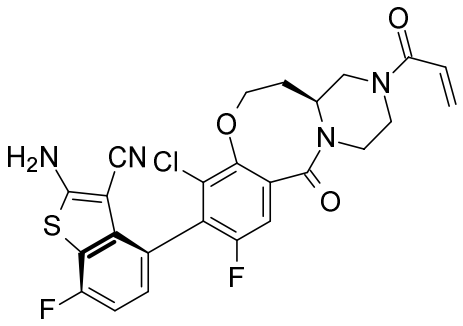
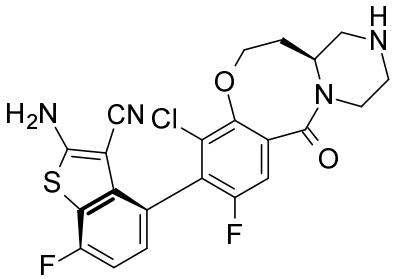
In an example, disclosed herein is a compound of the formula,



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or a pharmaceutically acceptable salt thereof,

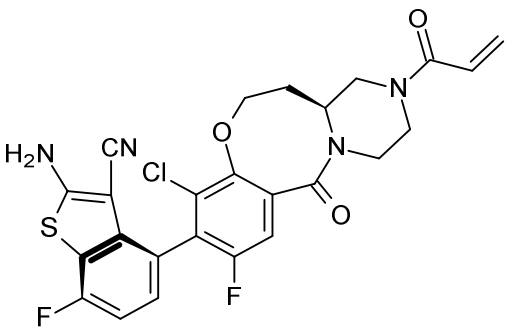
obtainable by combining citrate buffer, an acryloyl group, and 4-[(13aS)-10-chloro-8-fluoro-6-oxo-2,3,4,12,13,13a-hexahydro-1H-pyrazino[2,1-d][1,5]benzoxazocin-9-yl]-2-amino-7-fluoro-benzothiophene-3-carbonitrile, M atropisomer,



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wherein the Michael adduct impurity is present in an amount of less than 0.3% as measured by HPLC Analysis.

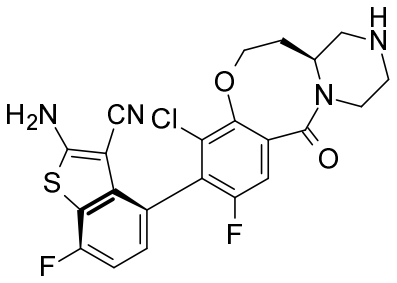
In an aspect, disclosed herein is a compound of the formula,



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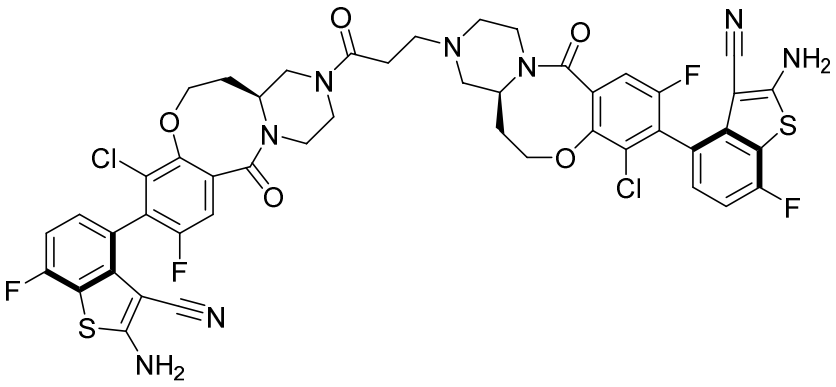
or a pharmaceutically acceptable salt thereof,

obtainable by combining citrate buffer, an acryloyl group, and 4-[(13aS)-10-chloro-8-fluoro-6-oxo-2,3,4,12,13,13a-hexahydro-1H-pyrazino[2,1-d][1,5]benzoxazocin-9-yl]-2-amino-7-fluoro-benzothiophene-3-carbonitrile, M atropisomer,



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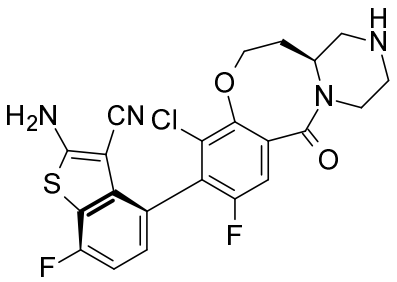
wherein Michael adduct impurity, 4-[(13aS)-2-[3-[(13aS)-9-(2-amino-3-cyano-7-fluoro-benzothiophen-4-yl)-10-chloro-8-fluoro-6-oxo-1,3,4,12,13,13a-hexahydropyrazino[2,1-d][1,5]benzoxazocin-2-yl]-3-oxo-propyl]-10-chloro-8-fluoro-6-oxo-1,3,4,12,13,13a-hexahydropyrazino[2,1-d][1,5]benzoxazocin-9-yl]-2-amino-7-fluoro-benzothiophene-3-carbonitrile, M,M atropisomer,



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is present in an amount of less than 0.3% as measured by HPLC Analysis.

The present disclosure also provides a pharmaceutical composition comprising a compound of Formula I, or a pharmaceutically acceptable salt thereof, obtainable by combining citrate buffer, an acryloyl group, and 4-[(13aS)-10-chloro-8-fluoro-6-oxo-2,3,4,12,13,13a-hexahydro-1H-pyrazino[2,1-d][1,5]benzoxazocin-9-yl]-2-amino-7-fluoro-benzothiophene-3-carbonitrile, M atropisomer,



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wherein the Michael adduct impurity is present in an amount of less than 0.3% as measured by HPLC Analysis, and a pharmaceutically acceptable carrier, diluent, or excipient.

A surprising result is that the use of a citrate buffer in a base catalyzed reaction lowers the Michael adduct impurity amount.

The present disclosure also provides a method of treating cancer wherein one or more cells express Kras G12C mutant protein, comprising administering to a patient in need thereof, a pharmaceutical composition comprising a compound of Formula I, or a pharmaceutically acceptable salt thereof, wherein the Michael adduct impurity is present in an amount of less than 0.3% as measured by HPLC Analysis. In various examples, the cancer is lung cancer, such as advanced non-small cell lung cancer, colorectal cancer, pancreatic cancer, bladder cancer, cervical cancer, endometrial cancer, ovarian cancer, cholangiocarcinoma, or esophageal cancer. In preferred examples, the cancer is advanced non-small cell lung cancer, pancreatic cancer, or colorectal cancer. In still more preferred examples, the cancer is non-small cell lung cancer.

In still yet another form, the present disclosure comprises a method of treating cancer, comprising administering to a patient in need thereof, a pharmaceutical composition comprising a compound of Formula I, or a pharmaceutically acceptable salt thereof,

wherein a Michael adduct impurity is present in an amount of less than 0.3% as measured by HPLC Analysis. In another example, the cancer is non-small cell lung carcinoma. In another example, the cancer is colorectal carcinoma. In yet another example, the cancer is mutant pancreatic cancer. In another example, the present disclosure comprising a method of treating Kras G12C mutant bearing cancers of other origins.

The present disclosure also provides a method of treating a patient with a cancer that has a KRAS G12C mutation comprising administering to a patient in need thereof a pharmaceutical composition comprising a compound of Formula I or a pharmaceutically acceptable salt thereof, wherein a Michael adduct impurity is present in an amount of less than 0.3% as measured by HPLC Analysis.

The present disclosure also provides a method of modulating a mutant Kras G12C enzyme in a patient in need thereof, by administering a pharmaceutical composition comprising a compound of Formula I or a pharmaceutically acceptable salt thereof, wherein a Michael adduct impurity is present in an amount of less than 0.3% as measured by HPLC Analysis. Preferably the method comprises inhibiting a human mutant Kras G12C enzyme.

In another aspect, disclosed herein is the compound, or a pharmaceutically acceptable salt thereof, disclosed herein, or a pharmaceutical composition disclosed herein, for use in therapy.

In another aspect, disclosed herein is the compound, or a pharmaceutically acceptable salt thereof, disclosed herein, or a pharmaceutical composition disclosed herein, for use in the treatment of cancer.

In another aspect, disclosed herein is the compound, or a pharmaceutically acceptable salt thereof, disclosed herein, or a pharmaceutical composition disclosed herein, for use in simultaneous, separate or sequential combination with one or more of a PD-1 inhibitor, a PD-L1 inhibitor, a CDK4/CDK6 inhibitor, or a pharmaceutically acceptable salt thereof, an EGFR inhibitor, or a pharmaceutically acceptable salt thereof, an ERK inhibitor, or a pharmaceutically acceptable salt thereof, a platinum agent, pemetrexed, an

Aurora A inhibitor, or a pharmaceutically acceptable salt thereof, or a SHP2 inhibitor, or pharmaceutically acceptable salts thereof, in the treatment of cancer.

In another aspect, disclosed herein is use of a compound disclosed herein, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating a patient for cancer, wherein one or more cells express KRas G12C mutant protein and wherein the cancer is selected from the group consisting of lung cancer, advanced non-small cell lung cancer, pancreatic cancer, cervical cancer, esophageal cancer, endometrial cancer, ovarian cancer, cholangiocarcinoma, and colorectal cancer.

In another aspect, disclosed herein is use of a pharmaceutical composition disclosed herein, in the manufacture of a medicament for treating a patient for cancer, wherein one or more cells express KRas G12C mutant protein and wherein the cancer is selected from the group consisting of lung cancer, advanced non-small cell lung cancer, pancreatic cancer, cervical cancer, esophageal cancer, endometrial cancer, ovarian cancer, cholangiocarcinoma, and colorectal cancer.

In another example, disclosed herein is a use of a pharmaceutical composition comprising a pharmaceutical composition comprising a compound of Formula I or a pharmaceutically acceptable salt thereof, wherein a Michael adduct impurity is present in an amount of less than 0.3% as measured by HPLC Analysis, in the manufacture of a medicament for treating a KRAS G12C mutant cancer, wherein the compound is administered at a dose between about 50 mg and about 200 mg, in simultaneous, separate or sequential combination with a second therapeutic agent, wherein the second therapeutic agent is selected from the group consisting of: one or more of a PD-1 inhibitor, or a pharmaceutically acceptable salt thereof, a PD-L1 inhibitor, or a pharmaceutically acceptable salt thereof, a CDK4/CDK6 inhibitor, or a pharmaceutically acceptable salt thereof, an EGFR inhibitor, or a pharmaceutically acceptable salt thereof, an ERK inhibitor, or a pharmaceutically acceptable salt thereof, a platinum agent, or a pharmaceutically acceptable salt thereof, an antifolate, or a pharmaceutically acceptable salt thereof, an Aurora A inhibitor, or a pharmaceutically acceptable salt thereof, and a SHP2 inhibitor, or pharmaceutically acceptable salts thereof.

In another example, disclosed herein is a use of a pharmaceutical composition comprising a compound of Formula I or a pharmaceutically acceptable salt thereof, wherein a Michael adduct impurity is present in an amount of less than 0.3% as measured by HPLC Analysis, in the manufacture of a medicament, administering to a patient in need thereof, a dose between about 50 mg and about 200 mg of the compound of Formula I, or a pharmaceutically acceptable salt thereof, in simultaneous, separate or sequential combination with a PD-1 or PD-L1 inhibitor, for treatment of a KRAS G12C mutant cancer. In another example, the PD-1 or PD-L1 inhibitor is pembrolizumab, wherein pembrolizumab is dosed (or administered) 200 mg once every three weeks. In another example, the PD-1 or PD-L1 inhibitor is nivolumab. In another example, the PD-1 or PD-L1 inhibitor is cimiplimab. In another example, the PD-1 or PD-L1 inhibitor is sintilimab. In another example, the PD-1 or PD-L1 inhibitor is atezolizumab. In another example, the PD-1 or PD-L1 inhibitor is avelumab. In another example, the PD-1 or PD-L1 inhibitor is durvalumab. In another example, the PD-1 or PD-L1 inhibitor is lodapilimab. In an example, the dose of the compound of Formula I, or a pharmaceutically acceptable salt thereof, is administered once a day. In an example, the dose of the compound of Formula I, or a pharmaceutically acceptable salt thereof, is administered twice a day. In an example, the dose of the compound of Formula I, or a pharmaceutically acceptable salt thereof, is selected from the group consisting of about 50 mg, about 100 mg, about 150 mg, and about 200 mg.

In another example, disclosed herein is a use of a pharmaceutical composition comprising a compound of Formula I or a pharmaceutically acceptable salt thereof, wherein a Michael adduct impurity is present in an amount of less than 0.3% as measured by HPLC Analysis, in the manufacture of a medicament, administering to a patient in need thereof, a dose between about 50 mg and about 200 mg of the compound of Formula I, or a pharmaceutically acceptable salt thereof, in simultaneous, separate or sequential combination with pembrolizumab in the treatment of KRAS G12C-mutant advanced NSCLC, wherein pembrolizumab is dosed intravenously at 200 mg once every three weeks. In an example, the dose of the compound of Formula I, or a pharmaceutically acceptable salt thereof, is administered once a day. In an example, the dose of the compound of Formula I, or a pharmaceutically acceptable salt thereof, is administered

twice a day. In an example, the dose of the compound of Formula I, or a pharmaceutically acceptable salt thereof, is selected from the group consisting of about 50 mg, about 100 mg, about 150 mg, and about 200 mg.

In another example, disclosed herein is a use of a pharmaceutical composition comprising a compound of Formula I or a pharmaceutically acceptable salt thereof, wherein a Michael adduct impurity is present in an amount of less than 0.3% as measured by HPLC Analysis, in the manufacture of a medicament, administering to a patient in need thereof, a dose of about 150 mg of the compound of Formula I, or a pharmaceutically acceptable salt thereof, in simultaneous, separate or sequential combination with pembrolizumab in the treatment of *KRAS* G12C-mutant advanced NSCLC. In an example, pembrolizumab is administered for up to thirty-five cycles. In an example, the patient in need thereof is treatment naïve to KRAS G12Ci, PD-1, or PD-L1 therapy. In an example, the patient in need thereof has received at least one treatment, including prior KRAS G12C inhibitor. In yet another example, the patient in need thereof has a tumor proportion score (TPS) status of 0% to 49%. In yet another example, the *KRAS* G12C-mutant advanced NSCLC has a tumor proportion score (TPS) status of 0% to 49%. In an example, the patient in need thereof has a tumor proportion score (TPS) status of 1% to 49%. In an example, the *KRAS* G12C-mutant advanced NSCLC has a tumor proportion score (TPS) status of 1% to 49%. In an example, the patient in need thereof has a tumor proportion score (TPS) status of greater than or equal to 50%. In an example, the *KRAS* G12C-mutant advanced NSCLC has a tumor proportion score (TPS) status of greater than or equal to 50%.

In another example, disclosed herein is a use of a pharmaceutical composition comprising a compound of Formula I or a pharmaceutically acceptable salt thereof, wherein a Michael adduct impurity is present in an amount of less than 0.3% as measured by HPLC Analysis, in the manufacture of a medicament, administering to a patient in need thereof, a dose of about 100 mg of the compound of Formula I, or a pharmaceutically acceptable salt thereof, in simultaneous, separate or sequential combination with pembrolizumab in the treatment of *KRAS* G12C-mutant advanced NSCLC. In an example, pembrolizumab is administered for up to thirty-five cycles. In an example, the patient in need thereof is treatment naïve to KRAS G12Ci, PD-1, or PD-L1 therapy. In an example, the patient

in need thereof has received at least one treatment, including prior KRAS G12C inhibitor. In yet another example, the patient in need thereof has a tumor proportion score (TPS) status of 0% to 49%. In yet another example, the *KRAS* G12C-mutant advanced NSCLC has a tumor proportion score (TPS) status of 0% to 49%. In an example, the patient in need thereof has a tumor proportion score (TPS) status of 1% to 49%. In an example, the *KRAS* G12C-mutant advanced NSCLC has a tumor proportion score (TPS) status of 1% to 49%. In an example, the patient in need thereof has a tumor proportion score (TPS) status of greater than or equal to 50%. In an example, the *KRAS* G12C-mutant advanced NSCLC has a tumor proportion score (TPS) status of greater than or equal to 50%.

In another example, disclosed herein is a use of a pharmaceutical composition comprising a compound of Formula I or a pharmaceutically acceptable salt thereof, wherein a Michael adduct impurity is present in an amount of less than 0.3% as measured by HPLC Analysis, in the manufacture of a medicament, administering to a patient in need thereof, a dose of about 50 mg of the compound of Formula I, or a pharmaceutically acceptable salt thereof, in simultaneous, separate or sequential combination with pembrolizumab in the treatment of *KRAS* G12C-mutant advanced NSCLC. In an example, pembrolizumab is administered for up to thirty-five cycles. In an example, the patient in need thereof is treatment naïve to KRAS G12Ci, PD-1, or PD-L1 therapy. In an example, the patient in need thereof has received at least one treatment, including prior KRAS G12C inhibitor. In yet another example, the patient in need thereof has a tumor proportion score (TPS) status of 0% to 49%. In yet another example, the *KRAS* G12C-mutant advanced NSCLC has a tumor proportion score (TPS) status of 0% to 49%. In an example, the patient in need thereof has a tumor proportion score (TPS) status of 1% to 49%. In an example, the *KRAS* G12C-mutant advanced NSCLC has a tumor proportion score (TPS) status of 1% to 49%. In an example, the patient in need thereof has a tumor proportion score (TPS) status of greater than or equal to 50%. In an example, the *KRAS* G12C-mutant advanced NSCLC has a tumor proportion score (TPS) status of greater than or equal to 50%.

In another example, disclosed herein is a use of a pharmaceutical composition comprising a compound of Formula I or a pharmaceutically acceptable salt thereof, wherein

a Michael adduct impurity is present in an amount of less than 0.3% as measured by HPLC Analysis, in the manufacture of a medicament, administering to a patient in need thereof, a dose of about 150 mg of the compound of Formula I, or a pharmaceutically acceptable salt thereof, in simultaneous, separate or sequential combination with pembrolizumab, pemetrexed, and cisplatin in the treatment of *KRAS* G12C-mutant advanced NSCLC. In an example, pembrolizumab is dosed (or administered) 200 mg once every three weeks. In an example, pemetrexed is dosed (or administered) 500 mg/m2 once every three weeks. In an example, cisplatin is dosed (or administered) 75 mg/m2 once every three weeks. In an example, pemetrexed and cisplatin are administered on the same day. In an example, pembrolizumab is administered for up to thirty-five cycles. In an example, cisplatin is administered for up to four cycles. In an example, the patient in need thereof is treatment naïve to KRAS G12Ci, PD-1, or PD-L1 therapy.

In another example, disclosed herein is a use of a pharmaceutical composition comprising a compound of Formula I or a pharmaceutically acceptable salt thereof, wherein a Michael adduct impurity is present in an amount of less than 0.3% as measured by HPLC Analysis, in the manufacture of a medicament, administering to a patient in need thereof, a dose of about 100 mg of the compound of Formula I, or a pharmaceutically acceptable salt thereof, in simultaneous, separate or sequential combination with pembrolizumab, pemetrexed, and cisplatin in the treatment of *KRAS* G12C-mutant advanced NSCLC. In an example, pembrolizumab is dosed (or administered) 200 mg once every three weeks. In an example, pemetrexed is dosed (or administered) 500 mg/m2 once every three weeks. In an example, cisplatin is dosed (or administered) 75 mg/m2 once every three weeks. In an example, pemetrexed and cisplatin are administered on the same day. In an example, pembrolizumab is administered for up to thirty-five cycles. In an example, cisplatin is administered for up to four cycles. In an example, the patient in need thereof is treatment naïve to KRAS G12Ci, PD-1, or PD-L1 therapy.

In another example, disclosed herein is a use of a pharmaceutical composition comprising a compound of Formula I or a pharmaceutically acceptable salt thereof, wherein a Michael adduct impurity is present in an amount of less than 0.3% as measured by HPLC Analysis, in the manufacture of a medicament, administering to a patient in need thereof, a dose of about 50 mg of the compound of Formula I, or a pharmaceutically acceptable salt

thereof, in simultaneous, separate or sequential combination with pembrolizumab, pemetrexed, and cisplatin in the treatment of *KRAS* G12C-mutant advanced NSCLC. In an example, pembrolizumab is dosed (or administered) 200 mg once every three weeks. In an example, pemetrexed is dosed (or administered) 500 mg/m2 once every three weeks. In an example, cisplatin is dosed (or administered) 75 mg/m2 once every three weeks. In an example, pemetrexed and cisplatin are administered on the same day. In an example, pembrolizumab is administered for up to thirty-five cycles. In an example, cisplatin is administered for up to four cycles. In an example, the patient in need thereof is treatment naïve to KRAS G12Ci, PD-1, or PD-L1 therapy.

In another example, disclosed herein is a use of a pharmaceutical composition comprising a compound of Formula I or a pharmaceutically acceptable salt thereof, wherein a Michael adduct impurity is present in an amount of less than 0.3% as measured by HPLC Analysis, in the manufacture of a medicament, administering to a patient in need thereof, a dose of about 150 mg of the compound of Formula I, or a pharmaceutically acceptable salt thereof, in simultaneous, separate or sequential combination with pembrolizumab, pemetrexed, and carboplatin in the treatment of *KRAS* G12C-mutant advanced NSCLC. In an example, pembrolizumab is dosed (or administered) 200 mg once every three weeks. In an example, pemetrexed is dosed (or administered) 500 mg/m2 once every three weeks. In an example, carboplatin is dosed (or administered) area under the curve (AUC) 5 mg/ml/minute once every three weeks for a maximum dose of 750 mg. In an example, pemetrexed and carboplatin are administered on the same day. In an example, pembrolizumab is administered for up to thirty-five cycles. In an example, carboplatin is administered for up to four cycles. In an example, the patient in need thereof is treatment naïve to KRAS G12Ci, PD-1, or PD-L1 therapy.

In another example, disclosed herein is a use of a pharmaceutical composition comprising a compound of Formula I or a pharmaceutically acceptable salt thereof, wherein a Michael adduct impurity is present in an amount of less than 0.3% as measured by HPLC Analysis, in the manufacture of a medicament, administering to a patient in need thereof, a dose of about 100 mg of the compound of Formula I, or a pharmaceutically acceptable salt thereof, in simultaneous, separate or sequential combination with pembrolizumab, pemetrexed, and carboplatin in the treatment of *KRAS* G12C-mutant advanced NSCLC. In

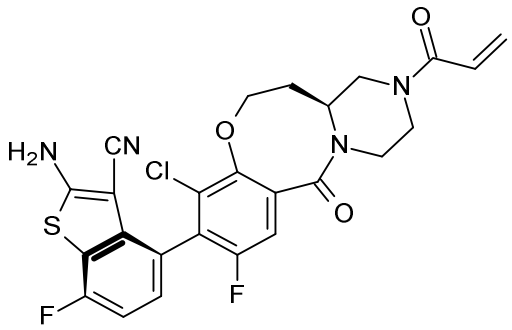
an example, pembrolizumab is dosed (or administered) 200 mg once every three weeks. In an example, pemetrexed is dosed (or administered) 500 mg/m2 once every three weeks. In an example, carboplatin is dosed (or administered) area under the curve (AUC) 5 mg/ml/minute once every three weeks for a maximum dose of 750 mg. In an example, pemetrexed and carboplatin are administered on the same day. In an example, pembrolizumab is administered for up to thirty-five cycles. In an example, carboplatin is administered for up to four cycles. In an example, the patient in need thereof is treatment naïve to KRAS G12Ci, PD-1, or PD-L1 therapy.

In another example, disclosed herein is a use of a pharmaceutical composition comprising a compound of Formula I or a pharmaceutically acceptable salt thereof, wherein a Michael adduct impurity is present in an amount of less than 0.3% as measured by HPLC Analysis, in the manufacture of a medicament, administering to a patient in need thereof, a dose of about 50 mg of the compound of Formula I, or a pharmaceutically acceptable salt thereof, in simultaneous, separate or sequential combination with pembrolizumab, pemetrexed, and carboplatin in the treatment of *KRAS* G12C-mutant advanced NSCLC. In an example, pembrolizumab is dosed (or administered) 200 mg once every three weeks. In an example, pemetrexed is dosed (or administered) 500 mg/m2 once every three weeks. In an example, carboplatin is dosed (or administered) area under the curve (AUC) 5 mg/ml/minute once every three weeks for a maximum dose of 750 mg. In an example, pemetrexed and carboplatin are administered on the same day. In an example, pembrolizumab is administered for up to thirty-five cycles. In an example, carboplatin is administered for up to four cycles. In an example, the patient in need thereof is treatment naïve to KRAS G12Ci, PD-1, or PD-L1 therapy.

The starting materials and intermediates leading to the compounds of the present disclosure, or salts thereof, may be prepared by a variety of procedures, some of which are illustrated in the following Preparations and Examples and by Preparations and Examples in the ‘877 reference. The starting materials and intermediates leading to the compounds of the present disclosure may be prepared by methods well known and appreciated in the art according to the following Preparations and Examples and by Preparations and Examples of the ‘877 reference. Suitable reaction conditions for the steps of these Preparations and Example are well known in the art and appropriate substitutions of

What is Claimed is:

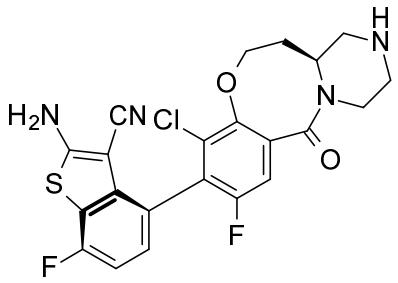
1. A method of preparing a compound of the formula,



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or a pharmaceutically acceptable salt thereof, the method comprising:

combining citrate buffer, an acryloyl group, and 4-[(13aS)-10-chloro-8-fluoro-6-oxo-2,3,4,12,13,13a-hexahydro-1H-pyrazino[2,1-d][1,5]benzoxazocin-9-yl]-2-amino-7-fluoro-benzothiophene-3-carbonitrile, M atropisomer,



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2. The method of claim 1, wherein the step of preparing is in a continuous stirred-tank reactor.

3. The method of claim 1 or 2, wherein the acryloyl group is acryloyl chloride, acryloyl bromide, or acryloyl anhydride.

4. The method of any one of claims 1 to 3, wherein the acryloyl group is within the range of approximately 1.05 eq to approximately 1.35 eq relative to the 4-[(13aS)-10-chloro-8-fluoro-6-oxo-2,3,4,12,13,13a-hexahydro-1H-pyrazino[2,1-d][1,5]benzoxazocin-9-yl]-2-amino-7-fluoro-benzothiophene-3-carbonitrile, M atropisomer.

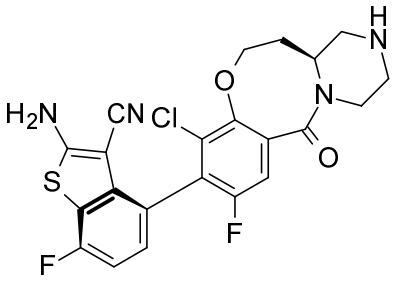
5. The method of any one of claims 1 to 4, wherein the acryloyl group is approximately 1.25 eq relative to the 4-[(13aS)-10-chloro-8-fluoro-6-oxo-2,3,4,12,13,13a-hexahydro-1H-pyrazino[2,1-d][1,5]benzoxazocin-9-yl]-2-amino-7-fluoro-benzothiophene-3-carbonitrile, M atropisomer.

6. The method of any one of claims 1 to 5, wherein the citrate buffer is within the range of approximately 2.0 pH to approximately 4.0 pH.

7. The method of any one of claims 2 to 6, wherein the continuous stirred-tank reactor is operated within the range of approximately 300 rpm to approximately 600 rpm.

8. The method of any one of claims 2 to 7, wherein the citrate buffer is added into the continuous stirred-tank reactor at a flow rate of approximately 3.6 mL/min or at a flow rate of approximately 0.8 mL/min.

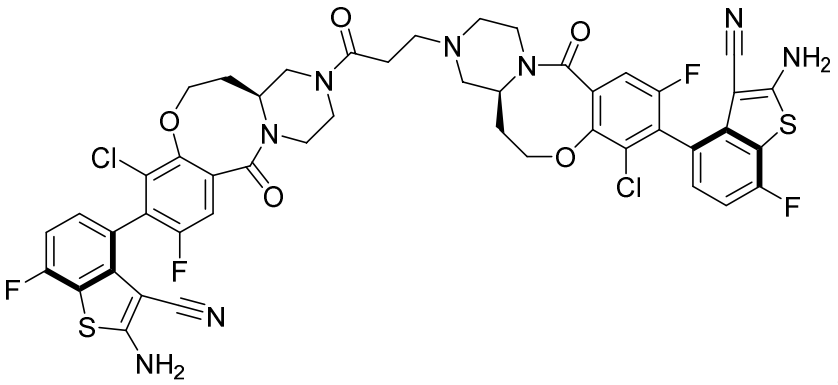
9. The method of any one of claims 2 to 8, wherein the 4-[(13aS)-10-chloro-8-fluoro-6-oxo-2,3,4,12,13,13a-hexahydro-1H-pyrazino[2,1-d][1,5]benzoxazocin-9-yl]-2-amino-7-fluoro-benzothiophene-3-carbonitrile, M atropisomer,



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is added into the continuous stirred-tank reactor at a flow rate of approximately 6.6 mL/min.

10. The method of any one of claims 1 to 9, wherein a Michael adduct impurity, 4-[(13aS)-2-[3-[(13aS)-9-(2-amino-3-cyano-7-fluoro-benzothiophen-4-yl)-10-chloro-8-fluoro-6-oxo-1,3,4,12,13,13a-hexahydropyrazino[2,1-d][1,5]benzoxazocin-2-yl]-3-oxo-propyl]-10-chloro-8-fluoro-6-oxo-1,3,4,12,13,13a-hexahydropyrazino[2,1-d][1,5]benzoxazocin-9-yl]-2-amino-7-fluoro-benzothiophene-3-carbonitrile, M,M atropisomer,

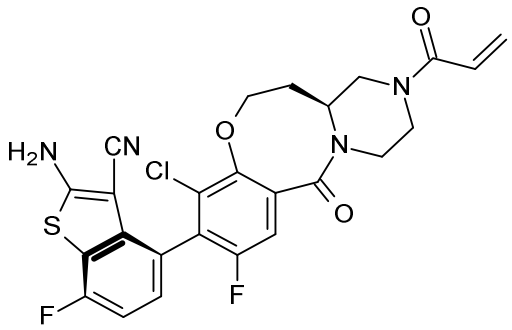


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is present in an amount of less than 0.3% as measured by HPLC Analysis.

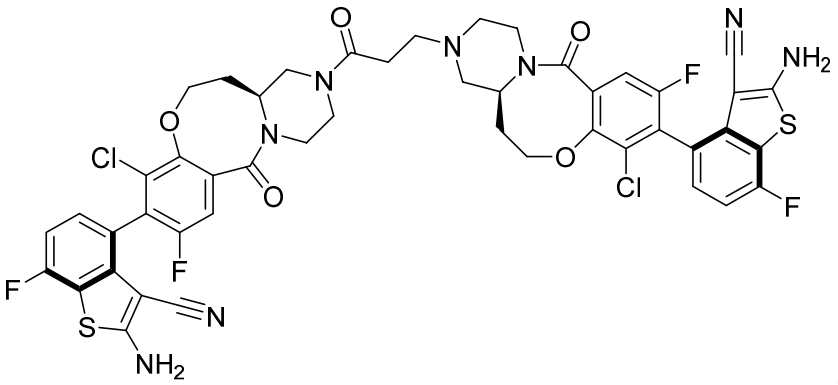
11. The method of claim 10, wherein the Michael adduct impurity is less than 0.15% as measured by HPLC Analysis.

12. A pharmaceutical composition comprising a compound of the formula,



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or a pharmaceutically acceptable salt thereof, wherein a Michael adduct impurity, 4-[(13aS)-2-[3-[(13aS)-9-(2-amino-3-cyano-7-fluoro-benzothiophen-4-yl)-10-chloro-8-fluoro-6-oxo-1,3,4,12,13,13a-hexahydropyrazino[2,1-d][1,5]benzoxazocin-2-yl]-3-oxo-propyl]-10-chloro-8-fluoro-6-oxo-1,3,4,12,13,13a-hexahydropyrazino[2,1-d][1,5]benzoxazocin-9-yl]-2-amino-7-fluoro-benzothiophene-3-carbonitrile, M,M atropisomer,



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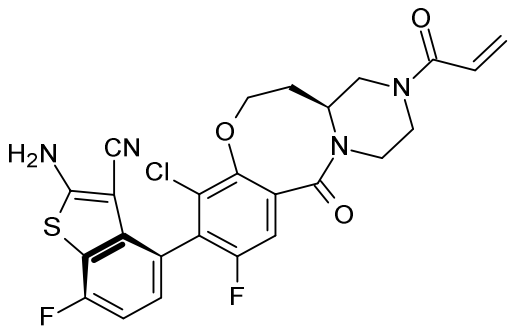
is present in an amount of less than 0.3% as measured by HPLC Analysis,

and a pharmaceutically acceptable carrier, diluent or excipient.

13. The pharmaceutical composition of claim 12, wherein the Michael adduct impurity is present in an amount of less than 0.15% as measured by HPLC Analysis.

14. Use of a pharmaceutical composition according to claim 12 or 13, in the manufacture of a medicament for treating a patient for cancer, wherein one or more cells express KRas G12C mutant protein and wherein the cancer is selected from the group consisting of lung cancer, advanced non-small cell lung cancer, pancreatic cancer, cervical cancer, esophageal cancer, endometrial cancer, ovarian cancer, cholangiocarcinoma, and colorectal cancer.

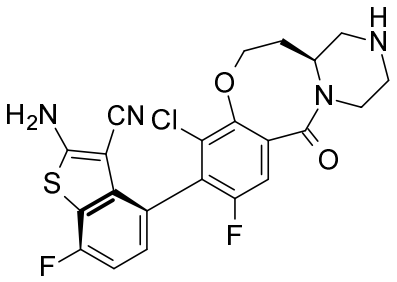
15. A compound of the formula,



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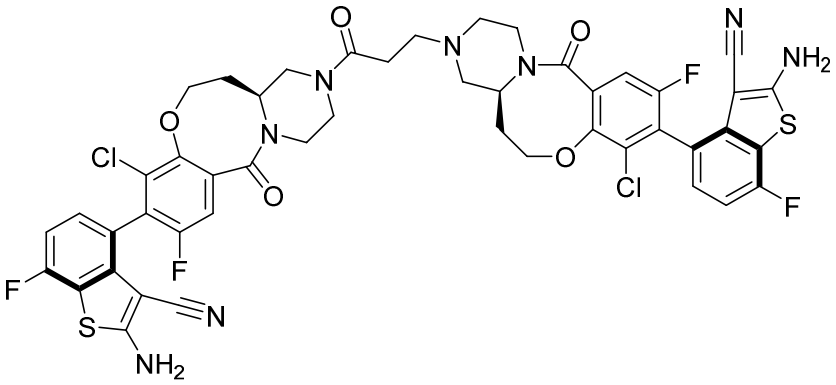
or a pharmaceutically acceptable salt thereof,

obtainable by combining citrate buffer, an acryloyl group, and 4-[(13aS)-10-chloro-8-fluoro-6-oxo-2,3,4,12,13,13a-hexahydro-1H-pyrazino[2,1-d][1,5]benzoxazocin-9-yl]-2-amino-7-fluoro-benzothiophene-3-carbonitrile, M atropisomer,



,

wherein Michael adduct impurity, 4-[(13aS)-2-[3-[(13aS)-9-(2-amino-3-cyano-7-fluoro-benzothiophen-4-yl)-10-chloro-8-fluoro-6-oxo-1,3,4,12,13,13a-hexahydropyrazino[2,1-d][1,5]benzoxazocin-2-yl]-3-oxo-propyl]-10-chloro-8-fluoro-6-oxo-1,3,4,12,13,13a-hexahydropyrazino[2,1-d][1,5]benzoxazocin-9-yl]-2-amino-7-fluoro-benzothiophene-3-carbonitrile, M,M atropisomer,



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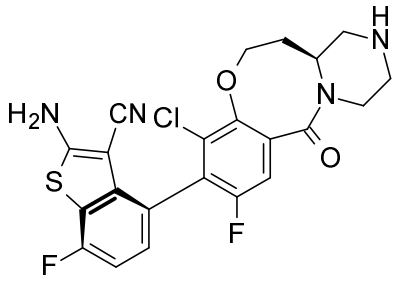
is present in an amount of less than 0.3% as measured by HPLC Analysis.

16. The compound of claim 15, wherein the step of combining is in a continuous stirred-tank reactor.

17. The compound of claim 15 or 16, wherein the citrate buffer is within the range of approximately 2.0 pH to approximately 4.0 pH.

18. The compound of claim 16 or 17, wherein the continuous stirred-tank reactor is operated within the range of approximately 300 rpm to approximately 600 rpm.

19. The compound of any one of claims 15 to 18, wherein the 4-[(13aS)-10-chloro-8-fluoro-6-oxo-2,3,4,12,13,13a-hexahydro-1H-pyrazino[2,1-d][1,5]benzoxazocin-9-yl]-2-amino-7-fluoro-benzothiophene-3-carbonitrile, M atropisomer,



,

is added into the continuous stirred-tank reactor at a flow rate of approximately 6.6 mL/min.

20. Use of a compound according to any one of claims 15 to 19, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating a patient for cancer, wherein one or more cells express KRas G12C mutant protein and wherein the cancer is selected from the group consisting of lung cancer, advanced non-small cell lung cancer, pancreatic cancer, cervical cancer, esophageal cancer, endometrial cancer, ovarian cancer, cholangiocarcinoma, and colorectal cancer.

21. The use according to claim 20, wherein the compound or a pharmaceutically acceptable salt thereof, is to be administered in simultaneous, separate or sequential combination with one or more of a PD-1 inhibitor, a PD-L1 inhibitor, a CDK4/CDK6 inhibitor, or a pharmaceutically acceptable salt thereof, an EGFR inhibitor, or a pharmaceutically acceptable salt thereof, an ERK inhibitor, or a pharmaceutically acceptable salt thereof, a platinum agent, pemetrexed, an Aurora A inhibitor, or a pharmaceutically acceptable salt thereof, a SHP2 inhibitor, or pharmaceutically acceptable salts thereof, or a pharmaceutically acceptable salt thereof.

22. The compound, or a pharmaceutically acceptable salt thereof, according to any one of claims 15 to 19, or a pharmaceutical composition according to claim 12 or 13, for use in therapy.

23. The compound, or a pharmaceutically acceptable salt thereof, according to any one of claims 15 to 19, or a pharmaceutical composition according to claim 12 or 13, for use in the treatment of cancer.

24. The compound, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition for use according to claim 23, wherein the cancer is selected from the group consisting of lung cancer, advanced non-small cell lung cancer, pancreatic cancer, cervical cancer, esophageal cancer, endometrial cancer, ovarian cancer, cholangiocarcinoma, and colorectal cancer.

25. The compound, or a pharmaceutically acceptable salt thereof, according to any one of claims 15 to 19, or a pharmaceutical composition according to claim 12 or 13, for use in simultaneous, separate or sequential combination with one or more of a PD-1 inhibitor, a PD-L1 inhibitor, a CDK4/CDK6 inhibitor, or a pharmaceutically acceptable salt thereof, an EGFR inhibitor, or a pharmaceutically acceptable salt thereof, an ERK inhibitor, or a pharmaceutically acceptable salt thereof, a platinum agent, pemetrexed, an Aurora A inhibitor, or a pharmaceutically acceptable salt thereof, or a SHP2 inhibitor, or pharmaceutically acceptable salts thereof, in the treatment of cancer.