



(12) **DEMANDE DE BREVET CANADIEN
CANADIAN PATENT APPLICATION**

(13) **A1**

(86) Date de dépôt PCT/PCT Filing Date: 2019/06/10
(87) Date publication PCT/PCT Publication Date: 2019/12/19
(85) Entrée phase nationale/National Entry: 2020/11/09
(86) N° demande PCT/PCT Application No.: US 2019/036397
(87) N° publication PCT/PCT Publication No.: 2019/241157
(30) Priorité/Priority: 2018/06/11 (US62/683,263)

(51) Cl.Int./Int.Cl. *C07D 471/04* (2006.01),
A61K 31/4375 (2006.01), *A61P 35/00* (2006.01)

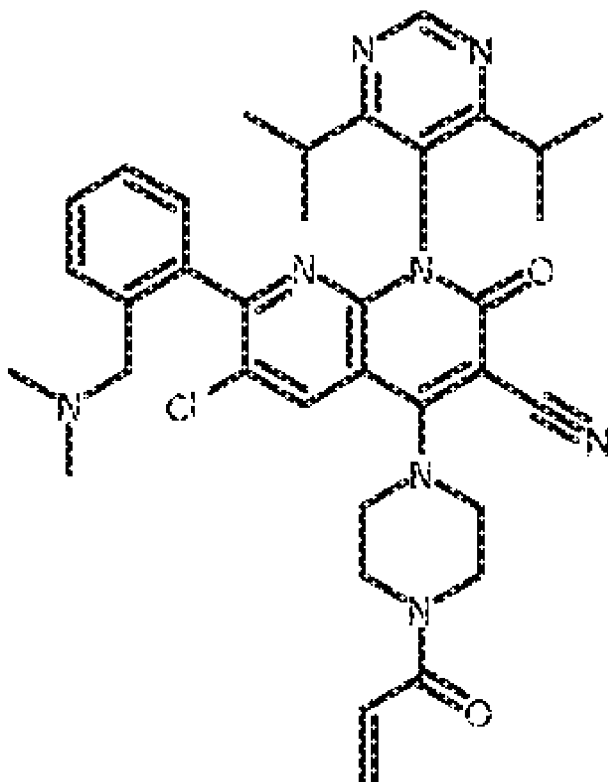
(71) Demandeur/Applicant:
AMGEN INC., US

(72) Inventeurs/Inventors:
CHEN, JIAN, US;
TAMAYO, NURIA A., US;
LIU, LONGBIN, US;
WANG, HUI-LING, US;
LANMAN, BRIAN ALAN, US;
WURZ, RYAN PAUL, US;
SHIN, YOUNGSOOK, US;
CEE, VICTOR J., US

(74) Agent: SMART & BIGGAR LLP

(54) Titre : INHIBITEURS DE KRAS G12C POUR LE TRAITEMENT DU CANCER

(54) Title: KRAS G12C INHIBITORS FOR TREATING CANCER



(57) **Abrégé/Abstract:**

Provided herein are KRAS G12C inhibitors, such as composition of the same, and methods of using the same. These inhibitors are useful for treating a number of disorders, including pancreatic, colorectal, and lung cancers.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property

Organization

International Bureau

(43) International Publication Date

19 December 2019 (19.12.2019)



(10) International Publication Number

WO 2019/241157 A1

(51) International Patent Classification:

C07D 471/04 (2006.01) A61P 35/00 (2006.01)

A61K 31/4375 (2006.01)

(21) International Application Number:

PCT/US2019/036397

(22) International Filing Date:

10 June 2019 (10.06.2019)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

62/683,263 11 June 2018 (11.06.2018) US

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

(72) Inventors: CHEN, Jian; One Amgen Center Drive, Thousand Oaks, California 91320 (US). TAMAYO, Nuria A.; One Amgen Center Drive, Thousand Oaks, California 91320 (US). LIU, Longbin; One Amgen Center Drive, Thousand Oaks, California 91320 (US). WANG, Hui-Ling; One Amgen Center Drive, Thousand Oaks, California 91320 (US). LANMAN, Brian Alan; One Amgen Center Drive, Thousand Oaks, California 91320 (US). WURZ, Ryan Paul; One Amgen Center Drive, Thousand Oaks, California 91320 (US). SHIN, Youngsook; One Amgen Center Drive, Thousand Oaks, California 91320 (US). CEE, Victor J.; One Amgen Center Drive, Thousand Oaks, California 91320 (US).

(74) Agent: REIDY, Joseph F.; One Amgen Center Drive, Thousand Oaks, 91320 (US).

(81) Designated States (unless otherwise indicated, for every

kind of national protection available): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every

kind of regional protection available): ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

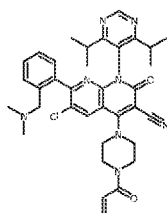
- as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))
- as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))

Published:

- with international search report (Art. 21(3))
- with sequence listing part of description (Rule 5.2(a))

(54) Title: KRAS G12C INHIBITORS FOR TREATING CANCER

(57) Abstract: Provided herein are KRAS G12C inhibitors, such as composition of the same, and methods of using the same. These inhibitors are useful for treating a number of disorders, including pancreatic, colorectal, and lung cancers.



WO 2019/241157 A1

KRAS G12C INHIBITORS FOR TREATING CANCER

FIELD OF THE INVENTION

[0001] The present application is being filed along with a sequence listing in electronic format. The sequence listing is provided as a file entitled A-2262-WO-PCT_SeqList_061019_ST25.txt, created June 10, 2019, which is 16 kb in size. The information in the electronic format of the sequence listing is incorporated herein by reference in its entirety.

[0002] The present invention relates to compounds that inhibit the KRAS G12C protein; methods of treating diseases or conditions, such as cancer, using the compounds; and pharmaceutical compositions containing the compounds.

BACKGROUND

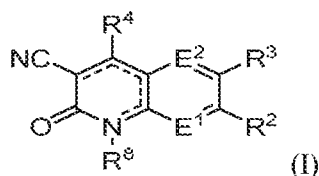
[0003] KRAS gene mutations are common in pancreatic cancer, lung adenocarcinoma, colorectal cancer, gall bladder cancer, thyroid cancer, and bile duct cancer. KRAS mutations are also observed in about 25% of patients with NSCLC, and some studies have indicated that KRAS mutations are a negative prognostic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

[0004] The compounds disclosed herein can be in the form of a pharmaceutically acceptable salt. The compounds provided can be formulated into a pharmaceutical formulation comprising a compound disclosed herein and a pharmaceutically acceptable excipient.

[0005] Also provided is a method of inhibiting KRAS G12C in a cell, comprising contacting the cell with a compound or composition disclosed herein. Further provided is a method of treating cancer in a subject comprising administering to the subject a therapeutically effective amount of a compound or composition disclosed herein. In some embodiments, the cancer is lung cancer, pancreatic cancer, or colorectal cancer.

SUMMARY

[0006] In one aspect of the present invention, the invention provides a compound having a structure of formula (I)



wherein

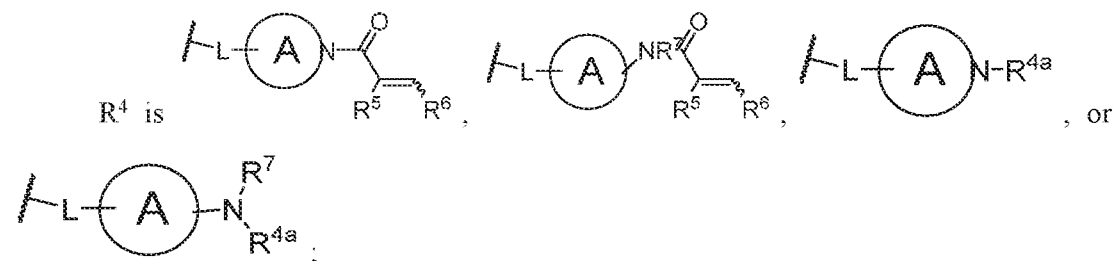
E^1 and E^2 are each independently N or CR^1 ;

=== is a single or double bond as necessary to give every atom its normal valence;

R^1 is independently H, hydroxy, $-C_{1-6}$ alkyl, $-C_{1-6}$ haloalkyl, $-C_{1-6}$ alkoxy, $-NH-C_{1-6}$ alkyl, $-N(C_{1-4}alkyl)_2$, cyano, or halo;

R^2 is halo, $-C_{1-6}$ alkyl, $-C_{1-6}$ haloalkyl, $-OR^{2a}$, $-N(R^{2a})_2$, $-C_{2-6}$ alkenyl, $-C_{2-6}$ alkynyl, $-C_{0-3}$ alkylene- C_{3-14} cycloalkyl, $-C_{0-3}$ alkylene- C_{2-14} heterocycloalkyl, aryl, heteroaryl, $-C_{0-3}$ alkylene- C_{6-14} aryl, or $-C_{0-3}$ alkylene- C_{2-14} heteroaryl, and each R^{2a} is independently H, $-C_{1-6}$ alkyl, $-C_{1-6}$ haloalkyl, $-C_{3-14}$ cycloalkyl, $-C_{2-14}$ heterocycloalkyl, $-C_{2-6}$ alkenyl, $-C_{2-6}$ alkynyl, aryl, or heteroaryl, or two R^{2a} substituents, together with the nitrogen atom to which they are attached, form a 3-7-membered ring;

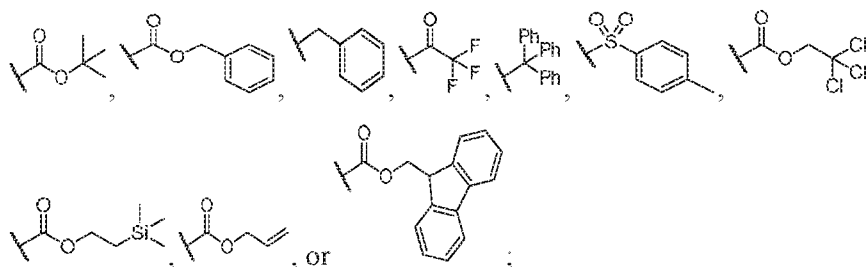
R^3 is halo, $-C_{1-6}$ alkyl, $-C_{1-6}$ haloalkyl, $-C_{1-6}$ alkoxy, C_{3-6} cycloalkyl, $-C_{2-14}$ heterocycloalkyl, $-C_{2-6}$ alkenyl, $-C_{2-6}$ alkynyl, aryl, or heteroaryl;



ring A is a monocyclic 4-7 membered ring or a bicyclic, bridged, fused, or spiro 6-11 membered ring;

L is a bond, $-C_{1-6}$ alkylene, $-O-C_{0-6}$ alkylene, $-S-C_{0-6}$ alkylene, or $-NH-C_{0-6}$ alkylene, and for $-C_{2-6}$ alkylene, $-O-C_{2-6}$ alkylene, $-S-C_{2-6}$ alkylene, and $NH-C_{2-6}$ alkylene, one carbon atom of the alkylene group can optionally be replaced with O, S, or NH;

R^{4a} is H, C_{1-6} alkyl, C_{2-6} alkynyl, C_{1-6} alkylene- $O-C_{1-4}$ alkyl, C_{1-6} alkylene-OH, C_{1-6} haloalkyl, cycloalkyl, heterocycloalkyl, C_{0-3} alkylene- C_{3-14} cycloalkyl, C_{0-3} alkylene- C_{2-14} heterocycloalkyl, aryl, heteroaryl, C_{0-3} alkylene- C_{6-14} aryl, or selected from



R^5 and R^6 are each independently H, halo, $-C_{1-6}$ alkyl, $-C_{2-6}$ alkynyl, $-C_{1-6}$ alkylene-O- C_{1-4} alkyl, $-C_{1-6}$ alkylene-OH, $-C_{1-6}$ haloalkyl, $-C_{1-6}$ alkyleneamine, $-C_{0-6}$ alkylene-amide, $-C_{0-3}$ alkylene-C(O)OH, $-C_{0-3}$ alkylene-C(O)OC $_{1-4}$ alkyl, $-C_{1-6}$ alkylene-O-aryl, $-C_{0-3}$ alkylene-C(O)C $_{1-4}$ alkylene-OH, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, $-C_{0-3}$ alkylene- C_{3-14} cycloalkyl, $-C_{0-3}$ alkylene- C_{2-14} heterocycloalkyl, $-C_{0-3}$ alkylene- C_{6-14} aryl, $-C_{0-3}$ alkylene- C_{2-14} heteroaryl, or cyano, or R^5 and R^6 , together with the atoms to which they are attached, form a 4-6 membered ring;

R^7 is H or C_{1-6} alkyl, or R^7 and R^5 , together with the atoms to which they are attached, form a 4-6 membered ring;

R^8 is H, $-C_{1-6}$ alkyl, $-C_{0-3}$ alkylene- C_{6-14} aryl, $-C_{0-3}$ alkylene- C_{3-14} heteroaryl, $-C_{0-3}$ alkylene- C_{3-14} cycloalkyl, $-C_{0-3}$ alkylene- C_{2-14} heterocycloalkyl, $-C_{1-6}$ alkoxy, $-O-C_{0-3}$ alkylene- C_{6-14} aryl, $-O-C_{0-3}$ alkylene- C_{3-14} heteroaryl, $-O-C_{0-3}$ alkylene- C_{3-14} cycloalkyl, $-O-C_{0-3}$ alkylene- C_{2-14} heterocycloalkyl, $-NH-C_{1-8}$ alkyl, $-N(C_{1-8}alkyl)_2$, $-NH-C_{0-3}$ alkylene- C_{6-14} aryl, $-NH-C_{0-3}$ alkylene- C_{2-14} heteroaryl, $-NH-C_{0-3}$ alkylene- C_{3-14} cycloalkyl, $-NH-C_{0-3}$ alkylene- C_{2-14} heterocycloalkyl, halo, cyano, or C_{1-6} alkylene-amine;

wherein the heteroaryl, spiroheterocycloalkyl and heterocycloalkyl groups of any of the R^2 , R^{2a} , R^3 , R^4 , R^{4a} , R^5 , R^6 , R^7 , and R^8 substituents have 1, 2, 3 or 4 heteroatoms independently selected from O, N or S, wherein the cycloalkyl, spirocycloalkyl, spiroheterocycloalkyl, and heterocycloalkyl groups may include a C=O group, and further wherein the spiroheterocycloalkyl, and heterocycloalkyl groups may include a S=O or SO₂;

wherein the $-C_{1-6}$ alkyl, $-C_{2-6}$ alkenyl, $-C_{2-6}$ alkynyl and the $-OC_{1-6}$ alkyl of any of the R^1 , R^2 , R^{2a} , R^3 , R^4 , R^{4a} , L, R^5 , R^6 , R^7 , and R^8 substituents is unsubstituted or substituted by 1, 2 or 3 R^9 substituents independently selected from OH, $-OC_{1-6}$ alkyl, $-C_{1-6}$ alkyl-O- C_{1-6} alkyl, halo, $-O$ -halo C_{1-6} alkyl, $-CN$, $-NR^aR^b$, $-(NR^aR^bR^c)_n$, $-OSO_2R^a$, $-SO_2R^a$, $-(CH_2CH_2O)_nCH_3$, $-(=O)$, $-C(=O)$,

$-C(=O)R^a$, $-OC(=O)R^a$, $-C(=O)OR^a$, $-C(=O)NR^aR^b$, $-O-SiR^aR^bR^c$, $-SiR^aR^bR^c$, $-O$ -(3- to 10-membered heterocycloalkyl), a 6- to 12-membered aryl or heteroaryl, a 5- to 12-membered

spirocycloalkyl or spiroheterocycloalkyl, a 3- to 12-membered cycloalkenyl, a 3- to 12-membered monocyclic or bicyclic cycloalkyl, or a 3- to 12-membered monocyclic or bicyclic heterocycloalkyl group, wherein the heteroaryl, spiroheterocycloalkyl and heterocycloalkyl groups have 1, 2, 3 or 4 heteroatoms independently selected from O, N or S, wherein the cycloalkyl, spirocycloalkyl, spiroheterocycloalkyl, and heterocycloalkyl groups may include a C=O group, and further wherein the spiroheterocycloalkyl, and heterocycloalkyl groups may include a S=O or SO₂;

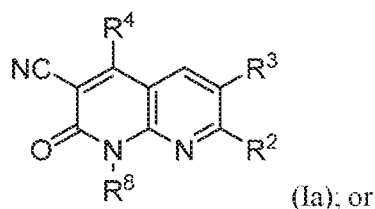
wherein the aryl, heteroaryl, cycloalkyl, and heterocycloalkyl group of any of the R¹, R², R^{2a}, R³, R⁴, R^{4a}, R⁵, R⁶, R⁷, R⁸ and R⁹ substituents can be unsubstituted or substituted with 1, 2, 3 or 4 R¹⁰ substituents independently selected from OH, halo, -NR^cR^d, -C₁₋₆alkyl, -OC₁₋₆alkyl, -C₁₋₆alkyl-OH, -C₁₋₆alkyl-O-C₁₋₆alkyl, C₁₋₆haloalkyl, -O-haloC₁₋₆alkyl, -SO₂R^c, -CN, -C(=O)NR^cR^d, -C(=O)R^c, -OC(=O)R^a, -C(=O)OR^c, a 6- to 12-membered aryl or heteroaryl, a 5- to 12-membered spirocycloalkyl or spiroheterocycloalkyl, a 3- to 12-membered cycloalkenyl, a 3- to 12-membered monocyclic or bicyclic cycloalkyl, or a 3- to 12-membered monocyclic or bicyclic heterocycloalkyl group, wherein the heteroaryl, spiroheterocycloalkyl, and heterocycloalkyl groups of R¹⁰ have 1, 2, 3 or 4 heteroatoms independently selected from O, N or S, wherein the cycloalkyl, spirocycloalkyl, and spiroheterocycloalkyl groups of R¹⁰ or the heterocycloalkyl group of R¹⁰ may include a C=O group, and further wherein the spiroheterocycloalkyl and heterocycloalkyl groups may include a S=O or SO₂;

wherein each R^a, R^b, R^c and R^d is independently hydrogen, OH, -C₁₋₆alkyl, -(CH₂CH₂O)_nCH₃, -NR¹¹R¹¹, -C₁₋₆alkyl-NR¹¹R¹¹, phenyl, -C₁₋₆alkyl-C(=O)OH, -C₁₋₆alkyl-C(=O)-O-C₁₋₆alkyl, -C₁₋₆alkyl-3- to 12-membered cycloalkyl, -C₁₋₆alkyl-3- to 12-membered heterocycloalkyl, -C₁₋₆alkyl-6- to 12-membered heteroaryl, a 6- to 12-membered aryl or heteroaryl, a 3- to 12-membered monocyclic or bicyclic cycloalkyl, or a 3- to 12-membered monocyclic or bicyclic heterocycloalkyl group, wherein the heteroaryl group, heterocycloalkyl group of R^a, R^b, R^c, and R^d or the heterocycloalkyl group of the -C₁₋₆alkyl-heterocycloalkyl group of R^a, R^b, R^c, and R^d has from 1, 2, 3, or 4 heteroatoms independently selected from O, N or S, wherein the cycloalkyl and heterocycloalkyl groups of R^a, R^b, R^c, and R^d and the heterocycloalkyl group of the -C₁₋₆alkyl-heterocycloalkyl groups of R^a, R^b, R^c, and R^d may include a double bond, and further wherein the cycloalkyl and heterocycloalkyl groups of R^a, R^b, R^c, and R^d and the heterocycloalkyl group of the -C₁₋₆alkyl-heterocycloalkyl groups of R^a, R^b, R^c, and R^d may contain a C=O group; and

the alkyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl groups of R^a , R^b , R^c , and R^d or the heterocycloalkyl groups of the $-C_{1-6}$ alkyl-heterocycloalkyl groups of R^a , R^b , R^c , and R^d can be unsubstituted or substituted with from 1, 2, 3, or 4 R^{12} substituents, wherein each R^{12} is independently selected from H, OH, halo, $-C_{1-6}$ alkyl, $N(CH_3)_2$, $-C_{1-6}$ haloalkyl, $C(=O)CH_3$, $-C(=O)OCH_3$, or $-C_{1-6}$ alkyl-O- C_{1-6} alkyl; or

a stereoisomer thereof, an atropisomer thereof, a pharmaceutically acceptable salt thereof, a pharmaceutically acceptable salt of the stereoisomer thereof, or a pharmaceutically acceptable salt of the atropisomer thereof.

[0007] In another aspect of the present invention, the present invention comprises a compound having a structure of formula (Ia)



a stereoisomer thereof, an atropisomer thereof, a pharmaceutically acceptable salt thereof, a pharmaceutically acceptable salt of the stereoisomer thereof, or a pharmaceutically acceptable salt of the atropisomer thereof.

[0008] One aspect of the present invention provides various compounds, stereoisomers, atropisomers, pharmaceutically acceptable salts, pharmaceutically acceptable salts of the stereoisomers, and pharmaceutically acceptable salts of the atropisomers as described in the embodiments set forth below.

[0009] Another aspect of the present invention provides a pharmaceutical composition that includes the compound of any of the embodiments or the pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier or diluent.

[0010] Another aspect of the present invention provides a method of treating cancer. Such methods include: administering to a patient in need thereof a therapeutically effective amount of the compound of any of the embodiments or a pharmaceutically acceptable salt thereof. In some such methods, the cancer is a hematologic malignancy. In some such methods, the cancer is selected from the group consisting of breast cancer, colorectal cancer, skin cancer, melanoma, ovarian cancer, kidney cancer, lung cancer, non-small cell lung cancer, lymphoma, non-Hodgkin's lymphoma, myeloma, multiple myeloma, leukemia, and acute myelogenous

leukemia. In some other such methods, the cancer is multiple myeloma. In some other such methods, the cancer is acute myelogenous leukemia. In some other such methods, the cancer is non-Hodgkin's lymphoma.

[0011] In another aspect, the method further includes administering to a patient in need thereof a therapeutically effective amount of one or more additional pharmaceutically active compounds. For example, in some such methods the one or more additional pharmaceutically active compounds is carfilzomib. In others, the one or more additional pharmaceutically active compounds is venetoclax. In still other such methods, the one or more additional pharmaceutically active compounds is cytarabine. In still other such methods, the one or more additional pharmaceutically active compounds is daratumumab. In still other such methods, the one or more additional pharmaceutically active compound is an MCL-1 inhibitor. In still other such methods, the MCL-1 inhibitor is AMG-176. In still other such methods, the one or more additional pharmaceutically active compounds is an immunomodulatory agent (IMiD).

[0012] Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this disclosure belongs. Methods and materials are described herein for use in the present disclosure; other, suitable methods and materials known in the art can also be used. The materials, methods, and examples are illustrative only and not intended to be limiting. All publications, patent applications, patents, sequences, database entries, and other references mentioned herein are incorporated by reference in their entirety. In case of conflict, the present specification, including definitions, will control.

[0013] Other features and advantages of the disclosure will be apparent from the following detailed description and figures, and from the Claims.

DETAILED DESCRIPTION

Definitions

Table 1: Abbreviations. The following abbreviations may be used herein:

AcOH	acetic acid
aq or aq.	aqueous
BOC or Boc	<i>tert</i> -butoxycarbonyl
COMU	([(1-cyano-2-ethoxy-2-oxoethylidene)amino]oxy)dimethylamino(morpholin-4-yl)carbenium hexafluorophosphate
CPhos	2-dicyclohexylphosphino-2',6'-bis(<i>N,N</i> -dimethylamino)biphenyl
cpme	cyclopentyl methyl ether

DCE	1,2-dichloroethane
DABCO	1,4-diazabicyclo[2.2.2]octane
DCM	dichloromethane
DMA	<i>N,N</i> -dimethylacetamide
DMAP	4-dimethylaminopyridine
DME	1,2-dimethoxyethane
DMF	<i>N,N</i> -dimethylformamide
DMSO	dimethyl sulfoxide
Dppf, DPPF or dppf eq or eq. or equiv.	1,1'-bis(diphenylphosphino)ferrocene equivalent
ESI or ES	electrospray ionization
Et	ethyl
Et ₂ O	diethyl ether
EtOAc	ethyl acetate
g	gram(s)
h	hour(s)
HBTU	<i>N,N,N',N'</i> -tetramethyl- <i>O</i> -(1 <i>H</i> -benzotriazol-1-yl)uronium hexafluorophosphate, <i>O</i> -(benzotriazol-1-yl)- <i>N,N,N',N'</i> -tetramethyluronium hexafluorophosphate
HPLC	high pressure liquid chromatography
iPr	isopropyl
iPr ₂ NEt or DIPEA	<i>N</i> -ethyl diisopropylamine (Hünig's base)
KHMDS	potassium hexamethyldisilazide
KOAc	potassium acetate
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
<i>m/z</i>	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)
mg	milligrams
min	minutes
mL	milliliters
MS	mass spectra
NaHMDS	sodium hexamethyldisilazide
NBS	<i>N</i> -bromosuccinimide
<i>n</i> -BuLi	<i>n</i> -butyllithium
NCS	<i>N</i> -chlorosuccinimide
NMR	nuclear magnetic resonance
Pd ₂ (dba) ₃	tris(dibenzylideneacetone)dipalladium(0)

Pd(dppf)Cl ₂ ·DCM, Pd(dppf)Cl ₂	[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-bottomed flask
RP-HPLC	reverse phase high pressure liquid chromatography
RT or rt or r.t.	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- <i>n</i> -butylammonium fluoride
TBDPS	tert-butyldiphenylsilyl
<i>t</i> -BuOH	<i>tert</i> -butanol
TEA or Et ₃ N	trimethylamine
TFA	trifluoroacetic acid
THF	tetrahydrofuran
UV	ultraviolet

[0014] 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.

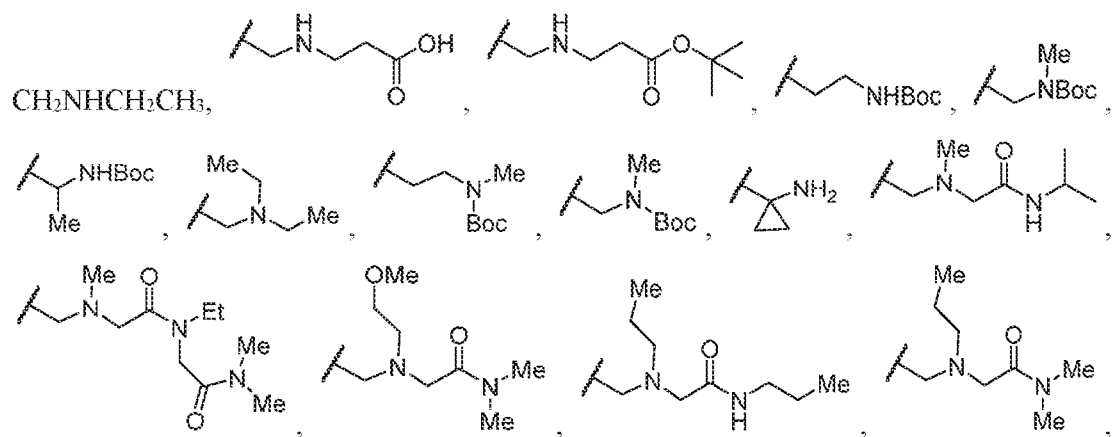
[0015] As used herein, the term “alkyl” refers to straight chained and branched C₁-C₈ hydrocarbon groups, including but not limited to, methyl, ethyl, *n*-propyl, *i*-propyl, *n*-butyl, *sec*-butyl, *t*-butyl, *n*-pentyl, 2-methylbutyl, 3-methylbutyl, 2,2-dimethylpropyl, *n*-hexyl, 2-methylpentyl, 3-methylpentyl, 4-methylpentyl, 2,2-dimethylbutyl, 2,3-dimethylbutyl, 3,3-dimethylbutyl, and 2-ethylbutyl. 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., -CH₂-), 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, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋

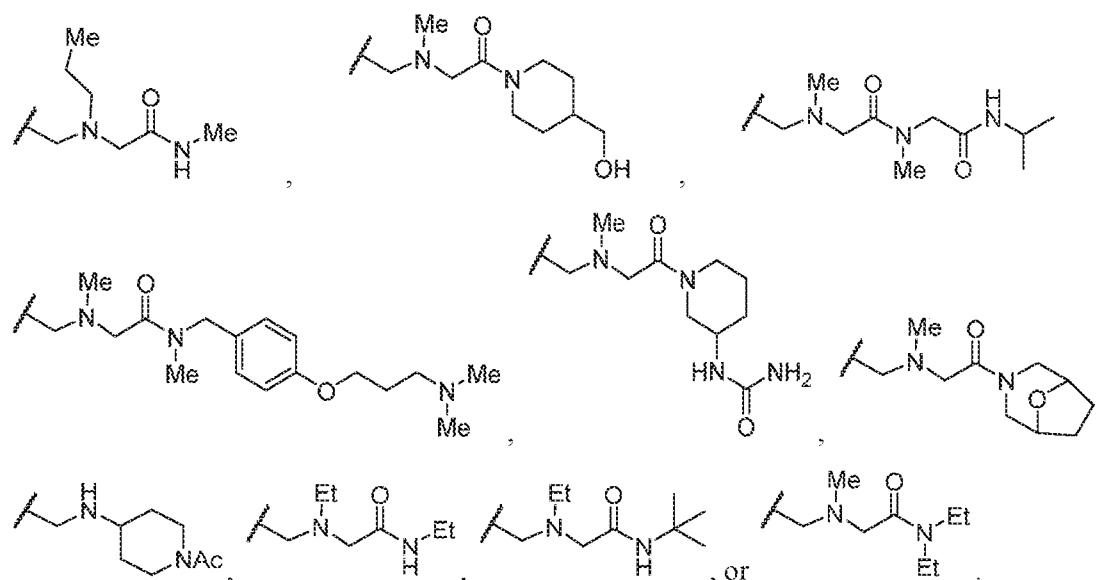
alkynyl, -NC, amino, -CO₂H, -CO₂C₁-C₆alkyl, -OCOC₁-C₆alkyl, C₃-C₁₀ cycloalkyl, C₃-C₁₀ heterocycloalkyl, C₅-C₁₀aryl, and C₅-C₁₀ heteroaryl. The term “haloalkyl” specifically refers to an alkyl group wherein at least one, e.g., one to six, or all of the hydrogens of the alkyl group are substituted with halo atoms.

[0016] The terms “alkenyl” and “alkynyl” indicate an alkyl group that further includes a double bond or a triple bond, respectively.

[0017] As used herein, the term “halo” refers to fluoro, chloro, bromo, and iodo. The term “alkoxy” is defined as -OR, wherein R is alkyl.

[0018] As used herein, the term “amino” or “amine” interchangeably refers to a -NR₂ 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., NR₃⁺. 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)NR₂. Some contemplated amino or amido groups (some with optional alkylene groups, e.g., alkylene-amino, or alkylene-amido) include CH₂NH₂, CH(CH₃)NH₂, CH(CH₃)₂NH₂, CH₂CH₂NH₂, CH₂CH₂N(CH₃)₂, CH₂NHCH₃, C(O)NHCH₃, C(O)N(CH₃)₂, CH₂C(O)NHphenyl, CH₂NHC(O)CH₃, CH₂NHCH₂CH₂OH, CH₂NHCH₂CO₂H, CH₂NH(CH₃)CH₂CO₂CH₃, CH₂NHCH₂CH₂OCH₃, CH₂NH(CH₃)CH₂CH₂OCH₃, CH₂NH(CH₃)CH₂C(O)N(CH₃)₂, CH₂NH(CH₃)CH₂C(O)NHCH₃, CH₂CH₂CCH₃, CH₂NMe₂, CH₂NH(CH₃)CH₂CH₂OH, CH₂NH(CH₃)CH₂CH₂F, CH₂N⁺(CH₃)₃, CH₂NHCH₂CHF₂,





[0019] Collectively, antibodies form a family of plasma proteins known as immunoglobulins and comprise of immunoglobulin domains. (Janeway et al., Immunobiology: The Immune System in Health and Disease, 4th ed., Elsevier Science Ltd./Garland Publishing, 1999. As used herein, the term “antibody” refers to a protein having a conventional immunoglobulin format, comprising heavy and light chains, and comprising variable and constant regions. For example, an antibody may be an IgG which is a “Y-shaped” structure of two identical pairs of polypeptide chains, each pair having one “light” (typically having a molecular weight of about 25 kDa) and one “heavy” chain (typically having a molecular weight of about 50-70 kDa). An antibody has a variable region and a constant region. In IgG formats, the variable region is generally about 100-110 or more amino acids, comprises three complementarity determining regions (CDRs), is primarily responsible for antigen recognition, and substantially varies among other antibodies that bind to different antigens. The constant region allows the antibody to recruit cells and molecules of the immune system. The variable region is made of the N-terminal regions of each light chain and heavy chain, while the constant region is made of the C-terminal portions of each of the heavy and light chains. (Janeway et al., “Structure of the Antibody Molecule and the Immunoglobulin Genes”, Immunobiology: The Immune System in Health and Disease, 4th ed. Elsevier Science Ltd./Garland Publishing, (1999)).

[0020] The general structure and properties of CDRs of antibodies have been described in the art. Briefly, in an antibody scaffold, the CDRs are embedded within a framework in the heavy and light chain variable region where they constitute the regions largely responsible for antigen binding and recognition. A variable region typically comprises at least three heavy or light chain CDRs (Kabat et al., 1991, Sequences of Proteins of Immunological Interest, Public

Health Service N.I.H., Bethesda, Md.; see also Chothia and Lesk, 1987, J. Mol. Biol. 196:901-917; Chothia et al., 1989, Nature 342: 877-883), within a framework region (designated framework regions 1-4, FR1, FR2, FR3, and FR4, by Kabat et al., 1991; see also Chothia and Lesk, 1987, *supra*).

[0021] Antibodies can comprise any constant region known in the art. Human light chains are classified as kappa and lambda light chains. Heavy chains are classified as mu, delta, gamma, alpha, or epsilon, and define the antibody's isotype as IgM, IgD, IgG, IgA, and IgE, respectively. IgG has several subclasses, including, but not limited to IgG1, IgG2, IgG3, and IgG4. IgM has subclasses, including, but not limited to, IgM1 and IgM2. Embodiments of the present disclosure include all such classes or isotypes of antibodies. The light chain constant region can be, for example, a kappa- or lambda-type light chain constant region, e.g., a human kappa- or lambda-type light chain constant region. The heavy chain constant region can be, for example, an alpha-, delta-, epsilon-, gamma-, or mu-type heavy chain constant regions, e.g., a human alpha-, delta-, epsilon-, gamma-, or mu-type heavy chain constant region. Accordingly, in exemplary embodiments, the antibody is an antibody of isotype IgA, IgD, IgE, IgG, or IgM, including any one of IgG1, IgG2, IgG3 or IgG4.

[0022] The antibody can be a monoclonal antibody or a polyclonal antibody. In some embodiments, the antibody comprises a sequence that is substantially similar to a naturally-occurring antibody produced by a mammal, e.g., mouse, rabbit, goat, horse, chicken, hamster, human, and the like. In this regard, the antibody can be considered as a mammalian antibody, e.g., a mouse antibody, rabbit antibody, goat antibody, horse antibody, chicken antibody, hamster antibody, human antibody, and the like. In certain aspects, the antibody is a human antibody. In certain aspects, the antibody is a chimeric antibody or a humanized antibody. The term "chimeric antibody" refers to an antibody containing domains from two or more different antibodies. A chimeric antibody can, for example, contain the constant domains from one species and the variable domains from a second, or more generally, can contain stretches of amino acid sequence from at least two species. A chimeric antibody also can contain domains of two or more different antibodies within the same species. The term "humanized" when used in relation to antibodies refers to antibodies having at least CDR regions from a non-human source which are engineered to have a structure and immunological function more similar to true human antibodies than the original source antibodies. For example, humanizing can involve grafting a CDR from a non-human antibody, such as a mouse antibody, into a human antibody. Humanizing also can involve select amino acid substitutions to make a non-human sequence more similar to a human sequence.

[0023] An antibody can be cleaved into fragments by enzymes, such as, e.g., papain and pepsin. Papain cleaves an antibody to produce two Fab fragments and a single Fc fragment. Pepsin cleaves an antibody to produce a F(ab')₂ fragment and a pFc' fragment. As used herein, the term "antigen binding antibody fragment" refers to a portion of an antibody molecule that is capable of binding to the antigen of the antibody and is also known as "antigen-binding fragment" or "antigen-binding portion". In exemplary instances, the antigen binding antibody fragment is a Fab fragment or a F(ab')₂ fragment.

[0024] The architecture of antibodies has been exploited to create a growing range of alternative formats that span a molecular-weight range of at least about 12–150 kDa and has a valency (n) range from monomeric (n = 1), to dimeric (n = 2), to trimeric (n = 3), to tetrameric (n = 4), and potentially higher; such alternative formats are referred to herein as "antibody protein products". Antibody protein products include those based on the full antibody structure and those that mimic antibody fragments which retain full antigen-binding capacity, e.g., scFvs, Fabs and VHH/VH (discussed below). The smallest antigen binding antibody fragment that retains its complete antigen binding site is the Fv fragment, which consists entirely of variable (V) regions. A soluble, flexible amino acid peptide linker is used to connect the V regions to a scFv (single chain fragment variable) fragment for stabilization of the molecule, or the constant (C) domains are added to the V regions to generate a Fab fragment [fragment, antigen-binding]. Both scFv and Fab fragments can be easily produced in host cells, e.g., prokaryotic host cells. Other antibody protein products include disulfide-bond stabilized scFv (ds-scFv), single chain Fab (scFab), as well as di- and multimeric antibody formats like dia-, tria- and tetra-bodies, or minibodies (miniAbs) that comprise different formats consisting of scFvs linked to oligomerization domains. The smallest fragments are VHH/VH of camelid heavy chain Abs as well as single domain Abs (sdAb). The building block that is most frequently used to create novel antibody formats is the single-chain variable (V)-domain antibody fragment (scFv), which comprises V domains from the heavy and light chain (VH and VL domain) linked by a peptide linker of ~15 amino acid residues. A peptibody or peptide-Fc fusion is yet another antibody protein product. The structure of a peptibody consists of a biologically active peptide grafted onto an Fc domain. Peptibodies are well-described in the art. See, e.g., Shimamoto et al., *mAbs* 4(5): 586-591 (2012).

[0025] Other antibody protein products include a single chain antibody (SCA); a diabody; a triabody; a tetrabody; bispecific or trispecific antibodies, and the like. Bispecific antibodies can be divided into five major classes: BslgG, appended IgG, BsAb fragments, bispecific

fusion proteins and BsAb conjugates. See, e.g., Spiess et al., *Molecular Immunology* 67(2) Part A: 97-106 (2015).

[0026] As used herein, the term “aryl” refers to a C₆₋₁₄ monocyclic or polycyclic aromatic group, preferably a C₆₋₁₀ monocyclic or bicyclic aromatic group, or C₁₀₋₁₄ 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 C₁₀₋₁₄ 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, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, -CF₃, -OCF₃, -NO₂, -CN, -NC, -OH, alkoxy, amino, -CO₂H, -CO₂C₁₋₆alkyl, -OCOC₁₋₆alkyl, C₃₋₁₀ cycloalkyl, C₃₋₁₀ heterocycloalkyl, C₅₋₁₀aryl, and C₅₋₁₀ heteroaryl.

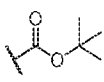
[0027] As used herein, the term “cycloalkyl” refers to a monocyclic or polycyclic non-aromatic carbocyclic ring, where the polycyclic ring can be fused, bridged, or spiro. The carbocyclic ring can have 3 to 10 carbon ring atoms. Contemplated carbocyclic rings include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, and cyclononyl.

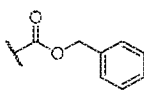
[0028] As used herein, the term “heterocycloalkyl” means a monocyclic or polycyclic (e.g., bicyclic), saturated or partially unsaturated, ring system containing 3 or more (e.g., 3 to 12, 4 to 10, 4 to 8, or 5 to 7) total atoms, of which one to five (e.g., 1, 2, 3, 4, or 5) of the atoms are independently selected from nitrogen, oxygen, and sulfur. Nonlimiting examples of heterocycloalkyl groups include azetidiny, pyrrolidiny, piperidiny, piperaziny, dihydropyrroly, morpholiny, thiomorpholiny, dihydropyridiny, oxacycloheptyl, dioxacycloheptyl, thiacycloheptyl, and diazacycloheptyl.

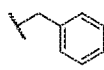
[0029] Unless otherwise indicated, a cycloalkyl or heterocycloalkyl group can be unsubstituted or substituted with one or more, and in particular one to four, groups. Some contemplated substituents include halo, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, -OCF₃, -NO₂, -CN, -NC, -OH, alkoxy, amino, -CO₂H, -CO₂C₁₋₆alkyl, -OCOC₁₋₈alkyl, C₃₋₁₀ cycloalkyl, C₃₋₁₀ heterocycloalkyl, C₅₋₁₀aryl, and C₅₋₁₀ heteroaryl.

[0030] 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 C₁₀₋₁₄ 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, benzothieryl, benzothiophenyl, benzotriazolyl, benzoxazolyl, furopyridyl, imidazopyridinyl, imidazothiazolyl, indoliziny, indolyl, indazolyl, isobenzofuranyl, isobenzothieryl, isoindolyl, isoquinoliny, isothiazolyl, naphthyridinyl, oxazolopyridinyl, phthalazinyl, pteridinyl, purinyl, pyridopyridyl, pyrrolopyridyl, quinoliny, quinoxaliny, quiazoliny, 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, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, -OCF₃, -NO₂, -CN, -NC, -OH, alkoxy, amino, -CO₂H, -CO₂C₁₋₆alkyl, -OCOC₁₋₆alkyl, C₃₋₁₀ cycloalkyl, C₃₋₁₀ heterocycloalkyl, C₅₋₁₀aryl, and C₅₋₁₀ heteroaryl.

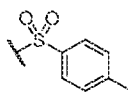
[0031] As used herein, the term Boc refers to the structure .

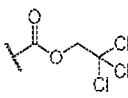
[0032] As used herein, the term Cbz refers to the structure .

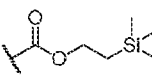
[0033] As used herein, the term Bn refers to the structure .

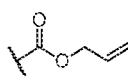
[0034] As used herein, the term trifluoroacetamide refers to the structure .

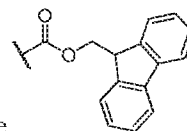
[0035] As used herein, the term trityl refers to the structure .

[0036] As used herein, the term tosyl refers to the structure .

[0037] As used herein, the term Troc refers to the structure .

[0038] As used herein, the term Teoc refers to the structure .

[0039] As used herein, the term Alloc refers to the structure .



[0040] As used herein, the term Fmoc refers to the structure

COMPOUNDS OF THE DISCLOSURE

[0041] 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 ^2H , ^3H , ^{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. ^3H , 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.

[0042] Substitution with heavier isotopes such as deuterium, i.e. ^2H , 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.

[0043] 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.

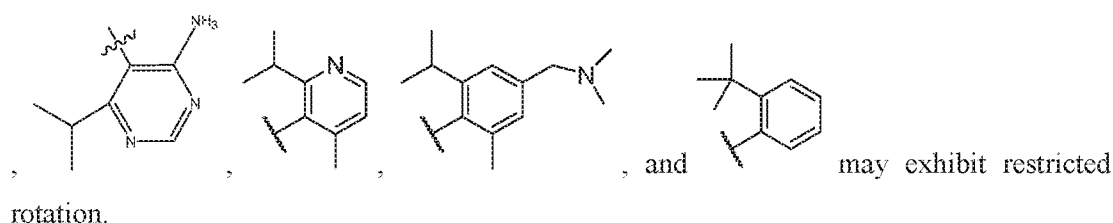
[0044] Isotopically-labeled compounds as disclosed herein can generally be prepared by conventional techniques known to those skilled in the art or by processes analogous to those described in the accompanying examples and schemes using an appropriate isotopically-labeled reagent in place of the non-labeled reagent previously employed.

[0045] 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.

[0046] 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

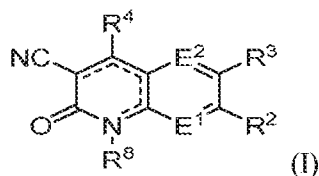
permitted. For example, groups such as, but not limited to, the following R⁸ groups



EMBODIMENTS

Embodiment 1

[0047] In one embodiment of the present invention, the present invention comprises a compound having a structure of formula (I)



R^5 and R^6 are each independently H, halo, $-C_{1-6}$ alkyl, $-C_{2-6}$ alkynyl, $-C_{1-6}$ alkylene-O- C_{1-4} alkyl, $-C_{1-6}$ alkylene-OH, $-C_{1-6}$ haloalkyl, $-C_{1-6}$ alkyleneamine, $-C_{0-6}$ alkylene-amide, $-C_{0-3}$ alkylene-C(O)OH, $-C_{0-3}$ alkylene-C(O)OC $_{1-4}$ alkyl, $-C_{1-6}$ alkylene-O-aryl, $-C_{0-3}$ alkylene-C(O)C $_{1-4}$ alkylene-OH, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, $-C_{0-3}$ alkylene- C_{3-14} cycloalkyl, $-C_{0-3}$ alkylene- C_{2-14} heterocycloalkyl, $-C_{0-3}$ alkylene- C_{6-14} aryl, $-C_{0-3}$ alkylene- C_{2-14} heteroaryl, or cyano, or R^5 and R^6 , together with the atoms to which they are attached, form a 4–6 membered ring;

R^7 is H or C_{1-6} alkyl, or R^7 and R^5 , together with the atoms to which they are attached, form a 4–6 membered ring;

R^8 is H, $-C_{1-6}$ alkyl, $-C_{0-3}$ alkylene- C_{6-14} aryl, $-C_{0-3}$ alkylene- C_{3-14} heteroaryl, $-C_{0-3}$ alkylene- C_{3-14} cycloalkyl, $-C_{0-3}$ alkylene- C_{2-14} heterocycloalkyl, $-C_{1-6}$ alkoxy, $-O-C_{0-3}$ alkylene- C_{6-14} aryl, $-O-C_{0-3}$ alkylene- C_{3-14} heteroaryl, $-O-C_{0-3}$ alkylene- C_{3-14} cycloalkyl, $-O-C_{0-3}$ alkylene- C_{2-14} heterocycloalkyl, $-NH-C_{1-8}$ alkyl, $-N(C_{1-8}alkyl)_2$, $-NH-C_{0-3}$ alkylene- C_{6-14} aryl, $-NH-C_{0-3}$ alkylene- C_{2-14} heteroaryl, $-NH-C_{0-3}$ alkylene- C_{3-14} cycloalkyl, $-NH-C_{0-3}$ alkylene- C_{2-14} heterocycloalkyl, halo, cyano, or C_{1-6} alkylene-amine;

wherein the heteroaryl, spiroheterocycloalkyl and heterocycloalkyl groups of any of the R^2 , R^{2a} , R^3 , R^4 , R^{4a} , R^5 , R^6 , R^7 , and R^8 substituents have 1, 2, 3 or 4 heteroatoms independently selected from O, N or S, wherein the cycloalkyl, spirocycloalkyl, spiroheterocycloalkyl, and heterocycloalkyl groups may include a C=O group, and further wherein the spiroheterocycloalkyl, and heterocycloalkyl groups may include a S=O or SO₂;

wherein the $-C_{1-6}$ alkyl, $-C_{2-6}$ alkenyl, $-C_{2-6}$ alkynyl and the $-OC_{1-6}$ alkyl of any of the R^1 , R^2 , R^{2a} , R^3 , R^4 , R^{4a} , L, R^5 , R^6 , R^7 , and R^8 substituents is unsubstituted or substituted by 1, 2 or 3 R^9 substituents independently selected from OH, $-OC_{1-6}$ alkyl, $-C_{1-6}$ alkyl-O- C_{1-6} alkyl, halo, $-O$ -halo C_{1-6} alkyl, $-CN$, $-NR^aR^b$, $-(NR^aR^bR^c)_n$, $-OSO_2R^a$, $-SO_2R^a$, $-(CH_2CH_2O)_nCH_3$, $-(=O)$, $-C(=O)$,

$-C(=O)R^a$, $-OC(=O)R^a$, $-C(=O)OR^a$, $-C(=O)NR^aR^b$, $-O-SiR^aR^bR^c$, $-SiR^aR^bR^c$, $-O$ -(3- to 10-membered heterocycloalkyl), a 6- to 12-membered aryl or heteroaryl, a 5- to 12-membered spirocycloalkyl or spiroheterocycloalkyl, a 3- to 12-membered cycloalkenyl, a 3- to 12-membered monocyclic or bicyclic cycloalkyl, or a 3- to 12-membered monocyclic or bicyclic heterocycloalkyl group, wherein the heteroaryl, spiroheterocycloalkyl and heterocycloalkyl groups have 1, 2, 3 or 4 heteroatoms independently selected from O, N or S, wherein the cycloalkyl, spirocycloalkyl, spiroheterocycloalkyl, and heterocycloalkyl groups may include a

C=O group, and further wherein the spiroheterocycloalkyl, and heterocycloalkyl groups may include a S=O or SO₂;

wherein the aryl, heteroaryl, cycloalkyl, and heterocycloalkyl group of any of the R¹, R², R^{2a}, R³, R⁴, R^{4a}, R⁵, R⁶, R⁷, R⁸ and R⁹ substituents can be unsubstituted or substituted with 1, 2, 3 or 4 R¹⁰ substituents independently selected from OH, halo, -NR^cR^d, -C₁₋₆alkyl, -OC₁₋₆alkyl, -C₁₋₆alkyl-OH, -C₁₋₆alkyl-O-C₁₋₆alkyl, C₁₋₆haloalkyl, -O-haloC₁₋₆alkyl, -SO₂R^c, -CN, -C(=O)NR^cR^d, -C(=O)R^c, -OC(=O)R^a, -C(=O)OR^c, a 6- to 12-membered aryl or heteroaryl, a 5- to 12-membered spirocycloalkyl or spiroheterocycloalkyl, a 3- to 12-membered cycloalkenyl, a 3- to 12-membered monocyclic or bicyclic cycloalkyl, or a 3- to 12-membered monocyclic or bicyclic heterocycloalkyl group, wherein the heteroaryl, spiroheterocycloalkyl, and heterocycloalkyl groups of R¹⁰ have 1, 2, 3 or 4 heteroatoms independently selected from O, N or S, wherein the cycloalkyl, spirocycloalkyl, and spiroheterocycloalkyl groups of R¹⁰ or the heterocycloalkyl group of R¹⁰ may include a C=O group, and further wherein the spiroheterocycloalkyl and heterocycloalkyl groups may include a S=O or SO₂;

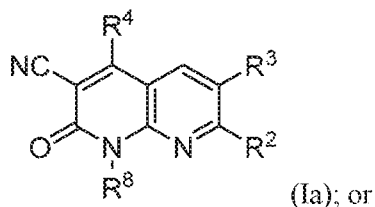
wherein each R^a, R^b, R^c and R^d is independently hydrogen, OH, -C₁₋₆alkyl, -(CH₂CH₂O)_nCH₃, -NR¹¹R¹¹, -C₁₋₆alkyl-NR¹¹R¹¹, phenyl, -C₁₋₆alkyl-C(=O)OH, -C₁₋₆alkyl-C(=O)-O-C₁₋₆alkyl, -C₁₋₆alkyl-3- to 12-membered cycloalkyl, -C₁₋₆alkyl-3- to 12-membered heterocycloalkyl, -C₁₋₆alkyl-6- to 12-membered heteroaryl, a 6- to 12-membered aryl or heteroaryl, a 3- to 12-membered monocyclic or bicyclic cycloalkyl, or a 3- to 12-membered monocyclic or bicyclic heterocycloalkyl group, wherein the heteroaryl group, heterocycloalkyl group of R^a, R^b, R^c, and R^d or the heterocycloalkyl group of the -C₁₋₆alkyl-heterocycloalkyl group of R^a, R^b, R^c, and R^d has from 1, 2, 3, or 4 heteroatoms independently selected from O, N or S, wherein the cycloalkyl and heterocycloalkyl groups of R^a, R^b, R^c, and R^d and the heterocycloalkyl group of the -C₁₋₆alkyl-heterocycloalkyl groups of R^a, R^b, R^c, and R^d may include a double bond, and further wherein the cycloalkyl and heterocycloalkyl groups of R^a, R^b, R^c, and R^d and the heterocycloalkyl group of the -C₁₋₆alkyl-heterocycloalkyl groups of R^a, R^b, R^c, and R^d may contain a C=O group; and

the alkyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl groups of R^a, R^b, R^c, and R^d or the heterocycloalkyl groups of the -C₁₋₆alkyl-heterocycloalkyl groups of R^a, R^b, R^c, and R^d can be unsubstituted or substituted with from 1, 2, 3, or 4 R¹² substituents, wherein each R¹² is independently selected from H, OH, halo, -C₁₋₆alkyl, N(CH₃)₂, -C₁₋₆haloalkyl, C(=O)CH₃, -C(=O)OCH₃, or -C₁₋₆alkyl-O-C₁₋₆alkyl; or

a stereoisomer thereof, an atropisomer thereof, a pharmaceutically acceptable salt thereof, a pharmaceutically acceptable salt of the stereoisomer thereof, or a pharmaceutically acceptable salt of the atropisomer thereof.

Embodiment 2

[0048] In another embodiment of the present invention, the present invention comprises a compound of embodiment 1 having a structure of formula (Ia)



a stereoisomer thereof, an atropisomer thereof, a pharmaceutically acceptable salt thereof, a pharmaceutically acceptable salt of the stereoisomer thereof, or a pharmaceutically acceptable salt of the atropisomer thereof.

Embodiment 3

[0049] In another embodiment of the present invention, the present invention comprises a compound of embodiment 1 wherein E¹ is N.

Embodiment 4

[0050] In another embodiment of the present invention, the present invention comprises a compound of embodiment 1 wherein E² is CR¹.

Embodiment 5

[0051] In another embodiment of the present invention, the present invention comprises a compound of embodiment 4 wherein R¹ is H.

Embodiment 7

[0052] In another embodiment of the present invention, the present invention comprises a compound of embodiment 6 wherein R² is a substituted aryl.

Embodiment 8

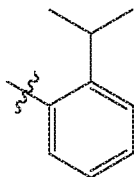
[0053] In another embodiment of the present invention, the present invention comprises a compound of embodiment 6 wherein R² is a fluorinated phenyl.

Embodiment 9

[0054] In another embodiment of the present invention, the present invention comprises a compound of embodiment 6 wherein R^2 is Cl.

Embodiment 10

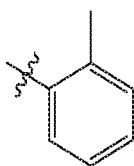
[0055] In another embodiment of the present invention, the present invention comprises a



compound of embodiment 6 wherein R^2 is

Embodiment 11

[0056] In another embodiment of the present invention, the present invention comprises a



compound of embodiment 6 wherein R^2 is

Embodiment 12

[0057] In another embodiment of the present invention, the present invention comprises a compound of any of one of embodiments 1-11 wherein R^3 is halo.

Embodiment 13

[0058] In another embodiment of the present invention, the present invention comprises a compound of embodiment 12 wherein R^3 is Cl.

Embodiment 14

[0059] In another embodiment of the present invention, the present invention comprises a compound of embodiment 12 wherein R^3 is F.

Embodiment 15

[0060] In another embodiment of the present invention, the present invention comprises a



compound of any of one of embodiments 1-14 wherein R^4 is

Embodiment 16

[0061] In another embodiment of the present invention, the present invention comprises a compound of embodiment 15 wherein L is a bond.

Embodiment 17

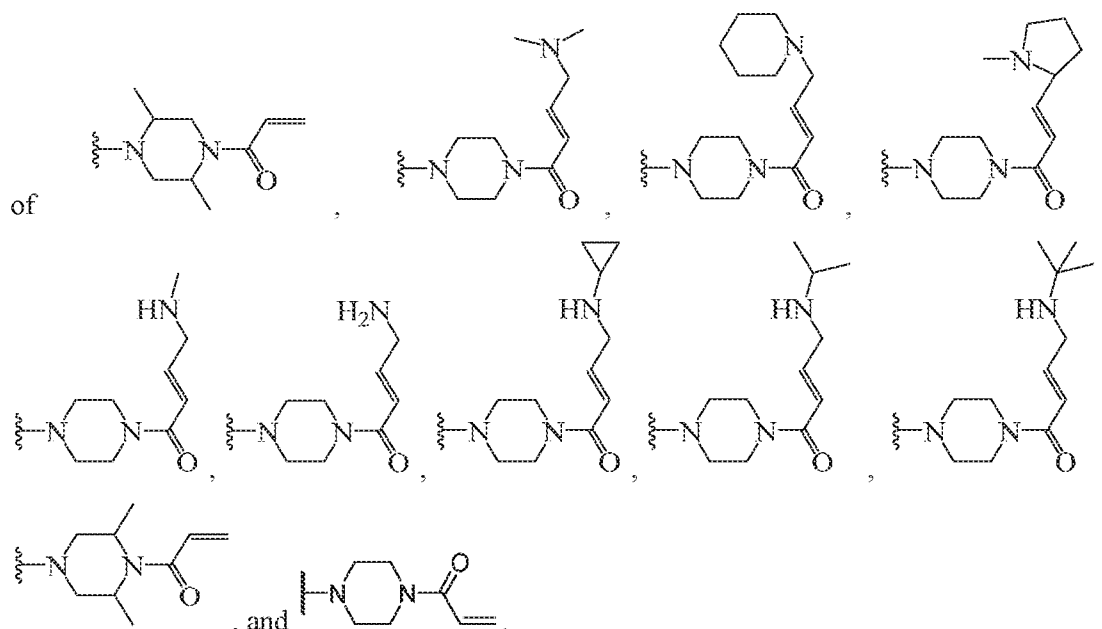
[0062] In another embodiment of the present invention, the present invention comprises a compound of embodiment 15 wherein ring A is a monocyclic 4–7 membered ring.

Embodiment 18

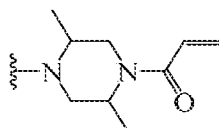
[0063] In another embodiment of the present invention, the present invention comprises a compound of embodiment 17 wherein A is an unsubstituted or substituted heterocycle.

Embodiment 19

[0064] In another embodiment of the present invention, the present invention comprises a compound of any one of embodiments 1-18, wherein R^4 is selected from the group consisting

**Embodiment 20**

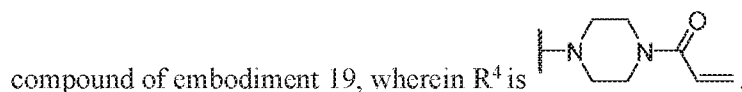
[0065] In another embodiment of the present invention, the present invention comprises a



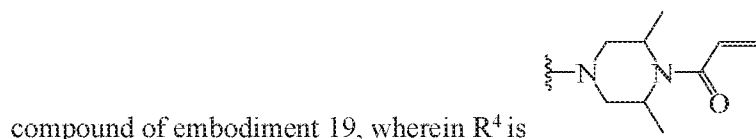
compound of embodiment 19, wherein R^4 is

Embodiment 21

[0066] In another embodiment of the present invention, the present invention comprises a

**Embodiment 22**

[0067] In another embodiment of the present invention, the present invention comprises a

**Embodiment 23**

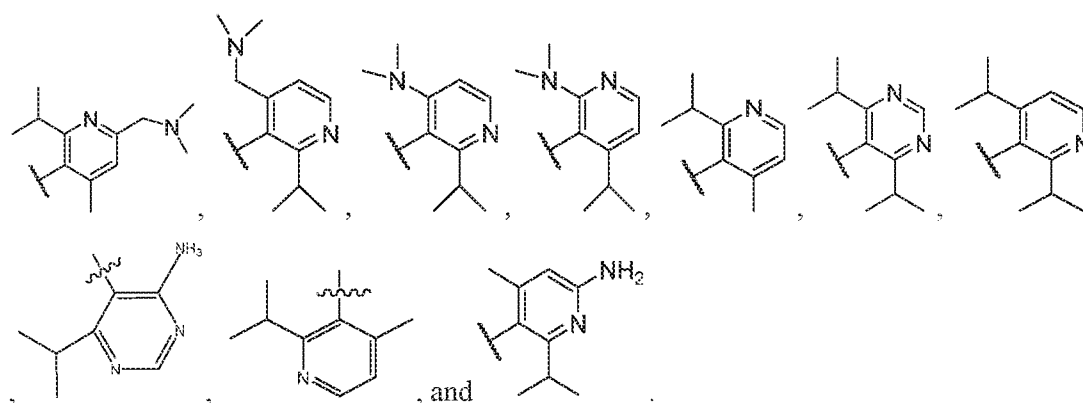
[0068] In another embodiment of the present invention, the present invention comprises a compound of any of one of embodiments 1-22 wherein R⁸ is -C₀₋₃alkylene-C₆₋₁₄aryl, or -C₀₋₃alkylene-C₃₋₁₄heteroaryl.

Embodiment 24

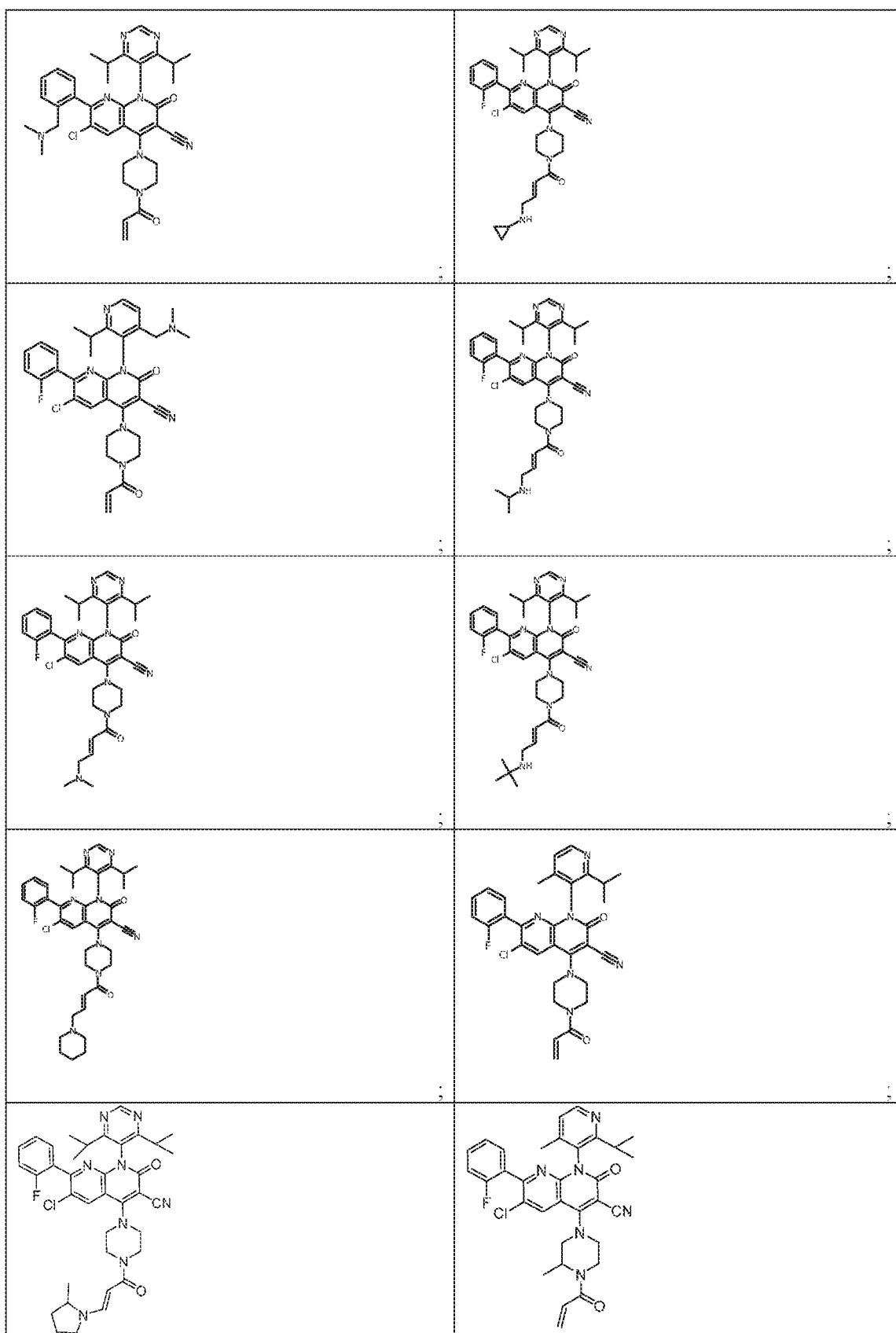
[0069] In another embodiment of the present invention, the present invention comprises a compound of claim 23 wherein R⁸ is -C₃₋₁₄heteroaryl.

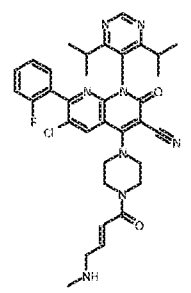
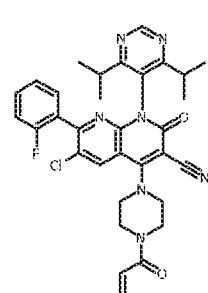
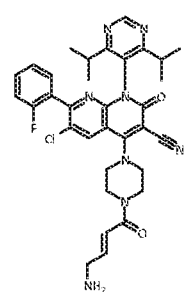
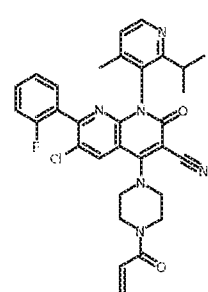
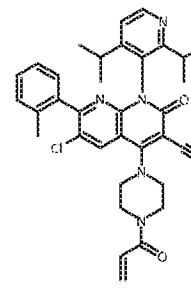
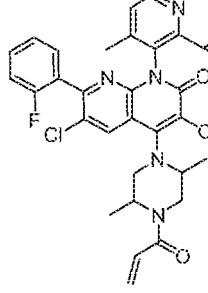
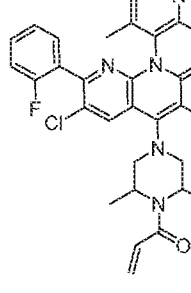
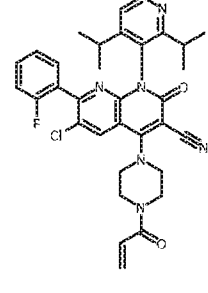
Embodiment 25

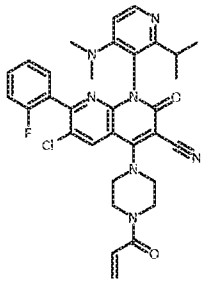
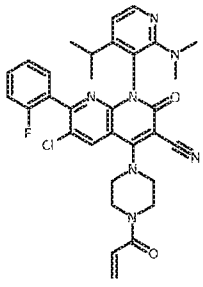
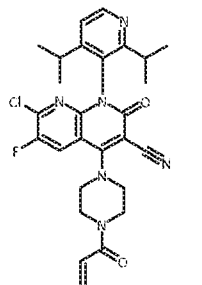
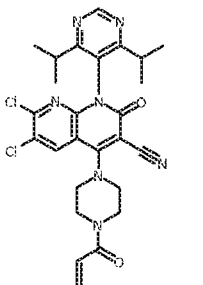
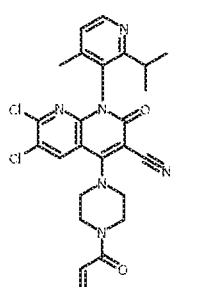
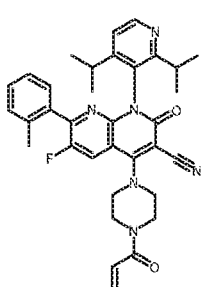
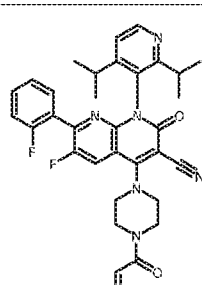
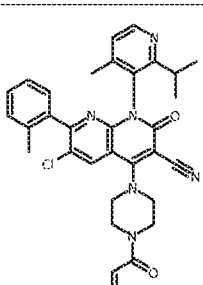
[0070] In another embodiment of the present invention, the present invention comprises a compound of embodiment 23, wherein R⁸ is selected from the group consisting of

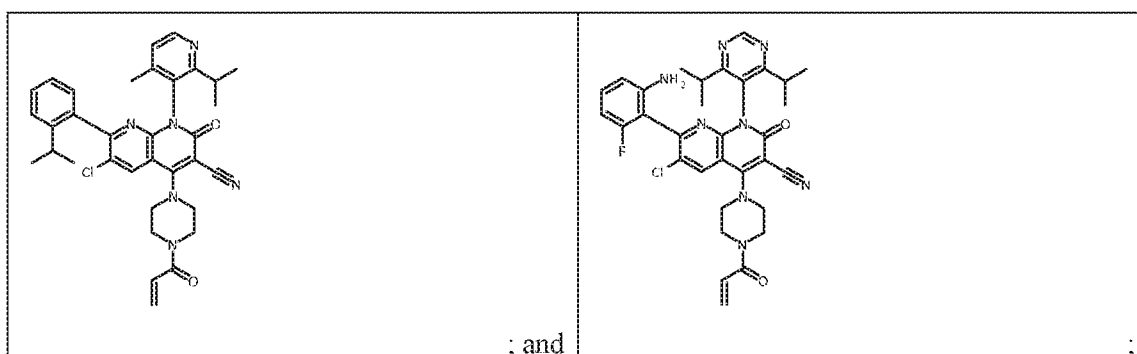
**Embodiment 26**

[0071] In another embodiment of the present invention, the present invention comprises a compound having a structure selected from the formula:



 1 2	 1 2
 1 2	 1 2
 1 2	 1 2
 1 2	 1 2

 1 2	 1 2
 1 2	 1 2
 1 2	 1 2
 1 2	 1 2



or a stereoisomer thereof, an atropisomer thereof, a pharmaceutically acceptable salt thereof, a pharmaceutically acceptable salt of the stereoisomer thereof, or a pharmaceutically acceptable salt of the atropisomer thereof.

Embodiment 27

[0072] In another embodiment of the present invention, the present invention comprises a compound of any one of embodiments 1-26 in the form of a pharmaceutically acceptable salt.

Embodiment 28

[0073] In another embodiment of the present invention, the present invention comprises a pharmaceutical composition comprising the compound of any one of embodiments 1-27 and a pharmaceutically acceptable excipient.

Embodiment 29

[0074] In another embodiment of the present invention, the present invention comprises a method of inhibiting KRAS G12C in a cell, comprising contacting the cell with the compound of any one of embodiments 1-27 or the composition of embodiment 28.

Embodiment 30

[0075] In another embodiment of the present invention, the present invention comprises a method of treating cancer in a subject comprising administering to the subject a therapeutically effective amount of the compound of any one of embodiments 1-26 or the composition of embodiment 27.

Embodiment 31

[0076] In another embodiment of the present invention, the present invention comprises the method of embodiment 30, wherein the cancer is lung cancer, pancreatic cancer, or colorectal cancer.

Embodiment 32

[0077] In another embodiment of the present invention, the present invention comprises the method of embodiment 31, wherein the cancer is lung cancer.

Embodiment 33

[0078] In another embodiment of the present invention, the present invention comprises the method of embodiment 31, wherein the cancer is pancreatic cancer.

Embodiment 34

[0079] In another embodiment of the present invention, the present invention comprises the method of embodiment 31, wherein the cancer is colorectal cancer.

Embodiment 35

[0080] In another embodiment of the present invention, the present invention comprises the method of embodiment 30, further comprising administering to the patient in need thereof a therapeutically effective amount of one or more additional pharmaceutically active compounds.

Embodiment 36

[0081] In another embodiment of the present invention, the present invention comprises the method of embodiment 35, wherein the one or more additional pharmaceutically active compounds is an anti-PD-1 antibody.

Embodiment 37

[0082] In another embodiment of the present invention, the present invention comprises the method of embodiment 36, wherein the anti-PD-1 antibody is pembrolizumab.

Embodiment 38

[0083] In another embodiment of the present invention, the present invention comprises the method of embodiment 36, wherein the anti-PD-1 antibody is nivolumab.

Embodiment 39

[0084] In another embodiment of the present invention, the present invention comprises the method of embodiment 36, wherein the anti-PD-1 antibody is AMG 404.

Embodiment 40

[0085] In another embodiment of the present invention, the present invention comprises the method of claim 35, wherein the one or more additional pharmaceutically active compounds is a MEK inhibitor.

Embodiment 41

[0086] In another embodiment of the present invention, the present invention comprises the method of embodiment 35, wherein the one or more additional pharmaceutically active compounds is daratumumab.

Embodiment 42

[0087] In another embodiment of the present invention, the present invention comprises the method of embodiment 35, wherein the one or more additional pharmaceutically active compounds is an immunomodulatory agent.

Embodiment 43

[0088] In another embodiment of the present invention, the present invention comprises the use of a compound according to any one of embodiments 1-27 for treating cancer in a subject.

Embodiment 44

[0089] In another embodiment of the present invention, the present invention comprises the compound according to any one of embodiments 1-27 in the preparation of a medicament for treating cancer.

Embodiment 45

[0090] In another embodiment of the present invention, the present invention comprises the compound according to embodiment 44, wherein the cancer is non-small cell lung cancer.

SYNTHESIS OF DISCLOSED COMPOUNDS

[0091] Compounds as disclosed herein can be synthesized via a number of specific methods. The examples which outline specific synthetic routes, and the generic schemes below are meant to provide guidance to the ordinarily skilled synthetic chemist, who will readily appreciate that the solvent, concentration, reagent, protecting group, order of synthetic steps, time, temperature, and the like can be modified as necessary, well within the skill and judgment of the ordinarily skilled artisan.

Pharmaceutical compositions, dosing, and routes of administration

[0092] 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 is described in more detail below.

[0093] 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.

[0094] 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.

[0095] 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.

[0096] 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, chlorprocaine, choline, diethanolamine, dicyclohexylamine, ethylenediamine, N-methylglucamine, and procaine.

[0097] 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.

[0098] 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.

[0099] 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.

[0100] 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).

[0101] 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.

[0102] 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.

[0103] 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.

[0104] 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.

[0105] 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.

[0106] 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.

[0107] 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.

[0108] 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.

[0109] 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.

[0110] 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.

[0111] 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.

[0112] 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.

[0113] 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.

[0114] 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%.

[0115] 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).

[0116] 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 1500

mg/day, about 5 mg/day to about 1000 mg/day, about 10 mg/day to about 750 mg/day, about 3 mg/day to about 350 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

[0117] 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.

[0118] 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).

[0119] 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.

[0120] 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.

[0121] 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.

[0122] 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 macroglobulinemia.

[0123] 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).

[0124] 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.

[0125] 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.

[0126] 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.

[0127] 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 myeloproliferative 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)).

[0128] 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.

[0129] 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%.

[0130] 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:

[0131] 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.

[0132] 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™, (doxorubicin) as well as a host of chemotherapeutic agents. Non-limiting examples of chemotherapeutic agents include alkylating agents such as thiotepa and cyclophosphamide (Cytosan™); alkyl sulfonates such as busulfan, improsulfan and piposulfan; aziridines such as benzodopa, carboquone, meturedopa, and uredopa; ethylenimines and methylamelamines including altretamine, triethylenemelamine, triethylenephosphoramide, triethylenethiophosphoramide 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, anthramycin, azaserine, bleomycins, cactinomycin, calicheamicin, carabycin, 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, epitostanol, mepitostane, testolactone; anti-adrenals such as aminoglutethimide, mitotane, trilostane; folic acid replenisher such as frolinic acid; aceglutone; 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.

[0133] 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).

[0134] 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.

[0135] 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.

[0136] 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.

[0137] 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.

[0138] 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.

[0139] 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, cetorelix, 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, gentuzumab 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-_{ns}, 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, masoprocil, 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, dexaminoxlutethimide, 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), 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.

[0140] 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.

[0141] 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.

[0142] 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".

[0143] 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 disintegrin 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).

[0144] Additional anti-angiogenic/anti-tumor agents include: SD-7784 (Pfizer, USA); cilengitide (Merck KGaA, Germany, EPO 770622); pegaptanib octasodium, (Gilead Sciences, USA); Alaphastatin, (BioActa, UK); M-PGA, (Celgene, USA, US 5712291); ilomastat, (Arriva, USA, US 5892112); emaxanib, (Pfizer, USA, US 5792783); vatalanib, (Novartis, Switzerland); 2-methoxyestradiol, (EntreMed, 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, (Boreon, 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, (Pracis, 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, USA); troponin I, (Harvard University, USA); SU 6668, (SUGEN, 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, USA); urokinase plasminogen activator inhibitor, (Dendreon, USA); oglufanide (pINN), (Melmotte, USA); HIF-1alpha 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); anginox, (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); TumStatins, (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).

[0145] 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-mercaptapurine 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.

[0146] 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; anacetin; AMG 102; AMG 176; AMG 386; AMG 479; AMG 655; AMG 745; AMG 951; and AMG 706, or a pharmaceutically acceptable salt thereof.

[0147] 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., hexamethylmelamine 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-dacarbazine (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), PI3K / 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.

[0148] 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.

[0149] 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, flucoronide, flumethasone, flunisolide, fluocinolone acetate, fluocinonide, fluocortin butyl, fluocortolone, fluorometholone, fluperolone acetate, fluprednidene acetate, fluprednisolone, flurandrenolide, fluticasone propionate, formocortol, 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.

[0150] 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 agents (IMiDs), such as thalidomide, lenalidomide, and pomalidomide, anti-PD-1, anti-PDL-1, anti-CTLA4, anti-LAG1, and anti-OX40 agents, GITR agonists, CAR-T cells, and BiTEs.

[0151] 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 (Erbix), 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.

[0152] 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, 1997; 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.

[0153] 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.* 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.

[0154] MEK inhibitors include, but are not limited to, tremetinib, CI-1040, AZD6244, PD318088, PD98059, PD334581, RDEA119, ARRY-142886, ARRY-438162, and PD-325901.

[0155] 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-morpholinyl)pyrido-[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-dihydroimidazo[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.

[0156] 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 Akt1 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 tricinibine (TCN or API-2 or NCI identifier: NSC 154020; Yang et al. (2004) *Cancer Res.* 64, 4394-9).

[0157] 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)-dihydrorapamycin, 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).

[0158] MCL-1 inhibitors include, but are not limited to, AMG-176, AMG 397, 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.

[0159] SHP inhibitors include, but are not limited to, SHP099.

[0160] Proteasome inhibitors include, but are not limited to, Kyprolis®(carfilzomib), Velcade®(bortezomib), and oprozomib.

[0161] 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.

[0162] Monoclonal antibodies include, but are not limited to, Darzalex® (daratumumab), Herceptin® (trastuzumab), Avastin® (bevacizumab), Rituxan® (rituximab), Lucentis® (ranibizumab), and Eylea® (aflibercept).

[0163] 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).

[0164] 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: Keytruda®(pembrolizumab), Opdivo®(niolumab), 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), Ipilimumab (to CTLA-4). Immune therapies also include genetically engineered T-cells (e.g., CAR-T cells) and bispecific antibodies (e.g., BiTEs).

[0165] In a particular embodiment, the compounds of the present invention are used in combination with an anti-PD-1 antibody, such as AMG 404. In a specific embodiment, the anti-PD-1 antibody (or antigen binding antibody fragment thereof) comprises 1, 2, 3, 4, 5, or all 6 the CDR amino acid sequences of SEQ ID NOs: 1-6 (representing HC CDR1, HC CDR2, HC CDR3, LC CDR1, LC CDR2, and LC CDR3, in that order). In specific embodiments, the anti-PD-1 antibody (or antigen binding antibody fragment thereof) comprises all 6 of the CDR amino acid sequences of SEQ ID NOs: 1-6. In other embodiments, the anti-PD-1 antibody (or antigen binding antibody fragment thereof) comprises (a) the heavy chain variable region amino acid sequence in SEQ ID NO: 7, or a variant sequence thereof which differs by only one or two amino acids or which has at least or about 70% sequence identity, or (b) the light chain variable region amino acid sequence in SEQ ID NO: 8 or a variant sequence thereof which differs by only one or two amino acids or which has at least or about 70% sequence identity. In an exemplary embodiment, the anti-PD-1 antibody (or antigen binding antibody fragment thereof) comprises the heavy chain variable region amino acid sequence in SEQ ID NO: 7 and the light chain variable region amino acid sequence in SEQ ID NO: 8. In other embodiments, the anti-PD-1 antibody (or antigen binding antibody fragment thereof) comprises (a) the heavy chain amino acid sequence of SEQ ID NO: 9 or a variant sequence thereof which differs by only one or two amino acids or which has at least or about 70% sequence identity; or (b) the

light chain amino acid sequence of SEQ ID NO: 10 or a variant sequence thereof which differs by only one or two amino acids or which has at least or about 70% sequence identity. In an exemplary embodiment, the anti-PD-1 antibody (or antigen binding antibody fragment thereof) comprises the heavy chain amino acid sequence of SEQ ID NO: 9 and the light chain amino acid sequence of SEQ ID NO: 10.

[0166] The present disclosure further provides nucleic acid sequences encoding the anti-PD-1 antibody (or an antigen binding portion thereof). In exemplary aspects, the antibody comprises 1, 2, 3, 4, 5, or all 6 CDRs encoded by the nucleic acid(s) of SEQ ID NOs: 11-16 (representing HC CDR1, HC CDR2, HC CDR3, LC CDR1, LC CDR2, and LC CDR3, in that order). In another exemplary aspect, the antibody comprises all 6 CDRs encoded by the nucleic acids of SEQ ID NOs: 11-16. In some embodiments, the anti-PD-1 antibody (or an antigen binding portion thereof) comprises (a) a heavy chain variable region encoded by SEQ ID NO: 17 or a variant sequence thereof which differs by only 1, 2, 3, 4, 5, or 6 nucleic acids or which has at least or about 70%, 85%, 90%, or 95% sequence identity, or (b) a light chain variable region encoded by SEQ ID NO: 18 or a variant sequence thereof which differs by only 1, 2, 3, 4, 5, or 6 nucleic acids or which has at least or about 70%, 85%, 90%, or 95% sequence identity. In an exemplary embodiment, the anti-PD-1 antibody (or an antigen binding portion thereof) comprises a heavy chain variable region encoded by SEQ ID NO: 17 and a light chain variable region encoded by SEQ ID NO: 18. In other embodiments, the anti-PD-1 antibody (or an antigen binding portion thereof) comprises (a) a heavy chain encoded by SEQ ID NO: 19 or a variant sequence thereof which differs by only 1, 2, 3, 4, 5, or 6 nucleic acids or which has at least or about 70%, 85%, 90%, or 95% sequence identity, or (b) a light chain encoded by SEQ ID NO: 20 or a variant sequence thereof which differs by only 1, 2, 3, 4, 5, or 6 nucleic acids or which has at least or about 70%, 85%, 90%, or 95% sequence identity. In an exemplary embodiment, the anti-PD-1 antibody (or an antigen binding portion thereof) comprises a heavy chain encoded by SEQ ID NO: 19 and a light chain encoded by SEQ ID NO: 20.

[0167] 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. 6,111,090, 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.:

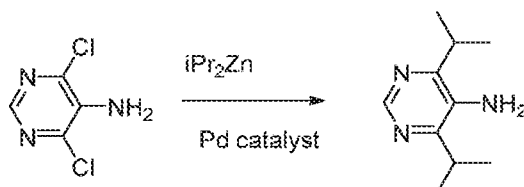
WO2005/055808, PCT Publication No.: WO 99/40196, PCT Publication No.: WO 2001/03720, PCT Publication No.: WO99/20758, PCT Publication No.: WO2006/083289, PCT Publication No.: WO 2005/115451, U.S. Pat. No. 7,618,632, and PCT Publication No.: WO 2011/051726.

[0168] 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.

[0169] 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.

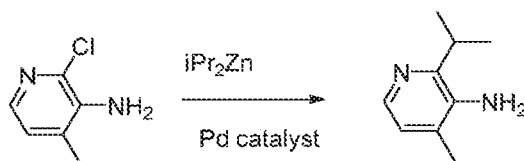
SECTION 1 – GENERAL PROCEDURES

1. 4,6-Diisopropylpyrimidin-5-amine (Intermediate A)



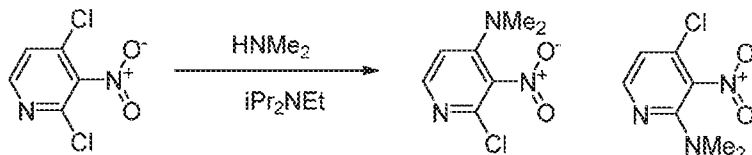
[0170] A solution of 4,6-dichloro-5-aminopyrimidine (3.00 g, 18.3 mmol, Combi-Blocks Inc., San Diego, CA) in THF (18 mL) was degassed by bubbling argon into the mixture for 5 min. 2-Propylzinc bromide (0.5 M solution in THF, 91.0 mL, 45.5 mmol, Sigma-Aldrich, St. Louis, MO) was added via syringe followed by XantPhos Pd G3 (434 mg, 0.5 mmol, Sigma-Aldrich, St. Louis, MO). The resulting mixture was stirred at rt for 16 h and then was filtered through a pad of Celite. The filter cake was rinsed with EtOAc, and the filtrate was collected and concentrated *in vacuo* to afford 4,6-diisopropylpyrimidin-5-amine (**Intermediate A**, 3.45 g). *m/z* (ESI, +ve ion): 180.2 (M+H)+.

2. 2-Isopropyl-4-methylpyridin-3-amine (Intermediate B)



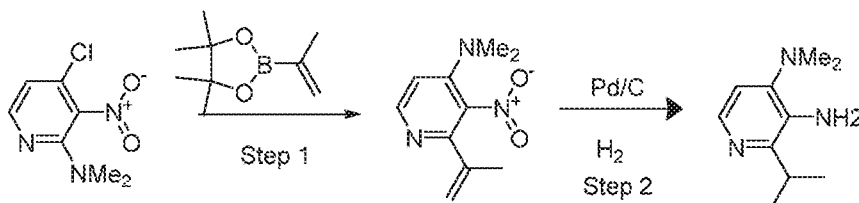
[0100] To a slurry of 3-amino-2-bromo-4-picoline (360 mg, 1.9 mmol, Combi-Blocks, San Diego, CA) in THF (4 mL) was added [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II), complex with DCM (79 mg, 0.1 mmol). The resulting slurry was degassed with argon for 2 min and then 2-propylzinc bromide (0.5 M solution in THF, 5.4 mL, 2.7 mmol, Sigma-Aldrich, St. Louis, MO) was added. The resulting solution was heated at 60 °C for 17 h, then the heating was stopped and the reaction was allowed to cool to rt. The reaction mixture was quenched with water (10 mL) and 1 N NaOH solution (20 mL) and then was extracted with EtOAc. The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by silica gel chromatography on silica gel (eluent: 0-15% MeOH/DCM) to provide 2-isopropyl-4-methylpyridin-3-amine (**Intermediate B**). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 7.66 (d, *J* = 4.6 Hz, 1 H), 6.78 (d, *J* = 4.8 Hz, 1 H), 4.72 (br s, 2 H), 3.14-3.25 (m, 1 H), 2.08 (s, 3 H), 1.14 (d, *J* = 6.8 Hz, 6 H). *m/z* (ESI, +ve ion): 151.1 (M+H)+.

3. 2-Chloro-*N,N*-dimethyl-3-nitropyridin-4-amine (**Intermediate C**) and 4-chloro-*N,N*-dimethyl-3-nitropyridin-2-amine (**intermediate D**)



[0171] To 2,4-dichloro-3-nitropyridine (7.0 g, 36 mmol, Ark Pharm, Inc.) in 10 ml acetonitrile was added triethylamine (6 ml, 43 mmol, Sigma-Aldrich, St. Louis, MO). The mixture was cooled to 0°C and dimethylamine 2N in THF (19 ml, 38 mmol) was slowly added. After 2.5h LCMS indicated the reaction was completed. Added 100 ml ethyl acetate, washed with brine, dried, and evaporated. After purification by chromatography purification on silica gel (0-100% ethyl acetate/heptane) gave 4-chloro-*N,N*-dimethyl-3-nitropyridin-2-amine (**intermediate D**) as the less polar peak: ¹H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 7.98 - 8.22 (m, 1 H) and 2-chloro-*N,N*-dimethyl-3-nitropyridin-4-amine (**Intermediate C**) as more polar peak: ¹H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 3.01 - 3.05 (m, 6 H) 6.61 - 6.70 (m, 1 H) 6.85 - 6.95 (m, 1 H) 7.80 - 7.87 (m, 1 H) 7.97 - 8.06 (m, 1 H).

4. 2-Isopropyl-*N,N*-4-dimethylpyridine-3,4-diamine (**Intermediate E**)



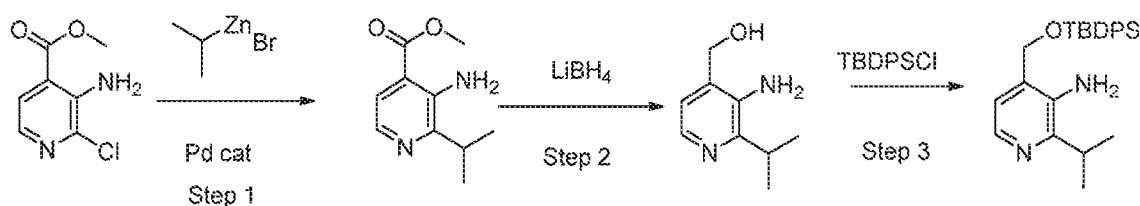
[0172] **Step 1: *N,N*-Dimethyl-3-nitro-2-(prop-1-en-2-yl)pyridin-4-amine.** To three neck flask was added 2-chloro-*N,N*-dimethyl-3-nitropyridin-4-amine (**Intermediate C**) (4.66 g, 23.1 mmol), 30 ml dioxane and 15 ml water. The mixture was stirred under nitrogen for 10 min. Sodium carbonate, anhydrous, powder (7.35 g, 69.3 mmol, Sigma-Aldrich, St. Louis, MO), (1,1'-bis(diphenylphosphino) ferrocene) dichloropalladium (1.0 g, 1.4 mmol, Sigma-Aldrich, St. Louis, MO), and 2-isopropenylboronic acid, pincol ester (8.3 g, 49.4 mmol, Combi-Blocks Inc.) was added and heated in a 100°C bath. After 5h, LCMS showed reaction completed and the mixture was cooled to RT. Ethyl acetate (200 ml) was added and washed with 50 ml brine, dried and evaporated. Purification by chromatography on silica gel (eluent: 30-40% ethyl acetate/heptane) gave *N,N*-dimethyl-3-nitro-2-(prop-1-en-2-yl)pyridin-4-amine as yellow solids. ¹H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 2.11 - 2.21 (m, 3 H) 2.95 -

3.01 (m, 6 H) 4.99 - 5.06 (m, 1 H) 5.16 - 5.23 (m, 1 H) 6.59 - 6.69 (m, 1 H) 8.19 - 8.28 (m, 1 H).

[0173] **Step 2: 2-Isopropyl-*N,N*-4-dimethylpyridine-3,4-diamine.** To *N,N*-dimethyl-3-nitro-2-(prop-1-en-2-yl)pyridin-4-amine (4.8 g, 23.2 mmol) in 60 ml EtOH solution was added palladium 10% on carbon (0.6 g, 5.6 mmol, Sigma-Aldrich, St. Louis, MO). The mixture was hydrogenated at 45PSI for 3 days. The mixture was filtered through a pad of celite, washed with ethyl acetate, evaporated and purified by chromatography on silica gel eluted with 30-40% (3/1 EtOAc/EtOH)/heptane gave 2-isopropyl-*N,N*-4-dimethylpyridine-3,4-diamine (**Intermediate E**).

[0174] 4-Isopropyl-*N,N*-2-dimethylpyridine-2,3-diamine (**Intermediate F**) was prepared from 4-chloro-*N,N*-dimethyl-3-nitropyridin-2-amine (**Intermediate D**) following the same sequence.

**5. 4-(((*tert*-Butyldiphenylsilyl)oxy)methyl)-2-isopropylpyridin-3-amine
(Intermediate G)**

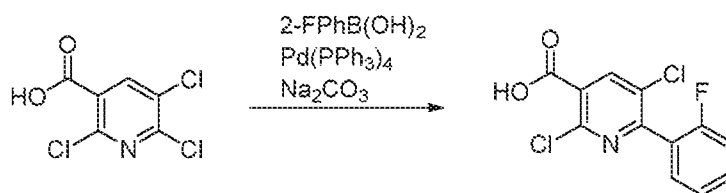


[0175] **Step 1: Methyl 3-amino-2-isopropylisonicotinate.** To a 1-L three necked round-bottomed flask equipped with Findenser condenser was added 3-amino-2-chloro-4-(methoxycarbonyl)pyridine (10.6 g, 56.8 mmol, Combi-Blocks Inc., San Diego, CA) and [(4,5-bis(diphenylphosphino)-9,9-dimethylxanthene)-2-(2'-amino-1,1'-biphenyl)]palladium(II) methanesulfonate (2.69 g, 2.8 mmol, Sigma-Aldrich, St. Louis, MO) in tetrahydrofuran (114 ml) under argon. 2-Propylzinc bromide 0.5M in tetrahydrofuran (148 ml, 73.8 mmol, Sigma-Aldrich, St. Louis, MO) was added via addition funnel over 4 min. The reaction mixture was then stirred at 50 °C for 40 min. The reaction mixture was cooled with ice water bath. Ice (~100 g) and Celite (~100 g) were added with stirring and the mixture was filtered through fine frit glass filter and washed with DCM to remove insoluble emulsions. The two layers were separated, and the aqueous layer was extracted with DCM (3x200 mL). The combined organic phases were dried over sodium sulfate, filtered and concentrated *in vacuo* to afford brown oil. The crude material was purified by chromatography on silica gel eluting with a gradient of 0% to 70% EtOAc in heptane, to provide methyl 3-amino-2-isopropylisonicotinate as yellow oil.

[0176] **Step 2. 3-Amino-2-isopropylpyridin-4-yl)methanol.** A 1L three-necked flask was equipped with condenser, charged with methyl 3-amino-2-isopropylisonicotinate (18.2 g, 94 mmol) and THF (185 mL). Lithium borohydride 2 M in THF (94 mL, 187 mmol, Sigma-Aldrich, St. Louis, MO) was added dropwise. The mixture was stirred at rt for 15 min. Then methanol (30.3 mL) was added slowly and the mixture was stirred at rt to 40 °C for 3.5 hours. Saturated NH₄Cl (~100 mL) was added slowly. The reaction mixture was concentrated *in vacuo* to remove most of THF. The residual mixture was diluted with water and extracted with EtOAc (4 x 150 mL). The combined organic phases were dried over Na₂SO₄, filtered and concentrated to give crude 3-amino-2-isopropylpyridin-4-yl)methanol for use directly in the next step.

[0177] **Step 3. 4-(((*tert*-Butyldiphenylsilyl)oxy)methyl)-2-isopropylpyridin-3-amine.** A 1L RBF was charged with (3-amino-2-isopropylpyridin-4-yl)methanol (15.6 g, 94 mmol), DIPEA (57.3 mL, 328 mmol, Sigma-Aldrich, St. Louis, MO) and 4-(dimethylamino) pyridine (0.57 g, 4.7 mmol, Sigma-Aldrich, St. Louis, MO) in dichloromethane (187 mL). *tert*-Butyldiphenylchlorosilane (31.7 mL, 122 mmol, Sigma-Aldrich, St. Louis, MO) was added dropwise. The mixture was stirred at rt for 3 hours. The mixture was washed with water. The organic phase was dried over sodium sulfate, filtered and concentrated *in vacuo* to afford yellow oil. The crude product was purified by chromatography on silica gel eluting with a gradient of 0% to 50% EtOAc in heptane, to provide 4-(((*tert*-butyldiphenylsilyl)oxy)methyl)-2-isopropylpyridin-3-amine (**Intermediate G**, 28.1 g, 69.4 mmol, 74.1 % yield) as a white solid.

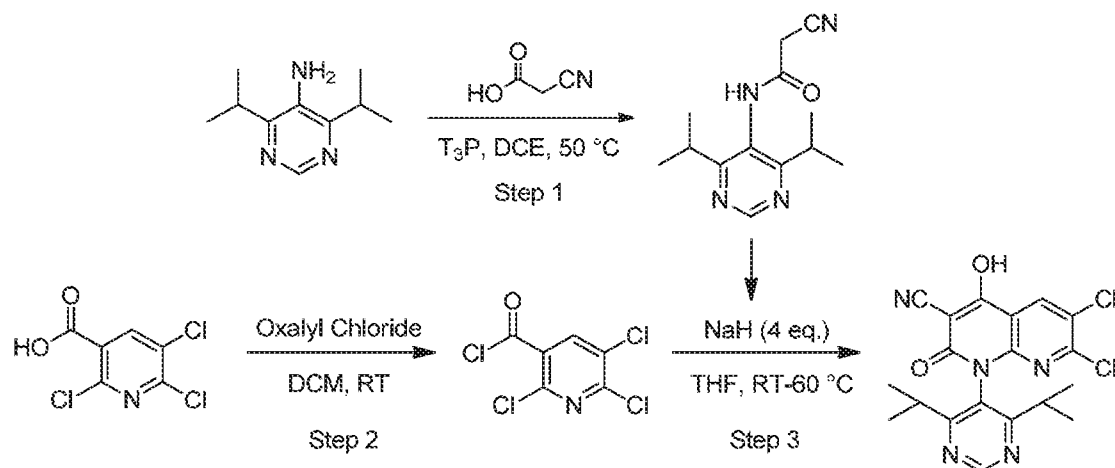
6. 2,5-Dichloro-6-(2-fluorophenyl)nicotinic acid (**Intermediate H**)



[0178] **2,5-Dichloro-6-(2-fluorophenyl)nicotinic acid.** A mixture of 2,5,6-trichloronicotinic acid (1.03 g, 4.54 mmol, Combi-Blocks, San Diego, CA), palladium tetrakis (0.13 g, 0.1 mmol, Sigma-Aldrich, St. Louis, MO), (2-fluorophenyl)boronic acid (0.70 g, 5.0 mmol, TCI America, Portland, OR), and sodium carbonate (2M in water, 6.8 mL, 13.6 mmol) in 1,4-dioxane (11 mL) was purged with nitrogen and heated to 80 °C for 1 h followed by 90 °C for 5 h. The reaction mixture was diluted with EtOAc (150 mL), washed with 1 N aqueous citric acid (2 x 100 mL); the organic layer was separated, dried over anhydrous Na₂SO₄, and

concentrated *in vacuo* to give 2,5-dichloro-6-(2-fluorophenyl)nicotinic acid (**Intermediate H**, 1.27 g, 4.4 mmol, 97% yield) as an amber oil. *m/z* (ESI, +ve ion): 285.8 (M+H)⁺.

7. **6,7-Dichloro-1-(4,6-diisopropylpyrimidin-5-yl)-4-hydroxy-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile (Intermediate I)**



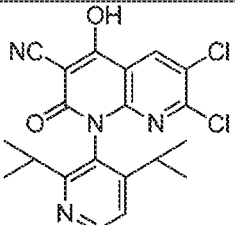
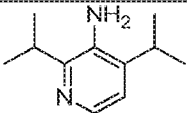
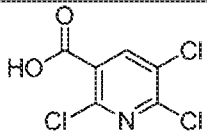
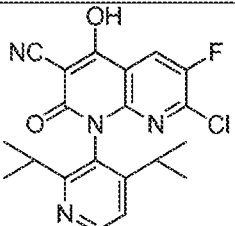
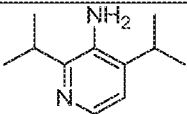
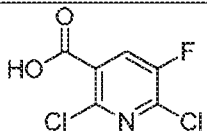
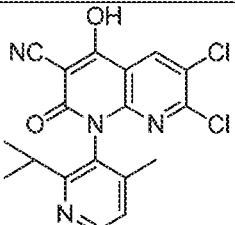
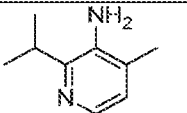
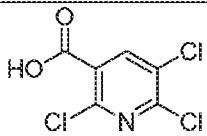
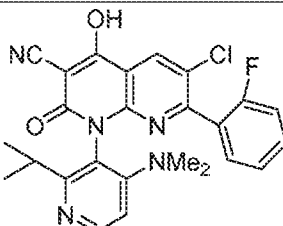
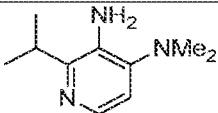
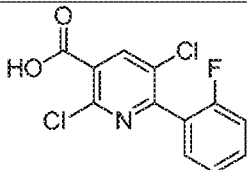
[0179] **Step 1: 2-Cyano-N-(4,6-diisopropylpyrimidin-5-yl)acetamide.** To 4,6-diisopropylpyrimidin-5-amine (6.9 g, 38.5 mmol, **Intermediate A**) and cyanoacetic acid (4.86 g, 57.1 mmol, Sigma-Aldrich, St. Louis, MO) were added 35 ml DCE, 1-propanephosphonic acid cyclic anhydride, 50 wt. % solution in ethyl acetate (45.8 ml, 77 mmol, Sigma-Aldrich, St. Louis, MO) and triethylamine, anhydrous (16.2 ml, 115 mmol, Sigma-Aldrich, St. Louis, MO). The mixture was heated to 50 °C for 30 min. The mixture was cooled to rt, added 300 ml ethyl acetate and 150 sat NaHCO₃, and stirred for 5 min. The organic layer was separated, washed with saturated NH₄Cl, dried and evaporated. Purification by chromatography on silica gel eluting with 0-50% (3/1 EtOAc/EtOH)/heptane gave 2-cyano-N-(4,6-diisopropylpyrimidin-5-yl)acetamide as a white solid.

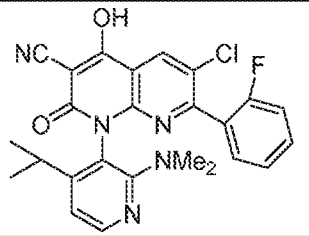
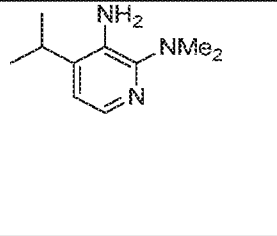
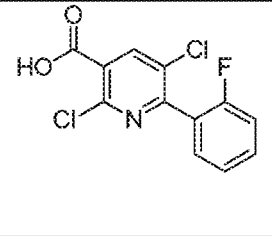
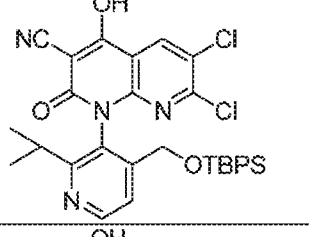
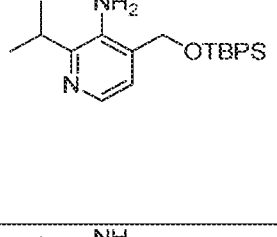
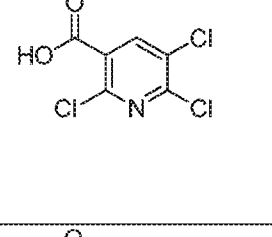
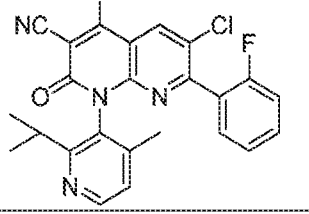
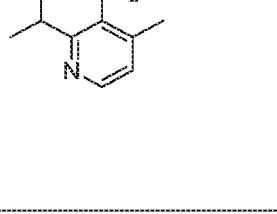
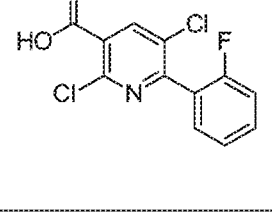
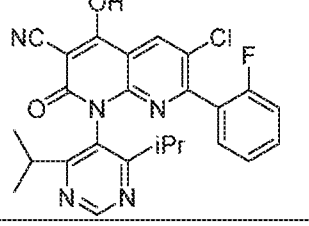
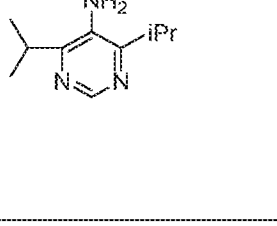
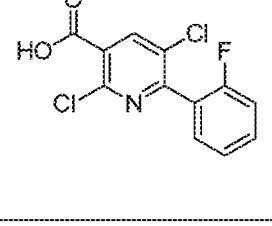
[0180] **Step 2: 2,5,6-Trichloronicotinoyl chloride.** To 2,5,6-trichloronicotinic acid (2.92 g, 12.9 mmol) in 20 ml DCM suspension was added 0.3 ml DMF and oxalyl chloride, 2.0 M solution in methylene chloride (9.67 ml, 19.3 mmol, Sigma-Aldrich, St. Louis, MO). The mixture was stirred at RT for 45 min, evaporated, dried *in vacuo* to give crude 2,5,6-trichloronicotinoyl chloride which used in the next step.

[0181] **Step 3: 6,7-Dichloro-1-(4,6-diisopropylpyrimidin-5-yl)-4-hydroxy-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile.** To 2-cyano-N-(4,6-diisopropylpyrimidin-5-yl)acetamide (3.1 g, 12.6 mmol) in 30 ml THF was added portion wise 60% sodium hydride (1.51 g, 37.8 mmol, Sigma-Aldrich, St. Louis, MO). The mixture was stirred for 15 min, and

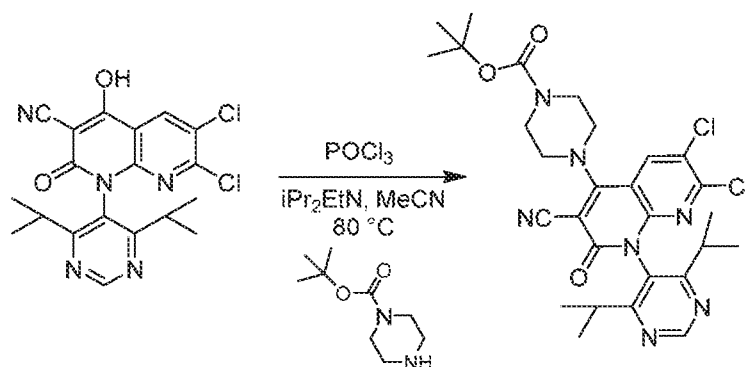
2,5,6-trichloronicotinoyl chloride (3.08 g, 12.6 mmol, Combi-Blocks, San Diego, CA) in 30 ml THF was slowly added. After 15 min the mixture was heated in 70 °C bath for 1h. Additional 0.5 g 60% NaH was added and the mixture was stirred for 10 min and heated at 90°C for 6h. The mixture was cooled to rt, Water (5 ml) was slowly added followed by 2N HCl (50 ml). The mixture was extracted with 100 ml EtOAc. The organic layer was washed with brine (3x), dried and evaporated. Purification by chromatography on silica gel eluting with 0-60% (3/1 EtOH/EtOAc)/heptane gave 6,7-dichloro-1-(4,6-diisopropylpyrimidin-5-yl)-4-hydroxy-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile (**Intermediate I**) as a yellow solid.

Table 2. The following ketones were prepared similarly from the appropriate aromatic amine and pyridine carboxylic acid.

Cpd #	ketone	Aromatic amine used	Pyridine carboxylic acid used
Intermediate J			
Intermediate K			
Intermediate L			
Intermediate M			

Intermediate N			
Intermediate O			
Intermediate P			
Intermediate Q			

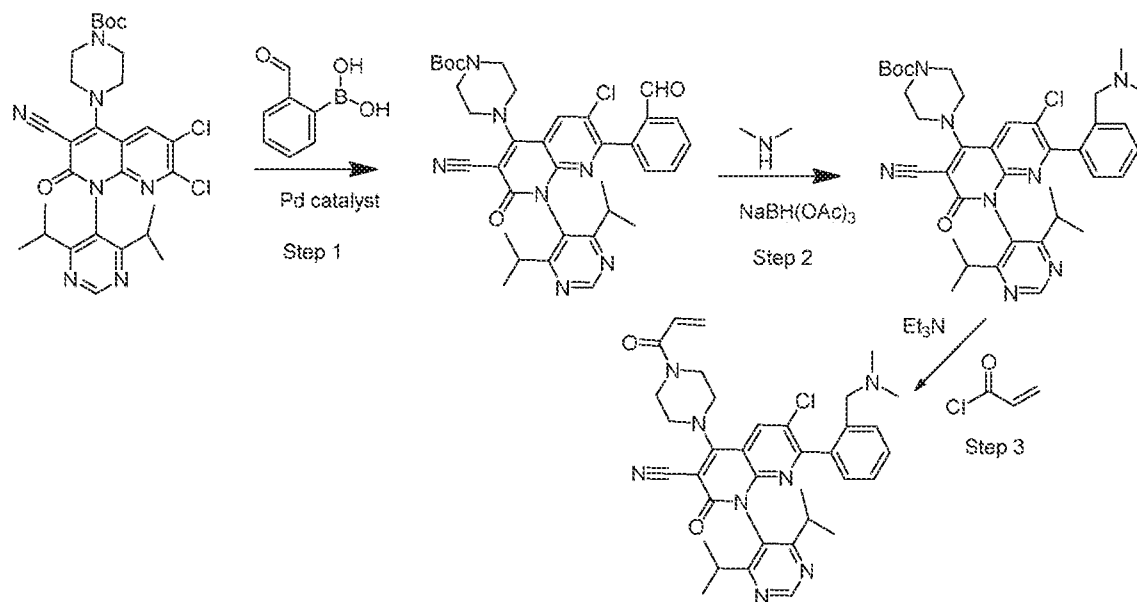
8. 4-(4-Acryloylpiperazin-1-yl)-6-chloro-1-(4,6-diisopropylpyrimidin-5-yl)-7-(2-fluorophenyl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile (**Intermediate R**)



[0182] To 6,7-dichloro-1-(4,6-diisopropylpyrimidin-5-yl)-4-hydroxy-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile (**Intermediate I**, 0.97 g, 2.3 mmol) in 10 ml acetonitrile was added diisopropylethylamine (1.2 ml, 7 mmol, Sigma-Aldrich, St. Louis, MO) and phosphorous oxychloride (0.3 ml, 3.4 mmol, Sigma-Aldrich, St. Louis, MO). The mixture was heated at 90 °C for 30 min. The mixture was cooled and evaporated, and dried *in vacuo*. It was dissolved in 10 ml acetonitrile and cooled in ice water bath. Diisopropylethylamine (1.22 ml, 6.96 mmol) and 1-(t-butoxycarbonyl)-piperazine (0.490 ml, 2.63 mmol, Sigma-Aldrich, St. Louis, MO) were added and the mixture was stirred at 0 °C for 1h and at RT for 16h. Ethyl acetate (60 ml) was added and the solution was washed with brine (3x), dried and evaporated. Purification by chromatography on silica gel eluting with 0-40% ethyl acetate/heptane gave 4-(4-acryloylpiperazin-1-yl)-6-chloro-1-(4,6-diisopropylpyrimidin-5-yl)-7-(2-fluorophenyl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile (**Intermediate R**) as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 0.92 - 1.00 (m, 6 H) 1.04 - 1.13 (m, 6 H) 1.40 - 1.55 (m, 9 H) 2.60 - 2.73 (m, 2 H) 3.56 - 3.70 (m, 4 H) 3.73 - 3.86 (m, 4 H) 8.38 - 8.65 (m, 1 H) 9.07 - 9.35 (m, 1 H); *m/z* (ESI, +ve ion): 586 (M+H)⁺.

Example 1

4-(4-Acryloylpiperazin-1-yl)-6-chloro-1-(4,6-diisopropylpyrimidin-5-yl)-7-(2-((dimethylamino)methyl)phenyl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile



[0183] Step 1. *tert*-Butyl 4-(6-chloro-3-cyano-1-(4,6-diisopropylpyrimidin-5-yl)-7-(2-formylphenyl)-2-oxo-1,2-dihydro-1,8-naphthyridin-4-yl)piperazine-1-carboxylate. *tert*-Butyl 4-(6,7-dichloro-3-cyano-1-(4,6-diisopropylpyrimidin-5-yl)-2-oxo-1,2-dihydro-1,8-naphthyridin-4-yl)piperazine-1-carboxylate (**Intermediate R**, 0.42 g, 0.7 mmol), 2-formylphenylboronic acid (0.127 g, 0.8 mmol, Sigma-Aldrich, St. Louis, MO), (1,1'-bis(diphenylphosphino)ferrocene) dichloropalladium (0.067 g, 0.09 mmol, Sigma-Aldrich, St. Louis, MO), and acetic acid cesium salt (0.13 g, 0.7 mmol, Sigma-Aldrich, St. Louis, MO) in two necked flask were flushed with N₂ for 5 min, added 4 ml THF. The mixture was heated at 90 °C for 1.5 h. It was cooled to RT and 15 ml EtOAc and 8 ml brine were added. Two layers were separated and organic layer was dried and evaporated. Purification by chromatography on silica gel eluting with 0-40% (3/1 EtOH/EtOAc)/heptane gave *tert*-butyl 4-(6-chloro-3-cyano-1-(4,6-diisopropylpyrimidin-5-yl)-7-(2-formylphenyl)-2-oxo-1,2-dihydro-1,8-naphthyridin-4-yl)piperazine-1-carboxylate as a white solid.

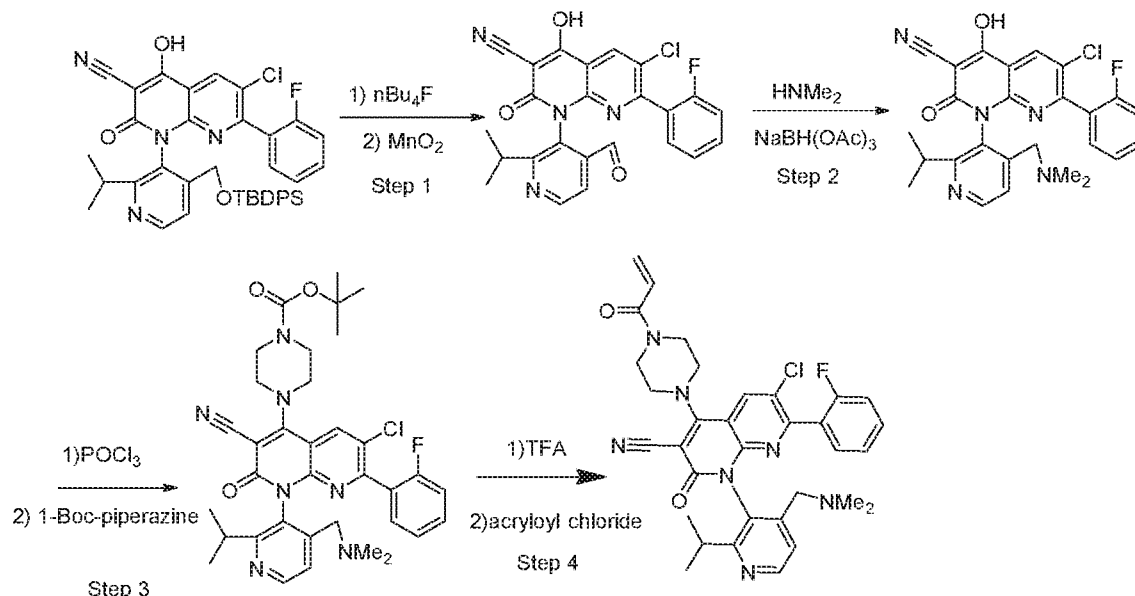
[0184] Step 2. *tert*-Butyl 4-(6-chloro-3-cyano-1-(4,6-diisopropylpyrimidin-5-yl)-7-(2-((dimethylamino)methyl)phenyl)-2-oxo-1,2-dihydro-1,8-naphthyridin-4-yl)piperazine-1-carboxylate. To *tert*-butyl 4-(6-chloro-3-cyano-1-(4,6-diisopropylpyrimidin-5-yl)-7-(2-formylphenyl)-2-oxo-1,2-dihydro-1,8-naphthyridin-4-yl)piperazine-1-carboxylate (0.2 g, 0.3

mmol) in 3 ml DCE was added dimethylamine (0.4 ml, 0.8 mmol) (2M in THF, Sigma-Aldrich, St. Louis, MO), sodium triacetoxyborohydride (0.18 g, 0.8 mmol, Sigma-Aldrich, St. Louis, MO), and 1 ml HOAc. After 5h, 10 ml each of DCM and 10% K₂CO₃ solution were added. The organic layer was separated, dried, and evaporated. Purification by chromatography on silica gel eluting with 0-30% (3/1 EtOH/EtOAc)/heptane gave *tert*-butyl 4-(6-chloro-3-cyano-1-(4,6-diisopropylpyrimidin-5-yl)-7-(2-((dimethylamino)methyl)phenyl)-2-oxo-1,2-dihydro-1,8-naphthyridin-4-yl)piperazine-1-carboxylate.

[0185] Step 3. 4-(4-Acryloylpiperazin-1-yl)-6-chloro-1-(4,6-diisopropylpyrimidin-5-yl)-7-(2-((dimethylamino)methyl)phenyl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile. *tert*-Butyl 4-(6-chloro-3-cyano-1-(4,6-diisopropylpyrimidin-5-yl)-7-(2-((dimethylamino)methyl)phenyl)-2-oxo-1,2-dihydro-1,8-naphthyridin-4-yl)piperazine-1-carboxylate (62 mg, 0.09 mmol) in 2 ml DCM and 1 ml TFA (Sigma-Aldrich, St. Louis, MO) was stirred for 30 min and evaporated. It was co-evaporated with 4x10 ml DCM. The residue was dissolved in 6 ml DCM, cooled to °C, added triethylamine, anhydrous (50 µl, 0.3 mmol, Sigma-Aldrich, St. Louis, MO) and acryloyl chloride (400 µl, 0.2 mmol, Sigma-Aldrich, St. Louis, MO). The mixture was stirred for 15 min and evaporated and purified by chromatography on silica gel eluting with 0-80% (3/1EtOH/EtOAc)/hep to give yellow oil. Further purification by chromatography on silica gel eluting with 0-90% (8% (2NNH₃ in MeOH) in DCM)/DCM, gave 4-(4-acryloylpiperazin-1-yl)-6-chloro-1-(4,6-diisopropylpyrimidin-5-yl)-7-(2-((dimethylamino)methyl)phenyl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile as a yellow solid. ¹H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 1.02 - 1.13 (m, 6 H) 1.19 - 1.27 (m, 6 H) 1.94 - 2.05 (m, 6 H) 2.05 - 2.15 (m, 2 H) 2.44 - 2.77 (m, 2 H) 3.79 - 4.12 (m, 8 H) 5.71 - 6.04 (m, 1 H) 6.29 - 6.54 (m, 1 H) 6.57 - 6.80 (m, 1 H) 6.90 - 7.08 (m, 1 H) , 1H overlapped with CHCl₃, 7.36 - 7.45 (m, 1 H) 7.45 - 7.52 (m, 1 H) 8.00 - 8.36 (m, 1 H) 8.97 - 9.33 (m, 1 H). *m/z* (ESI, +ve ion): 638.9 (M+H)⁺.

Example 2

4-(4-Acryloylpiperazin-1-yl)-6-chloro-1-(4-((dimethylamino)methyl)-2-isopropylpyridin-3-yl)-7-(2-fluorophenyl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile



[0186] **Step 1:** 6-Chloro-7-(2-fluorophenyl)-1-(4-formyl-2-isopropylpyridin-3-yl)-4-hydroxy-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile. To 1-(4-(((*tert*-butyldiphenylsilyl)oxy)methyl)-2-isopropylpyridin-3-yl)-6-chloro-7-(2-fluorophenyl)-4-hydroxy-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile (**Intermediate O**, 3.0 g, 4.2 mmol) in 40 ml THF was added $n\text{Bu}_4\text{NF}$ (1M in THF, 5.2 ml, Sigma-Aldrich, St. Louis, MO). After 22h, 200 ml ethyl acetate and 60 ml sat ammonium chloride were added. The organic layer was, separated, washed with 2xsat NH_4Cl , dried and evaporated. Purification by chromatography on silica gel eluting with 20-90% (3/1 EtOAc/EtOH)/hep gave the alcohol.

6-Chloro-7-(2-fluorophenyl)-4-hydroxy-1-(4-(hydroxymethyl)-2-isopropylpyridin-3-yl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile (1.48 g, 3.1 mmol) in 40 ml DCM was stirred with manganese (IV) oxide (7.4 g, 85 mmol, Sigma-Aldrich, St. Louis, MO) at RT for 2 days. The mixture was filtered through celite and evaporated to give crude aldehyde.

[0187] **Step 2:** To 6-chloro-1-(4-((dimethylamino)methyl)-2-isopropylpyridin-3-yl)-7-(2-fluorophenyl)-4-hydroxy-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile. To 6-chloro-7-(2-fluorophenyl)-1-(4-formyl-2-isopropylpyridin-3-yl)-4-hydroxy-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile (1.05 g, 2.2 mmol) in 12 ml DCE was added dimethylamine 2M in THF (2.3 ml, 4.6 mmol, Sigma-Aldrich, St. Louis, MO). The mixture

was stirred for 5 min, and sodium triacetoxymethylborohydride (0.80 g, 3.7 mmol, Sigma-Aldrich, St. Louis, MO) was added. After 2h, the mixture was diluted with 20 ml DCM and 20 ml sat NaHCO₃. The organic layer was separated, dried and evaporated. Purification by chromatography on silica gel eluting with 20-100% (7% 2M NH₃/MeOH in 3/1 EtOAc/EtOH)/heptane gave 6-chloro-1-(4-((dimethylamino)methyl)-2-isopropylpyridin-3-yl)-7-(2-fluorophenyl)-4-hydroxy-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile as a yellow solid.

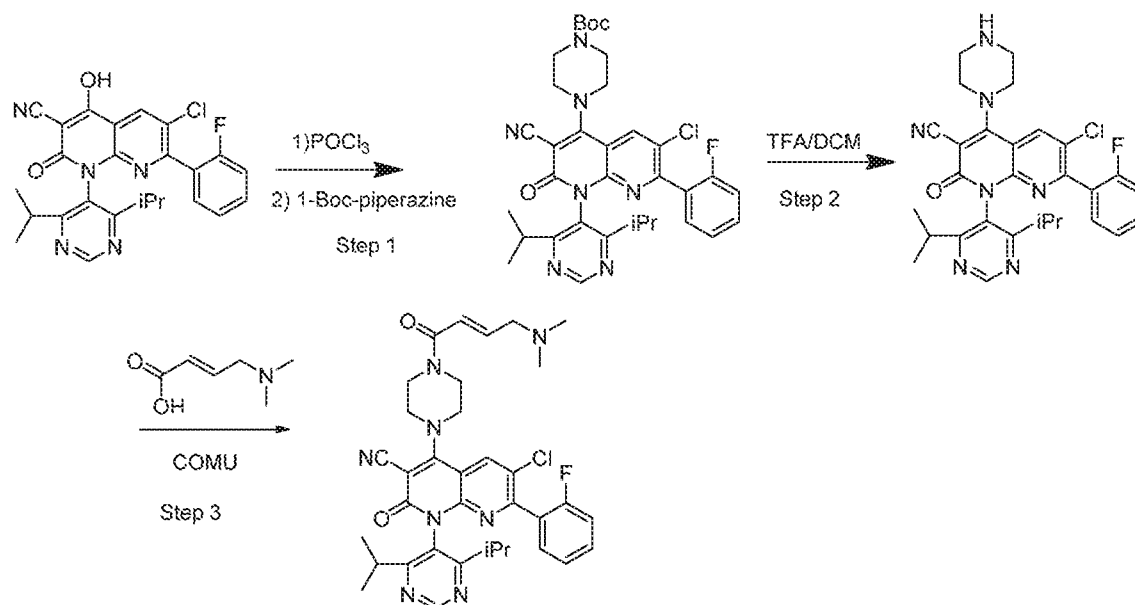
[0188] **Step 3: *tert*-Butyl 4-(6-chloro-3-cyano-1-(4-((dimethylamino)methyl)-2-isopropylpyridin-3-yl)-7-(2-fluorophenyl)-2-oxo-1,2-dihydro-1,8-naphthyridin-4-yl)piperazine-1-carboxylate.** To 6-chloro-1-(4-((dimethylamino)methyl)-2-isopropylpyridin-3-yl)-7-(2-fluorophenyl)-4-hydroxy-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile (0.82 g, 1.6 mmol) in 12 ml acetonitrile suspension was added triethylamine, anhydrous (3 ml, 21.3 mmol, Sigma-Aldrich, St. Louis, MO) and phosphoroxchloride (0.5 ml, 5.3 mmol, Sigma-Aldrich, St. Louis, MO). The mixture was heated to 75 °C for 30 min. The mixture was cooled to RT, evaporated, and dissolved in 20 ml DCM. 1.5 ml TEA and 1-(*t*-butoxycarbonyl)-piperazine (0.621 g, 3.3 mmol, Sigma-Aldrich, St. Louis, MO) was added. After 6h, LCMS showed the chloride starting material still present. 1-(*t*-Butoxycarbonyl)-piperazine (0.3 g) was added and the mixture was stirred for additional 16h. 40 ml DCM and 10 ml brine were added, and the organic layer was separated, dried and evaporated. Purification by chromatography on silica gel eluting with 10-40% (10% 2N NH₃/MeOH(3/1 EtOAc/EtOH))/heptane gave *tert*-butyl 4-(6-chloro-3-cyano-1-(4-((dimethylamino)methyl)-2-isopropylpyridin-3-yl)-7-(2-fluorophenyl)-2-oxo-1,2-dihydro-1,8-naphthyridin-4-yl)piperazine-1-carboxylate.

[0189] **Step 4: 4-(4-Acryloylpiperazin-1-yl)-6-chloro-1-(4-((dimethylamino)methyl)-2-isopropylpyridin-3-yl)-7-(2-fluorophenyl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile.** To *tert*-butyl 4-(6-chloro-3-cyano-1-(4-((dimethylamino)methyl)-2-isopropylpyridin-3-yl)-7-(2-fluorophenyl)-2-oxo-1,2-dihydro-1,8-naphthyridin-4-yl)piperazine-1-carboxylate (0.8 g, 1.2 mmol) in 6 ml DCM was added 4 ml TFA (Sigma-Aldrich, St. Louis, MO). The mixt was stirred for 10 min and evaporated and dried *in vacuo*. The residue was dissolved in 6 ml DCM and cooled in ice water bath, and was added triethylamine, anhydrous (1.0 ml, 7 mmol). Acryloyl chloride 0.5M in DCM (pre-made) (4.5 ml, 2.2 mmol, Sigma-Aldrich, St. Louis, MO) was added. After 10 min the mixture was evaporated. Purification by chromatography on silica gel eluting with 10-30% (10% 2N NH₃ in MeOH in (3/1 EtOAc/EtOH) solution)/heptane gave 4-(4-acryloylpiperazin-1-yl)-6-chloro-1-(4-((dimethylamino)methyl)-2-isopropylpyridin-3-yl)-7-(2-fluorophenyl)-2-oxo-1,2-

dihydro-1,8-naphthyridine-3-carbonitrile as a yellow solid. ^{19}F NMR (376 MHz, $\text{DMSO}-d_6$) δ ppm -114.33 (s, 1 F). ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm 0.89 - 0.98 (m, 3 H) 1.04 - 1.11 (m, 3 H) 1.82 - 1.95 (m, 6 H) 2.65 - 2.77 (m, 1 H) 2.92 - 3.09 (m, 2 H) 3.77 - 3.97 (m, 8 H) 5.75 - 5.81 (m, 1 H) 6.16 - 6.25 (m, 1 H) 6.85 - 6.97 (m, 1 H) 7.09 - 7.17 (m, 1 H) 7.21 - 7.32 (m, 2 H) 7.33 - 7.37 (m, 1 H) 7.45 - 7.54 (m, 1 H) 8.39 - 8.63 (m, 2 H). m/z (ESI, +ve ion): 614.0 ($\text{M}+\text{H}$) $^+$.

Example 3

(*E*)-6-Chloro-1-(4,6-diisopropylpyrimidin-5-yl)-4-(4-(4-(dimethylamino)but-2-enoyl)piperazin-1-yl)-7-(2-fluorophenyl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile



[0190] **Step 1:** *tert*-Butyl 4-(6-chloro-3-cyano-1-(4,6-diisopropylpyrimidin-5-yl)-7-(2-fluorophenyl)-2-oxo-1,2-dihydro-1,8-naphthyridin-4-yl)piperazine-1-carboxylate. 6-Chloro-1-(4,6-diisopropylpyrimidin-5-yl)-7-(2-fluorophenyl)-4-hydroxy-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile (**Intermediate Q**, 0.37 g, 0.7 mmol) in 6 ml acetonitrile was heated with diisopropylethylamine (0.5 ml, 2.8 mmol, Sigma-Aldrich, St. Louis, MO) and phosphorous oxychloride (0.1 mL, 1.0 mmol, Sigma-Aldrich, St. Louis, MO) at 90 °C for 45 min. The reaction mixture was evaporated and dried *in vacuo*. The residue was dissolved in 8 ml DCM, cooled to 0 °C, and 1 ml Hunigs base and 1-(*t*-butoxycarbonyl)-piperazine (0.18 g, 0.9 mmol, Sigma-Aldrich, St. Louis, MO) were added. After 30 min, 25 ml DCM was added. The organic layer was washed with brine, dried and evaporated. Purification by

chromatography on silica gel eluting with 0-20% (3/1 EtOH/EtOAc)/hep gave *tert*-butyl 4-(6-chloro-3-cyano-1-(4,6-diisopropylpyrimidin-5-yl)-7-(2-fluorophenyl)-2-oxo-1,2-dihydro-1,8-naphthyridin-4-yl)piperazine-1-carboxylate as a yellow solid: ^1H NMR (400 MHz, DMSO- d_6) δ ppm 0.87 - 0.94 (m, 6 H) 1.03 - 1.13 (m, 6 H) 1.43 - 1.51 (m, 9 H) 2.64 - 2.75 (m, 2 H) 3.60 - 3.71 (m, 4 H) 3.77 - 3.89 (m, 4 H) 7.11 - 7.19 (m, 1 H) 7.23 - 7.36 (m, 2 H) 7.45 - 7.56 (m, 1 H) 8.47 - 8.54 (m, 1 H) 9.05 - 9.13 (m, 1 H). ^{19}F NMR (376 MHz, DMSO- d_6) δ ppm -114.61 (s, 1 F)

[0191] Step 2: 6-Chloro-1-(4,6-diisopropylpyrimidin-5-yl)-7-(2-fluorophenyl)-2-oxo-4-(piperazin-1-yl)-1,2-dihydro-1,8-naphthyridine-3-carbonitrile. *tert*-Butyl 4-(6-chloro-3-cyano-1-(4,6-diisopropylpyrimidin-5-yl)-7-(2-fluorophenyl)-2-oxo-1,2-dihydro-1,8-naphthyridin-4-yl)piperazine-1-carboxylate (1.3 g, 2.0 mmol) in 12 ml DCM and trifluoroacetic acid (8 ml, 107 mmol, Sigma-Aldrich, St. Louis, MO) was stirred for 1h, and evaporated. The residue was dissolved in 50 ml EtOAc and stirred with sat NaHCO_3 . The organic layer was separated, washed with brine, dried and evaporated to give 6-chloro-1-(4,6-diisopropylpyrimidin-5-yl)-7-(2-fluorophenyl)-2-oxo-4-(piperazin-1-yl)-1,2-dihydro-1,8-naphthyridine-3-carbonitrile as a yellow solid.

Step 3: (*E*)-6-Chloro-1-(4,6-diisopropylpyrimidin-5-yl)-4-(4-(4-(dimethylamino)but-2-enoyl)piperazin-1-yl)-7-(2-fluorophenyl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile.

6-Chloro-1-(4,6-diisopropylpyrimidin-5-yl)-7-(2-fluorophenyl)-2-oxo-4-(piperazin-1-yl)-1,2-dihydro-1,8-naphthyridine-3-carbonitrile (0.1 g, 0.18 mmol) in 1 ml DMF was added *trans*-4-dimethylaminocrotonic acid hydrochloride (0.056 g, 0.3 mmol, Matrix Scientific), diisopropylethylamine (0.25 ml, 1.431 mmol), and COMU (0.23 g, 0.5 mmol, Combi-Blocks, San Diego, CA). After 17h, 30 ml EtOAc was added, and organic layer was washed with brine, dried and evaporated. Purification by chromatography on silica gel eluting with 0-60% (3/1 EtOH/EtOAc)/heptane first then 60% (15% (2N NH_3 in MeOH) in DCM solution)/heptane gave (*E*)-6-Chloro-1-(4,6-diisopropylpyrimidin-5-yl)-4-(4-(4-(dimethylamino)but-2-enoyl)piperazin-1-yl)-7-(2-fluorophenyl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile. ^1H NMR (400 MHz, DMSO- d_6) δ ppm 0.82 - 0.98 (m, 6 H) 1.08 (br d, $J=4.35$ Hz, 6 H) 2.09 - 2.29 (m, 6 H) 2.63 - 2.78 (m, 2 H) 3.01 - 3.16 (m, 2 H) 3.74 - 4.08 (m, 8 H) 6.48 - 6.91 (m, 2 H) 7.08 - 7.65 (m, 4 H) 8.41 - 8.71 (m, 1 H) 8.94 - 9.30 (m, 1 H). ^{19}F NMR (376 MHz, DMSO- d_6) δ ppm -114.60 (br s, 1 F). m/z (ESI, +ve ion): 656.9 ($\text{M}+\text{H}$) $^+$.

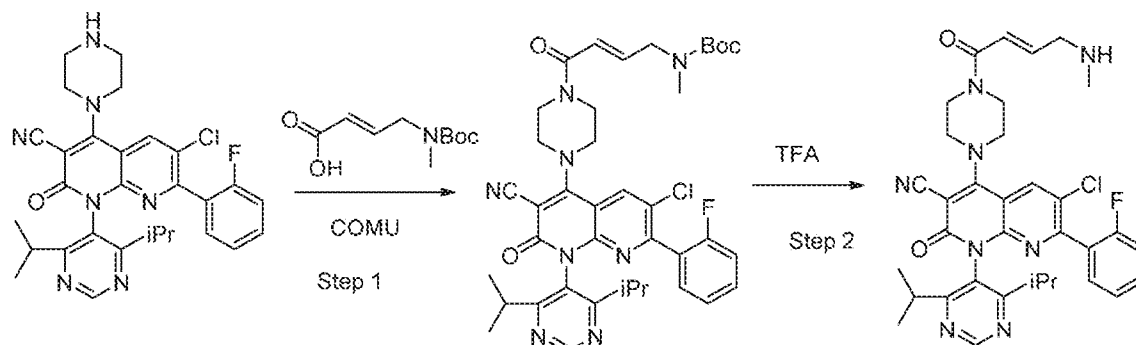
Table 3. The following compounds were similarly prepared by varying the carboxylic acid in Step 3. The general synthesis of the three intermediates of Examples 3.1, 3.2 and 4, is known in the literature and one of ordinary skill in the art would understand and appreciate any

changes to the general synthesis to make the specific intermediates of Examples 3.1, 3.2, 4 and 4.1.

Ex. #	Chemical Structure	Acid used in Step 3
3.1		 (<i>E</i>)-4-(piperidin-1-yl)but-2-enoic acid hydrochloride Reference: U.S. Patent No. 7,772,243
3.2		 (<i>E</i>)-4-(piperidin-1-yl)but-2-enoic acid hydrochloride Reference: U.S. Patent No. 7,772,243

Example 4

(*E*)-6-Chloro-1-(4,6-diisopropylpyrimidin-5-yl)-7-(2-fluorophenyl)-4-(4-(4-(methylamino)but-2-en-1-yl)piperazin-1-yl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile trifluoroacetate salt



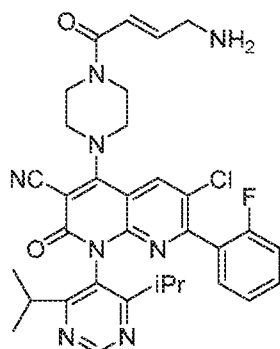
[0192] Step 1: *tert*-Butyl (*E*)-(4-(4-(6-chloro-3-cyano-1-(4,6-diisopropylpyrimidin-5-yl)-7-(2-fluorophenyl)-2-oxo-1,2-dihydro-1,8-naphthyridin-4-yl)piperazin-1-yl)-4-oxobut-2-en-1-yl)(methyl)carbamate. To 6-chloro-1-(4,6-diisopropylpyrimidin-5-yl)-7-(2-

fluorophenyl)-2-oxo-4-(piperazin-1-yl)-1,2-dihydro-1,8-naphthyridine-3-carbonitrile (0.33 g, 0.6 mmol, from Step 2, Example 3) in 3 ml DMF was added (*E*)-4-((*tert*-butoxycarbonyl)(methylamino)but-2-enoic acid (0.24 g, 1.1 mmol)(can be synthesized as described for Example 17b in U.S. Patent No. 9,951,077), COMU (0.55 g, 1.2 mmol, Combi-Blocks, San Diego, CA), and diisopropylethylamine (0.3 ml, 1.7 mmol). The mixture was stirred at RT for 1h. 50 ml EtOAc was added and washed with brine (3x), dried and evaporated. Purification by chromatography on silica gel eluting with 0-40% (3/1 EtOAc-EtOH)/heptane gave *tert*-butyl (*E*)-(4-(4-(6-chloro-3-cyano-1-(4,6-diisopropylpyrimidin-5-yl)-7-(2-fluorophenyl)-2-oxo-1,2-dihydro-1,8-naphthyridin-4-yl)piperazin-1-yl)-4-oxobut-2-en-1-yl)(methyl)carbamate.

[0193] Step 2: (*E*)-6-Chloro-1-(4,6-diisopropylpyrimidin-5-yl)-7-(2-fluorophenyl)-4-(4-(4-(methylamino)but-2-enoyl)piperazin-1-yl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile trifluoroacetate salt. *tert*-Butyl (*E*)-(4-(4-(6-chloro-3-cyano-1-(4,6-diisopropylpyrimidin-5-yl)-7-(2-fluorophenyl)-2-oxo-1,2-dihydro-1,8-naphthyridin-4-yl)piperazin-1-yl)-4-oxobut-2-en-1-yl)(methyl)carbamate (0.16 g, 0.2 mmol) in 3 ml DCM was added 2 ml TFA. After 1.5h, the mixture was evaporated, added 5xDCM, evaporated to give (*E*)-6-Chloro-1-(4,6-diisopropylpyrimidin-5-yl)-7-(2-fluorophenyl)-4-(4-(4-(methylamino)but-2-enoyl)piperazin-1-yl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile trifluoroacetate salt as a colored foam. ¹⁹F NMR (376 MHz, METHANOL-*d*₄) δ ppm -115.72 (s, 1 F) -77.42 (s, 1 F).

¹H NMR (400 MHz, METHANOL-*d*₄) δ ppm 0.93 - 1.02 (m, 6 H) 1.12 - 1.18 (m, 6 H) 1.98 - 2.00 (m, 3 H) 2.66 - 2.73 (m, 2 H) 3.82 - 3.89 (m, 2 H) 3.91 - 4.04 (m, 8 H) 6.70 - 6.82 (m, 1 H) 6.89 - 6.99 (m, 1 H) 7.10 - 7.24 (m, 3 H) 7.42 - 7.54 (m, 1 H) 8.46 - 8.52 (m, 1 H) 8.99 - 9.06 (m, 1 H). *m/z* (ESI, +ve ion): 643.1 (M+H)⁺.

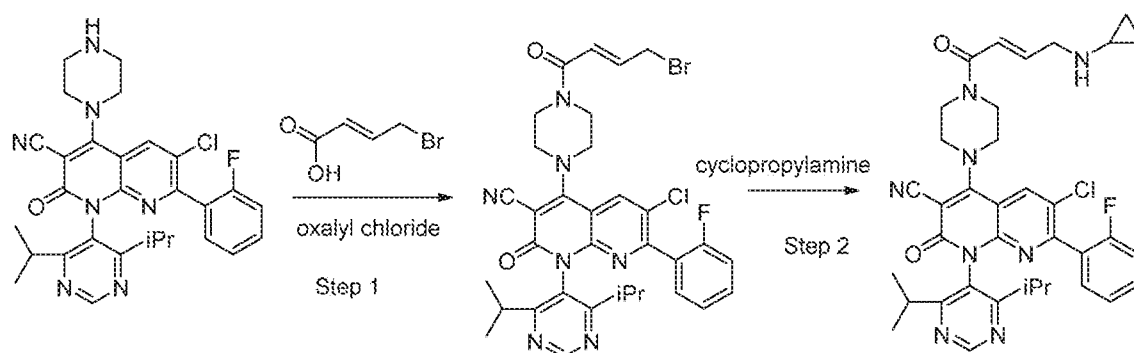
Example 4.1 (*E*)-4-(4-(4-aminobut-2-enoyl)piperazin-1-yl)-6-chloro-1-(4,6-diisopropylpyrimidin-5-yl)-7-(2-fluorophenyl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile



The compound was prepared from (*E*)-4-((tert-butoxycarbonyl)amino)but-2-enoic acid (can be synthesized as described for Intermediate 34 in PCT Appl. No. PCT/US2016/065954; International Publication No. WO 2017100662) following the procedure of Example 4. ¹F NMR showed 2 TFA present. ¹⁹F NMR (376 MHz, DMSO-*d*₆) δ ppm -114.60 (s, 1 F), -74.47 (s, 1 F). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 0.88 - 0.93 (m, 6 H) 1.05 - 1.11 (m, 6 H) 2.64 - 2.72 (m, 2 H) 3.65 - 3.75 (m, 2 H) 3.81 - 3.96 (m, 8 H) 6.64 - 6.77 (m, 1 H) 6.83 - 6.93 (m, 1 H) 7.09 - 7.18 (m, 1 H) 7.23 - 7.36 (m, 2 H) 7.46 - 7.66 (m, 1 H) 7.89 - 8.18 (m, 3 H) 8.38 - 8.65 (m, 1 H) 8.95 - 9.20 (m, 1 H). *m/z* (ESI, +ve ion): 629.2 (M+H)⁺.

Example 5

(*E*)-6-Chloro-4-(4-(4-(cyclopropylamino)but-2-enoyl)piperazin-1-yl)-1-(4,6-diisopropylpyrimidin-5-yl)-7-(2-fluorophenyl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile

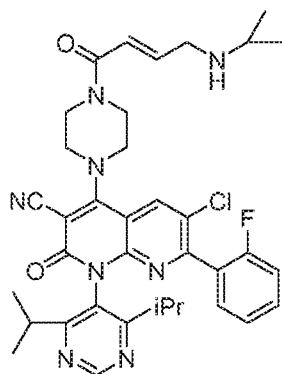


[0194] **Step 1:** (*E*)-4-(4-(4-Bromobut-2-enoyl)piperazin-1-yl)-6-chloro-1-(4,6-diisopropylpyrimidin-5-yl)-7-(2-fluorophenyl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile. To (*E*)-4-bromobut-2-enoic acid (0.25 g, 1.5 mmol, Enamine) in 3 ml DCM was added several drops of DMF and oxalyl chloride, 2.0M solution in methylene chloride (1.5 ml, 3.0 mmol). After 30 min at RT the mixture was evaporated and dried *in vacuo*. The residue was dissolved 6 ml THF and 6 ml DCM and slowly added to precooled solution of (*S*)-6-

chloro-1-(4,6-diisopropylpyrimidin-5-yl)-7-(2-fluorophenyl)-4-(2-methylpiperazin-1-yl)pyrido[2,3-d]pyrimidin-2(1H)-one (from Step 2, Example 3, 0.63 g, 1.2 mmol) and triethylamine, anhydrous (0.33 ml, 2.3 mmol) in 12 ml THF cooled in an ice/NaCl bath (temp only -10 °C to -15 °C. the bath temp went up -5 °C to -10 °C after addition). The cooling bath was allowed to warm up to RT. After 3h, 150 ml EtOAc and brine/sat NaHCO₃ were added. The organic layer was separated, dried and evaporated. Purification by chromatography on silica gel eluting with 0-60% EtOAc/heptane gave (*E*)-4-(4-(4-bromobut-2-enoyl)piperazin-1-yl)-6-chloro-1-(4,6-diisopropylpyrimidin-5-yl)-7-(2-fluorophenyl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile.

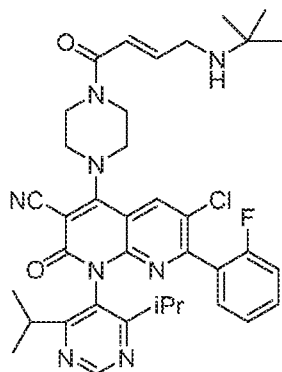
[0195] **Step 2: (*E*)-6-chloro-4-(4-(4-(cyclopropylamino)but-2-enoyl)piperazin-1-yl)-1-(4,6-diisopropylpyrimidin-5-yl)-7-(2-fluorophenyl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile.** The mixture of (*E*)-4-(4-(4-bromobut-2-enoyl)piperazin-1-yl)-6-chloro-1-(4,6-diisopropylpyrimidin-5-yl)-7-(2-fluorophenyl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile (0.18 g, 0.26 mmol) and cyclopropylamine (77 µl, 1.1 mmol) in 1.5 ml acetonitrile was stirred at RT for 5h. The mixture was evaporated and purified by prep HPLC (Phenomenex Gemini C18 column, 150×30 mm, 10µ, 110 Å, 10-100% 0.1% TFA in MeCN/H₂O) to give (*E*)-6-chloro-4-(4-(4-(cyclopropylamino)but-2-enoyl)piperazin-1-yl)-1-(4,6-diisopropylpyrimidin-5-yl)-7-(2-fluorophenyl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile as bis TFA. ¹H NMR (400 MHz, METHANOL-*d*₄) δ ppm 0.86 - 0.99 (m, 4 H) 1.00 - 1.06 (m, 6 H) 1.16 - 1.23 (m, 6 H) 2.66 - 2.80 (m, 2 H) 2.81 - 2.90 (m, 1 H) 3.91 - 4.15 (m, 10 H) 6.74 - 6.90 (m, 1 H) 6.95 - 7.06 (m, 1 H) 7.14 - 7.29 (m, 3 H) 7.43 - 7.57 (m, 1 H) 8.48 - 8.58 (m, 1 H) 9.00 - 9.12 (m, 1 H). ¹⁹F NMR (376 MHz, METHANOL-*d*₄) δ ppm -119.71 - -118.25 (m, 6 F) -83.14 - -71.43 (m, 1 F). *m/z* (ESI, +ve ion): 669.0 (M+H)⁺.

[0196] **Example. 5.1: (*E*)-6-chloro-1-(4,6-diisopropylpyrimidin-5-yl)-7-(2-fluorophenyl)-4-(4-(4-(isopropylamino)but-2-enoyl)piperazin-1-yl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile**



[0197] The compound was prepared according to the procedure of Example 5 using isopropylamine in Step 2. ^1H NMR (400 MHz, METHANOL- d_4) δ ppm 0.97 - 1.06 (m, 6 H) 1.16 - 1.22 (m, 6 H) 1.37 - 1.43 (m, 6 H) 2.69 - 2.80 (m, 2 H) 3.88 - 3.95 (m, 2 H) 3.95 - 4.07 (m, 8 H) 4.09 - 4.16 (m, 1 H) 6.75 - 6.87 (m, 1 H) 6.97 - 7.06 (m, 1 H) 7.14 - 7.26 (m, 3 H) 7.44 - 7.59 (m, 1 H) 8.50 - 8.56 (m, 1 H) 9.02 - 9.12 (m, 1 H). ^{19}F NMR (376 MHz, METHANOL- d_4) δ ppm -115.73 (s, 6 F) -79.92 - -74.06 (m, 1 F). consistent with 2TFA. m/z (ESI, +ve ion): 671.2 (M+H) $^+$.

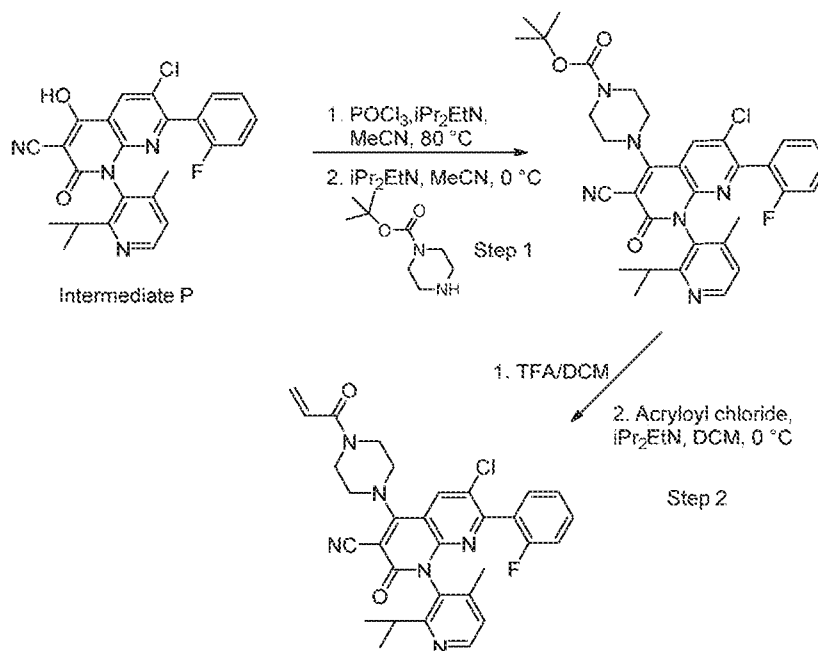
[0198] Example. 5.2: (*E*)-4-(4-(4-(tert-butylamino)but-2-enoyl)piperazin-1-yl)-6-chloro-1-(4,6-diisopropylpyrimidin-5-yl)-7-(2-fluorophenyl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile



[0199] The compound was prepared according to the procedure of Example 5 using *tert*-butylamine: m/z (ESI, +ve ion): 685.3 (M+H) $^+$. ^1H NMR (400 MHz, METHANOL- d_4) δ ppm 0.95 - 1.00 (m, 6 H) 1.14 - 1.18 (m, 6 H) 1.40 - 1.44 (m, 9 H) 2.61 - 2.76 (m, 2 H) 3.84 - 3.90 (m, 2 H) 3.92 - 4.06 (m, 8 H) 6.70 - 6.83 (m, 1 H) 6.94 - 7.03 (m, 1 H) 7.07 - 7.27 (m, 4 H) 7.42 - 7.52 (m, 1 H) 8.41 - 8.57 (m, 1 H) 8.95 - 9.11 (m, 1 H). ^{19}F NMR (376 MHz, METHANOL- d_4) δ ppm -115.73 (s, 1 F) -78.45 - -76.11 (m, 1 F)

Example 6

4-(4-Acryloylpiperazin-1-yl)-6-chloro-7-(2-fluorophenyl)-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile



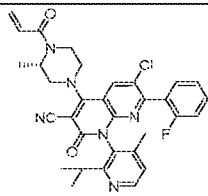
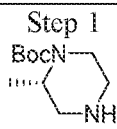
[0200] Step 1: *tert*-Butyl 4-(6-chloro-3-cyano-7-(2-fluorophenyl)-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-1,2-dihydro-1,8-naphthyridin-4-yl)piperazine-1-carboxylate.

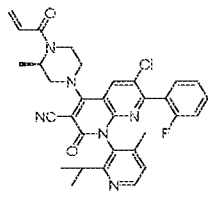
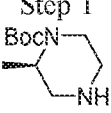
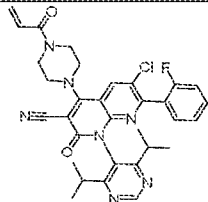
To a solution of 6-chloro-7-(2-fluorophenyl)-4-hydroxy-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile (**Intermediate P**, 250 mg, 0.5 mmol) and $i\text{Pr}_2\text{EtN}$ (0.29 mL, 1.6 mmol) in acetonitrile (5 mL) was added phosphorus oxychloride (0.08 mL, 0.8 mmol, Sigma-Aldrich, St. Louis, MO), and the resulting solution was stirred at 80°C for 30 min. The reaction mixture was allowed to cool to rt and the solvent was removed under vacuum. The residue obtained was dissolved in acetonitrile (4 mL) and $i\text{Pr}_2\text{EtN}$ (0.29 mL, 1.6 mmol) was added. The mixture was cooled to 0°C and *tert*-butyl piperazine-1-carboxylate (207 mg, 1.1 mmol, Sigma-Aldrich, St. Louis, MO) in acetonitrile (0.5 mL) was added. After stirring at rt for 20 min, satd NaHCO_3 (5 mL) and EtOAc (5 mL) were added. The organic layer was taken, washed with water, dried over Na_2SO_4 , filtered, and concentrated *in vacuo*. Chromatographic purification of the residue (silica gel, 0–25% EtOAc:EtOH (3:1) in heptane) provided *tert*-butyl 4-(6-chloro-3-cyano-7-(2-fluorophenyl)-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-1,2-dihydro-1,8-naphthyridin-4-yl)piperazine-1-carboxylate as a light yellow solid: m/z (ESI, +ve) 617.0 ($\text{M}+\text{H}$)⁺.

[0201] **Step 2:** 4-(4-Acryloylpiperazin-1-yl)-6-chloro-7-(2-fluorophenyl)-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile. To a 50-mL round bottomed flask was added *tert*-butyl 4-(6-chloro-3-cyano-7-(2-fluorophenyl)-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-1,2-dihydro-1,8-naphthyridin-4-yl)piperazine-1-carboxylate (246 mg, 0.4 mmol), trifluoroacetic acid (2 mL, 17.5 mmol), and DCM (4 mL). The reaction mixture was stirred at rt for 30 min and the solvent was removed under vacuum to provide 6-chloro-7-(2-fluorophenyl)-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-4-(piperazin-1-yl)-1,2-dihydro-1,8-naphthyridine-3-carbonitrile as a trifluoroacetate salt: *m/z* (ESI, +ve) 517.0 (M+H)⁺. The crude salt was dissolved in DCM (5 mL) and *i*Pr₂EtN (0.28 mL, 1.6 mmol) was added. The reaction mixture was cooled to 0 °C and acryloyl chloride (0.036 mL, 0.44 mmol, Sigma-Aldrich, St. Louis, MO) in DCM (0.5 mL) was added. The reaction mixture was stirred at 0 °C for 30 min and quenched with saturated aqueous NaHCO₃ (5 mL) and extracted with EtOAc (10 mL). The organic layer was separated, washed with brine (5 mL), dried over Na₂SO₄, filtered, and concentrated *in vacuo*. Chromatographic purification of the residue (silica gel, 0–50% EtOAc:EtOH (3:1) in heptane) provided 4-(4-acryloylpiperazin-1-yl)-6-chloro-7-(2-fluorophenyl)-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile as a light yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.50 (s, 1 H), 8.44 (d, *J*=4.77 Hz, 1 H), 7.47 - 7.57 (m, 1 H), 7.25 - 7.34 (m, 2 H), 7.22 (d, *J*=5.18 Hz, 1 H), 7.19 (td, *J*=7.26, 1.45 Hz, 1 H), 6.92 (dd, *J*=16.59, 10.37 Hz, 1 H), 6.21 (dd, *J*=16.79, 2.28 Hz, 1 H), 5.75 - 5.80 (m, 1 H), 3.79 - 4.00 (m, 8 H), 2.66 (quin, *J*=6.63 Hz, 1 H), 1.93 (s, 3 H), 1.07 (d, *J*=6.63 Hz, 3 H), 0.91 (d, *J*=6.63 Hz, 3 H). *m/z* (ESI, +ve) 571.0 (M+H)⁺.

[0202] The following compounds were prepared according to the above route from substituted 1-Boc-piperazines in Step 1.

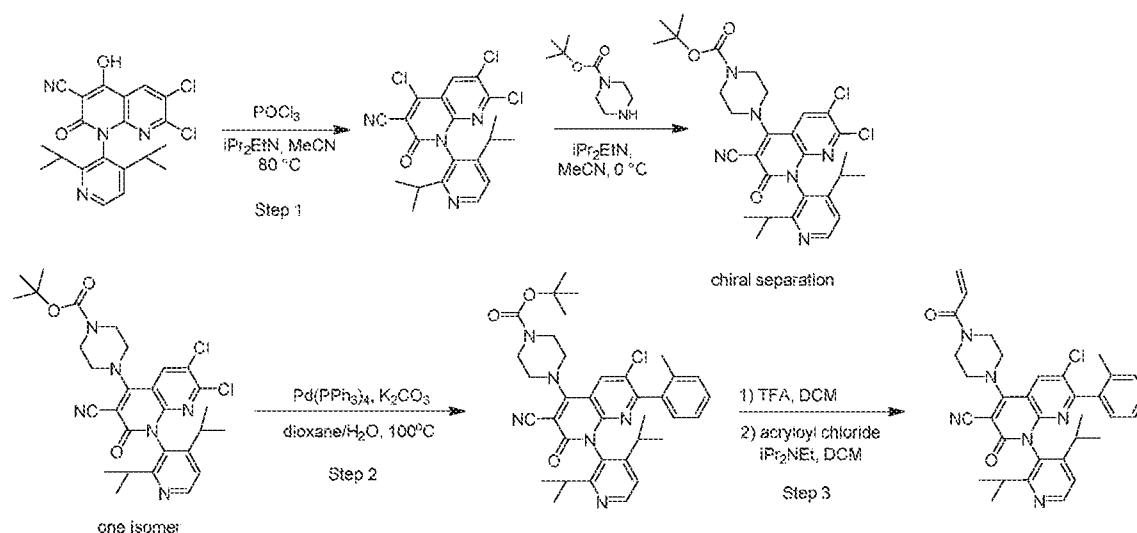
Table 4. List of compounds prepared according to the described route

Ex.#	Chemical Structure	Name	Reagent change
6.1		(S)-4-(4-acryloyl-3-methylpiperazin-1-yl)-6-chloro-7-(2-fluorophenyl)-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile	Step 1  Combi-Blocks Inc., San Diego, CA

6.2		(R)-4-(4-acryloyl-3-methylpiperazin-1-yl)-6-chloro-7-(2-fluorophenyl)-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile	Step 1  Combi-Blocks Inc., San Diego, CA
6.3		4-(4-acryloylpiperazin-1-yl)-6-chloro-1-(4,6-diisopropylpyrimidin-5-yl)-7-(2-fluorophenyl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile	Step 1 intermediate Q

Example 7

4-(4-Acryloylpiperazin-1-yl)-6-chloro-1-(2,4-diisopropylpyridin-3-yl)-2-oxo-7-(o-tolyl)-1,2-dihydro-1,8-naphthyridine-3-carbonitrile



[0203] **Step 1. Racemic *tert*-butyl 4-(6,7-dichloro-3-cyano-1-(2,4-diisopropylpyridin-3-yl)-2-oxo-1,2-dihydro-1,8-naphthyridin-4-yl)piperazine-1-carboxylate.** To a 250-mL round bottomed flask was added 6,7-dichloro-1-(2,4-diisopropylpyridin-3-yl)-4-hydroxy-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile (**Intermediate K**, 2.8 g, 6.7 mmol) and diisopropylethylamine (3.5 ml, 20.1 mmol) in CH₃CN (24 mL). Then POCl₃ (0.94 ml, 10.1 mmol) was added dropwise. The reaction mixture was heated at 80 °C for 3 h. The reaction mixture was allowed to cool to room temperature and the solvent was removed under vacuum.

[0204] The residue was redissolved in CH₃CN (24 mL) and diisopropylethylamine (3.5 mL, 20.1 mmol) was added. The reaction was cooled to 0 °C and 1-Boc-piperazine (1.63 g, 8.7 mmol, Aldrich) was added in one portion. The reaction mixture was stirred at 0 °C for 1 h, warmed to RT, treated with saturated NaHCO₃, and extracted with EtOAc (3x). The organic extract was washed with water and dried over Na₂SO₄, filtered and concentrated *in vacuo*. The crude material was purified by chromatography on silica gel, eluting with a gradient of 0% to 25 % 3:1 EtOAc:EtOH in heptane to provide *tert*-butyl 4-(6,7-dichloro-3-cyano-1-(2,4-diisopropylpyridin-3-yl)-2-oxo-1,2-dihydro-1,8-naphthyridin-4-yl)piperazine-1-carboxylate (1.48 g, 2.5 mmol, 38 % yield) as yellow solid. *m/z* (ESI, +ve ion): 585.0 (M+1).

[0205] (*M*)-*tert*-Butyl 4-(6,7-dichloro-3-cyano-1-(2,4-diisopropylpyridin-3-yl)-2-oxo-1,2-dihydro-1,8-naphthyridin-4-yl)piperazine-1-carboxylate and (*P*)-*tert*-butyl 4-(6,7-dichloro-3-cyano-1-(2,4-diisopropylpyridin-3-yl)-2-oxo-1,2-dihydro-1,8-naphthyridin-4-yl)piperazine-1-carboxylate The above material was purified by preparative SFC purification to give both (*M*) and (*P*) isomers:

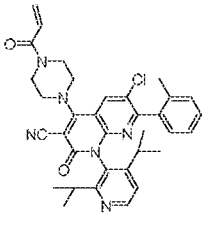
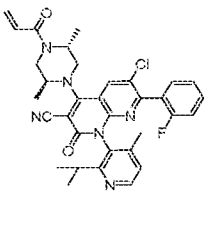
[0206] [OX-H (5μm, 21x250 mm) column, F=80ml, 35% Methanol, 65% carbon dioxide, back pressure= 90 bar, 1.2 ml injection] to give: peak 1: 580 mg, chemical purity:>99.0%, D.E. > 99.0 %. ¹H NMR (400 MHz, CHLOROFORM-*d*) δ 8.67 (d, *J*=5.18 Hz, 1H), 8.11 (s, 1H), 7.22 (d, *J*=5.18 Hz, 1H), 3.67-3.81 (m, 8H), 2.26-2.56 (m, 2H), 1.52 (s, 9H), 1.19 (dd, *J*=6.84, 12.02 Hz, 6H), 1.03 (dd, *J*=6.84, 18.45 Hz, 6H) and peak 2: 650 mg, chemical purity:>99.0%, D.E. 96.3%. ¹H NMR (400 MHz, CHLOROFORM-*d*) δ 8.67 (d, *J*=5.18 Hz, 1H), 8.11 (s, 1H), 7.22 (d, *J*=4.98 Hz, 1H), 3.67-3.84 (m, 8H), 2.29-2.53 (m, 2H), 1.52 (s, 9H), 1.19 (dd, *J*=6.84, 12.02 Hz, 6H), 1.03 (dd, *J*=6.84, 18.45 Hz, 6H).

[0207] Step 2. *tert*-Butyl 4-(6-chloro-3-cyano-1-(2,4-diisopropylpyridin-3-yl)-2-oxo-7-(*o*-tolyl)-1,2-dihydro-1,8-naphthyridin-4-yl)piperazine-1-carboxylate. To a vial containing *tert*-butyl 4-(6,7-dichloro-3-cyano-1-(2,4-diisopropylpyridin-3-yl)-2-oxo-1,2-dihydro-1,8-naphthyridin-4-yl)piperazine-1-carboxylate (210 mg, 0.36 mmol, one isomer) was added *o*-tolylboronic acid (54 mg, 0.4 mmol, Sigma-Aldrich Corporation), Pd(PPh₃)₄ (25 mg, 0.022 mmol), and potassium carbonate (99 mg, 0.72 mmol). The vial was evacuated under vacuum and then flushed with nitrogen. 1,4-Dioxane (897 μl) and water (299 μl) were then added and the reaction mixture was heated at 100°C for 1 h. The reaction mixture was cooled to RT, partitioned between EtOAc and brine. The aqueous layer was back extracted with EtOAc (2x) and the combined organics was dried (Na₂SO₄) and concentrated. The crude material was purified by chromatography on silica gel eluting with a gradient of 0% to 50% 3:1 EtOAc:EtOH in heptane, to provide *tert*-butyl 4-(6-chloro-3-cyano-1-(2,4-diisopropylpyridin-3-yl)-2-oxo-7-

(*o*-tolyl)-1,2-dihydro-1,8-naphthyridin-4-yl)piperazine-1-carboxylate (164 mg, 0.26 mmol, 71 % yield) as light-yellow solid. *m/z* (ESI, +ve ion): 641.3 (M+1).

[0208] **Step 3.** 4-(4-Acryloylpiperazin-1-yl)-6-chloro-1-(2,4-diisopropylpyridin-3-yl)-2-oxo-7-(*o*-tolyl)-1,2-dihydro-1,8-naphthyridine-3-carbonitrile To *tert*-butyl 4-(6-chloro-3-cyano-1-(2,4-diisopropylpyridin-3-yl)-2-oxo-7-(*o*-tolyl)-1,2-dihydro-1,8-naphthyridin-4-yl)piperazine-1-carboxylate (164 mg, 0.26 mmol) dissolved in dichloromethane (1.3 ml) was added trifluoroacetic acid (400 μ l, 5.4 mmol). The reaction mixture was stirred at RT for 1 h. The reaction mixture was concentrated *in vacuo* and the residue was re-dissolved in dichloromethane (1.3 mL) and 1,1'-dimethyltriethylamine (134 μ l, 0.77 mmol) was added followed by dropwise addition of acryloyl chloride (23 μ l, 0.28 mmol, Sigma-Aldrich Corporation) at 0°C. The reaction was stirred at 0°C for 30 min. The reaction mixture was purified by chromatography on silica gel eluting with a gradient of 0% to 60% EtOAc in heptane, to give 4-(4-acryloylpiperazin-1-yl)-6-chloro-1-(2,4-diisopropylpyridin-3-yl)-2-oxo-7-(*o*-tolyl)-1,2-dihydro-1,8-naphthyridine-3-carbonitrile (63 mg, 0.1 mmol, 41.4 % yield) as white solid. *m/z* (ESI, +ve ion): 595.3 (M+1). ¹H NMR (400 MHz, CHLOROFORM-*d*) δ 8.53 (d, *J*=5.18 Hz, 1H), 8.15 (s, 1H), 8.03 (s, 1H), 7.16 (d, *J*=7.67 Hz, 2H), 7.10 (d, *J*=5.18 Hz, 1H), 6.96 (d, *J*=7.46 Hz, 1H), 6.57-6.66 (m, 1H), 6.39 (dd, *J*=1.76, 16.69 Hz, 1H), 5.81 (dd, *J*=1.76, 10.47 Hz, 1H), 3.72-4.02 (m, 8H), 2.52 (quin, *J*=6.63 Hz, 1H), 2.38-2.46 (m, 1H), 1.94 (s, 3H), 1.16 (dd, *J*=6.74, 11.09 Hz, 6H), 0.97 (d, *J*=6.84 Hz, 3H), 0.92 (d, *J*=6.84 Hz, 3H).

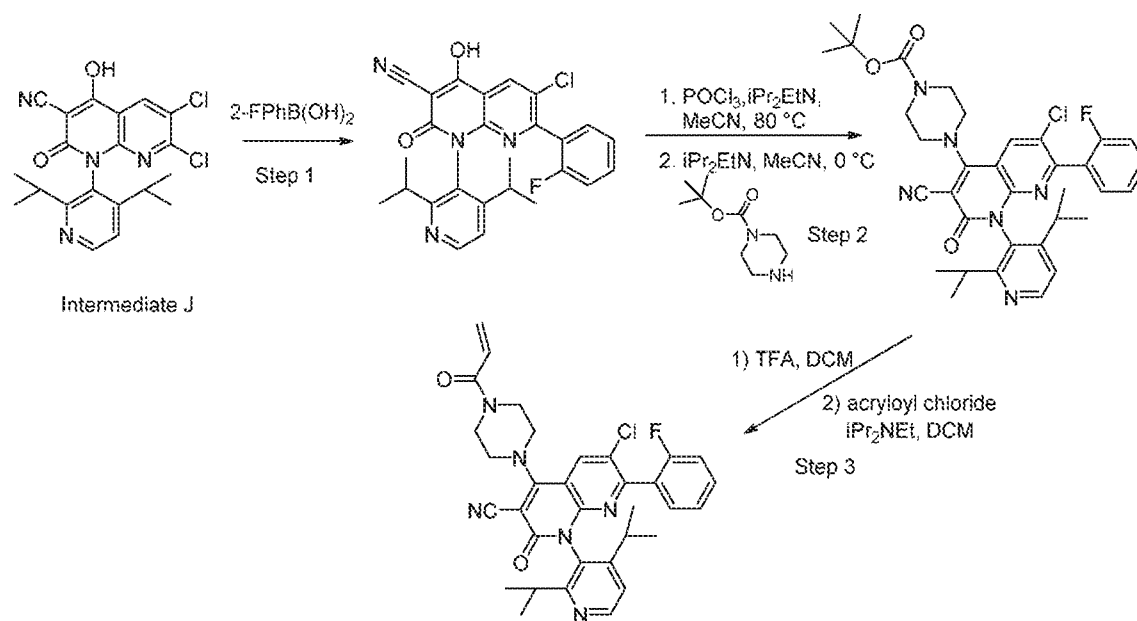
Table 5: List of compounds prepared according to the described route

Ex.#	Chemical Structure	Name	Reagent and method change
7.1		4-(4-acryloylpiperazin-1-yl)-6-chloro-1-(2,4-diisopropylpyridin-3-yl)-2-oxo-7-(<i>o</i> -tolyl)-1,2-dihydro-1,8-naphthyridine-3-carbonitrile	Step 2 use the other atropisomeric intermediate
7.2		4-((2 <i>S</i> ,5 <i>R</i>)-4-acryloyl-2,5-dimethylpiperazin-1-yl)-6-chloro-7-(2-fluorophenyl)-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile	Step 1 Use Intermediate L No chiral separation Step 2 use 2-fluorophenylboronic acid Step 3 use <i>tert</i> -butyl (2 <i>R</i> ,5 <i>S</i>)-2,5-dimethylpiperazine-1-carboxylate,

			Enovation Chem., LLC, Bridgewater, NJ
7.3		4-((3 <i>R</i> ,5 <i>S</i>)-4-acryloyl-3,5-dimethylpiperazin-1-yl)-6-chloro-7-(2-fluorophenyl)-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile	Step 1 Use Intermediate L No chiral separation Step 2 use 2-fluorophenylboronic acid Step 3 use <i>tert</i> -butyl (2 <i>R</i> ,6 <i>S</i>)-2,6-dimethylpiperazine-1-carboxylate ArkPharma, Arlington Heights, IL

Example 8

Racemic 4-(4-Acryloylpiperazin-1-yl)-6-chloro-1-(2,4-diisopropylpyridin-3-yl)-7-(2-fluorophenyl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile



[0209] Step 1: 6-Chloro-1-(2,4-diisopropylpyridin-3-yl)-7-(2-fluorophenyl)-4-hydroxy-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile. To 6,7-dichloro-1-(2,4-diisopropylpyridin-3-yl)-4-hydroxy-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile (Intermediate J, 335 mg, 0.8 mmol), potassium carbonate (222 mg, 1.6 mmol), Pd(PPh₃)₄ (56

mg, 0.048 mmol, Sigma-Aldrich, St. Louis, MO), and 2-fluorobenzeneboronic acid (124 mg, 0.9 mmol) was added 1,4-dioxane (2 ml) and water (669 μ l) and the reaction mixture was heated at 100°C for 3 h. The reaction mixture was cooled to RT, partitioned between EtOAc and brine. The aqueous layer was back extracted with EtOAc (2x) and the combined organics was dried (Na_2SO_4) and concentrated. The crude material was purified by chromatography on silica gel column eluting with a gradient of 0% to 50% 3:1 EtOAc/EtOH in heptane, to provide 6-chloro-1-(2,4-diisopropylpyridin-3-yl)-7-(2-fluorophenyl)-4-hydroxy-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile (326 mg, 0.68 mmol, 85 % yield) as yellow solid. m/z (ESI, +ve ion): 477.2 (M+1).

[0210] **Step 2:** *tert*-Butyl 4-(6-chloro-3-cyano-1-(2,4-diisopropylpyridin-3-yl)-7-(2-fluorophenyl)-2-oxo-1,2-dihydro-1,8-naphthyridin-4-yl)piperazine-1-carboxylate. To 6-chloro-1-(2,4-diisopropylpyridin-3-yl)-7-(2-fluorophenyl)-4-hydroxy-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile (326 mg, 0.7 mmol), diisopropylethylamine (358 μ l, 2.0 mmol), and POCl_3 (96 μ l, 1.0 mmol) was added CH_3CN (2.3 mL). The reaction mixture was heated at 80 °C for 1 h. The reaction mixture was allowed to cool to room temperature and the solvent was removed under vacuum. The residue was re-dissolved in CH_3CN (2.3 mL) and diisopropylethylamine (358 μ l, 2.0 mmol) was added. The reaction was cooled to 0 °C and 1-Boc-piperazine (166 mg, 0.9 mmol, Sigma-Aldrich, St. Louis, MO) was added in one portion. After stirring at RT for 2 h, saturated NaHCO_3 was added and the aqueous layer was extracted with EtOAc (3x). The organic extract was washed with water and dried over Na_2SO_4 , filtered and concentrated *in vacuo*. The crude material was purified by chromatography on silica gel eluting with a gradient of 0% to 25 % EtOAc:EtOH (3:1) in heptanes to provide *tert*-butyl 4-(6-chloro-3-cyano-1-(2,4-diisopropylpyridin-3-yl)-7-(2-fluorophenyl)-2-oxo-1,2-dihydro-1,8-naphthyridin-4-yl)piperazine-1-carboxylate (270 mg, 0.4 mmol, 61 % yield) as orange solid. m/z (ESI, +ve ion): 645.2 (M+1).

[0211] **Step 3: Racemic 4-(4-acryloylpiperazin-1-yl)-6-chloro-1-(2,4-diisopropylpyridin-3-yl)-7-(2-fluorophenyl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile** *tert*-Butyl 4-(6-chloro-3-cyano-1-(2,4-diisopropylpyridin-3-yl)-7-(2-fluorophenyl)-2-oxo-1,2-dihydro-1,8-naphthyridin-4-yl)piperazine-1-carboxylate (0.52 g, 0.8 mmol) in dichloromethane (4.1 ml) was stirred with trifluoroacetic acid (1.3 ml, 17.4 mmol) for 1 h. The mixture was concentrated *in vacuo* and the residue was re-dissolved in dichloromethane (2 mL). 1,1'-Dimethyltriethylamine (0.43 ml, 2.4 mmol) was added followed by dropwise addition of acryloyl chloride (0.073 ml, 0.9 mmol) at 0°C. The reaction was stirred at 0°C for 30 min. The reaction mixture was purified by chromatography on silica gel eluting

with a gradient of 0% to 50% 3:1 EtOAc/EtOH in hexane, to give 4-(4-acryloylpiperazin-1-yl)-6-chloro-1-(2,4-diisopropylpyridin-3-yl)-7-(2-fluorophenyl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile (0.23 g, 0.19 mmol, 46 % yield). m/z (ESI, +ve ion): 599.3 (M+1). ^1H NMR (400 MHz, CHLOROFORM-*d*) δ 8.67 (d, $J=5.39$ Hz, 1H), 8.18 (s, 1H), 7.36-7.46 (m, 1H), 7.22 (d, $J=5.18$ Hz, 1H), 7.03-7.18 (m, 3H), 6.64 (dd, $J=10.57, 16.79$ Hz, 1H), 6.41 (dd, $J=1.66, 16.79$ Hz, 1H), 5.84 (dd, $J=1.66, 10.57$ Hz, 1H), 3.78-4.10 (m, 8H), 2.57 (td, $J=6.82, 13.53$ Hz, 1H), 2.47 (td, $J=6.84, 13.68$ Hz, 1H), 1.23 (d, $J=6.84$ Hz, 3H), 1.18 (d, $J=6.84$ Hz, 3H), 1.02 (d, $J=6.84$ Hz, 3H), 0.95 (d, $J=6.84$ Hz, 3H).

Examples 8.1 and 8.2: The above material (Example 8) was purified by preparative SFC Purification [OX-H (5 μ m, 21x250 mm), F=8 0ml, 30% methanol, 70% carbon dioxide, back pressure= 90 bar, 1.0 ml injection] to give:

Example 8.1 as peak 1: 14-(4-acryloylpiperazin-1-yl)-6-chloro-1-(2,4-diisopropylpyridin-3-yl)-7-(2-fluorophenyl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile as off-white solid, chemical purity: > 99.0%, D.E. > 99.0%; m/z (ESI, +ve ion): 599.3 (M+1). ^1H NMR (400 MHz, CHLOROFORM-*d*) δ 8.58 (d, $J=5.18$ Hz, 1H), 8.17 (s, 1H), 7.36-7.47 (m, 1H), 7.05-7.19 (m, 4H), 6.64 (dd, $J=10.37, 16.79$ Hz, 1H), 6.41 (dd, $J=1.66, 16.79$ Hz, 1H), 5.83 (dd, $J=1.76, 10.47$ Hz, 1H), 3.78-4.08 (m, 8H), 2.48-2.60 (m, 1H), 2.38-2.48 (m, 1H), 1.18 (dd, $J=6.84, 10.78$ Hz, 6H), 0.90-1.02 (m, 6H). ^{19}F NMR (376 MHz, CHLOROFORM-*d*) δ -113.03 (s, 1F).

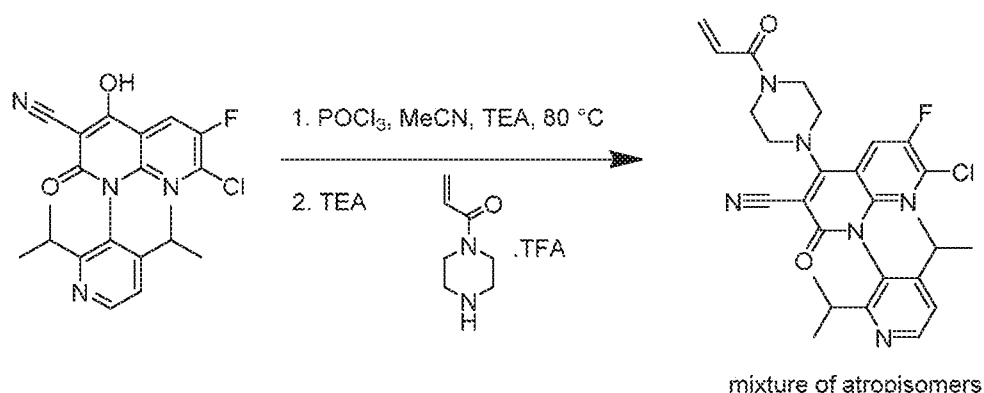
Example 8.2 as peak 2: 4-(4-acryloylpiperazin-1-yl)-6-chloro-1-(2,4-diisopropylpyridin-3-yl)-7-(2-fluorophenyl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile as off-white solid, chemical purity >99.0%, D.E. 98.2%. m/z (ESI, +ve ion): 599.3 (M+1). ^1H NMR (400 MHz, CHLOROFORM-*d*) δ 8.58 (d, $J=5.18$ Hz, 1H), 8.17 (s, 1H), 7.34-7.47 (m, 1H), 7.03-7.19 (m, 4H), 6.64 (dd, $J=10.57, 16.79$ Hz, 1H), 6.41 (dd, $J=1.66, 16.79$ Hz, 1H), 5.83 (dd, $J=1.76, 10.47$ Hz, 1H), 3.76-4.12 (m, 8H), 2.49-2.63 (m, 1H), 2.37-2.49 (m, 1H), 1.18 (dd, $J=6.74, 10.68$ Hz, 6H), 0.90-1.02 (m, 6H). ^{19}F NMR (376 MHz, CHLOROFORM-*d*) δ -113.03 (s, 1F).

Table 6: List of compounds prepared according to the described route

Ex.#	Chemical Structure	Name	Reagents
8.3		4-(4-acryloylpiperazin-1-yl)-6-chloro-1-(4-(dimethylamino)-2-isopropylpyridin-3-yl)-7-(2-fluorophenyl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile	Intermediate M
8.4		4-(4-acryloylpiperazin-1-yl)-6-chloro-1-(2-(dimethylamino)-4-isopropylpyridin-3-yl)-7-(2-fluorophenyl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile	Intermediate N

Example 9

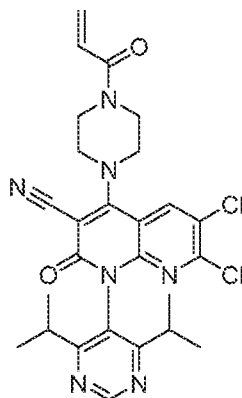
4-(4-Acryloylpiperazin-1-yl)-7-chloro-1-(2,4-diisopropylpyridin-3-yl)-6-fluoro-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile



[0212] Phosphorous oxychloride (0.334 mL, 3.57 mmol) was added dropwise to a solution of 7-chloro-1-(2,4-diisopropylpyridin-3-yl)-6-fluoro-4-hydroxy-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile (**Intermediate K**, 1.1 g, 2.7 mmol) and triethylamine (1.157 mL, 8.23 mmol) in acetonitrile (10 mL) under argon. The mixture was heated to 80 °C for 1 h and concentrated *in vacuo*. The residue was dissolved in acetonitrile (10 mL) and treated with triethylamine (7.71 mL, 54.9 mmol) and 1-(piperazin-1-yl)prop-2-en-1-one bis(2,2,2-trifluoroacetate) (1.314 g, 3.57 mmol, eNovation, LLC). The reaction mixture was stirred at

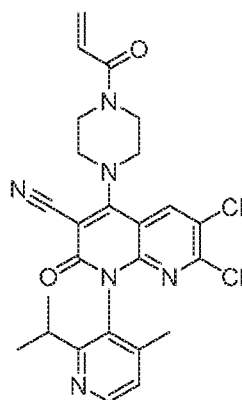
RT for 12 hours, diluted with water, and extracted with EtOAc (2X). The organic extracts were combined, concentrated *in vacuo* and the residue was purified by chromatography on silica gel eluting with 0-80% EtOAc/EtOH (3:1) in heptane to afford 4-(4-acryloylpiperazin-1-yl)-7-chloro-1-(2,4-diisopropylpyridin-3-yl)-6-fluoro-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile (0.102 g, 0.098 mmol) as a mixture of atropisomers. ^1H NMR (400 MHz, CHLOROFORM-*d*) δ 8.71 (d, $J=5.18$ Hz, 1H), 7.88 (d, $J=7.67$ Hz, 1H), 7.26-7.29 (m, 1H), 6.66 (dd, $J=10.57, 16.79$ Hz, 1H), 6.40-6.47 (m, 1H), 5.86 (dd, $J=1.66, 10.57$ Hz, 1H), 3.99 (br s, 4H), 3.71-3.90 (m, 4H), 2.36-2.54 (m, 2H), 1.24 (d, $J=6.63$ Hz, 3H), 1.21 (d, $J=6.63$ Hz, 3H), 1.09 (d, $J=6.63$ Hz, 3H), 1.04 (d, $J=6.84$ Hz, 3H). ^{19}F NMR (376 MHz, CHLOROFORM-*d*) δ -124.74 (s, 1F). m/z (ESI, +ve ion): 523.1 (M+H) $^+$.

[0213] Example 9.1 4-(4-acryloylpiperazin-1-yl)-6,7-dichloro-1-(4,6-diisopropylpyrimidin-5-yl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile



[0214] The compound was prepared from Intermediate I according to the procedure for Example 9. ^1H NMR (400 MHz, DMSO-*d*₆) δ ppm 0.93 - 1.01 (m, 6 H) 1.05 - 1.12 (m, 6 H) 2.61 - 2.75 (m, 2 H) 3.72 - 3.95 (m, 8 H) 5.62 - 5.97 (m, 1 H) 6.10 - 6.38 (m, 1 H) 6.83 - 7.01 (m, 1 H) 8.36 - 8.73 (m, 1 H) 8.97 - 9.77 (m, 1 H). m/z (ESI, +ve ion): 539.8 (M+H) $^+$.

Example 9.2 4-(4-acryloylpiperazin-1-yl)-6,7-dichloro-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile.

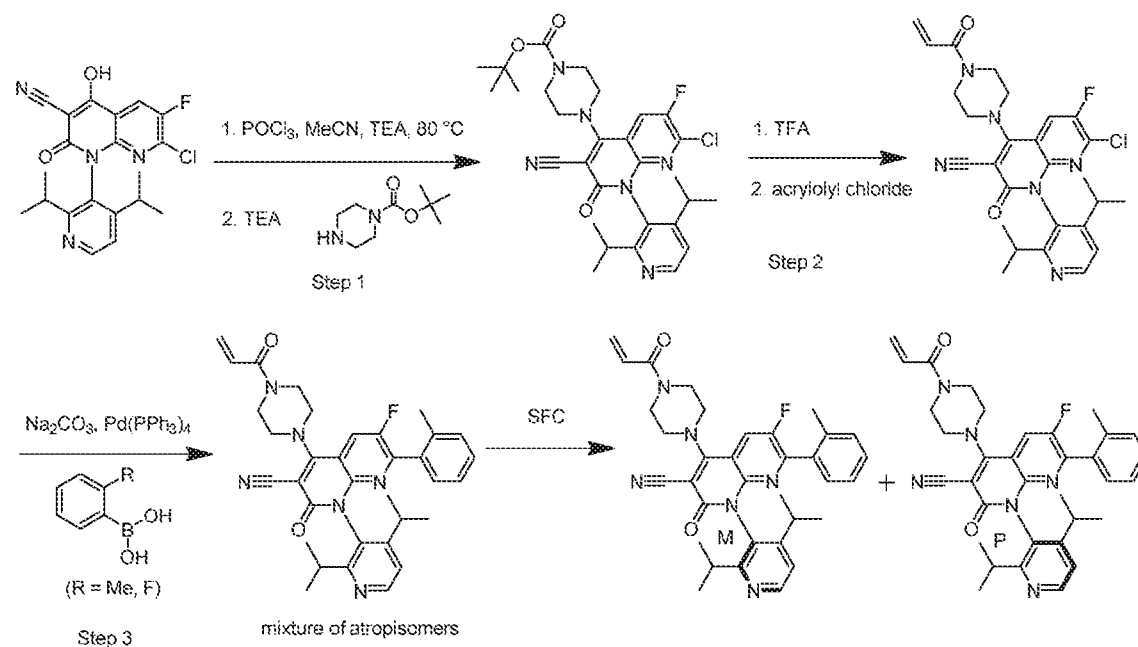


The compound was prepared from Intermediate L according to the procedure for Example 9.

^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm 0.95 - 1.02 (m, 3 H) 1.04 - 1.11 (m, 3 H) 1.89 - 1.96 (m, 3 H) 2.56 - 2.70 (m, 1 H) 3.74 - 3.95 (m, 8 H) 5.70 - 5.83 (m, 1 H) 6.10 - 6.28 (m, 1 H) 6.82 - 6.99 (m, 1 H) 7.26 - 7.36 (m, 1 H) 8.46 - 8.56 (m, 2 H). m/z (ESI, +ve ion): 511.1 (M+H)⁺.

Example 10

4-(4-Acryloylpiperazin-1-yl)-1-(2,4-diisopropylpyridin-3-yl)-6-fluoro-2-oxo-7-(o-tolyl)-1,2-dihydro-1,8-naphthyridine-3-carbonitrile



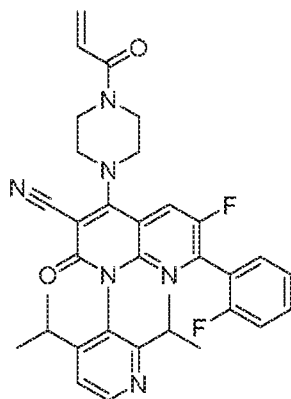
[0215] **Step 1:** *tert*-Butyl 4-(7-chloro-3-cyano-1-(2,4-diisopropylpyridin-3-yl)-6-fluoro-2-oxo-1,2-dihydro-1,8-naphthyridin-4-yl)piperazine-1-carboxylate. Following the procedure described in example 9, 1-(*t*-butoxycarbonyl)-piperazine (0.657 g, 3.5 mmol, Sigma-Aldrich, St. Louis, MO) was used to afford *tert*-butyl 4-(7-chloro-3-cyano-1-(2,4-diisopropylpyridin-3-yl)-6-fluoro-2-oxo-1,2-dihydro-1,8-naphthyridin-4-yl)piperazine-1-carboxylate (0.71 g, 1.2 mmol, 49 % yield). *m/z* (ESI, +ve ion): 569.3 (M+H)⁺.

[0216] **Step 2:** 4-(4-Acryloylpiperazin-1-yl)-7-chloro-1-(2,4-diisopropylpyridin-3-yl)-6-fluoro-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile. TFA (1.86 mL, 24.9 mmol) was added to a solution of *tert*-butyl 4-(7-chloro-3-cyano-1-(2,4-diisopropylpyridin-3-yl)-6-fluoro-2-oxo-1,2-dihydro-1,8-naphthyridin-4-yl)piperazine-1-carboxylate (0.71 g, 1.2 mmol) in dichloromethane (5 mL). The resulting mixture was stirred at rt for 1 hour and then concentrated *in vacuo*. The residue was suspended in DCM (5 mL) and treated with TEA (0.710 mL, 5 mmol) followed by acryloyl chloride (0.16 mL, 2 mmol). The reaction was stirred at rt for 10 minutes, quenched with water, and extracted with EtOAc (2X). The organic layers were combined, concentrated, and the residue purified by chromatography on silica gel eluting with 0-80% EtOAc/EtOH (3:1) in heptane to afford 4-(4-acryloylpiperazin-1-yl)-7-chloro-1-(2,4-diisopropylpyridin-3-yl)-6-fluoro-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile (0.610 g, 1.1 mmol, 93 % yield). ¹H NMR (400 MHz, CHLOROFORM-*d*) δ 8.69 (d, *J*=5.18 Hz, 1H), 7.86 (d, *J*=7.67 Hz, 1H), 7.23-7.26 (m, 1H), 6.62 (dd, *J*=10.57, 16.79 Hz, 1H), 6.40 (dd, *J*=1.76, 16.69 Hz, 1H), 5.83 (dd, *J*=1.66, 10.57 Hz, 1H), 3.96 (br s, 4H), 3.78 (br s, 4H), 2.32-2.52 (m, 2H), 1.22 (br d, *J*=6.63 Hz, 3H), 1.18 (d, *J*=6.63 Hz, 3H), 1.07 (br d, *J*=6.43 Hz, 3H), 1.01 (d, *J*=6.84 Hz, 3H). ¹⁹F NMR (376 MHz, CHLOROFORM-*d*) δ -124.72 (s, 1F). *m/z* (ESI, +ve ion): 523.1 (M+H)⁺.

[0217] **Step 3:** 4-(4-Acryloylpiperazin-1-yl)-1-(2,4-diisopropylpyridin-3-yl)-6-fluoro-2-oxo-7-(*o*-tolyl)-1,2-dihydro-1,8-naphthyridine-3-carbonitrile. A mixture of 4-(4-acryloylpiperazin-1-yl)-7-chloro-1-(2,4-diisopropylpyridin-3-yl)-6-fluoro-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile (0.250 g, 0.478 mmol), *o*-tolylboronic acid (0.097 g, 0.717 mmol, Sigma-Aldrich Corporation), sodium carbonate (0.15 g, 1.4 mmol) and tetrakis(triphenylphosphine)palladium(0) (0.055 g, 0.048 mmol) in 1,4-dioxane (3 mL)/ water (2 mL) was stirred at 90 °C for 1 h. The reaction mixture was diluted with water and extracted with EtOAc. The organic was concentrated and the residue purified by chromatography on silica gel eluting with 0-90% EtOAc/EtOH (3:1) in heptane to afford 4-(4-acryloylpiperazin-1-yl)-1-(2,4-diisopropylpyridin-3-yl)-6-fluoro-2-oxo-7-(*o*-tolyl)-1,2-dihydro-1,8-naphthyridine-3-carbonitrile (0.11 g, 0.09 mmol, 19 % yield) as a mixture of atropisomers. ¹H

NMR (400 MHz, CHLOROFORM-*d*) δ 8.58 (br d, $J=4.98$ Hz, 1H), 7.86 (d, $J=9.12$ Hz, 1H), 7.26-7.32 (m, 1H), 7.09-7.23 (m, 4H), 6.62 (dd, $J=10.57, 16.79$ Hz, 1H), 6.35-6.44 (m, 1H), 5.81 (dd, $J=1.66, 10.57$ Hz, 1H), 3.91-4.06 (m, 4H), 3.82 (br s, 4H), 2.39-2.60 (m, 2H), 1.98 (s, 3H), 1.13-1.22 (m, 6H), 0.97 (br d, $J=6.01$ Hz, 3H), 0.91 (d, $J=6.63$ Hz, 3H). ^{19}F NMR (376 MHz, CHLOROFORM-*d*) δ -126.76 (s, 1F). m/z (ESI, +ve ion): 579.4 (M+H) $^{+}$.

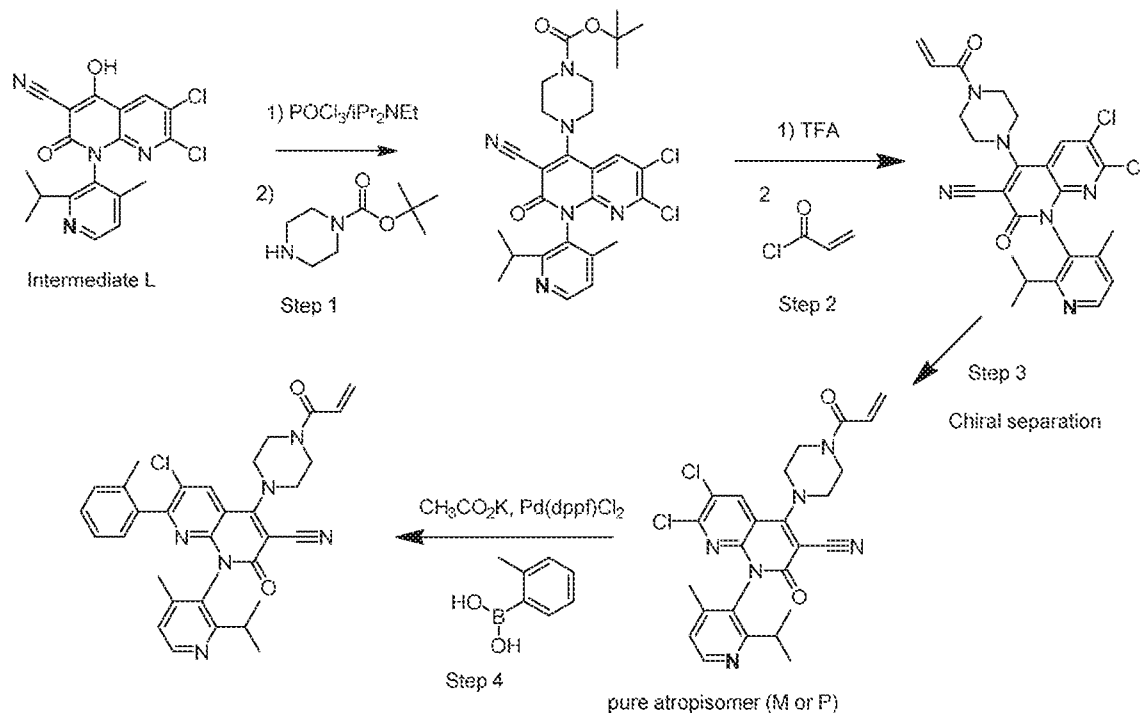
Example 10.1 4-(4-acryloylpiperazin-1-yl)-1-(2,4-diisopropylpyridin-3-yl)-6-fluoro-7-(2-fluorophenyl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile.



[0218] The compound was prepared according to the procedure of Example 10 using 2-fluorophenylboronic acid (Sigma-Aldrich, St. Louis, MO). ^1H NMR (400 MHz, CHLOROFORM-*d*) δ 8.65 (d, $J=5.18$ Hz, 1H), 7.92 (d, $J=9.12$ Hz, 1H), 7.38-7.49 (m, 1H), 7.11-7.26 (m, 4H), 6.66 (dd, $J=10.57, 16.79$ Hz, 1H), 6.34-6.50 (m, 1H), 5.85 (dd, $J=1.76, 10.47$ Hz, 1H), 3.94-4.11 (m, 4H), 3.86 (br s, 4H), 2.44-2.63 (m, 2H), 1.18-1.26 (m, 6H), 1.02 (br d, $J=6.63$ Hz, 3H), 0.96 (d, $J=6.84$ Hz, 3H). ^{19}F NMR (376 MHz, CHLOROFORM-*d*) δ -112.53 - -112.64 (s, 1F), -125.66 - -125.77 (s, 1F) (signals split due to the presence of atropisomers). m/z (ESI, +ve ion): 583.4 (M+H) $^{+}$.

Example 11

4-(4-Acryloylpiperazin-1-yl)-6-chloro-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-7-(o-tolyl)-1,2-dihydro-1,8-naphthyridine-3-carbonitrile



[0219] Step 1: *tert*-Butyl 4-(6,7-dichloro-3-cyano-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-1,2-dihydro-1,8-naphthyridin-4-yl)piperazine-1-carboxylate. The compound was prepared from Intermediate L according to the procedure described for Intermediate 9.

[0220] Step 2: 4-(4-Acryloylpiperazin-1-yl)-6,7-dichloro-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile. To *tert*-butyl 4-(6,7-dichloro-3-cyano-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-1,2-dihydro-1,8-naphthyridin-4-yl)piperazine-1-carboxylate (6.26 g, 11.2 mmol) in 20 ml DCM was added 15 ml TFA. The mixture was stirred for 15 min and evaporated. DCM (5x20 ml) was added and evaporated. The residue was dried *in vacuo*, dissolved in 40 ml DCM and cooled in an ice water bath. Diisopropylethylamine (13ml, 74.4 mmol) and acryloyl chloride (1.5 ml, 18.4 mmol) was added. After 10 min 100 ml DCM and 50 ml brine were added and the two layers were separated. The organic layer was dried, evaporated and purified by chromatography on silica gel eluting with 25%-70% (3/1 EtOAc/EtOH)/hep to give 4-(4-acryloylpiperazin-1-yl)-6,7-dichloro-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 0.95 - 1.02 (m, 3 H) 1.04 - 1.11 (m, 3 H) 1.89 - 1.96 (m, 3 H) 2.56 - 2.70 (m, 1 H) 3.74 - 3.95 (m, 8 H) 5.70 - 5.83 (m, 1 H) 6.10 - 6.28

(m, 1 H) 6.82 - 6.99 (m, 1 H) 7.26 - 7.36 (m, 1 H) 8.46 - 8.56 (m, 2 H). m/z (ESI, +ve ion): 511.1 (M+H)⁺.

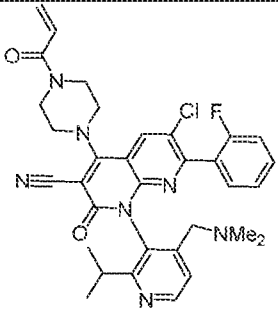
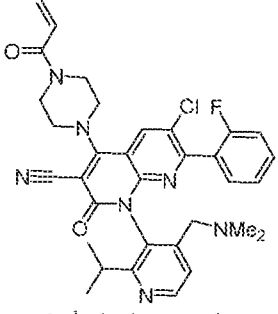
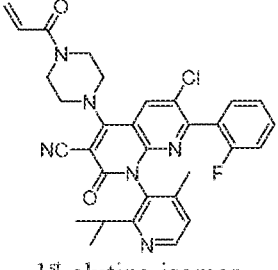
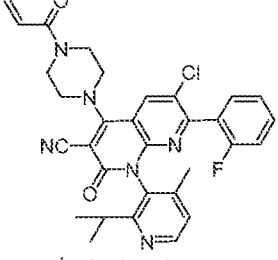
[0221] Step 3: 4-(4-Acryloylpiperazin-1-yl)-6,7-dichloro-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile single atropisomers. 4-(4-Acryloylpiperazin-1-yl)-6,7-dichloro-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile was purified by was purified via preparative SFC using an OX (250 X 30 mm, 5u), a mobile phase of 30% iPrOH:ACN 1:1 mixture using a flowrate of 150 mL/min. to generate peak 1 with an ee of >99% (chemical purity >99%) and peak 2 with an ee of 97.53% (chemical purity 97.53%). Peak assignment determined by SFC with OX column using 30% iPrOH:ACN 1:1 mixture.

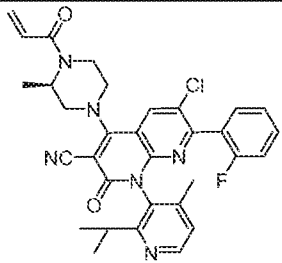
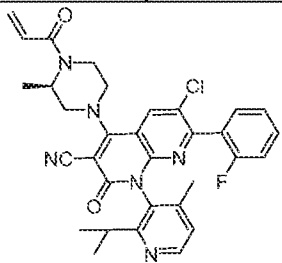
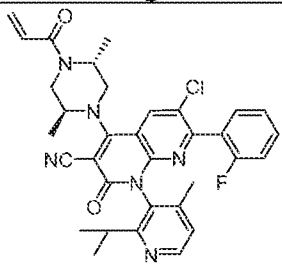
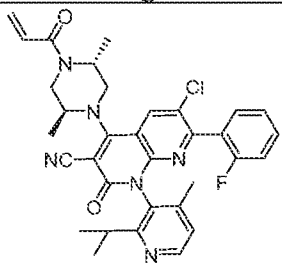
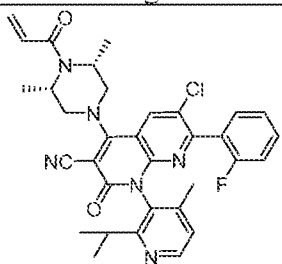
[0222] Step 4: 4-(4-Acryloylpiperazin-1-yl)-6-chloro-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-7-(o-tolyl)-1,2-dihydro-1,8-naphthyridine-3-carbonitrile. A mixture of 4-(4-acryloylpiperazin-1-yl)-6,7-dichloro-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile, first eluting peak from SFC separation (0.156 g, 0.305 mmol), *o*-tolylboronic acid (0.050 g, 0.36 mmol), potassium acetate (0.090 g, 0.9 mmol), and (1,1'-bis(diphenylphosphino) ferrocene) dichloropalladium (0.022 g, 0.03 mmol) in 1,4-dioxane (1 mL)/water (0.4 mL) was stirred at 90 °C for 1 h. The resulting mixture was diluted with water and extracted with EtOAc (2X). The organic was concentrated *in vacuo* and the residue purified by chromatography on silica gel eluting with 0-80% EtOAc/EtOH, (3:1) in heptane to afford 4-(4-acryloylpiperazin-1-yl)-6-chloro-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-7-(o-tolyl)-1,2-dihydro-1,8-naphthyridine-3-carbonitrile (0.021 g, 0.037 mmol, 12% yield). ¹H NMR (400 MHz, CHLOROFORM-*d*) δ 8.48 (d, *J*=4.77 Hz, 1H), 8.18 (s, 1H), 7.28-7.32 (m, 1H), 7.14-7.22 (m, 2H), 7.01-7.12 (m, 2H), 6.64 (dd, *J*=10.57, 16.79 Hz, 1H), 6.40 (dd, *J*=1.66, 16.79 Hz, 1H), 5.82 (dd, *J*=1.55, 10.47 Hz, 1H), 3.99 (br s, 4H), 3.84 (br s, 4H), 2.49-2.65 (m, 1H), 1.97 (d, *J*=6.63 Hz, 6H), 1.19 (d, *J*=6.63 Hz, 3H), 0.98 (d, *J*=6.63 Hz, 3H). m/z (ESI, +ve ion): 567.4 (M+H)⁺.

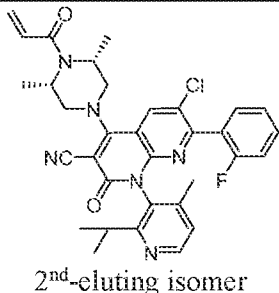
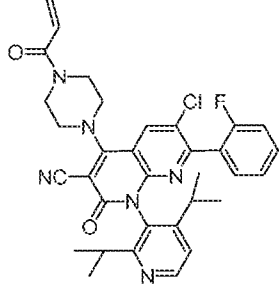
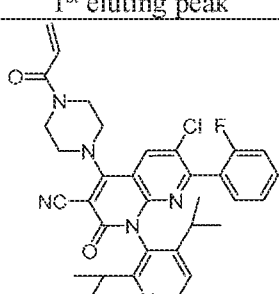
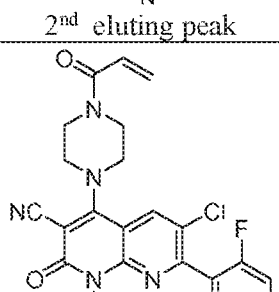
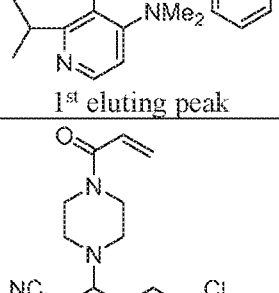
Table 7: List of compounds prepared according to the described route

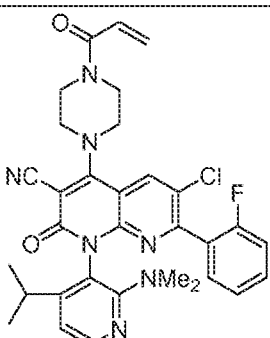
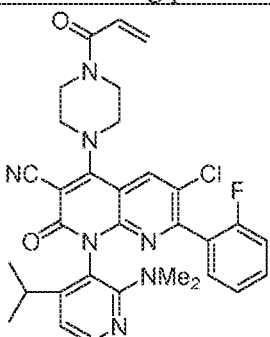
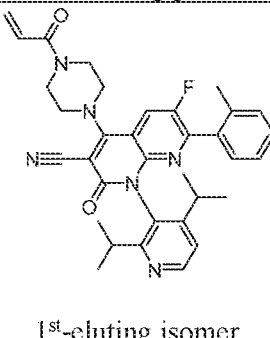
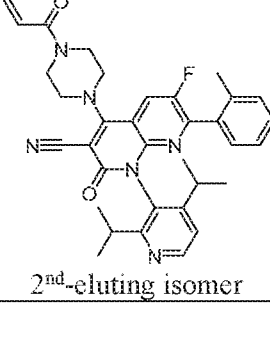
Ex.#	Chemical Structure	Name	Reagents
11.1		4-(4-acryloylpiperazin-1-yl)-6-chloro-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-7-(o-tolyl)-1,2-dihydro-1,8-naphthyridine-3-carbonitrile	4-(4-acryloylpiperazin-1-yl)-6,7-dichloro-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile (second eluting peak) and o-tolylboronic acid
11.2		4-(4-acryloylpiperazin-1-yl)-6-chloro-1-(2-isopropyl-4-methylpyridin-3-yl)-7-(2-isopropylphenyl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile	4-(4-acryloylpiperazin-1-yl)-6,7-dichloro-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile (first eluting peak) and [2-(1-methylethyl)phenyl]-boronic acid (Combi-Blocks Inc.)
11.3		4-(4-acryloylpiperazin-1-yl)-6-chloro-1-(2-isopropyl-4-methylpyridin-3-yl)-7-(2-isopropylphenyl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile	4-(4-acryloylpiperazin-1-yl)-6,7-dichloro-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile (second eluting peak) and [2-(1-methylethyl)phenyl]-boronic acid
11.4		4-(4-acryloylpiperazin-1-yl)-7-(2-amino-6-fluorophenyl)-6-chloro-1-(4,6-diisopropylpyrimidin-5-yl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile	Using Ex.9.1 and (2-amino-6-fluorophenyl)boronic acid pinacol ester

Table 8. Chiral Separated Compound Examples

Ex.#	Chemical Structure	Name	Racemic SM / separation conditions
2.1	 1st eluting peak	4-(4-acryloylpiperazin-1-yl)-6-chloro-1-(4-((dimethylamino)methyl)-2-isopropylpyridin-3-yl)-7-(2-fluorophenyl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile	SFC: OX, 250 X 21 mm, 5 μ m, 55:45 CO ₂ : (methanol/0.2% TEA), 70 g/min, 102 bar
2.2	 2nd eluting peak	4-(4-acryloylpiperazin-1-yl)-6-chloro-1-(4-((dimethylamino)methyl)-2-isopropylpyridin-3-yl)-7-(2-fluorophenyl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile	SFC: OX, 250 X 21 mm, 5 μ m, 55:45 CO ₂ : (methanol/0.2% TEA), 70 g/min, 102 bar
6.4	 1st-eluting isomer	4-(4-acryloylpiperazin-1-yl)-6-chloro-7-(2-fluorophenyl)-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile	SFC: AS-H, 21 x 250 mm, 5 μ m, 20% MeOH in CO ₂ , 80 g/min, 100 bar
6.5	 2nd-eluting isomer	4-(4-acryloylpiperazin-1-yl)-6-chloro-7-(2-fluorophenyl)-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile	SFC: AS-H, 21 x 250 mm, 5 μ m, 20% MeOH in CO ₂ , 80 g/min, 100 bar

6.6	 1st-eluting isomer	(<i>R</i>)-4-(4-acryloyl-3-methylpiperazin-1-yl)-6-chloro-7-(2-fluorophenyl)-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile	SFC: OX-H, 21 x 250 mm, 5 μm, 40% MeOH in CO ₂ , 80 g/min, 100 bar
6.7	 2nd-eluting isomer	(<i>R</i>)-4-(4-acryloyl-3-methylpiperazin-1-yl)-6-chloro-7-(2-fluorophenyl)-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile	SFC: OX-H, 21 x 250 mm, 5 μm, 40% MeOH in CO ₂ , 80 g/min, 100 bar
7.4	 1st-eluting isomer	4-((2 <i>S</i> ,5 <i>R</i>)-4-acryloyl-2,5-dimethylpiperazin-1-yl)-6-chloro-7-(2-fluorophenyl)-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile	SFC: Chirapak ID, 21 x 250 mm, 5 μm, 25% MeOH in CO ₂ , 70 g/min, 151 bar
7.5	 2nd-eluting isomer	4-((2 <i>S</i> ,5 <i>R</i>)-4-acryloyl-2,5-dimethylpiperazin-1-yl)-6-chloro-7-(2-fluorophenyl)-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile	SFC: Chirapak ID, 21 x 250 mm, 5 μm, 25% MeOH in CO ₂ , 70 g/min, 151 bar
7.6	 1st-eluting isomer	4-((3 <i>R</i> ,5 <i>S</i>)-4-acryloyl-3,5-dimethylpiperazin-1-yl)-6-chloro-7-(2-fluorophenyl)-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile	SFC: OD-H, 21 x 250 mm, 5 μm, 40% MeOH in CO ₂ , 80 g/min, 120 bar

7.7	 2nd-eluting isomer	4-((3 <i>R</i> ,5 <i>S</i>)-4-acryloyl-3,5-dimethylpiperazin-1-yl)-6-chloro-7-(2-fluorophenyl)-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile	SFC: OD-H, 21 x 250 mm, 5 μ m, 40% MeOH in CO ₂ , 80 g/min, 120 bar
8.1	 1st eluting peak	4-(4-acryloylpiperazin-1-yl)-6-chloro-1-(2,4-diisopropylpyridin-3-yl)-7-(2-fluorophenyl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile	SFC: OD-H, 21 x 250 mm, 5 μ m, 30% MeOH in CO ₂ , 80 g/min, 90 bar
8.2	 2nd eluting peak	4-(4-acryloylpiperazin-1-yl)-6-chloro-1-(2,4-diisopropylpyridin-3-yl)-7-(2-fluorophenyl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile	SFC: OD-H, 21 x 250 mm, 5 μ m, 30% MeOH in CO ₂ , 80 g/min, 90 bar
8.5	 1st eluting peak	4-(4-acryloylpiperazin-1-yl)-6-chloro-1-(4-(dimethylamino)-2-isopropylpyridin-3-yl)-7-(2-fluorophenyl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile	SFC: OD-H, 21 x 250 mm, 5 μ m, 25% MeOH with 0.2% TEA, 75% CO ₂ , 80 g/min, 90 bar
8.6		4-(4-acryloylpiperazin-1-yl)-6-chloro-1-(4-(dimethylamino)-2-isopropylpyridin-3-yl)-7-(2-fluorophenyl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile	SFC: OD-H, 21 x 250 mm, 5 μ m, 25% MeOH with 0.2% TEA, 75% CO ₂ , 80 g/min, 90 bar

	2 nd eluting peak		
8.7	 1 st eluting peak	4-(4-acryloylpiperazin-1-yl)-6-chloro-1-(2-(dimethylamino)-4-isopropylpyridin-3-yl)-7-(2-fluorophenyl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile	SFC: OD-H, 21 x 250 mm, 5 μm, 25% MeOH with 0.2% TEA, 75% CO ₂ , 80 g/min, 90 bar
8.8	 2 nd eluting peak	4-(4-acryloylpiperazin-1-yl)-6-chloro-1-(2-(dimethylamino)-4-isopropylpyridin-3-yl)-7-(2-fluorophenyl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile	SFC: OD-H, 21 x 250 mm, 5 μm, 25% MeOH with 0.2% TEA, 75% CO ₂ , 80 g/min, 90 bar
10.2	 1 st -eluting isomer	4-(4-acryloylpiperazin-1-yl)-1-(2,4-diisopropylpyridin-3-yl)-6-fluoro-2-oxo-7-(o-tolyl)-1,2-dihydro-1,8-naphthyridine-3-carbonitrile	SFC: OD-H, 21 x 250 mm, 5 μm, 40% MeOH in CO ₂ , 80 g/min, 120 bar
10.3	 2 nd -eluting isomer	4-(4-acryloylpiperazin-1-yl)-1-(2,4-diisopropylpyridin-3-yl)-6-fluoro-2-oxo-7-(o-tolyl)-1,2-dihydro-1,8-naphthyridine-3-carbonitrile	SFC: OD-H, 21 x 250 mm, 5 μm, 40% MeOH in CO ₂ , 80 g/min, 120 bar

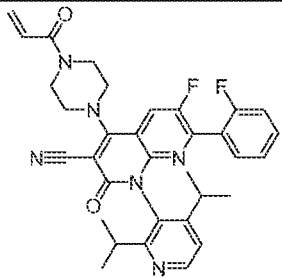
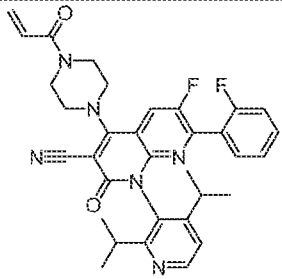
10.4	 1st-eluting isomer	4-(4-acryloylpiperazin-1-yl)-1-(2,4-diisopropylpyridin-3-yl)-6-fluoro-7-(2-fluorophenyl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile	SFC: OX-H, 21x250 mm, 5 μ m, a mobile 5-95% (0.1% TFA in Water/0.1% TFA in MeCN), 0.8 ml/min
10.5	 2nd-eluting isomer	4-(4-acryloylpiperazin-1-yl)-1-(2,4-diisopropylpyridin-3-yl)-6-fluoro-7-(2-fluorophenyl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile	SFC: OX-H, 21x250 mm, 5 μ m, a mobile 5-95% (0.1% TFA in Water/0.1% TFA in MeCN), 0.8 ml/min

Table 9: Analytical Data

Ex. #	LRMS: m/z (ESI, +ve ion): (M+H) ⁺	NMR
1	638.9	¹ H NMR (400 MHz, CHLOROFORM- <i>d</i>) δ ppm 1.02 - 1.13 (m, 6 H) 1.19 - 1.27 (m, 6 H) 1.94 - 2.05 (m, 6 H) 2.05 - 2.15 (m, 2 H) 2.44 - 2.77 (m, 2 H) 3.79 - 4.12 (m, 8 H) 5.71 - 6.04 (m, 1 H) 6.29 - 6.54 (m, 1 H) 6.57 - 6.80 (m, 1 H) 6.90 - 7.08 (m, 1 H), 1H overlap with CHCl ₃ , 7.36 - 7.45 (m, 1 H) 7.45 - 7.52 (m, 1 H) 8.00 - 8.36 (m, 1 H) 8.97 - 9.33 (m, 1 H)
2	614.0	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 7.91 - 8.08 (m, 1 H), 7.49 - 7.67 (m, 2 H), 7.41 (br d, <i>J</i> =5.8 Hz, 1 H), 7.21 (br s, 1 H), 6.76 - 6.98 (m, 1 H), 6.52 - 6.67 (m, 1 H), 6.09 - 6.29 (m, 1 H), 5.75 (br s, 1 H), 4.61 - 4.96 (m, 1 H), 4.23 - 4.48 (m, 1 H), 3.93 - 4.21 (m, 2 H), 3.50 - 3.77 (m, 1H), 3.33 - 3.49 (m, 1 H), 3.23 - 3.28 (m, 1 H), 2.94 - 3.24 (m, 1 H), 1.27 (br d, <i>J</i> =9.3 Hz, 6 H), 1.09 (br s, 3 H).
2.1	614.2	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 0.88 - 1.01 (m, 3 H) 1.03 - 1.15 (m, 3 H) 1.79 - 1.98 (m, 6 H) 2.65 - 2.80 (m, 1 H) 2.91 - 3.11 (m, 2 H) 3.70 - 4.00 (m, 8 H) 5.69 - 5.95 (m, 1 H) 6.03 - 6.31 (m, 1 H) 6.68 - 7.01 (m, 1 H) 7.09 - 7.20 (m, 1 H) 7.21 - 7.40 (m, 3 H) 7.43 - 7.58 (m, 1 H) 8.40 - 8.67 (m, 2 H) ¹⁹ F NMR (376 MHz, DMSO- <i>d</i> ₆) δ ppm -122.64 - -110.35 (m, 1 F)
2.2	614.2	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 0.87 - 0.99 (m, 3 H) 1.03 - 1.14 (m, 3 H) 1.80 - 1.99 (m, 6 H) 2.65 - 2.80 (m, 1 H) 2.90 - 3.12 (m, 2 H) 3.74 - 3.99 (m, 8 H) 5.68 - 5.82 (m, 1 H) 6.14 -

		6.26 (m, 1 H) 6.84 - 7.00 (m, 1 H) 7.09 - 7.18 (m, 1 H) 7.20 - 7.38 (m, 3 H) 7.45 - 7.56 (m, 1 H) 8.42 - 8.59 (m, 2 H) ¹⁹ F NMR (376 MHz, DMSO- <i>d</i> ₆) δ ppm -114.34 (s, 1 F)
3	656.9	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 0.82 - 0.98 (m, 6 H) 1.08 (br d, <i>J</i> =4.35 Hz, 6 H) 2.09 - 2.29 (m, 6 H) 2.63 - 2.78 (m, 2 H) 3.01 - 3.16 (m, 2 H) 3.74 - 4.08 (m, 8 H) 6.48 - 6.91 (m, 2 H) 7.08 - 7.65 (m, 4 H) 8.41 - 8.71 (m, 1 H) 8.94 - 9.30 (m, 1 H). ¹⁹ F NMR (376 MHz, DMSO- <i>d</i> ₆) δ ppm -114.60 (br s, 1 F)
3.1	696.8	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 0.84 - 0.98 (m, 6 H) 1.03 - 1.13 (m, 6 H) 1.35 - 1.45 (m, 2 H) 1.47 - 1.60 (m, 4 H) 2.28 - 2.44 (m, 4 H) 2.63 - 2.76 (m, 2 H) 3.04 - 3.22 (m, 2 H) 3.75 - 3.96 (m, 8 H) 3.98 - 4.09 (m, 1 H) 6.59 - 6.84 (m, 2 H) 7.09 - 7.20 (m, 1 H) 7.25 - 7.37 (m, 2 H) 7.45 - 7.60 (m, 1 H) 8.37 - 8.65 (m, 1 H) 8.98 - 9.26 (m, 1 H) ¹⁹ F NMR (376 MHz, DMSO- <i>d</i> ₆) δ ppm -117.96 - -110.35 (m, 1 F)
3.2	682.8	¹ H NMR (400 MHz, CHLOROFORM- <i>d</i>) δ ppm 1.05 - 1.17 (m, 6 H) 1.25 - 1.33 (m, 6 H) 1.78 - 2.08 (m, 3 H) 2.11 - 2.24 (m, 1 H) 2.29 - 2.40 (m, 1 H) 2.41 - 2.47 (m, 3 H) 2.59 - 2.74 (m, 2 H) 2.84 - 2.99 (m, 1 H) 3.20 - 3.33 (m, 1 H) 3.86 - 4.02 (m, 4 H) 4.03 - 4.16 (m, 4 H) 6.52 - 6.68 (m, 1 H) 6.91 - 7.07 (m, 1 H) 7.15 - 7.26 (m, 3 H) 7.50 - 7.63 (m, 1 H) 8.21 (s, 1 H) 9.15 - 9.29 (m, 1 H)
4	643.1	¹ H NMR (400 MHz, METHANOL- <i>d</i> ₄) δ ppm 0.93 - 1.02 (m, 6 H) 1.12 - 1.18 (m, 6 H) 1.98 - 2.00 (m, 3 H) 2.66 - 2.73 (m, 2 H) 3.82 - 3.89 (m, 2 H) 3.91 - 4.04 (m, 8 H) 6.70 - 6.82 (m, 1 H) 6.89 - 6.99 (m, 1 H) 7.10 - 7.24 (m, 3 H) 7.42 - 7.54 (m, 1 H) 8.46 - 8.52 (m, 1 H) 8.99 - 9.06 (m, 1 H) ¹⁹ F NMR (376 MHz, METHANOL- <i>d</i> ₄) δ ppm -115.72 (s, 1 F) - 77.42 (s, 1 F)
4.1	629.2	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 0.88 - 0.93 (m, 6 H) 1.05 - 1.11 (m, 6 H) 2.64 - 2.72 (m, 2 H) 3.65 - 3.75 (m, 2 H) 3.81 - 3.96 (m, 8 H) 6.64 - 6.77 (m, 1 H) 6.83 - 6.93 (m, 1 H) 7.09 - 7.18 (m, 1 H) 7.23 - 7.36 (m, 2 H) 7.46 - 7.66 (m, 1 H) 7.89 - 8.18 (m, 3 H) 8.38 - 8.65 (m, 1 H) 8.95 - 9.20 (m, 1 H) ¹⁹ F NMR (376 MHz, DMSO- <i>d</i> ₆) δ ppm -114.60 (s, 1 F), -74.47 (s, 1 F).
5	669.0	¹ H NMR (400 MHz, METHANOL- <i>d</i> ₄) δ ppm 0.86 - 0.99 (m, 4 H) 1.00 - 1.06 (m, 6 H) 1.16 - 1.23 (m, 6 H) 2.66 - 2.80 (m, 2 H) 2.81 - 2.90 (m, 1 H) 3.91 - 4.15 (m, 10 H) 6.74 - 6.90 (m, 1 H) 6.95 - 7.06 (m, 1 H) 7.14 - 7.29 (m, 3 H) 7.43 - 7.57 (m, 1 H) 8.48 - 8.58 (m, 1 H) 9.00 - 9.12 (m, 1 H). ¹⁹ F NMR (376 MHz, METHANOL- <i>d</i> ₄) δ ppm -119.71 - -118.25 (m, 6 F) -83.14 - -71.43 (m, 1 F)
5.1	671.2	¹ H NMR (400 MHz, METHANOL- <i>d</i> ₄) δ ppm 0.97 - 1.06 (m, 6 H) 1.16 - 1.22 (m, 6 H) 1.37 - 1.43 (m, 6 H) 2.69 - 2.80 (m, 2 H) 3.88 - 3.95 (m, 2 H) 3.95 - 4.07 (m, 8 H) 4.09 - 4.16 (m, 1 H) 6.75 - 6.87 (m, 1 H) 6.97 - 7.06 (m, 1 H) 7.14 - 7.26 (m, 3 H) 7.44 - 7.59 (m, 1 H) 8.50 - 8.56 (m, 1 H) 9.02 - 9.12 (m, 1 H).

		¹⁹ F NMR (376 MHz, METHANOL- <i>d</i> ₄) δ ppm -115.73 (s, 6 F) - 79.92 - -74.06 (m, 1 F)
5.2	685.3	¹ H NMR (400 MHz, METHANOL- <i>d</i> ₄) δ ppm 0.95 - 1.00 (m, 6 H) 1.14 - 1.18 (m, 6 H) 1.40 - 1.44 (m, 9 H) 2.61 - 2.76 (m, 2 H) 3.84 - 3.90 (m, 2 H) 3.92 - 4.06 (m, 8 H) 6.70 - 6.83 (m, 1 H) 6.94 - 7.03 (m, 1 H) 7.07 - 7.27 (m, 4 H) 7.42 - 7.52 (m, 1 H) 8.41 - 8.57 (m, 1 H) 8.95 - 9.11 (m, 1 H) ¹⁹ F NMR (376 MHz, METHANOL- <i>d</i> ₄) δ ppm -115.73 (s, 1 F) - 78.45 - -76.11 (m, 1 F)
6	571.0	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.50 (s, 1 H), 8.44 (d, <i>J</i> =4.77 Hz, 1 H), 7.47 - 7.57 (m, 1 H), 7.25 - 7.34 (m, 2 H), 7.22 (d, <i>J</i> =5.18 Hz, 1 H), 7.19 (td, <i>J</i> =7.26, 1.45 Hz, 1 H), 6.92 (dd, <i>J</i> =16.59, 10.37 Hz, 1 H), 6.21 (dd, <i>J</i> =16.79, 2.28 Hz, 1 H), 5.75 - 5.80 (m, 1 H), 3.79 - 4.00 (m, 8 H), 2.66 (quin, <i>J</i> =6.63 Hz, 1 H), 1.93 (s, 3 H), 1.07 (d, <i>J</i> =6.63 Hz, 3 H), 0.91 (d, <i>J</i> =6.63 Hz, 3 H)
6.1	585.0	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.51 (d, <i>J</i> =3.52 Hz, 1 H), 8.44 (d, <i>J</i> =4.98 Hz, 1 H), 7.45 - 7.57 (m, 1 H), 7.15 - 7.36 (m, 4 H), 6.89 (dd, <i>J</i> =16.69, 10.47 Hz, 1 H), 6.19 (dd, <i>J</i> =16.79, 2.28 Hz, 1 H), 5.72 - 5.84 (m, 1 H), 4.23 - 4.94 (m, 2 H), 4.14 (br d, <i>J</i> =11.82 Hz, 1 H), 3.94 (br s, 2 H), 3.47 - 3.63 (m, 2 H), 2.54 - 2.82 (m, 1 H), 1.84 - 2.01 (m, 3 H), 1.33 (br t, <i>J</i> =5.70 Hz, 3 H), 1.07 (dd, <i>J</i> =10.78, 6.63 Hz, 3 H), 0.92 (dd, <i>J</i> =6.63, 0.83 Hz, 3 H).
6.2	585.0	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.51 (d, <i>J</i> =3.52 Hz, 1 H), 8.44 (d, <i>J</i> =4.77 Hz, 1 H), 7.48 - 7.56 (m, 1 H), 7.15 - 7.37 (m, 4 H), 6.89 (dd, <i>J</i> =16.69, 10.47 Hz, 1 H), 6.20 (dd, <i>J</i> =16.79, 2.28 Hz, 1 H), 5.76 (dd, <i>J</i> =10.57, 1.87 Hz, 1 H), 4.23 - 4.99 (m, 2 H), 4.14 (br d, <i>J</i> =12.85 Hz, 1 H), 3.94 (br s, 2 H), 3.55 (br d, <i>J</i> =10.57 Hz, 1 H), 2.53 - 2.82 (m, 1 H), 1.94 - 2.05 (m, 3 H), 1.92 - 1.93 (m, 1 H), 1.33 (br t, <i>J</i> =5.80 Hz, 3 H), 1.07 (dd, <i>J</i> =10.78, 6.63 Hz, 3 H), 0.92 (dd, <i>J</i> =6.63, 0.83 Hz, 3 H).
6.3	600.0	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 9.10 (s, 1H), 8.52 (s, 1H), 7.48-7.55 (m, 1H), 7.25-7.34 (m, 2H), 7.15 (dt, <i>J</i> =1.66, 7.46 Hz, 1H), 6.92 (dd, <i>J</i> =10.47, 16.69 Hz, 1H), 6.21 (dd, <i>J</i> =2.38, 16.69 Hz, 1H), 5.74-5.80 (m, 1H), 3.80-3.98 (m, 8H), 2.65-2.74 (m, 2H), 1.08 (d, <i>J</i> =6.63 Hz, 6H), 0.90 (d, <i>J</i> =6.63 Hz, 6H). ¹⁹ F NMR (376 MHz, DMSO- <i>d</i> ₆) δ ppm -114.60 (s, 1F).
6.4	571.0	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.50 (s, 1 H), 8.43 (d, <i>J</i> =4.98 Hz, 1 H), 7.46 - 7.57 (m, 1 H), 7.14 - 7.37 (m, 4 H), 6.92 (dd, <i>J</i> =16.69, 10.47 Hz, 1 H), 6.21 (dd, <i>J</i> =16.69, 2.38 Hz, 1 H), 5.73 - 5.84 (m, 1 H), 3.77 - 3.98 (m, 8 H), 2.66 (quin, <i>J</i> =6.63 Hz, 1 H), 1.93 (s, 3 H), 1.07 (d, <i>J</i> =6.63 Hz, 3 H), 0.91 (d, <i>J</i> =6.63 Hz, 3 H). ¹⁹ F NMR (376 MHz, DMSO- <i>d</i> ₆) δ ppm -114.02 (s, 1 F)
6.5	571.0	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.50 (s, 1 H), 8.43 (d, <i>J</i> =4.98 Hz, 1 H), 7.46 - 7.62 (m, 1 H), 7.24 - 7.34 (m, 2 H), 7.22 (d, <i>J</i> =5.39 Hz, 1 H), 7.19 (td, <i>J</i> =7.46, 1.87 Hz, 1 H), 6.92 (dd, <i>J</i> =16.69, 10.47 Hz, 1 H), 6.21 (dd, <i>J</i> =16.59, 2.28 Hz, 1 H), 5.74 -

		5.80 (m, 1 H), 3.82 - 3.96 (m, 8 H), 2.66 (quin, $J=6.63$ Hz, 1 H), 1.93 (s, 3 H), 1.07 (d, $J=6.63$ Hz, 3 H), 0.91 (d, $J=6.84$ Hz, 3 H). ^{19}F NMR (376 MHz, $\text{DMSO-}d_6$) δ ppm – 114.00 (s, 1 F)
6.6	585.0	^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ ppm 8.51 (s, 1 H), 8.44 (d, $J=4.98$ Hz, 1 H), 7.48 - 7.56 (m, 1 H), 7.17 - 7.34 (m, 4 H), 6.89 (dd, $J=16.69$, 10.47 Hz, 1 H), 6.20 (dd, $J=16.69$, 2.38 Hz, 1 H), 5.76 (dd, $J=10.37$, 2.07 Hz, 1 H), 4.20 - 4.97 (m, 2 H), 4.15 (br d, $J=12.44$ Hz, 1 H), 3.93 (br s, 2 H), 3.47 - 3.62 (m, 1 H), 3.24 - 3.26 (m, 1 H), 2.73 (quin, $J=6.63$ Hz, 1 H), 1.89 (s, 3 H), 1.33 (br d, $J=6.63$ Hz, 3 H), 1.08 (d, $J=6.63$ Hz, 3 H), 0.92 (d, $J=6.63$ Hz, 3 H). ^{19}F NMR (376 MHz, $\text{DMSO-}d_6$) δ ppm – 114.06 (s, 1 F)
6.7	585.0	^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ ppm 8.52 (s, 1 H), 8.44 (d, $J=4.98$ Hz, 1 H), 7.46 - 7.56 (m, 1 H), 7.24 - 7.35 (m, 2 H), 7.22 (d, $J=4.98$ Hz, 1 H), 7.19 (td, $J=7.46$, 1.87 Hz, 1 H), 6.89 (dd, $J=16.69$, 10.47 Hz, 1 H), 6.19 (dd, $J=16.79$, 2.28 Hz, 1 H), 5.76 (dd, $J=10.37$, 2.07 Hz, 1 H), 4.25 - 4.97 (m, 2 H), 4.14 (br d, $J=13.06$ Hz, 1 H), 3.94 (br s, 2 H), 3.45 - 3.64 (m, 1 H), 3.24 - 3.26 (m, 1 H), 2.53 - 2.63 (m, 1 H), 1.97 (s, 3 H), 1.32 (br d, $J=6.43$ Hz, 3 H), 1.05 (d, $J=6.63$ Hz, 3 H), 0.92 (d, $J=6.84$ Hz, 3 H). ^{19}F NMR (376 MHz, $\text{DMSO-}d_6$) δ ppm – 113.8 (s, 1 F)
7	595.3	^1H NMR (400 MHz, $\text{CHLOROFORM-}d$) δ 8.53 (d, $J=5.18$ Hz, 1H), 8.15 (s, 1H), 8.03 (s, 1H), 7.16 (d, $J=7.67$ Hz, 2H), 7.10 (d, $J=5.18$ Hz, 1H), 6.96 (d, $J=7.46$ Hz, 1H), 6.57-6.66 (m, 1H), 6.39 (dd, $J=1.76$, 16.69 Hz, 1H), 5.81 (dd, $J=1.76$, 10.47 Hz, 1H), 3.72-4.02 (m, 8H), 2.52 (quin, $J=6.63$ Hz, 1H), 2.38-2.46 (m, 1H), 1.94 (s, 3H), 1.16 (dd, $J=6.74$, 11.09 Hz, 6H), 0.97 (d, $J=6.84$ Hz, 3H), 0.92 (d, $J=6.84$ Hz, 3H).
7.1	595.3	^1H NMR (400 MHz, $\text{CHLOROFORM-}d$) δ 8.58 (d, $J=5.18$ Hz, 1H), 8.17 (s, 1H), 7.27-7.32 (m, 1H), 7.11-7.21 (m, 3H), 6.91-7.03 (m, 1H), 6.64 (dd, $J=10.57$, 16.79 Hz, 1H), 6.41 (dd, $J=1.66$, 16.79 Hz, 1H), 5.83 (dd, $J=1.76$, 10.47 Hz, 1H), 3.99 (br s, 4H), 3.79-3.92 (m, 4H), 2.50-2.63 (m, 1H), 2.39-2.50 (m, 1H), 1.96 (s, 3H), 1.18 (dd, $J=6.74$, 13.79 Hz, 6H), 1.00 (d, $J=6.84$ Hz, 3H), 0.94 (d, $J=6.84$ Hz, 3H).
7.2	599.0	^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ ppm 8.41 - 8.47 (m, 2 H), 7.45 - 7.58 (m, 1 H), 7.16 - 7.35 (m, 4 H), 6.74 - 7.04 (m, 1 H), 6.20 (br d, $J=16.38$ Hz, 1 H), 5.76 (dd, $J=10.37$, 2.07 Hz, 1 H), 3.65 - 5.03 (m, 5 H), 3.56 (br d, $J=12.23$ Hz, 1 H), 2.53 - 2.63 (m, 1 H), 2.00 (s, 3 H), 1.26 - 1.45 (m, 6 H), 1.01 - 1.14 (m, 3 H), 0.92 - 0.95 (m, 3 H). ^{19}F NMR (376 MHz, $\text{DMSO-}d_6$) δ ppm – 113.8 (s, 1 F)
7.3	599.0	^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ ppm 8.67 (s, 1 H), 8.44 (d, $J=4.98$ Hz, 1 H), 7.46 - 7.56 (m, 1 H), 7.14 - 7.38 (m, 4 H), 6.88 (dd, $J=16.69$, 10.47 Hz, 1 H), 6.22 (dd, $J=16.59$, 2.28 Hz, 1 H), 5.77 (dd, $J=10.37$, 1.87 Hz, 1 H), 4.66 (br s, 2 H), 3.94 (br t, $J=14.93$ Hz, 2 H), 3.71 (ddd, $J=12.59$, 7.83, 4.46 Hz, 2 H), 2.67 (quin, $J=6.63$ Hz, 1 H), 1.94 (s, 3 H), 1.52 (d, $J=6.63$ Hz, 6 H), 1.07 (d, $J=6.63$ Hz, 3 H), 0.92 (d, $J=6.63$ Hz, 3 H)

7.4	599.0	¹ H NMR (400 MHz, <i>DMSO-d</i> ₆) δ ppm 8.40 - 8.45 (m, 2 H), 7.44 - 7.57 (m, 1 H), 7.16 - 7.36 (m, 4 H), 6.71 - 7.00 (m, 1 H), 6.20 (dd, <i>J</i> =16.69, 1.97 Hz, 1 H), 5.76 (dd, <i>J</i> =10.37, 1.66 Hz, 1 H), 3.91 - 5.02 (m, 5 H), 3.57 (br d, <i>J</i> =12.44 Hz, 1 H), 2.79 (quin, <i>J</i> =6.58 Hz, 1 H), 1.87 (s, 3 H), 1.30 (br s, 6 H), 1.09 (d, <i>J</i> =6.63 Hz, 3 H), 0.94 (d, <i>J</i> =6.84 Hz, 3 H). ¹⁹ F NMR (376 MHz, <i>DMSO-d</i> ₆) δ ppm - 114.2 (s, 1 F)
7.5	599.0	¹ H NMR (400 MHz, <i>DMSO-d</i> ₆) δ ppm 8.26 - 8.64 (m, 2 H), 7.42 - 7.67 (m, 1 H), 7.11 - 7.38 (m, 4 H), 6.73 - 7.03 (m, 1 H), 6.20 (br d, <i>J</i> =16.59 Hz, 1 H), 5.76 (dd, <i>J</i> =10.37, 2.49 Hz, 1 H), 4.45 - 4.63 (m, 2 H), 3.65 - 4.38 (m, 3 H), 3.55 (br d, <i>J</i> =12.44 Hz, 1 H), 2.53 - 2.62 (m, 1 H), 2.00 (s, 3 H), 1.29 (br s, 6 H), 1.05 (d, <i>J</i> =6.63 Hz, 3 H), 0.93 (d, <i>J</i> =6.63 Hz, 3 H).). ¹⁹ F NMR (376 MHz, <i>DMSO-d</i> ₆) δ ppm - 113.9 (s, 1 F)
7.6	599.0	¹ H NMR (400 MHz, <i>DMSO-d</i> ₆) δ ppm 8.67 (s, 1 H), 8.44 (d, <i>J</i> =4.98 Hz, 1 H), 7.47 - 7.57 (m, 1 H), 7.25 - 7.36 (m, 2 H), 7.18 - 7.25 (m, 2 H), 6.88 (dd, <i>J</i> =16.59, 10.57 Hz, 1 H), 6.22 (dd, <i>J</i> =16.69, 2.38 Hz, 1 H), 5.77 (dd, <i>J</i> =10.57, 2.28 Hz, 1 H), 4.61 - 4.72 (m, 2 H), 3.94 (br t, <i>J</i> =14.93 Hz, 2 H), 3.71 (ddd, <i>J</i> =12.59, 7.93, 4.56 Hz, 2 H), 2.68 (quin, <i>J</i> =6.58 Hz, 1 H), 1.94 (s, 3 H), 1.53 (d, <i>J</i> =6.63 Hz, 6 H), 1.07 (d, <i>J</i> =6.63 Hz, 3 H), 0.92 (d, <i>J</i> =6.63 Hz, 3 H). ¹⁹ F NMR (376 MHz, <i>DMSO-d</i> ₆) δ ppm - 114.0 (s, 1 F)
7.7	599.0	¹ H NMR (400 MHz, <i>DMSO-d</i> ₆) δ ppm 8.67 (s, 1 H), 8.44 (d, <i>J</i> =4.98 Hz, 1 H), 7.47 - 7.57 (m, 1 H), 7.25 - 7.36 (m, 2 H), 7.18 - 7.25 (m, 2 H), 6.88 (dd, <i>J</i> =16.59, 10.57 Hz, 1 H), 6.22 (dd, <i>J</i> =16.69, 2.38 Hz, 1 H), 5.77 (dd, <i>J</i> =10.57, 2.07 Hz, 1 H), 4.60 - 4.73 (m, 2 H), 3.87 - 4.00 (m, 2 H), 3.71 (ddd, <i>J</i> =12.49, 7.83, 4.77 Hz, 2 H), 2.68 (quin, <i>J</i> =6.63 Hz, 1 H), 1.94 (s, 3 H), 1.53 (d, <i>J</i> =6.63 Hz, 6 H), 1.07 (d, <i>J</i> =6.63 Hz, 3 H), 0.92 (d, <i>J</i> =6.63 Hz, 3 H). ¹⁹ F NMR (376 MHz, <i>DMSO-d</i> ₆) δ ppm - 114.1 (s, 1 F)
8	599.3	¹ H NMR (400 MHz, CHLOROFORM- <i>d</i>) δ 8.67 (d, <i>J</i> =5.39 Hz, 1H), 8.18 (s, 1H), 7.36-7.46 (m, 1H), 7.22 (d, <i>J</i> =5.18 Hz, 1H), 7.03-7.18 (m, 3H), 6.64 (dd, <i>J</i> =10.57, 16.79 Hz, 1H), 6.41 (dd, <i>J</i> =1.66, 16.79 Hz, 1H), 5.84 (dd, <i>J</i> =1.66, 10.57 Hz, 1H), 3.78-4.10 (m, 8H), 2.57 (td, <i>J</i> =6.82, 13.53 Hz, 1H), 2.47 (td, <i>J</i> =6.84, 13.68 Hz, 1H), 1.23 (d, <i>J</i> =6.84 Hz, 3H), 1.18 (d, <i>J</i> =6.84 Hz, 3H), 1.02 (d, <i>J</i> =6.84 Hz, 3H), 0.95 (d, <i>J</i> =6.84 Hz, 3H).
8.1	599.3	¹ H NMR (400 MHz, CHLOROFORM- <i>d</i>) δ 8.58 (d, <i>J</i> =5.18 Hz, 1H), 8.17 (s, 1H), 7.36-7.47 (m, 1H), 7.05-7.19 (m, 4H), 6.64 (dd, <i>J</i> =10.37, 16.79 Hz, 1H), 6.41 (dd, <i>J</i> =1.66, 16.79 Hz, 1H), 5.83 (dd, <i>J</i> =1.76, 10.47 Hz, 1H), 3.78-4.08 (m, 8H), 2.48-2.60 (m, 1H), 2.38-2.48 (m, 1H), 1.18 (dd, <i>J</i> =6.84, 10.78 Hz, 6H), 0.90-1.02 (m, 6H). ¹⁹ F NMR (376 MHz, CHLOROFORM- <i>d</i>) δ -113.03 (s, 1F).
8.2	599.3	¹ H NMR (400 MHz, CHLOROFORM- <i>d</i>) δ 8.58 (d, <i>J</i> =5.18 Hz, 1H), 8.17 (s, 1H), 7.34-7.47 (m, 1H), 7.03-7.19 (m, 4H), 6.64 (dd, <i>J</i> =10.57, 16.79 Hz, 1H), 6.41 (dd, <i>J</i> =1.66, 16.79 Hz, 1H), 5.83 (dd, <i>J</i> =1.76, 10.47 Hz, 1H), 3.76-4.12 (m, 8H), 2.49-2.63

		(m, 1H), 2.37-2.49 (m, 1H), 1.18 (dd, $J=6.74, 10.68$ Hz, 6H), 0.90-1.02 (m, 6H). ^{19}F NMR (376 MHz, CHLOROFORM- d) δ -113.03 (s, 1F).
8.3	600.0	^1H NMR (400 MHz, DMSO- d_6) δ ppm 0.86 - 0.93 (m, 3 H) 1.05 - 1.13 (m, 3 H) 2.57 - 2.70 (m, 1 H) 2.73 - 2.85 (m, 6 H) 3.79 - 3.95 (m, 8 H) 5.72 - 5.81 (m, 1 H) 6.14 - 6.27 (m, 1 H) 6.82 - 6.97 (m, 2 H) 7.22 - 7.28 (m, 1 H) 7.30 - 7.37 (m, 2 H) 7.49 - 7.62 (m, 1 H) 8.15 - 8.24 (m, 1 H) 8.45 - 8.56 (m, 1 H)
8.4	600.0	^1H NMR (400 MHz, DMSO- d_6) δ ppm 0.80 - 0.86 (m, 3 H) 1.01 - 1.09 (m, 3 H) 2.40 - 2.47 (m, 1 H) 2.59 - 2.66 (m, 6 H) 3.80 - 3.90 (m, 8 H) 5.71 - 5.82 (m, 1 H) 6.15 - 6.25 (m, 1 H) 6.83 - 6.97 (m, 2 H) 7.15 - 7.24 (m, 1 H) 7.26 - 7.37 (m, 2 H) 7.48 - 7.59 (m, 1 H) 8.07 - 8.16 (m, 1 H) 8.46 - 8.51 (m, 1 H) ^{19}F NMR (376 MHz, DMSO- d_6) δ ppm -113.86 (s, 1 F)
8.5	600.0	^1H NMR (400 MHz, DMSO- d_6) δ ppm 0.78 - 0.95 (m, 3 H) 1.02 - 1.12 (m, 3 H) 2.54 - 2.62 (m, 1 H) 2.63 - 2.79 (m, 6 H) 3.73 - 4.02 (m, 8 H) 5.69 - 5.87 (m, 1 H) 6.09 - 6.31 (m, 1 H) 6.75 - 6.85 (m, 1 H) 6.86 - 7.01 (m, 1 H) 7.17 - 7.41 (m, 3 H) 7.47 - 7.65 (m, 1 H) 8.10 - 8.30 (m, 1 H) 8.43 - 8.61 (m, 1 H). containing 1 eq TEA peaks. confirmed by ms. ^{19}F NMR (376 MHz, DMSO- d_6) δ ppm -127.32 - -105.08 (m, 1 F)
8.6	600.0	^1H NMR (400 MHz, DMSO- d_6) δ ppm 0.79 - 0.89 (m, 3 H) 1.01 - 1.09 (m, 3 H) 2.52 - 2.56 (m, 1 H) 2.59 - 2.70 (m, 6 H) 3.62 - 3.99 (m, 8 H) 5.72 - 5.83 (m, 1 H) 6.11 - 6.30 (m, 1 H) 6.68 - 6.79 (m, 1 H) 6.84 - 6.98 (m, 1 H) 7.14 - 7.25 (m, 1 H) 7.27 - 7.38 (m, 2 H) 7.45 - 7.60 (m, 1 H) 8.15 - 8.26 (m, 1 H) 8.42 - 8.54 (m, 1 H). ^{19}F NMR (376 MHz, DMSO- d_6) δ ppm -123.81 - -104.20 (m, 1 F)
8.7	600.0	^1H NMR (400 MHz, DMSO- d_6) δ ppm 0.79 - 0.88 (m, 3 H) 1.00 - 1.09 (m, 3 H) 2.39 - 2.47 (m, 1 H) 2.57 - 2.64 (m, 6 H) 3.74 - 3.97 (m, 8 H) 5.70 - 5.84 (m, 1 H) 6.13 - 6.27 (m, 1 H) 6.83 - 6.97 (m, 2 H) 7.15 - 7.23 (m, 1 H) 7.25 - 7.36 (m, 2 H) 7.47 - 7.60 (m, 1 H) 8.08 - 8.15 (m, 1 H) 8.43 - 8.54 (m, 1 H) ^{19}F NMR (376 MHz, DMSO- d_6) δ ppm -113.82 (s, 1 F)
8.8	600.0	^1H NMR (400 MHz, DMSO- d_6) δ ppm 0.79 - 0.89 (m, 4 H) 0.81 - 0.86 (m, 3 H) 1.00 - 1.09 (m, 4 H) 1.01 - 1.08 (m, 3 H) 2.39 - 2.47 (m, 1 H) 2.56 - 2.68 (m, 7 H) 3.80 - 3.96 (m, 8 H) 5.71 - 5.81 (m, 1 H) 6.14 - 6.25 (m, 1 H) 6.82 - 6.98 (m, 2 H) 7.14 - 7.24 (m, 1 H) 7.26 - 7.37 (m, 2 H) 7.46 - 7.59 (m, 1 H) 8.07 - 8.15 (m, 1 H) 8.43 - 8.54 (m, 1 H) ^{19}F NMR (376 MHz, DMSO- d_6) δ ppm -113.82 (s, 1 F)
9	523.1	^1H NMR (400 MHz, CHLOROFORM- d) δ 8.71 (d, $J=5.18$ Hz, 1H), 7.88 (d, $J=7.67$ Hz, 1H), 7.26-7.29 (m, 1H), 6.66 (dd, $J=10.57, 16.79$ Hz, 1H), 6.40-6.47 (m, 1H), 5.86 (dd, $J=1.66, 10.57$ Hz, 1H), 3.99 (br s, 4H), 3.71-3.90 (m, 4H), 2.36-2.54 (m, 2H), 1.24 (d, $J=6.63$ Hz, 3H), 1.21 (d, $J=6.63$ Hz, 3H), 1.09 (d, $J=6.63$ Hz, 3H), 1.04 (d, $J=6.84$ Hz, 3H). ^{19}F NMR (376 MHz, CHLOROFORM- d) δ -124.74 (s, 1F)

9.1	539.8	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 0.93 - 1.01 (m, 6 H) 1.05 - 1.12 (m, 6 H) 2.61 - 2.75 (m, 2 H) 3.72 - 3.95 (m, 8 H) 5.62 - 5.97 (m, 1 H) 6.10 - 6.38 (m, 1 H) 6.83 - 7.01 (m, 1 H) 8.36 - 8.73 (m, 1 H) 8.97 - 9.77 (m, 1 H)
9.2	511.1	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 0.95 - 1.02 (m, 3 H) 1.04 - 1.11 (m, 3 H) 1.89 - 1.96 (m, 3 H) 2.56 - 2.70 (m, 1 H) 3.74 - 3.95 (m, 8 H) 5.70 - 5.83 (m, 1 H) 6.10 - 6.28 (m, 1 H) 6.82 - 6.99 (m, 1 H) 7.26 - 7.36 (m, 1 H) 8.46 - 8.56 (m, 2 H)
10	579.4	¹ H NMR (400 MHz, CHLOROFORM- <i>d</i>) δ 8.58 (br d, <i>J</i> =4.98 Hz, 1H), 7.86 (d, <i>J</i> =9.12 Hz, 1H), 7.26-7.32 (m, 1H), 7.09-7.23 (m, 4H), 6.62 (dd, <i>J</i> =10.57, 16.79 Hz, 1H), 6.35-6.44 (m, 1H), 5.81 (dd, <i>J</i> =1.66, 10.57 Hz, 1H), 3.91-4.06 (m, 4H), 3.82 (br s, 4H), 2.39-2.60 (m, 2H), 1.98 (s, 3H), 1.13-1.22 (m, 6H), 0.97 (br d, <i>J</i> =6.01 Hz, 3H), 0.91 (d, <i>J</i> =6.63 Hz, 3H). ¹⁹ F NMR (376 MHz, CHLOROFORM- <i>d</i>) δ -126.76 (s, 1F).
10.1	583.4	¹ H NMR (400 MHz, CHLOROFORM- <i>d</i>) δ 8.65 (d, <i>J</i> =5.18 Hz, 1H), 7.92 (d, <i>J</i> =9.12 Hz, 1H), 7.38-7.49 (m, 1H), 7.11-7.26 (m, 4H), 6.66 (dd, <i>J</i> =10.57, 16.79 Hz, 1H), 6.34-6.50 (m, 1H), 5.85 (dd, <i>J</i> =1.76, 10.47 Hz, 1H), 3.94-4.11 (m, 4H), 3.86 (br s, 4H), 2.44-2.63 (m, 2H), 1.18-1.26 (m, 6H), 1.02 (br d, <i>J</i> =6.63 Hz, 3H), 0.96 (d, <i>J</i> =6.84 Hz, 3H). ¹⁹ F NMR (376 MHz, CHLOROFORM- <i>d</i>) δ -112.53 - -112.64 (s, 1F), -125.66 - -125.77 (s, 1F) (signals split due to the presence of atropisomers).
10.2	579.4	¹ H NMR (400 MHz, CHLOROFORM- <i>d</i>) δ 8.59 (d, <i>J</i> =4.98 Hz, 1H), 7.89 (d, <i>J</i> =9.33 Hz, 1H), 7.28-7.34 (m, 1H), 7.14-7.22 (m, 4H), 6.65 (dd, <i>J</i> =10.57, 16.79 Hz, 1H), 6.37-6.46 (m, 1H), 5.83 (dd, <i>J</i> =1.66, 10.57 Hz, 1H), 3.99 (br s, 4H), 3.84 (br s, 4H), 2.41-2.61 (m, 2H), 2.00 (s, 3H), 1.18 (dd, <i>J</i> =6.84, 9.74 Hz, 6H), 0.91-1.00 (m, 3H), 0.95 (d, <i>J</i> =12.44 Hz, 3H). ¹⁹ F NMR (376 MHz, CHLOROFORM- <i>d</i>) δ -126.78 (s, 1F).
10.3	579.4	¹ H NMR (400 MHz, CHLOROFORM- <i>d</i>) δ 8.59 (d, <i>J</i> =5.18 Hz, 1H), 7.89 (d, <i>J</i> =9.33 Hz, 1H), 7.28-7.34 (m, 1H), 7.14-7.22 (m, 4H), 6.65 (dd, <i>J</i> =10.57, 16.79 Hz, 1H), 6.36-6.47 (m, 1H), 5.84 (dd, <i>J</i> =1.76, 10.47 Hz, 1H), 4.00 (br s, 4H), 3.84 (br s, 4H), 2.41-2.61 (m, 2H), 2.00 (s, 3H), 1.19 (br d, <i>J</i> =9.54 Hz, 3H), 1.18 (br d, <i>J</i> =9.95 Hz, 3H), 0.88-1.04 (m, 3H), 0.96 (d, <i>J</i> =12.44 Hz, 3H). ¹⁹ F NMR (376 MHz, CHLOROFORM- <i>d</i>) δ -126.78 (s, 1F)
10.4	583.4	¹ H NMR (400 MHz, CHLOROFORM- <i>d</i>) δ 8.57 (d, <i>J</i> =4.98 Hz, 1H), 7.86 (d, <i>J</i> =9.12 Hz, 1H), 7.32-7.43 (m, 1H), 7.02-7.19 (m, 4H), 6.60 (dd, <i>J</i> =10.37, 16.79 Hz, 1H), 6.28-6.41 (m, 1H), 5.78 (dd, <i>J</i> =1.66, 10.57 Hz, 1H), 3.94 (br s, 4H), 3.79 (br s, 4H), 2.36-2.57 (m, 2H), 1.15 (br d, <i>J</i> =9.54 Hz, 3H), 1.13 (br d, <i>J</i> =9.74 Hz, 3H), 0.94 (d, <i>J</i> =6.84 Hz, 3H), 0.89 (d, <i>J</i> =6.84 Hz, 3H). ¹⁹ F NMR (376 MHz, CHLOROFORM- <i>d</i>) δ -112.52 - -112.63 (d, 1F), -125.68 - -125.78 (d, 1F)
10.5	583.3	¹ H NMR (400 MHz, CHLOROFORM- <i>d</i>) δ 8.57 (d, <i>J</i> =5.18 Hz, 1H), 7.86 (d, <i>J</i> =9.33 Hz, 1H), 7.32-7.43 (m, 1H), 7.04-7.17 (m, 4H), 6.60 (dd, <i>J</i> =10.57, 16.79 Hz, 1H), 6.32-6.40 (m, 1H), 5.78 (dd, <i>J</i> =1.76, 10.47 Hz, 1H), 3.94 (br s, 4H), 3.79 (br s, 4H), 2.36-2.56 (m, 2H), 1.13 (br d, <i>J</i> =9.74 Hz, 3H), 1.15 (br d, <i>J</i> =9.54 Hz,

		3H), 0.91 (br d, $J=12.65$ Hz, 3H), 0.83-1.00 (m, 3H). ^{19}F NMR (376 MHz, CHLOROFORM- d) δ -112.52 - -112.63 (d, 1F), -125.67 - -125.78 (d, 1F).
11	567.4	^1H NMR (400 MHz, CHLOROFORM- d) δ 8.48 (d, $J=4.77$ Hz, 1H), 8.18 (s, 1H), 7.28-7.32 (m, 1H), 7.14-7.22 (m, 2H), 7.01-7.12 (m, 2H), 6.64 (dd, $J=10.57$, 16.79 Hz, 1H), 6.40 (dd, $J=1.66$, 16.79 Hz, 1H), 5.82 (dd, $J=1.55$, 10.47 Hz, 1H), 3.99 (br s, 4H), 3.84 (br s, 4H), 2.49-2.65 (m, 1H), 1.97 (d, $J=6.63$ Hz, 6H), 1.19 (d, $J=6.63$ Hz, 3H), 0.98 (d, $J=6.63$ Hz, 3H)
11.1	567.2	^1H NMR (400 MHz, CHLOROFORM- d) δ 8.46 (d, $J=4.98$ Hz, 1H), 8.16 (s, 1H), 7.23-7.33 (m, 1H), 7.11-7.20 (m, 2H), 7.02-7.07 (m, 2H), 6.62 (dd, $J=10.37$, 16.79 Hz, 1H), 6.37 (dd, $J=1.66$, 16.79 Hz, 1H), 5.80 (dd, $J=1.66$, 10.37 Hz, 1H), 3.96 (br s, 4H), 3.82 (br s, 4H), 2.57 (quin, $J=6.69$ Hz, 1H), 1.94 (d, $J=6.84$ Hz, 6H), 1.16 (d, $J=6.63$ Hz, 3H), 0.96 (d, $J=6.84$ Hz, 3H).
11.2	595.3	^1H NMR (400 MHz, CHLOROFORM- d) δ 8.46 (br s, 1H), 8.15 (s, 1H), 7.31-7.37 (m, 1H), 7.25-7.31 (m, 1H), 7.15 (t, $J=7.46$ Hz, 1H), 6.97-7.11 (m, 1H), 6.91 (d, $J=7.46$ Hz, 1H), 6.60 (dd, $J=10.57$, 16.79 Hz, 1H), 6.37 (dd, $J=1.66$, 16.79 Hz, 1H), 5.80 (dd, $J=1.55$, 10.47 Hz, 1H), 3.96 (br s, 4H), 3.82 (br s, 4H), 2.60 (br s, 1H), 2.45 (br s, 1H), 1.85-2.08 (m, 3H), 1.21 (br s, 3H), 0.79-1.11
11.3	595.3	^1H NMR (400 MHz, CHLOROFORM- d) δ 8.44 (br s, 1H), 8.15 (s, 1H), 7.32-7.37 (m, 1H), 7.25-7.32 (m, 1H), 7.15 (t, $J=7.36$ Hz, 1H), 6.97-7.09 (m, 1H), 6.92 (d, $J=7.67$ Hz, 1H), 6.61 (dd, $J=10.57$, 16.79 Hz, 1H), 6.38 (dd, $J=1.55$, 16.69 Hz, 1H), 5.80 (dd, $J=1.66$, 10.57 Hz, 1H), 3.96 (br s, 4H), 3.82 (br s, 4H), 2.58 (br s, 1H), 2.46 (br s, 1H), 1.94 (br s, 3H), 1.20 (br d, $J=9.54$ Hz, 3H), 0.97 (br s, 6H), 0.85-0.90 (m, 3H).
11.4	614.8	^1H NMR (400 MHz, DMSO- d_6) δ ppm 0.79 - 0.90 (m, 3 H) 0.95 - 1.16 (m, 9 H) 2.56 - 2.69 (m, 1 H) 2.75 - 2.90 (m, 1 H) 3.75 - 4.09 (m, 8 H) 4.96 - 5.20 (m, 2 H) 5.68 - 5.86 (m, 1 H) 6.11 - 6.25 (m, 1 H) 6.27 - 6.37 (m, 1 H) 6.39 - 6.53 (m, 1 H) 6.84 - 6.98 (m, 1 H) 7.00 - 7.14 (m, 1 H) 8.48 (s, 1 H) 9.09 (s, 1 H) ^{19}F NMR (376 MHz, DMSO- d_6) δ ppm -116.22 (s, 1 F).

BIOLOGICAL ANALYSIS

For compounds in Table 10, the following assay conditions were employed:

[0223] **Coupled Nucleotide Exchange Assay:** Purified GDP-bound KRAS protein (aa 1-169), containing both G12C and C118A amino acid substitutions and an *N*-terminal His-tag, was pre-incubated in assay buffer (25 mM HEPES pH 7.4, 10 mM MgCl_2 , and 0.01% Triton X-100) with a compound dose-response titration for 5 min (see Table 10). Following compound pre-incubation, purified SOS protein (aa 564-1049) and GTP (Roche 10106399001) were added to the assay wells and incubated for an additional 30 min. To determine the extent

of inhibition of SOS-mediated nucleotide exchange, purified GST-tagged cRAF (aa 1-149), nickel chelate AlphaLISA acceptor beads (PerkinElmer AL108R), and AlphaScreen glutathione donor beads (PerkinElmer 6765302) were added to the assay wells and incubated for 10 minutes. The assay plates were then read on a PerkinElmer EnVision Multilabel Reader, using AlphaScreen® technology, and data were analyzed using a 4-parameter logistic model to calculate IC₅₀ values.

[0224] Phospho-ERK1/2 MSD Assay: MIA PaCa-2 (ATCC® CRL-1420™) and A549 (ATCC® CCL-185™) cells were cultured in RPMI 1640 Medium (ThermoFisher Scientific 11875093) containing 10% fetal bovine serum (ThermoFisher Scientific 16000044) and 1x penicillin-streptomycin-glutamine (ThermoFisher Scientific 10378016). Sixteen hours prior to compound treatment, MIA PaCa-2 were seeded in 96-well cell culture plates at a density of 25,000 cells/well and incubated at 37°C, 5% CO₂. A compound dose-response titration was diluted in growth media, added to appropriate wells of a cell culture plate, and then incubated at 37°C, 5% CO₂ for 2 (see Table 10). Following compound treatment, cells were stimulated with 10 ng/mL EGF (Roche 11376454001) for 10 min, washed with ice-cold Dulbecco's phosphate-buffered saline, no Ca²⁺ or Mg²⁺ (ThermoFisher Scientific 14190144), and then lysed in RIPA buffer (50 mM Tris-HCl pH 7.5, 1% Igepal, 0.5% sodium deoxycholate, 150 mM NaCl, and 0.5% sodium dodecyl sulfate) containing protease inhibitors (Roche 4693132001) and phosphatase inhibitors (Roche 4906837001). Phosphorylation of ERK1/2 in compound-treated lysates was assayed using Phospho-ERK1/2 Whole Cell Lysate kits (Meso Scale Discovery K151DWD) according to the manufacturer's protocol. Assay plates were read on a Meso Scale Discovery Sector Imager 6000, and data were analyzed using a 4-parameter logistic model to calculate IC₅₀ values.

Table 10: Biochemical and cellular activity of compounds

Ex.#	Coupled exchange IC ₅₀ (5 min; μ M)	p-ERK IC ₅₀ (2 h; MIA PaCa-2, μ M)
1	4.13	-
2	0.061	0.16
2.1	0.18	0.14
2.2	5.71	-
3	0.4	0.72
3.1	1.02	4.47
3.2	0.71	1.26
4	0.34	0.30
4.1	0.18	0.16
5	0.70	0.76
5.1	0.44	0.56
5.2	0.44	0.39
6	0.17	0.17
6.1	1.57	-
6.2	0.28	0.14
6.3	0.07	0.04
6.4	0.73	-
6.5	0.10	0.06
6.6	0.92	-
6.7	0.20	0.15
7	0.15	0.22
7.1	0.14	0.14
7.2	4.3	-
7.3	0.18	0.26
7.4	17.6	-
7.5	2.27	-
7.6	0.32	-
7.7	0.18	0.26
8	0.06	0.12

8.1	0.07	0.32
8.2	0.12	0.16
8.3	0.42	-
8.4	0.24	0.24
8.5	3.26	-
8.6	0.25	0.16
8.7	1.55	-
8.8	0.09	0.05
9	82.1	-
9.1	25.1	-
9.2	36	-
10	0.94	-
10.1	0.65	-
10.2	0.45	-
10.3	0.83	-
10.4	0.44	-
10.5	0.36	-
11	0.71	-
11.1	0.15	0.12
11.2	1.96	-
11.3	0.05	0.09
11.4	0.13	0.09

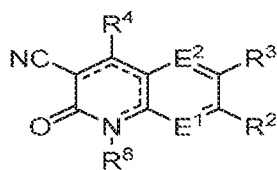
(-) denotes "not tested"

[0225] The present invention is described in connection with preferred embodiments. However, it should be appreciated that the invention is not limited to the disclosed embodiments. It is understood that, given the description of the embodiments of the invention herein, various modifications can be made by a person skilled in the art. Such modifications are encompassed by the claims below.

CLAIMS

What is claimed is:

1. A compound having a structure of formula (I)



(I)

wherein

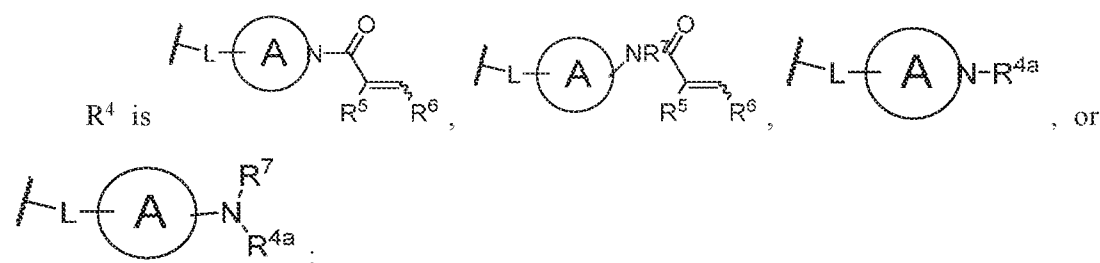
E^1 and E^2 are each independently N or CR^1 ;

=== is a single or double bond as necessary to give every atom its normal valence;

R^1 is independently H, hydroxy, $-C_{1-6}$ alkyl, $-C_{1-6}$ haloalkyl, $-C_{1-6}$ alkoxy, $-NH-C_{1-6}$ alkyl, $-N(C_{1-4}alkyl)_2$, cyano, or halo;

R^2 is halo, $-C_{1-6}$ alkyl, $-C_{1-6}$ haloalkyl, $-OR^{2a}$, $-N(R^{2a})_2$, $-C_{2-6}$ alkenyl, $-C_{2-6}$ alkynyl, $-C_{0-3}$ alkylene- C_{3-14} cycloalkyl, $-C_{0-3}$ alkylene- C_{2-14} heterocycloalkyl, aryl, heteroaryl, $-C_{0-3}$ alkylene- C_{6-14} aryl, or $-C_{0-3}$ alkylene- C_{2-14} heteroaryl, and each R^{2a} is independently H, $-C_{1-6}$ alkyl, $-C_{1-6}$ haloalkyl, $-C_{3-14}$ cycloalkyl, $-C_{2-14}$ heterocycloalkyl, $-C_{2-6}$ alkenyl, $-C_{2-6}$ alkynyl, aryl, or heteroaryl, or two R^{2a} substituents, together with the nitrogen atom to which they are attached, form a 3-7-membered ring;

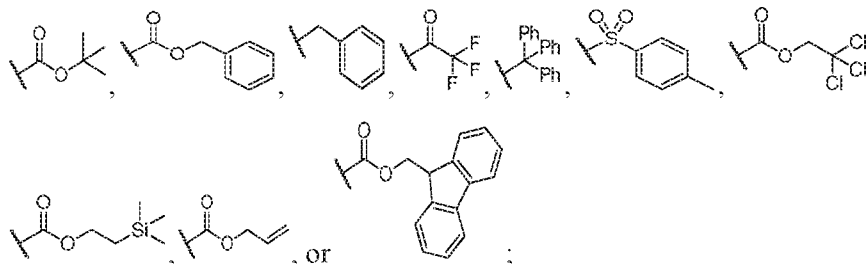
R^3 is halo, $-C_{1-6}$ alkyl, $-C_{1-6}$ haloalkyl, $-C_{1-6}$ alkoxy, C_{3-6} cycloalkyl, $-C_{2-14}$ heterocycloalkyl, $-C_{2-6}$ alkenyl, $-C_{2-6}$ alkynyl, aryl, or heteroaryl;



ring A is a monocyclic 4-7 membered ring or a bicyclic, bridged, fused, or spiro 6-11 membered ring;

L is a bond, $-C_{1-6}$ alkylene, $-O-C_{0-6}$ alkylene, $-S-C_{0-6}$ alkylene, or $-NH-C_{0-6}$ alkylene, and for $-C_{2-6}$ alkylene, $-O-C_{2-6}$ alkylene, $-S-C_{2-6}$ alkylene, and $NH-C_{2-6}$ alkylene, one carbon atom of the alkylene group can optionally be replaced with O, S, or NH;

R^{4a} is H, C_{1-6} alkyl, C_{2-6} alkynyl, C_{1-6} alkylene-O- C_{1-4} alkyl, C_{1-6} alkylene-OH, C_{1-6} haloalkyl, cycloalkyl, heterocycloalkyl, C_{0-3} alkylene- C_{3-14} cycloalkyl, C_{0-3} alkylene- C_{2-14} heterocycloalkyl, aryl, heteroaryl, C_{0-3} alkylene- C_{6-14} aryl, or selected from



R^5 and R^6 are each independently H, halo, $-C_{1-6}$ alkyl, $-C_{2-6}$ alkynyl, $-C_{1-6}$ alkylene-O- C_{1-4} alkyl, $-C_{1-6}$ alkylene-OH, $-C_{1-6}$ haloalkyl, $-C_{1-6}$ alkyleneamine, $-C_{0-6}$ alkylene-amide, $-C_{0-3}$ alkylene- $C(O)OH$, $-C_{0-3}$ alkylene- $C(O)OC_{1-4}$ alkyl, $-C_{1-6}$ alkylene-O-aryl, $-C_{0-3}$ alkylene- $C(O)C_{1-4}$ alkylene-OH, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, $-C_{0-3}$ alkylene- C_{3-14} cycloalkyl, $-C_{0-3}$ alkylene- C_{2-14} heterocycloalkyl, $-C_{0-3}$ alkylene- C_{6-14} aryl, $-C_{0-3}$ alkylene- C_{2-14} heteroaryl, or cyano, or R^5 and R^6 , together with the atoms to which they are attached, form a 4–6 membered ring;

R^7 is H or C_{1-6} alkyl, or R^7 and R^5 , together with the atoms to which they are attached, form a 4–6 membered ring;

R^8 is H, $-C_{1-6}$ alkyl, $-C_{0-3}$ alkylene- C_{6-14} aryl, $-C_{0-3}$ alkylene- C_{3-14} heteroaryl, $-C_{0-3}$ alkylene- C_{3-14} cycloalkyl, $-C_{0-3}$ alkylene- C_{2-14} heterocycloalkyl, $-C_{1-6}$ alkoxy, $-O-C_{0-3}$ alkylene- C_{6-14} aryl, $-O-C_{0-3}$ alkylene- C_{3-14} heteroaryl, $-O-C_{0-3}$ alkylene- C_{3-14} cycloalkyl, $-O-C_{0-3}$ alkylene- C_{2-14} heterocycloalkyl, $-NH-C_{1-8}$ alkyl, $-N(C_{1-8}alkyl)_2$, $-NH-C_{0-3}$ alkylene- C_{6-14} aryl, $-NH-C_{0-3}$ alkylene- C_{2-14} heteroaryl, $-NH-C_{0-3}$ alkylene- C_{3-14} cycloalkyl, $-NH-C_{0-3}$ alkylene- C_{2-14} heterocycloalkyl, halo, cyano, or C_{1-6} alkylene-amine;

wherein the heteroaryl, spiroheterocycloalkyl and heterocycloalkyl groups of any of the R^2 , R^{2a} , R^3 , R^4 , R^{4a} , R^5 , R^6 , R^7 , and R^8 substituents have 1, 2, 3 or 4 heteroatoms independently selected from O, N or S, wherein the cycloalkyl, spirocycloalkyl, spiroheterocycloalkyl, and heterocycloalkyl groups may include a $C=O$ group, and further wherein the spiroheterocycloalkyl, and heterocycloalkyl groups may include a $S=O$ or SO_2 ;

wherein the $-C_{1-6}$ alkyl, $-C_{2-6}$ alkenyl, $-C_{2-6}$ alkynyl and the $-OC_{1-6}$ alkyl of any of the R^1 , R^2 , R^{2a} , R^3 , R^4 , R^{4a} , L , R^5 , R^6 , R^7 , and R^8 substituents is unsubstituted or substituted by 1, 2 or 3 R^9 substituents independently selected from OH, $-OC_{1-6}$ alkyl, $-C_{1-6}$ alkyl-O- C_{1-6} alkyl, halo, -

O-haloC₁₋₆alkyl, -CN, -NR^aR^b, -(NR^aR^bR^c)_n, -OSO₂R^a, -SO₂R^a, -(CH₂CH₂O)_nCH₃, -(=O), -C(=O),

-C(=O)R^a, -OC(=O)R^a, -C(=O)OR^a, -C(=O)NR^aR^b, -O-SiR^aR^bR^c, -SiR^aR^bR^c, -O-(3- to 10-membered heterocycloalkyl), a 6- to 12-membered aryl or heteroaryl, a 5- to 12-membered spirocycloalkyl or spiroheterocycloalkyl, a 3- to 12-membered cycloalkenyl, a 3- to 12-membered monocyclic or bicyclic cycloalkyl, or a 3- to 12-membered monocyclic or bicyclic heterocycloalkyl group, wherein the heteroaryl, spiroheterocycloalkyl and heterocycloalkyl groups have 1, 2, 3 or 4 heteroatoms independently selected from O, N or S, wherein the cycloalkyl, spirocycloalkyl, spiroheterocycloalkyl, and heterocycloalkyl groups may include a C=O group, and further wherein the spiroheterocycloalkyl, and heterocycloalkyl groups may include a S=O or SO₂;

wherein the aryl, heteroaryl, cycloalkyl, and heterocycloalkyl group of any of the R¹, R², R^{2a}, R³, R⁴, R^{4a}, R⁵, R⁶, R⁷, R⁸ and R⁹ substituents can be unsubstituted or substituted with 1, 2, 3 or 4 R¹⁰ substituents independently selected from OH, halo, -NR^cR^d, -C₁₋₆alkyl, -OC₁₋₆alkyl, -C₁₋₆alkyl-OH, -C₁₋₆alkyl-O-C₁₋₆alkyl, C₁₋₆haloalkyl, -O-haloC₁₋₆alkyl, -SO₂R^c, -CN, -C(=O)NR^cR^d, -C(=O)R^c, -OC(=O)R^a, -C(=O)OR^c, a 6- to 12-membered aryl or heteroaryl, a 5- to 12-membered spirocycloalkyl or spiroheterocycloalkyl, a 3- to 12-membered cycloalkenyl, a 3- to 12-membered monocyclic or bicyclic cycloalkyl, or a 3- to 12-membered monocyclic or bicyclic heterocycloalkyl group, wherein the heteroaryl, spiroheterocycloalkyl, and heterocycloalkyl groups of R¹⁰ have 1, 2, 3 or 4 heteroatoms independently selected from O, N or S, wherein the cycloalkyl, spirocycloalkyl, and spiroheterocycloalkyl groups of R¹⁰ or the heterocycloalkyl group of R¹⁰ may include a C=O group, and further wherein the spiroheterocycloalkyl and heterocycloalkyl groups may include a S=O or SO₂;

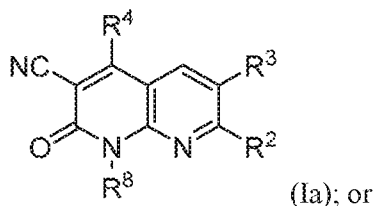
wherein each R^a, R^b, R^c and R^d is independently hydrogen, OH, -C₁₋₆alkyl, -(CH₂CH₂O)_nCH₃, -NR¹¹R¹¹, -C₁₋₆alkyl-NR¹¹R¹¹, phenyl, -C₁₋₆alkyl-C(=O)OH, -C₁₋₆alkyl-C(=O)-O-C₁₋₆alkyl, -C₁₋₆alkyl-3- to 12-membered cycloalkyl, -C₁₋₆alkyl-3- to 12-membered heterocycloalkyl, -C₁₋₆alkyl-6- to 12-membered heteroaryl, a 6- to 12-membered aryl or heteroaryl, a 3- to 12-membered monocyclic or bicyclic cycloalkyl, or a 3- to 12-membered monocyclic or bicyclic heterocycloalkyl group, wherein the heteroaryl group, heterocycloalkyl group of R^a, R^b, R^c, and R^d or the heterocycloalkyl group of the -C₁₋₆alkyl-heterocycloalkyl group of R^a, R^b, R^c, and R^d has from 1, 2, 3, or 4 heteroatoms independently selected from O, N or S, wherein the cycloalkyl and heterocycloalkyl groups of R^a, R^b, R^c, and R^d and the heterocycloalkyl group of the -C₁₋₆alkyl-heterocycloalkyl groups of R^a, R^b, R^c, and R^d may

include a double bond, and further wherein the cycloalkyl and heterocycloalkyl groups of R^a , R^b , R^c , and R^d and the heterocycloalkyl group of the $-C_{1-6}alkyl-heterocycloalkyl$ groups of R^a , R^b , R^c , and R^d may contain a $C=O$ group;

the alkyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl groups of R^a , R^b , R^c , and R^d or the heterocycloalkyl groups of the $-C_{1-6}alkyl-heterocycloalkyl$ groups of R^a , R^b , R^c , and R^d can be unsubstituted or substituted with from 1, 2, 3, or 4 R^{12} substituents, wherein each R^{12} is independently selected from H, OH, halo, $-C_{1-6}alkyl$, $N(CH_3)_2$, $-C_{1-6}haloalkyl$, $C(=O)CH_3$, $-C(=O)OCH_3$, or $-C_{1-6}alkyl-O-C_{1-6}alkyl$; or

a stereoisomer thereof, an atropisomer thereof, a pharmaceutically acceptable salt thereof, a pharmaceutically acceptable salt of the stereoisomer thereof, or a pharmaceutically acceptable salt of the atropisomer thereof.

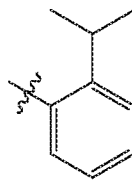
2. A compound of claim 1 having a structure of formula (Ia)



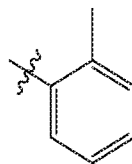
a stereoisomer thereof, an atropisomer thereof, a pharmaceutically acceptable salt thereof, a pharmaceutically acceptable salt of the stereoisomer thereof, or a pharmaceutically acceptable salt of the atropisomer thereof.

3. The compound of claim 1 wherein E^1 is N.
4. The compound of claim 1 wherein E^2 is CR^1 .
5. The compound of claim 4 wherein R^1 is H.
6. The compound of any of one of claims 1-5 wherein R^2 is selected from a halo, or an unsubstituted or substituted aryl.
7. The compound of claim 6 wherein R^2 is a substituted aryl.
8. The compound of claim 6 wherein R^2 is a fluorinated phenyl.

9. The compound of claim 6 wherein R^2 is Cl.



10. The compound of claim 6 wherein R^2 is



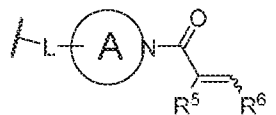
11. The compound of claim 6 wherein R^2 is

12. The compound of any of one of claims 1-11 wherein R^3 is halo.

13. The compound of claim 12 wherein R^3 is Cl.

14. The compound of claim 12 wherein R^3 is F.

15. The compound of any of one of claims 1-14 wherein R^4 is

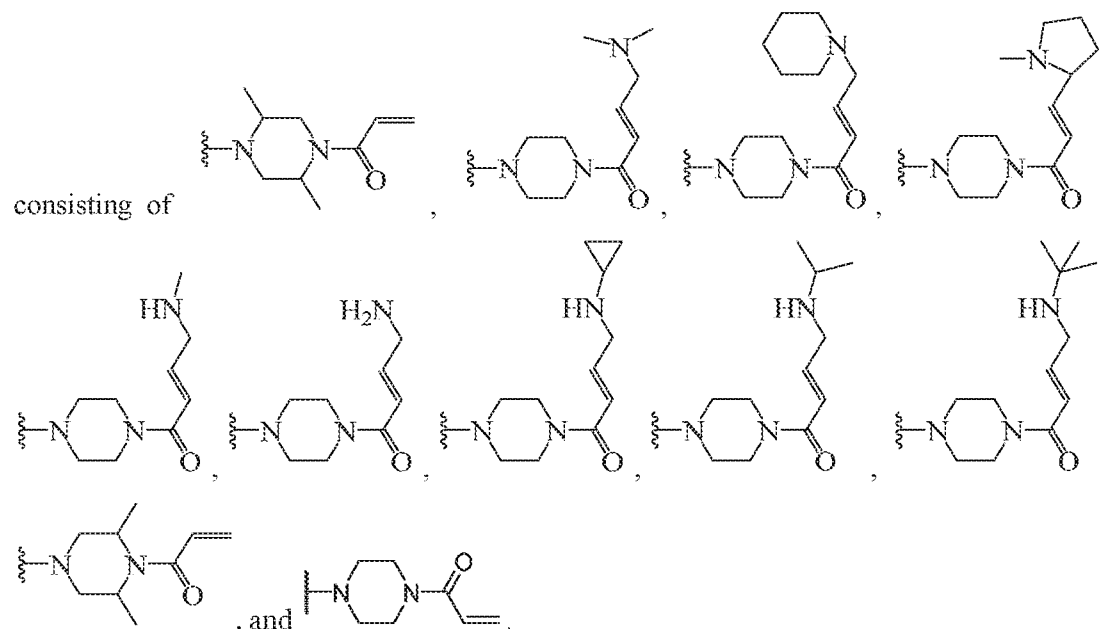


16. The compound of claim 15 wherein L is a bond.

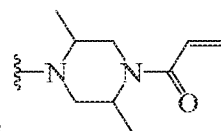
17. The compound of claim 15 wherein ring A is a monocyclic 4-7 membered ring.

18. The compound of claim 17 wherein A is an unsubstituted or substituted heterocycle.

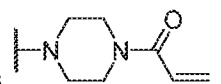
19. The compound of any one of claims 1-18, wherein R^4 is selected from the group



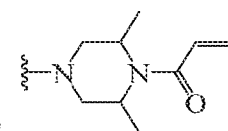
20. The compound of claim 19, wherein R^4 is



21. The compound of claim 19, wherein R^4 is



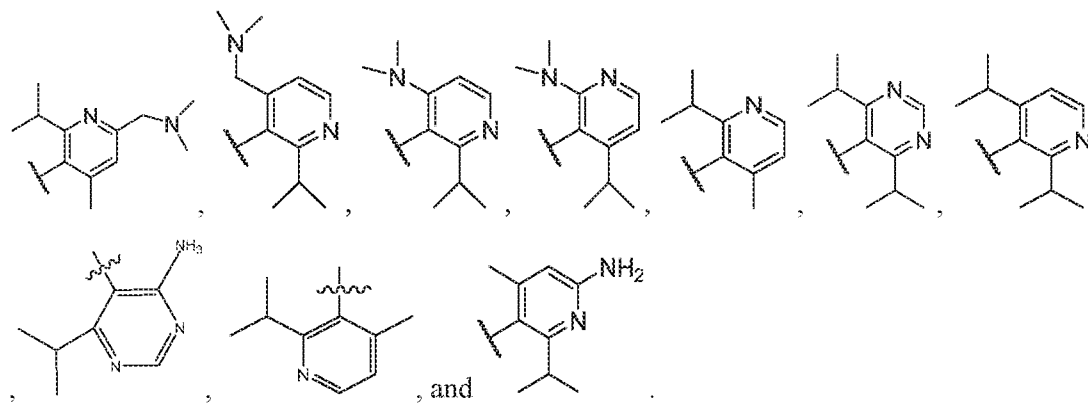
22. The compound of claim 19, wherein R^4 is



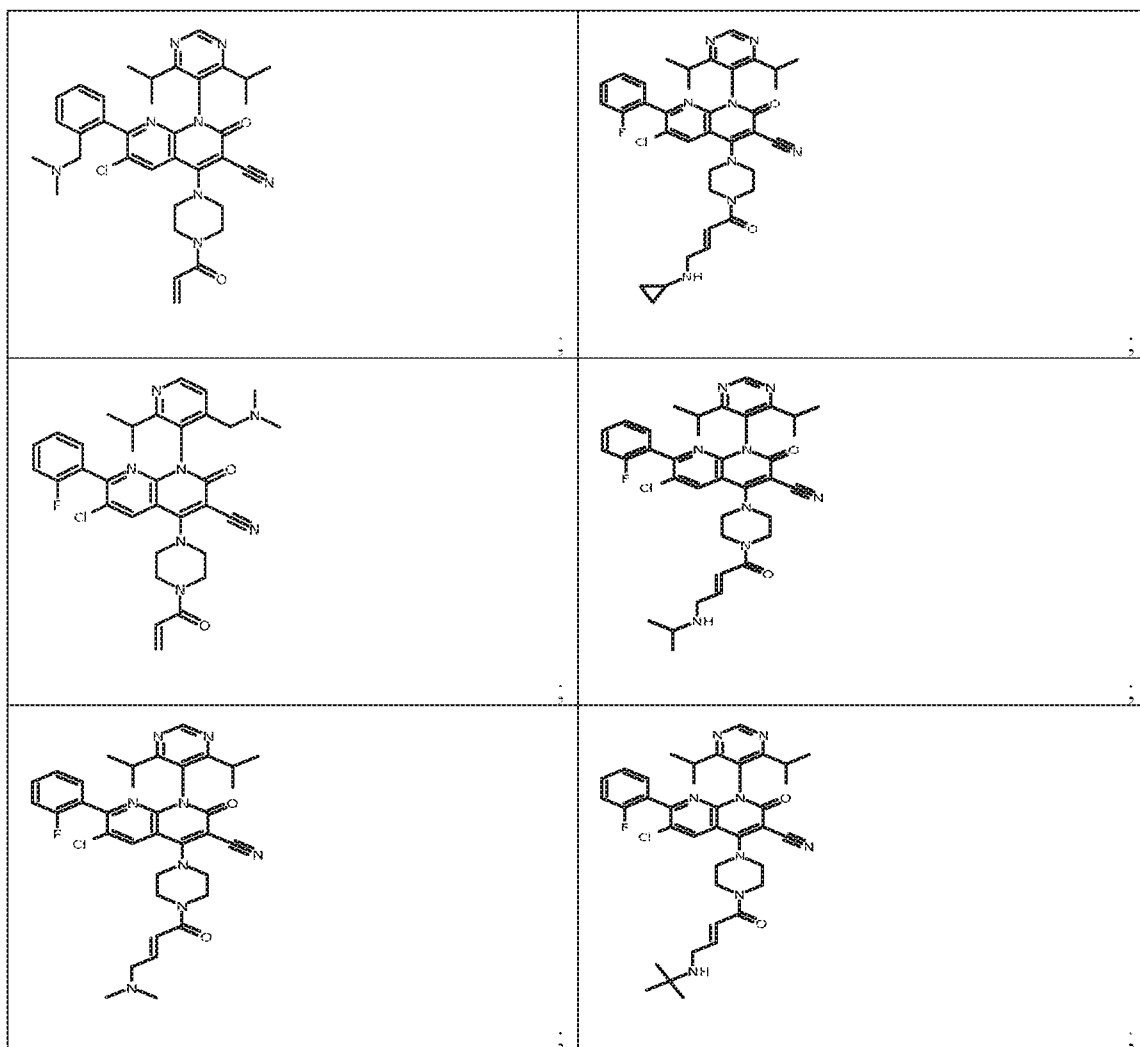
23. The compound of any one of claims 1-22 wherein R^8 is $-C_{0-3}$ alkylene- C_6-14 aryl, or $-C_{0-3}$ alkylene- C_{3-14} heteroaryl.

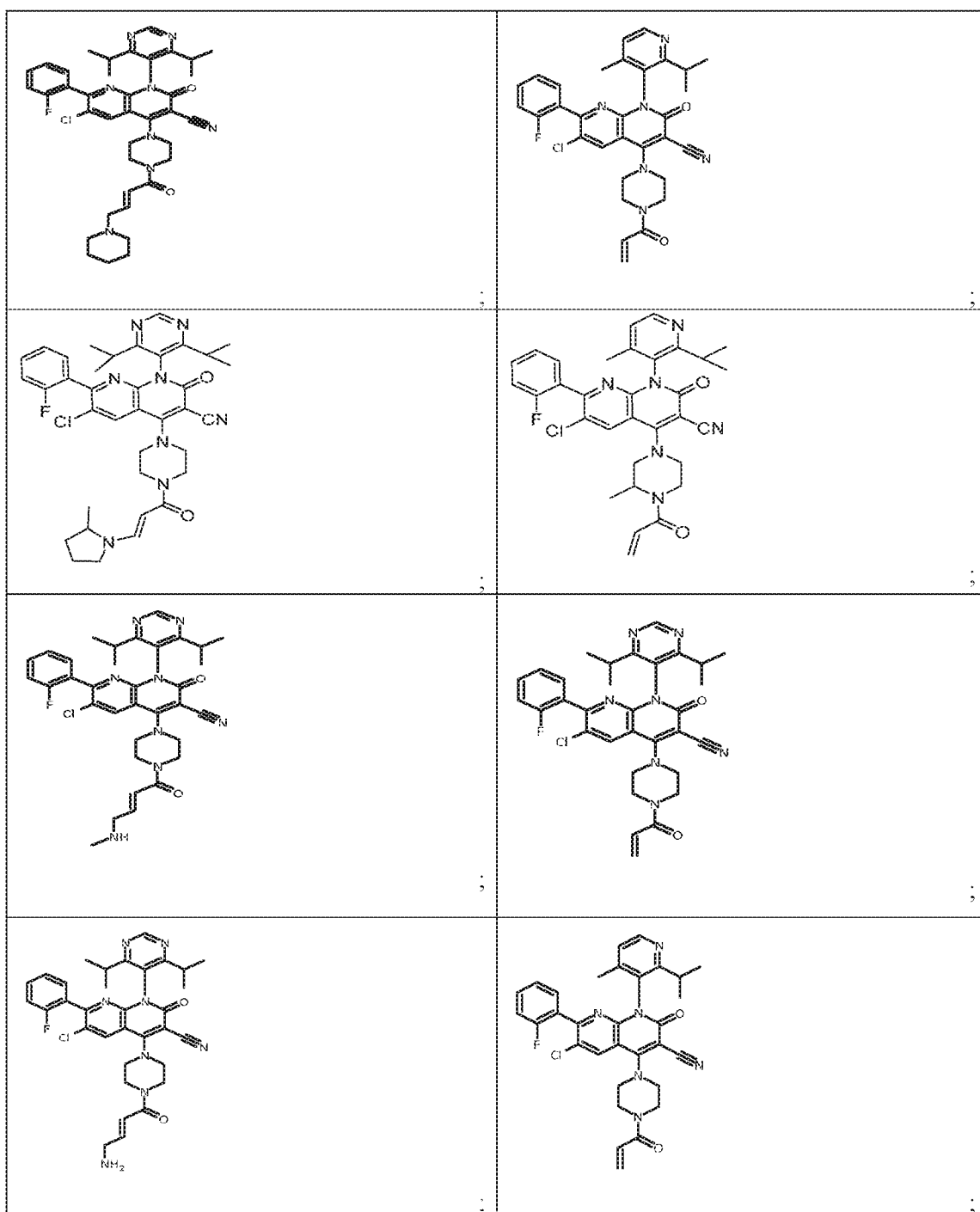
24. The compound of claim 23 wherein R^8 is $-C_{3-14}$ heteroaryl.

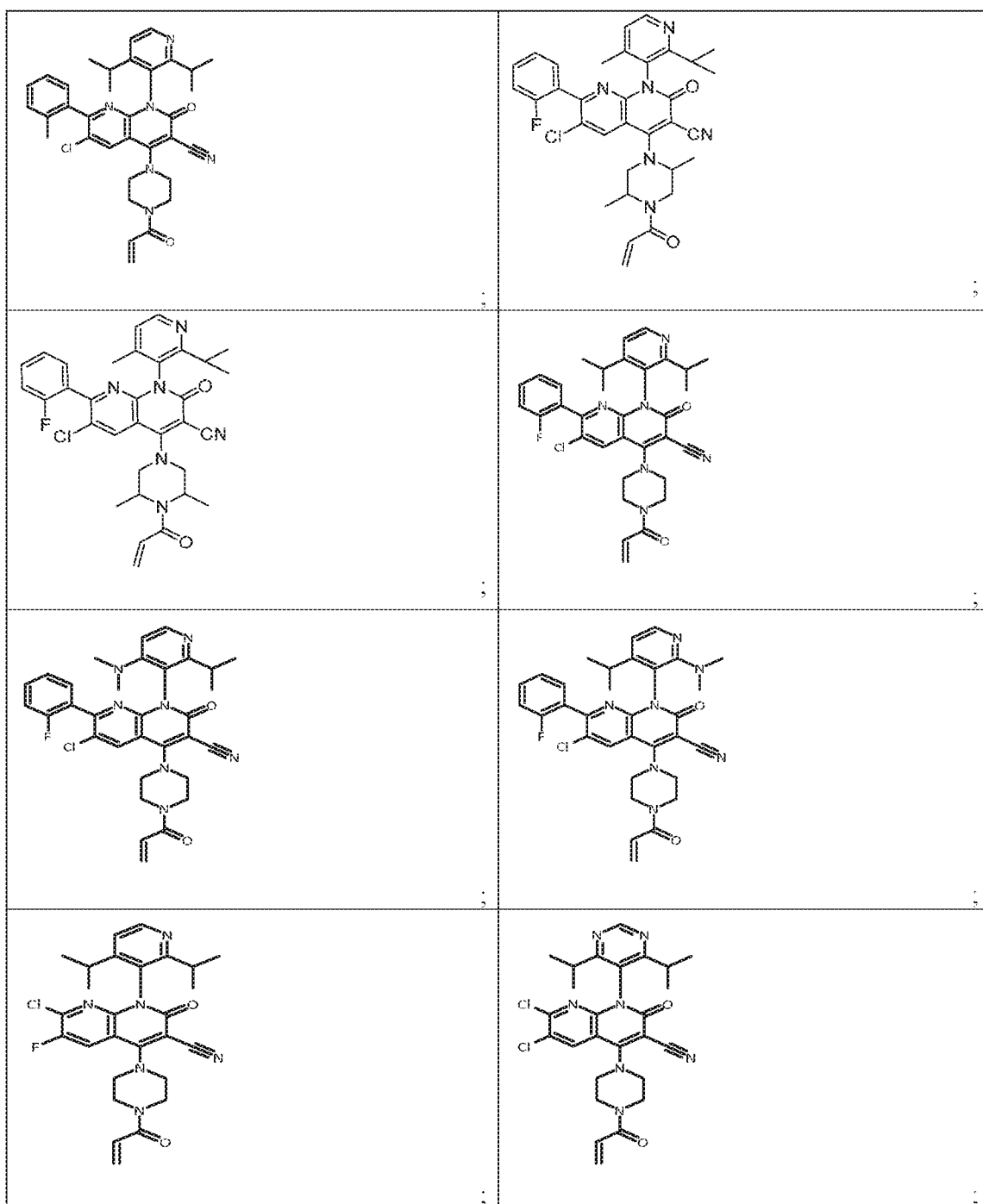
25. The compound of claim 23, wherein R⁸ is selected from the group consisting of

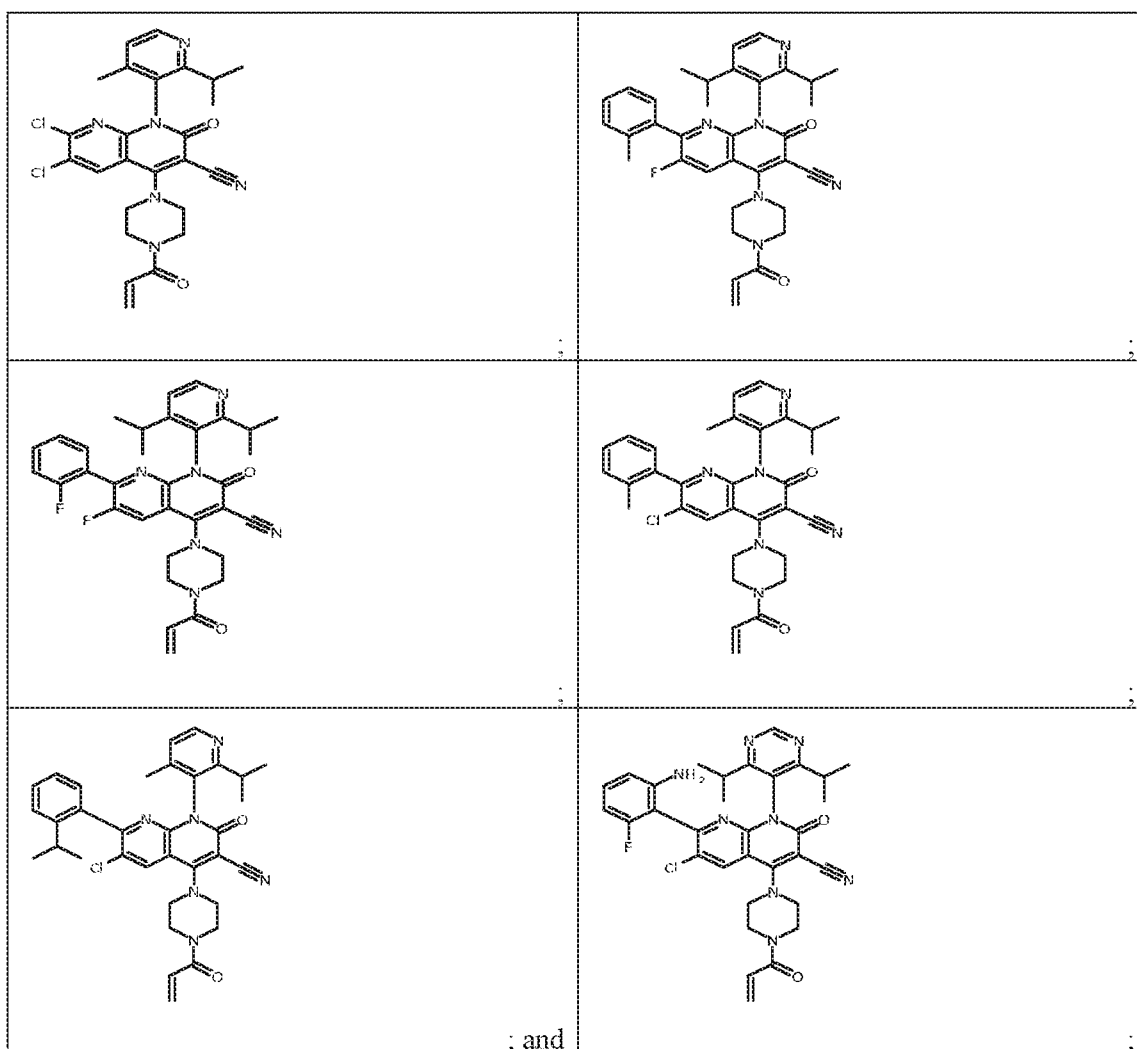


26. A compound having a structure selected from the formula:









or a stereoisomer thereof, an atropisomer thereof, a pharmaceutically acceptable salt thereof, a pharmaceutically acceptable salt of the stereoisomer thereof, or a pharmaceutically acceptable salt of the atropisomer thereof.

27. The compound of any one of claims 1-26 in the form of a pharmaceutically acceptable salt.

28. A pharmaceutical composition comprising the compound of any one of claims 1-27 and a pharmaceutically acceptable excipient.

29. A method of inhibiting KRAS G12C in a cell, comprising contacting the cell with the compound of any one of claims 1-27 or the composition of claim 28.

30. A method of treating cancer in a subject comprising administering to the subject a therapeutically effective amount of the compound of any one of claims 1-26 or the composition of claim 27.

31. The method of claim 30, wherein the cancer is lung cancer, pancreatic cancer, or colorectal cancer.

32. The method of claim 31, wherein the cancer is lung cancer.

33. The method of claim 31, wherein the cancer is pancreatic cancer.

34. The method of claim 31, wherein the cancer is colorectal cancer.

35. The method of claim 30, further comprising administering to the patient in need thereof a therapeutically effective amount of one or more additional pharmaceutically active compounds.

36. The method of claim 35, wherein the one or more additional pharmaceutically active compounds is an anti-PD-1 antibody.

37. The method of claim 36, wherein the one or more additional pharmaceutically active compounds is pembrolizumab.

38. The method of claim 36, wherein the one or more additional pharmaceutically active compounds is nivolumab.

39. The method of claim 36, wherein the one or more additional pharmaceutically active compounds is AMG 404.

40. The method of claim 35, wherein the one or more additional pharmaceutically active compounds is a MEK inhibitor.

41. The method of claim 35, wherein the one or more additional pharmaceutically active compounds is daratumumab.

42. The method of claim 35, wherein the one or more additional pharmaceutically active compounds is an immunomodulatory agent.

43. Use of a compound according to any one of claims 1-27 for treating cancer in a subject.

44. A compound according to any one of claims 1-27 in the preparation of a medicament for treating cancer.

45. The compound according to claim 44, wherein the cancer is non-small cell lung cancer.

