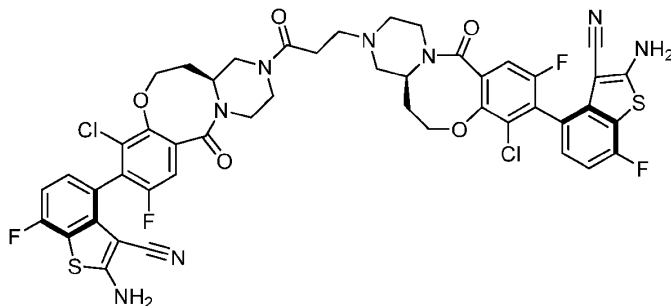


-1-

PROCESS FOR MAKING A KRAS G12C INHIBITOR

The present disclosure relates to processes that can be used to prepare the compound of Formula I, and pharmaceutically acceptable salts thereof, and pharmaceutical compositions comprising the compound of Formula I, wherein a Michael adduct impurity is present in an amount of less than 0.3% as measured by HPLC Analysis. The compound of Formula I and pharmaceutical compositions can be used to treat cancer.

WO 2021/118877 (hereinafter “the ‘877 reference”) discloses certain KRas G12C inhibitors, or salts thereof, that can be used to treat cancer. Methods of preparing these compounds are also disclosed. The methods disclosed in the ‘877 reference use a phosphate buffer. These methods result in greater quantities of impurities than desired. These impurities include, in greater quantities than desired, 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,



which can be difficult to remove.

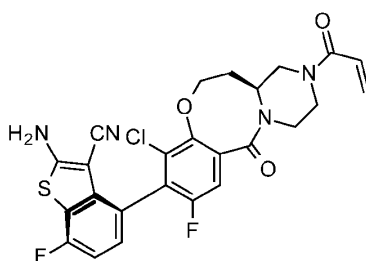
Accordingly, there is a need for an alternative process for the preparation of the compound of Formula I. It would be useful to develop new processes that can be used to prepare the compound of Formula I that contain less impurities, especially the Michael adduct impurity.

-2-

SUMMARY

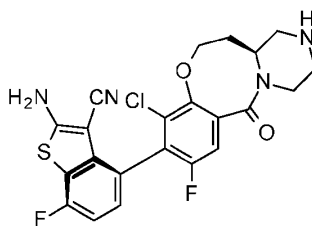
Disclosed herein are methods of making the compound of Formula I, or pharmaceutically acceptable salts thereof. Also disclosed herein are the compound of Formula I, or pharmaceutically acceptable salts thereof, obtainable by using newly developed processes.

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



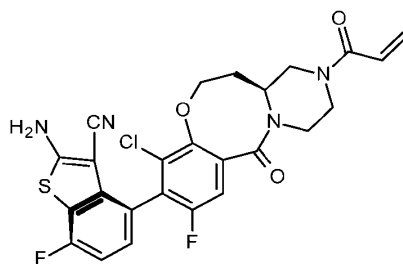
or a pharmaceutically acceptable salt thereof, the method comprising:

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



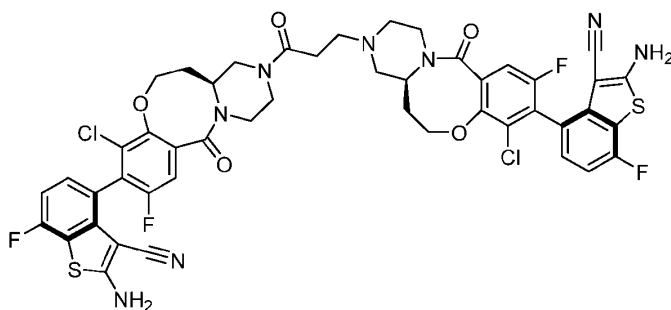
-3-

In another aspect, disclosed herein is a pharmaceutical composition comprising a compound of the formula,



or a pharmaceutically acceptable salt thereof, wherein a Michael adduct impurity,

5 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,



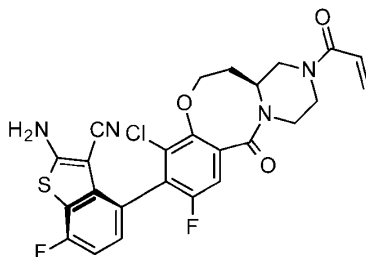
10

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

and a pharmaceutically acceptable carrier, diluent or excipient.

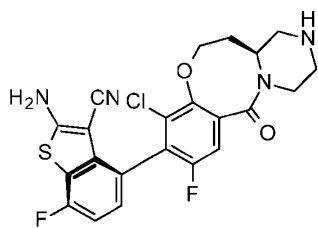
-4-

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



or a pharmaceutically acceptable salt thereof,

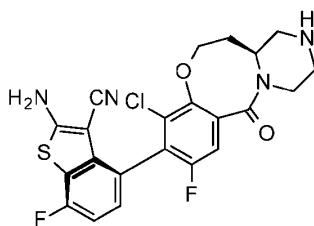
obtainable by combining citrate buffer, an acryloyl group, and 4-[(13aS)-10-chloro-
5 8-fluoro-6-oxo-2,3,4,12,13,13a-hexahydro-1H-pyrazino[2,1-d][1,5]benzoxazin-9-yl]-2-
amino-7-fluoro-benzothiophene-3-carbonitrile, M atropisomer,



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

-5-

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,



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.

10 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 embodiments, 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 embodiments, the cancer is advanced non-small cell lung cancer, pancreatic cancer, or colorectal cancer. In still more preferred embodiments, 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 embodiment, the cancer is non-small cell lung carcinoma. In another embodiment, the cancer is colorectal carcinoma. In yet another embodiment, the cancer is mutant pancreatic cancer. In another embodiment, 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 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 aspect, 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
5 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 embodiment, the PD-1 or PD-L1 inhibitor is pembrolizumab, wherein pembrolizumab is dosed (or administered) 200 mg once every three weeks. In another
10 embodiment, the PD-1 or PD-L1 inhibitor is nivolumab. In another embodiment, the PD-1 or PD-L1 inhibitor is cimiplimab. In another embodiment, the PD-1 or PD-L1 inhibitor is sintilimab. In another embodiment, the PD-1 or PD-L1 inhibitor is atezolizumab. In another embodiment, the PD-1 or PD-L1 inhibitor is avelumab. In another embodiment, the PD-1 or PD-L1 inhibitor is durvalumab. In another embodiment, the PD-1 or PD-L1
15 inhibitor is lodapilimab. In an embodiment, the dose of the compound of Formula I, or a pharmaceutically acceptable salt thereof, is administered once a day. In an embodiment, the dose of the compound of Formula I, or a pharmaceutically acceptable salt thereof, is administered twice a day. In an embodiment, the dose of the compound of Formula I, or a pharmaceutically acceptable salt thereof, is selected from the group consisting of about 50
20 mg, about 100 mg, about 150 mg, and about 200 mg.

In another aspect, 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
25 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 embodiment, the dose of the compound of Formula I, or a pharmaceutically
30 acceptable salt thereof, is administered once a day. In an embodiment, the dose of the compound of Formula I, or a pharmaceutically acceptable salt thereof, is administered

twice a day. In an embodiment, 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 aspect, 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 embodiment, pembrolizumab is administered for up to thirty-five cycles. In an embodiment, the patient in need thereof is treatment naïve to *KRAS* G12Ci, PD-1, or PD-L1 therapy. In an embodiment, the patient in need thereof has received at least one treatment, including prior *KRAS* G12C inhibitor. In yet another embodiment, the patient in need thereof has a tumor proportion score (TPS) status of 0% to 49%. In yet another embodiment, the *KRAS* G12C-mutant advanced NSCLC has a tumor proportion score (TPS) status of 0% to 49%. In an embodiment, the patient in need thereof has a tumor proportion score (TPS) status of 1% to 49%. In an embodiment, the *KRAS* G12C-mutant advanced NSCLC has a tumor proportion score (TPS) status of 1% to 49%. In an embodiment, the patient in need thereof has a tumor proportion score (TPS) status of greater than or equal to 50%. In an embodiment, the *KRAS* G12C-mutant advanced NSCLC has a tumor proportion score (TPS) status of greater than or equal to 50%.

In another aspect, 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 embodiment, pembrolizumab is administered for up to thirty-five cycles. In an embodiment, the patient in need thereof is treatment naïve to *KRAS* G12Ci, PD-1, or PD-L1 therapy. In an embodiment, the patient

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

In another aspect, 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 embodiment, pembrolizumab is administered for up to thirty-five cycles. In an embodiment, the patient in need thereof is treatment naïve to *KRAS* G12Ci, PD-1, or PD-L1 therapy. In an embodiment, the patient in need thereof has received at least one treatment, including prior *KRAS* G12C inhibitor. In yet another embodiment, the patient in need thereof has a tumor proportion score (TPS) status of 0% to 49%. In yet another embodiment, the *KRAS* G12C-mutant advanced NSCLC has a tumor proportion score (TPS) status of 0% to 49%. In an embodiment, the patient in need thereof has a tumor proportion score (TPS) status of 1% to 49%. In an embodiment, the *KRAS* G12C-mutant advanced NSCLC has a tumor proportion score (TPS) status of 1% to 49%. In an embodiment, the patient in need thereof has a tumor proportion score (TPS) status of greater than or equal to 50%. In an embodiment, the *KRAS* G12C-mutant advanced NSCLC has a tumor proportion score (TPS) status of greater than or equal to 50%.

In another aspect, 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, 5
pemetrexed, and cisplatin in the treatment of *KRAS* G12C-mutant advanced NSCLC. In an embodiment, pembrolizumab is dosed (or administered) 200 mg once every three weeks. In an embodiment, pemetrexed is dosed (or administered) 500 mg/m² once every three weeks. In an embodiment, cisplatin is dosed (or administered) 75 mg/m² once every three weeks. In an embodiment, pemetrexed and cisplatin are administered on the same day. In 10
an embodiment, pembrolizumab is administered for up to thirty-five cycles. In an embodiment, cisplatin is administered for up to four cycles. In an embodiment, the patient in need thereof is treatment naïve to *KRAS* G12C_i, PD-1, or PD-L1 therapy.

In another aspect, disclosed herein is a use of a pharmaceutical composition comprising a compound of Formula I or a pharmaceutically acceptable salt thereof, wherein 15
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 20
embodiment, pembrolizumab is dosed (or administered) 200 mg once every three weeks. In an embodiment, pemetrexed is dosed (or administered) 500 mg/m² once every three weeks. In an embodiment, cisplatin is dosed (or administered) 75 mg/m² once every three weeks. In an embodiment, pemetrexed and cisplatin are administered on the same day. In an embodiment, pembrolizumab is administered for up to thirty-five cycles. In an 25
embodiment, cisplatin is administered for up to four cycles. In an embodiment, the patient in need thereof is treatment naïve to *KRAS* G12C_i, PD-1, or PD-L1 therapy.

In another aspect, disclosed herein is a use of a pharmaceutical composition comprising a compound of Formula I or a pharmaceutically acceptable salt thereof, wherein 30
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 embodiment, pembrolizumab is dosed (or administered) 200 mg once every three weeks. In an embodiment, pemetrexed is dosed (or administered) 500 mg/m² once every three weeks. In an embodiment, cisplatin is dosed (or administered) 75 mg/m² once every three weeks. In an embodiment, pemetrexed and cisplatin are administered on the same day. In an embodiment, pembrolizumab is administered for up to thirty-five cycles. In an embodiment, cisplatin is administered for up to four cycles. In an embodiment, the patient in need thereof is treatment naïve to *KRAS* G12C_i, PD-1, or PD-L1 therapy.

10 In another aspect, 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 embodiment, pembrolizumab is dosed (or administered) 200 mg once every three weeks. In an embodiment, pemetrexed is dosed (or administered) 500 mg/m² once every three weeks. In an embodiment, 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 embodiment, pemetrexed and carboplatin are administered on the same day. In an embodiment, pembrolizumab is administered for up to thirty-five cycles. In an embodiment, carboplatin is administered for up to four cycles. In an embodiment, the patient in need thereof is treatment naïve to *KRAS* G12C_i, PD-1, or PD-L1 therapy.

25 In another aspect, 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

30

an embodiment, pembrolizumab is dosed (or administered) 200 mg once every three weeks. In an embodiment, pemetrexed is dosed (or administered) 500 mg/m² once every three weeks. In an embodiment, 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
5 embodiment, pemetrexed and carboplatin are administered on the same day. In an embodiment, pembrolizumab is administered for up to thirty-five cycles. In an embodiment, carboplatin is administered for up to four cycles. In an embodiment, the patient in need thereof is treatment naïve to KRAS G12C_i, PD-L1, or PD-L1 therapy.

In another aspect, disclosed herein is a use of a pharmaceutical composition
10 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,
15 pemetrexed, and carboplatin in the treatment of *KRAS* G12C-mutant advanced NSCLC. In an embodiment, pembrolizumab is dosed (or administered) 200 mg once every three weeks. In an embodiment, pemetrexed is dosed (or administered) 500 mg/m² once every three weeks. In an embodiment, 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
20 embodiment, pemetrexed and carboplatin are administered on the same day. In an embodiment, pembrolizumab is administered for up to thirty-five cycles. In an embodiment, carboplatin is administered for up to four cycles. In an embodiment, the patient in need thereof is treatment naïve to KRAS G12C_i, PD-L1, or PD-L1 therapy.

The starting materials and intermediates leading to the compounds of the present
25 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
30 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

solvents and co-reagents are within the skill of the art. Likewise, it will be appreciated by those skilled in the art that synthetic intermediates may be isolated and/or purified by various well-known techniques as needed or desired, and that frequently, it will be possible to use various intermediates directly in subsequent synthetic steps with little or no purification. As an illustration, the starting materials and intermediates leading to compounds of the preparations and examples can be isolated, for example, by silica gel purification, isolated directly by filtration, or crystallization. Furthermore, the skilled artisan will appreciate that in some circumstances, the order in which moieties are introduced is not critical. The particular order of steps required to produce the compounds of the present disclosure is dependent upon the particular compound being synthesized, the starting materials, and the relative liability of the substituted moieties, as is well appreciated by the skilled chemist. All substituents, unless otherwise indicated, are as previously defined, and all reagents are well known and appreciated in the art.

The specific synthetic steps for each of the routes described may be combined in different ways, or in conjunction with steps from different routes, to prepare compounds or salts of the present disclosure. The products of each step in the Preparations below can be recovered by conventional methods, including extraction, evaporation, precipitation, chromatography, filtration, trituration, and crystallization.

The compounds of the present disclosure can be prepared in a number of ways well known to those skilled in the art of organic synthesis. By way of example, compounds of the present disclosure can be synthesized using the methods described below, together with synthetic methods known in the art of synthetic organic chemistry, or variations thereon as appreciated by those skilled in the art. Preferred methods include but are not limited to those methods described below.

Definitions

Certain abbreviations are defined as follows: "ACN" refers to acetonitrile; "APCI-MS" refers to atmospheric pressure chemical ionization mass spectrometry; "Boc" refers to *tert*-butoxycarbonyl; "CDI" refers to 1,1'-carbonyldiimidazole; "CDMT" refers to 2-chloro-4,6-dimethoxy-1,3,5-triazine; "DCC" refers to 1,3-dicyclohexylcarbodiimide;

“DCM” refers to dichloromethane; “DIC” refers to 1,3-diisopropylcarbodiimide; “DIPEA” or “DIEA” refers to N,N-diisopropylethylamine; “DMAC” or “DMA” refer to dimethylacetamide; “DMAP” refers to 4-dimethylaminopyridine; “DMF” refers to N,N-dimethylformamide; “DMSO” refers to dimethylsulfoxide; “DMSO-d6” refers to deuterated dimethylsulfoxide; “EDCI” refers to 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride; “EtOAc” refers to ethyl acetate; “EtOH” refers to ethanol or ethyl alcohol; “H₃PO₄” refers to phosphoric acid; “HATU” refers to O-(7-Azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate; “HOAt” refers to 1-hydroxy-7-azobenzotriazole; “HBTU” refers to 3-[bis(dimethylamino)methyl]methyl-3H-benzotriazol-1-oxide hexafluorophosphate; “HOBt” refers to 1-hydroxybenzotriazole hydrate; “HPLC” refers to high-performance liquid chromatography; “MeOH” refers to methanol; “2-MeTHF” refers to 2-methyltetrahydrofuran; “MP (DSC)” refers to melting point by differential scanning calorimetry; “MTBE” refers to methyl *tert*-butyl ether; “NCS” refers to N-chlorosuccinimide; “NMM” refers to N-methylmorpholine; “NMP” refers to N-methyl-2-pyrrolidone; “NMR” refers to nuclear magnetic resonance; “PyBOP” refers to (benzotriazol-1-yl-oxytripyrrolidinophosphonium hexafluorophosphate); “PyBrOP” refers to bromo(tri-pyrrolidinyl)phosphoniumhexafluorophosphate; and “TEA” refers to triethylamine; “TFA” refers to trifluoroacetic acid; “THF” refers to tetrahydrofuran.

20 An “acryloyl group” is any alpha,beta unsaturated carbonyl conjugated to a terminal alkene (CH₂=CH-C(O)-), such as acryloyl chloride, acryloyl bromide, or acryloyl anhydride.

A “base” is a molecule that is a proton acceptor, or a molecule that can neutralize an acid. Examples of bases include but are not limited to, K₂CO₃.

25 A “citrate buffer” is any salt, ester, or polyatomic anion including a derivative of citric acid.

A “citric acid buffer” is any buffer including citric acid.

The terms “continuous manufacturing” (herein after “CM”), “flow”, and “flow chemistry” involve the continuous feeding of input materials into, the transformation of in-

process materials within, and the concomitant removal of output materials from a manufacturing process, such as a continuous stirred-tank reactor. The terms are applicable to CM for new products (e.g., new drugs, generic drugs, biosimilars) and the conversion of batch manufacturing to CM for existing products. (See for example, FDA, "Q13
5 Continuous Manufacturing of Drug Substances and Drug Products, Guidance for Industry", March 2023). A continuous stirred-tank reactor is a vessel in which reactants are added and products are removed continuously and the reactor contents are stirred using internal agitation.

The terms "batch", "batch manufacturing" and "batch chemistry" involve a specific
10 quantity of material produced in a process or series of processes so that it is expected to be homogeneous within specified limits. The batch size can be defined either by a fixed quantity or by the amount produced in a fixed time interval. (See for example, FDA, "Q7 Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients, Guidance for Industry", September 2016).

15 A "catalyst" is a substance that increases the rate of a chemical reaction without itself undergoing any permanent chemical change.

As used herein, the terms "treating", "to treat", or "treatment", includes slowing, reducing, or reversing the progression or severity of an existing symptom, disorder, condition, which can include specifically slowing the growth of a cancerous lesion or
20 progression of abnormal cell growth and/or cell division.

The term "PD-1" as used herein refers to programmed death receptor 1. The term "PD-L1" as used herein refers to programmed death ligand 1.

The term "CDK4/CDK6 inhibitor" as used herein refers to any chemical that inhibits the function of CDK4/CDK6.

25 The term "EGFR inhibitor" as used herein refers to any chemical that inhibits the function of EGFR.

The term "ERK" refers to extracellular signal-regulated kinases. The term "ERK inhibitor" as used herein refers to any chemical that inhibits the function of ERK.

The term “platinum agent” as used herein refers to any platinum containing chemical that inhibits cancer.

The term “antifolate” as used herein refers to any chemical that inhibits the function of folic acid. In an embodiment, the antifolate is pemetrexed.

5 The term “Aurora A inhibitor” as used herein refers to any chemical that inhibits the function of Aurora A kinase.

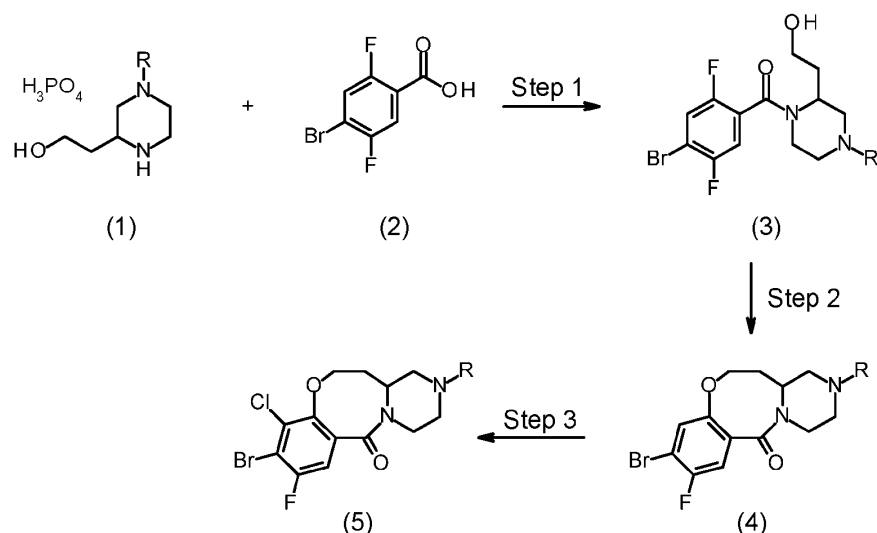
The term “SHP2 inhibitor” as used herein refers to any chemical that inhibits the function of SHP2.

10 Pharmaceutical compositions containing the compounds of Formula I as described herein may be prepared using a pharmaceutically acceptable carrier, diluent, or excipient. Examples of pharmaceutical compositions and processes for their preparation can be found in “Remington: The Science and Practice of Pharmacy”, Loyd, V., *et al.* Eds., 22nd Ed., Mack Publishing Co., 2012. Non-limiting examples of pharmaceutically acceptable carriers, diluents, and excipients include the following: saline, water, starch, sugars,
15 mannitol, and silica derivatives; binding agents such as carboxymethyl cellulose, alginates, gelatin, and polyvinyl-pyrrolidone; kaolin and bentonite; and polyethyl glycols.

20 Compounds of the present disclosure can be synthesized in part by following the steps outlined in the following Schemes 1 – 1a which comprise different sequences of assembling intermediates or compounds. Starting materials are either commercially available or made by known procedures in the reported literature or as illustrated below.

-17-

Scheme 1



In Step 1 of Scheme 1, the protected piperazine-2-ethanol, compound (1), is coupled with 4-bromo-2,5-difluoro-benzoic acid, compound (2), in an amide bond formation using a coupling reagent such as CDMT with an organic base such as NMM in a solvent system such as acetonitrile and water and an inorganic base such as K₂CO₃. R is a protecting group developed for the amino group, such as carbamates and amides. Such protecting groups are well known and appreciated in the art, such as carbamate protecting groups including allyloxycarbonyl, fluorenylmethoxycarbonyl, or benzyloxycarbonyl. A common and preferred protecting group can be Boc. One skilled in the art will recognize that there are a number of methods and reagents for amide formation resulting from the reaction of carboxylic acids and amines. For example, the reaction of the amine compound with an appropriate carboxylic acid in the presence of a coupling reagent with or without an organic base such as DIPEA or TEA can provide compound (3). Other coupling reagents include carbodiimides, such as DCC, DIC, EDCI or a carbonyldiimidazole such as CDI. Amide coupling additives, such as HOBt and HOAt can also be used to enhance the reaction. Additionally, uronium or phosphonium salts of non-nucleophilic anions, such as HBTU, HATU, PyBOP, and PyBrOP could be used in place of the more traditional coupling reagents. An additive such as DMAP may be used to enhance the reaction. Alternatively,

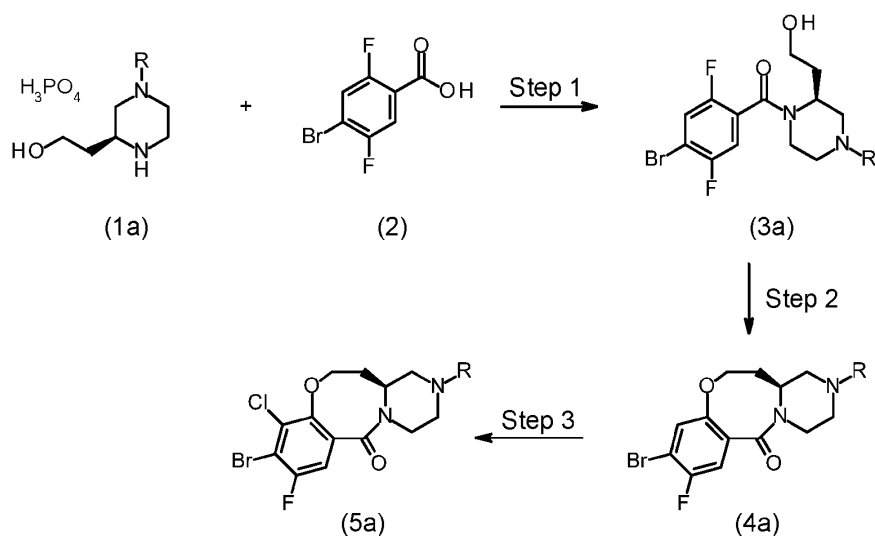
-18-

the acid chloride of compound (2) can be used in the presence of a base, such as TEA or pyridine to give compound (3).

In Step 2, the intramolecular cyclization of compound (3) is completed using an appropriate base such as potassium *tert*-butoxide, sodium *tert*-amylate, sodium *tert*-butoxide, sodium *tert*-pentoxide, DIPEA, TEA, DBU, sodium hydride in a solvent such as DMF to give compound 4. Other possible solvents could be NMP, DMAc, DMSO, and THF. This intramolecular cyclization of compound (3) to compound (4) may be conducted by slowly adding a solution of compound (3) to an excess of base so as to minimize intermolecular reaction derived impurities.

In Step 3, compound (4) can be chlorinated with under acidic conditions using an acid such as TFA, H_3PO_4 , with a chlorinating agent such as trichloroisocyanuric acid or NCS in a solvent such as acetonitrile or DMF to give compound (5).

Scheme 1a



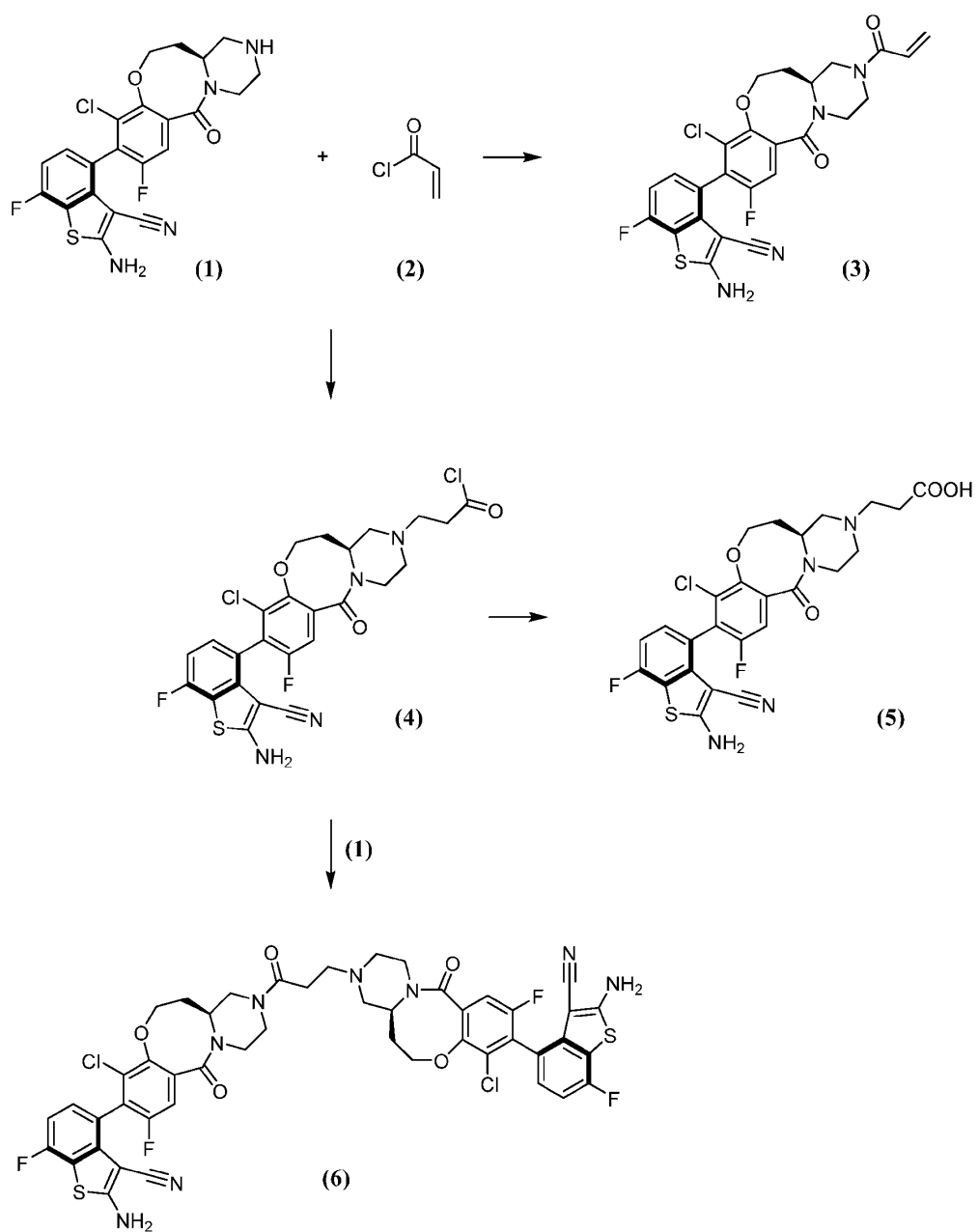
Scheme 1a illustrates a chiral synthesis of compound (5a). Compound (1a) can be prepared as described by Medicinal Chemistry route to 1, Development of an Alternative Route to the Bicyclic Piperazine, Retrosynthetic analysis of bicyclic piperazine core 2, and/or Coupling, cyclization, reduction, and Michael addition to afford Piperazine 24 in

Org Proc Res Dev., 2011, 15(6). 1328-1335. Compounds (3a), (4a), and (5a) can be prepared as described in Scheme 1.

Scheme 2 depicts the formation of products arising from reaction of amine (1) with acryloyl chloride (2). With a 1,2-addition, the compound of Formula I (3) is achieved. A
5 1,4-addition produces an amine impurity, acid chloride (4). Reaction of either acid chloride (4) or compound of Formula I (3) with an additional molecule of amine (1) results in Michael adduct impurity (6), while hydrolysis of acid chloride (4) with water results in acid impurity (5).

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Scheme 2

*tert*-Butyl

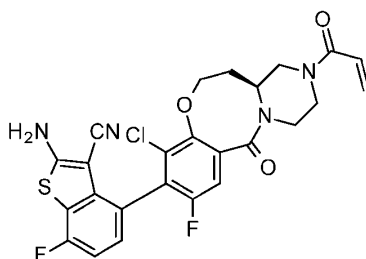
(S)-9-bromo-10-fluoro-12-oxo-1,2,4,4a,5,6-hexahydro-3H,12H-

benzo[b]pyrazino[1,2-e][1,5]oxazocine-3-carboxylate is synthesized using a 7-step sequence beginning with commercially available S-aspartic acid, which is the source of the stereocenter.

It is known that significant impurity rejection including rejection of the R-enantiomer can be achieved in the isolation of intermediates. *tert*-Butyl (S)-9-bromo-10-fluoro-12-oxo-1,2,4,4a,5,6-hexahydro-3H,12H-benzo[b]pyrazino[1,2-e][1,5]oxazocine-3-carboxylate can be isolated by crystallization with significant impurity rejection. Steps and Schemes are used to control process and reagent impurities.

DETAILED DESCRIPTION

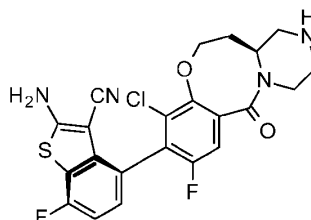
A KRAS G12C inhibitor of interest is 4-[(13aS)-10-chloro-8-fluoro-6-oxo-2-prop-2-enoyl-1,3,4,12,13,13a-hexahydropyrazino[2,1-d][1,5]benzoxazocin-9-yl]-2-amino-7-fluoro-benzothiophene-3-carbonitrile, which has the following structure:



This compound was disclosed as Example 35 in the '877 reference. As disclosed therein, this compound exists as atropisomers. The atropisomers may be separated. See Preparations 167 and 168 of the '877 reference. The desired diastereomer is taught in Preparation 168 of the '877 reference.

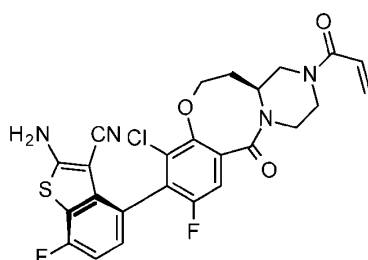
This desired diastereomer corresponds to an M atropisomer. The second diastereomer may be further processed to 4-[(13aS)-10-chloro-8-fluoro-6-oxo-2,3,4,12,13,13a-hexahydro-1H-pyrazino[2,1-d][1,5]benzoxazocin-9-yl]-2-amino-7-fluoro-benzothiophene-3-carbonitrile, M atropisomer, which has the following structure:

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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 in the '877 reference may be further processed to Example 35, M atropisomer in the '877 reference.

Example 35, M atropisomer is 4-[(13aS)-10-chloro-8-fluoro-6-oxo-2-prop-2-enoyl-1,3,4,12,13,13a-hexahydropyrazino[2,1-d][1,5]benzoxazocin-9-yl]-2-amino-7-fluoro-benzothiophene-3-carbonitrile, M atropisomer (hereinafter "Formula I") having the following structure:



(Formula I).

The compound of Formula I is currently undergoing clinical testing (ClinicalTrials.gov Identifier: NCT04956640) to assess its utility in treating patients having cancer that is treatable by inhibiting KRAS G12C. The compound of Formula I may be used, either as a monotherapy, in combination with one or more other therapeutic agents, or as part of neoadjuvant, adjuvant, advanced, or metastatic therapy, to treat cancer. Such cancers include but are not limited to lung cancer, colorectal cancer, pancreatic cancer, bladder cancer, cervical cancer, endometrial cancer, ovarian cancer, cholangiocarcinoma or esophageal cancer.

Compounds of the preparations and examples can be isolated, for example, by silica gel purification, isolated directly by filtration, or crystallization. Furthermore, the skilled artisan will appreciate that in some circumstances, the order in which moieties are introduced is not critical. The particular order of steps required to produce the compounds of the present disclosure is dependent upon the particular compound being synthesized, the starting compound, and the relative liability of the substituted moieties, as is well appreciated by the skilled chemist. All substituents, unless otherwise indicated, are as previously defined, and all reagents are well known and appreciated in the art.

Certain stereochemical centers have been left unspecified and certain substituents have been eliminated in the following schemes for the sake of clarity and are not intended to limit the teaching of the schemes in any way. It will be understood that all stereoisomers are encompassed. Specific stereoisomers can be prepared by stereospecific synthesis using enantiomerically pure or enriched starting materials and/or reagents. Alternatively, enantiomers can be separated using methods known in the art, such as chiral chromatography or by converting the enantiomers to diastereomeric salts, separating the diastereomeric salts, converting the diastereomeric salt into a non-salt form and isolating the enantiomer. Individual isomers, enantiomers, and diastereomers may be separated or resolved by one of ordinary skill in the art at any convenient point in the synthesis of compounds of the disclosure, by methods such as selective crystallization techniques or chiral chromatography (See for example, J. Jacques, et al., "*Enantiomers, Racemates, and Resolutions*", John Wiley and Sons, Inc., 1981, and E.L. Eliel and S.H. Wilen, "*Stereochemistry of Organic Compounds*", Wiley-Interscience, 1994).

Additionally, the intermediates described in the following schemes contain a number of nitrogen or oxygen protecting groups. The variable protecting group may be the same or different in each occurrence depending on the particular reaction conditions and the particular transformations to be performed. The protection and deprotection conditions are well known to the skilled artisan and are described in the literature (See for example "*Greene's Protective Groups in Organic Synthesis*", Fourth Edition, by Peter G.M. Wuts and Theodora W. Greene, John Wiley and Sons, Inc. 2007).

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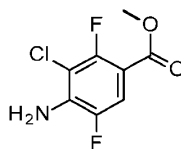
One of skill in the art will also appreciate that the compound of Formula I, described herein, or pharmaceutically acceptable salts thereof, can be deuterated (where a hydrogen can be replaced by a deuterium) and such molecules are within the scope of the compounds disclosed herein.

5

Preparations and Examples

Preparation 1

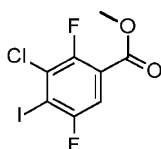
Methyl 4-amino-3-chloro-2,5-difluoro-benzoate



The title compound was prepared in the same manner as the method of the '877
10 reference; Preparation 31. ES/MS m/z: 222 [M+H]⁺.

Preparation 2

Methyl 3-chloro-2,5-difluoro-4-iodobenzoate

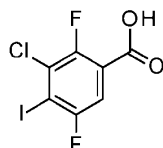


Cuprous iodide (22.7 g, 119 mmol), ACN (100 mL), and *tert*-butyl nitrite (17.7 mL,
15 149 mmol) were combined and stirred for 45 minutes at room temperature. A solution of
methyl 4-amino-3-chloro-2,5-difluoro-benzoate (22.1 g, 100 mmol) in ACN (100 mL) was
added. The reaction mixture was stirred at 40°C for three hours, allowed to cool to room
temperature, filtered through diatomaceous earth, and rinsed with DCM. The filtrate was
concentrated *in vacuo* and purified by silica gel flash chromatography (10% EtOAc in
20 hexanes) to give the title compound as a white solid (17.8 g, 54%). ¹H NMR (CDCl₃) δ
7.60 (dd, *J*=5.6, 7.6 Hz, 1H), 3.98 (s, 3H).

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Preparation 3

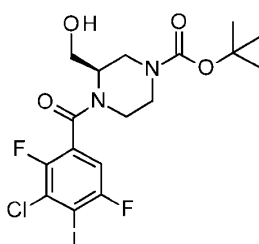
3-Chloro-2,5-difluoro-4-iodo-benzoic acid



MeOH (50 mL) was added to a solution of methyl 3-chloro-2,5-difluoro-4-iodo-
5 benzoate (16.8 g, 50.5 mmol) in THF (125 mL). The reaction mixture was cooled in an ice bath. 1N aqueous NaOH (150 mL, 150 mmol) was added in three portions. The reaction mixture was allowed to stir at room temperature for 30 minutes and concentrated *in vacuo* to remove organic solvents. The aqueous remainder was cooled with ice chips and the pH adjusted to ~2 with 5N aqueous HCl (25 mL). The aqueous layer was extracted with EtOAc
10 (3x). The combined organic extracts were dried over sodium sulfate, filtered, and concentrated *in vacuo* to give the title compound (15.8 g, 98%). ¹H NMR δ (DMSO-d₆) 13.91 (s, 1H), 7.68 (dd, *J*=5.8, 7.8 Hz, 1H).

Preparation 4

15 *tert*-Butyl (3R)-4-(3-chloro-2,5-difluoro-4-iodo-benzoyl)-3-(hydroxymethyl)piperazine-1-carboxylate



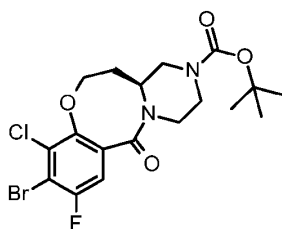
HATU (3.31 g, 8.53 mmol) was added to a solution of 3-chloro-2,5-difluoro-4-iodo-benzoic acid (2.99 g, 9.39 mmol) and DIEA (6.7 mL, 38 mmol) in THF (100 mL). The reaction mixture was stirred at room temperature for one hour. A solution of *tert*-butyl
20 (3R)-3-(hydroxymethyl)piperazine-1-carboxylate (1.92 g, 8.52 mmol) in THF (5 mL) was

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added dropwise. The reaction mixture was stirred at room temperature for 14 hours and 60°C for three hours, then diluted with EtOAc and water. The organic layer was washed with water, 1N aqueous NaOH, and brine. The aqueous layer was extracted with EtOAc, which was washed with brine. The combined organic extracts were dried over sodium sulfate, filtered, and concentrated *in vacuo*. The crude was purified by silica gel flash chromatography (10-50% EtOAc in hexanes) to give the title compound as a white solid (3.82 g, 82%). ES/MS m/z ($^{35}\text{Cl}/^{37}\text{Cl}$) 461/463 [M-*tert*-Butyl+H] $^{+}$.

Preparation 5

10 *tert*-Butyl (13aS)-9-bromo-10-chloro-8-fluoro-6-oxo-1,3,4,12,13,13a-hexahydropyrazino[2,1-d][1,5]benzoxazocine-2-carboxylate

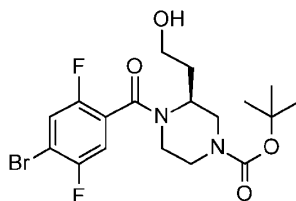


The title compound was prepared in the same manner as the method of the '877 reference; Preparation 117. ES/MS m/z ($^{79}\text{Br}/^{81}\text{Br}$) 407/409 [M-*tert*-Butyl+H] $^{+}$.

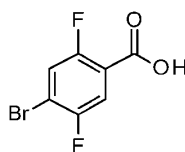
-27-

Preparation 20

tert-Butyl (3S)-4-(4-bromo-2,5-difluoro-benzoyl)-3-(2-hydroxyethyl)piperazine-1-carboxylate



- 5 CDMT (802.8 g, 4.57 mol) was added to a reactor along with acetonitrile (20.0 L) and the mixture was cooled to 0 °C. NMM (708.2 g, 7.00 mol) was added and the mixture was stirred for 30 min at 0 °C. 4-bromo-2,5-difluorobenzoic acid (794.8 g, 3.35 mol),



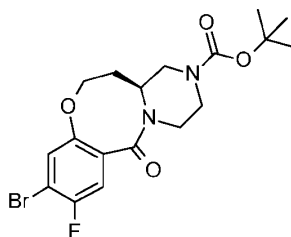
- was added and the mixture was stirred for 1 h at 0 °C. In a separate vessel, K₂CO₃ (842 g, 6.09 mol), water (5.0 L), and *tert*-butyl (3S)-3-(2-hydroxyethyl)piperazine-1-carboxylate:phosphoric acid (1:1) (1000 g, 3.05 mol) were combined. The aqueous piperazine solution was added to the acetonitrile coupling solution over 5 min while maintaining an internal temperature of 0 °C. The mixture was stirred for 2.5 h at 0 °C. The bottom layer was drained from the reactor. The reaction mixture was stirred for an additional 64 h at 0 °C, then concentrated to 2 L/kg. 2-MeTHF (10.0 L) and n-heptane (3.0 L) were added. 1 M aq. NaHCO₃ (10.0 L) was added and the mixture was stirred for 15 min. The layers were allowed to separate and the bottom layer was drained. 1 M aq. NaHCO₃ (10.0 L) was added and the mixture was stirred for 15 min. The layers were allowed to separate and the bottom layer was drained. Aq. HCl (0.05 M, 5.0 L) was added and the mixture was stirred for 15 min. The layers were allowed to separate and the bottom layer was drained. Water (5.0 L) was added and the mixture was stirred for 15 min. The

-28-

layers were allowed to separate and the bottom layer was drained. The upper layer was concentrated to 2 L/kg and 2-MeTHF (1.0 L) was added. The mixture was concentrated to 2 L/kg and 2-MeTHF (1.0 L) was added. The mixture was concentrated to 2 L/kg and DMF (2.7 L) was added to give the title compound as a DMF solution (4.03 kg, 31.2% assay, 2.80 mol, 92% yield), which was used without further manipulation. An analytical sample was prepared by chromatography and exhibited the following spectroscopic characteristics: APCI-MS found 471 and 473 ($M+Na^+$): 1H NMR (500 MHz, d_6 -DMSO + TFA, multiple rotamers present) δ 7.84 (m, 1H), 7.53 (br s, 1H), 4.71 (br s, 0.5H), 4.33 – 4.27 (m, 0.5H), 4.12 – 3.72 (m, 2H), 3.65 (br s, 0.5H), 3.47 (br, 1H), 3.38 – 3.11 (m, 2H), 3.11 – 2.56 (m, 2.5H), 1.68 (m, 2H), 1.39 (s 9H).

Preparation 21

tert-Butyl (13aS)-9-bromo-8-fluoro-6-oxo-1,3,4,12,13,13a-hexahydropyrazino[2,1-d][1,5]benzoxazocine-2-carboxylate



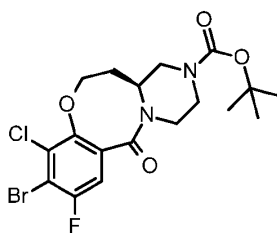
Sodium *tert*-pentoxide (462 g, 4.20 mol) was added to a reactor along with DMF (9.1 L). The mixture was stirred to form a solution and cooled to 0 °C. The DMF solution of *tert*-butyl (3S)-4-(4-bromo-2,5-difluoro-benzoyl)-3-(2-hydroxyethyl)piperazine-1-carboxylate (4.03 kg, 31.2% assay, 2.80 mol) was added over 8 h at 0 °C. The total mass of the product solution at this point is 12.95 kg. A portion of the solution (1.30 kg) was placed in a separate reactor. Water (2.6 kg) was added to a clean reactor. The 1.30 kg of product solution was added to the water over 3 h at 25 °C. The mixture was stirred for 64 h at 25 °C. The resulting solids were isolated by filtration and washed with a mixture of DMF (0.3 L) and water (0.3 L). The crude solids were added to a reactor along with EtOH (628 mL). The mixture was heated to 55 °C and stirred for 30 min. Water (314 mL) was added over 2

-29-

h and the mixture was held at 55 °C for an additional 30 min. The slurry was cooled to 20 °C over 2 h, then held at 20 °C for 2 h. The resulting solids were isolated by filtration and washed with a mixture of water (60 mL) and EtOH (60 mL). The product was dried under vacuum at 50 °C for 16 h to give the title compound (98.2 g, 73% yield). APCI-MS found 451 and 453 ($M+Na^{-1}$); 1H NMR (400 MHz, d_6 -DMSO-) δ 7.32 (d, J = 6.0 Hz, 1H), 7.28 (d, J = 9.2 Hz, 1H), 4.24–4.18 (m, 2H), 4.05–3.91 (m, 2H), 3.87–3.76 (m, 2H), 3.06 (br, 1H), 2.95–2.80 (brn, 2H), 2.06 (m, 1H), 1.76 (m, 1H), 1.04 (s, 9H).

Alternative Synthesis of Preparation 5

10 *tert*-Butyl (13aS)-9-bromo-10-chloro-8-fluoro-6-oxo-1,3,4,12,13,13a-hexahydropyrazino[2,1-d][1,5]benzoxazocine-2-carboxylate

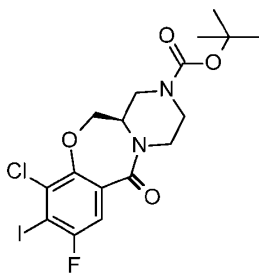


tert-Butyl (13aS)-9-bromo-8-fluoro-6-oxo-1,3,4,12,13,13a-hexahydropyrazino[2,1-d][1,5]benzoxazocine-2-carboxylate (2.00 g, 4.66 mmol) was added to a reactor along with acetonitrile (20 mL) and the mixture was cooled to 5 °C. Trichloroisocyanuric acid (1.08 g, 4.66 mmol) was added and the mixture was stirred at 5 °C for 5 min. A solution of phosphoric acid (0.96 mL, 14.0 mmol; stock solution was 1.92 mL of phosphoric acid in 4.0 mL of acetonitrile) was added over 2 min and the mixture was stirred at 5 °C for 23 h. Aq. K_2CO_3 (40%, 20 mL) was added and the mixture was stirred at 5 °C for 30 min, warmed to 20 °C, and stirred at 20 °C for 2 h. Ethyl acetate (20 mL) and water (20 mL) were added and the mixture was stirred until solids dissolved. Solids reappeared after sitting for 1 h. Aq. $NaHSO_3$ (5%, 10 mL) was added and the mixture was stirred overnight. Aq. K_2CO_3 (40%, 4 mL) and di-*tert*-butyl dicarbonate (0.20 g, 0.93 mmol) were added and the mixture was stirred overnight. The mixture was concentrated to 2-3 volumes and isopropanol (4 volumes) was added. The mixture was concentrated to 2-3 volumes and isopropanol (4 volumes) was added. The mixture was concentrated to 2-3

volumes and isopropanol (2 volumes) was added. The mixture was stirred at 57 °C. Water (4 volumes) was added over 1 h and the mixture was stirred at 57 °C for 2 h. The mixture was cooled and stirred overnight at 20°C, filtered, and washed with 1:2 isopropanol:water (3 volumes). The product was dried under vacuum at 50 °C for 3 h to give the title compound (1.85 g, 86% yield).

Preparation 6

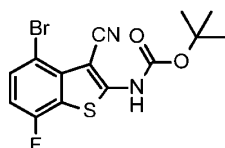
tert-Butyl (4aR)-7-chloro-9-fluoro-8-iodo-11-oxo-2,4,4a,5-tetrahydro-1H-pyrazino[2,1-c][1,4]benzoxazepine-3-carboxylate



10 *tert*-Butyl (3R)-4-(3-chloro-2,5-difluoro-4-iodo-benzoyl)-3-
(hydroxymethyl)piperazine-1-carboxylate (4.59 g, 8.88 mmol) in DMF (150 mL) was
cooled to 0°C. Sodium hydride (0.89 g, 22 mmol, 60 mass% in paraffin oil) was added.
After four hours at 0°C, the reaction mixture was quenched with saturated aqueous sodium
bicarbonate and diluted with water and diethyl ether. The aqueous layer was extracted with
15 diethyl ether (4x). The combined organic extracts were washed with water (3x) and brine,
dried over sodium sulfate, filtered, and concentrated *in vacuo*. The crude was purified by
silica gel flash chromatography (15-40% EtOAc in hexanes) to give the title compound as
a white solid (3.82 g, 82%). ES/MS *m/z* (³⁵Cl/³⁷Cl) 441/443 [M-*tert*-Butyl+H]⁺.

Preparation 7

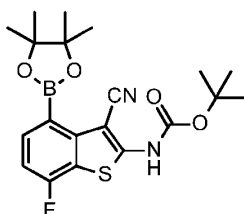
tert-Butyl N-(4-bromo-3-cyano-7-fluoro-benzothiophen-2-yl)carbamate



The title compound was prepared in the same manner as the method of the ‘877
reference; Preparation 14. ES/MS m/z (⁷⁹Br/⁸¹Br) 315/317 [M-*tert*-Butyl+H]⁺.

Preparation 8

tert-Butyl N-[3-cyano-7-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzothiophen-2-yl]carbamate

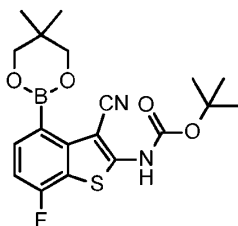


A mixture of *tert*-butyl N-(4-bromo-3-cyano-7-fluorobenzothiophen-2-yl)carbamate (3.10 g, 8.35 mmol), bis(pinacolato)diboron (21.0 g, 82.7 mmol), and potassium acetate (2.50 g, 25.5 mmol) in 1,4-dioxane (50 mL) was flushed with nitrogen (direct sparge) for 10 minutes. 1,1'-Bis(diphenylphosphino)ferrocene-palladium(II)dichloride dichloromethane complex (1.0 g, 1.2 mmol) was added. The reaction flask was sealed and heated at 80-85°C for 3.5 hours. The reaction mixture was filtered through diatomaceous earth. The filtrate was diluted with water and extracted with EtOAc (2x). The combined organic extracts were washed with brine, dried over sodium sulfate, filtered, and concentrated *in vacuo*. The crude was purified by silica gel flash chromatography (10-50% (20% acetone in DCM) in hexanes) to give the title compound (4.45 g, 87%). ES/MS *m/z* 363 [M-*tert*-Butyl+H]⁺.

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Preparation 9

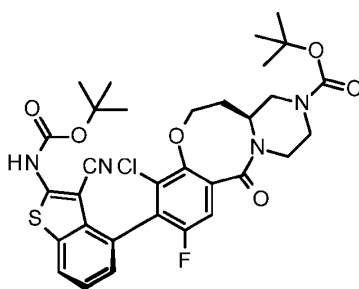
tert-Butyl N-[3-cyano-4-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)-7-fluoro-benzothiophen-2-yl]carbamate



5 The title compound was prepared in the same manner as the method of the '877 reference; Preparation 15. ¹H NMR (DMSO-d₆) δ 11.6 (s, 1H), 7.61 (m, 1H), 7.20 (m, 1H), 3.78 (s, 4H), 1.54 (s, 9H), 1.03 (s, 6H).

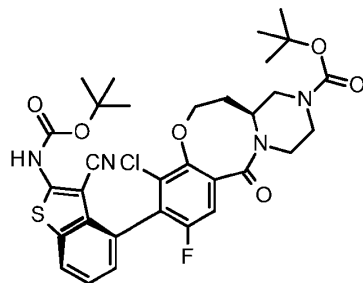
Preparations 10 and 11

10 *tert*-Butyl (13aS)-9-[2-(*tert*-butoxycarbonylamino)-3-cyano-benzothiophen-4-yl]-10-chloro-8-fluoro-6-oxo-1,3,4,12,13,13a-hexahydropyrazino[2,1-d][1,5]benzoxazocine-2-carboxylate, P and M atropisomers



P atropisomer

-33-

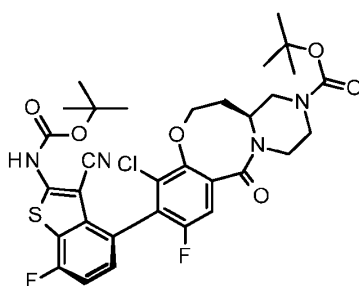


M atropisomer

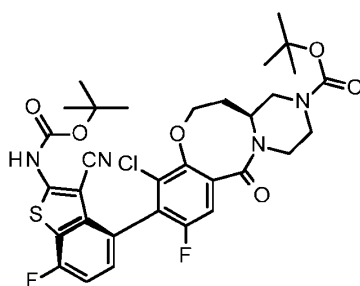
The title compounds were prepared in the same manner as the method of the '877 reference; Preparation 167. The mixture of atropisomers were separated by silica gel flash chromatography (0-30% acetone in hexanes). Preparation 10 (P atropisomer) was the first
5 compound to elute off the column. Preparation 11 (M atropisomer) was the second compound to elute off the column. For both, ES/MS m/z ($^{35}\text{Cl}/^{37}\text{Cl}$) 657/659 $[\text{M}+\text{H}]^+$.

Preparations 12 and 13

tert-Butyl (13a*S*)-9-[2-(*tert*-butoxycarbonylamino)-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]benzoxazocine-2-carboxylate, P and M atropisomers



P atropisomer



M atropisomer

The title compounds were prepared in the same manner as the method of the '877 reference; Preparations 167 and 168: A mixture of *tert*-butyl (13a*S*)-9-bromo-10-chloro-8-fluoro-6-oxo-1,3,4,12,13,13a-hexahydropyrazino[2,1-d][1,5]benzoxazocine-2-carboxylate (10.0 g, 21.6 mmol), *tert*-butyl N-[3-cyano-4-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)-7-fluoro-benzothiophen-2-yl]carbamate (12.3 g, 30.4 mmol), potassium carbonate (8.94 g, 64.7 mmol), and dichloro[(*S*)-(-)-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl]palladium(II) (also known as "(*S*)-(-)-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl palladium dichloride") (3.84 g, 4.42 mmol) was added to 1,4-dioxane (215 mL) that had been flushed with nitrogen (direct sparge) for 30 minutes. The reaction flask was sealed and heated at 105°C for 14 hours. Additional *tert*-butyl N-[3-cyano-4-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)-7-fluoro-benzothiophen-2-

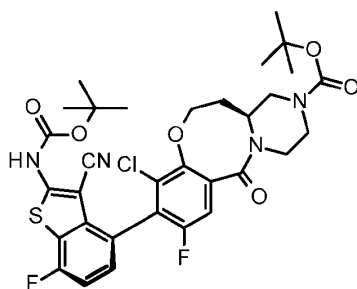
yl]carbamate (3.54 g, 8.75 mmol) and dichloro[(S)-(-)-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl]palladium(II) (0.97 g, 1.12 mmol) were added. The reaction flask was sealed and heated at 105°C for 14 hours.

The reaction mixture was filtered through diatomaceous earth, and rinsed with
5 EtOAc. The filtrate was concentrated *in vacuo* and diluted with EtOAc, water, and brine. The aqueous layer was extracted with EtOAc. The combined organic extracts were dried over magnesium sulfate, filtered, and concentrated *in vacuo*. The crude was purified by silica gel flash chromatography (10-40% acetone in hexanes). Preparation 12 (P atropisomer) eluted first, followed by Preparation 13 (M atropisomer). Impure fractions of
10 P atropisomer were further purified by silica gel flash chromatography. This gave the two title compounds (P atropisomer, 0.35 g, 2%; M atropisomer, 5.6 g, 38%). For both, ES/MS m/z 619 [M-*tert*-Butyl+H]⁺.

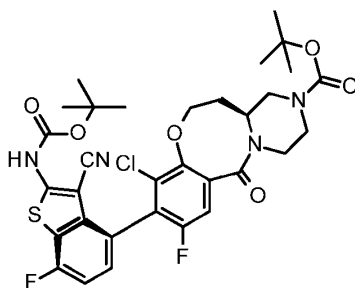
Catalyst Screen of Preparations 12 and 13

tert-Butyl (13aS)-9-[2-(*tert*-butoxycarbonylamino)-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]benzoxazocine-2-carboxylate, P and M atropisomers

5



P atropisomer



M atropisomer

In a glove box, a mixture of *tert*-butyl (13aS)-9-bromo-10-chloro-8-fluoro-6-oxo-1,3,4,12,13,13a-hexahydropyrazino[2,1-d][1,5]benzoxazocine-2-carboxylate (0.025 g, 0.054 mmol), *tert*-butyl N-[3-cyano-4-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)-7-fluoro-benzothiophen-2-yl]carbamate (0.030 g, 0.074 mmol), potassium carbonate (0.022 g, 0.16 mmol), and catalyst (0.0081 mmol) was added to 1,4-dioxane (1 mL) in a vial. The vial was sealed and heated at 105°C for 19 hours, then cooled to room temperature. Reaction monitoring by LCMS showed the following reaction progression and ratio of atropisomers:

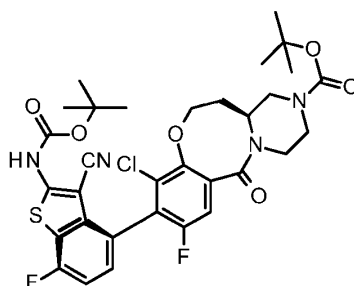
Table 1:

Catalyst	Reaction Progression (% loss of limiting reactant)	Ratio of Prep 12 : Prep 13 P : M atropisomers
Dichloro[(S)-(-)-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl]palladium(II)	100	1 : 4
Dichloro[(R)-(+)-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl]palladium(II)	100	1 : 2
Dichloro 1,1'-bis(diphenylphosphino)ferrocene palladium (II) dichloromethane	100	1 : 2
Dichloro(1,2-bis(diphenylphosphino)ethane)palladium(II)	71	1 : 2
Dichloro(1,3-bis(diphenylphosphino)propane)palladium(II)	56	1 : 2
Dichloro[1,4-bis(diphenylphosphino)butane]palladium(II)	85	1 : 2
Dichloro{bis[2-(diphenylphosphino)phenyl]ether}palladium(II)	100	2 : 3
Dichloro[9,9-dimethyl-4,5-bis(diphenylphosphino)xanthene]palladium(II)	4	
Dibromo[1,1'-bis(diphenylphosphino)ferrocene]palladium(II)	100	1 : 2

[(1,2,3- η)-2-Buten-1-yl]chloro[dicyclohexyl(2',6'-dimethoxy[1,1'-biphenyl]-2-yl)phosphine- κ P]palladium	28	1 : 4
[(1,2,3- η)-2-Butenyl]chloro(tricyclohexylphosphine)palladium	100	2 : 3
trans-Dichlorobis(tricyclohexylphosphine)palladium(II)	21	

Alternative Synthesis of Preparation 13

5 *tert*-Butyl (13aS)-9-[2-(*tert*-butoxycarbonylamino)-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]benzoxazocine-2-carboxylate, M atropisomer



M atropisomer

To a small flask, in a glove box, was added palladium (II) acetate (0.119 g, 0.528 mmol), (S)-(-)-2,2'-bis(diphenylphosphino)-1,1'-binaphthalene (0.364 g, 0.580 mmol) and toluene (25 mL), which would make diacetate[(S)-(-)-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl]palladium(II). The mixture was capped and stirred for 1 hour. *tert*-Butyl 10 *tert*-Butyl (13aS)-9-bromo-10-chloro-8-fluoro-6-oxo-1,3,4,12,13,13a-hexahydropyrazino[2,1-d][1,5]benzoxazocine-2-carboxylate (0.500 g, 1.06 mmol) and a solution of potassium carbonate in water (2 mL, made from 0.241 g potassium carbonate in 2 mL water) were added. The mixture was heated at 60°C for 6 hours. The organic and aqueous layers were

separated. The organic layer was dried over magnesium sulfate and filtered. The solids were rinsed with toluene (25 mL), which was added to the original filtrate.

To a second flask was added *tert*-butyl (13aS)-9-bromo-10-chloro-8-fluoro-6-oxo-1,3,4,12,13,13a-hexahydropyrazino[2,1-d][1,5]benzoxazocine-2-carboxylate (9.51 g, 20.16 mmol) and cesium carbonate (31.1 g, 95.0 mmol). The flask was cycled through vacuum and nitrogen four times.

To a third flask was added *tert*-butyl N-[3-cyano-4-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)-7-fluoro-benzothiophen-2-yl]carbamate (10.9 g, 25.3 mmol), 1,1,1-tris(hydroxymethyl)ethane (1.69 g), and THF (50 mL). The mixture was stirred for 25 min.

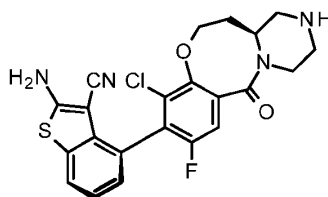
10 To the second flask was added the ligand-catalyst filtrate and THF (50 mL). The mixture was heated at 60°C under nitrogen. The contents of the third flask were added dropwise (6 mL/hour). After 10 total hours of heating, HPLC analysis showed complete conversion of bromide starting material to product in a 4.36:1 M:P atropisomer ratio.

15 After 12 total hours of heating, the mixture was allowed to cool to room temperature. Water (100 mL) was added and the organic and aqueous layers were separated. 20% brine (50 mL) was added and the organic and aqueous layers were separated. A portion (~20%) of the organic layer (26.2 g) was distilled to ~10 mL, diluted with isopropyl acetate (20 mL), distilled to ~10 mL, diluted with isopropyl acetate (20 mL), and distilled to ~10 mL. The resulting suspension was filtered and dried under vacuum to
20 give the title compound (1.85 g). HPLC analysis showed 98.23% M atropisomer and 0.76% P atropisomer.

-40-

Preparation 16

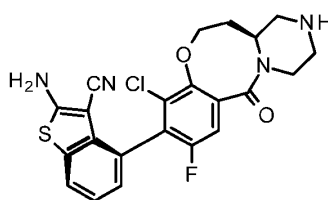
4-[(13aS)-10-Chloro-8-fluoro-6-oxo-2,3,4,12,13,13a-hexahydro-1H-pyrazino[2,1-d][1,5]benzoxazocin-9-yl]-2-amino-benzothiophene-3-carbonitrile, P atropisomer



5 TFA (4 mL) was added to a solution of *tert*-butyl (13aS)-9-[2-(*tert*-butoxycarbonylamino)-3-cyano-benzothiophen-4-yl]-10-chloro-8-fluoro-6-oxo-1,3,4,12,13,13a-hexahydropyrazino[2,1-d][1,5]benzoxazocine-2-carboxylate, P atropisomer (0.98 g, 1.5 mmol) in DCM (5 mL). The reaction mixture was stirred at room temperature for three hours, concentrated *in vacuo*, and purified by silica gel flash chromatography (4-10% 7N ammoniated MeOH in DCM) to give the title compound (0.57 g, 84%). ES/MS m/z ($^{35}\text{Cl}/^{37}\text{Cl}$) 457/459 $[\text{M}+\text{H}]^+$.

Preparation 17

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-benzothiophene-3-carbonitrile, M atropisomer



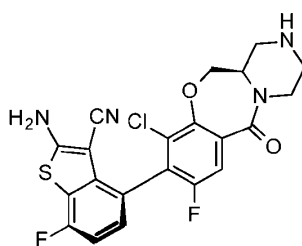
15

The title compound was prepared in the same manner as the method of the '877 reference; Preparation 187. ES/MS m/z ($^{35}\text{Cl}/^{37}\text{Cl}$) 457/459 $[\text{M}+\text{H}]^+$.

-41-

Preparation 18

4-[(4aR)-7-Chloro-9-fluoro-11-oxo-1,2,3,4,4a,5-hexahydropyrazino[2,1-c][1,4]benzoxazepin-8-yl]-2-amino-7-fluoro-benzothiophene-3-carbonitrile, P atropisomer



5

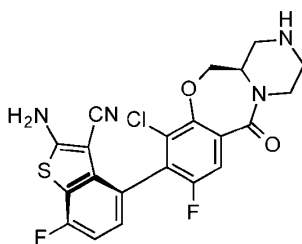
TFA (2 mL) was added to a solution of *tert*-butyl (4aR)-8-[2-(*tert*-butoxycarbonylamino)-3-cyano-7-fluoro-benzothiophen-4-yl]-7-chloro-9-fluoro-11-oxo-2,4,4a,5-tetrahydro-1H-pyrazino[2,1-c][1,4]benzoxazepine-3-carboxylate, P atropisomer (0.018 g, 0.027 mmol) in DCM (2 mL). The reaction mixture was stirred at room temperature for 30 minutes, concentrated *in vacuo*, and purified by silica gel flash chromatography (0-10% MeOH in DCM, then 0-10% 7N ammoniated MeOH in DCM) to give the title compound (0.013 g, 100%). ES/MS *m/z* ($^{35}\text{Cl}/^{37}\text{Cl}$) 461/463 $[\text{M}+\text{H}]^+$.

10

-42-

Preparation 19

4-[(4aR)-7-Chloro-9-fluoro-11-oxo-1,2,3,4,4a,5-hexahydropyrazino[2,1-c][1,4]benzoxazepin-8-yl]-2-amino-7-fluoro-benzothiophene-3-carbonitrile, M atropisomer



5

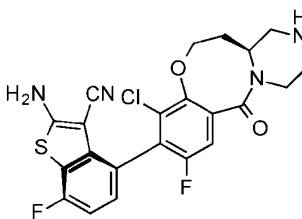
TFA (2.5 mL) was added to an ice-cooled solution of *tert*-butyl (4aR)-8-[2-(*tert*-butoxycarbonylamino)-3-cyano-7-fluoro-benzothiophen-4-yl]-7-chloro-9-fluoro-11-oxo-2,4,4a,5-tetrahydro-1H-pyrazino[2,1-c][1,4]benzoxazepine-3-carboxylate, M atropisomer (0.20 g, 0.31 mmol) in DCM (2.5 mL). The reaction mixture was stirred at room temperature for two hours, concentrated *in vacuo*, and purified by silica gel flash chromatography (0-10% 7N ammoniated MeOH in DCM) to give the title compound (0.13 g, 89%). ES/MS m/z ($^{35}\text{Cl}/^{37}\text{Cl}$) 461/463 $[\text{M}+\text{H}]^+$.

10

Preparation 22

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

15

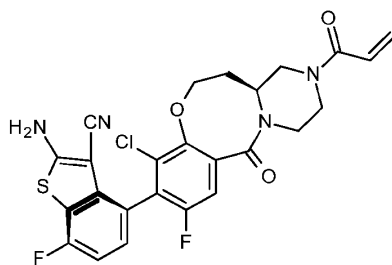


-43-

tert-Butyl (13aS)-9-[2-(*tert*-butoxycarbonylamino)-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]benzoxazocine-2-carboxylate, M atropisomer (100.0 g, 148.1 mmol) was added to a reactor with EtOH (300 mL). A solution of HCl in EtOH (30%, 216 g, 1.78 mol) was added over 30 min with stirring. The mixture was heated to 40 °C for 20 h, then cooled to 0 °C with stirring. A mixture of KOH (118.8 g, 1.80 mol) in water (1.0 L) was gradually added with stirring. The EtOH was removed by distillation. The residue was extracted with 2-MeTHF (1.0 L) and again with 2-MeTHF (500 mL). The organic extracts were combined, washed with saturated aqueous NaCl (3 × 0.5 L), and concentrated to ~200 mL. Acetonitrile (1.0 L) was added in a dropwise manner. The mixture was stirred and cooled to 0 °C for 1 h. The solids were collected by filtration, washed with acetonitrile (200 mL), and dried under vacuum to afford the title compound as a white solid (66.4 g, 85% yield). APCI-MS 475 (M+H⁺).

Example 1

4-[(13aS)-10-Chloro-8-fluoro-6-oxo-2-prop-2-enoyl-1,3,4,12,13,13a-hexahydropyrazino[2,1-d][1,5]benzoxazocin-9-yl]-2-amino-7-fluoro-benzothiophene-3-carbonitrile, M atropisomer



(Example 1)

HCl gas was bubbled for five minutes into an ice-cooled solution of *tert*-butyl (13aS)-9-[2-(*tert*-butoxycarbonylamino)-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]benzoxazocine-2-carboxylate, M atropisomer (0.786 g, 1.17 mmol) in DCM (12 mL) and 2-propanol (12 mL). The reaction mixture was stirred at room temperature for five hours, then cooled in an ice bath. HCl gas was bubbled into the reaction mixture for five minutes. The reaction

mixture was stirred at room temperature for 14 hours, then concentrated *in vacuo*. The residue was twice diluted with n-heptane and concentrated *in vacuo*. MTBE (50 mL) was added. The mixture was stirred at room temperature for ten minutes, then filtered to give the deprotected material as a dihydrochloride salt.

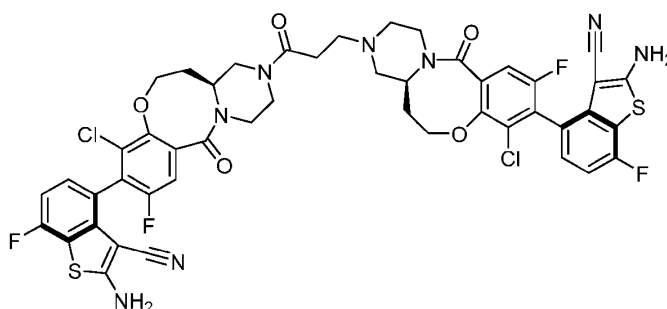
5 The dihydrochloride salt was dissolved in water (12 mL). 2-Methyltetrahydrofuran (12 mL) was added. A solution of potassium carbonate (0.81 g, 5.82 mmol) in water (12 mL) was added. The mixture was vigorously stirred while being cooled in an ice bath. Acryloyl chloride (0.10 mL, 1.28 mmol) in 2-methyltetrahydrofuran (5 mL) was added dropwise. After five minutes, diluted with brine and 2-methyltetrahydrofuran. The
10 aqueous layer was extracted with 2-methyltetrahydrofuran (2x). The combined organic extracts were washed with water, dried over magnesium sulfate, filtered, and concentrated *in vacuo*. The crude was purified by silica gel flash chromatography (20-30% B in A; A:3:1 EtOAc:hexanes; B: 4:1 EtOAc:MeOH) to give the title compound (0.409 g, 66%). ES/MS m/z ($^{35}\text{Cl}/^{37}\text{Cl}$) 529/531 $[\text{M}+\text{H}]^+$.

15 Alternative Synthesis 1 of Example 1: Flow Chemistry

4-[(13aS)-10-Chloro-8-fluoro-6-oxo-2-prop-2-enoyl-1,3,4,12,13,13a-hexahydropyrazino[2,1-d][1,5]benzoxazocin-9-yl]-2-amino-7-fluoro-benzothiophene-3-carbonitrile, M atropisomer

To a continuous stirred-tank reactor (105 mL, 15°C) was added material from feed
20 A [monopotassium phosphate (25.02 g), dipotassium phosphate (2.61 g), and water (to 600 mL volume); pH ~ 5.8; flow rate 4.73 g/min], feed B [acryloyl chloride (13.15 g, 1.15 eq) and 2-methyltetrahydrofuran (6 volumes); flow rate 2.48 g/min], and feed C [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 (60 g, 0.126 mol),
25 2-methyltetrahydrofuran (6 volumes), and water (0.2 volumes); flow rate 2.97 g/min]. The mixture in the reactor was pumped to a second continuous stirred-tank reactor (105 mL, 15°C) at a flow rate of 10.5 g/min, and then collected in a separate receiving bottle. HPLC analysis conditions ("HPLC analysis") comprise an Inertsil ODS-3V column (4.6 x 250 mm; 5 mm) eluted with 20% to 95% ACN in 0.1% aqueous H_3PO_4 using an Agilent 1260

chromatograph with UV detector. HPLC analysis showed 0.33% 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-
 5 d][1,5]benzoxazocin-9-yl]-2-amino-7-fluoro-benzothiophene-3-carbonitrile, M,M
 atropisomer,



“MA impurity” as shown in Table 2. This MA impurity is a Michael adduct
 wherein unreacted [4-[(13aS)-10-chloro-8-fluoro-6-oxo-2,3,4,12,13,13a-hexahydro-1H-
 10 pyrazino[2,1-d][1,5]benzoxazocin-9-yl]-2-amino-7-fluoro-benzothiophene-3-carbonitrile,
 M atropisomer reacts with the compound of Formula I and thereby forms a dimer. It is
 possible for trace amounts of the corresponding M,P atropisomer dimer may be present.
 The final mixture layers were separated. The aqueous phase was extracted with 2-
 methyltetrahydrofuran (5 volumes). The combined organic phases were washed with
 15 aqueous sodium bicarbonate (5 wt%, 10 volumes) twice and aqueous sodium chloride
 (10%, 10 volumes) once. The organic phase was concentrated to 10 volumes, diluted with
 isopropanol (10 volumes), concentrated to 10 volumes, diluted with isopropanol (10
 volumes), stirred at 15°C for 2 hours, filtered, washed, and dried to give crude title
 compound (~60 g).

20 Crude title compound (~50 g) was dissolved in 4:1 THF:MeOH (11 volumes) at
 35°C, diluted with methylcyclohexane (0.58 volumes), seeded (2.5 wt%), and stirred for
 30 min. Methylcyclohexane (12.3 volumes) was added steadily over 10-12 hours. The
 mixture was stirred overnight at 35°C, filtered, washed with methylcyclohexane (2
 volumes), and dried to give the title compound (46.4 g, 84% adjusted yield).

Alternative Synthesis 2 of Example 1: Batch Chemistry

4-[(13aS)-10-Chloro-8-fluoro-6-oxo-2-prop-2-enoyl-1,3,4,12,13,13a-hexahydropyrazino[2,1-d][1,5]benzoxazocin-9-yl]-2-amino-7-fluoro-benzothiophene-3-carbonitrile, M atropisomer

- 5 A batch reaction (one-sixth scale) was carried out, in which a solution of acryloyl chloride (2.19 g, 1.15 eq) in 2-methyltetrahydrofuran (6 volumes) was added in a dropwise manner over 30 min to a solution of 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 (10 g, 21 mmol) in 2-methyltetrahydrofuran
10 (6 volumes) and pH 5.8 buffer [monopotassium phosphate (4.17 g), dipotassium phosphate (0.435 g), and water (to 100 mL volume)]. HPLC analysis after 25 min showed 1.63% MA impurity as shown in Table 2.

Alternative Synthesis 3 of Example 1: Flow Chemistry

- 4-[(13aS)-10-Chloro-8-fluoro-6-oxo-2-prop-2-enoyl-1,3,4,12,13,13a-hexahydropyrazino[2,1-d][1,5]benzoxazocin-9-yl]-2-amino-7-fluoro-benzothiophene-3-carbonitrile, M atropisomer
15

- To a continuous stirred-tank reactor (55 mL, 12°C-13°C, 300 rpm) was added material from feed A [monopotassium phosphate (25.02 g), dipotassium phosphate (2.61 g), and water (to 600 mL volume); pH ~ 5.8; flow rate 2.3 mL/min], feed B [acryloyl
20 chloride (8.38 g, 1.25 eq) and 2-methyltetrahydrofuran (6 volumes); flow rate 1.6 mL/min], and feed C [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 (36.01 g, 0.076 mol), 2-methyltetrahydrofuran (6 volumes), and water (0.4
25 volumes); flow rate 1.6 mL/min]. The mixture in the reactor was pumped to a receiving bottle at 15 mL/min. Material from feed A, B, and C was dispensed for 20 minutes at the flow rates specified above before pausing the system and taking a reactor sample of the organic for HPLC analysis. HPLC analysis conditions ("HPLC analysis") comprise an Inertsil ODS-3V column (4.6 x 250 mm; 5 mm) eluted with 20% to 95% ACN in 0.1% aqueous H₃PO₄ using an Agilent 1260 chromatograph with UV detector. HPLC analysis

showed 0.32% MA impurity as shown in Table 2. It is possible for trace amounts of the corresponding M,P atropisomer dimer may be present.

Alternative Synthesis 4 of Example 1: Flow Chemistry

5 4-[(13aS)-10-Chloro-8-fluoro-6-oxo-2-prop-2-enoyl-1,3,4,12,13,13a-hexahydropyrazino[2,1-d][1,5]benzoxazocin-9-yl]-2-amino-7-fluoro-benzothiophene-3-carbonitrile, M atropisomer

To a continuous stirred-tank reactor (55 mL, 12°C-13°C, 300 rpm) was added material from feed A [citric acid (29.30 g), sodium citrate dihydrate (3.10 g), and water (to 500 mL volume); heat to dissolve, pH ~ 3.0; flow rate 2.3 mL/min], feed B [acryloyl chloride (2.54 g, 1.25 eq) and 2-methyltetrahydrofuran (6 volumes); flow rate 1.6 mL/min], and feed C [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 (8.05 g, 0.017 mol), 2-methyltetrahydrofuran (6 volumes), and water (0.4 volumes); flow rate 1.6 mL/min]. The mixture in the reactor was pumped to a receiving bottle at 15 mL/min. Material from feed A, B, and C was dispensed for 20 minutes at the flow rates specified above before pausing the system and taking a reactor sample of the organic for HPLC analysis. HPLC analysis conditions ("HPLC analysis") comprise an Inertsil ODS-3V column (4.6 x 250 mm; 5 mm) eluted with 20% to 95% ACN in 0.1% aqueous H₃PO₄ using an Agilent 1260 chromatograph with UV detector. HPLC analysis showed 0.14% MA impurity as shown in Table 2. It is possible for trace amounts of the corresponding M,P atropisomer dimer may be present.

Alternative Synthesis 5 of Example 1: Flow Chemistry

25 4-[(13aS)-10-Chloro-8-fluoro-6-oxo-2-prop-2-enoyl-1,3,4,12,13,13a-hexahydropyrazino[2,1-d][1,5]benzoxazocin-9-yl]-2-amino-7-fluoro-benzothiophene-3-carbonitrile, M atropisomer

To a continuous stirred-tank reactor (110 mL, 450 rpm) was added material from feed A [citric acid monohydrate (78.22 g), sodium citrate dihydrate (30.94 g), and water (to 1 L volume); heat to dissolve, pH ~ 3.0; flow rate 3.6 mL/min], feed B [acryloyl chloride

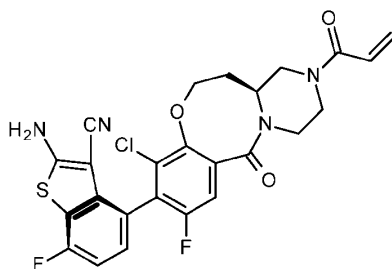
-48-

(10.20 g, 1.25 eq) and 2-methyltetrahydrofuran (2 volumes); flow rate 0.8 mL/min], and feed C [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 (21.96 g, 0.046 mol), 2-methyltetrahydrofuran (18 volumes), and water (0.6
 5 volumes); flow rate 6.6 mL/min]. The mixture in the reactor was pumped to a receiving bottle at 20 mL/min. Material from feed A, B, and C was dispensed for 30 minutes at the flow rates specified above before pausing the system and taking a reactor sample of the organic for HPLC analysis. HPLC analysis conditions ("HPLC analysis") comprise an CSH Phenyl Hexyl column (3.0 x 100 mm, 2.5 mm) eluted with 20% to 95% ACN in 0.1%
 10 aqueous TFA using an Agilent 1260 chromatograph with UV detector. HPLC analysis showed 0.07% MA impurity as shown in Table 2. It is possible for trace amounts of the corresponding M,P atropisomer dimer may be present.

A surprising result is that the use of a higher rpm, such as the range of approximately 300 rpm to approximately 800 rpm, the range of approximately 400 rpm to approximately
 15 500 rpm, and specific examples, such as approximately 300 rpm, approximately 450 rpm, or approximately 600 rpm, in the continuous stirred-tank reactor lowers the Michael adduct impurity amount.

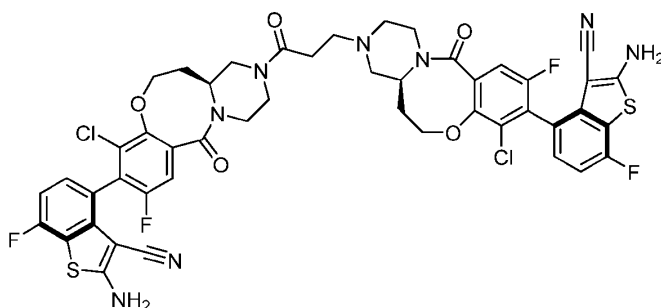
Alternative Synthesis 6 of Example 1: Flow Chemistry

4-[(13aS)-10-Chloro-8-fluoro-6-oxo-2-prop-2-enoyl-1,3,4,12,13,13a-
 20 hexahydropyrazino[2,1-d][1,5]benzoxazocin-9-yl]-2-amino-7-fluoro-benzothiophene-3-carbonitrile, M atropisomer



To a continuous stirred-tank reactor (110 mL, 10-11°C, 600 rpm) was added

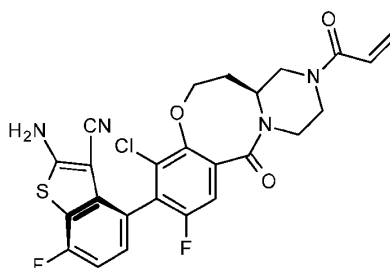
material from feed A [citric acid monohydrate (39.0 g), sodium citrate dihydrate (4.15 g), and water (to 0.5 L volume); heat to dissolve, pH ~ 3.0; flow rate 3.6 mL/min], feed B [acryloyl chloride (8.30 g, 1.25 eq) and 2-methyltetrahydrofuran (2 volumes); flow rate 0.8 mL/min], and feed C [4-[(13aS)-10-chloro-8-fluoro-6-oxo-2,3,4,12,13,13a-hexahydro-1H-pyrazino[2,1-d][1,5]benzoxazocin-9-yl]-2-amino-7-fluoro-benzothiophene-3-carbonitrile, M atropisomer (21.96 g, 0.046 mol), 2-methyltetrahydrofuran (18 volumes), and water (0.6 volumes); flow rate 6.6 mL/min]. The mixture in the reactor was pumped to a receiving bottle at 20 mL/min. Material from feed A, B, and C was dispensed for 30 minutes at the flow rates specified above before pausing the system and taking a reactor sample of the organic for HPLC analysis. HPLC analysis conditions ("HPLC analysis") comprise an CSH Phenyl Hexyl column (3.0 x 100 mm, 2.5 mm) eluted with 20% to 95% ACN in 0.1% aqueous TFA using an Agilent 1260 chromatograph with UV detector. HPLC analysis showed 0.06% 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,



“MA impurity” as shown in Table 2. This MA impurity is a Michael adduct wherein unreacted [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 reacts with the compound of Formula I and thereby forms a dimer. It is possible for trace amounts of the corresponding M,P atropisomer dimer may be present.

Alternative Synthesis 7 of Example 1: Semi-Batch Chemistry

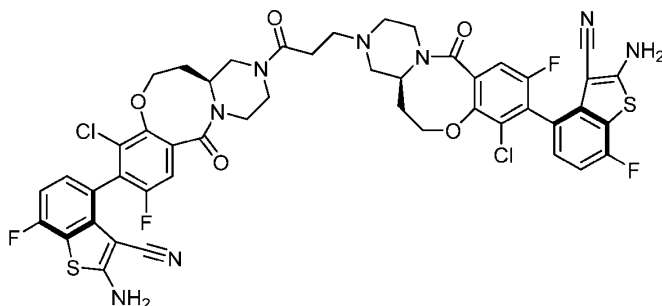
4-[(13aS)-10-Chloro-8-fluoro-6-oxo-2-prop-2-enoyl-1,3,4,12,13,13a-hexahydropyrazino[2,1-d][1,5]benzoxazocin-9-yl]-2-amino-7-fluoro-benzothiophene-3-carbonitrile, M atropisomer



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To a round bottom flask (100 mL, 1.6°C, 430 rpm) was added material from feed A [citric acid monohydrate (78.22 g), sodium citrate dihydrate (30.94 g), and water (to 1 L volume); heat to dissolve, pH ~ 3.0; 20 mL charged to flask] and feed C [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 (2.0010 g, 0.046 mol), 2-methyltetrahydrofuran (18 volumes), and water (0.6 volumes)]. 4.2 mL of feed B [acryloyl chloride (0.625 mL, 1.25 eq) and 2-methyltetrahydrofuran (2 volumes); flow rate 4.42 mL/min] was added to the round bottom flask using a syringe pump and stirred for 10 minutes before sampling. HPLC analysis conditions ("HPLC analysis") comprise an CSH Phenyl Hexyl column (3.0 x 100 mm, 2.5 mm) eluted with 20% to 95% ACN in 0.1% aqueous TFA using an Agilent 1260 chromatograph with UV detector. HPLC analysis showed 0.16% 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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“MA impurity” as shown in Table 2. This MA impurity is a Michael adduct wherein unreacted [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 reacts with the compound of Formula I and thereby forms a dimer. It is possible for trace amounts of the corresponding M,P atropisomer dimer may be present.

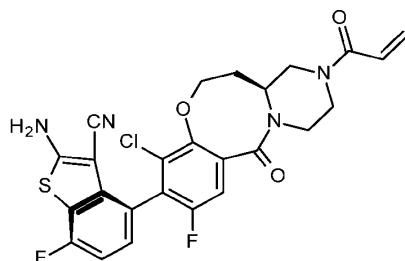
Table 2

Alternative Synthesis of Example 1	% MA impurity
Alternative Synthesis 1 of Example 1, for comparison	0.33
Alternative Synthesis 2 of Example 1, for comparison	1.63
Alternative Synthesis 3 of Example 1, for comparison	0.32
Alternative Synthesis 4 of Example 1	0.14
Alternative Synthesis 5 of Example 1	0.07
Alternative Synthesis 6 of Example 1	0.06
Alternative Synthesis 7 of Example 1	0.16

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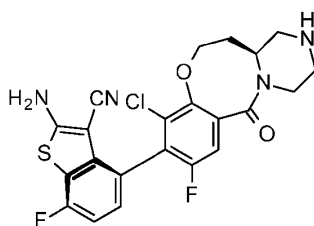
What is Claimed is:

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



or a pharmaceutically acceptable salt thereof, the method comprising:

- 5 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,



2. The method of claim 1, wherein the step of preparing is in a continuous stirred-tank reactor.
3. The method of claims 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 acryloyl chloride.
5. The method of any one of claims 1 to 4, 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.

6. The method of any one of claims 1 to 5, 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.

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

8. The method of any one of claims 1 to 7, wherein the citrate buffer is approximately 3.0 pH.

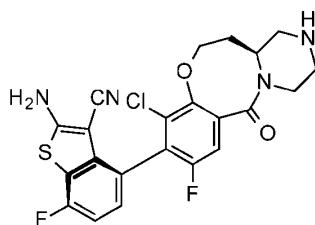
9. The method of any one of claims 2 to 8, wherein the continuous stirred-tank reactor is operated within the range of approximately 300 rpm to approximately 600 rpm.

10. The method of any one of claims 2 to 9, wherein the continuous stirred-tank reactor is operated at approximately 450 rpm.

11. The method of any one of claims 2 to 10, wherein the citrate buffer is added into the continuous stirred-tank reactor at a flow rate of approximately 3.6 mL/min.

12. The method of any one of claims 2 to 11, wherein the acryloyl group is added into the continuous stirred-tank reactor at a flow rate of approximately 0.8 mL/min.

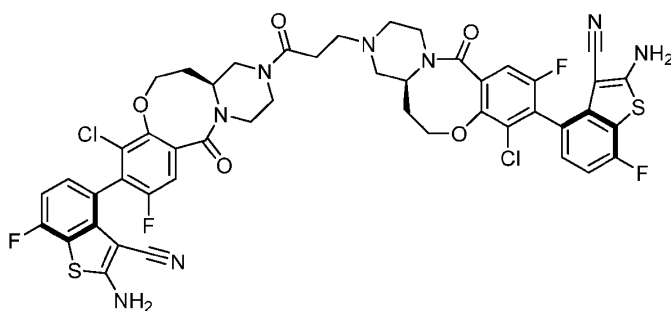
13. The method of any one of claims 2 to 12, wherein the 4-[(13aS)-10-chloro-8-fluoro-6-oxo-2,3,4,12,13,13a-hexahydro-1H-pyrazino[2,1-d][1,5]benzoxazocin-9-yl]-2-amino-7-fluoro-benzothiophene-3-carbonitrile, M atropisomer,



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

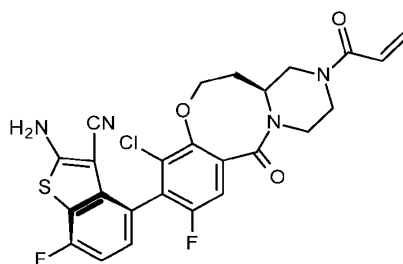
14. The method of any one of claims 1 to 13, wherein a Michael adduct impurity, 4-[(13aS)-2-[3-[(13aS)-9-(2-amino-3-cyano-7-fluoro-benzothiophen-4-yl)-10-chloro-8-fluoro-6-oxo-1,3,4,12,13,13a-hexahydropyrazino[2,1-d][1,5]benzoxazocin-2-yl]-3-oxo-propyl]-10-chloro-8-fluoro-6-oxo-1,3,4,12,13,13a-hexahydropyrazino[2,1-d][1,5]benzoxazocin-9-yl]-2-amino-7-fluoro-benz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



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

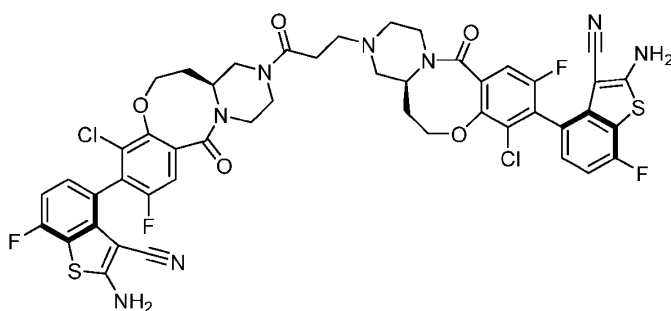
15. The method of claims 14 wherein the Michael adduct impurity is less than 0.15% as measured by HPLC Analysis.

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



- 15 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,

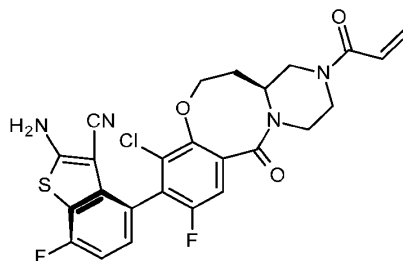
and a pharmaceutically acceptable carrier, diluent or excipient.

17. The pharmaceutical composition of claim 16, wherein the Michael adduct impurity is present in an amount of less than 0.15% as measured by HPLC Analysis.

- 10 18. A method of treating a patient for cancer wherein one or more cells express KRas G12C mutant protein, comprising administering to a patient in need thereof, a pharmaceutical composition according to claims 16 or 17, 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,
- 15 cholangiocarcinoma, and colorectal cancer.

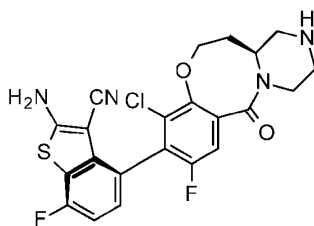
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19. A compound of the formula,



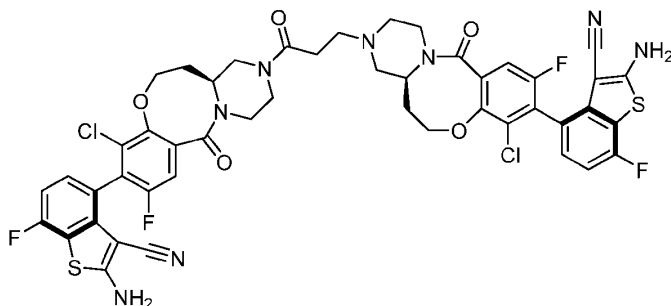
or a pharmaceutically acceptable salt thereof,

obtainable by combining citrate buffer, an acryloyl group, and 4-[(13aS)-10-chloro-
 5 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-
 10 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.

20. The compound of claim 19, wherein the step of combining is in a continuous stirred-tank reactor.

5 21. The compound of claims 19 or 20, wherein the acryloyl group is acryloyl chloride, acryloyl bromide, or acryloyl anhydride.

22. The compound of any one of claims 19 to 21, wherein the acryloyl group is acryloyl chloride.

10 23. The compound of any one of claims 19 to 22, 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.

15 24. The compound of any one of claims 19 to 23, 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.

25. The compound of any one of claims 19 to 24, wherein the citrate buffer is within the range of approximately 2.0 pH to approximately 4.0 pH.

20 26. The compound of any one of claims 19 to 25, wherein the citrate buffer is approximately 3.0 pH.

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27. The compound of any one of claims 19 to 26, wherein the Michael adduct impurity is present in an amount of less than 0.15% as measured by HPLC Analysis.

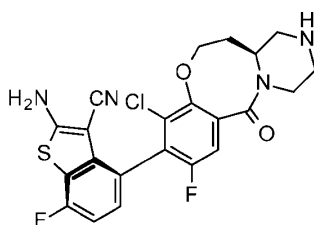
28. The compound of any one of claims 20 to 27, wherein the continuous stirred-tank reactor is operated within the range of approximately 300 rpm to approximately 5 600 rpm.

29. The compound of any one of claims 20 to 28, wherein the continuous stirred-tank reactor is operated at approximately 450 rpm.

30. The compound of any one of claims 20 to 29, wherein the citrate buffer is added into the continuous stirred-tank reactor at a flow rate of approximately 3.6 mL/min.

10 31. The compound of any one of claims 20 to 30, wherein the acryloyl group is added into the continuous stirred-tank reactor at a flow rate of approximately 0.8 mL/min.

32. The compound of any one of claims 20 to 31, 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.

33. A method of treating a patient for cancer wherein one or more cells express KRas G12C mutant protein, comprising administering to a patient in need thereof, an effective amount of a compound according to any one of claims 19 to 32, or a 20 pharmaceutically acceptable salt thereof, 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.

34. The method according to claims 18 or 33 wherein the cancer is non-small cell lung cancer.

5 35. The method according to claims 18 or 33, wherein the cancer is advanced non-small cell lung cancer.

36. The method according to claims 18 or 33, wherein the cancer is colorectal cancer.

10 37. The method according to claims 18 or 33, wherein the cancer is pancreatic cancer.

38. The method according to claims 18 or 33, wherein the patient has a cancer that was determined to have one or more cells expressing the KRas G12C mutant protein prior to administration of the compound or a pharmaceutically acceptable salt thereof.

15 39. A method of treating a patient with a cancer that has a KRAS G12C mutation comprising administering to the patient in need thereof a compound according to any one of claims 19 to 32, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition according to claims 16 or 17.

20 40. The method according to claim 39, wherein the patient is also administered an effective amount of 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.

25 41. The method according to claim 40, wherein the patient has not received prior therapy with a KRAS G12C inhibitor, or a pharmaceutically acceptable salt thereof.

42. The method according to claim 40, wherein the patient has not received prior therapy with an effective amount of 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.

43. The method according to claim 40, wherein the patient received prior therapy with an effective amount of 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.

44. The method according to claim 40, wherein the patient received prior therapy with a KRAS G12C inhibitor, or a pharmaceutically acceptable salt thereof.

45. The compound, or a pharmaceutically acceptable salt thereof, according to any one of claims 19 to 32, or a pharmaceutical composition according to claims 16 or 17, for use in therapy.

46. The compound, or a pharmaceutically acceptable salt thereof, according to any one of claims 19 to 32, or a pharmaceutical composition according to any one of claims 16 or 17, for use in the treatment of cancer.

47. The compound, or a pharmaceutically acceptable salt thereof, for use according to claim 46, 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.

48. The compound, or a pharmaceutically acceptable salt thereof, according to any one of claims 19 to 32, or a pharmaceutical composition according to any one of claims

16 or 17, 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, 5 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.