

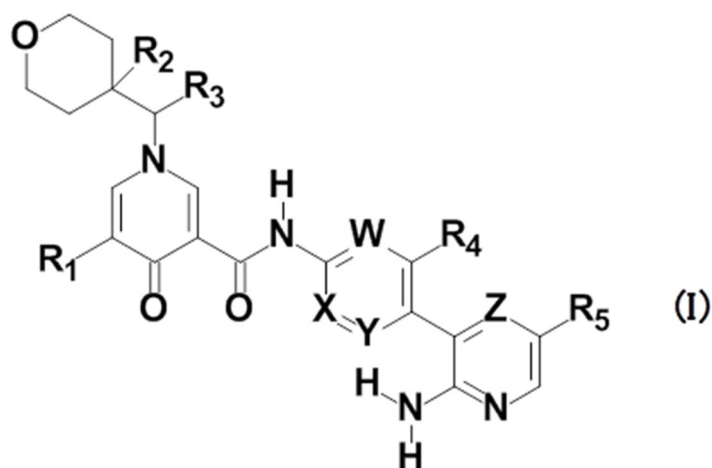
thereof has high Axl inhibitory specificity and low inhibitory activity against Mer, and further found that this compound or salt thereof induces no retinal toxicity in a long-term administration test using mice.

Specifically, the present invention relates to the following [1] to [53]:

[1]

A compound represented by the general formula (I) or a pharmaceutically acceptable salt thereof:

[Formula 1]



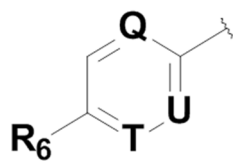
wherein

W, X, and Y each independently represent a nitrogen atom, C-H, C-F, or C-Cl,

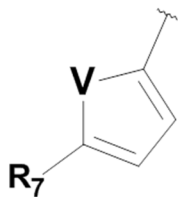
Z represents a nitrogen atom, C-H, C-F, C-Cl, or C-C₁-C₆ alkyl or C-C₁-C₆ alkoxy group,

R₁ represents a group represented by the following formula (II-1) or (II-2):

[Formula 2]



(II-1)



(II-2)

wherein in the formula (II-1),

Q represents a nitrogen atom, C-H, or C-F,

T represents a nitrogen atom or C-H,

U represents a nitrogen atom or C-H, and

R₆ represents a halogen atom, a C₁-C₆ alkyl group, a C₃-C₆ cycloalkyl group, a cyano group, or a trifluoromethoxy group, and

in the formula (II-2),

V represents a sulfur atom or an oxygen atom, and

R₇ represents a C₁-C₆ alkyl group,

R₂ represents a hydrogen atom, a halogen atom, a C₁-C₆ alkyl group, a C₁-C₆ alkoxy group, or a cyano group,

R₃ represents a hydrogen atom or a C₁-C₆ alkyl group,

R₄ represents a hydrogen atom, a halogen atom, or a C₁-C₆ alkyl group, and

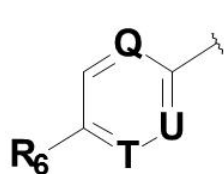
R₅ represents a hydrogen atom or a group represented by the following formula (III-1), (III-2), (III-3), or (III-4):

W, X, and Y each independently represent a nitrogen atom, C-H, C-F, or C-Cl.

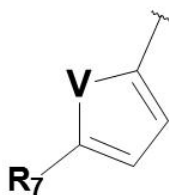
Z represents a nitrogen atom, C-H, C-F, C-C₁-C₆ alkoxy group, C-C₁-C₆ alkoxy group, or C-Cl.

R₁ represents a group represented by the following formula (II-1) or (II-2):

[Formula 14]



(II-1)



(II-2)

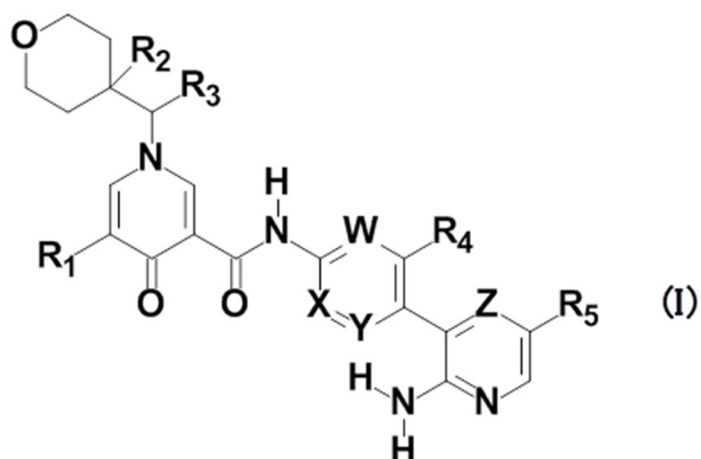
wherein in the formula (II-1), Q represents a nitrogen atom, C-H, or C-F, T represents a nitrogen atom or C-H, U represents a nitrogen atom or C-H, and R₆ represents a halogen atom, a C₁-C₆ alkyl group, a C₃-C₆ cycloalkyl group, a cyano group, or a trifluoromethoxy group, and in the formula (II-2), V represents a sulfur atom or an oxygen atom, and R₇ represents a C₁-C₆ alkyl group.

R₂ represents a hydrogen atom, a halogen atom, a C₁-C₆ alkyl group, a C₁-C₆ alkoxy group, or a cyano group. In this context, the C₁-C₆ alkyl group is preferably a methyl group, an ethyl group, or a propyl group. The C₁-C₆ alkoxy group is preferably a methoxy group or an ethoxy group.

R₃ represents a hydrogen atom or a C₁-C₆ alkyl group. The C₁-C₆ alkyl group is preferably a methyl group, an ethyl group, or a propyl group.

Claims

1. A compound represented by the general formula (I) or a pharmaceutically acceptable salt thereof:

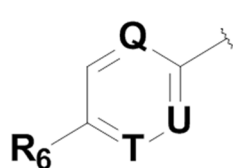


wherein

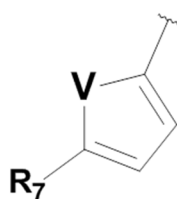
W, X, and Y each independently represent a nitrogen atom, C-H, C-F, or C-Cl,

Z represents a nitrogen atom, C-H, C-F, C-Cl, C-C₁-C₆ alkyl or C-C₁-C₆ alkoxy group,

R₁ represents a group represented by the following formula (II-1) or (II-2):



(II-1)



(II-2)

wherein in the formula (II-1),

Q represents a nitrogen atom, C-H, or C-F,

T represents a nitrogen atom or C-H,

U represents a nitrogen atom or C-H, and

R₆ represents a halogen atom, a C₁-C₆ alkyl group, a C₃-C₆ cycloalkyl group, a cyano group, or a trifluoromethoxy group, and

in the formula (II-2),

V represents a sulfur atom or an oxygen atom, and

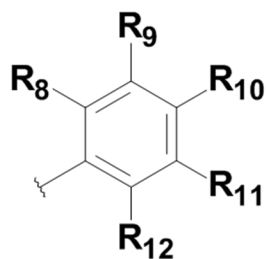
R₇ represents a C₁-C₆ alkyl group,

R₂ represents a hydrogen atom, a halogen atom, a C₁-C₆ alkyl group, a C₁-C₆ alkoxy group, or a cyano group,

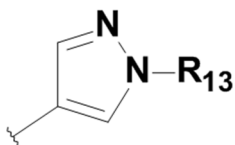
R₃ represents a hydrogen atom or a C₁-C₆ alkyl group,

R₄ represents a hydrogen atom, a halogen atom, or a C₁-C₆ alkyl group, and

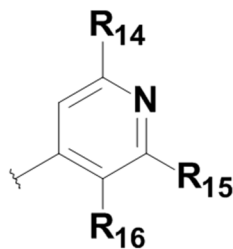
R₅ represents a hydrogen atom or a group represented by the following formula (III-1), (III-2), (III-3), or (III-4):



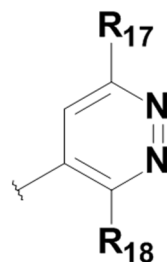
(III-1)



(III-2)



(III-3)



(III-4)

wherein in the formula (III-1),

R₈ and R₁₂ each independently represent a hydrogen atom or a deuterium atom,

R₉ represents a hydrogen atom, a halogen atom, or a C₁-C₆ alkoxy group,

R₁₀ represents a hydrogen atom, a C₁-C₆ alkyl group optionally substituted by a heterocycloalkyl group, or a C₁-C₆ alkoxy group optionally substituted by a heterocycloalkyl group optionally substituted by a C₁-C₆ alkyl group, and

R₁₁ represents a hydrogen atom, a C₁-C₆ alkoxy group, or a deuterium-substituted C₁-C₆ alkoxy group,

in the formula (III-2),

R₁₃ represents a C₁-C₆ alkyl group optionally substituted by a heterocycloalkyl group, or a heterocycloalkyl group,

in the formula (III-3),

R₁₄ represents a hydrogen atom or a C₁-C₆ alkyl group,

R₁₅ represents a hydrogen atom, a C₁-C₆ alkyl group, or a C₁-C₆ alkoxy group, and

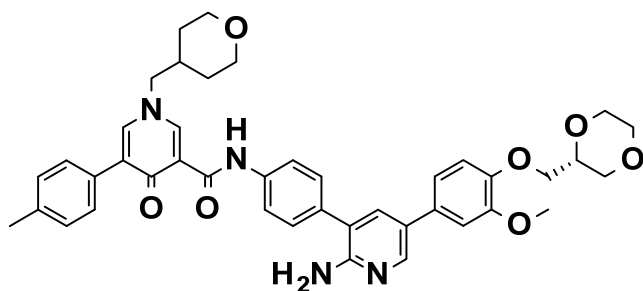
R₁₆ represents a hydrogen atom or a halogen atom, and

in the formula (III-4),

R₁₇ represents a C₁-C₆ alkoxy group, and

R₁₈ represents a C₁-C₆ alkoxy group.

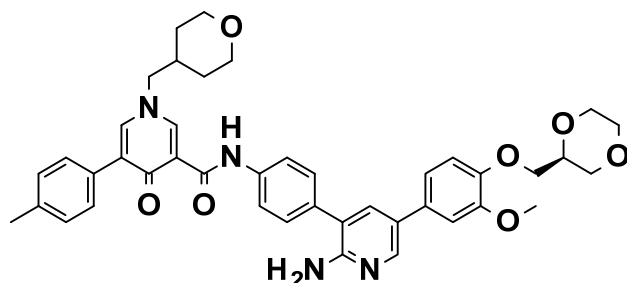
2. A compound according to claim 1 which is N-[4-(2-Amino-5-{4-[(2R)-1,4-dioxan-2-ylmethoxy]-3-methoxyphenyl}pyridin-3-yl)phenyl]-5-(4-methylphenyl)-4-oxo-1-(tetrahydro-2H-pyran-4-ylmethyl)-1,4-dihydropyridine-3-carboxamide represented by the following formula:



or a pharmaceutically acceptable salt thereof.

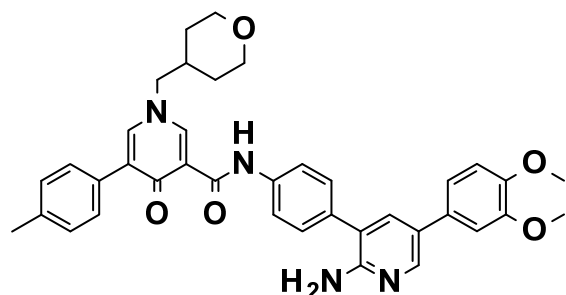
3. A compound according to claim 1 which is N-[4-(2-Amino-5-{4-[(2S)-1,4-dioxan-2-ylmethoxy]-3-methoxyphenyl}pyridin-3-

yl)phenyl]-5-(4-methylphenyl)-4-oxo-1-(tetrahydro-2H-pyran-4-ylmethyl)-1,4-dihydropyridine-3-carboxamide represented by the following formula:



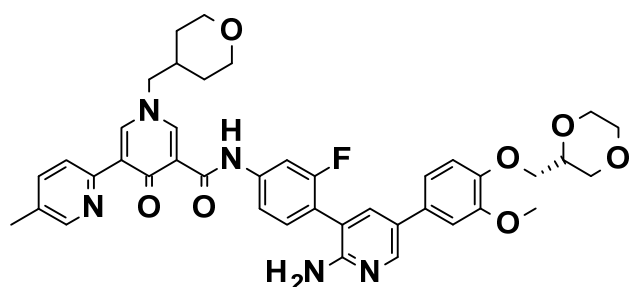
or a pharmaceutically acceptable salt thereof.

4. A compound according to claim 1 which is N-{4-[2-Amino-5-(3,4-dimethoxyphenyl)pyridin-3-yl]phenyl}-5-(4-methylphenyl)-4-oxo-1-(tetrahydro-2H-pyran-4-ylmethyl)-1,4-dihydropyridine-3-carboxamide represented by the following formula:



or a pharmaceutically acceptable salt thereof.

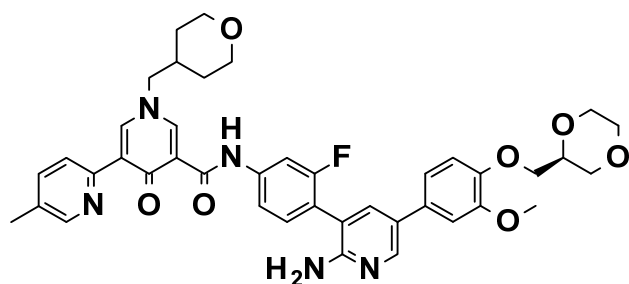
5. A compound according to claim 1 which is N-[4-(2-Amino-5-{4-[(2R)-1,4-dioxan-2-ylmethoxy]-3-methoxyphenyl}pyridin-3-yl)-3-fluorophenyl]-5-methyl-4'-oxo-1'-(tetrahydro-2H-pyran-4-ylmethyl)-1',4'-dihydro-2,3'-bipyridine-5'-carboxamide represented by the following formula:



or a pharmaceutically acceptable salt thereof.

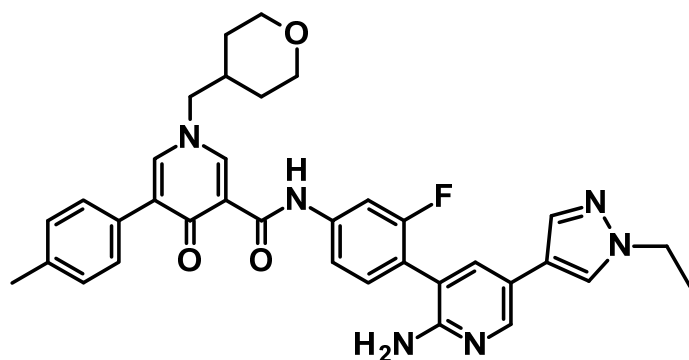
6. A compound according to claim 1 which is selected from the group consisting of:

N-[4-(2-Amino-5-{4-[(2S)-1,4-dioxan-2-ylmethoxy]-3-methoxyphenyl}pyridin-3-yl)-3-fluorophenyl]-5-methyl-4'-oxo-1'-(tetrahydro-2H-pyran-4-ylmethyl)-1',4'-dihydro-2,3'-bipyridine-5'-carboxamide represented by the following formula:



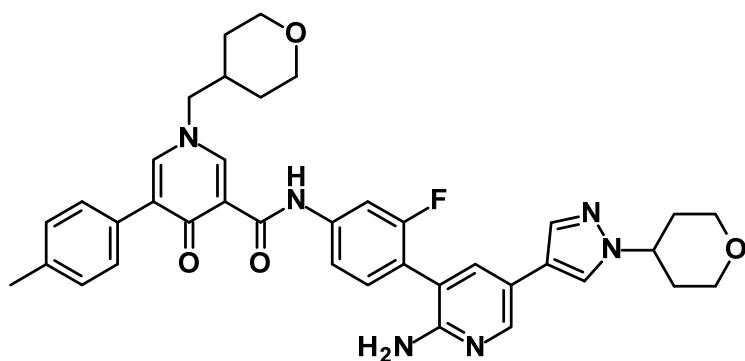
or a pharmaceutically acceptable salt thereof;

N-{4-[2-Amino-5-(1-ethyl-1H-pyrazol-4-yl)pyridin-3-yl]-3-fluorophenyl}-5-(4-methylphenyl)-4-oxo-1-(tetrahydro-2H-pyran-4-ylmethyl)-1,4-dihydropyridine-3-carboxamide represented by the following formula:



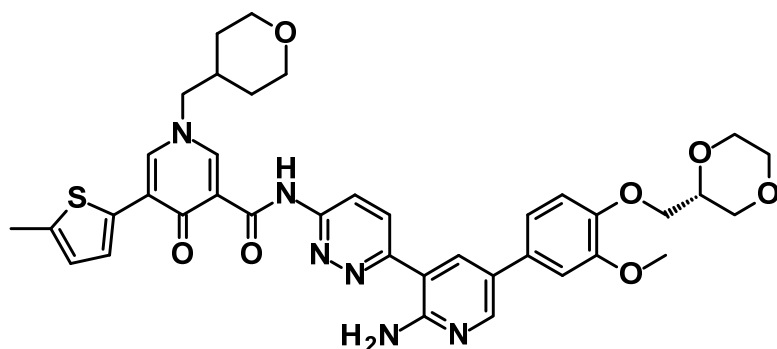
or a pharmaceutically acceptable salt thereof;

N-(4-{2-Amino-5-[1-(tetrahydro-2H-pyran-4-yl)-1H-pyrazol-4-yl]pyridin-3-yl}-3-fluorophenyl)-5-(4-methylphenyl)-4-oxo-1-(tetrahydro-2H-pyran-4-ylmethyl)-1,4-dihydropyridine-3-carboxamide represented by the following formula:

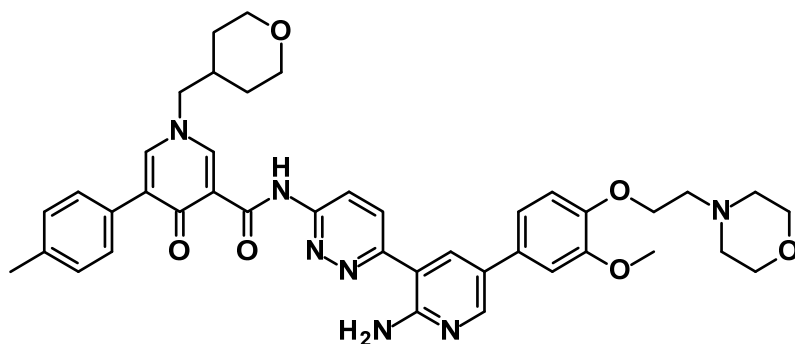


or a pharmaceutically acceptable salt thereof;

N-[6-(2-Amino-5-{4-[(2R)-1,4-dioxan-2-ylmethoxy]-3-methoxyphenyl}pyridin-3-yl)pyridazin-3-yl]-5-(5-methylthiophen-2-yl)-4-oxo-1-(tetrahydro-2H-pyran-4-ylmethyl)-1,4-dihydropyridine-3-carboxamide represented by the following formula:



or a pharmaceutically acceptable salt thereof; and
 N-[6-(2-Amino-5-{3-methoxy-4-[2-(morpholin-4-yl)ethoxy]phenyl}pyridin-3-yl)pyridazin-3-yl]-5-(4-methylphenyl)-4-oxo-1-(tetrahydro-2H-pyran-4-ylmethyl)-1,4-dihydropyridine-3-carboxamide represented by the following formula:



or a pharmaceutically acceptable salt thereof.

7. A hydrobromide, nitrate, sulfate, phosphate, methanesulfonate, ethanesulfonate, benzenesulfonate, or p-toluenesulfonate of a compound according to claim 2.
8. A methanesulfonate of a compound according to claim 4.

9. A methanesulfonate, phosphate, naphthalene-1,5-disulfonate, or sulfate of a compound according to claim 5.

10. A crystal of a methanesulfonate according to claim 7, wherein the crystal exhibits characteristic peaks at diffraction angles $2\theta = 3.74, 7.56, 8.96, 11.38, 12.36, 14.78, 15.60, 16.16, 18.70$, and 24.10 in a powder X-ray diffraction pattern obtained by irradiation with copper $K\alpha$ radiation (wavelength $\lambda = 1.54$ angstroms).

11. A crystal of a hydrobromide according to claim 7, wherein the crystal exhibits characteristic peaks at diffraction angles $2\theta = 3.84, 7.72, 9.40, 11.62, 14.92, 15.48, 16.70, 18.88, 19.32$, and 24.40 in a powder X-ray diffraction pattern obtained by irradiation with copper $K\alpha$ radiation (wavelength $\lambda = 1.54$ angstroms).

12. A crystal of a nitrate according to claim 7, wherein the crystal exhibits characteristic peaks at diffraction angles $2\theta = 3.82, 7.66, 9.28, 9.52, 11.54, 15.26, 15.54, 16.62, 19.24$, and 24.56 in a powder X-ray diffraction pattern obtained by irradiation with copper $K\alpha$ radiation (wavelength $\lambda = 1.54$ angstroms).

13. A crystal of a sulfate according to claim 7, wherein the crystal exhibits characteristic peaks at diffraction angles $2\theta = 3.74, 7.56, 8.92, 9.58, 11.36, 12.38, 14.68, 15.64, 16.06$, and 24.38 in a powder X-ray diffraction pattern obtained by irradiation with copper $K\alpha$ radiation (wavelength $\lambda = 1.54$ angstroms).

14. A crystal of a phosphate according to claim 7, wherein the crystal exhibits characteristic peaks at diffraction angles $2\theta =$

3.74, 7.56, 8.80, 9.56, 11.34, 14.56, 15.74, 23.68, 24.34, and 24.68 in a powder X-ray diffraction pattern obtained by irradiation with copper K α radiation (wavelength λ = 1.54 angstroms).

15. A crystal of an ethanesulfonate according to claim 7, wherein the crystal exhibits characteristic peaks at diffraction angles 2θ = 6.72, 7.90, 12.02, 13.40, 16.90, 17.88, 19.00, 19.80, 21.26, and 24.18 in a powder X-ray diffraction pattern obtained by irradiation with copper K α radiation (wavelength λ = 1.54 angstroms).

16. A crystal of a benzenesulfonate according to claim 7, wherein the crystal exhibits characteristic peaks at diffraction angles 2θ = 9.22, 10.60, 10.82, 11.10, 13.40, 15.78, 17.50, 18.66, 21.02, and 26.10 in a powder X-ray diffraction pattern obtained by irradiation with copper K α radiation (wavelength λ = 1.54 angstroms).

17. A crystal of a p-toluenesulfonate according to claim 7, wherein the crystal exhibits characteristic peaks at diffraction angles 2θ = 4.18, 5.12, 13.44, 14.98, 16.96, 17.44, 18.92, 19.72, 20.16, and 23.04 in a powder X-ray diffraction pattern obtained by irradiation with copper K α radiation (wavelength λ = 1.54 angstroms).

18. A crystal of a phosphate according to claim 9, wherein the crystal exhibits characteristic peaks at diffraction angles 2θ = 4.28, 8.42, 8.64, 10.54, 12.72, 13.48, 15.90, 17.00, 17.46, and 21.26 in a powder X-ray diffraction pattern obtained by irradiation with copper K α radiation (wavelength λ = 1.54 angstroms).

19. A crystal of a sulfate according to claim 9, wherein the crystal exhibits characteristic peaks at diffraction angles $2\theta = 3.66, 6.42, 7.32, 9.76, 11.00, 12.88, 18.42, 19.62, 20.54,$ and 24.22 in a powder X-ray diffraction pattern obtained by irradiation with copper $K\alpha$ radiation (wavelength $\lambda = 1.54$ angstroms).

20. A crystal of a sulfate according to claim 9, wherein the crystal exhibits characteristic peaks at diffraction angles $2\theta = 3.64, 6.40, 7.32, 9.76, 17.38, 18.42, 19.64, 20.56, 22.90,$ and 24.20 in a powder X-ray diffraction pattern obtained by irradiation with copper $K\alpha$ radiation (wavelength $\lambda = 1.54$ angstroms).

21. A crystal of a sulfate according to claim 9, wherein the crystal exhibits characteristic peaks at diffraction angles $2\theta = 3.64, 6.40, 7.30, 9.76, 17.34, 18.38, 19.34, 20.56, 21.52,$ and 22.94 in a powder X-ray diffraction pattern obtained by irradiation with copper $K\alpha$ radiation (wavelength $\lambda = 1.54$ angstroms).

22. A crystal of a sulfate according to claim 9, wherein the crystal exhibits characteristic peaks at diffraction angles $2\theta = 3.62, 6.38, 7.28, 9.74, 17.30, 18.36, 19.54, 20.52, 22.86,$ and 24.14 in a powder X-ray diffraction pattern obtained by irradiation with copper $K\alpha$ radiation (wavelength $\lambda = 1.54$ angstroms).

23. A crystal of a sulfate according to claim 9, wherein the crystal exhibits characteristic peaks at diffraction angles $2\theta = 3.64, 6.40, 7.30, 9.76, 12.86, 18.40, 19.62, 20.54, 22.92,$ and 24.20 in a powder X-ray diffraction pattern obtained by

irradiation with copper K α radiation (wavelength λ = 1.54 angstroms).

24. A crystal of a sulfate according to claim 9, wherein the crystal exhibits characteristic peaks at diffraction angles 2θ = 3.64, 6.36, 7.30, 18.36, 19.04, 19.42, 19.70, 20.12, 20.42, and 21.32 in a powder X-ray diffraction pattern obtained by irradiation with copper K α radiation (wavelength λ = 1.54 angstroms).

25. A crystal of a sulfate according to claim 9, wherein the crystal exhibits characteristic peaks at diffraction angles 2θ = 5.62, 7.18, 9.22, 10.36, 15.56, 16.40, and 20.86 in a powder X-ray diffraction pattern obtained by irradiation with copper K α radiation (wavelength λ = 1.54 angstroms).

26. A crystal of a naphthalene-1,5-disulfonate according to claim 9, wherein the crystal exhibits characteristic peaks at diffraction angles 2θ = 6.14, 6.98, 11.24, 14.84, 17.48, 19.54, 20.94, 22.38, 23.20, and 24.70 in a powder X-ray diffraction pattern obtained by irradiation with copper K α radiation (wavelength λ = 1.54 angstroms).

27. A crystal of a naphthalene-1,5-disulfonate according to claim 9, wherein the crystal exhibits characteristic peaks at diffraction angles 2θ = 9.24, 9.58, 14.00, 14.46, 16.70, 17.02, 18.22, 20.24, 21.64, and 25.52 in a powder X-ray diffraction pattern obtained by irradiation with copper K α radiation (wavelength λ = 1.54 angstroms).

28. An Ax1 inhibitor comprising a compound according to any one of claims 1 to 6 or a pharmaceutically acceptable salt thereof.

29. A pharmaceutical composition comprising a compound according to any one of claims 1 to 6 or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.

30. A medicament comprising a compound according to any one of claims 1 to 6 or a pharmaceutically acceptable salt thereof as an active ingredient.

31. A compound according to any one of claims 1 to 6 or a pharmaceutically acceptable salt thereof, a pharmaceutical composition according to claim 29 or a medicament according to claim 30 for use in therapy.

32. A compound according to any one of claims 1 to 6 or a pharmaceutically acceptable salt thereof, a pharmaceutical composition according to claim 29 or a medicament according to claim 30 for use in the treatment of a hyperproliferative disease.

33. A compound according to any one of claims 1 to 6 or a pharmaceutically acceptable salt thereof, a pharmaceutical composition according to claim 29 or a medicament according to claim 30 for use in the treatment of a cancer, the prevention of cancer metastasis, overcoming drug resistance of a cancer, or the inhibition of drug resistance acquisition of a cancer.

34. A compound, a pharmaceutical composition or a medicament for use in the treatment of a cancer, the prevention of cancer metastasis, overcoming drug resistance of a cancer, or the inhibition of drug resistance acquisition of a cancer according to claim 33, wherein the cancer is selected from breast cancer, colon cancer, prostate cancer, lung cancer, gastric cancer, ovary cancer, endometrial cancer, kidney cancer, hepatocellular

cancer, thyroid gland cancer, uterus cancer, esophagus cancer, squamous cell cancer, leukemia, osteosarcoma, melanoma, glioblastoma, neuroblastoma, and pancreatic cancer.