

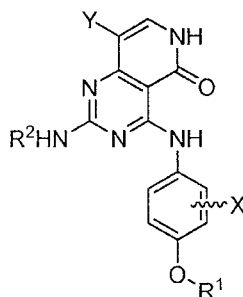
8-Bromo-4-(4-(3-fluorophenoxy)phenylamino)-2-(1-methylpiperidin-4-ylamino)pyrido[4,3-d]pyrimidin-5(6H)-one hydrochloride (238);

A 40 mL reaction vial was charged with **238e** (0.90 g, 1.90 mmol) in 15 mL DMF. The clear solution was cooled to -10 °C. To this, was added m-CPBA (1.48 g, 6.00 mmol) at -10 °C. The reaction was allowed to warm up to room temperature, and then stirred for additional 30 min at RT. To the mixture was added TEA (0.83 mL, 6.00 mmol) and 1-methylpiperidin-4-amine (685 mg, 6.00 mmol), and then it was stirred at room temperature for 1 hour with monitoring the reaction by LC-MS. The solvent was removed under reduced pressure yielding light brown oily residue. The residue was dissolved in methylene chloride and washed with saturated aqueous sodium bicarbonate solution. The separated organic layer was dried over sodium sulfate, and then concentrated under reduced pressure to yield a solid. The solid was dissolved in a minimum amount of methylene chloride and treated with excess of n-hexanes yielding pale yellow solids. The resulted solids were collected by filtration, rinsed with n-hexanes and then dried in the air yielding a pale yellow solid. The solid was dissolved in the mixture of DCM and methanol. To the clear solution was added 4N HCl in dioxane (12.0 mL), then it was stirred at room temperature for 6 hours. The solvent was removed under reduced pressure yielding the desired product (**238**, 90% yield).

8-Bromo-2-(1-methylpiperidin-4-ylamino)-4-(4-phenoxyphenylamino)pyrido[4,3-d]pyrimidin-5(6H)-one hydrochloride (226);
Prepared from (**226c**) by the method of (**238**). MS (ESI) m/z 521 [M+1]⁺, 523 [M+3]⁺. ¹H NMR (400M Hz /CDCl₃) δ (ppm) 11.62(s, 0.7H), 11.42(s, 0.3H), 11.09(b, 1H), 7.70-7.79(m, 2H), 7.56(m, 1H), 7.32-7.39(m, 2H), 7.02-7.14(m, 5H), 5.79(d, J=7.32Hz, 0.7H), 5.43(d, J=7.04Hz, 0.3H), 3.88(m, 0.3H), 3.75(m, 0.7H), 2.90(m, 2H), 2.01-2.37(m, 7H), 1.66(m, 2H).

CLAIMS

1. A compound represented by Formula (I):



Formula (I)

wherein:

R¹ is aryl, arylalkyl, C₅-C₆cycloalkyl or C₅-C₆cycloalkyl methyl optionally substituted with R³;

R³ is independently fluoro, chloro, bromo, iodo, C₁-C₆alkyl, or CF₃;

- 10 X is F, Cl, Br, I, CH₃, or CF₃;

Y is chloro, bromo, iodo, -C₁-C₃alkyl or phenyl;

- R² is C₃-C₆cycloalkyl or C₄-C₇heterocycloalkyl, wherein the C₃-C₆cycloalkyl is optionally substituted at carbon atoms with 1 or 2 R⁴, and wherein the C₄-C₇heterocycloalkyl has 1 or 2 heteroatoms selected from the group consisting of
15 nitrogen, oxygen, sulfur, sulfone, or sulfoxide, and is independently substituted at carbon with R⁴ or at nitrogen with R⁵;

R⁴ is hydroxyl, hydroxyl(C₁-C₆)alkyl, amino, amino(C₁-C₆)alkyl, NHC₁-C₃alkyl, N(C₁-C₃alkyl)₂, C₁-C₃alkyl or halo;

- R⁵ is H, C₁-C₃alkyl or C(O)C₁-C₃alkyl, wherein the C₁-C₃alkyl group is
20 optionally substituted with 1-3 fluorine atoms;
or a pharmaceutically acceptable salt thereof.

2. The compound of Claim 1, wherein R¹ represents phenyl, benzyl, cyclohexyl, cyclopentyl, cyclohexyl methyl, or cyclopentyl methyl optionally
25 substituted with R².

3. The compound of Claim 1 or Claim 2, wherein R² represents piperidine or pyrrolidine substituted at nitrogen with R⁵.
4. The compound of any one of claims 1-3, where R⁵ is methyl, ethyl,
5 trifluoroethyl, or iso-propyl.
5. The compound of any one of claims 1-4, wherein R³ represents H or F.
6. The compound of claim 5, wherein the compound is 8-bromo-2-((1-
10 methylpiperidin-4-yl)amino)-4-((3-phenoxyphenyl)amino)pyrido[4,3-d]pyrimidin-
5(6H)-one hydrochloride or 8-bromo-4-((3-(3-fluorophenoxy) phenyl)amino)-2-((1-
methylpiperidin-4-yl)amino)pyrido[4,3-d]pyrimidin-5(6H)-one hydrochloride.
7. The compound of any one of claims 1-3, wherein Y represents bromo.
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8. The compound of Claim 1, wherein X represents fluorine or methyl.
9. The compound of claim 8, wherein the compound is 8-bromo-4-((3-fluoro-4-
phenoxyphenyl)amino)-2-((1-methylpiperidin-4-yl)amino) pyrido[4,3-d]pyrimidin-
20 5(6H)-one hydrochloride.
10. An isomeric compound of Claim 1.
11. A pharmaceutical formulation comprising a compound or a pharmaceutically
25 acceptable salt thereof of any one of claims 1-10 in combination with a
pharmaceutically acceptable carrier, diluent or excipient.
12. Use of a compound or a pharmaceutically acceptable salt thereof as defined
in claim 1, for preparing a medicament for the treatment of diseases which can be
30 treated by inhibition of the FLT3, MER, VEGFR3 and Aurora-B enzyme.
13. A compound or pharmaceutically acceptable salt thereof of claim 1, for use
in the treatment of hematological malignancies such as leukemias, lymphomas (non-

Hodgkin's lymphoma), Hodgkin's disease (also called Hodgkin's lymphoma), and myeloma for instance, acute lymphocytic leukemia (ALL), acute myeloid leukemia (AML), acute promyelocytic leukemia (APL), chronic lymphocytic leukemia (CLL), chronic myeloid leukemia (CML), chronic neutrophilic leukemia (CNL), acute undifferentiated leukemia (AUL), anaplastic large-cell lymphoma (ALCL), prolymphocytic leukemia (PML), juvenile myelomonocytic leukemia (JMML), adult T-cell ALL, AML with trilineage myelodysplasia (AML/TMDS), mixed lineage leukemia (MLL), myelodysplastic syndromes (MDSs), myeloproliferative disorders (MPD), multiple myeloma, (MM) and myeloid sarcoma. Aberrant expression FLT3 has been documented in both adult and childhood leukemias including acute myeloid leukemia (AML), AML with trilineage myelodysplasia (AML/TMDS), acute lymphoblastic leukemia (ALL), and myelodysplastic syndrome (MDS).

14. A compound or pharmaceutically acceptable salt thereof of claim 1, for use in the treatment of autoimmune diseases such as autoimmune encephalomyelitis, multiple sclerosis, Langerhans cell histiocytosis and systemic lupus erythematosus.

15. A compound or pharmaceutically acceptable salt thereof of claim 1, for use in the treatment of malignant solid tumors such as gastric cancer, breast cancer, non-small cell lung cancer, cervical cancer, colorectal cancer, prostate cancer, Kaposi sarcoma, head and neck squamous cell carcinoma, endometrial carcinoma and mesothelioma.

16. A method for treating a disease or condition mediated by FLT3, MER, VEGFR3 or Aurora-B, the method comprising administering to a subject in need thereof an effective amount of a compound or a pharmaceutically acceptable salt thereof of any one of claims 1-10.

17. The method of claim 16, wherein said compound is administered singly or in combination with one or more additional therapeutic agents.

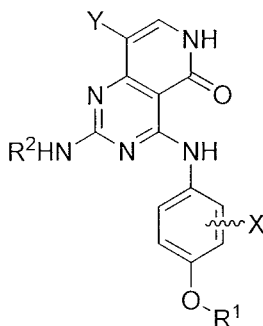
18. The method of claim 16 or claim 17, wherein said compound is administered via intravenous administration, subcutaneous administration, inhalation, oral administration, rectal administration, parenteral, intravitreal administration, intramuscular administration, intranasal administration, dermal administration, topical administration, optic administration, ophthalmic administration, buccal administration, tracheal administration, bronchial administration, or sublingual administration.

8-bromo-4-((4-(3-fluorophenoxy)phenyl)amino)-2-((1-methylpiperidin-4-yl)amino) pyrido[4,3-d]pyrimidin-5(6H)-one (238); A 40 mL reaction vial was charged with **238e** (0.90 g, 1.90 mmol) in 15 mL DMF. The clear solution was cooled to -10 °C. To this, was added m-CPBA (1.48 g, 6.00 mmol) at -10 °C. The reaction was allowed to warm up to room temperature, and then stirred for additional 30 min at RT. To the mixture was added TEA (0.83 mL, 6.00 mmol) and 1-methylpiperidin-4-amine (685 mg, 6.00 mmol), and then it was stirred at room temperature for 1 hour with monitoring the reaction by LC-MS. The solvent was removed under reduced pressure yielding light brown oily residue. The residue was dissolved in methylene chloride and washed with saturated aqueous sodium bicarbonate solution. The separated organic layer was dried over sodium sulfate, and then concentrated under reduced pressure to yield a solid. The solid was dissolved in a minimum amount of methylene chloride and treated with excess of n-hexanes yielding pale yellow solids. The resulted solids were collected by filtration, rinsed with n-hexanes and then dried in the air yielding a pale yellow solid. The solid was dissolved in the mixture of DCM and methanol. To the clear solution was added 4N HCl in dioxane (12.0 mL), then it was stirred at room temperature for 6 hours. The solvent was removed under reduced pressure yielding the desired product (**238**, 90% yield).

8-Bromo-2-(1-methylpiperidin-4-ylamino)-4-(4-phenoxyphenylamino)pyrido[4,3-d]pyrimidin-5(6H)-one hydrochloride (226); Prepared from (**226c**) by the method of (**238**). MS (ESI) m/z 521 $[M+1]^+$, 523 $[M+3]^+$. ^1H NMR (400M Hz, CDCl_3) δ (ppm) 11.62(s, 0.7H), 11.42(s, 0.3H), 11.09(b, 1H), 7.70-7.79(m, 2H), 7.56(m, 1H), 7.32-7.39(m, 2H), 7.02-7.14(m, 5H), 5.79(d, $J=7.32\text{Hz}$, 0.7H), 5.43(d, $J=7.04\text{Hz}$, 0.3H), 3.88(m, 0.3H), 3.75(m, 0.7H), 2.90(m, 2H), 2.01-2.37(m, 7H), 1.66(m, 2H).

CLAIMS

1. A compound represented by Formula (I):



Formula (I)

wherein:

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R³ is independently fluoro, chloro, bromo, iodo, C₁-C₆alkyl, or CF₃;

X is H, F, Cl, Br, I, CH₃, or CF₃;

Y is chloro, bromo, iodo, -C₁-C₃alkyl or phenyl;

R² is C₄-C₇heterocycloalkyl, wherein the C₄-C₇heterocycloalkyl has 1 or 2 nitrogen atoms in the C₄-C₇heterocycloalkyl ring, and is substituted at nitrogen with R⁵;

and

R⁵ is C₁-C₃alkyl or C(O)C₁-C₃alkyl, wherein the C₁-C₃alkyl group is optionally substituted with 1-3 fluorine atoms;

or a pharmaceutically acceptable salt thereof.

2. The compound of claim 1, wherein R¹ represents phenyl, benzyl, cyclohexyl, cyclopentyl, cyclohexyl methyl, or cyclopentyl methyl optionally substituted with R³.

3. The compound of claim 1, wherein R² represents piperidine substituted at nitrogen with R⁵.

4. The compound of claim 1, where R⁵ is methyl, ethyl, trifluoroethyl, or iso-propyl.
5. The compound of claim 4, wherein the compound is 8-bromo-2-((1-methylpiperidin-4-yl)amino)-4-((4-phenoxyphenyl)amino)pyrido[4,3-d]pyrimidin-5(6H)-one, 8-bromo-4-((4-(3-fluorophenoxy)phenyl)amino)-2-((1-methylpiperidin-4-yl)amino) pyrido[4,3-d]pyrimidin-5(6H)-one, or 8-bromo-4-((3-(3-fluorophenoxy) phenyl)amino)-2-((1-methylpiperidin-4-yl)amino)pyrido[4,3-d]pyrimidin-5(6H)-one.
6. The compound of claim 1, wherein Y represents bromo.
7. The compound of claim 1, wherein X represents H, fluorine or methyl.
8. The compound of claim 7, wherein the compound is 8-bromo-4-((3-fluoro-4-phenoxyphenyl)amino)-2-((1-methylpiperidin-4-yl)amino) pyrido[4,3-d]pyrimidin-5(6H)-one hydrochloride.
9. A stereoisomeric compound of claim 1.
10. A pharmaceutical formulation comprising a compound or a pharmaceutically acceptable salt thereof of claim 1 in combination with a pharmaceutically acceptable carrier, diluent or excipient.
11. A method of inhibiting FLT3 activity in a cell, the method comprising contacting the cell with an effective amount of a compound or a pharmaceutically acceptable salt thereof of claim 1, such that FLT3 activity is inhibited.

12. A method for the treatment of a hematological malignancy, wherein the hematological malignancy is selected from the group consisting of acute lymphocytic leukemia (ALL), acute myeloid leukemia (AML), chronic lymphocytic leukemia (CLL), chronic myeloid leukemia (CML), and myeloproliferative disorders (MPD), the method comprising administering to a subject in need thereof an effective amount of a compound or a pharmaceutically acceptable salt thereof of claim 1.
13. The method of claim 12, wherein said compound is administered singly or in combination with one or more additional therapeutic agents.
14. The method of claim 12, wherein said compound is administered via intravenous administration, subcutaneous administration, inhalation, oral administration, rectal administration, parenteral, intravitreal administration, intramuscular administration, intranasal administration, dermal administration, topical administration, optic administration, ophthalmic administration, buccal administration, tracheal administration, bronchial administration, or sublingual administration.