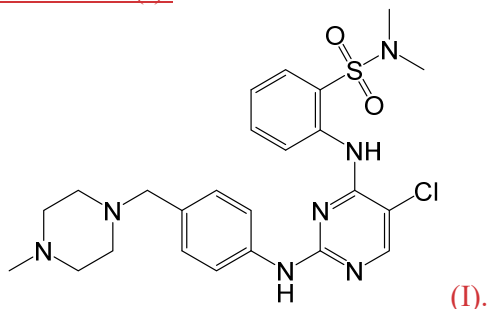


SUMMARY OF THE INVENTION

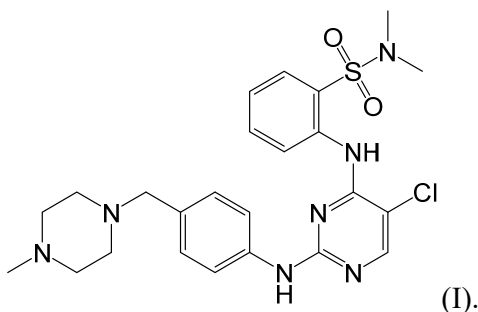
In one aspect of the present disclosure, there is provided a crystalline form of a tartrate salt of the compound of structure (I):



5 In another aspect of the present disclosure, there is provided a composition comprising the crystalline form disclosed herein.

In a further aspect of the present disclosure, there is provided a unit dose comprising the composition disclosed herein, wherein the composition is a pharmaceutical composition and the unit dose comprises about 1-100 mg of the tartrate salt.

10 In one ~~aspect~~example, the present disclosure provides a tartrate salt of the compound of structure (I):



In some embodiments, the tartrate salt disclosed herein may have a molar ratio of tartaric acid to the compound of structure (I) of about 1:1 to about 2:1. For example, the
15 tartrate salt may have a molar ratio of tartaric acid to the compound of structure (I) of about 2:1. Any of the tartrate salts disclosed herein may be a salt of L-(+)-tartaric acid.

In another ~~aspected~~example, the present disclosure provides a crystalline form of any of the tartrate salts disclosed herein. In some embodiments, the crystalline form is crystalline Form A, having a molar ratio of tartaric acid to the compound of structure (I) of about 2:1. In
20 some examples, Form A can be in substantially pure form. In some embodiments, the

crystalline form comprises Form A. In some embodiments, the crystalline form consists essentially of Form A.

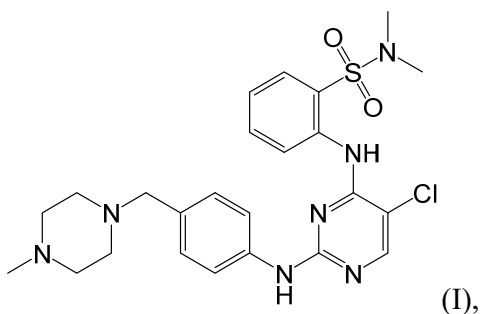
Any of the crystalline forms disclosed herein may be characterized by an x-ray powder diffraction (XRPD) pattern comprising peaks, in units 2-theta, at 11.2 ± 0.2 , 17.1 ± 0.2 , and 19.9 ± 0.2 . Optionally, the crystalline form may further comprise a peak, in units 2-theta, at 15.4 ± 0.2 . Alternatively or in addition, the crystalline form may further comprise a peak, in units 2-theta, at 7.0 ± 0.2 . In some examples, the crystalline form as disclosed herein can be characterized by an XRPD pattern comprising three or more peaks, in units of 2-theta, selected from 7.0 ± 0.2 , 11.2 ± 0.2 , 15.4 ± 0.2 , 16.3 ± 0.2 , 17.1 ± 0.2 , 19.9 ± 0.2 , 21.6 ± 0.2 , and 25.5 ± 0.2 . In othe examples, the XRPD pattern may comprise 4, 5, 6, 7, or 8 peaks, in units of 2-theta, selected from 7.0 ± 0.2 , 11.2 ± 0.2 , 15.4 ± 0.2 , 16.3 ± 0.2 , 17.1 ± 0.2 , 19.9 ± 0.2 , 21.6 ± 0.2 , and 25.5 ± 0.2 . In one specific example, the XRPD pattern is substantially identical to the XRPD pattern shown in Figure 61.

Further, the present disclosure provides a unit dose comprising any of the pharmaceutical compositions disclosed herein. The unit dose may comprise about 1-100 mg of the tartrate salt. In some embodiments, the unit dose disclosed herein may comprise about 1 mg, 4 mg, 16 mg, 25 mg, 50 mg, 75 mg, or 100 mg of the tartrate salt. In some
5 embodiments, the unit dose can be formulated in a gelatin hard capsule for oral administration.

In another aspectexample, the present disclosure provides a method of treating a cancer, the method comprising administering to a subject (e.g., a human) in need thereof a therapeutically effective amount of any of the tartrate salts disclosed herein, any of the
10 crystalline forms disclosed herein, any of the pharmaceutical compositions comprising such, or any of the unit doses also disclosed herein.

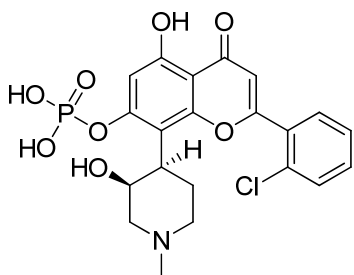
In some embodiments, the method disclosed herein comprises administering to the subject a therapeutically effective amount of a tartrate salt having a molar ratio of tartaric acid to the compound of structure (I) of about 2:1. In some examples, the method comprises
15 administering to the subject a therapeutically effective amount of the crystalline Form A, which may be in substantially pure form.

In a further aspectexample, provided herein is a method of treating cancer in a subject comprising administering to the subject a compound of structure (I):



or a pharmaceutically acceptable salt or crystalline form thereof. The compound, or
20 pharmaceutically acceptable salt, or crystalline form thereof, can be administered to the subject orally once daily at a dose from about 1.5 mg/m² to about 65 mg/m², or at a dose of about 20 mg to about 100 mg. The subject may have any of the tumor (e.g., advanced solid tumor) or hematopoietic cancer as disclosed herein. In some embodiments, the subject may
25 have undergone one or more prior cancer therapy, e.g., those disclosed herein.

other examples, the one or more therapeutic agents may comprises an immune checkpoint inhibitor, for example, a PD-1 or PD-L1 inhibitor. Examples of PD-1 inhibitors include, but are not limited to, pembrolizumab, nivolumab, or a combination thereof. Examples of PD-L1 inhibitors include, but are not limited to, atezolizumab, avelumab, durvalumab, or a combination thereof. Alternatively or in addition, the one or more therapeutic agents may comprise a CDK inhibitor, for example, a CDK9 inhibitor, which, in some instances, may be alvocidib, or a pharmaceutically acceptable salt or prodrug thereof. In some examples, the CDK9 inhibitor is a prodrug of alvocidib, which may have the following structure (II'):



(II'), or a pharmaceutically acceptable salt or zwitterionic form thereof.

In some examples, the one or more therapeutic agents comprise a platinum-based chemotherapeutic agents.

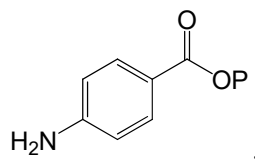
Exemplary additional therapeutic agents to be used in combination with the compound of structure (I), or a pharmaceutically acceptable salt thereof (e.g., any of the tartarate salts disclosed herein) may comprise carboplatin, gemcitabine, bevacizumab, topotecan, rucaparib, olaparib, niraparib, nivolumab, pembrolizumab, atezolizumab, avelumab, durvalumab, ipilimumab, or a combination thereof.

In yet another ~~aspect~~example, the present disclosure provides a method comprising administering an effective amount of a compound of structure (I):

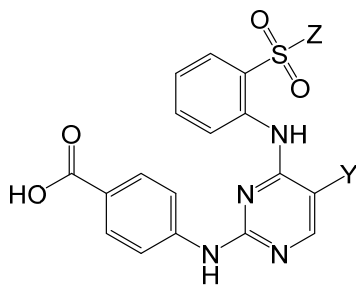
Z is halo or $\text{-NR}^1(\text{R}^2)$; and

R^1 and R^2 are, each independently, hydrogen or $\text{C}_1\text{-C}_8$ alkyl,

with a compound having the following structure:

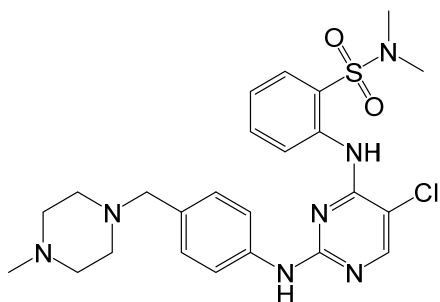


5 wherein P is H or a protecting group, to obtain a compound having the following structure:



In some embodiments, X can be halo or sulfonate (e.g., chloro). Alternatively or in addition, P can be H; Y can be chloro; Z can be $\text{-NR}^1(\text{R}^2)$; R^1 can be $\text{C}_1\text{-C}_8$ alkyl (e.g., methyl); and/or R^2 can be $\text{C}_1\text{-C}_8$ alkyl (e.g., methyl).

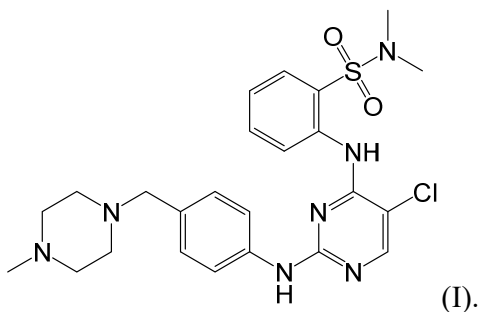
10 In yet another ~~aspect~~example, the present disclosure provides a method for preparing a tartrate salt of the compound of structure (I):



(I). The method may comprise admixing the compound of structure (I) with tartaric acid. In some examples, the tartaric acid can be L-(+)-tartaric acid. In some embodiments, the tartrate salt is of crystalline Form A, and the method comprises: (a) dissolving the compound of structure (I) in a solvent comprising anisole and ethanol to afford a first solution; (b) adding a solution of (L)-tartaric acid in ethanol to the first solution to afford a second solution; and (c) allowing the tartrate salt of structure (I) to crystallize from the second solution.

CLAIMS

1. A crystalline form of a tartrate salt of the compound of structure (I):



5

~~2. The tartrate salt of claim 1, having a molar ratio of tartaric acid to the compound of structure (I) of about 1:1 to about 2:1.~~

10

~~3. The tartrate salt of claim 2, having a molar ratio of tartaric acid to the compound of structure (I) of about 2:1.~~

~~4. The tartrate salt of any one of claims 1-3, wherein the tartrate salt is a salt of L-(+)-tartaric acid.~~

15

~~5. A crystalline form of the tartrate salt of any one of claims 1-4.~~

~~62.~~ The crystalline form of claim 15, which is crystalline Form A, having a molar ratio of tartaric acid to the compound of structure (I) of about 2:1.

20

3. The crystalline form of claim 2, characterized by an x-ray powder diffraction (XRPD) pattern comprising peaks, in units 2-theta, at 11.2±0.2, 17.1±0.2, and 19.9±0.2.

25

4. The crystalline form of claim 2, characterized by an XRPD pattern comprising three or more peaks, in units of 2-theta, selected from 7.0±0.2, 11.2±0.2, 15.4±0.2, 16.3±0.2, 17.1±0.2, 19.9±0.2, 21.6±0.2, and 25.5±0.2.

5. A composition comprising the crystalline form of claim 1.
6. The composition of claim 5, comprising crystalline Form A in substantially pure form.
- 5 7. The composition of claim 5, wherein the composition is a pharmaceutical composition that is formulated for oral administration.
8. A unit dose comprising the composition of claim 5, wherein the composition is a pharmaceutical composition and the unit dose comprises about 1-100 mg of the tartrate salt.
- 10 9. The crystalline form of claim 1, wherein the tartrate salt is a salt of L-(+)-tartaric acid.
10. The crystalline form of claim 2, wherein Form A is in substantially pure form.
- 15 11. The crystalline form of claim 4, wherein the XRPD pattern is substantially identical to the XRPD pattern shown in FIG. 61A.
7. ~~— The crystalline form of claim 6, comprising Form A.~~
- 20 8. ~~— The crystalline form of claim 7, consisting essentially of Form A.~~
9. ~~— The crystalline form of claim 8, wherein Form A is in substantially pure form.~~
10. ~~— The crystalline form of any one of claims 7-9, characterized by an x-ray powder~~
25 ~~diffraction (XRPD) pattern comprising peaks, in units 2 theta, at 11.2 ± 0.2 , 17.1 ± 0.2 , and 19.9 ± 0.2 .~~
11. ~~— The crystalline form of claim 10, further comprising a peak, in units 2 theta, at 15.4 ± 0.2 .~~
- 30

12. — The crystalline form of claim 11, further comprising a peak, in units 2θ , at 7.0 ± 0.2 .
13. — The crystalline form of any one of claims 7-9, characterized by an XRPD pattern comprising three or more peaks, in units of 2θ , selected from 7.0 ± 0.2 , 11.2 ± 0.2 , 15.4 ± 0.2 , 16.3 ± 0.2 , 17.1 ± 0.2 , 19.9 ± 0.2 , 21.6 ± 0.2 , and 25.5 ± 0.2 .
14. — The crystalline form of claim 13, wherein the XRPD pattern comprises 4, 5, 6, 7, or 8 peaks, in units of 2θ , selected from 7.0 ± 0.2 , 11.2 ± 0.2 , 15.4 ± 0.2 , 16.3 ± 0.2 , 17.1 ± 0.2 , 19.9 ± 0.2 , 21.6 ± 0.2 , and 25.5 ± 0.2 .
15. — The crystalline form of claim 14, wherein the XRPD pattern is substantially identical to the XRPD pattern shown in Figure 61.
16. — The crystalline form of any one of claims 7-15, characterized by a differential scanning calorimetry (DSC) thermogram comprising an endotherm peak in units $^{\circ}\text{C}$ of about 185.0 - 194.0 .
17. — The crystalline form of claim 16, wherein the endotherm peak has an onset temperature of about 186.3°C .
18. — The crystalline form of claim 17, characterized by a DSC thermogram comprising endotherm peaks in units $^{\circ}\text{C}$ at about 107.8 , about 152.1 , and about 189.1 .
19. — The crystalline form of claim 18, wherein the DSC thermogram is substantially identical to the thermogram shown in Figure 64.
20. — The crystalline form of any one of claims 7-19, characterized by a thermogravimetric analysis (TGA) thermogram showing weight loss of about 1.8% at 160°C .

21. — The crystalline form of claim 20, wherein the TGA thermogram is substantially identical to the thermogram shown in Figure 64.
22. — The crystalline form of any one of claims 7-21, having an initial purity of at least 99% and a subsequent purity of at least 99% after being stored for up to about 15 days at about $25^{\circ}\text{C} \pm 2^{\circ}\text{C}$ at a relative humidity of $60 \pm 5\%$.
23. — The crystalline form of any one of claims 7-22, having an initial purity of at least 99% and a subsequent purity of at least 99% after being stored for up to about 15 days at about $40^{\circ}\text{C} \pm 2^{\circ}\text{C}$ at a relative humidity of $75 \pm 5\%$.
24. — A composition comprising a tartrate salt of any one of claims 1-4, or a crystalline form of any one of claims 5-23.
25. — The composition of claim 24, comprising Form A in substantially pure form.
26. — The composition of claim 25, comprising at least 90% Form A by weight.
27. — The composition of claim 25 or claim 26, consisting essentially of crystalline Form A.
28. — The composition of any one of claims 24-27, wherein the composition is a pharmaceutical composition and further comprises a pharmaceutically acceptable carrier or diluent.
29. — The pharmaceutical composition of claim 28, further comprising one or more additional therapeutic agents.
30. — The pharmaceutical composition of claim 29, wherein the one or more additional therapeutic agents are independently selected from hormone therapeutic agents, chemotherapeutic agents, immunotherapeutic agents, cell growth factors, and agents to inhibit cell growth factor receptor action.

- ~~31. — The pharmaceutical composition of any one of claims 24–30, wherein the pharmaceutical composition is formulated for oral administration.~~
- 5 ~~32. — The pharmaceutical composition of claim 31, wherein the pharmaceutical composition is formulated as a capsule or tablet.~~
- ~~33. — A unit dose comprising a pharmaceutical composition of any one of claims 24–32, wherein unit dose comprises about 1–100 mg of the tartrate salt.~~
- 10 ~~34. — The unit dose of claim 33, comprising about 1 mg, 4 mg, 16 mg, 25 mg, 50 mg, 75 mg, or 100 mg of the tartrate salt.~~
- ~~35. — The unit dose of claim 33 or 34, wherein the unit dose is formulated in a gelatin hard capsule for oral administration.~~
- 15 ~~36. — A method of treating a cancer, the method comprising administering to a subject in need thereof a therapeutically effective amount of the tartrate salt of any one of claims 1–4, or the crystalline form of any one of claims 5–23, or the pharmaceutical composition of any one of claims 24–32, or the unit dose of any one of claims 33–35.~~
- 20 ~~37. — The method of claim 36, comprising administering to the subject a therapeutically effective amount of a tartrate salt having a molar ratio of tartaric acid to the compound of structure (I) of about 2:1.~~
- 25 ~~38. — The method of claim 37, comprising administering to the subject a therapeutically effective amount of the crystalline Form A.~~
- ~~39. — The method of claim 38, wherein Form A is in substantially pure form.~~
- 30 ~~40. — The method of any one of claims 36–39, wherein the subject is a human.~~

41. — The method of any one of claims 36-40, wherein the cancer is a solid tumor or a hematological cancer.

42. — The method of claim 41, wherein the solid tumor is a tumor of the bones, digestive organs, reproductive organs, head, neck, lung, heart, skin, nervous system, endocrine system, neuroendocrine system, urinary system, soft tissue, or brain.

43. — The method of claim 41, wherein the hematopoietic cancer is multiple myeloma, myelodysplastic syndrome (MDS), acute myelogenous leukemia (AML), acute lymphoblastic leukemia (ALL), acute lymphocytic leukemia, chronic lymphogenous leukemia, chronic lymphocytic leukemia (CLL), small lymphocytic lymphoma (SLL), mantle cell lymphoma, diffuse large B-cell lymphoma, follicular lymphoma, or non-Hodgkin's lymphoma.

44. — The method of any one of claims 41-43, wherein the cancer is an advanced solid tumor and/or has shown disease progress after receiving one or more prior cancer therapy.

45. — The method of any one of claims 41-44, wherein the solid tumor is a resistant, recurrent, refractory, or relapsed solid tumor.

46. — The method of claim 44 or claim 45, wherein the one or more prior cancer therapy comprises a hormone therapeutic agent, a chemotherapeutic agent, an immunotherapeutic agent, or a cell surface receptor inhibitor.

47. — The method of claim 46, wherein the chemotherapeutic agent is an alkylating agent, a platinum-based agent, an antimetabolite, an anti-cancer antibiotic, or a plant-derived anti-cancer agent.

48. — The method of claim 47, wherein the chemotherapeutic agent is selected from the group consisting of carboplatin, cisplatin, miboplatin, nedaplatin, and oxaliplatin.

49. — ~~The method of claim 44 or claim 45, wherein the one or more prior cancer therapy comprises immunotherapy, chemotherapy, or a combination thereof.~~
- 5 50. — ~~The method of any one of claims 41-42 and 44-49, wherein the solid tumor is selected from the group consisting of non-small-cell lung cancer (NSCLC), colorectal carcinoma (CRC), ovarian cancer, melanoma, breast carcinoma, neuroendocrine carcinoma, prostate adenocarcinoma, cholangiocarcinoma, uterine carcinoma, and pancreatic cancer.~~
- 10 51. — ~~The method of any one of claims 36-50, wherein the subject has at least stable disease after receiving an immunotherapy.~~
52. — ~~The method of claim 51, wherein the subject has received up to two cycles of the immunotherapy.~~
- 15 53. — ~~The method of any one of claims 36-52, wherein the subject has EGFR⁺ NSCLC.~~
54. — ~~The method of claim 53, wherein the subject has demonstrated disease progression after receiving one or more chemotherapies comprising one or more tyrosine kinase inhibitors (TKIs).~~
- 20 55. — ~~The method of claim 54, wherein the one or more TKIs comprise an EGFR TKI.~~
56. — ~~The method of any one of claims 53-55, wherein the subject has at least stable disease after taking up to two lines of the TKIs.~~
- 25 57. — ~~The method of any one of claims 36-52, wherein the subject has BRAF⁺, KRAS⁺, or NRAS⁺ mutated colorectal carcinoma (CRC).~~
58. — ~~The method of any one of claims 36-52, wherein the subject has persistent or recurrent ovarian cancer.~~
- 30

59. — The method of claim 58, wherein the subject is refractory or resistant to a platinum-based agent, has undergone prior therapy, or both.
60. — The method of claim 59, wherein the platinum-based agent is carboplatin, cisplatin,
5 miboplatin, nedaplatin, or oxaliplatin.
—
61. — The method of any one of claims 36-52, wherein the subject has BRAF-mutated melanoma.
- 10 62. — The method of claim 61, wherein the subject has progressed disease after an immunotherapy, a chemotherapy comprising one or more BRAF/MEK inhibitors, or a combination thereof.
63. — The method of any one of claims 36-62, wherein the subject is resistant to an
15 immunotherapy and wherein the method further comprising subjecting the subject to the same immunotherapy.
64. — The method of claim 63, wherein the immunotherapy comprises an anti-PD-1 or an anti-PD-L1 agent.
20
65. — The method of any one of claims 36-62, wherein the subject is resistant to a chemotherapy comprising a TKI, and wherein the method further comprising subjecting the subject to the same chemotherapy.
- 25 66. — The method of claim 65, wherein the subject is not taking steroids at an amount equivalent to 15 mg/day of prednisone.
67. — The method of claim 65 or claim 66, wherein the method further comprises administering to the subject concomitant steroids.
30

~~68.—The method of any one of claims 36–67, wherein the subject is free of an anticancer therapy at least within the month prior to the first dosing of the tartrate salt, free of CYP2C19-metabolizers, and/or H2-receptor antagonists at least within 7 days prior to the first dosing of the tartrate salt.~~

5

~~69.—The method of any one of claims 36–68, wherein the subject is administered orally the tartrate salt, the crystalline form thereof, or the pharmaceutical composition comprising such at a daily dose of about 1.0, 1.5, 3.0, 6.0, 9.0, 12.0, 16.0, 21.0, 28.0, 37.0, 49.0, or 65.0 mg/m² of the tartrate salt.~~

10

~~70.—The method of any one of claims 36–68, wherein the subject is administered orally the tartrate salt, the crystalline form thereof, or the pharmaceutical composition at a daily dose of the tartrate salt of about 20–100 mg, optionally about 25–75 mg.~~

15

~~71.—The method of claim 70, wherein the daily dose of the tartrate salt is about 20mg, about 25mg, about 30mg, about 35mg, about 40mg, about 45mg, about 50 mg, about 55mg, about 60mg, about 65mg, about 70mg, about 75mg, about 80mg, about 85mg, about 90mg, about 95mg, or about 100mg.~~

20

~~72.—The method of any one of claims 36–71, wherein the method comprises one or more treatment cycles, each consisting of about 28 days, and wherein in each treatment cycle, the tartrate salt, the crystalline form thereof, or the pharmaceutical composition is administered to the subject daily for 21 days, followed by a drug holiday period of seven days.~~

25

~~73.—The method of claim 44 or claim 45, wherein the hematological cancer is chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL).~~

~~74.—The method of claim 73, wherein the subject has undergone one or more prior therapies for CLL or SLL.~~

30

- ~~75.—The method of claim 73 or claim 74, wherein the subject is intolerant to the prior therapies or has progressive disease after the prior therapies.~~
- 5 ~~76.—The method of claim 75, wherein the prior therapies comprise a B-cell receptor antagonist, a BCL-2 antagonist, or a combination thereof.~~
- ~~77.—The method of any one of claims 73-76, wherein the subject is not concurrently treated by another cancer therapy.~~
- 10 ~~78.—The method of any one of claims 73-77, wherein the subject is administered orally the tartrate salt, the crystalline form thereof, or the pharmaceutical composition at a daily dose of about 20 mg-100 mg of the tartrate salt, optionally about 25-75 mg.~~
- 15 ~~79.—The method of claim 78, wherein the daily dose of the tartrate salt is about 25 mg, about 33 mg, about 45 mg, about 50 mg, about 58 mg, about 75 mg, or about 100 mg.~~
- ~~80.—The method of any one of claims 73-79, further comprising administering to the subject a BTK inhibitor.~~
- 20 ~~81.—The method of claim 80, wherein the BTK inhibitor is selected from the group consisting of ibrutinib, acalabrutinib, zanubrutinib, and LOXO-305.~~
-
- ~~82.—The method of claim 81, wherein the BTK inhibitor is ibrutinib.~~
- 25 ~~83.—The method of any one of claims 80-82, wherein the subject was subject to a prior treatment of the BTK inhibitor and has progressed on the BTK inhibitor treatment.~~
- ~~84.—The method of any one of claims 80-83, wherein the subject is administered the tartrate salt, the crystalline form thereof, or the pharmaceutical composition comprising such~~
- 30 ~~at a daily dose of about 20 mg-100 mg of the tartrate salt.~~

85. — The method of claim 84, wherein the daily dose of the tartrate salt is about 20 mg, about 25 mg, about 33 mg, about 45 mg, about 50 mg, about 58 mg, about 75 mg, or about 100 mg.

5 86. — The method of any one of claims 73–85, further comprising monitoring the subject for tumor lysis syndrome (TLS).

87. — The method of any one of claims 73–86, further comprising administering to the subject an antibiotic, an anti-viral agent, an anti-fungal agent, or a combination thereof.

10

88. — The method of any one of claims 73–87, wherein the method comprises one or more treatment cycles, each consisting of about 28 days, and wherein in each cycle, the subject is administered the tartrate salt, the crystalline form thereof, or the pharmaceutical composition comprising such orally once daily for 28 days.

15

89. — The method of any one of claims 36–88, wherein the subject has an elevated level of soluble AXL, AXL expression and/or phosphorylation, growth arrest specific 6 (GAS6), a mesenchymal transcription factor, or a combination thereof, as relative to a reference level of soluble AXL, GAS6, or the mesenchymal transcription factor.

20

90. — The method of claim 36–89, further comprising, prior to the administering step, identifying a subject having an elevated level of soluble AXL, AXL expression and/or phosphorylation, growth arrest specific 6 (GAS6), a mesenchymal transcription factor, or a combination thereof, as relative to a reference level of soluble AXL, GAS6, or the mesenchymal transcription factor.

25

91. — The method of claim 90, wherein the identifying step is performed by obtaining a peripheral blood sample or a bone marrow sample of a candidate subject, and measuring the level of soluble AXL, the level of GAS6, the level of the mesenchymal transcription factor, or a combination thereof in the peripheral blood sample or the bone marrow sample.

30

92. — ~~The method of any one of claims 36-91, further comprising, after the administering step, examining the subject for one or more symptoms of diarrhea, nausea, vomiting, dysgeusia, anemia, and thrombocytopenia.~~
- 5 93. — ~~The method of claim 92, further comprising lowering the daily dose of the tartrate salt or terminating the treatment if the one or more symptoms are detected.~~
94. — ~~The method of any one of claims 36-93, further comprising administering an effective amount of one or more therapeutic agents to the subject.~~
- 10 95. — ~~The method of claim 94, wherein the one or more therapeutic agents comprise one or more tyrosine kinase inhibitors.~~
96. — ~~The method of claim 95, wherein the one or more tyrosine kinase inhibitors comprises~~
15 ~~an EGFR inhibitor.~~
97. — ~~The method of claim 95 or claim 96, wherein the one or more therapeutic agents comprise an immune checkpoint inhibitor.~~
- 20 98. — ~~The method of claim 97, wherein the immune checkpoint inhibitor is a PD-1 or PD-L1 inhibitor.~~
99. — ~~The method of claim 98, wherein the immune checkpoint inhibitor is a PD-1 inhibitor, which is pembrolizumab, nivolumab, or a combination thereof.~~
- 25 100. — ~~The method of claim 98, wherein the immune checkpoint inhibitor is a PD-L1 inhibitor, which is atezolizumab, avelumab, durvalumab, or a combination thereof.~~
101. — ~~The method of any one of claims 95-100, wherein the one or more therapeutic agents~~
30 ~~comprise a CDK inhibitor.~~

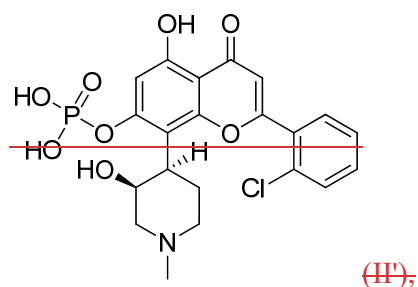
~~102. The method of claim 101, wherein the CDK inhibitor is a CDK9 inhibitor.~~

~~103. The method of claim 102, wherein the CDK9 inhibitor is alvocidib, or a pharmaceutically acceptable salt or prodrug thereof.~~

5

~~104. The method of claim 103, wherein the CDK9 inhibitor is a prodrug of alvocidib.~~

~~105. The method of claim 104, wherein the prodrug has the following structure (II):~~

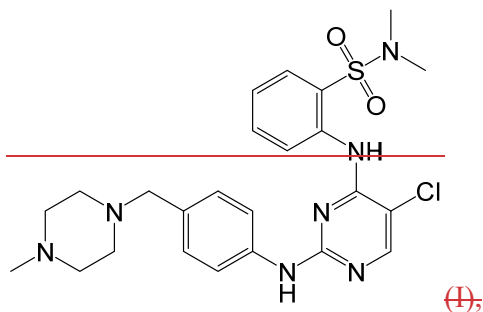


10 ~~or a pharmaceutically acceptable salt or zwitterionic form thereof.~~

~~106. The method of any one of claims 95-105, wherein the one or more therapeutic agents comprise a platinum-based chemotherapeutic agents.~~

15 ~~107. The method of claim 95, wherein the one or more therapeutic agents comprise carboplatin, gemcitabine, bevacizumab, topotecan, rucaparib, olaparib, niraparib, nivolumab, pembrolizumab, atezolizumab, avelumab, durvalumab, ipilimumab, or a combination thereof.~~

~~108. A method of treating cancer in a subject comprising administering to the subject a compound of structure (I):~~



20

~~or a pharmaceutically acceptable salt or crystalline form thereof, wherein:~~

~~the compound, or pharmaceutically acceptable salt, or crystalline form thereof, is administered to the subject orally once daily at a dose from about 1.5 mg/m² to about 65 mg/m², or at a dose of about 20 mg to about 100 mg, optionally about 25 mg to about 75 mg.~~

5 ~~109.—The method of claim 108, wherein the compound of structure (I), or pharmaceutically acceptable salt, or crystalline form thereof, is administered orally at a dose of about 1.0, about 1.5, about 3.0, about 6.0, about 9.0, about 12.0, about 16.0, about 21.0, about 28.0, about 37.0, about 49.0, or about 65.0 mg/m².~~

10 ~~110.—The method of claim 109, wherein the compound of structure (I), or pharmaceutically acceptable salt, or crystalline form thereof, is administered to the subject as a single anti-cancer agent at a daily dose of about 20mg, about 25mg, about 30mg, about 35mg, about 40mg, about 45mg, about 50 mg, about 55mg, about 60mg, about 65mg, about 70mg, about 75mg, about 80mg, about 85mg, about 90mg, about 95mg, or about 100mg.~~

15 ~~111.—The method of claim 108, wherein the compound of structure (I), or pharmaceutically acceptable salt, or crystalline form thereof, is administered orally to the subject concurrently with a second anti-cancer agent and the daily dose of the compound of structure (I), or pharmaceutically acceptable salt, or crystalline form thereof is about 20 mg, about 25 mg,~~
20 ~~about 33 mg, about 45 mg, about 50 mg, about 58 mg, about 75 mg, or about 100 mg.~~

~~112.—The method of claim 108, wherein the second anti-cancer agent is a BTK inhibitor.~~

25 ~~113.—The method of claim 112, wherein the BTK inhibitor is selected from the group consisting of ibrutinib, acalabrutinib, zanubrutinib, and LOXO-305.~~

~~114.—The method of claim 113, wherein the BTK inhibitor is ibrutinib.~~

30 ~~115.—The method of any one of claims 112-114, wherein the subject received a prior treatment of the BTK inhibitor and has progressed on the BTK inhibitor treatment.~~

~~116.—The method of any one of claims 108–115, wherein the subject is a human patient having a solid tumor or a hematopoietic cancer.~~

5 ~~117.—The method of claim 116, wherein the human patient has an advanced solid tumor.~~

~~118.—The method of claim 116 or claim 117, wherein the solid tumor is a tumor of the bones, digestive organs, reproductive organs, head, neck, lung, heart, skin, nervous system, endocrine system, neuroendocrine system, urinary system, or soft tissue.~~

10

~~119.—The method of claim 116, wherein the hematopoietic cancer is multiple myeloma, myelodysplastic syndrome (MDS), acute myelogenous leukemia (AML), acute lymphoblastic leukemia (ALL), acute lymphocytic leukemia, chronic lymphogenous leukemia, chronic lymphocytic leukemia (CLL), small lymphocytic lymphoma (SLL), mantle cell lymphoma, diffuse large B-cell lymphoma, follicular lymphoma, or non-Hodgkin's lymphoma.~~

15

~~120.—The method of any one of claims 116–119, wherein the cancer is an advanced solid tumor and/or has shown disease progress after receiving one or more prior cancer therapy.~~

20 ~~121.—The method of any one of claims 116–120, wherein the solid tumor is a resistant, recurrent, refractory, or relapsed solid tumor.~~

~~122.—The method of claim 120 or claim 121, wherein the one or more prior cancer therapy comprises a hormone therapeutic agent, a chemotherapeutic agent, an immunotherapeutic agent, or a cell surface receptor inhibitor.~~

25

~~123.—The method of claim 122, wherein the chemotherapeutic agent is an alkylating agent, a platinum-based agent, an antimetabolite, an anti-cancer antibiotic, or a plant-derived anti-cancer agent.~~

30

- ~~124.—The method of claim 123, wherein the chemotherapeutic agent is selected from the group consisting of carboplatin, cisplatin, miboplatin, nedaplatin, and oxaliplatin.~~
- 5 ~~125.—The method of claim 123 or claim 124, wherein the one or more prior cancer therapy comprises immunotherapy, chemotherapy, or a combination thereof.~~
- ~~126.—The method of claim 125, wherein the solid tumor is selected from the group consisting of non-small cell lung cancer (NSCLC), colorectal carcinoma (CRC), ovarian cancer, melanoma, breast carcinoma, neuroendocrine carcinoma, prostate adenocarcinoma, cholangiocarcinoma, uterine carcinoma, and pancreatic cancer.~~
- 10 ~~127.—The method of any one of claims 108–126, wherein the subject has at least stable disease after receiving an immunotherapy.~~
- ~~–~~
- 15 ~~128.—The method of claim 127, wherein the subject has received up to two cycles of the immunotherapy.~~
- ~~129.—The method of any one of claims 108–128, wherein the subject has EGFR⁺ NSCLC.~~
- 20 ~~130.—The method of claim 129, wherein the subject has demonstrated disease progression after receiving one or more chemotherapies comprising one or more tyrosine kinase inhibitors (TKIs).~~
- ~~131.—The method of claim 130, wherein the one or more TKIs comprise an EGFR TKI.~~
- 25 ~~132.—The method of any one of claims 129–131, wherein the subject has at least stable disease after taking up to two lines of the TKIs.~~
- ~~133.—The method of any one of claims 108–128, wherein the subject has BRAF⁺, KRAS⁺, or NRAS⁺ mutated colorectal carcinoma (CRC).~~
- 30

~~134.—The method of any one of claims 108–133, wherein the subject has persistent or recurrent ovarian cancer.~~

~~135.—The method of claim 134, wherein the subject is refractory or resistant to a platinum-based agent, has undergone prior therapy, or both.~~

~~136.—The method of claim 135, wherein the platinum-based agent is carboplatin, cisplatin, miboplatin, nedaplatin, or oxaliplatin.~~

~~—~~

~~137.—The method of any one of claims 108–128, wherein the subject has BRAF-mutated melanoma.~~

~~138.—The method of claim 137, wherein the subject has progressed disease after an immunotherapy, a chemotherapy comprising one or more BRAF/MEK inhibitors, or a combination thereof.~~

~~139.—The method of any one of claims 108–138, wherein the subject is resistant to an immunotherapy and wherein the method further comprising subjecting the subject to the same immunotherapy.~~

~~140.—The method of claim 139, wherein the immunotherapy comprises an anti-PD-1 or an anti-PD-L1 agent.~~

~~141.—The method of any one of claims 108–140, wherein the subject is resistant to a chemotherapy comprising a TKI, and wherein the method further comprising subjecting the subject to the same chemotherapy.~~

~~142.—The method of claim 141, wherein the subject is not taking steroids at an amount equivalent to 15 mg/day of prednisone.~~

- 143.—The method of claim 141 or claim 142, wherein the method further comprises administering to the subject concomitant steroids.—
- 144.—The method of any one of claims 108–143, wherein the subject is free of an anticancer therapy at least within the month prior to the first dosing of the tartrate salt, free of CYP2C19-metabolizers, and/or H2-receptor antagonists at least within 7 days prior to the first dosing of the tartrate salt.
- 145.—The method of any one of claims 108–144, wherein the method comprises one or more treatment cycles, each consisting of 28 days, and wherein in each cycle, the tartrate salt, the crystalline form thereof, or the pharmaceutical composition comprising such is administered to the subject daily for 21 days, followed by a drug holiday period of seven days.—
- 146.—The method of claim 120 or claim 121, wherein the hematological cancer is chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL).
- 147.—The method of claim 146, wherein the subject has undergone one or more prior therapies for CLL or SLL.
- 148.—The method of claim 146 or claim 147, wherein the subject is intolerant to the prior therapies or has progressive disease after the prior therapies.
- 149.—The method of claim 148, wherein the prior therapies comprise a B-cell receptor-antagonist, a BCL-2 antagonist, or a combination thereof.
- 150.—The method of any one of claims 146–149, wherein the subject is not concurrently treated by another cancer therapy.
- 151.—The method of any one of claims 146–150, further comprising monitoring the subject for tumor lysis syndrome (TLS).

- ~~152.—The method of any one of claims 146–151, further comprising administering to the subject an antibiotic, an anti-viral agent, an anti-fungal agent, or a combination thereof.~~
- 5 ~~153.—The method of any one of claims 146–152, wherein the method comprises one or more treatment cycles, each consisting of about 28 days, and wherein in each cycle, the subject is administered the tartrate salt, the crystalline form thereof, or the pharmaceutical composition comprising such orally once daily for 28 days.~~
- 10 ~~154.—The method of any one of claims 108–153, wherein the subject has an elevated level of soluble AXL, AXL expression and/or phosphorylation, growth-arrest specific 6 (GAS6), a mesenchymal transcription factor, or a combination thereof, as relative to a reference level of soluble AXL, GAS6, or the mesenchymal transcription factor.~~
- 15 ~~155.—The method of any one of claims 108–154, further comprising, prior to the administering step, identifying a subject having an elevated level of soluble AXL, AXL expression and/or phosphorylation, growth-arrest specific 6 (GAS6), a mesenchymal transcription factor, or a combination thereof, as relative to a reference level of soluble AXL, GAS6, or the mesenchymal transcription factor.~~
- 20 ~~156.—The method of claim 155, wherein the identifying step is performed by obtaining a peripheral blood sample or a bone marrow sample of a candidate subject, and measuring the level of soluble AXL, the level of GAS6, the level of the mesenchymal transcription factor, or a combination thereof in the peripheral blood sample or the bone marrow sample.~~
- 25 ~~157.—The method of any one of claims 108–156, further comprising, after the administering step, examining the subject for one or more symptoms of diarrhea, nausea, vomiting, dysgeusia, anemia, and thrombocytopenia.~~
- 30 ~~158.—The method of claim 157, further comprising lowering the daily dose of the tartrate salt or terminating the treatment if the one or more symptoms are detected.~~

~~159.—The method of any one of claims 108–158, further comprising administering an effective amount of one or more therapeutic agents to the subject.~~

5 ~~160.—The method of claim 159, wherein the one or more therapeutic agents comprise one or more tyrosine kinase inhibitors.~~

~~161.—The method of claim 160, wherein the one or more tyrosine kinase inhibitors comprises an EGFR inhibitor.~~

10

~~162.—The method of any one of claims 159–161, wherein the one or more therapeutic agents comprise an immune checkpoint inhibitor.~~

15

~~163.—The method of claim 162, wherein the immune checkpoint inhibitor is a PD-1 or PD-L1 inhibitor.~~

~~164.—The method of claim 163, wherein the immune checkpoint inhibitor is a PD-1 inhibitor, which is pembrolizumab, nivolumab, or a combination thereof.~~

20

~~165.—The method of claim 163, wherein the immune checkpoint inhibitor is a PD-L1 inhibitor, which is atezolizumab, avelumab, durvalumab, or a combination thereof.~~

~~166.—The method of any one of claims 159–165, wherein the one or more therapeutic agents comprise a CDK inhibitor.~~

25

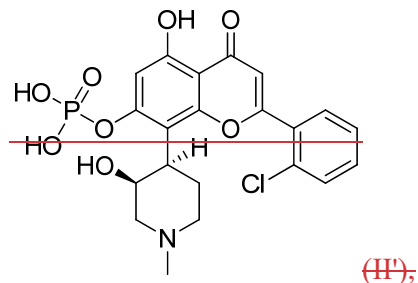
~~167.—The method of claim 166, wherein the CDK inhibitor is a CDK9 inhibitor.~~

~~168.—The method of claim 167, wherein the CDK9 inhibitor is alvocidib, or a pharmaceutically acceptable salt or prodrug thereof.~~

30

~~169.—The method of claim 168, wherein the CDK9 inhibitor is a prodrug of alvocidib.~~

~~170.—The method of claim 169, wherein the prodrug has the following structure (II'):~~



~~or a pharmaceutically acceptable salt or zwitterionic form thereof.~~

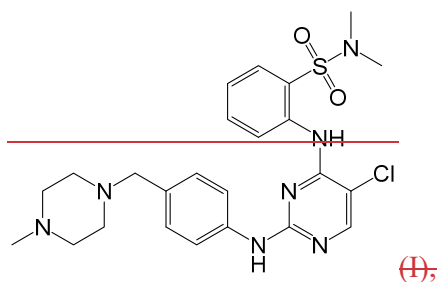
5

~~171.—The method of any one of claims 159-170, wherein the one or more therapeutic agents comprise a platinum-based chemotherapeutic agents.—~~

~~172.—The method of claim 159, wherein the one or more therapeutic agents comprise carboplatin, gemcitabine, bevacizumab, topotecan, rucaparib, olaparib, niraparib, nivolumab, pembrolizumab, atezolizumab, avelumab, durvalumab, ipilimumab, or a combination thereof.~~

10

~~173.—A method of treating a cancer, the method comprising administering an effective amount of a compound of structure (I):~~



15

~~or a pharmaceutically acceptable salt thereof, to a subject in need thereof, wherein the cancer is selected from the group consisting of EGFR+ non-small cell lung cancer; BRAF-, KRAS-, or NRAS-mutated colorectal carcinoma; persistent or recurrent ovarian carcinoma; BRAF-mutated melanoma, inflammatory breast cancer, and triple negative breast cancer.~~

20

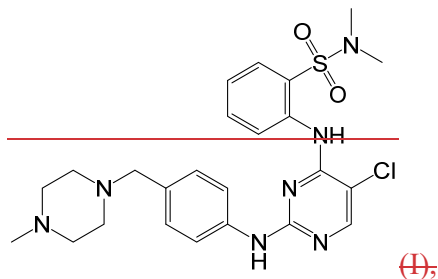
174.—The method of claim 173, wherein the subject has shown disease progress after receiving one or more prior cancer therapy.

175.—The method of claim 173 or claim 174, wherein the cancer is a resistant, refractory, recurrent, or relapsed cancer.

176.—The method of claim 174, wherein the one or more prior cancer therapy comprises a hormone therapeutic agent, a chemotherapeutic agent, an immunotherapeutic agent, or a cell surface receptor inhibitor.

10

177.—A method of treating a cancer, the method comprising administering an effective amount of a compound of structure (I):



178.—The method of claim 177, wherein the solid tumor is a tumor of the bones, digestive organs, reproductive organs, head, neck, lung, heart, skin, nervous system, endocrine system, neuroendocrine system, urinary system, or soft tissue.

179.—The method of claim 177, wherein the hematopoietic cancer is multiple myeloma, myelodysplastic syndrome (MDS), acute myelogenous leukemia (AML), acute lymphoblastic leukemia (ALL), acute lymphocytic leukemia, chronic lymphogenous leukemia, chronic lymphocytic leukemia (CLL), small lymphocytic lymphoma (SLL), mantle cell lymphoma, diffuse large B-cell lymphoma, follicular lymphoma, or non-Hodgkin's lymphoma.

25

~~180.—The method of any one of claims 177-179, wherein the prior chemotherapy and/or immunotherapy comprises a hormone therapeutic agent, a chemotherapeutic agent, an immunotherapeutic agent, or a cell surface receptor inhibitor.—~~

5

~~181.—The method of claim 180, wherein the chemotherapeutic agent is an alkylating agent, a platinum-based agent, an antimetabolite, an anti-cancer antibiotic, or a plant-derived anti-cancer agent.~~

10 ~~182.—The method of claim 181, wherein the chemotherapeutic agent is selected from the group consisting of carboplatin, cisplatin, miboplatin, nedaplatin, and oxaliplatin.~~

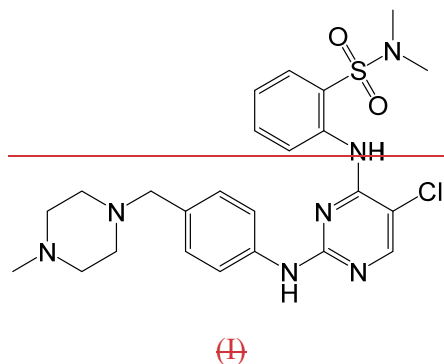
~~183.—The method of any one of claims 177-181, wherein the subject is treated concurrently with the chemotherapy, the immunotherapy, or the combination thereof.~~

15

~~184.—The method of any one of claims 177-183, wherein the subject is resistant to an immunotherapy and wherein the method further comprising subjecting the subject to the same immunotherapy.~~

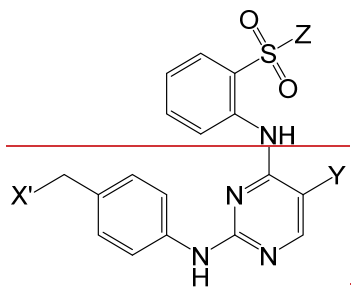
20 ~~185.—The method of any one of claims 177-183, wherein the subject is resistant to a chemotherapy comprising a TKI, and wherein the method further comprising subjecting the subject to the same chemotherapy.~~

~~186.—A method for preparing a compound of structure (I):~~



25

or a pharmaceutically acceptable salt thereof, the method comprising reacting a compound having the following structure:



or a pharmaceutically acceptable salt thereof, wherein:

5 X' is a leaving group;

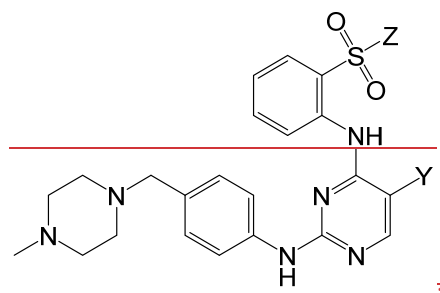
Y is halo;

Z is halo or -NR¹(R²); and

R¹ and R² are, each independently, hydrogen or C₁-C₈ alkyl,

with N-methylpiperazine, or a salt thereof, to obtain a compound having the following

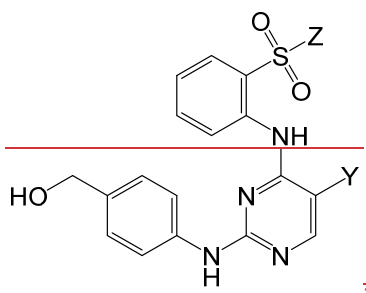
10 structure:



or a pharmaceutically acceptable salt thereof.

187. The method of claim 186, further comprising the step of:

15 reacting a compound having the following structure:



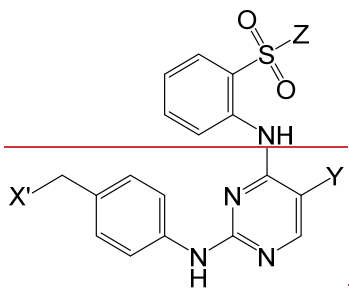
or a pharmaceutically acceptable salt thereof, wherein:

Y is halo;

Z is halo or $\text{NR}^1(\text{R}^2)$; and

R^1 and R^2 are, each independently, hydrogen or $\text{C}_1\text{--C}_8$ alkyl,

5 with an activating agent to obtain the compound having the structure:



or a pharmaceutically acceptable salt thereof.

188. The method of claim 187, wherein the activating agent comprises a sulfonyl chloride functional group.

10

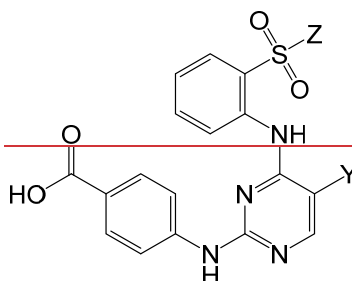
189. The method of any one of claims 186–188, wherein X' is halo or sulfonate.

190. The method of claim 189, wherein X' is chloro.

15

191. The method of claim 190, wherein the activating agent is thionyl chloride.

192. The method of claim 187, further comprising the step:
reacting a compound having the following structure:



20

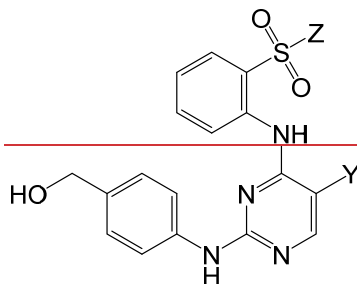
or a pharmaceutically acceptable salt thereof, wherein:

Y is halo;

~~Z is halo or $\text{NR}^+(\text{R}^2)$; and~~

~~R^1 and R^2 are, each independently, hydrogen or $\text{C}_1\text{--C}_8$ alkyl,~~

~~with a reducing agent to obtain the compound having the structure:~~

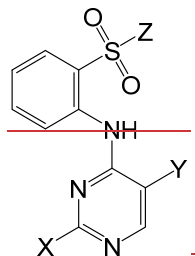


5

~~193. The method of claim 192, wherein the reducing agent is lithium aluminum hydride, diborane, sodium borohydride, borane, or combinations thereof.~~

~~194. The method of any one of claims 186–193, wherein the reducing agent is borane.~~

10 ~~195. The method of claim 192, further comprising:
reacting a compound having the following structure:~~



~~or a pharmaceutically acceptable salt thereof, wherein~~

~~X is a leaving group;~~

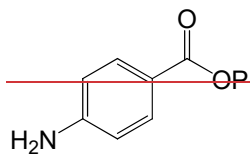
15

~~Y is halo;~~

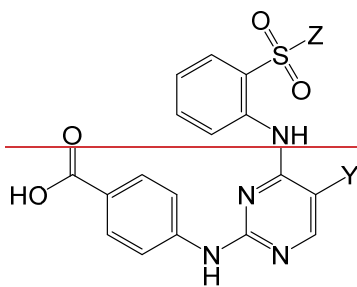
~~Z is halo or $\text{NR}^+(\text{R}^2)$; and~~

~~R^1 and R^2 are, each independently, hydrogen or $\text{C}_1\text{--C}_8$ alkyl,~~

~~with a compound having the following structure:~~



20 ~~wherein P is H or a protecting group, to obtain a compound having the following structure:~~



~~196. The method of claim 195, wherein X is halo or sulfonate.~~

5 ~~197. The method of claim 196, wherein X is chloro.~~

~~198. The method of any one of claims 195-197, wherein P is H.~~

~~199. The method of any one of claims 186-198, wherein Y is chloro.~~

10

~~200. The method of any one of claims 186-199, wherein Z is $\text{NR}^+(\text{R}^2)$.~~

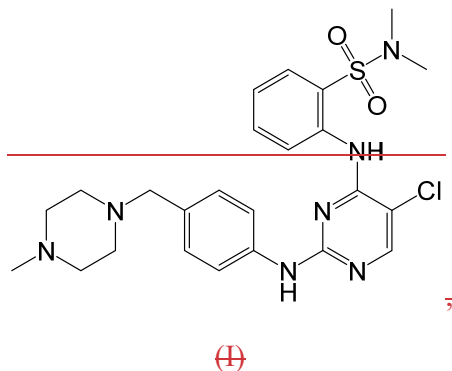
~~201. The method of any one of claims 186-200, wherein R^+ is $\text{C}_1\text{-C}_8$ alkyl.~~

15 ~~202. The method of claim 201, wherein R^+ is methyl.~~

~~203. The method of any one of claims 186-202, wherein R^2 is $\text{C}_1\text{-C}_8$ alkyl.~~

~~204. The method of claim 203, wherein R^2 is methyl.~~

205.—A method for preparing a tartrate salt of the compound of structure (I):



5 the method comprising admixing the compound of structure (I) with tartaric acid.

206.—The method of claim 205, wherein the tartaric acid is L (+) tartaric acid.

10

207.—The method of claim 205 or claim 206, wherein the tartrate salt is of crystalline Form A, and the method comprises:

(a) —dissolving the compound of structure (I) in a solvent comprising anisole and ethanol to afford a first solution;

15

(b) —adding a solution of (L) tartaric acid in ethanol to the first solution to afford a second solution; and

(c) —allowing the tartrate salt of structure (I) to crystallize from the second solution.

20

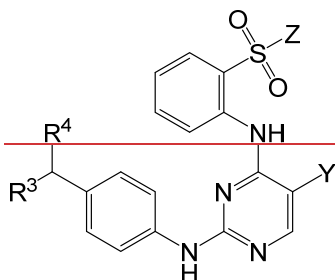
208.—The method of claim 207, wherein the solvent of step (a) comprises anisole and ethanol in a ratio of about 2.5:1 (w/w) and/or has a temperature of about 70 °C.

209.—The method of claim 207 or claim 208, wherein the molar ratio of (L) tartaric acid in step (b) to the compound of structure (I) in step (a) is about 2:1 and/or wherein the solution of tartaric acid is added to the first solution over the course of about an hour.

25

210. ~~The method of any one of claims 207-209, wherein the second solution is cooled to about 20 °C and/or is stirred for about 5 hours.~~

211. ~~A compound having the following structure (III):~~



~~(III)~~

~~or a pharmaceutically acceptable salt, stereoisomer or tautomer thereof, wherein:~~

~~Y is halo;~~

~~Z is halo or NR¹(R²);~~

~~R¹ and R² are, each independently, hydrogen or C₁-C₈ alkyl;~~

~~R³ is halo or OR^a;~~

~~R⁴ is hydrogen or oxo; and~~

~~R^a is hydrogen or C₁-C₈ alkyl.~~

212. ~~The compound of claim 211, wherein Y is chloro.~~

213. ~~The compound of claim 211 or claim 212, wherein Z is NR¹(R²).~~

214. ~~The compound of claim 213, wherein R¹ and R² are C₁-C₈ alkyl.~~

215. ~~The compound of claim 213, wherein R¹ and R² are methyl.~~

216. ~~The compound of any one of claims 211-215, wherein R³ is OR^a.~~

217. ~~The compound of claim 216, wherein R^a is H.~~

~~218. The compound of any one of claims 211-217, wherein R² is halo.~~

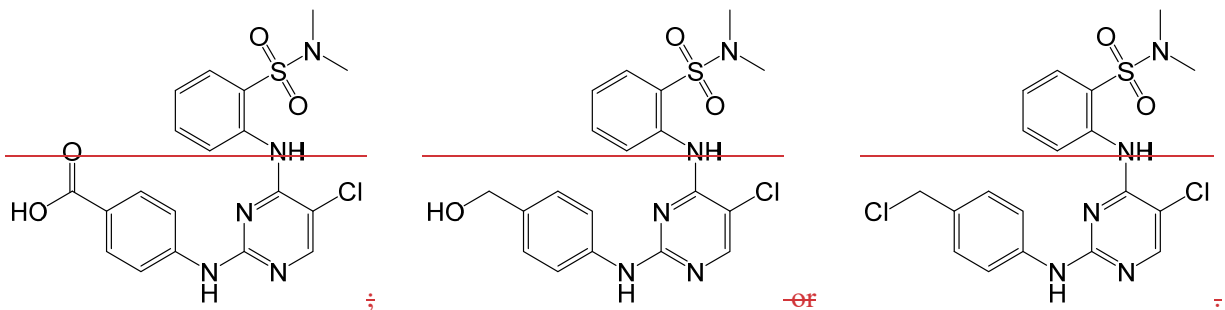
~~219. The compound of claim 218, wherein R³ is chloro.~~

5

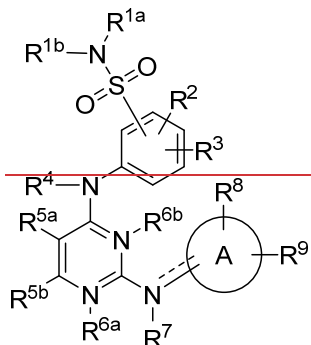
~~220. The compound of any one of claims 211-219, wherein R⁴ is hydrogen.~~

~~221. The compound of any one of claims 211-220, wherein R⁴ is oxo.~~

10 ~~222. The compound of any one of claims 211-221, wherein the compound has one of the following structures:~~



~~223. A compound having the following structure (I):~~



15

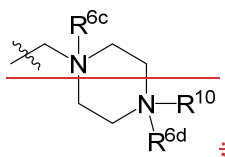
~~or a stereoisomer, pharmaceutically acceptable salt, tautomer or prodrug thereof,~~

~~wherein:~~

~~A represents a 6-membered aromatic ring or a 6-membered carbocyclic ring;~~

~~R^{1a} and R^{1b} are each independently H, C₁-C₆ alkyl, or -OH;~~

~~R² and R³ are each independently H, C₁-C₆ alkyl, or halo;~~
~~R⁴ is H, C₁-C₆ alkyl, or OH;~~
~~R^{5a} and R^{5b} are each independently H, C₁-C₆ alkyl, or halo;~~
~~R^{6a}, R^{6b}, R^{6c} and R^{6d} are each independently absent or O-;~~
~~R⁷ is H, C₁-C₆ alkyl, OH or absent;~~
~~R⁸ is absent or has the following structure:~~



~~R⁹ is absent or alkenyl, provided that at least one of R⁸ or R⁹ is present;~~
~~R¹⁰ is H or C₁-C₆ alkyl; and~~

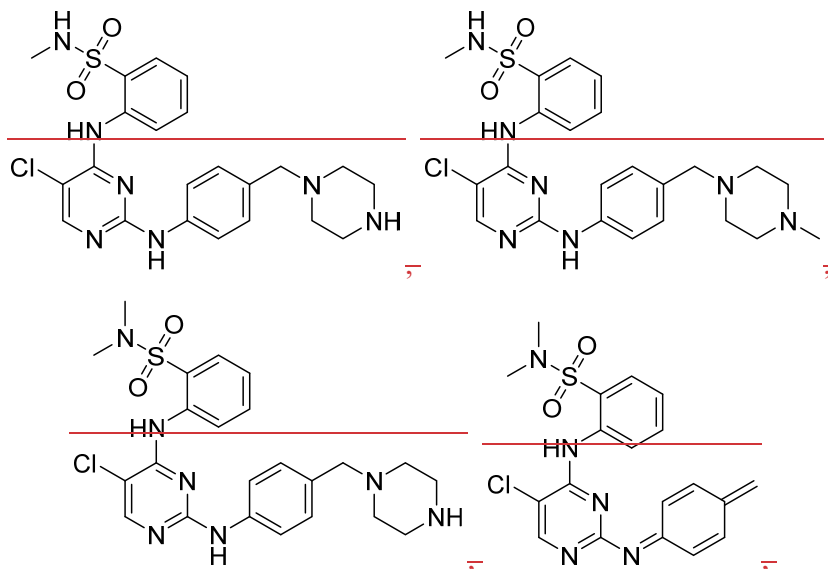
~~==== represents a double or single bond; and~~

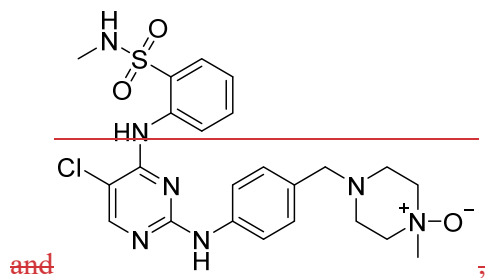
~~all valencies are satisfied;~~

~~provided that if R^{1a} and R^{1b} are both methyl, then:~~

- ~~a. — at least one of R^{6a}, R^{6b}, R^{6c}, R^{6d} and R⁹ is O-;~~
- ~~b. — R⁷ is C₁-C₆ alkyl, OH or absent; and/or~~
- ~~c. — R¹⁰ is H.~~

~~224. The compound of claim 223, wherein the compound is selected from the group consisting of:~~





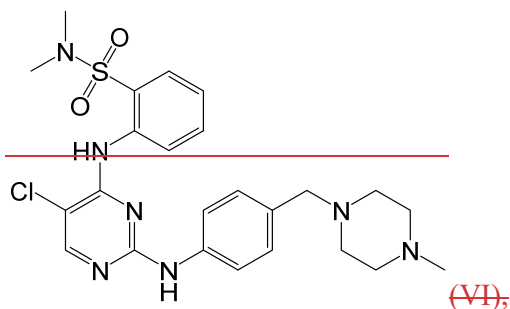
and pharmaceutically acceptable salts thereof.

225.—A pharmaceutical composition comprising a compound of any one of claims 211–224,
or a stereoisomer, pharmaceutically acceptable salt, tautomer or prodrug thereof, and a
pharmaceutically acceptable carrier, diluent or excipient.

226.—A method for treating cancer in a subject, the method comprising administering an
effective amount of a compound of any one of claims 211–224, or a stereoisomer,
pharmaceutically acceptable salt, tautomer or prodrug thereof, or a pharmaceutical
composition according to claim 223.

227.—A method of determining a metabolic profile of a subject, the method comprising:
contacting a population of cells of the subject with a therapeutic agent; and determining a
concentration of a first metabolite that is a compound of any one of claims 211–224.—

228.—The method of claim 227, wherein the therapeutic agent is a compound that has the
following structure (VI):



or a pharmaceutically acceptable salt or crystalline form thereof.

~~229.—The method of any one of claims 36, 108, 177, and 226, wherein the cancer is melanoma, breast cancer, or brain tumor.~~

~~230.—The method of claim 229, wherein the melanoma is metastatic melanoma.~~

5

~~231.—The method of claim 230, wherein the breast cancer is inflammatory breast cancer and/or triple negative breast cancer.~~

~~232.—The method of claim 229, wherein the brain tumor is glioblastoma multiforme (GBM).~~

10

~~233.—The method of any one of claims 229–232, wherein the subject shows disease progression, recurrence, or relapse after treatment with an immunotherapy.~~

~~234.—The method of any one of claims 229–233, further comprising administering an immunotherapeutic agent to the subject.~~

15

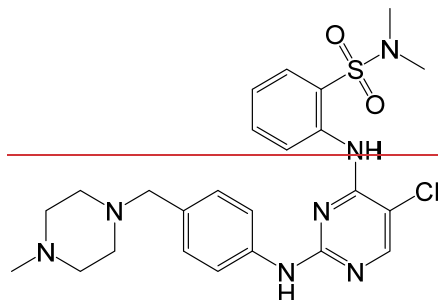
~~235.—The method of claim 234, wherein the immunotherapy is a checkpoint inhibitor or a CTLA-4 inhibitor.~~

~~236.—The method of claim 234, wherein the immunotherapeutic agent is pembrolizumab.~~

20

~~237.—The method of any one of claims 173–185, wherein the method is performed under the conditions set forth in any one of claims 69–72 and 78–107.~~

238.—A method for treating ascites in a subject in need thereof, the method comprising administering to the subject a compound of structure (I):



(I);

5 or a pharmaceutically acceptable salt thereof, wherein the ascites is caused by a cancer.

239.—The method of claim 238, comprising administering to the subject a therapeutically effective amount of the tartrate salt of any one of claims 1-4, or a crystalline form of any one of claims 5-23, or a pharmaceutical composition of any one of claims 24-32, or a unit dose of
10 any one of claims 33-35.

240.—The method of claim 239, comprising administering to the subject a therapeutically effective amount of a tartrate salt having a molar ratio of tartaric acid to the compound of structure (I) of about 2:1.

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241.—The method of claim 239, comprising administering to the subject a therapeutically effective amount of the crystalline Form A.

242.—The method of any one of claims 238-241, wherein the cancer is a hematological cancer or a solid tumor cancer.

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243.—The method of any one of claims 238-242, wherein the cancer is ovarian cancer.

244.—The method of any one of claims 238-243, wherein the cancer is ovarian clear cell carcinoma.

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245.—A method of treating ascites in a subject in need thereof, the method comprising administering to the subject a subject a compound of claim 223 or 224, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 225, wherein the ascites is caused by a cancer.

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246.—The method of claim 245, wherein the cancer is a hematological cancer or a solid tumor cancer.

247.—The method of claim 245 or 246, wherein the cancer is ovarian cancer.

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248.—The method of any one of claims 245–247, wherein the cancer is ovarian clear cell carcinoma.

249.—A method of reversing the epithelial-to-mesenchymal transition (EMT) in a cancer, the method comprising administering to a subject having said cancer a therapeutically effective amount of a tartarate salt of any one of claims 1–4, a crystalline form of any one of claims 5–23, a pharmaceutical composition of any one of claims 24–32, or a unit dose of any one of claims 33–35.

250.—The method of claim 249, wherein the cancer is a solid tumor or a hematopoietic cancer.

251.—The method of claim 250, wherein the cancer is multiple myeloma, myelodysplastic syndrome (MDS), acute myelogenous leukemia (AML), acute lymphoblastic leukemia (ALL), acute lymphocytic leukemia, chronic lymphogenous leukemia, chronic lymphocytic leukemia (CLL), small lymphocytic lymphoma (SLL), mantle cell lymphoma, diffuse large B-cell lymphoma, follicular lymphoma, or non-Hodgkin's lymphoma.

252.—The method of claim 250, wherein the cancer is non-small cell lung cancer (NSCLC), colorectal carcinoma (CRC), ovarian cancer, melanoma, breast carcinoma, neuroendocrine carcinoma, prostate adenocarcinoma, cholangiocarcinoma, uterine carcinoma, or pancreatic

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cancer.

~~253.—The method of any one of claims 249–252, wherein reversal of the EMT is concomitant with treatment with one or more additional therapeutic agents.~~

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~~254.—The method of claim 253, wherein the one or more additional therapeutic agents are independently selected from an immune checkpoint inhibitor, an EGFR inhibitor, a PARP inhibitor, or a combination of a BRAF inhibitor and an MEK inhibitor.~~

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