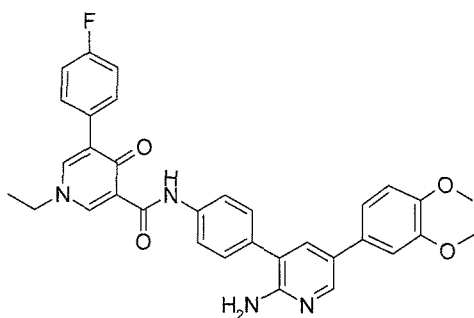
A 1 N aqueous sodium hydroxide solution (0.16 ml) was added to a solution of the compound obtained in the above Step 1 (24 mg) in methanol (1.0 ml) at room temperature, and the mixture was stirred for two hours. The solvent was distilled off under reduced pressure and a 1 N aqueous hydrochloric acid solution was added. The organic layer was extracted with chloroform and then dried over sodium sulfate. The solvent was distilled off

under reduced pressure to give 22 mg of the title compound as a solid.

$^1\text{H-NMR}$ (CDCl_3) δ : 1.60 (3H, t, $J = 7.6$ Hz), 4.12 (2H, q, $J = 7.3$ Hz), 7.12-7.20 (2H, m), 7.51-7.64 (3H, m), 8.55 (1H, d, $J = 2.3$ Hz).

MS (ESI) m/z : 262 ($\text{M}+\text{H}$) $^+$.

[Step 3] N-{4-[2-Amino-5-(3,4-dimethoxyphenyl)pyridin-3-yl]phenyl}-1-ethyl-5-(4-fluorophenyl)-4-oxo-1,4-dihydropyridine-3-carboxamide



DIPEA (80 μl) was added to a solution of the compound obtained in the above Step 2 (60 mg) and COMU (128 mg) in DMF (2.0 ml) at room temperature, and the mixture was stirred for 30 minutes. The compound obtained in Step 2 of Example 1 (81 mg) was added at room temperature, and the mixture was stirred for 16 hours. A saturated aqueous sodium bicarbonate solution was then added, and the organic layer was extracted with ethyl acetate and dried over sodium sulfate. The solvent was distilled off under reduced pressure, and the residue was purified by silica gel column chromatography [ethyl

acetate:dichloromethane:methanol = 5:5:1 (v/v)]. The resulting solid was crystallized from ethyl acetate and diisopropyl ether to give 107 mg of the title compound as a solid.

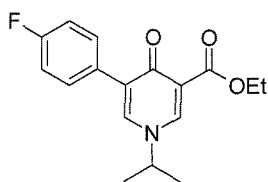
$^1\text{H-NMR}$ (CDCl_3) δ : 1.60 (3H, t, $J = 7.2$ Hz), 3.92 (3H, s), 3.94 (3H, s), 4.09 (2H, q, $J = 7.2$ Hz), 4.63 (2H, s), 6.90-7.21 (5H, m), 7.46-7.61 (6H, m), 7.84-7.90 (2H, m), 8.27 (1H, d, $J = 2.3\text{Hz}$), 8.66 (1H, d, $J = 2.3$ Hz).

MS (ESI) m/z : 565 ($\text{M}+\text{H}$) $^+$.

Example 4

N-{4-[2-Amino-5-(3,4-dimethoxyphenyl)pyridin-3-yl]phenyl}-5-(4-fluorophenyl)-4-oxo-1-(propan-2-yl)-1,4-dihydropyridine-3-carboxamide

[Step 1] Ethyl 5-(4-fluorophenyl)-4-oxo-1-(propan-2-yl)-1,4-dihydropyridine-3-carboxylate



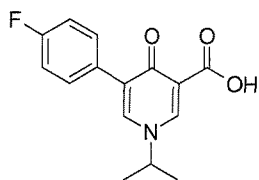
N,N-Dimethylformamide dimethylacetal (3.6 ml) was added to a solution of ethyl 4-(4-fluorophenyl)-3-oxobutanoate (1200 mg) in n-propyl acetate (13 ml) at room temperature, and the mixture was stirred at 90°C for four hours. The solvent was distilled off under reduced pressure, and ethanol (18 ml) was added, followed by the addition of 2-propylamine (688 μl). After stirring at

60°C for one hour, 2-propylamine (459 μ l) was added and the mixture was further stirred at 60°C for one hour. The solvent was distilled off under reduced pressure, and the residue was purified by silica gel column chromatography [chloroform:methanol = 300:1 $\rightarrow$ 80:1 (v/v)] to give 620 mg of the title compound as an oily substance.

$^1\text{H-NMR}$ (CDCl_3) δ : 1.39 (3H, t, $J = 7.1$ Hz), 1.55 (6H, d, $J = 6.9$ Hz), 4.13-4.25 (1H, m), 4.39 (2H, q, $J = 7.1$ Hz), 7.04-7.12 (2H, m), 7.42 (1H, d, $J = 2.8$ Hz), 7.54-7.61 (2H, m), 8.23 (1H, d, $J = 2.8$ Hz).

MS (ESI) m/z : 304 ($\text{M}+\text{H}$) $^+$.

[Step 2] 5-(4-Fluorophenyl)-4-oxo-1-(propan-2-yl)-1,4-dihydropyridine-3-carboxylic acid

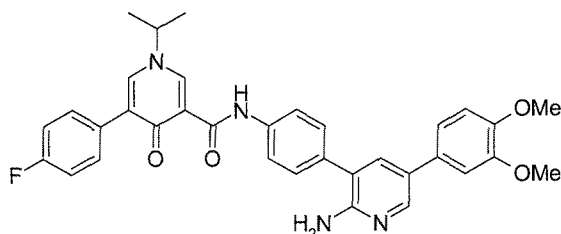


A 1 N aqueous sodium hydroxide solution (4.0 ml) was added to a solution of the compound obtained in the above Step 1 (620 mg) in methanol (4.0 ml) at room temperature, and the mixture was stirred for one hour. The solvent was distilled off under reduced pressure and a 1 N aqueous hydrochloric acid solution was added. The precipitated solid was collected by filtration to give 327 mg of the title compound as a solid.

$^1\text{H-NMR}$ (CDCl_3) δ : 1.62 (6H, d, J = 6.9 Hz), 4.28-4.41 (1H, m), 7.12-7.20 (2H, m), 7.55-7.62 (2H, m), 7.67 (1H, d, J = 2.3 Hz), 8.60 (1H, d, J = 2.3 Hz).

MS(ESI) m/z : 276 ($\text{M}+\text{H}$) $^+$.

[Step 3] N-{4-[2-Amino-5-(3,4-dimethoxyphenyl)pyridin-3-yl]phenyl}-5-(4-fluorophenyl)-4-oxo-1-(propan-2-yl)-1,4-dihydropyridine-3-carboxamide



DIPEA (42 μl) was added to a solution of the compound obtained in the above Step 2 (45 mg) and COMU (91 mg) in DMF (1.0 ml) at room temperature, and the mixture was stirred for 40 minutes. The compound obtained in Step 2 of Example 1 (58 mg) was added at room temperature. The mixture was stirred for 16 hours, followed by the addition of water. The precipitated solid was collected by filtration and purified by silica gel column chromatography [chloroform:methanol = 300:1 $\rightarrow$ 30:1 (v/v)] to give 56 mg of the title compound as a solid.

$^1\text{H-NMR}$ (CDCl_3) δ : 1.62 (6H, d, J = 6.4 Hz), 3.92 (3H, s), 3.94 (3H, s), 4.28-4.38 (1H, m), 4.72 (2H, s), 6.94 (1H, d, J = 8.3 Hz), 7.01-7.11 (2H, m), 7.14-7.21 (2H, m),

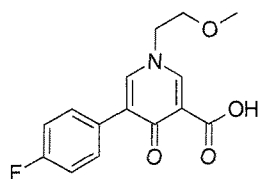
7.46-7.61 (6H, m), 7.85-7.91 (2H, m), 8.26 (1H, d, $J = 2.3$ Hz), 8.72 (1H, d, $J = 2.3$ Hz).

MS (ESI) m/z : 579 (M+H)⁺.

Example 5

N-{4-[2-Amino-5-(3,4-dimethoxyphenyl)pyridin-3-yl]phenyl}-5-(4-fluorophenyl)-1-(2-methoxyethyl)-4-oxo-1,4-dihydropyridine-3-carboxamide

[Step 1] 5-(4-Fluorophenyl)-1-(2-methoxyethyl)-4-oxo-1,4-dihydropyridine-3-carboxylic acid



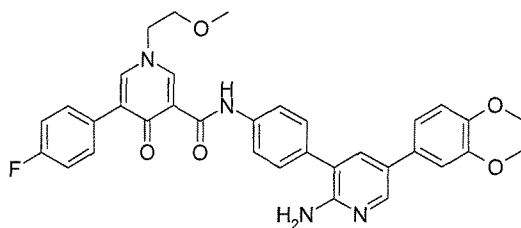
1-Bromo-2-methoxyethane (95 μ l) was added to a suspension of ethyl 5-(4-fluorophenyl)-4-oxo-1,4-dihydropyridine-3-carboxylate (200 mg) and cesium carbonate (499 mg) in DMF (4 ml) at room temperature. The reaction mixture was stirred at room temperature for four hours. The reaction mixture was stirred at 50°C overnight. Cesium carbonate (499 mg) and 1-bromo-2-methoxyethane (95 μ l) were added to the reaction mixture at 50°C. The reaction mixture was stirred at 50°C for nine hours. The reaction mixture was stirred at 80°C for three days and returned to room temperature. A 1 N aqueous sodium hydroxide solution (4 ml) was added to the reaction mixture at room temperature. The reaction

mixture was stirred at room temperature for five hours. A 1 N aqueous hydrochloric acid solution and water were added to the reaction mixture. The precipitated solid was collected by filtration, washed with water and then washed with a mixed solvent of hexane and diethyl ether [5:1 (v/v)] to give 113 mg of the title compound as a solid.

$^1\text{H-NMR}$ (CDCl_3) δ : 3.39 (3H, s), 3.74 (2H, t, $J = 4.8$ Hz), 4.17 (2H, t, $J = 4.8$ Hz), 7.13-7.19 (2H, m), 7.56-7.61 (2H, m), 7.69 (1H, d, $J = 2.8$ Hz), 8.54 (1H, d, $J = 2.3$ Hz).

MS (ESI) m/z : 292 ($\text{M}+\text{H}$) $^+$.

[Step 2] N-{4-[2-Amino-5-(3,4-dimethoxyphenyl)pyridin-3-yl]phenyl}-5-(4-fluorophenyl)-1-(2-methoxyethyl)-4-oxo-1,4-dihydropyridine-3-carboxamide



HOAt (21 mg), HATU (89 mg), DMAP (10 mg) and DIPEA (46 μl) were added to a solution of the compound obtained in the above Step 1 (50 mg) in DMF (1 ml) at room temperature. The reaction mixture was stirred at room temperature for 3.5 hours. The compound obtained in Step 2 of Example 1 (50 mg) was added to the reaction mixture at room temperature. The reaction mixture was stirred at

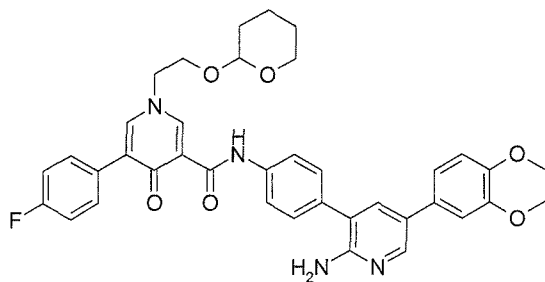
room temperature overnight. Water was added to the reaction mixture, and the precipitated solid was collected by filtration. The resulting solid was purified by PLC [ethyl acetate:methanol = 8:1 (v/v)], and the eluate was concentrated under reduced pressure. The residue was purified by PLC [dichloromethane:methanol = 15:1 (v/v)] to give 60 mg of the title compound as a solid.

$^1\text{H-NMR}$ (CDCl_3) δ : 3.40 (3H, s), 3.76 (2H, t, $J = 4.8$ Hz), 3.92 (3H, s), 3.94 (3H, s), 4.15 (2H, t, $J = 4.8$ Hz), 4.65 (2H, s), 6.90-7.20 (5H, m), 7.48-7.60 (6H, m), 7.87 (2H, d, $J = 8.7$ Hz), 8.27 (1H, d, $J = 2.3$ Hz), 8.64 (1H, d, $J = 1.8$ Hz).

MS (ESI) m/z : 595 ($\text{M}+\text{H}$) $^+$.

Example 6

N-{4-[2-Amino-5-(3,4-dimethoxyphenyl)pyridin-3-yl]phenyl}-5-(4-fluorophenyl)-4-oxo-1-[2-(tetrahydro-2H-pyran-2-yloxy)ethyl]-1,4-dihydropyridine-3-carboxamide (racemate)



2-(2-Bromoethoxy)tetrahydro-2H-pyran (83 μl) was added to a suspension of the compound of Reference

Example 9 and cesium carbonate (237 mg) in DMF (2 ml) at room temperature. The reaction mixture was stirred at 50°C overnight. The reaction mixture was returned to room temperature, and a 1 N aqueous sodium hydroxide solution (2 ml) was added at room temperature. The reaction mixture was stirred at room temperature for one hour. A 1 N aqueous hydrochloric acid solution and water were added to the reaction mixture, followed by extraction with ethyl acetate. The organic layer was washed with water and brine, and then dried over sodium sulfate and filtered. The filtrate was then concentrated under reduced pressure to give 5-(4-fluorophenyl)-4-oxo-1-[2-(tetrahydro-2H-pyran-2-yloxy)ethyl]-1,4-dihydropyridine-3-carboxylic acid as an oily substance.

5-(4-Fluorophenyl)-4-oxo-1-[2-(tetrahydro-2H-pyran-2-yloxy)ethyl]-1,4-dihydropyridine-3-carboxylic acid was dissolved in DMF (2 ml), and HOAt (41 mg), HATU (170 mg), DMAP (18 mg) and DIPEA (88 μ l) were added at room temperature. The reaction mixture was stirred at room temperature for three hours. The compound obtained in Step 2 of Example 1 (96 mg) was added to the reaction mixture at room temperature, followed by stirring overnight. Water was added to the reaction mixture, and the precipitated solid was collected by filtration to give 281 mg of the crude purified title compound as a solid. 141 mg of the solid was purified by PLC [dichloromethane:methanol = 20:1 (v/v)], and the eluate

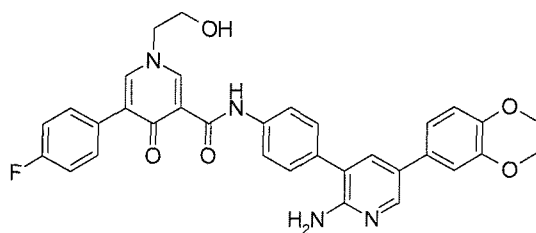
was concentrated under reduced pressure. The residue was purified by PLC [ethyl acetate:methanol = 15:1 (v/v)] to give 72 mg of the title compound.

$^1\text{H-NMR}$ (CDCl_3) δ : 1.44-1.80 (6H, m), 3.47-3.51 (1H, m), 3.59-3.67 (1H, m), 3.75-3.81 (1H, m), 3.91 (3H, s), 3.94 (3H, s), 4.08-4.23 (3H, m), 4.59-4.69 (3H, m), 6.93 (1H, d, $J = 8.3$ Hz), 7.02-7.11 (2H, m), 7.14-7.18 (2H, m), 7.46-7.51 (2H, m), 7.55-7.58 (3H, m), 7.66 (1H, d, $J = 2.3$ Hz), 7.84-7.89 (2H, m), 8.26 (1H, d, $J = 2.8$ Hz), 8.68 (1H, d, $J = 2.3$ Hz).

MS (ESI) m/z : 665 ($\text{M}+\text{H}$) $^+$.

Example 7

N-{4-[2-Amino-5-(3,4-dimethoxyphenyl)pyridin-3-yl]phenyl}-5-(4-fluorophenyl)-1-(2-hydroxyethyl)-4-oxo-1,4-dihydropyridine-3-carboxamide



The crude purified N-{4-[2-amino-5-(3,4-dimethoxyphenyl)pyridin-3-yl]phenyl}-5-(4-fluorophenyl)-4-oxo-1-[2-(tetrahydro-2H-pyran-2-yloxy)ethyl]-1,4-dihydropyridine-3-carboxamide obtained in Example 6 (141 mg) was dissolved in methanol (4 ml) and dichloromethane (2 ml). A 4 N solution of hydrochloric acid in dioxane

(4 ml) was added to the reaction mixture at room temperature. The reaction mixture was stirred at room temperature for 2.5 hours. A saturated sodium bicarbonate solution was added to the reaction mixture, and the organic layer was extracted with ethyl acetate, washed with brine and dried over sodium sulfate. After filtration, the filtrate was concentrated under reduced pressure, the residue was purified by silica gel column chromatography [ethyl acetate:methanol = 100:0 -> 19:1 -> 9:1 (v/v)], and the eluate was concentrated under reduced pressure. The residue was purified by PLC [dichloromethane:methanol = 8:1 (v/v)] to give 9 mg of the title compound.

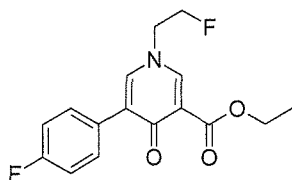
¹H-NMR (CDCl₃) δ: 3.91 (3H, s), 3.93 (3H, s), 4.05-4.14 (4H, m), 4.98 (2H, br s), 6.92 (1H, d, J = 8.7 Hz), 6.98-7.14 (4H, m), 7.44-7.54 (4H, m), 7.59 (2H, t, J = 2.5 Hz), 7.80 (2H, d, J = 8.3 Hz), 8.14 (1H, d, J = 2.3 Hz), 8.64 (1H, d, J = 2.3 Hz).

MS (ESI) m/z: 581 (M+H)⁺.

Example 8

N-{4-[2-Amino-5-(3,4-dimethoxyphenyl)pyridin-3-yl]phenyl}-1-(2-fluoroethyl)-5-(4-fluorophenyl)-4-oxo-1,4-dihydropyridine-3-carboxamide

[Step 1] Ethyl 1-(2-fluoroethyl)-5-(4-fluorophenyl)-4-oxo-1,4-dihydropyridine-3-carboxylate

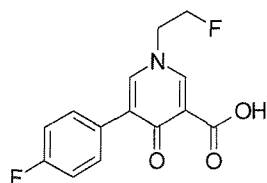


2-Fluoroethyl 4-methylbenzenesulfonate (1.00 g) was added to a suspension of ethyl 5-(4-fluorophenyl)-4-oxo-1,4-dihydropyridine-3-carboxylate (1.00 g) and cesium carbonate (2.49 g) in DMF (9 ml) at room temperature. The reaction mixture was stirred at 80°C for two hours. The reaction mixture was returned to room temperature and diluted by adding ethyl acetate. The organic layer was washed with water and brine and dried over sodium sulfate. After filtration, the filtrate was concentrated under reduced pressure, the residue was purified by silica gel column chromatography [ethyl acetate:hexane:methanol = 1:1:0 -> 7:3:0 -> 1:0:0 -> 19:0:1 (v/v)] to give 0.35 g of the title compound as an oily substance.

$^1\text{H-NMR}$ (CDCl_3) δ : 1.32-1.40 (3H, m), 4.11-4.38 (4H, m), 4.63-4.84 (2H, m), 6.99-7.09 (2H, m), 7.41-7.58 (3H, m), 8.12-8.18 (1H, m).

MS (ESI) m/z : 308 ($\text{M}+\text{H}$) $^+$.

[Step 2] 1-(2-Fluoroethyl)-5-(4-fluorophenyl)-4-oxo-1,4-dihydropyridine-3-carboxylic acid

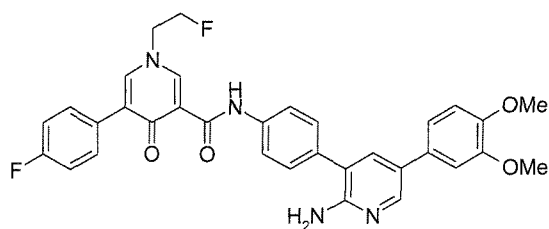


Potassium carbonate (390 mg) and water (5 ml) were added to a solution of the compound obtained in the above Step 1 (347 mg) in methanol (10 ml) at room temperature. The reaction mixture was stirred at room temperature overnight. A 1 N aqueous hydrochloric acid solution and water were added to the reaction mixture, and the precipitated solid was collected by filtration and dried to give 210 mg of the title compound as a solid.

$^1\text{H-NMR}$ (CD_3OD) δ : 4.47-4.59 (2H, m), 4.75-4.89 (2H, m), 7.16-7.22 (2H, m), 7.67-7.72 (2H, m), 8.20 (1H, d, J = 2.3 Hz), 8.74 (1H, d, J = 1.8 Hz).

MS (ESI) m/z : 280 ($\text{M}+\text{H}$) $^+$.

[Step 3] N-{4-[2-Amino-5-(3,4-dimethoxyphenyl)pyridin-3-yl]phenyl}-1-(2-fluoroethyl)-5-(4-fluorophenyl)-4-oxo-1,4-dihydropyridine-3-carboxamide



DIPEA (47 μl) was added to a solution of the compound obtained in the above Step 2 (38 mg) and COMU (76 mg) in DMF (0.9 ml) at room temperature, and the mixture was stirred for 15 minutes. The compound obtained in Step 2 of Example 1 (48 mg) was added at room temperature. The mixture was stirred for five hours, followed by the addition of water. The organic layer was

extracted with ethyl acetate, and then washed with water and brine and dried over sodium sulfate. The solvent was distilled off under reduced pressure, and the residue was purified by silica gel column chromatography

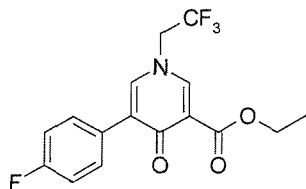
[chloroform:methanol = 300:1 -> 30:1 (v/v)] to give 30 mg of the title compound as a solid.

$^1\text{H-NMR}$ (CDCl_3) δ : 3.92 (3H, s), 3.94 (3H, s), 4.25-4.37 (2H, m), 4.66 (2H, s), 4.74-4.91 (2H, m), 6.94 (1H, d, J = 8.3 Hz), 7.02-7.11 (2H, m), 7.14-7.20 (2H, m), 7.47-7.60 (6H, m), 7.84-7.89 (2H, m), 8.27 (1H, d, J = 2.5 Hz), 8.65 (1H, d, J = 2.5 Hz).

MS (ESI) m/z : 583 ($\text{M}+\text{H}$) $^+$.

Example 9

N-{4-[2-Amino-5-(3,4-dimethoxyphenyl)pyridin-3-yl]phenyl}-5-(4-fluorophenyl)-4-oxo-1-(2,2,2-trifluoroethyl)-1,4-dihydropyridine-3-carboxamide
[Step 1] Ethyl 5-(4-fluorophenyl)-4-oxo-1-(2,2,2-trifluoroethyl)-1,4-dihydropyridine-3-carboxylate



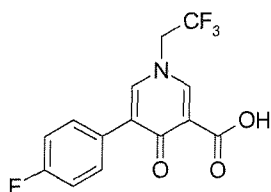
A mixed solution of ethyl 4-(4-fluorophenyl)-3-oxobutanoate (0.95 g), N,N-dimethylformamide dimethylacetal (1.59 g) and toluene (7 ml) was stirred at 100°C to 105°C for 14 hours while methanol was distilled

off. After cooling to room temperature, the residue was concentrated under reduced pressure. Further, 7 ml of toluene was added and the residue was concentrated to one-third its volume under reduced pressure. Toluene (3.5 ml) was added to give a solution of ethyl 5-(dimethylamino)-2-[(dimethylamino)methylene]-4-(4-fluorophenyl)-3-oxopent-4-enoate. This solution was cooled to 0°C to 5°C, trifluoroethyl amine (0.43 ml) and a 4.3 M solution of hydrogen chloride in ethyl acetate (1.57 ml) were added, and the mixture was stirred at 100°C to 105°C for three hours. After cooling to room temperature, the layers were separated by adding water, and the organic layer was concentrated to 3.5 ml. Toluene (1.4 ml) was added, followed by stirring at room temperature. The resulting solid was collected by filtration to give 1.07 g of the title compound as a solid.

¹H-NMR (CDCl₃) δ: 1.39 (3H, t, J = 7.3 Hz), 4.33-4.42 (4H, m), 7.05-7.13 (2H, m), 7.32-7.37 (1H, m), 7.50-7.58 (2H, m), 8.13 (1H, d, J = 2.7 Hz).

MS (ESI) m/z: 344 (M+H)⁺

[Step 2] 5-(4-Fluorophenyl)-4-oxo-1-(2,2,2-trifluoroethyl)-1,4-dihydropyridine-3-carboxylic acid

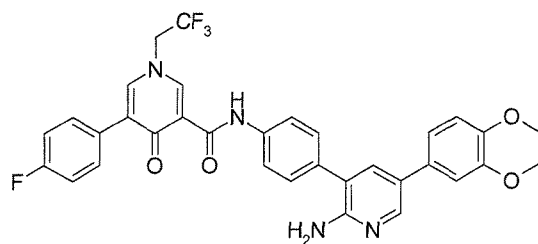


A 1 N aqueous sodium hydroxide solution (0.8 ml) was added to a solution of the compound obtained in the above Step 1 (118 mg) in methanol (0.7 ml) at room temperature, and the mixture was stirred for two hours. The solvent was distilled off under reduced pressure and a 1 N aqueous hydrochloric acid solution was added. The precipitated solid was collected by filtration to give the title compound (87 mg).

$^1\text{H-NMR}$ (CDCl_3) δ : 4.55 (2H, q, $J = 7.6$ Hz), 7.14-7.22 (2H, m), 7.52-7.60 (3H, m), 8.55 (1H, d, $J = 2.3$ Hz).

MS (ESI) m/z : 316 ($\text{M}+\text{H}$) $^+$.

[Step 3] N-{4-[2-Amino-5-(3,4-dimethoxyphenyl)pyridin-3-yl]phenyl}-5-(4-fluorophenyl)-4-oxo-1-(2,2,2-trifluoroethyl)-1,4-dihydropyridine-3-carboxamide



HOAt (25 mg), HATU (106 mg), DMAP (11 mg) and DIPEA (55 μl) were added to a solution of the compound obtained in the above Step 2 (60 mg) in DMF (1 ml) at room temperature. The reaction mixture was stirred at room temperature for 3.5 hours. The compound obtained in Step 2 of Example 1 (65 mg) was added to the reaction mixture at room temperature. The reaction mixture was stirred at

room temperature overnight. Water was added to the reaction mixture, and the precipitated solid was collected by filtration. The resulting solid was purified by PLC [developed with ethyl acetate], and the eluate was concentrated under reduced pressure. The residue was purified by PLC [dichloromethane:methanol = 20:1 (v/v)] to give 70 mg of the title compound as a solid.

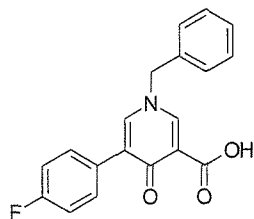
$^1\text{H-NMR}$ (CDCl_3) δ : 3.91 (3H, s), 3.94 (3H, s), 4.53 (2H, q, $J = 7.8$ Hz), 4.65 (2H, s), 6.94 (1H, d, $J = 8.7$ Hz), 7.04 (1H, d, $J = 2.3$ Hz), 7.09 (1H, dd, $J = 8.3, 2.3$ Hz), 7.16-7.20 (2H, m), 7.48-7.57 (6H, m), 7.85 (2H, dt, $J = 9.0, 2.3$ Hz), 8.27 (1H, d, $J = 2.8$ Hz), 8.66 (1H, d, $J = 2.3$ Hz), 12.46 (1H, s).

MS (ESI) m/z : 619 ($\text{M}+\text{H}$) $^+$.

Example 10

N-{4-[2-Amino-5-(3,4-dimethoxyphenyl)pyridin-3-yl]phenyl}-1-benzyl-5-(4-fluorophenyl)-4-oxo-1,4-dihydropyridine-3-carboxamide

[Step 1] 1-Benzyl-5-(4-fluorophenyl)-4-oxo-1,4-dihydropyridine-3-carboxylic acid

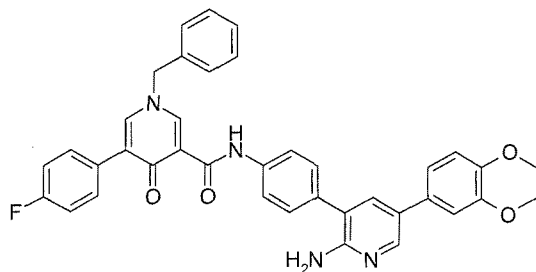


55% sodium hydride (131 mg) dispersed in oil was added to a solution of 5-(4-fluorophenyl)-4-oxo-1,4-dihydropyridine-3-carboxylic acid (233 mg) in DMF (5 ml) under ice cooling, and the mixture was stirred at room temperature for one hour. Benzyl bromide (356 μ l) was then added and the mixture was stirred for two days. A 1 N aqueous sodium hydroxide solution was then added, followed by stirring overnight. A 10% aqueous citric acid solution was added to the reaction solution, and the precipitate was collected by filtration to give the title compound (253 mg) as a solid.

^1H -NMR (CDCl_3) δ : 5.19 (2H, s), 7.09-7.15 (2H, m), 7.26-7.30 (2H, m), 7.43-7.47 (3H, m), 7.51-7.56 (2H, m), 7.63 (1H, d, $J = 2.3$ Hz), 8.62 (1H, d, $J = 2.3$ Hz).

MS(ESI) m/z : 324 ($\text{M}+\text{H}$) $^+$.

[Step 2] N-{4-[2-Amino-5-(3,4-dimethoxyphenyl)pyridin-3-yl]phenyl}-1-benzyl-5-(4-fluorophenyl)-4-oxo-1,4-dihydropyridine-3-carboxamide



HOAt (14 mg), HATU (57 mg), DMAP (6 mg) and DIPEA (29 μ l) were added to a solution of the compound obtained in the above Step 1 (35 mg) in DMF (1 ml) at room

temperature. The reaction mixture was stirred at room temperature for three hours. The compound obtained in Step 2 of Example 1 (32 mg) was added to the reaction mixture at room temperature. The reaction mixture was stirred at room temperature overnight. Water was added to the reaction mixture, and the precipitated solid was collected by filtration, purified by PLC [chloroform:methanol = 9:1 (v/v)] and lyophilized with a dioxane-water mixed solvent to give 37 mg of the title compound as a solid.

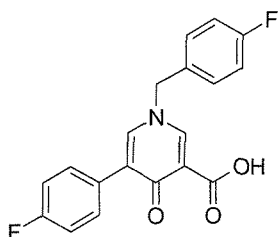
$^1\text{H-NMR}$ (CDCl_3) δ : 3.91 (3H, s), 3.94 (3H, s), 4.73 (2H, br s), 5.17 (2H, s), 6.93 (1H, d, $J = 8.7$ Hz), 7.03 (1H, d, $J = 2.3$ Hz), 7.07-7.17 (3H, m), 7.28-7.32 (2H, m), 7.43-7.58 (9H, m), 7.86 (2H, d, $J = 8.7$ Hz), 8.25 (1H, d, $J = 2.3$ Hz), 8.74 (1H, d, $J = 2.3$ Hz).

MS (ESI) m/z : 627 ($\text{M}+\text{H}$) $^+$.

Example 11

N-{4-[2-Amino-5-(3,4-dimethoxyphenyl)pyridin-3-yl]phenyl}-1-(4-fluorobenzyl)-5-(4-fluorophenyl)-4-oxo-1,4-dihydropyridine-3-carboxamide

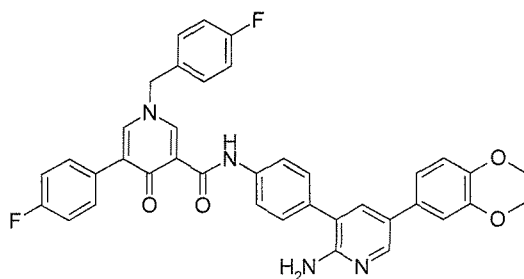
[Step 1] 1-(4-Fluorobenzyl)-5-(4-fluorophenyl)-4-oxo-1,4-dihydropyridine-3-carboxylic acid



1-(Bromomethyl)-4-fluorobenzene (122 μ l) was added to a suspension of ethyl 5-(4-fluorophenyl)-4-oxo-1,4-dihydropyridine-3-carboxylate (200 mg) and cesium carbonate (499 mg) in DMF (4 ml) at room temperature. The reaction mixture was stirred at room temperature overnight. A 1 N aqueous sodium hydroxide solution (4 ml) was added to the reaction mixture at room temperature. The reaction mixture was stirred at room temperature for two hours. A 1 N aqueous hydrochloric acid solution and water were added to the reaction mixture, and the precipitated solid was collected by filtration, washed with water and then dried to give 250 mg of the title compound as a solid.

$^1\text{H-NMR}$ (CDCl_3) δ : 5.15 (2H, s), 7.10-7.19 (4H, m), 7.26-7.30 (2H, m), 7.51-7.60 (3H, m), 8.60 (1H, d, $J = 1.8$ Hz).
MS (ESI) m/z : 342 ($\text{M}+\text{H}$) $^+$.

[Step 2] N-{4-[2-Amino-5-(3,4-dimethoxyphenyl)pyridin-3-yl]phenyl}-1-(4-fluorobenzyl)-5-(4-fluorophenyl)-4-oxo-1,4-dihydropyridine-3-carboxamide



HOAt (21 mg), HATU (89 mg), DMAP (10 mg) and DIPEA (46 μ l) were added to a solution of the compound obtained

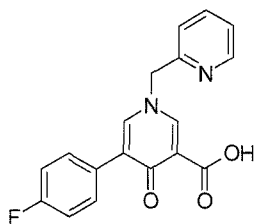
in the above Step 1 (58 mg) in DMF (1 ml) at room temperature. The reaction mixture was stirred at room temperature for one hour. The compound obtained in Step 2 of Example 1 (50 mg) was added to the reaction mixture, followed by stirring at room temperature overnight. Water was added to the reaction mixture, and the precipitated solid was collected by filtration. The resulting solid was purified by PLC [developed with ethyl acetate], and the eluate was concentrated under reduced pressure. The residue was purified by PLC [dichloromethane:methanol = 30:1 (v/v)] to give 61 mg of the title compound as a solid.

$^1\text{H-NMR}$ (CDCl_3) δ : 3.91 (3H, s), 3.94 (3H, s), 4.66 (2H, s), 5.13 (2H, s), 6.93 (1H, d, $J = 7.8$ Hz), 7.02-7.18 (6H, m), 7.25-7.32 (2H, m), 7.47-7.57 (6H, m), 7.85 (2H, d, $J = 8.3$ Hz), 8.26 (1H, d, $J = 1.8$ Hz), 8.71 (1H, d, $J = 1.8$ Hz).

MS (ESI) m/z : 645 ($\text{M}+\text{H}$) $^+$.

Example 12

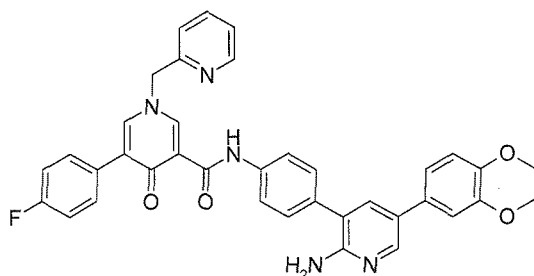
N-{4-[2-Amino-5-(3,4-dimethoxyphenyl)pyridin-3-yl]phenyl}-5-(4-fluorophenyl)-4-oxo-1-(pyridin-2-ylmethyl)-1,4-dihydropyridine-3-carboxamide
[Step 1] 5-(4-Fluorophenyl)-4-oxo-1-(pyridin-2-ylmethyl)-1,4-dihydropyridine-3-carboxylic acid



2-(Bromomethyl)pyridine hydrobromide (126 mg) was added to a suspension of ethyl 5-(4-fluorophenyl)-4-oxo-1,4-dihydropyridine-3-carboxylate (100 mg) and cesium carbonate (437 mg) in DMF (2 ml) at room temperature. The reaction mixture was stirred at room temperature overnight. The reaction mixture was stirred at 80°C for four hours and returned to room temperature. A 1 N aqueous sodium hydroxide solution (2 ml) was added to the reaction mixture at room temperature. The reaction mixture was stirred at room temperature for 1.5 hours. A 1 N aqueous hydrochloric acid solution and water were added to the reaction mixture, and the precipitated solid was collected by filtration, washed with water and then dried to give 94 mg of the title compound as a solid.

¹H-NMR (CDCl₃) δ: 5.23 (2H, s), 7.11-7.17 (2H, m), 7.30-7.38 (2H, m), 7.56-7.62 (2H, m), 7.76-7.87 (2H, m), 8.63 (2H, s).

[Step 2] N-{4-[2-Amino-5-(3,4-dimethoxyphenyl)pyridin-3-yl]phenyl}-5-(4-fluorophenyl)-4-oxo-1-(pyridin-2-ylmethyl)-1,4-dihydropyridine-3-carboxamide



HOAt (18 mg), HATU (75 mg), DMAP (8 mg) and DIPEA (62 μ l) were added to a solution of the compound obtained in the above Step 1 (47 mg) in DMF (1 ml) at room temperature. The reaction mixture was stirred at room temperature for one hour. The compound obtained in Step 2 of Example 1 (42 mg) was added to the reaction mixture at room temperature. The reaction mixture was stirred at room temperature overnight. HATU (75 mg) was added to the reaction mixture at room temperature. The reaction mixture was stirred at 50°C for one hour and returned to room temperature. Water was added to the reaction mixture, and the precipitated solid was collected by filtration. The resulting solid was purified by PLC [ethyl acetate:methanol = 8:1 (v/v)], and the eluate was concentrated under reduced pressure. The residue was purified by PLC [dichloromethane:methanol = 15:1 (v/v)] to give 65 mg of the title compound as a solid.

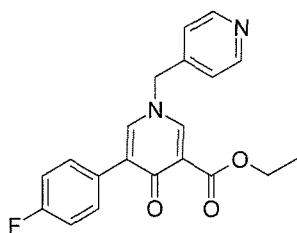
$^1\text{H-NMR}$ (CDCl_3) δ : 3.91 (3H, s), 3.94 (3H, s), 4.68 (2H, s), 5.24 (2H, s), 6.93 (1H, d, J = 8.3 Hz), 7.03-7.17 (4H, m), 7.28-7.36 (2H, m), 7.48 (2H, d, J = 8.7 Hz), 7.55-7.59 (3H, m), 7.72-7.80 (2H, m), 7.86 (2H, d, J = 8.7 Hz),

8.26 (1H, d, $J = 2.3$ Hz), 8.63-8.65 (1H, m), 8.75 (1H, d, $J = 2.3$ Hz).

MS (ESI) m/z : 628 (M+H)⁺.

Example 13

N-{4-[2-Amino-5-(3,4-dimethoxyphenyl)pyridin-3-yl]phenyl}-5-(4-fluorophenyl)-4-oxo-1-(pyridin-4-ylmethyl)-1,4-dihydropyridine-3-carboxamide
[Step 1] Ethyl 5-(4-fluorophenyl)-4-oxo-1-(pyridin-4-ylmethyl)-1,4-dihydropyridine-3-carboxylate



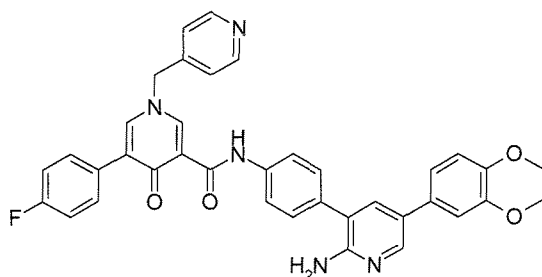
4-(Bromomethyl)pyridine hydrobromide (290 mg) was added to a suspension of ethyl 5-(4-fluorophenyl)-4-oxo-1,4-dihydropyridine-3-carboxylate (200 mg) and cesium carbonate (998 mg) in DMF (5 ml) at room temperature. The reaction mixture was stirred at 100°C overnight. The reaction mixture was returned to room temperature and diluted by adding ethyl acetate. The organic layer was washed with water and brine and dried over sodium sulfate. After filtration, the filtrate was concentrated under reduced pressure, the residue was purified by silica gel column chromatography [chloroform:methanol = 10:0 -> 19:1 -> 9:1 (v/v)], and the eluate was concentrated under

reduced pressure. The residue was purified by PLC [dichloromethane:methanol = 10:1 (v/v)] to give 126 mg of the title compound as an oily substance.

$^1\text{H-NMR}$ (CDCl_3) δ : 1.37 (3H, t, $J = 7.1$ Hz), 4.36 (2H, q, $J = 7.2$ Hz), 5.08 (2H, s), 7.02-7.14 (4H, m), 7.35 (1H, d, $J = 2.8$ Hz), 7.50-7.56 (2H, m), 8.19 (1H, d, $J = 2.3$ Hz), 8.67-8.69 (2H, m)

MS (ESI) m/z : 353 ($\text{M}+\text{H}$) $^+$.

[Step 2] N-{4-[2-Amino-5-(3,4-dimethoxyphenyl)pyridin-3-yl]phenyl}-5-(4-fluorophenyl)-4-oxo-1-(pyridin-4-ylmethyl)-1,4-dihydropyridine-3-carboxamide



Potassium hydroxide (136 mg) was added to a solution of the compound obtained in the above Step 1 (126 mg) in methanol (4 ml) at room temperature. The reaction mixture was stirred at room temperature for 37 hours. A 1 N aqueous hydrochloric acid solution (0.54 ml) was added to the reaction mixture. The reaction mixture was concentrated under reduced pressure and dried. The resulting solid was dissolved in DMF (2 ml), and HOAt (40 mg), HATU (169 mg), DMAP (18 mg) and DIPEA (88 μl) were added at room temperature. The reaction mixture was

stirred at room temperature for four hours. The compound obtained in Step 2 of Example 1 (95 mg) was added to the reaction mixture at room temperature. The reaction mixture was stirred at room temperature overnight. HATU (169 mg) was added to the reaction mixture at room temperature. The reaction mixture was stirred at 50°C for two hours and returned to room temperature. Water was added to the reaction mixture, and the precipitated solid was collected by filtration. The resulting solid was purified by PLC [ethyl acetate:methanol = 8:1 (v/v)], and the eluate was concentrated under reduced pressure. The residue was purified by PLC [dichloromethane:methanol = 15:1 (v/v)], and the eluate was concentrated under reduced pressure. The residue was purified by amino PLC [dichloromethane:methanol = 15:1 (v/v)] to give 107 mg of the title compound as a solid.

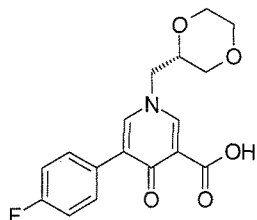
¹H-NMR (CDCl₃) δ: 3.91 (3H, s), 3.94 (3H, s), 4.64 (2H, s), 5.19 (2H, s), 6.94 (1H, d, J = 8.3 Hz), 7.03-7.17 (6H, m), 7.48-7.57 (6H, m), 7.86 (2H, d, J = 8.3 Hz), 8.27 (1H, d, J = 2.3 Hz), 8.69-8.72 (3H, m).

MS (ESI) m/z: 628 (M+H)⁺.

Example 14

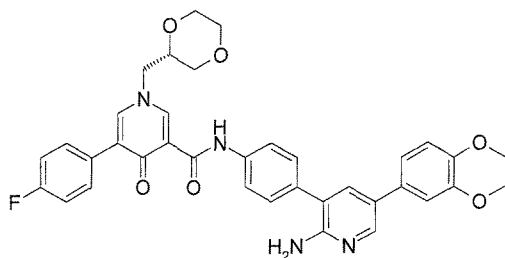
N-{4-[2-Amino-5-(3,4-dimethoxyphenyl)pyridin-3-yl]phenyl}-1-[(2S)-1,4-dioxan-2-ylmethyl]-5-(4-fluorophenyl)-4-oxo-1,4-dihydropyridine-3-carboxamide

[Step 1] 1-[(2S)-1,4-Dioxan-2-ylmethyl]-5-(4-fluorophenyl)-4-oxo-1,4-dihydropyridine-3-carboxylic acid



(2R)-1,4-Dioxan-2-ylmethyl methanesulfonate (95 mg) was added to a suspension of ethyl 5-(4-fluorophenyl)-4-oxo-1,4-dihydropyridine-3-carboxylate (100 mg) and cesium carbonate (264 mg) in DMF (2 ml) at room temperature. The reaction mixture was stirred at room temperature overnight. (2R)-1,4-Dioxan-2-ylmethyl methanesulfonate (32 mg) was added at room temperature. The reaction mixture was stirred at 80°C overnight. (2R)-1,4-Dioxan-2-ylmethyl methanesulfonate (32 mg) was added at room temperature. The reaction mixture was stirred at 100°C for three hours and then returned to room temperature. A 1 N aqueous sodium hydroxide solution (2 ml) was added to the reaction mixture at room temperature. The reaction mixture was stirred at room temperature for one hour. A 1 N aqueous hydrochloric acid solution and water were added to the reaction mixture, and the precipitated solid was collected by filtration, washed with water and then dried to give 101 mg of the title compound as a solid. MS (ESI) m/z : 334 (M+H)⁺.

[Step 2] N-{4-[2-Amino-5-(3,4-dimethoxyphenyl)pyridin-3-yl]phenyl}-1-[(2S)-1,4-dioxan-2-ylmethyl]-5-(4-fluorophenyl)-4-oxo-1,4-dihydropyridine-3-carboxamide



HOAt (21 mg), HATU (89 mg), DMAP (10 mg) and DIPEA (46 μ l) were added to a solution of the compound obtained in the above Step 1 (57 mg) in DMF (1 ml) at room temperature. The reaction mixture was stirred at room temperature for three hours. The compound obtained in Step 2 of Example 1 (50 mg) was added to the reaction mixture at room temperature. The reaction mixture was stirred at room temperature overnight. Water was added to the reaction mixture, and the precipitated solid was collected by filtration. The resulting solid was purified by PLC [dichloromethane:methanol = 20:1 (v/v)], and the eluate was concentrated under reduced pressure. The residue was purified by PLC [ethyl acetate:methanol = 15:1 (v/v)] to give 75 mg of the title compound as a solid.

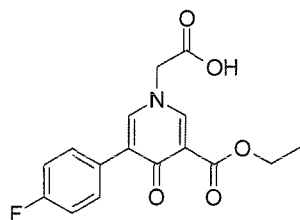
$^1\text{H-NMR}$ (CDCl_3) δ : 3.33-3.38 (1H, m), 3.55-4.03 (8H, m), 3.91 (3H, s), 3.94 (3H, s), 4.68 (2H, s), 6.93 (1H, d, J = 8.3 Hz), 7.04-7.19 (4H, m), 7.49 (2H, d, J = 8.3 Hz),

7.55-7.60 (4H, m), 7.86 (2H, d, $J = 8.3$ Hz), 8.26 (1H, d, $J = 2.3$ Hz), 8.61 (1H, d, $J = 2.8$ Hz).

MS (ESI) m/z : 637 ($M+H$)⁺.

Example 15

N-{4-[2-Amino-5-(3,4-dimethoxyphenyl)pyridin-3-yl]phenyl}-5-(4-fluorophenyl)-1-[2-(methylamino)-2-oxoethyl]-4-oxo-1,4-dihydropyridine-3-carboxamide
[Step 1] [3-(Ethoxycarbonyl)-5-(4-fluorophenyl)-4-oxopyridin-1(4H)-yl]acetic acid



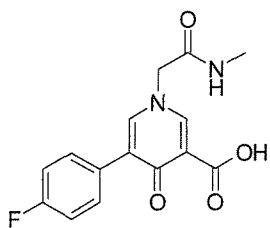
tert-Butyl bromoacetate (341 μ l) was added to a suspension of ethyl 5-(4-fluorophenyl)-4-oxo-1,4-dihydropyridine-3-carboxylate (400 mg) and cesium carbonate (998 mg) in DMF (8 ml) at room temperature. The reaction mixture was stirred at room temperature overnight. The reaction mixture was diluted by adding ethyl acetate. The organic layer was washed with water and brine, dried over sodium sulfate and filtered, and the filtrate was then concentrated under reduced pressure. Dichloromethane (15 ml) and TFA (0.59 ml) were added to the residue at room temperature. The reaction mixture was stirred at room temperature for two hours. TFA (1.00 ml) was added to the reaction mixture at room temperature.

The reaction mixture was stirred overnight. TFA (4.00 ml) was added to the reaction mixture at room temperature. The reaction mixture was stirred overnight. Water was added to the reaction mixture, and the organic layer was extracted with ethyl acetate, washed with brine and dried over sodium sulfate. After filtration, the filtrate was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography [chloroform:methanol = 19:1 -> 17:3 (v/v)] to give 320 mg of the title compound as a solid.

^1H -NMR (CDCl_3) δ : 1.47 (3H, t, J = 7.1 Hz), 4.57 (2H, q, J = 7.2 Hz), 5.38 (2H, s), 7.16-7.22 (2H, m), 7.57-7.62 (2H, m), 8.50 (1H, s), 9.06 (1H, s).

MS (ESI) m/z : 320 ($\text{M}+\text{H}$) $^+$.

[Step 2] 5-(4-Fluorophenyl)-1-[2-(methylamino)-2-oxoethyl]-4-oxo-1,4-dihydropyridine-3-carboxylic acid

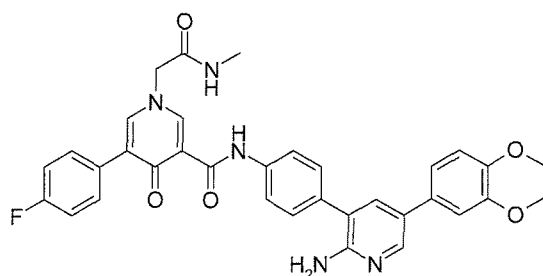


Methylamine (2 M solution in THF; 0.63 ml), EDC.HCl (96 mg), HOBT (35 mg) and DMF (3 ml) were added to the compound obtained in the above Step 1 (80 mg) at room temperature. The reaction mixture was stirred overnight. The reaction mixture was stirred at 50°C for five hours. Water (1 ml) was added to the reaction mixture at 50°C.

The reaction mixture was stirred at 50°C for 1.5 hours and returned to room temperature. A 1 N aqueous sodium hydroxide solution (2 ml) was added to the reaction mixture at room temperature. The reaction mixture was stirred at room temperature for 0.5 hour. A 1 N aqueous hydrochloric acid solution and water were added to the reaction mixture, and the organic layer was extracted with dichloromethane and dried over sodium sulfate. After filtration, the filtrate was concentrated under reduced pressure, and the residue was washed with water to give 22 mg of the title compound as a solid.

$^1\text{H-NMR}$ (CD_3OD) δ : 2.81 (3H, s), 4.94 (2H, s), 7.15-7.21 (2H, m), 7.65-7.72 (2H, m), 8.10 (1H, s), 8.65 (1H, s).
MS (ESI) m/z : 305 ($\text{M}+\text{H}$) $^+$.

[Step 3] N-{4-[2-Amino-5-(3,4-dimethoxyphenyl)pyridin-3-yl]phenyl}-5-(4-fluorophenyl)-1-[2-(methylamino)-2-oxoethyl]-4-oxo-1,4-dihydropyridine-3-carboxamide



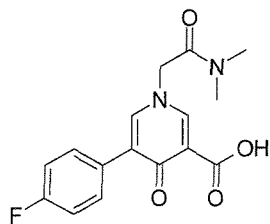
HOAt (9 mg), HATU (37 mg), DMAP (4 mg) and DIPEA (20 μl) were added to a solution of the compound obtained in the above Step 2 (22 mg) in DMF (1 ml) at room temperature. The reaction mixture was stirred at room

temperature for 3.5 hours. The compound obtained in Step 2 of Example 1 (21 mg) was added to the reaction mixture at room temperature. The reaction mixture was stirred at room temperature overnight. Water was added to the reaction mixture, and the precipitated solid was collected by filtration and washed with acetone to give 13 mg of the title compound as a solid.

$^1\text{H-NMR}$ (DMSO-D_6) δ : 2.64-2.66 (3H, m), 3.74 (3H, s), 3.80 (3H, s), 4.91 (2H, s), 5.65 (2H, s), 6.96 (1H, d, $J = 8.7$ Hz), 7.10-7.17 (2H, m), 7.27 (2H, t, $J = 8.9$ Hz), 7.50 (2H, d, $J = 8.7$ Hz), 7.58 (1H, d, $J = 2.8$ Hz), 7.66-7.71 (2H, m), 7.80 (2H, d, $J = 8.7$ Hz), 8.09 (1H, d, $J = 1.8$ Hz), 8.22 (2H, d, $J = 2.3$ Hz), 8.64 (1H, d, $J = 2.3$ Hz).
 MS(ESI) m/z : 608 ($\text{M}+\text{H}$) $^+$.

Example 16

N-{4-[2-Amino-5-(3,4-dimethoxyphenyl)pyridin-3-yl]phenyl}-1-[2-(dimethylamino)-2-oxoethyl]-5-(4-fluorophenyl)-4-oxo-1,4-dihydropyridine-3-carboxamide
[Step 1] 1-[2-(Dimethylamino)-2-oxoethyl]-5-(4-fluorophenyl)-4-oxo-1,4-dihydropyridine-3-carboxylic acid



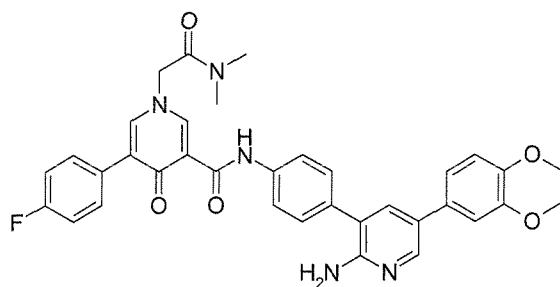
33 mg of the title compound was obtained as a solid from the compound obtained in Step 1 of Example 15 (100

mg) and dimethylamine (2 M solution in THF; 1.55 ml) by a reaction similar to that in Step 2 of Example 15.

$^1\text{H-NMR}$ (DMSO-D_6) δ : 2.89 (3H, s), 3.00 (3H, s), 5.27 (2H, s), 7.28-7.34 (2H, m), 7.68-7.73 (2H, m), 8.28 (1H, d, J = 1.8 Hz), 8.68 (1H, d, J = 2.3 Hz).

MS(ESI) m/z : 319 ($\text{M}+\text{H}$) $^+$.

[Step 2] N-{4-[2-Amino-5-(3,4-dimethoxyphenyl)pyridin-3-yl]phenyl}-1-[2-(dimethylamino)-2-oxoethyl]-5-(4-fluorophenyl)-4-oxo-1,4-dihydropyridine-3-carboxamide



HOAt (13 mg), HATU (53 mg), DMAP (6 mg) and DIPEA (29 μl) were added to a solution of the compound obtained in the above Step 1 (33 mg) in DMF (1 ml) at room temperature. The reaction mixture was stirred at room temperature for three hours. The compound obtained in Step 2 of Example 1 (30 mg) was added to the reaction mixture at room temperature. The reaction mixture was stirred at room temperature overnight. Water was added to the reaction mixture, and the precipitated solid was collected by filtration. The resulting solid was purified by PLC [ethyl acetate:methanol = 6:1 (v/v)], and the eluate was concentrated under reduced pressure. The

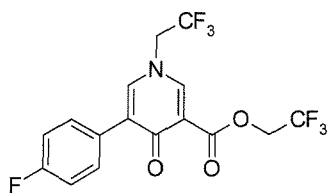
residue was purified by PLC [dichloromethane:methanol = 20:1 (v/v)] to give 10 mg of the title compound as a solid.

$^1\text{H-NMR}$ (CDCl_3) δ : 3.06 (3H, s), 3.12 (3H, s), 3.92 (3H, s), 3.94 (3H, s), 4.67 (2H, s), 4.81 (2H, s), 6.94 (1H, d, $J = 8.3$ Hz), 7.03-7.16 (4H, m), 7.45-7.50 (3H, m), 7.55-7.60 (3H, m), 7.86 (2H, d, $J = 8.3$ Hz), 8.26 (1H, d, $J = 2.3$ Hz), 8.51 (1H, d, $J = 2.8$ Hz).

MS (ESI) m/z : 622 ($\text{M}+\text{H}$) $^+$.

Example 17

N-{4-[2-Amino-5-(3,4-dimethoxyphenyl)pyridin-3-yl]phenyl}-1-(2,2-difluoro-2-methoxyethyl)-5-(4-fluorophenyl)-4-oxo-1,4-dihydropyridine-3-carboxamide
[Step 1] 2,2,2-Trifluoroethyl 5-(4-fluorophenyl)-4-oxo-1-(2,2,2-trifluoroethyl)-1,4-dihydropyridine-3-carboxylate



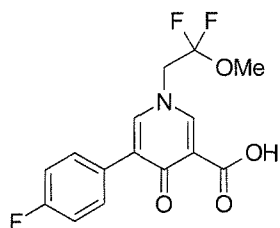
2,2,2-Trifluoroethyl trifluoromethanesulfonate (371 μl) was added to a suspension of 5-(4-fluorophenyl)-4-oxo-1,4-dihydropyridine-3-carboxylic acid (100 mg) and cesium carbonate (838 mg) in DMF (2 ml) at room temperature. The reaction mixture was stirred at room temperature for three hours and diluted by adding ethyl acetate. The organic layer was washed with water and

brine and dried over sodium sulfate. After filtration, the filtrate was concentrated under reduced pressure, and the residue was purified by PLC [ethyl acetate:hexane = 2:1 (v/v)] to give 123 mg of the title compound as a solid.

$^1\text{H-NMR}$ (CDCl_3) δ : 4.37-4.46 (2H, m), 4.65-4.71 (2H, m), 7.05-7.12 (2H, m), 7.34-7.39 (1H, m), 7.49-7.56 (2H, m), 8.16 (1H, d, $J = 2.4$ Hz).

MS (ESI) m/z : 398 ($\text{M}+\text{H}$) $^+$.

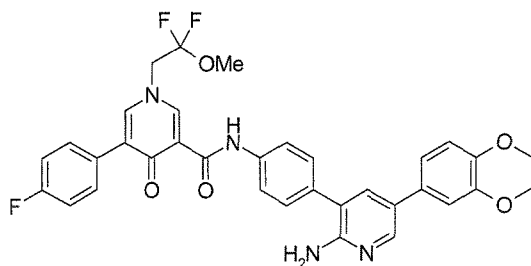
[Step 2] 1-(2,2-Difluoro-2-methoxyethyl)-5-(4-fluorophenyl)-4-oxo-1,4-dihydropyridine-3-carboxylic acid



Methanol (2 ml) and a 1 N aqueous sodium hydroxide solution (2 ml) were added to a solution of the compound obtained in the above Step 1 (123 mg) in THF (2 ml) at room temperature. The reaction mixture was stirred at room temperature for three hours. The reaction mixture was stirred at 50°C for one hour. The reaction mixture was stirred at 80°C overnight. A 1 N aqueous sodium hydroxide solution (3 ml) was added to the reaction mixture, and the mixture was stirred at 80°C overnight and returned to room temperature. A 1 N aqueous hydrochloric acid solution and water were added to the

reaction mixture. The precipitated solid was collected by filtration, washed with water and then washed with a mixed solvent of hexane and diethyl ether [4:1 (v/v)] and dried to give 58 mg of the title compound as a solid.

[Step 3] N-{4-[2-Amino-5-(3,4-dimethoxyphenyl)pyridin-3-yl]phenyl}-1-(2,2-difluoro-2-methoxyethyl)-5-(4-fluorophenyl)-4-oxo-1,4-dihydropyridine-3-carboxamide



HOAt (25 mg), HATU (105 mg), DMAP (11 mg) and DIPEA (54 μ l) were added to a solution of the compound obtained in the above Step 2 (58 mg) in DMF (1 ml) at room temperature. The reaction mixture was stirred at room temperature for three hours. The compound obtained in Step 2 of Example 1 (59 mg) was added to the reaction mixture at room temperature. The reaction mixture was stirred at room temperature overnight. Water was added to the reaction mixture, and the precipitated solid was collected by filtration. The resulting solid was purified by PLC [developed with ethyl acetate], and the eluate was concentrated under reduced pressure. The residue was purified by PLC [dichloromethane:methanol = 20:1 (v/v)], and the eluate was concentrated under

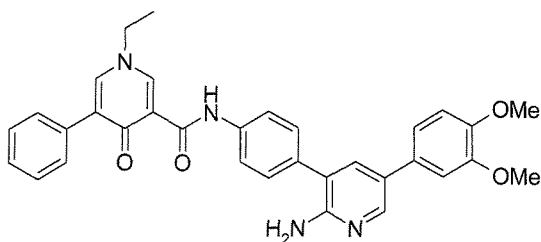
reduced pressure. The residue was purified by PLC (NH)
[dichloromethane:methanol = 30:1 (v/v)] to give 16 mg of
the title compound as a solid.

$^1\text{H-NMR}$ (CDCl_3) δ : 3.66 (3H, s), 3.91 (3H, s), 3.94 (3H,
s), 4.32 (2H, t, $J = 7.3$ Hz), 4.69 (2H, s), 6.91-6.95 (1H,
m), 7.03-7.05 (1H, m), 7.06-7.10 (1H, m), 7.14-7.20 (2H,
m), 7.47-7.58 (6H, m), 7.84-7.88 (2H, m), 8.26 (1H, d, J
 $= 2.3$ Hz), 8.62 (1H, d, $J = 2.3$ Hz).

MS (ESI) m/z : 631 ($\text{M}+\text{H}$) $^+$.

Example 18

N-{4-[2-Amino-5-(3,4-dimethoxyphenyl)pyridin-3-
yl]phenyl}-1-ethyl-4-oxo-5-phenyl-1,4-dihydropyridine-3-
carboxamide



DIPEA (601 μl) was added to a solution of 1-ethyl-4-
oxo-5-phenyl-1,4-dihydropyridine-3-carboxylic acid (420
mg) and COMU (961 mg) in DMF (5.0 ml) at room temperature,
and the mixture was stirred for 20 minutes. The compound
obtained in Step 2 of Example 1 (610 mg) was added at
room temperature. The mixture was stirred for 15 hours,
followed by the addition of water. The organic layer was
extracted with ethyl acetate, and then washed with water

and brine and dried over sodium sulfate. The solvent was distilled off under reduced pressure, and the residue was purified by silica gel column chromatography [chloroform:methanol = 300:1 -> 60:1 (v/v)] to give 700 mg of the title compound as a solid.

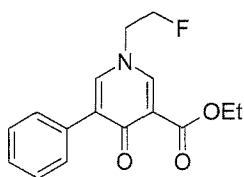
$^1\text{H-NMR}$ (CDCl_3) δ : 1.58-1.64 (3H, m), 3.92 (3H, s), 3.95 (3H, s), 4.09 (2H, q, $J = 7.3$ Hz), 4.70 (2H, s), 6.94 (1H, d, $J = 8.3$ Hz), 7.02-7.12 (2H, m), 7.39-7.61 (9H, m), 7.85-7.91 (2H, m), 8.26 (1H, d, $J = 2.8$ Hz), 8.66 (1H, d, $J = 2.8$ Hz).

MS(ESI) m/z : 547 ($\text{M}+\text{H}$) $^+$.

Example 19

N-{4-[2-Amino-5-(3,4-dimethoxyphenyl)pyridin-3-yl]phenyl}-1-(2-fluoroethyl)-4-oxo-5-phenyl-1,4-dihydropyridine-3-carboxamide

[Step 1] Ethyl 1-(2-fluoroethyl)-4-oxo-5-phenyl-1,4-dihydropyridine-3-carboxylate



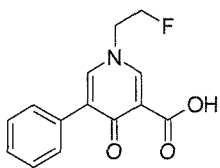
Ethyl 4-oxo-5-phenyl-1,4-dihydropyridine-3-carboxylate (190 mg) was suspended in DMF (2.5 ml). Cesium carbonate (509 mg) and 2-fluoroethyl 4-methylbenzenesulfonate (256 mg) were added sequentially and the mixture was stirred at 50°C for three hours. A 1

N aqueous hydrochloric acid solution was added under ice cooling, and the organic layer was extracted with ethyl acetate, washed with water and brine and then dried over sodium sulfate. The solvent was distilled off under reduced pressure, and the residue was purified by silica gel column chromatography [chloroform:methanol = 300:1 -> 40:1 (v/v)] to give 181 mg of the title compound as an oily substance.

$^1\text{H-NMR}$ (CDCl_3) δ : 1.39 (3H, t, $J = 7.2$ Hz), 4.09-4.22 (2H, m), 4.38 (2H, q, $J = 7.2$ Hz), 4.68-4.73 (1H, m), 4.79-4.85 (1H, m), 7.31-7.43 (4H, m), 7.56-7.61 (2H, m), 8.16 (1H, d, $J = 2.8$ Hz).

MS (ESI) m/z : 290 ($\text{M}+\text{H}$) $^+$.

[Step 2] 1-(2-Fluoroethyl)-4-oxo-5-phenyl-1,4-dihydropyridine-3-carboxylic acid



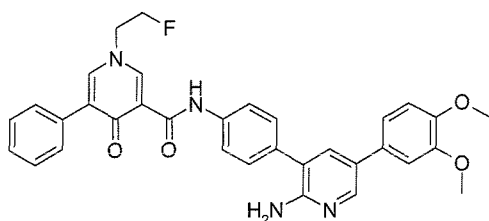
A 1 N aqueous sodium hydroxide solution (1.2 ml) was added to a solution of the compound obtained in the above Step 1 (181 mg) in methanol (1.5 ml) at room temperature, and the mixture was stirred for two hours. The solvent was distilled off under reduced pressure and a 1 N aqueous hydrochloric acid solution was added. The

precipitated solid was collected by filtration to give 98 mg of the title compound.

$^1\text{H-NMR}$ (CDCl_3) δ : 4.26-4.39 (2H, m), 4.74-4.91 (2H, m), 7.40-7.51 (3H, m), 7.56-7.62 (2H, m), 7.68 (1H, d, $J = 2.0$ Hz), 8.56 (1H, d, $J = 2.0$ Hz).

MS (ESI) m/z : 262 ($\text{M}+\text{H}$) $^+$.

[Step 3] N-{4-[2-Amino-5-(3,4-dimethoxyphenyl)pyridin-3-yl]phenyl}-1-(2-fluoroethyl)-4-oxo-5-phenyl-1,4-dihydropyridine-3-carboxamide



DIPEA (133 μl) was added to a solution of the compound obtained in the above Step 2 (100 mg) and COMU (213 mg) in DMF (5.0 ml) at room temperature, and the mixture was stirred for one hour. The compound obtained in Step 2 of Example 1 (135 mg) was added at room temperature. The mixture was stirred for five hours, followed by the addition of water. The organic layer was extracted with ethyl acetate, and then washed with water and brine and dried over sodium sulfate. The solvent was distilled off under reduced pressure, and the residue was purified by silica gel column chromatography [chloroform:methanol = 19:1 (v/v)] to give 192 mg of the title compound as a solid.

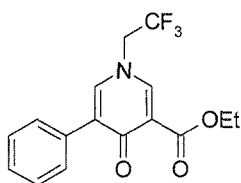
$^1\text{H-NMR}$ (CDCl_3) δ : 3.92 (3H, s), 3.94 (3H, s), 4.27 (1H, t, $J = 4.6$ Hz), 4.33 (1H, t, $J = 4.4$ Hz), 4.64 (2H, s), 4.77 (1H, t, $J = 4.6$ Hz), 4.88 (1H, t, $J = 4.4$ Hz), 6.94 (1H, d, $J = 8.3$ Hz), 7.04 (1H, d, $J = 2.3$ Hz), 7.09 (1H, dd, $J = 8.3, 1.8$ Hz), 7.40-7.51 (5H, m), 7.56-7.60 (4H, m), 7.87 (2H, d, $J = 8.7$ Hz), 8.27 (1H, d, $J = 2.3$ Hz), 8.65 (1H, d, $J = 2.8$ Hz).

MS (ESI) m/z : 565 ($\text{M}+\text{H}$) $^+$.

Example 20

N-{4-[2-Amino-5-(3,4-dimethoxyphenyl)pyridin-3-yl]phenyl}-4-oxo-5-phenyl-1-(2,2,2-trifluoroethyl)-1,4-dihydropyridine-3-carboxamide

[Step 1] Ethyl 4-oxo-5-phenyl-1-(2,2,2-trifluoroethyl)-1,4-dihydropyridine-3-carboxylate



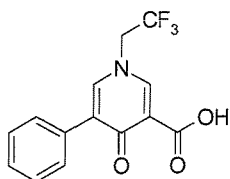
Ethyl 4-oxo-5-phenyl-1,4-dihydropyridine-3-carboxylate (100 mg) was suspended in DMF (1.5 ml). Cesium carbonate (268 mg) and 2,2,2-trifluoroethyl trifluoromethanesulfonate (83 μl) were added sequentially and the mixture was stirred at room temperature for three hours. A 1 N aqueous hydrochloric acid solution was added under ice cooling, followed by extraction with ethyl acetate. The organic layer was washed with water

and brine and then dried over sodium sulfate. The solvent was distilled off under reduced pressure, and the residue was purified by silica gel column chromatography [chloroform:methanol = 300:1 $\rightarrow$ 40:1 (v/v)] to give 159 mg of the title compound as an oily substance.

$^1\text{H-NMR}$ (CDCl_3) δ : 1.39 (3H, t, $J = 7.1$ Hz), 4.33-4.42 (4H, m), 7.33-7.44 (4H, m), 7.51-7.58 (2H, m), 8.13 (1H, d, $J = 2.8$ Hz).

MS (ESI) m/z : 326 ($\text{M}+\text{H}$) $^+$.

[Step 2] 4-Oxo-5-phenyl-1-(2,2,2-trifluoroethyl)-1,4-dihydropyridine-3-carboxylic acid

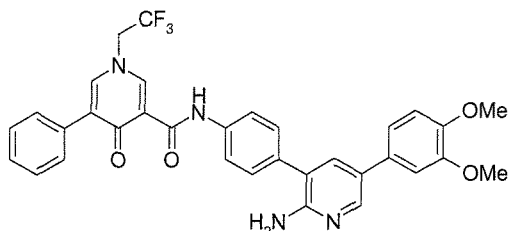


A 1 N aqueous sodium hydroxide solution (0.73 ml) was added to a solution of the compound obtained in the above Step 1 (158 mg) in methanol (2.0 ml) at room temperature, and the mixture was stirred for two hours. The solvent was distilled off under reduced pressure and a 1 N aqueous hydrochloric acid solution was added. The precipitated solid was collected by filtration to give 90 mg of the title compound.

$^1\text{H-NMR}$ (CDCl_3) δ : 4.54 (2H, q, $J = 7.6$ Hz), 7.42-7.64 (6H, m), 8.54 (1H, d, $J = 2.8$ Hz).

MS (ESI) m/z : 296 ($\text{M}-\text{H}$) $^-$.

[Step 3] N-{4-[2-Amino-5-(3,4-dimethoxyphenyl)pyridin-3-yl]phenyl}-4-oxo-5-phenyl-1-(2,2,2-trifluoroethyl)-1,4-dihydropyridine-3-carboxamide



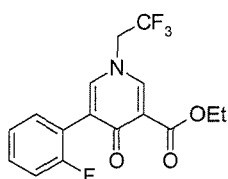
DIPEA (289 μ l) was added to a solution of the compound obtained in the above Step 2 (247 mg) and COMU (462 mg) in DMF (2.5 ml) at room temperature, and the mixture was stirred for 10 minutes. The compound obtained in Step 2 of Example 1 (267 mg) was added at room temperature. The mixture was stirred for 17 hours, followed by the addition of water. The organic layer was extracted with ethyl acetate, and then washed with water and brine and dried over sodium sulfate. The solvent was distilled off under reduced pressure, and the residue was purified by silica gel column chromatography [chloroform:methanol = 300:1 $\rightarrow$ 40:1 (v/v)] to give 320 mg of the title compound as a solid.

$^1\text{H-NMR}$ (CDCl_3) δ : 3.92 (3H, s), 3.94 (3H, s), 4.51 (2H, q, $J = 7.8$ Hz), 4.65 (2H, s), 6.94 (1H, d, $J = 8.3$ Hz), 7.02-7.11 (2H, m), 7.42-7.59 (9H, m), 7.83-7.89 (2H, m), 8.27 (1H, d, $J = 2.8$ Hz), 8.64 (1H, d, $J = 2.8$ Hz).

MS(ESI) m/z : 601 ($\text{M}+\text{H}$) $^+$.

Example 21

N-{4-[2-Amino-5-(3,4-dimethoxyphenyl)pyridin-3-yl]phenyl}-5-(2-fluorophenyl)-4-oxo-1-(2,2,2-trifluoroethyl)-1,4-dihydropyridine-3-carboxamide
[Step 1] Ethyl 5-(2-fluorophenyl)-4-oxo-1-(2,2,2-trifluoroethyl)-1,4-dihydropyridine-3-carboxylate

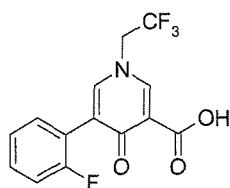


The compound obtained in Reference Example 1 (110 mg) was suspended in DMF (1.5 ml). Cesium carbonate (274 mg) and 2,2,2-trifluoroethyl trifluoromethanesulfonate (85 μ l) were added sequentially and the mixture was stirred at room temperature for four hours. A 1 N aqueous hydrochloric acid solution was added under ice cooling, followed by extraction with ethyl acetate. The organic layer was washed with water and brine and then dried over sodium sulfate. The solvent was distilled off under reduced pressure, and the residue was purified by silica gel column chromatography [chloroform:methanol = 300:1 $\rightarrow$ 60:1 (v/v)] to give 134 mg of the title compound as an oily substance.

$^1\text{H-NMR}$ (CDCl_3) δ : 1.38 (3H, t, $J = 7.1$ Hz), 4.33-4.41 (4H, m), 7.09-7.22 (2H, m), 7.30-7.38 (1H, m), 7.45 (1H, br s), 7.55-7.61 (1H, m), 8.15 (1H, d, $J = 2.8$ Hz).

MS(ESI) m/z : 344 ($\text{M}+\text{H}$) $^+$.

[Step 2] 5-(2-Fluorophenyl)-4-oxo-1-(2,2,2-trifluoroethyl)-1,4-dihydropyridine-3-carboxylic acid

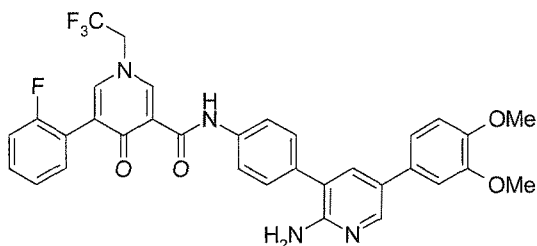


A 1 N aqueous sodium hydroxide solution (0.78 ml) was added to a solution of the compound obtained in the above Step 1 (134 mg) in methanol (1.2 ml) at room temperature, and the mixture was stirred for two hours. The solvent was distilled off under reduced pressure and a 1 N aqueous hydrochloric acid solution was added. The precipitated solid was collected by filtration to give 103 mg of the title compound.

$^1\text{H-NMR}$ (CDCl_3) δ : 4.54 (2H, q, $J = 7.8$ Hz), 7.17-7.30 (2H, m), 7.40-7.48 (1H, m), 7.55-7.61 (1H, m), 7.70 (1H, br s), 8.57 (1H, d, $J = 2.3$ Hz).

MS (ESI) m/z : 316 ($\text{M}+\text{H}$) $^+$.

[Step 3] N-{4-[2-Amino-5-(3,4-dimethoxyphenyl)pyridin-3-yl]phenyl}-5-(2-fluorophenyl)-4-oxo-1-(2,2,2-trifluoroethyl)-1,4-dihydropyridine-3-carboxamide



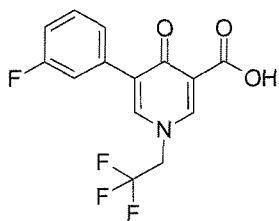
DIPEA (35 μ l) was added to a solution of the compound obtained in the above Step 2 (32 mg) and COMU (57 mg) in DMF (1.0 ml) at room temperature, and the mixture was stirred for 20 minutes. The compound obtained in Step 2 of Example 1 (36 mg) was added at room temperature. The mixture was stirred for seven hours, followed by the addition of a 1 N aqueous hydrochloric acid solution. After extraction with ethyl acetate, the organic layer was washed with water and brine and then dried over sodium sulfate. The solvent was distilled off under reduced pressure, and the residue was purified by silica gel column chromatography [chloroform:methanol = 300:1 $\rightarrow$ 30:1 (v/v)] to give 49 mg of the title compound as a solid.

$^1\text{H-NMR}$ (CDCl_3) δ : 3.92 (3H, s), 3.94 (3H, s), 4.51 (2H, q, $J = 7.8$ Hz), 4.62 (2H, s), 6.94 (1H, d, $J = 8.3$ Hz), 7.02-7.11 (2H, m), 7.18-7.31 (2H, m), 7.40-7.62 (6H, m), 7.82-7.87 (2H, m), 8.27 (1H, d, $J = 2.3$ Hz), 8.66 (1H, d, $J = 2.3$ Hz), 12.40 (1H, s).

MS(ESI) m/z : 619 ($\text{M}+\text{H}$) $^+$.

Example 22

N-{4-[2-Amino-5-(3,4-dimethoxyphenyl)pyridin-3-yl]phenyl}-5-(3-fluorophenyl)-4-oxo-1-(2,2,2-trifluoroethyl)-1,4-dihydropyridine-3-carboxamide
[Step 1] 5-(3-Fluorophenyl)-4-oxo-1-(2,2,2-trifluoroethyl)-1,4-dihydropyridine-3-carboxylic acid

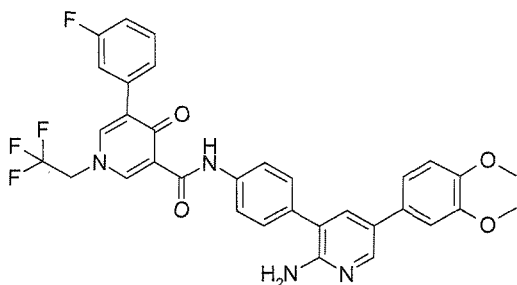


The compound obtained in Reference Example 2 (75 mg) was suspended in DMF. Cesium carbonate (140 mg) and 2,2,2-trifluoroethyl trifluoromethanesulfonate (54 μ l) were added sequentially and the mixture was stirred at room temperature for four hours. The reaction solution was filtered. After washing with a small amount of DMF, a 1 N aqueous sodium hydroxide solution (0.57 ml) was added to the filtrate at room temperature, and the mixture was stirred for three hours. The solvent was distilled off under reduced pressure and a 1 N aqueous hydrochloric acid solution was added. The precipitated solid was collected by filtration to give 77 mg of the title compound.

$^1\text{H-NMR}$ (CDCl_3) δ : 4.56 (2H, q, $J = 7.8$ Hz), 7.12-7.19 (1H, m), 7.30-7.38 (2H, m), 7.41-7.49 (1H, m), 7.61-7.65 (1H, m), 8.54-8.59 (1H, m).

MS (ESI) m/z : 316 ($M+H$) $^+$.

[Step 2] N-{4-[2-Amino-5-(3,4-dimethoxyphenyl)pyridin-3-yl]phenyl}-5-(3-fluorophenyl)-4-oxo-1-(2,2,2-trifluoroethyl)-1,4-dihydropyridine-3-carboxamide



DIPEA (64 μ l) was added to a solution of the carboxylic acid obtained in the above Step 1 (77 mg) and COMU (136 mg) in DMF (1.0 ml) at room temperature, and the mixture was stirred for 30 minutes. The compound obtained in Step 2 of Example 1 (73 mg) was added at room temperature. The mixture was stirred for 15 hours, followed by the addition of water. The precipitated solid was collected by filtration, and the resulting solid was purified by silica gel column chromatography [ethyl acetate:dichloromethane:methanol = 10:10:1 (v/v)] and then crystallized from dichloromethane and diisopropyl ether to give 92 mg of the title compound as a solid.

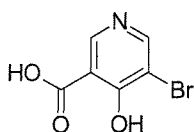
$^1\text{H-NMR}$ (CDCl_3) δ : 3.92 (3H, s), 3.94 (3H, s), 4.48-4.56 (2H, m), 4.62 (2H, s), 6.90-7.19 (4H, m), 7.21-7.36 (2H, m), 7.42-7.61 (5H, m), 7.82-7.89 (2H, m), 8.25-8.30 (1H, m), 8.62-8.66 (1H, m), 12.43 (1H, s).

MS (ESI) m/z : 619 ($\text{M}+\text{H}$) $^+$.

Example 23

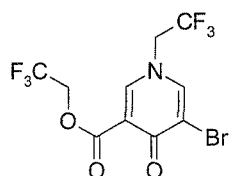
N-{4-[2-Amino-5-(3,4-dimethoxyphenyl)pyridin-3-yl]phenyl}-6'-fluoro-4-oxo-1-(2,2,2-trifluoroethyl)-1,4-dihydro-3,3'-bipyridine-5-carboxamide

[Step 1] 5-Bromo-4-hydroxypyridine-3-carboxylic acid



A solution of methyllithium in ether (1 M, 4.8 ml) was added to a solution of 3,5-dibromopyridin-4-ol (1200 mg) in THF (10 ml) at -78°C , and the mixture was stirred for 30 minutes. A solution of n-butyllithium in hexane (1.65 M, 6.0 ml) was added at -78°C , and the mixture was stirred for one hour. Dry ice was added at -78°C and the mixture was stirred at 0°C for 20 minutes, followed by the addition of a 4 N aqueous hydrochloric acid solution. The precipitated solid was collected by filtration and washed with water to give a mixture of the title compound and 3,5-dibromopyridin-4-ol.

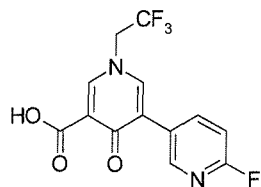
[Step 2] 2,2,2-Trifluoroethyl 5-bromo-4-oxo-1-(2,2,2-trifluoroethyl)-1,4-dihydropyridine-3-carboxylate



DMF (5 ml), cesium carbonate (2140 mg) and 2,2,2-trifluoroethyl trifluoromethanesulfonate (945 μl) were

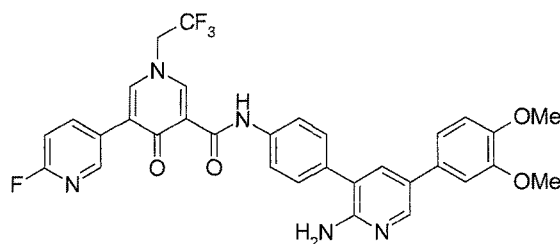
added sequentially to the compound obtained in the above Step 1, and the mixture was stirred at room temperature for two hours. A 1 N aqueous hydrochloric acid solution was added, followed by extraction with ethyl acetate. The organic layer was washed with a saturated aqueous sodium bicarbonate solution and brine and then dried over sodium sulfate. The solvent was distilled off under reduced pressure, and the residue was purified by silica gel column chromatography [chloroform:methanol = 300:1 -> 30:1 (v/v)] to give the title compound as a mixture with an inseparable by-product.

[Step 3] 6'-Fluoro-4-oxo-1-(2,2,2-trifluoroethyl)-1,4-dihydro-3,3'-bipyridine-5-carboxylic acid



The compound obtained in the above Step 2 was suspended in a mixed solvent of 1,4-dioxane/water (7.0/0.7 ml). (6-Fluoropyridin-3-yl)boronic acid (420 mg), potassium carbonate (659 mg) and tetrakis(triphenylphosphine)palladium (138 mg) were added sequentially, and the mixture was stirred at 100°C for seven hours. The mixture was left to cool, followed by the addition of a 1 N aqueous hydrochloric acid solution. The organic layer was extracted with chloroform and dried

[Step 4] N-{4-[2-Amino-5-(3,4-dimethoxyphenyl)pyridin-3-yl]phenyl}-6'-fluoro-4-oxo-1-(2,2,2-trifluoroethyl)-1,4-dihydro-3,3'-bipyridine-5-carboxamide



DIPEA (31 μ l) was added to a solution of the compound obtained in the above Step 3 and COMU (49 mg) in DMF (1.0 ml) at room temperature, and the mixture was stirred for 20 minutes. The compound obtained in Step 2 of Example 1 (31 mg) was added at room temperature. The mixture was stirred for seven hours, followed by the addition of water. After extraction with ethyl acetate, the organic layer was washed with water and brine and then dried over sodium sulfate. The solvent was distilled off under reduced pressure, and the residue was purified by PLC [chloroform:methanol = 15:1 (v/v)] to give 21 mg of the title compound as a solid.

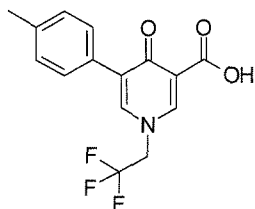
$^1\text{H-NMR}$ (CDCl_3) δ : 3.92 (3H, s), 3.94 (3H, s), 4.55 (2H, q, $J = 7.8$ Hz), 4.64 (2H, s), 6.94 (1H, d, $J = 8.3$ Hz), 7.02-7.12 (3H, m), 7.49-7.60 (4H, m), 7.82-7.88 (2H, m), 8.16-8.22 (1H, m), 8.26-8.33 (2H, m), 8.68 (1H, d, $J = 2.3$ Hz), 12.29 (1H, s).

MS(ESI) m/z : 620 ($\text{M}+\text{H}$) $^+$.

Example 24

N-{4-[2-Amino-5-(3,4-dimethoxyphenyl)pyridin-3-yl]phenyl}-5-(4-methylphenyl)-4-oxo-1-(2,2,2-trifluoroethyl)-1,4-dihydropyridine-3-carboxamide

[Step 1] 5-(4-Methylphenyl)-4-oxo-1-(2,2,2-trifluoroethyl)-1,4-dihydropyridine-3-carboxylic acid

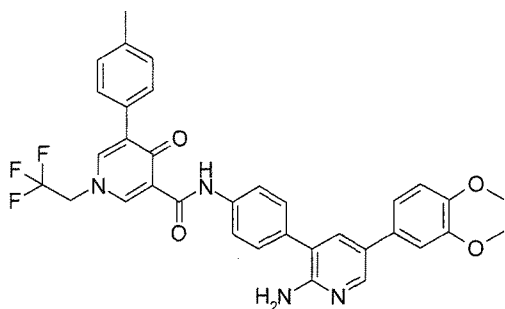


71 mg of the title compound was obtained from the compound obtained in Reference Example 3 (75 mg) and 2,2,2-trifluoroethyl trifluoromethanesulfonate (55 μl) as raw materials by a reaction similar to that in Step 1 of Example 22.

$^1\text{H-NMR}$ (CDCl_3) δ : 2.41 (3H, s), 4.52 (2H, q, $J = 7.6$ Hz), 7.23-7.32 (2H, m), 7.43-7.49 (2H, m), 7.57-7.61 (1H, m), 8.50-8.54 (1H, m).

MS(ESI) m/z : 312 ($\text{M}+\text{H}$) $^+$.

[Step 2] N-{4-[2-Amino-5-(3,4-dimethoxyphenyl)pyridin-3-yl]phenyl}-5-(4-methylphenyl)-4-oxo-1-(2,2,2-trifluoroethyl)-1,4-dihydropyridine-3-carboxamide



60 mg of the title compound was obtained as a solid from the carboxylic acid obtained in the aforementioned Step 1 (71 mg) and the compound obtained in Step 2 of Example 1 (67 mg) as raw materials by a reaction similar to that in Step 3 of Example 3.

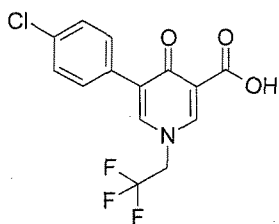
$^1\text{H-NMR}$ (CDCl_3) δ : 2.42 (3H, s), 3.92 (3H, s), 3.94 (3H, s), 4.45-4.54 (2H, m), 4.63 (2H, s), 6.90-7.14 (3H, m), 7.20-7.33 (2H, m), 7.42-7.59 (6H, m), 7.83-7.89 (2H, m), 8.25-8.30 (1H, m), 8.60-8.64 (1H, m), 12.55 (1H, s).

MS (ESI) m/z : 615 ($\text{M}+\text{H}$) $^+$.

Example 25

N-{4-[2-Amino-5-(3,4-dimethoxyphenyl)pyridin-3-yl]phenyl}-5-(4-chlorophenyl)-4-oxo-1-(2,2,2-trifluoroethyl)-1,4-dihydropyridine-3-carboxamide

[Step 1] 5-(4-Chlorophenyl)-4-oxo-1-(2,2,2-trifluoroethyl)-1,4-dihydropyridine-3-carboxylic acid

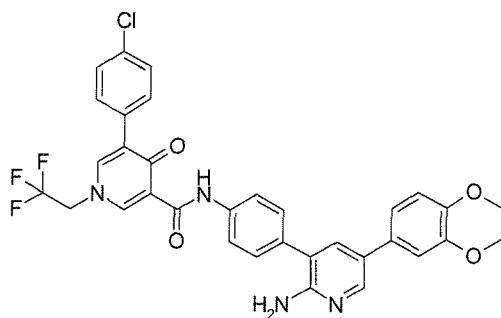


76 mg of the title compound was obtained from the compound obtained in Reference Example 4 (75 mg) and 2,2,2-trifluoroethyl trifluoromethanesulfonate (51 μ l) as raw materials by a reaction similar to that in Step 1 of Example 22.

$^1\text{H-NMR}$ (CDCl_3) δ : 4.51-4.60 (2H, m), 7.42-7.56 (4H, m), 7.59-7.63 (1H, m), 8.54-8.57 (1H, m).

MS(ESI) m/z : 332 ($\text{M}+\text{H}$) $^+$.

[Step 2] N-{4-[2-Amino-5-(3,4-dimethoxyphenyl)pyridin-3-yl]phenyl}-5-(4-chlorophenyl)-4-oxo-1-(2,2,2-trifluoroethyl)-1,4-dihydropyridine-3-carboxamide



107 mg of the title compound was obtained as a solid from the compound obtained in the above Step 1 (76 mg) and the compound obtained in Step 2 of Example 1 (68 mg) as raw materials by a reaction similar to that in Step 3 of Example 3.

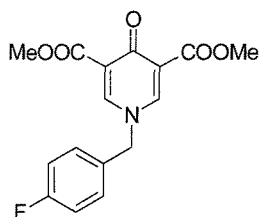
$^1\text{H-NMR}$ (CDCl_3) δ : 3.92 (3H, s), 3.94 (3H, s), 4.47-4.56 (2H, m), 4.63 (2H, s), 6.91-7.12 (3H, m), 7.44-7.59 (8H, m), 7.82-7.88 (2H, m), 8.26-8.29 (1H, m), 8.62-8.66 (1H, m), 12.43 (1H, s).

MS(ESI) m/z : 635 ($\text{M}+\text{H}$) $^+$.

Example 26

N-{4-[2-Amino-5-(3,4-dimethoxyphenyl)pyridin-3-yl]phenyl}-1-(4-fluorobenzyl)-4-oxo-5-(pyrrolidin-1-ylcarbonyl)-1,4-dihydropyridine-3-carboxamide

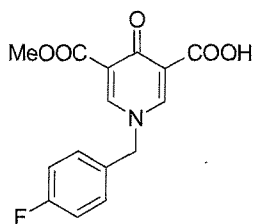
[Step 1] Dimethyl 1-(4-fluorobenzyl)-4-oxo-1,4-dihydropyridine-3,5-dicarboxylate



N,N-Dimethylformamide dimethylacetal (25.6 ml) was added to a solution of dimethyl 1,3-acetone-dicarboxylate (7.22 ml) in n-butyl acetate (150 ml), and the mixture was stirred at 100°C for 1.5 hours. The reaction mixture was concentrated under reduced pressure, and methanol (100 ml) and 4-fluorobenzylamine (8.6 ml) were added to the residue. The mixture was heated under reflux overnight. The reaction mixture was concentrated under reduced pressure, and the residue was then purified by silica gel chromatography [chloroform:methanol = 9:1 (v/v)] to give the title compound (6.24 g) as a solid.

$^1\text{H-NMR}$ (CDCl_3) δ : 3.87 (6H, s), 5.00 (2H, s), 7.11-7.16 (2H, m), 7.22-7.26 (2H, m), 8.10 (2H, s).
 MS (ESI) : m/z 320 ($\text{M}+\text{H}$) $^+$.

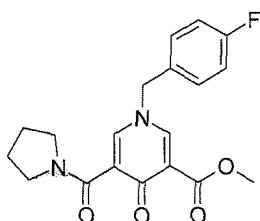
[Step 2] 1-(4-Fluorobenzyl)-5-(methoxycarbonyl)-4-oxo-1,4-dihydropyridine-3-carboxylic acid



1 N sodium hydroxide (19.5 ml) was added to a solution of the compound obtained in the above Step 1 (6.24 g) in methanol (50 ml), and the mixture was stirred at room temperature overnight. Subsequently, the mixture was stirred at 50°C for one day, and 1 N sodium hydroxide (19.5 ml) was further added, followed by stirring for two days. The reaction mixture was returned to room temperature and the precipitate was then collected by filtration. Methanol (200 ml) and acidic resin IR-120B (20 g) were added to the resulting solid, and the mixture was heated under reflux for one day. The resin was separated by filtration, and the filtrate was concentrated under reduced pressure. The precipitate was then collected by filtration from a mixed solvent of acetic acid and ethyl ether to give the title compound (1.48 g) as a solid.

$^1\text{H-NMR}$ (DMSO-D_6) δ : 3.81 (3H, s), 5.46 (2H, s), 7.25-7.30 (2H, m) 7.53-7.59 (2H, m), 8.84 (1H, d, $J = 2.3$ Hz), 8.93 (1H, d, $J = 1.8$ Hz).

[Step 3] Methyl 1-(4-fluorobenzyl)-4-oxo-5-(pyrrolidin-1-ylcarbonyl)-1,4-dihydropyridine-3-carboxylate

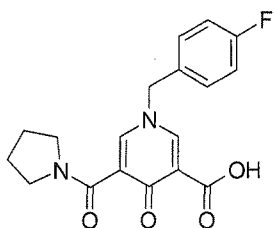


EDC.HCl (106 mg) and pyrrolidine (71 μl) were added to a solution of the compound obtained in the above Step 2 (130 mg) and HOBt (29 mg) in DMF (1.6 ml) at room temperature, followed by stirring for 90 minutes. The mixture was further stirred at 60°C for three hours, and water was then added at room temperature, followed by extraction with ethyl acetate. The organic layer was washed with brine and then dried over sodium sulfate. The solvent was distilled off under reduced pressure, and the residue was purified by silica gel column chromatography [chloroform:methanol = 300:1 $\rightarrow$ 30:1 (v/v)] to give 45 mg of the title compound as an oily substance.

$^1\text{H-NMR}$ (CDCl_3) δ : 1.81-1.96 (4H, m), 3.45 (2H, t, $J = 6.4$ Hz), 3.57 (2H, t, $J = 6.7$ Hz), 3.88 (3H, s), 4.96 (2H, s), 7.10-7.17 (2H, m), 7.22-7.28 (2H, m), 7.63 (1H, d, $J = 2.5$ Hz), 8.19 (1H, d, $J = 2.5$ Hz).

MS (ESI) m/z : 359 (M+H)⁺.

[Step 4] 1-(4-Fluorobenzyl)-4-oxo-5-(pyrrolidin-1-ylcarbonyl)-1,4-dihydropyridine-3-carboxylic acid

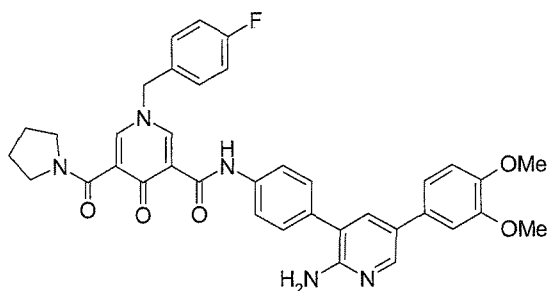


A 1 N aqueous sodium hydroxide solution (0.26 ml) was added to a solution of the compound obtained in the above Step 3 (45 mg) in methanol (1.0 ml) at room temperature, and the mixture was stirred for 90 minutes. The solvent was distilled off under reduced pressure and a 1 N aqueous hydrochloric acid solution was added. The precipitated solid was collected by filtration to give 33 mg of the title compound.

¹H-NMR (CDCl₃) δ : 1.86-2.01 (4H, m), 3.43 (2H, t, J = 6.7 Hz), 3.61 (2H, t, J = 6.9 Hz), 5.10 (2H, s), 7.12-7.19 (2H, m), 7.26-7.30 (2H, m), 7.87 (1H, d, J = 2.5 Hz), 8.54 (1H, d, J = 2.5 Hz).

MS (ESI) m/z : 345 (M+H)⁺.

[Step 5] N-{4-[2-Amino-5-(3,4-dimethoxyphenyl)pyridin-3-yl]phenyl}-1-(4-fluorobenzyl)-4-oxo-5-(pyrrolidin-1-ylcarbonyl)-1,4-dihydropyridine-3-carboxamide



46 mg of the title compound was obtained as a solid from the compound obtained in the above Step 4 (29 mg) and the compound obtained in Step 2 of Example 1 (30 mg) as raw materials by a reaction similar to that in Step 3 of Example 3.

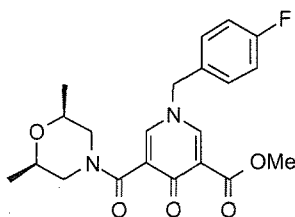
$^1\text{H-NMR}$ (CDCl_3) δ : 1.88-2.03 (4H, m), 3.46 (2H, t, $J = 6.4$ Hz), 3.64 (2H, t, $J = 6.7$ Hz), 3.92 (3H, s), 3.94 (3H, s), 4.63 (2H, s), 5.09 (2H, s), 6.94 (1H, d, $J = 8.3$ Hz), 7.02-7.18 (4H, m), 7.27-7.32 (2H, m), 7.47-7.51 (2H, m), 7.55-7.58 (1H, m), 7.75 (1H, d, $J = 2.8$ Hz), 7.82-7.87 (2H, m), 8.27 (1H, d, $J = 2.3$ Hz), 8.65 (1H, d, $J = 2.8$ Hz), 12.46 (1H, s).

MS (ESI) m/z : 648 ($\text{M}+\text{H}$) $^+$.

Example 27

N-{4-[2-Amino-5-(3,4-dimethoxyphenyl)pyridin-3-yl]phenyl}-5-{[(2R,6S)-2,6-dimethylmorpholin-4-yl]carbonyl}-1-(4-fluorobenzyl)-4-oxo-1,4-dihydropyridine-3-carboxamide

[Step 1] Methyl 5-{[(2R,6S)-2,6-dimethylmorpholin-4-yl]carbonyl}-1-(4-fluorobenzyl)-4-oxo-1,4-dihydropyridine-3-carboxylate

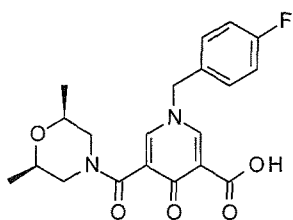


DIPEA (228 μ l) was added to a solution of the compound obtained in Step 2 of Example 26 (200 mg) and COMU (365 mg) in DMF (2.5 ml) at room temperature, and the mixture was stirred for 15 minutes. *cis*-2,6-Dimethylmorpholine (162 μ l) was added and the mixture was stirred for four hours. A 1 N hydrochloric acid solution was added at room temperature, and the organic layer was extracted with ethyl acetate, washed with brine and then dried over sodium sulfate. The solvent was distilled off under reduced pressure, and the residue was purified by silica gel column chromatography [chloroform:methanol = 300:1 $\rightarrow$ 30:1 (v/v)] to give 30 mg of the title compound as an oily substance.

$^1\text{H-NMR}$ (CDCl_3) δ : 1.11 (3H, d, J = 6.4 Hz), 1.22 (3H, d, J = 6.4 Hz), 2.46-2.55 (1H, m), 2.83-2.94 (1H, m), 3.21-3.28 (1H, m), 3.59-3.79 (2H, m), 3.88 (3H, s), 4.43-4.51 (1H, m), 4.99 (2H, s), 7.11-7.17 (2H, m), 7.22-7.31 (2H, m), 7.62 (1H, d, J = 2.8 Hz), 8.21 (1H, d, J = 2.8 Hz).

MS (ESI) m/z : 403 ($\text{M}+\text{H}$) $^+$.

[Step 2] 5-{[(2*R*,6*S*)-2,6-Dimethylmorpholin-4-yl]carbonyl}-1-(4-fluorobenzyl)-4-oxo-1,4-dihydropyridine-3-carboxylic acid

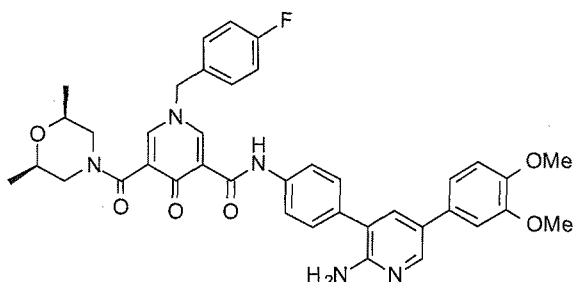


A 1 N aqueous sodium hydroxide solution (0.14 ml) was added to a solution of the compound obtained in the above Step 1 (30 mg) in methanol (1.0 ml) at room temperature, and the mixture was stirred for two hours. The solvent was distilled off under reduced pressure and a 1 N aqueous hydrochloric acid solution was added. The organic layer was extracted with chloroform and then dried over sodium sulfate. The solvent was distilled off under reduced pressure to give 28 mg of the title compound as an oily substance.

$^1\text{H-NMR}$ (CDCl_3) δ : 1.14 (3H, d, $J = 6.4$ Hz), 1.24 (3H, d, $J = 6.0$ Hz), 2.49-2.58 (1H, m), 2.82-2.92 (1H, m), 3.15-3.23 (1H, m), 3.61-3.78 (2H, m), 4.44-4.52 (1H, m), 5.11 (2H, s), 7.13-7.20 (2H, m), 7.27-7.32 (2H, m), 7.86 (1H, d, $J = 2.3$ Hz), 8.56 (1H, d, $J = 2.3$ Hz).

MS (ESI) m/z : 389 ($\text{M}+\text{H}$) $^+$.

[Step 3] N-{4-[2-Amino-5-(3,4-dimethoxyphenyl)pyridin-3-yl]phenyl}-5-[(2R,6S)-2,6-dimethylmorpholin-4-yl]carbonyl}-1-(4-fluorobenzyl)-4-oxo-1,4-dihydropyridine-3-carboxamide



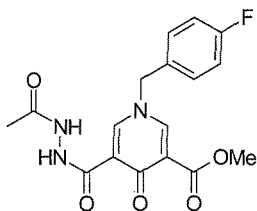
24 mg of the title compound was obtained as a solid from the compound obtained in the above Step 2 (28 mg) and the compound obtained in Step 2 of Example 1 (25 mg) as raw materials by a reaction similar to that in Step 3 of Example 3.

$^1\text{H-NMR}$ (CDCl_3) δ : 1.15 (3H, d, $J = 6.4$ Hz), 1.25 (3H, d, $J = 6.0$ Hz), 2.52-2.61 (1H, m), 2.86-2.97 (1H, m), 3.24-3.31 (1H, m), 3.64-3.76 (2H, m), 3.92 (3H, s), 3.94 (3H, s), 4.50-4.56 (1H, m), 4.63 (2H, s), 5.10 (2H, s), 6.94 (1H, d, $J = 8.3$ Hz), 7.02-7.11 (2H, m), 7.12-7.19 (2H, m), 7.27-7.33 (2H, m), 7.48-7.53 (2H, m), 7.57 (1H, d, $J = 2.3$ Hz), 7.72 (1H, d, $J = 2.8$ Hz), 7.82-7.87 (2H, m), 8.27 (1H, d, $J = 2.3$ Hz), 8.66 (1H, d, $J = 2.8$ Hz), 12.37 (1H, s).

MS (ESI) m/z : 692 ($\text{M}+\text{H}$) $^+$.

Example 28

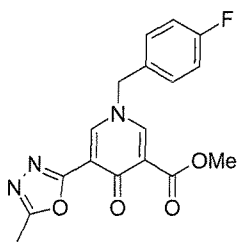
N-{4-[2-Amino-5-(3,4-dimethoxyphenyl)pyridin-3-yl]phenyl}-1-(4-fluorobenzyl)-5-(5-methyl-1,3,4-oxadiazol-2-yl)-4-oxo-1,4-dihydropyridine-3-carboxamide
[Step 1] Methyl 5-[(2-acetylhydrazinyl)carbonyl]-1-(4-fluorobenzyl)-4-oxo-1,4-dihydropyridine-3-carboxylate



159 mg of the title compound was obtained from the compound obtained in Step 2 of Example 26 (250 mg) and acetohydrazide (76 mg) as raw materials by a reaction similar to that in Step 1 of Example 27.

$^1\text{H-NMR}$ (CDCl_3) δ : 2.09 (3H, s), 3.91 (3H, s), 5.08 (2H, s), 7.11-7.18 (2H, m), 7.23-7.28 (2H, m), 7.95-8.00 (1H, m), 8.22 (1H, d, $J = 2.5$ Hz), 8.47 (1H, d, $J = 2.5$ Hz), 12.21 (1H, d, $J = 5.5$ Hz).

[Step 2] Methyl 1-(4-fluorobenzyl)-5-(5-methyl-1,3,4-oxadiazol-2-yl)-4-oxo-1,4-dihydropyridine-3-carboxylate



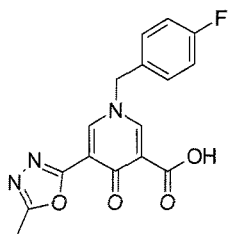
Hexachloroethane (260 mg), the compound obtained in the above Step 1 (159 mg) and triethylamine (368 μl) were added sequentially to a solution of triphenylphosphine (346 mg) in dichloromethane (3.0 ml) under ice cooling. The mixture was gradually warmed to room temperature and then stirred for 18 hours. Water was added, followed by extraction with ethyl acetate. The organic layer was

washed with brine and then dried over sodium sulfate. The solvent was distilled off under reduced pressure, and the residue was purified by silica gel column chromatography [chloroform:methanol = 300:1 → 30:1 (v/v)] to give 105 mg of the title compound as an oily substance.

$^1\text{H-NMR}$ (CDCl_3) δ : 2.60 (3H, s), 3.91 (3H, s), 5.04 (2H, s), 7.10-7.18 (2H, m), 7.24-7.30 (2H, m), 8.21-8.25 (2H, m).

MS (ESI) m/z : 344 ($\text{M}+\text{H}$) $^+$.

[Step 3] 1-(4-Fluorobenzyl)-5-(5-methyl-1,3,4-oxadiazol-2-yl)-4-oxo-1,4-dihydropyridine-3-carboxylic acid

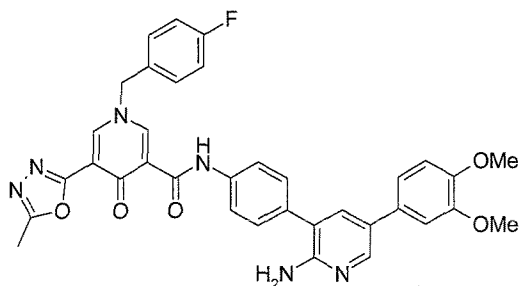


A 1 N aqueous sodium hydroxide solution (0.66 ml) was added to a mixed solution of the compound obtained in the above Step 2 (113 mg) in methanol (1.5 ml)/tetrahydrofuran (0.2 ml) at room temperature, and the mixture was stirred for two hours. The solvent was distilled off under reduced pressure and a 1 N aqueous hydrochloric acid solution was added. The precipitated solid was collected by filtration to give 74 mg of the title compound.

$^1\text{H-NMR}$ (CDCl_3) δ : 2.66 (3H, s), 5.19 (2H, s), 7.14-7.21 (2H, m), 7.28-7.35 (2H, m), 8.49 (1H, d, $J = 2.3$ Hz), 8.63 (1H, d, $J = 2.3$ Hz).

MS (ESI) m/z : 330 ($\text{M}+\text{H}$) $^+$.

[Step 4] N-{4-[2-Amino-5-(3,4-dimethoxyphenyl)pyridin-3-yl]phenyl}-1-(4-fluorobenzyl)-5-(5-methyl-1,3,4-oxadiazol-2-yl)-4-oxo-1,4-dihydropyridine-3-carboxamide



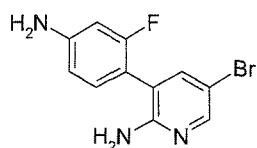
42 mg of the title compound was obtained as a solid from the compound obtained in the above Step 3 (28 mg) and the compound obtained in Step 2 of Example 1 (30 mg) as raw materials by a reaction similar to that in Step 3 of Example 3.

$^1\text{H-NMR}$ (CDCl_3) δ : 2.68 (3H, s), 3.92 (3H, s), 3.94 (3H, s), 4.63 (2H, s), 5.18 (2H, s), 6.94 (1H, d, $J = 8.3$ Hz), 7.02-7.20 (4H, m), 7.30-7.35 (2H, m), 7.48-7.59 (3H, m), 7.83-7.88 (2H, m), 8.28 (1H, d, $J = 2.8$ Hz), 8.38 (1H, d, $J = 2.3$ Hz), 8.74 (1H, d, $J = 2.8$ Hz), 12.32 (1H, s).

MS (ESI) m/z : 633 ($\text{M}+\text{H}$) $^+$.

Example 29

N-{4-[2-Amino-5-(3,4-dimethoxyphenyl)pyridin-3-yl]-3-fluorophenyl}-5-(4-fluorophenyl)-4-oxo-1-(2,2,2-trifluoroethyl)-1,4-dihydropyridine-3-carboxamide
[Step 1] 3-(4-Amino-2-fluorophenyl)-5-bromopyridin-2-amine

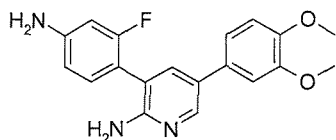


5-Bromo-3-iodopyridin-2-amine (300 mg), 3-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (238 mg), tetrakis(triphenylphosphine)palladium (58 mg) and potassium carbonate (416 mg) were suspended in dioxane (5 ml) and water (0.5 ml), and the suspension was heated under reflux at 80°C for two days. After leaving to cool, a saturated aqueous sodium bicarbonate solution was added, and the organic layer was extracted with ethyl acetate and dried over sodium sulfate. The solvent was distilled off under reduced pressure, and the residue was purified by silica gel column chromatography [hexane:ethyl acetate = 1:2 (v/v)] to give 248 mg of the title compound as a solid.

$^1\text{H-NMR}$ (CDCl_3) δ : 3.92 (2H, s), 4.50 (2H, s), 6.44-6.56 (2H, m), 7.06-7.13 (1H, m), 7.43-7.48 (1H, m), 8.08-8.12 (1H, m).

MS (ESI) m/z : 282, 284 ($\text{M}+\text{H}$) $^+$.

[Step 2] 3-(4-Amino-2-fluorophenyl)-5-(3,4-dimethoxyphenyl)pyridin-2-amine

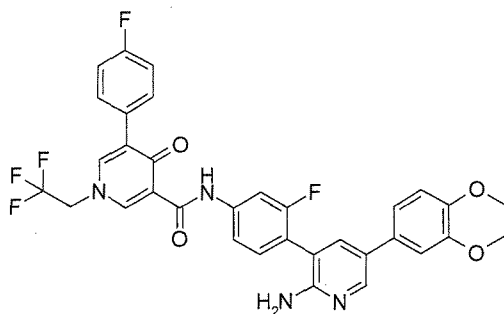


The compound obtained in the above Step 1 (2.00 g), 3,4-dimethoxyphenylboronic acid (1.42 g), [1,1'-bis(diphenylphosphino)ferrocene]palladium(II) dichloride-dichloromethane adduct (0.29 g) and potassium carbonate (2.94 g) were suspended in dioxane (20 ml) and water (4.0 ml), and the suspension was refluxed at 100°C for four hours. After leaving to cool, a saturated aqueous sodium bicarbonate solution was added, and the organic layer was extracted with ethyl acetate and dried over sodium sulfate. The solvent was distilled off under reduced pressure, and the residue was purified by silica gel column chromatography [ethyl acetate:dichloromethane:methanol = 10:10:1 (v/v)]. The resulting solid was recrystallized from dichloromethane and diisopropyl ether to give 1.93 g of the title compound as a solid.

$^1\text{H-NMR}$ (CDCl_3) δ : 3.91 (3H, s), 3.94 (3H, s), 4.51 (2H, s), 6.49-6.58 (2H, m), 6.91-7.21 (4H, m), 7.55 (1H, d, J = 2.4 Hz), 8.28 (1H, d, J = 2.4 Hz).

MS(ESI) m/z : 340 ($\text{M}+\text{H}$) $^+$.

[Step 3] N-{4-[2-Amino-5-(3,4-dimethoxyphenyl)pyridin-3-yl]-3-fluorophenyl}-5-(4-fluorophenyl)-4-oxo-1-(2,2,2-trifluoroethyl)-1,4-dihydropyridine-3-carboxamide



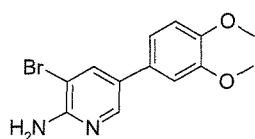
DIPEA (83 μ l) was added to a solution of the compound obtained in Step 2 of Example 9 (75 mg) and COMU (132 mg) in DMF (1.0 ml) at room temperature, and the mixture was stirred for one hour. The compound obtained in the above Step 2 (70 mg) was added at room temperature. The mixture was stirred for 23 hours, followed by the addition of water. The precipitated solid was collected by filtration, and the resulting solid was purified by silica gel column chromatography [ethyl acetate] and then subjected to lyophilization using dioxane to give 119 mg of the title compound as a solid.

$^1\text{H-NMR}$ (CDCl_3) δ : 3.91 (3H, s), 3.94 (3H, s), 4.48-4.61 (4H, m), 6.90-7.22 (5H, m), 7.34-7.61 (6H, m), 7.86-7.93 (1H, m), 8.30-8.33 (1H, m), 8.62-8.66 (1H, m).

MS (ESI) m/z : 637 ($\text{M}+\text{H}$) $^+$.

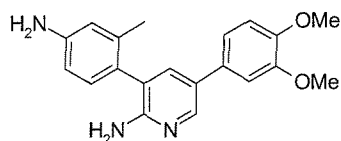
Example 30

N-{4-[2-Amino-5-(3,4-dimethoxyphenyl)pyridin-3-yl]-3-methylphenyl}-5-(4-fluorophenyl)-4-oxo-1-(2,2,2-trifluoroethyl)-1,4-dihydropyridine-3-carboxamide
[Step 1] 3-Bromo-5-(3,4-dimethoxyphenyl)pyridin-2-amine



3-Bromo-5-iodopyridin-2-amine (7.50 g), 3,4-dimethoxyphenylboronic acid (4.79 g), tetrakis(triphenylphosphine)palladium (1.45 g) and potassium carbonate (10.4 g) were suspended in dioxane (100 ml) and water (10 ml), and the suspension was heated at 80°C for 9.5 hours. After leaving to cool, a saturated aqueous ammonium chloride solution was added, and the organic layer was extracted with ethyl acetate and dried over sodium sulfate. The solvent was distilled off under reduced pressure, and the residue was purified by silica gel column chromatography [ethyl acetate] to give 7.36 g of the title compound as a solid.
MS (ESI) m/z: 309, 311 (M+H)⁺.

[Step 2] 3-(4-Amino-2-methylphenyl)-5-(3,4-dimethoxyphenyl)pyridin-2-amine

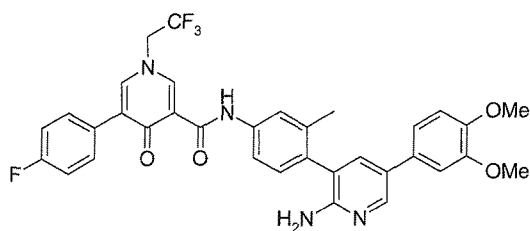


Water (0.1 ml), potassium carbonate (55 mg) and [1,1'-bis(diphenylphosphino)ferrocene]palladium(II) dichloride-dichloromethane adduct (5.4 mg) were added to a solution of the compound obtained in the above Step 1 (41 mg) and 3-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (34 mg) in 1,4-dioxane (1.0 ml), and the mixture was stirred at 100°C for 26 hours. After leaving to cool, the reaction solution was diluted with ethyl acetate. The organic layer was washed with water and brine and dried over sodium sulfate. The solvent was distilled off under reduced pressure, and the residue was purified by silica gel column chromatography [chloroform:methanol = 300:1 → 40:1 (v/v)] to give 29 mg of the title compound as a solid.

¹H-NMR (CDCl₃) δ: 2.14 (3H, s), 3.72 (2H, s), 3.91 (3H, s), 3.93 (3H, s), 4.41 (2H, s), 6.55-6.68 (2H, m), 6.90-6.95 (1H, m), 6.99-7.10 (3H, m), 7.45-7.50 (1H, m), 8.27 (1H, d, J = 2.3 Hz).

MS (ESI) m/z: 336 (M+H)⁺.

[Step 3] N-{4-[2-Amino-5-(3,4-dimethoxyphenyl)pyridin-3-yl]-3-methylphenyl}-5-(4-fluorophenyl)-4-oxo-1-(2,2,2-trifluoroethyl)-1,4-dihydropyridine-3-carboxamide



DIPEA (16 μ l) was added to a solution of the compound obtained in Step 2 of Example 9 (20 mg) and COMU (35 mg) in DMF (0.8 ml) at room temperature, and the mixture was stirred for 15 minutes. 3-(4-Amino-2-methylphenyl)-5-(3,4-dimethoxyphenyl)pyridin-2-amine obtained in the above Step 2 (27 mg) was added at room temperature. After stirring for three hours, water was added. The precipitated solid was collected by filtration and purified by silica gel column chromatography [chloroform:methanol = 300:1 $\rightarrow$ 50:1 (v/v)] to give 16 mg of the title compound as a solid.

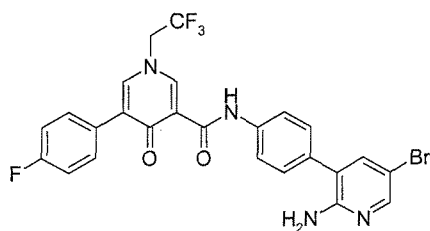
$^1\text{H-NMR}$ (CDCl_3) δ : 2.23 (3H, s), 3.91 (3H, s), 3.94 (3H, s), 4.43 (2H, s), 4.51 (2H, q, $J = 7.8$ Hz), 6.93 (1H, d, $J = 8.6$ Hz), 7.01-7.11 (2H, m), 7.15-7.25 (3H, m), 7.49-7.58 (4H, m), 7.68-7.73 (2H, m), 8.30 (1H, d, $J = 2.3$ Hz), 8.64 (1H, d, $J = 2.3$ Hz), 12.40 (1H, s).

MS(ESI) m/z : 633(M+H) $^+$.

Example 31

N-[4-(2-Amino-5-phenylpyridin-3-yl)phenyl]-5-(4-fluorophenyl)-4-oxo-1-(2,2,2-trifluoroethyl)-1,4-dihydropyridine-3-carboxamide

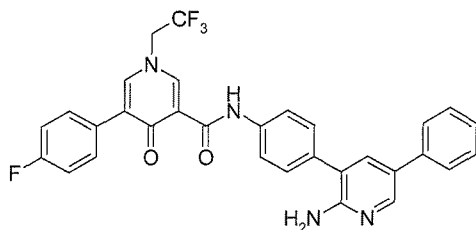
[Step 1] N-[4-(2-Amino-5-bromopyridin-3-yl)phenyl]-5-(4-fluorophenyl)-4-oxo-1-(2,2,2-trifluoroethyl)-1,4-dihydropyridine-3-carboxamide



DIPEA (414 μ l) was added to a solution of the compound obtained in Step 2 of Example 9 (500 mg) and COMU (883 mg) in DMF (8.0 ml) at room temperature, and the mixture was stirred for 25 minutes. The compound obtained in Step 1 of Example 1 (440 mg) was added at room temperature. The mixture was stirred for 19 hours, followed by the addition of water. The precipitated solid was collected by filtration, suspended in chloroform/diisopropyl ether and then collected by filtration to give 800 mg of the title compound.

$^1\text{H-NMR}$ (CDCl_3) δ : 4.52 (2H, q, $J = 7.8$ Hz), 4.62 (2H, s), 7.14-7.22 (2H, m), 7.39-7.58 (6H, m), 7.80-7.86 (2H, m), 8.09 (1H, d, $J = 2.8$ Hz), 8.63 (1H, d, $J = 2.8$ Hz), 12.47 (1H, s).

[Step 2] N-[4-(2-Amino-5-phenylpyridin-3-yl)phenyl]-5-(4-fluorophenyl)-4-oxo-1-(2,2,2-trifluoroethyl)-1,4-dihydropyridine-3-carboxamide



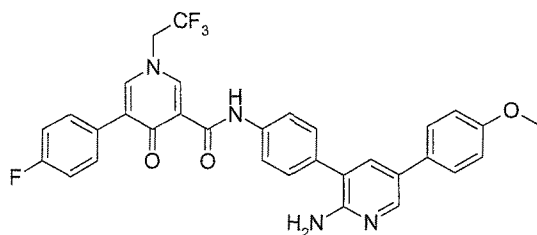
Water (0.1 ml), potassium carbonate (70 mg) and tetrakis(triphenylphosphine)palladium (19 mg) were added to a solution of the compound obtained in the above Step 1 (95 mg) and phenylboronic acid (25 mg) in 1,2-dimethoxyethane (1.5 ml), and the mixture was stirred at 80°C for 21 hours. After leaving to cool, the reaction solution was diluted with ethyl acetate. The organic layer was washed with water and brine and dried over sodium sulfate. The solvent was distilled off under reduced pressure, and the residue was purified by silica gel column chromatography [chloroform:methanol = 300:1 -> 40:1 (v/v)] to give 39 mg of the title compound as a solid.

¹H-NMR (CDCl₃) δ: 4.52 (2H, q, J = 7.8 Hz), 4.68 (2H, s), 7.14-7.21 (2H, m), 7.29-7.35 (1H, m), 7.39-7.64 (10H, m), 7.82-7.88 (2H, m), 8.31 (1H, d, J = 2.3 Hz), 8.64 (1H, d, J = 2.3 Hz).

MS (ESI) m/z: 559 (M+H)⁺.

Example 32

N-{4-[2-Amino-5-(4-methoxyphenyl)pyridin-3-yl]phenyl}-5-(4-fluorophenyl)-4-oxo-1-(2,2,2-trifluoroethyl)-1,4-dihydropyridine-3-carboxamide



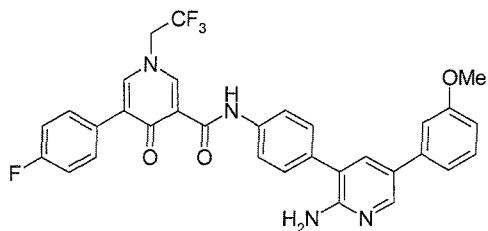
50 mg of the title compound was obtained as a solid from the compound obtained in Step 1 of Example 31 (95 mg) and 4-methoxyphenylboronic acid (31 mg) as raw materials by a reaction similar to that in Step 2 of Example 31.

$^1\text{H-NMR}$ (DMSO-D_6) δ : 3.78 (3H, s), 5.28 (2H, q, $J = 8.6$ Hz), 5.68 (2H, s), 6.95-7.01 (2H, m), 7.28-7.36 (2H, m), 7.51-7.60 (5H, m), 7.65-7.72 (2H, m), 7.78-7.85 (2H, m), 8.22 (1H, d, $J = 2.3$ Hz), 8.28 (1H, d, $J = 1.8$ Hz), 8.88 (1H, d, $J = 2.3$ Hz).

MS(ESI) m/z : 589 ($\text{M}+\text{H}$) $^+$.

Example 33

N-{4-[2-Amino-5-(3-methoxyphenyl)pyridin-3-yl]phenyl}-5-(4-fluorophenyl)-4-oxo-1-(2,2,2-trifluoroethyl)-1,4-dihydropyridine-3-carboxamide



Water (0.1 ml), potassium carbonate (70 mg) and tetrakis(triphenylphosphine)palladium (19 mg) were added to a solution of the compound obtained in Step 1 of Example 31 (95 mg) and 3-methoxyphenylboronic acid (31 mg) in 1,4-dioxane (1.5 ml), and the mixture was stirred at 90°C for 17 hours. After leaving to cool, the reaction solution was diluted with ethyl acetate. The

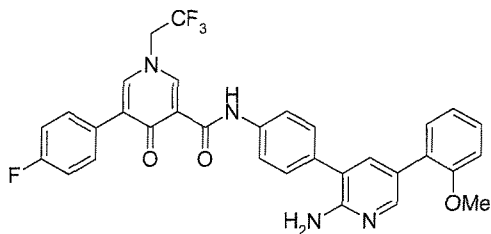
organic layer was washed with water and brine and dried over sodium sulfate. The solvent was distilled off under reduced pressure, and the residue was purified by silica gel column chromatography [ethyl acetate:methanol = 300:1 -> 100:1 (v/v)] to give 10 mg of the title compound as a solid.

$^1\text{H-NMR}$ (CDCl_3) δ : 3.86 (3H, s), 4.52 (2H, q, $J = 8.0$ Hz), 4.67 (2H, s), 6.84-6.90 (1H, m), 7.05-7.09 (1H, m), 7.11-7.22 (3H, m), 7.31-7.38 (1H, m), 7.47-7.63 (6H, m), 7.82-7.88 (2H, m), 8.31 (1H, d, $J = 2.8$ Hz), 8.64 (1H, d, $J = 2.8$ Hz), 12.46 (1H, s).

MS(ESI) m/z : 589 ($\text{M}+\text{H}$) $^+$.

Example 34

N-{4-[2-Amino-5-(2-methoxyphenyl)pyridin-3-yl]phenyl}-5-(4-fluorophenyl)-4-oxo-1-(2,2,2-trifluoroethyl)-1,4-dihydropyridine-3-carboxamide



Water (0.1 ml), potassium carbonate (70 mg) and [1,1'-bis(diphenylphosphino)ferrocene]palladium(II) dichloride-dichloromethane adduct (6.9 mg) were added to a solution of the compound obtained in Step 1 of Example 31 (95 mg) and 2-methoxyphenylboronic acid (31 mg) in 1,2-dimethoxyethane (1.5 ml), and the mixture was stirred

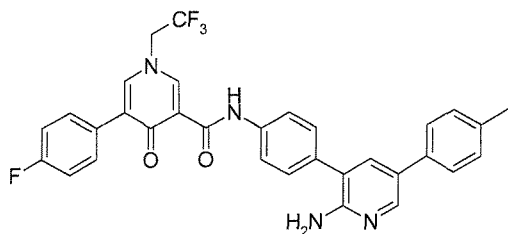
at 80°C for 20 hours. After leaving to cool, the reaction solution was diluted with ethyl acetate. The organic layer was washed with water and brine and dried over sodium sulfate. The solvent was distilled off under reduced pressure, and the residue was purified by silica gel column chromatography [hexane:ethyl acetate = 3:1 -> 1:3 (v/v)] to give 34 mg of the title compound as a solid.

¹H-NMR (CDCl₃) δ: 3.83 (3H, s), 4.45-4.55 (2H, m), 4.63 (2H, s), 6.94-7.07 (2H, m), 7.15-7.34 (4H, m), 7.49-7.62 (6H, m), 7.83 (2H, d, J = 8.6 Hz), 8.25 (1H, d, J = 2.3 Hz), 8.64 (1H, s), 12.43 (1H, s).

MS(ESI) m/z: 589(M+H)⁺.

Example 35

N-{4-[2-Amino-5-(4-methylphenyl)pyridin-3-yl]phenyl}-5-(4-fluorophenyl)-4-oxo-1-(2,2,2-trifluoroethyl)-1,4-dihydropyridine-3-carboxamide



20 mg of the title compound was obtained as a solid from the compound obtained in Step 1 of Example 31 (95 mg) and 4-methylphenylboronic acid (27 mg) as raw materials by a reaction similar to that in Example 34.

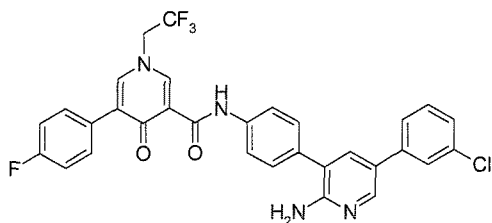
¹H-NMR (CDCl₃) δ: 2.38 (3H, s), 4.51 (2H, q, J = 7.8 Hz), 4.63 (2H, s), 7.15-7.25 (4H, m), 7.42-7.62 (8H, m), 7.82-

7.87 (2H, m), 8.30 (1H, d, J = 2.3 Hz), 8.64 (1H, d, J = 2.3 Hz), 12.45 (1H, s).

MS (ESI) m/z: 573 (M+H)⁺.

Example 36

N-{4-[2-Amino-5-(3-chlorophenyl)pyridin-3-yl]phenyl}-5-(4-fluorophenyl)-4-oxo-1-(2,2,2-trifluoroethyl)-1,4-dihydropyridine-3-carboxamide



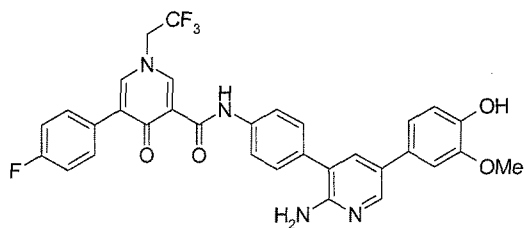
44 mg of the title compound was obtained as a solid from the compound obtained in Step 1 of Example 31 (95 mg) and 3-chlorophenylboronic acid (32 mg) as raw materials by a reaction similar to that in Example 34.

¹H-NMR (CDCl₃) δ: 4.52 (2H, q, J = 7.6 Hz), 4.75 (2H, s), 7.15-7.22 (2H, m), 7.27-7.44 (3H, m), 7.46-7.61 (7H, m), 7.83-7.89 (2H, m), 8.28 (1H, d, J = 2.3 Hz), 8.65 (1H, d, J = 2.3 Hz), 12.46 (1H, s).

MS (ESI) m/z: 593 (M+H)⁺.

Example 37

N-{4-[2-Amino-5-(4-hydroxy-3-methoxyphenyl)pyridin-3-yl]phenyl}-5-(4-fluorophenyl)-4-oxo-1-(2,2,2-trifluoroethyl)-1,4-dihydropyridine-3-carboxamide



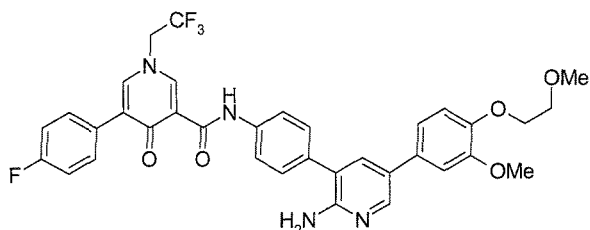
Water (0.1 ml), potassium carbonate (70 mg) and [1,1'-bis(diphenylphosphino)ferrocene]palladium(II) dichloride-dichloromethane adduct (6.9 mg) were added to a solution of the compound obtained in Step 1 of Example 31 (95 mg) and 2-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (51 mg) in 1,4-dioxane (1.5 ml), and the mixture was stirred at 100°C for four hours. After leaving to cool, the reaction solution was diluted with ethyl acetate. The organic layer was washed with water and brine and dried over sodium sulfate. The solvent was distilled off under reduced pressure, and the residue was purified by silica gel column chromatography [chloroform:methanol = 300:1 → 30:1 (v/v)] to give 43 mg of the title compound as a solid.

¹H-NMR (CDCl₃) δ: 3.95 (3H, s), 4.52 (2H, q, J = 7.8 Hz), 4.65 (2H, s), 5.64 (1H, s), 6.95-7.07 (3H, m), 7.15-7.22 (2H, m), 7.47-7.58 (6H, m), 7.83-7.88 (2H, m), 8.25 (1H, d, J = 2.3 Hz), 8.64 (1H, d, J = 2.3 Hz), 12.46 (1H, s). MS(ESI) m/z: 605 (M+H)⁺.

Example 38

N-(4-{2-Amino-5-[3-methoxy-4-(2-methoxyethoxy)phenyl]pyridin-3-yl}phenyl)-5-(4-

fluorophenyl)-4-oxo-1-(2,2,2-trifluoroethyl)-1,4-dihydropyridine-3-carboxamide



34 mg of the title compound was obtained as a solid from the compound obtained in Step 1 of Example 31 (95 mg) and 2-[3-methoxy-4-(2-methoxyethoxy)phenyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (62 mg) as raw materials by a reaction similar to that in Example 34.

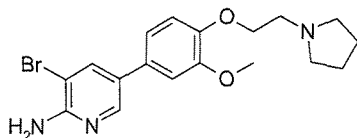
$^1\text{H-NMR}$ (CDCl_3) δ : 3.46 (3H, s), 3.78-3.83 (2H, m), 3.92 (3H, s), 4.18-4.23 (2H, m), 4.52 (2H, q, $J = 7.8$ Hz), 4.63 (2H, s), 6.96-7.09 (3H, m), 7.15-7.22 (2H, m), 7.47-7.59 (6H, m), 7.83-7.88 (2H, m), 8.27 (1H, d, $J = 2.3$ Hz), 8.64 (1H, d, $J = 2.3$ Hz), 12.46 (1H, s).

MS (ESI) m/z : 663 ($\text{M}+\text{H}$) $^+$.

Example 39

N-[4-(2-Amino-5-{3-methoxy-4-[2-(pyrrolidin-1-yl)ethoxy]phenyl}pyridin-3-yl)phenyl]-5-(4-fluorophenyl)-4-oxo-1-(2,2,2-trifluoroethyl)-1,4-dihydropyridine-3-carboxamide

[Step 1] 3-Bromo-5-[3-methoxy-4-(2-pyrrolidin-1-ylethoxy)phenyl]pyridin-2-amine



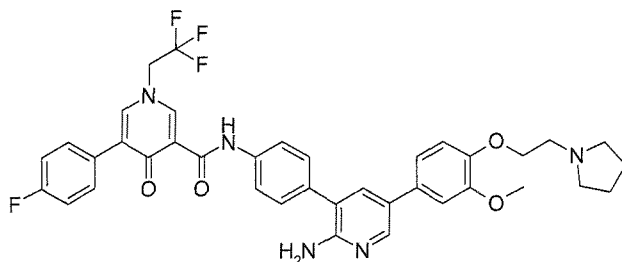
1-{2-[2-Methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy]ethyl}pyrrolidine (5.81 g), tetrakis(triphenylphosphine)palladium (0.97 g) and potassium carbonate (6.94 g) were added to a solution of 3-bromo-5-iodopyridin-2-amine (5.00 g) in dioxane (40 ml) and water (4 ml) at room temperature. The reaction mixture was stirred at 80°C overnight. The reaction mixture was returned to room temperature and a saturated aqueous sodium bicarbonate solution was added, followed by extraction with ethyl acetate. The organic layer was dried over magnesium sulfate. After filtration, the filtrate was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography [chloroform:methanol = 50:1 → 20:1 → 10:1 (v/v)] to give 4.03 g of the title compound as an oily substance.

¹H-NMR (CDCl₃) δ: 1.24 (4H, s), 2.63-2.68 (4H, m), 2.98 (2H, t, J = 6.4 Hz), 3.92 (3H, s), 4.19 (2H, t, J = 6.4 Hz), 4.91 (2H, s), 6.93-7.02 (3H, m), 7.85 (1H, d, J = 1.8 Hz), 8.22 (1H, d, J = 2.3 Hz).

MS (ESI) m/z: 392, 394 (M+H)⁺.

[Step 2] N-[4-(2-Amino-5-{3-methoxy-4-[2-(pyrrolidin-1-yl)ethoxy]phenyl}pyridin-3-yl)phenyl]-5-(4-fluorophenyl)-

4-oxo-1-(2,2,2-trifluoroethyl)-1,4-dihydropyridine-3-carboxamide



COMU (391 mg) and DIPEA (159 μ l) were added to a solution of the compound obtained in Step 2 of Example 9 (216 mg) in DMF (2 ml) at room temperature. The reaction mixture was stirred at room temperature for 15 minutes. 4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (100 mg) was added to the reaction mixture at room temperature. The reaction mixture was stirred at 50°C overnight. Then the reaction mixture was stirred at 80°C for two days. Water was added to the reaction mixture, followed by extraction with ethyl acetate. The organic layer was dried over sodium sulfate and filtered, and the filtrate was then concentrated under reduced pressure. The residue was purified by silica gel column chromatography [hexane:ethyl acetate = 1:1 $\rightarrow$ 1:3 $\rightarrow$ 0:100 (v/v)], and the eluate was concentrated under reduced pressure. The compound obtained in the above Step 1 (76 mg), tetrakis(triphenylphosphine)palladium (22 mg) and potassium carbonate (40 mg) were added to a solution of part of the resulting oily substance (50 mg) in dioxane (3 ml) and water (0.3 ml) at room temperature.

The reaction mixture was stirred at 100°C for two days and returned to room temperature. The reaction mixture was concentrated under reduced pressure, the residue was purified by silica gel column chromatography (NH) [ethyl acetate:methanol = 100:0 -> 9:1 (v/v)], and the eluate was concentrated under reduced pressure. The residue was purified by PLC (NH) [dichloromethane:methanol = 15:1 (v/v)], and the eluate was concentrated under reduced pressure. The residue was purified by PLC (NH) [dichloromethane:methanol = 40:1 (v/v)] to give 1.8 mg of the title compound as an oily substance.

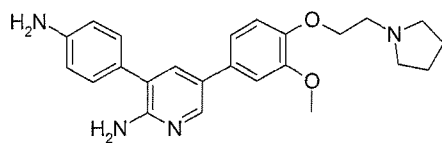
¹H-NMR (CDCl₃) δ: 1.80-1.88 (4H, m), 2.62-2.72 (4H, m), 2.99 (2H, t, J = 6.2 Hz), 3.92 (3H, s), 4.20 (2H, t, J = 6.2 Hz), 4.52 (2H, q, J = 7.6 Hz), 4.66 (2H, s), 6.97-7.20 (5H, m), 7.47-7.59 (6H, m), 7.85 (2H, d, J = 7.3 Hz), 8.27 (1H, s), 8.64 (1H, s), 12.46 (1H, s).

MS (ESI) m/z: 702 (M+H)⁺.

Example 40

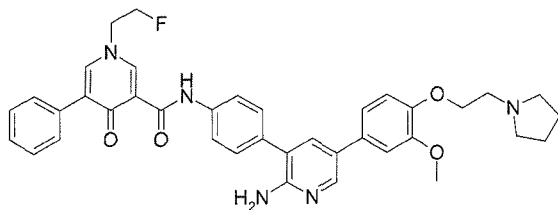
N-(4-{2-Amino-5-[3-methoxy-4-(2-pyrrolidin-1-ylethoxy)phenyl]pyridin-3-yl}phenyl)-1-(2-fluoroethyl)-4-oxo-5-phenyl-1,4-dihydropyridine-3-carboxamide

[Step 1] 3-(4-Aminophenyl)-5-[3-methoxy-4-(2-pyrrolidin-1-ylethoxy)phenyl]pyridin-2-amine



4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (285 mg), tetrakis(triphenylphosphine)palladium (110 mg) and potassium carbonate (396 mg) were added to a solution of the compound obtained in Step 1 of Example 39 (375 mg) in dioxane (10 ml) and water (1 ml) at room temperature. The reaction mixture was stirred at 100°C for five hours. The reaction mixture was returned to room temperature, followed by extraction with chloroform. The organic layer was dried over magnesium sulfate. After filtration, the filtrate was concentrated under reduced pressure, and the residue was purified by column chromatography [chloroform:methanol = 19:1 (v/v)] to give 407 mg of the title compound as an oily substance. MS (ESI) m/z : 405 (M+H)⁺.

[Step 2] N-(4-{2-Amino-5-[3-methoxy-4-(2-pyrrolidin-1-ylethoxy)phenyl]pyridin-3-yl}phenyl)-1-(2-fluoroethyl)-4-oxo-5-phenyl-1,4-dihydropyridine-3-carboxamide



DIPEA (67 μ l) was added to a solution of the compound obtained in Step 2 of Example 19 (50 mg) and COMU (106 mg) in DMF (5.0 ml) at room temperature, and the mixture was stirred for one hour. The compound

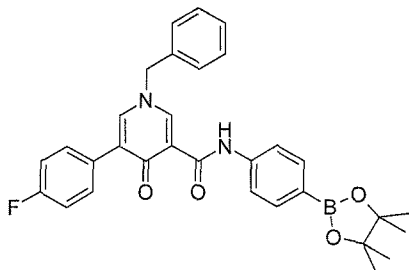
obtained in the above Step 1 (85 mg) was added at room temperature. The mixture was stirred for five hours, followed by the addition of water. The organic layer was extracted with ethyl acetate, and then washed with water and brine and dried over sodium sulfate. The solvent was distilled off under reduced pressure, and the residue was purified by reverse phase HPLC [acetonitrile:water:formic acid] to give 51 mg of the title compound as a solid.

¹H-NMR (CDCl₃) δ: 1.79-1.85 (4H, m), 2.62-2.69 (4H, m), 2.97 (2H, t, J = 6.4 Hz), 3.92 (3H, s), 4.19 (2H, t, J = 6.4 Hz), 4.27 (1H, t, J = 4.6 Hz), 4.33 (1H, t, J = 4.6 Hz), 4.64 (2H, s), 4.76 (1H, t, J = 4.6 Hz), 4.88 (1H, t, J = 4.6 Hz), 6.95 (1H, d, J = 8.3 Hz), 7.03 (1H, d, J = 2.3 Hz), 7.07 (1H, dd, J = 8.3, 1.8 Hz), 7.39-7.51 (5H, m), 7.55-7.60 (4H, m), 7.87 (2H, dt, J = 8.3, 2.3 Hz), 8.26 (1H, d, J = 2.3 Hz), 8.65 (1H, d, J = 2.8 Hz).

MS(ESI) m/z: 648 (M+H)⁺.

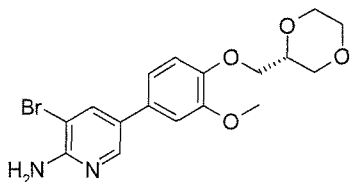
Example 41

N-[4-(2-Amino-5-{4-[(2R)-1,4-dioxan-2-ylmethoxy]-3-methoxyphenyl}pyridin-3-yl)phenyl]-1-benzyl-5-(4-fluorophenyl)-4-oxo-1,4-dihydropyridine-3-carboxamide
[Step 1] 1-Benzyl-5-(4-fluorophenyl)-4-oxo-N-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-1,4-dihydropyridine-3-carboxamide



EDC.HCl (152 mg), HOBt (73 mg) and 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (128 mg) were added to a solution of 1-benzyl-5-(4-fluorophenyl)-4-oxo-1,4-dihydropyridine-3-carboxylic acid (171 mg) in DMF (3 ml) at room temperature. The reaction mixture was stirred at 50°C overnight. EDC.HCl (76 mg) and 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (64 mg) were added to the reaction mixture at 50°C. The reaction mixture was stirred at 50°C overnight. The reaction mixture was then stirred at 80°C overnight. The reaction mixture was returned to room temperature and diluted by adding water. The precipitated solid was collected by filtration. The resulting solid was purified by silica gel column chromatography [hexane:ethyl acetate = 5:1 -> 4:1 -> 3:1 -> 1:1 (v/v)] to give 112 mg of the title compound as a solid. MS (ESI) m/z: 525 (M+H)⁺.

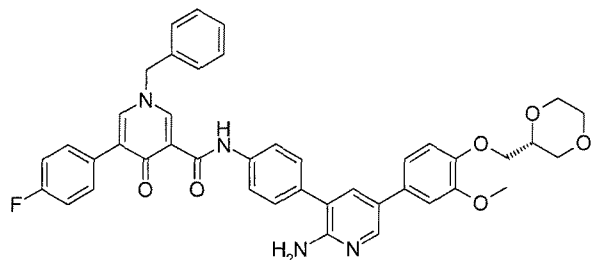
[Step 2] 3-Bromo-5-{4-[(2R)-1,4-dioxan-2-ylmethoxy]-3-methoxyphenyl}pyridin-2-amine



The compound obtained in Reference Example 7 (2.64 g), 3-bromo-5-iodopyridin-2-amine (2.25 g), tetrakis(triphenylphosphine)palladium (430 mg) and potassium carbonate (3.12 g) were suspended in dioxane (30 ml) and water (6 ml), and the suspension was stirred at 80°C overnight. After leaving to cool, the reaction solution was diluted with chloroform, followed by washing with water. The organic layer was dried over sodium sulfate, and the solvent was distilled off under reduced pressure. The residue was then purified by silica gel column chromatography [ethyl acetate:hexane = 1:1 -> chloroform:methanol = 19:1 (v/v)] to give 2.05 g of the title compound as a solid.

MS (ESI) m/z: 395, 397 (M+H)⁺.

[Step 3] N-[4-(2-Amino-5-{4-[(2R)-1,4-dioxan-2-ylmethoxy]-3-methoxyphenyl}pyridin-3-yl)phenyl]-1-benzyl-5-(4-fluorophenyl)-4-oxo-1,4-dihydropyridine-3-carboxamide



The compound obtained in the above Step 2 (93 mg), tetrakis(triphenylphosphine)palladium (49 mg) and potassium carbonate (88 mg) were added to a solution of the compound obtained in the above Step 1 (112 mg) in dioxane (3 ml) and water (0.3 ml) at room temperature. The reaction mixture was stirred at 100°C overnight. The reaction mixture was returned to room temperature and diluted by adding ethyl acetate. The organic layer was washed with water and brine, dried over sodium sulfate and filtered, and the filtrate was then concentrated under reduced pressure. The residue was purified by PLC [developed with ethyl acetate], and the eluate was concentrated under reduced pressure. The residue was purified by PLC [dichloromethane:methanol = 15:1 (v/v)] to give 57 mg of the title compound as a solid.

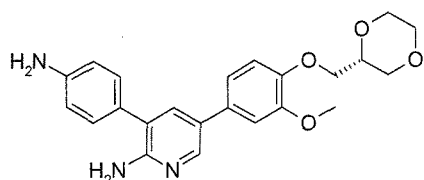
$^1\text{H-NMR}$ (CDCl_3) δ : 3.52-3.83 (5H, m), 3.89 (3H, s), 3.93-4.09 (4H, m), 4.72 (2H, s), 5.15 (2H, s), 6.95 (1H, d, J = 8.3 Hz), 7.01-7.06 (2H, m), 7.09-7.15 (2H, m), 7.25-7.30 (2H, m), 7.40-7.56 (9H, m), 7.82-7.87 (2H, m), 8.25 (1H, d, J = 2.3 Hz), 8.73 (1H, d, J = 2.3 Hz).

MS (ESI) m/z : 713 ($\text{M}+\text{H}$) $^+$.

Example 42

N-[4-(2-Amino-5-{4-[(2R)-1,4-dioxan-2-ylmethoxy]-3-methoxyphenyl}pyridin-3-yl)phenyl]-5-(4-fluorophenyl)-4-oxo-1-(2,2,2-trifluoroethyl)-1,4-dihydropyridine-3-carboxamide

[Step 1] 3-(4-Aminophenyl)-5-{4-[(2R)-1,4-dioxan-2-ylmethoxy]-3-methoxyphenyl}pyridin-2-amine



The compound obtained in Step 2 of Example 41 (2.05 g), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (1.14 g), tetrakis(triphenylphosphine)palladium (0.3 g), and potassium carbonate (2.15 g) were suspended in dioxane (30 ml) and water (6 ml), and the suspension was stirred at 100°C for two hours. After leaving to cool, the reaction solution was diluted with chloroform, followed by washing with water. The organic layer was dried over anhydrous sodium sulfate. The solvent was distilled off under reduced pressure, and the residue was purified by silica gel column chromatography [ethyl acetate:hexane = 1:1 -> chloroform:ethanol = 19:1 (v/v)] to give 1.27 g of the title compound as a solid.

MS (ESI) m/z : 408 (M+H)⁺.

COc1cc(OC[C@H]2OCCO2)ccc1-c3cc(N)cnc3-c4ccc(NC(=O)c5cc(C(F)(F)F)nc(=O)c5-c6ccc(F)cc6)cc4

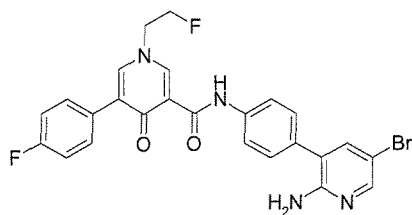
COMU (82 mg) and DIPEA (51 μ l) were added to a solution of the compound obtained in Step 2 of Example 9 (51 mg) in DMF (1 ml), and the mixture was stirred at room temperature for five minutes. The compound obtained in the above Step 1 (60 mg) was added at room temperature, and the mixture was stirred at room temperature for five hours. Water was added to the reaction solution, followed by extraction with ethyl acetate. The organic layer was dehydrated with sodium sulfate, and the solvent was distilled off under reduced pressure. The resulting residue was suspended in ethyl acetate and diisopropyl ether. The solid obtained by filtration was subjected to silica gel column chromatography [ethyl acetate:methanol = 99:1 $\rightarrow$ 9:1 (v/v)] and then purified by reverse phase HPLC [acetonitrile:water:formic acid] to give 14 mg of the title compound as a solid.

$^1\text{H-NMR}$ (CDCl_3) δ : 3.50-3.55 (1H, m), 3.61-3.69 (1H, m), 3.70-3.76 (1H, m), 3.78-3.85 (2H, m), 3.88 (3H, s), 3.92-3.99 (2H, m), 4.00-4.08 (2H, m), 4.50 (2H, q, $J = 7.8$ Hz), 4.60-4.66 (2H, m), 6.94 (1H, d, $J = 8.2$ Hz), 6.99-7.05 (2H, m), 7.13-7.19 (2H, m), 7.45-7.50 (3H, m), 7.50-7.55 (3H, m), 7.83 (2H, d, $J = 8.7$ Hz), 8.24 (1H, d, $J = 1.8$ Hz), 8.62 (1H, d, $J = 2.3$ Hz), 12.43 (1H, s).

MS (ESI) m/z : 705 ($\text{M}+\text{H}$) $^+$.

Example 43

N-[4-(2-Amino-5-{4-[(2R)-1,4-dioxan-2-ylmethoxy]-3-methoxyphenyl}pyridin-3-yl)phenyl]-1-(2-fluoroethyl)-5-(4-fluorophenyl)-4-oxo-1,4-dihydropyridine-3-carboxamide
[Step 1] N-[4-(2-Amino-5-bromopyridin-3-yl)phenyl]-1-(2-fluoroethyl)-5-(4-fluorophenyl)-4-oxo-1,4-dihydropyridine-3-carboxamide

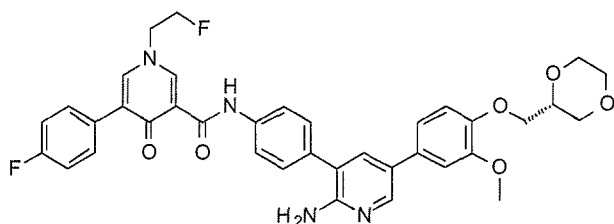


DIPEA (114 μl) was added to a solution of the compound obtained in Step 2 of Example 8 (91 mg) and COMU (181 mg) in DMF (2.0 ml) at room temperature, and the mixture was stirred for 20 minutes. The compound obtained in Step 1 of Example 1 (95 mg) was added at room temperature. The mixture was stirred for six hours, followed by the addition of water. After extraction with

ethyl acetate, the organic layer was washed with brine and then dried over sodium sulfate. The solvent was distilled off under reduced pressure, and the residue was purified by silica gel column chromatography [chloroform:methanol = 300:1 → 30:1 (v/v)] to give 139 mg of the title compound as a solid.

¹H-NMR (CDCl₃) δ: 4.24-4.36 (2H, m), 4.63 (2H, s), 4.73-4.91 (2H, m), 7.13-7.21 (2H, m), 7.39-7.44 (2H, m), 7.48 (1H, d, J = 2.3 Hz), 7.53-7.60 (3H, m), 7.82-7.88 (2H, m), 8.08 (1H, d, J = 2.3 Hz), 8.64 (1H, d, J = 2.3 Hz).
MS (ESI) m/z: 525 (M+H)⁺.

[Step 2] N-[4-(2-Amino-5-{4-[(2R)-1,4-dioxan-2-ylmethoxy]-3-methoxyphenyl}pyridin-3-yl)phenyl]-1-(2-fluoroethyl)-5-(4-fluorophenyl)-4-oxo-1,4-dihydropyridine-3-carboxamide



Water (0.1 ml), potassium carbonate (61 mg) and tetrakis(triphenylphosphine)palladium (17 mg) were added to a solution of the compound obtained in the above Step 1 (77 mg) and the compound obtained in Reference Example 7 (56 mg) in 1,4-dioxane (1.4 ml), and the mixture was stirred at 100°C for six hours. After leaving to cool, the reaction solution was diluted with chloroform. The

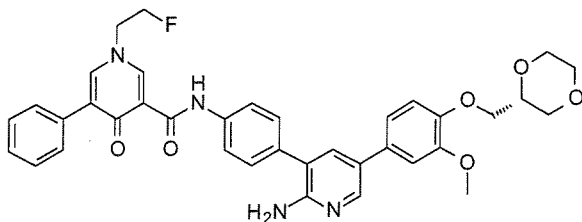
organic layer was washed with water and then dried over sodium sulfate. The solvent was distilled off under reduced pressure, and the residue was purified by reverse phase HPLC [acetonitrile:water:formic acid] to give 35 mg of the title compound as a solid.

$^1\text{H-NMR}$ (CDCl_3) δ : 3.51-3.88 (5H, m), 3.90 (3H, s), 3.94-4.16 (4H, m), 4.24-4.37 (2H, m), 4.64 (2H, s), 4.74-4.91 (2H, m), 6.94-7.08 (3H, m), 7.14-7.20 (2H, m), 7.46-7.60 (6H, m), 7.83-7.90 (2H, m), 8.26 (1H, d, $J = 2.5$ Hz), 8.65 (1H, d, $J = 2.5$ Hz).

MS (ESI) m/z : 669 ($\text{M}+\text{H}$) $^+$.

Example 44

N-[4-(2-Amino-5-{4-[(2R)-1,4-dioxan-2-ylmethoxy]-3-methoxyphenyl}pyridin-3-yl)phenyl]-1-(2-fluoroethyl)-4-oxo-5-phenyl-1,4-dihydropyridine-3-carboxamide



DIPEA (60 μl) was added to a solution of the compound obtained in Step 2 of Example 19 (50 mg) and COMU (96 mg) in DMF (3.0 ml) at room temperature, and the mixture was stirred for one hour. The compound obtained in Step 1 of Example 42 (70 mg) was added at room temperature. The mixture was stirred for five hours, followed by the addition of water. The organic layer was

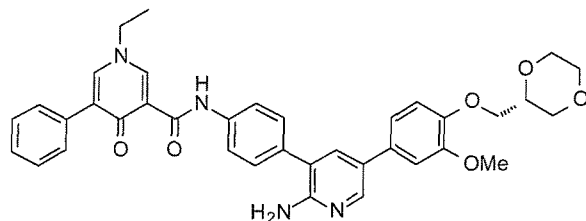
extracted with ethyl acetate, and then washed with water and brine and dried over sodium sulfate. The solvent was distilled off under reduced pressure, and the residue was purified by silica gel column chromatography [chloroform:methanol = 19:1 -> 9:1 (v/v)] to give 87 mg of the title compound as a solid.

$^1\text{H-NMR}$ (CDCl_3) δ : 3.51-3.88 (5H, m), 3.90 (3H, s), 3.94-4.11 (4H, m), 4.27 (1H, t, $J = 4.6$ Hz), 4.33 (1H, t, $J = 4.4$ Hz), 4.65 (2H, s), 4.77 (1H, t, $J = 4.4$ Hz), 4.88 (1H, t, $J = 4.4$ Hz), 6.96 (1H, d, $J = 8.3$ Hz), 7.02-7.07 (2H, m), 7.39-7.51 (5H, m), 7.56-7.60 (4H, m), 7.87 (2H, d, $J = 8.7$ Hz), 8.26 (1H, d, $J = 2.3$ Hz), 8.65 (1H, d, $J = 2.8$ Hz).

MS (ESI) m/z : 651 ($\text{M}+\text{H}$) $^+$.

Example 45

N-[4-(2-Amino-5-{4-[(2R)-1,4-dioxan-2-ylmethoxy]-3-methoxyphenyl}pyridin-3-yl)phenyl]-1-ethyl-4-oxo-5-phenyl-1,4-dihydropyridine-3-carboxamide



DIPEA (240 μl) was added to a solution of 1-ethyl-4-oxo-5-phenyl-1,4-dihydropyridine-3-carboxylic acid (168 mg) and COMU (384 mg) in DMF (2.3 ml) at room temperature, and the mixture was stirred for 20 minutes. The compound

obtained in Step 1 of Example 42 (295 mg) was added at room temperature. The mixture was stirred for 15 hours, followed by the addition of water. The organic layer was extracted with ethyl acetate, and then washed with water and brine and dried over sodium sulfate. The solvent was distilled off under reduced pressure, and the residue was purified by silica gel column chromatography

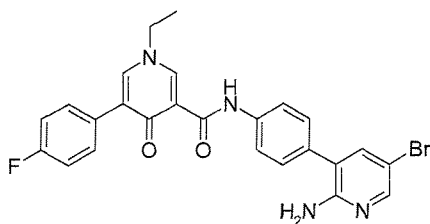
[chloroform:methanol = 300:1 -> 30:1 (v/v)] to give 235 mg of the title compound as a solid.

$^1\text{H-NMR}$ (CDCl_3) δ : 1.57-1.63 (3H, m), 3.50-3.59 (1H, m), 3.63-3.89 (4H, m), 3.91 (3H, s), 3.94-4.14 (6H, m), 4.80 (2H, s), 6.94-7.08 (3H, m), 7.39-7.51 (5H, m), 7.54-7.61 (4H, m), 7.86-7.91 (2H, m), 8.24 (1H, d, $J = 2.5$ Hz), 8.66 (1H, d, $J = 2.5$ Hz).

MS (ESI) m/z : 633 ($\text{M}+\text{H}$) $^+$.

Example 46

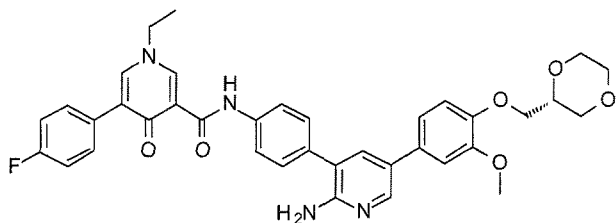
N-[4-(2-Amino-5-{4-[(2R)-1,4-dioxan-2-ylmethoxy]-3-methoxyphenyl}pyridin-3-yl)phenyl]-1-ethyl-5-(4-fluorophenyl)-4-oxo-1,4-dihydropyridine-3-carboxamide
[Step 1] N-[4-(2-Amino-5-bromopyridin-3-yl)phenyl]-1-ethyl-5-(4-fluorophenyl)-4-oxo-1,4-dihydropyridine-3-carboxamide



DIPEA (120 μ l) was added to a solution of the compound obtained in Step of Example 3 (80 mg) and COMU (192 mg) in DMF (1.5 ml) at room temperature, and the mixture was stirred for 10 minutes. The compound obtained in Step 1 of Example 1 (100 mg) was added at room temperature. The mixture was stirred for four hours, followed by the addition of water. The precipitated solid was collected by filtration to give 174 mg of the title compound.

$^1\text{H-NMR}$ (CDCl_3) δ : 1.60 (3H, t, $J = 7.3$ Hz), 4.09 (2H, q, $J = 7.3$ Hz), 4.71 (2H, s), 7.13-7.21 (2H, m), 7.38-7.44 (2H, m), 7.47-7.61 (4H, m), 7.83-7.88 (2H, m), 8.08 (1H, d, $J = 2.3$ Hz), 8.65 (1H, d, $J = 2.3$ Hz).

[Step 2] N-[4-(2-Amino-5-{4-[(2R)-1,4-dioxan-2-ylmethoxy]-3-methoxyphenyl}pyridin-3-yl)phenyl]-1-ethyl-5-(4-fluorophenyl)-4-oxo-1,4-dihydropyridine-3-carboxamide



Water (0.1 ml), potassium carbonate (65 mg) and tetrakis(triphenylphosphine)palladium (18 mg) were added to a solution of the compound obtained in the above Step 1 (80 mg) and the compound obtained in Reference Example 7 (61 mg) in 1,4-dioxane (1.5 ml), and the mixture was

stirred at 100°C for seven hours. After leaving to cool, the reaction solution was diluted with ethyl acetate. The organic layer was washed with water and brine and then dried over sodium sulfate. The solvent was distilled off under reduced pressure, and the residue was purified by silica gel column chromatography [ethyl acetate:methanol = 300:1 -> 50:1 (v/v)] to give 21 mg of the title compound as a solid.

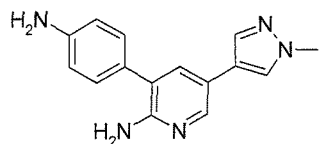
¹H-NMR (CDCl₃) δ: 1.60 (3H, t, J = 7.3 Hz), 3.51-3.60 (1H, m), 3.63-3.87 (4H, m), 3.91 (3H, s), 3.94-4.14 (6H, m), 4.64 (2H, s), 6.92-7.08 (3H, m), 7.13-7.20 (2H, m), 7.46-7.60 (6H, m), 7.84-7.90 (2H, m), 8.26 (1H, d, J = 2.3 Hz), 8.66 (1H, d, J = 2.3 Hz).

MS (ESI) m/z: 651 (M+H)⁺.

Example 47

N-{4-[2-Amino-5-(1-methyl-1H-pyrazol-4-yl)pyridin-3-yl]phenyl}-1-ethyl-5-(4-fluorophenyl)-4-oxo-1,4-dihydropyridine-3-carboxamide

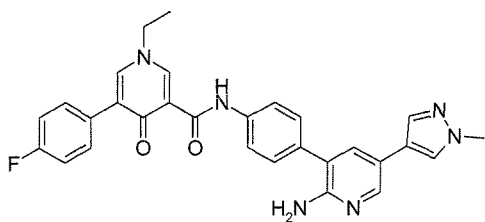
[Step 1] 3-(4-Aminophenyl)-5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-amine



Water (5 ml), potassium carbonate (1742 mg) and tetrakis(triphenylphosphine)palladium (242 mg) were added to a solution of the compound obtained in Step 1 of

Example 1 (1110 mg) and 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (874 mg) in 1,4-dioxane (50 ml), and the mixture was stirred at 100°C for five hours. After leaving to cool, the reaction solution was diluted with chloroform. The organic layer was washed with water and brine and dried over sodium sulfate. The solvent was distilled off under reduced pressure, and the residue was purified by silica gel column chromatography [chloroform:methanol = 96:4 (v/v)] to give 638 mg of the title compound as a solid.
MS (ESI) m/z : 266 (M+H)⁺.

[Step 2] N-{4-[2-Amino-5-(1-methyl-1H-pyrazol-4-yl)pyridin-3-yl]phenyl}-1-ethyl-5-(4-fluorophenyl)-4-oxo-1,4-dihydropyridine-3-carboxamide



DIPEA (29 μ l) was added to a solution of the compound obtained in Step 2 of Example 3 (22 mg) and COMU (47 mg) in DMF (1.0 ml) at room temperature, and the mixture was stirred for 20 minutes. The compound obtained in the above Step 1 (25 mg) was added at room temperature. The mixture was stirred for 7 hours, followed by the addition of water. The organic layer was extracted with ethyl acetate, and then washed with water

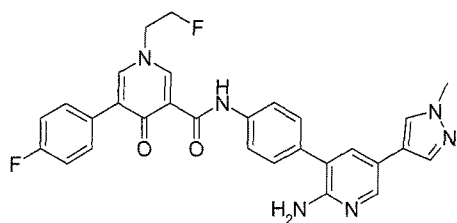
and brine and dried over sodium sulfate. The solvent was distilled off under reduced pressure, and the residue was purified by PLC (NH) [chloroform:methanol = 30:1 (v/v)] to give 22 mg of the title compound as a solid.

$^1\text{H-NMR}$ (CDCl_3) δ : 1.57-1.62 (3H, m), 3.94 (3H, s), 4.09 (2H, q, $J = 7.5$ Hz), 4.58 (2H, s), 7.14-7.20 (2H, m), 7.44-7.49 (3H, m), 7.52-7.60 (4H, m), 7.69 (1H, s), 7.84-7.89 (2H, m), 8.19 (1H, d, $J = 2.5$ Hz), 8.66 (1H, d, $J = 2.5$ Hz).

MS(ESI) m/z : 509 ($\text{M}+\text{H}$) $^+$.

Example 48

N-{4-[2-Amino-5-(1-methyl-1H-pyrazol-4-yl)pyridin-3-yl]phenyl}-1-(2-fluoroethyl)-5-(4-fluorophenyl)-4-oxo-1,4-dihydropyridine-3-carboxamide



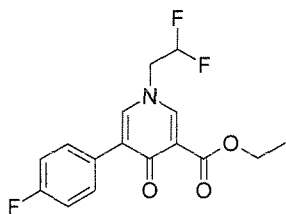
61 mg of the title compound was obtained as a solid from the compound obtained in Step 2 of Example 8 (96 mg) and the compound obtained in Step 1 of Example 47 (70 mg) as raw materials by a reaction similar to that in Step 2 of Example 47.

$^1\text{H-NMR}$ (CDCl_3) δ : 3.94 (3H, s), 4.25-4.36 (2H, m), 4.58 (2H, s), 4.74-4.91 (2H, m), 7.15-7.19 (2H, m), 7.44-7.49

(3H, m), 7.54-7.59 (4H, m), 7.69 (1H, s), 7.83-7.88 (2H, m), 8.20 (1H, d, $J = 2.3$ Hz), 8.65 (1H, d, $J = 2.3$ Hz).
MS(ESI) m/z : 527 (M+H)⁺.

Example 49

N-{4-[2-Amino-5-(1-methyl-1H-pyrazol-4-yl)pyridin-3-yl]phenyl}-1-(2,2-difluoroethyl)-5-(4-fluorophenyl)-4-oxo-1,4-dihydropyridine-3-carboxamide
[Step 1] Ethyl 1-(2,2-difluoroethyl)-5-(4-fluorophenyl)-4-oxo-1,4-dihydropyridine-3-carboxylate

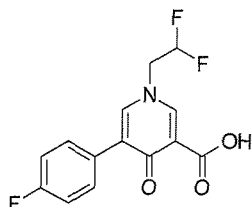


0.31 g of the title compound was obtained as an oily substance from ethyl 5-(4-fluorophenyl)-4-oxo-1,4-dihydropyridine-3-carboxylate (1.50 g) and 2,2-difluoroethyl trifluoromethanesulfonate (2.20 g) as raw materials by a reaction similar to that in Step 1 of Example 8.

¹H-NMR (CDCl₃) δ : 1.38 (3H, t, $J = 7.1$ Hz), 4.15-4.26 (2H, m), 4.37 (2H, q, $J = 7.1$ Hz), 5.95-6.28 (1H, m), 7.04-7.11 (2H, m), 7.36 (1H, d, $J = 2.3$ Hz), 7.51-7.57 (2H, m), 8.13 (1H, d, $J = 2.3$ Hz).

MS(ESI) m/z : 326 (M+H)⁺.

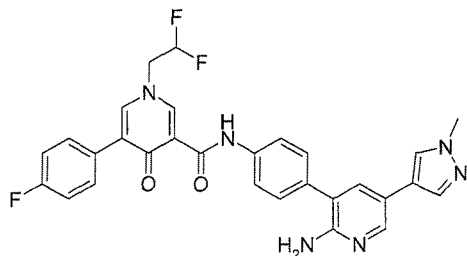
[Step 2] 1-(2,2-Difluoroethyl)-5-(4-fluorophenyl)-4-oxo-1,4-dihydropyridine-3-carboxylic acid



Potassium carbonate (0.33 g) and water (2 ml) were added to a solution of the compound obtained in the above Step 1 (0.31 g) in methanol (4 ml) at room temperature. The reaction mixture was stirred at room temperature overnight. A 1 N aqueous hydrochloric acid solution and water were added to the reaction mixture, and the precipitated solid was collected by filtration, washed with water and then dried to give 0.19 g of the title compound as a solid.

MS (ESI) m/z : 298 (M+H)⁺.

[Step 3] N-{4-[2-Amino-5-(1-methyl-1H-pyrazol-4-yl)pyridin-3-yl]phenyl}-1-(2,2-difluoroethyl)-5-(4-fluorophenyl)-4-oxo-1,4-dihydropyridine-3-carboxamide



53 mg of the title compound was obtained as a solid from the compound obtained in the above Step 2 (86 mg)

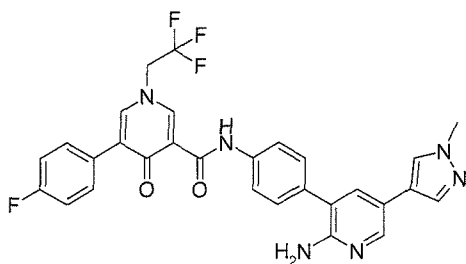
and the compound obtained in Step 1 of Example 47 (70 mg) as raw materials by a reaction similar to that in Step 3 of Example 1.

$^1\text{H-NMR}$ (CDCl_3) δ : 3.92 (3H, s), 4.26-4.38 (2H, m), 4.61 (2H, s), 5.97-6.32 (1H, m), 7.13-7.17 (2H, m), 7.43-7.55 (7H, m), 7.67 (1H, s), 7.82 (2H, d, $J = 8.3$ Hz), 8.17 (1H, d, $J = 1.8$ Hz), 8.60 (1H, d, $J = 2.8$ Hz).

MS (ESI) m/z : 545 ($\text{M}+\text{H}$) $^+$.

Example 50

N-{4-[2-Amino-5-(1-methyl-1H-pyrazol-4-yl)pyridin-3-yl]phenyl}-5-(4-fluorophenyl)-4-oxo-1-(2,2,2-trifluoroethyl)-1,4-dihydropyridine-3-carboxamide



HOBt (51 mg), HATU (215 mg), DMAP (23 mg) and DIPEA (131 μl) were added to a solution of the compound obtained in Step 2 of Example 9 (131 mg) in DMF (2 ml) at room temperature. The reaction mixture was stirred at room temperature for 1.5 hours. The compound obtained in Step 1 of Example 47 (100 mg) was added to the reaction mixture at room temperature. The reaction mixture was stirred at 50°C for 1.5 hours and returned to room temperature. Water was added to the reaction mixture,

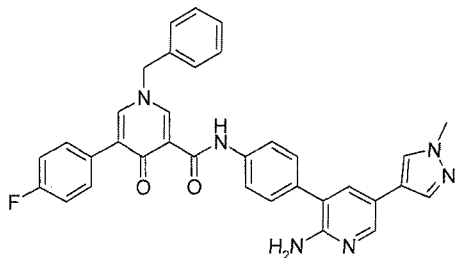
and the precipitated solid was collected by filtration. The resulting solid was purified by PLC [dichloromethane:methanol = 15:1 (v/v)] to give 64 mg of the title compound as a solid.

$^1\text{H-NMR}$ (CDCl_3) δ : 3.94 (3H, s), 4.51 (2H, q, $J = 7.8$ Hz), 4.60 (2H, s), 7.15-7.23 (2H, m), 7.46-7.57 (7H, m), 7.69 (1H, s), 7.84 (2H, d, $J = 8.3$ Hz), 8.19 (1H, d, $J = 2.3$ Hz), 8.64 (1H, d, $J = 2.3$ Hz), 12.45 (1H, s).

MS (ESI) m/z : 563 ($\text{M}+\text{H}$) $^+$.

Example 51

N-{4-[2-Amino-5-(1-methyl-1H-pyrazol-4-yl)pyridin-3-yl]phenyl}-1-benzyl-5-(4-fluorophenyl)-4-oxo-1,4-dihydropyridine-3-carboxamide



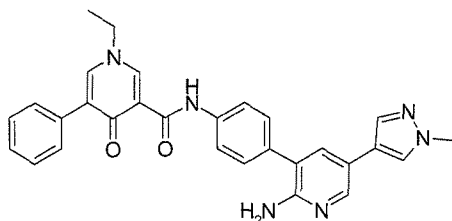
39 mg of the title compound was obtained as a solid from the compound obtained in Step 1 of Example 10 (67 mg) and the compound obtained in Step 1 of Example 47 (50 mg) as raw materials by a reaction similar to that in Step 3 of Example 1.

$^1\text{H-NMR}$ (CDCl_3) δ : 3.93 (3H, s), 4.61 (2H, s), 5.16 (2H, s), 7.09-7.16 (2H, m), 7.25-7.30 (2H, m), 7.40-7.48 (6H,

m), 7.48-7.55 (4H, m), 7.68 (1H, s), 7.84 (2H, d, $J = 8.3$ Hz), 8.19 (1H, d, $J = 2.3$ Hz), 8.73 (1H, d, $J = 2.3$ Hz).
MS(ESI) m/z : 571 (M+H)⁺.

Example 52

N-{4-[2-Amino-5-(1-methyl-1H-pyrazol-4-yl)pyridin-3-yl]phenyl}-1-ethyl-4-oxo-5-phenyl-1,4-dihydropyridine-3-carboxamide



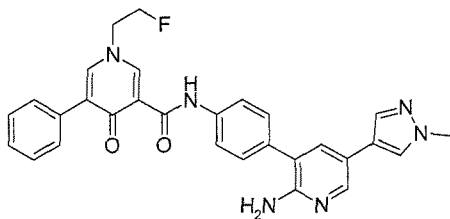
22 mg of the title compound was obtained as a solid from 1-ethyl-4-oxo-5-phenyl-1,4-dihydropyridine-3-carboxylic acid (20 mg) and the compound obtained in Step 1 of Example 47 (25 mg) as raw materials by a reaction similar to that in Step 2 of Example 47.

¹H-NMR (CDCl₃) δ : 1.58-1.62 (3H, m), 3.94 (3H, s), 4.03-4.14 (2H, m), 4.58 (2H, s), 7.38-7.60 (10H, m), 7.69 (1H, s), 7.83-7.90 (2H, m), 8.20 (1H, d, $J = 2.29$ Hz), 8.66 (1H, d, $J = 2.75$ Hz).

MS(ESI) m/z : 491 (M+H)⁺.

Example 53

N-{4-[2-Amino-5-(1-methyl-1H-pyrazol-4-yl)pyridin-3-yl]phenyl}-1-(2-fluoroethyl)-4-oxo-5-phenyl-1,4-dihydropyridine-3-carboxamide



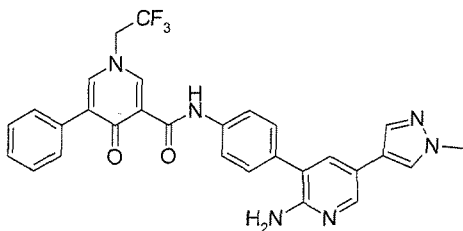
42 mg of the title compound was obtained as a solid from the compound obtained in Step 2 of Example 19 (38 mg) and the compound obtained in Step 1 of Example 47 (42 mg) as raw materials by a reaction similar to that in Step 2 of Example 47.

¹H-NMR (CDCl₃) δ: 3.94 (3H, s), 4.24-4.37 (2H, m), 4.58 (2H, s), 4.74-4.91 (2H, m), 7.41-7.60 (10H, m), 7.69 (1H, s), 7.83-7.89 (2H, m), 8.20 (1H, d, J = 2.5 Hz), 8.65 (1H, d, J = 2.5 Hz).

MS (ESI) m/z: 509 (M+H)⁺.

Example 54

N-{4-[2-Amino-5-(1-methyl-1H-pyrazol-4-yl)pyridin-3-yl]phenyl}-4-oxo-5-phenyl-1-(2,2,2-trifluoroethyl)-1,4-dihydropyridine-3-carboxamide



47 mg of the title compound was obtained as a solid from the compound obtained in Step 2 of Example 20 (41 mg) and the compound obtained in Step 1 of Example 47 (40

mg) as raw materials by a reaction similar to that in Step 2 of Example 47.

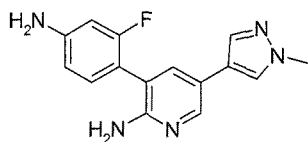
$^1\text{H-NMR}$ (CDCl_3) δ : 3.94 (3H, s), 4.45-4.64 (4H, m), 7.42-7.58 (10H, m), 7.69 (1H, s), 7.82-7.88 (2H, m), 8.20 (1H, d, $J = 2.3$ Hz), 8.64 (1H, d, $J = 2.3$ Hz).

MS(ESI) m/z : 545 ($\text{M}+\text{H}$) $^+$.

Example 55

N-{4-[2-Amino-5-(1-methyl-1H-pyrazol-4-yl)pyridin-3-yl]-3-fluorophenyl}-1-(2-fluoroethyl)-4-oxo-5-phenyl-1,4-dihydropyridine-3-carboxamide

[Step 1] 3-(4-Amino-2-fluorophenyl)-5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-amine

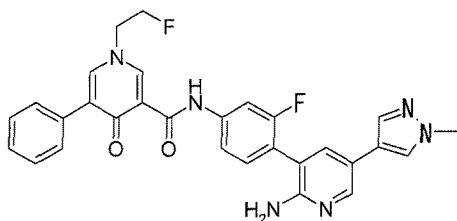


The compound obtained in Step 1 of Example 29 (2 g), 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (1.62 g), tetrakis(triphenylphosphine)palladium (0.41 g) and potassium carbonate (2.94 g) were suspended in dioxane (10 ml) and water (1 ml), and the suspension was heated under reflux at 100°C for 61 hours. After leaving to cool, a saturated aqueous sodium bicarbonate solution was added, and the organic layer was extracted with ethyl acetate and dried over sodium sulfate. The solvent was distilled off under reduced pressure, and the residue was

purified by silica gel column chromatography [ethyl acetate:methanol = 10:1 (v/v)] to give 1.88 g of the title compound as a solid.

MS (ESI) m/z : 284 (M+H)⁺.

[Step 2] N-{4-[2-Amino-5-(1-methyl-1H-pyrazol-4-yl)pyridin-3-yl]-3-fluorophenyl}-1-(2-fluoroethyl)-4-oxo-5-phenyl-1,4-dihydropyridine-3-carboxamide



51 mg of the title compound was obtained as a solid from the compound obtained in Step 2 of Example 19 (50 mg) and the compound obtained in the above Step 1 (60 mg) as raw materials by a reaction similar to that in Step 2 of Example 47.

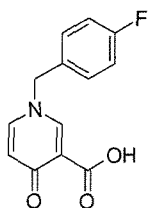
¹H-NMR (CDCl₃) δ : 3.94 (3H, s), 4.28 (1H, t, J = 4.4 Hz), 4.34 (1H, t, J = 4.6 Hz), 4.53 (2H, s), 4.77 (1H, t, J = 4.6 Hz), 4.88 (1H, t, J = 4.6 Hz), 7.34 (1H, t, J = 8.3 Hz), 7.37-7.54 (5H, m), 7.54-7.60 (4H, m), 7.68 (1H, d, J = 0.9 Hz), 7.91 (1H, dd, J = 12.2, 2.1 Hz), 8.23 (1H, d, J = 2.3 Hz), 8.64 (1H, d, J = 2.3 Hz).

MS (ESI) m/z : 527 (M+H)⁺.

Example 56

N-{4-[2-Amino-5-(1-methyl-1H-pyrazol-4-yl)pyridin-3-yl]phenyl}-1-(4-fluorobenzyl)-4-oxo-1,4-dihydropyridine-3-carboxamide

[Step 1] 1-(4-Fluorobenzyl)-4-oxo-1,4-dihydropyridine-3-carboxylic acid

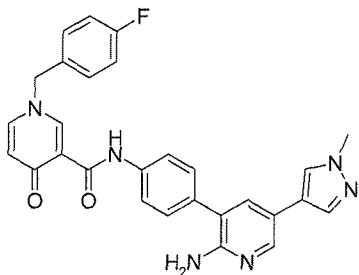


0.91 g of the title compound was obtained as a solid from ethyl 4-oxo-1,4-dihydropyridine-3-carboxylate (0.75 g) and 1-(bromomethyl)-4-fluorobenzene (1.38 ml) as raw materials by a reaction similar to that in Step 1 of Example 11.

$^1\text{H-NMR}$ (CDCl_3) δ : 5.11 (2H, s), 6.72-6.77 (1H, m), 7.11-7.18 (2H, m), 7.24-7.27 (2H, m), 7.49-7.55 (1H, m), 8.56-8.60 (1H, m).

MS (ESI) m/z : 248 ($\text{M}+\text{H}$) $^+$.

[Step 2] N-{4-[2-Amino-5-(1-methyl-1H-pyrazol-4-yl)pyridin-3-yl]phenyl}-1-(4-fluorobenzyl)-4-oxo-1,4-dihydropyridine-3-carboxamide



33 mg of the title compound was obtained as a solid from the compound obtained in the above Step 1 (72 mg) and the compound obtained in Step 1 of Example 47 (70 mg) as raw materials by a reaction similar to that in Step 2 of Example 47.

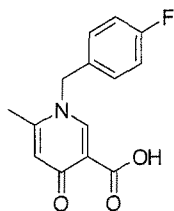
$^1\text{H-NMR}$ (CDCl_3) δ : 3.94 (3H, s), 4.59 (2H, s), 5.08 (2H, s), 6.66 (1H, d, $J = 7.8$ Hz), 7.10-7.17 (2H, m), 7.23-7.28 (2H, m), 7.41 (1H, dd, $J = 7.6, 2.5$ Hz), 7.45-7.49 (3H, m), 7.55 (1H, s), 7.69 (1H, s), 7.82-7.86 (2H, m), 8.20 (1H, s), 8.66 (1H, d, $J = 2.3$ Hz).

MS (ESI) m/z : 495 ($\text{M}+\text{H}$) $^+$.

Example 57

N-{4-[2-Amino-5-(1-methyl-1H-pyrazol-4-yl)pyridin-3-yl]phenyl}-1-(4-fluorobenzyl)-6-methyl-4-oxo-1,4-dihydropyridine-3-carboxamide

[Step 1] 1-(4-Fluorobenzyl)-6-methyl-4-oxo-1,4-dihydropyridine-3-carboxylic acid

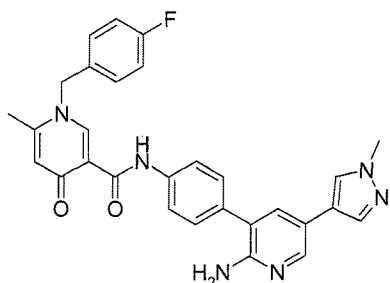


0.86 g of the title compound was obtained as a solid from ethyl 6-methyl-4-oxo-1,4-dihydropyridine-3-carboxylate (0.75 g) and 1-(bromomethyl)-4-fluorobenzene (1.27 ml) as raw materials by a reaction similar to that in Step 1 of Example 11.

$^1\text{H-NMR}$ (CDCl_3) δ : 2.36 (3H, s), 5.20 (2H, s), 6.62 (1H, s), 7.05-7.14 (4H, m), 8.55 (1H, s).

MS (ESI) m/z : 262 ($\text{M}+\text{H}$) $^+$.

[Step 2] N-{4-[2-Amino-5-(1-methyl-1H-pyrazol-4-yl)pyridin-3-yl]phenyl}-1-(4-fluorobenzyl)-6-methyl-4-oxo-1,4-dihydropyridine-3-carboxamide



58 mg of the title compound was obtained as a solid from the compound obtained in the above Step 1 (76 mg) and the compound obtained in Step 1 of Example 47 (70 mg) as raw materials by a reaction similar to that in Step 2 of Example 47.

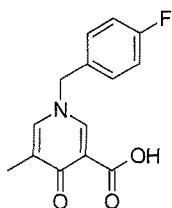
$^1\text{H-NMR}$ (CDCl_3) δ : 2.31 (3H, s), 3.94 (3H, s), 4.61 (2H, s), 5.17 (2H, s), 6.54 (1H, d, $J = 0.9$ Hz), 7.06-7.14 (4H, m), 7.45-7.49 (3H, m), 7.56 (1H, s), 7.69 (1H, d, $J = 0.9$ Hz), 7.82-7.87 (2H, m), 8.20 (1H, d, $J = 2.3$ Hz), 8.63 (1H, s).

MS (ESI) m/z : 509 ($\text{M}+\text{H}$) $^+$.

Example 58

N-{4-[2-Amino-5-(1-methyl-1H-pyrazol-4-yl)pyridin-3-yl]phenyl}-1-(4-fluorobenzyl)-5-methyl-4-oxo-1,4-dihydropyridine-3-carboxamide

[Step 1] 1-(4-Fluorobenzyl)-5-methyl-4-oxo-1,4-dihydropyridine-3-carboxylic acid

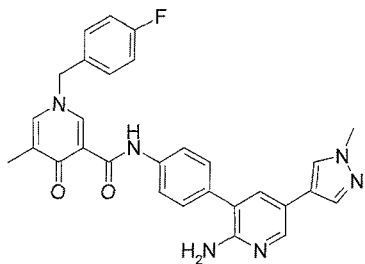


0.35 g of the title compound was obtained as a solid from the compound obtained in Reference Example 5 (0.40 g) and 1-(bromomethyl)-4-fluorobenzene (0.35 ml) as raw materials by a reaction similar to that in Step 1 of Example 11.

$^1\text{H-NMR}$ (DMSO- D_6) δ : 2.11 (3H, d, $J = 0.9$ Hz), 5.30 (2H, s), 7.14-7.18 (2H, m), 7.41-7.45 (2H, m), 8.01-8.02 (1H, m), 8.73 (1H, d, $J = 1.8$ Hz).

MS (ESI) m/z : 262 ($\text{M}+\text{H}$) $^+$.

[Step 2] N-{4-[2-Amino-5-(1-methyl-1H-pyrazol-4-yl)pyridin-3-yl]phenyl}-1-(4-fluorobenzyl)-5-methyl-4-oxo-1,4-dihydropyridine-3-carboxamide



28 mg of the title compound was obtained as a solid from the compound obtained in the above Step 1 (70 mg) and the compound obtained in Step 1 of Example 47 (75 mg) as raw materials by a reaction similar to that in Step 2 of Example 47.

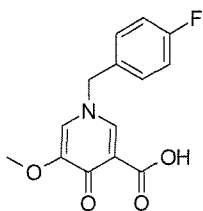
$^1\text{H-NMR}$ (CDCl_3) δ : 2.13 (3H, s), 3.94 (3H, s), 4.58 (2H, s), 5.06 (2H, s), 7.14 (2H, d, $J = 8.3$ Hz), 7.23-7.26 (2H, m), 7.34-7.37 (1H, m), 7.44-7.49 (3H, m), 7.55 (1H, s), 7.69 (1H, s), 7.86 (2H, d, $J = 7.8$ Hz), 8.20 (1H, d, $J = 2.3$ Hz), 8.64 (1H, d, $J = 2.3$ Hz).

MS(ESI) m/z : 509 ($\text{M}+\text{H}$) $^+$.

Example 59

N-{4-[2-Amino-5-(1-methyl-1H-pyrazol-4-yl)pyridin-3-yl]phenyl}-1-(4-fluorobenzyl)-5-methoxy-4-oxo-1,4-dihydropyridine-3-carboxamide

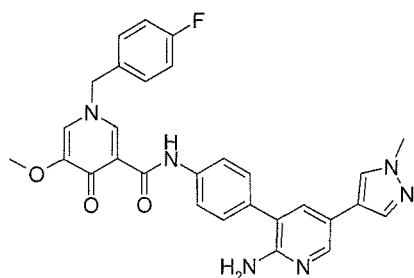
[Step 1] 1-(4-Fluorobenzyl)-5-methoxy-4-oxo-1,4-dihydropyridine-3-carboxylic acid



1-(Bromomethyl)-4-fluorobenzene (74 μl) was added to a suspension of the compound obtained in Reference Example 6 (92 mg) and potassium carbonate (129 mg) in DMF (2 ml) at room temperature. The reaction mixture was stirred at room temperature for two hours. A 1 N aqueous

sodium hydroxide solution (1 ml) was added to the reaction mixture at room temperature, and the reaction mixture was stirred at room temperature for 2.5 hours. Methanol (2 ml) was added to the reaction mixture at room temperature, and the reaction mixture was stirred at room temperature for two hours. A 1 N aqueous sodium hydroxide solution (1.0 ml) and methanol (10 ml) were added to the reaction mixture at room temperature, and the reaction mixture was stirred at 50°C overnight. A 1 N aqueous hydrochloric acid solution and water were then added to the reaction mixture, and the precipitated solid was collected by filtration, washed with water and then dried to give 109 mg of the title compound as a solid. ¹H-NMR (CDCl₃) δ: 3.82 (3H, s), 5.12 (2H, s), 7.03 (1H, d, J = 2.3 Hz), 7.13-7.18 (2H, m), 7.23-7.26 (2H, m), 8.48 (1H, d, J = 2.3 Hz). MS (ESI) m/z: 278 (M+H)⁺.

[Step 2] N-{4-[2-Amino-5-(1-methyl-1H-pyrazol-4-yl)pyridin-3-yl]phenyl}-1-(4-fluorobenzyl)-5-methoxy-4-oxo-1,4-dihydropyridine-3-carboxamide



50 mg of the title compound was obtained as a solid from the compound obtained in the above Step 1 (50 mg) and the compound obtained in Step 1 of Example 47 (57 mg) as raw materials by a reaction similar to that in Step 2 of Example 47.

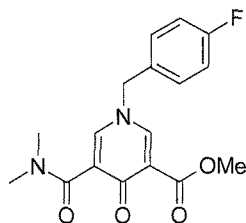
$^1\text{H-NMR}$ (CDCl_3) δ : 3.81 (3H, s), 3.94 (3H, s), 4.58 (2H, s), 5.11 (2H, s), 6.95 (1H, d, $J = 2.3$ Hz), 7.12-7.17 (2H, m), 7.23-7.28 (2H, m), 7.45-7.49 (3H, m), 7.55 (1H, s), 7.69 (1H, s), 7.84 (2H, d, $J = 8.7$ Hz), 8.20 (1H, d, $J = 2.3$ Hz), 8.59 (1H, d, $J = 2.3$ Hz).

MS(ESI) m/z : 525 ($\text{M}+\text{H}$) $^+$.

Example 60

$\text{N}'\text{-}\{4\text{-}[2\text{-Amino-5-(1-methyl-1H-pyrazol-4-yl)pyridin-3-yl]phenyl}\}\text{-1-(4-fluorobenzyl)-N,N-dimethyl-4-oxo-1,4-dihydropyridine-3,5-dicarboxamide}$

[Step 1] Methyl 5-(dimethylcarbamoyl)-1-(4-fluorobenzyl)-4-oxo-1,4-dihydropyridine-3-carboxylate

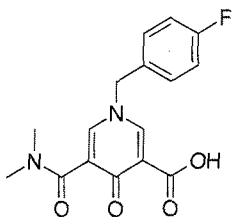


38 mg of the title compound was obtained as an oily substance from the compound obtained in Step 2 of Example 26 (200 mg) and dimethylamine (2 M solution in THF, 0.66 ml) as raw materials by a reaction similar to that in Step 1 of Example 27.

$^1\text{H-NMR}$ (CDCl_3) δ : 2.96 (3H, s), 3.05 (3H, s), 3.89 (3H, s), 4.96 (2H, s), 7.10-7.17 (2H, m), 7.22-7.29 (2H, m), 7.58 (1H, d, $J = 2.8$ Hz), 8.21 (1H, d, $J = 2.8$ Hz).

MS (ESI) m/z : 333 ($\text{M}+\text{H}$) $^+$.

[Step 2] 5-(Dimethylcarbamoyl)-1-(4-fluorobenzyl)-4-oxo-1,4-dihydropyridine-3-carboxylic acid

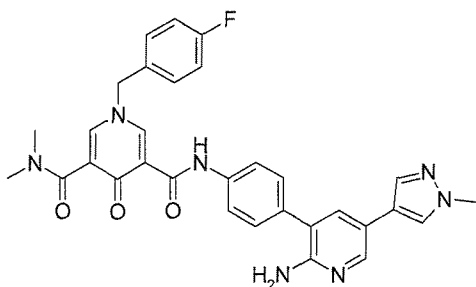


18 mg of the title compound was obtained from the compound obtained in the above Step 1 (38 mg) as a raw material by a reaction similar to that in Step 4 of Example 26.

$^1\text{H-NMR}$ (CDCl_3) δ : 2.96 (3H, s), 3.10 (3H, s), 5.10 (2H, s), 7.12-7.19 (2H, m), 7.25-7.31 (2H, m), 7.82 (1H, d, $J = 2.3$ Hz), 8.55 (1H, d, $J = 2.3$ Hz).

MS (ESI) m/z : 319 ($\text{M}+\text{H}$) $^+$.

[Step 3] N'-{4-[2-Amino-5-(1-methyl-1H-pyrazol-4-yl)pyridin-3-yl]phenyl}-1-(4-fluorobenzyl)-N,N-dimethyl-4-oxo-1,4-dihydropyridine-3,5-dicarboxamide



23 mg of the title compound was obtained as a solid from the compound obtained in the above Step 2 (18 mg) and the compound obtained in Step 1 of Example 47 (16 mg) as raw materials by a reaction similar to that in Step 2 of Example 47.

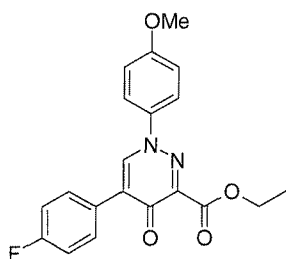
$^1\text{H-NMR}$ (CDCl_3) δ : 3.00 (3H, s), 3.12 (3H, s), 3.94 (3H, s), 4.57 (2H, s), 5.10 (2H, s), 7.11-7.18 (2H, m), 7.27-7.33 (2H, m), 7.43-7.50 (3H, m), 7.55 (1H, s), 7.68-7.72 (2H, m), 7.80-7.86 (2H, m), 8.20 (1H, d, $J = 2.3$ Hz), 8.66 (1H, d, $J = 2.8$ Hz), 12.42 (1H, s).

MS(ESI) m/z : 566($\text{M}+\text{H}$) $^+$.

Example 61

N-{4-[2-Amino-5-(1-methyl-1H-pyrazol-4-yl)pyridin-3-yl]phenyl}-5-(4-fluorophenyl)-1-(4-methoxyphenyl)-4-oxo-1,4-dihydropyridazine-3-carboxamide

[Step 1] Ethyl 5-(4-fluorophenyl)-1-(4-methoxyphenyl)-4-oxo-1,4-dihydropyridazine-3-carboxylate

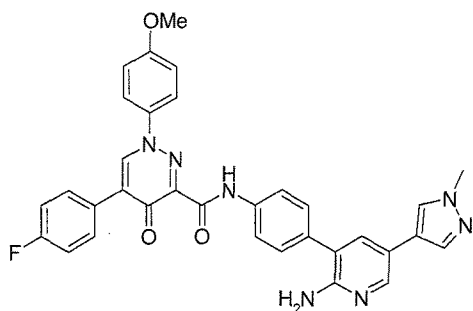


A 0.67 N aqueous hydrochloric acid solution (3 ml) was added to 4-methoxyaniline (165 mg), and a solution of sodium nitrite (138 mg) in water (1 ml) was added at 0°C. The reaction mixture was stirred at 0°C for five minutes. A suspension of sodium acetate (329 mg) and ethyl 4-(4-fluorophenyl)-3-oxobutanoate (300 mg) in ethanol (3 ml) was added to the reaction mixture at 0°C. The reaction mixture was stirred at room temperature overnight. The reaction mixture was diluted with water, followed by extraction with ethyl acetate. The organic layer was washed with brine and dried over sodium sulfate. After filtration, the filtrate was concentrated under reduced pressure. N,N-Dimethylformamide dimethylacetal (3 ml) was added to the resulting oily substance at room temperature. The reaction mixture was stirred at 110°C for 1.5 hours and returned to room temperature. The reaction mixture was diluted with water, followed by extraction with ethyl acetate. The organic layer was washed with water and brine and dried over sodium sulfate. After filtration, the filtrate was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography [ethyl acetate:hexane] to give 345 mg of the title compound as an oily substance.

¹H-NMR (CDCl₃) δ: 1.42 (3H, t, J = 7.1 Hz), 3.87 (3H, s), 4.48 (2H, q, J = 7.1 Hz), 7.01-7.04 (2H, m), 7.11-7.17 (2H, m), 7.51-7.55 (2H, m), 7.75-7.80 (2H, m), 8.30 (1H, s).

MS (ESI) m/z : 369 (M+H)⁺.

[Step 2] N-{4-[2-Amino-5-(1-methyl-1H-pyrazol-4-yl)pyridin-3-yl]phenyl}-5-(4-fluorophenyl)-1-(4-methoxyphenyl)-4-oxo-1,4-dihydropyridazine-3-carboxamide

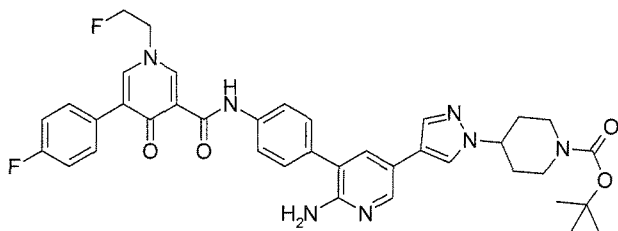


Cerium(IV) ammonium nitrate (1540 mg) and water (5 ml) were added to a solution of the compound obtained in the above Step 1 (345 mg) in acetonitrile (5 ml) at 0°C. The reaction mixture was stirred at 0°C for 30 minutes, and an aqueous sodium thiosulfate solution was added to the reaction mixture. The reaction mixture was concentrated under reduced pressure, and the residue was washed with water, washed with a mixed solvent of ethyl acetate and hexane [1:1 (v/v)] and then dried. 19 mg of the title compound was obtained as a solid from part of the resulting solid (70 mg) and the compound obtained in Step 1 of Example 47 (60 mg) as raw materials by a reaction similar to that in Step 2 of Example 47.

¹H-NMR (CDCl₃) δ : 3.89 (3H, s), 3.94 (3H, s), 4.65 (2H, s), 7.03-7.08 (2H, m), 7.19-7.25 (2H, m), 7.46-7.57 (4H,

MS (ESI) m/z : 588 (M+H)⁺.

N-{4-[2-Amino-5-(1-piperidin-4-yl-1H-pyrazol-4-yl)pyridin-3-yl]phenyl}-1-(2-fluoroethyl)-5-(4-fluorophenyl)-4-oxo-1,4-dihydropyridine-3-carboxamide
[Step 1] tert-Butyl 4-(4-{6-amino-5-[4-({[1-(2-fluoroethyl)-5-(4-fluorophenyl)-4-oxo-1,4-dihydropyridin-3-yl]carbonyl}amino)phenyl]pyridin-3-yl}-1H-pyrazol-1-yl)piperidine-1-carboxylate

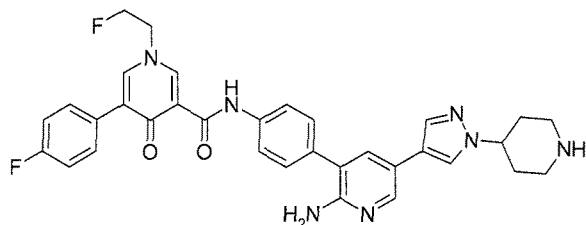


Water (0.5 ml), cesium carbonate (60 mg) and tetrakis(triphenylphosphine)palladium (16 mg) were added to a solution of the compound obtained in Step 1 of Example 43 (75 mg) and tert-butyl 4-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazol-1-yl]piperidine-1-carboxylate (59 mg) in dimethoxyethane (4 ml), and the mixture was stirred under microwave irradiation at 100°C for 10 minutes. After leaving to cool, the reaction product was purified by silica gel column chromatography [chloroform:methanol = 99:1 -> 9:1

(v/v)]. Further, the resulting crude purified product was crystallized from ethyl acetate to give 120 mg of the title compound as a solid.

MS (ESI) m/z : 696 (M+H)⁺.

[Step 2] N-{4-[2-Amino-5-(1-piperidin-4-yl-1H-pyrazol-4-yl)pyridin-3-yl]phenyl}-1-(2-fluoroethyl)-5-(4-fluorophenyl)-4-oxo-1,4-dihydropyridine-3-carboxamide



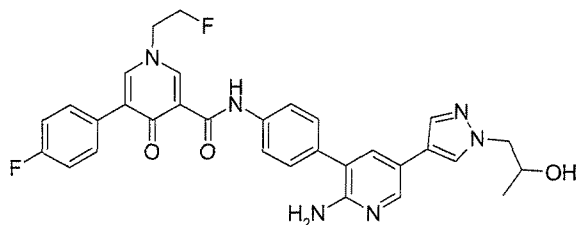
TFA (1 ml) was added dropwise to a solution of the compound obtained in the above Step 1 (120 mg) in dichloromethane (1 ml) under ice cooling, and the mixture was stirred at room temperature. The solvent was distilled off under reduced pressure, and the resulting residue was purified by silica gel column chromatography (NH) [chloroform:methanol = 99:1 → 19:1 (v/v)] to give 60 mg of the title compound as a solid.

¹H-NMR (DMSO-D₆) δ : 1.74-1.82 (2H, m), 1.95-1.98 (2H, m), 2.56-2.64 (2H, m), 3.02-3.05 (2H, m), 4.12-4.17 (1H, m), 4.52-4.59 (2H, m), 4.80-4.91 (2H, m), 5.54 (2H, s), 7.28-7.32 (2H, m), 7.49 (2H, d, J = 8.6 Hz), 7.57 (1H, d, J = 2.3 Hz), 7.72-7.75 (2H, m), 7.80-7.82 (3H, m), 8.15 (1H, s), 8.22 (2H, dd, J = 8.0, 2.3 Hz), 8.77 (1H, d, J = 2.3 Hz).

MS (ESI) m/z : 596 (M+H)⁺.

Example 63

N-(4-{2-Amino-5-[1-(2-hydroxypropyl)-1H-pyrazol-4-yl]pyridin-3-yl}phenyl)-1-(2-fluoroethyl)-5-(4-fluorophenyl)-4-oxo-1,4-dihydropyridine-3-carboxamide (racemate)



43 mg of the title compound was obtained as a solid from the compound obtained in Step 1 of Example 43 (80 mg) and 1-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazol-1-yl]propan-2-ol (50 mg) as raw materials by a reaction similar to that in Step 1 of Example 62.

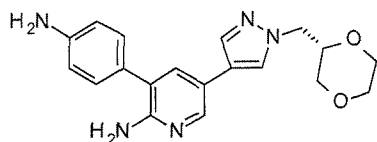
¹H-NMR (CDCl₃) δ : 1.25 (3H, d, J = 6.4 Hz), 3.39 (1H, s), 3.98-4.06 (1H, m), 4.16-4.37 (4H, m), 4.59 (2H, s), 4.74-4.91 (2H, m), 7.14-7.20 (2H, m), 7.44-7.49 (3H, m), 7.54-7.63 (4H, m), 7.74 (1H, s), 7.83-7.89 (2H, m), 8.20 (1H, d, J = 2.3 Hz), 8.65 (1H, d, J = 2.3 Hz).

MS (ESI) m/z : 571 (M+H)⁺.

Example 64

N-[4-(2-Amino-5-{1-[(2S)-1,4-dioxan-2-ylmethyl]}-1H-pyrazol-4-yl)pyridin-3-yl}phenyl]-1-ethyl-5-(4-fluorophenyl)-4-oxo-1,4-dihydropyridine-3-carboxamide

[Step 1] 3-(4-Aminophenyl)-5-{1-[(2S)-1,4-dioxan-2-ylmethyl]-1H-pyrazol-4-yl}pyridin-2-amine

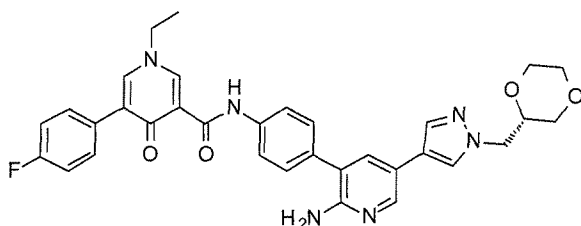


4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (10.0 g) was added to a suspension of cesium carbonate (75.6 g) in 1,4-dioxane (200 ml), followed by stirring. (2R)-1,4-Dioxan-2-ylmethyl methanesulfonate (12.1 g) and tetra-n-butylammonium iodide (0.95 g) were then added, and the mixture was stirred at 100°C for six hours. After cooling the reaction solution to room temperature, 3-(4-aminophenyl)-5-bromopyridin-2-amine (10.9 g) and [1,1'-bis(diphenylphosphino)ferrocene]palladium(II) dichloride-dichloromethane adduct (2.1 g) were added, and the mixture was stirred at 100°C for one hour. The reaction solution was returned to room temperature, ethyl acetate was added, and the insoluble matter was then removed by filtration. The resulting organic layer was washed sequentially with water and brine and then dried over anhydrous sodium sulfate. The solvent was distilled off under reduced pressure, and the residue was purified by silica gel column chromatography [chloroform:methanol = 99:1 → 19:1 (v/v)] to give 10.3 g of the title compound as a solid.

$^1\text{H-NMR}$ (CDCl_3) δ : 3.28-3.33 (1H, m), 3.55-3.83 (7H, m), 3.95-4.01 (1H, m), 4.16 (1H, s), 4.17 (1H, s), 4.56 (2H, br s), 6.77-6.79 (2H, m), 7.26-7.29 (2H, m), 7.43 (1H, d, $J = 2.3$ Hz), 7.63 (1H, s), 7.70-7.70 (1H, m), 8.17 (1H, d, $J = 2.3$ Hz).

MS(ESI) m/z : 352 ($\text{M}+\text{H}$) $^+$.

[Step 2] N-[4-(2-Amino-5-{1-[(2S)-1,4-dioxan-2-ylmethyl]-1H-pyrazol-4-yl}pyridin-3-yl)phenyl]-1-ethyl-5-(4-fluorophenyl)-4-oxo-1,4-dihydropyridine-3-carboxamide



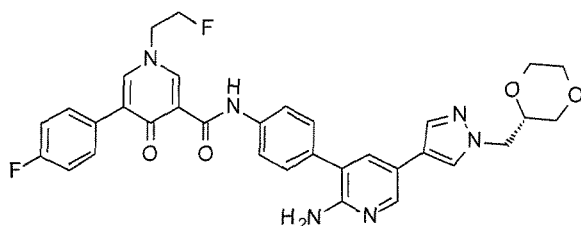
58 mg of the title compound was obtained as a solid from the compound obtained in Step 2 of Example 3 (35 mg) and the compound obtained in the above Step 1 (52 mg) as raw materials by a reaction similar to that in Step 2 of Example 47.

$^1\text{H-NMR}$ (CDCl_3) δ : 1.60 (3H, t, $J = 7.3$ Hz), 3.31 (1H, dd, $J = 11.5, 10.1$ Hz), 3.54-3.63 (1H, m), 3.67-3.85 (4H, m), 3.94-4.02 (1H, m), 4.05-4.20 (4H, m), 4.58 (2H, s), 7.14-7.20 (2H, m), 7.44-7.49 (3H, m), 7.51-7.60 (3H, m), 7.64 (1H, s), 7.71 (1H, s), 7.84-7.90 (2H, m), 8.21 (1H, d, $J = 2.5$ Hz), 8.66 (1H, d, $J = 2.5$ Hz).

MS(ESI) m/z : 595 ($\text{M}+\text{H}$) $^+$.

Example 65

N-[4-(2-Amino-5-{1-[(2S)-1,4-dioxan-2-ylmethyl]-1H-pyrazol-4-yl}pyridin-3-yl)phenyl]-1-(2-fluoroethyl)-5-(4-fluorophenyl)-4-oxo-1,4-dihydropyridine-3-carboxamide



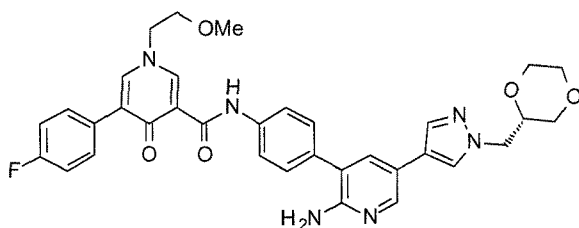
88 mg of the title compound was obtained as a solid from the compound obtained in Step 2 of Example 8 (40 mg) and the compound obtained in Step 1 of Example 64 (55 mg) as raw materials by a reaction similar to that in Step 2 of Example 47.

$^1\text{H-NMR}$ (CDCl_3) δ : 3.27-3.36 (1H, m), 3.54-3.63 (1H, m), 3.67-3.85 (4H, m), 3.95-4.03 (1H, m), 4.15-4.19 (2H, m), 4.25-4.37 (2H, m), 4.58 (2H, br s), 4.74-4.91 (2H, m), 7.14-7.20 (2H, m), 7.44-7.49 (3H, m), 7.54-7.60 (3H, m), 7.65 (1H, s), 7.71 (1H, s), 7.84-7.88 (2H, m), 8.22 (1H, d, $J = 2.5$ Hz), 8.65 (1H, d, $J = 2.5$ Hz).

MS (ESI) m/z : 613 ($\text{M}+\text{H}$) $^+$.

Example 66

N-[4-(2-Amino-5-{1-[(2S)-1,4-dioxan-2-ylmethyl]-1H-pyrazol-4-yl}pyridin-3-yl)phenyl]-5-(4-fluorophenyl)-1-(2-methoxyethyl)-4-oxo-1,4-dihydropyridine-3-carboxamide



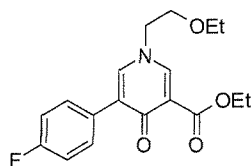
44 mg of the title compound was obtained as a solid from the compound obtained in Step 1 of Example 5 (33 mg) and the compound obtained in Step 1 of Example 64 (44 mg) as raw materials by a reaction similar to that in Step 2 of Example 47.

$^1\text{H-NMR}$ (CDCl_3) δ : 3.27-3.35 (1H, m), 3.40 (3H, s), 3.53-3.62 (1H, m), 3.67-3.85 (6H, m), 3.94-4.03 (1H, m), 4.08-4.15 (4H, m), 4.57 (2H, s), 7.13-7.20 (2H, m), 7.44-7.49 (3H, m), 7.54-7.61 (3H, m), 7.64 (1H, d, $J = 0.92$ Hz), 7.71 (1H, d, $J = 0.92$ Hz), 7.84-7.89 (2H, m), 8.20-8.23 (1H, m), 8.64 (1H, d, $J = 2.8$ Hz).

MS (ESI) m/z : 625 ($\text{M}+\text{H}$) $^+$.

Example 67

N-[4-(2-Amino-5-{1-[(2S)-1,4-dioxan-2-ylmethyl]-1H-pyrazol-4-yl}pyridin-3-yl)phenyl]-1-(2-ethoxyethyl)-5-(4-fluorophenyl)-4-oxo-1,4-dihydropyridine-3-carboxamide
[Step 1] Ethyl 1-(2-ethoxyethyl)-5-(4-fluorophenyl)-4-oxo-1,4-dihydropyridine-3-carboxylate

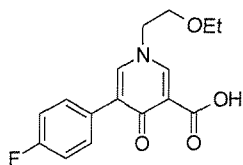


251 mg of the title compound was obtained as a solid from ethyl 5-(4-fluorophenyl)-4-oxo-1,4-dihydropyridine-3-carboxylate (270 mg) and 2-bromoethyl ethyl ether (196 μ l) as raw materials by a reaction similar to that in Step 1 of Example 19.

$^1\text{H-NMR}$ (CDCl_3) δ : 1.19 (3H, t, $J = 6.9$ Hz), 1.38 (3H, t, $J = 7.1$ Hz), 3.51 (2H, q, $J = 6.9$ Hz), 3.73 (2H, t, $J = 4.9$ Hz), 4.01 (2H, t, $J = 4.9$ Hz), 4.37 (2H, q, $J = 7.1$ Hz), 7.03-7.11 (2H, m), 7.46 (1H, d, $J = 2.5$ Hz), 7.54-7.62 (2H, m), 8.19 (1H, d, $J = 2.5$ Hz).

MS (ESI) m/z : 334 ($\text{M}+\text{H}$) $^+$.

[Step 2] 1-(2-Ethoxyethyl)-5-(4-fluorophenyl)-4-oxo-1,4-dihydropyridine-3-carboxylic acid

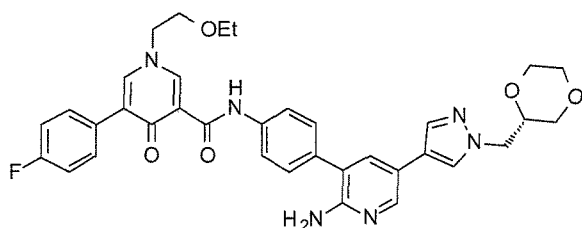


109 mg of the title compound was obtained from the compound obtained in the above Step 1 (250 mg) as a raw material by a reaction similar to that in Step 2 of Example 19.

$^1\text{H-NMR}$ (CDCl_3) δ : 1.19 (3H, t, $J = 7.1$ Hz), 3.53 (2H, q, $J = 7.1$ Hz), 3.78 (2H, t, $J = 4.8$ Hz), 4.16 (2H, t, $J = 4.8$ Hz), 7.12-7.19 (2H, m), 7.55-7.63 (2H, m), 7.73 (1H, d, $J = 2.3$ Hz), 8.54 (1H, d, $J = 2.3$ Hz).

MS (ESI) m/z : 306 ($\text{M}+\text{H}$) $^+$.

[Step 3] N-[4-(2-Amino-5-{1-[(2S)-1,4-dioxan-2-ylmethyl]-1H-pyrazol-4-yl}pyridin-3-yl)phenyl]-1-(2-ethoxyethyl)-5-(4-fluorophenyl)-4-oxo-1,4-dihydropyridine-3-carboxamide



59 mg of the title compound was obtained as a solid from the compound obtained in the above Step 2 (37 mg) and the compound obtained in Step 1 of Example 64 (47 mg) as raw materials by a reaction similar to that in Step 2 of Example 47.

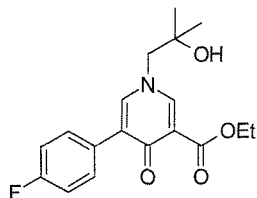
¹H-NMR (CDCl₃) δ: 1.20 (3H, t, J = 6.9 Hz), 3.31 (1H, dd, J = 11.92, 10.1 Hz), 3.50-3.62 (3H, m), 3.67-3.85 (6H, m), 3.94-4.03 (1H, m), 4.10-4.19 (4H, m), 4.59 (2H, s), 7.13-7.20 (2H, m), 7.43-7.50 (3H, m), 7.54-7.61 (2H, m), 7.62-7.66 (2H, m), 7.71 (1H, d, J = 0.92 Hz), 7.83-7.90 (2H, m), 8.21 (1H, d, J = 2.5 Hz), 8.65 (1H, d, J = 2.5 Hz).

MS (ESI) m/z: 639 (M+H)⁺.

Example 68

N-[4-(2-Amino-5-{1-[(2S)-1,4-dioxan-2-ylmethyl]-1H-pyrazol-4-yl}pyridin-3-yl)phenyl]-5-(4-fluorophenyl)-1-(2-hydroxy-2-methylpropyl)-4-oxo-1,4-dihydropyridine-3-carboxamide

[Step 1] Ethyl 5-(4-fluorophenyl)-1-(2-hydroxy-2-methylpropyl)-4-oxo-1,4-dihydropyridine-3-carboxylate

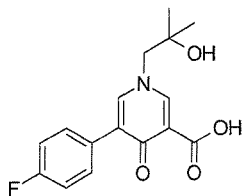


Ethyl 5-(4-fluorophenyl)-4-oxo-1,4-dihydropyridine-3-carboxylate (400 mg) was suspended in DMF (5.0 ml). Cesium carbonate (1200 mg), 1-chloro-2-methyl-2-propanol (345 μ l) and tetra-n-butylammonium iodide (56 mg) were added sequentially, and the mixture was stirred at 70°C for 10 hours. A 1 N aqueous hydrochloric acid solution was added at room temperature, the insoluble matter was removed by filtration through celite, followed by extraction with ethyl acetate. The organic layer was washed with water and brine and then dried over sodium sulfate. The solvent was distilled off under reduced pressure, and the residue was purified by silica gel column chromatography [chloroform:methanol = 300:1 $\rightarrow$ 60:1 (v/v)] to give 57 mg of the title compound as a solid.

$^1\text{H-NMR}$ (CDCl_3) δ : 1.32 (6H, s), 1.37 (3H, t, $J = 7.1\text{Hz}$), 3.43 (1H, s), 3.79 (2H, s), 4.36 (2H, q, $J = 7.1\text{ Hz}$), 7.00-7.09 (2H, m), 7.45-7.49 (1H, m), 7.51-7.60 (2H, m), 8.16 (1H, d, $J = 2.3\text{ Hz}$).

MS (ESI) m/z : 334 ($\text{M}+\text{H}$) $^+$.

[Step 2] 5-(4-Fluorophenyl)-1-(2-hydroxy-2-methylpropyl)-4-oxo-1,4-dihydropyridine-3-carboxylic acid

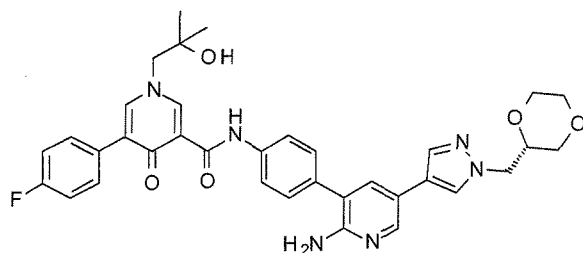


42 mg of the title compound was obtained from the compound obtained in the above Step 1 (77 mg) as a raw material by a reaction similar to that in Step 2 of Example 19.

$^1\text{H-NMR}$ (CDCl_3) δ : 1.35 (6H, s), 3.96 (2H, s), 7.10-7.18 (2H, m), 7.56-7.64 (2H, m), 7.77 (1H, d, $J = 2.3$ Hz), 8.54 (1H, d, $J = 2.3$ Hz).

MS (ESI) m/z : 306 ($\text{M}+\text{H}$) $^+$.

[Step 3] N-[4-(2-Amino-5-{1-[(2S)-1,4-dioxan-2-ylmethyl]-1H-pyrazol-4-yl}pyridin-3-yl)phenyl]-5-(4-fluorophenyl)-1-(2-hydroxy-2-methylpropyl)-4-oxo-1,4-dihydropyridine-3-carboxamide



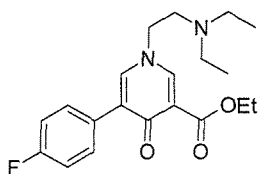
52 mg of the title compound was obtained as a solid from the compound obtained in the above Step 2 (37 mg) and the compound obtained in Step 1 of Example 64 (47 mg) as raw materials by a reaction similar to that in Step 2 of Example 47.

$^1\text{H-NMR}$ (CDCl_3) δ : 1.37 (6H, s), 3.27-3.35 (1H, m), 3.54-3.62 (1H, m), 3.67-3.85 (4H, m), 3.92-4.03 (3H, m), 4.15-4.20 (2H, m), 4.58 (2H, s), 7.11-7.19 (2H, m), 7.43-7.49 (3H, m), 7.54-7.61 (2H, m), 7.64 (1H, s), 7.68 (1H, d, $J = 2.3$ Hz), 7.71 (1H, s), 7.83-7.89 (2H, m), 8.21 (1H, d, $J = 2.3$ Hz), 8.61 (1H, d, $J = 2.3$ Hz).

MS (ESI) m/z : 639 ($\text{M}+\text{H}$) $^+$.

Example 69

N-[4-(2-Amino-5-{1-[(2S)-1,4-dioxan-2-ylmethyl]-1H-pyrazol-4-yl}pyridin-3-yl)phenyl]-1-[2-(diethylamino)ethyl]-5-(4-fluorophenyl)-4-oxo-1,4-dihydropyridine-3-carboxamide
[Step 1] Ethyl 1-[2-(diethylamino)ethyl]-5-(4-fluorophenyl)-4-oxo-1,4-dihydropyridine-3-carboxylate



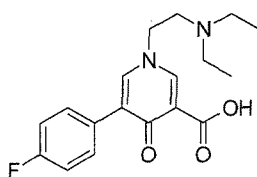
Ethyl 5-(4-fluorophenyl)-4-oxo-1,4-dihydropyridine-3-carboxylate (270 mg) was suspended in DMF (3.0 ml). Cesium carbonate (1180 mg) and 2-bromo-N,N-diethylethylamine hydrobromide (405 mg) were added sequentially, and the mixture was stirred at 50°C for six hours. A 1 N aqueous hydrochloric acid solution was added under ice cooling, and the insoluble matter was then removed by filtration through celite. After

extraction with ethyl acetate, the organic layer was washed with water and brine and then dried over sodium sulfate. The solvent was distilled off under reduced pressure, and the residue was purified by silica gel column chromatography [chloroform:methanol = 300:1 -> 60:1 (v/v)] to give 89 mg of the title compound as an oily substance.

$^1\text{H-NMR}$ (CDCl_3) δ : 0.96 (6H, t, $J = 7.1$ Hz), 1.39 (3H, t, $J = 7.2$ Hz), 2.49-2.57 (4H, m), 2.77 (2H, t, $J = 5.7$ Hz), 3.85 (2H, t, $J = 5.7$ Hz), 4.38 (2H, q, $J = 7.2$ Hz), 7.03-7.11 (2H, m), 7.42 (1H, d, $J = 2.3$ Hz), 7.54-7.61 (2H, m), 8.20 (1H, d, $J = 2.3$ Hz).

MS(ESI) m/z : 361 ($\text{M}+\text{H}$) $^+$.

[Step 2] 1-[2-(Diethylamino)ethyl]-5-(4-fluorophenyl)-4-oxo-1,4-dihydropyridine-3-carboxylic acid



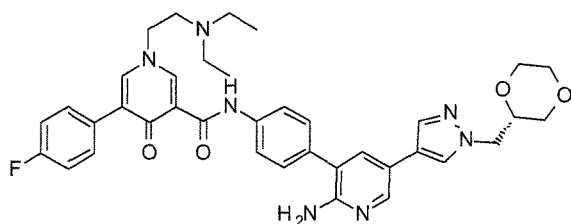
A 1 N aqueous sodium hydroxide solution (0.50 ml) was added to a solution of the compound obtained in the above Step 1 (89 mg) in methanol (0.8 ml) at room temperature, and the mixture was stirred for three hours. The solvent was distilled off under reduced pressure and a 1 N aqueous hydrochloric acid solution was added, followed by extraction with chloroform. The organic

layer was dried over sodium sulfate, and the solvent was distilled off under reduced pressure to give 53 mg of the title compound.

$^1\text{H-NMR}$ (CDCl_3) δ : 0.89-1.11 (6H, m), 2.48-2.75 (4H, m), 2.80-3.03 (2H, m), 3.91-4.28 (2H, m), 7.11-7.19 (2H, m), 7.56-7.64 (2H, m), 7.78 (1H, br s), 8.59 (1H, br s).

MS (ESI) m/z : 333 ($\text{M}+\text{H}$) $^+$.

[Step 3] N-[4-(2-Amino-5-{1-[(2S)-1,4-dioxan-2-ylmethyl]-1H-pyrazol-4-yl}pyridin-3-yl)phenyl]-1-[2-(diethylamino)ethyl]-5-(4-fluorophenyl)-4-oxo-1,4-dihydropyridine-3-carboxamide



46 mg of the title compound was obtained as a solid from the compound obtained in the above Step 2 (39 mg) and the compound obtained in Step 1 of Example 64 (45 mg) as raw materials by a reaction similar to that in Step 2 of Example 47.

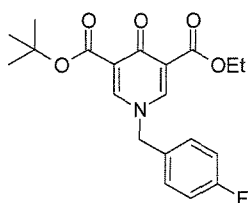
$^1\text{H-NMR}$ (CDCl_3) δ : 0.97 (6H, t, $J = 7.1$ Hz), 2.56 (4H, q, $J = 7.1$ Hz), 2.80-2.86 (2H, m), 3.31 (1H, dd, $J = 11.7$, 9.9 Hz), 3.53-3.63 (1H, m), 3.67-3.85 (4H, m), 3.94-4.02 (3H, m), 4.15-4.19 (2H, m), 4.58 (2H, s), 7.13-7.20 (2H, m), 7.43-7.50 (3H, m), 7.53-7.61 (3H, m), 7.65 (1H, s),

7.71 (1H, s), 7.84-7.90 (2H, m), 8.21 (1H, d, $J = 2.3$ Hz),
8.63 (1H, d, $J = 2.3$ Hz).

MS (ESI) m/z : 666 (M+H)⁺.

Example 70

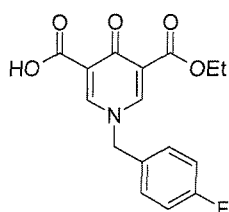
N'-[4-(2-Amino-5-{1-[(2S)-1,4-dioxan-2-ylmethyl]-1H-pyrazol-4-yl}pyridin-3-yl)phenyl]-N,N-diethyl-1-(4-fluorobenzyl)-4-oxo-1,4-dihydropyridine-3,5-dicarboxamide
[Step 1] tert-Butyl ethyl 1-(4-fluorobenzyl)-4-oxo-1,4-dihydropyridine-3,5-dicarboxylate



N,N-Dimethylformamide dimethylacetal (11.0 ml) was added to a solution of tert-butyl ethyl 3-oxopentanedicarboxylate (4.76 g) in n-butyl acetate (60 ml), and the mixture was stirred at 100°C for 90 minutes. The solvent was distilled off under reduced pressure, and the residue was then dissolved in ethanol (40 ml). 4-Fluorobenzylamine (2.59 ml) was added and the mixture was stirred at 70°C for five hours. The solvent was distilled off under reduced pressure, and the residue was purified by silica gel column chromatography [chloroform:methanol = 300:1 → 50:1 (v/v)] to give 5.8 g of the title compound as an oily substance.

$^1\text{H-NMR}$ (CDCl_3) δ : 1.35 (3H, t, $J = 7.1$ Hz), 1.55 (9H, s), 4.35 (2H, q, $J = 7.1$ Hz), 4.95 (2H, s), 7.09-7.17 (2H, m), 7.19-7.25 (2H, m), 7.94 (1H, d, $J = 2.8$ Hz), 8.04 (1H, d, $J = 2.8$ Hz).

[Step 2] 5-(Ethoxycarbonyl)-1-(4-fluorobenzyl)-4-oxo-1,4-dihydropyridine-3-carboxylic acid

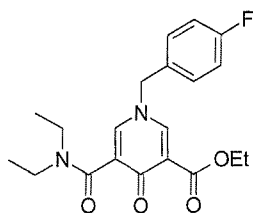


TFA (40 ml) was added to a solution of the compound obtained in the above Step 1 (5.81 g) in dichloromethane (40 ml) under ice cooling. The mixture was gradually warmed to room temperature and stirred for two hours. The solvent was distilled off under reduced pressure, and diethyl ether was added to the residue. The precipitated solid was collected by filtration to give 3.7 g of the title compound.

$^1\text{H-NMR}$ (CDCl_3) δ : 1.40 (3H, t, $J = 7.1$ Hz), 4.41 (2H, q, $J = 7.1$ Hz), 5.13 (2H, s), 7.13-7.20 (2H, m), 7.25-7.30 (2H, m), 8.33 (1H, d, $J = 2.5$ Hz), 8.55 (1H, d, $J = 2.5$ Hz).

MS (ESI) m/z : 320 ($\text{M}+\text{H}$) $^+$.

[Step 3] Ethyl 5-(diethylcarbamoyl)-1-(4-fluorobenzyl)-4-oxo-1,4-dihydropyridine-3-carboxylate

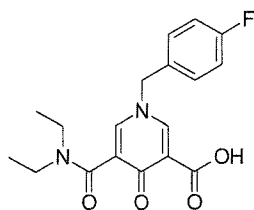


Diethylamine (130 μ l) and 1H-benzotriazol-1-yloxytripyrrolidinophosphonium hexafluorophosphate (528 mg) were added to a solution of the compound obtained in Step 2 (270 mg) in dichloromethane (3.0 ml) at room temperature, and the mixture was stirred for five hours. The solvent was distilled off under reduced pressure, and the residue was purified by silica gel column chromatography [chloroform:methanol = 300:1 $\rightarrow$ 30:1 (v/v)] to give 160 mg of the title compound as an oily substance.

$^1\text{H-NMR}$ (CDCl_3) δ : 1.02 (3H, t, $J = 7.1$ Hz), 1.20 (3H, t, $J = 7.1$ Hz), 1.36 (3H, t, $J = 7.1$ Hz), 3.19-3.26 (2H, m), 3.47 (2H, q, $J = 7.1$ Hz), 4.35 (2H, q, $J = 7.1$ Hz), 4.97 (2H, s), 7.08-7.16 (2H, m), 7.21-7.25 (2H, m), 7.45 (1H, d, $J = 2.8$ Hz), 8.17 (1H, d, $J = 2.8$ Hz).

MS (ESI) m/z : 375 ($\text{M}+\text{H}$) $^+$.

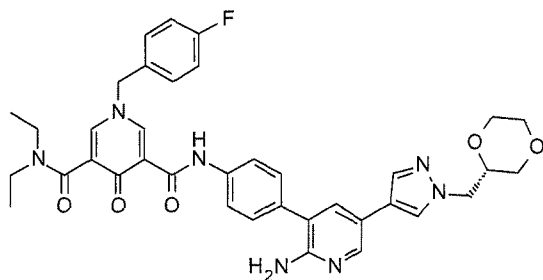
[Step 4] 5-(Diethylcarbamoyl)-1-(4-fluorobenzyl)-4-oxo-1,4-dihydropyridine-3-carboxylic acid



110 mg of the title compound was obtained from the compound obtained in the above Step 3 (160 mg) as a raw material by a reaction similar to that in Step 2 of Example 19.

$^1\text{H-NMR}$ (CDCl_3) δ : 1.10 (3H, t, $J = 7.2$ Hz), 1.24 (3H, t, $J = 7.2$ Hz), 3.22 (2H, q, $J = 7.2$ Hz), 3.53 (2H, q, $J = 7.2$ Hz), 5.09 (2H, s), 7.11-7.19 (2H, m), 7.22-7.29 (2H, m), 7.70 (1H, d, $J = 2.3$ Hz), 8.54 (1H, d, $J = 2.3$ Hz).
MS(ESI) m/z : 347 ($\text{M}+\text{H}$) $^+$.

[Step 5] N'-[4-(2-Amino-5-{1-[(2S)-1,4-dioxan-2-ylmethyl]-1H-pyrazol-4-yl}pyridin-3-yl)phenyl]-N,N-diethyl-1-(4-fluorobenzyl)-4-oxo-1,4-dihydropyridine-3,5-dicarboxamide



30 mg of the title compound was obtained as a solid from the compound obtained in the above Step 4 (40 mg) and the compound obtained in Step 1 of Example 64 (45 mg) as raw materials by a reaction similar to that in Step 2 of Example 47.

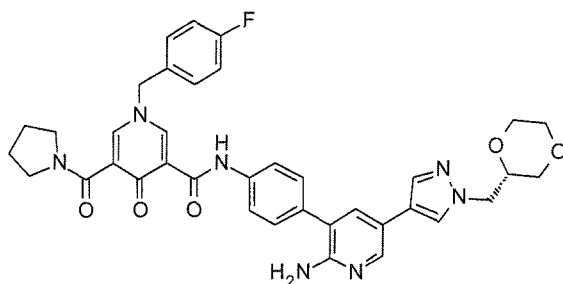
$^1\text{H-NMR}$ (CDCl_3) δ : 1.09 (3H, t, $J = 7.1$ Hz), 1.24-1.30 (3H, m), 3.23-3.35 (3H, m), 3.50-3.62 (3H, m), 3.67-3.86 (4H, m), 3.94-4.02 (1H, m), 4.15-4.19 (2H, m), 4.58 (2H, s),

5.09 (2H, s), 7.11-7.18 (2H, m), 7.27-7.32 (2H, m), 7.44-7.49 (3H, m), 7.57 (1H, d, J = 2.8 Hz), 7.65 (1H, s), 7.71 (1H, s), 7.81-7.86 (2H, m), 8.21 (1H, d, J = 2.3 Hz), 8.66 (1H, d, J = 2.3 Hz), 12.39 (1H, s).

MS(ESI) m/z: 680 (M+H)⁺.

Example 71

N-[4-(2-Amino-5-{1-[(2S)-1,4-dioxan-2-ylmethyl]-1H-pyrazol-4-yl}pyridin-3-yl)phenyl]-1-(4-fluorobenzyl)-4-oxo-5-(pyrrolidin-1-ylcarbonyl)-1,4-dihydropyridine-3-carboxamide



25 mg of the title compound was obtained as a solid from the compound obtained in Step 4 of Example 26 (38 mg) and the compound obtained in Step 1 of Example 64 (42 mg) as raw materials by a reaction similar to that in Step 2 of Example 47.

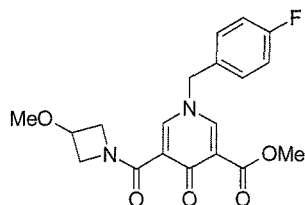
¹H-NMR (CDCl₃) δ: 1.87-2.03 (4H, m), 3.27-3.35 (1H, m), 3.27-3.35 (2H, m), 3.54-3.85 (7H, m), 3.94-4.02 (1H, m), 4.16-4.19 (2H, m), 4.58 (2H, s), 5.09 (2H, s), 7.11-7.18 (2H, m), 7.27-7.32 (2H, m), 7.44-7.49 (3H, m), 7.65 (1H, d, J = 0.9 Hz), 7.70-7.76 (2H, m), 7.81-7.86 (2H, m),

8.21 (1H, d, J = 2.5 Hz), 8.65 (1H, d, J = 2.5 Hz), 12.46 (1H, s).

MS (ESI) m/z: 678 (M+H)⁺.

Example 72

N-[4-(2-Amino-5-{1-[(2S)-1,4-dioxan-2-ylmethyl]-1H-pyrazol-4-yl}pyridin-3-yl)phenyl]-1-(4-fluorobenzyl)-5-[(3-methoxyazetidin-1-yl)carbonyl]-4-oxo-1,4-dihydropyridine-3-carboxamide
[Step 1] Methyl 1-(4-fluorobenzyl)-5-[(3-methoxyazetidin-1-yl)carbonyl]-4-oxo-1,4-dihydropyridine-3-carboxylate



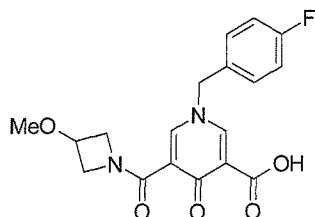
3-Methoxyazetidine hydrochloride (67 mg), 1H-benzotriazol-1-yloxytripyrrolidinophosphonium hexafluorophosphate (206 mg) and triethylamine (100 μ l) were added to a solution of the compound obtained in Step 2 of Example 26 (110 mg) in dichloromethane/DMF (2.0/0.5 ml) at room temperature, and the mixture was stirred for seven hours. After adding a small amount of water, the mixture was diluted with ethyl acetate, followed by drying over sodium sulfate. The solvent was distilled off under reduced pressure, and the residue was purified by silica gel column chromatography [chloroform:methanol

= 300:1 -> 20:1 (v/v)] to give 63 mg of the title compound as an oily substance.

$^1\text{H-NMR}$ (CDCl_3) δ : 3.27 (3H, s), 3.88 (3H, s), 3.96-4.07 (2H, m), 4.17-4.32 (2H, m), 4.48-4.55 (1H, m), 4.97 (2H, s), 7.10-7.16 (2H, m), 7.22-7.26 (2H, m), 7.88 (1H, d, J = 2.5 Hz), 8.16 (1H, d, J = 2.5 Hz).

MS (ESI) m/z : 375 ($\text{M}+\text{H}$) $^+$.

[Step 2] 1-(4-Fluorobenzyl)-5-[(3-methoxyazetidin-1-yl)carbonyl]-4-oxo-1,4-dihydropyridine-3-carboxylic acid



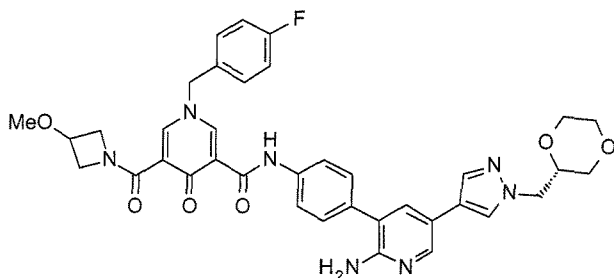
44 mg of the title compound was obtained from the compound obtained in the above Step 1 (63 mg) as a raw material by a reaction similar to that in Step 2 of Example 19.

$^1\text{H-NMR}$ (CDCl_3) δ : 3.30 (3H, s), 4.00-4.06 (2H, m), 4.20-4.35 (2H, m), 4.43-4.49 (1H, m), 5.10 (2H, s), 7.13-7.18 (2H, m), 7.27-7.32 (2H, m), 8.10 (1H, d, J = 2.3 Hz), 8.54 (1H, d, J = 2.3 Hz).

MS (ESI) m/z : 361 ($\text{M}+\text{H}$) $^+$.

[Step 3] N-[4-(2-Amino-5-{1-[(2S)-1,4-dioxan-2-ylmethyl]-1H-pyrazol-4-yl}pyridin-3-yl)phenyl]-1-(4-fluorobenzyl)-

5-[(3-methoxyazetidin-1-yl)carbonyl]-4-oxo-1,4-dihydropyridine-3-carboxamide



42 mg of the title compound was obtained as a solid from the compound obtained in the above Step 2 (40 mg) and the compound obtained in Step 1 of Example 64 (43 mg) as raw materials by a reaction similar to that in Step 2 of Example 47.

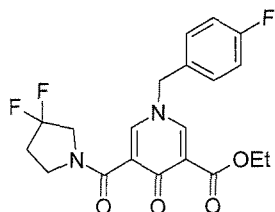
$^1\text{H-NMR}$ (CDCl_3) δ : 3.28-3.34 (4H, m), 3.54-3.84 (5H, m), 3.95-4.09 (3H, m), 4.16-4.20 (2H, m), 4.23-4.63 (5H, m), 5.10 (2H, s), 7.11-7.19 (2H, m), 7.27-7.33 (2H, m), 7.46-7.50 (3H, m), 7.65 (1H, s), 7.72 (1H, s), 7.81-7.86 (2H, m), 7.97 (1H, d, $J = 2.3$ Hz), 8.22 (1H, d, $J = 2.3$ Hz), 8.65 (1H, d, $J = 2.3$ Hz), 12.46 (1H, s).

MS(ESI) m/z : 694 ($\text{M}+\text{H}$) $^+$.

Example 73

N-[4-(2-Amino-5-{1-[(2S)-1,4-dioxan-2-ylmethyl]-1H-pyrazol-4-yl}pyridin-3-yl)phenyl]-5-[(3,3-difluoropyrrolidin-1-yl)carbonyl]-1-(4-fluorobenzyl)-4-oxo-1,4-dihydropyridine-3-carboxamide

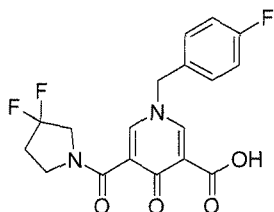
[Step 1] Ethyl 5-[(3,3-difluoropyrrolidin-1-yl)carbonyl]-1-(4-fluorobenzyl)-4-oxo-1,4-dihydropyridine-3-carboxylate



148 mg of the title compound was obtained as an isomeric mixture from the compound obtained in Step 2 of Example 70 (220 mg) and 3,3-difluoropyrrolidine hydrochloride (148 mg) as raw materials by a reaction similar to that in Step 1 of Example 72.

MS (ESI) m/z : 409 (M+H)⁺.

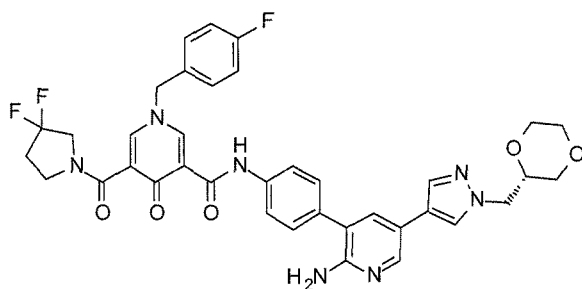
[Step 2] 5-[(3,3-Difluoropyrrolidin-1-yl)carbonyl]-1-(4-fluorobenzyl)-4-oxo-1,4-dihydropyridine-3-carboxylic acid



118 mg of the title compound was obtained as an isomeric mixture from the compound obtained in the above Step 1 (148 mg) as a raw material by a reaction similar to that in Step 2 of Example 19.

MS (ESI) m/z : 381 (M+H)⁺.

[Step 3] N-[4-(2-Amino-5-{1-[(2S)-1,4-dioxan-2-ylmethyl]-1H-pyrazol-4-yl}pyridin-3-yl)phenyl]-5-[(3,3-difluoropyrrolidin-1-yl)carbonyl]-1-(4-fluorobenzyl)-4-oxo-1,4-dihydropyridine-3-carboxamide

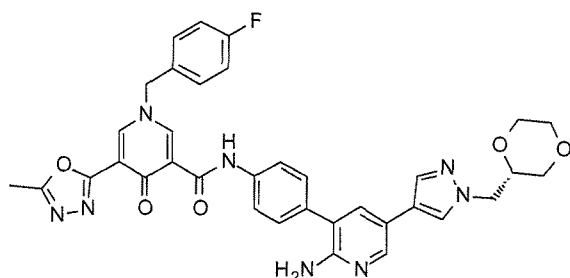


52 mg of the title compound was obtained as a solid from the compound obtained in the above Step 2 (40 mg) and the compound obtained in Step 1 of Example 64 (41 mg) as raw materials by a reaction similar to that in Step 2 of Example 47.

¹H-NMR (DMSO-D₆) δ: 3.21-3.93 (13H, m), 4.10-4.15 (2H, m), 5.39 (2H, s), 5.56 (2H, s), 7.25-7.33 (2H, m), 7.47-7.58 (5H, m), 7.75-7.85 (3H, m), 8.07 (1H, s), 8.20 (1H, d, J = 2.3 Hz), 8.35 (1H, d, J = 2.3 Hz), 8.85-8.91 (1H, m).
MS (ESI) m/z: 714 (M+H)⁺.

Example 74

N-[4-(2-Amino-5-{1-[(2S)-1,4-dioxan-2-ylmethyl]-1H-pyrazol-4-yl}pyridin-3-yl)phenyl]-1-(4-fluorobenzyl)-5-(5-methyl-1,3,4-oxadiazol-2-yl)-4-oxo-1,4-dihydropyridine-3-carboxamide



53 mg of the title compound was obtained as a solid from the compound obtained in Step 3 of Example 28 (39 mg) and the compound obtained in Step 1 of Example 64 (46 mg) as raw materials by a reaction similar to that in Step 2 of Example 47.

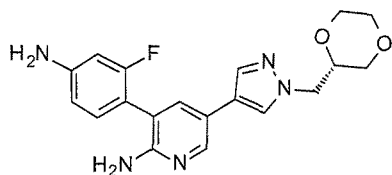
$^1\text{H-NMR}$ (CDCl_3) δ : 2.68 (3H, s), 3.31 (1H, dd, $J = 11.5$, 10.1 Hz), 3.54-3.63 (1H, m), 3.67-3.85 (4H, m), 3.94-4.03 (1H, m), 4.15-4.20 (2H, m), 4.58 (2H, s), 5.18 (2H, s), 7.13-7.20 (2H, m), 7.29-7.36 (2H, m), 7.46-7.51 (3H, m), 7.65 (1H, s), 7.71 (1H, s), 7.82-7.88 (2H, m), 8.22 (1H, d, $J = 2.3$ Hz), 8.38 (1H, d, $J = 2.8$ Hz), 8.74 (1H, d, $J = 2.8$ Hz), 12.32 (1H, s).

MS (ESI) m/z : 663 ($\text{M}+\text{H}$) $^+$.

Example 75

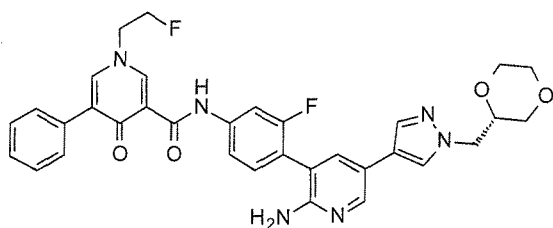
N-[4-(2-Amino-5-{1-[(2S)-1,4-dioxan-2-ylmethyl]-1H-pyrazol-4-yl}pyridin-3-yl)-3-fluorophenyl]-1-(2-fluoroethyl)-4-oxo-5-phenyl-1,4-dihydropyridine-3-carboxamide

[Step 1] 3-(4-Amino-2-fluorophenyl)-5-{1-[(2S)-1,4-dioxan-2-ylmethyl]-1H-pyrazol-4-yl}pyridin-2-amine



Water (1.5 ml), cesium carbonate (1730 mg) and tetrakis(triphenylphosphine)palladium (204 mg) were added to a solution of the compound obtained in Step 1 of Example 29 (500 mg) and the compound obtained in Reference Example 8 (782 mg) in 1,4-dioxane (15 ml). The mixture was stirred under microwave irradiation at 100°C for one hour. After leaving to cool, the reaction solution was diluted with chloroform. The organic layer was washed with water and brine and dried over sodium sulfate. The solvent was distilled off under reduced pressure, and the residue was purified by silica gel column chromatography [chloroform:methanol = 19:1 (v/v)] to give 450 mg of the title compound as a solid. MS (ESI) m/z: 370 (M+H)⁺.

[Step 2] N-[4-(2-Amino-5-{1-[(2S)-1,4-dioxan-2-ylmethyl]-1H-pyrazol-4-yl}pyridin-3-yl)-3-fluorophenyl]-1-(2-fluoroethyl)-4-oxo-5-phenyl-1,4-dihydropyridine-3-carboxamide



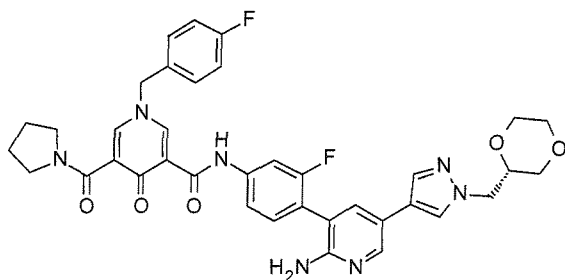
57 mg of the title compound was obtained as a solid from the compound obtained in Step 2 of Example 19 (34 mg) and the compound obtained in the above Step 1 (53 mg) as raw materials by a reaction similar to that in Step 2 of Example 47.

$^1\text{H-NMR}$ (CDCl_3) δ : 3.26-3.35 (1H, m), 3.53-3.63 (1H, m), 3.67-3.85 (4H, m), 3.94-4.02 (1H, m), 4.15-4.19 (2H, m), 4.25-4.37 (2H, m), 4.49 (2H, s), 4.74-4.91 (2H, m), 7.31-7.37 (1H, m), 7.40-7.52 (5H, m), 7.55-7.61 (3H, m), 7.64 (1H, s), 7.71 (1H, s), 7.88-7.95 (1H, m), 8.26 (1H, d, $J = 2.5$ Hz), 8.64 (1H, d, $J = 2.5$ Hz).

MS(ESI) m/z : 613 ($M+H$) $^+$.

Example 76

N-[4-(2-Amino-5-{1-[(2S)-1,4-dioxan-2-ylmethyl]-1H-pyrazol-4-yl}pyridin-3-yl)-3-fluorophenyl]-1-(4-fluorobenzyl)-4-oxo-5-(pyrrolidin-1-ylcarbonyl)-1,4-dihydropyridine-3-carboxamide



28 mg of the title compound was obtained as a solid from the compound obtained in Step 4 of Example 26 (38 mg) and the compound obtained in Step 1 of Example 75 (45

mg) as raw materials by a reaction similar to that in Step 2 of Example 47.

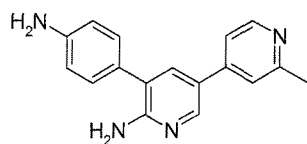
$^1\text{H-NMR}$ (CDCl_3) δ : 1.87-2.03 (4H, m), 3.31 (1H, dd, $J = 11.7, 9.9$ Hz), 3.42-3.49 (2H, m), 3.53-3.85 (7H, m), 3.94-4.02 (1H, m), 4.15-4.19 (2H, m), 4.49 (2H, s), 5.10 (2H, s), 7.11-7.19 (2H, m), 7.27-7.38 (3H, m), 7.41-7.46 (1H, m), 7.49 (1H, d, $J = 2.3$ Hz), 7.64 (1H, s), 7.71 (1H, s), 7.75 (1H, d, $J = 2.3$ Hz), 7.84-7.91 (1H, m), 8.26 (1H, d, $J = 2.5$ Hz), 8.64 (1H, d, $J = 2.5$ Hz).

MS (ESI) m/z : 696 ($\text{M}+\text{H}$) $^+$.

Example 77

N-[4-(6-Amino-2'-methyl-3,4'-bipyridin-5-yl)phenyl]-5-(4-fluorophenyl)-4-oxo-1-(2,2,2-trifluoroethyl)-1,4-dihydropyridine-3-carboxamide

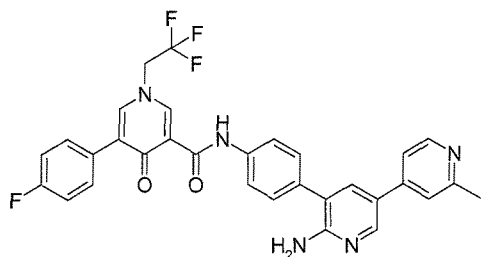
[Step 1] 5-(4-Aminophenyl)-2'-methyl-3,4'-bipyridin-6-amine



871 mg of the title compound was obtained as a solid from the compound obtained in Step 1 of Example 1 (2.0 g) and 2-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (1.66 g) as raw materials by a reaction similar to that in Step 1 of Example 47.

MS (ESI) m/z : 277 ($\text{M}+\text{H}$) $^+$.

[Step 2] N-[4-(6-Amino-2'-methyl-3,4'-bipyridin-5-yl)phenyl]-5-(4-fluorophenyl)-4-oxo-1-(2,2,2-trifluoroethyl)-1,4-dihydropyridine-3-carboxamide



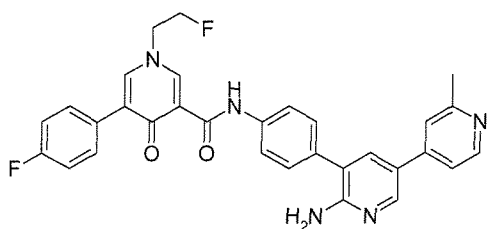
6.5 mg of the title compound was obtained as a solid from the compound obtained in Step 2 of Example 9 (63 mg) and the compound obtained in the above Step 1 (50 mg) as raw materials by a reaction similar to that in Step 3 of Example 1.

$^1\text{H-NMR}$ (CDCl_3) δ : 2.58 (3H, s), 4.50 (2H, q, $J = 7.9$ Hz), 4.77 (2H, s), 7.14-7.20 (2H, m), 7.31 (1H, s), 7.45-7.55 (6H, m), 7.63 (1H, d, $J = 2.3$ Hz), 7.85 (2H, d, $J = 8.7$ Hz), 8.36 (1H, d, $J = 2.3$ Hz), 8.48 (1H, d, $J = 5.0$ Hz), 8.62 (1H, d, $J = 2.8$ Hz), 12.46 (1H, s).

MS (ESI) m/z : 574 ($\text{M}+\text{H}$) $^+$.

Example 78

N-[4-(6-Amino-2'-methyl-3,4'-bipyridin-5-yl)phenyl]-1-(2-fluoroethyl)-5-(4-fluorophenyl)-4-oxo-1,4-dihydropyridine-3-carboxamide



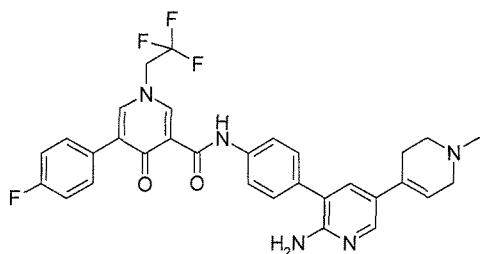
Water (0.1 ml), potassium carbonate (48 mg) and tetrakis(triphenylphosphine)palladium (13 mg) were added to a solution of the compound obtained in Step 1 of Example 43 (61 mg) and 2-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (28 mg) in 1,4-dioxane (1.2 ml), and the mixture was stirred at 100°C for six hours. After leaving to cool, the reaction solution was diluted with chloroform. The organic layer was washed with water and then dried over sodium sulfate. The solvent was distilled off under reduced pressure, and the residue was purified by silica gel column chromatography [chloroform:methanol = 300:1 → 10:1 (v/v)] to give 24 mg of the title compound as a solid.

¹H-NMR (CDCl₃) δ: 2.61 (3H, s), 4.24-4.37 (2H, m), 4.74-4.92 (4H, m), 7.13-7.21 (2H, m), 7.27-7.36 (3H, m), 7.45-7.67 (5H, m), 7.84-7.91 (2H, m), 8.38 (1H, d, J = 2.3 Hz), 8.51 (1H, d, J = 5.0 Hz), 8.65 (1H, d, J = 2.3 Hz).

MS (ESI) m/z: 538 (M+H)⁺.

Example 79

N-[4-(6-Amino-1'-methyl-1',2',3',6'-tetrahydro-3,4'-bipyridin-5-yl)phenyl]-5-(4-fluorophenyl)-4-oxo-1-(2,2,2-trifluoroethyl)-1,4-dihydropyridine-3-carboxamide

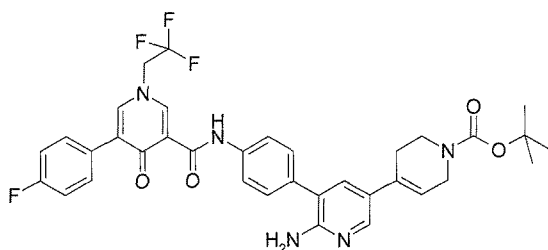


40 mg of the title compound was obtained as a solid from the compound obtained in Step 1 of Example 31 (100 mg) and 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2,3,6-tetrahydropyridine (48 mg) as raw materials by a reaction similar to that in Step 1 of Example 62.

$^1\text{H-NMR}$ ($\text{DMSO-}D_6$) δ : 2.26 (3H, s), 2.44-2.46 (2H, m), 2.52-2.54 (2H, m), 2.96-2.98 (2H, m), 5.25-5.30 (2H, m), 5.63 (2H, br s), 6.03 (1H, br s), 7.30-7.34 (2H, m), 7.39 (1H, d, $J = 2.3$ Hz), 7.47 (2H, d, $J = 8.6$ Hz), 7.66-7.69 (2H, m), 7.80 (2H, d, $J = 8.6$ Hz), 8.03 (1H, d, $J = 2.3$ Hz), 8.28 (1H, d, $J = 2.3$ Hz), 8.87 (1H, d, $J = 2.3$ Hz).
 MS(ESI) m/z : 578 ($\text{M}+\text{H}$) $^+$.

Example 80

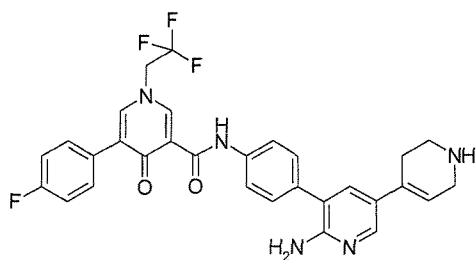
N-[4-(1'-Acetyl-6-amino-1',2',3',6'-tetrahydro-3,4'-bipyridin-5-yl)phenyl]-5-(4-fluorophenyl)-4-oxo-1-(2,2,2-trifluoroethyl)-1,4-dihydropyridine-3-carboxamide
 [Step 1] tert-Butyl 6-amino-5-[4-({[5-(4-fluorophenyl)-4-oxo-1-(2,2,2-trifluoroethyl)-1,4-dihydropyridin-3-yl]carbonyl}amino)phenyl]-3',6'-dihydro-3,4'-bipyridine-1' (2'H)-carboxylate



300 mg of the title compound was obtained as a solid from the compound obtained in Step 1 of Example 31 (500 mg) and tert-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate (302 mg) as raw materials by a reaction similar to that in Step 1 of Example 62.

MS (ESI) m/z : 664 (M+H)⁺.

[Step 2] N-[4-(6-Amino-1',2',3',6'-tetrahydro-3,4'-bipyridin-5-yl)phenyl]-5-(4-fluorophenyl)-4-oxo-1-(2,2,2-trifluoroethyl)-1,4-dihydropyridine-3-carboxamide

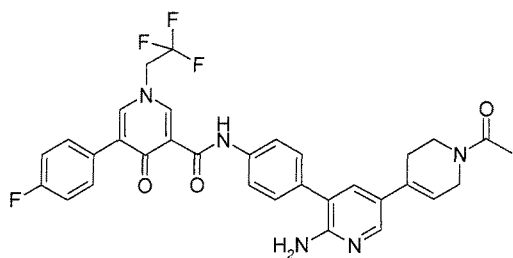


A 4 N solution of hydrochloric acid in dioxane (1.1 ml) was added dropwise to a solution of the compound obtained in the above Step 1 (300 mg) in dichloromethane (5 ml) under ice cooling, and the mixture was then stirred at room temperature for five days. The solvent

was distilled off under reduced pressure to give 300 mg of a hydrochloride of the title compound as a solid.

MS (ESI) m/z : 564 (M+H)⁺.

[Step 3] N-[4-(1'-Acetyl-6-amino-1',2',3',6'-tetrahydro-3,4'-bipyridin-5-yl)phenyl]-5-(4-fluorophenyl)-4-oxo-1-(2,2,2-trifluoroethyl)-1,4-dihydropyridine-3-carboxamide



Triethylamine (32 μ l) and acetic anhydride (12 μ l) were added dropwise to a solution of the compound obtained in the above Step 2 (75 mg) in DMF (3 ml) under ice cooling, and the mixture was stirred at room temperature. The solvent was distilled off under reduced pressure, and the resulting residue was purified by reverse phase HPLC [acetonitrile:water:formic acid] and then purified by silica gel column chromatography (NH) [chloroform:methanol = 99:1 $\rightarrow$ 9:1 (v/v)]. Further, the resulting crude purified product was crystallized from ethyl acetate to give 35 mg of the title compound as a solid.

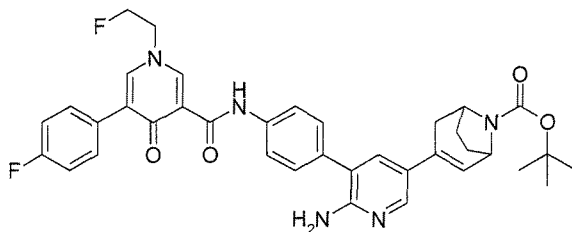
¹H-NMR (DMSO-D₆) δ : 2.02-2.06 (3H, m), 3.33-3.37 (2H, m), 3.59-3.65 (2H, m), 4.04-4.11 (2H, m), 5.25-5.30 (2H, m), 5.68 (2H, s), 6.06 (1H, s), 7.30-7.34 (2H, m), 7.42 (1H,

dd, $J = 8.0, 2.3$ Hz), 7.48 (2H, d, $J = 8.6$ Hz), 7.66-7.69 (2H, m), 7.80 (2H, d, $J = 8.6$ Hz), 8.05 (1H, dd, $J = 8.0, 2.3$ Hz), 8.28 (1H, d, $J = 2.3$ Hz), 8.87 (1H, d, $J = 2.3$ Hz).

MS(ESI) m/z : 606 (M+H)⁺.

Example 81

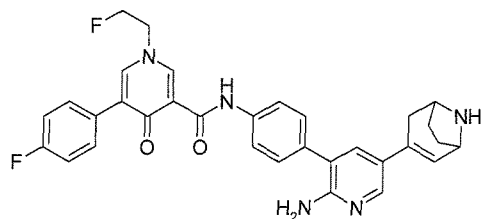
N-{4-[5-(8-Acetyl-8-azabicyclo[3.2.1]oct-2-en-3-yl)-2-aminopyridin-3-yl]phenyl}-1-(2-fluoroethyl)-5-(4-fluorophenyl)-4-oxo-1,4-dihydropyridine-3-carboxamide
[Step 1] tert-Butyl 3-{6-amino-5-[4-({[1-(2-fluoroethyl)-5-(4-fluorophenyl)-4-oxo-1,4-dihydropyridin-3-yl]carbonyl}amino)phenyl]pyridin-3-yl}-8-azabicyclo[3.2.1]oct-2-ene-8-carboxylate



152 mg of the title compound was obtained as a solid using the compound obtained in Step 1 of Example 43 (150 mg) and tert-butyl 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-8-azabicyclo[3.2.1]oct-2-ene-8-carboxylate (105 mg) by a reaction similar to that in Step 1 of Example 62.

MS(ESI) m/z : 654 (M+H)⁺.

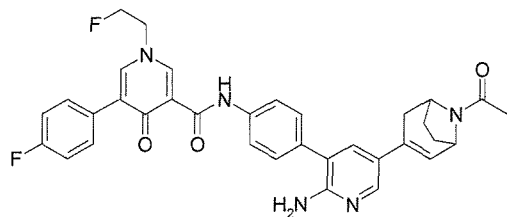
[Step 2] N-{4-[2-Amino-5-(8-azabicyclo[3.2.1]oct-2-en-3-yl)pyridin-3-yl]phenyl}-1-(2-fluoroethyl)-5-(4-fluorophenyl)-4-oxo-1,4-dihydropyridine-3-carboxamide



77 mg of the title compound was obtained as a solid from the compound obtained in the above Step 1 (152 mg) as a raw material by a reaction similar to that in Step 2 of Example 62.

MS (ESI) m/z : 554 (M+H)⁺.

[Step 3] N-{4-[5-(8-Acetyl-8-azabicyclo[3.2.1]oct-2-en-3-yl)-2-aminopyridin-3-yl]phenyl}-1-(2-fluoroethyl)-5-(4-fluorophenyl)-4-oxo-1,4-dihydropyridine-3-carboxamide



65 mg of the title compound was obtained as a solid from the compound obtained in the above Step 2 (77 mg) as a raw material by a reaction similar to that in Step 3 of Example 80.

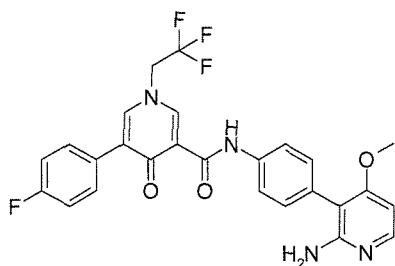
¹H-NMR (DMSO-D₆) δ : 1.62-1.88 (2H, m), 1.99-2.00 (3H, m), 2.19-2.40 (2H, m), 2.84-2.95 (1H, m), 3.30-3.32 (1H, m), 4.42-4.73 (4H, m), 4.78-4.93 (2H, m), 5.68-5.69 (2H, m),

6.38-6.43 (1H, m), 7.28-7.33 (2H, m), 7.37-7.38 (1H, m), 7.45 (2H, d, $J = 8.6$ Hz), 7.72-7.76 (2H, m), 7.80 (2H, d, $J = 8.6$ Hz), 8.00 (1H, t, $J = 2.3$ Hz), 8.23 (1H, d, $J = 2.3$ Hz), 8.77 (1H, d, $J = 2.3$ Hz).

MS(ESI) m/z : 596(M+H)⁺.

Example 82

N-[4-(2-Amino-4-methoxypyridin-3-yl)phenyl]-5-(4-fluorophenyl)-4-oxo-1-(2,2,2-trifluoroethyl)-1,4-dihydropyridine-3-carboxamide



COMU (391 mg) and DIPEA (159 μ l) were added to a solution of the compound obtained in Step 2 of Example 9 (216 mg) in DMF (2 ml) at room temperature. The reaction mixture was stirred at room temperature for 15 minutes. 4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (100 mg) was added to the reaction mixture at room temperature. The reaction mixture was stirred at 50°C overnight. The reaction mixture was then stirred at 80°C for two days. Water was added to the reaction mixture, followed by extraction with ethyl acetate. The organic layer was dried over sodium sulfate and filtered, and the filtrate was then concentrated under reduced pressure.

The residue was purified by silica gel column chromatography [hexane:ethyl acetate = 1:1 -> 1:3 -> 0:100 (v/v)], and the eluate was concentrated under reduced pressure. 3-Iodo-4-methoxypyridine-2-amine (47 mg), tetrakis(triphenylphosphine)palladium (14 mg) and potassium carbonate (52 mg) were added to a solution of part of the resulting oily substance (65 mg) in dioxane (3 ml) and water (0.3 ml) at room temperature. The reaction mixture was stirred at 100°C overnight, returned to room temperature and diluted by adding ethyl acetate. After purification by silica gel column chromatography (NH) [developed with ethyl acetate], the eluate was concentrated under reduced pressure. The residue was purified by reverse phase HPLC [acetonitrile:water:formic acid] to give 5.6 mg of the title compound as a solid.

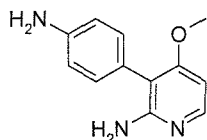
¹H-NMR (CDCl₃) δ: 3.76 (3H, s), 4.50 (2H, q, J = 7.9 Hz), 4.69 (2H, s), 6.40 (1H, d, J = 6.0 Hz), 7.10-7.34 (4H, m), 7.49-7.56 (3H, m), 7.82-7.84 (2H, m), 7.96 (1H, d, J = 6.0 Hz), 8.63 (1H, d, J = 2.3 Hz), 12.40 (1H, s).

MS (ESI) m/z: 513 (M+H)⁺.

Example 83

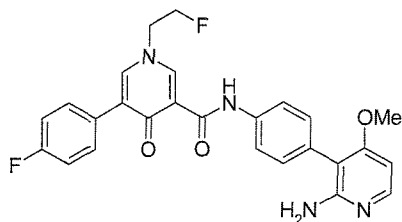
N-[4-(2-Amino-4-methoxypyridin-3-yl)phenyl]-1-(2-fluoroethyl)-5-(4-fluorophenyl)-4-oxo-1,4-dihydropyridine-3-carboxamide

[Step 1] 3-(4-Aminophenyl)-4-methoxypyridin-2-amine



3-Iodo-4-methoxypyridin-2-amine (350 mg), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (322 mg), [1,1'-bis(diphenylphosphino)ferrocene]palladium(II) dichloride-dichloromethane adduct (81 mg) and cesium fluoride (580 mg) were suspended in methanol (5.0 ml), and the suspension was heated under reflux at 80°C for 19 hours. After leaving to cool, a saturated aqueous ammonium chloride solution was added, and the organic layer was extracted with ethyl acetate and dried over sodium sulfate. The solvent was distilled off under reduced pressure, and the residue was purified by silica gel column chromatography [ethyl acetate:dichloromethane:methanol = 5:5:1 (v/v)] to give 245 mg of the title compound as a solid. MS (ESI) m/z : 216 (M+H)⁺.

[Step 2] N-[4-(2-Amino-4-methoxypyridin-3-yl)phenyl]-1-(2-fluoroethyl)-5-(4-fluorophenyl)-4-oxo-1,4-dihydropyridine-3-carboxamide



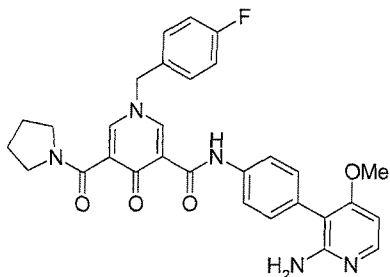
69 mg of the title compound was obtained as a solid from the compound obtained in Step 2 of Example 8 (40 mg) and the compound obtained in the above Step 1 (34 mg) as raw materials by a reaction similar to that in Step 2 of Example 47.

$^1\text{H-NMR}$ (CDCl_3) δ : 3.75 (3H, s), 4.24-4.38 (4H, m), 4.73-4.91 (2H, m), 6.39 (1H, d, $J = 6.0$ Hz), 7.14-7.20 (2H, m), 7.29-7.35 (2H, m), 7.53-7.60 (3H, m), 7.81-7.87 (2H, m), 7.99 (1H, d, $J = 6.0$ Hz), 8.64 (1H, d, $J = 2.8$ Hz).

MS(ESI) m/z : 477 ($\text{M}+\text{H}$) $^+$.

Example 84

N-[4-(2-Amino-4-methoxypyridin-3-yl)phenyl]-1-(4-fluorobenzyl)-4-oxo-5-(pyrrolidin-1-ylcarbonyl)-1,4-dihydropyridine-3-carboxamide



36 mg of the title compound was obtained as a solid from the compound obtained in Step 4 of Example 26 (38 mg) and the compound obtained in Step 1 of Example 83 (26 mg) as raw materials by a reaction similar to that in Step 2 of Example 47.

$^1\text{H-NMR}$ (CDCl_3) δ : 1.87-2.03 (4H, m), 3.41-3.67 (4H, m), 3.75 (3H, s), 4.33 (2H, s), 5.08 (2H, s), 6.39 (1H, d, J

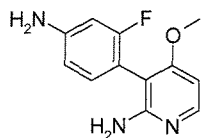
= 6.0 Hz), 7.11-7.18 (2H, m), 7.27-7.35 (4H, m), 7.74 (1H, d, J = 2.8 Hz), 7.79-7.84 (2H, m), 8.00 (1H, d, J = 6.0 Hz), 8.65 (1H, d, J = 2.8 Hz), 12.40 (1H, s).

MS (ESI) m/z: 542 (M+H)⁺.

Example 85

N-[4-(2-Amino-4-methoxypyridin-3-yl)-3-fluorophenyl]-5-(4-fluorophenyl)-4-oxo-1-(2,2,2-trifluoroethyl)-1,4-dihydropyridine-3-carboxamide

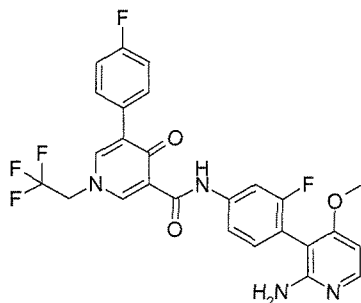
[Step 1] 3-(4-Amino-2-fluorophenyl)-4-methoxypyridin-2-amine



146 mg of the title compound was obtained as a solid from 3-iodo-4-methoxypyridin-2-ylamine (250 mg) and 4-amino-2-fluorophenylboronic acid pinacol ester (261 mg) as raw materials by a reaction similar to that in Step 1 of Example 83.

MS (ESI) m/z: 234 (M+H)⁺.

[Step 2] N-[4-(2-Amino-4-methoxypyridin-3-yl)-3-fluorophenyl]-5-(4-fluorophenyl)-4-oxo-1-(2,2,2-trifluoroethyl)-1,4-dihydropyridine-3-carboxamide



66 mg of the title compound was obtained as a solid from the compound obtained in Step 2 of Example 9 (75 mg) and the compound obtained in the above Step 1 (55 mg) as raw materials by a reaction similar to that in Step 3 of Example 1.

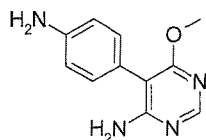
$^1\text{H-NMR}$ (CDCl_3) δ : 3.77 (3H, s), 4.31 (2H, s), 4.51 (2H, q, $J = 7.9$ Hz), 6.37-6.41 (1H, m), 7.15-7.35 (3H, m), 7.39-7.46 (1H, m), 7.49-7.59 (3H, m), 7.82-7.88 (1H, m), 8.02-8.05 (1H, m), 8.60-8.64 (1H, m), 12.5 (1H, s).

MS (ESI) m/z : 531 ($\text{M}+\text{H}$) $^+$.

Example 86

N-[4-(4-Amino-6-methoxypyrimidin-5-yl)phenyl]-5-(4-fluorophenyl)-4-oxo-1-(2,2,2-trifluoroethyl)-1,4-dihydropyridine-3-carboxamide

[Step 1] 5-(4-Aminophenyl)-6-methoxypyrimidin-4-amine

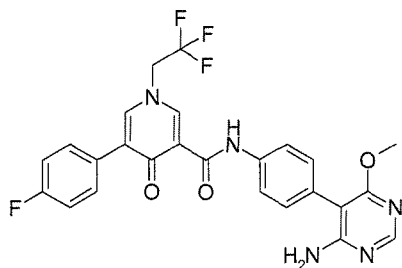


121 mg of the title compound was obtained as a solid from 5-bromo-6-methoxypyrimidin-4-amine (242 mg) and 4-

(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (200 mg) as raw materials by a reaction similar to that in Step 2 of Example 1.

MS (ESI) m/z : 217 (M+H)⁺.

[Step 2] N-[4-(4-Amino-6-methoxypyrimidin-5-yl)phenyl]-5-(4-fluorophenyl)-4-oxo-1-(2,2,2-trifluoroethyl)-1,4-dihydropyridine-3-carboxamide



15 mg of the title compound was obtained as a solid from the compound obtained in Step 2 of Example 9 (60 mg) and the compound obtained in the above Step 1 (45 mg) as raw materials by a reaction similar to that in Step 2 of Example 47.

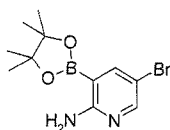
¹H-NMR (CDCl₃) δ : 3.89 (3H, s), 4.51 (2H, q, J = 7.8 Hz), 4.72 (2H, s), 7.16-7.20 (2H, m), 7.34 (2H, d, J = 8.7 Hz), 7.49-7.58 (3H, m), 7.83 (2H, d, J = 8.3 Hz), 8.27 (1H, s), 8.63 (1H, d, J = 2.8 Hz), 12.42 (1H, s).

MS (ESI) m/z : 514 (M+H)⁺.

Example 87

N-[2'-Amino-5'-(3,4-dimethoxyphenyl)-2,3'-bipyridin-5-yl]-5-(4-fluorophenyl)-4-oxo-1-(2,2,2-trifluoroethyl)-1,4-dihydropyridine-3-carboxamide

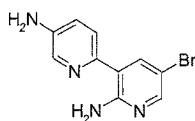
[Step 1] 5-Bromo-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-amine



N-Bromosuccinimide (255 mg) was added to a solution of 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-amine (300 mg) in DMF (6.8 ml) at room temperature, and the mixture was stirred for four hours. Water was added and the precipitated solid was collected by filtration to give 210 mg of the title compound.

$^1\text{H-NMR}$ (CDCl_3) δ : 1.31 (12H, s), 5.42 (2H, s), 7.88 (1H, d, $J = 2.93$ Hz), 8.10 (1H, d, $J = 2.93$ Hz).

[Step 2] 5'-Bromo-2,3'-bipyridine-2',5-diamine



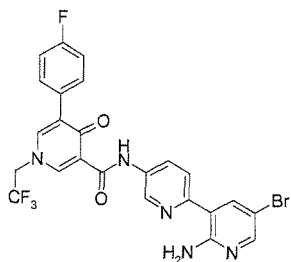
Tetrakis(triphenylphosphine)palladium (41 mg), 6-iodopyridin-3-amine (216 mg) and potassium carbonate (291 mg) were added to a solution of the compound obtained in the above Step 1 (210 mg) in dioxane (3.5 ml) and water (0.3 ml), and the mixture was stirred at 80°C for four hours. The reaction solution was further stirred at 90°C

for four hours and then diluted with ethyl acetate. The organic layer was washed with water and brine. After drying over sodium sulfate, the solvent was distilled off under reduced pressure, and the residue was purified by silica gel column chromatography [n-hexane:ethyl acetate = 19:1 -> 1:1 (v/v)] to give 136 mg of the title compound as a solid.

$^1\text{H-NMR}$ (CDCl_3) δ : 3.83 (2H, s), 6.64 (2H, s), 7.10 (1H, dd, $J = 8.54, 3.05$ Hz), 7.45-7.51 (1H, m), 7.78-7.83 (1H, m), 8.03-8.12 (2H, m).

MS (ESI) m/z :265 ($\text{M}+\text{H}$) $^+$.

[Step 3] N-(2'-Amino-5'-bromo-2,3'-bipyridin-5-yl)-5-(4-fluorophenyl)-4-oxo-1-(2,2,2-trifluoroethyl)-1,4-dihydropyridine-3-carboxamide



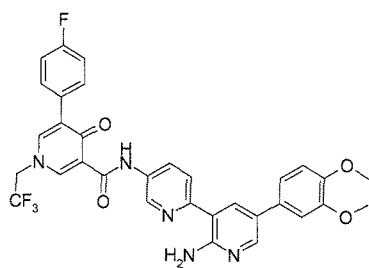
179 mg of the title compound was obtained from the compound obtained in Step 2 of Example 9 (140 mg) and the compound obtained in the above Step 2 (130 mg) as raw materials by a reaction similar to that in Step 1 of Example 31.

$^1\text{H-NMR}$ (DMSO-D_6) δ : 5.23-5.33 (2H, m), 7.29-7.37 (2H, m), 7.58 (2H, s), 7.65-7.72 (2H, m), 8.03-8.09 (2H, m), 8.17

(1H, d, $J = 2.44$ Hz), 8.28-8.35 (2H, m), 8.88-8.92 (1H, m), 8.97 (1H, d, $J = 2.44$ Hz), 12.85 (1H, s).

MS (ESI) m/z : 562 (M+H)⁺.

[Step 4] N-[2'-Amino-5'-(3,4-dimethoxyphenyl)-2,3'-bipyridin-5-yl]-5-(4-fluorophenyl)-4-oxo-1-(2,2,2-trifluoroethyl)-1,4-dihydropyridine-3-carboxamide



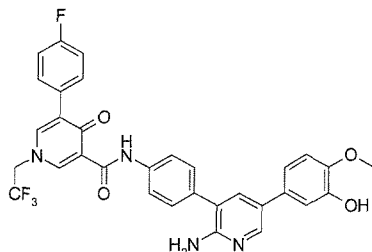
38 mg of the title compound was obtained as a solid from the compound obtained in the above Step 3 (95 mg) and 3,4-dimethoxyphenylboronic acid (37 mg) as raw materials by a reaction similar to that in Step 2 of Example 31.

¹H-NMR (CDCl₃) δ : 3.91 (3H, s), 3.94 (3H, s), 4.50 (2H, q, $J = 7.65$ Hz), 6.58-6.73 (2H, m), 6.93 (1H, d, $J = 8.30$ Hz), 7.01-7.10 (2H, m), 7.13-7.20 (2H, m), 7.48-7.55 (3H, m), 7.73-7.78 (1H, m), 7.94-7.98 (1H, m), 8.26-8.32 (2H, m), 8.59-8.63 (1H, m), 8.92 (1H, d, $J = 2.44$ Hz), 12.58 (1H, s).

MS (ESI) m/z : 620 (M+H)⁺.

Example 88

N-{4-[2-Amino-5-(3-hydroxy-4-methoxyphenyl)pyridin-3-yl]phenyl}-5-(4-fluorophenyl)-4-oxo-1-(2,2,2-trifluoroethyl)-1,4-dihydropyridine-3-carboxamide



58 mg of the title compound was obtained from the compound obtained in Step 1 of Example 31 (95 mg) and 2-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (51 mg) as raw materials by a reaction similar to that in Step 2 of Example 31.

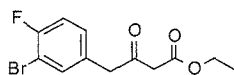
¹H-NMR (CDCl₃) δ: 3.93 (3H, s), 4.51 (2H, q, J = 7.53 Hz), 4.57-4.66 (2H, m), 5.70 (1H, s), 6.88-6.93 (1H, m), 7.00-7.05 (1H, m), 7.11-7.22 (3H, m), 7.46-7.59 (6H, m), 7.81-7.88 (2H, m), 8.27 (1H, d, J = 2.44 Hz), 8.64 (1H, d, J = 2.44 Hz), 12.45 (1H, s).

MS (ESI) m/z: 605 (M+H)⁺.

Example 89

N-{4-[2-Amino-5-(3,4-dimethoxyphenyl)pyridin-3-yl]phenyl}-5-(4-fluoro-3-bromophenyl)-4-oxo-1-(2,2,2-trifluoroethyl)-1,4-dihydropyridine-3-carboxamide

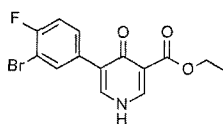
[Step 1] Ethyl 4-(3-bromo-4-fluorophenyl)-3-oxobutanoate



Magnesium chloride (3.7 g) was added to a suspension of 3-ethoxy-3-oxopropanoic acid potassium salt (5.5 g) in THF (100 ml), and the mixture was stirred at room temperature for 2.5 hours (Reaction Solution 1). In another vessel, carbonyldiimidazole (4.2 g) was added in small portions to a solution of 2-(3-bromo-4-fluorophenyl)acetic acid (5 g) in THF (50 ml) at room temperature, and the mixture was stirred for 30 minutes (Reaction Solution 2). Reaction Solution 2 was added to Reaction Solution 1 at room temperature, and the mixture was stirred at 60°C for three hours. Hydrochloric acid (1 N aqueous solution, 200 ml) was added, followed by extraction with ethyl acetate. The resulting organic layer was washed sequentially with water, a saturated aqueous sodium bicarbonate solution and brine and then dried over anhydrous sodium sulfate. The solvent was distilled off under reduced pressure to give 7 g of the title compound as an oily substance.

MS (ESI)m/z:305 (M+H)⁺.

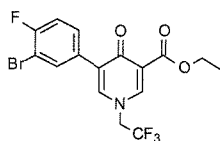
[Step 2] Ethyl 5-(3-bromo-4-fluorophenyl)-4-oxo-1,4-dihydropyridine-3-carboxylate



1,3,5-Triazine (2.1 g) and sodium ethoxide (20% solution in ethanol, 9.4 ml) were added to a solution of

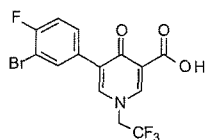
the compound obtained in the above Step 1 (7 g) in ethanol (70 ml), and the mixture was stirred at 85°C for five hours. The reaction solution was distilled off under reduced pressure, and the residue was diluted with water and then neutralized by adding hydrochloric acid (1 N solution). The precipitated solid was collected by filtration and washed sequentially with water and ethyl acetate to give 5.4 g of the title compound as a solid. MS (ESI)m/z:342 (M+H)⁺.

[Step 3] Ethyl 5-(3-bromo-4-fluorophenyl)-4-oxo-1-(2,2,2-trifluoroethyl)-1,4-dihydropyridine-3-carboxylate



6.0 g of the title compound was obtained as an oily substance from the compound obtained in the above Step 2 (5.4 g) and 2,2,2-trifluoroethyl trifluoromethanesulfonate (5.2 g) as raw materials by a reaction similar to that in Step 1 of Example 20. MS (ESI)m/z:424 (M+H)⁺.

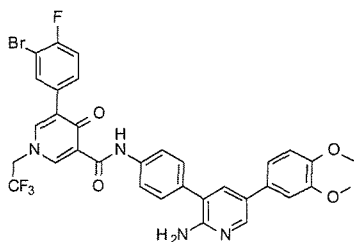
[Step 4] 5-(3-Bromo-4-fluorophenyl)-4-oxo-1-(2,2,2-trifluoroethyl)-1,4-dihydropyridine-3-carboxylic acid



5.3 g of the title compound was obtained as a solid from the compound obtained in the above Step 3 (6.0 g) as a raw material by a reaction similar to that in Step 2 of Example 20.

MS (ESI) m/z : 396 ($M+H$)⁺.

[Step 5] N-{4-[2-Amino-5-(3,4-dimethoxyphenyl)pyridin-3-yl]phenyl}-5-(4-fluoro-3-bromophenyl)-4-oxo-1-(2,2,2-trifluoroethyl)-1,4-dihydropyridine-3-carboxamide



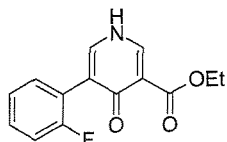
2.5 g of the title compound was obtained as a solid from the compound obtained in the above Step 4 (1.6 g) and the compound obtained in Step 2 of Example 1 (1.6 g) as raw materials by a reaction similar to that in Step 3 of Example 20.

¹H-NMR (CDCl₃) δ : 3.92 (3H, s), 3.94 (3H, s), 4.50-4.62 (4H, m), 6.93-6.95 (1H, m), 7.04 (1H, d, J = 1.8 Hz), 7.09 (1H, d, J = 8.5 Hz), 7.22-7.26 (1H, m), 7.49-7.53 (4H, m), 7.57 (1H, d, J = 2.4 Hz), 7.78 (1H, dd, J = 6.7, 1.8 Hz), 7.85 (2H, d, J = 8.5 Hz), 8.28 (1H, d, J = 2.4 Hz), 8.65 (1H, d, J = 2.4 Hz), 12.37 (1H, s).

MS (ESI); m/z : 699 [$M+H$]⁺.

Reference Example 1

Ethyl 5-(2-fluorophenyl)-4-oxo-1,4-dihydropyridine-3-carboxylate

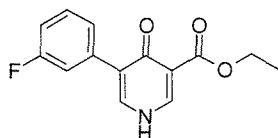


A solution of sodium ethoxide in ethanol (20%, 1270 μ l) was added to a solution of ethyl 4-(2-fluorophenyl)-3-oxobutanoate (697 mg) and 1,3,5-triazine (277 mg) in ethanol (8.0 ml) at room temperature, and the mixture was stirred at 85°C for four hours. The solvent was distilled off under reduced pressure, followed by dilution with water. A 1 N aqueous hydrochloric acid solution was added, and the precipitated solid was collected by filtration and washed with ethyl acetate to give 406 mg of the title compound as a solid.

$^1\text{H-NMR}$ (DMSO-D_6) δ : 1.25 (3H, t, $J = 7.20$ Hz), 4.19 (2H, q, $J = 7.20$ Hz), 7.18-7.25 (2H, m), 7.36-7.42 (2H, m), 7.81 (1H, s), 8.25 (1H, s).

Reference Example 2

Ethyl 5-(3-fluorophenyl)-4-oxo-1,4-dihydropyridine-3-carboxylate



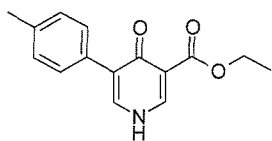
2.97 g of the title compound was obtained as a solid from 4-(3-fluoro-phenyl)-3-oxobutyric acid ethyl ester (4.40 g) and 1,3,5-triazine (1.75 g) by a reaction similar to that in Reference Example 1.

$^1\text{H-NMR}$ (DMSO-D_6) δ : 1.26 (3H, t, $J = 7.1$ Hz), 4.19 (2H, q, $J = 7.1$ Hz), 7.10-7.19 (1H, m), 7.38-7.55 (3H, m), 7.89-7.96 (1H, m), 8.16-8.23 (1H, m), 12.0 (1H, br s).

MS (ESI) m/z : 262 ($\text{M}+\text{H}$) $^+$

Reference Example 3

Ethyl 5-(4-methylphenyl)-4-oxo-1,4-dihydropyridine-3-carboxylate



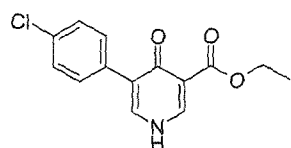
1.86 g of the title compound was obtained as a solid from 4-(4-methylphenyl)-3-oxobutyric acid ethyl ester (2.97 g) and 1,3,5-triazine (1.20 g) by a reaction similar to that in Reference Example 1.

$^1\text{H-NMR}$ (DMSO-D_6) δ : 1.26 (3H, t, $J = 7.1$ Hz), 2.32 (3H, s), 4.19 (2H, q, $J = 7.1$ Hz), 7.16-7.21 (2H, m), 7.46-7.50 (2H, m), 7.79 (1H, br s), 8.17 (1H, br s), 11.9 (1H, br s).

MS (ESI) m/z : 258 ($\text{M}+\text{H}$) $^+$

Reference Example 4

Ethyl 5-(4-chlorophenyl)-4-oxo-1,4-dihydropyridine-3-carboxylate

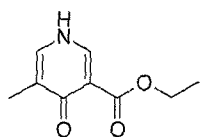


1.87 g of the title compound was obtained as a solid from 4-(4-chlorophenyl)-3-oxobutyric acid ethyl ester (2.97 g) and 1,3,5-triazine (1.10 g) by a reaction similar to that in Reference Example 1.

MS (ESI) m/z : 278 (M+H)⁺

Reference Example 5

Ethyl 5-methyl-4-oxo-1,4-dihydropyridine-3-carboxylate

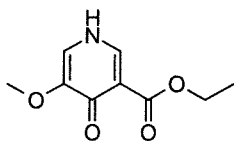


928 mg of the title compound was obtained as a solid from ethyl 3-oxopentanoate (1.4 ml) and 1,3,5-triazine (930 mg) by a reaction similar to that in Reference Example 1.

¹H-NMR (DMSO-D₆) δ : 1.24 (3H, t, J = 7.1 Hz), 1.84 (3H, s), 4.16 (2H, q, J = 7.2 Hz), 7.61 (1H, s), 8.15 (1H, d, J = 3.2 Hz), 11.58 (1H, s).

Reference Example 6

Ethyl 5-methoxy-4-oxo-1,4-dihydropyridine-3-carboxylate

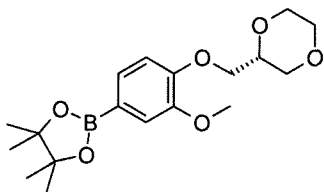


92 mg of the title compound was obtained as a solid from ethyl 4-methoxy-3-oxobutanoate (1.3 ml) and 1,3,5-triazine (920 mg) by a reaction similar to that in Reference Example 1.

$^1\text{H-NMR}$ (DMSO-D_6) δ : 1.24 (3H, t, $J = 7.1$ Hz), 3.66 (3H, s), 4.17 (2H, q, $J = 7.2$ Hz), 7.35 (1H, s), 8.10 (1H, s), 11.67 (1H, s).

Reference Example 7

2-(4-{[(2R)-1,4-dioxan-2-yl]methoxy}-3-methoxyphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane



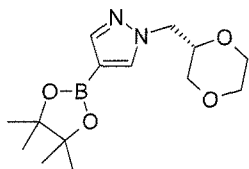
2-Methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (10.2 g), (2R)-1,4-dioxan-2-ylmethyl methanesulfonate (8.0 g) and potassium carbonate (11.2 g) were suspended in DMF (200 ml), and the suspension was stirred at 90°C for 16 hours. After leaving to cool, the insoluble matter was removed and the solvent was distilled off under reduced pressure. The residue was purified by silica gel column chromatography

[hexane:ethyl acetate = 2:1 (v/v)] to give 14.3 g of the title compound.

MS (ESI) m/z : 351 (M+H)⁺

Reference Example 8

1-[(2S)-1,4-Dioxan-2-ylmethyl]-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole

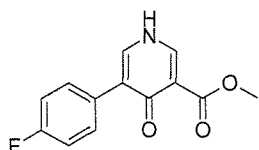


4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (2.5 g) was added to a suspension of cesium carbonate (2.50 g) in 1,4-dioxane (30 ml). After stirring, (2R)-1,4-dioxan-2-ylmethyl methanesulfonate (2.78 g) was added and the mixture was stirred at 90°C for four hours. After leaving to cool, the reaction solution was filtered, and the filtrate was concentrated. The residue was purified by silica gel column chromatography [chloroform:methanol = 19:1 (v/v)] to give 3.79 g of the title compound.

MS (ESI) m/z : 295 (M+H)⁺

Reference Example 9

Methyl 5-(4-fluorophenyl)-4-oxo-1,4-dihydropyridine-3-carboxylate



Thionyl chloride (0.8 ml) was added to a suspension of 5-(4-fluorophenyl)-4-oxo-1,4-dihydropyridine-3-carboxylic acid (400 mg) in methanol (9 ml) at 0°C. The reaction mixture was stirred at 70°C overnight. The reaction mixture was returned to room temperature and concentrated under reduced pressure. The resulting residue was washed with saturated aqueous sodium bicarbonate and water and then further washed with diethyl ether to give 304 mg of the title compound as a solid.

$^1\text{H-NMR}$ (DMSO- D_6) δ : 3.72 (3H, s), 7.17-7.24 (2H, m), 7.61-7.65 (2H, m), 7.85 (1H, s), 8.21 (1H, s), 11.96 (1H, s).

MS (ESI) m/z : 248 (M+H) $^+$.

In Examples of the present invention, X-ray diffraction data were measured using the following instrument and measurement conditions.

Instrument manufacturer: Rigaku Co., Ltd.

Instrument: RINT TTR-III

Radiation source: Cu-K α radiation

Wavelength ($\text{\AA}$): 1.54

Detector: Scintillation counter

Optical system: Parallel beam method

Tube voltage (kV): 50

Tube current (mA): 300

Scanning field 2θ (deg): 2 to 40

Sampling step (deg): 0.02

Scanning speed (deg/min): 20 or 2

Sample holder: Nonreflective sample holder

Example 90

N-{4-[2-Amino-5-(3,4-dimethoxyphenyl)pyridin-3-yl]phenyl}-5-(4-fluorophenyl)-4-oxo-1-(2,2,2-trifluoroethyl)-1,4-dihydropyridine-3-carboxamide hydrochloride

Acetonitrile (383 μ l), a 5.788 mol/L aqueous hydrochloric acid solution (5.67 μ l, 1.05 eq.) and water (4.15 μ l) were added to N-{4-[2-amino-5-(3,4-dimethoxyphenyl)pyridin-3-yl]phenyl}-5-(4-fluorophenyl)-4-oxo-1-(2,2,2-trifluoroethyl)-1,4-dihydropyridine-3-carboxamide (19.64 mg, 31.75 μ mol) at room temperature. After stirring at 40°C for about 24 hours, the precipitated solid was collected by filtration. The solid was then dried at room temperature to give the title compound (12.42 mg). Yield: 60%.

For the powder X-ray diffraction ($\text{CuK}\alpha$, $\lambda = 1.54 \text{ \AA}$, scanning speed = 20°/min) of the resulting crystals, the diffraction pattern is shown in FIG. 1, and peaks having a relative intensity of 28 or more based on the maximum peak intensity as 100 in FIG. 1 are shown in Table 1.

[Table 1]

Peak No.	2θ	d value	Relative intensity	Peak No.	2θ	d value	Relative intensity
1	7.44	11.87	31	9	23.02	3.86	34
2	10.00	8.84	28	10	23.70	3.75	92
3	13.48	6.56	42	11	24.54	3.62	37
4	14.86	5.96	37	12	25.92	3.43	28
5	16.10	5.50	32	13	28.46	3.13	32
6	19.30	4.60	40				
7	20.30	4.37	100				
8	22.62	3.93	37				

Example 91

N-{4-[2-Amino-5-(3,4-dimethoxyphenyl)pyridin-3-yl]phenyl}-5-(4-fluorophenyl)-4-oxo-1-(2,2,2-trifluoroethyl)-1,4-dihydropyridine-3-carboxamide monohydrochloride

The compound of Step 3 of Example 9 (15.7 g) was suspended in ethanol (50 ml), and 4 N hydrochloric acid-dioxane (12.69 ml) was added at room temperature. After stirring at room temperature, the solvent was distilled off under reduced pressure. The residue was suspended in acetonitrile, and the suspension was stirred overnight. The resulting solid was collected by filtration, and the solid was then suspended in hexane, followed by stirring for three days. The resulting solid was collected by filtration and then dried under reduced pressure to give 15.7 g of the title compound as a solid.

MS (ESI) m/z: 619 (M+H)⁺.

Elemental analysis for C₃₃H₂₆F₄N₄O₄·1HCl·1.75H₂O

Calculated: C, 57.73; H, 4.33; F, 11.06; N, 8.16; Cl, 5.16.

Found: C, 57.71; H, 4.15; F, 11.89; N, 8.18; Cl, 5.12.

For the powder X-ray diffraction ($\text{CuK}\alpha$, $\lambda = 1.54 \text{ \AA}$, scanning speed = $2^\circ/\text{min}$), the diffraction pattern is shown in FIG. 2, and peaks having a relative intensity of 31 or more based on the maximum peak intensity as 100 in FIG. 2 are shown in Table 2.

[Table 2]

Peak No.	2θ	d value	Relative intensity	Peak No.	2θ	d value	Relative intensity
1	4.32	20.44	52	7	20.54	4.32	64
2	9.10	9.71	100	8	20.70	4.29	76
3	15.52	5.70	41	9	23.54	3.78	82
4	18.32	4.84	40	10	24.14	3.68	80
5	18.54	4.78	41	11	25.34	3.51	47
6	19.22	4.61	43	12	27.02	3.30	42

Example 92

N-{4-[2-Amino-5-(3,4-dimethoxyphenyl)pyridin-3-yl]phenyl}-5-(4-fluorophenyl)-4-oxo-1-(2,2,2-trifluoroethyl)-1,4-dihydropyridine-3-carboxamide hydrochloride hydrate

Water (36 ml) and a 1.004 mol/L aqueous hydrochloric acid solution of (3.54 ml, 1.10 eq.) were added to N-{4-[2-amino-5-(3,4-dimethoxyphenyl)pyridin-3-yl]phenyl}-5-(4-fluorophenyl)-4-oxo-1-(2,2,2-trifluoroethyl)-1,4-dihydropyridine-3-carboxamide (2.00 g, 3.23 mmol) at room temperature. The mixture was stirred at 40°C for six days and then stirred at room temperature for 30 minutes.

The precipitated solid was collected by filtration and dried at room temperature. Water (38 ml) and a 1.004 mol/L aqueous hydrochloric acid solution (1.61 ml, 0.50 eq.) were added to the collected solid at room temperature. The mixture was stirred at 40°C for about 12 hours and then stirred at room temperature for 30 minutes. The precipitated solid was collected by filtration and then dried under reduced pressure at room temperature for three hours to give the title compound (2.19 g). Yield: 100%.

For the powder X-ray diffraction (CuK α , λ = 1.54 Å, scanning speed = 2°/min) of the resulting crystals, the diffraction pattern is shown in FIG. 3, and peaks having a relative intensity of 51 or more based on the maximum peak intensity as 100 in FIG. 3 are shown in Table 3.

[Table 3]

Peak No.	2 θ	d value	Relative intensity	Peak No.	2 θ	d value	Relative intensity
1	13.86	6.38	51	6	22.58	3.93	51
2	15.04	5.89	64	7	23.82	3.73	54
3	19.76	4.49	58	8	24.10	3.69	62
4	20.58	4.31	100	9	24.36	3.65	76
5	22.26	3.99	51	10	24.88	3.58	69

Example 93

N-{4-[2-Amino-5-(3,4-dimethoxyphenyl)pyridin-3-yl]phenyl}-5-(4-fluorophenyl)-4-oxo-1-(2,2,2-trifluoroethyl)-1,4-dihydropyridine-3-carboxamide monohydrochloride

The compound of Step 3 of Example 9 (28.91 g) was suspended in ethanol (100 ml), and 4 N hydrochloric acid-dioxane (23.37 ml) was added at room temperature. After stirring at room temperature for two hours, the solvent was distilled off under reduced pressure, and the residue was recrystallized from ethanol/isopropyl ether (50 ml/150 ml). The resulting solid was collected by filtration, washed with isopropyl ether and then dried under reduced pressure to give 30.83 g of the title compound as a solid.

$^1\text{H-NMR}$ (CDCl_3) δ : 3.93 (3H, s), 3.94 (3H, s), 4.66-4.73 (2H, m), 6.92-7.05 (3H, m), 7.18 (2H, t, $J = 8.5$ Hz), 7.44 (2H, d, $J = 8.5$ Hz), 7.51-7.58 (3H, m), 7.90-7.96 (4H, m), 8.72 (1H, d, $J = 1.8$ Hz), 12.65 (1H, s).

MS(ESI) m/z : 619 ($\text{M}+\text{H}$) $^+$.

Elemental analysis for $\text{C}_{33}\text{H}_{26}\text{F}_4\text{N}_4\text{O}_4 \cdot 1\text{HCl} \cdot 0.05$ isopropyl ether $\cdot 1.25\text{H}_2\text{O}$

Calculated: C, 58.59; H, 4.46; F, 11.13; N, 8.21; Cl, 5.19.

Found: C, 58.43; H, 4.16; F, 11.19; N, 8.11; Cl, 5.24.

For the powder X-ray diffraction ($\text{CuK}\alpha$, $\lambda = 1.54 \text{ \AA}$, scanning speed = $2^\circ/\text{min}$), the diffraction pattern is shown in FIG. 4, and peaks having a relative intensity of 31 or more based on the maximum peak intensity as 100 in FIG. 4 are shown in Table 4.

[Table 4]

Peak No.	2θ	d value	Relative intensity	Peak No.	2θ	d value	Relative intensity
1	5.34	16.54	100	7	17.54	5.05	33
2	7.22	12.23	31	8	23.24	3.82	44
3	8.20	10.77	35	9	23.72	3.75	35
4	11.68	7.57	33	10	25.12	3.54	31
5	14.54	6.09	30	11	26.16	3.40	31
6	15.74	5.63	32				

Example 94

N-{4-[2-Amino-5-(3,4-dimethoxyphenyl)pyridin-3-yl]phenyl}-5-(4-fluorophenyl)-4-oxo-1-(2,2,2-trifluoroethyl)-1,4-dihydropyridine-3-carboxamide monohydrochloride dihydrate

Acetone (3.0 ml), water (1.87 ml) and a 1.004 mol/l aqueous hydrochloric acid solution (2.70 ml, 1.10 eq.) were added to N-{4-[2-amino-5-(3,4-dimethoxyphenyl)pyridin-3-yl]phenyl}-5-(4-fluorophenyl)-4-oxo-1-(2,2,2-trifluoroethyl)-1,4-dihydropyridine-3-carboxamide (1.52 g, 2.46 mmol) at room temperature. The mixture was stirred at 40°C for about 11 hours and then stirred at room temperature for about 30 minutes, and the precipitated solid was collected by filtration. The solid was then dried under reduced pressure at room temperature for about three hours to give the title compound (1.60 g). Yield: 94%.

N-{4-[2-Amino-5-(3,4-dimethoxyphenyl)pyridin-3-yl]phenyl}-5-(4-fluorophenyl)-4-oxo-1-(2,2,2-trifluoroethyl)-1,4-dihydropyridine-3-carboxamide

monohydrochloride dihydrate is represented as elements;
analytical values (theoretical values): C; 57.15%
(57.35%), H; 4.46% (4.52%), N; 7.99% (8.11%), F; 11.23%
(11.00%) Cl; 5.11% (5.13%)

For the powder X-ray diffraction ($\text{CuK}\alpha$, $\lambda = 1.54 \text{ \AA}$,
scanning speed = $20^\circ/\text{min}$), the diffraction pattern is
shown in FIG. 5, and peaks having a relative intensity of
33 or more based on the maximum peak intensity as 100 in
FIG. 5 are shown in Table 5.

[Table 5]

Peak No.	2θ	d value	Relative intensity	Peak No.	2θ	d value	Relative intensity
1	11.02	8.02	59	6	24.70	3.60	100
2	11.86	7.46	66	7	25.80	3.45	45
3	15.56	5.69	44	8	26.04	3.42	40
4	18.20	4.87	60	9	26.26	3.39	33
5	22.12	4.02	41	10	28.62	3.12	43

Example 95

N-{4-[2-Amino-5-(3,4-dimethoxyphenyl)pyridin-3-yl]phenyl}-5-(4-fluorophenyl)-4-oxo-1-(2,2,2-trifluoroethyl)-1,4-dihydropyridine-3-carboxamide hydrochloride

Acetone (200 μl) was added to N-{4-[2-amino-5-(3,4-dimethoxyphenyl)pyridin-3-yl]phenyl}-5-(4-fluorophenyl)-4-oxo-1-(2,2,2-trifluoroethyl)-1,4-dihydropyridine-3-carboxamide hydrochloride hydrate described in Example 92 (22.72 mg) at room temperature, and the mixture was stirred at 40°C for about 24 hours. After leaving to stand at room temperature for about 30 minutes, the

precipitated solid was collected by filtration. The solid was then dried at room temperature to give the title compound (21.11 mg). Yield: 89%.

For the powder X-ray diffraction ($\text{CuK}\alpha$, $\lambda = 1.54 \text{ \AA}$, scanning speed = $20^\circ/\text{min}$) of the resulting crystals, the diffraction pattern is shown in FIG. 6, and peaks having a relative intensity of 17 or more based on the maximum peak intensity as 100 in FIG. 6 are shown in Table 6.

[Table 6]

Peak No.	2θ	d value	Relative intensity	Peak No.	2θ	d value	Relative intensity
1	3.58	24.66	100	6	9.62	9.19	44
2	4.56	19.36	28	7	10.28	8.60	20
3	6.60	13.38	22	8	13.06	6.77	27
4	6.72	13.14	27	9	24.52	3.63	21
5	7.20	12.27	17				

Example 96

N-{4-[2-Amino-5-(3,4-dimethoxyphenyl)pyridin-3-yl]phenyl}-5-(4-fluorophenyl)-4-oxo-1-(2,2,2-trifluoroethyl)-1,4-dihydropyridine-3-carboxamide hydrochloride

Tetrahydrofuran (200 μl) was added to N-{4-[2-amino-5-(3,4-dimethoxyphenyl)pyridin-3-yl]phenyl}-5-(4-fluorophenyl)-4-oxo-1-(2,2,2-trifluoroethyl)-1,4-dihydropyridine-3-carboxamide hydrochloride hydrate described in Example 92 (21.27 mg) at room temperature, and the mixture was stirred at 40°C for about 24 hours. After leaving to stand at room temperature for about 30 minutes, the precipitated solid was collected by

filtration. The solid was then dried at room temperature to give the title compound (18.37 mg). Yield: 86%.

For the powder X-ray diffraction ($\text{CuK}\alpha$, $\lambda = 1.54 \text{ \AA}$, scanning speed = $20^\circ/\text{min}$) of the resulting crystals, the diffraction pattern is shown in FIG. 7, and peaks having a relative intensity of 31 or more based on the maximum peak intensity as 100 in FIG. 7 are shown in Table 7.

[Table 7]

Peak No.	2 θ	d value	Relative intensity	Peak No.	2 θ	d value	Relative intensity
1	7.78	11.35	94	8	19.34	4.59	100
2	8.14	10.85	34	9	20.08	4.42	47
3	8.88	9.95	40	10	22.36	3.97	40
4	12.54	7.05	33	11	24.66	3.61	66
5	15.68	5.65	31	12	25.74	3.46	39
6	16.36	5.41	37	13	26.70	3.34	44
7	18.76	4.73	47	14	28.02	3.18	34

Example 97

N-{4-[2-Amino-5-(3,4-dimethoxyphenyl)pyridin-3-yl]phenyl}-5-(4-fluorophenyl)-4-oxo-1-(2,2,2-trifluoroethyl)-1,4-dihydropyridine-3-carboxamide hydrochloride

Ethanol (14.8 ml), concentrated hydrochloric acid (as 12 mol/l) (219 μl , 1.05 eq.) and water (6 μl) were added to N-{4-[2-amino-5-(3,4-dimethoxyphenyl)pyridin-3-yl]phenyl}-5-(4-fluorophenyl)-4-oxo-1-(2,2,2-trifluoroethyl)-1,4-dihydropyridine-3-carboxamide (1.50 g, 2.43 mmol) at room temperature. The mixture was stirred at 40°C for about 11 hours and then stirred at room

temperature for one hour, and the precipitated solid was collected by filtration. The solid was then dried under reduced pressure at room temperature for three hours to give the title compound (1.54 g). Yield: 97%.

N-{4-[2-Amino-5-(3,4-dimethoxyphenyl)pyridin-3-yl]phenyl}-5-(4-fluorophenyl)-4-oxo-1-(2,2,2-trifluoroethyl)-1,4-dihydropyridine-3-carboxamide hydrochloride is represented as elements; analytical values (theoretical values): C; 60.41% (60.51%), H; 4.20% (4.15%), N; 8.48% (8.55%), F; 11.89% (11.60%), Cl; 5.26% (5.41%)

For the powder X-ray diffraction ($\text{CuK}\alpha$, $\lambda = 1.54 \text{ \AA}$, scanning speed = $2^\circ/\text{min}$), the diffraction pattern is shown in FIG. 8, and peaks having a relative intensity of 30 or more based on the maximum peak intensity as 100 in FIG. 8 are shown in Table 8.

[Table 8]

Peak No.	2θ	d value	Relative intensity	Peak No.	2θ	d value	Relative intensity
1	5.78	15.28	38	8	20.74	4.28	35
2	8.90	9.93	40	9	22.42	3.96	31
3	13.66	6.48	66	10	24.66	3.61	68
4	14.42	6.14	88	11	25.12	3.54	66
5	16.84	5.26	57	12	25.60	3.48	34
6	17.56	5.05	100	13	26.96	3.30	30
7	19.26	4.60	36				

Example 98

N-{4-[2-Amino-5-(3,4-dimethoxyphenyl)pyridin-3-yl]phenyl}-5-(4-fluorophenyl)-4-oxo-1-(2,2,2-

trifluoroethyl)-1,4-dihydropyridine-3-carboxamide
hydrochloride

1-Propanol (401 μ l), a 5.877 mmol/L aqueous hydrochloric acid solution (6.22 μ l, 1.10 eq.) and water (4.1 μ l) were added to N-{4-[2-amino-5-(3,4-dimethoxyphenyl)pyridin-3-yl]phenyl}-5-(4-fluorophenyl)-4-oxo-1-(2,2,2-trifluoroethyl)-1,4-dihydropyridine-3-carboxamide (20.55 mg, 33.22 μ mol) at room temperature, and the mixture was stirred at 40°C for about 24 hours. After leaving to stand at room temperature for about 30 minutes, the precipitated solid was collected by filtration. The solid was then dried at room temperature to give the title compound (19.65 mg). Yield: 90%.

For the powder X-ray diffraction ($\text{CuK}\alpha$, $\lambda = 1.54 \text{ \AA}$, scanning speed = 20°/min) of the resulting crystals, the diffraction pattern is shown in FIG. 9, and peaks having a relative intensity of 38 or more based on the maximum peak intensity as 100 in FIG. 9 are shown in Table 9.

[Table 9]

Peak No.	2 θ	d value	Relative intensity	Peak No.	2 θ	d value	Relative intensity
1	11.12	7.95	93	7	22.36	3.97	38
2	14.82	5.97	49	8	22.68	3.92	80
3	18.86	4.70	51	9	23.00	3.86	67
4	20.32	4.37	44	10	24.10	3.69	48
5	20.66	4.30	38	11	25.26	3.52	45
6	21.64	4.10	48	12	27.00	3.30	100

Example 99

N-{4-[2-Amino-5-(3,4-dimethoxyphenyl)pyridin-3-yl]phenyl}-5-(4-fluorophenyl)-4-oxo-1-(2,2,2-trifluoroethyl)-1,4-dihydropyridine-3-carboxamide hydrochloride

Acetone (400 μ l) was added to a mixture of three crystal forms of N-{4-[2-amino-5-(3,4-dimethoxyphenyl)pyridin-3-yl]phenyl}-5-(4-fluorophenyl)-4-oxo-1-(2,2,2-trifluoroethyl)-1,4-dihydropyridine-3-carboxamide hydrochloride described in Examples 92, 93 and 94 (22.15 mg) at room temperature, and the mixture was stirred for about 24 hours. The precipitated crystals were collected by filtration and dried at room temperature to give the title compound (19.45 mg). Yield: 88%.

For the powder X-ray diffraction ($\text{CuK}\alpha$, $\lambda = 1.54 \text{ \AA}$, scanning speed = $20^\circ/\text{min}$) of the resulting crystals, the diffraction pattern is shown in FIG. 10, and peaks having a relative intensity of 38 or more based on the maximum peak intensity as 100 in FIG. 10 are shown in Table 10.

[Table 10]

Peak No.	2θ	d value	Relative intensity	Peak No.	2θ	d value	Relative intensity
1	7.80	11.33	60	7	19.66	4.51	52
2	12.18	7.26	93	8	20.20	4.39	61
3	12.78	6.92	38	9	21.20	4.23	100
4	16.20	5.47	58	10	24.52	3.63	41
5	16.82	5.27	47	11	25.68	3.47	47
6	19.20	4.62	48	12	26.78	3.33	43

Example 100

N-{4-[2-Amino-5-(3,4-dimethoxyphenyl)pyridin-3-yl]phenyl}-5-(4-fluorophenyl)-4-oxo-1-(2,2,2-trifluoroethyl)-1,4-dihydropyridine-3-carboxamide monohydrochloride hydrate

Water (60 ml), 1-propanol (90 ml) and concentrated hydrochloric acid (as 36%, d = 1.18) (0.17 ml, 0.1 eq.) were added to the compound of Example 94 (14.00 g, 20 mmol) at room temperature. After heating to 90°C, the insoluble matter was collected by filtration and the mother liquor was cooled to room temperature. After stirring at the same temperature for about three hours and then stirring at 0°C for about 27 hours, the precipitated solid was collected by filtration. The solid was then dried under reduced pressure at 40°C and 50°C overnight to give the title compound (12.10 g). Yield: 88%. The obtained crystals were used as seed crystals.

1-Propanol (144 ml), water (96 ml) and concentrated hydrochloric acid (as 36%, d = 1.18) (3.1 ml, 1.1 eq.) were added to the compound of Step 3 of Example 9 (20.00 g, 32.33 mmol) at room temperature. The mixture was warmed to 83°C. After confirming dissolution, the solution was cooled to 0°C. The seed crystals obtained above (20 mg) were then seeded, and the mixture was stirred for about 17 hours. The precipitated solid was then collected by filtration. The solid was then dried

under reduced pressure at 40°C overnight to give the title compound (18.26 g). Yield: 82%.

N-{4-[2-Amino-5-(3,4-dimethoxyphenyl)pyridin-3-yl]phenyl}-5-(4-fluorophenyl)-4-oxo-1-(2,2,2-trifluoroethyl)-1,4-dihydropyridine-3-carboxamide hydrochloride dihydrate is represented as: C; 57.84% (57.35%), H; 4.23% (4.52%), N; 8.17% (8.11%), F; 11.44% (11.00%), Cl; 5.23% (5.13%).

For the powder X-ray diffraction (CuK α , λ = 1.54 Å, scanning speed = 2°/min), the diffraction pattern is shown in FIG. 11, and peaks having a relative intensity of 37 or more based on the maximum peak intensity as 100 in FIG. 11 are shown in Table 11.

[Table 11]

Peak No.	2 θ	d value	Relative intensity	Peak No.	2 θ	d value	Relative intensity
1	2.80	31.53	73	6	14.86	5.96	69
2	6.86	12.87	39	7	17.40	5.09	44
3	7.88	11.21	57	8	22.40	3.97	37
4	11.60	7.62	100	9	23.78	3.74	38
5	13.68	6.47	54	10	25.74	3.46	40

Example 101

N-{4-[2-Amino-5-(3,4-dimethoxyphenyl)pyridin-3-yl]phenyl}-5-(4-fluorophenyl)-4-oxo-1-(2,2,2-trifluoroethyl)-1,4-dihydropyridine-3-carboxamide monohydrochloride hydrate

2-Propanol (50 ml), concentrated hydrochloric acid (as 36%, d = 1.18) (0.76 ml, 1.1 eq.) and 1.5% aqueous 2-propanol (50 ml) were added to the compound of Step 3 of

Example 9 (5.00 g, 8.08 mmol) at room temperature. After warming to 40°C, the compound of Example 93 (10 mg) was seeded. The mixture was stirred at 40°C for about two hours and then stirred at room temperature for 30 minutes, and the precipitated solid was collected by filtration. The solid was then dried under reduced pressure at 40°C overnight to give the title compound (5.02 g). Yield: 92%.

N-{4-[2-Amino-5-(3,4-dimethoxyphenyl)pyridin-3-yl]phenyl}-5-(4-fluorophenyl)-4-oxo-1-(2,2,2-trifluoroethyl)-1,4-dihydropyridine-3-carboxamide hydrochloride monohydrate is represented as: C; 59.07% (58.89%), H; 4.06% (4.34%), N; 8.31% (8.32%), F; 11.58% (11.29%), Cl; 5.27% (5.27%)

For the powder X-ray diffraction ($\text{CuK}\alpha$, $\lambda = 1.54 \text{ \AA}$, scanning speed = $2^\circ/\text{min}$), the diffraction pattern is shown in FIG. 12, and peaks having a relative intensity of 17 or more based on the maximum peak intensity as 100 in FIG. 12 are shown in Table 12.

[Table 12]

Peak No.	2 θ	d value	Relative intensity	Peak No.	2 θ	d value	Relative intensity
1	5.32	16.60	23	7	19.78	4.48	17
2	7.98	11.07	69	8	21.76	4.08	17
3	10.68	8.28	100	9	23.08	3.85	29
4	11.70	7.56	19	10	25.30	3.52	25
5	14.84	5.96	43	11	25.68	3.47	17
6	16.02	5.53	25				

Example 102

N-{4-[2-Amino-5-(3,4-dimethoxyphenyl)pyridin-3-yl]phenyl}-5-(4-fluorophenyl)-4-oxo-1-(2,2,2-trifluoroethyl)-1,4-dihydropyridine-3-carboxamide monohydrochloride

Ethanol (40 ml) was added to the compound of Example 96 (2.00 g, 3.05 mmol as hydrochloride anhydride) at room temperature. The mixture was stirred at room temperature for about 19 hours and then stirred at 40°C for about 33 hours, and the precipitated solid was collected by filtration. The solid was then dried under reduced pressure at 40°C overnight to give the title compound (1.62 g). Yield: 81%.

N-{4-[2-Amino-5-(3,4-dimethoxyphenyl)pyridin-3-yl]phenyl}-5-(4-fluorophenyl)-4-oxo-1-(2,2,2-trifluoroethyl)-1,4-dihydropyridine-3-carboxamide hydrochloride is represented as: C; 60.34% (60.51%), H; 4.11% (4.15%), N; 8.47% (8.55%), F; 11.77% (11.60%), Cl; 5.35% (5.41%)

For the powder X-ray diffraction ($\text{CuK}\alpha$, $\lambda = 1.54 \text{ \AA}$, scanning speed = $2^\circ/\text{min}$), the diffraction pattern is shown in FIG. 13, and peaks having a relative intensity of 49 or more based on the maximum peak intensity as 100 in FIG. 13 are shown in Table 13.

[Table 13]

Peak No.	2θ	d value	Relative intensity	Peak No.	2θ	d value	Relative intensity
1	8.10	10.91	67	8	20.72	4.28	81
2	10.60	8.34	49	9	20.94	4.24	75
3	12.06	7.33	50	10	22.86	3.89	78
4	14.16	6.25	56	11	23.90	3.72	100
5	14.58	6.07	70	12	24.32	3.66	97
6	15.60	5.68	76	13	27.14	3.28	51
7	18.16	4.88	71				

Example 103

N-{4-[2-Amino-5-(3,4-dimethoxyphenyl)pyridin-3-yl]phenyl}-5-(4-fluorophenyl)-4-oxo-1-(2,2,2-trifluoroethyl)-1,4-dihydropyridine-3-carboxamide monohydrochloride hydrate

Acetonitrile (39 ml), 6 N hydrochloric acid (565 µl, 1.05 eq.) and water (420 µl) were added to the compound of Step 3 of Example 9 (2.00 g, 3.23 mmol) at room temperature. The mixture was stirred at 40°C for about seven hours, followed by the addition of water (8.75 ml). After confirming dissolution, the solution was stirred at 0°C for about 10 hours and then allowed to stand at room temperature for about three days, and the precipitated solid was collected by filtration. The solid was then dried at room temperature to give the title compound (0.54 g). Yield: 24%.

N-{4-[2-Amino-5-(3,4-dimethoxyphenyl)pyridin-3-yl]phenyl}-5-(4-fluorophenyl)-4-oxo-1-(2,2,2-trifluoroethyl)-1,4-dihydropyridine-3-carboxamide

hydrochloride trihydrate is represented as: C; 55.73% (55.90%), H; 4.37% (4.69%), N; 8.07% (7.90%), F; 10.85% (10.72%), Cl; 4.98% (5.00%)

For the powder X-ray diffraction ($\text{CuK}\alpha$, $\lambda = 1.54 \text{ \AA}$, scanning speed = $2^\circ/\text{min}$), the diffraction pattern is shown in FIG. 14, and peaks having a relative intensity of 17 or more based on the maximum peak intensity as 100 in FIG. 14 are shown in Table 14.

[Table 14]

Peak No.	2θ	d value	Relative intensity	Peak No.	2θ	d value	Relative intensity
1	3.60	24.52	69	7	15.30	5.79	23
2	6.22	14.20	100	8	16.40	5.40	20
3	9.56	9.24	71	9	19.52	4.54	19
4	10.42	8.48	18	10	22.12	4.02	18
5	14.04	6.30	18	11	26.42	3.37	17
6	14.66	6.04	23				

Example 104

N-{4-[2-Amino-5-(3,4-dimethoxyphenyl)pyridin-3-yl]phenyl}-5-(4-fluorophenyl)-4-oxo-1-(2,2,2-trifluoroethyl)-1,4-dihydropyridine-3-carboxamide monohydrochloride hydrate

40% aqueous 1-propanol (28 ml) and concentrated hydrochloric acid (36%, $d = 1.18$) (0.14 ml, 0.56 eq.) were added to the compound of Example 100 (2.00 g, 2.89 mmol) at room temperature. The mixture was stirred at 0°C for about 21 hours, and the precipitated solid was then collected by filtration. The solid was then dried

at room temperature to give the title compound (1.89 g).

Yield: 88%.

N-{4-[2-Amino-5-(3,4-dimethoxyphenyl)pyridin-3-yl]phenyl}-5-(4-fluorophenyl)-4-oxo-1-(2,2,2-trifluoroethyl)-1,4-dihydropyridine-3-carboxamide hydrochloride pentahydrate is represented as: C; 53.06% (53.19%), H; 4.78% (5.01%), N; 7.46% (7.52%), F; 10.46% (10.20%), Cl; 5.01% (4.76%)

For the powder X-ray diffraction (CuK α , λ = 1.54 Å, scanning speed = 2°/min), the diffraction pattern is shown in FIG. 15, and peaks having a relative intensity of 42 or more based on the maximum peak intensity as 100 in FIG. 15 are shown in Table 15.

[Table 15]

Peak No.	2 θ	d value	Relative intensity	Peak No.	2 θ	d value	Relative intensity
1	5.46	16.17	88	7	16.56	5.35	100
2	7.98	11.07	50	8	22.00	4.04	59
3	9.54	9.26	45	9	23.54	3.78	63
4	11.00	8.04	81	10	24.00	3.70	48
5	14.00	6.32	56	11	26.56	3.35	42
6	15.36	5.76	49				

Example 105

N-{4-[2-Amino-5-(3,4-dimethoxyphenyl)pyridin-3-yl]phenyl}-5-(4-fluorophenyl)-4-oxo-1-(2,2,2-trifluoroethyl)-1,4-dihydropyridine-3-carboxamide monohydrochloride

1 N aqueous hydrochloric acid (400 μ l) was added to a suspension of the compound of Step 3 of Example 9 (50 mg) in ethanol (400 μ l) at room temperature, and ethanol

(300 μ l) was then further added to form a solution. After stirring at room temperature for 30 minutes, the solid was precipitated, so the mixture was allowed to stand overnight. The reaction solution was added dropwise to water (7 ml), and the mixture was stirred for five days. The precipitate was collected by filtration and air-dried to give 52 mg of the title compound as a solid.

$^1\text{H-NMR}$ (CDCl_3) δ : 3.93 (3H, s), 3.94 (3H, s), 4.66-4.73 (2H, m), 6.92-7.05 (3H, m), 7.18 (2H, t, $J = 8.5$ Hz), 7.44 (2H, d, $J = 8.5$ Hz), 7.51-7.58 (3H, m), 7.90-7.96 (4H, m), 8.72 (1H, d, $J = 1.8$ Hz), 12.65 (1H, s).

MS (ESI) m/z : 619 ($\text{M}+\text{H}$) $^+$.

For the powder X-ray diffraction ($\text{CuK}\alpha$, $\lambda = 1.54$ Å, scanning speed = $2^\circ/\text{min}$), the diffraction pattern is shown in FIG. 16, and peaks having a relative intensity of 12 or more based on the maximum peak intensity as 100 in FIG. 16 are shown in Table 16.

[Table 16]

Peak No.	2θ	d value	Relative intensity	Peak No.	2θ	d value	Relative intensity
1	5.64	15.66	28	7	16.18	5.47	28
2	6.92	12.76	24	8	17.04	5.20	70
3	8.06	10.96	100	9	21.84	4.07	12
4	11.32	7.81	42	10	22.50	3.95	12
5	13.92	6.36	14	11	23.82	3.73	12
6	14.40	6.15	55	12	24.28	3.66	18

(Test Example 1: Cell-free Axl kinase inhibitory activity)

A kinase dilution solution containing 170 ng/ml of AXL (a fusion protein of amino acids 464-885 of the intracellular domain of human AXL with glutathione transferase, expressed using the baculovirus expression system and purified by glutathione sepharose chromatography; Carna Biosciences, Inc., catalog No. 08-107) was prepared using a kinase reaction buffer (100 mM HEPES (pH 7.4), 0.003% Brij-35, 0.004% Tween-20, 1 mM DTT, 10 mM MgCl_2), and added at 19 μl to each well of a 384-well plate.

Next, the test compound was diluted with DMSO, and this diluted solution was added at 1 μl to each well.

After preincubation at room temperature for 30 minutes, a solution containing 1.5 μM of a substrate peptide (FL-Peptide 30 (5FAM-KKKKEEIYFFF- CONH_2), Caliper Life Sciences, catalog No. 760430) and 10 μM of ATP was prepared, and this was added at 5 μl to each well to initiate kinase reaction. The plate was incubated at 28°C for 1.5 hours, and 40 μl of a termination buffer (100 mM HEPES (pH 7.4), 0.015% Brij-35, 40 mM EDTA, 0.1% Coating Reagent 3) was added to each well to terminate the reaction.

The substrate peptide and the phosphorylated peptide in the reaction solution were separated and quantified by EZ Reader II (Caliper Life Sciences).

The kinase reaction was evaluated by the product ratio ($\text{P}/(\text{P}+\text{S})$) calculated from the peak height of the

substrate peptide (S) and the peak height of the phosphorylated peptide (P).

The inhibition was determined by the following formula (automatically calculated by the software of the EZ Reader II system):

$$\text{Inhibition (\%)} = 100 \times (1 - C_i/C_0)$$

where C_i represents the product ratio when the test compound is added, and C_0 represents the product ratio when DMSO is added in place of the test compound.

IC₅₀ was determined from inhibition data for 12 test compound concentrations by nonlinear regression (four-parameter logistic regression) using the following formula.

$$\text{Inhibition (\%)} = \text{Bottom} + (\text{Top} - \text{Bottom}) / (1 + ([\text{Compound}] / \text{IC}_{50})^{\text{slope}})$$

The compounds of Examples 3, 5, 9, 11, 12, 13, 15, 17, 24, 26 to 29, 38, 39, 40, 42, 50, 51, 62, 64, 71, 74, 76, 77, 80 and 85 had an inhibitory activity of $0.1 \text{ nM} \leq \text{IC}_{50} < 1 \text{ nM}$. The compounds of Examples 1, 2, 4, 6, 7, 8, 10, 14, 16, 18 to 23, 25, 30, 31, 33, 34, 37, 41, 43 to 49, 52 to 58, 60, 61, 63, 65, 66, 67, 69, 70, 72, 75, 78, 79, 82, 86, 87, 88 and 89 had an inhibitory activity of $1 \text{ nM} \leq \text{IC}_{50} < 10 \text{ nM}$. The compounds of Examples 32, 35, 36, 59, 68, 73, 83 and 84 had an inhibitory activity of $10 \text{ nM} \leq \text{IC}_{50} < 20 \text{ nM}$. The compound of Example 81 had an inhibitory activity of $\text{IC}_{50} = 23 \text{ nM}$.

(Test Example 2: Intracellular Axl phosphorylation inhibitory activity)

A phosphorylated Axl (hereinafter pAxl) inhibitory test was performed using the human non-small-cell lung cancer-derived cell strain NCI-H1299.

NCI-H1299 cells were suspended in a medium (RPMI 1640 medium containing 10% fetal bovine serum), inoculated into a 96-well multiwell plate at 15000 cells/100 μ l/well and cultured at 37°C in the presence of 5% CO₂ for one day. On the following day, the medium was removed, 100 μ l of a fresh medium was added and the cells were cultured at 37°C in the presence of 5% CO₂ for one day. The test compound was dissolved in DMSO and diluted with a medium to prepare a sample solution (DMSO concentration: 2%). 25 μ l of such a medium or sample-added medium was added to each well (DMSO concentration: 0.4%), and the plate was incubated at 37°C in the presence of 5% CO₂ for one hour.

GAS6 (R&D, catalog No.: 885-GS) was diluted to 6 μ g/ml with a medium, and the diluted solution was added at 25 μ l to each well. After stirring, the plate was incubated at 37°C in the presence of 5% CO₂ for 10 minutes.

The supernatant was discarded, and a solution of a 37% formalin solution diluted to 4% with phosphate buffer (PBS) (hereinafter 4% formalin solution) was added at 0.1

ml to each well. The plate was allowed to stand at room temperature for 10 minutes. Next, the 4% formalin solution was discarded, 0.2 ml of a solution of Triton X-100 diluted to 0.1% with PBS (hereinafter wash buffer) was added and discarded using a decanter, and the excess moisture was removed on a paper towel.

Subsequently, 110 μ l of NaN_3 and H_2O_2 were added to wash buffer at 0.1% (hereinafter quenching buffer), and 0.1 ml of the quenching buffer was added to each well, and the plate was allowed to stand at room temperature for 15 minutes.

The buffer was discarded, 0.2 ml of wash buffer was added and discarded using a decanter, and the excess moisture was removed on a paper towel. Skim milk (Nacalai Tesque) was added to wash buffer at a final concentration of 5% (blocking buffer), 0.25 ml of the blocking buffer was added to each well, and the plate was allowed to stand at room temperature for one hour.

The blocking buffer was discarded, anti-phospho-Axl (Y702) (D12B2) rabbit monoclonal antibody (Cell Signaling, catalog No. 5724) was reacted at a concentration of 1/1000, and the plate was allowed to stand at 4°C overnight. A washing operation with wash buffer was repeated five times, and Peroxidase AffiniPure Donkey Anti-Rabbit IgG (H+L) (Jackson ImmunoResearch, catalog No. 711-035-152) was reacted at a concentration of 1/2000 at room temperature for one hour. A similar washing

operation was performed, and 0.05 ml of Super Signal ELISA Pico Chemiluminescent Substrate (Thermo Scientific, catalog No. 37069) was added. After lightly stirring, the plate was incubated for 20 minutes. Luminescence was then measured by ARVO sx (PerkinElmer), and the pAxl (Y702) level was measured.

pAxl inhibitory activity was determined by the following formula.

$$\text{Inhibition \%} = 100 - (A-B) \times 100 / (T-B)$$

A: Measurement of the test compound

B: Luminescence value of the reaction solution with a positive control compound added at a concentration that inhibits phosphorylation at almost 100% (e.g., the luminescence value of the reaction solution with 1 μ M BMS-777607 added)

T: Luminescence value of the reaction solution with a compound not added

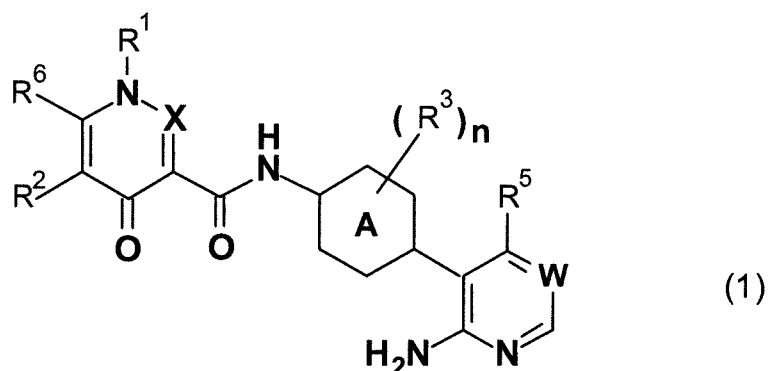
The 50% inhibitory concentration (IC_{50}) was determined from pAxl inhibitory activity data at multiple concentrations by GraphPad Prism 4.

The compounds of Examples 2 to 5, 8 to 13, 15 to 17, 19 to 21, 23 to 29, 37 to 67, 70, 71, 73 to 78, 80, 82, 83, 85, 86, 87 and 88 had an inhibitory activity of $0 \text{ nM} < IC_{50} < 50 \text{ nM}$. The compounds of Examples 1, 7, 14, 18, 22, 30, 33, 34, 72, 79 and 89 had an inhibitory activity of $50 \text{ nM} \leq IC_{50} < 100 \text{ nM}$. The compounds of Examples 6, 31,

32, 35, 36, 68, 69, 81 and 84 had an inhibitory activity of $100 \text{ nM} \leq \text{IC}_{50} < 500 \text{ nM}$.

Claims

1. A compound represented by the general formula (1):



wherein in the formula (1),

A represents a phenylene group or a six-membered heteroarylene group, where the amino group bonded to A and the nitrogen-containing heterocycle are para-positioned relative to each other,

R^1 represents a C_1 - C_6 alkyl group which may have one or more substituents selected from Group 1, an aryl group which may have one or more substituents selected from Group 2, a heteroaryl group which may have one or more substituents selected from Group 2, or a hydrogen atom,

R^2 represents a C_1 - C_6 alkyl group which may have one or more substituents selected from Group 1, a C_1 - C_6 alkoxy group which may have one or more substituents selected from a halogen atom and a

hydroxyl group, $-\text{CONR}^{\text{A}}\text{R}^{\text{B}}$ where R^{A} and R^{B} each independently represents a $\text{C}_1\text{-C}_6$ alkyl group which may have one or more substituents selected from a halogen atom, a $\text{C}_1\text{-C}_6$ alkoxy group and a hydroxyl group, or a hydrogen atom, or R^{A} and R^{B} together with the nitrogen atom to which they are bonded may form a three- to seven-membered heterocycloalkyl group which may have one or more substituents selected from a halogen atom, a $\text{C}_1\text{-C}_6$ alkyl group, a $\text{C}_1\text{-C}_6$ alkoxy group and a hydroxyl group, a cycloalkyl group which may have one or more substituents selected from Group 2, a phenyl group which may have one or more substituents selected from Group 2, a heteroaryl group which may have one or more substituents selected from Group 2, or a hydrogen atom,

R^3 is a substituent on A where n represents an integer from 0 to 4, and each R^3 may be identical to or different from each other when n is two or more, and represents a $\text{C}_1\text{-C}_6$ alkyl group which may have one or more substituents selected from Group 1, a $\text{C}_1\text{-C}_6$ alkoxy group which may have one or more substituents selected from a halogen atom and a hydroxyl group, a $\text{C}_1\text{-C}_6$ alkylthio group which may have one or more substituents

selected from a halogen atom and a hydroxyl group, a halogen atom, or a hydroxyl group, R^5 represents a C_1 - C_6 alkyl group which may have one or more substituents selected from Group 1, $-OR^C$ where R^C represents a C_1 - C_6 alkyl group which may have one or more substituents selected from a C_1 - C_6 alkoxy group, a halogen atom and a hydroxyl group, a three- to seven-membered heterocycloalkyl group which may have one or more substituents selected from a halogen atom, a C_1 - C_6 alkyl group and a hydroxyl group, or a hydrogen atom, a C_1 - C_6 alkylthio group which may have one or more substituents selected from a halogen atom and a hydroxyl group, or a hydrogen atom,

R^6 represents a hydrogen atom, or a C_1 - C_6 alkyl group which may have one or more substituents selected from Group 1,

W represents $C-R^4$ or a nitrogen atom where R^4 represents a C_1 - C_6 alkyl group which may have one or more substituents selected from Group 1, a C_1 - C_6 alkoxy group which may have one or more substituents selected from a C_1 - C_6 alkoxy group, a heterocycloalkyl group, a halogen atom and a hydroxyl group, a cycloalkyl group which may have one or more substituents selected from

Group 3, a cycloalkenyl group which may have one or more substituents selected from Group 3, a heterocycloalkyl group which may have one or more substituents selected from Group 3, a heterocycloalkenyl group which may have one or more substituents selected from Group 3, an aryl group which may have one or more substituents selected from Group 3, a heteroaryl group which may have one or more substituents selected from Group 3, a halogen atom, or a hydrogen atom, and X represents CH or a nitrogen atom, or a salt thereof,

Group 1:

a halogen atom,

$-NR^A R^B$ and $-CONR^A R^B$ where R^A and R^B each independently represents a C_1 - C_6 alkyl group which may have one or more substituents selected from a halogen atom, a C_1 - C_6 alkoxy group and a hydroxyl group, or a hydrogen atom, or R^A and R^B together with the nitrogen atom to which they are bonded may form a three- to seven-membered heterocycloalkyl group which may have one or more substituents selected from a halogen atom, a C_1 - C_6 alkyl group, a C_1 - C_6 alkoxy group and a hydroxyl group,

-OR^C where R^C represents a C₁-C₆ alkyl group which may have one or more substituents selected from a C₁-C₆ alkoxy group, a halogen atom and a hydroxyl group, a three- to seven-membered heterocycloalkyl group which may have one or more substituents selected from a halogen atom, a C₁-C₆ alkyl group and a hydroxyl group, or a hydrogen atom,

an aryl group which may have one or more substituents selected from a C₁-C₆ alkyl group which may have one or more substituents selected from a halogen atom and a hydroxyl group, a C₁-C₆ alkoxy group, an oxo group and a halogen atom, a heteroaryl group which may have one or more substituents selected from a C₁-C₆ alkyl group which may have one or more substituents selected from a halogen atom and a hydroxyl group, a C₁-C₆ alkoxy group, an oxo group, a hydroxyl group and a halogen atom,

a three- to seven-membered cycloalkyl group which may have one or more substituents selected from a C₁-C₆ alkyl group which may have one or more substituents selected from a halogen atom and a hydroxyl group, a C₁-C₆ alkoxy group, an oxo group, a hydroxyl group and a halogen atom,

and

a three- to seven-membered heterocycloalkyl group which may have one or more substituents selected from a C₁-C₆ alkyl group which may have one or more substituents selected from a halogen atom and a hydroxyl group, a C₁-C₆ alkoxy group, an oxo group, a hydroxyl group and a halogen atom

Group 2: a C₁-C₆ alkyl group which may have one or more substituents selected from a halogen atom and a hydroxyl group, a C₁-C₆ alkoxy group, an oxo group, a hydroxyl group and a halogen atom

Group 3: a C₁-C₆ alkyl group which may have one or more substituents selected from Group 1, a C₁-C₆ acyl group,

a C₁-C₆ alkylthio group which may have one or more substituents selected from a halogen atom and a hydroxyl group,

-CONR^AR^B where R^A and R^B each independently represents a C₁-C₆ alkyl group which may have one or more substituents selected from a halogen atom, a C₁-C₆ alkoxy group and a hydroxyl group, or a hydrogen atom, or R^A and R^B together with the nitrogen atom to which they are bonded may form a three- to seven-membered heterocycloalkyl group which may have one or more substituents

selected from a halogen atom, a C₁-C₆ alkyl group, a C₁-C₆ alkoxy group and a hydroxyl group, -OR^c where R^c represents a C₁-C₆ alkyl group which may have one or more substituents selected from a C₁-C₆ alkoxy group, a halogen atom, a three- to seven-membered heterocycloalkyl group and a hydroxyl group, a three- to seven-membered heterocycloalkyl group which may have one or more substituents selected from a halogen atom, a C₁-C₆ alkyl group and a hydroxyl group, or a hydrogen atom, and a heterocycloalkyl group which may have one or more substituents selected from Group 2.

2. A compound or salt thereof according to claim 1, wherein A is a phenylene group.

3. A compound or salt thereof according to claim 1 or 2, wherein W is C-R⁴.

4. A compound or salt thereof according to any one of claims 1 to 3, wherein n is 0.

5. A compound or salt thereof according to any one of claims 1 to 4, wherein R⁵ is a hydrogen atom.

7. A compound according to any one of claims 1 to 5 which is N-{4-[2-Amino-5-(3,4-dimethoxyphenyl)pyridin-3-yl]phenyl}-5-(4-fluorophenyl)-4-oxo-1-(2,2,2-trifluoroethyl)-1,4-dihydropyridine-3-carboxamide or a salt thereof.
8. A compound according to any one of claims 1 to 5 which is N-{4-[2-Amino-5-(3,4-dimethoxyphenyl)pyridin-3-yl]phenyl}-5-(4-fluorophenyl)-4-oxo-1-(2,2,2-trifluoroethyl)-1,4-dihydropyridine-3-carboxamide hydrochloride.
9. A crystal of a compound according to any one of claims 1 to 5 which is N-{4-[2-amino-5-(3,4-dimethoxyphenyl)pyridin-3-yl]phenyl}-5-(4-fluorophenyl)-4-oxo-1-(2,2,2-trifluoroethyl)-1,4-dihydropyridine-3-carboxamide hydrochloride.
10. A crystal according to claim 9, which has an X-ray diffraction pattern shown in any one of Figures 1 to 16 in a powder X-ray diffraction diagram obtained by irradiation with copper K α radiation (wavelength $\lambda = 1.54 \text{ \AA}$).
11. A crystal according to claim 9, which has characteristic peaks at diffraction angles 2θ of

7.44, 10.00, 13.48, 14.86, 16.10, 19.30, 20.30, 22.62, 23.02, 23.70, 24.54, 25.92 and 28.46 in a powder X-ray diffraction diagram obtained by irradiation with copper K α radiation (wavelength λ = 1.54 Å).

12. A crystal according to claim 9, which has characteristic peaks at diffraction angles 2θ of 4.32, 9.10, 15.52, 18.32, 18.54, 19.22, 20.54, 20.70, 23.54, 24.14, 25.34 and 27.02 in a powder X-ray diffraction diagram obtained by irradiation with copper K α radiation (wavelength λ = 1.54 Å).

13. A crystal according to claim 9, which has characteristic peaks at diffraction angles 2θ of 13.86, 15.04, 19.76, 20.58, 22.26, 22.58, 23.82, 24.10, 24.36 and 24.88 in a powder X-ray diffraction diagram obtained by irradiation with copper K α radiation (wavelength λ = 1.54 Å).

14. A crystal according to claim 9, which has characteristic peaks at diffraction angles 2θ of 5.34, 7.22, 8.20, 11.68, 14.54, 15.74, 17.54, 23.24, 23.72, 25.12 and 26.16 in a powder X-ray diffraction

diagram obtained by irradiation with copper $K\alpha$ radiation (wavelength $\lambda = 1.54 \text{ \AA}$).

15. A crystal according to claim 9, which has characteristic peaks at diffraction angles 2θ of 11.02, 11.86, 15.56, 18.20, 22.12, 24.70, 25.80, 26.04, 26.26 and 28.62 in a powder X-ray diffraction diagram obtained by irradiation with copper $K\alpha$ radiation (wavelength $\lambda = 1.54 \text{ \AA}$).

16. A crystal according to claim 9, which has characteristic peaks at diffraction angles 2θ of 3.58, 4.56, 6.60, 6.72, 7.20, 9.62, 10.28, 13.06 and 24.52 in a powder X-ray diffraction diagram obtained by irradiation with copper $K\alpha$ radiation (wavelength $\lambda = 1.54 \text{ \AA}$).

17. A crystal according to claim 9, which has characteristic peaks at diffraction angles 2θ of 7.78, 8.14, 8.88, 12.54, 15.68, 16.36, 18.76, 19.34, 20.08, 22.36, 24.66, 25.74, 26.70 and 28.02 in a powder X-ray diffraction diagram obtained by irradiation with copper $K\alpha$ radiation (wavelength $\lambda = 1.54 \text{ \AA}$).

18. A crystal according to claim 9, which has characteristic peaks at diffraction angles 2θ of 5.78, 8.90, 13.66, 14.42, 16.84, 17.56, 19.26, 20.74, 22.42, 24.66, 25.12, 25.60 and 26.96 in a powder X-ray diffraction diagram obtained by irradiation with copper $K\alpha$ radiation (wavelength $\lambda = 1.54 \text{ \AA}$).

19. A crystal according to claim 9, which has characteristic peaks at diffraction angles 2θ of 11.12, 14.82, 18.86, 20.32, 20.66, 21.64, 22.36, 22.68, 23.00, 24.10, 25.26 and 27.00 in a powder X-ray diffraction diagram obtained by irradiation with copper $K\alpha$ radiation (wavelength $\lambda = 1.54 \text{ \AA}$).

20. A crystal according to claim 9, which has characteristic peaks at diffraction angles 2θ of 7.80, 12.18, 12.78, 16.20, 16.82, 19.20, 19.66, 20.20, 21.20, 24.52, 25.68 and 26.78 in a powder X-ray diffraction diagram obtained by irradiation with copper $K\alpha$ radiation (wavelength $\lambda = 1.54 \text{ \AA}$).

21. A crystal according to claim 9, which has characteristic peaks at diffraction angles 2θ of 2.80, 6.86, 7.88, 11.60, 13.68, 14.86, 17.40, 22.40,

23.78 and 25.74 in a powder X-ray diffraction diagram obtained by irradiation with copper K α radiation (wavelength $\lambda = 1.54 \text{ \AA}$).

22. A crystal according to claim 9, which has characteristic peaks at diffraction angles 2θ of 5.32, 7.98, 10.68, 11.70, 14.84, 16.02, 19.78, 21.76, 23.08, 25.30 and 25.68 in a powder X-ray diffraction diagram obtained by irradiation with copper K α radiation (wavelength $\lambda = 1.54 \text{ \AA}$).

23. A crystal according to claim 9, which has characteristic peaks at diffraction angles 2θ of 8.10, 10.60, 12.06, 14.16, 14.58, 15.60, 18.16, 20.72, 20.94, 22.86, 23.90, 24.32 and 27.14 in a powder X-ray diffraction diagram obtained by irradiation with copper K α radiation (wavelength $\lambda = 1.54 \text{ \AA}$).

24. A crystal according to claim 9, which has characteristic peaks at diffraction angles 2θ of 3.60, 6.22, 9.56, 10.42, 14.04, 14.66, 15.30, 16.40, 19.52, 22.12 and 26.42 in a powder X-ray diffraction diagram obtained by irradiation with copper K α radiation (wavelength $\lambda = 1.54 \text{ \AA}$).

25. A crystal according to claim 9, which has characteristic peaks at diffraction angles 2θ of 5.46, 7.98, 9.54, 11.00, 14.00, 15.36, 16.56, 22.00, 23.54, 24.00 and 26.56 in a powder X-ray diffraction diagram obtained by irradiation with copper $K\alpha$ radiation (wavelength $\lambda = 1.54 \text{ \AA}$).

26. A crystal according to claim 9, which has characteristic peaks at diffraction angles 2θ of 5.64, 6.92, 8.06, 11.32, 14.40, 16.18, 17.04, 21.84, 22.50, 23.82 and 24.28 in a powder X-ray diffraction diagram obtained by irradiation with copper $K\alpha$ radiation (wavelength $\lambda = 1.54 \text{ \AA}$).

27. An Axl inhibitor comprising a compound or salt thereof according to any one of claims 1 to 6, or a crystal thereof.

28. A medicine comprising a compound or salt thereof according to any one of claims 1 to 6, or a crystal thereof as an active ingredient.

29. A compound or salt thereof according to any one of claims 1 to 6, or a crystal thereof, for use in medicine.

30. A pharmaceutical composition comprising a compound or salt thereof according to any one of claims 1 to 6, or a crystal thereof, and a pharmaceutically acceptable carrier.

31. A medicine according to claim 28, a compound or salt thereof according to any one of claims 1 to 6, or a crystal thereof, or a pharmaceutical composition according to claim 30 for use in treating a disease caused by Axl kinase hyperfunction, a disease associated with Axl kinase hyperfunction and/or a disease accompanied by Axl kinase hyperfunction.

32. A medicine according to claim 28, a compound or salt thereof according to any one of claims 1 to 6, or a crystal thereof, or a pharmaceutical composition according to claim 30, for use in treating hyperproliferative disease, treating cancer, preventing cancer metastasis, or overcoming drug resistance.

33. A medicine, a compound or salt thereof, or a crystal thereof, or a pharmaceutical composition for use according to claim 32, wherein the cancer is selected from breast cancer, colon cancer, prostate

cancer, lung cancer, gastric cancer, ovarian cancer, endometrial cancer, renal cancer, hepatocellular carcinoma, thyroid cancer, uterine cancer, esophageal cancer, squamous cell carcinoma, leukemia, osteosarcoma, melanoma, glioblastoma, neuroblastoma and pancreatic cancer.