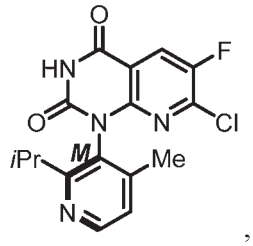
IMPROVED SYNTHESIS OF KEY INTERMEDIATE OF KRAS G12C INHIBITOR COMPOUND

FIELD OF THE INVENTION

The present invention relates to an improved, efficient, scalable process to prepare intermediate compounds, such as compound 5M, having the structure 

, useful for the synthesis of compounds that inhibit KRAS G12C mutations.

BACKGROUND

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.

BRIEF DESCRIPTION OF THE FIGURES

Figure 1 shows the crystal arrangement of composition 4a.

Figure 2-1 shows XRPD overlay of Dione racemate Type A~E.

Figure 2-2 shows XRPD overlay of (1S)-(-)-camphanic acid cocrystal.

Figure 2-3 shows XRPD overlay of (+)-2, 3-dibenzoyl-D-tartaric acid cocrystal.

Figure 2-4 shows XRPD overlay of D-(+)-malic acid cocrystal.

Figure 2-5 shows XRPD overlay of M-Dione cocrystal at different temperatures.

Figure 2-6 shows XRPD overlay of P-Dione cocrystal at different temperatures.

Figure 2-7 shows XRPD overlay of M-Dione cocrystal and P-Dione cocrystal mixture at different temperatures.

Figure 2-8 shows XRPD Overlay of Dione racemate at different temperatures (I/II).

Figure 2-9 shows XRPD overlay of Dione racemate at different temperatures (II/II).

Figure 2-10 shows Ternary Phase Diagram of M/P-Dione cocrystals.

Figure 2-11 shows Ternary phase diagram of M/P-Dione.

Figure 3-1 shows XRPD of Dione racemate Type A.

Figure 3-2 shows TGA/DSC overlay of Dione racemate Type A.

Figure 3-3 shows ^{1}H NMR spectrum of Dione racemate Type A.

Figure 3-4 shows PLM image of Dione racemate Type A.

Figure 3-5 shows XRPD of Dione racemate Type B.

Figure 3-6 shows TGA/DSC overlay of Dione racemate Type B.

Figure 3-7 shows ^{1}H NMR spectrum of Dione racemate Type B.

Figure 3-8 shows XRPD of Dione racemate Type C.

Figure 3-9 shows TGA/DSC overlay of Dione racemate Type C.

Figure 3-10 shows ^{1}H NMR spectrum of Dione racemate Type C.

Figure 3-11 shows XRPD of Dione racemate Type D.

Figure 3-12 shows TGA/DSC overlay of Dione racemate Type D.

Figure 3-13 shows ^{1}H NMR spectrum of Dione racemate Type D.

Figure 3-14 shows XRPD of Dione racemate Type E.

Figure 3-15 shows TGA/DSC overlay of Dione racemate Type E.

Figure 3-16 shows ^{1}H NMR spectrum of Dione racemate Type E.

Figure 3-17 shows XRPD of M-Dione cocrystal Type A.

Figure 3-18 shows TGA/DSC overlay of M-Dione cocrystal Type A.

Figure 3-19 shows ^{1}H NMR spectrum of M-Dione cocrystal Type A.

Figure 3-20 shows XRPD of P-Dione cocrystal Type A.

Figure 3-21 shows TGA/DSC overlay of P-Dione cocrystal Type A.

Figure 3-22 shows ^{1}H NMR spectrum of P-Dione cocrystal Type A.

Figure 3-23 shows XRPD overlay of Dione racemate forms.

Figure 3-24 shows XRPD of competitive slurry samples.

Figure 3-25 shows XRPD overlay of prepared P-Dione cocrystal.

Figure 3-26 shows ^{1}H NMR spectrum overlay of M/P-Dione cocrystals.

Figure 3-27 shows XRPD overlay of prepared P-Dione cocrystal.

Figure 4-1 shows Inter-conversion diagram of M-Dione DBTA Cocrystal crystal forms.

Figure 5-1 shows XRPD overlay of M-dione DBTA cocrystal crystal forms (Type A ~ E).

Figure 5-2 shows XRPD overlay of M-dione DBTA cocrystal crystal forms (Type F ~ K).

Figure 5-3 shows XRPD overlay of M-dione DBTA cocrystal crystal forms (Type L ~ Q).

Figure 5-4 shows XRPD pattern of Type A.

Figure 5-5 shows TGA/DSC curves of Type A.

Figure 5-6 shows ^{1}H NMR of Type A.

Figure 5-7 shows XRPD overlay of Type B.

Figure 5-8 shows TGA/DSC curves of Type B.

Figure 5-9 shows ^{1}H NMR of Type B.

Figure 5-10 shows XRPD pattern of Type C.

Figure 5-11 shows TGA/DSC curves of Type C.

Figure 5-12 shows ^{1}H NMR of Type C.

Figure 5-13 shows XRPD pattern of Type D.

Figure 5-14 shows TGA/DSC curves of Type D.

Figure 5-15 shows ^{1}H NMR of Type D.

Figure 5-16 shows XRPD pattern of Type E.

Figure 5-17 shows TGA/DSC curves of Type E.

Figure 5-18 shows ^{1}H NMR of Type E.

Figure 5-19 shows XRPD pattern of Type F.

Figure 5-20 shows TGA/DSC curves of Type F.

Figure 5-21 shows ^{1}H NMR of Type F.

Figure 5-22 shows XRPD pattern of Type G.

Figure 5-23 shows TGA/DSC curves of Type G.

Figure 5-24 shows ^{1}H NMR of Type G.

Figure 5-25 shows XRPD pattern of Type H.

Figure 5-26 shows TGA/DSC curves of Type H.

Figure 5-27 shows ^{1}H NMR of Type H.

Figure 5-28 shows XRPD pattern of Type I.

Figure 5-29 shows TGA/DSC curves of Type I.

Figure 5-30 shows ^{1}H NMR of Type I.

Figure 5-31 shows XRPD pattern of Type J.

Figure 5-32 shows TGA/DSC curves of Type J.

Figure 5-33 shows ^{1}H NMR of Type J.

Figure 5-34 shows XRPD pattern of Type K.

Figure 5-35 shows TGA/DSC curves of Type K.

Figure 5-36 shows ^{1}H NMR of Type K.

Figure 5-37 shows XRPD pattern of Type L.

Figure 5-38 shows TGA/DSC curves of Type L.

Figure 5-39 shows ^{1}H NMR of Type L.

Figure 5-40 shows XRPD pattern of Type M.

Figure 5-41 shows TGA/DSC curves of Type M.

Figure 5-42 shows ^{1}H NMR of Type M.

Figure 5-43 shows XRPD pattern of Type N.

Figure 5-44 shows TGA/DSC curves of Type N.

Figure 5-45 shows ^{1}H NMR of Type N.

Figure 5-46 shows XRPD pattern of Type O.

Figure 5-47 shows TGA/DSC curves of Type O.

Figure 5-48 shows ^{1}H NMR of Type O.

Figure 5-49 shows XRPD pattern of Type P.

Figure 5-50 shows TGA/DSC curves of Type P.

Figure 5-51 shows ^{1}H NMR of Type P.

Figure 5-52 shows XRPD pattern of Type Q.

Figure 5-53 shows TGA/DSC curves of Type Q.

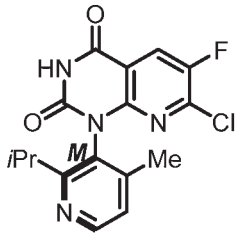
Figure 5-54 shows ^{1}H NMR of Type Q.

Figure 6-1 shows HPLC of M-5 from resolution with 1,3-diphenyl-3-oxopropanesulfonic acid.

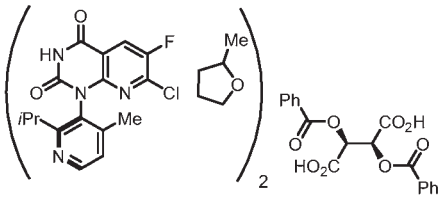
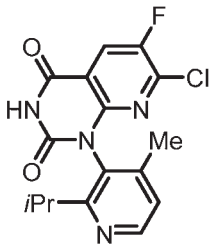
Figure 6-2 shows HPLC of 5 (P-atropisomer excess) from resolution with 1,3-diphenyl-3-oxopropanesulfonic acid.

SUMMARY

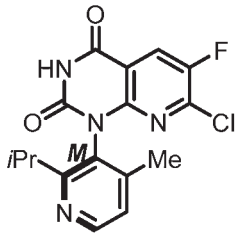
The present invention relates to improved preparation of a compound having the following chemical structure:



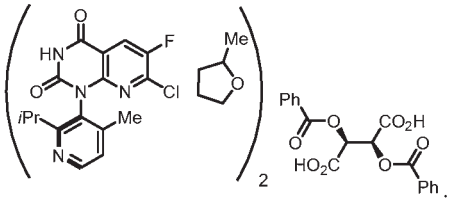
and key intermediates thereof, i.e., compositions and compounds comprising the following chemical structures:


; and

.

The present invention additional relates to a method of preparing Compound 5M having the following chemical structure


.

The present invention additional relates to a composition comprising a 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 XRPD	Ultraviolet X-Ray Powder Diffraction

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.

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.

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

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

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.

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.

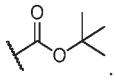
As used herein, the term "cycloalkyl" refers to a monocyclic or polycyclic non-aromatic carbocyclic ring, where the polycyclic ring can be fused, bridged, or spiro. The carbocyclic ring can have 3 to 10 carbon ring atoms. Contemplated carbocyclic rings include, but are not limited to, cyclopropyl, cyclobutyl,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

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.

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.

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,

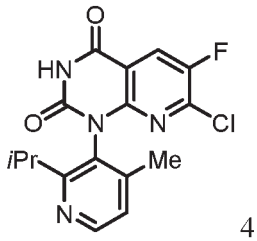
isoquinolinyl, isothiazolyl, naphthyridinyl, oxazolopyridinyl, phthalazinyl, pteridinyl, purinyl, pyridopyridyl, pyrrolopyridyl, quinolinyl, quinoxalinyl, quiazolinyl, thiadiazolopyrimidyl, and thienopyridyl. Unless otherwise indicated, a heteroaryl group can be unsubstituted or substituted with one 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, $-CO_2H$, $-CO_2C_{1-8}$alkyl, $-OCOC_{1-8}$alkyl, C_3-C_{10} cycloalkyl, C_3-C_{10} heterocycloalkyl, C_5-C_{10}aryl, and C_5-C_{10} heteroaryl.

As used herein, the term Boc refers to the structure .

EMBODIMENTS

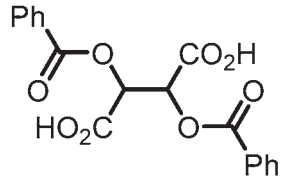
Embodiment 1

In one embodiment of the invention, the present invention comprises a composition, the composition comprising a compound of Formula 4:



4

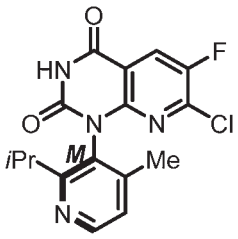
and a compound of Formula B:



B.

Embodiment 2

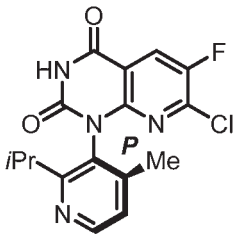
In another embodiment of the present invention, the present invention comprises the composition of embodiment 1, wherein the compound of Formula 4 is a compound of Formula 5M:



5M.

Embodiment 3

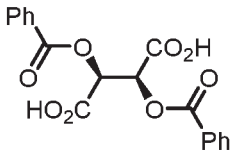
In another embodiment of the present invention, the present invention comprises the composition of embodiment 1, wherein the compound of Formula 4 is a compound of Formula 5P:



5P.

Embodiment 4

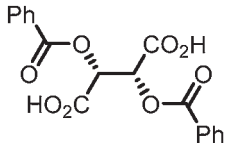
In another embodiment of the present invention, the present invention comprises the composition of any one of embodiments 1-3, wherein the compound of Formula B is a compound of formula B1:



B1.

Embodiment 5

In another embodiment of the present invention, the present invention comprises the composition of any one of embodiments 1-3, wherein the compound of Formula B is a compound of formula B2:



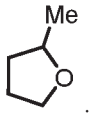
B2.

Embodiment 6

In another embodiment of the present invention, the present invention comprises the composition of any one of embodiments 1-5, wherein the composition comprises a 2 to 1 ratio of the compound of Formula 4 to the compound of Formula B.

Embodiment 7

In another embodiment of the present invention, the present invention comprises the composition of any one of embodiments 1-6, wherein the composition further comprises 2-methyltetrahydrofuran having the formula:

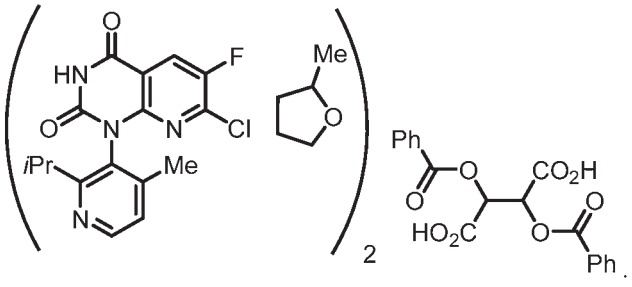


Embodiment 8

In another embodiment of the present invention, the present invention comprises the composition of any one of embodiments 1-7, wherein the ratio of the 2-methyltetrahydrofuran to the compound of formula B is 2 to 1.

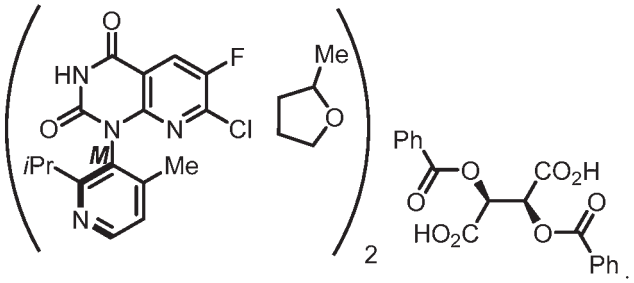
Embodiment 9

In another embodiment of the present invention, the present invention comprises the composition of embodiment 1, wherein the composition has the formula:



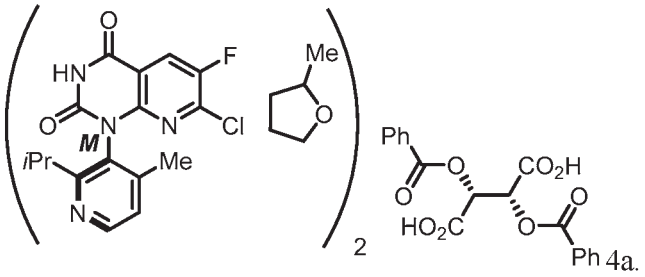
Embodiment 10

In another embodiment of the present invention, the present invention comprises the composition of embodiment 9, wherein the composition has the formula:



Embodiment 11

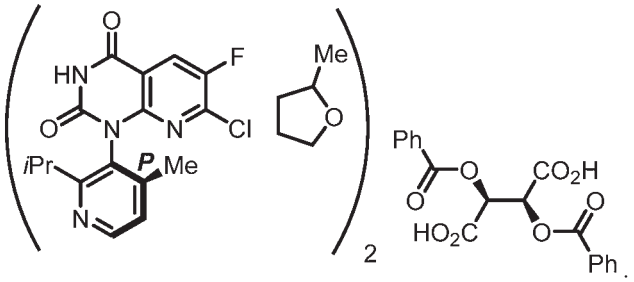
In another embodiment of the present invention, the present invention comprises the composition of embodiment 9, wherein the composition has the formula:



4a.

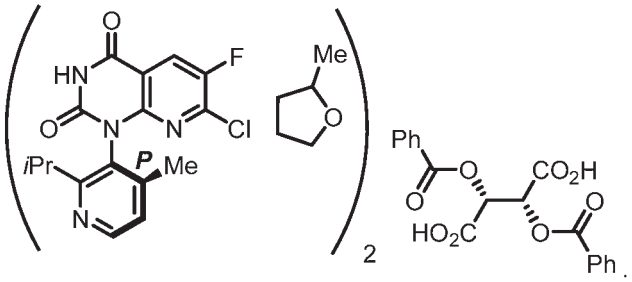
Embodiment 12

In another embodiment of the present invention, the present invention comprises the composition of embodiment 9, wherein the composition has the formula:



Embodiment 13

In another embodiment of the present invention, the present invention comprises the composition of embodiment 9, wherein the composition has the formula:

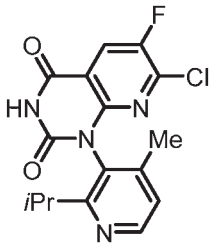


Embodiment 14

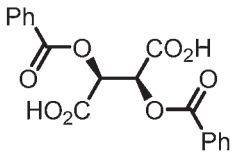
In another embodiment of the present invention, the present invention comprises the composition of any one of embodiments 1-13, wherein the composition is in a crystalline state.

Embodiment 15

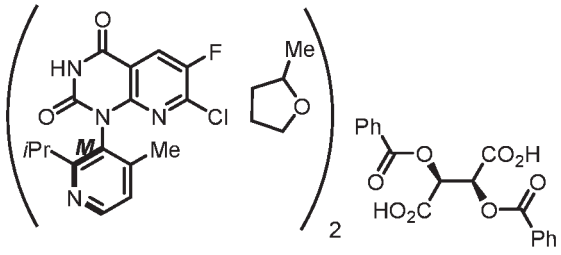
In another embodiment of the present invention, the present invention comprises a method of making a composition of formula 4a, the method comprising reacting a compound 4, having the following chemical structure:



4, with a compound B1, having the formula:



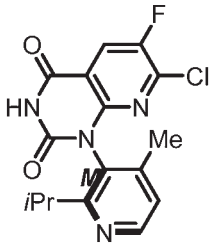
in the presence of 2-methyltetrahydrofuran to form the composition of formula 4a, having the structure:



4a.

Embodiment 16

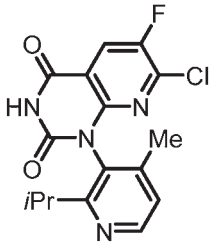
In another embodiment of the present invention, the present invention comprises a method of obtaining a compound of formula 5M, having the following chemical structure:



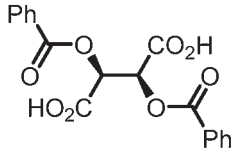
5M,

the method comprising:

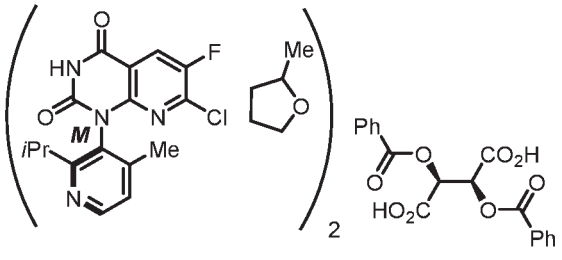
a) reacting a compound 4, having the following chemical structure:



4, with a compound B1, having the formula:



in the presence of 2-methyltetrahydrofuran to form a composition of formula 4a, having the structure:



4a as crystals;

b) isolating composition 4a, and

c) treating the isolated composition 4a with a base to produce the compound of formula 5M.

Embodiment 17

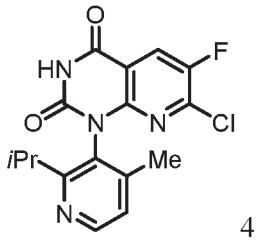
In another embodiment of the present invention, the present invention comprises the method according to Embodiment 16, wherein the base is Na_2HPO_4.

Embodiment 18

In another embodiment of the present invention, the present invention comprises the method according to Embodiment 16, wherein the base is $NaHCO_3$.

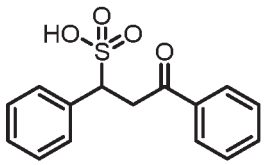
Embodiment 19

In another embodiment of the present invention, the present invention comprises the composition, the composition comprising a compound of Formula 4:



4

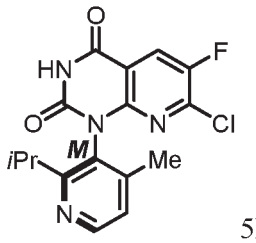
and a compound of Formula 11:



11.

Embodiment 20

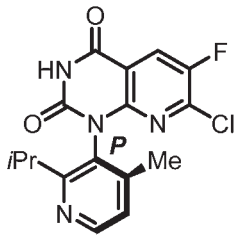
In another embodiment of the present invention, the present invention comprises the composition of embodiment 19, wherein the compound of Formula 4 is a compound of Formula 5M:



5M.

Embodiment 21

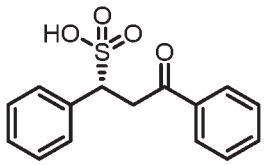
In another embodiment of the present invention, the present invention comprises the composition of embodiment 19, wherein the compound of Formula 4 is a compound of Formula 5P:



5P.

Embodiment 22

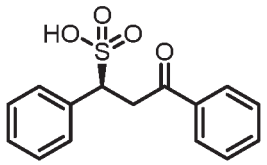
In another embodiment of the present invention, the present invention comprises the composition of any one of embodiments 19-21, wherein the compound of Formula 11 is a compound of formula 11a:



11a.

Embodiment 23

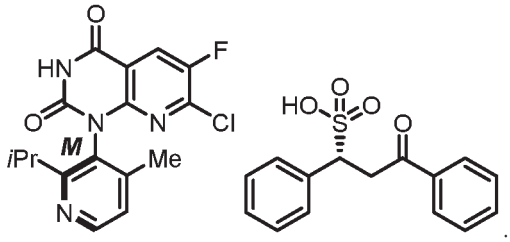
In another embodiment of the present invention, the present invention comprises the composition of any one of embodiments 19-21, wherein the compound of Formula 11 is a compound of formula 11b



11b.

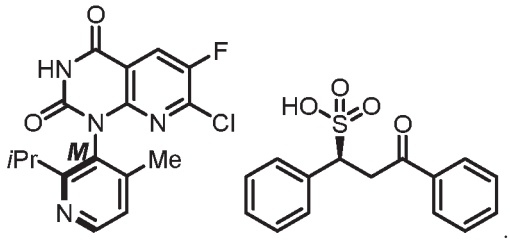
Embodiment 24

In another embodiment of the present invention, the present invention comprises the composition of embodiment 19, wherein the composition has the formula:



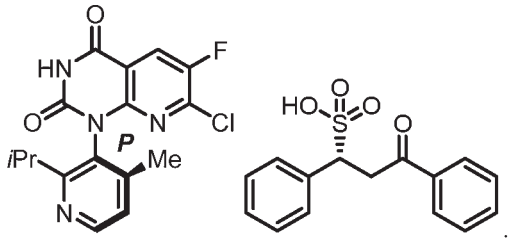
Embodiment 25

In another embodiment of the present invention, the present invention comprises the composition of embodiment 19, wherein the composition has the formula:



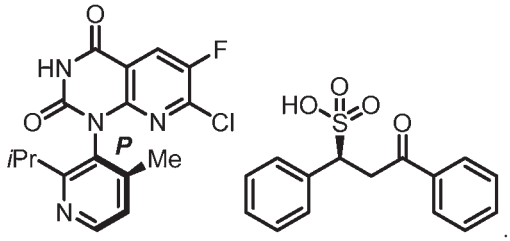
Embodiment 26

In another embodiment of the present invention, the present invention comprises the composition of embodiment 19, wherein the composition has the formula:



Embodiment 27

In another embodiment of the present invention, the present invention comprises the composition of embodiment 19, wherein the composition has the formula:

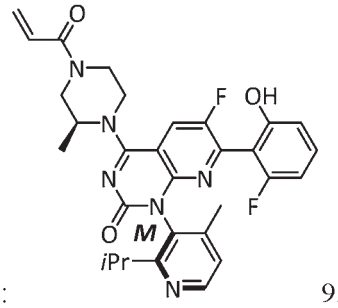


Embodiment 28

In another embodiment of the present invention, the present invention comprises the composition of any one of embodiments 19-27, wherein the composition comprises a 1 to 1 ratio of the compound of Formula 4 to the compound of Formula 11.

Embodiment 29

In another embodiment of the present invention, the present invention comprises the the method of embodiment 16, wherein the compound of formula 5M is used to generate a compound having the Formula 9:



9.

Embodiment 30

The method of embodiment 29, 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

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

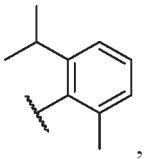
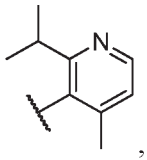
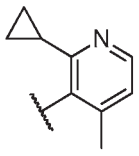
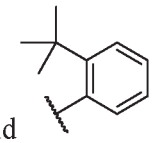
The compounds disclosed herein include all pharmaceutically acceptable isotopically-labeled compounds wherein one or more atoms of the compounds disclosed herein are replaced by atoms having the same atomic number, but an atomic mass or mass number different from the atomic mass or mass number usually 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 radiolabelled 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.

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.

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.

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.

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.

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.

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 invention.

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.

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.

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.

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

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%.

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.

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

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

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.

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.

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.

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.

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.

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.

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.

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.

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).

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.

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.

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.

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.

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.

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.

For administration by inhalation, compounds of the present invention 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.

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.

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.

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.

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.

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.

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 invention 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.

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%.

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).

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 invention 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

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.

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).

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.

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.

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.

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.

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).

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.

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.

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.

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)).

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.

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%.

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

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.

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.

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).

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.

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.

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.

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.

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.

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.

The compounds of the invention 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.

In some embodiments, the combination comprises a composition of the present invention 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.

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 invention 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".

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).

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).

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.

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 invention 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.

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.

The compounds of the present invention 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.

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 invention 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.

The compounds of the present invention 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.

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.

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.

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.

The $KRAS^{G12C}$ inhibitors of the present invention can be used in combination with MEK inhibitors. Particular MEK inhibitors that can be used in the combinations of the present invention 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 invention 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 invention includes cobimetinib. MEK inhibitors include, but are not limited to, CI-1040, AZD6244, PD318088, PD98059, PD334581, RDEA119, ARRY-142886, and ARRY-438162.

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 bismesylate 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.

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).

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).

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.

$KRAS^{G12C}$ inhibitors can also be used in combination with SHP2 inhibitors in the present invention. 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.

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

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.

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

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).

Anti-PD-1 inhibitors, including but not limited to antibodies include, but are not limited to, pembrolizumab (Keytruda®) 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).

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.

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.

As one aspect of the present invention contemplates the treatment of the disease/conditions with a combination of pharmaceutically active compounds that may be administered separately, the invention further relates to combining separate pharmaceutical compositions in kit form. The kit comprises two separate pharmaceutical compositions: a compound of the present invention, 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.

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

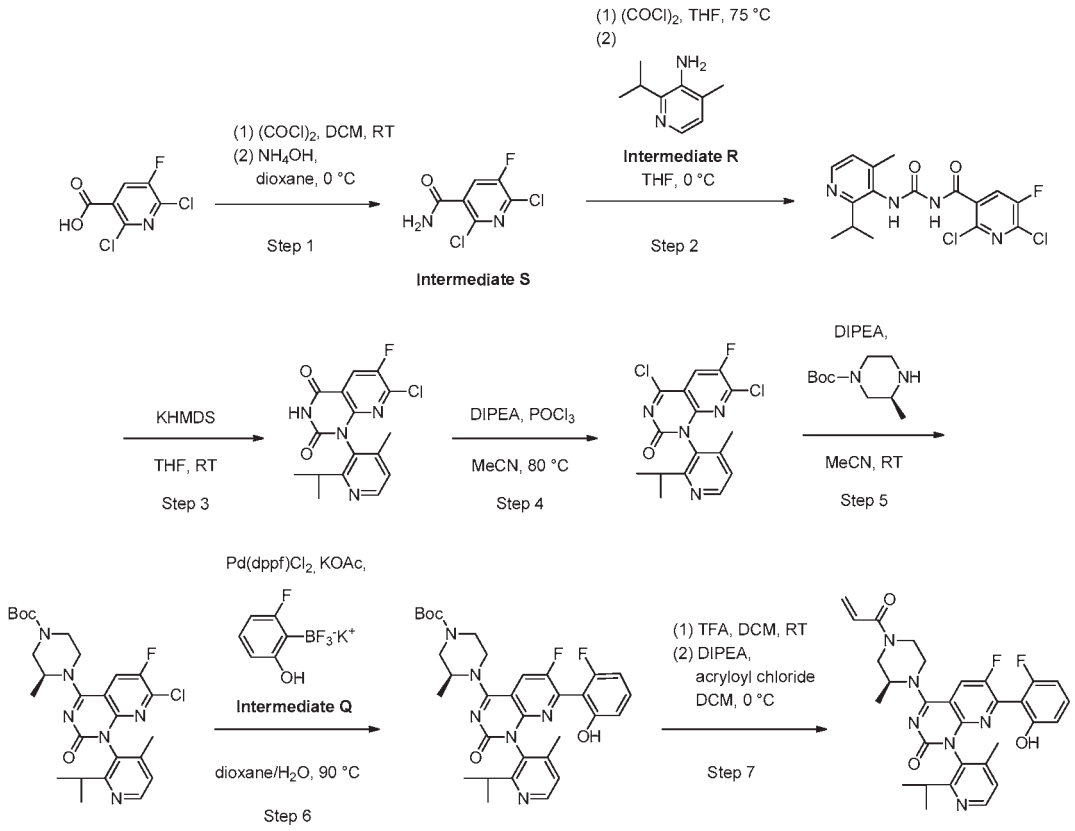
The processes presented below illustrate specific embodiments of the present invention. These processes are meant to be representative and are not intended to limit the scope of the claims in any manner.

Related Processes of the invention

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 invention and are not intended to be construed as limiting the scope of the present invention.

A synthesis of Compound 9 and the relevant intermediates is described in U.S. Serial No. 15/984,855, filed May 21, 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, 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.



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 $(M+H)^+$.

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$(M+H)^+$.

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 $(M+H)^+$.

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 $(M+H)^+$.

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

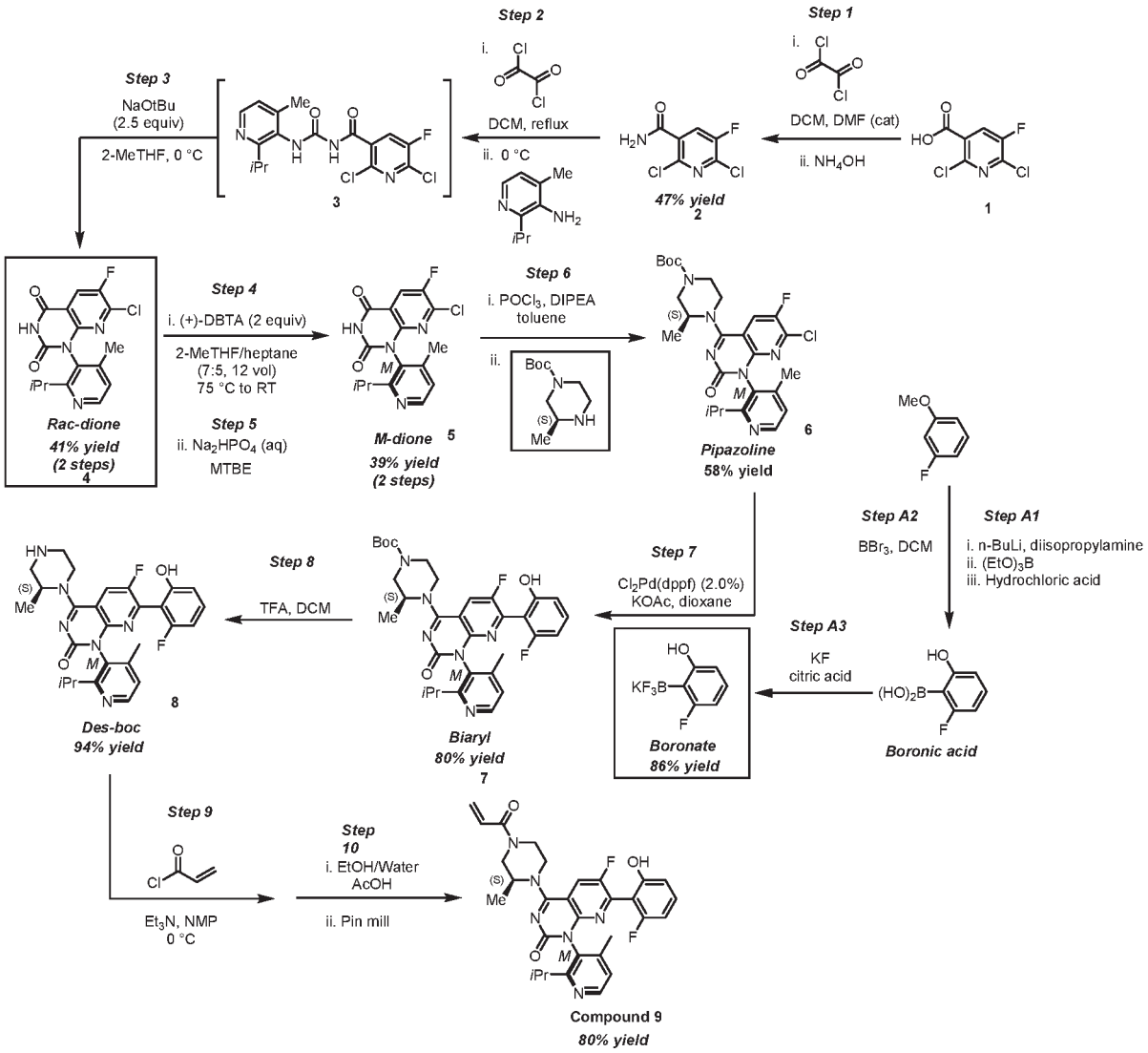
mmol), followed by (*S*)-4-*N*-Boc-2-methyl piperazine (3.23 g, 16.1 mmol, Combi-Blocks, Inc., San Diego, CA, USA). The resulting mixture was warmed to room temperature and stirred for 1 h, then was diluted with cold saturated aqueous sodium bicarbonate solution (200 mL) and EtOAc (300 mL). The mixture 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 $(M+H)^+$.

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 $(M+H)^+$.

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

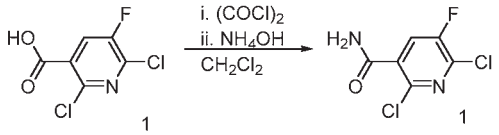
4-(6-fluoro-7-(2-fluoro-6-hydroxyphenyl)-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-1,2-dihydropyrido[2,3-*d*]pyrimidin-4-yl)-3-methylpiperazine-1-carboxylate (6.3 g, 10.4 mmol) in DCM (30 mL). The resulting mixture was stirred at room temperature for 1 h and then was concentrated. The residue was dissolved 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 $(M+H)^+$.

The present invention comprises the following steps wherein the resolution of the rac-Dione in Steps 4 and 5 promotes the successful separation of the atropisomers:


Step 1
i. DCM, DMF (cat)
ii. NH4OH
1
47% yield
2
Step 2
i. DCM, reflux
ii. 0 °C
Step 3
NaOtBu
(2.5 equiv)
2-MeTHF, 0 °C
3
Rac-dione
41% yield
(2 steps)
4
Step 4
i. (+)-DBTA (2 equiv)
2-MeTHF/heptane
(7:5, 12 vol)
75 °C to RT
Step 5
ii. Na2HPO4 (aq)
MTBE
M-dione
39% yield
(2 steps)
5
Step 6
i. POCl3, DIPEA
toluene
ii.
Pipazoline
58% yield
6
Step A1
i. n-BuLi, diisopropylamine
ii. (EtO)3B
iii. Hydrochloric acid
Step A2
BBr3, DCM
Boronic acid
Step A3
KF
citric acid
Boronate
86% yield
Step 7
Cl2Pd(dppf) (2.0%)
KOAc, dioxane
Biaryl
80% yield
7
Step 8
TFA, DCM
Des-boc
94% yield
8
Step 9
Et3N, NMP
0 °C
Step 10
i. EtOH/Water
AcOH
ii. Pin mill
Compound 9
80% yield

Representative Process Description of the Invention

Step 1



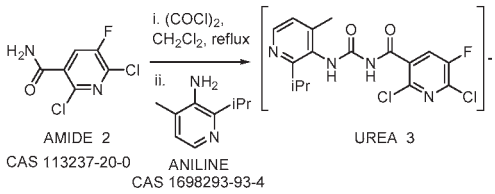
ACID
CAS 82671-06-5

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

To a solution of 2,6-dichloro-5-fluoro-3-pyridinecarboxylic acid (Compound 1) (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 2).

Step 2

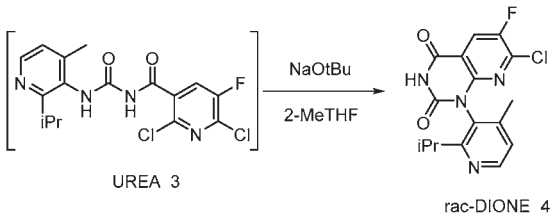


Material	CAS #	MW (g/mol)	Equivalents / Volumes	Moles	Theoretical
Amide (2,6-dichloro-5-fluoronicotinamide)	113237-20-0	209.99	1.0 equiv.	77.8	16.27 kg
Oxalyl Chloride	79-37-8	126.93	1.2 equiv.	93.8	11.9 kg (7.9 L)
Dichloromethane	75-09-2	84.93	N/A	N/A	730.7 kg (551.5 L)
Aniline DCM Solution 2-isopropyl-4-methylpyridin-3-amine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

In reactor A, a solution of 2,6-dichloro-5-fluoronicotinamide (Compound 2) (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) (12.9kg; 85.9mol) followed by dichloromethane (102.6 kg). The ANILINE solution was azeodried via vacuum distillation while maintaining a 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 3

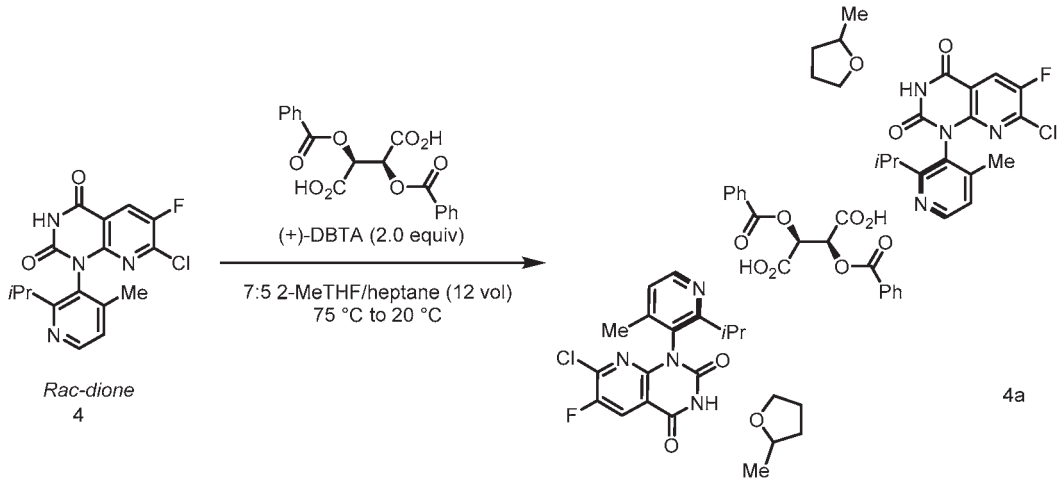


Material	CAS #	MW (g/mol)	Equivalents / Volumes	Moles	Theoretical
Urea, solution in DCM 2,6-dichloro-5-fluoro-*N*-{[4-methyl-2-(propan-2-yl)pyridin-3-yl]carbamoyl}pyridine-3-carboxamide	N/A	385.22	1.0 equiv.	38.9	208.3 kg (15 kg contained weight)
2-methyltetrahydrofuran	96-47-9	86.13	N/A	N/A	308 kg (358 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

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) repeateding if necessary to achieve a target pH of ≥ 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 4

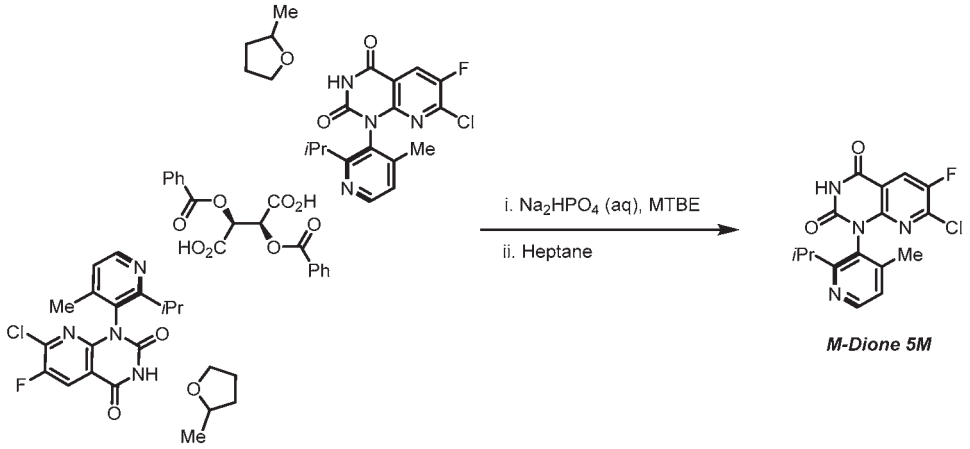


Material	CAS #	MW (g/mol)	Equivalents / Volumes	Moles	Theoretical
Rac-dione	N/A	348.76	1.0		
(+)-2,3-dibenzoyl-D-tartaric acid	17026-42-5	358.30	2.0		
2-methyltetrahydrofuran	96-47-9	86.13	7.0		
heptane	142-82-5	100.21	2.0		
heptane	142-82-5	100.21	3.0		
2-methyltetrahydrofuran	96-47-9	86.13	4.0		
heptane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

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 5



M-Dione 5M

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

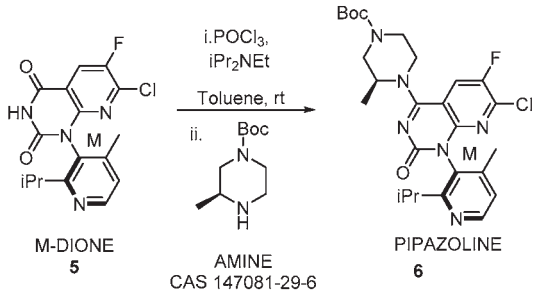
Material	CAS #	MW (g/mol)	Equivalents / Volumes	Moles	Theoretical
M-Dione/DBTA/Me-THF cocrystal	N/A	1228.08	1.0	74.2	46.9 kg (25.9 kg corrected for M-dione)
Methyl *tert*-butyl ether	1634-04-4	88.15	45.0	17593	2100 L
Disodium hydrogen phosphate	7558-79-4	141.96	2.0	148.4	21.1 kg
USP purified water					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

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.

The first-generation process highlighted above has been successfully scaled on 200+ kg of rac-dione starting material (Compound 5). 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 6

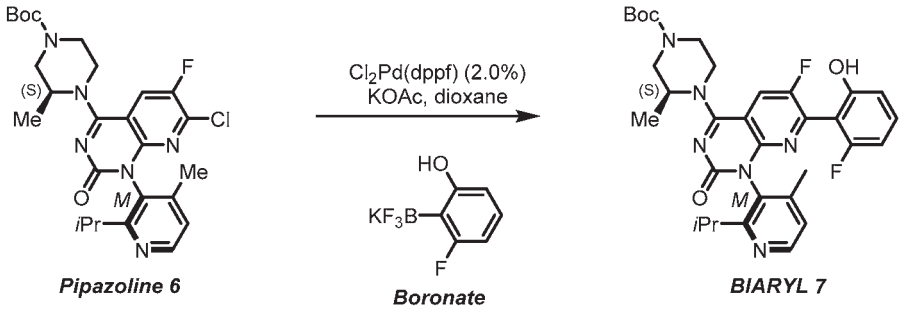


Material	CAS #	MW (g/mol)	Equivalents / Volumes	Moles	Theoretical
M-DIONE	N/A	348.76	1 equiv.	9.8	3.7 kg
Toluene	108-88-3	92.14	N/A	375	34.6 kg (40 L)
Phosphoryl chloride	10025-87-3	153.33	1.2 equiv.	11.7	1.8 kg (1.1 L)
N,N-Diisopropylethylamine	7087-68-5	129.24	3.0 equiv.	29.4	3.8 kg (5.1 L)
(s)-1-Boc-3-methylpiperazine	147081-29-6	200.28	1.1 equiv.	10.8	2.214 kg
Sodium bicarbonate	144-55-8	84.01	N/A	N/A	973 g
Dichloromethane	75-09-2	84.93	N/A	871	74 kg (55.6 L)
Sodium Chloride	7647-14-5	58.44	N/A	103	6.0 kg
Ethyl acetate	141-78-6	88.11	N/A	288	25.4 kg (28.2 L)

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) (3.7kg; 9.8mol) was combined in reactor (A) with 10.5kg of toluene and distilled down to an oil to remove water while maintaining a set point of 45 °C. Toluene (21kg) was added to the residue and the mixture stirred for 30min at 40-45 °C. The contents where cooled to 22 °C then phosphoryl chloride (1.8kg; 11.7mol) added. The mixture was cooled to 0-5 °C before adding N,N-Diisopropylethylamine (2.5 kg; 19.34mol) while maintaining a temperature < 5 °C. The solution was aged for 3h at 22 °C. In

a separate reactor (B), (s)-1-boc-3-methylpiperazine (2.21kg; 10.8mol) and N,N-diisopropylethylamine (1.26kg; 9.75mol)) where combined in toluene (6kg) and then charged to reactor (A) while maintaining < 25 °C. The reaction mixture was aged for 15min at 22C then quenched with sodium bicarbonate (973g) in water (12.9L) while maintaining a temperature <25 C. The mixture was stirred for 30min then DCM (36.8kg) added while continuing to stir for 1h. The layers were allowed to separate, and the lower organic layer drained to reactor (C). The aqueous layer in reactor (A) was back extracted using DCM (18.4kg) and the combined organic layers washed with brine solution (6.0 kg NaCl; 16.5 kg DI water). The organic layer was distilled under atmospheric pressure maintaining an internal temperature between 45-55 C. DCM is replaced during the distillation to azeotropically dry the solution. Following the distillation, the solution volume was adjusted to 19L using DCM. The solution was cooled to 30 C and polish filtered. The filtrate was combined with ethyl acetate (8.5 kg) and then distilled at atmospheric pressure until 11-13kg is collected in the receiver. The solution was seeded with 30g of authentic product and aged for 1h at 25-30 °C then further distilled under atmospheric pressure at 45-55 C internal temperature until 8.2kg of distillate had been collected. The slurry was cooled to 22 °C and aged overnight then further cooled to 0-5 °C. The product was collected by filtration and washed twice using ethyl acetate (4.2kg each). The cake was dried with nitrogen and vacuum to afford *tert*-butyl (3*S*)-4-{7-chloro-6-fluoro-(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 (Compound 6, PIPAZOLINE).

Step 7



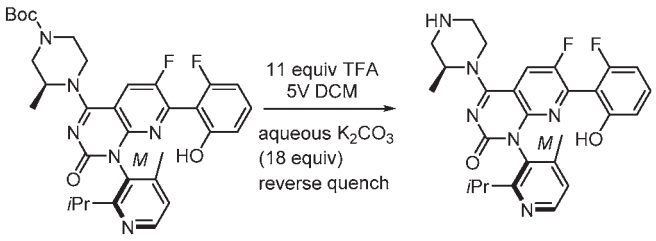
Pipazoline 6 *Boronate* *BIARYL 7*

Material	CAS #	MW (g/mol)	Equivalents / Volumes	Moles	Theoretical
[1,1'-Bis(diphenylphosphino)ferrocene] dichloropalladium(II)	72287-26-4	731.714	0.020	1.01	0.74 kg
Dichloromethane	75-09-2	84.93		N/A	400 kg
1,4-Dioxane	123-91-1	88.1052	5.0	N/A	168 kg
Ethylenediaminetetraacetic acid disodium salt dihydrate	6381-92-6	336.207	1.0	45.2	15.2 kg
Heptane	142-82-5	100.21			200 kg
Nitrogen					As needed
Pipazoline	N/A	531.0	1.0	45.2	24.0 kg
Potassium acetate	127-08-2	98.1417	5.0	225.99	22.2 kg
Potassium trifluoro(2-fluoro-6-hydroxyphenyl)borate	N/A	233.03	1.20	54.24	12.6 kg
2-Propanol	67-63-0	66.10		N/A	850 kg
Si-Thiol	N/A	N/A		N/A	13.2 kg
Sodium hydroxide	1310-73-2	40.00			6.5 kg
USP purified water					As needed

To a reactor was added degassed dioxane (74.2 kg), *tert*-butyl (3*S*)-4-{7-chloro-6-fluoro-(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 (Compound 6, Pipazoline) (24.0 kg, 45.2

mol), potassium acetate (22.2 kg, 45.2 mol), and (dppf)$PdCl_2$ (0.74 kg, 1.01 mol). The reactor was inerted with nitrogen gas. The solution was sparged with nitrogen gas until the oxygen content was < 500 mg/L. The reaction was heated to 87.5 °C. A solution of potassium trifluoro(2-fluoro-6-hydroxyphenyl)borate (12.6 kg, 54.3 mol) in degassed dioxane (49.4 kg) and degassed water (14.4 kg) with oxygen content < 500 mg/L was transferred to the reaction, maintaining an internal temperature of 82.5 °C ± 7.5 °C. The reaction was adjusted to 87.5 °C ± 1.5 °C and stirred for 75 min ± 15 min. A 1.0 M EDTA solution (47.3 kg) followed by water (40.1 kg) was charged to the reactor while maintaining an internal temperature of 85 °C ± 5 °C. The reaction was cooled to 20 °C ± 3 °C over > 2 h and then stirred for > 16 h. The reaction was filtered and the crude solids were rinsed with water (3 x 120 kg). The solids were rinsed with a mixture of heptane (28.8 kg) and 2-propanol (33.1 kg) and then dried at < 50 °C for > 10 h. A clean reactor was loaded with crude solids and dichloromethane (240 kg). The contents were stirred at 20 °C ± 5 °C for > 30 min. To the reactor was added Si-Thiol (144 kg) and dichloromethane (14.9 kg). The reaction was stirred at 20 °C ± 5 °C for 18 h. The reaction was filtered and rinsed with dichloromethane (84 kg). The solution was distilled and solvent swapped to 2-propanol. The reaction was heated to 60 °C ± 3 °C and heptane (108 kg) was charged while maintaining a reaction temperature of 60 °C ± 3 °C. The reaction was stirred for 45 min and then cooled and stirred at 20 °C ± 5 °C for 2.5 h. The reaction was filtered and rinsed with 50% v/v heptane/2-propanol (61.9 kg). The isolated solids were dried at < 50 °C for > 12 h to afford *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 (Compound 7, BIARYL).

Step 8

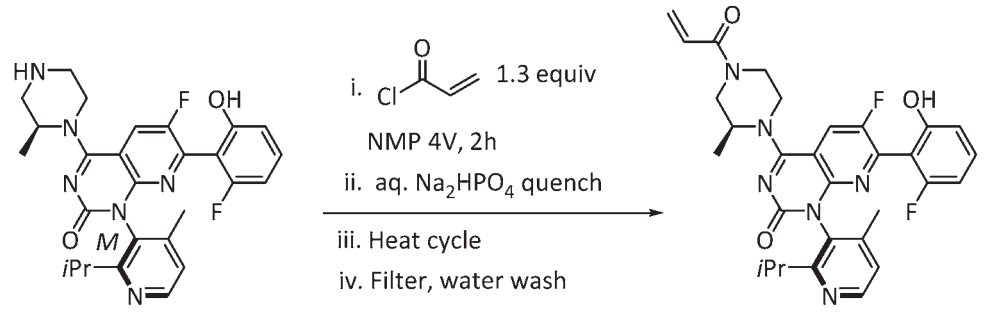


General Note: All equivalents and volumes are reported in reference to BIARYL 7

Material	CAS #	MW (g/mol)	Equivalents / Volumes	Moles	Theoretical
BIARYL 7	NA	606.67	1.0 equiv.	5.27	2.75 kg
TFA	76-05-1	114.02	11 equiv.	49.7	5.67 kg
DCM	74-09-2	84.93	5 vol	NA	13.71 L
Methanol	67-56-1	32.04	5 vol	NA	13.71 L
Water	7732-18-5	18.02	20 vol	NA	54.8 L
Potassium Carbonate	584-08-7	138.20	18 equiv.	94.91	11.24 kg
DCM	74-09-2	84.93	1 vol	NA	2.75 L
Water	7732-18-5	18.02	10 vol	NA	27.5 L
Water	7732-18-5	18.02	10 vol	NA	27.5 L

To a reactor 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 (Compound 7, BIARYL) (2.75 kg, 5.27 mol), DCM (13.7 L), and TFA (5.67 kg, 49.7 mol). The reaction was stirred for 8-16 h at 20 ± 5 °C. To a second reactor was added potassium carbonate (11.24 kg), water (54.8 L), and methanol (13.7 L) to form a homogenous solution. The reaction mixture was added to the potassium carbonate solution over 2 h. The mixture was stirred at 20 ± 5 °C for an additional 12 h. The resulting slurry was filtered and rinsed with water (2 x 27.5 L). 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 (Compound 8, DESBOC).

Step 9



Des-BOC 8 **Crude 9**

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

Material	CAS #	MW (g/mol)	Equivalents / Volumes	mmol	mass	volume
Des-BOS	NA	506.56	1.0 equiv.	308.4	156.25g	
Acryloyl chloride[1]	814-68-6	90.51	1.3 equiv.	401.0	36.29g	-
						-
NMP N-methyl pyrrolidinone[2]	872-50-4	99.13	4 vol	NA	-	625mL
Water	7732-18-5	18.02	20 vol	NA	3125g	3125mL
Na_2HPO4[3]	7558-79-4	141.96	4 equiv.	1233.6	175.12g	-
Water	7732-18-5	18.02	20 vol	NA	3125g	3,125mL

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 (Compound 8, DESBOC) (156.25g) was combined with N-methyl pyrrolidinone (625mL) and stirred at ambient temperature. To the resulting solution was added acryloyl chloride (36.29g; 401.0mmol) while maintaining < 30 °C internal temperature. The contents where stirred for 2h at 25 C. In a separate reactor a solution of disodium phosphate (175.1g; 1234mmol) in DI

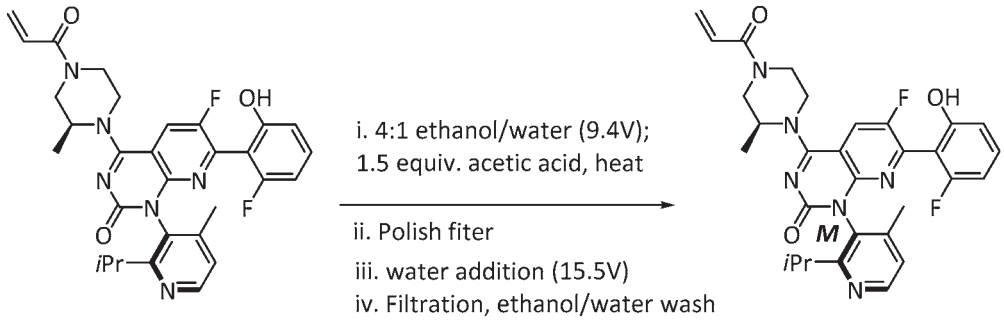
[1] acryloyl chloride was added over 7mins on this scale. Avoid over cooling reaction. Colder reaction temperatures led to slower reaction time leading to higher levels of m/z 1066 impurity as the starting material reacts with the product. Ideal temp range is 22-25 C

[2] NMP content of dried cake typically 1-2wt%.

[3] Disodium phosphate in table is as anhydrous basis. Hydrate may be used, adjust mass accordingly to obtain desired mmol.

water (3.1L) was prepared. The crude product solution was then transferred to the reactor containing the disodium phosphate solution over >2h at 25 °C. The slurry was heated to 45 °C midway through the addition and after complete addition, aged for 2h at the same temperature. The mixture was cooled to 25 C and aged for 4h before collecting the solids by vacuum filtration. The solids where washed twice with water (1.5L each) and the product dried under nitrogen and vacuum to afford the product 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 Compound 9).[4]

Step 10



Crude Compound 9 ***Compound 9***

General Note: All equivalents and volumes are reported in reference to crude drug substance

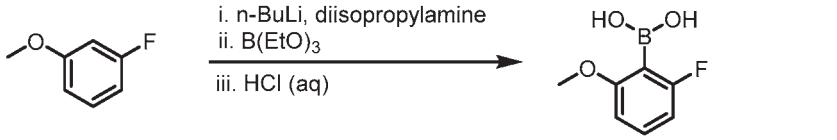
Material	CAS #	MW (g/mol)	Equivalents / Volumes	mmol	mass	volume
Crude Compound 9	NA	560.60	1.0 equiv.	253.9	142.33g	-
Ethanol (200 proof)	64-17-5	-	7.5 V	-	-	1067mL
USP Water	-	18.02	1.9V	-	-	270 mL
Acetic acid	64-19-7	60.05	1.5 equiv.	380.8	22.87g	21.82mL
WFI Water	-	18.02	15.5 vol	-	-	2200mL
Ethanol (for wash)	64-17-5	-	2.5 V	-	-	356 mL
WFI Water (for wash)	-	-	5.0 V	-	-	712 mL
Compound 9 seed[5]	-	560.60	0	-	0.3-0.7g	-

[4] Results for this lead lot: 154.06g isolated mass, 93%wt, 82.9% corrected yield, 18,000ppm NMP

[5] 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. 0.25%- 0.5% is seed is target amount.

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 Compound 9) (142.33g; 253.9mmol) was combined with ethanol (996mL) and water (270mL). Acetic acid (21.8ml; 380.8mmol) was added and the mixture heated to 75 °C to form a solution which was polish filtered into a clean reactor. The solution was cool to 45 °C and then water (1067mL) was added while maintaining an internal temperature > 40 °C. The solution was seeded with authentic Compound 9 and the resulting mixture aged for 30min. Water (1138mL) was then added over 2h. The mixture was cooled to 25 °C and aged for 8h after which the solid was collected by vacuum filtration and washed using a mixture of ethanol (355.8mL) and water (711.6mL). 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 (Compound 9).

Step A1 Reaction Scheme and Charge Table

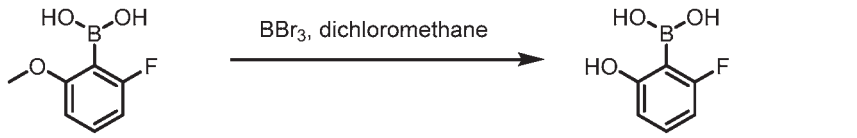


3-fluoroanisole (2-fluoro-6-methoxyphenyl)boronic acid

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)	109-72-8	64.06	1.5	1.78	N/A	0.712
diisopropylamine	108-18-9	101.19	1.4	1.66	168	0.233
Triethylborate	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)	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

Reactor A was charged with THF (6 vol) and Diisopropylamine (1.4 equiv). The resulting solution was cooled to -70 °C and 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. $B(EtO)_3$ (2.0 equiv) was added slowly and kept at -70 °C for 10 min. The reaction mixture was quenched with 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.

Step A2 Reaction Scheme and Charge Table



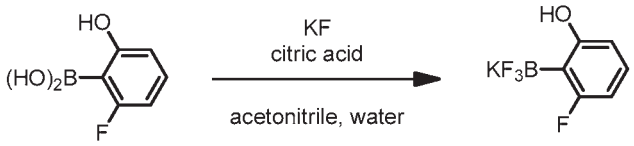
(2-fluoro-6-methoxyphenyl)boronic acid (2-fluoro-6-hydroxyphenyl)boronic acid

Material	CAS #	MW (g/mol)	Equivalents / Volumes	mol	Mass (g)	Volume (L)
(2-fluoro-6-methoxyphenyl)boronic acid.	78495-63-3	169.95	1.0	0.118	20	N/A
Boron tribromide	10294-33-4	250.52	1.5	0.177	44.2	0.017
Dichloromethane	75-09-2	84.93	4 vol	N/A	N/A	0.080
Water	7732-18-5	18.02	13 vol	N/A	N/A	0.26
Methyl tert-butyl ether	1634-04-4	88.15	13 Vol	N/A	N/A	0.26
Heptane	142-82-5	100.20	10 Vol	N/A	N/A	0.20

Reactor A was charged with dichloromethane (4 vol) and 2-fluoro-6-methoxy-4-methylphenylboronic acid (1 equiv). The reaction mixture was cooled to -30 °C and 1.5 BBr_3 (1.5 equiv) was added dropwise. When the addition completed, the mixture was warmed to 25 °C and stirred 2 h. The reaction mixture was quenched into ice cold (0-5 °C) water (10 vol). MTBE (10 vol) was added and the mixture warmed to 25 °C and stirred for 1-2 h or until all

solids dissolved. The aqueous phase was separated and extracted with MTBE (3 vol). The combined organic extracts were washed with water (3 vol) and then concentrated to 1 total volumes. Heptane (10 vol) was added to the mixture and stirred for 2 h. The resulting product was isolated by filtration and dried at < 30 °C to afford (2-fluoro-6-hydroxyphenyl)boronic acid.

Step A3 Reaction Scheme and Charge Table



Boronic acid ***Boronate***

Material	CAS #	MW (g/mol)	Equivalents / Volumes	mol	Mass (kg)	Volume (L)
(2-fluoro-6-hydroxyphenyl)boronic acid	1256345-60-4	155.92	1.0	89.79	14.00	N/A
Citric acid monohydrate	5949-29-1	210.14	1.64	147.26	30.94	N/A
Acetonitrile	75-05-8	41.05	21 Vol	N/A	220.1	294
Potassium fluoride	7789-23-3	58.10	4.00	359.16	20.87	N/A
USP Water	7732-18-5	18.02	2.0 Vol	N/A	28.00	28.00
Celite	N/A	N/A	N/A	N/A	7.00	N/A
2-Propanol	67-63-0	60.10	25 Vol	N/A	275	350

Step A3

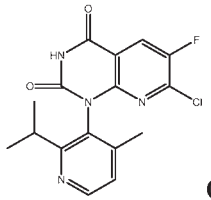
Potassium Fluoride (21.0kg; 20.87mol) was combined with water (28L) in a reactor (reactor A) and the contents stirred for 30min. In a separate reactor (reactor B), (2-fluoro-6-hydroxyphenyl)boronic acid (14.00 kg, 89.79mol) was charged followed by acetonitrile (206.1kg) and citric acid (30.94kg; 147.26mol) at 25 C. The contents of reactor A was added to reactor B at 25C and stirred at that temperature for 10h. The reaction mixture was filtered through a bed of celite (7.0kg) and rinsed with acetonitrile (42kg). The filtrate was combined with isopropanol (56 kg) and then distilled under vacuum at a temperature < 35 °C replacing

the distilled volume to the reactor with isopropanol and repeated as needed to complete the solvent swap from acetonitrile to isopropanol. The slurry was cooled to 15C and aged for 1h before filtered and washing with 28kg of isopropanol. The cake was dried using vacuum and nitrogen and packaged to afford Compound A3.

Resolution of the M-Dione Compound 5

Chromatographic Resolution of M-dione intermediate

Numerous chiral chromatographic techniques and methods were used to isolate the M-dione from Compound 4. The techniques and stationary phases are well known in the art and are outlined in Table 1.



Compound 4

Table 1

Technique	Stationary Phase	Mobile Phase	Yield^
SFC	Chiralpak® AD	40% methanol / 60% CO2 *	~95%
HPLC	Chiralpak® AD	90/10/0.1 ethanol/ methanol/ triethylamine	~94%
HPLC	Chiralpak® IG	60/40/0.1 ethanol/ methanol/ Triethylamine	~92%
Simulated Moving Bed (SMB)	Chiralpak® IC	Acetonitrile	~ 96%

^Yield is defined as % of available M-Dione that was recovered at the required purity of > 98% ee.

* This separation was performed multiple times. For each lot of material, the mobile phase may have been slightly modified to accommodate for variations in the lots. Additional mobile phases used for purification included:

1) 25/75 methanol/CO_2,

2) 30/70 methanol/CO_2, and

3) 50/50 methanol/CO_2.

The SFC, HPLC, and SMB techniques are well known in the art and the Chiralpak® stationary phases are commercially available from commercial sources, such as Fisher Scientific and Daicel Corporation.

However, it is desired to develop a more efficient process to isolate the M-Dione (Compound 5).

Classical resolution

The present invention is directed to the development of a viable classical resolution process for M/P-Dione racemate (Compound 4).

A total of 100 cocrystal screening experiments were performed and three potential cocrystals of Dione were identified. Based on the highest area ratio of M/P-Dione in the residual solid and lowest area ratio in the supernatant, (+)-2, 3-dibenzoyl-D-tartaric acid (DBTA) was selected as the chiral reagent for resolution.

According to the results from 100 cocrystal screening experiments and 20 more solvent screening, 2-MeTHF/n-heptane was found to provide a better resolution result than other solvent systems. Based on the solubility results of M-Dione cocrystal and P-Dione cocrystal in different ratios of 2-MeTHF and n-heptane, 2-MeTHF/n-heptane (1.4:1, v/v) was selected as the optimal solvent composition for resolution.

In order to find out any possible form conversion to Dione racemate or M/P-Dione during crystallization process of chiral resolution, the solubility of M-Dione cocrystal, P-Dione cocrystal, M+P-Dione cocrystal mixture (1:1, w/w), Dione racemate and DBTA were determined at different temperatures in 2-MeTHF/n-heptane (1.4:1, v/v). No form change was observed for M-Dione cocrystal and P-Dione cocrystal at different temperatures for 7 days. However, Dione racemate Type C was obtained after stirring of a mixture of M+P-Dione cocrystal mixture (1:1, w/w) at different temperatures for 7 days. Dione racemate Type D (20 and 30 °C) or Dione racemate Type C (40, 50, 60 and 65 °C) were observed after stirring of Dione racemate at corresponding temperatures for 7 days. A solubility of ~100 mg/mL was observed under all the temperatures for DBTA.

To further optimize the resolution process, the ternary phase diagram of M/P-Dione cocrystal was drawn based on the equilibrium solubility results and no eutectic point was obtained likely because racemate Type C could crystallize out when both M-Dione cocrystal and P-Dione cocrystal were present. Another ternary phase diagram of M/P-Dione was drawn based on the equilibrium solubility results and no eutectic point was obtained likely because

Dione racemate Type C or Type D could crystallize out when both M-Dione and P-Dione were present.

In summary, a chiral reagent (DBTA) and a solvent system ((2-MeTHF/n-heptane (1.4:1, v/v)) were identified for resolution of Dione racemate. Small scale crystallization process using the resolving reagent and solvent system could achieve a yield of 39% and ee purity of 99% for M-Dione. In addition, polymorphism of Dione racemate was observed and investigated during screening experiments.

2 Screening Experiment

2.1 Cocrystal Screening

A total of 100 cocrystal screening experiments were performed using 20 acids and 5 solvent systems (Results summarized in Table 2-1). In general, Dione racemate and acid in the molar ratio at 1:1 was mixed and stirred at RT for 3 days before isolation for XRPD. Based on the XRPD results, three potential acids that could form cocrystals of Dione racemate were identified, including (1S)-(−)-camphanic acid (Figure 2-2), (+)-2, 3-dibenzoyl-D-tartaric acid (Figure 2-3) and D-(+)-malic acid (Figure 2-4). Four new freebase crystal forms were also obtained based on XRPD results, which were assigned as Dione racemate Type B~E.

As showed in Table 2-2, the supernatant and residual solid of the three potential cocrystals were further tested by HPLC. The ratio of M-Dione/P-Dione was measured and summarized in Table 2-2. As a result, DBTA cocrystal showed an area ratio of M-Dione/P-Dione at 0.11 in the supernatant and 4.4 in the residual solid, which suggested that M-Dione and P-Dione showed a good resolution after forming cocrystal with DBTA. Thus, DBTA was selected as the chiral reagent for further resolution optimization.

Table 2-1 Summary of cocrystal screening experiments

Solvent / Acid	Acetone	H_2O/ACN (1:1, v/v)	EtOAc	2-MeTHF/n-heptane (1:1, v/v)	MTBE/n-heptane (1:1, v/v)
blank	Type B^+	Type C^+	Type C^+	Type D^+	Type E^+
L-Aspartic acid	Type B	Type C	Type C+acid	Type D	Type E
(R)-1,4-Benzodioxane-2-carboxylic acid	Type B	Type C	Type C	Type D	Type E+acid
(1S)-(−)-Camphanic acid	Type B	Type C	**Cocrystal Type A***	**Cocrystal Type B***	**Cocrystal Type A***
(−)-Camphoric acid	Type B	Type C+ acid	Type C+acid	Type D	Type E+acid

Solvent / Acid	Acetone	H_2O/ACN (1:1, v/v)	EtOAc	2-MeTHF/n-heptane (1:1, v/v)	MTBE/n-heptane (1:1, v/v)
(+)-2,3-Dibenzoyl-D-tartaric acid	Type B	Type C	Amorphous	**Cocrystal Type A[#]**	**Cocrystal Type A[#]**
D-Glutamic acid	Type B	Type C	Type C+acid	Type D	Type E
D-(+)-Malic acid	Type B	Type C	**Cocrystal Type A[$]**	Type D	Type E
(R)-(−)-Mandelic acid	Type B	Type C	Type C	Type D	Type E+acid
(−)-Menthyloxyacetic acid	Type B	Type C	Type C	Type D	Type E
(S)-(+)-α-Methoxyphenylacetic acid	Type B	Type C	Type C	Type D	Type E
(R)-(+)-α-Methoxy-α-trifluoromethylphenylacetic acid	Type B	Type C	Type C	Type D	Type E
(R)-(−)-5-Oxo-2-tetrahydrofurancarboxylic acid	Type B	Type C	Type C	Type D	Type E
(R)-(+)-N-(1-Phenylethyl)succinamic acid	Type B	Type C	Type C	Type D	Type E+acid
(S)-(+)-2-Phenylpropionic acid	Type B	Type C	Type C	Type D	Type E
L-Pyroglutamic acid	Type B	Type C	Type C	Type D	Type E+acid
D-(−)-Quinic acid	Type B+acid	Type C	Type C+acid	Type D+acid	Type E+acid
L-(+)-Tartaric acid	Type B	Type C	Type C	Type D	Type E
L-Ascorbic acid	Type B+acid	Type C	Type C+acid	Type D	Type E
N,N-Bis[(R)-(−)-1-phenylethyl]phthalamic acid	Type B	Type C	Type C	Type D	Type E+acid
(S)-phenylsuccinic acid	Type B	Type C	Type C+acid	Type D	Type E+acid

[+] Denotes crystal form of free rac-dione (no co-crystal formed), *: (1S)-(−)-Camphanic acid cocrystal, [#] : (+)-2,3-Dibenzoyl-D-tartaric acid cocrystal, [$]: D-(+)-Malic acid cocrystal

Table 2-2 HPLC data summary of three cocrystals

Peak area / Sample	Supernatant			Solid		
	P-Dione (area)	M-Dione (area)	**M/P**	P-Dione (area)	M-Dione (area)	**M/P**
(1S)-(-)-Camphanic acid cocrystal Type A(810465-06-C3)	9021.4	8274.2	**0.9**	6418.6	6360.4	**1.0**
(1S)-(-)-Camphanic acid cocrystal Type B (810465-06-D3)	4673.2	4303.4	**0.9**	4768.3	4736.9	**1.0**
DBTA cocrystal Type A (810465-06-D5)	17673.1	1858.6	**0.11**	1180.2	5249.8	**4.4**
D-(+)-Malic acid cocrystal Type A (810465-06-C7)	11382.6	10696.5	**0.9**	6443.3	6366.7	**1.0**

2.2 Solvent Screening

To select a suitable solvent to further resolute M-Dione and P-Dione, the area ratio from HPLC of M/P-Dione was collected in 20 more solvent/solvent mixtures. As listed in Table 2-3, 2-MeTHF showed the best resolution with the M-Dione/P-Dione area ratio of 0.7 in the supernatant and 4.1 in the residual solid. However, 2-MeTHF/n-heptane (1:1, v/v) showed a better resolution result during cocrystal screening (Table 2-2), thus 2-MeTHF/n-heptane was selected for further optimization. The area ratio from HPLC of M/P-Dione was collected in different ratios of 2-MeTHF/n-heptane with different acid/base ratios. Results in Table 2-4 showed that higher ratio of acid/FB (2:1 or 1.5:1) in 2-MeTHF/n-heptane (8:1 or 4:1, v/v) is desirable to improve the ratio of M/P-Dione in isolated solids.

The solubility of M-cocrystal and P-cocrystal in different ratios of 2-MeTHF/n-heptane was also performed at 5 and 25 ºC, which were summarized in Table 2-5. M-cocrystal was provided by client and P-cocrystal was prepared via reverse anti-solvent and anti-solvent (the experimental details refer to Section 4.3). The solubility result in Table 2-5 showed that the volume ratio of 2-MeTHF/n-heptane at 1.5:1 could afford the best resolution at RT. More resolution experiments were performed by client, from which a volume ratio of 1.4:1 showed the best resolution result. Thus, the volume ratio of 2-MeTHF/n-heptane at 1.4:1 was selected as the solvent system for resolution.

Table 2-3 Solvent screening of Dione racemate DBTA cocrystal (M-Dione/P-Dione area ratio)

Solvent	Supernatant	Solid	Solvent	Supernatant	Solid
2-MeTHF	0.7	4.1	DMSO/n-heptane (1:1, v/v)	NA	NA
MTBE	0.04	3.5	DMF/n-heptane (1:1, v/v)	0.9	1.0
MeOH	0.9	1.0	Toluene/n-heptane (1:1, v/v)	0.8	1.0
IPA	1.0	1.0	Acetic acid	NA	NA
EtOH/n-heptane (1:1, v/v)	0.9	1.0	Formic acid	NA	NA
MIBK	0.9	1.0	DCM	NA	NA
MEK	1.0	1.0	Cumene	0.9	1.0
IPAc	0.9	1.0	1-Butanol	0.9	1.0
THF	NA	NA	n-Propanol	0.9	1.0
NMP	NA	NA	1,3-Dimethyl-2-imidazolidinone	0.9	1.0

NA: A clear solution was obtained and no solid was isolated.

Table 2-4 Results of acid/base ratio and 2-MeTHF/n-heptane ratio screening with Dione racemate DBTA cocrystal (M-Dione/P-Dione area ratio)

Acid/base ratio / 2-MeTHF/n-heptane (v/v)	2:1			1.5:1			1:1.5			1:2		
	Form	L	S	Form	L	S	Form	L	S	Form	L	S
8:1	CA	0.4	13.4	CA	0.4	8.9	CA	0.5	7.0	CA	0.6	2.6
4:1	CA	0.3	8.7	CA	0.3	6.2	CA	0.4	6.2	CA	0.4	5.7
2:1	CA	0.2	6.0	CA	0.2	5.6	CA	0.2	4.7	CA	0.2	5.2
1:2	CA	0.3	1.2	CA	0.1	1.3	CA	0.1	1.4	CA	0.1	1.7
1:4	DA	1.4	1.0	CA	0.4	1.0	CA+ DA	0.1	1.0	CA	0.1	1.0
1:8	CA+ DA	0.9	1.0	DA	0.5	1.0	DA	0.3	1.0	DA	0.3	1.0

L: Supernatant, S: Solid, CA: Cocrystal Type A, DA: Dione racemate Type A

Table 2-5 2-MeTHF/n-heptane ratio screening of M/P-Dione cocrystals

Temperature (°C)	2-MeTHF/n-heptane (v/v)	M-Dione cocrystal		P-Dione cocrystal	
		Solubility (mg/mL)	XRPD	Solubility (mg/mL)	XRPD
5	1:1	11.3	Type A*	38.5	Type A#
	1.5:1	17.3	Type A*	60.8	Type A#
	2:1	22.2	Type A*	66.9	Type A#
	3:1	28.6	Type A*	86.6	Type A#
	4:1	30.8	Type A*	82.9	Type A#
	6:1	47.1	Type A*	92.1	NA
	8:1	55.1	Type A*	90.6	NA
25	1:1	13.4	Type A*	52.9	Type A#
	1.5:1	20.3	Type A*	80.8	Type A#
	2:1	28.1	Type A*	81.7	Type A#
	3:1	39.0	Type A*	87.0	NA
	4:1	43.0	Type A*	86.5	NA
	6:1	53.2	Type A*	81.9	NA
	8:1	65.0	Type A*	89.2	NA

*: M-cocrystal Type A, #: P-cocrystal Type A

2.3 Solubility of Dione DBTA cocrystal, Dione racemate and DBTA

The 7-day equilibrium solubility of M-Dione cocrystal, P-Dione cocrystal, M+P-Dione cocrystal mixture (1:1, w/w) and Dione racemate were set up at different temperatures (20, 30, 40, 50, 60, 65, 75 and 80 °C) in 2-MeTHF/n-heptane (1.4:1, v/v). Color change was observed at 75 and 80 °C after 5 days suggestive of degradation, so the solubility was not collected.

No form change was observed upon stirring of M-cocrystal and P-cocrystal at different temperatures for 7 days (Figure 2-5 and Figure 2-6). Dione racemate Type C was obtained after stirring of a mixture of M-Dione cocrystal and P-Dione cocrystal mixture (1:1, w/w) at different temperatures for 7 days (Figure 2-7). Dione racemate Type D (20 and 30 °C) and Dione racemate Type C (40, 50, 60 and 65 °C) were observed after stirring of Dione racemate at different temperature for 7 days (Figure 2-8 and Figure 2-9).

The 5-day equilibrium solubility of DBTA was set up at different temperatures (20, 30, 40, 50, 60 and 65 °C) in 2-MeTHF/n-heptane (1.4:1, v/v). A solubility of ~100 mg/mL was observed

under all the temperatures. No significant difference was observed with varying temperatures (Table 2-7).

Table 2-6 Solubility of Dione DBTA cocrystal, mixture of M/P-Dione cocrystal, Dione reaemante in 2-MeTHF/n-heptane (1.4:1, v/v)

Sample ID	Material	Temperature (°C)	Solubility (mg/mL)		Crystal Form
			M-Dione	P-Dione	
1-01-A1	M-Dione cocrystal	20	13.1	-	M-cocrystal Type A
1-01-A2		30	15.8	-	M-cocrystal Type A
1-01-A3		40	18.4	-	M-cocrystal Type A
1-01-A4		50	17.2	-	M-cocrystal Type A
1-01-A5		60	34.6	-	M-cocrystal Type A
1-01-A6		65	35.4	-	M-cocrystal Type A
1-01-B1	P-Dione, cocrystal	20	-	39.4	P-cocrystal Type A
1-01-B2		30	-	56.5	P-cocrystal Type A
1-01-B3		40	-	55.8	P-cocrystal Type A
1-01-B4		50	-	79.9	P-cocrystal Type A
1-01-B5		60	-	113.9	P-cocrystal Type A
1-01-B6		65	-	110.0	P-cocrystal Type A
1-01-C1	M+P-Dione cocrystal mixture	20	7.3	10.4	Dione racemate Type C
1-01-C2		30	9.2	16.0	Dione racemate Type C
1-01-C3		40	9.8	12.2	Dione racemate Type C
1-01-C4		50	12.1	21.9	Dione racemate Type C
1-01-C5		60	18.7	26.7	Dione racemate Type C
1-01-C6		65	13.4*	18.0*	Dione racemate Type C
1-01-D1	Dione racemate	20	18.0	15.2	Dione racemate Type D
1-01-D2		30	20.1	17.1	Dione racemate Type D
1-01-D3		40	11.5	9.9	Dione racemate Type C
1-01-D4		50	14.2	11.8	Dione racemate Type C
1-01-D5		60	13.7	11.7	Dione racemate Type C
1-01-D6		65	15.3	13.1	Dione racemate Type C

5

Table 2-7 Solubility of DBTA in 2-MeTHF/n-heptane (1.4:1, v/v)

Sample ID	Temperature (°C)	Solubility (mg/mL)
1-15-A1	20	99.1
1-15-A2	30	100.3
1-15-A3	40	98.9
1-15-A4	50	88.0
1-15-A5	60	105.0
1-15-A6	65	96.1

2.4 Ternary Phase Diagram

2.4.1 M/P-Dione cocrystals

M-Dione cocrystal and P-Dione cocrystal were weighed as corresponding mass listed in the Table 2-8 and were stirred in 2-MeTHF/n-heptane (1.4:1, v/v) at RT for 72 hours. The ternary phase diagram of M/P-Dione cocrystal was drawn based on 72-hour equilibrium solubility data and no eutectic point was obtained (Figure 2-10).

Table 2-8 Solubility data summary for M/P-Dione cocrystals

#	Weight of M-cocrystal (mg)	Weight of P-cocrystal (mg)	de (%)	Supernatant				Solid		
				[M] mg/mL	[P] mg/mL	de (%)	[M]/[P]	M mg	P mg	de (%)
1	50.7	0	100.0	22.9	0.0	100.0	NA	27.8	0.0	100.0
2	0	99.7	-100.0	0.0	81.2	-100.0	NA	0.0	18.5	-100.0
3	21.1	83.4	-59.6	5.1	59.4	-84.2	11.680	16.0	24.0	-20.0
4	41	83.5	-34.1	5.9	45.0	-76.9	7.658	35.1	38.5	-4.6
5	84	85	-0.6	11.5	23.7	-34.9	2.070	72.5	61.3	8.4
6	167.7	83.1	33.7	12.2	20.8	-26.2	1.711	155.5	62.3	42.8
7	49.7	50.4	-0.7	17.5	40.8	-40.0	2.331	32.2	9.6	54.1
8	49.7	25	33.1	19.9	21.8	-4.6	1.095	29.8	3.2	80.7
9	49.2	12.2	60.3	21.3	9.6	37.9	0.451	27.9	2.6	82.9

2.4.2 M/P-Dione

M-Dione and P-Dione were weighed as corresponding mass listed in the Table 2-9 and were stirring in 2-MeTHF/n-heptane (1.4:1, v/v) at RT for 5 days. The ternary phase diagram was drawn based on 5-day equilibrium solubility data in 1.0 mL of 2-MeTHF/n-heptane (1.4:1,

v/v) at RT. M-Dione Type A, P-Dione Type A, Dione racemate Type C and Type D were observed in the residual solid of solubility samples. No eutectic points were obtained in the phase diagram (Figure 2-11).

Table 2-9 Data summary of Ternary Phase Diagram for M/P-Dione

#	Weight of M-Dione (mg)	Weight of P-Dione (mg)	de (%)	Supernatant				Solid			XRPD
				[M] mg/mL	[P] mg/mL	de (%)	[M]/[P]	M mg	P mg	de (%)	
1	99.3	0	100.0	80.1	0	100.0	NA	19.2	0.0	100.0	A
2	0	100.6	-100.0	0	77.1	-100.0	NA	0.0	23.5	-100.0	A
3	20.2	119.3	-71.0	7.7	50.3	-73.6	0.2	12.5	69.0	-69.2	A+RD
4	89.8	90.3	-0.3	16.2	17.5	-3.9	0.9	73.6	72.8	0.6	RD
5	121.1	40.7	49.7	53.0	1.6	94.2	33.4	68.1	39.1	27.0	A+RC
6	90.2	19.5	64.4	52.6	1.4	94.8	37.6	37.6	18.1	35.0	A+RC
7	41.6	39.9	2.1	9.8	9.0	4.4	1.1	31.8	30.9	1.4	RC
8	39.2	120.3	-50.8	7.6	48.1	-72.8	0.2	31.6	72.2	-39.1	A+RD
9	119.1	20.5	70.6	54.1	1.6	94.4	34.5	65.0	18.9	54.9	A+RC

RC: Dione racemate Type C; RD: Dione racemate Type D; A: M or P-Dione Type A (the XRPD patterns of M-Dione Type A and P-Dione Type A were same and were not distinguished).

3 Solid State Characterization of Crystal Forms

A total of five Dione racemate crystal forms and two cocrystal forms were obtained. All these forms were characterized by XRPD, TGA, DSC, PLM and ^{1}H NMR and summarized in Table 2-10. The solid state characterization data suggested Dione racemate Type A and Type D were identified as 2-MeTHF solvates, Type B as an acetone solvate, Type C as an anhydrate, and Type E as a MTBE solvate.

Both M-Dione cocrystal Type A and P-Dione cocrystal Type A were found to be as 2-MeTHF solvates. All the characterization data are demonstrated in Figure 3-1 to Figure 3-22.

Table 2-10 Summary of crystal forms

Sample ID	Crystal form	Endotherm (peak, °C)	TGA (wt%)	^{1}H NMR (wt%)
5-05-A	Dione racemate Type A	110.2, 248.6, 213.4*	2.5 (150 °C)	2.4 (2-MeTHF)
1-10-A1	Dione racemate Type B	113.4, 126.0, 250.9	9.8 (150 °C)	6.2 (acetone)
1-01-D5	Dione racemate Type C	251.9	3.0 (150 °C)	ND&
1-01-D1	Dione racemate Type D	120.5, 253.3	15.4 (150 °C)	12.0 (2-MeTHF)
1-10-A4	Dione racemate Type E	151.6, 158.6, 248.7	14.7 (160 °C)	7.5 (MTBE)

5-17-A	M-Dione cocrystal Type A	109.6, 119.2	6.6 (125 °C)	10.6 (2-MeTHF)
5-16-A	P-Dione cocrystal Type A	88.3, 112.3, 132.8	9.2 (140 °C)	10.6 (2-MeTHF)

*: exothermic peak; &: not detected.

3.1.1 Competitive Slurry of Dione Racemate Forms

Dione racemate Type B~E were successfully re-produced via slurry of Dione racemate Type A in acetone, H_2O/ACN (1:1, v/v), 2-MeTHF/n-heptane (1.4:1, v/v) and MTBE/n-heptane (1:1, v/v) at RT, respectively.

Around 5 mg of each Dione racemate forms (Type A~E) were weighed into an HPLC vial, 0.3 mL of saturated Dione racemate solution in 2-MeHTF/n-heptane (1.4:1, v/v) was added into the vial and the mixture was then stirred at 20, 30, 40, 50, 60 and 65 °C for 5 days.

All the freebase forms converted to Dione racemate Type C via competitive slurry in 2-MeHTF/n-heptane (1.4:1, v/v) at target temperatures, suggesting Dione racemate Type C is the most thermodynamically stable form in 2-MeHTF/n-heptane (1.4:1, v/v) from 20 to 65 °C.

Table 2-11 Competitive slurry results

Starting Form	Experiment ID	Solvent	Temperature (°C)	Solid Form
Dione racemate Type A~E	1-16-B1	2-MeTHF/n-heptane (1.4:1, v/v)	20	Dione racemate Type C
	1-16-B2		30	Dione racemate Type C
	1-16-B3		40	Dione racemate Type C
	1-16-B4		50	Dione racemate Type C
	1-16-B5		60	Dione racemate Type C
	1-16-B6		65	Dione racemate Type C

3.2 Preparation of P-Dione cocrystal

3.2.1 Small Scale

2 g P-dione and 1 g DBTA were dissolved in 18 mL 2-MeTHF at 65 °C to get an almost clear solution. 18 mL heptane was added to this solution in 1 h. The solution was cooled to 20 °C over 4 h and aged overnight. The solution was evaporated using air blow at RT for about1h and a yellowish oily-like paste was obtained. Another 54 mL heptane was added to

the mixture with stirring for 2 h. The suspension was filtered. The solid sample was assigned as 810465-16-A.

3.2.2 Large Scale

10 g P-dione and 5 g DBTA were dissolved in 100 mL 2-MeTHF at 65 °C. The solution was filtered by 0.45 μm PTFE filter and a clear solution was obtained. The clear solution was added dropwise to a suspension of 400 mL heptane containing ~1 g seeds (810465-16-A) produced from the first run. The suspension was kept stirring at RT for 5 h before isolation. About 10 g of the P-Dione cocrystal (810465-20-A) was produced with a yield of ~66%.

4 Instruments and Methods

4.1 XRPD

For XRPD analysis, PANalytical X-ray powder diffract meters were used in reflection mode. The XRPD parameters used are listed in Table 4-1.

Table 4-1 Parameters for XRPD test

Parameters	**PANalytical**	**PANalytical**	**PANalytical**
Model	Empyrean	X' Pert^3	X' Pert^3
X-Ray wavelength	Cu, kα, Kα1 (Å): 1.540598, Kα2 (Å): 1.544426 Kα2/Kα1 intensity ratio: 0.50	Cu, kα, Kα1 (Å): 1.540598, Kα2 (Å): 1.544426 Kα2/Kα1 intensity ratio: 0.50	Cu, kα Kα1 (Å): 1.540598, Kα2 (Å): 1.544426 Kα2/Kα1 intensity ratio: 0.50
X-Ray tube setting	45 kV, 40 mA	45 kV, 40 mA	45 kV, 40 mA
Divergence slit	Automatic	1/8°	Fixed 1/8°
Scan mode	Continuous	Continuous	Continuous
Scan range (°2TH)	3°-40°	3°-40°	3°-40°
Scan step time (s)	17.8	46.7	18.9
Step size (°2TH)	0.0167	0.0263	0.0131
Test Time	5 min 30 s	5 min 04 s	4 min 15 s

4.2 TGA and DSC

TGA data were collected using a TA discovery 550, Q500 and Q5000 TGA from TA Instruments. DSC was performed using Q500, Q5000 and Discovery 2500 DSC from TA Instruments. Detailed parameters used are listed in Table **4-2** 4-2.

Table 4-2 Parameters for TGA and DSC tests

Parameters	TGA	DSC
Method	Ramp	Ramp
Sample pan	Aluminum, open	Aluminum, crimped
Temperature	RT – 350 °C	25 °C - 300 °C
Heating rate	10 °C/min	10 °C/min
Purge gas	N_2	N_2

4.3 HPLC

Agilent 1100/1260 HPLC was utilized to test solubility, with detailed methods listed in Table 4-3.

Table 4-3 HPLC method for solubility test

HPLC	Agilent 1100 with DAD detector
Column	CHIRALPAK IC-3, 4.6x100mm, 3um
Mobile phase	A: n-Heptane
	B: MeOH/EtOH (1:1, v/v)
Isocratic elution	A:B=75:25, 60:40
Run time	10.0 min
Post time	0.0 min
Flow rate	1.0 mL/min
Injection volume	5 µL
Detector wavelength	UV at 215 nm
Column temperature	40 °C
Sampler temperature	RT
Diluent	EtOH

Table 4-4 HPLC method for solubility test (DBTA)

HPLC	Agilent 1260 with DAD detector
Column	Agilent ZORBAX 300SB-C3, 150×4.6 mm, 3.5 µm
Mobile phase	A: 0.05% TFA in H_2O
	B: 0.05% TFA in ACN
Isoctatic elution	A:B=65:35

Run time	5.0 min
Post time	0.0 min
Flow rate	0.6 mL/min
Injection volume	5 µL
Detector wavelength	UV at 215 nm
Column temperature	40 °C
Sampler temperature	RT
Diluent	EtOH

4.4 ^{1}H NMR

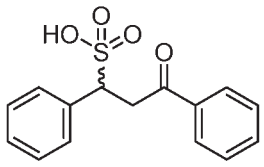
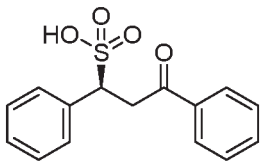
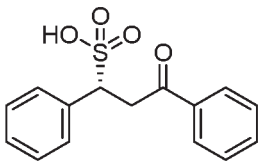
^{1}H NMR spectrum was collected on Bruker 400M NMR Spectrometer using DMSO-d_6 as solvent.

4.5 PLM

Polarized light microscopic picture was captured on Nikon DS-Fi2 upright microscope at room temperature.

Additional screening of compound 5 with 1,3-diphenyl-3-oxopropanesulfonic acid 11b.

Due to the low basicity of the pyridine moiety in compound **5** and the limited 'hits' in terms of the formation of crystalline salts using the standard screening set, it was chosen to screen racemic compound 4 with 1,3-diphenyl-3-oxopropanesulfonic acid 11b on a 0.06 mmol scale.

 **11-RAC**	 **11a** (+)-enantiomer	 **11b** (-)-enantiomer

Gram scale resolution of racemic compound 5: A 250 mL round-bottom flask was charged with 2.0 g racemic compound 4 (5.7 mmol, 1.0 eq.) in 200 mL EtOH:AcOH (90:10 v:v). After the material had dissolved, 832 mg of sulfonic acid 11b (2.9 mmol, 0.5 eq.) was added to the solution. The clear solution was left to stir for 15 hours at a stirring speed of 800 rpm. A white precipitate had formed which was isolated from the mother liquor. The isolated salt was suspended in CH_2Cl_2 which was treated with a concentrated aqueous $NaHCO_3$ solution

using a separatory funnel. The organic layer was isolated and the basic aqueous layer was extracted with CH_2Cl_2 (2x). The organic layers were combined and dried over Na_2SO_3. Evaporation of the solvent yielded 415 mg of (M)-5 (96% ee) (see Figure 6-1).

The clear mother liquor was evaporated to dryness. The yellow oily material was dissolved in CH_2Cl_2 and treated with a concentrated aqueous $NaHCO_3$ solution using a separatory funnel. The organic layer was isolated and the basic aqueous layer was extracted with CH_2Cl_2 (2x). The organic layers were combined and dried over Na_2SO_3. Evaporation of the solvent yielded 1579 mg of 5 (23% ee in (P)-atropisomer; Figure 6-2).

Polymorph Screening on M-Dione DBTA Cocrystal

5 Characterization of Crystal Forms of M-Dione DBTA Cocrystal

Polymorph screening experiments for the M-Dione were set up under 100 conditions using methods of slurry conversion, slow evaporation, slow cooling, anti-solvent addition, vapor diffusion, temperature cycling, and wet grinding. A total of 17 crystal forms (Type A ~ Q) were obtained from the screening. The form relationship is shown in Figure 4-1. The detailed characterization data are provided in Table 5-1 and the overlays of XRPD patterns are shown in Figure 5-1. Solid state characterization results suggested Type G is a hydrate, while the other Types are solvates.

5.1 Instruments and Methods

5.1.1 XRPD

XRPD was performed with a Panalytical X'Pert^3 Powder XRPD on a Si zero-background holder. The 2θ position was calibrated against a Panalytical Si reference standard disc. The parameters used are listed in Table 5-a.

Table 5-a Parameters for XRPD test

Parameters	Reflection Mode
X-Ray wavelength	Cu, kα Kα1 (Å): 1.540598, Kα2 (Å): 1.544426, Kα2/Kα1 intensity ratio: 0.50
X-Ray tube setting	45 kV, 40 mA
Divergence slit	Fixed 1/8º
Scan mode	Continuous
Scan range (º 2TH)	3-40
Scan step time [s]	18.87
Step size (º 2TH)	0.0131
Test Time	4 min 15 s

5.1.2 TGA/DSC

TGA data was collected using a TA Discovery 550 TGA from TA Instrument. DSC was performed using a TA Q2000 DSC from TA Instrument. DSC was calibrated with Indium reference standard and the TGA was calibrated using nickel reference standard. Detailed parameters used are listed in Table 5-b.

Table 5-b Parameters for TGA and DSC test

Parameters	TGA	DSC
Method	Ramp	Ramp
Sample pan	Platinum, open	Aluminum, crimped
Temperature	RT – desired temperature	
Heating rate	10 °C/min	
Purge gas	N_2	

5.2 Polymorph Screening

The solubility of Type A (3-05-A) was estimated at RT. Approximately 2 mg solids were added into a 3-mL glass vial. Solvents in Table 5-c were then added stepwise (50/50/200/700μL) into the vials until the solids were dissolved or a total volume of 2 mL was

reached. Results summarized in Table 5-c were used to guide the solvent selection in polymorph screening.

Polymorph screening experiments were performed using different crystallization or solid transition methods. The methods utilized and crystal types identified are summarized in Table 5-c.

Table 5-c Approximate solubility of starting material (6010013-05-A) at RT

Solvent	Solubility (mg/mL)	Solvent	Solubility (mg/mL)
MTBE	S<3.1	Acetone	S>52.0
H_2O	2.4<S<8.0	DMF	S>40.0
n-Heptane	3.0<S<10.0	Anisole	S>40.0
Toluene	2.7<S<9.0	Acetic acid	S>40.0
Hexanes	2.9<S<9.7	THF	S>50.0
IPA	26.0<S<52.0	ACN	S>46.0
2-MeTHF	24.0<S<48.0	CHCl3	S>50.0
1,4-Dioxane	25.0<S<50.0	EtOAc	S>72.0
n-BuOH	23.0<S<46.0	DMSO	S>72.0
MIBK	38.0<S<76.0	MeOH	S>78.0
BuOAc	S>28.0	EtOH	S>68.0
IPAc	S>32.0	--	--

Table 5-d Summary of polymorph screening experiments

Method	No. of Experiments	Crystal Type
Slurry at RT/5°C	37	Type A ~ G, Type J, Type N, Type N
Slow Evaporation	16	Type A, Type C, Type D, Type J, Type K, Type L, Type N, Type O
Slow Cooling	9	Type C, Type J, Type L, Type O
Anti-solvent Addition	9	Type A, Type C, Type H and Type I
Liquid Vapor Diffusion	5	Type L, Type M, Type Q
Solid Vapor Diffusion	6	Type A and M
Temperature Cycling	7	Type A, Type G, Type O

Method	No. of Experiments	Crystal Type
Wet Grinding	10	Type A
Total	99	Type A~Q

5.2.1 Slurry at RT

Slurry experiments were conducted at RT in different solvent systems. About 20 mg of Type A (3-05-A) was suspended in 0.2 mL of solvent in a 3-mL glass vial. After the suspension was stirred magnetically for 13 days at RT, the remaining solids were isolated for XRPD analysis. Results summarized in Table 5-e indicated that Type A~D and Type J were obtained.

Table 5-e Summary of slurry experiments at RT

Experiment ID	Solvent (v:v)	Solid Form
3-07-A1	MTBE	Type B
3-07-A2	H_2O	Type A
3-07-A3	n-Heptane	Low crystallinity
3-07-A4	Toluene	Low crystallinity
3-07-A5	Hexanes	Type A
3-07-A6*	IPA	Type A
3-07-A7*	2-MeTHF	Type B
3-07-A8*	1,4-Dioxane	Type J
3-07-A9	n-BuOH	Low crystallinity
3-07-A10*	MIBK	Type A
3-07-A11	BuOAc	Type C
3-07-A12	IPAc	Type D
3-07-A13*	Acetone	Amorphous
3-07-A14*	DMF	Type P
3-07-A15	Anisole	Type E
3-07-A16	THF/n-Heptane(1:9)	Low crystallinity
3-07-A17	2-MeTHF/n-Heptane(1:9)	Type A
3-07-A18	IPA/H2O(1:9)	Type A
3-07-A19	IPAc/H2O(1:9)	Type F
3-07-A20	n-BuOH/H2O(1:9)	Type A
3-07-A21	n-BuOH/MTBE(1:9)	Type A

Experiment ID	Solvent (v:v)	Solid Form
3-07-A22	CHCl3/MTBE(1:9)	Type A
3-07-A23*	MeOH/H2O (937:63, aw=0.2)	Amorphous
3-07-A24*	MeOH/H2O (844:156, aw=0.4)	Type N
3-07-A25*	MeOH/H2O (693:304, aw=0.6)	Type G
3-07-A26	MeOH/H2O (569:431, aw=0.8)	Type G

*: Solid obtained via slow evaporation at RT

5.2.2 Slow Evaporation

Slow evaporation experiments were performed under 16 conditions. Briefly, 20 mg of Type A (3-05-A) was dissolved in 0.2~0.8 mL of solvent in a 20-mL glass vial. If no dissolution was achieved, suspensions were filtered using a PTFE (pore size of 0.2 μm) and the filtrates were used for the following steps. The visually clear solutions were covered by Parafilm® with 5~10 pinholes and subjected to evaporation at RT. The solids were isolated for XRPD analysis. The results summarized in Table 5-f indicated that Type A, Type C, Type D, Type J, Type K, Type L, Type N, Type O were obtained.

Table 5-f Summary of slow evaporation experiments

Experiment ID	Solvent (v:v)	Solid Form
3-08-A1	Acetic acid	Amorphous
3-08-A2	THF	Type J
3-08-A3	ACN	Amorphous
3-08-A4	CHCl3	Amorphous
3-08-A5	EtOAc	Type C
3-08-A6	DMSO	Amorphous
3-08-A7	MeOH	Amorphous
3-08-A8	EtOH	Type N
3-08-A9	1,4-Dioxane	Type J
3-08-A10	n-BuOH	Type A
3-08-A11	MIBK	Type O

3-08-A12	BuOAc	Type C
3-08-A13	IPAc	Type D
3-08-A14	Acetone	Type K
3-08-A15	DMF	Gel
3-08-A16	2-MeTHF	Type L

5.2.3 Slow Cooling

Slow cooling experiments were conducted in 9 solvent systems. About 20 mg of Type A (3-05-A) was suspended in 1 mL of solvent in a 3-mL glass vial at RT. The suspension was then heated to 50 °C, equilibrated for two hour and filtered using a PTFE membrane (pore size of 0.20 μm). Filtrates were slowly cooled down to 5 °C at a rate of 0.1 °C/min. Results summarized in Table 5-g indicated Type C, Type G, Type J, Type L and Type O s were observed.

Table 5-g Summary of slow cooling experiments

Experiment ID	**Solvent (v:v)**	**Solid Form**
3-09-A1*	IPA	Type O
3-09-A2	2-MeTHF	Type L
3-09-A3*	1,4-Dioxane	Type J
3-09-A4*	n-BuOH	Type L
3-09-A5*	Acetic acid	Type G (Low crystallinity)
3-09-A6	THF	Type J
3-09-A7*	ACN	Amorphous
3-09-A8	CHCl3	Low crystallinity
3-09-A9*	EtOAc	Type C

*: Solids obtained from evaporation at RT.

5.2.4 Anti-solvent Addition

A total of 9 anti-solvent addition experiments were carried out. About 20 mg of starting material (3-05-A) was dissolved in 0.2-1.4 mL solvent to obtain a clear solution. The solution was magnetically stirred followed by addition of 0.2 mL anti-solvent stepwise till precipitate appeared or the total amount of anti-solvent reached 15.0 mL. The obtained precipitate was isolated for XRPD analysis. Results in Table 5-h showed that Type A, Type C, Type H and Type I were obtained.

Table 5-h Summary of anti-solvent addition experiments

Experiment ID	Solvent	Anti-solvent	Solid Form
3-10-A1*	H2O	Acetone	Type H
3-10-A2		THF	Amorphous
3-10-A3*		DMSO	Type I
3-10-A4*	MTBE	EtOH	Type A
3-10-A5*		CHCl3	Type A
3-10-A6		EtOAc	Type A
3-10-A7*	n-heptane	Acetone	Type C
3-10-A8*		2-MeTHF	Type A
3-10-A9*		IPAc	Type C

*: Solids obtained from evaporation at RT.

5.2.5 Liquid Vapor Diffusion

Five liquid vapor diffusion experiments were conducted. Approximate 20 mg of starting material (3-05-A) was dissolved in appropriate solvent to obtain a clear solution in a 3-mL vial. This solution was then placed into a 20-mL vial with 3 mL of volatile solvents. The 20-mL vial was sealed with a cap and kept at RT allowing sufficient time for organic vapor to interact with the solution. The precipitates were isolated for XRPD analysis. The results summarized in Table 5-i showed that Type L, Type M and Type Q were generated.

Table 5-i Summary of liquid vapor diffusion experiments

Experiment ID	**Solvent**	**Anti-solvent**	**Solid Form**
3-11-A1	MIBK	n-Heptane	Type Q
3-11-A2	EtOAc	IPA	Type M
3-11-A3	THF	MTBE	Type L
3-11-A4	2-MeTHF	n-Heptane	Type L
3-11-A5*	DMF	Toluene	Gel

*: Solids were obtained via evaporation at RT.

5.2.6 Solid Vapor Diffusion

Solid vapor diffusion experiments were conducted using 6 different solvents. Approximate 10 mg of starting material (3-05-A) was weighed into a 3-mL vial, which was placed into a 20-mL vial with 2 mL of volatile solvent. The 20-mL vial was sealed with a cap and kept at RT for 7 days allowing solvent vapor to interact with sample. The solids were tested

by XRPD and the results summarized in Table 5-j showed that Type A and Type M were generated.

Table 5-j Summary of solid vapor diffusion experiments

Experiment ID	Solvent	Solid Form
3-12-A1	EtOH	Type M
3-12-A2	MTBE	Type A
3-12-A3	H2O	Type A
3-12-A4	acetone	Amorphous
3-12-A5	2-MeTHF	Type A
3-12-A6	IPAc	Type A

5.2.7 Temperature Cycling

Temperature cycling experiments were conducted in 7 solvent systems. About 20 mg of starting material (3-05-A) was suspended in 1 mL of solvent in a 3-mL glass vial at RT. The suspension was then heated to 50 °C, equilibrated for one hour and filtered using a PTFE membrane (pore size of 0.20 μm). Filtrates were slowly cooled down to 5 °C at a rate of 0.2 °C/min and then heat to 50 °C at a rate of 1 °C/min. Repeat the cycle one more time and then cooling to 5 °C at a rate of 0.2 °C/min. The samples were stored 5 °C before solids were isolated and analyzed using XRPD. Results summarized in Table 5-k indicated Type A, Type G and Type O were observed.

Table 5-k Summary of temperature cycling experiments

Experiment ID	Solvent (v:v)	Solid Form
3-13-A1*	2-MeTHF	Type A
3-13-A2*	MeOH	Type G
3-13-A3*	MIBK	Type A
3-13-A4*	ACN	Amorphous
3-13-A5	CHCl3	Low crystallinity
3-13-A6*	Toluene	Amorphous
3-13-A7*	IPA	Type O

*: Solids obtained from evaporation at RT.

5.2.8 Slurry at 5 °C

Slurry experiments were conducted at 5 °C in different solvent systems. About 20 mg of starting material (3-05-A) was suspended in 0.2 mL of solvent in a 3-mL glass vial. After the suspension was stirred magnetically for 7 days at 5 °C, the remaining solids were isolated for XRPD analysis. Results summarized in Table 5-l indicated that Type A, Type C ~Type E and Type J were obtained.

Table 5-l Summary of slurry experiments at 5 °C

Experiment ID	Solvent (v:v)	Solid Form
3-14-A1*	BuOAc	Type C
3-14-A2*	IPAc	Type D
3-14-A3*	Acetone	Low crystallinity
3-14-A4*	DMF	Gel
3-14-A5	Anisole	Type E
3-14-A6*	2MeTHF	Type A
3-14-A7*	ACN	Low crystallinity
3-14-A8*	CHCl3	Low crystallinity
3-14-A9*	EtOAc	Low crystallinity
3-14-A10*	MeOH	Type C
3-14-A11*	THF	Type J

*: Solids obtained from evaporation at RT.

5.2.9 Wet Grinding

Wet grinding experiments were performed under five conditions. Briefly, 10 mg of Type A (3-05-A) was put in mortar and grinding in ~20 μL of solvent for 5min. The solids were isolated for XRPD analysis. The results summarized in Table 5-m indicated that Type A was obtained.

Table 5-m Summary of wet grinding experiments

Experiment ID	Solvent (v:v)	Solid Form
3-15-A1	MTBE	Amorphous
3-15-A2	H_2O	Amorphous
3-15-A3	n-Heptane	Amorphous
3-15-A4	Toluene	Amorphous
3-15-A5	Hexanes	Amorphous
3-15-A6	IPA	Amorphous

3-15-A7	2-MeTHF	Type A (low crystallinity)
3-15-A8	1,4-Dioxane	Type A
3-15-A9	n-BuOH	Amorphous
3-15-A10	MIBK	Amorphous

Table 5-1 Characterization of M-dione DBTA cocrystal crystal forms

Crystal Form (Batch No.)	**Preparation Conditions**	**Weight Loss in TGA (%)**	**DSC Endo. (Peak, °C)**	**Form ID**
Type A (3-05-A)	Classic resolution with DBTA (2-MeTHF)	7.31 up to 125°C	109.4 120.0	2-MeTHF solvate
Type B (3-07-A1)	Slurry at RT (MTBE)	7.21 up to 125°C	115.7	MTBE solvate
Type C (3-08-A5)	Slow Evaporation (EtOAc)	7.99 up to 125°C	92.7 116.4	EtOAc solvate
Type D (3-07-A12)	Slurry at RT (IPAc)	7.51 up to 130 °C.	75.4, 110.5, 148.0, 116.6 , 265.9(exo).	IPAc solvate
Type E (3-07-A15)	Slurry at RT (Anisole)	8.63 up to 125°C	103.8 119.0	Anisole Solvate
Type F (3-07-A19)	Slurry at RT IPAc/H_2O (v:v 1:9)	6.2 up to 130 °C	86.5, 107.9	IPAc solvate
Type G (3-07-A26)	Slurry at RT (MeOH/H_2O aw=0.8)	6.44 up to 100°C	86.0 127.2 133.1	Hydrate

Type H (3-10-A1)	Anti-Solvent (Acetone/H_2O)	3.58 up to 130°C	107.6	Acetone solvate
Type I (3-10-A3)	Anti-Solvent (DMSO/H_2O)	7.26 up to 150 °C	128.9	DMSO solvate
Type J (3-08-A2)	Slow Evaporation (THF)	7.27% by 125°C	115.7	THF Solvate
Type K (3-08-A14)	Slow Evaporation (Acetone)	5.71 up to 150 °C.	96.7, 119.8 147.4 157.4°C(exo).	Acetone solvate
Type L (3-11-A4)	Liquid Vapor Diffusion (2-MeTHF/n-Heptane)	7.94 up to 130 °C	126.2	2-MeTHF solvate
Type M (3-11-A2)	Liquid Vapor Diffusion (EtOAc/IPA)	3.73 up to 150°C	122.6	IPA solvate
Type N (3-08-A8)	Slow Evaporation (EtOH)	4.08 up to 150°C	85.4, 126.5 150.9	EtOH solvate
Type O (3-08-A11)	Slow Evaporation (MIBK)	2.03 up to 130°C	106.2, 151.2	MIBK solvate
Type P (3-07-A14)	Slow Evaporation (DMF)	8.33 up to 130°C	89.9	DMF solvate
Type Q (3-11-A1)	Liquid Vapor Diffusion (MIBK/n-Heptane)	6.00 up to 120°C	92.9, 148.9 170.0	MIBK solvate

5.3 Type A

Type A (3-05-A) was provided by client. The XRPD result showed in Figure 5-4 suggested crystalline. As shown by TGA and DSC data in Figure 5-5, a weight loss of 7.3% up to 125 °C and two endotherms at 109.4 and 120.0 °C (peak) were observed. As displayed in Figure 5-6, the presence of 2-MeTHF was evidenced in ^{1}H NMR spectrum. Based on the results, Type A was considered as a 2-MeTHF solvate.

5.4 Type B

Type B sample (3-07-A1) was obtained via slurry of Type A in MTBE at RT. XRPD pattern shown in Figure 5-7 suggested crystalline. As shown by TGA and DSC data in Figure 5-10, a weight loss of 7.2% up to 125 °C and an endotherm at 115.7°C (peak) were observed. As displayed in Figure 5-9, the presence of MTBE was evidenced in ^{1}H NMR spectrum. Based on the results, Type B was likely a MTBE solvate.

5.5 Type C

Type C sample (3-08-A5) was obtained via slow evaporation in EtOAc at RT. XRPD pattern shown in Figure 5-10 suggested crystalline. TGA and DSC data displayed in Figure 5-11 indicated a weight loss of 8.0% up to 125 °C and two endotherms at 92.7 °C and 116.4 °C (peak). As displayed in Figure 5-12, the presence of EtOAc was evidenced in ^{1}H NMR spectrum. Based on the results, Type C was likely an EtOAc solvate.

5.6 Type D

Type D (3-07-A12) was obtained by slurry of Type A in IPAc at RT. The XRPD result showed in Figure 5-13 suggested crystalline. As shown by TGA and DSC data in Figure 5-14, a weight loss of 7.5% up to 130 °C and endotherms at 75.4 °C, 110.5 °C, 148.0 °C and 116.6 °C (peak) and an exotherm at 265.9 °C were observed. As displayed in Figure 5-15, the presence of IPAc was evidenced in ^{1}H NMR spectrum. Based on the results, Type D was likely an IPAc solvate.

5.7 Type E

Type E (3-07-A15) was obtained via slurry of Type A in anisole at RT. The XRPD result showed in Figure 5-16 suggested crystalline. As shown by TGA and DSC data in Figure 5-17, a weight loss of 8.6% up to 125 °C and two endotherms at 103.8 °C and 119.0 °C (peak) were observed. As displayed in Figure 5-18, the presence of IPAc was evidenced in ^{1}H NMR spectrum. Based on the results, Type E was likely an anisole solvate.

5.8 Type F

Type F (3-07-A19) was obtained via slurry of Type A in IPAc/H_2O (v:v 1:9) at RT. The XRPD result showed in Figure 5-19 suggested crystalline. As shown by TGA and DSC

data in Figure 5-20, a weight loss of 6.2% up to 130 °C and two endotherms at 86.5 °C and 107.9 °C (peak) were observed. As displayed in Figure 5-18, the presence of IPAc was evidenced in ^{1}H NMR spectrum. Based on the results, Type F was likely an IPAc solvate.

5.9 Type G

Type G (3-07-A26) was obtained via slurry of Type A in MeOH/H_2O (aw=0.8) at RT. The XRPD result showed in Figure 5-22 suggested crystalline state. As shown by TGA and DSC data in Figure 5-23, a weight loss of 6.4% up to 100 °C and endotherms at 86.0°C, 127.2 °C and 133.1 °C (peak) were observed. As displayed in Figure 5-24, no signal for MeOH or MeTHF was observed in solution ^{1}HNMR spectrum. Based on the results, Type G was likely a hydrate.

5.10 Type H

Type H (3-10-A1) was obtained via anti-solvent addition using Acetone/H_2O. The XRPD result showed in Figure 5-25 suggested crystalline. As shown by TGA and DSC data in Figure 5-26, a weight loss of 3.6% up to 130 °C and an endotherm at 107.6 °C (peak) were observed. As displayed in Figure 5-27, the presence of acetone was evidenced in ^{1}H NMR spectrum. Based on the results, Type H was likely an acetone solvate.

5.11 Type I

Type I (3-10-A3) was obtained via anti-solvent addition using DMSO/H_2O. The XRPD result showed in Figure 5-28 suggested crystalline. As shown by TGA and DSC data in Figure 5-29, a weight loss of 7.3% up to 150 °C and an endotherm at 128.9 °C (peak) were observed. As displayed in Figure 5-30, the presence of DMSO was evidenced in ^{1}H NMR spectrum. Based on the results, Type I was likely a DMSO solvate.

5.12 Type J

Type J (3-08-A2) was obtained via slow evaporation in THF. The XRPD result showed in Figure 5-31 suggested crystalline. As shown by TGA and DSC data in Figure 5-32, a weight loss of 7.3% up to 125 °C and an endotherm at 115.7 °C (peak) were observed. As displayed in Figure 5-33, the presence of THF was evidenced in ^{1}H NMR spectrum. Based on the results, Type J was likely a THF solvate.

5.13 Type K

Type K (3-08-A14) was obtained via slow evaporation in acetone. The XRPD result showed in Figure 5-34 suggested crystalline. As shown by TGA and DSC data in Figure 5-35, a weight loss of 5.7% up to 150 °C and endotherms at 96.7 °C, 119.8 °C and 147.4 °C (peak) and an exotherm at 157.4 °C (peak) were observed. As displayed in Figure 5-36, the presence

of acetone was evidenced in ^{1}H NMR spectrum. Based on the results, Type K was likely an acetone solvate.

5.14 Type L

Type L (3-11-A4) was obtained via liquid vapor diffusion in 2-MeTHF/n-Heptane. The XRPD result showed in Figure 5-37 suggested crystalline with preferred orientation. As shown by TGA and DSC data in Figure 5-38, a weight loss of 7.9% up to 130 °C and an endotherm at 126.2 °C (peak) were observed. As displayed in Figure 5-39, the presence of acetone was evidenced while no signal for n-heptane was observed in ^{1}H NMR spectrum. Based on the results, Type L was likely a 2-MeTHF solvate.

5.15 Type M

Type M (3-11-A2) was obtained from liquid vapor diffusion in EtOAc/IPA. The XRPD result showed in Figure 5-40 suggested crystalline. As shown by TGA and DSC data in Figure 5-41, a weight loss of 3.7% up to 150 °C and an endotherm at 122.6 °C (peak) were observed. As displayed in Figure 5-42, the presence of IPA was evidenced while no signal for EtOAc was observed in ^{1}H NMR. Based on the results, Type M was likely an IPA solvate.

5.16 Type N

Type N (3-08-A8) was obtained via slow evaporation in EtOH. The XRPD result showed in Figure 5-43 suggested crystalline. As shown by TGA and DSC data in Figure 5-44, a weight loss of 4.1% up to 150 °C and endotherms at 85.4 °C, 126.5 °C and 150.9 °C (peak) were observed. As displayed in Figure 5-45, the presence of EtOH was evidenced in ^{1}H NMR spectrum. Based on the results, Type N was likely an EtOH solvate.

5.17 Type O

Type O (3-08-A11) was obtained via slow evaporation in MIBK. The XRPD result showed in Figure 5-46 suggested crystalline. As shown by TGA and DSC data in Figure 5-47, a weight loss of 2.0% up to 130 °C and two endotherms at 106.2°C and 151.2°C (peak) were observed. As displayed in Figure 5-48, the presence of MIBK was evidenced in ^{1}H NMR spectrum. Based on the results, Type O was likely a MIBK solvate.

5.18 Type P

Type P (3-07-A14) was obtained via slow evaporation in DMF. The XRPD result showed in Figure 5-49 suggested crystalline. As shown by TGA and DSC data in Figure 5-50, a weight loss of 8.3% up to 130 °C and an endotherm at 89.9 °C (peak) were observed. As displayed in Figure 5-51, the presence of DMF was evidenced in ^{1}H NMR spectrum. Based on the results, Type P was likely a DMF solvate.

5.19 Type Q

Type Q (3-11-A1) was obtained via liquid vapor diffusion in MIBK/n-Heptane. The XRPD result showed in Figure 5-52 suggested crystalline. As shown by TGA and DSC data in Figure 5-53, a weight loss of 6.0% up to 120 °C and endotherms at 92.9 °C, 148.9 °C and 170.0 °C (peak) were observed. As displayed in Figure 5-54, the presence of MIBK was evidenced while no signal of N-Heptane observed in ^{1}H NMR spectrum. Based on the results, Type Q was likely a MIBK solvate.

6. Crystal data and Experimental for Composition 4a

Experimental. Single colourless plate-shaped crystals of (**Composition 4a**) were used as received. A suitable crystal (0.28×0.18×0.09) mm^3 was selected and mounted on a nylon loop with paratone oil on a Bruker APEX-II CCD diffractometer. The crystal was kept at T = 173(2) K during data collection. Using **Olex2** (Dolomanov et al., 2009), the structure was solved with the XT (Sheldrick, 2015) structure solution program, using the Intrinsic Phasing solution method. The model was refined with version of **XL** (Sheldrick, 2008) using Least Squares minimisation.

Crystal Data. $C_{65}H_{72}Cl_2F_2N_8O_{15}$, M_r = 1314.20, triclinic, $P\bar{1}$ (No. 1), a = 11.5683(10) Å, b = 11.6705(10) Å, c = 13.9593(12) Å, α = 68.1780(10)°, β = 69.4150(10)°, γ = 87.7760(10)°, V = 1628.7(2) Å^3, T = 173(2) K, Z = 1, Z' = 1, μ(MoKα) = 0.178, 26758 reflections measured, 11949 unique (R_{int} = 0.0528) which were used in all calculations. The final wR_2 was 0.2465 (all data) and R_1 was 0.0835 (I > 2(I)).p

Table 6-2: Fractional Atomic Coordinates (×10^4) and Equivalent Isotropic Displacement Parameters (Å^2×10^3) for **COMPOSITION 4A**. U_{eq} is defined as 1/3 of the trace of the orthogonalised U_{ij}.

Atom	x	y	z	U_{eq}
O1C	5607(5)	3451(5)	6493(5)	44.9(14)
O2C	6723(6)	4580(6)	6921(5)	49.9(15)
O3C	3704(5)	3216(6)	5826(5)	45.6(14)
O4C	2800(6)	3841(6)	4560(6)	55.9(16)
O5C	3369(5)	5630(6)	6567(5)	50.2(15)
O6C	3636(5)	3990(6)	7917(5)	50.8(15)
O7C	5703(6)	2984(7)	4257(5)	55.4(16)

Atom	x	y	z	U_{eq}
O8C	6595(5)	4867(6)	3832(5)	49.1(15)
C1C	5032(7)	4527(8)	6031(7)	41(2)
C2C	4615(7)	4267(8)	5203(7)	39.1(19)
C3C	3928(8)	4667(8)	6968(7)	42(2)
C4C	5705(8)	3954(9)	4361(7)	42(2)
C5C	6393(8)	3601(8)	6961(7)	42(2)
C6C	6820(9)	2403(8)	7493(8)	49(2)
C7C	7721(15)	2378(12)	7941(13)	98(3)
C8C	8179(15)	1311(13)	8410(13)	94(3)
C9C	7697(17)	223(14)	8497(14)	107(5)
C10C	6708(16)	185(12)	8178(13)	98(3)
C11C	6265(15)	1303(12)	7665(13)	94(3)
C12C	2953(8)	3028(9)	5341(7)	44(2)
C13C	2359(9)	1762(9)	5860(8)	54(2)
C14C	1223(9)	1501(10)	5822(8)	56(2)
C15C	671(11)	300(12)	6312(10)	75(3)
C16C	1261(14)	-658(13)	6805(13)	98(5)
C17C	2446(14)	-407(13)	6720(13)	97(4)
C18C	2954(13)	800(12)	6325(12)	87(4)
Cl1B	6935(2)	1601(2)	11106(2)	66.0(7)
F1B	4643(5)	1859(6)	10647(5)	66.7(16)
O1B	8509(6)	7968(6)	7303(6)	58.0(17)
O2B	4575(6)	6378(7)	8234(6)	66.1(19)
N1B	7896(6)	6005(6)	8607(6)	40.4(16)
N2B	7345(6)	3931(7)	9798(6)	42.2(17)
N3B	6567(7)	7139(7)	7745(6)	49.2(18)
N4B	11242(6)	5811(7)	8040(6)	47.4(18)
C1B	7710(8)	7096(9)	7832(8)	48(2)
C2B	7030(8)	4974(8)	9152(6)	40(2)
C3B	6537(8)	2952(9)	10275(7)	47(2)
C4B	5411(8)	2909(8)	10151(7)	47(2)

Atom	x	y	z	U_{eq}
C5B	5070(8)	3977(10)	9543(7)	49(2)
C6B	5884(8)	5054(9)	9031(7)	44(2)
C7B	5584(8)	6210(9)	8328(8)	50(2)
C8B	9103(7)	5996(7)	8717(7)	41(2)
C9B	9205(8)	6331(8)	9550(7)	43(2)
C10B	10370(9)	6393(9)	9588(7)	49(2)
C11B	11350(8)	6131(8)	8840(7)	44(2)
C12B	10113(7)	5734(7)	7981(7)	38.9(19)
C13B	8078(9)	6634(9)	10360(8)	55(2)
C14B	10040(9)	5292(9)	7127(8)	54(2)
C15B	10546(10)	4041(10)	7234(10)	65(3)
C16B	10688(11)	6301(12)	5939(9)	73(3)
Cl1A	11316(3)	-588(3)	4003(3)	82.7(9)
F1A	13799(6)	-251(6)	4033(5)	77.9(18)
O1A	12158(6)	6025(6)	1115(6)	57.3(17)
O2A	15430(6)	4363(7)	1981(6)	63.4(18)
N1A	11949(6)	3944(6)	2039(6)	38.9(16)
N2A	11735(7)	1804(7)	3004(6)	48.6(19)
N3A	13776(6)	5170(7)	1580(6)	45.5(18)
N4A	8608(6)	4153(7)	2689(6)	46.4(18)
C1A	12607(8)	5110(9)	1551(7)	47(2)
C2A	12449(7)	2876(8)	2555(7)	40(2)
C3A	12216(10)	797(10)	3464(8)	56(2)
C4A	13389(10)	813(9)	3546(8)	56(3)
C5A	14083(9)	1886(10)	3114(8)	54(2)
C6A	13638(8)	2995(8)	2564(7)	44(2)
C7A	14365(8)	4199(9)	2043(8)	48(2)
C8A	10709(7)	3834(8)	2039(6)	37.4(19)
C9A	10540(8)	3371(9)	1305(8)	47(2)
C10A	9326(8)	3313(8)	1314(7)	47(2)
C11A	8421(8)	3689(8)	2008(7)	45(2)

Atom	x	y	z	U_{eq}
C12A	9733(7)	4227(7)	2738(7)	39.4(19)
C13A	11568(8)	2995(10)	522(8)	55(2)
C14A	9890(8)	4703(9)	3549(7)	50(2)
C15A	9619(11)	6056(11)	3255(11)	71(3)
C16A	9045(10)	3875(11)	4734(8)	64(3)
O3S	355(10)	1070(10)	9718(9)	116(3)
C11S	-300(40)	-220(40)	11630(40)	142(14)
C11T	-1050(40)	-700(50)	11410(40)	190(20)
C12S	160(30)	-310(30)	10410(20)	180(9)
C13S	1360(40)	-510(50)	10600(40)	151(11)
C13T	1220(40)	-820(40)	9990(40)	151(11)
C14S	2240(20)	280(20)	9240(20)	155(8)
C15S	1510(20)	1150(20)	8834(18)	139(7)
O2S	6461(8)	-721(8)	5995(7)	83(2)
C6S	5780(20)	-1920(20)	5275(19)	145(7)
C7S	6000(20)	-720(20)	5170(20)	155(8)
C8S	7200(30)	-180(30)	4150(30)	241(15)
C9S	7990(20)	670(20)	4390(20)	153(7)
C10S	7490(30)	340(30)	5490(30)	202(11)
O1S	4966(9)	7468(9)	1097(8)	99(3)
C1S	5930(20)	8160(20)	2110(20)	176(9)
C2S	5018(15)	7306(16)	2147(14)	105(5)
C3S	3770(20)	7280(20)	2920(20)	146(7)
C4S	3200(30)	8270(30)	2170(30)	207(12)
C5S	4180(20)	8430(20)	990(20)	162(8)

Table 6-3: Anisotropic Displacement Parameters ($\times 10^4$) **COMPOSITION 4A**. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2} \times U_{11} + ... + 2hka^* \times b^* \times U_{12}]$\$

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
O1C	37(3)	57(4)	52(3)	-27(3)	-25(3)	9(3)
O2C	47(4)	54(4)	52(4)	-21(3)	-21(3)	4(3)

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
O3C	33(3)	63(4)	39(3)	-21(3)	-10(3)	-3(3)
O4C	52(4)	68(4)	53(4)	-20(4)	-26(3)	1(3)
O5C	34(3)	56(4)	53(4)	-19(3)	-11(3)	9(3)
O6C	44(3)	71(4)	35(4)	-21(3)	-11(3)	3(3)
O7C	46(4)	71(5)	56(4)	-34(4)	-15(3)	3(3)
O8C	33(3)	56(4)	55(4)	-22(3)	-11(3)	7(3)
C1C	31(4)	48(5)	47(5)	-20(4)	-14(4)	1(4)
C2C	35(5)	42(5)	41(5)	-16(4)	-14(4)	2(4)
C3C	37(5)	52(5)	39(5)	-21(4)	-14(4)	2(4)
C4C	36(5)	51(5)	45(5)	-17(4)	-22(4)	6(4)
C5C	40(5)	48(5)	35(4)	-16(4)	-11(4)	5(4)
C6C	58(6)	45(5)	51(5)	-22(4)	-26(5)	10(4)
C7C	141(9)	68(6)	117(8)	-37(6)	-85(8)	23(6)
C8C	124(9)	77(6)	120(8)	-41(6)	-86(7)	41(6)
C9C	155(14)	87(10)	133(13)	-53(9)	-107(12)	68(10)
C10C	141(9)	68(6)	117(8)	-37(6)	-85(8)	23(6)
C11C	124(9)	77(6)	120(8)	-41(6)	-86(7)	41(6)
C12C	35(5)	65(6)	38(5)	-26(5)	-15(4)	3(4)
C13C	50(6)	59(6)	56(6)	-23(5)	-23(5)	6(5)
C14C	47(6)	71(7)	58(6)	-31(5)	-22(5)	1(5)
C15C	54(6)	101(10)	73(8)	-34(7)	-22(6)	-21(6)
C16C	96(10)	81(9)	114(11)	-3(8)	-67(9)	-27(8)
C17C	98(10)	73(8)	110(11)	-10(8)	-51(9)	-2(7)
C18C	88(9)	77(8)	102(10)	-20(7)	-56(8)	-9(7)
Cl1B	67.9(16)	57.4(14)	64.2(16)	-10.1(12)	-27.3(13)	-6.4(12)
F1B	67(4)	76(4)	55(3)	-19(3)	-22(3)	-23(3)
O1B	41(4)	55(4)	71(4)	-12(3)	-23(3)	-6(3)
O2B	36(4)	89(5)	78(5)	-31(4)	-28(3)	11(3)
N1B	23(3)	42(4)	51(4)	-12(3)	-13(3)	-6(3)
N2B	33(4)	54(5)	35(4)	-14(3)	-10(3)	-5(3)
N3B	40(4)	58(5)	48(4)	-12(4)	-23(4)	2(4)

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
N4B	35(4)	47(4)	59(5)	-17(4)	-18(4)	7(3)
C1B	38(5)	55(6)	58(6)	-27(5)	-22(4)	9(5)
C2B	37(5)	53(5)	27(4)	-15(4)	-9(4)	1(4)
C3B	46(5)	55(6)	40(5)	-19(4)	-14(4)	6(4)
C4B	49(5)	54(6)	36(5)	-16(4)	-14(4)	-12(4)
C5B	29(5)	83(7)	35(5)	-25(5)	-9(4)	-6(5)
C6B	32(5)	64(6)	37(5)	-21(4)	-10(4)	-8(4)
C7B	38(5)	67(6)	50(5)	-23(5)	-19(4)	3(4)
C8B	34(5)	43(5)	48(5)	-15(4)	-19(4)	2(4)
C9B	39(5)	51(5)	42(5)	-22(4)	-12(4)	1(4)
C10B	49(6)	59(6)	42(5)	-20(4)	-20(4)	10(4)
C11B	42(5)	50(5)	46(5)	-17(4)	-23(4)	4(4)
C12B	28(4)	42(5)	47(5)	-17(4)	-14(4)	2(3)
C13B	44(5)	62(6)	52(6)	-25(5)	-8(4)	7(5)
C14B	40(5)	62(6)	61(6)	-26(5)	-18(5)	0(4)
C15B	52(6)	72(7)	89(8)	-52(6)	-22(6)	7(5)
C16B	66(7)	99(9)	50(6)	-23(6)	-21(5)	-10(6)
Cl1A	84(2)	60.8(16)	85(2)	-4.6(15)	-34.1(16)	-3.2(14)
F1A	89(5)	73(4)	76(4)	-21(3)	-45(4)	31(3)
O1A	45(4)	60(4)	64(4)	-17(4)	-23(3)	1(3)
O2A	42(4)	87(5)	76(5)	-38(4)	-33(3)	8(3)
N1A	26(3)	53(4)	37(4)	-16(3)	-12(3)	1(3)
N2A	41(4)	59(5)	37(4)	-13(4)	-9(3)	0(4)
N3A	31(4)	58(4)	51(4)	-27(4)	-12(3)	-4(3)
N4A	36(4)	59(5)	40(4)	-16(4)	-12(3)	1(3)
C1A	44(5)	57(6)	41(5)	-21(4)	-16(4)	2(5)
C2A	30(4)	65(6)	33(4)	-26(4)	-13(4)	12(4)
C3A	61(6)	65(6)	48(6)	-20(5)	-28(5)	6(5)
C4A	57(6)	55(6)	60(6)	-29(5)	-19(5)	18(5)
C5A	54(6)	79(7)	48(5)	-36(5)	-27(5)	18(5)
C6A	34(5)	59(6)	45(5)	-26(4)	-15(4)	13(4)

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
C7A	35(5)	72(6)	47(5)	-34(5)	-13(4)	5(5)
C8A	32(4)	46(5)	30(4)	-10(4)	-12(4)	6(4)
C9A	33(5)	61(6)	48(5)	-18(4)	-16(4)	5(4)
C10A	38(5)	59(6)	46(5)	-17(4)	-18(4)	-5(4)
C11A	30(5)	59(6)	38(5)	-14(4)	-8(4)	-1(4)
C12A	31(4)	47(5)	34(4)	-9(4)	-10(4)	3(4)
C13A	39(5)	91(7)	41(5)	-34(5)	-10(4)	12(5)
C14A	36(5)	73(6)	46(5)	-31(5)	-12(4)	5(4)
C15A	64(7)	81(8)	78(8)	-44(6)	-22(6)	6(6)
C16A	58(6)	96(8)	39(5)	-21(5)	-25(5)	16(6)
O3S	113(8)	120(8)	98(7)	-25(6)	-37(6)	19(7)

Table 6-3: Bond Lengths in Å for **COMPOSITION 4A**.

Atom	Atom	Length/Å
O1C	C1C	1.439(10)
O1C	C5C	1.341(10)
O2C	C5C	1.194(10)
O3C	C2C	1.427(10)
O3C	C12C	1.341(10)
O4C	C12C	1.215(11)
O5C	C3C	1.313(10)
O6C	C3C	1.193(10)
O7C	C4C	1.194(10)
O8C	C4C	1.306(10)
C1C	C2C	1.525(11)
C1C	C3C	1.528(12)
C2C	C4C	1.532(12)
C5C	C6C	1.478(13)
C6C	C7C	1.386(16)
C6C	C11C	1.358(16)
C7C	C8C	1.358(17)

Atom	Atom	Length/Å
C8C	C9C	1.35(2)
C9C	C10C	1.373(19)
C10C	C11C	1.411(17)
C12C	C13C	1.454(14)
C13C	C14C	1.384(13)
C13C	C18C	1.366(16)
C14C	C15C	1.375(15)
C15C	C16C	1.375(18)
C16C	C17C	1.368(19)
C17C	C18C	1.375(18)
Cl1B	C3B	1.732(10)
F1B	C4B	1.339(10)
O1B	C1B	1.212(11)
O2B	C7B	1.221(11)
N1B	C1B	1.398(12)
N1B	C2B	1.381(10)
N1B	C8B	1.458(10)

Atom	Atom	Length/Å
N2B	C2B	1.344(11)
N2B	C3B	1.305(11)
N3B	C1B	1.367(11)
N3B	C7B	1.385(12)
N4B	C11B	1.346(11)
N4B	C12B	1.346(10)
C2B	C6B	1.391(12)
C3B	C4B	1.378(13)
C4B	C5B	1.357(13)
C5B	C6B	1.389(12)
C6B	C7B	1.456(14)
C8B	C9B	1.400(12)
C8B	C12B	1.369(12)
C9B	C10B	1.372(12)
C9B	C13B	1.526(13)
C10B	C11B	1.359(13)
C12B	C14B	1.492(13)
C14B	C15B	1.526(14)
C14B	C16B	1.562(15)
Cl1A	C3A	1.714(11)
F1A	C4A	1.336(11)
O1A	C1A	1.216(11)
O2A	C7A	1.223(11)
N1A	C1A	1.386(11)
N1A	C2A	1.405(11)
N1A	C8A	1.446(10)
N2A	C2A	1.331(11)
N2A	C3A	1.321(12)
N3A	C1A	1.373(12)
N3A	C7A	1.368(12)
N4A	C11A	1.335(11)

Atom	Atom	Length/Å
N4A	C12A	1.335(11)
C2A	C6A	1.394(12)
C3A	C4A	1.402(14)
C4A	C5A	1.324(14)
C5A	C6A	1.419(13)
C6A	C7A	1.453(13)
C8A	C9A	1.393(12)
C8A	C12A	1.398(12)
C9A	C10A	1.405(12)
C9A	C13A	1.485(13)
C10A	C11A	1.339(13)
C12A	C14A	1.497(12)
C14A	C15A	1.527(16)
C14A	C16A	1.541(14)
O3S	C12S	1.51(3)
O3S	C15S	1.44(2)
C11S	C12S	1.64(5)
C11T	C12S	1.51(3)
C12S	C13S	1.49(5)
C12S	C13T	1.39(5)
C13S	C14S	1.70(5)
C13T	C14S	1.55(5)
C14S	C15S	1.39(3)
O2S	C7S	1.43(2)
O2S	C10S	1.52(3)
C6S	C7S	1.38(3)
C7S	C8S	1.54(4)
C8S	C9S	1.57(4)
C9S	C10S	1.34(3)
O1S	C2S	1.429(18)
O1S	C5S	1.41(2)

Atom	Atom	Length/Å
C1S	C2S	1.45(3)
C2S	C3S	1.46(3)
C3S	C4S	1.53(3)
C4S	C5S	1.59(4)

Table 6-4: Bond Angles in for **COMPOSITION 4A**.

Atom	**Atom**	**Atom**	**Angle/°**
C5C	O1C	C1C	116.5(6)
C12C	O3C	C2C	117.1(7)
O1C	C1C	C2C	105.3(6)
O1C	C1C	C3C	108.6(7)
C3C	C1C	C2C	111.5(7)
O3C	C2C	C1C	106.6(6)
O3C	C2C	C4C	108.9(6)
C1C	C2C	C4C	110.9(7)
O5C	C3C	C1C	109.9(7)
O6C	C3C	O5C	126.1(8)
O6C	C3C	C1C	124.0(8)
O7C	C4C	O8C	127.3(8)
O7C	C4C	C2C	122.3(8)
O8C	C4C	C2C	110.4(7)
O1C	C5C	C6C	110.8(8)
O2C	C5C	O1C	124.1(8)
O2C	C5C	C6C	125.1(8)
C7C	C6C	C5C	119.6(9)
C11C	C6C	C5C	121.9(9)
C11C	C6C	C7C	118.1(10)
C8C	C7C	C6C	122.4(12)
C9C	C8C	C7C	119.1(13)
C10C	C9C	C8C	120.6(12)
C9C	C10C	C11C	119.5(13)
C6C	C11C	C10C	119.7(12)
O3C	C12C	C13C	112.4(8)
O4C	C12C	O3C	122.7(8)
O4C	C12C	C13C	124.9(8)
C14C	C13C	C12C	120.6(9)
C18C	C13C	C12C	120.4(9)

Atom	Atom	Atom	Angle/°
C18C	C13C	C14C	118.8(10)
C15C	C14C	C13C	120.1(10)
C16C	C15C	C14C	120.5(10)
C15C	C16C	C17C	118.7(12)
C16C	C17C	C18C	120.4(14)
C13C	C18C	C17C	120.5(12)
C1B	N1B	C8B	115.5(7)
C2B	N1B	C1B	121.7(7)
C2B	N1B	C8B	122.6(7)
C3B	N2B	C2B	116.6(7)
C1B	N3B	C7B	126.9(8)
C12B	N4B	C11B	118.8(8)
O1B	C1B	N1B	121.2(8)
O1B	C1B	N3B	122.4(9)
N3B	C1B	N1B	116.3(8)
N1B	C2B	C6B	119.7(8)
N2B	C2B	N1B	117.3(7)
N2B	C2B	C6B	123.1(8)
N2B	C3B	Cl1B	116.9(7)
N2B	C3B	C4B	125.0(8)
C4B	C3B	Cl1B	118.0(7)
F1B	C4B	C3B	121.5(8)
F1B	C4B	C5B	120.2(8)
C5B	C4B	C3B	118.3(8)
C4B	C5B	C6B	119.2(8)
C2B	C6B	C7B	120.9(8)
C5B	C6B	C2B	117.7(8)
C5B	C6B	C7B	121.2(8)
O2B	C7B	N3B	121.3(9)
O2B	C7B	C6B	124.9(9)
N3B	C7B	C6B	113.8(7)

Atom	Atom	Atom	Angle/°
C9B	C8B	N1B	118.0(7)
C12B	C8B	N1B	120.2(7)
C12B	C8B	C9B	121.7(7)
C8B	C9B	C13B	121.4(8)
C10B	C9B	C8B	116.6(8)
C10B	C9B	C13B	122.0(8)
C11B	C10B	C9B	119.9(8)
N4B	C11B	C10B	123.0(8)
N4B	C12B	C8B	119.9(8)
N4B	C12B	C14B	116.2(7)
C8B	C12B	C14B	123.8(7)
C12B	C14B	C15B	113.0(8)
C12B	C14B	C16B	110.5(8)
C15B	C14B	C16B	111.7(9)
C1A	N1A	C2A	121.5(7)
C1A	N1A	C8A	118.9(7)
C2A	N1A	C8A	119.5(7)
C3A	N2A	C2A	116.6(8)
C7A	N3A	C1A	126.9(8)
C12A	N4A	C11A	120.6(7)
O1A	C1A	N1A	120.7(8)
O1A	C1A	N3A	122.4(8)
N3A	C1A	N1A	116.9(8)
N2A	C2A	N1A	116.6(7)
N2A	C2A	C6A	124.3(8)
C6A	C2A	N1A	119.1(8)
N2A	C3A	Cl1A	116.6(7)
N2A	C3A	C4A	123.7(9)
C4A	C3A	Cl1A	119.7(8)
F1A	C4A	C3A	119.7(9)
C5A	C4A	F1A	121.1(9)

Atom	Atom	Atom	Angle/°
C5A	C4A	C3A	119.2(9)
C4A	C5A	C6A	119.7(9)
C2A	C6A	C5A	116.4(9)
C2A	C6A	C7A	121.0(8)
C5A	C6A	C7A	122.6(8)
O2A	C7A	N3A	120.9(9)
O2A	C7A	C6A	124.4(9)
N3A	C7A	C6A	114.7(8)
C9A	C8A	N1A	118.0(7)
C9A	C8A	C12A	122.2(7)
C12A	C8A	N1A	119.7(7)
C8A	C9A	C10A	115.9(8)
C8A	C9A	C13A	123.3(8)
C10A	C9A	C13A	120.7(8)
C11A	C10A	C9A	119.5(8)
C10A	C11A	N4A	123.5(8)
N4A	C12A	C8A	118.2(8)
N4A	C12A	C14A	118.8(7)
C8A	C12A	C14A	123.0(7)
C12A	C14A	C15A	110.2(8)
C12A	C14A	C16A	109.8(8)
C15A	C14A	C16A	111.6(9)
C15S	O3S	C12S	101.0(16)
O3S	C12S	C11S	98(2)
C11T	C12S	O3S	114(3)
C13S	C12S	O3S	101(3)
C13S	C12S	C11T	119(4)
C13T	C12S	O3S	108(3)
C13T	C12S	C11S	124(4)
C12S	C13S	C14S	94(3)
C12S	C13T	C14S	106(3)

Atom	Atom	Atom	Angle/°
C15S	C14S	C13S	105(2)
C15S	C14S	C13T	98(2)
C14S	C15S	O3S	109.6(18)
C7S	O2S	C10S	109.8(17)
O2S	C7S	C8S	98(2)
C6S	C7S	O2S	110(2)
C6S	C7S	C8S	105(2)
C7S	C8S	C9S	108(3)
C10S	C9S	C8S	104(3)
C9S	C10S	O2S	110(2)
C5S	O1S	C2S	99.3(14)
O1S	C2S	C1S	115.3(16)
O1S	C2S	C3S	109.3(14)
C1S	C2S	C3S	113.3(18)
C2S	C3S	C4S	102.4(19)
C3S	C4S	C5S	100(2)
O1S	C5S	C4S	110(2)

Table 6-5: Hydrogen Fractional Atomic Coordinates ($\times 10^4$) and Equivalent Isotropic Displacement Parameters ($Å^2 \times 10^3$) for **COMPOSITION 4A**. U_{eq} is defined as 1/3 of the trace of the orthogonalised U_{ij}.

Atom	x	y	z	U_{eq}
H5C	2738	5676	7079	75
H8C	7257	4612	3523	74
H1C	5642	5286	5648	49
H2C	4246	5000	4813	47
H7C	8030	3133	7918	117
H8CA	8829	1329	8674	113
H9C	8046	-520	8781	129
H10C	6325	-589	8302	117
H11C	5582	1286	7440	113
H14C	824	2153	5456	67

Atom	x	y	z	U_{eq}
H15C	-125	131	6310	90
H16C	854	-1479	7197	118
H17C	2922	-1070	6936	117
H18C	3724	966	6375	104
H3B	6442	7830	7268	59
H5B	4284	3988	9467	59
H10B	10491	6619	10136	58
H11B	12147	6175	8883	53
H13A	7637	7233	9947	82
H13B	8351	6990	10789	82
H13C	7521	5873	10864	82
H14B	9141	5177	7246	64
H15A	11415	4105	7168	98
H15B	10492	3806	6645	98
H15D	10055	3410	7957	98
H16A	10303	7074	5885	109
H16B	10596	6013	5392	109
H16D	11573	6448	5797	109
H3A	14191	5912	1268	55
H5A	14875	1914	3171	65
H10A	9147	3010	831	57
H11A	7601	3622	2016	54
H13D	12178	3715	8	83
H13E	11236	2674	104	83
H13F	11970	2347	938	83
H14A	10773	4660	3501	60
H15E	9817	6386	3737	106
H15F	8738	6107	3360	106
H15G	10127	6543	2480	106
H16E	8174	3966	4816	96
H16F	9227	4126	5267	96

Atom	x	y	z	U_{eq}
H16G	9198	3006	4874	96
H11D	403	121	11721	212
H11E	-600	-1054	12212	212
H11F	-968	318	11703	212
H11G	-1060	-259	11882	290
H11H	-1114	-1599	11825	290
H11I	-1750	-509	11154	290
H12S	128	-753	9931	215
H12A	-557	-686	10345	215
H13G	1497	-1393	10872	182
H13H	1451	-115	11089	182
H13I	1087	-1267	9548	182
H13J	1458	-1412	10592	182
H14D	3019	696	9168	186
H14E	2460	-284	8839	186
H14F	2628	537	9673	186
H14G	2896	104	8645	186
H15H	1338	997	8243	167
H15I	1947	1996	8512	167
H6SA	6575	-2283	5108	218
H6SB	5393	-1922	4756	218
H6SC	5233	-2417	6034	218
H7S	5282	-222	5136	186
H8SA	7003	307	3490	290
H8SB	7680	-861	4007	290
H9SA	8880	527	4152	184
H9SB	7923	1561	4003	184
H10D	7155	1055	5667	243
H10E	8144	66	5812	243
H1SA	6626	7716	2249	264
H1SB	5541	8496	2685	264

Atom	x	y	z	U_{eq}
H1SC	6226	8839	1383	264
H2S	5277	6457	2441	126
H3SA	3789	7506	3528	175
H3SB	3293	6455	3231	175
H4SA	3168	9048	2302	249
H4SB	2364	7965	2275	249
H5SA	3745	8410	500	195
H5SB	4689	9246	647	195

Table 6-4: Hydrogen Bond information for **COMPOSITION 4A**.

D	H	A	d(D-H)/Å	d(H-A)/Å	d(D-A)/Å	D-H-A/deg
O5C	H5C	N4B[1]	0.84	1.82	2.656(9)	170.9
O8C	H8C	N4A	0.84	1.79	2.624(9)	171.6
N3B	H3B	O2S[2]	0.88	1.94	2.805(12)	168.1
C14B	H14B	N1B	1.00	2.44	2.937(12)	110.1
N3A	H3A	O1S[3]	0.88	1.95	2.798(12)	160.7

——

[1]-1+x,+y,+z; [2]+x,1+y,+z; [3]1+x,+y,+z

Table 6-5: Atomic Occupancies for all atoms that are not fully occupied in **COMPOSITION 4A**.

Atom	Occupancy
C11S	0.5
H11D	0.5
H11E	0.5
H11F	0.5
C11T	0.5
H11G	0.5
H11H	0.5
H11I	0.5
H12S	0.5

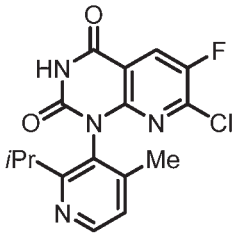
Atom	Occupancy
H12A	0.5
C13S	0.5
H13G	0.5
H13H	0.5
C13T	0.5
H13I	0.5
H13J	0.5
H14D	0.5
H14E	0.5
H14F	0.5
H14G	0.5

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

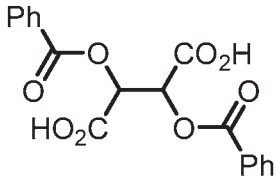
What is claimed is:

1. A composition, the composition comprising a compound of Formula 4:



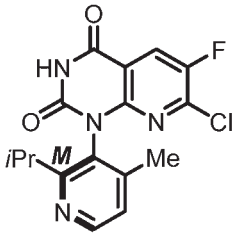
4

and a compound of Formula B:



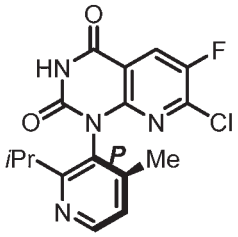
B.

2. The composition of claim 1, wherein the compound of Formula 4 is a compound of Formula 5M:



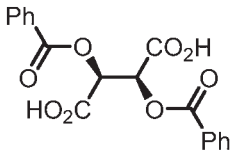
5M.

3. The composition of claim 1, wherein the compound of Formula 4 is a compound of Formula 5P:

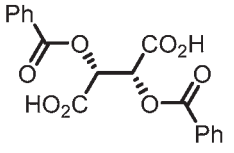


5P.

4. The composition of any one of claims 1-3, wherein the compound of Formula B is a compound of formula B1:

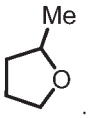

B1.

5. The composition of any one of claims 1-3, wherein the compound of Formula B is a compound of formula B2:


B2.

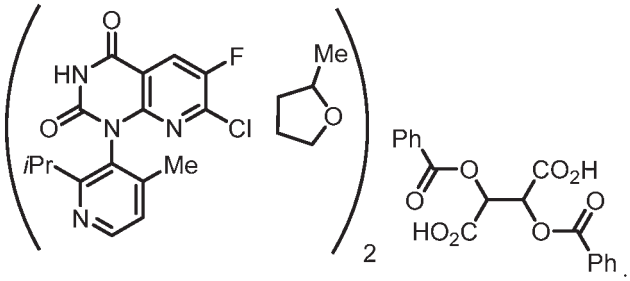
6. The composition of any one of claims 1-3, wherein the composition comprises a 2 to 1 ratio of the compound of Formula 4 to the compound of Formula B.

7. The composition of any one of claims 1-3, wherein the composition further comprises 2-methyltetrahydrofuran having the formula:

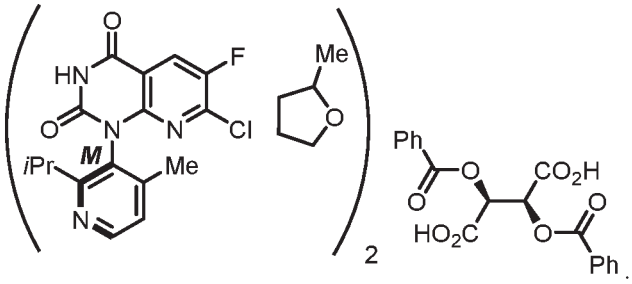

.

8. The composition of any one of claims 1-3, wherein the ratio of the 2-methyltetrahydrofuran to the compound of formula B is 2 to 1.

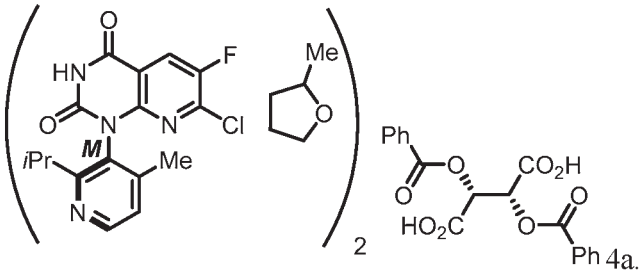
9. The composition of claim 1, wherein the composition has the formula:


.

10. The composition of claim 9, wherein the composition has the formula:

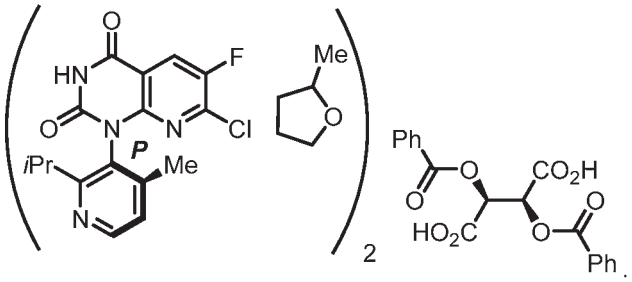

.

11. The composition of claim 9, wherein the composition has the formula:

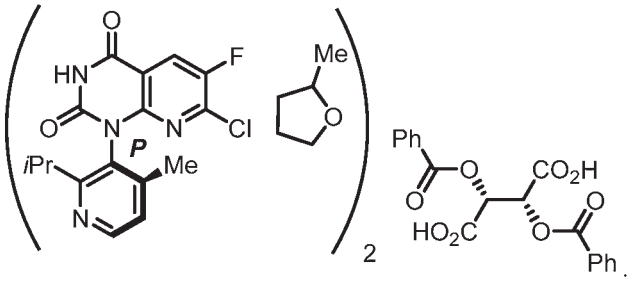


4a.

12. The composition of claim 9, wherein the composition has the formula:

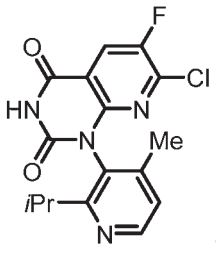


13. The composition of claim 9, wherein the composition has the formula:

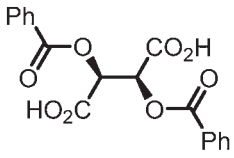


14. The composition of any one of claims 1-13, wherein the composition is in a crystalline state.

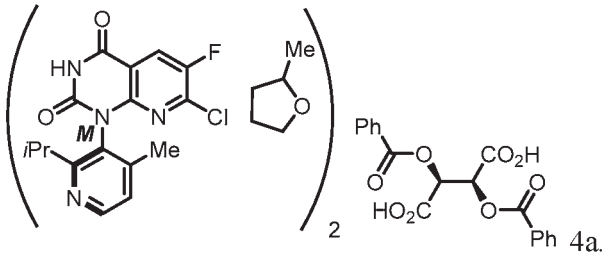
15. A method of making a composition of formula 4a, the method comprising reacting a compound 4, having the following chemical structure:



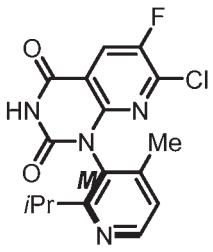
4, with a compound B1, having the formula:



in the presence of 2-methyltetrahydrofuran to form the composition of formula 4a,

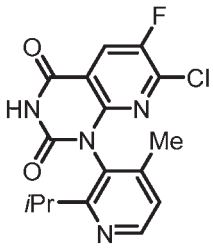
having the structure:  4a.

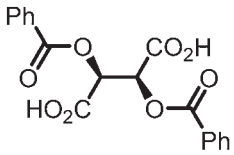
16. A method of obtaining a compound of formula 5M, having the following chemical structure:

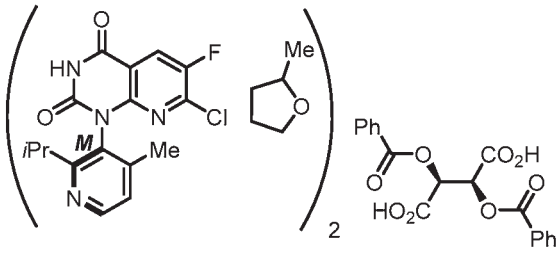
 5M,

the method comprising:

a) reacting a compound 4, having the following chemical structure:

 4, with a compound B1, having the formula:



in the presence of 2-methyltetrahydrofuran to form a composition of formula 4a, having the structure:  4a as crystals;

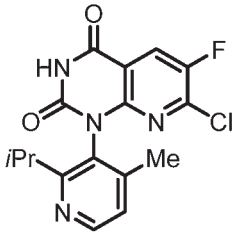
b) isolating composition 4a, and

c) treating the isolated composition 4a with a base to produce the compound of formula 5M.

17. The method according to Claim 16, wherein the base is Na_2HPO_4.

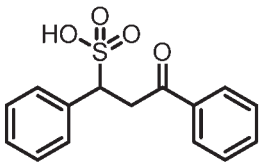
18. The method according to Claim 16, wherein the base is $NaHCO_3$.

19. A composition, the composition comprising a compound of Formula 4:



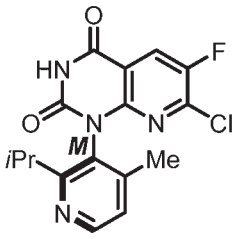
4

and a compound of Formula 11:



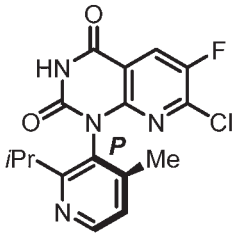
11.

20. The composition of claim 19, wherein the compound of Formula 4 is a compound of Formula 5M:



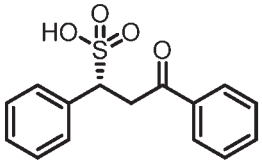
5M.

21. The composition of claim 19, wherein the compound of Formula 4 is a compound of Formula 5P:



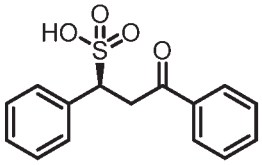
5P.

22. The composition of any one of claims 19-21, wherein the compound of Formula 11 is a compound of formula 11a:



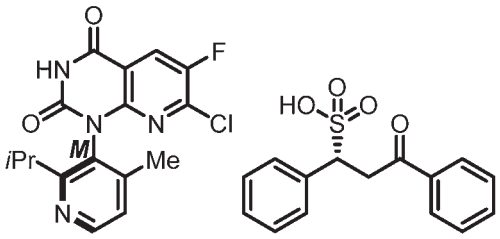
11a.

23. The composition of any one of claims 19-21, wherein the compound of Formula 11 is a compound of formula 11b:



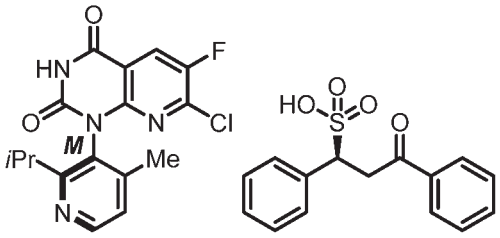
11b.

24. The composition of claim 19, wherein the composition has the formula:



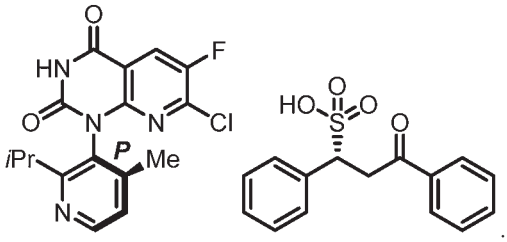
.

25. The composition of claim 19, wherein the composition has the formula:

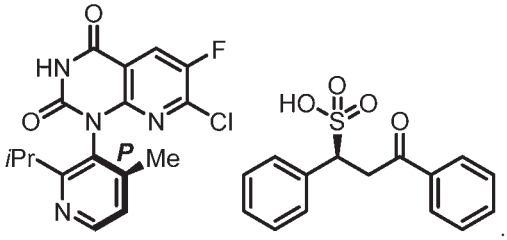


.

26. The composition of claim 19, wherein the composition has the formula:

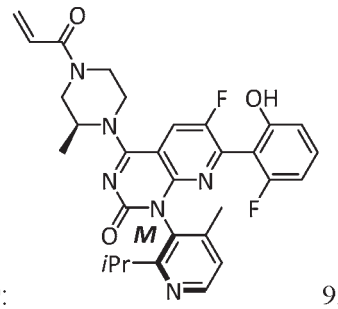


27. The composition of claim 19, wherein the composition has the formula:



28. The composition of any one of claims 19-27, wherein the composition comprises a 1 to 1 ratio of the compound of Formula 4 to the compound of Formula 11.

29. The method of claim 16, wherein the compound of formula 5M is used to generate a compound having the Formula 9:



9.

30. The method of claim 29, wherein the method further comprises mixing the compound of Formula 9 with at least one pharmaceutically acceptable excipient to form a pharmaceutical composition.