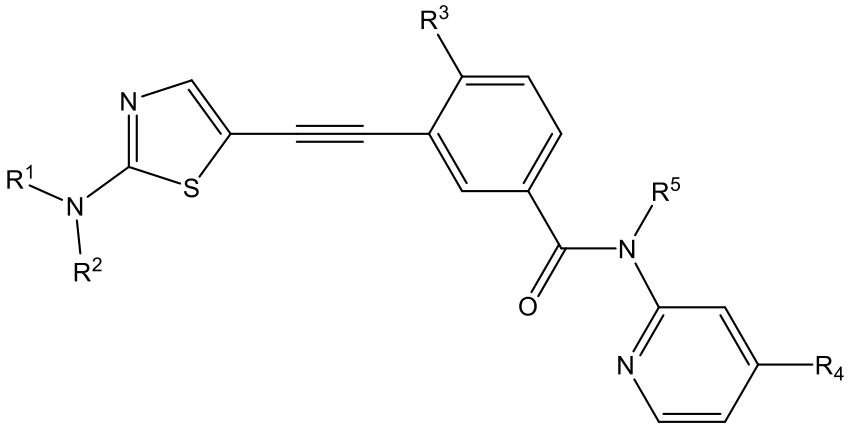
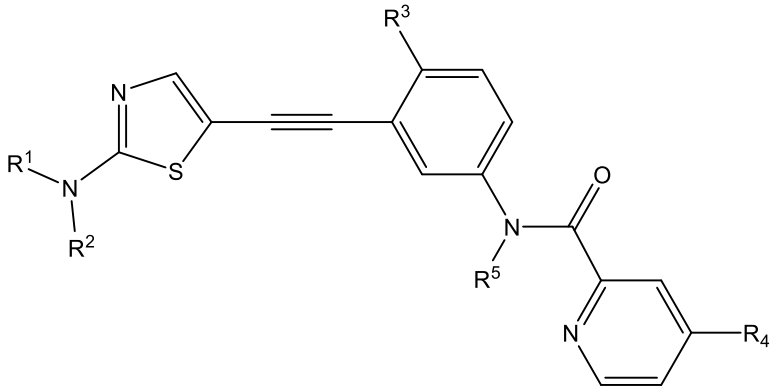
Claims

1. A compound of one of the following formulae (Ig) or (Ih):



(Ig), or



(Ih),

or a pharmaceutically acceptable salt thereof,

wherein:

R^1 is H;

R^2 is -C(O)R^8 or –C(O)NR^9R^{10};

R^3 is (C_1-C_6) alkyl, (C_1-C_6) alkoxy, (C_1-C_6) haloalkyl, (C_1-C_6) haloalkoxy, halogen, or OH;

R^4 is (C_1-C_6) alkyl, (C_1-C_6) alkoxy, (C_1-C_6) haloalkyl, (C_1-C_6) haloalkoxy, halogen, -OH, CN, -($C(R^6)_2)_p$-heterocycloalkyl wherein the heterocycloalkyl comprises a 4- to 7-membered ring and 1 to 3 heteroatoms selected from N, O, and S , or -($C(R^6)_2)_p$-heteroaryl wherein the heteroaryl comprises a 5- or 6-membered ring and 1 to 3 heteroatoms selected from N, O, and S, and wherein the heterocycloalkyl or heteroaryl is optionally substituted with one or more substituents each independently selected from (C_1-C_6) alkyl, -NH_2, (C_1-C_6) alkylamino, and (C_1-C_6) dialkylamino;

R^5 is H, (C_1-C_6) alkyl, or (C_1-C_6) haloalkyl;

each R^6 is independently H or (C_1-C_6) alkyl;

R^8 is (C_2-C_6) alkyl, (C_3-C_7) cycloalkyl, (C_2-C_6) alkenyl, (C_1-C_3) alkoxy, (C_1-C_6) haloalkyl, (C_1-C_6) haloalkoxy, or 4 to 7-membered heterocycloalkyl comprising 1 to 3 heteroatoms selected from N, O, and S;

R^9 is H, (C_1-C_6) alkyl, (C_1-C_6) haloalkyl, (C_3-C_7) cycloalkyl, or 4 to 7-membered heterocycloalkyl comprising 1 to 3 heteroatoms selected from N, O, or S;

R^{10} is H, (C_1-C_6) alkyl, (C_1-C_6) haloalkyl, (C_3-C_7) cycloalkyl, or 4 to 7-membered heterocycloalkyl comprising 1 to 3 heteroatoms selected from N, O, or S, wherein the cycloalkyl or heterocycloalkyl is optionally substituted with one or more substituents each independently selected from (C_1-C_6) alkyl, -NH_2, (C_1-C_6) alkylamino, (C_1-C_6) dialkylamino, and -OH, and wherein the (C_1-C_6) alkyl is optionally substituted with one or more R^{11};

or R^9 and R^{10} together with the nitrogen atom to which they are attached form a 4- to 7-membered heterocycloalkyl ring comprising 1 to 3 heteroatom selected from N, O, and S, optionally substituted with one or more substituent each independently selected from (C_1-C_6) alkyl, (C_1-C_6) hydroxyalkyl, -$(CH_2)_q$-NH_2, -$(CH_2)_q$-(C_1-C_6) alkylamino, -$(CH_2)_q$-(C_1-C_6) dialkylamino, -C(O)(C_1-C_6) alkyl, -OH, and 4- to 7-membered heterocycloalkyl comprising 1 to 3 heteroatom selected from N, O, and S, and optionally substituted with one or more (C_1-C_6) alkyl;

R^{11} is (C_1-C_6) alkoxy, -OH, -NH_2, (C_1-C_6) alkylamino, (C_1-C_6) dialkylamino, 5- or 6-membered heteroaryl comprising 1 to 3 heteroatoms selected from N, O, or S, or 4- to 7-membered heterocycloalkyl comprising 1 to 3 heteroatoms selected from N, O, or S, wherein the heterocycloalkyl is optionally substituted with one or more substituents each independently selected from (C_1-C_6) alkyl and OH; and

each p and q is independently 0, 1 or 2.

2. The compound of claim 1, wherein R^5 is H.

3. The compound of claim 1, wherein R^4 is (C_1-C_6) haloalkyl.

4. The compound of claim 1, wherein R^4 is CF_3.

5. The compound of claim 1, wherein R^3 is methyl.

6. The compound of claim 1, wherein R^2 is –C(O)NR^9R^{10}.

7. The compound of claim 1, wherein

R^2 is –C(O)NR^9R^{10}; wherein

R^9 is (C_1-C_6) alkyl and R^{10} is unsubstituted (C_1-C_6) alkyl or (C_1-C_6) alkyl substituted with one R^{11}, optionally wherein R^{11} is –OH; or

R^9 and R^{10} together with the nitrogen atom to which they are attached form a 4- to 6-membered heterocycloalkyl ring comprising 1 to 3 heteroatom selected from N, O, and S, optionally substituted with one or more substituents each independently selected from (C_1-C_6) alkyl, (C_1-C_6) hydroxyalkyl, -$(CH_2)_q$-(C_1-C_6) dialkylamino, -C(O)(C_1-C_6) alkyl, OH, or 6-membered heterocycloalkyl comprising 1 to 3 heteroatom selected from N, O, and S, and optionally substituted with (C_1-C_6) alkyl.

8. The compound of claim 7, wherein R^9 is (C_1-C_6) alkyl and R^{10} is (C_1-C_6) alkyl substituted with one R^{11}.

9. The compound of claim 8, wherein R^{11} is -OH.

10. The compound of claim 7, wherein R^9 and R^{10} together with the nitrogen atom to which they are attached form a 4- to 6-membered heterocycloalkyl ring comprising 1 to 3 heteroatom selected from N, O, and S, optionally substituted with one or more substituents each independently selected from (C_1-C_6) alkyl, (C_1-C_6) hydroxyalkyl, -$(CH_2)_q$-(C_1-C_6) dialkylamino, -C(O)(C_1-C_6) alkyl, OH, or 6-membered heterocycloalkyl comprising 1 to 3 heteroatom selected from N, O, and S, and optionally substituted with (C_1-C_6) alkyl.

11. The compound of claim 7, wherein R^9 and R^{10} together with the nitrogen atom to which they are attached form a heterocycloalkyl ring that is azetidinyl, morpholinyl, piperidinyl, or piperazinyl, and which is optionally substituted with one or more substituent each independently selected from (C_1-C_6) alkyl, (C_1-C_6) hydroxyalkyl, -$(CH_2)_q$-(C_1-C_6) dialkylamino, -C(O)(C_1-C_6) alkyl, -OH, and 6-membered heterocycloalkyl comprising 1 to 3 heteroatom selected from N, O, and S, and optionally substituted with one or more (C_1-C_6) alkyl.

12. The compound of claim 1, wherein

R^2 is –C(O)NR^9R^{10}

R^3 is (C_1-C_6) alkyl or halogen;

R^4 is (C_1-C_6) haloalkyl;

R^5 is H;

R^9 and R^{10} together with the nitrogen atom to which they are attached form a 4- to 6-membered heterocycloalkyl ring comprising 1 to 3 heteroatom selected from N, O, and S, optionally substituted with one or more substituents each independently selected from (C_1-C_6) alkyl, (C_1-C_6) hydroxyalkyl, -$(CH_2)_q$-(C_1-C_6) dialkylamino, -C(O)(C_1-C_6) alkyl, OH, or 6-membered heterocycloalkyl comprising 1 to 3 heteroatom selected from N, O, and S, and optionally substituted with (C_1-C_6) alkyl; and

q is 0, 1 or 2.

13. The compound of claim 12, wherein R^4 is CF_3.

14. The compound of claim 12, wherein R^3 is methyl.

~~15. The compound of claim 12, wherein R^9 and R^{10} together with the nitrogen atom to which they are attached form a heterocycloalkyl ring that is azetidinyl, pyrrolidinyl, morpholinyl, piperidinyl, or piperazinyl, and which is optionally substituted with one or more substituent each independently selected from -(C_1-C_6) alkyl, (C_1-C_6) hydroxyalkyl, -$(CH_2)_q$-(C_1-C_6) dialkylamino, -C(O)(C_1-C_6) alkyl, -OH, and 6-membered heterocycloalkyl comprising 1 to 3 heteroatom selected from N, O, and S, and optionally substituted with one or more (C_1-C_6) alkyl.~~

~~16. The compound of claim 15, wherein said azetidinyl, pyrrolidinyl, morpholinyl, piperidinyl, or piperazinyl is substituted with one substituent that is (C_1-C_6) alkyl, (C_1-C_6) hydroxyalkyl, -$(CH_2)_q$-(C_1-C_6) dialkylamino, -C(O)(C_1-C_6) alkyl, or -OH.~~

~~17. The compound of claim 12, wherein~~

~~R^9 and R^{10} together with the nitrogen atom to which they are attached form an azetidine ring, wherein the azetidine ring is substituted with methyl and -OH;~~

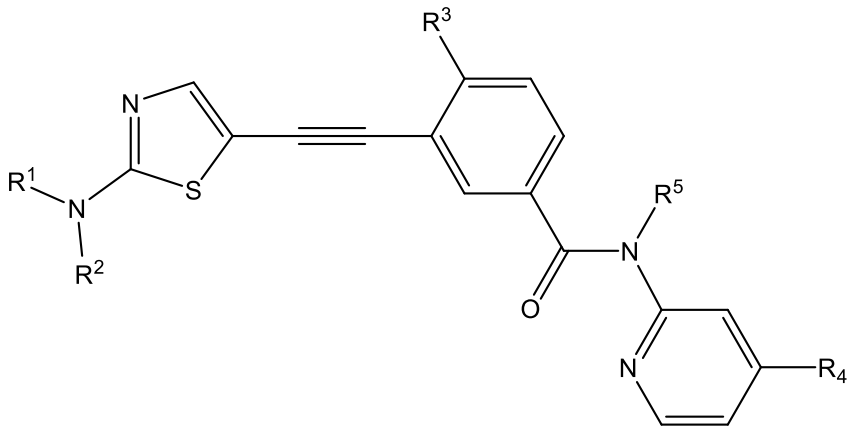
~~R^9 and R^{10} together with the nitrogen atom to which they are attached form a pyrrolidine ring, wherein the pyrrolidine ring is substituted with dimethylamino;~~

~~R^9 and R^{10} together with the nitrogen atom to which they are attached form a piperazine ring, wherein said piperazine ring is unsubstituted or substituted by methyl or -C(O)CH_3;~~

~~R^9 and R^{10} together with the nitrogen atom to which they are attached form a piperidine ring, wherein the piperidine ring is substituted with methyl, hydroxyethyl, or N-methylpiperazine; or~~

~~R^9 and R^{10} together with the nitrogen atom to which they are attached form a morpholine ring, wherein the morpholine ring is unsubstituted or substituted with $-CH_2N(CH_3)_2$.~~

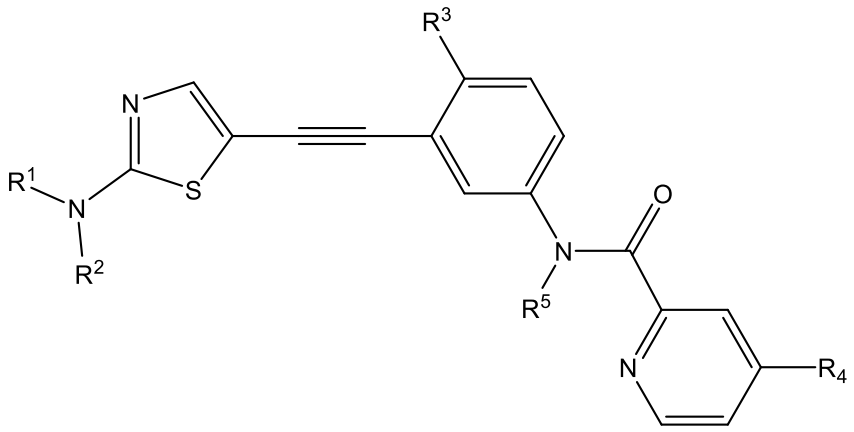
15.~~18.~~ The compound of claim 12, wherein the compound has a structure that is:



(Ig),

or a pharmaceutically acceptable salt thereof.

16.~~19.~~ The compound of claim 12, wherein the compound has a structure that is:



(Ih),

or a pharmaceutically acceptable salt thereof.

17.~~20.~~ A compound that is selected from the group consisting of:

3-((2-(3,3-dimethylureido)thiazol-5-yl)ethynyl)-4-methyl-N-(4-(trifluoromethyl)pyridin-2-yl)benzamide;

4-methyl-N-(4-(trifluoromethyl)pyridin-2-yl)-3-((2-ureidothiazol-5-yl)ethynyl)benzamide;

methyl (5-((2-methyl-5-((4-(trifluoromethyl)pyridin-2-yl)carbamoyl)phenyl)ethynyl)thiazol-2-yl)carbamate;

4-methyl-3-((2-(3-methylureido)thiazol-5-yl)ethynyl)-N-(4-(trifluoromethyl)pyridin-2-yl)benzamide;

3-((2-(3-(2-methoxyethyl)ureido)thiazol-5-yl)ethynyl)-4-methyl-N-(4-(trifluoromethyl)pyridin-2-yl)benzamide;

4-methyl-3-((2-(3-(2-morpholinoethyl)ureido)thiazol-5-yl)ethynyl)-N-(4-(trifluoromethyl)pyridin-2-yl)benzamide;

3-((2-(3-(2-methoxyethyl)-3-methylureido)thiazol-5-yl)ethynyl)-4-methyl-N-(4-(trifluoromethyl)pyridin-2-yl)benzamide;

3-((2-(3-ethyl-3-methylureido)thiazol-5-yl)ethynyl)-4-methyl-N-(4-(trifluoromethyl)pyridin-2-yl)benzamide;

3-((2-(3-(2-(dimethylamino)ethyl)-3-methylureido)thiazol-5-yl)ethynyl)-4-methyl-N-(4-(trifluoromethyl)pyridin-2-yl)benzamide;

3-((2-(3-(2-hydroxyethyl)-3-methylureido)thiazol-5-yl)ethynyl)-4-methyl-N-(4-(trifluoromethyl)pyridin-2-yl)benzamide;

3-((2-(3-(2-(dimethylamino)ethyl)ureido)thiazol-5-yl)ethynyl)-4-methyl-N-(4-(trifluoromethyl)pyridin-2-yl)benzamide;

4-methyl-3-((2-(3-(2-(pyrrolidin-1-yl)ethyl)ureido)thiazol-5-yl)ethynyl)-N-(4-(trifluoromethyl)pyridin-2-yl)benzamide;

4-methyl-3-((2-(3-((1-methylpiperidin-4-yl)methyl)ureido)thiazol-5-yl)ethynyl)-N-(4-(trifluoromethyl)pyridin-2-yl)benzamide;

4-methyl-3-((2-(3-(2-(4-methylpiperazin-1-yl)ethyl)ureido)thiazol-5-yl)ethynyl)-N-(4-(trifluoromethyl)pyridin-2-yl)benzamide;

3-((2-(3-(2-hydroxy-2-methylpropyl)ureido)thiazol-5-yl)ethynyl)-4-methyl-N-(4-(trifluoromethyl)pyridin-2-yl)benzamide;

4-methyl-3-((2-(3-methyl-3-(2-(4-methylpiperazin-1-yl)ethyl)ureido)thiazol-5-yl)ethynyl)-N-(4-(trifluoromethyl)pyridin-2-yl)benzamide;

3-((2-(3-cyclopropylureido)thiazol-5-yl)ethynyl)-4-methyl-N-(4-(trifluoromethyl)pyridin-2-yl)benzamide;

3-((2-(3-(2-(3-hydroxypyrrolidin-1-yl)ethyl)ureido)thiazol-5-yl)ethynyl)-4-methyl-N-(4-(trifluoromethyl)pyridin-2-yl)benzamide;

4-methyl-3-((2-(3-methyl-3-(2-(pyrrolidin-1-yl)ethyl)ureido)thiazol-5-yl)ethynyl)-N-(4-(trifluoromethyl)pyridin-2-yl)benzamide;

4-methyl-3-((2-(3-methyl-3-((1-methylpyrrolidin-2-yl)methyl)ureido)thiazol-5-yl)ethynyl)-N-(4-(trifluoromethyl)pyridin-2-yl)benzamide;

3-((2-(3-(2-hydroxy-2-methylpropyl)-3-methylureido)thiazol-5-yl)ethynyl)-4-methyl-N-(4-(trifluoromethyl)pyridin-2-yl)benzamide;

3-((2-(3-(4-hydroxycyclohexyl)-3-methylureido)thiazol-5-yl)ethynyl)-4-methyl-N-(4-(trifluoromethyl)pyridin-2-yl)benzamide;

4-methyl-N-(5-((2-methyl-5-((4-(trifluoromethyl)pyridin-2-yl)carbamoyl)phenyl)ethynyl)thiazol-2-yl)piperazine-1-carboxamide;

3-hydroxy-3-methyl-N-(5-((2-methyl-5-((4-(trifluoromethyl)pyridin-2-yl)carbamoyl)phenyl)ethynyl)thiazol-2-yl)azetidine-1-carboxamide;

4-methyl-N-(5-((2-methyl-5-((4-(trifluoromethyl)pyridin-2-yl)carbamoyl)phenyl)ethynyl)thiazol-2-yl)piperidine-1-carboxamide;

4-methyl-3-((2-(3-(pyridin-4-ylmethyl)ureido)thiazol-5-yl)ethynyl)-N-(4-(trifluoromethyl)pyridin-2-yl)benzamide;

4-(2-hydroxyethyl)-N-(5-((2-methyl-5-((4-(trifluoromethyl)pyridin-2-yl)carbamoyl)phenyl)ethynyl)thiazol-2-yl)piperazine-1-carboxamide;

4-methyl-3-((2-(3-methyl-3-(2-(methylamino)ethyl)ureido)thiazol-5-yl)ethynyl)-N-(4-(trifluoromethyl)pyridin-2-yl)benzamide;

4-methyl-3-((2-(3-methyl-3-(1-methylpiperidin-4-yl)ureido)thiazol-5-yl)ethynyl)-N-(4-(trifluoromethyl)pyridin-2-yl)benzamide;

N-(5-((2-methyl-5-((4-(trifluoromethyl)pyridin-2-yl)carbamoyl)phenyl)ethynyl)thiazol-2-yl)piperazine-1-carboxamide;

3-((2-(3-(4-aminobutyl)ureido)thiazol-5-yl)ethynyl)-4-methyl-N-(4-(trifluoromethyl)pyridin-2-yl)benzamide;

4-methyl-3-((2-(3-methyl-3-(1-methylpiperidin-3-yl)ureido)thiazol-5-yl)ethynyl)-N-(4-(trifluoromethyl)pyridin-2-yl)benzamide;

3-((2-(3-(4-aminocyclohexyl)-3-methylureido)thiazol-5-yl)ethynyl)-4-methyl-N-(4-(trifluoromethyl)pyridin-2-yl)benzamide;

2-((dimethylamino)methyl)-N-(5-((2-methyl-5-((4-(trifluoromethyl)pyridin-2-yl)carbamoyl)phenyl)ethynyl)thiazol-2-yl)morpholine-4-carboxamide;

N-(5-((2-methyl-5-((4-(trifluoromethyl)pyridin-2-yl)carbamoyl)phenyl)ethynyl)thiazol-2-yl)morpholine-4-carboxamide;

3-((2-(3-(3-aminopropyl)ureido)thiazol-5-yl)ethynyl)-4-methyl-N-(4-(trifluoromethyl)pyridin-2-yl)benzamide;

4-acetyl-N-(5-((2-methyl-5-((4-(trifluoromethyl)pyridin-2-yl)carbamoyl)phenyl)ethynyl)thiazol-2-yl)piperazine-1-carboxamide;

3-((2-(3-(2-aminoethyl)ureido)thiazol-5-yl)ethynyl)-4-methyl-N-(4-(trifluoromethyl)pyridin-2-yl)benzamide;

4-methyl-3-((2-(3-methyl-3-(1-methylazetidin-3-yl)ureido)thiazol-5-yl)ethynyl)-N-(4-(trifluoromethyl)pyridin-2-yl)benzamide;

3-(dimethylamino)-N-(5-((2-methyl-5-((4-(trifluoromethyl)pyridin-2-yl)carbamoyl)phenyl)ethynyl)thiazol-2-yl)pyrrolidine-1-carboxamide;

N-(5-((2-methyl-5-((4-(trifluoromethyl)pyridin-2-yl)carbamoyl)phenyl)ethynyl)thiazol-2-yl)-4-(4-methylpiperazin-1-yl)piperidine-1-carboxamide;

2-fluoro-5-((2-(3-methylureido)thiazol-5-yl)ethynyl)-N-(4-(trifluoromethyl)pyridin-2-yl)benzamide;

2-fluoro-N-(4-(trifluoromethyl)pyridin-2-yl)-5-((2-ureidothiazol-5-yl)ethynyl)benzamide;

3-((2-(3-methylureido)thiazol-5-yl)ethynyl)-N-(4-(trifluoromethyl)pyridin-2-yl)benzamide;

4-fluoro-3-((2-(3-methylureido)thiazol-5-yl)ethynyl)-N-(4-(trifluoromethyl)pyridin-2-yl)benzamide;

3-((2-(3-(2-methoxyethyl)-3-methylureido)thiazol-5-yl)ethynyl)-4-methyl-N-(4-(pyrrolidin-1-ylmethyl)-3-(trifluoromethyl)phenyl)benzamide;

N-(2-methoxy-3-(trifluoromethyl)phenyl)-3-((2-(3-(2-methoxyethyl)-3-methylureido)thiazol-5-yl)ethynyl)-4-methylbenzamide;

N-(4-cyano-3-(trifluoromethyl)phenyl)-3-((2-(3-(2-methoxyethyl)-3-methylureido)thiazol-5-yl)ethynyl)-4-methylbenzamide;

3-((2-(cyclopropanecarboxamido)thiazol-5-yl)ethynyl)-4-methyl-N-(4-(trifluoromethyl)pyridin-2-yl)benzamide;

3-((2-(cyclopropanecarboxamido)thiazol-5-yl)ethynyl)-4-methyl-N-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)benzamide;

3-((2-acetamidothiazol-5-yl)ethynyl)-4-methyl-N-(4-(trifluoromethyl)pyridin-2-yl)benzamide;

4-methyl-3-((2-pivalamidothiazol-5-yl)ethynyl)-N-(4-(trifluoromethyl)pyridin-2-yl)benzamide;

N-(4-methyl-3-((2-(3-methyl-3-(1-methylpiperidin-4-yl)ureido)thiazol-5-yl)ethynyl)phenyl)-4-(trifluoromethyl)picolinamide;

N-(3-((2-(3-(2-methoxyethyl)-3-methylureido)thiazol-5-yl)ethynyl)-4-methylphenyl)-4-(trifluoromethyl)picolinamide;

N-(4-methyl-3-((2-(3-methyl-3-(2-(4-methylpiperazin-1-yl)ethyl)ureido)thiazol-5-yl)ethynyl)phenyl)-4-(trifluoromethyl)picolinamide;

N-(3-((2-(3,3-dimethylureido)thiazol-5-yl)ethynyl)-4-methylphenyl)-3-(trifluoromethoxy)benzamide;

N-(4-methyl-3-((2-(3-methylureido)thiazol-5-yl)ethynyl)phenyl)-4-(trifluoromethyl)picolinamide;

N-(3-((2-(3-(2-(dimethylamino)ethyl)-3-methylureido)thiazol-5-yl)ethynyl)-4-methylphenyl)-4-(trifluoromethyl)picolinamide;

N-(3-((2-(3-(2-(diethylamino)ethyl)-3-methylureido)thiazol-5-yl)ethynyl)-4-methylphenyl)-4-(trifluoromethyl)picolinamide;

N-(3-((2-(3-(2-hydroxyethyl)-3-methylureido)thiazol-5-yl)ethynyl)-4-methylphenyl)-4-(trifluoromethyl)picolinamide;

N-(3-((2-(3-(2-methoxyethyl)-3-methylureido)thiazol-5-yl)ethynyl)phenyl)-4-(trifluoromethyl)picolinamide; and

N-(4-fluoro-3-((2-(3-(2-methoxyethyl)-3-methylureido)thiazol-5-yl)ethynyl)phenyl)-4-(trifluoromethyl)picolinamide;

or a pharmaceutically acceptable salt thereof.

18.~~21.~~ A pharmaceutical composition comprising a compound of any one of claims 1-17~~20~~, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable diluent, excipient or carrier.

19.~~22.~~ Use of the compound according to any one of claims 1-17~~20~~, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for treating a c-Kit-mediated disease or disorder,-wherein said cKit-mediated disease or disorder is selected from cell proliferative disorder, a fibrotic disorder, a metabolic disorder, multiple sclerosis, asthma, an allergic reaction, inflammatory arthritis, and mastocytosis.

20.~~23~~ The use of claim 19~~22~~, wherein said cell proliferative disorder is cancer, optionally wherein

said cancer is selected from the group consisting of leukemia, mast cell tumor, small cell lung cancer, testicular cancer, cancer of the gastrointestinal tract, cancer of the central nervous system, cancer of the female genital tract, sarcoma of neuroectodermal origin, and Schwann cell neoplasia associated with neurofibromatosis; or

said cancer is selected from the group consisting of small cell lung carcinoma, acute myeloid leukemia (AML), neuroblastoma, malignant melanomas, colorectal cancer,systemic mastocytosis (SM), and gastrointestinal stromal tumors (GISTs).