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(71) Applicant: **AMGEN INC.** [US/US]; One Amgen Center Drive, Thousand Oaks, California 91320-1799 (US).

(72) Inventors: **PARSONS, Andrew T.**; One Amgen Center Drive, Law Dept - Patent Operations, MS 28-5-A, Thousand Oaks, California 91320-1799 (US). **BEAVER, Matthew**; One Amgen Center Drive, Law Dept - Patent Operations, MS 28-5-A, Thousand Oaks, California 91320-1799 (US).

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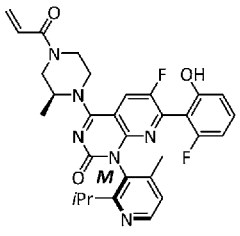
(54) Title: IMPROVED SYNTHESIS OF KRAS G12C INHIBITOR COMPOUND

(57) Abstract: The present disclosure relates to an improved, efficient, scalable process to prepare intermediate compounds, such as 2,2',2"-(1,3,5,2,4,6-trioxatriborinane-2,4,6-triyl)tris(3-fluorophenol), useful for the synthesis of compounds, such as Compound 9, for the treatment of KRAS G12C mutated cancers.



Compound 9

WO 2021/097212 A1

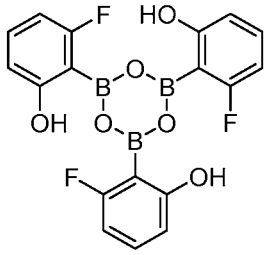
IMPROVED SYNTHESIS OF KRAS G12C INHIBITOR COMPOUND

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of U.S. Provisional Application No. 62/935,502, filed on November 14, 2019, which is incorporated by reference herein in its entirety.

FIELD

[0002] The present disclosure relates to an improved, efficient, scalable process to prepare intermediate compounds, such as compound of Formula 6A, having the structure,



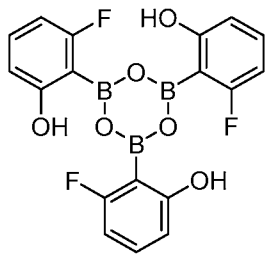
useful for the synthesis of compounds for the treatment of KRAS G12C mutated cancers.

BACKGROUND

[0003] KRAS gene mutations are common in pancreatic cancer, lung adenocarcinoma, colorectal cancer, gall bladder cancer, thyroid cancer, and bile duct cancer. KRAS mutations are also observed in about 25% of patients with NSCLC, and some studies have indicated that KRAS mutations are a negative prognostic factor in patients with NSCLC. Recently, V-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog (KRAS) mutations have been found to confer resistance to epidermal growth factor receptor (EGFR) targeted therapies in colorectal cancer; accordingly, the mutational status of KRAS can provide important information prior to the prescription of TKI therapy. Taken together, there is a need for new medical treatments for patients with pancreatic cancer, lung adenocarcinoma, or colorectal cancer, especially those who have been diagnosed to have such cancers characterized by a KRAS mutation, and including those who have progressed after chemotherapy.

SUMMARY

[0004] The present disclosure relates to improved preparation of a compound having the following chemical structure:



DETAILED DESCRIPTION

Definitions

Abbreviations: The following abbreviations may be used herein:

ACN	Acetonitrile
AcOH	acetic acid
aq or aq.	Aqueous
BOC or Boc	tert-butyloxycarbonyl
BuOH	n-butanol
BuOAc	Butanol acetate
cpme	cyclopentyl methyl ether
$CHCl_3$	Trichloromethane
DCE	1,2-dichloroethane
DABCO	1,4-diazabicyclo[2.2.2]octane
DCM	Dichloromethane
DMA	N,N-Dimethylacetamide
DMAP	4-dimethylaminopyridine
DME	1,2-dimethoxyethane
DMF	N,N-dimethylformamide
DMSO	dimethyl sulfoxide
Dppf, DPPF or dppf	1,1'-bis(diphenylphosphino)ferrocene
eq or eq. or equiv.	Equivalent
ESI or ES	electrospray ionization
Et	Ethyl
Et_2O	diethyl ether
EtOAc	ethyl acetate

EtOH	ethanol
g	Grams
h	Hour
H_20	water
HPLC	high pressure liquid chromatography
iPr	Isopropyl
IPA	Isopropyl alcohol
IPAc	Isopropyl acetate
iPr_2NEt or DIPEA	N-ethyl diisopropylamine (Hünig's base)
KHMDS	potassium hexamethyldisilazide
KOAc	potassium acetate
LDA	Lithium diisopropylamide
Lawesson's reagent	2,4-bis(4-methoxyphenyl)-2,4-dithioxo-1,3,2,4-dithiadiphosphetane, 2,4-Bis-(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane 2,4-disulfide
LC MS, LCMS, LC-MS or LC/MS	liquid chromatography mass spectroscopy
LG	Leaving group (e.g., halogen, mesylate, triflate)
LHMDS or LiHMDS	lithium hexamethyldisilazide
m/z	mass divided by charge
Me	Methyl
MeCN	Acetonitrile
MeOH	Methanol
Met	Metal species for cross-coupling (e.g., MgX, ZnX, SnR_3, SiR_3, $B(OR)_2$)
2-MeTHF	2-Methyltetrahydrofuran
mg	Milligrams
min	Minutes
MIBK	4-Methyl-2-pentanone
mL	Milliliters
MS	mass spectra
MTBE	Methyl tert-butyl ether

n-BuLi	n-butyl Lithium
NaHMDS	sodium hexamethyldisilazide
NBS	N-bromosuccinimide
NCS	N-chlorosuccinimide
NMR	nuclear magnetic resonance
$Pd_2(dba)_3$	tris(dibenzylideneacetone)dipalladium(0)
$Pd(dppf)Cl_2 \cdot DCM$	[1,1′-Bis(diphenylphosphino)ferrocene]dichloropalladium(II), complex with dichloromethane
$Pd(PPh_3)_4$	Tetrakis(triphenylphosphine)palladium(0)
Ph	Phenyl
PR or PG or Prot. group	protecting group
rbf	round-bottom flask
RP-HPLC	reverse phase high pressure liquid chromatography
RT or rt	room temperature
sat. or satd.	saturated
SFC	supercritical fluid chromatography
SPhos Pd G3 or SPhos G3	(2-Dicyclohexylphosphino-2′,6′-dimethoxybiphenyl) [2-(2′-amino-1,1′-biphenyl)]palladium(II) methanesulfonate
TBAF	tetra-*n*-butylammonium fluoride
TBTU	*N*,*N*,*N*′,*N*′-Tetramethyl-*O*-(benzotriazol-1-yl)uronium tetrafluoroborate
t-BuOH	*tert*-butanol
TEA or Et_3N	Trimethylamine
TFA	trifluoroacetic acid
THF	Tetrahydrofuran
UV	Ultraviolet
XRPD	X-Ray Powder Diffraction

[0005] The use of the terms “a,” “an,” “the,” and similar referents in the context of describing the invention (especially in the context of the claims) are to be construed to cover both the singular and the plural, unless otherwise indicated. Recitation of ranges of values

herein merely are intended to serve as a shorthand method of referring individually to each separate value falling within the range, unless otherwise indicated herein, and each separate value is incorporated into the specification as if it were individually recited herein. The use of any and all examples, or exemplary language (e.g., "such as") provided herein, is intended to better illustrate the invention and is not a limitation on the scope of the invention unless otherwise claimed. No language in the specification should be construed as indicating any non-claimed element as essential to the practice of the invention.

[0006] As used herein, the term "alkyl" refers to straight chained and branched C1-C_8 hydrocarbon groups, including but not limited to, methyl, ethyl, n-propyl, i-propyl, n-butyl, sec-butyl, t-butyl, n-pentyl, 2-methylbutyl, 3-methylbutyl, 2,2-dimethylpropyl, n-hexyl, 2-methylpentyl, 3-methylpentyl, 4-methylpentyl, 2,2-dimethylbutyl, 2,3-dimethylbutyl, 3,3-dimethylbutyl, and 2-ethybutyl. The term C_{m-n} means the alkyl group has "m" to "n" carbon atoms. The term "alkylene" refers to an alkyl group having a substituent. An alkyl (e.g., methyl), or alkylene (e.g., -CH_2-), group can be substituted with one or more, and typically one to three, of independently selected, for example, halo, trifluoromethyl, trifluoromethoxy, hydroxy, alkoxy, nitro, cyano, alkylamino, C_1-$_8$alkyl, C_2-$_8$alkenyl, C_2-$_8$alkynyl, -NC, amino, -CO_2H, -CO_2C_1-C_8alkyl, -$OCOC_1$-C_8alkyl, C_3-C_{10} cycloalkyl, C_3-C_{10} heterocycloalkyl, C_5-C_{10}aryl, and C_5-C_{10} heteroaryl. The term "haloalkyl" specifically refers to an alkyl group wherein at least one, e.g., one to six, or all of the hydrogens of the alkyl group are substituted with halo atoms.

[0007] The terms "alkenyl" and "alkynyl" indicate an alkyl group that further includes a double bond or a triple bond, respectively.

[0008] As used herein, the term "halo" refers to fluoro, chloro, bromo, and iodo. The term "alkoxy" is defined as -OR, wherein R is alkyl.

[0009] As used herein, the term "amino" or "amine" interchangeably refers to a -NR_2 group, wherein each R is, e.g., H or a substituent. In some embodiments, the amino group is further substituted to form an ammonium ion, e.g., NR_3^+. Ammonium moieties are specifically included in the definition of "amino" or "amine." Substituents can be, for example, an alkyl, alkoxy, cycloalkyl, heterocycloalkyl, amide, or carboxylate. An R group may be further substituted, for example, with one or more, e.g., one to four, groups selected from halo, cyano, alkenyl, alkynyl, alkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, urea, carbonyl, carboxylate, amine, and amide. An "amide" or "amido" group interchangeably

refers to a group similar to an amine or amino group but further including a C(O), e.g., -C(O)NR_2.

[0010] As used herein, the term "aryl" refers to a C_{6-14} monocyclic or polycyclic aromatic group, preferably a C_{6-10} monocyclic or bicyclic aromatic group, or C_{10-14} polycyclic aromatic group. Examples of aryl groups include, but are not limited to, phenyl, naphthyl, fluorenyl, azulenyl, anthryl, phenanthryl, pyrenyl, biphenyl, and terphenyl. Aryl also refers to C_{10-14} bicyclic and tricyclic carbon rings, where one ring is aromatic and the others are saturated, partially unsaturated, or aromatic, for example, dihydronaphthyl, indenyl, indanyl, or tetrahydronaphthyl (tetralinyl). Unless otherwise indicated, an aryl group can be unsubstituted or substituted with one or more, and in particular one to four, groups independently selected from, for example, halo, C_{1-8}alkyl, C_{2-8}alkenyl, C_{2-8}alkynyl, -CF_3, -OCF_3, -NO_2, -CN, -NC, -OH, alkoxy, amino, -CO_2H, -CO_2C_1-C_8alkyl, -$OCOC_1$-C_8alkyl, C_3-C_{10} cycloalkyl, C_3-C_{10} heterocycloalkyl, C_5-C_{10}aryl, and C_5-C_{10} heteroaryl.

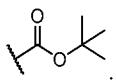
[0011] As used herein, the term "cycloalkyl" refers to a monocyclic or polycyclic non-aromatic carbocyclic ring, where the polycyclic ring can be fused, bridged, or spiro. The carbocyclic ring can have 3 to 10 carbon ring atoms. Contemplated carbocyclic rings include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, and cyclononyl.

[0012] As used herein, the term "heterocycloalkyl" means a monocyclic or polycyclic (e.g., bicyclic), saturated or partially unsaturated, ring system containing 3 or more (e.g., 3 to 12, 4 to 10, 4 to 8, or 5 to 7) total atoms, of which one to five (e.g., 1, 2, 3, 4, or 5) of the atoms are independently selected from nitrogen, oxygen, and sulfur. Nonlimiting examples of heterocycloalkyl groups include azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, dihydropyrrolyl, morpholinyl, thiomorpholinyl, dihydropyridinyl, oxacycloheptyl, dioxacycloheptyl, thiacycloheptyl, and diazacycloheptyl.

[0013] Unless otherwise indicated, a cycloalkyl or heterocycloalkyl group can be unsubstituted or substituted with one or more, and in particular one to four, groups. Some contemplated substituents include halo, C_{1-8}alkyl, C_{2-8}alkenyl, C_{2-8}alkynyl, -OCF_3, -NO_2, -CN, -NC, -OH, alkoxy, amino, -CO_2H, -CO_2C_1-C_8alkyl, -$OCOC_1$-C_8alkyl, C_3-C_{10} cycloalkyl, C_3-C_{10} heterocycloalkyl, C_5-C_{10}aryl, and C_5-C_{10} heteroaryl.

[0014] As used herein, the term "heteroaryl" refers to a monocyclic or polycyclic ring system (for example, bicyclic) containing one to three aromatic rings and containing one to

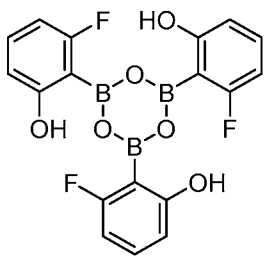
four (e.g., 1, 2, 3, or 4) heteroatoms selected from nitrogen, oxygen, and sulfur in an aromatic ring. In certain embodiments, the heteroaryl group has from 5 to 20, from 5 to 15, from 5 to 10 ring, or from 5 to 7 atoms. Heteroaryl also refers to C_{10-14} bicyclic and tricyclic rings, where one ring is aromatic and the others are saturated, partially unsaturated, or aromatic. Examples of heteroaryl groups include, but are not limited to, furanyl, imidazolyl, isothiazolyl, isoxazolyl, oxadiazolyl, oxazolyl, pyrazinyl, pyrazolyl, pyridazinyl, pyridyl, pyrimidinyl, pyrrolyl, thiadiazolyl, thiazolyl, thienyl, tetrazolyl, triazinyl, triazolyl, benzofuranyl, benzimidazolyl, benzoisoxazolyl, benzopyranyl, benzothiadiazolyl, benzothiazolyl, benzothienyl, benzothiophenyl, benzotriazolyl, benzoxazolyl, furopyridyl, imidazopyridinyl, imidazothiazolyl, indolizinyl, indolyl, indazolyl, isobenzofuranyl, isobenzothienyl, isoindolyl, isoquinolinyl, isothiazolyl, naphthyridinyl, oxazolopyridinyl, phthalazinyl, pteridinyl, purinyl, pyridopyridyl, pyrrolopyridyl, quinolinyl, quinoxalinyl, quiazolinyl, thiadiazolopyrimidyl, and thienopyridyl. Unless otherwise indicated, a heteroaryl group can be unsubstituted or substituted with one or more, and in particular one to four or one or two, substituents. Contemplated substituents include halo, C_{1-8}alkyl, C_{2-8}alkenyl, C_{2-8}alkynyl, $-OCF_3$, $-NO_2$, -CN, -NC, -OH, alkoxy, amino, $-CO_2H$, $-CO_2C_1$-C_8alkyl, $-OCOC_1$-C_8alkyl, C_3-C_{10} cycloalkyl, C_3-C_{10} heterocycloalkyl, C_5-C_{10}aryl, and C_5-C_{10} heteroaryl.

[0015] As used herein, the term Boc refers to the structure  .

EMBODIMENTS

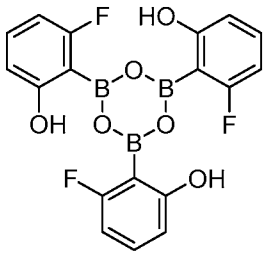
Embodiment 1

[0016] In one embodiment of the disclosure, the present disclosure comprises a compound of Formula 6A



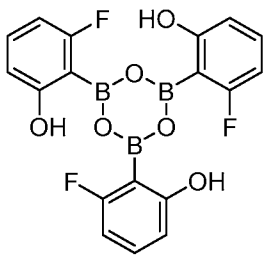
Embodiment 2

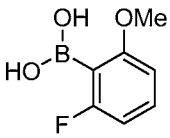
[0017] In another embodiment of the present disclosure, the present disclosure comprises a composition, the composition comprising a compound of Formula 6A:



Embodiment 3

[0018] In another embodiment of the present disclosure, the present disclosure comprises a method of making a compound of formula 6A:



the method comprising reacting a mixture comprising a compound having the structure:  with an acid with at least one solvent.

Embodiment 4

[0019] In another embodiment of the present disclosure, the present disclosure comprises the method of embodiment 3, wherein the acid is BBr_3.

Embodiment 5

[0020] In another embodiment of the present disclosure, the present disclosure comprises the method of embodiment 3, wherein the at least one solvent is dichloromethane.

Embodiment 6

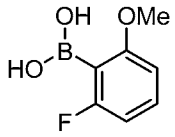
[0021] In another embodiment of the present disclosure, the present disclosure comprises the method of embodiment 3, wherein the at least one solvent is heptane.

Embodiment 7

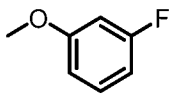
[0022] In another embodiment of the present disclosure, the present disclosure comprises the method of embodiment 3, wherein the mixture is cooled to approximately -20 °C.

Embodiment 8

[0023] In another embodiment of the present disclosure, the present disclosure comprises the method of embodiment 3, wherein the method of making a compound of the structure:



comprises mixing a compound having the structure:



with a reagent, a first base, a secondary amine base, a catalyst, and an acid.

Embodiment 9

[0024] In another embodiment of the present disclosure, the present disclosure comprises the method of embodiment 8, wherein the first base in n-Butyl lithium.

Embodiment 10

[0025] In another embodiment of the present disclosure, the present disclosure comprises the method of embodiment 8, wherein the secondary amine base is diisopropylamine.

Embodiment 11

[0026] In another embodiment of the present disclosure, the present disclosure comprises the method of embodiment 8, wherein the catalyst is triethylamine hydrochloride.

Embodiment 12

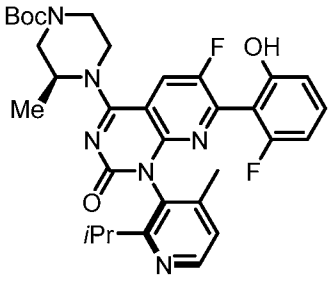
[0027] In another embodiment of the present disclosure, the present disclosure comprises the method of embodiment 8, wherein the reagent is triethyl borate.

Embodiment 13

[0028] In another embodiment of the present disclosure, the present disclosure comprises the method of embodiment 8, wherein the acid is HCl.

Embodiment 14

[0029] In another embodiment of the present disclosure, the present disclosure comprises the method of embodiment 3, wherein the compound of formula 6A is used to generate a compound having the Formula 7:



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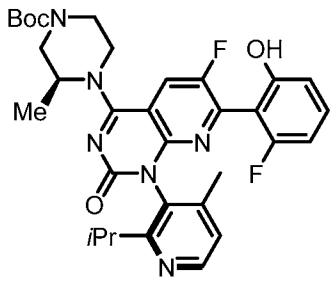
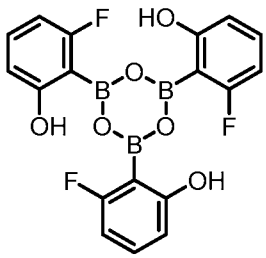
Embodiment 15

[0030] In another embodiment of the present disclosure, the present disclosure comprises a method of making a compound of Formula 7:



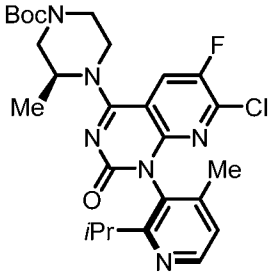
,

comprising the steps of reacting a compound of Formula 6A:



,

with a compound of Formula 6:

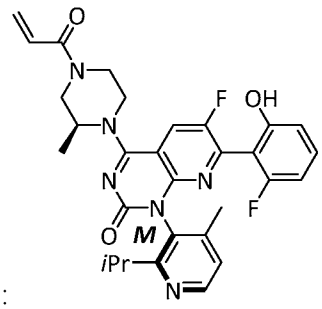


,

in the presence of $Pd(dpePhos)Cl_2$, and KOAc.

Embodiment 16

[0031] In another embodiment of the present disclosure, the present disclosure comprises the method of embodiment 3, wherein the compound of formula 6A is used to generate a compound having the Formula 9:



9.

Embodiment 17

[0032] In another embodiment of the present disclosure, the present disclosure comprises the method of embodiment 16, wherein the method further comprises mixing the compound of Formula 9 with at least one pharmaceutically acceptable excipient to form a pharmaceutical composition.

Compounds of the disclosure

[0033] Provided herein are KRAS inhibitors having structures discussed in more detail below.

[0034] The compounds disclosed herein include all pharmaceutically acceptable isotopically-labeled compounds wherein one or more atoms of the compounds disclosed herein are replaced by atoms having the same atomic number, but an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes that can be incorporated into the disclosed compounds include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, fluorine, chlorine, and iodine, such as ^{2}H, ^{3}H, ^{11}C, ^{13}C, ^{14}C, ^{13}N, ^{15}N, ^{15}O, ^{17}O, ^{18}O, ^{31}P, ^{32}P, ^{35}S, ^{18}F, ^{36}Cl, ^{123}I, and ^{125}I, respectively. These radiolabeled compounds could be useful to help determine or measure the effectiveness of the compounds, by characterizing, for example, the site or mode of action, or binding affinity to pharmacologically important site of action. Certain isotopically-labeled compounds of the disclosure, for example, those incorporating a radioactive isotope, are useful in drug and/or substrate tissue distribution studies. The radioactive isotopes tritium, i.e. ^{3}H, and carbon-14,

i.e. ^{14}C, are particularly useful for this purpose in view of their ease of incorporation and ready means of detection.

[0035] Substitution with heavier isotopes such as deuterium, i.e. ^{2}H, may afford certain therapeutic advantages resulting from greater metabolic stability, for example, increased in vivo half-life or reduced dosage requirements, and hence are preferred in some circumstances.

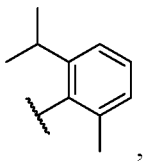
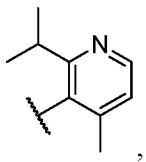
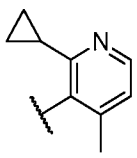
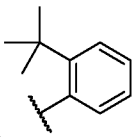
[0036] Substitution with positron emitting isotopes, such as ^{11}C, ^{18}F, ^{15}O and ^{13}N, can be useful in Positron Emission Topography (PET) studies for examining substrate receptor occupancy. Isotopically-labeled compounds of structure (I) can generally be prepared by conventional techniques known to those skilled in the art or by processes analogous to those described in the Preparations and Examples as set out below using an appropriate isotopically-labeled reagent in place of the non-labeled reagent previously employed.

[0037] Isotopically-labeled compounds as disclosed herein can generally be prepared by conventional techniques known to those skilled in the art or by processes analogous to those described in the accompanying examples and schemes using an appropriate isotopically-labeled reagent in place of the non-labeled reagent previously employed.

[0038] Certain of the compounds as disclosed herein may exist as stereoisomers (i.e., isomers that differ only in the spatial arrangement of atoms) including optical isomers and conformational isomers (or conformers). The compounds disclosed herein include all stereoisomers, both as pure individual stereoisomer preparations and enriched preparations of each, and both the racemic mixtures of such stereoisomers as well as the individual diastereomers and enantiomers that may be separated according to methods that are known to those skilled in the art. Additionally, the compounds disclosed herein include all tautomeric forms of the compounds.

[0039] Certain of the compounds disclosed herein may exist as atropisomers, which are conformational stereoisomers that occur when rotation about a single bond in the molecule is prevented, or greatly slowed, as a result of steric interactions with other parts of the molecule. The compounds disclosed herein include all atropisomers, both as pure individual atropisomer preparations, enriched preparations of each, or a non-specific mixture of each. Where the rotational barrier about the single bond is high enough, and interconversion between conformations is slow enough, separation and isolation of the isomeric species may

be permitted. For example, groups such as, but not limited to, the following groups

 ,  ,  and  may exhibit restricted rotation.

[0040] The term "monohydrate" means a salt of Compound 9 having about one associated water molecule. Those skilled in the art appreciate that the exact number of the associated water molecules may vary slightly at any time with variable temperature, pressure, and other environmental influence. All slight variations of the number of the associated water molecules are contemplated to be within the scope of the present disclosure.

[0041] The term "dihydrate" means a salt of Compound 9 having about two associated water molecules. Those skilled in the art appreciate that the exact number of the associated water molecules may vary slightly at any time with variable temperature, pressure, and other environmental influence. All slight variations of the number of the associated water molecules are contemplated to be within the scope of the present invention.

[0042] The term "co-crystal" means a crystalline material comprising two or more compounds at ambient temperature (20 °C to 25 °C., preferably 20 °C.), of which at least two are held together by weak interaction, wherein at least one of the compounds is a co-crystal former and the other is Compound 5. Weak interaction is being defined as an interaction which is neither ionic nor covalent and includes for example: hydrogen bonds, van der Waals forces, and π-π interactions.

[0043] The term "amorphous form" or "amorphous" means a material that lacks long range order and as such does not show distinct X-ray diffraction peaks, i.e. a Bragg diffraction peak. The XRPD pattern of an amorphous material is characterized by one or more amorphous halos.

[0044] The term "amorphous halo" is an approximately bell-shaped maximum in the X-ray powder pattern of an amorphous substance.

[0045] The term "substantially pure" refers to a solid form of Compound 9 having purity greater than about 95%, specifically greater than about 99.5%, more specifically greater than about 99.8% and still more specifically greater than about 99.9%.

[0046] The term "patient" means animals, such as dogs, cats, cows, horses, sheep and humans. Particular patients are mammals. The term patient includes males and females.

[0047] The terms "treating", "treat" or "treatment" and the like include preventative (e.g., prophylactic) and palliative treatment.

[0048] The term "excipient" means any pharmaceutically acceptable additive, carrier, diluent, adjuvant, or other ingredient, other than the active pharmaceutical ingredient (API), which is typically included for formulation and/or administration to a patient.

Pharmaceutical compositions, dosing, and routes of administration

[0049] Also provided herein are pharmaceutical compositions that include a compound as disclosed herein, together with a pharmaceutically acceptable excipient, such as, for example, a diluent or carrier. Compounds and pharmaceutical compositions suitable for use in the present invention include those wherein the compound can be administered in an effective amount to achieve its intended purpose. Administration of the compound described in more detail below.

[0050] Suitable pharmaceutical formulations can be determined by the skilled artisan depending on the route of administration and the desired dosage. *See, e.g.*, Remington's Pharmaceutical Sciences, 1435-712 (18th ed., Mack Publishing Co, Easton, Pennsylvania, 1990). Formulations may influence the physical state, stability, rate of in vivo release and rate of in vivo clearance of the administered agents. Depending on the route of administration, a suitable dose may be calculated according to body weight, body surface areas or organ size. Further refinement of the calculations necessary to determine the appropriate treatment dose is routinely made by those of ordinary skill in the art without undue experimentation, especially in light of the dosage information and assays disclosed herein as well as the pharmacokinetic data obtainable through animal or human clinical trials.

[0051] The phrases "pharmaceutically acceptable" or "pharmacologically acceptable" refer to molecular entities and compositions that do not produce adverse, allergic, or other untoward reactions when administered to an animal or a human. As used herein, "pharmaceutically acceptable" includes any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents and the like. The use of such excipients for pharmaceutically active substances is well known in the art. Except insofar as any conventional media or agent is incompatible with the therapeutic compositions, its use in therapeutic compositions is contemplated. Supplementary active ingredients also can be incorporated into the compositions. In exemplary embodiments, the formulation may comprise corn syrup solids, high-oleic safflower oil, coconut oil, soy oil, L-

leucine, calcium phosphate tribasic, L-tyrosine, L-proline, L-lysine acetate, DATEM (an emulsifier), L-glutamine, L-valine, potassium phosphate dibasic, L-isoleucine, L-arginine, L-alanine, glycine, L-asparagine monohydrate, L-serine, potassium citrate, L-threonine, sodium citrate, magnesium chloride, L-histidine, L-methionine, ascorbic acid, calcium carbonate, L-glutamic acid, L-cystine dihydrochloride, L-tryptophan, L-aspartic acid, choline chloride, taurine, m-inositol, ferrous sulfate, ascorbyl palmitate, zinc sulfate, L-carnitine, alpha-tocopheryl acetate, sodium chloride, niacinamide, mixed tocopherols, calcium pantothenate, cupric sulfate, thiamine chloride hydrochloride, vitamin A palmitate, manganese sulfate, riboflavin, pyridoxine hydrochloride, folic acid, beta-carotene, potassium iodide, phylloquinone, biotin, sodium selenate, chromium chloride, sodium molybdate, vitamin D3 and cyanocobalamin.

[0052] The compound can be present in a pharmaceutical composition as a pharmaceutically acceptable salt. As used herein, "pharmaceutically acceptable salts" include, for example base addition salts and acid addition salts.

[0053] Pharmaceutically acceptable base addition salts may be formed with metals or amines, such as alkali and alkaline earth metals or organic amines. Pharmaceutically acceptable salts of compounds may also be prepared with a pharmaceutically acceptable cation. Suitable pharmaceutically acceptable cations are well known to those skilled in the art and include alkaline, alkaline earth, ammonium and quaternary ammonium cations. Carbonates or hydrogen carbonates are also possible. Examples of metals used as cations are sodium, potassium, magnesium, ammonium, calcium, or ferric, and the like. Examples of suitable amines include isopropylamine, trimethylamine, histidine, N,N'-dibenzylethylenediamine, chloroprocaine, choline, diethanolamine, dicyclohexylamine, ethylenediamine, N-methylglucamine, and procaine.

[0054] Pharmaceutically acceptable acid addition salts include inorganic or organic acid salts. Examples of suitable acid salts include the hydrochlorides, formates, acetates, citrates, salicylates, nitrates, phosphates. Other suitable pharmaceutically acceptable salts are well known to those skilled in the art and include, for example, formic, acetic, citric, oxalic, tartaric, or mandelic acids, hydrochloric acid, hydrobromic acid, sulfuric acid or phosphoric acid; with organic carboxylic, sulfonic, sulfo or phospho acids or N-substituted sulfamic acids, for example acetic acid, trifluoroacetic acid (TFA), propionic acid, glycolic acid, succinic acid, maleic acid, hydroxymaleic acid, methylmaleic acid, fumaric acid, malic acid, tartaric acid, lactic acid, oxalic acid, gluconic acid, glucaric acid, glucuronic acid, citric acid,

benzoic acid, cinnamic acid, mandelic acid, salicylic acid, 4-aminosalicylic acid, 2-phenoxybenzoic acid, 2-acetoxybenzoic acid, embonic acid, nicotinic acid or isonicotinic acid; and with amino acids, such as the 20 alpha amino acids involved in the synthesis of proteins in nature, for example glutamic acid or aspartic acid, and also with phenylacetic acid, methanesulfonic acid, ethanesulfonic acid, 2-hydroxyethanesulfonic acid, ethane 1,2-disulfonic acid, benzenesulfonic acid, 4-methylbenzenesulfonic acid, naphthalene 2-sulfonic acid, naphthalene 1,5-disulfonic acid, 2- or 3-phosphoglycerate, glucose 6-phosphate, N-cyclohexylsulfamic acid (with the formation of cyclamates), or with other acid organic compounds, such as ascorbic acid.

[0055] Pharmaceutical compositions containing the compounds disclosed herein can be manufactured in a conventional manner, e.g., by conventional mixing, dissolving, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping, or lyophilizing processes. Proper formulation is dependent upon the route of administration chosen.

[0056] For oral administration, suitable compositions can be formulated readily by combining a compound disclosed herein with pharmaceutically acceptable excipients such as carriers well known in the art. Such excipients and carriers enable the present compounds to be formulated as tablets, pills, dragees, capsules, liquids, gels, syrups, slurries, suspensions and the like, for oral ingestion by a patient to be treated. Pharmaceutical preparations for oral use can be obtained by adding a compound as disclosed herein with a solid excipient, optionally grinding a resulting mixture, and processing the mixture of granules, after adding suitable auxiliaries, if desired, to obtain tablets or dragee cores. Suitable excipients include, for example, fillers and cellulose preparations. If desired, disintegrating agents can be added. Pharmaceutically acceptable ingredients are well known for the various types of formulation and may be for example binders (e.g., natural or synthetic polymers), lubricants, surfactants, sweetening and flavoring agents, coating materials, preservatives, dyes, thickeners, adjuvants, antimicrobial agents, antioxidants and carriers for the various formulation types.

[0057] When a therapeutically effective amount of a compound disclosed herein is administered orally, the composition typically is in the form of a solid (e.g., tablet, capsule, pill, powder, or troche) or a liquid formulation (e.g., aqueous suspension, solution, elixir, or syrup).

[0058] When administered in tablet form, the composition can additionally contain a functional solid and/or solid carrier, such as a gelatin or an adjuvant. The tablet, capsule, and powder can contain about 1 to about 95% compound, and preferably from about 15 to about 90% compound.

[0059] When administered in liquid or suspension form, a functional liquid and/or a liquid carrier such as water, petroleum, or oils of animal or plant origin can be added. The liquid form of the composition can further contain physiological saline solution, sugar alcohol solutions, dextrose or other saccharide solutions, or glycols. When administered in liquid or suspension form, the composition can contain about 0.5 to about 90% by weight of a compound disclosed herein, and preferably about 1 to about 50% of a compound disclosed herein. In one embodiment contemplated, the liquid carrier is non-aqueous or substantially non-aqueous. For administration in liquid form, the composition may be supplied as a rapidly-dissolving solid formulation for dissolution or suspension immediately prior to administration.

[0060] When a therapeutically effective amount of a compound disclosed herein is administered by intravenous, cutaneous, or subcutaneous injection, the composition is in the form of a pyrogen-free, parenterally acceptable aqueous solution. The preparation of such parenterally acceptable solutions, having due regard to pH, isotonicity, stability, and the like, is within the skill in the art. A preferred composition for intravenous, cutaneous, or subcutaneous injection typically contains, in addition to a compound disclosed herein, an isotonic vehicle. Such compositions may be prepared for administration as solutions of free base or pharmacologically acceptable salts in water suitably mixed with a surfactant, such as hydroxypropylcellulose. Dispersions also can be prepared in glycerol, liquid polyethylene glycols, and mixtures thereof and in oils. Under ordinary conditions of storage and use, these preparations can optionally contain a preservative to prevent the growth of microorganisms.

[0061] Injectable compositions can include sterile aqueous solutions, suspensions, or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions, suspensions, or dispersions. In all embodiments the form must be sterile and must be fluid to the extent that easy syringability exists. It must be stable under the conditions of manufacture and storage and must resist the contaminating action of microorganisms, such as bacteria and fungi, by optional inclusion of a preservative. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (e.g., glycerol, propylene glycol, and liquid polyethylene glycol, and the like), suitable mixtures thereof, and vegetable

oils. In one embodiment contemplated, the carrier is non-aqueous or substantially non-aqueous. The proper fluidity can be maintained, for example, by the use of a coating, such as lecithin, by the maintenance of the required particle size of the compound in the embodiment of dispersion and by the use of surfactants. The prevention of the action of microorganisms can be brought about by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, thimerosal, and the like. In many embodiments, it will be preferable to include isotonic agents, for example, sugars or sodium chloride. Prolonged absorption of the injectable compositions can be brought about by the use in the compositions of agents delaying absorption, for example, aluminum monostearate and gelatin.

[0062] Sterile injectable solutions are prepared by incorporating the active compounds in the required amount in the appropriate solvent with various of the other ingredients enumerated above, as required, followed by filtered sterilization. Generally, dispersions are prepared by incorporating the various sterilized active ingredients into a sterile vehicle which contains the basic dispersion medium and the required other ingredients from those enumerated above. In the embodiment of sterile powders for the preparation of sterile injectable solutions, the preferred methods of preparation are vacuum-drying and freeze-drying techniques which yield a powder of the active ingredient plus any additional desired ingredient from a previously sterile-filtered solution thereof.

[0063] Slow release or sustained release formulations may also be prepared in order to achieve a controlled release of the active compound in contact with the body fluids in the GI tract, and to provide a substantially constant and effective level of the active compound in the blood plasma. For example, release can be controlled by one or more of dissolution, diffusion, and ion-exchange. In addition, the slow release approach may enhance absorption via saturable or limiting pathways within the GI tract. For example, the compound may be embedded for this purpose in a polymer matrix of a biological degradable polymer, a water-soluble polymer or a mixture of both, and optionally suitable surfactants. Embedding can mean in this context the incorporation of micro-particles in a matrix of polymers. Controlled release formulations are also obtained through encapsulation of dispersed micro-particles or emulsified micro-droplets via known dispersion or emulsion coating technologies.

[0064] For administration by inhalation, compounds of the present disclosure are conveniently delivered in the form of an aerosol spray presentation from pressurized packs or a nebulizer, with the use of a suitable propellant. In the embodiment of a pressurized aerosol, the dosage unit can be determined by providing a valve to deliver a metered amount.

Capsules and cartridges of, e.g., gelatin, for use in an inhaler or insufflator can be formulated containing a powder mix of the compound and a suitable powder base such as lactose or starch.

[0065] The compounds disclosed herein can be formulated for parenteral administration by injection (e.g., by bolus injection or continuous infusion). Formulations for injection can be presented in unit dosage form (e.g., in ampules or in multidose containers), with an added preservative. The compositions can take such forms as suspensions, solutions, or emulsions in oily or aqueous vehicles, and can contain formulatory agents such as suspending, stabilizing, and/or dispersing agents.

[0066] Pharmaceutical formulations for parenteral administration include aqueous solutions of the compounds in water-soluble form. Additionally, suspensions of the compounds can be prepared as appropriate oily injection suspensions. Suitable lipophilic solvents or vehicles include fatty oils or synthetic fatty acid esters. Aqueous injection suspensions can contain substances which increase the viscosity of the suspension. Optionally, the suspension also can contain suitable stabilizers or agents that increase the solubility of the compounds and allow for the preparation of highly concentrated solutions. Alternatively, a present composition can be in powder form for constitution with a suitable vehicle (e.g., sterile pyrogen-free water) before use.

[0067] Compounds disclosed herein also can be formulated in rectal compositions, such as suppositories or retention enemas (e.g., containing conventional suppository bases). In addition to the formulations described previously, the compounds also can be formulated as a depot preparation. Such long-acting formulations can be administered by implantation (e.g., subcutaneously or intramuscularly) or by intramuscular injection. Thus, for example, the compounds can be formulated with suitable polymeric or hydrophobic materials (for example, as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt.

[0068] In particular, a compound disclosed herein can be administered orally, buccally, or sublingually in the form of tablets containing excipients, such as starch or lactose, or in capsules or ovules, either alone or in admixture with excipients, or in the form of elixirs or suspensions containing flavoring or coloring agents. Such liquid preparations can be prepared with pharmaceutically acceptable additives, such as suspending agents. A compound also can be injected parenterally, for example, intravenously, intramuscularly,

subcutaneously, or intracoronarily. For parenteral administration, the compound is best used in the form of a sterile aqueous solution which can contain other substances, for example, salts, or sugar alcohols, such as mannitol, or glucose, to make the solution isotonic with blood.

[0069] For veterinary use, a compound disclosed herein is administered as a suitably acceptable formulation in accordance with normal veterinary practice. The veterinarian can readily determine the dosing regimen and route of administration that is most appropriate for a particular animal.

[0070] In some embodiments, all the necessary components for the treatment of KRAS-related disorder using a compound as disclosed herein either alone or in combination with another agent or intervention traditionally used for the treatment of such disease may be packaged into a kit. Specifically, the present disclosure provides a kit for use in the therapeutic intervention of the disease comprising a packaged set of medicaments that include the compound disclosed herein as well as buffers and other components for preparing deliverable forms of said medicaments, and/or devices for delivering such medicaments, and/or any agents that are used in combination therapy with the compound disclosed herein, and/or instructions for the treatment of the disease packaged with the medicaments. The instructions may be fixed in any tangible medium, such as printed paper, or a computer readable magnetic or optical medium, or instructions to reference a remote computer data source such as a world wide web page accessible via the internet.

[0071] A "therapeutically effective amount" means an amount effective to treat or to prevent development of, or to alleviate the existing symptoms of, the subject being treated. Determination of the effective amounts is well within the capability of those skilled in the art, especially in light of the detailed disclosure provided herein. Generally, a "therapeutically effective dose" refers to that amount of the compound that results in achieving the desired effect. For example, in one preferred embodiment, a therapeutically effective amount of a compound disclosed herein decreases KRAS activity by at least 5%, compared to control, at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, or at least 90%.

[0072] The amount of compound administered can be dependent on the subject being treated, on the subject's age, health, sex, and weight, the kind of concurrent treatment (if any),

severity of the affliction, the nature of the effect desired, the manner and frequency of treatment, and the judgment of the prescribing physician. The frequency of dosing also can be dependent on pharmacodynamic effects on arterial oxygen pressures. However, the most preferred dosage can be tailored to the individual subject, as is understood and determinable by one of skill in the art, without undue experimentation. This typically involves adjustment of a standard dose (e.g., reduction of the dose if the patient has a low body weight).

[0073] While individual needs vary, determination of optimal ranges of effective amounts of the compound is within the skill of the art. For administration to a human in the curative or prophylactic treatment of the conditions and disorders identified herein, for example, typical dosages of the compounds of the present disclosure can be about 0.05 mg/kg/day to about 50 mg/kg/day, for example at least 0.05 mg/kg, at least 0.08 mg/kg, at least 0.1 mg/kg, at least 0.2 mg/kg, at least 0.3 mg/kg, at least 0.4 mg/kg, or at least 0.5 mg/kg, and preferably 50 mg/kg or less, 40 mg/kg or less, 30 mg/kg or less, 20 mg/kg or less, or 10 mg/kg or less, which can be about 2.5 mg/day (0.5 mg/kg x 5kg) to about 5000 mg/day (50mg/kg x 100kg), for example. For example, dosages of the compounds can be about 0.1 mg/kg/day to about 50 mg/kg/day, about 0.05 mg/kg/day to about 10 mg/kg/day, about 0.05 mg/kg/day to about 5 mg/kg/day, about 0.05 mg/kg/day to about 3 mg/kg/day, about 0.07 mg/kg/day to about 3 mg/kg/day, about 0.09 mg/kg/day to about 3 mg/kg/day, about 0.05 mg/kg/day to about 0.1 mg/kg/day, about 0.1 mg/kg/day to about 1 mg/kg/day, about 1 mg/kg/day to about 10 mg/kg/day, about 1 mg/kg/day to about 5 mg/kg/day, about 1 mg/kg/day to about 3 mg/kg/day, about 3 mg/day to about 500 mg/day, about 5 mg/day to about 250 mg/day, about 10 mg/day to about 100 mg/day, about 3 mg/day to about 10 mg/day, or about 100 mg/day to about 250 mg/day. Such doses may be administered in a single dose or it may be divided into multiple doses.

Methods of using KRAS G12C inhibitors

[0074] The present disclosure provides a method of inhibiting RAS-mediated cell signaling comprising contacting a cell with an effective amount of one or more compounds disclosed herein. Inhibition of RAS-mediated signal transduction can be assessed and demonstrated by a wide variety of ways known in the art. Non-limiting examples include a showing of (a) a decrease in GTPase activity of RAS; (b) a decrease in GTP binding affinity or an increase in GDP binding affinity; (c) an increase in K off of GTP or a decrease in K off of GDP; (d) a decrease in the levels of signaling transduction molecules downstream in the RAS pathway, such as a decrease in pMEK, pERK, or pAKT levels; and/or (e) a decrease in binding of RAS

complex to downstream signaling molecules including but not limited to Raf. Kits and commercially available assays can be utilized for determining one or more of the above.

[0075] The disclosure also provides methods of using the compounds or pharmaceutical compositions of the present disclosure to treat disease conditions, including but not limited to conditions implicated by G12C KRAS, HRAS or NRAS mutation (e.g., cancer).

[0076] In some embodiments, a method for treatment of cancer is provided, the method comprising administering an effective amount of any of the foregoing pharmaceutical compositions comprising a compound as disclosed herein to a subject in need thereof. In some embodiments, the cancer is mediated by a KRAS, HRAS or NRAS G12C mutation. In various embodiments, the cancer is pancreatic cancer, colorectal cancer or lung cancer. In some embodiments, the cancer is gall bladder cancer, thyroid cancer, and bile duct cancer.

[0077] In some embodiments the disclosure provides method of treating a disorder in a subject in need thereof, wherein the said method comprises determining if the subject has a KRAS, HRAS or NRAS G12C mutation and if the subject is determined to have the KRAS, HRAS or NRAS G12C mutation, then administering to the subject a therapeutically effective dose of at least one compound as disclosed herein or a pharmaceutically acceptable salt thereof.

[0078] The disclosed compounds inhibit anchorage-independent cell growth and therefore have the potential to inhibit tumor metastasis. Accordingly, another embodiment the disclosure provides a method for inhibiting tumor metastasis, the method comprising administering an effective amount a compound disclosed herein.

[0079] KRAS, HRAS or NRAS G12C mutations have also been identified in hematological malignancies (e.g., cancers that affect blood, bone marrow and/or lymph nodes). Accordingly, certain embodiments are directed to administration of a disclosed compounds (e.g., in the form of a pharmaceutical composition) to a patient in need of treatment of a hematological malignancy. Such malignancies include, but are not limited to leukemias and lymphomas. For example, the presently disclosed compounds can be used for treatment of diseases such as Acute lymphoblastic leukemia (ALL), Acute myelogenous leukemia (AML), Chronic lymphocytic leukemia (CLL), small lymphocytic lymphoma (SLL), Chronic myelogenous leukemia (CML), Acute monocytic leukemia (AMoL) and/ or other leukemias. In other embodiments, the compounds are useful for treatment of lymphomas such as all subtypes of Hodgkins lymphoma or non-Hodgkins lymphoma. In

various embodiments, the compounds are useful for treatment of plasma cell malignancies such as multiple myeloma, mantle cell lymphoma, and Waldenstrom's macroglubunemia.

[0080] Determining whether a tumor or cancer comprises a G12C KRAS, HRAS or NRAS mutation can be undertaken by assessing the nucleotide sequence encoding the KRAS, HRAS or NRAS protein, by assessing the amino acid sequence of the KRAS, HRAS or NRAS protein, or by assessing the characteristics of a putative KRAS, HRAS or NRAS mutant protein. The sequence of wild-type human KRAS, HRAS or NRAS is known in the art, (e.g. Accession No. NP203524).

[0081] Methods for detecting a mutation in a KRAS, HRAS or NRAS nucleotide sequence are known by those of skill in the art. These methods include, but are not limited to, polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) assays, polymerase chain reaction-single strand conformation polymorphism (PCR-SSCP) assays, real-time PCR assays, PCR sequencing, mutant allele-specific PCR amplification (MASA) assays, direct sequencing, primer extension reactions, electrophoresis, oligonucleotide ligation assays, hybridization assays, TaqMan assays, SNP genotyping assays, high resolution melting assays and microarray analyses. In some embodiments, samples are evaluated for G12C KRAS, HRAS or NRAS mutations by real-time PCR. In real-time PCR, fluorescent probes specific for the KRAS, HRAS or NRAS G12C mutation are used. When a mutation is present, the probe binds and fluorescence is detected. In some embodiments, the KRAS, HRAS or NRAS G12C mutation is identified using a direct sequencing method of specific regions (e.g., exon 2 and/or exon 3) in the KRAS, HRAS or NRAS gene. This technique will identify all possible mutations in the region sequenced.

[0082] Methods for detecting a mutation in a KRAS, HRAS or NRAS protein are known by those of skill in the art. These methods include, but are not limited to, detection of a KRAS, HRAS or NRAS mutant using a binding agent (e.g., an antibody) specific for the mutant protein, protein electrophoresis and Western blotting, and direct peptide sequencing.

[0083] Methods for determining whether a tumor or cancer comprises a G12C KRAS, HRAS or NRAS mutation can use a variety of samples. In some embodiments, the sample is taken from a subject having a tumor or cancer. In some embodiments, the sample is a fresh tumor/cancer sample. In some embodiments, the sample is a frozen tumor/cancer sample. In some embodiments, the sample is a formalin-fixed paraffin-embedded sample. In some embodiments, the sample is a circulating tumor cell (CTC) sample. In some embodiments,

the sample is processed to a cell lysate. In some embodiments, the sample is processed to DNA or RNA.

[0084] The disclosure also relates to a method of treating a hyperproliferative disorder in a mammal that comprises administering to said mammal a therapeutically effective amount of a compound as disclosed herein, or a pharmaceutically acceptable salt thereof. In some embodiments, said method relates to the treatment of a subject who suffers from a cancer such as acute myeloid leukemia, cancer in adolescents, adrenocortical carcinoma childhood, AIDS-related cancers (e.g. Lymphoma and Kaposi's Sarcoma), anal cancer, appendix cancer, astrocytomas, atypical teratoid, basal cell carcinoma, bile duct cancer, bladder cancer, bone cancer, brain stem glioma, brain tumor, breast cancer, bronchial tumors, Burkitt lymphoma, carcinoid tumor, atypical teratoid, embryonal tumors, germ cell tumor, primary lymphoma, cervical cancer, childhood cancers, chordoma, cardiac tumors, chronic lymphocytic leukemia (CLL), chronic myelogenous leukemia (CML), chronic myleoproliferative disorders, colon cancer, colorectal cancer, craniopharyngioma, cutaneous T-cell lymphoma, extrahepatic ductal carcinoma in situ (DCIS), embryonal tumors, CNS cancer, endometrial cancer, ependymoma, esophageal cancer, esthesioneuroblastoma, ewing sarcoma, extracranial germ cell tumor, extragonadal germ cell tumor, eye cancer, fibrous histiocytoma of bone, gall bladder cancer, gastric cancer, gastrointestinal carcinoid tumor, gastrointestinal stromal tumors (GIST), germ cell tumor, gestational trophoblastic tumor, hairy cell leukemia, head and neck cancer, heart cancer, liver cancer, Hodgkin lymphoma, hypopharyngeal cancer, intraocular melanoma, islet cell tumors, pancreatic neuroendocrine tumors, kidney cancer, laryngeal cancer, lip and oral cavity cancer, liver cancer, lobular carcinoma in situ (LCIS), lung cancer, lymphoma, metastatic squamous neck cancer with occult primary, midline tract carcinoma, mouth cancer, multiple endocrine neoplasia syndromes, multiple myeloma/plasma cell neoplasm, mycosis fungoides, myelodysplastic syndromes,myelodysplastic/myeloproliferative neoplasms, multiple myeloma, merkel cell carcinoma, malignant mesothelioma, malignant fibrous histiocytoma of bone and osteosarcoma, nasal cavity and paranasal sinus cancer, nasopharyngeal cancer, neuroblastoma, non-hodgkin lymphoma, non-small cell lung cancer (NSCLC), oral cancer, lip and oral cavity cancer, oropharyngeal cancer, ovarian cancer, pancreatic cancer, papillomatosis, paraganglioma, paranasal sinus and nasal cavity cancer, parathyroid cancer, penile cancer, pharyngeal cancer, pleuropulmonary blastoma, primary central nervous system (CNS) lymphoma, prostate cancer, rectal cancer, transitional cell cancer,

retinoblastoma, rhabdomyosarcoma, salivary gland cancer, skin cancer, stomach (gastric) cancer, small cell lung cancer, small intestine cancer, soft tissue sarcoma, T-Cell lymphoma, testicular cancer, throat cancer, thymoma and thymic carcinoma, thyroid cancer, transitional cell cancer of the renal pelvis and ureter, trophoblastic tumor, unusual cancers of childhood, urethral cancer, uterine sarcoma, vaginal cancer, vulvar cancer, or viral-induced cancer. In some embodiments, said method relates to the treatment of a non-cancerous hyperproliferative disorder such as benign hyperplasia of the skin (e. g., psoriasis), restenosis, or prostate (e. g., benign prostatic hypertrophy (BPH)).

[0085] In some embodiments, the methods for treatment are directed to treating lung cancers, the methods comprise administering an effective amount of any of the above described compound (or a pharmaceutical composition comprising the same) to a subject in need thereof. In certain embodiments the lung cancer is a non- small cell lung carcinoma (NSCLC), for example adenocarcinoma, squamous-cell lung carcinoma or large-cell lung carcinoma. In some embodiments, the lung cancer is a small cell lung carcinoma. Other lung cancers treatable with the disclosed compounds include, but are not limited to, glandular tumors, carcinoid tumors and undifferentiated carcinomas.

[0086] The disclosure further provides methods of modulating a G12C Mutant KRAS, HRAS or NRAS protein activity by contacting the protein with an effective amount of a compound of the disclosure. Modulation can be inhibiting or activating protein activity. In some embodiments, the disclosure provides methods of inhibiting protein activity by contacting the G12C Mutant KRAS, HRAS or NRAS protein with an effective amount of a compound of the disclosure in solution. In some embodiments, the disclosure provides methods of inhibiting the G12C Mutant KRAS, HRAS or NRAS protein activity by contacting a cell, tissue, or organ that expresses the protein of interest. In some embodiments, the disclosure provides methods of inhibiting protein activity in subject including but not limited to rodents and mammal (e.g., human) by administering into the subject an effective amount of a compound of the disclosure. In some embodiments, the percentage modulation exceeds 25%, 30%, 40%, 50%, 60%, 70%, 80%, or 90%. In some embodiments, the percentage of inhibiting exceeds 25%, 30%, 40%, 50%, 60%, 70%, 80%, or 90%.

[0087] In some embodiments, the disclosure provides methods of inhibiting KRAS, HRAS or NRAS G12C activity in a cell by contacting said cell with an amount of a compound of the disclosure sufficient to inhibit the activity of KRAS, HRAS or NRAS G12C in said cell. In some embodiments, the disclosure provides methods of inhibiting KRAS, HRAS or NRAS

G12C activity in a tissue by contacting said tissue with an amount of a compound of the disclosure sufficient to inhibit the activity of KRAS, HRAS or NRAS G12C in said tissue. In some embodiments, the disclosure provides methods of inhibiting KRAS, HRAS or NRAS G12C activity in an organism by contacting said organism with an amount of a compound of the disclosure sufficient to inhibit the activity of KRAS, HRAS or NRAS G12C in said organism. In some embodiments, the disclosure provides methods of inhibiting KRAS, HRAS or NRAS G12C activity in an animal by contacting said animal with an amount of a compound of the disclosure sufficient to inhibit the activity of KRAS, HRAS or NRAS G12C in said animal. In some embodiments, the disclosure provides methods of inhibiting KRAS, HRAS or NRAS G12C activity in a mammal by contacting said mammal with an amount of a compound of the disclosure sufficient to inhibit the activity of KRAS, HRAS or NRAS G12C in said mammal. In some embodiments, the disclosure provides methods of inhibiting KRAS, HRAS or NRAS G12C activity in a human by contacting said human with an amount of a compound of the disclosure sufficient to inhibit the activity of KRAS, HRAS or NRAS G12C in said human. The present disclosure provides methods of treating a disease mediated by KRAS, HRAS or NRAS G12C activity in a subject in need of such treatment.

Combination Therapy

[0088] The present disclosure also provides methods for combination therapies in which an agent known to modulate other pathways, or other components of the same pathway, or even overlapping sets of target enzymes are used in combination with a compound of the present disclosure, or a pharmaceutically acceptable salt thereof. In one aspect, such therapy includes but is not limited to the combination of one or more compounds of the disclosure with chemotherapeutic agents, therapeutic antibodies, and radiation treatment, to provide a synergistic or additive therapeutic effect.

[0089] Many chemotherapeutics are presently known in the art and can be used in combination with the compounds of the disclosure. In some embodiments, the chemotherapeutic is selected from the group consisting of mitotic inhibitors, alkylating agents, anti-metabolites, intercalating antibiotics, growth factor inhibitors, cell cycle inhibitors, enzymes, topoisomerase inhibitors, biological response modifiers, anti- hormones, angiogenesis inhibitors, and anti-androgens. Non-limiting examples are chemotherapeutic agents, cytotoxic agents, and non-peptide small molecules such as Gleevec® (Imatinib Mesylate), Kyprolis® (carfilzomib), Velcade® (bortezomib), Casodex (bicalutamide), Iressa® (gefitinib), Venclexta™ (venetoclax) and Adriamycin™, (docorubicin) as well as a

host of chemotherapeutic agents. Non-limiting examples of chemotherapeutic agents include alkylating agents such as thiotepa and cyclosphosphamide (Cytoxan™); alkyl sulfonates such as busulfan, improsulfan and piposulfan; aziridines such as benzodopa, carboquone, meturedopa, and uredopa; ethylenimines and methylamelamines including altretamine, triethylenemelamine, trietylenephosphoramide, triethylenethiophosphaoramide and trimethylolomelamine; nitrogen mustards such as chlorambucil, chlornaphazine, chlorocyclophosphamide, estramustine, ifosfamide, mechlorethamine, mechlorethamine oxide hydrochloride, melphalan, novembichin, phenesterine, prednimustine, trofosfamide, uracil mustard; nitrosureas such as carmustine, chlorozotocin, fotemustine, lomustine, nimustine, ranimustine; antibiotics such as aclacinomysins, actinomycin, authramycin, azaserine, bleomycins, cactinomycin, calicheamicin, carabicin, carminomycin, carzinophilin, Casodex™, chromomycins, dactinomycin, daunorubicin, detorubicin, 6-diazo-5-oxo- L-norleucine, doxorubicin, epirubicin, esorubicin, idarubicin, marcellomycin, mitomycins, mycophenolic acid, nogalamycin, olivomycins, peplomycin, potfiromycin, puromycin, quelamycin, rodorubicin, streptonigrin, streptozocin, tubercidin, ubenimex, zinostatin, zorubicin; anti-metabolites such as methotrexate and 5-fluorouracil (5-FU); folic acid analogues such as denopterin, methotrexate, pteropterin, trimetrexate; purine analogs such as fludarabine, 6-mercaptopurine, thiamiprine, thioguanine; pyrimidine analogs such as ancitabine, azacitidine, 6-azauridine, carmofur, cytarabine, dideoxyuridine, doxifluridine, enocitabine, floxuridine, androgens such as calusterone, dromostanolone propionate, epitiostanol, mepitiostane, testolactone; anti-adrenals such as aminoglutethimide, mitotane, trilostane; folic acid replenisher such as frolinic acid; aceglatone; aldophosphamide glycoside; aminolevulinic acid; amsacrine; bestrabucil; bisantrene; edatraxate; defofamine; demecolcine; diaziquone; elfomithine; elliptinium acetate; etoglucid; gallium nitrate; hydroxyurea; lentinan; lonidamine; mitoguazone; mitoxantrone; mopidamol; nitracrine; pentostatin; phenamet; pirarubicin; podophyllinic acid; 2-ethylhydrazide; procarbazine; PSK; razoxane; sizofiran; spirogermanium; tenuazonic acid; triaziquone; 2,2',2''-trichlorotriethylamine; urethan; vindesine; dacarbazine; mannomustine; mitobronitol; mitolactol; pipobroman; gacytosine; arabinoside ("Ara-C"); cyclophosphamide; thiotepa; taxanes, e.g. paclitaxel and docetaxel; retinoic acid; esperamicins; capecitabine; and pharmaceutically acceptable salts, acids or derivatives of any of the above.

[0090] Also included as suitable chemotherapeutic cell conditioners are anti-hormonal agents that act to regulate or inhibit hormone action on tumors such as anti-estrogens

including for example tamoxifen, (Nolvadex™), raloxifene, aromatase inhibiting 4(5)-imidazoles, 4-hydroxytamoxifen, trioxifene, keoxifene, LY 117018, onapristone, and toremifene (Fareston); and anti-androgens such as flutamide, nilutamide, bicalutamide, leuprolide, and goserelin; chlorambucil; gemcitabine; 6-thioguanine; mercaptopurine; methotrexate; platinum analogs such as cisplatin and carboplatin; vinblastine; platinum; etoposide (VP-16); ifosfamide; mitomycin C; mitoxantrone; vincristine; vinorelbine; navelbine; novantrone; teniposide; daunomycin; aminopterin; xeloda; ibandronate; camptothecin-11 (CPT-11); topoisomerase inhibitor RFS 2000; difluoromethylornithine (DMFO).

[0091] Where desired, the compounds or pharmaceutical composition of the present disclosure can be used in combination with commonly prescribed anti-cancer drugs such as Herceptin®, Avastin®, Erbitux®, Rituxan®, Taxol®, Arimidex®, Taxotere®, ABVD, AVICINE, Abagovomab, Acridine carboxamide, Adecatumumab, 17-N-Allylamino-17-demethoxygeldanamycin, Alpharadin, Alvocidib, 3-Aminopyridine-2-carboxaldehyde thiosemicarbazone, Amonafide, Anthracenedione, Anti-CD22 immunotoxins, Antineoplastic, Antitumorigenic herbs, Apaziquone, Atiprimod, Azathioprine, Belotecan, Bendamustine, BIBW 2992, Biricodar, Brostallicin, Bryostatin, Buthionine sulfoximine, CBV (chemotherapy), Calyculin, cell-cycle nonspecific antineoplastic agents, Dichloroacetic acid, Discodermolide, Elsamitrucin, Enocitabine, Epothilone, Eribulin, Everolimus, Exatecan, Exisulind, Ferruginol, Forodesine, Fosfestrol, ICE chemotherapy regimen, IT-101, Imexon, Imiquimod, Indolocarbazole, Irofulven, Laniquidar, Larotaxel, Lenalidomide, Lucanthone, Lurtotecan, Mafosfamide, Mitozolomide, Nafoxidine, Nedaplatin, Olaparib, Ortataxel, PAC-1, Pawpaw, Pixantrone, Proteasome inhibitor, Rebeccamycin, Resiquimod, Rubitecan, SN-38, Salinosporamide A, Sapacitabine, Stanford V, Swainsonine, Talaporfin, Tariquidar, Tegafur-uracil, Temodar, Tesetaxel, Triplatin tetranitrate, Tris(2-chloroethyl)amine, Troxacitabine, Uramustine, Vadimezan, Vinflunine, ZD6126 or Zosuquidar.

[0092] This disclosure further relates to a method for using the compounds or pharmaceutical compositions provided herein, in combination with radiation therapy for inhibiting abnormal cell growth or treating the hyperproliferative disorder in the mammal. Techniques for administering radiation therapy are known in the art, and these techniques can be used in the combination therapy described herein. The administration of the compound of the disclosure in this combination therapy can be determined as described herein.

[0093] Radiation therapy can be administered through one of several methods, or a combination of methods, including without limitation external-beam therapy, internal radiation therapy, implant radiation, stereotactic radiosurgery, systemic radiation therapy, radiotherapy and permanent or temporary interstitial brachytherapy. The term "brachytherapy," as used herein, refers to radiation therapy delivered by a spatially confined radioactive material inserted into the body at or near a tumor or other proliferative tissue disease site. The term is intended without limitation to include exposure to radioactive isotopes (e.g. At-211, I-131, I-125, Y-90, Re-186, Re-188, Sm- 153, Bi-212, P-32, and radioactive isotopes of Lu). Suitable radiation sources for use as a cell conditioner of the present disclosure include both solids and liquids. By way of non-limiting example, the radiation source can be a radionuclide, such as I-125, I-131, Yb-169, Ir-192 as a solid source, I-125 as a solid source, or other radionuclides that emit photons, beta particles, gamma radiation, or other therapeutic rays. The radioactive material can also be a fluid made from any solution of radionuclide(s), e.g., a solution of I-125 or I-131, or a radioactive fluid can be produced using a slurry of a suitable fluid containing small particles of solid radionuclides, such as Au-198, Y-90. Moreover, the radionuclide(s) can be embodied in a gel or radioactive micro spheres.

[0094] The compounds or pharmaceutical compositions of the disclosure can be used in combination with an amount of one or more substances selected from anti-angiogenesis agents, signal transduction inhibitors, antiproliferative agents, glycolysis inhibitors, or autophagy inhibitors.

[0095] Anti-angiogenesis agents, such as MMP-2 (matrix-metalloproteinase 2) inhibitors, MMP-9 (matrix-metalloproteinase 9) inhibitors, and COX-11 (cyclooxygenase 11) inhibitors, can be used in conjunction with a compound of the disclosure and pharmaceutical compositions described herein. Anti-angiogenesis agents include, for example, rapamycin, temsirolimus (CCI-779), everolimus (RAD001), sorafenib, sunitinib, and bevacizumab. Examples of useful COX-II inhibitors include alecoxib, valdecoxib, and rofecoxib. Examples of useful matrix metalloproteinase inhibitors are described in WO 96/33172 WO 96/27583 European Patent Publication EP0818442, European Patent Publication EP1004578 , WO 98/07697, WO 98/03516, WO 98/34918, WO 98/34915, WO 98/33768, WO 98/30566, European Patent Publication 606046, European Patent Publication 931 788, WO 90/05719, WO 99/52910, WO 99/52889, WO 99/29667, WO1999007675, European Patent Publication EP1786785, European Patent Publication No. EP1181017, United States Publication No.

US20090012085, United States Publication US5863 949, United States Publication US5861 510, and European Patent Publication EP0780386, all of which are incorporated herein in their entireties by reference. Preferred MMP-2 and MMP-9 inhibitors are those that have little or no activity inhibiting MMP-1. More preferred, are those that selectively inhibit MMP-2 and/or AMP-9 relative to the other matrix- metalloproteinases (i. e., MAP-1, MMP-3, MMP-4, MMP-5, MMP-6, MMP- 7, MMP- 8, MMP-10, MMP-11, MMP-12, andMMP-13). Some specific examples of MMP inhibitors useful in the disclosure are AG-3340, RO 32-3555, and RS 13-0830.

[0096] The present compounds may also be used in co-therapies with other anti-neoplastic agents, such as acemannan, aclarubicin, aldesleukin, alemtuzumab, alitretinoin, altretamine, amifostine, aminolevulinic acid, amrubicin, amsacrine, anagrelide, anastrozole, ANCER, ancestim, ARGLABIN, arsenic trioxide, BAM 002 (Novelos), bexarotene, bicalutamide, broxuridine, capecitabine, celmoleukin, cetrorelix, cladribine, clotrimazole, cytarabine ocfosfate, DA 3030 (Dong-A), daclizumab, denileukin diftitox, deslorelin, dexrazoxane, dilazep, docetaxel, docosanol, doxercalciferol, doxifluridine, doxorubicin, bromocriptine, carmustine, cytarabine, fluorouracil, HIT diclofenac, interferon alfa, daunorubicin, doxorubicin, tretinoin, edelfosine, edrecolomab, eflornithine, emitefur, epirubicin, epoetin beta, etoposide phosphate, exemestane, exisulind, fadrozole, filgrastim, finasteride, fludarabine phosphate, formestane, fotemustine, gallium nitrate, gemcitabine, gemtuzumab zogamicin, gimeracil/oteracil/tegafur combination, glycopine, goserelin, heptaplatin, human chorionic gonadotropin, human fetal alpha fetoprotein, ibandronic acid, idarubicin, (imiquimod, interferon alfa, interferon alfa, natural, interferon alfa-2, interferon alfa-2a, interferon alfa-2b, interferon alfa-N1, interferon alfa-$_{n3}$, interferon alfacon-1, interferon alpha, natural, interferon beta, interferon beta-1a, interferon beta-1b, interferon gamma, natural interferon gamma-1a, interferon gamma-1b, interleukin-1 beta, iobenguane, irinotecan, irsogladine, lanreotide, LC 9018 (Yakult), leflunomide, lenograstim, lentinan sulfate, letrozole, leukocyte alpha interferon, leuprorelin, levamisole + fluorouracil, liarozole, lobaplatin, lonidamine, lovastatin, masoprocol, melarsoprol, metoclopramide, mifepristone, miltefosine, mirimostim, mismatched double stranded RNA, mitoguazone, mitolactol, mitoxantrone, molgramostim, nafarelin, naloxone + pentazocine, nartograstim, nedaplatin, nilutamide, noscapine, novel erythropoiesis stimulating protein, NSC 631570 octreotide, oprelvekin, osaterone, oxaliplatin, paclitaxel, pamidronic acid, pegaspargase, peginterferon alfa-2b, pentosan polysulfate sodium, pentostatin, picibanil, pirarubicin, rabbit antithymocyte

polyclonal antibody, polyethylene glycol interferon alfa-2a, porfimer sodium, raloxifene, raltitrexed, rasburiembodiment, rhenium Re 186 etidronate, RII retinamide, rituximab, romurtide, samarium (153 Sm) lexidronam, sargramostim, sizofiran, sobuzoxane, sonermin, strontium-89 chloride, suramin, tasonermin, tazarotene, tegafur, temoporfin, temozolomide, teniposide, tetrachlorodecaoxide, thalidomide, thymalfasin, thyrotropin alfa, topotecan, toremifene, tositumomab-iodine 131, trastuzumab, treosulfan, tretinoin, trilostane, trimetrexate, triptorelin, tumor necrosis factor alpha, natural, ubenimex, bladder cancer vaccine, Maruyama vaccine, melanoma lysate vaccine, valrubicin, verteporfin, vinorelbine, VIRULIZIN, zinostatin stimalamer, or zoledronic acid; abarelix; AE 941 (Aeterna), ambamustine, antisense oligonucleotide, bcl-2 (Genta), APC 8015 (Dendreon), cetuximab, decitabine, dexaminoglutethimide, diaziquone, EL 532 (Elan), EM 800 (Endorecherche), eniluracil, etanidazole, fenretinide, filgrastim SD01 (Amgen), fulvestrant, galocitabine, gastrin 17 immunogen, HLA-B7 gene therapy (Vical), granulocyte macrophage colony stimulating factor, histamine dihydrochloride, ibritumomab tiuxetan, ilomastat, IM 862 (Cytran), interleukin-2, iproxifene, LDI 200 (Milkhaus), leridistim, lintuzumab, CA 125 MAb (Biomira), cancer MAb (Japan Pharmaceutical Development), HER-2 and Fc MAb (Medarex), idiotypic 105AD7 MAb (CRC Technology), idiotypic CEA MAb (Trilex), LYM-1-iodine 131 MAb (Techniclone), polymorphic epithelial mucin-yttrium 90 MAb (Antisoma), marimastat, menogaril, mitumomab, motexafin gadolinium, MX 6 (Galderma), nelarabine, nolatrexed, P 30 protein, pegvisomant, pemetrexed, porfiromycin, prinomastat, RL 0903 (Shire), rubitecan, satraplatin, sodium phenylacetate, sparfosic acid, SRL 172 (SR Pharma), SU 5416 (SUGEN, now Pfizer, Inc.), TA 077 (Tanabe), tetrathiomolybdate, thaliblastine, thrombopoietin, tin ethyl etiopurpurin, tirapazamine, cancer vaccine (Biomira), melanoma vaccine (New York University), melanoma vaccine (Sloan Kettering Institute), melanoma oncolysate vaccine (New York Medical College), viral melanoma cell lysates vaccine (Royal Newcastle Hospital), or valspodar.

[0097] The compounds of the disclosure may further be used with VEGFR inhibitors. Other compounds described in the following patents and patent applications can be used in combination therapy: US 6,258,812, US 2003/0105091, WO 01/37820, US 6,235,764, WO 01/32651, US 6,630,500, US 6,515,004, US 6,713,485, US 5,521,184, US 5,770,599, US 5,747,498, WO 02/68406, WO 02/66470, WO 02/55501, WO 04/05279, WO 04/07481, WO 04/07458, WO 04/09784, WO 02/59110, WO 99/45009, WO 00/59509, WO 99/61422, US 5,990,141, WO 00/12089, and WO 00/02871.

[0098] In some embodiments, the combination comprises a composition of the present disclosure in combination with at least one anti-angiogenic agent. Agents are inclusive of, but not limited to, *in vitro* synthetically prepared chemical compositions, antibodies, antigen binding regions, radionuclides, and combinations and conjugates thereof. An agent can be an agonist, antagonist, allosteric modulator, toxin or, more generally, may act to inhibit or stimulate its target (e.g., receptor or enzyme activation or inhibition), and thereby promote cell death or arrest cell growth.

[0099] Exemplary anti-angiogenic agents include ERBITUX™ (IMC-C225), KDR (kinase domain receptor) inhibitory agents (e.g., antibodies and antigen binding regions that specifically bind to the kinase domain receptor), anti-VEGF agents (e.g., antibodies or antigen binding regions that specifically bind VEGF, or soluble VEGF receptors or a ligand binding region thereof) such as AVASTIN™ or VEGF-TRAP™, and anti-VEGF receptor agents (e.g., antibodies or antigen binding regions that specifically bind thereto), EGFR inhibitory agents (e.g., antibodies or antigen binding regions that specifically bind thereto) such as Vectibix (panitumumab), IRESSA™ (gefitinib), TARCEVA™ (erlotinib), anti-Ang1 and anti-Ang2 agents (e.g., antibodies or antigen binding regions specifically binding thereto or to their receptors, e.g., Tie2/Tek), and anti-Tie2 kinase inhibitory agents (e.g., antibodies or antigen binding regions that specifically bind thereto). The pharmaceutical compositions of the present disclosure can also include one or more agents (e.g., antibodies, antigen binding regions, or soluble receptors) that specifically bind and inhibit the activity of growth factors, such as antagonists of hepatocyte growth factor (HGF, also known as Scatter Factor), and antibodies or antigen binding regions that specifically bind its receptor "c-met".

[00100] Other anti-angiogenic agents include Campath, IL-8, B-FGF, Tek antagonists (Ceretti et al., U.S. Publication No. 2003/0162712; U.S. Patent No. 6,413,932), anti-TWEAK agents (e.g., specifically binding antibodies or antigen binding regions, or soluble TWEAK receptor antagonists; see, Wiley, U.S. Patent No. 6,727,225), ADAM distintegrin domain to antagonize the binding of integrin to its ligands (Fanslow et al., U.S. Publication No. 2002/0042368), specifically binding anti-eph receptor and/or anti-ephrin antibodies or antigen binding regions (U.S. Patent Nos. 5,981,245; 5,728,813; 5,969,110; 6,596,852; 6,232,447; 6,057,124 and patent family members thereof), and anti-PDGF-BB antagonists (e.g., specifically binding antibodies or antigen binding regions) as well as antibodies or antigen binding regions specifically binding to PDGF-BB ligands, and PDGFR kinase inhibitory agents (e.g., antibodies or antigen binding regions that specifically bind thereto).

[0100] Additional anti-angiogenic/anti-tumor agents include: SD-7784 (Pfizer, USA); cilengitide.(Merck KGaA, Germany, EPO 770622); pegaptanib octasodium, (Gilead Sciences, USA); Alphastatin, (BioActa, UK); M-PGA, (Celgene, USA, US 5712291); ilomastat, (Arriva, USA, US 5892112); emaxanib, (Pfizer, USA, US 5792783); vatalanib, (Novartis, Switzerland); 2-methoxyestradiol, (EntreMed, now CASI Pharamaceuticals, USA); TLC ELL-12, (Elan, Ireland); anecortave acetate, (Alcon, USA); alpha-D148 Mab, (Amgen, USA); CEP-7055,(Cephalon, USA); anti-Vn Mab, (Crucell, Netherlands) DAC:antiangiogenic, (ConjuChem, Canada); Angiocidin, (InKine Pharmaceutical, USA); KM-2550, (Kyowa Hakko, Japan); SU-0879, (Pfizer, USA); CGP-79787, (Novartis, Switzerland, EP 970070); ARGENT technology, (Ariad, USA); YIGSR-Stealth, (Johnson & Johnson, USA); fibrinogen-E fragment, (BioActa, UK); angiogenesis inhibitor, (Trigen, UK); TBC-1635, (Encysive Pharmaceuticals, USA); SC-236, (Pfizer, USA); ABT-567, (Abbott, USA); Metastatin, (EntreMed, USA); angiogenesis inhibitor, (Tripep, Sweden); maspin, (Sosei, Japan); 2-methoxyestradiol, (Oncology Sciences Corporation, USA); ER-68203-00, (IVAX, USA); Benefin, (Lane Labs, USA); Tz-93, (Tsumura, Japan); TAN-1120, (Takeda, Japan); FR-111142, (Fujisawa, Japan, JP 02233610); platelet factor 4, (RepliGen, USA, EP 407122); vascular endothelial growth factor antagonist, (Borean, Denmark); bevacizumab (pINN), (Genentech, USA); angiogenesis inhibitors, (SUGEN, USA); XL 784, (Exelixis, USA); XL 647, (Exelixis, USA); MAb, alpha5beta3 integrin, second generation, (Applied Molecular Evolution, USA and MedImmune, USA); gene therapy, retinopathy, (Oxford BioMedica, UK); enzastaurin hydrochloride (USAN), (Lilly, USA); CEP 7055, (Cephalon, USA and Sanofi-Synthelabo, France); BC 1, (Genoa Institute of Cancer Research, Italy); angiogenesis inhibitor, (Alchemia, Australia); VEGF antagonist, (Regeneron, USA); rBPI 21 and BPI-derived antiangiogenic, (XOMA, USA); PI 88, (Progen, Australia); cilengitide (pINN), (Merck KGaA, German; Munich Technical University, Germany, Scripps Clinic and Research Foundation, USA); cetuximab (INN), (Aventis, France); AVE 8062, (Ajinomoto, Japan); AS 1404, (Cancer Research Laboratory, New Zealand); SG 292, (Telios, USA); Endostatin, (Boston Childrens Hospital, USA); ATN 161, (Attenuon, USA); ANGIOSTATIN, (Boston Childrens Hospital, USA); 2-methoxyestradiol, (Boston Childrens Hospital, USA); ZD 6474, (AstraZeneca, UK); ZD 6126, (Angiogene Pharmaceuticals, UK); PPI 2458, (Praecis, USA); AZD 9935, (AstraZeneca, UK); AZD 2171, (AstraZeneca, UK); vatalanib (pINN), (Novartis, Switzerland and Schering AG, Germany); tissue factor pathway inhibitors, (EntreMed, USA); pegaptanib (Pinn), (Gilead Sciences, USA); xanthorrhizol, (Yonsei University, South Korea); vaccine, gene-based, VEGF-2, (Scripps Clinic and

Research Foundation, USA); SPV5.2, (Supratek, Canada); SDX 103, (University of California at San Diego, USA); PX 478, (ProlX, USA); METASTATIN, (EntreMed, now CASI Pharmaceuticals, USA); troponin I, (Harvard University, USA); SU 6668, (SUGEN, now Pfizer, Inc., USA); OXI 4503, (OXiGENE, USA); o-guanidines, (Dimensional Pharmaceuticals, USA); motuporamine C, (British Columbia University, Canada); CDP 791, (Celltech Group, UK); atiprimod (pINN), (GlaxoSmithKline, UK); E 7820, (Eisai, Japan); CYC 381, (Harvard University, USA); AE 941, (Aeterna, Canada); vaccine, angiogenesis, (EntreMed, now CASI Pharmaceuticals, USA); urokinase plasminogen activator inhibitor, (Dendreon, USA); oglufanide (pINN), (Melmotte, USA); HIF-1alfa inhibitors, (Xenova, UK); CEP 5214, (Cephalon, USA); BAY RES 2622, (Bayer, Germany); Angiocidin, (InKine, USA); A6, (Angstrom, USA); KR 31372, (Korea Research Institute of Chemical Technology, South Korea); GW 2286, (GlaxoSmithKline, UK); EHT 0101, (ExonHit, France); CP 868596, (Pfizer, USA); CP 564959, (OSI, USA); CP 547632, (Pfizer, USA); 786034, (GlaxoSmithKline, UK); KRN 633, (Kirin Brewery, Japan); drug delivery system, intraocular, 2-methoxyestradiol, (EntreMed, USA); anginex, (Maastricht University, Netherlands, and Minnesota University, USA); ABT 510, (Abbott, USA); AAL 993, (Novartis, Switzerland); VEGI, (ProteomTech, USA); tumor necrosis factor-alpha inhibitors, (National Institute on Aging, USA); SU 11248, (Pfizer, USA and SUGEN USA); ABT 518, (Abbott, USA); YH16, (Yantai Rongchang, China); S-3APG , (Boston Childrens Hospital, USA and EntreMed, USA); MAb, KDR, (ImClone Systems, USA); MAb, alpha5 beta1, (Protein Design, USA); KDR kinase inhibitor, (Celltech Group, UK, and Johnson & Johnson, USA); GFB 116, (South Florida University, USA and Yale University, USA); CS 706, (Sankyo, Japan); combretastatin A4 prodrug, (Arizona State University, USA); chondroitinase AC, (IBEX, Canada); BAY RES 2690, (Bayer, Germany); AGM 1470, (Harvard University, USA, Takeda, Japan, and TAP, USA); AG 13925, (Agouron, USA); Tetrathiomolybdate, (University of Michigan, USA); GCS 100, (Wayne State University, USA) CV 247, (Ivy Medical, UK); CKD 732, (Chong Kun Dang, South Korea); MAb, vascular endothelium growth factor, (Xenova, UK); irsogladine (INN), (Nippon Shinyaku, Japan); RG 13577, (Aventis, France); WX 360, (Wilex, Germany); squalamine (pINN), (Genaera, USA); RPI 4610, (Sirna, USA); cancer therapy, (Marinova, Australia); heparanase inhibitors, (InSight, Israel); KL 3106, (Kolon, South Korea); Honokiol, (Emory University, USA); ZK CDK, (Schering AG, Germany); ZK Angio, (Schering AG, Germany); ZK 229561, (Novartis, Switzerland, and Schering AG, Germany); XMP 300, (XOMA, USA); VGA 1102, (Taisho, Japan); VEGF receptor modulators, (Pharmacopeia, USA); VE-

cadherin-2 antagonists , (ImClone Systems, USA); Vasostatin, (National Institutes of Health, USA);vaccine, Flk-1, (ImClone Systems, USA); TZ 93, (Tsumura, Japan); TumStatin, (Beth Israel Hospital, USA); truncated soluble FLT 1 (vascular endothelial growth factor receptor 1), (Merck & Co, USA); Tie-2 ligands, (Regeneron, USA); and, thrombospondin 1 inhibitor, (Allegheny Health, Education and Research Foundation, USA).

[0101] Autophagy inhibitors include, but are not limited to chloroquine, 3- methyladenine, hydroxychloroquine (Plaquenil™), bafilomycin A1, 5-amino-4- imidazole carboxamide riboside (AICAR), okadaic acid, autophagy-suppressive algal toxins which inhibit protein phosphatases of type 2A or type 1, analogues of cAMP, and drugs which elevate cAMP levels such as adenosine, LY204002, N6-mercaptopurine riboside, and vinblastine. In addition, antisense or siRNA that inhibits expression of proteins including but not limited to ATG5 (which are implicated in autophagy), may also be used.

[0102] Additional pharmaceutically active compounds/agents that can be used in the treatment of cancers and that can be used in combination with one or more compound of the present disclosure include: epoetin alfa; darbepoetin alfa; panitumumab; pegfilgrastim; palifermin; filgrastim; denosumab; ancestim; AMG 102; AMG 176; AMG 386; AMG 479; AMG 655; AMG 745; AMG 951; and AMG 706, or a pharmaceutically acceptable salt thereof.

[0103] In certain embodiments, a composition provided herein is conjointly administered with a chemotherapeutic agent. Suitable chemotherapeutic agents may include, natural products such as vinca alkaloids (e.g., vinblastine, vincristine, and vinorelbine), paclitaxel, epidipodophyllotoxins (e.g., etoposide and teniposide), antibiotics (e.g., dactinomycin (actinomycin D), daunorubicin, doxorubicin, and idarubicin), anthracyclines, mitoxantrone, bleomycins, plicamycin (mithramycin), mitomycin, enzymes (e.g., L-asparaginase which systemically metabolizes L-asparagine and deprives cells which do not have the capacity to synthesize their own asparagine), antiplatelet agents, antiproliferative/antimitotic alkylating agents such as nitrogen mustards (e.g., mechlorethamine, cyclophosphamide and analogs, melphalan, and chlorambucil), ethylenimines and methylmelamines (e.g., hexaamethylmelaamine and thiotepa), CDK inhibitors (e.g., seliciclib, UCN-01, P1446A-05, PD-0332991, dinaciclib, P27-00, AT-7519, RGB286638, and SCH727965), alkyl sulfonates (e.g., busulfan), nitrosoureas (e.g., carmustine (BCNU) and analogs, and streptozocin), trazenes-dacarbazinine (DTIC), antiproliferative/antimitotic antimetabolites such as folic acid analogs (e.g., methotrexate), pyrimidine analogs (e.g., fluorouracil, floxuridine, and

cytarabine), purine analogs and related inhibitors (e.g., mercaptopurine, thioguanine, pentostatin and 2-chlorodeoxyadenosine), aromatase inhibitors (e.g., anastrozole, exemestane, and letrozole), and platinum coordination complexes (e.g., cisplatin and carboplatin), procarbazine, hydroxyurea, mitotane, aminoglutethimide, histone deacetylase (HDAC) inhibitors (e.g., trichostatin, sodium butyrate, apicidan, suberoyl anilide hydroamic acid, vorinostat, LBH 589, romidepsin, ACY-1215, and panobinostat), mTor inhibitors (e.g., temsirolimus, everolimus, ridaforolimus, and sirolimus), KSP(Eg5) inhibitors (e.g., Array 520), DNA binding agents (e.g., Zalypsis), PI3K delta inhibitor (e.g., GS-1101 and TGR-1202), PI3K delta and gamma inhibitor (e.g., CAL-130), multi-kinase inhibitor (e.g., TG02 and sorafenib), hormones (e.g., estrogen) and hormone agonists such as leutinizing hormone releasing hormone (LHRH) agonists (e.g., goserelin, leuprolide and triptorelin), BAFF-neutralizing antibody (e.g., LY2127399), IKK inhibitors, p38MAPK inhibitors, anti-IL-6 (e.g., CNTO328), telomerase inhibitors (e.g., GRN 163L), aurora kinase inhibitors (e.g., MLN8237), cell surface monoclonal antibodies (e.g., anti-CD38 (HUMAX-CD38), anti-CS1 (e.g., elotuzumab), HSP90 inhibitors (e.g., 17 AAG and KOS 953), P13K / Akt inhibitors (e.g., perifosine), Akt inhibitor (e.g., GSK-2141795), PKC inhibitors (e.g., enzastaurin), FTIs (e.g., Zarnestra™), anti-CD138 (e.g., BT062), Torc1/2 specific kinase inhibitor (e.g., INK128), kinase inhibitor (e.g., GS-1101), ER/UPR targeting agent (e.g., MKC-3946), cFMS inhibitor (e.g., ARRY-382), JAK1/2 inhibitor (e.g., CYT387), PARP inhibitor (e.g., olaparib and veliparib (ABT-888)), BCL-2 antagonist. Other chemotherapeutic agents may include mechlorethamine, camptothecin, ifosfamide, tamoxifen, raloxifene, gemcitabine, navelbine, sorafenib, or any analog or derivative variant of the foregoing.

[0104] The compounds of the present disclosure may also be used in combination with radiation therapy, hormone therapy, surgery and immunotherapy, which therapies are well known to those skilled in the art.

[0105] In certain embodiments, a pharmaceutical composition provided herein is conjointly administered with a steroid. Suitable steroids may include, but are not limited to, 21-acetoxypregnenolone, alclometasone, algestone, amcinonide, beclomethasone, betamethasone, budesonide, chloroprednisone, clobetasol, clocortolone, cloprednol, corticosterone, cortisone, cortivazol, deflazacort, desonide, desoximetasone, dexamethasone, diflorasone, diflucortolone, difuprednate, enoxolone, fluazacort, flucloronide, flumethasone, flunisolide, fluocinolone acetonide, fluocinonide, fluocortin butyl, fluocortolone, fluorometholone, fluperolone acetate, fluprednidene acetate, fluprednisolone, flurandrenolide,

fluticasone propionate, formocortal, halcinonide, halobetasol propionate, halometasone, hydrocortisone, loteprednol etabonate, mazipredone, medrysone, meprednisone, methylprednisolone, mometasone furoate, paramethasone, prednicarbate, prednisolone, prednisolone 25-diethylaminoacetate, prednisolone sodium phosphate, prednisone, prednival, prednylidene, rimexolone, tixocortol, triamcinolone, triamcinolone acetonide, triamcinolone benetonide, triamcinolone hexacetonide, and salts and/or derivatives thereof. In a particular embodiment, the compounds of the present disclosure can also be used in combination with additional pharmaceutically active agents that treat nausea. Examples of agents that can be used to treat nausea include: dronabinol; granisetron; metoclopramide; ondansetron; and prochlorperazine; or a pharmaceutically acceptable salt thereof.

[0106] The compounds of the present disclosure may also be used in combination with an additional pharmaceutically active compound that disrupts or inhibits RAS-RAF-ERK or PI3K-AKT-TOR signaling pathways. In other such combinations, the additional pharmaceutically active compound is a PD-1 and PD-L1 antagonist. The compounds or pharmaceutical compositions of the disclosure can also be used in combination with an amount of one or more substances selected from EGFR inhibitors, MEK inhibitors, PI3K inhibitors, AKT inhibitors, TOR inhibitors, Mcl-1 inhibitors, BCL-2 inhibitors, SHP2 inhibitors, proteasome inhibitors, and immune therapies, including monoclonal antibodies, immunomodulatory imides (IMiDs), anti-PD-1, anti-PDL-1, anti-CTLA4, anti-LAG1, and anti-OX40 agents, GITR agonists, CAR-T cells, and BiTEs.

[0107] EGFR inhibitors include, but are not limited to, small molecule antagonists, antibody inhibitors, or specific antisense nucleotide or siRNA. Useful antibody inhibitors of EGFR include cetuximab (Erbitux), panitumumab (Vectibix), zalutumumab, nimotuzumab, and matuzumab. Small molecule antagonists of EGFR include gefitinib, erlotinib (Tarceva), and most recently, lapatinib (TykerB). See e.g., Yan L, et. al., *Pharmacogenetics and Pharmacogenomics In Oncology Therapeutic Antibody Development*, BioTechniques 2005; 39(4): 565-8, and Paez J G, et. al., *EGFR Mutations In Lung Cancer Correlation With Clinical Response To Gefitinib Therapy*, Science 2004; 304(5676): 1497-500.

[0108] Non-limiting examples of small molecule EGFR inhibitors include any of the EGFR inhibitors described in the following patent publications, and all pharmaceutically acceptable salts and solvates of said EGFR inhibitors: European Patent Application EP 520722, published Dec. 30, 1992; European Patent Application EP 566226, published Oct. 20, 1993; PCT International Publication WO 96/33980, published Oct. 31, 1996; U.S. Pat.

No. 5,747,498, issued May 5, 1998; PCT International Publication WO 96/30347, published Oct. 3, 1996; European Patent Application EP 787772, published Aug. 6, 1997; PCT International Publication WO 97/30034, published Aug. 21, 1997; PCT International Publication WO 97/30044, published Aug. 21, 1997; PCT International Publication WO 97/38994, published Oct. 23, 1997; PCT International Publication WO 97/49688, published Dec. 31, 1997; European Patent Application EP 837063, published Apr. 22, 1998; PCT International Publication WO 98/02434, published Jan. 22, 1998; PCT International Publication WO 97/38983, published Oct. 23, 1997; PCT International Publication WO 95/19774, published Jul. 27, 1995; PCT International Publication WO 95/19970, published Jul. 27, 1995; PCT International Publication WO 97/13771, published Apr. 17, 1997; PCT International Publication WO 98/02437, published Jan. 22, 1998; PCT International Publication WO 98/02438, published Jan. 22, 1998; PCT International Publication WO 97/32881, published Sep. 12, 1997; German Application DE 19629652, published Jan. 29, 1998; PCT International Publication WO 98/33798, published Aug. 6, 1998; PCT International Publication WO 97/32880, published Sep. 12, 1997; PCT International Publication WO 97/32880 published Sep. 12, 1997; European Patent Application EP 682027, published Nov. 15, 1995; PCT International Publication WO 97/02266, published Jan. 23, 197; PCT International Publication WO 97/27199, published Jul. 31, 1997; PCT International Publication WO 98/07726, published Feb. 26, 1998; PCT International Publication WO 97/34895, published Sep. 25, 1997; PCT International Publication WO 96/31510′, published Oct. 10, 1996; PCT International Publication WO 98/14449, published Apr. 9, 1998; PCT International Publication WO 98/14450, published Apr. 9, 1998; PCT International Publication WO 98/14451, published Apr. 9, 1998; PCT International Publication WO 95/09847, published Apr. 13, 1995; PCT International Publication WO 97/19065, published May 29, 1997; PCT International Publication WO 98/17662, published Apr. 30, 1998; U.S. Pat. No. 5,789,427, issued Aug. 4, 1998; U.S. Pat. No. 5,650,415, issued Jul. 22, 1997; U.S. Pat. No. 5,656,643, issued Aug. 12, 1997; PCT International Publication WO 99/35146, published Jul. 15, 1999; PCT International Publication WO 99/35132, published Jul. 15, 1999; PCT International Publication WO 99/07701, published Feb. 18, 1999; and PCT International Publication WO 92/20642 published Nov. 26, 1992. Additional non-limiting examples of small molecule EGFR inhibitors include any of the EGFR inhibitors described in Traxler, P., 1998, Exp. Opin. Ther. Patents 8(12):1599-1625.

[0109] Antibody-based EGFR inhibitors include any anti-EGFR antibody or antibody fragment that can partially or completely block EGFR activation by its natural ligand. Non-limiting examples of antibody-based EGFR inhibitors include those described in Modjtahedi, H., et al., 1993, Br. J. Cancer 67:247-253; Teramoto, T., et al., 1996, Cancer 77:639-645; Goldstein et al., 1995, Clin. Cancer Res. 1:1311-1318; Huang, S. M., et al., 1999, Cancer Res. 15:59(8):1935-40; and Yang, X., et al., 1999, Cancer Res. 59:1236-1243. Thus, the EGFR inhibitor can be monoclonal antibody Mab E7.6.3 (Yang, 1999 supra), or Mab C225 (ATCC Accession No. HB-8508), or an antibody or antibody fragment having the binding specificity thereof.

[0110] The $KRAS^{G12C}$ inhibitors of the present disclosure can be used in combination with MEK inhibitors. Particular MEK inhibitors that can be used in the combinations of the present disclosure include PD-325901, trametinib, pimasertib, MEK162 [also known as binimetinib], TAK-733, GDC-0973 and AZD8330. A particular MEK inhibitor that can be used along with $KRAS^{G12C}$ inhibitor in the combinations of the present disclosure is trametinib (tradename: Mekinist®, commercially available from Novartis Pharmaceuticals Corp.). Another particular MEK inhibitor is N-(((2R)-2,3-dihydroxypropyl)oxy)-3,4-difluoro-2-((2-fluoro-4-iodophenyl)amino)benzamide, also known as AMG 1009089, 1009089 or PD-325901. Another particular MEK inhibitor that can be used in the combinations of the present disclosure includes cobimetinib. MEK inhibitors include, but are not limited to, CI-1040, AZD6244, PD318088, PD98059, PD334581, RDEA119, ARRY-142886, and ARRY-438162.

[0111] PI3K inhibitors include, but are not limited to, wortmannin, 17-hydroxywortmannin analogs described in WO 06/044453, 4-[2-(1H-Indazol-4-yl)-6-[[4-(methylsulfonyl)piperazin-1-yl]methyl]thieno[3,2-d]pyrimidin-4-yl]morpholine (also known as GDC 0941 and described in PCT Publication Nos. WO 09/036,082 and WO 09/055,730), 2-Methyl-2-[4-[3-methyl-2-oxo-8-(quinolin-3-yl)-2,3-dihydroimidazo[4,5-c]quinolin-1-yl]phenyl]propionitrile (also known as BEZ 235 or NVP-BEZ 235, and described in PCT Publication No. WO 06/122806), (S)-1-(4-((2-(2-aminopyrimidin-5-yl)-7-methyl-4-morpholinothieno[3,2-d]pyrimidin-6-yl)methyl)piperazin-1-yl)-2-hydroxypropan-1-one (described in PCT Publication No. WO 2008/070740), LY294002 (2-(4-Morpholinyl)-8-phenyl-4H-1-benzopyran-4-one available from Axon Medchem), PI 103 hydrochloride (3-[4-(4-morpholinylpyrido-[3′,2′:4,5]furo[3,2-d]pyrimidin-2-yl]phenol hydrochloride available from Axon Medchem), PIK 75 (N′-[(1E)-(6-bromoimidazo[1,2-a]pyridin-3-yl)methylene]-

N,2-dimethyl-5-nitrobenzenesulfono-hydrazide hydrochloride available from Axon Medchem), PIK 90 (N-(7,8-dimethoxy-2,3-dihydro-imidazo[1,2-c]quinazolin-5-yl)-nicotinamide available from Axon Medchem), GDC-0941 bismesylate (2-(1H-Indazol-4-yl)-6-(4-methanesulfonyl-piperazin-1-ylmethyl)-4-morpholin-4-yl-thieno[3,2-d]pyrimidine available from Axon Medchem), AS-252424 (5-[1-[5-(4-Fluoro-2-hydroxy-phenyl)-furan-2-yl]-meth-(Z)-ylidene]-thiazolidine-2,4-dione available from Axon Medchem), and TGX-221 (7-Methyl-2-(4-morpholinyl)-9-[1-(phenylamino)ethyl]-4H-pyrido-[1,2-a]pyrimidin-4-one available from Axon Medchem), XL-765, and XL-147. Other PI3K inhibitors include demethoxyviridin, perifosine, CAL101, PX-866, BEZ235, SF1126, INK1117, IPI-145, BKM120, XL147, XL765, Palomid 529, GSK1059615, ZSTK474, PWT33597, IC87114, TG100-115, CAL263, PI-103, GNE-477, CUDC-907, and AEZS-136.

[0112] AKT inhibitors include, but are not limited to, Akt-1-1 (inhibits Akt1) (Barnett et al. (2005) *Biochem. J.,* 385 (Pt. 2), 399-408); Akt-1-1,2 (inhibits Ak1 and 2) (Barnett et al. (2005) *Biochem. J.* 385 (Pt. 2), 399-408); API-59CJ-Ome (e.g., Jin et al. (2004) *Br. J. Cancer* 91, 1808-12); 1-H-imidazo[4,5-c]pyridinyl compounds (e.g., WO05011700); indole-3-carbinol and derivatives thereof (e.g., U.S. Pat. No. 6,656,963; Sarkar and Li (2004) *J Nutr.* 134(12 Suppl), 3493S-3498S); perifosine (e.g., interferes with Akt membrane localization; Dasmahapatra et al. (2004) *Clin. Cancer Res.* 10(15), 5242-52, 2004); phosphatidylinositol ether lipid analogues (e.g., Gills and Dennis (2004) *Expert. Opin. Investig. Drugs* 13, 787-97); and triciribine (TCN or API-2 or NCI identifier: NSC 154020; Yang et al. (2004) *Cancer Res.* 64, 4394-9).

[0113] TOR inhibitors include, but are not limited to, AP-23573, CCI-779, everolimus, RAD-001, rapamycin, temsirolimus, ATP-competitive TORC1/TORC2 inhibitors, including PI-103, PP242, PP30 and Torin 1. Other TOR inhibitors in FKBP12 enhancer; rapamycins and derivatives thereof, including: CCI-779 (temsirolimus), RAD001 (Everolimus; WO 9409010) and AP23573; rapalogs, e.g. as disclosed in WO 98/02441 and WO 01/14387, e.g. AP23573, AP23464, or AP23841; 40-(2-hydroxyethyl)rapamycin, 40-[3-hydroxy(hydroxymethyl)methylpropanoate]-rapamycin (also called CC1779), 40-epi-(tetrazolyt)-rapamycin (also called ABT578), 32-deoxorapamycin, 16-pentynyloxy-32(S)-dihydrorapanycin, and other derivatives disclosed in WO 05005434; derivatives disclosed in U.S. Pat. No. 5,258,389, WO 94/090101, WO 92/05179, U.S. Pat. No. 5,118,677, U.S. Pat. No. 5,118,678, U.S. Pat. No. 5,100,883, U.S. Pat. No. 5,151,413, U.S. Pat. No. 5,120,842, WO 93/111130, WO 94/02136, WO 94/02485, WO 95/14023, WO 94/02136, WO 95/16691,

WO 96/41807, WO 96/41807 and U.S. Pat. No. 5,256,790; phosphorus-containing rapamycin derivatives (e.g., WO 05016252); 4H-1-benzopyran-4-one derivatives (e.g., U.S. Provisional Application No. 60/528,340).

[0114] MCl-1 inhibitors include, but are not limited to, AMG-176, MIK665, and S63845. The myeloid cell leukemia-1 (MCL-1) protein is one of the key anti-apoptotic members of the B-cell lymphoma-2 (BCL-2) protein family. Over-expression of MCL-1 has been closely related to tumor progression as well as to resistance, not only to traditional chemotherapies but also to targeted therapeutics including BCL-2 inhibitors such as ABT-263.

[0115] $KRAS^{G12C}$ inhibitors can also be used in combination with SHP2 inhibitors in the present disclosure. SHP2 inhibitors that can be used in the present combinations include, but are not limited to, SHP099, and RMC-4550 or RMC-4630, from Revolutions Medicines in Redwood City, CA.

[0116] Proteasome inhibitors include, but are not limited to, Kyprolis®(carfilzomib), Velcade®(bortezomib), and oprozomib.

[0117] Immune therapies include, but are not limited to, anti-PD-1 agents, anti-PDL-1 agents, anti-CTLA-4 agents, anti-LAG1 agents, and anti-OX40 agents.

[0118] Monoclonal antibodies include, but are not limited to, Darzalex® (daratumumab), Herceptin® (trastuzumab), Avastin® (bevacizumab), Rituxan® (rituximab), Lucentis® (ranibizumab), and Eylea® (aflibercept).

[0119] Immunomodulatory agents (IMiDs) are a class of immunomodulatory drugs (drugs that adjust immune responses) containing an imide group. The IMiD class includes thalidomide and its analogues (lenalidomide, pomalidomide, and apremilast).

[0120] Anti-PD-1 inhibitors, including but not limited to antibodies include, but are not limited to, pembrolizumab (Keytruda®), AMG 404 and nivolumab (Opdivo®). Exemplary anti-PD-1 antibodies and methods for their use are described by Goldberg et al., *Blood* 110(1):186-192 (2007), Thompson et al., *Clin. Cancer Res.* 13(6):1757-1761 (2007), and Korman et al., International Application No. PCT/JP2006/309606 (publication no. WO 2006/121168 A1), each of which are expressly incorporated by reference herein. include: Yervoy™ (ipilimumab) or Tremelimumab (to CTLA-4), galiximab (to B7.1), BMS-936558 (to PD-1), MK-3475 (to PD-1), AMP224 (to B7DC), BMS-936559 (to B7-H1), MPDL3280A (to B7-H1), MEDI-570 (to ICOS), AMG557 (to B7H2), MGA271 (to B7H3), IMP321 (to LAG-3), BMS-663513 (to CD137), PF-05082566 (to CD137), CDX-1127 (to CD27), anti-

OX40 (Providence Health Services), huMAbOX40L (to OX40L), Atacicept (to TACI), CP-870893 (to CD40), Lucatumumab (to CD40), Dacetuzumab (to CD40), Muromonab-CD3 (to CD3), Ipilumumab (to CTLA-4). Immune therapies also include genetically engineered T-cells (e.g., CAR-T cells) and bispecific antibodies (e.g., BiTEs).

[0121] GITR agonists include, but are not limited to, GITR fusion proteins and anti-GITR antibodies (e.g., bivalent anti-GITR antibodies), such as, a GITR fusion protein described in U.S. Pat. No. 6,111,090box.c, European Patent No.: 090505B1, U.S. Pat. No. 8,586,023, PCT Publication Nos.: WO 2010/003118 and 2011/090754, or an anti-GITR antibody described, e.g., in U.S. Pat. No. 7,025,962, European Patent No.: 1947183B1, U.S. Pat. No. 7,812,135, U.S. Pat. No. 8,388,967, U.S. Pat. No. 8,591,886, European Patent No.: EP 1866339, PCT Publication No.: WO 2011/028683, PCT Publication No.: WO 2013/039954, PCT Publication No.: WO2005/007190, PCT Publication No.: WO 2007/133822, PCT Publication No.: WO2005/055808, PCT Publication No.: WO 99/40196, PCT Publication No.: WO 2001/03720, PCT Publication No.: WO99/20758, PCT Publication No.: WO2006/083289, PCT Publication No.: WO 2005/115451, U.S. Pat. No. 7,618,632, and PCT Publication No.: WO 2011/051726.

[0122] The compounds described herein can be used in combination with the agents disclosed herein or other suitable agents, depending on the condition being treated. Hence, in some embodiments the one or more compounds of the disclosure will be co-administered with other agents as described above. When used in combination therapy, the compounds described herein are administered with the second agent simultaneously or separately. This administration in combination can include simultaneous administration of the two agents in the same dosage form, simultaneous administration in separate dosage forms, and separate administration. That is, a compound described herein and any of the agents described above can be formulated together in the same dosage form and administered simultaneously. Alternatively, a compound of the disclosure and any of the agents described above can be simultaneously administered, wherein both the agents are present in separate formulations. In another alternative, a compound of the present disclosure can be administered just followed by and any of the agents described above, or vice versa. In some embodiments of the separate administration protocol, a compound of the disclosure and any of the agents described above are administered a few minutes apart, or a few hours apart, or a few days apart.

[0123] As one aspect of the present disclosure contemplates the treatment of the disease/conditions with a combination of pharmaceutically active compounds that may be

administered separately, the disclosure further relates to combining separate pharmaceutical compositions in kit form. The kit comprises two separate pharmaceutical compositions: a compound of the present disclosure, and a second pharmaceutical compound. The kit comprises a container for containing the separate compositions such as a divided bottle or a divided foil packet. Additional examples of containers include syringes, boxes, and bags. In some embodiments, the kit comprises directions for the use of the separate components. The kit form is particularly advantageous when the separate components are preferably administered in different dosage forms (e.g., oral and parenteral), are administered at different dosage intervals, or when titration of the individual components of the combination is desired by the prescribing health care professional.

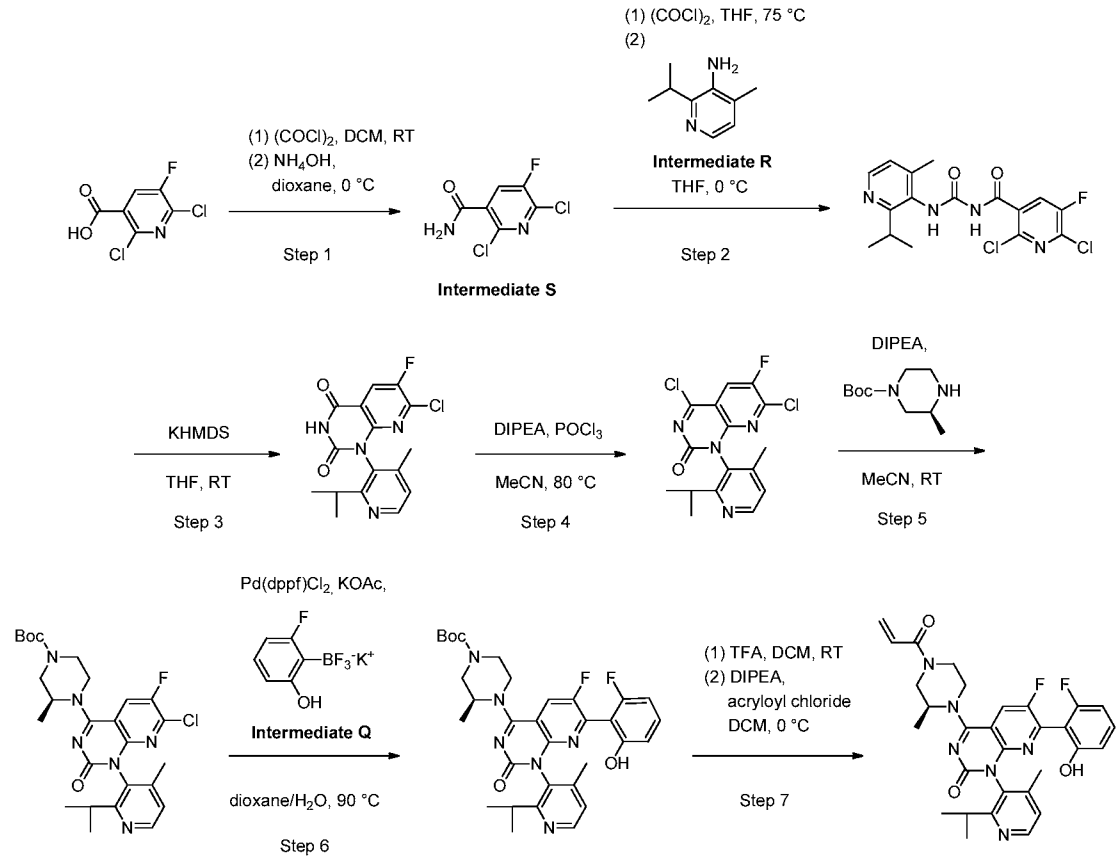
[0124] All patents and other publications recited herein are hereby incorporated by reference.

[0125] The processes presented below illustrate specific embodiments of the present disclosure. These processes are meant to be representative and are not intended to limit the scope of the claims in any manner.

Related Synthetic Processes

[0126] The following intermediate compounds of 6-Fluoro-7-(2-fluoro-6-hydroxyphenyl)-1-(4-methyl-2-(2-propanyl)-3-pyridinyl)-4-((2*S*)-2-methyl-4-(2-propenoyl)-1-piperazinyl)pyrido[2,3-*d*]pyrimidin-2(1H)-one are representative examples of the disclosure and are not intended to be construed as limiting the scope of the present invention.

[0127] A synthesis of Compound 9 and the relevant intermediates is described in U.S. Serial No. 15/984,855, filed May 21, 2018 (U.S. Publication No. 2018/0334454, November 22, 2018) which claims priority to and the benefit claims the benefit of U.S. Provisional Application No. 62/509,629, filed on May 22, 2017, both of which are incorporated herein by reference in their entireties for all purposes. 6-Fluoro-7-(2-fluoro-6-hydroxyphenyl)-1-(4-methyl-2-(2-propanyl)-3-pyridinyl)-4-((2*S*)-2-methyl-4-(2-propenoyl)-1-piperazinyl)pyrido[2,3-*d*]pyrimidin-2(1H)-one was prepared using the following process, in which the isomers of the final product were isolated via chiral chromatography.



[0128] Step 1: 2,6-Dichloro-5-fluoronicotinamide (Intermediate S). To a mixture of 2,6-dichloro-5-fluoro-nicotinic acid (4.0 g, 19.1 mmol, AstaTech Inc., Bristol, PA) in dichloromethane (48 mL) was added oxalyl chloride (2M solution in DCM, 11.9 mL, 23.8 mmol), followed by a catalytic amount of DMF (0.05 mL). The reaction was stirred at room temperature overnight and then was concentrated. The residue was dissolved in 1,4-dioxane (48 mL) and cooled to 0 °C. Ammonium hydroxide solution (28.0-30% NH3 basis, 3.6 mL, 28.6 mmol) was added slowly via syringe. The resulting mixture was stirred at 0 °C for 30 min and then was concentrated. The residue was diluted with a 1:1 mixture of EtOAc/Heptane and agitated for 5 min, then was filtered. The filtered solids were discarded, and the remaining mother liquor was partially concentrated to half volume and filtered. The filtered solids were washed with heptane and dried in a reduced-pressure oven (45 °C) overnight to provide 2,6-dichloro-5-fluoronicotinamide. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.23 (d, J = 7.9 Hz, 1 H) 8.09 (br s, 1 H) 7.93 (br s, 1 H). m/z (ESI, +ve ion): 210.9 $(M+H)^+$.

[0129] Step 2: 2,6-Dichloro-5-fluoro-*N*-((2-isopropyl-4-methylpyridin-3-yl)carbamoyl)nicotinamide. To an ice-cooled slurry of 2,6-dichloro-5-fluoronicotinamide

(**Intermediate S**, 5.0 g, 23.9 mmol) in THF (20 mL) was added oxalyl chloride (2 M solution in DCM, 14.4 mL, 28.8 mmol) slowly via syringe. The resulting mixture was heated at 75 °C for 1 h, then heating was stopped, and the reaction was concentrated to half volume. After cooling to 0 °C, THF (20 mL) was added, followed by a solution of 2-isopropyl-4-methylpyridin-3-amine (**Intermediate R**, 3.59 g, 23.92 mmol) in THF (10 mL), dropwise via cannula. The resulting mixture was stirred at 0 °C for 1 h and then was quenched with a 1:1 mixture of brine and saturated aqueous ammonium chloride. The mixture was extracted with EtOAc (3x) and the combined organic layers were dried over anhydrous sodium sulfate and concentrated to provide 2,6-dichloro-5-fluoro-*N*-((2-isopropyl-4-methylpyridin-3-yl)carbamoyl)nicotinamide. This material was used without further purification in the following step. *m/z* (ESI, +ve ion): 385.1$(M+H)^+$.

[0130] Step 3: 7-Chloro-6-fluoro-1-(2-isopropyl-4-methylpyridin-3-yl)pyrido[2,3-*d*]pyrimidine-2,4(1H,3H)-dione. To an ice-cooled solution of 2,6-dichloro-5-fluoro-*N*-((2-isopropyl-4-methylpyridin-3-yl)carbamoyl)nicotinamide (9.2 g, 24.0 mmol) in THF (40 mL) was added KHMDS (1 M solution in THF, 50.2 mL, 50.2 mmol) slowly via syringe. The ice bath was removed and the resulting mixture was stirred for 40 min at room temperature. The reaction was quenched with saturated aqueous ammonium chloride and extracted with EtOAc (3x). The combined organic layers were dried over anhydrous sodium sulfate and concentrated. The residue was purified by silica gel chromatography (eluent: 0-50% 3:1 EtOAc-EtOH/heptane) to provide 7-chloro-6-fluoro-1-(2-isopropyl-4-methylpyridin-3-yl)pyrido[2,3-*d*]pyrimidine-2,4(1H,3H)-dione. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 12.27 (br s, 1H), 8.48-8.55 (m, 2 H), 7.29 (d, J = 4.8 Hz, 1 H), 2.87 (quin, J = 6.6 Hz, 1 H), 1.99-2.06 (m, 3 H), 1.09 (d, J = 6.6 Hz, 3 H), 1.01 (d, J = 6.6 Hz, 3 H). ^{19}F NMR (376 MHz, DMSO-d_6) δ: -126.90 (s, 1 F). *m/z* (ESI, +ve ion): 349.1 $(M+H)^+$.

[0131] Step 4: 4,7-Dichloro-6-fluoro-1-(2-isopropyl-4-methylpyridin-3-yl)pyrido[2,3-*d*]pyrimidin-2(1H)-one. To a solution of 7-chloro-6-fluoro-1-(2-isopropyl-4-methylpyridin-3-yl)pyrido[2,3-*d*]pyrimidine-2,4(1H,3H)-dione (4.7 g, 13.5 mmol) and DIPEA (3.5 mL, 20.2 mmol) in acetonitrile (20 mL) was added phosphorus oxychloride (1.63 mL, 17.5 mmol), dropwise via syringe. The resulting mixture was heated at 80 °C for 1 h, and then was cooled to room temperature and concentrated to provide 4,7-dichloro-6-fluoro-1-(2-isopropyl-4-methylpyridin-3-yl)pyrido[2,3-*d*]pyrimidin-2(1H)-one. This material was used without further purification in the following step. *m/z* (ESI, +ve ion): 367.1 $(M+H)^+$.

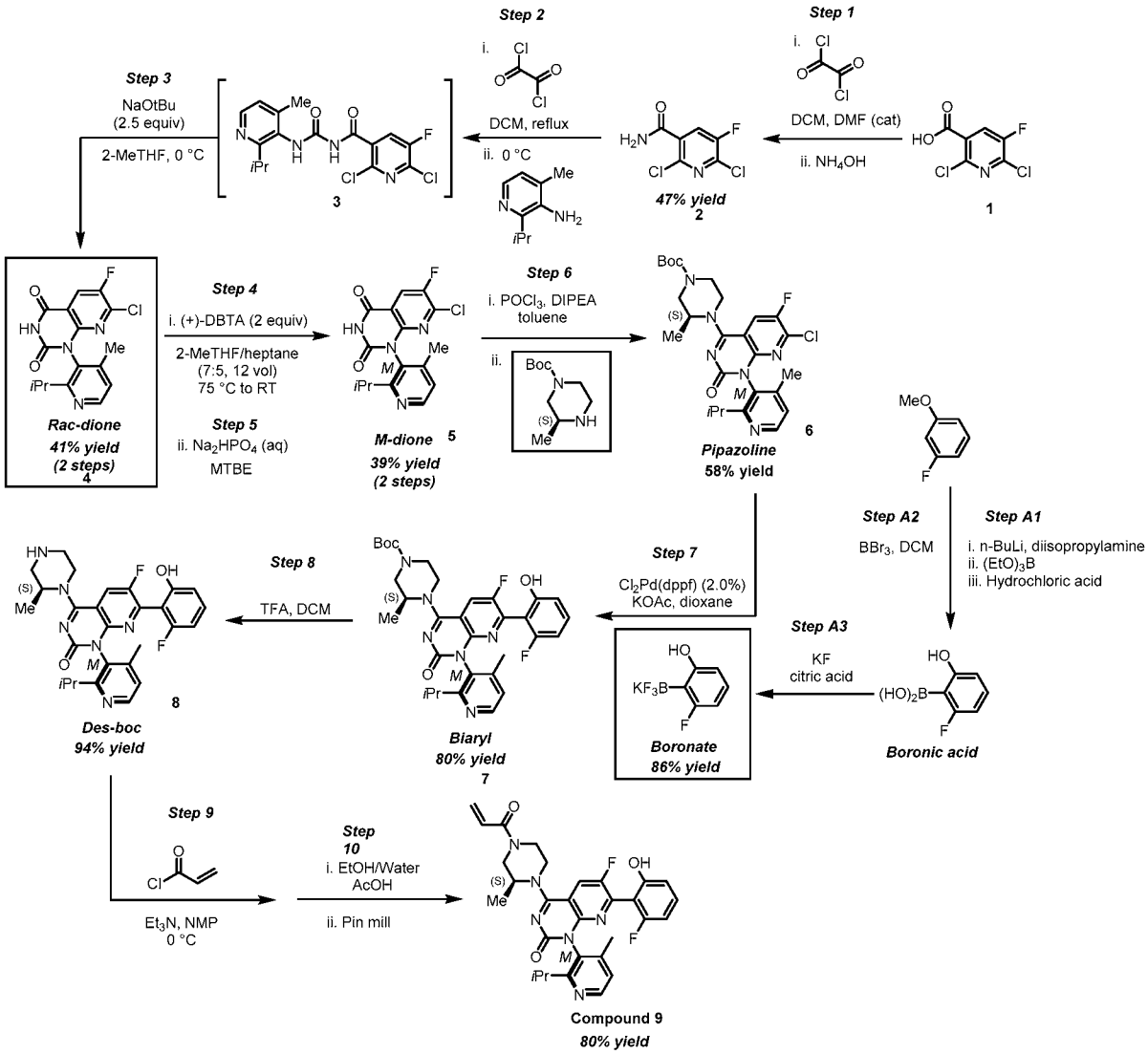
[0132] Step 5: (*S*)-*tert*-Butyl 4-(7-chloro-6-fluoro-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-1,2-dihydropyrido[2,3-*d*]pyrimidin-4-yl)-3-methylpiperazine-1-carboxylate. To an ice-cooled solution of 4,7-dichloro-6-fluoro-1-(2-isopropyl-4-methylpyridin-3-yl)pyrido[2,3-*d*]pyrimidin-2(1H)-one (13.5 mmol) in acetonitrile (20 mL) was added DIPEA (7.1 mL, 40.3 mmol), followed by (*S*)-4-*N*-Boc-2-methyl piperazine (3.23 g, 16.1 mmol, Combi-Blocks, Inc., San Diego, CA, USA). The resulting mixture was warmed to room temperature and stirred for 1 h, then was diluted with cold saturated aqueous sodium bicarbonate solution (200 mL) and EtOAc (300 mL). The mixture was stirred for an additional 5 min, the layers were separated, and the aqueous layer was extracted with more EtOAc (1x). The combined organic layers were dried over anhydrous sodium sulfate and concentrated. The residue was purified by silica gel chromatography (eluent: 0-50% EtOAc/heptane) to provide (*S*)-*tert*-butyl 4-(7-chloro-6-fluoro-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-1,2-dihydropyrido[2,3-*d*]pyrimidin-4-yl)-3-methylpiperazine-1-carboxylate. *m/z* (ESI, +ve ion): 531.2 $(M+H)^+$.

[0133] Step 6: (3*S*)-*tert*-Butyl 4-(6-fluoro-7-(2-fluoro-6-hydroxyphenyl)-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-1,2-dihydropyrido[2,3-*d*]pyrimidin-4-yl)-3-methylpiperazine-1-carboxylate. A mixture of (*S*)-*tert*-butyl 4-(7-chloro-6-fluoro-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-1,2-dihydropyrido[2,3-*d*]pyrimidin-4-yl)-3-methylpiperazine-1-carboxylate (4.3 g, 8.1 mmol), potassium trifluoro(2-fluoro-6-hydroxyphenyl)borate (**Intermediate Q**, 2.9 g, 10.5 mmol), potassium acetate (3.2 g, 32.4 mmol) and [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II), complex with dichloromethane (661 mg, 0.81 mmol) in 1,4-dioxane (80 mL) was degassed with nitrogen for 1 min. De-oxygenated water (14 mL) was added, and the resulting mixture was heated at 90 °C for 1 h. The reaction was allowed to cool to room temperature, quenched with half-saturated aqueous sodium bicarbonate, and extracted with EtOAc (2x) and DCM (1x). The combined organic layers were dried over anhydrous sodium sulfate and concentrated. The residue was purified by silica gel chromatography (eluent: 0-60% 3:1 EtOAc-EtOH/heptane) to provide (3*S*)-*tert*-butyl 4-(6-fluoro-7-(2-fluoro-6-hydroxyphenyl)-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-1,2-dihydropyrido[2,3-*d*]pyrimidin-4-yl)-3-methylpiperazine-1-carboxylate. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 10.19 (br s, 1 H), 8.38 (d, J = 5.0 Hz, 1 H), 8.26 (dd, J = 12.5, 9.2 Hz, 1 H), 7.23-7.28 (m, 1 H), 7.18 (d, J = 5.0 Hz, 1 H), 6.72 (d, J = 8.0 Hz, 1 H), 6.68 (t, J = 8.9 Hz, 1 H), 4.77-4.98 (m, 1 H), 4.24 (br t, J = 14.2 Hz, 1 H), 3.93-4.08 (m, 1 H), 3.84 (br d, J=12.9 Hz, 1 H), 3.52-3.75 (m, 1 H), 3.07-3.28 (m, 1 H), 2.62-2.74

(m, 1 H), 1.86-1.93 (m, 3 H), 1.43-1.48 (m, 9 H), 1.35 (dd, J = 10.8, 6.8 Hz, 3 H), 1.26-1.32 (m, 1 H), 1.07 (dd, J = 6.6, 1.7 Hz, 3 H), 0.93 (dd, J = 6.6, 2.1 Hz, 3 H). ^{19}F NMR (376 MHz, DMSO-d_6) δ: -115.65 (s, 1 F), -128.62 (s, 1 F). *m/z* (ESI, +ve ion): 607.3 $(M+H)^+$.

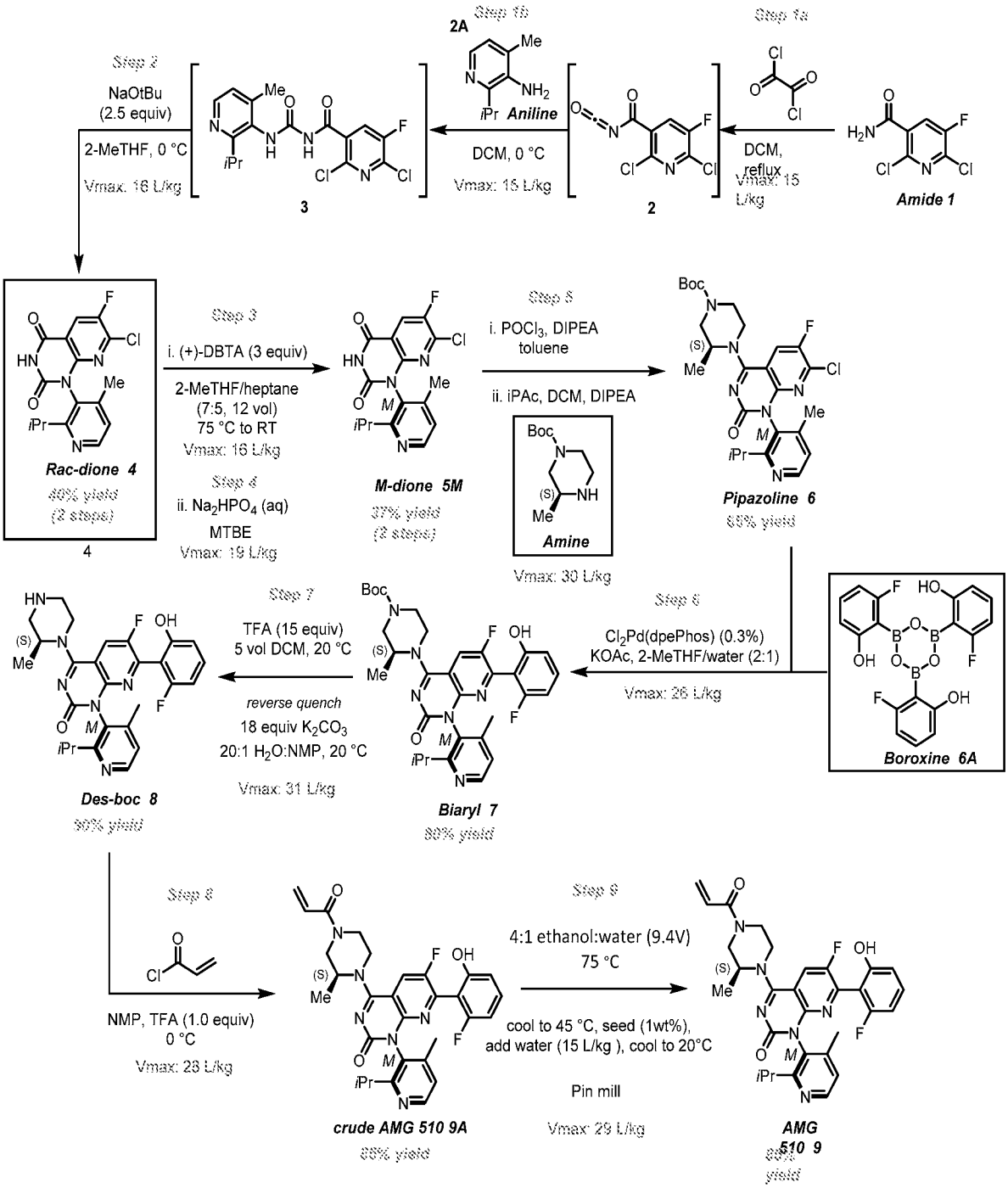
[0134] Step 7: 6-Fluoro-7-(2-fluoro-6-hydroxyphenyl)-1-(4-methyl-2-(2-propanyl)-3-pyridinyl)-4-((2*S*)-2-methyl-4-(2-propenoyl)-1-piperazinyl)pyrido[2,3-*d*]pyrimidin-2(1H)-one. Trifluoroacetic acid (25 mL, 324 mmol) was added to a solution of (3*S*)-*tert*-butyl 4-(6-fluoro-7-(2-fluoro-6-hydroxyphenyl)-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-1,2-dihydropyrido[2,3-*d*]pyrimidin-4-yl)-3-methylpiperazine-1-carboxylate (6.3 g, 10.4 mmol) in DCM (30 mL). The resulting mixture was stirred at room temperature for 1 h and then was concentrated. The residue was dissolved in DCM (30 mL), cooled to 0 °C, and sequentially treated with DIPEA (7.3 mL, 41.7 mmol) and a solution of acryloyl chloride (0.849 mL, 10.4 mmol) in DCM (3 mL; added dropwise via syringe). The reaction was stirred at 0 °C for 10 min, then was quenched with half-saturated aqueous sodium bicarbonate and extracted with DCM (2x). The combined organic layers were dried over anhydrous sodium sulfate and concentrated. The residue was purified by silica gel chromatography (eluent: 0-100% 3:1 EtOAc-EtOH/heptane) to provide 6-fluoro-7-(2-fluoro-6-hydroxyphenyl)-1-(4-methyl-2-(2-propanyl)-3-pyridinyl)-4-((2*S*)-2-methyl-4-(2-propenoyl)-1-piperazinyl)pyrido[2,3-*d*]pyrimidin-2(1H)-one. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 10.20 (s, 1 H), 8.39 (d, J = 4.8 Hz, 1 H), 8.24-8.34 (m, 1 H), 7.23-7.32 (m, 1 H), 7.19 (d, J = 5.0 Hz, 1 H), 6.87 (td, J = 16.3, 11.0 Hz, 1 H), 6.74 (d, J = 8.6 Hz, 1 H), 6.69 (t, J = 8.6 Hz, 1 H), 6.21 (br d, J = 16.2 Hz, 1 H), 5.74-5.80 (m, 1 H), 4.91 (br s, 1 H), 4.23-4.45 (m, 2 H), 3.97-4.21 (m, 1 H), 3.44-3.79 (m, 2 H), 3.11-3.31 (m, 1 H), 2.67-2.77 (m, 1 H), 1.91 (s, 3 H), 1.35 (d, J = 6.8 Hz, 3 H), 1.08 (d, J = 6.6 Hz, 3 H), 0.94 (d, J = 6.8 Hz, 3 H). ^{19}F NMR (376 MHz, DMSO-d_6) δ ppm -115.64 (s, 1 F), -128.63 (s, 1 F). *m/z* (ESI, +ve ion): 561.2 $(M+H)^+$.

[0135] Another synthesis of Compound 9 and the relevant intermediates was described in a U.S. provisional patent application filed November 16, 2018, which is incorporated herein by reference in its entirety for all purposes.

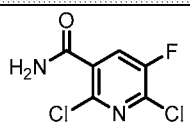


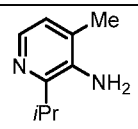
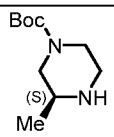
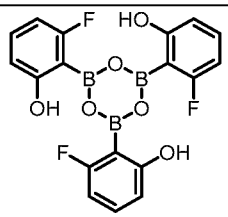
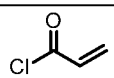
Representative Synthetic Processes

[0136] The present disclosure comprises the following steps wherein the synthesis and utilization of the boroxine intermediate is a novel and inventive step in the manufacture of AMG 510 (Compound 9):

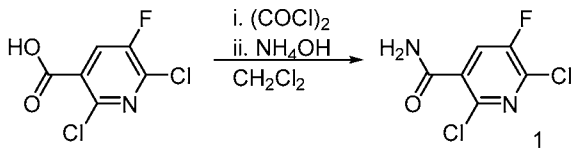


Raw Materials

Material	Structure	CAS #	MW (g/mol)
(2,6-dichloro-5-fluoronicotinamide) Compound 1	 Amide	113237-20-0	209.99

2-isopropyl-4-methylpyridin-3-amine Compound 2A	 ***Aniline***	1698293-93-4	150.22
(s)-1-Boc-3-methylpiperazine	 ***Amine***	147081-29-6	200.28
2,2',2''-(1,3,5,2,4,6-trioxatriborinane-2,4,6-triyl)tris(3-fluorophenol) Compound 6A	 ***Boroxine***	N/A	413.71
Acryloyl chloride	 ***Chloride***	814-68-6	90.51
Note: Des-boc content in the Amine and 3-chloropropionyl chloride content in the acryloyl chloride need to be controlled in these incoming starting materials to ensure sufficient final drug substance quality			

Step 1a



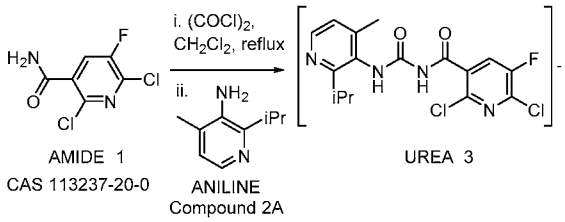
ACID
CAS 82671-06-5

AMIDE
CAS 113237-20-0

Material	CAS #	MW (g/mol)	Equivalents / Volumes	Moles	Theoretical
2,6-dichloro-5-fluoro-3-pyridinecarboxylic acid	82671-06-5	209.99	1.0 equiv.	119.1	25 kg
DCM	74-09-2	84.93	16.51 equiv.	2354.9	200 kg
DMF	68-12-2	73.09	0.068 equiv.	8.1	592 g (627 mL)
Oxalyl Chloride	79-37-8	126.93	1.25 equiv.	148.9	18.9 kg
Ammonium Hydroxide	1336-21-6	35.05	5 equiv.	595.5	40.2 L
Water	7732-18-5	18.02	N/A	N/A	261 L

[0137] To a solution of 2,6-dichloro-5-fluoro-3-pyridinecarboxylic acid (25kg; 119.1mol) in dichloromethane (167kg) and DMF (592g) was added Oxalyl chloride (18.9kg; 148.9mol) while maintaining an internal temp between 15-20 °C. Additional dichloromethane (33kg) was added as a rinse and the reaction mixture stirred for 2h. The reaction mixture is cooled then quenched with ammonium hydroxide (40.2L; 595.5mol) while maintaining internal temperature 0 ± 10°C. The resulting slurry was stirred for 90min then the product collected by filtration. The filtered solids were washed with DI water (3X 87L) and dried to provide 2,6-dichloro-5-fluoronicotinamide (Compound 1).

Step 1b

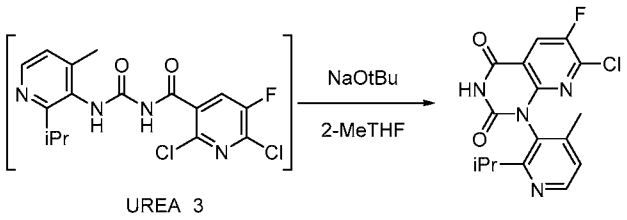


Material	CAS #	MW (g/mol)	Equivalents / Volumes	Moles	Theoretical
Amide (2,6-dichloro-5-fluoronicotinamide)	113237-20-0	209.99	1.0 equiv.	77.8	16.27 kg
Oxalyl Chloride	79-37-8	126.93	1.2 equiv.	93.8	11.9 kg (7.9 L)
Dichloromethane	75-09-2	84.93	N/A	N/A	730.7 kg (551.5 L)
Aniline DCM Solution 2-isopropyl-4-methylpyridin-3-amine	1698293-93-4	150.22	1.1 equiv.	85.9	12.9 kg (Aniline contained wt)

[0138] In reactor A, a solution of 2,6-dichloro-5-fluoronicotinamide (Compound 1) (16.27kg; 77.8mol) in dichloromethane (359.5kg) was added oxalyl chloride (11.9kg; 93.8mol) while maintaining temp ≤ 25°C for 75min. The resulting solution was then headed to 40°C ± 3°C and aged for 3h. Using vacuum, the solution was distilled to remove dichloromethane until the solution was below the agitator. Dichloromethane (300 kg) was then added and the mixture cooled to 0 ± 5°C. To a clean, dry reactor (reactor B) was added,2-isopropyl-4-methylpyridin-3-amine (ANILINE Compound 2A) (12.9kg; 85.9mol) followed by dichloromethane (102.6 kg). The ANILINE solution was azeodried via vacuum distillation while maintaining an internal temperature between 20-25 °), replacing with additional dichloromethane until the solution was dry by KF analysis (limit ≤ 0.05%). The solution volume was adjusted to approx. 23L volume with dichloromethane. The dried ANILINE solution was then added to reactor A while maintaining an internal temperature of

0 ± 5°C throughout the addition. The mixture was then heated to 23 °C and aged for 1h. the solution was polish filtered into a clean reactor to afford 2,6-dichloro-5-fluoro-N-((2-isopropyl-4-methylpyridin-3-yl)carbamoyl)nicotinamide (Compound 3) as a solution in DCM and used directly in the next step.

Step 2

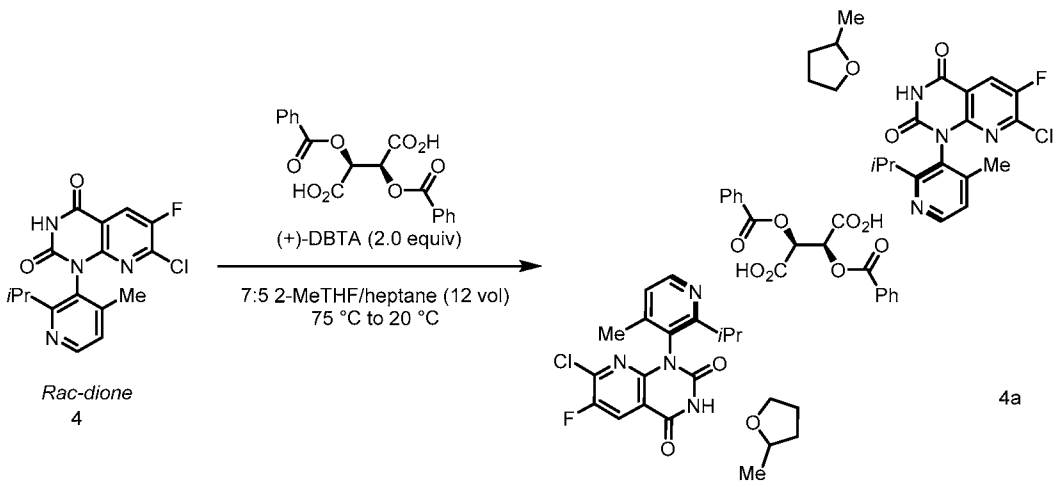


Material	CAS #	MW (g/mol)	Equivalents / Volumes	Moles	Theoretical
Urea, solution in DCM 2,6-dichloro-5-fluoro-*N*-{[4-methyl-2-(propan-2-yl)pyridin-3-yl]carbamoyl}pyridine-3-carboxamide	N/A	385.22	1.0 equiv.	38.9	208.3 kg (15 kg contained weight)
2-methyltetrahydrofuran	96-47-9	86.13	N/A	N/A	308 kg (358 L)
Sodium tert-butoxide	865-48-5	96.11	2.0 equiv	97.8	9.4 kg
Ammonium Chloride	12125-02-9	53.49	N/A	430	23.0 kg
Hydrochloric Acid	7467-01-0	36.46	N/A	41	1.6 kg
Magnesium Sulfate	7487-88-9	120.37	N/A	195	23.5 kg
Sodium Chloride	7647-14-5	58.44	N/A	282	16.5 kg
Heptane	142-82-5	100.21	N/A	N/A	94 L
10% citric acid					75 kg

[0139] A dichloromethane solution of 2,6-dichloro-5-fluoro-*N*-{[4-methyl-2-(propan-2-yl)pyridin-3-yl]carbamoyl}pyridine-3-carboxamide (UREA (Compound 3)) (15kg contained; 38.9mol) was solvent exchanged into 2-MeTHF using vacuum distillation while maintaining internal temperature of 20-25 °C. The reactor volume was adjusted to 40L and then

additional 2-MeTHF was charged (105.4 kg). Sodium t-butoxide was added (9.4 kg; 97.8mol) while maintaining 5-10 °C. The contents where warmed to 23 °C and stirred for 3h. The contents where then cooled to 0-5C and ammonium chloride added (23.0kg; 430mol) as a solution in 60L of DI water. The mixture was warmed to 20 C and DI water added (15L) and further aged for 30min. Agitation was stopped and the layers separated. The aqueous layer was removed and to the organic layer was added DI water(81.7L). A mixture of conc HCl (1.5kg) and water (9L) was prepared then added to the reactor slowly until pH measured between 4-5. The layers were separated, and the aqueous layer back extracted using 2-MeTHF (42.2kg). The two organic layers combined and washed with a 10% citric acid solution (75kg) followed by a mixture of water (81.7L) and saturated NaCl (19.8 kg). The organic layer was then washed with saturated sodium bicarbonate (75kg) repeating if necessary to achieve a target pH of $\geq$ 7.0 of the aqueous. The organic layer was washed again with brine (54.7kg) and then dried over magnesium sulfate (5kg). The mixture was filtered to remove magnesium sulfate rinsing the filtered bed with 2-MeTHF (49.2 kg). The combined filtrate and washes where distilled using vacuum to 40L volume. The concentrated solution was heated to 55 °C and heptane (10-12kg) slowly added until cloud point. The solution was cooled to 23 °C over 2h then heptane (27.3 kg) was added over 2h. The product slurry was aged for 3h at 20-25 °C then filtered and washed with a mixture of 2-MeTHF (2.8kg) and heptane (9kg). The product was dried using nitrogen and vacuum to afford solid 7-chloro-6-fluoro-1-(2-isopropyl-4-methylpyridin-3-yl)pyrido[2,3-d]pyrimidine-2,4(1H,3H)-dione (rac-DIONE (Compound 4)).

Step 3



Rac-dione
4

4a

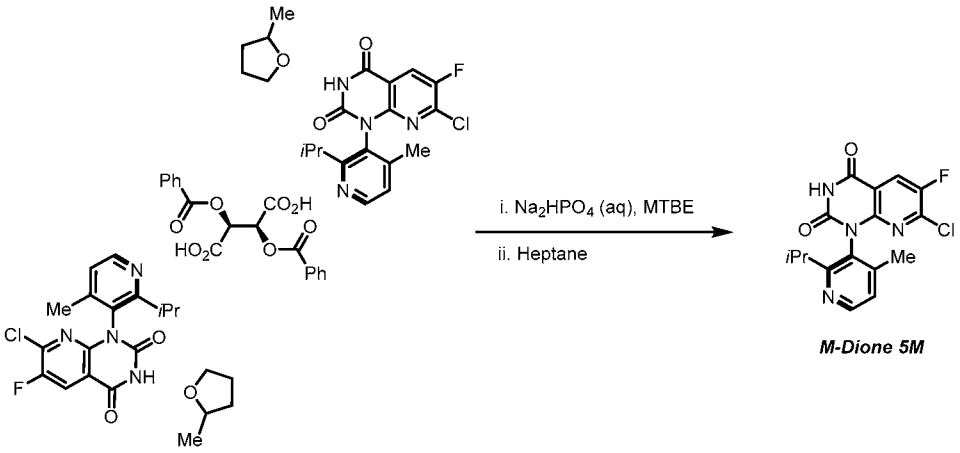
M-dione DBTA co-crystal

Material	CAS #	MW (g/mol)	Equivalents / Volumes	Moles	Theoretical
Rac-dione (Compound 4)	N/A	348.76	1.0		
(+)-2,3-dibenzoyl-D-tartaric acid	17026-42-5	358.30	2.0		
2-methyltetrahydrofuran	96-47-9	86.13	7.0		
heptane	142-82-5	100.21	2.0		
heptane	142-82-5	100.21	3.0		
2-methyltetrahydrofuran	96-47-9	86.13	4.0		
heptane	142-82-5	100.21	2.0		

[0140] To a vessel, an agitated suspension of Compound 4, (1.0 eq.) in 2-methylterahydrofuran (7.0 L/kg) was added (+)-2,3-dibenzoyl-D-tartaric acid (2.0 eq.) under an atmosphere of nitrogen. 2-MeTHF is chiral, but it is used as a racemic mixture. The different enantiomers of 2-MeTHF are incorporated randomly into the co-crystal. The resulting suspension was warmed to 75°C and aged at 75°C until full dissolution was observed (≤ 30 mins.). The resulting solution was polish filtered at 75°C into a secondary vessel. To the polish filtered solution was charged n-Heptane (2.0 L/kg) at a rate that maintained the internal temperature above 65°C. The solution was then cooled to 60°C, seeded with crystals (0.01 kg/kg) and allowed to age for 30 minutes. The resulting suspension

was cooled to 20°C over 4 hours and then sampled for chiral purity analysis by HPLC. To the suspension, n-Heptane (3.0 L/kg) was charged and then aged for 4 hours at 20°C under an atmosphere of nitrogen. The suspension was filtered, and the isolated solids were washed two times with (2:1) n-Heptane:2-methyltetrahydrofuran (3.0 L/kg). The material was dried with nitrogen and vacuum to afford M-Dione:DBTA: Me-THF complex (Compound 4a).

Step 4



M-Dione 5M

M-Dione/DBTA/2-MeTHF cocrystal 4a

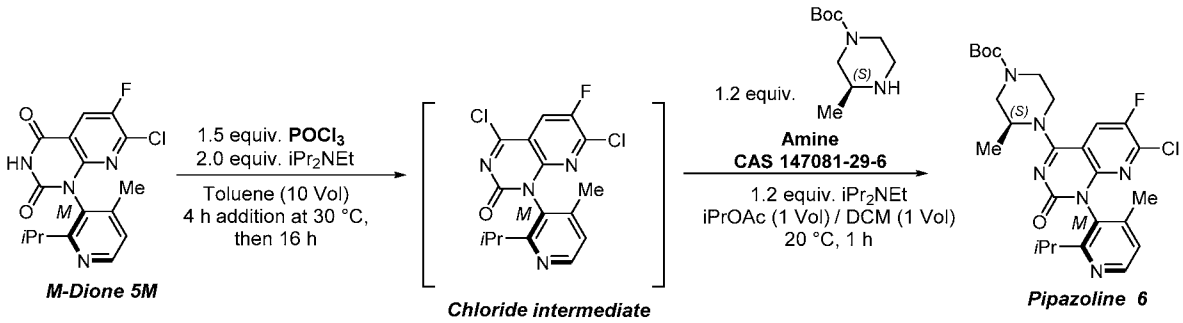
Material	CAS #	MW (g/mol)	Equivalents / Volumes	Moles	Theoretical
M-Dione/DBTA/Me-THF cocrystal (Compound 4a)	N/A	1228.08	1.0	74.2	46.9 kg (25.9 kg corrected for M-dione)
Methyl *tert*-butyl ether	1634-04-4	88.15	45.0	17593	2100 L
Disodium hydrogen phosphate	7558-79-4	141.96	2.0	148.4	21.1 kg
USP purified water					As needed
Magnesium sulfate	7487-88-9	120.37	N/A	N/A	25 kg
Heptane	142-82-5	100.20	60.0	19322	2835 L

[0141] To vessel A, a suspension of disodium hydrogen phosphate (21.1 kg, 2.0 equiv) in DI water (296.8 L, 6.3 L/kg) was agitated until dissolution was observed (≥ 30 min.). To vessel B, a suspension of the M-Dione:DBTA: Me-THF complex (Composition 4a)[46.9 kg (25.9 kg corrected for M-dione, 1.0 equiv.)] in methyl tert-butyl ether (517.8 L, 11.0 L/kg) was agitated for 15 to 30 minutes. The resulting solution from vessel A was added to vessel B, and then the mixture was agitated for more than 3 hours. The agitation was stopped, and the biphasic mixture was left to separate for more than 30 minutes. The lower aqueous phase was removed and then back extracted with methyl tert-butyl ether (77.7 L, 1.7 L/kg). The organic phases were combined in vessel B and dried with magnesium sulfate (24.8 kg, 0.529 kg/kg). The resulting suspension from vessel B was agitated for more than three hours and then filtered into vessel C. To vessel B, a methyl tert-butyl ether (46.9 L, 1.0 L/kg) rinse was charged and then filtered into vessel C. The contents of vessel C were cooled to 10 °C and then distilled under vacuum while slowly being warmed to 35°C. Distillation was continued until 320-350 kg (6.8-7.5 kg/kg) of methyl tert-butyl ether was collected. After cooling the contents of vessel C to 20°C, n-Heptane (278.7 L, 5.9 L/kg) was charged over one hour and then distilled under vacuum while slowly being warmed to 35°C. Distillation was continued until a 190-200 kg (4.1-4.3 kg/kg) mixture of methyl tert-butyl ether and n-Heptane was collected. After cooling the contents of vessel C to 20°C, n-Heptane (278.7 L, 5.9 L/kg) was charged a second time over one hour and then distilled under vacuum while slowly being warmed to 35°C. Distillation was continued until a 190-200 kg (4.1-4.3 kg/kg) mixture of methyl tert-butyl ether and n-Heptane was collected. After cooling the contents of vessel C to 20°C, n-Heptane (195.9 L, 4.2 L/kg) was charged a third time over one hour and then sampled for solvent composition by GC analysis. The vessel C suspension continued to agitate for more than one hour. The suspension was filtered, and then washed with a n-Heptane (68.6 L, 1.5 L/kg) rinse from vessel C. The isolated solids were dried at 50°C, and a sample was submitted for stock suitability. Afforded 7-chloro-6-fluoro-(1*M*)-1-[4-methyl-2-(propan-2-yl)pyridin-3-yl]pyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (M-DIONE) Compound 5M.

[0142] The first-generation process highlighted above has been successfully scaled on 200+ kg of rac-dione starting material (Compound 4). In this process, seeding the crystallization with the thermodynamically-stable rac-dione crystal form (which exhibits low solubility) would cause a batch failure. Based on our subsequent studies, we found that increasing the DBTA equivalents and lowering the seed temperature by adjusting heptane

charge schedule improves robustness of the process. The improved process is resistant to the presence of the thermodynamically-stable rac-dione crystal form and promotes successful separation of atropisomers. Subsequent batches will incorporate the improved process for large scale manufacture.

Step 5



Material	CAS #	MW (g/mol)	Equivalents	L/kg input
M-Dione 5M	N/A	348.76	1 equiv.	1 equiv.
Toluene-1	108-88-3	92.14		10.0 L/kg
Toluene-2	108-88-3	92.14		0.5 L/kg
Toluene-3	108-88-3	92.14		4.5 L/kg
Phosphoryl chloride	10025-87-3	153.33	1.5 equiv.	
N,N-Diisopropylethylamine-1	7087-68-5	129.24	2.0 equiv.	
N,N-Diisopropylethylamine-2	7087-68-5	129.24	1.2 equiv.	
(s)-1-Boc-3-methylpiperazine	147081-29-6	200.28	1.2 equiv.	
Sodium bicarbonate	144-55-8	84.01	4.5 equiv.	
Water-1		18.01		15.0 L/kg
Dichloromethane	75-09-2	84.93		1.0 L/kg
isopropyl acetate-1	108-21-4	102.132		1.0 L/kg
Water-2		18.01		5.0 L/kg
Water-3		18.01		5.0 L/kg
isopropyl acetate-2	108-21-4	102.132		5.0 L/kg
isopropyl acetate-3	108-21-4	102.132		5.0 L/kg
acetone	67-64-1	58.08		10.0 L/kg
Water-4		18.01		10.0 L/kg
1:1 Acetone/water	N/A	N/A		5.0 L/kg

Note: All L/kg amounts are relative to *M-Dione* input; All equiv. amounts are relative to M-Dione input after adjusted by potency.

[0143] M-Dione (Compound 5M, 1.0 equiv.) and Toluene-1 (10.0 L/kg) was charged to Vessel A. The resulting solution was dried by azeotropic distillation under vacuum at 45 °C until 5.0 L/kg of solvents has been removed. The contents of Vessel A were then cooled to 20 °C.

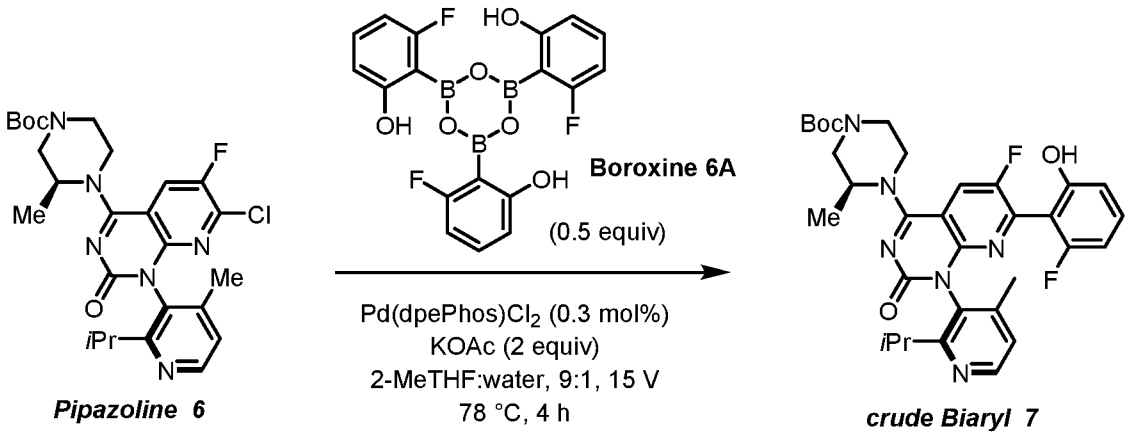
[0144] Vessel C was charged with Toluene-3 (4.5 L/kg), Phosphoryl chloride (1.5 equiv.) and *N,N*-Diisopropylethylamine-1 (2.0 equiv.) while maintaining the internal temperature below 20 ± 5 °C.

Upon finishing charging, Vessel C was warmed to 30 ± 5 °C. The contents of Vessel A were then transferred to Vessel C over 4 hours while maintaining the internal temperature at 30 ± 5°C. Vessel A was rinsed with Toluene-2 (0.5 L/kg) and transferred to Vessel C. The contents of Vessel C were agitated at 30°C for an additional 3 hours. The contents of Vessel C were cooled to 20 ± 5 °C. A solution of (*s*)-1-boc-3-methylpiperazine (1.2 equiv.), *N,N*-Diisopropylethylamine-2 (1.2 equiv.) in isopropyl acetate-1 (1.0 L/kg) was prepared in Vessel D. The solution of Vessel D was charged to vessel C while maintaining a batch temperature of 20 ± 5 °C (Note: Exotherm is observed). Upon the end of transfer, Vessel D was rinsed with additional dichloromethane (1.0 L/kg) and transferred to Vessel C. The contents of Vessel C were agitated for an additional 60 minutes at 20 °C. A solution of sodium bicarbonate [water-1 (15.0 L/kg + Sodium bicarbonate (4.5 equiv.)] was then charged into Vessel C over an hour while maintaining an internal temperature at 20 ± 5 °C throughout the addition. The contents of Vessel C were agitated for at least 12 hours at which point the Pipazoline (Compound 6) product was isolated by filtration in an agitated filter dryer. The cake was washed with water-2 and -3 (5.0 L/kg x 2 times, agitating each wash for 15 minutes) and isopropyl acetate-2 and 3 (5.0 L/kg x 2 times, agitating each wash for 15 min). The cake as dried under nitrogen for 12 hours.

Acetone Re-slurry (Optional):

[0145] Pipazoline (Compound 6) and acetone (10.0 L/kg) were charged to Vessel E. The suspension was heated to 50 °C for 2 hours. Water-4 (10.0 L/kg) was charged into Vessel E over 1 hour. Upon completion of water addition, the mixture was cooled to 20 °C over 1 hour. The contents of Vessel E were filtered to isolate the product, washing the cake with 1:1 acetone/water mixture (5.0 L/kg). The cake was dried under nitrogen for 12 hours.

Step 6



General Note: All equivalents and volumes are reported in reference to Pipazoline input

Material	CAS #	MW (g/mol)	Equivalents	L/kg or kg/kg input
Pipazoline (Compound 6)		531	1.0 equiv	-
Boroxine (Compound 6 A)	N/A	413.71	0.5 equiv	-
Boroxine (Compound 6A)	N/A	413.71	0.1 equiv	-
2-methyltetrahydrofuran	96-47-9	86.13	-	9.0 L/kg
2-methyltetrahydrofuran	96-47-9	86.13	-	0.5 L/kg
$Pd(dpePhos)Cl_2$	205319-06-8	715.9	0.003 equiv	-
$Pd(dpePhos)Cl_2$	205319-06-8	715.9	0.001 equiv	-
Wet 2-methyltetrahydrofuran	96-47-9	86.13	-	4.5 L/kg
Water	7732-18-5	18.02	-	6.5 L/kg
Potassium Acetate	127-08-2	98.14	2.0 equiv	-
Biaryl Seed		606.7	-	0.002 kg/kg
Wet 2-methyltetrahydrofuran	96-47-9	86.13	-	0.02 L/kg
Heptane	142-82-5	100.20		5.0 L/kg
Water	7732-18-5	18.02	-	5.0 L/kg
Isopropanol	67-63-0	66.10	-	2.5 L/kg
Water	7732-18-5	18.02	-	2.5 L/kg
Isopropanol	67-63-0	66.10	-	2.5 L/kg
Isopropanol	67-63-0	66.10	-	2.5 L/kg
Heptane	142-82-5	100.20		2.5 L/kg

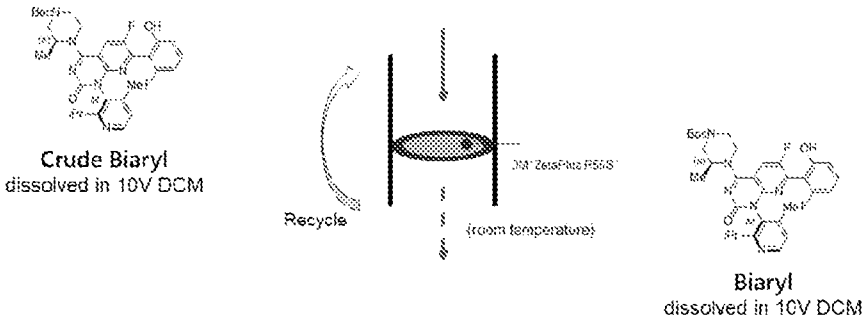
Note: All L/kg and kg/kg amounts are relative to *Pipazoline* input

[0146] Reactor A is charged with *Pipazoline* (Compound 6, 1.0 equiv), degassed 2-MeTHF (9.0 L/kg) and a solution of potassium acetate (2.0 equiv) in degassed water (6.5 L/kg). The resulting mixture is warmed to 75 ± 5 °C and then, charge a slurry of

$Pd(dpePhos)Cl_2$ (0.003 equiv) in 2-MeTHF (0.5 L/kg). Within 2 h of catalyst charge, a solution of freshly prepared *Boroxine* (Compound 6A, 0.5 equiv) in wet degassed 2-MeTHF (4.0 L/kg, KF > 4.0%) is charged over the course of >1 hour, but < 2 hours, rinsing with an additional portion of wet 2-MeTHF (0.5 L/kg) after addition is complete. After reaction completion (<0.15 area % Pipazoline remaining, typically <1 h after boroxine addition is complete), 0.2 wt% (0.002 kg/kg) of *Biaryl* seed is added as a slurry in 0.02 L/kg wet 2-MeTHF, and the resulting seed bed is aged for > 60 min. Heptane (5.0 L/kg) is added over 2 hours at 75 ± 5 °C. The batch is then cooled to 20 ± 5 °C over 2 hours and aged for an additional 2 h. The slurry is then filtered and cake washed with 1 x 5.0L/kg water, 1 x 5.0L/kg 1:1 iPrOH:water followed by 1 x 5.0 L/kg 1:1 iPrOH:heptane (resuspension wash: the cake is resuspended by agitator and allow to set before filtering) . The cake (Biaryl, Compound 7) is then dried under vacuum with a nitrogen sweep.

Note: If the reaction stalls, an additional charge of catalyst and boroxine is required

Step 7 Charcoal Filtration for Pd removal



General Note: All equivalents and volumes are reported in reference to crude Biaryl input

	Material	CAS #	MW (g/mol)	Equivalents	L/kg or kg/kg input
Initial dissolution	Crude Biaryl	N/A	606.67	1.0	-
	Dichloromethane	75-09-2	84.93	-	10 L/kg
	3M "Zeta Plus R55SP" Carbon Disk				
rinse	Dichloromethane	75-09-2	84.93	-	1.0 L/kg

Note: All L/kg and kg/kg amounts are relative to *crude Biaryl* input

[0147] In a clean Vessel A, charge crude Biaryl (1 equiv) and charge DCM (10 L/kg). Agitate content for > 60 minutes at 22 ± 5 °C, observing dissolution. Pass crude Biaryl from

Vessel A, through a bag filter and carbon filters at a flux ≤ 3 L^2/min/m and collect filtrate in clean Vessel B. Charge DCM rinse (1 L/kg) to Vessel A, and through carbon filters to collect in vessel B.

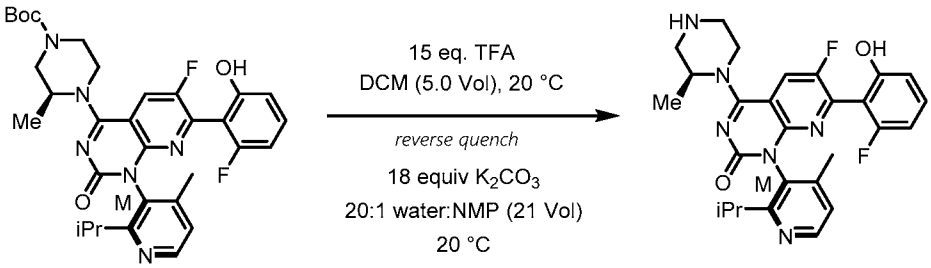
[0148] From filtrate in Vessel B, pull a solution sample for IPC Pd content. Sample is concentrated to solid and analyzed by ICP-MS. IPC: Pd ≤ 25 ppm with respect to Biaryl.

a. If Pd content is greater than 25 ppm with respect to Biaryl on first or second IPC sample, pass solution through carbon filter a second time at ≤ 3 L^2/min/m^2, rinsing with 1 L/kg DCM; sample filtrate for IPC.

b. If Pd content remains greater than 25 ppm after third IPC, install and condition fresh carbon discs. Pass Biaryl filtrate through refreshed carbon filter, washing with 1 L/kg DCM. Sample for IPC.

[0149] Distill and refill to appropriate concentration. Prepare for distillation of recovered filtrate by concentrating to ≤ 4 L/kg DCM, and recharge to reach 5.25 ± 0.25 L/kg DCM prior to moving into Step 7 Boc-deprotection reaction.

Step 7



Biaryl ***Des-Boc***

General Note: All equivalents and volumes are reported in reference to crude Biaryl input

Material	CAS #	MW (g/mol)	Equivalents	L/kg or kg/kg input
Biaryl Compound 8	NA	606.67	1.0	-
Dichloromethane	74-09-2	84.93	-	5.0 L/kg
TFA	76-05-1	114.02	15.0	1.9 L/kg
Potassium Carbonate	584-08-7	138.2	18.0	4.1 kg/kg
Water	7732-18-5	18.02	-	20.0 L/kg
1-methyl-2-pyrrolidinone	872-50-4	99.13	-	1.0 L/kg
Dichloromethane	74-09-2	84.93	-	1.0 L/kg
Water	7732-18-5	18.02	-	10.0 L/kg
Water	7732-18-5	18.02	-	10.0 L/kg

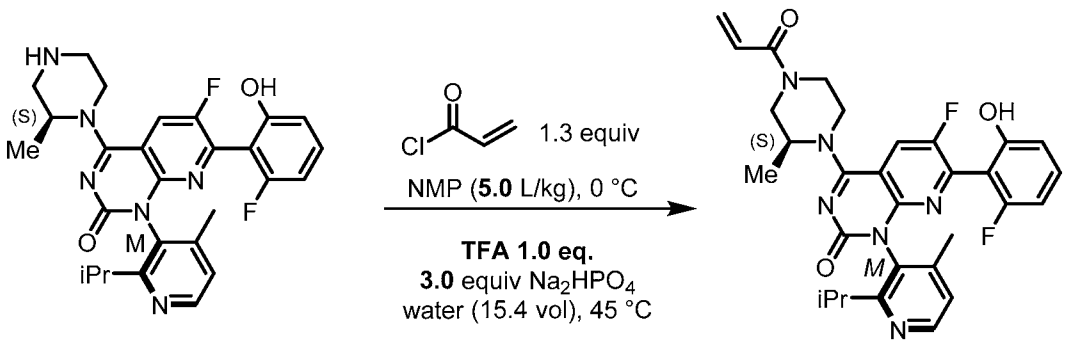
Note: *All L/kg and kg/kg amounts are relative to Biaryl input*

[0150] To Reactor A was added: *tert*-butyl (3*S*)-4-{6-fluoro-7-(2-fluoro-6-hydroxyphenyl)-(1*M*)-1-[4-methyl-2-(propan-2-yl)pyridin-3-yl]-2-oxo-1,2-dihydropyrido[2,3-*d*]pyrimidin-4-yl}-3-methylpiperazine-1-carboxylate (*Biaryl*) (1.0 equiv), dichloromethane (5.0 L/kg), and the TFA (15.0 equiv, 1.9 L/kg) is charged slowly to maintain the internal temperature at 20 ± 5 °C. The reaction was stirred for 4 h at 20 ± 5 °C.

[0151] To Reactor B was added: potassium carbonate (18.0 equiv), water (20.0 L/kg), and NMP (1.0) to form a homogenous solution. While agitating at the *maximum acceptable rate* for the equipment, the reaction mixture in A was transferred into the potassium carbonate solution in B over 30 minutes (~ 0.24 L/kg/min rate). The mixture was stirred at 20 ± 5 °C for an additional 12 h.

[0152] The resulting slurry was filtered and rinsed with water (2 x 10 L/kg). The wet cake was dried for 24 h to give 6-fluoro-7-(2-fluoro-6-hydroxyphenyl)-4-[(2*S*)-2-methylpiperazin-1-yl]-(1*M*)-1-[4-methyl-2-(propan-2-yl)pyridin-3-yl]pyrido[2,3-*d*]pyrimidin-2(1*H*)-one (*Des-Boc, Compound 8*).

Step 8



Des-Boc 8 ***Crude AMG 510 9A***

General Note: All equivalents and volumes are reported in reference to Des-Boc input

	Material	CAS #	MW (g/mol)	Equivalents	L/kg or kg/kg input
reaction	Des-Boc Compound 8	N/A	506.6	1.0	-
	TFA	76-05-1	114.02	1.0	
	1-Methyl-2-Pyrrolidinone	872-50-4	99.1	-	4.2
	1-Methyl-2-Pyrrolidinone	872-50-4	99.1	-	0.8
	Acryloyl Chloride	814-68-6	90.5	1.3	-
quench soln.	Sodium Phosphate Dibasic	7558-79-4	142.0	3.0 eq	
	Water	7732-18-5	18.0	-	15.0 L/kg
	AMG 510 Seed	N/A	560.6	0.005	0.005 kg/kg
	Water	7732-18-5	18.0	-	0.4 L/kg
rinse	1-Methyl-2-Pyrrolidinone	872-50-4	99.1	-	0.5 L/kg
wash	Water	7732-18-5	18.02	-	10.0 L/kg

Note: All L/kg and kg/kg amounts are relative to Des-Boc input

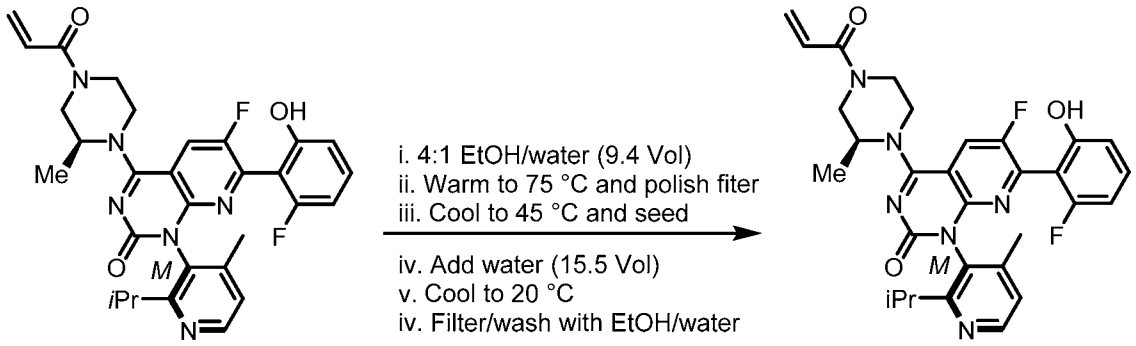
[0153] *Des-Boc* (Compound 8, 1.0 equiv) and NMP (4.2 L/kg) are charged to Vessel A under nitrogen, charge the TFA (1.0 equiv.) slowly to maintain the Tr <25 °C. The mixture is aged at 25 °C until full dissolution is observed (about 0.5 hour). The solution is then polish filtered through a 0.45 micron filter into Vessel B, washing with a NMP (0.8 L/kg). The filtrate and wash are combined, and then cooled to 0 °C. To the resulting solution, Acryloyl Chloride (1.3 equiv.) is added while maintaining temperature < 10 C. The reaction mixture is then aged at 5 ±5°C until completed by IPC (ca. 1.5 hrs).

Preparation of Aqueous Disodium Phosphate Quench:

[0154] Disodium Phosphate (3.0 equiv) and Water (15.0 L/kg) are charged to Vessel C. The mixture is aged at 25 °C until full dissolution is observed. The solution is warmed to 45 ±5°C. A seed slurry of *AMG 510* (0.005 equiv.) in Water (0.4 L/kg) is prepared and added to Vessel C while maintaining temperature at 45 ±5°C.

[0155] The reaction mixture in Vessel B is transferred to Vessel C (quench solution) while maintaining temperature at 45 ±5°C (ca. 1 hrs). Vessel B is washed with a portion of NMP (0.5 L/kg). The product slurry is aged for 2 hrs at 45 ±5°C, cooled to 20 °C over 3 hrs, aged at 20 °C for a minimum of 12 hrs, filtered and washed with Water (2 x 10.0 L/kg). The product is dried using nitrogen and vacuum to afford *Crude AMG 510 (Compound 9A).*

Step 9



Crude AMG 510 9A ***AMG 510 Compound 9***

General Note: All equivalents and volumes are reported in reference to crude AMG 510 input

Material	CAS #	MW (g/mol)	Equivalents	L/kg or kg/kg input
Crude AMG 510 Compound 9A	NA	560.60	1.0	-
Ethanol	64-17-5		-	7.5 L/kg
Water	-	18.02	-	1.9 L/kg
AMG 510 seed[1]	-	560.60	0.015	0.015 kg/kg
Water	--	18.02	-	15.0 L/kg
Ethanol (for wash)	64-17-5	-	2.5 V	2.5 L/kg
Water (for wash)	-	-	5.0 V	5.0 L/kg

Note: All L/kg and kg/kg amounts are relative to *Crude AMG 510* input

[0156] Reactor A was charged with 6-fluoro-7-(2-fluoro-6-hydroxyphenyl)-(1*M*)-1-[4-methyl-2-(propan-2-yl)pyridin-3-yl]-4-[(2*S*)-2-methyl-4-(prop-2-enoyl)piperazin-1-yl]pyrido[2,3-*d*]pyrimidin-2(1*H*)-one (***Crude AMG 510***) (1.0 equiv), ethanol (7.5 L/kg), and water (1.9 L/kg). The mixture heated to 75 °C and polish filtered into a clean Reactor B. The solution was cool to 45 °C and seeded with authentic milled AMG 510 seed (0.015 ± 0.005

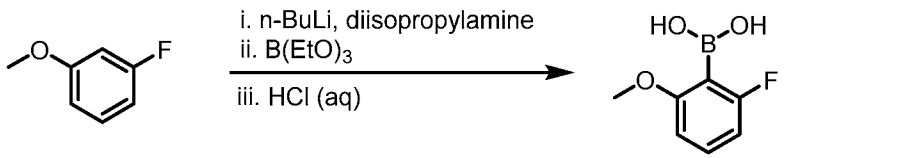
[1] Seed performs best when reduced in particle size via milling or with other type of mechanical grinding if mill is not available (mortar/ pestle). Actual seed utilized will be based on seed availability. 1.0-2.0% is seed is target amount.

kg/kg); the resulting slurry was aged for 30 min. Water (15.0 L/kg) was added over 5h while maintaining an internal temperature > 40 °C; the mixture was aged for an additional 2h.

[0157] The mixture was cooled to 20 °C over 3 hours and aged for 8h, after which the solid was collected by filtration and washed using a mixture of ethanol (2.5 L/kg) and water (5.0 L/kg). The solid was dried using vacuum and nitrogen to obtain 6-fluoro-7-(2-fluoro-6-hydroxyphenyl)-(1*M*)-1-[4-methyl-2-(propan-2-yl)pyridin-3-yl]-4-[(2*S*)-2-methyl-4-(prop-2-enoyl)piperazin-1-yl]pyrido[2,3-*d*]pyrimidin-2(1*H*)-one (***AMG 510, Compound 9***).

Compound 6A Boroxine Synthesis:

Lithiation/borylation



3-fluoroanisole

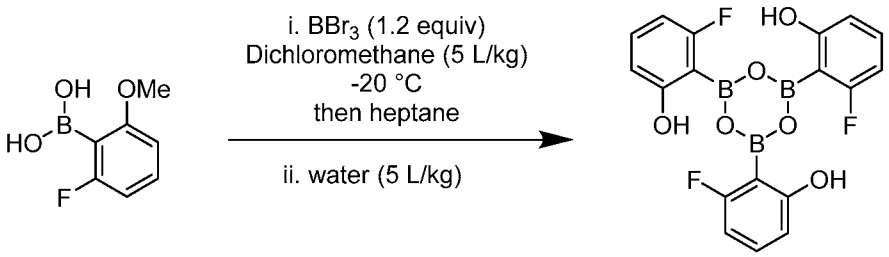
(2-fluoro-6-methoxyphenyl)boronic acid
79% yield

Material	CAS #	MW (g/mol)	Equivalents / Volumes	mol	Mass (g)	Volume (L)
3-Fluoroanisole	456-49-5	126.13	1.0	1.19	150	0.136
n-butyllithium (2.5 M in hexane) (first base)	109-72-8	64.06	1.5	1.78	N/A	0.712
Diisopropylamine (secondary amine base)	108-18-9	101.19	1.4	1.66	168	0.233
Triethylamine hydrochloride (catalyst)	554-68-7	137.65	0.01	0.012	1.65	N/A
Triethylborate (reagent)	150-46-9	145.99	2.0	2.38	347.5	0.405
Tetrahydrofuran	109-99-9	72.11	12 vol	N/A	N/A	1.8

Hydrochloric acid (2N) (acid)	7647-01-0	36.46	10 vol	N/A	N/A	1.5
Methyl tert-butyl ether	1634-04-4	88.15	12 Vol	N/A	N/A	1.8
Heptane	142-82-5	100.20	10.5 Vol	N/A	N/A	1.575

[0158] Reactor A was charged with THF (6 vol), a secondary amine base, Diisopropylamine (1.4 equiv), and a catalyst, such as triethylamine hydrochloride (0.01 equiv.). The resulting solution was cooled to -70 °C and a first base, n-BuLi (2.5 M in hexane, 1.5 equiv) was slowly added. After addition is complete, a solution of 3-fluoroanisole (1.0 equiv) in THF (6 vol) was added slowly and kept at -70 °C for 5 min. Concurrently or subsequently, a reagent, $B(EtO)_3$ (2.0 equiv), was added slowly and kept at -70 °C for 10 min. The reaction mixture was quenched with an acid, 2N HCl. The quenched reaction mixture was extracted with MTBE (3 x 4 vol). The combined organic phases were concentrated to 1.5-3 total volumes. Heptane (7-9 vol) was added drop-wise and the mixture was cooled to 0-10 °C and stirred for 3 h. The mixture was filtrated and rinsed with heptane (1.5 vol). The solid was dried under nitrogen at < 30 °C to afford (2-fluoro-6-methoxyphenyl)boronic acid.

Demethylation:



Boroxine Compound 6A
60% yield

Material	CAS #	MW (g/mol)	Equivalents	L/kg or kg/kg input
(2-fluoro-6-methoxyphenyl)boronic acid	78495-63-3	169.95	1.0	-
Boron tribromide	10294-33-4	250.52	1.2	1.8 kg/kg
Dichloromethane	74-09-2	84.93	-	4.0 L/kg
Dichloromethane	74-09-2	84.93	-	4.0 L/kg
Water	7732-18-5	18.02	-	3.0 L/kg
Water	7732-18-5	18.02	-	3.0 L/kg
Saturated sodium bicarbonate solution			As needed	
Dichloromethane	74-09-2	84.93	-	5.0 L/kg
Concentrate hydrochloric acid			As needed	
Water	7732-18-5	18.02	-	3.0 L/kg
Water	7732-18-5	18.02	-	3.0 L/kg
Ethanol				
Water				
Water	7732-18-5	18.02	-	3.0 L/kg
Water	7732-18-5	18.02	-	3.0 L/kg

Note: All L/kg and kg/kg amounts are relative to (2-fluoro-6-methoxyphenyl)boronic acid input

[0159] To a reactor, charge dichloromethane (solvent, 4.0 L/kg) and an acid, BBr_3 (1.2 equiv), and cool to -20 °C. To this solution, a suspension of (2-fluoro-6-methoxyphenyl)boronic acid (1.0 equiv) in dichloromethane (4.0 L/kg) was added into the BBr_3/DCM mixture while keeping temperature -15 to -25 °C. The reaction was allowed to proceed for approximately 2 hours while monitored by HPLC [≤1% (2-fluoro-6-methoxyphenyl)boronic acid] before reverse quenching into water (3.0 L/kg). The precipitated solid was then isolated by filtration and slurried with water (3.0 L/kg) on the

filter prior to deliquoring. The filtrates were adjusted to pH 4-6 by the addition of sodium bicarbonate. The bottom organic phase was separated and the resulting aqueous layer was washed with dichloromethane (solvent, 5.0 Vol) and adjusted to pH = 1 by addition of concentrated hydrochloric acid. The resulting solids were isolated by filtration, washing the cake with water (2 x 5.0 L/kg)

Purification via Reslurry (required)

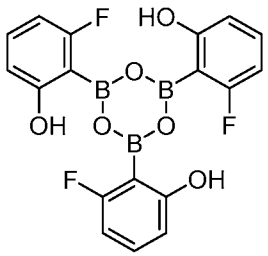
[0160] The combined crude solids were charged into a reactor and slurried with 5% EtOH/water (5.0 L/kg) at 20 °C for >1 h. The purified product was then isolated by filtration and rinsed with water (2 x 3 L/kg) before drying on the filter at < 30 °C to with nitrogen/vacuum to afford 2,2',2"-(1,3,5,2,4,6-trioxatriborinane-2,4,6-triyl)tris(3-fluorophenol) (**Boroxine, Compound 6A**).

[0161] The foregoing is merely illustrative of the invention and is not intended to limit the invention to the disclosed uses. Variations and changes, which are routine to one skilled in the art, are intended to be within the scope and nature of the invention, which are defined in the appended claims. All mentioned references, patents, applications and publications, are hereby incorporated by reference in their entirety, as if here written.

CLAIMS

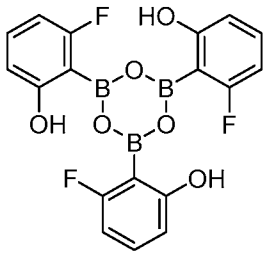
What is claimed is:

1. A compound of Formula 6A:



.

2. A composition, the composition comprising a compound of Formula 6A:



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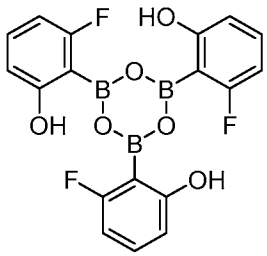
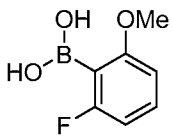
3. A method of making a compound of formula 6A:



,

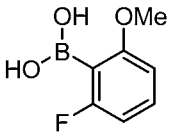
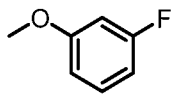
the method comprising reacting a mixture comprising a compound having the structure:  with an acid with at least one solvent.

4. Then method of claim 3, wherein the acid is BBr_3.

5. The method of claim 3, wherein the at least one solvent is dichloromethane.

6. The method of claim 3, wherein the at least one solvent is heptane.

7. The method of claim 3, wherein the mixture is cooled to approximately -20 °C.

8. The method of claim 3, wherein the method of making a compound of the structure:  comprises mixing a compound having the structure:  with a reagent, a first base, a secondary amine base, a catalyst, and an acid.

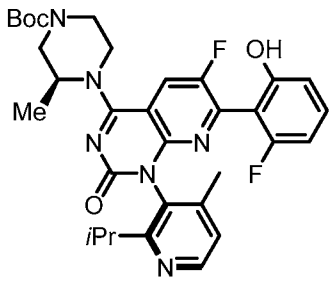
9. The method of claim 8, wherein the first base in n-Butyl lithium.

10. The method of claim 8, wherein the secondary amine base is diisopropylamine.

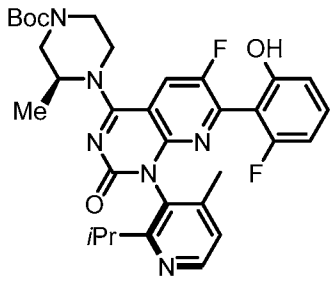
11. The method of claim 8, wherein the catalyst is triethylamine hydrochloride.

12. The method of claim 8, wherein the reagent is triethyl borate.

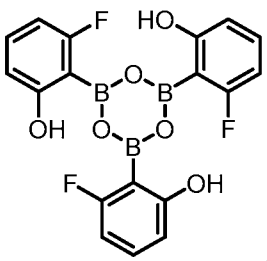
13. The method of claim 8, wherein the acid is HCl.

14. The method of claim 3, wherein the compound of formula 6A is used to generate a compound having the Formula 7:  .

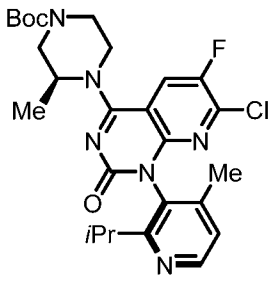
15. The method of making a compound of Formula 7,

 ,

comprising the steps of reacting a compound of Formula 6A,

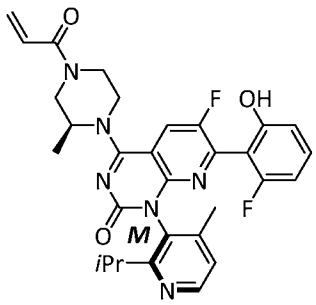
 ,

with a compound of Formula 6,



, in the presence of $Pd(dpePhos)Cl_2$, and KOAc.

16. The method of claim 3, wherein the compound of formula 6A is used to generate a compound having the Formula 9:



9.

17. The method of claim 16, wherein the method further comprises mixing the compound of Formula 9 with at least one pharmaceutically acceptable excipient to form a pharmaceutical composition.