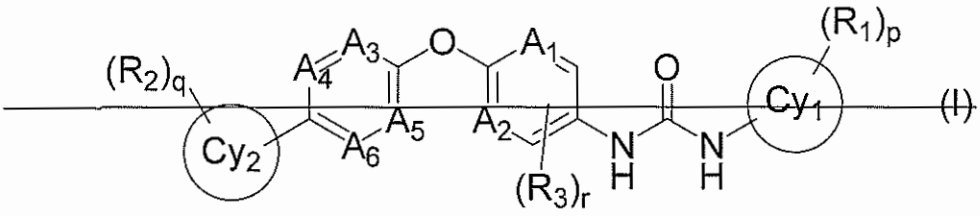
CLAIMS

1. ~~A compound~~ 1-(2-(4-(2-amino-5-fluoropyridin-3-yl)phenoxy)pyrimidin-5-yl)-3-(2-(pyridin-3-yl)-5-(trifluoromethyl)phenyl)urea. ~~represented by the general formula (I):~~



~~wherein:~~

~~a ring Cy_1 represents a C3-10 monocyclic carbocycle or bicyclic carbocycle or a 4- to 10-membered monocyclic heterocycle or bicyclic heterocycle;~~

~~a ring Cy_2 represents a 4- to 10-membered monocyclic heterocycle or bicyclic heterocycle excluding a heterocycle 1,3-thiazol-5-yl group;~~

~~R_1 represents:~~

~~(1) a halogen;~~

~~(2) a C1-6 alkyl group, C2-6 alkenyl group or C2-6 alkynyl group optionally substituted with a substituent selected from the group consisting of (i) a halogen and (ii) a hydroxy group;~~

~~(3) a C5-6 monocyclic carbocycle optionally substituted with one or two R_5 groups;~~

~~(4) a 5- to 6-membered monocyclic heterocycle optionally substituted with one or two R_5 groups;~~

~~(5) $-S(O)_{m1}-R_6$;~~

~~(6) $-SO_2NR_7R_8$;~~

~~(7) $-C(O)OR_9$;~~

~~(8) $-NR_{10}C(O)R_{11}$;~~

~~(9) $-C(O)NR_{12}R_{13}$;~~

~~(10) $-OR_{14}$;~~

~~(11) $-NR_{15}R_{16}$;~~

~~(12) a cyano group; or~~

~~(13) a nitro group;~~

~~R_5 represents:~~

~~(1) a halogen;~~

~~(2) $-S(O)_{m2}-R_{17}$;~~

~~(3) $-SO_2NR_{18}R_{19}$;~~

~~(4) $-C(O)OR_{20}$;~~

~~(5) $-NR_{21}C(O)R_{22}$;~~

~~(6) $-C(O)NR_{23}R_{24}$;~~

~~(7) $-OR_{25}$;~~

~~(8) $-NR_{26}R_{27}$;~~

~~(9) a cyano group;~~

~~(10) a nitro group; or~~

~~(11) a C1-3 alkyl group optionally substituted with a substituent selected from the group consisting of (i) a halogen, (ii) a hydroxy group and (iii) an oxo group;~~

~~when two R_5 groups are present, the R_5 groups may be independently the same or different;~~

~~when, further, two R_5 groups are respectively and independently a C1-3 alkyl group or a hydroxy group and the R_5 groups are attached to carbon atoms adjacent to each other on the C5-6 monocyclic carbocycle or the 5- to 6-membered monocyclic heterocycle, the R_5 groups may together form a ring;~~

~~R_6 to R_{27} respectively and independently represent (1) a hydrogen atom or (2) a C1-6 alkyl group optionally substituted with (i) a halogen or (ii) a hydroxy group;~~

~~when R_{18} and R_{19} are respectively and independently a C1-6 alkyl group, R_{18} and R_{19} groups may together form a ring;~~

~~R_2 represents:~~

~~(1) a halogen;~~

~~(2) a C1-6 alkyl group optionally substituted with (i) a halogen or (ii) a hydroxy group;~~

~~(3) a C3-6 cycloalkyl group optionally substituted with (i) a halogen or (ii) a hydroxy group;~~

~~(4) a C1-6 alkoxy group optionally substituted with a halogen;~~
~~(5) $-NR_{28}R_{29}$;~~
~~(6) a 3- to 7-membered monocyclic heterocycle; or~~
~~(7) O-(3- to 7-membered monocyclic heterocycle);~~
~~R_{28} and R_{29} respectively and independently represent (1) a hydrogen atom or (2) a C1-6 alkyl group optionally substituted with (i) a halogen or (ii) a hydroxy group;~~
~~A_1 and A_2 respectively and independently represent $=CR_3-$ or $=N-$;~~
~~A_3, A_4, A_5 and A_6 respectively and independently represent $=CR_4-$ or $=N-$;~~
~~R_3 and R_4 respectively and independently represent a hydrogen atom or a halogen;~~
~~m1 represents an integer of 0 to 2;~~
~~m2 represents an integer of 0 to 2;~~
~~p represents an integer of 0 to 7;~~
~~q represents an integer of 0 to 7;~~
~~r represents an integer of 0 to 2;~~
~~provided that when p, q and r respectively represent an integer of 2 or more, R_1, R_2 and R_3 groups may be respectively and independently the same or different, a salt thereof, an N-oxide thereof, a solvate thereof or a prodrug thereof.~~

2. A salt of 1-(2-(4-(2-amino-5-fluoropyridin-3-yl)phenoxy)pyrimidin-5-yl)-3-(2-(pyridin-3-yl)-5-(trifluoromethyl)phenyl)urea.

~~The compound according to claim 1, wherein the ring Cy_2 is a 5- to 10-membered monocyclic aromatic heterocycle or bicyclic aromatic heterocycle excluding a heterocycle 1,3-thiazol-5-yl group.~~

3. A pharmaceutical composition comprising 1-(2-(4-(2-amino-5-fluoropyridin-3-yl)phenoxy)pyrimidin-5-yl)-3-(2-(pyridin-3-yl)-5-(trifluoromethyl)phenyl)urea or a salt thereof, as an

active ingredient.

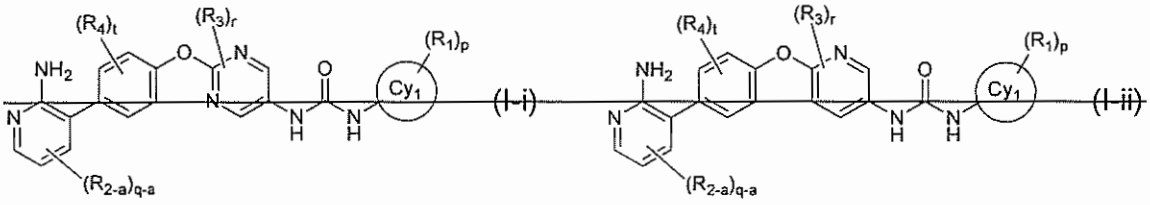
~~The compound according to claim 1 or 2, wherein the ring Cy_2 is a pyridine ring, a pyrimidine ring, a pyrazolopyrimidine ring, an imidazopyridazine ring, an imidazopyridine ring, a pyrrolopyridine ring, an imidazopyrazine ring or a pyrazolopyridine ring.~~

4. A prophylactic and/or therapeutic agent for pain, comprising 1-(2-(4-(2-amino-5-fluoropyridin-3-yl)phenoxy)pyrimidin-5-yl)-3-(2-(pyridin-3-yl)-5-(trifluoromethyl)phenyl)urea or a salt thereof, as an active ingredient.

~~The compound according to any one of claims 1 to 3, wherein one of A_1 and A_2 is =N- and the other is =CH- or both are =N- and A_3, A_4, A_5 and A_6 are =CH-.~~

5. The prophylactic and/or therapeutic agent according to claim 4, wherein the pain is pain of osteoarthritis, cancer pain, chronic low back pain, low back pain of osteoporosis, pain of bone fracture, pain of rheumatoid arthritis, neuropathic pain, postherpetic pain, pain of diabetic neuropathy, fibromyalgia, pain of pancreatitis, pain of interstitial cystitis, pain of endometriosis, pain of irritable bowel syndrome, migraine, postoperative pain or pain of pulpitis.

~~The compound according to claim 1, wherein the general formula (I) is represented by the general formula (I-i) or the general formula (I-ii):~~

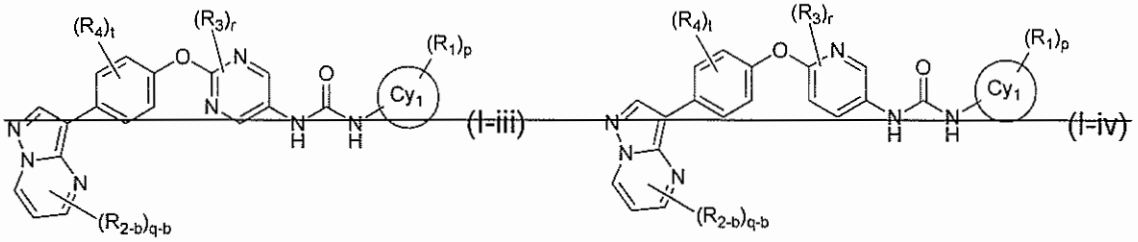


~~wherein R_{2-a} represents the same meaning as R_2; q a represents an integer of 0 to 3; t represents an integer of 0~~

~~to 4; and other symbols represent the same meanings as those described in claim 1, provided that when q a and t represent an integer of 2 or more, R_{2-a} and R_4 groups may be respectively and independently the same or different.~~

6. The use of 1-(2-(4-(2-amino-5-fluoropyridin-3-yl)phenoxy)pyrimidin-5-yl)-3-(2-(pyridin-3-yl)-5-(trifluoromethyl)phenyl)urea or a salt thereof, as an active ingredient in the manufacture of a prophylactic and/or therapeutic agent for the treatment of pain.

~~compound according to claim 1, wherein the general formula (I) is represented by the general formula (I-iii) or the general formula (I-iv):~~



~~wherein R_{2-b} represents the same meaning as R_2; q-b represents an integer of 0 to 4; and other symbols represent the same meanings as those described in claims 1 and 5, provided that when q-b represents an integer of 2 or more, R_{2-b} groups may be respectively and independently the same or different.~~

7. The use according to claim 6, wherein the pain is pain of osteoarthritis, cancer pain, chronic low back pain, low back pain of osteoporosis, pain of bone fracture, pain of rheumatoid arthritis, neuropathic pain, postherpetic pain, pain of diabetic neuropathy, fibromyalgia, pain of pancreatitis, pain of interstitial cystitis, pain of endometriosis, pain of irritable bowel syndrome, migraine, postoperative pain or pain of pulpitis.

~~The compound according to any one of claims 1 to 6, wherein the ring Cy_1 is a benzene ring or a 5- to 6-membered monocyclic aromatic heterocycle.~~

~~8. The compound according to claim 57, wherein the ring Cy_1 is a benzene ring, a pyridine ring or a pyrazole ring.~~

~~9. The compound according to any one of claims 1 to 45, which is:~~

~~(1) 1-(2-(1*H*-pyrazol-1-yl)-5-(trifluoromethyl)phenyl)-3-(2-(4-(2-amino-5-chloropyridin-3-yl)phenoxy)pyrimidin-5-yl)urea;~~

~~(2) 1-(2-(4-(2-amino-5-chloropyridin-3-yl)phenoxy)pyrimidin-5-yl)-3-(2-(4-methyl-1*H*-1,2,3-triazol-1-yl)-5-(trifluoromethyl)-phenyl)urea;~~

~~(3) 1-(2-(4-(2-amino-5-chloropyridin-3-yl)phenoxy)pyrimidin-5-yl)-3-(5-(trifluoromethyl)-2-(3-(trifluoromethyl)-1*H*-pyrazol-1-yl)phenyl)urea;~~

~~(4) 1-(2-(4-(2-amino-5-chloropyridin-3-yl)phenoxy)pyrimidin-5-yl)-3-(2-chloro-5-(trifluoromethyl)phenyl)urea;~~

~~(5) 1-(2-(1*H*-pyrazol-1-yl)-5-(trifluoromethyl)phenyl-3-(6-(4-(2-amino-5-chloropyridin-3-yl)phenoxy)pyridin-3-yl)urea;~~

~~(6) 1-(2-(1*H*-1,2,3-triazol-1-yl)-5-(trifluoromethyl)phenyl-3-(6-(4-(2-amino-5-chloropyridin-3-yl)phenoxy)pyridin-3-yl)urea;~~

~~(7) 1-(6-(4-(2-amino-5-chloropyridin-3-yl)phenoxy)pyridin-3-yl)-3-(2-(pyridin-3-yl)-5-(trifluoromethyl)phenyl)urea;~~

~~(8) 1-(2-(4-(2-amino-5-chloropyridin-3-yl)phenoxy)pyrimidin-5-yl)-3-(2-(1-methyl-1*H*-pyrazol-5-yl)-5-(trifluoromethyl)-phenyl)urea;~~

~~(9) 1-(2-(1*H*-1,2,3-triazol-1-yl)-5-(trifluoromethyl)phenyl)-3-(2-(4-(2-amino-5-fluoropyridin-3-yl)phenoxy)pyrimidin-5-yl)-urea;~~

~~(10) 1-(2-(4-(2-amino-5-fluoropyridin-3-yl)phenoxy)pyrimidin-5-yl)-3-(2-(pyridin-3-yl)-5-(trifluoromethyl)phenyl)urea;~~

~~(11) 1-(2-(1*H*-pyrazol-1-yl)-4-(trifluoromethyl)phenyl)-3-(2-~~

~~(4-(2-amino-5-chloropyridin-3-yl)phenoxy)pyrimidin-5-yl)urea;~~

~~(12) 1-(2-(4-(2-amino-5-chloropyridin-3-yl)phenoxy)pyrimidin-5-yl)-3-(2-fluoro-4-(trifluoromethyl)phenyl)urea;~~

~~(13) 1-(2-(4-(2-amino-5-chloropyridin-3-yl)phenoxy)pyrimidin-5-yl)-3-(2-chloro-4-(trifluoromethyl)phenyl)urea;~~

~~(14) 1-(2-{4-[2-amino-5-(trifluoromethyl)-3-pyridinyl]phenoxy}-5-pyrimidinyl)-3-{5-(trifluoromethyl)-2-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]phenyl}urea;~~

~~(15) 1-{2-[4-(2-amino-5-chloro-3-pyridinyl)phenoxy]-5-pyrimidinyl}-3-[4-(trifluoromethyl)-2-biphenylyl]urea;~~

~~(16) 1-{2-[4-(2-amino-5-fluoro-3-pyridinyl)phenoxy]-5-pyrimidinyl}-3-[4-(trifluoromethyl)-2-biphenylyl]urea;~~

~~(17) 1-{2-[4-(2-amino-5-chloro-3-pyridinyl)phenoxy]-5-pyrimidinyl}-3-[2-(4-chloro-1*H*-pyrazol-1-yl)-5-(trifluoromethyl)-phenyl]urea;~~

~~(18) 1-{2-[4-(2-amino-5-chloro-3-pyridinyl)phenoxy]-5-pyrimidinyl}-3-{5-chloro-2-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]phenyl}urea;~~

~~(19) 1-{2-[4-(2-amino-5-chloro-3-pyridinyl)phenoxy]-5-pyrimidinyl}-3-[2,4-bis(trifluoromethyl)phenyl]urea;~~

~~(20) 1-(2-{4-[2-amino-5-(trifluoromethyl)-3-pyridinyl]phenoxy}-5-pyrimidinyl)-3-[2-(4-chloro-1*H*-pyrazol-1-yl)-5-(trifluoromethyl)phenyl]urea;~~

~~(21) 1-{2-[4-(2-amino-5-fluoro-3-pyridinyl)phenoxy]-5-pyrimidinyl}-3-[2-(methylsulfonyl)-5-(trifluoromethyl)-phenyl]urea;~~

~~(22) 1-(2-{4-[2-amino-5-(trifluoromethyl)-3-pyridinyl]-phenoxy}-5-pyrimidinyl)-3-[2-(methylsulfonyl)-5-(trifluoromethyl)phenyl]urea;~~

~~(23) 1-{2-[4-(2-amino-5-chloro-3-pyridinyl)phenoxy]-5-pyrimidinyl}-3-[2-(methylsulfonyl)-5-(trifluoromethyl)-phenyl]urea; or~~

~~(24) 2-{[(2-{4-[2-amino-5-(trifluoromethyl)-3-pyridinyl]-phenoxy}-5-pyrimidinyl)carbamoyl]amino}-N,N-dimethyl-4-~~

~~(trifluoromethyl)benzenesulfonamide.~~

~~10. The compound according to any one of claims 1 to 4 and 6, which is:~~

~~(1) 1-(2-(4-(5-(azetidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)phenoxy)pyrimidin-5-yl)-3-(2-(pyridin-3-yl)-5-(trifluoromethyl)phenyl)urea;~~

~~(2) 1-(2-(4-(5-(azetidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)phenoxy)pyrimidin-5-yl)-3-(2-(1-methyl-1*H*-pyrazol-5-yl)-5-(trifluoromethyl)phenyl)urea;~~

~~(3) 1-(2-(4-(5-methoxypyrazolo[1,5-a]pyrimidin-3-yl)phenoxy)-pyrimidin-5-yl)-3-(2-(pyridin-3-yl)-5-(trifluoromethyl)-phenyl)urea;~~

~~(4) 1-(2-(4-(pyrazolo[1,5-a]pyrimidin-3-yl)phenoxy)pyrimidin-5-yl)-3-(2-(pyridin-3-yl)-5-(trifluoromethyl)phenyl)urea;~~

~~(5) 1-(2-{4-[5-(dimethylamino)pyrazolo[1,5-a]pyrimidin-3-yl]phenoxy}-5-pyrimidinyl)-3-[2-(3-pyridinyl)-5-(trifluoromethyl)phenyl]urea;~~

~~(6) 1-(2-{4-[5-(dimethylamino)pyrazolo[1,5-a]pyrimidin-3-yl]phenoxy}-5-pyrimidinyl)-3-[2-(1-methyl-1*H*-pyrazol-5-yl)-5-(trifluoromethyl)phenyl]urea;~~

~~(7) 1-{2-[4-(5-methylpyrazolo[1,5-a]pyrimidin-3-yl)phenoxy]-5-pyrimidinyl}-3-[2-(3-pyridinyl)-5-(trifluoromethyl)-phenyl]urea;~~

~~(8) 1-(2-{4-[5-(ethylamino)pyrazolo[1,5-a]pyrimidin-3-yl]-phenoxy}-5-pyrimidinyl)-3-[3′-methyl-4-(trifluoromethyl)-2-biphenylyl]urea;~~

~~(9) 1-(2-{4-[5-(dimethylamino)pyrazolo[1,5-a]pyrimidin-3-yl]-phenoxy}-5-pyrimidinyl)-3-[4-(trifluoromethyl)-2-biphenylyl]-urea;~~

~~(10) 1-(2-{4-[5-(dimethylamino)pyrazolo[1,5-a]pyrimidin-3-yl]-phenoxy}-5-pyrimidinyl)-3-[3′-methyl-4-(trifluoromethyl)-2-biphenylyl]urea; or~~

~~(11) 1-(2-{4-[5-(dimethylamino)pyrazolo[1,5-a]pyrimidin-3-yl]-~~

~~phenoxy}-5-pyrimidinyl)-3-[2'-methyl-4-(trifluoromethyl)-2-biphenylyl]urea.~~

~~11. A pharmaceutical composition comprising the compound represented by the general formula (I) according to claim 1, a salt thereof, an N-oxide thereof, a solvate thereof or a prodrug thereof as an active ingredient.~~

~~12. The composition according to claim 11, which is a Trk inhibitor.~~

~~13. The composition according to claim 11, which is a prophylactic and/or therapeutic agent for Trk related disease.~~

~~14. The composition according to claim 13, wherein the Trk-related disease is pain, cancer, pruritus, lower urinary tract dysfunction, asthma, allergic rhinitis, inflammatory bowel disease or Chagas disease.~~

~~15. The composition according to claim 14, wherein the pain is pain of osteoarthritis, cancer pain, chronic low back pain, low back pain of osteoporosis, pain of bone fracture, pain of rheumatoid arthritis, neuropathic pain, postherpetic pain, pain of diabetic neuropathy, fibromyalgia, pain of pancreatitis, pain of interstitial cystitis, pain of endometriosis, pain of irritable bowel syndrome, migraine, postoperative pain or pain of pulpitis.~~

~~16. A medicament which is a combination of the compound represented by the general formula (I) according to claim 1, a salt thereof, an N-oxide thereof, a solvate thereof or a prodrug thereof and at least one selected from acetaminophen, a nonsteroid antiinflammatory drug, an opioid, an antidepressant, an anticepileptic agent, an N-methyl-D-aspartate antagonist, a muscle relaxant, an antiarrhythmic~~

~~agent, a steroid and a bisphosphonate.~~

~~17. A method for prophylaxis and/or therapy of Trk related disease, comprising administering, to a patient, an effective amount of the compound represented by the general formula (I) according to claim 1, a salt thereof, an N-oxide thereof, a solvate thereof or a prodrug thereof.~~

~~18. The compound represented by the general formula (I) according to claim 1, a salt thereof, an N-oxide thereof, a solvate thereof or a prodrug thereof for prophylaxis and/or therapy of Trk-related disease.~~

~~19. A method for inhibiting Trk, comprising administering, to a patient, an effective amount of the compound represented by the general formula (I) according to claim 1, a salt thereof, an N-oxide thereof, a solvate thereof or a prodrug thereof.~~

~~20. Use of the compound represented by the general formula (I) according to claim 1, a salt thereof, an N-oxide thereof, a solvate thereof or a prodrug thereof for manufacturing a prophylactic and/or therapeutic agent for Trk related disease.~~

CLAIMS

1. 1-(2-(4-(2-amino-5-fluoropyridin-3-yl)phenoxy)pyrimidin-5-yl)-3-(2-(pyridin-3-yl)-5-(trifluoromethyl)phenyl)urea.

2. A salt of 1-(2-(4-(2-amino-5-fluoropyridin-3-yl)phenoxy)pyrimidin-5-yl)-3-(2-(pyridin-3-yl)-5-(trifluoromethyl)phenyl)urea.

3. A pharmaceutical composition comprising 1-(2-(4-(2-amino-5-fluoropyridin-3-yl)phenoxy)pyrimidin-5-yl)-3-(2-(pyridin-3-yl)-5-(trifluoromethyl)phenyl)urea or a salt thereof, as an active ingredient.

4. A prophylactic and/or therapeutic agent for pain, comprising 1-(2-(4-(2-amino-5-fluoropyridin-3-yl)phenoxy)pyrimidin-5-yl)-3-(2-(pyridin-3-yl)-5-(trifluoromethyl)phenyl)urea or a salt thereof, as an active ingredient.

5. The prophylactic and/or therapeutic agent according to claim 4, wherein the pain is pain of osteoarthritis, cancer pain, chronic low back pain, low back pain of osteoporosis, pain of bone fracture, pain of rheumatoid arthritis, neuropathic pain, postherpetic pain, pain of diabetic neuropathy, fibromyalgia, pain of pancreatitis, pain of interstitial cystitis, pain of endometriosis, pain of irritable bowel syndrome, migraine, postoperative pain or pain of pulpitis.

6. The use of 1-(2-(4-(2-amino-5-fluoropyridin-3-yl)phenoxy)pyrimidin-5-yl)-3-(2-(pyridin-3-yl)-5-(trifluoromethyl)phenyl)urea or a salt thereof, as an active ingredient in the manufacture of a prophylactic and/or therapeutic agent for the treatment of pain.

7. The use according to claim 6, wherein the pain is pain of osteoarthritis, cancer pain, chronic low back pain, low back pain of osteoporosis, pain of bone fracture, pain of rheumatoid arthritis, neuropathic pain, postherpetic pain, pain of diabetic neuropathy, fibromyalgia, pain of pancreatitis, pain of interstitial cystitis, pain of endometriosis, pain of irritable bowel syndrome, migraine, postoperative pain or pain of pulpitis.