COMBINATION THERAPY USING A PTPN11 INHIBITOR AND A KRAS G12C INHIBITOR

CROSS-REFERENCES TO RELATED APPLICATIONS

[0001] This application claims priority to U.S. Provisional Application No. 63/250,883 filed September 30, 2021, which is incorporated herein in its entirety for all purposes.

STATEMENT AS TO RIGHTS TO INVENTIONS MADE UNDER FEDERALLY SPONSORED RESEARCH AND DEVELOPMENT

[0002] NOT APPLICABLE

REFERENCE TO A "SEQUENCE LISTING," A TABLE, OR A COMPUTER PROGRAM LISTING APPENDIX SUBMITTED ON A COMPACT DISK

[0003] NOT APPLICABLE

BACKGROUND

[0004] The mitogen-activated protein kinase (MAPK) signaling pathway plays critical roles in the regulation of diverse cellular activities, including cell proliferation, survival, differentiation, and motility. The MAPK signal transduction pathway is mediated by receptor tyrosine kinases (RTKs). Dysregulation of the MAPK pathway occurs in more than one-third of all malignancies. The classical MAPK pathway consists of Ras (a family of related proteins which is expressed in all animal cell lineages and organs), Raf (a family of three serine/threonine-specific protein kinases that are related to retroviral oncogenes), MEK (mitogen-activated protein kinase kinase), and ERK (extracellular signal-regulated kinases), sequentially relaying proliferative signals generated at the cell surface receptors into the nucleus through cytoplasmic signaling. RTKs and components of the MAPK pathway, such as RAS and RAF, are frequently activated by mutation in human cancers, resulting in constitutive pathway activation. Several RTK and MAPK pathway inhibitors, including epidermal growth factor receptor (EGFR), anaplastic lymphoma kinase (ALK), and MAPK inhibitors, have been approved for the treatment of solid tumors in which activation of these pathways is the oncogenic driver.

[0005] KRAS (Kirsten rat sarcoma 2 viral oncogene homolog) is a part of the RAS/MAPK pathway. KRAS is one of the most prevalent oncogenes in a variety of human cancers.

Although there is compelling evidence that oncogenic KRAS drives tumorigenesis, efforts to target mutant KRAS have been stalled for many years. Recently, progress has been made in the development of therapeutics against cancers characterized by KRAS having a G12C mutation, which is present in ~15% of lung adenocarcinoma and 0%–8% of other cancers. Results from early-stage clinical trials indicate that many cancer patients in this subgroup could significantly benefit from these novel therapeutics. The first KRAS G12C inhibitor, sotorasib, received accelerated approval by the Food and Drug Administration (FDA) for the treatment of adult patients with KRAS G12C-mutated locally advanced or metastatic NSCLC, as determined by an FDA-approved test, who have received at least one prior systemic therapy. Another KRAS G12C inhibitor, adagrasib, has been granted FDA breakthrough therapy designation for the same indication. Additional KRAS G12C inhibitors are also under investigation.

[0006] Despite progress with inhibitors of RTK and MAPK pathway inhibitors, resistance to these pathway inhibitors have been observed in both clinical and nonclinical studies. Such resistance may be driven by activation or upregulation of other components of the pathway. Accordingly, monotherapies comprising RTK and MAPK pathway inhibitors may not be sufficient for treating tumors that have developed or may develop resistance to approved pathway inhibitors

[0007] Protein-tyrosine phosphatase non-receptor type 11 (PTPN11, also known as Src Homology-2 phosphatase (SHP2)) is a non-receptor protein tyrosine phosphatase encoded by the PTPN11 gene. SHP2 plays a key role in the RTK-mediated MAPK signal transduction pathway. This PTP contains two tandem Src homology-2 (SH2) domains, which function as phospho-tyrosine binding domains, a catalytic domain, and a C-terminal tail. In the basal state the protein typically exists in an inactive, self-inhibited conformation with the N-terminal SH2 domain blocking the active site. When stimulated by signal transduction mediated by cytokines and growth factor binding of phosphorylated proteins to the SH2 domains the auto-inhibition is relieved, this makes the active site available for dephosphorylation of PTPN11 substrates (MG Mohl, BG Neel, *Curr. Opin. Genetics Dev.* 2007, 17, 23–30. KS Grossmann, *Adv. Cancer Res.* 2010, 106, 53-89. W.Q. Huang et. al. *Curr. Cancer Drug Targets* 2014, 14, 567-588. C. Gordon et. al. *Cancer Metastasis Rev.* 2008, 27, 179-192.).

[0008] Germ-line and somatic mutations in PTPN11 have been reported in several human diseases resulting in gain-of-function in the catalytic activity, including Noonan Syndrome and Leopard Syndrome; as well as multiple cancers such as juvenile myelomonocytic leukemia, neuroblastoma, myelodysplastic syndrome, B cell acute lymphoblastic leukemia/lymphoma, melanoma, acute myeloid leukemia and cancers of the breast, lung and colon (MG Mohl, BG Neel, *Curr. Opin. Genetics Dev.* 2007, 17, 23–30). Recent studies have demonstrated that single PTPN11 mutations are able to induce Noonan syndrome, JMML-like myeloproliferative disease and acute leukemia in mice. These mutations disrupt the auto-inhibition between the N-SH2 domains and the catalytic site allowing constitutive access of substrates to the catalytic site of the enzyme (E. Darian et al, *Proteins,* 2011, 79, 1573-1588. Z-H Yu et al, *JBC*, 2013, 288, 10472, W Qiu et al *BMC Struct. Biol.* 2014, 14, 10).

[0009] PTPN11 is widely expressed in most tissues and plays a regulatory role in various cell signaling events that are important for a diversity of cell functions that includes proliferation, differentiation, cell cycle maintenance, epithelial-mesenchymal transition (EMT), mitogenic activation, metabolic control, transcription regulation, and cell migration, through multiple signaling pathways including the Ras-MAPK, the JAK-STAT or the PI3K-AKT pathways (Tajan, M. et. al. *Eur. J. Medical Genetics*, 2015, 58, 509-525. Prahallad, A. et. al. *Cell Reports,* 2015, 12, 1978-1985).

[0010] Additionally there is growing evidence that PTPN11/SHP2 is implicated in immune evasion during tumorigenesis, and hence a SHP2 inhibitor could stimulate the immune response in cancer patients (*Cancer Res.* 2015 Feb 1;75(3):508-18. T Yokosuka T, *J Exp Med.* 2012, 209(6), 1201. S Amarnath *Sci Transl Med.* 2011, 3, 111ra120. T Okazaki, *PNAS* 2001, 98:24, 13866-71).

[0011] As cancers may have or develop resistance to RTK and MAPK pathway inhibitors including KRAS G12C inhibitors, there remains a need for effective and safe therapeutic agents, including agents that may be used in combination, to treat cancers.

BRIEF SUMMARY

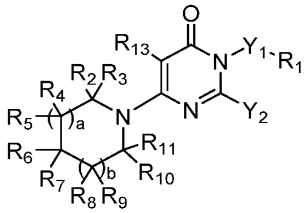
[0012] The present disclosure provides methods of treating diseases and disorders (e.g., cancers) by administering both a PTPN11 inhibitor (e.g., a compound represented by formula (I), such as formula (10b), as described herein) and a KRAS G12C inhibitor.

[0013] In a first aspect, the present disclosure provides a method of treating cancer in a subject, the method including administering to the subject:

a) a therapeutically effective amount of a PTPN11 inhibitor; and

b) a therapeutically effective amount of a KRAS G12C inhibitor,

wherein the PTPN11 inhibitor is represent by formula (I):

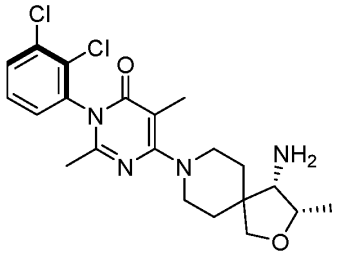


(I)

or a pharmaceutically acceptable salt, hydrate, solvate, stereoisomer, conformational isomer, tautomer, or a combination thereof, wherein the subscripts a and b, Y_1, Y_2, and R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_9, R_{10}, R_{11}, and R_{13} are as provided herein.

[0014] In a second aspect, the present disclosure provides a method of treating a solid tumor (e.g., an advanced non-small cell lung cancer) in a subject, the method including administering to a subject in need thereof:

a) a therapeutically effective amount of a compound represented by formula (10b):



(10b),

or a pharmaceutically acceptable salt, hydrate, solvate, stereoisomer, conformational isomer, tautomer, or a combination thereof; and

b) a therapeutically effective amount of a KRAS G12C inhibitor,

wherein the subject has a KRAS mutation (e.g., as described herein). In some embodiments, the KRAS G12C inhibitor is not sotorasib.

[0015] In a third aspect, the present disclosure provides a pharmaceutical composition for treating cancer in a subject, the composition including:

a) a therapeutically effective amount of a PTPN11 inhibitor; and

b) a therapeutically effective amount of a KRAS G12C inhibitor,

together with a pharmaceutically acceptable carrier or excipient,

wherein the PTPN11 inhibitor is represent by formula (I) as defined and described herein.

[0016] In a fourth aspect, the present disclosure provides a kit for treating a disease or disorder (e.g., cancer) in a subject, the kit including:

a) a therapeutically effective amount of a PTPN11 inhibitor; and

b) a therapeutically effective amount of a KRAS G12C inhibitor,

together with instruction for effective administration,

wherein the PTPN11 inhibitor is represent by formula (I) as defined and described herein.

BRIEF DESCRIPTION OF THE DRAWINGS

[0017] **FIGs. 1A-1E** show the compound of formula (10b) in combination with Compound A (i.e., 6-fluoro-7-(2-fluoro-6-hydroxyphenyl)-1-[4-methyl-2-(propan-2-yl)pyridin-3-yl]-4-[(2S)-2-methyl-4-(prop-2-enoyl)piperazin-1-yl]pyrido[2,3-d]pyrimidin-2(1H)-one) suppresses the growth of NCI-H358 subcutaneous tumors at tolerated doses in a mouse model. **FIGs. 1A, 1B, and 1D** show tumor volume monitored bi-weekly by caliper. **FIGs. 1C and 1E** show body weights recorded. Data represent mean±SEM. N=8 mice/group for **FIGs. 1B-1E** and N=10 mice/group for **FIG. 1A**.

[0018] **FIGs. 2A** and **2B** show changes in tumor volume and body weight in mice bearing NCI-H358 subcutaneous cell line-derived tumors upon treatment with compound of formula (10b) alone or in combination with sotorasib (AMG 510).

[0019] **FIGs. 3A** and **3B** show changes in tumor volume and body weight in mice bearing NCI-H2122 subcutaneous cell line-derived tumors upon treatment with compound of formula (10b) alone or in combination with sotorasib (AMG 510).

[0020] **FIGs. 4A-4D** show in vitro viability data for the compound of formula (10b) and sotorasib (AMG 510) in an NCI-H358 ($KRAS^{G12C}$) model. **FIG. 4A**: 3D viability at various concentrations of formula (10b). **FIG. 4B**: Bliss energy scoring for combinations of AMG 510 and formula (10b). **FIG. 4C**: fold change in DUSP6 levels. **FIG. 4D**: fold change in SPRY4 levels. As shown in **FIGs. 4C-4D**, the combination of AMG 510 and formula (10b) suppressed DUSP6 and SPRY4 levels relative to either agent alone.

[0021] **FIGs. 5A-5E** show 3D proliferation assays in MiaPaca-2 KRAS G12C mutant cell lines. **FIG. 5A**: Single agent growth inhibition of Adagrasib and formula (10b) on MiaPaCa-2 cells. The cells were treated with the combination of serial dilution of Adagrasib and Compound (10b) for 5 days. CTG assay was performed for cell viability evaluation (Data represent mean ± SE, n = 3). **FIG. 5B**: Dose-response matrix and **FIG. 5C**: synergy scores, produced from the 8x8 matrix by Loewe synergy model analysis. **FIGs. 5D-5E**: Drug combination dose-response curves of Adagrasib and formula (10b) on MiaPaCa-2 cells.

[0022] **FIGs. 6A-6E** show 3D proliferation assay in human NSCLC NCI-H358 KRAS G12C mutant cell line. **FIG. 6A**: Single agent growth inhibition of Adagrasib and formula (10b) on NCI-H358 cells. The cells were treated with the combination of serial dilution of Adagrasib and formula (10b) for 5 days. CTG assay was performed for cell viability evaluation (Data represent mean ± SD, n = 3). **FIG. 6B**: Dose-response matrix and **FIG. 6C**: synergy scores produced from the 8x8 matrix by Loewe synergy model analysis. **FIGs. 6D-6E**: Drug combination dose-response curves of Adagrasib and formula (10b) on NCI-H358 cells.

[0023] **FIGs. 7A-7E** show 3D proliferation assay in CRC patient-derived organoid models S002375 with KRAS G12C mutation. **FIG. 7A**: Single agent growth inhibition of Adagrasib and formula (10b) on S002375 cells. The cells were treated with the combination of serial dilution of Adagrasib and formula (10b) for 5 days. CTG assay was performed for cell viability evaluation (Data represent mean ± SD, n = 3). **FIG. 7B**: Dose-response matrix and **FIG. 7C**: synergy scores produced from the 8x8 matrix by Loewe synergy model analysis. **FIGs. 7D-7E**: Drug combination dose-response curves of Adagrasib and formula (10b) on S002375 cells.

[0024] **FIG. 8** shows an overall design of a clinical study of Compound (10b) in combination with a KRAS G12C inhibitor in patients with advanced non-small cell lung cancer with a KRAS mutation, as described in Example 5.

[0025] **FIG. 9** shows a flowchart for a trial conducted using the BOIN Design. Abbreviations: BOIN=Bayesian optimal interval design; DLT=dose limiting toxicity; MTD=maximum tolerated dose. Note: $\lambda e = 19.7\%$ and $\lambda d = 29.8\%$. In practice, with 6 patients/cohort, if the DLT rate is $\leq 1/6$ then escalate the dose, if the DLT rate is $\geq 2/6$ then de-escalate the dose.

DETAILED DESCRIPTION

I. GENERAL

[0026] The present disclosure provides a combination therapy method of treating a disease or disorder (e.g., cancer, such as a solid tumor) in a subject. The method includes administering to the subject a) a therapeutically effective amount of a PTPN11 inhibitor; and b) a therapeutically effective amount of a KRAS G12C inhibitor, wherein the PTPN11 inhibitor is represented by formula (I) as defined and described herein (e.g., a compound represented by formula (10b)). In particular, the cancer is characterized by a KRAS mutation, such as a mutation other than a Q61X mutation, e.g., a KRAS G12C mutation. In some instances, the cancer is a solid tumor, such as an advanced or metastatic non-small cell lung cancer (NSCLC). The KRAS G12C inhibitor may at least partially inhibit KRAS G12C kinase. The KRAS G12C inhibitor may be a selective KRAS G12C inhibitor (e.g., having greater selectivity for KRAS having a G12C mutation over KRAS having another mutation such as a G12D mutation). The KRAS G12C inhibitor may be a covalent inhibitor (e.g., capable of covalently modifying cysteine 12). The KRAS G12C inhibitor may be a noncolvanet inhibitor. The KRAS G12C inhibitor may bind to an inactive ("GDP") form of KRAS. The KRAS G12C inhibitor may bind to an active ("GTP") form of KRAS. The KRAS G12C inhibitor may bind to both inactive ("GDP") and active ("GTP") forms of KRAS. Also provided are a pharmaceutical composition thereof and a kit thereof for treating a disease or disorder (e.g., cancer) in a subject.

II. DEFINITIONS

[0027] As used herein, the terms below have the meanings indicated.

[0028] "Comprise," "include," and "have," and the derivatives thereof, are used herein interchangeably as comprehensive, open-ended terms. For example, use of "comprising," "including," or "having" means that whatever element is comprised, had, or included, is not the only element encompassed by the subject of the clause that contains the verb.

[0029] When ranges of values are disclosed, and the notation "from n_1 … to n_2" or "between n_1 … and n_2" is used, where n_1 and n_2 are the numbers, then unless otherwise specified, this notation is intended to include the numbers themselves and the range between them. This range may be integral or continuous between and including the end values. By way of example, the range "from 2 to 6 carbons" is intended to include two, three, four, five, and six carbons, since carbons come in integer units. Compare, by way of example, the range "from 1 to 3 μM (micromolar)," which is intended to include 1 μM, 3 μM, and everything in between to any number of significant figures (e.g., 1.255 μM, 2.1 μM, 2.9999 μM, etc.).

[0030] "About," as used herein, is intended to qualify the numerical values which it modifies, denoting such a value as variable within a margin of error. When no particular margin of error, such as a standard deviation to a mean value given in a chart or table of data, is recited, the term "about" should be understood to mean that range which would encompass the recited value and the range which would be included by rounding up or down to that figure as well, taking into account significant figures.

[0031] "Acyl," as used herein, alone or in combination, refers to a carbonyl attached to an alkenyl, alkyl, aryl, cycloalkyl, heteroaryl, heterocycle, or any other moiety were the atom attached to the carbonyl is carbon. An "acetyl" group refers to a $-C(O)CH_3$ group. An "alkylcarbonyl" or "alkanoyl" group refers to an alkyl group attached to the parent molecular moiety through a carbonyl group. Examples of such groups include methylcarbonyl and ethylcarbonyl. Examples of acyl groups include formyl, alkanoyl and aroyl.

[0032] "Alkenyl," as used herein, alone or in combination, refers to a straight-chain or branched-chain hydrocarbon radical having one or more double bonds and containing from 2 to 20 carbon atoms. In certain embodiments, said alkenyl will comprise from 2 to 6 carbon atoms. The term "alkenylene" refers to a carbon-carbon double bond system attached at two or more positions such as ethenylene [(-CH=CH-),(-C::C-)]. Examples of suitable alkenyl radicals

include ethenyl, propenyl, 2-methylpropenyl, 1,4-butadienyl and the like. Unless otherwise specified, the term "alkenyl" may include "alkenylene" groups.

[0033] "Alkynyl" refers to either a straight chain or branched hydrocarbon having at least 2 carbon atoms and at least one triple bond and having the number of carbon atom indicated (i.e., C_{2-6} means to two to six carbons). Alkynyl can include any number of carbons, such as C_2, C_{2-3}, C_{2-4}, C_{2-5}, C_{2-6}, C_{2-7}, C_{2-8}, C_{2-9}, C_{2-10}, C_3, C_{3-4}, C_{3-5}, C_{3-6}, C_4, C_{4-5}, C_{4-6}, C_5, C_{5-6}, and C_6. Examples of alkynyl groups include, but are not limited to, acetylenyl, propynyl, 1-butynyl, 2-butynyl, butadiynyl, 1-pentynyl, 2-pentynyl, isopentynyl, 1,3-pentadiynyl, 1,4-pentadiynyl, 1-hexynyl, 2-hexynyl, 3-hexynyl, 1,3-hexadiynyl, 1,4-hexadiynyl, 1,5-hexadiynyl, 2,4-hexadiynyl, and 1,3,5-hexatriynyl.

[0034] "Alkoxy," as used herein, alone or in combination, refers to an alkyl ether radical, wherein the term alkyl is as defined below. Examples of suitable alkyl ether radicals include methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, iso-butoxy, sec-butoxy, tert-butoxy, and the like.

[0035] "Alkyl," as used herein, alone or in combination, refers to a straight-chain or branched-chain alkyl radical containing from 1 to 20 carbon atoms. In certain embodiments, said alkyl will comprise from 1 to 10 carbon atoms. In further embodiments, said alkyl will comprise from 1 to 8 carbon atoms. Alkyl groups are unsubstituted or substituted as defined herein. Examples of alkyl radicals include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, pentyl, iso-amyl, hexyl, octyl, noyl and the like. The term "alkylene," as used herein, alone or in combination, refers to a saturated aliphatic group derived from a straight or branched chain saturated hydrocarbon attached at two or more positions, such as methylene ($-CH_2-$). Unless otherwise specified, the term "alkyl" may include "alkylene" groups.

[0036] "Alkylamino," as used herein, alone or in combination, refers to an alkyl group attached to the parent molecular moiety through an amino group. Suitable alkylamino groups may be mono- or dialkylated, forming groups such as, for example, N-methylamino, N-ethylamino, N,N-dimethylamino, N,N-ethylmethylamino and the like.

[0037] "Alkylthio," as used herein, alone or in combination, refers to an alkyl thioether (R–S–) radical wherein the term alkyl is as defined above and wherein the sulfur may be singly or

doubly oxidized. Examples of suitable alkyl thioether radicals include methylthio, ethylthio, n-propylthio, isopropylthio, n-butylthio, iso-butylthio, sec-butylthio, tert-butylthio, methanesulfonyl, ethanesulfinyl, and the like.

[0038] "Amido" and "carbamoyl," as used herein, alone or in combination, refer to an amino group as described below attached to the parent molecular moiety through a carbonyl group, or vice versa. The "amido" group as used herein incudes a "C-amido" and "N-amido" groups. The term "C-amido" as used herein, alone or in combination, refers to a -C(O)N(RR') group with R and R' as defined herein or as defined by the specifically enumerated "R" groups designated. In some embodiments, the "amido" group includes -C(O)NH_2, C_{1-4}alkylamido, and di(C_{1-4}alkyl)amido. The term "C_{1-4}alkylamido", as used herein, refers to -C(O)NH(C_{1-4}alkyl), wherein C_{1-4}alkyl is as defined herein. The term "N-amido" as used herein, alone or in combination, refers to a RC(O)N(R')- group, with R and R' as defined herein or as defined by the specifically enumerated "R" groups designated. The term "acylamino" as used herein, alone or in combination, embraces an acyl group attached to the parent moiety through an amino group. An example of an "acylamino" group is acetylamino ($CH_3C(O)NH$-).

[0039] "Amino," as used herein, alone or in combination, refers to -NRR', wherein R and R' are independently selected from hydrogen, alkyl, acyl, heteroalkyl, aryl, cycloalkyl, heteroaryl, and heterocycloalkyl, any of which may themselves be unsubstituted or substituted. Additionally, R and R' may combine to form heterocycloalkyl, either of which is unsubstituted or substituted.

[0040] "Aryl," as used herein, alone or in combination, means a carbocyclic aromatic system containing one, two or three rings wherein such polycyclic ring systems are fused together. The term "aryl" embraces aromatic groups such as phenyl, naphthyl, anthracenyl, and phenanthryl.

[0041] "Arylalkenyl" or "aralkenyl," as used herein, alone or in combination, refers to an aryl group attached to the parent molecular moiety through an alkenyl group.

[0042] "Arylalkoxy" or "aralkoxy," as used herein, alone or in combination, refers to an aryl group attached to the parent molecular moiety through an alkoxy group.

[0043] "Arylalkyl" or "aralkyl," as used herein, alone or in combination, refers to an aryl group attached to the parent molecular moiety through an alkyl group.

[0044] "Aryloxy," as used herein, alone or in combination, refers to an aryl group attached to the parent molecular moiety through an oxy.

[0045] "Carbamate," as used herein, alone or in combination, refers to an ester of carbamic acid (-NHCOO-) which may be attached to the parent molecular moiety from either the nitrogen or acid end, and which is unsubstituted or substituted as defined herein.

[0046] "O-carbamyl" as used herein, alone or in combination, refers to a -OC(O)NRR', group - with R and R' as defined herein.

[0047] "N-carbamyl" as used herein, alone or in combination, refers to a ROC(O)NR'- group, with R and R' as defined herein.

[0048] "Carbonyl," as used herein, when alone includes formyl [-C(O)H] and in combination is a -C(O)- group.

[0049] "Carboxyl" or "carboxy," as used herein, refers to -C(O)OH or the corresponding "carboxylate" anion, such as is in a carboxylic acid salt. An "O-carboxy" group refers to a RC(O)O- group, where R is as defined herein. A "C-carboxy" group refers to a -C(O)OR groups where R is as defined herein.

[0050] "Cyano," as used herein, alone or in combination, refers to -CN.

[0051] "Cycloalkyl," or, alternatively, "carbocycle," as used herein, alone or in combination, refers to a saturated or partially saturated monocyclic, bicyclic or tricyclic alkyl group wherein each cyclic moiety contains from 3 to 12 carbon atom ring members and which may optionally be a benzo fused ring system which is unsubstituted or substituted as defined herein. The term "cycloalkenyl" refers to a cycloalkyl group having one or two double bonds. In certain embodiments, said cycloalkyl (or cycloalkenyl) will comprise from 5 to 7 carbon atoms. Examples of such groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclobutenyl, cyclopentenyl, cyclohexenyl, tetrahydronapthyl, indanyl, octahydronaphthyl, 2,3-dihydro-1H-indenyl, adamantyl and the like. "Bicyclic" and "tricyclic" as used herein are intended to include both fused ring systems, such as decahydronaphthalene, octahydronaphthalene as well as the multicyclic (multicentered) saturated or partially unsaturated

type. The latter type of isomer is exemplified in general by, bicyclo[1,1,1]pentane, camphor, adamantane, and bicyclo[3,2,1]octane.

[0052] "Ester," as used herein, alone or in combination, refers to a carboxy group bridging two moieties linked at carbon atoms.

[0053] "Ether," as used herein, alone or in combination, refers to an oxy group bridging two moieties linked at carbon atoms.

[0054] "Halo," or "halogen," as used herein, alone or in combination, refers to fluorine, chlorine, bromine, or iodine.

[0055] "Haloalkoxy," as used herein, alone or in combination, refers to a haloalkyl group attached to the parent molecular moiety through an oxygen atom.

[0056] "Haloalkyl," as used herein, alone or in combination, refers to an alkyl radical having the meaning as defined above wherein one or more hydrogens are replaced with a halogen. Specifically embraced are monohaloalkyl, dihaloalkyl and polyhaloalkyl radicals. A monohaloalkyl radical, for one example, may have an iodo, bromo, chloro, or fluoro atom within the radical. Dihalo and polyhaloalkyl radicals may have two or more of the same halo atoms or a combination of different halo radicals. Examples of haloalkyl radicals include fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, pentafluoroethyl, heptafluoropropyl, difluorochloromethyl, dichlorofluoromethyl, difluoroethyl, difluoropropyl, dichloroethyl and dichloropropyl. "Haloalkylene" refers to a haloalkyl group attached at two or more positions. Examples include fluoromethylene (-CFH-), difluoromethylene (-CF_2 -), chloromethylene (-CHCl-) and the like.

[0057] "Heteroalkyl," as used herein, alone or in combination, refers to a stable straight or branched chain, or a combination thereof, fully saturated or containing from 1 to 3 degrees of unsaturation, consisting of the stated number of carbon atoms and from one to three heteroatoms selected from N, O, and S, and wherein the N and S atoms may optionally be oxidized and the N heteroatom may optionally be quaternized. The heteroatom(s) may be placed at any interior position of the heteroalkyl group. Up to two heteroatoms may be consecutive, such as, for example, -CH_2-NH-OCH_3.

[0058] "Heteroaryl," as used herein, alone or in combination, refers to a 3 to 15 membered unsaturated heteromonocyclic ring, or a fused monocyclic, bicyclic, or tricyclic ring system in which at least one of the fused rings is aromatic, which contains at least one atom selected from N, O, and S. In certain embodiments, said heteroaryl will comprise from 1 to 4 heteroatoms as ring members. In further embodiments, said heteroaryl will comprise from 1 to 2 heteroatoms as ring members. In certain embodiments, said heteroaryl will comprise from 5 to 7 atoms. The term also embraces fused polycyclic groups wherein heterocyclic rings are fused with aryl rings, wherein heteroaryl rings are fused with other heteroaryl rings, wherein heteroaryl rings are fused with heterocycloalkyl rings, or wherein heteroaryl rings are fused with cycloalkyl rings. Examples of heteroaryl groups include pyrrolyl, pyrrolinyl, imidazolyl, pyrazolyl, pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, triazolyl, pyranyl, furyl, thienyl, oxazolyl, isoxazolyl, oxadiazolyl, thiazolyl, thiadiazolyl, isothiazolyl, indolyl, isoindolyl, indolizinyl, benzimidazolyl, quinolyl, isoquinolyl, quinoxalinyl, quinazolinyl, indazolyl, benzotriazolyl, benzodioxolyl, benzopyranyl, benzoxazolyl, benzoxadiazolyl, benzothiazolyl, benzothiadiazolyl, benzofuryl, benzothienyl, chromonyl, coumarinyl, benzopyranyl, tetrahydroquinolinyl, tetrazolopyridazinyl, tetrahydroisoquinolinyl, thienopyridinyl, furopyridinyl, pyrrolopyridinyl and the like. Exemplary tricyclic heterocyclic groups include carbazolyl, benzidolyl, phenanthrolinyl, dibenzofuranyl, acridinyl, phenanthridinyl, xanthenyl and the like.

[0059] "Heterocycloalkyl" and, interchangeably, "heterocycle," as used herein, alone or in combination, each refer to a saturated, partially unsaturated, or fully unsaturated (but nonaromatic) monocyclic, bicyclic, or tricyclic heterocyclic group containing at least one heteroatom as a ring member, wherein each said heteroatom may be independently selected from nitrogen, oxygen, and sulfur. In certain embodiments, said heterocycloalkyl will comprise from 1 to 4 heteroatoms as ring members. In further embodiments, said heterocycloalkyl will comprise from 1 to 2 heteroatoms as ring members. In certain embodiments, said heterocycloalkyl will comprise from 3 to 8 ring members in each ring. In further embodiments, said heterocycloalkyl will comprise from 3 to 7 ring members in each ring. In yet further embodiments, said heterocycloalkyl will comprise from 5 to 6 ring members in each ring. "Heterocycloalkyl" and "heterocycle" are intended to include sulfones, sulfoxides, N-oxides of tertiary nitrogen ring members, and carbocyclic fused and benzo fused ring systems; additionally, both terms also include systems where a heterocycle ring is fused to an aryl group,

as defined herein, or an additional heterocycle group. Examples of heterocycle groups include aziridinyl, azetidinyl, 1,3-benzodioxolyl, dihydroisoindolyl, dihydroisoquinolinyl, dihydrocinnolinyl, dihydrobenzodioxinyl, dihydro[1,3]oxazolo[4,5-b]pyridinyl, benzothiazolyl, dihydroindolyl, dihydropyridinyl, 1,3-dioxanyl, 1,4-dioxanyl, 1,3-dioxolanyl, isoindolinyl, morpholinyl, piperazinyl, pyrrolidinyl, tetrahydropyridinyl, piperidinyl, thiomorpholinyl, and the like. The heterocycle groups are unsubstituted or substituted unless specifically prohibited.

[0060] "Hydrazinyl" as used herein, alone or in combination, refers to two amino groups joined by a single bond, i.e., -N-N-.

[0061] "Hydroxy," as used herein, alone or in combination, refers to -OH.

[0062] "Hydroxyalkyl," as used herein, alone or in combination, refers to a hydroxy group attached to the parent molecular moiety through an alkyl group.

[0063] "Iminohydroxy," as used herein, alone or in combination, refers to =N(OH) and =N-O-.

[0064] "Lower amino," as used herein, alone or in combination, refers to -NRR', wherein R and R' are independently selected from hydrogen and lower alkyl, either of which is unsubstituted or substituted.

[0065] "Mercaptyl" as used herein, alone or in combination, refers to an RS- group, where R is as defined herein.

[0066] "Nitro," as used herein, alone or in combination, refers to $-NO_2$.

[0067] "Oxy" or "oxa," as used herein, alone or in combination, refer to –O–.

[0068] "Oxo," as used herein, alone or in combination, refers to =O.

[0069] "Perhaloalkoxy" refers to an alkoxy group where all of the hydrogen atoms are replaced by halogen atoms.

[0070] "Perhaloalkyl" as used herein, alone or in combination, refers to an alkyl group where all of the hydrogen atoms are replaced by halogen atoms.

[0071] "Ring," or equivalently, "cycle," as used herein, in reference to a chemical structure or portion thereof, means a group in which every atom is a member of a common cyclic structure.

A ring can be saturated or unsaturated, including aromatic, unless otherwise provided, and may have between 3 and 9 members. If the ring is a heterocycle, it may contain between 1 and 4 heteroatoms or heteroatom-comprising groups selected from B, N, O, S, C(O), S(O)m. Unless specifically prohibited, a ring is unsubstituted or substituted.

[0072] "Sulfonate," "sulfonic acid," and "sulfonic," as used herein, alone or in combination, refer to the $–SO_3H$ group and its anion as the sulfonic acid is used in salt formation.

[0073] "Sulfanyl," as used herein, alone or in combination, refers to –S–.

[0074] "Sulfinyl," as used herein, alone or in combination, refers to –S(O)–.

[0075] "Sulfonyl," as used herein, alone or in combination, refers to $–S(O)_2–$.

[0076] "N-sulfonamido" refers to a $RS(=O)_2NR'$- group with R and R' as defined herein.

[0077] "S-sulfonamido" refers to a $-S(=O)_2NRR'$, group, with R and R' as defined herein.

[0078] "Thia" and "thio," as used herein, alone or in combination, refer to a –S– group or an ether wherein the oxygen is replaced with sulfur. The oxidized derivatives of the thio group, namely sulfinyl and sulfonyl, are included in the definition of thia and thio.

[0079] "Thiol," as used herein, alone or in combination, refers to an –SH group.

[0080] "Thiocarbonyl," as used herein, when alone includes thioformyl –C(S)H and in combination is a –C(S)– group.

[0081] "N-thiocarbamyl" refers to an ROC(S)NR'– group, with R and R' as defined herein.

[0082] "O-thiocarbamyl" refers to a –OC(S)NRR', group with R and R' as defined herein.

[0083] "Thiocyanato" refers to a –CNS group.

[0084] Any definition herein may be used in combination with any other definition to describe a composite structural group. By convention, the trailing element of any such definition is that which attaches to the parent moiety. For example, the composite group alkylamido would represent an alkyl group attached to the parent molecule through an amido group, and the term alkoxyalkyl would represent an alkoxy group attached to the parent molecule through an alkyl group.

[0085] "Bond" refers to a covalent linkage between two atoms, or two moieties when the atoms joined by the bond are considered to be part of larger substructure. A bond may be single, double, or triple unless otherwise specified. A dashed line between two atoms in a drawing of a molecule indicates that an additional bond may be present or absent at that position.

[0086] "Salt" refers to acid or base salts of the compounds of the present disclosure. Illustrative examples of pharmaceutically acceptable acid addition salts are mineral acid (hydrochloric acid, hydrobromic acid, phosphoric acid, and the like) salts and organic acid (acetic acid, propionic acid, glutamic acid, citric acid and the like) salts. Examples of pharmaceutically acceptable base addition salts include sodium, potassium, calcium, ammonium, organic amino, or magnesium salt, or a similar salt. It is understood that the pharmaceutically acceptable salts are non-toxic. Additional information on suitable pharmaceutically acceptable salts can be found in Remington's Pharmaceutical Sciences, 17th ed., Mack Publishing Company, Easton, Pa., 1985, which is incorporated herein by reference.

[0087] "Solvate" refers to a compound provided herein or a salt thereof, that further includes a stoichiometric or non-stoichiometric amount of solvent bound by non-covalent intermolecular forces.

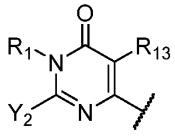
[0088] "Hydrate" refers to a compound that is complexed to a water molecule. The compounds of the present disclosure can be complexed with ½ water molecule or from 1 to 10 water molecules.

[0089] Asymmetric centers exist in the compounds disclosed herein. These centers are designated by the symbols "R" or "S," depending on the configuration of substituents around the chiral carbon atom. It should be understood that the present disclosure encompasses all stereochemical isomeric forms, including diastereomeric, enantiomeric, and epimeric forms, as well as d-isomers and 1-isomers, and mixtures thereof. Individual stereoisomers of compounds can be prepared synthetically from commercially available starting materials which contain chiral centers or by preparation of mixtures of enantiomeric products followed by separation such as conversion to a mixture of diastereomers followed by separation or recrystallization, chromatographic techniques, direct separation of enantiomers on chiral chromatographic columns, or any other appropriate method. Starting compounds of particular stereochemistry are

either commercially available or can be made and resolved by various techniques. Additionally, the compounds disclosed herein may exist as geometric isomers. The present disclosure includes all cis, trans, syn, anti, entgegen (E), and zusammen (Z) isomers as well as the appropriate mixtures thereof. Additionally, compounds may exist as tautomers; all tautomeric isomers are provided by this present disclosure. Additionally, the compounds disclosed herein can exist in unsolvated as well as solvated forms with pharmaceutically acceptable solvents such as water, ethanol, and the like. In general, the solvated forms are considered equivalent to the unsolvated forms.

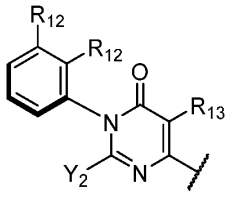
[0090] "Tautomer", as use herein, alone or in combination, refers to one of two or more isomers that rapidly interconvert. Generally, this interconversion is sufficiently fast so that an individual tautomer is not isolated in the absence of another tautomer. The ratio of the amount of tautomers can be dependent on solvent composition, ionic strength, and pH, as well as other solution parameters. The ratio of the amount of tautomers can be different in a particular solution and in the microenvironment of a biomolecular binding site in said solution. Examples of tautomers include keto / enol, enamine / imine, and lactam / lactim tautomers. Additional examples of tautomers also include 2-hydroxypyridine / 2(1*H*)-pyridone and 2-aminopyridine / 2(1*H*)-iminopyridone tautomers.

[0091] Conformational isomers exist in the compounds disclosed herein. When R_1 is aryl or heteroaryl in the formula:

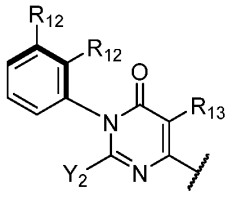


,

the aryl or heteroaryl group can orient in different conformations in relation to the pyrimidinone moiety, as represented by:



(S_a form), and



(R_a form).

These forms are designated by the symbols "S_a" or "R_a", depending on the conformation of the aryl or heteroaryl group in relation to the pyrimidinone moiety. Examples of "S_a" and "R_a" forms can be found in Examples 1-20 of International Patent Application No. PCT/US2019/045903, which is incorporated herein in its entirety for all purposes. The compound of formula (10b) is substantially in a "R_a" form.

[0092] "Pharmaceutically acceptable" refers to those compounds (salts, hydrates, solvates, stereoisomers, conformational isomers, tautomers, etc.) which are suitable for use in contact with the tissues of patients without undue toxicity, irritation, and allergic response, are commensurate with a reasonable benefit/risk ratio, and are effective for their intended use. The compounds disclosed herein can exist as pharmaceutically acceptable salts, as defined and described herein.

[0093] "Combination therapy" means the administration of two or more therapeutic agents to treat a therapeutic condition or disorder described in the present disclosure. Such administration encompasses co-administration of these therapeutic agents in a substantially simultaneous manner, such as in a single capsule having a fixed ratio of active ingredients or in multiple, separate capsules for each active ingredient. In addition, such administration also encompasses use of each type of therapeutic agent in a sequential manner. In either case, the treatment regimen will provide beneficial effects of the drug combination in treating the conditions or disorders described herein.

[0094] "PTPN11 inhibitor" is used herein to refer to a compound that exhibits an IC_{50} with respect to PTPN11 activity of no more than about 100 micromolar (μM) and more typically not more than about 50 μM, as measured in the PTPN11 assay described generally in International Patent Application No. PCT/US2019/045903 (e.g., the enzymatic activity of recombinant human PTPN11 proteins of Example 21). "IC_{50}" is that concentration of inhibitor which reduces the activity of an enzyme (e.g., PTPN11) to half-maximal level. In certain embodiments, compounds disclosed in PCT/US2019/045903 exhibit an IC_{50} of no more than about 10 μM for inhibition of PTPN11; in further embodiments, compounds exhibit an IC_{50} of no more than about 1 μM for inhibition of PTPN11; in yet further embodiments, compounds exhibit an IC_{50} of not more than about 200 nM for inhibition of PTPN11; in yet further embodiments, compounds exhibit an IC_{50} of not more than about 100 nM for inhibition of PTPN11; and in yet further embodiments, compounds exhibit an IC_{50} of not more than about 50 nM for inhibition of

PTPN11, as measured in the PTPN11 assay described therein. In certain embodiments, the compound of formula (2b) exhibits an IC_{50} of no more than 150 nM for inhibition of PTPN11 (e.g., a PTPN11-E76K mutant enzyme). In certain embodiments, the compound of formula (10b) exhibits an IC_{50} of no more than 50 nM for inhibition of PTPN11 (e.g., a PTPN11-E76K mutant enzyme).

[0095] "Therapeutically effective amount" refers to an amount of a compound or of a pharmaceutical composition useful for treating or ameliorating an identified disease or condition, or for exhibiting a detectable therapeutic or inhibitory effect. The exact amounts will depend on the purpose of the treatment, and will be ascertainable by one skilled in the art using known techniques (*see*, *e.g.*, Lieberman, *Pharmaceutical Dosage Forms* (vols. 1-3, 1992); Lloyd, *The Art, Science and Technology of Pharmaceutical Compounding* (1999); Pickar, *Dosage Calculations* (1999); and *Remington: The Science and Practice of Pharmacy*, 20th Edition, 2003, Gennaro, Ed., Lippincott, Williams & Wilkins).

[0096] "Treat", "treating", and "treatment" refer to any indicia of success in the treatment or amelioration of an injury, pathology, or condition, including any objective or subjective parameter such as abatement; remission; diminishing of symptoms or making the injury, pathology or condition more tolerable to the patient; slowing in the rate of degeneration or decline; making the final point of degeneration less debilitating; and/or improving a patient's physical or mental well-being. The treatment or amelioration of symptoms can be based on objective or subjective parameters; including the results of a physical examination, neuropsychiatric exams, and/or a psychiatric evaluation.

[0097] "Administering" refers to therapeutic provision of the compound or a form thereof to a subject, such as by oral administration or intravenous administration.

[0098] "Patient" or "subject" refers to a living organism suffering from or prone to a disease or condition that can be treated by administration of a pharmaceutical composition as provided herein. Non-limiting examples include humans, non-human primates (e.g., monkeys), goats, pigs, sheep, cows, deer, horses, bovines, rats, mice, rabbits, hamsters, guinea pigs, cats, dogs, and other non-mammalian animals. In some embodiments, the subject is human. In some embodiments, a subject is an adult (e.g., at least 18 years of age).

[0099] "Composition," as used herein, is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product, which results, directly or indirectly, from combination of the specified ingredients in the specified amounts. By "pharmaceutically acceptable" it is meant the carrier, diluent or excipient must be compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

[0100] "Pharmaceutically acceptable excipient" refers to a substance that aids the administration of an active agent to and absorption by a subject. Pharmaceutical excipients useful in the present disclosure include, but are not limited to, binders, fillers, disintegrants, lubricants, coatings, sweeteners, flavors and colors. Other pharmaceutical excipients can be useful in the present disclosure.

[0101] "Tablet" refers to solid pharmaceutical formulations with and without a coating. The term "tablet" also refers to tablets having one, two, three or even more layers, wherein each of the before mentioned types of tablets may be without or with one or more coatings. In some embodiments, tablets of the present disclosure can be prepared by roller compaction or other suitable means known in the art. The term "tablet" also comprises mini, melt, chewable, effervescent, and orally disintegrating tablets. Tablets include the compound of formula (I) or (10b) and one or more pharmaceutical excipients (e.g., fillers, binders, glidants, disintegrants, surfactants, binders, lubricants, and the like). Optionally, a coating agent can be also included. For the purposes of calculating percent weight of the tablet formulation, the amount of coating agent is not included in the calculation. That is, the percent weights reported herein are of the uncoated tablet.

[0102] Unless specifically indicated otherwise, the content of the compound of formula (I) or (10b) in, e.g., a tablet formulation is calculated based on the normalized weight of the compound of formula (I) or (10b) on a salt-free and anhydrous basis. That is, the salt and/or water content in the compound of formula (I) or (10b) is not included in the calculation.

[0103] "KRAS G12C inhibitor" as used herein refers to a compound which targets, decreases, or inhibits the synthesis or biological activity of KRAS (Kirsten rat sarcoma 2 viral oncogene homolog) by selectively modifying mutant cysteine 12 in G12C mutated KRAS. The KRAS G12C inhibitor may at least partially inhibit KRAS G12C. The KRAS G12C inhibitor may be a

selective KRAS G12C inhibitor (e.g., having greater selectivity for KRAS having a G12C mutation over KRAS having another mutation such as a G12D mutation). In those cases, the selective KRAS G12C inhibitor may have high potency for KRAS G12C, along with low affinity for other KRAS mutations. The KRAS G12C inhibitor may be a covalent inhibitor (e.g., capable of covalently modifying cysteine 12). The KRAS G12C inhibitor may be a noncolvanet inhibitor. The KRAS G12C inhibitor may bind to an inactive ("GDP") form of KRAS. The KRAS G12C inhibitor may bind to an active ("GTP") form of KRAS. The KRAS G12C inhibitor may bind to both inactive ("GDP") and active ("GTP") forms of KRAS. Examples of KRAS G12C inhibitors include sotorasib (AMG 510), adagrasib (MRTX-849), MRTX1257, ARS-853, ARS-1620, JNJ-74699157 (ARS-3248), JDQ443, GDC-6036, JAB-21822, BI 1823911, MK-1084, LY3537982, and LY3499446.

[0104] "KRAS-positive cancer" refers to a cancer with the KRAS gene rearranged, mutated, or amplified. "KRAS G12C-positive cancer" refers to a cancer with the KRAS G12C gene rearranged, mutated, or amplified.

[0105] "A cancer resistant to a KRAS inhibitor" and/or "a cancer that is a KRAS-positive cancer resistant to a KRAS inhibitor" refer to a cancer or tumor that either fails to respond favorably to treatment with a prior KRAS inhibitor, or alternatively, recurs or relapses after responding favorably to a KRAS inhibitor. "A cancer resistant to a KRAS G12C inhibitor" and/or "a cancer that is a KRAS G12C-positive cancer resistant to a KRAS G12C inhibitor" refer to a cancer or tumor that either fails to respond favorably to treatment with a prior KRAS G12C inhibitor, or alternatively, recurs or relapses after responding favorably to a KRAS G12C inhibitor.

[0106] "Jointly therapeutically effective amount" as used herein means the amount at which the therapeutic agents, when given separately (in a chronologically staggered manner, especially a sequence-specific manner) to a warm-blooded animal, especially to a human to be treated, show an (additive, but preferably synergistic) interaction (joint therapeutic effect). Whether this is the case can be determined *inter alia* by following the blood levels, showing that both compounds are present in the blood of the human to be treated at least during certain time intervals.

[0107] "Synergistic effect" as used herein refers to an effect of at least two therapeutic agents: a PTPN11 inhibitor as defined herein; and a KRAS G12C inhibitor as defined herein, which is greater than the simple addition of the effects of each drug administered by themselves. The effect can be, for example, slowing the symptomatic progression of a proliferative disease, such as cancer, particularly lung cancer (e.g., non-small cell lung cancer), or symptoms thereof. Analogously, a "synergistically effective amount" refers to the amount needed to obtain a synergistic effect.

[0108] "A," "an," or "a(n)", when used in reference to a group of substituents or "substituent group" herein, mean at least one. For example, where a compound is substituted with "an" alkyl or aryl, the compound is substituted with at least one alkyl and/or at least one aryl, wherein each alkyl and/or aryl is optionally different. In another example, where a compound is substituted with "a" substituent group, the compound is substituted with at least one substituent group, wherein each substituent group is optionally different.

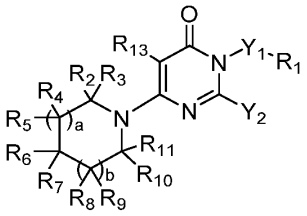
III. COMBINATION THERAPY

[0109] In a first aspect, the present disclosure provides a method of treating cancer in a subject. The method includes administering to the subject:

a) a therapeutically effective amount of a PTPN11 inhibitor; and

b) a therapeutically effective amount of a KRAS G12C inhibitor

wherein the PTPN11 inhibitor is represent by formula (I):



(I),

or a pharmaceutically acceptable salt, hydrate, solvate, stereoisomer, conformational isomer, tautomer, or a combination thereof,

wherein:

subscript a is 0 or 1;

subscript b is 0 or 1;

Y_1 is a direct bond or $CR_{17}R_{18}$;

Y_2 is selected from the group consisting of C_{1-4}alkyl, amino, C_{1-4}alkylC(O)O-, C_{1-4}alkylamino and C_{1-4}aminoalkyl;

R_1 is selected from the group consisting of C_{6-10}aryl, C_{3-8}cycloalkyl, C_{3-8}cycloalkenyl, and a 5-10 membered heteroaryl group having 1 to 4 heteroatoms or groups as ring vertices independently selected from N, C(O), O, and S; said aryl or heteroaryl of R_1 is unsubstituted or substituted with 1 to 5 R_{12} groups independently selected from the group consisting of halo, hydroxy, amino, C_{1-4}alkylamino, di(C_{1-4}alkyl)amino, cyano, C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}hydroxyalkyl, C_{1-4}haloalkyl, C_{1-4}aminoalkyl, C_{3-8}cycloalkyl, C_{3-8}cycloalkenyl, $NR_{15}C(O)R_{14}$, $NR_{15}C(O)OR_{14}$, $NR_{14}C(O)NR_{15}R_{16}$, $NR_{15}S(O)R_{14}$, $NR_{15}S(O)_2R_{14}$, $C(O)NR_{15}R_{16}$, $S(O)NR_{15}R_{16}$, $S(O)_2NR_{15}R_{16}$, $C(O)R_{14}$, $C(O)OR_{14}$, OR_{14}, SR_{14}, $S(O)R_{14}$, and $S(O)_2R_{14}$;

R_2, R_3, R_{10}, and R_{11} are each independently selected from the group consisting of hydrogen, C_{1-4}alkyl, and C_{3-8}cycloalkyl;

R_4, R_5, R_8, and R_9 are each independently selected from the group consisting of hydrogen, cyano, C_{1-4}alkyl, C_{1-4}alkoxy, amino, hydroxy, C_{3-8}cycloalkyl, halo, and C_{1-4}alkylamino;

R_6 is selected from the group consisting of amino, C_{1-4}aminoalkyl, and C_{1-4}alkylamino;

R_7 is selected from the group consisting of hydrogen, amido, cyano, halo, and hydroxy, or is selected from the group consisting of C_{1-4}alkyl, C_{1-4}hydroxyalkyl, C_{3-6}cycloalkyl, phenyl, and 5- or 6- membered heteroaryl, any of which is unsubstituted or substituted with 1 to 5 groups independently selected from the group consisting of amino, halo, hydroxy, cyano, C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}haloalkyl, C_{1-4}haloalkoxy, C_{1-4}alkylamino, and C_{1-4}aminoalkyl;

or R_6 and R_7 together with the carbon atom to which they are both attached form a 3- to 7-membered saturated or unsaturated ring, having 0 to 3 heteroatoms or groups as ring vertices independently selected from N, C(O), O, and $S(O)_m$; subscript m is 0, 1, or 2; and said saturated or unsaturated ring formed by R_6 and R_7 is unsubstituted or substituted with 1 to 3 groups independently selected from the group consisting of amino, halo, hydroxy, cyano, C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}haloalkyl, C_{1-4}haloalkoxy, C_{1-4}alkylamino and C_{1-4}aminoalkyl;

any two groups of R_2, R_3, R_4, R_5, R_7, R_8, R_9, R_{10} and R_{11} can form a 5 to 6 membered ring, having 0 to 2 heteroatoms as ring vertices elected from N, O and S;

any two groups of R_2, R_4, R_6, R_8 and R_{10} can form a direct bond, or a 1 or 2 atom carbon bridge;

R_{13} is selected from the group consisting of hydrogen, halo, cyano, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}hydroxyalkyl, C_{1-6} dihydroxyalkyl, -NH-NHR_{19}, -NHR_{19}, -OR_{19}, -$NHC(O)R_{19}$, -$NHC(O)NHR_{19}$, -$NHS(O)_2NHR_{19}$, -$NHS(O)_2R_{19}$, -$C(O)OR_{19}$, -$C(O)NR_{19}R_{20}$, -$C(O)NH(CH_2)_qOH$, -$C(O)NH(CH_2)_qR_{21}$, -$C(O)R_{21}$, -NH_2, -OH, -$S(O)_2NR_{19}R_{20}$, C_{3-8}cycloalkyl, aryl, heterocyclyl having 1-5 heteroatoms as ring vertices selected from N, O, S and P, and heteroaryl having 1-5 heteroatoms as ring vertices selected from N, O, S and P; subscript q is an integer of from 0 to 6; and each of aryl, heteroaryl, heterocyclyl and cycloalkyl of R_{13} is unsubstituted or substituted with 1 to 3 groups independently selected from the group consisting of C_{1-4}alkyl, –OH, -NH_2, -OR_{21}, halo, cyano, and oxo;

R_{14}, R_{15} and R_{16} are each independently selected from the group consisting of hydrogen, C_{1-4}alkyl, C_{3-8}cycloalkyl, C_{6-10}aryl and 5-10 membered heteroaryl, any of which is unsubstituted or substituted with one or more groups independently selected from the group consisting of amido, amino, halo, hydroxy, cyano, C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}haloalkyl, C_{1-4}haloalkoxy, C_{1-4}alkylamino and C_{1-4}aminoalkyl;

R_{17} and R_{18} are each independently selected from the group consisting of hydrogen, C_{1-4}alkyl, and CF_3;

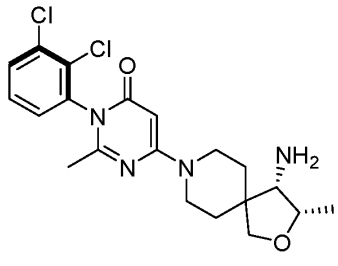
R_{19} and R_{20} are each independently selected from the group consisting of hydrogen, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}hydroxyalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl and C_{3-6}cycloalkyl; and

each R_{21} is independently selected from the group consisting of hydrogen, -OH, C_{1-6} alkyl, C_{1-6}haloalkyl, C_{1-6}hydroxyalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl and C_{3-6}cycloalkyl.

III-1: PTPN11 Inhibitors and/or KRAS G12C Inhibitors

[0110] The PTPN11 inhibitor represented by formula (I) is further described according to **Section IV. Compounds**. In some embodiments, the PTPN11 inhibitor of formula (I) is any one of embodiments as described in **Section IV. Compounds**.

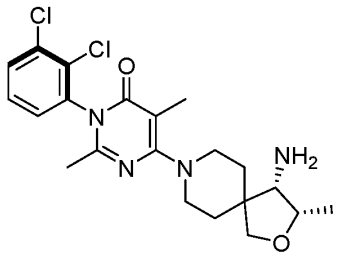
[0111] In some embodiments, the PTPN11 inhibitor is represented by formula (2b):



(2b),

having the name of 6-((3*S*,4*S*)-4-amino-3-methyl-2-oxa-8-azaspiro[4.5]decan-8-yl)-3-(*R*$_a$)-(2,3-dichlorophenyl)-2-methylpyrimidin-4(3*H*)-one.

[0112] In some embodiments, the PTPN11 inhibitor is represented by formula (10b):

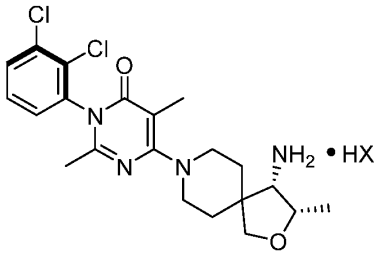


(10b),

having the name of 6-((3*S*,4*S*)-4-amino-3-methyl-2-oxa-8-azaspiro[4.5]decan-8-yl)-3-(*R*$_a$)-(2,3-dichlorophenyl)-2,5-dimethylpyrimidin-4(3*H*)-one.

[0113] The compound of any one of formula (I), formula (2b), and formula (10b) can be in a pharmaceutically acceptable salt form or in a neutral form, each of which is optionally in a solvate or a hydrate form.

[0114] In some embodiments, the compound of any one of formula (I), formula (2b), and formula (10b) is in a pharmaceutically acceptable salt form. In some embodiments, a pharmaceutically acceptable acid addition salt of the compound of formula (10b) is represented by formula (10b-HX):



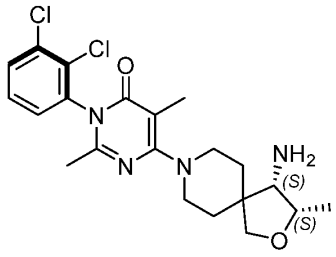
(10b-HX),

wherein HX is a pharmaceutically acceptable acid addition.

[0115] Examples of acceptable acid addition salts include those derived from inorganic acids like hydrochloric, hydrobromic, nitric, carbonic, monohydrogencarbonic, phosphoric, monohydrogenphosphoric, dihydrogenphosphoric, sulfuric, monohydrogensulfuric, hydriodic, or phosphorous acids and the like, as well as the salts derived from organic acids like acetic, propionic, isobutyric, maleic, malonic, benzoic, succinic, suberic, fumaric, lactic, mandelic, phthalic, benzenesulfonic, p-tolylsulfonic, citric, tartaric, methanesulfonic, and the like.

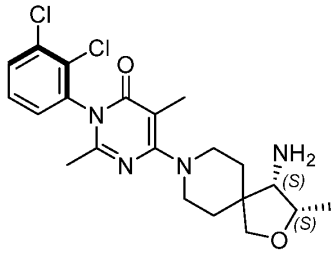
[0116] In some embodiments, the compound of any one of Formula (I), formula (2b), and formula (10b) is in a neutral form. In some embodiments, the compound of formula (10b) is in a neutral form.

[0117] In some embodiments, the compound of formula (10b) has a substantially moiety of 6-((3*S*,4*S*)-4-amino-3-methyl-2-oxa-8-azaspiro[4.5]decan-8-yl) with stereochemistry as shown in formula (10b):

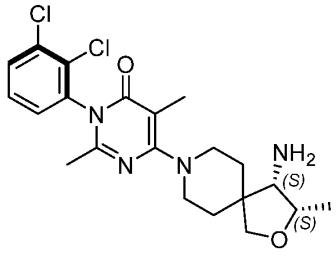


(10b).

[0118] In some embodiments, the compound of formula (10b) is substantially in a R_a conformation as shown in formula (10b):

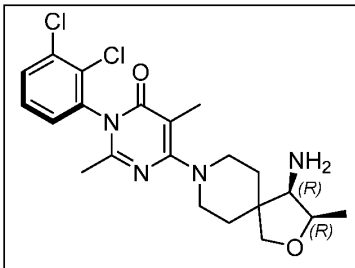
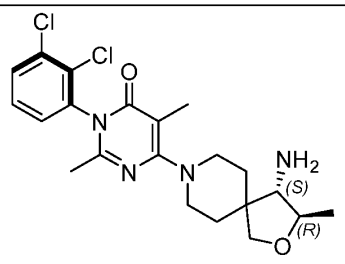
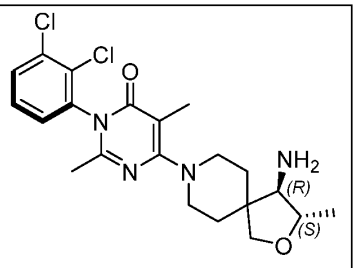
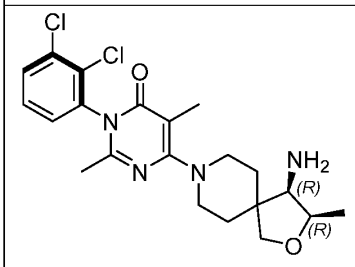
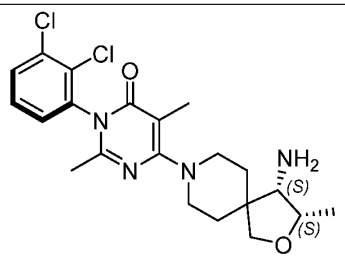
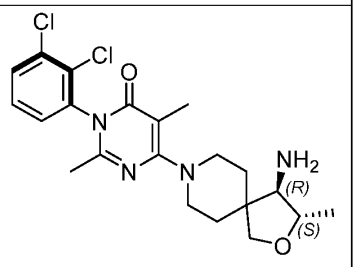

(10b).

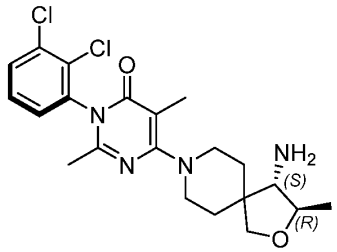
[0119] In some embodiments, the compound of formula (10b) is represented by the formula:


(10b),

having the name of 6-((3*S*,4*S*)-4-amino-3-methyl-2-oxa-8-azaspiro[4.5]decan-8-yl)-3-(R_a)-(2,3-dichlorophenyl)-2,5-dimethylpyrimidin-4(3*H*)-one.

[0120] In some embodiments, the compound of formula (10b) includes one or more corresponding enantiomer, diastereomers, and/or conformational isomers, as represented by formulae, respectively:

 enantiomer (*3R*, *4R*, S_a)	 diastereomer (*3R*, *4S*, R_a)	 diastereomer (*3S*, *4R*, S_a)
		

diastereomer (*3R*, *4R*, R_a)	diastereomer (*3S*, *4S*, S_a)	diastereomer (*3S*, *4R*, R_a)
 diastereomer (*3R*, *4S*, S_a)		

[0121] In some embodiments, the compound of formula (10b) has a purity of at least about 95 area% determined by a chiral high-performance liquid chromatography (HPLC). In some embodiments, the compound of formula (10b) has a purity of from about 95 area% to about 99 area%, from about 96 area% to about 99 area%, from about 97 area% to about 99 area%, or from about 98 area% to about 99 area%, determined by a chiral high-performance liquid chromatography (HPLC). In some embodiments, the compound of formula (10b) has a purity of from about 98 area% to about 99 area%.

[0122] In some embodiments, the compound of formula (10b) includes one or more corresponding enantiomer, diastereomers, and/or conformational isomers, as represented by the formulae above; and a total of the one or more isomers is no more than about 5 area% determined by a chiral high-performance liquid chromatography (HPLC).

[0123] In some embodiments, the corresponding enantiomer, diastereomers, and/or conformational isomers of the compound of formula (10b) are present in the compound of formula (10b) meet acceptance criteria as follows: enantiomer (*3R*, *4R*, S_a) $\leq$ 0.5 area%; diastereomer (*3R*, *4S*, R_a) $\leq$ 1.2 area%; diastereomer (*3S*, *4R*, S_a) $\leq$ 0.5 area%; diastereomer (*3R*, *4R*, R_a) $\leq$ 0.5 area%; diastereomer (*3S*, *4S*, S_a) $\leq$ 0.5 area%; diastereomer (*3S*, *4R*, R_a) $\leq$ 0.5 area%; and diastereomer (*3R*, *4S*, S_a) $\leq$ 0.5 area%, each of which is determined by a chiral high-performance liquid chromatography (HPLC). In some embodiments, the compound of formula (10b) has a purity of at least about 95 area%, wherein enantiomer (*3R*, *4R*, S_a) < 0.5 area%; diastereomer (*3R*, *4S*, R_a) < 1.2 area%; diastereomer (*3S*, *4R*, S_a) < 0.5 area%; diastereomer (*3R*, *4R*, R_a) < 0.5 area%; diastereomer (*3S*, *4S*, S_a) < 0.5 area%; diastereomer (*3S*, *4R*, R_a) < 0.5

area%; and diastereomer (*3R*, *4S*, S_a) < 0.5 area%, each of which is determined by a chiral high-performance liquid chromatography (HPLC). In some embodiments, the compound of formula (10b) has a purity of from about 95 area% to about 99 area%, from about 96 area% to about 99 area%, from about 97 area% to about 99 area%, or from about 98 area% to about 99 area%, wherein enantiomer (*3R*, *4R*, S_a) < 0.5 area%; diastereomer (*3R*, *4S*, R_a) < 1.2 area%; diastereomer (*3S*, *4R*, S_a) < 0.5 area%; diastereomer (*3R*, *4R*, R_a) < 0.5 area%; diastereomer (*3S*, *4S*, S_a) < 0.5 area%; diastereomer (*3S*, *4R*, R_a) < 0.5 area%; and diastereomer (*3R*, *4S*, S_a) < 0.5 area%, each of which is determined by a chiral high-performance liquid chromatography (HPLC). In some embodiments, the compound of formula (10b) has a purity of from about 98 area% to about 99 area%, wherein enantiomer (*3R*, *4R*, S_a) is not detected; diastereomer (*3R*, *4S*, R_a) is about 0.86 area%; diastereomer (*3S*, *4R*, S_a) is not detected; diastereomer (*3R*, *4R*, R_a) is about 0.07 area%; diastereomer (*3S*, *4S*, S_a) is not detected; diastereomer (*3S*, *4R*, R_a) is not detected; and diastereomer (*3R*, *4S*, S_a) is not detected, each of which is determined by a chiral high-performance liquid chromatography (HPLC).

[0124] In some embodiments, the compound of any one of formula (I), formula (2b), formula (10b), and formula (10b-HX) is in a solvate and/or a hydrate form.

[0125] The KRAS G12C inhibitor can be an inhibitor described for use in the treatment of a cancer. In some embodiments, the KRAS G12C inhibitor at least partially inhibits KRAS G12C kinase. In some embodiments, the KRAS G12C inhibitor is a selective KRAS G12C inhibitor (e.g., having greater selectivity for KRAS having a G12C mutation over KRAS having another mutation such as a G12D mutation). In some embodiments, the KRAS G12C inhibitor is a covalent inhibitor (e.g., capable of covalently modifying cysteine 12). In some embodiments, the KRAS G12C inhibitor is a noncolvanet inhibitor. In some embodiments, the KRAS G12C inhibitor is an inhibitor of the inactive ("GDP") form of KRAS. In some embodiments, the KRAS G12C inhibitor is an inhibitor of the active ("GTP") form of KRAS. In some embodiments, the KRAS G12C inhibitor is an inhibitor both the inactive ("GDP") and active ("GTP") forms of KRAS.

[0126] In some embodiments, the KRAS G12C inhibitor is sotorasib (AMG 510), adagrasib (MRTX-849), MRTX1257, ARS-853, ARS-1620, JNJ-74699157 (ARS-3248), JDQ443, GDC-6036, JAB-21822, BI 1823911, MK-1084, LY3537982, or LY3499446. In some embodiments,

the KRAS G12C inhibitor is adagrasib (MRTX-849). In some embodiments, the KRAS G12C inhibitor is not sotorasib (AMG 510), when the PTPN11 inhibitor is a compound of formula (10b).

[0127] In some embodiments, the PTPN11 inhibitor is represented by formula (2b); and the KRAS G12C inhibitor is sotorasib (AMG 510), adagrasib (MRTX-849), MRTX1257, ARS-853, ARS-1620, JNJ-74699157 (ARS-3248), JDQ443, GDC-6036, JAB-21822, BI 1823911, MK-1084, LY3537982, or LY3499446. In some embodiments, the PTPN11 inhibitor is represented by formula (2b); and the KRAS G12C inhibitor is sotorasib (AMG 510) or adagrasib (MRTX-849). In some embodiments, the PTPN11 inhibitor is represented by formula (2b); and the KRAS G12C inhibitor is sotorasib (AMG 510). In some embodiments, the PTPN11 inhibitor is represented by formula (2b); and the KRAS G12C inhibitor is adagrasib (MRTX-849).

[0128] In some embodiments, the PTPN11 inhibitor is represented by formula (10b); and the KRAS G12C inhibitor is adagrasib (MRTX-849), MRTX1257, ARS-853, ARS-1620, JNJ-74699157 (ARS-3248), JDQ443, GDC-6036, JAB-21822, BI 1823911, MK-1084, LY3537982, or LY3499446. In some embodiments, the PTPN11 inhibitor is represented by formula (10b); and the KRAS G12C inhibitor is adagrasib (MRTX-849).

III-2. Cancer/Solid Tumor

[0129] The cancer can be any cancer that responds to the treatment of a PTPN11 inhibitor and/or a KRAS G12C inhibitor (e.g., sotorasib or adagrasib). In some embodiments, the cancer is caused and/or characterized by a KRAS mutation, such as a KRAS G12C mutation. In some embodiments, the cancer is characterized by a KRAS mutation other than a Q61X mutation. In some embodiments, the cancer is a KRAS-positive cancer. In some embodiments, the cancer is a KRAS G12C-positive cancer (e.g., a cancer characterized by a G12C mutation in KRAS).

[0130] The cancer can be characterized by a solid tumor or a liquid tumor. In some embodiments, the cancer includes a solid tumor. In some embodiments, the cancer includes a liquid tumor.

[0131] In some embodiments, the cancer is lung cancer, colorectal cancer, pancreatic cancer, urothelial carcinoma, stomach cancer, mesothelioma, or a combination thereof. In some embodiments, the cancer is non-small cell lung cancer (NSCLC). In some embodiments, the

cancer is NSCLC characterized by a KRAS mutation, such as a KRAS G12C mutation. In some embodiments, a KRAS protein includes a G12C mutation. In some embodiments, the cancer is NSCLC characterized by a G12C mutation in KRAS. In some embodiments, the cancer is NSCLC characterized by a mutation in an epidermal growth factor receptor (EGFR) protein. In some embodiments, the cancer is NSCLC that is not characterized by a mutation in EGFR or anaplastic lymphoma kinase (ALK).

[0132] In some embodiments, the cancer is a KRAS G12C-positive cancer (e.g., a cancer characterized by a G12C mutation in KRAS). In some embodiments, the KRAS G12C-positive cancer is non-small cell lung cancer, small bowel cancer, appendiceal cancer, colorectal cancer, cancer of unknown primary, endometrial cancer, mixed cancer types, pancreatic cancer, hepatobiliary cancer, small cell lung cancer, cervical cancer, germ cell cancer, ovarian cancer, gastrointestinal neuroendocrine cancer, bladder cancer, myelodysplastic/myeloproliferative neoplasms, head and neck cancer, esophagogastric cancer, soft tissue sarcoma, mesothelioma, thyroid cancer, leukemia, or melanoma. In some embodiments, the cancer is small bowel cancer, appendiceal cancer, endometrial cancer, hepatobiliary cancer, small cell lung cancer, cervical cancer, germ cell tumor, ovarian cancer, gastrointestinal neuroendocrine tumor, bladder cancer, myelodysplastic/myeloproliferative neoplasms, head and neck cancer, esophagogastric cancer, soft tissue sarcoma, mesothelioma, thyroid cancer, leukemia, or melanoma. In some embodiments, the KRAS G12C-positive cancer is non-small cell lung cancer, colorectal cancer, pancreatic cancer, appendiceal cancer, endometrial cancer, cancer of unknown primary, ampullary cancer, gastric cancer, small bowel cancer, sinonasal cancer, bile duct cancer, or melanoma. In some embodiments, the cancer is an advanced or metastatic KRAS G12C-positive solid tumor (e.g., lung cancer, colorectal cancer, pancreatic cancer, urothelial carcinoma, stomach cancer, mesothelioma, or a combination thereof). In some embodiments, the cancer is an advanced or metastatic KRAS G12C-positive non-small cell lung cancer (NSCLC). In some embodiments, the cancer is an advanced or metastatic KRAS G12C-positive solid tumor, provided that the solid tumor is other than non-small cell lung cancer (NSCLC).

[0133] The cancer can also be any cancer that is resistant to the treatment of a KRAS G12C inhibitor. In some embodiments, the cancer is resistant to a KRAS G12C inhibitor, as defined and described herein. In some embodiments, the cancer is resistant to a KRAS G12C inhibitor

that is an inhibitor of the inactive ("GDP") form of KRAS. In some embodiments, the cancer is resistant to a KRAS G12C inhibitor that is an inhibitor of the active ("GTP") form of KRAS. In some embodiments, the cancer is resistant to a KRAS G12C inhibitor that is an inhibitor of both the inactive ("GDP") and active ("GTP") forms of KRAS.

[0134] In some embodiments, the cancer is characterized by intrinsic and/or acquired resistance to a KRAS G12C inhibitor as defined and described herein. In some embodiments, the cancer is a KRAS G12C-positive cancer resistant to a KRAS G12C inhibitor as defined and described herein. In some embodiments, the cancer is a KRAS G12C-positive cancer characterized by intrinsic and/or acquired resistance to a KRAS G12C inhibitor as defined and described herein.

[0135] In some embodiments, the cancer is characterized by intrinsic and/or acquired resistance to another therapy such as a KRAS modulator, platinum-based therapy, or taxane therapy. In some embodiments, the cancer is characterized by intrinsic and/or acquired resistance to a KRAS G12C inhibitor. In some embodiments, the cancer is characterized by intrinsic and/or acquired resistance to a KRAS G12C inhibitor selected from the group consisting of sotorasib (AMG 510), adagrasib (MRTX-849), MRTX1257, ARS-853, ARS-1620, JNJ-74699157 (ARS-3248), JDQ443, GDC-6036, JAB-21822, BI 1823911, MK-1084, LY3537982, and LY3499446. In some embodiments, the cancer is characterized by intrinsic and/or acquired resistance to sotorasib (AMG 510). In some embodiments, the cancer is characterized by intrinsic and/or acquired resistance to adagrasib (MRTX-849).

[0136] In some embodiments, the cancer is resistant to a KRAS G12C inhibitor selected from the group consisting of sotorasib (AMG 510), adagrasib (MRTX-849), MRTX1257, ARS-853, ARS-1620, JNJ-74699157 (ARS-3248), JDQ443, GDC-6036, JAB-21822, BI 1823911, MK-1084, LY3537982, and LY3499446. In some embodiments, the cancer is resistant to sotorasib (AMG 510) or adagrasib (MRTX-849). In some embodiments, the cancer is resistant to sotorasib (AMG 510). In some embodiments, the cancer is resistant to adagrasib (MRTX-849). In some embodiments, the cancer is a KRAS G12C-positive cancer resistant to a KRAS G12C inhibitor selected from the group consisting of sotorasib (AMG 510), adagrasib (MRTX-849), MRTX1257, ARS-853, ARS-1620, JNJ-74699157 (ARS-3248), JDQ443, GDC-6036, JAB-21822, BI 1823911, MK-1084, LY3537982, and LY3499446. In some embodiments, the cancer

is a KRAS G12C-positive cancer resistant to sotorasib (AMG 510) or adagrasib (MRTX-849). In some embodiments, the cancer is a KRAS G12C-positive cancer resistant to sotorasib (AMG 510). In some embodiments, the cancer is a KRAS G12C-positive cancer resistant to adagrasib (MRTX-849).

[0137] The solid tumor can be any solid tumor that responds to the treatment of a PTPN11 inhibitor and a KRAS G12C inhibitor (e.g., sotorasib or adagrasib). In some embodiments, the solid tumor is a tumor with one or more genes in KRAS rearranged, mutated, or amplified, provided that the tumor is other than caused by one or more additional activating mutations in BRAF V600X, PTPN11 (SHP2), or KRAS Q61X.

[0138] In some embodiments, the solid tumor is an advanced or metastatic non-small cell lung cancer (NSCLC) caused by a mutation in KRAS. In some embodiments, the solid tumor is an advanced or metastatic non-small cell lung cancer (NSCLC) caused by a mutation in KRAS, provided that the tumor is other than caused by one or more additional activating mutations in BRAF V600X, PTPN11 (SHP2), or KRAS Q61X. In some embodiments, the solid tumor is a KRAS G12C-positive solid tumor. In some embodiments, the solid tumor is an advanced or metastatic KRASG12C-positive non-small cell lung cancer (NSCLC).

[0139] The solid tumor can also be any tumor that is resistant to the treatment of a KRAS G12C inhibitor (e.g., sotorasib (AMG 510), adagrasib (MRTX-849), MRTX1257, ARS-853, ARS-1620, JNJ-74699157 (ARS-3248), JDQ443, GDC-6036, JAB-21822, BI 1823911, MK-1084, LY3537982, and LY3499446). In some embodiments, the solid tumor is resistant to a KRAS G12C inhibitor. In some embodiments, the solid tumor is characterized by intrinsic and/or acquired resistance to a KRAS G12C inhibitor as defined and described herein. In some embodiments, the solid tumor is a KRAS G12C-positive solid tumor resistant to a KRAS G12C inhibitor. In some embodiments, the solid tumor is a KRAS G12C-positive solid tumor characterized by intrinsic and/or acquired resistance to a KRAS G12C inhibitor. In some embodiments, the solid tumor is resistant to the treatment of a KRAS G12C inhibitor selected from the group consisting of sotorasib (AMG 510), adagrasib (MRTX-849), MRTX1257, ARS-853, ARS-1620, JNJ-74699157 (ARS-3248), JDQ443, GDC-6036, JAB-21822, BI 1823911, MK-1084, LY3537982, and LY3499446. In some embodiments, the solid tumor is resistant to sotorasib (AMG 510). In some embodiments, the solid tumor is resistant to adagrasib (MRTX-

849). In some embodiments, the solid tumor is a KRAS-positive solid tumor resistant to the treatment of a KRAS G12C inhibitor selected from the group consisting of sotorasib (AMG 510), adagrasib (MRTX-849), MRTX1257, ARS-853, ARS-1620, JNJ-74699157 (ARS-3248), JDQ443, GDC-6036, JAB-21822, BI 1823911, MK-1084, LY3537982, and LY3499446. In some embodiments, the solid tumor is a KRAS-positive solid tumor resistant to sotorasib (AMG 510). In some embodiments, the solid tumor is a KRAS-positive solid tumor resistant to adagrasib (MRTX-849). In some embodiments, the solid tumor is a KRAS G12C-positive solid tumor resistant to the treatment of a KRAS G12C inhibitor selected from the group consisting of sotorasib (AMG 510), adagrasib (MRTX-849), MRTX1257, ARS-853, ARS-1620, JNJ-74699157 (ARS-3248), JDQ443, GDC-6036, JAB-21822, BI 1823911, MK-1084, LY3537982, and LY3499446. In some embodiments, the solid tumor is a KRAS G12C-positive solid tumor resistant to sotorasib (AMG 510). In some embodiments, the solid tumor is a KRAS G12C-positive solid tumor resistant to adagrasib (MRTX-849).

[0140] In some embodiments, the cancer (e.g., solid tumor) is characterized by one or more mutations in the MAPK pathway, such as one or more mutations in KRAS, NRAS, HRAS, CRAF, BRAF, NRAF, MAPK/ERK, MAPKK/MEK, NF1, EGFR, IGFR, PDGFR, VEGFR, FGFR, CCKR, NGFR, EphR, AXLR, KEAP-1, TIE receptor, RYK receptor, DDR receptor, RET receptor, ROS receptor, LTK receptor, ROR receptor, MuSK receptor, or a combination thereof.

[0141] In some embodiments, the cancer or solid tumor is resistant to the treatment of an inhibitor that targets, decreases, or inhibits synthesis, expression, or biological activity in the MAPK pathway, such as an inhibitor targeting one or more of KRAS, NRAS, HRAS, CRAF, BRAF, NRAF, MAPK/ERK, MAPKK/MEK, NF1, EGFR, IGFR, PDGFR, VEGFR, FGFR, CCKR, NGFR, EphR, AXLR, KEAP-1, TIE receptor, RYK receptor, DDR receptor, RET receptor, ROS receptor, LTK receptor, ROR receptor, MuSK receptor, or a combination thereof. In some embodiments, the cancer or solid tumor is characterized by intrinsic and/or acquired resistance to an inhibitor that targets, decreases, or inhibits synthesis, expression, or biological activity in the MAPK pathway, such as an inhibitor targeting one or more of KRAS NRAS, HRAS, CRAF, BRAF, NRAF, MAPK/ERK, MAPKK/MEK, NF1, IGFR, PDGFR, VEGFR, FGFR, CCKR, NGFR, EphR, AXLR, KEAP-1, TIE receptor, RYK receptor, DDR receptor,

RET receptor, ROS receptor, LTK receptor, ROR receptor, MuSK receptor, or a combination thereof. Examples of MEK inhibitors include cobimetinib, trametinib, binimetinib, mirdametinib, and selumetinib. Examples of BRAF inhibitors include sorafenib, regorafenib, vemurafenib, encorafenib, and dabrafenib. Examples of EGFR inhibitors include erlotinib, cetuximab, panitumumab, vandetanib, afatinib, gefitinib, osimertinib, necitumumab, brigatinib, neratinib, dacomitinib, amivantamab (JNJ-61186372), mobocertinib (TAK-788), BLU-945, varlitinib, tarloxitinib, poziotinib, and lapatinib.

[0142] In any one of embodiments, a standard of care or curative therapy is unavailable for treating the cancer or solid tumor, as described herein.

III-3: Subject

[0143] In some embodiments, the subject is human. In some embodiments, the subject is under the care of a medical practitioner, such as a physician. In some embodiments, the subject has been diagnosed with the cancer. In some embodiments, the subject has relapsed. In some embodiments, the subject has previously entered remission. In some embodiments, the subject has previously undergone, is undergoing, or will undergo a monotherapy course of treatment. In some embodiments, the subject has previously undergone, is undergoing, or will undergo radiation therapy. In some embodiments, the subject has previously undergone, is undergoing, or will undergo immunotherapy. In some embodiments, the subject has previously undergone, is undergoing, or will undergo chemotherapy. In some embodiments, the subject has previously undergone, is undergoing, or will undergo a platinum-based chemotherapy. In some embodiments, the subject has previously undergone, is undergoing, or will undergo a therapeutic regimen comprising administration of a KRAS modulator (e.g., KRAS inhibitor). In some embodiments, the subject has previously undergone, is undergoing, or will undergo a therapeutic regimen comprising administration of an anti-PD-1/PD-L1 inhibitor (e.g., checkpoint inhibitor).

[0144] The subject can have an advanced (e.g., primary, metastatic, or recurrent) solid tumor with a KRAS G12C mutation (e.g., as described herein) as assessed by molecular diagnostic using an appropriate clinically validated and/or FDA approved test and with no available standard of care or curative therapies. In some embodiments, the subject has a KRAS G12C mutation (e.g., as described herein), as assessed by molecular diagnostic using an appropriate

clinically validated and/or FDA approved test within at least two (2) years prior to the admission to the treatment as described herein.

[0145] In some embodiments, the subject has a cancer characterized by one or more mutations in KRAS (e.g., as described herein), provided that the cancer is characterized by a KRAS G12C mutation. In some embodiments, the subject has a cancer characterized by a KRAS G12C mutation that is not characterized by a KRAS Q61X mutation. In some embodiments, the subject has a cancer characterized by a KRAS G12C mutation and an additional mutation at codon 13 (e.g., a G13D, G13A, G13C, G13R, G13S, and G13V mutation). In some embodiments, the subject has a cancer characterized by a KRAS G12C mutation and an additional mutation at codon 61.

[0146] In some embodiments, the subject has one or more mutations in the MAPK pathway. In some embodiments, the one or more mutations in the MAPK pathway are one or more mutations other than a BRAF mutation comprising V600X mutation, provided that the subject also has a KRAS G12C mutation. In some embodiments, the subject has one or more mutations in the MAPK pathway selected from the group consisting of one or more mutations in NRAS, HRAS, CRAF, BRAF, NRAF, MAPK/ERK, MAPK/MEK, NF1, IGFR, PDGFR, VEGFR, FGFR, CCKR, NGFR, EphR, AXLR, KEAP-1, TIE receptor, RYK receptor, DDR receptor, RET receptor, ROS receptor, LTK receptor, ROR receptor, and MuSK receptor, provided that the subject also has a KRAS G12C mutation. In some embodiments, the subject has a mutation in NRAS. In some embodiments, the subject has a mutation in HRAS. In some embodiments, the subject has a mutation in CRAF. In some embodiments, the subject has a mutation in BRAF (except for V600X mutation). In some embodiments, the subject has a mutation in NRAF. In some embodiments, the subject has a mutation in MAPK/ERK. In some embodiments, the subject has a mutation in MAPKK/MEK. In some embodiments, the subject has a mutation in NF1. In some embodiments, the subject has a mutation in IGFR. In some embodiments, the subject has a mutation in PDGFR. In some embodiments, the subject has a mutation in VEGFR. In some embodiments, the subject has a mutation in FGFR. In some embodiments, the subject has a mutation in CCKR. In some embodiments, the subject has a mutation in NGFR. In some embodiments, the subject has a mutation in EphR. In some embodiments, the subject has a mutation in AXLR. In some embodiments, the subject has a mutation in TIE receptor. In some

embodiments, the subject has a mutation in RYK receptor. In some embodiments, the subject has a mutation in DDR receptor. In some embodiments, the subject has a mutation in RET receptor. In some embodiments, the subject has a mutation in ROS receptor. In some embodiments, the subject has a mutation in LTK receptor. In some embodiments, the subject has a mutation in ROR receptor. In some embodiments, the subject has a mutation in MuSK receptor.

[0147] In some embodiments, the subject has a mutation in EGFR, provided that the subject also has a KRAS G12C mutation. In some embodiments, subject has an EGFR mutation including an EGFR exon 19 deletion, exon 20 insertion, L858X mutation, T790X mutation, C797X mutation, G719X mutation, L861X mutation, S768X mutation, E709X mutation, or any combination thereof. In some embodiments, subject has an EGFR mutation including an EGFR exon 19 deletion, and/or exon 20 insertion. In some embodiments, subject has an EGFR exon 19 deletion. In some embodiments, subject has an EGFR exon 20 insertion.

[0148] In some embodiments, the subject does not have a mutation in *PTPN11*, such as an E76K mutation.

[0149] In some embodiments, the subject has the solid tumor progressed or recurred on or after at least one prior line of a systemic therapy including a platinum-based doublet chemotherapy and/or an anti-PD-1/PD-L1 therapy, each of which is given in monotherapy or both of which are given in combination therapy.

[0150] In some embodiments, the subject has a measurable disease according to response evaluation criteria in solid tumors (RECIST). In some embodiments, treatment of the subject with the compound of formula (I) or (10b) and the KRAS G12C inhibitor causes a measurable change in disease state according to RECIST.

[0151] In some embodiments, the subject has not previously participated in an interventional clinical study within a period of at least about four (4) weeks or five (5) half-lives of an agent used in the interventional clinical study, whichever is shorter prior to initiation of the treatment with the compound of formula (I) or (10b) in combination with the KRAS G12C inhibitor.

[0152] In some embodiments, the subject has not previously received a radiotherapy or a proton therapy including i) a limited field of radiation for palliation within a period of about one

(1) week, or ii) a radiation to more than about 30% of bone marrow or a wide field of radiation within a period of about four (4) weeks, prior to initiation of the treatment with the compound of formula (I) or (10b) in combination with the KRAS G12C inhibitor.

[0153] In some embodiments, the subject has not taken or is not taking a) one or more of strong or moderate inducers or inhibitors of CYP3A4 and/or P-gp inducers or inhibitors (including herbal supplements or food products containing grapefruit juice, star fruit, or Seville oranges) within a period of about 14 days or five (5) half-lives, whichever is longer prior to initiation of the treatment with the compound of formula (I) or (10b) in combination with the KRAS G12C inhibitor; b) a drug that is a known substrate of CYP3A4, P-gp, multidrug and toxin extrusion protein (MATE)1, and/or MATE2-K transporters within a period of about 14 days or five (5) half-lives, whichever is longer prior to initiation of the treatment with the compound of formula (I) or (10b) in combination with the KRAS G12C inhibitor; and/or one or more acid reducing agents, such as proton pump inhibitors (PPIs) or H2 receptor antagonists within a period of about 14 days or five (5) half-lives, whichever is longer prior to initiation of the treatment with the compound of formula (I) or (10b) in combination with the KRAS G12C inhibitor.

[0154] In some embodiments, the subject does not have inadequate organ functions including adequate hematological, renal, hepatic, and coagulating functions, as defined below:

Hematological

a. Absolute neutrophil count <1,500/μL;
b. Platelets <100,000/μL; and
c. Hemoglobin <9 g/dL without transfusion for ≤2 weeks or erythropoiesis-stimulating agents (e.g., Epo, Procrit) for ≤6 weeks.

Renal

d. Serum creatinine > 1.5 × ULN, unless creatinine clearance ≥ 40 mL/min (measured or calculated using the Cockcroft-Gault formula)

Hepatic

e. Serum total bilirubin ≥1.5× institutional upper limit of normal (ULN) or ≥3.0× institutional ULN if the patient has a diagnosis of Gilbert syndrome or hemolytic anemia as confirmed by the investigator; and

f. Aspartate aminotransferase/serum glutamic-oxaloacetic transaminase (AST/SGOT) and/or alanine aminotransferase/serum glutamic-pyruvic transaminase (ALT/SGPT) >2.5×ULN.

Coagulation

g. International normalized ratio (INR) or prothrombin time (PT) >1.5×ULN unless the patient is receiving anticoagulant therapy and as long as PT or activated partial thromboplastin time (aPTT) is within the therapeutic range of intended use of anticoagulants; and

h. Activated partial thromboplastin time >1.5×ULN unless the patient is receiving anticoagulant therapy and as long as PT or aPTT is within the therapeutic range of intended use of anticoagulants.

[0155] In some embodiments, the subject does not have active hepatitis B infection, hepatitis C infection, or human immunodeficiency virus (HIV) infection with measurable viral load.

[0156] In some embodiments, the subject does not have has a life-threatening illness, medical condition, an active uncontrolled infection, or an organ system dysfunction (e.g., ascites, coagulopathy, or encephalopathy).

[0157] In some embodiments, the subject does not have one or more cardiac-related diseases or findings:

a) History of significant cardiovascular disease (e.g., cerebrovascular accident, myocardial infarction or unstable angina), within the last 6 months before starting the treatment;

b) Clinically significant cardiac disease, including New York Heart Association Class II or higher heart failure;

c) History of left ventricular ejection fraction (LVEF) <50% within the previous 12 months before starting the treatment;

d) Resting corrected QT interval (QTc) >470 msec, derived as the averaged from three electrocardiograms (ECGs), using the ECG machines provided; and/or

e) Any clinically significant abnormalities in rhythm, conduction, or morphology of resting ECG (e.g., third degree heart block, Mobitz Type II heart block, ventricular arrhythmias, uncontrolled atrial fibrillation).

[0158] In some embodiments, the subject has not been diagnosed of an additional invasive malignancy within the previous 3 years, provided that the additional invasive malignancy is other than curatively treated non-melanomatous skin cancer, superficial urothelial carcinoma, in situ cervical cancer, or any other curatively treated malignancy that is not expected to require treatment for recurrence during the course of the treatment with the compound of formula (I) or (10b) in combination with the KRAS G12C inhibitor.

[0159] In some embodiments, the subject does not have one or more untreated brain metastases from non-brain tumors.

[0160] In some embodiments, the subject who has had brain metastases resected or have received radiation therapy ending at least 4 weeks prior to the initiation of the treatment (e.g., Cycle 1, Day 1) with the compound of formula (I) or (10b) in combination with the KRAS G12C inhibitor is eligible, provided that the subject meets all of the following criteria prior to the initiation of the treatment: a) residual neurological symptoms related to the CNS treatment Grade ≤ 2; b) on a stable or decreasing dose of ≤ 10 mg daily prednisone (or equivalent) for at least 2 weeks prior to Cycle 1, Day 1, if applicable; and c) follow-up magnetic resonance imaging (MRI) within 4 weeks prior to Cycle 1, Day 1 shows no new lesions appearing.

[0161] In some embodiments, the subject has not undergone a major surgery within 4 weeks prior to the enrollment for the treatment with the compound of formula (I) or (10b) in combination with the KRAS G12C inhibitor, provided that the surgery or procedure is other than peripherally inserted central catheter line placement, thoracentesis, paracentesis, biopsies, or abscess drainage.

[0162] In some embodiments, the subject does not have a history of hypersensitivity to the KRAS G12C inhibitor or the compound of formula (I) or (10b), active or inactive excipients of the KRAS G12C inhibitor or the compound of formula (I) or (10b) or drugs with a similar chemical structure or class to either the KRAS G12C inhibitor or the compound of formula (I) or (10b), dependent on which combination the subject could receive.

[0163] In some embodiments, the subject does not have one or more additional activating mutations in BRAF V600X, PTPN11 (SHP2), and/or KRAS Q61X. In some embodiments, the subject does not have a tumor harboring one or more additional activating mutations in BRAF V600X, PTPN11 (SHP2), and/or KRAS Q61X.

[0164] In some embodiments, the subject is not previously treated with a KRAS G12C inhibitor (e.g., as described herein). In some embodiments, the subject is not previously treated with sotorasib or adagrasib. In some embodiments, the subject is not previously treated with sotorasib. In some embodiments, the subject is not previously treated with adagrasib. In some embodiments, the subject was previously treated with a KRAS G12C inhibitor. In some embodiments, the subject was previously treated with sotorasib. In some embodiments, the subject was previously treated with a KRAS G12C inhibitor other than sotorasib. In some embodiments, the subject was previously treated with adagrasib. In some embodiments, the subject is not previously treated with a PTPN11 inhibitor (e.g., SHP2 inhibitor). In some embodiments, the subject is not previously treated with a PTPN11 inhibitor (e.g., SHP2 inhibitor), provided that the PTPN11 inhibitor is other than the compound of formula (I) or (10b). In some embodiments, the subject is not previously treated with a PTPN11 inhibitor selected from the group consisting of TNO-155, RMC-4630, RLY-1971, JAB-3068, JAB-3312, PF-07284892, and ERAS601. In some embodiments, the subject is not previously treated with the compound of formula (I) or (10b). In some embodiments, the subject has previously been treated with a SHP2 inhibitor including any one of TNO-155, RMC-4630, RLY-1971, JAB-3068, JAB-3312, PF-07284892, ERAS601, and the compound of formula (I) or (10b). In some embodiments, the subject has previously been treated with the compound of formula (I) or (10b).

[0165] In some embodiments, the subject does not have a gastrointestinal illness (e.g., post gastrectomy, short bowel syndrome, uncontrolled Crohn's disease, celiac disease with villous atrophy, or chronic gastritis), which may preclude absorption of the compound of formula (I) or (10b).

[0166] In some embodiments, the subject is not on dialysis.

[0167] In some embodiments, the subject does not have a history of allogenic bone marrow transplant.

[0168] Further inclusion and exclusion criteria for subjects who may benefit from treatment with the compound of formula (I) or (10b) in combination with the KRAS G12C inhibitor, such as subjects enrolled in a clinical study of the SHP2 Inhibitor Compound (10b) in combination with the KRAS G12C inhibitor, are described in Example 5.

[0169] In some embodiments, the subject meets all of inclusion criteria of 1) to 11) as described in Example 5. In some embodiments, the subject meets all of inclusion criteria of 1) to 11) as described in Example 5, provided that the subject does not meet any one of exclusion criteria of 1) to 17) as described in Example 5.

III-4: Treatment Cycle and Dose Adjustment

[0170] Treatment with the compound of formula (I) or (10b) in combination with the KRAS G12C inhibitor can include one or more treatment cycles (e.g., at least 1, 2, 3, or more treatment cycles). In some embodiments, the treatment includes one or more treatment cycles (e.g., at least 1, 2, 3, or more treatment cycles). In some embodiments, the treatment includes at least 2, 3, or more treatment cycles. In some embodiments, the treatment includes 2 to 3 treatment cycles. In some embodiments, the treatment includes 3 treatment cycles. In some embodiments, the treatment includes more than 3 treatment cycles.

[0171] In some embodiments, each of one or more treatment cycles has a duration of about 28 days; and the compound of formula (I) or (10b) is administered daily. In some embodiments, each of one or more treatment cycles has a duration of about 28 days; and the KRAS G12C inhibitor is administered daily. In some embodiments, each of one or more treatment cycles has a duration of about 28 days; the compound of formula (I) or (10b) is administered daily; and the KRAS G12C inhibitor is administered daily.

[0172] The treatment may include a dose escalation period, during which, after a previous treatment cycle, a dose of the compound of formula (I) or (10b) or the KRAS G12C inhibitor can be adjusted (e.g., dose escalation or de-escalation) or retained. Dose adjustment may be based at least in part on a safety evaluation (e.g., a dose-limiting toxicity (DLT) assessment).

[0173] In some embodiments, a subject begins treatment with the compound of formula (I) or (10b) and the KRAS G12C inhibitor at a first compound dose level and a first KRAS G12C inhibitor dose level, and is subsequently treated at a second compound dose level and a second

KRAS G12C inhibitor dose level, where the second compound dose level differs from the first compound dose level and/or the second KRAS G12C inhibitor dose level differs from the first KRAS G12C inhibitor dose level. In some embodiments, the second KRAS G12C inhibitor dose level is lower than the first KRAS G12C inhibitor dose level. In some embodiments, the second KRAS G12C inhibitor dose level is higher than the first KRAS G12C inhibitor dose level. In some embodiments, the second compound dose level is lower than the first compound dose level. In some embodiments, the second compound dose level is higher than the first compound dose level. In some embodiments, the administration of KRAS G12C inhibitor in combination with the compound of formula (I) or (10b) includes one or more dose escalations (e.g., dose increases), dose retentions, or dose de-escalations (e.g., dose reductions) of KRAS G12C inhibitor and/or the compound of formula (I) or (10b). In some embodiments, the administration of KRAS G12C inhibitor in combination with the compound of formula (I) or (10b) includes one or more dose escalations, dose retentions, or dose de-escalations of KRAS G12C inhibitor. In some embodiments, the administration of KRAS G12C inhibitor in combination with the compound of formula (I) or (10b) includes one or more dose de-escalations of KRAS G12C inhibitor. In some embodiments, the administration of KRAS G12C inhibitor in combination with the compound of formula (I) or (10b) includes one or more dose escalations of KRAS G12C inhibitor. In some embodiments, the administration of KRAS G12C inhibitor in combination with the compound of formula (I) or (10b) includes one or more dose escalations, dose retentions, or dose de-escalations of the compound of formula (I) or (10b). In some embodiments, the administration of KRAS G12C inhibitor in combination with the compound of formula (I) or (10b) includes one or more dose de-escalations (e.g., dose reductions) of the compound of formula (I) or (10b). In some embodiments, the administration of KRAS G12C inhibitor in combination with the compound of formula (I) or (10b) includes one or more dose escalations (e.g., dose increases) of the compound of formula (I) or (10b). In some embodiments, the administration of KRAS G12C inhibitor in combination with the compound of formula (I) or (10b) includes one or more dose escalations (e.g., dose increases), dose retentions, or dose de-escalations (e.g., dose reductions) of KRAS G12C inhibitor and/or the compound of formula (I) or (10b), each of which is determined by a safety or dose-limiting toxicity (DLT) assessment (e.g., relevant to a cohort of subjects). In some embodiments, the administration of KRAS G12C inhibitor in combination with the compound of formula (I) or (10b) includes one or

more dose escalations, dose retentions, or dose de-escalations of the compound of formula (I) or (10b), each of which is determined by a dose-limiting toxicity (DLT) assessment, as described in Example 5 and **FIG. 9**.

[0174] In some embodiments, the administration of the compound of formula (I) or (10b) includes a dose escalation after a previous treatment cycle, when a dose-limiting toxicity (DLT) rate is less than, e.g., about 19.7% as determined by a DLT assessment (e.g., relevant to a cohort of subjects). In some embodiments, the administration of the compound of formula (I) or (10b) includes a dose escalation in a second treatment cycle after a first treatment cycle, when a dose-limiting toxicity (DLT) rate is less than, e.g., about 19.7% as determined by a DLT assessment (e.g., relevant to a cohort of subjects). In some embodiments, the administration of the compound of formula (I) or (10b) includes a dose escalation in a third treatment cycle after a second treatment cycle, when a dose-limiting toxicity (DLT) rate is less than, e.g., about 19.7% as determined by a DLT assessment (e.g., relevant to a cohort of subjects).

[0175] In some embodiments, the administration of the compound of formula (I) or (10b) includes a dose de-escalation after a previous treatment cycle, when a dose-limiting toxicity rate is more than, e.g., about 29.8% as determined by a DLT assessment (e.g., relevant to a cohort of subjects). In some embodiments, the administration of the compound of formula (I) or (10b) includes a dose retention in a second treatment cycle after a first treatment cycle, when a dose-limiting toxicity rate is more than, e.g., about 29.8% as determined by a DLT assessment (e.g., relevant to a cohort of subjects). In some embodiments, the administration of the compound of formula (I) or (10b) includes a dose retention in a third treatment cycle after a second treatment cycle, when a dose-limiting toxicity rate is more than, e.g., about 29.8% as determined by a DLT assessment (e.g., relevant to a cohort of subjects).

[0176] In some embodiments, the administration of the compound of formula (I) or (10b) includes a dose retention after a previous treatment cycle, when a dose-limiting toxicity rate is in a range of from about 21.9% to about 29.8% as determined by a DLT assessment (e.g., relevant to a cohort of subjects). In some embodiments, the administration of the compound of formula (I) or (10b) includes a dose retention in a second treatment cycle after a first treatment cycle, when a dose-limiting toxicity rate is in a range of from about 21.9% to about 29.8% as determined by a DLT assessment (e.g., relevant to a cohort of subjects). In some embodiments,

the administration of the compound of formula (I) or (10b) includes a dose retention in a third treatment cycle after a second treatment cycle, when a dose-limiting toxicity rate is in a range of from about 21.9% to about 29.8% as determined by a DLT assessment (e.g., relevant to a cohort of subjects).

[0177] After the dose escalation period, the treatment further includes a dose expansion/optimization period. In some embodiments of the dose expansion/optimization period, the compound of formula (I) or (10b) is administered at a dose regimen (e.g., Dose Regimen 1 or Dose Regimen 2) determined during the dose escalation period.

[0178] In some embodiments, the administration of the compound of formula (I) or (10b) includes one or more dose adjustments. In some embodiments, the administration of the compound of formula (I) or (10b) includes one or more dose adjustments during the dose expansion/optimization period. In some embodiments, the administration of the compound of formula (I) or (10b) includes one or more dose adjustments during the dose expansion/optimization period; and the one or more dose adjustments are determined according to a safety evaluation by Safety Review Committee (SRC).

[0179] In any one of embodiments as described herein, the KRAS G12C inhibitor in a total daily dosage is not adjusted (e.g., any dose escalation and/or de-escalation are not allowed during the treatment).

[0180] In some embodiments, dosing adjustments, delays, and discontinuations of the compound of formula (I) or (10b) and/or the KRAS G12C inhibitor are further based on the criteria of Example 5.

III-5: Therapeutically Effective Amount/Administration

[0181] The compound of formula (I) or (10b) and the KRAS G12C inhibitor can be provided in jointly therapeutically effective amounts or in synergistically effective amounts, or each of which can be used at a dose different than when each is used alone. In some embodiments, the compound of formula (I) or (10b) and the KRAS G12C inhibitor are provided in jointly therapeutically effective amounts. In some embodiments, the compound of formula (I) or (10b) and the KRAS G12C inhibitor are provided in synergistically effective amounts. In some embodiments, the compound of formula (I) or (10b) and/or the KRAS G12C inhibitor is used at

a dose different than when it is used alone (e.g., as in a monotherapy treatment). In some embodiments, the compound of formula (I) or (10b) and the KRAS G12C inhibitor are each used at a dose different than when each is used alone. In some embodiments, the compound of formula (I) or (10b) and the KRAS G12C inhibitor are each used at a dose lower than when each is used alone. In some embodiments, the compound of formula (I) or (10b) is used at a dose lower than when it is used alone. In some embodiments, the KRAS G12C inhibitor is used at a dose lower than when it is used alone. In some embodiments, the compound of formula (I) or (10b) is used at a dose higher than when it is used alone. In some embodiments, the KRAS G12C inhibitor is used at a dose higher than when it is used alone.

[0182] The compound of formula (I) or (10b) and the KRAS G12C inhibitor can be administered concomitantly or sequentially. In some embodiments, the compound of formula (I) or (10b) and the KRAS G12C inhibitor are administered concomitantly. In some embodiments, the compound of formula (I) or (10b) and the KRAS G12C inhibitor are administered in a pharmaceutical composition including the compound of formula (I) or (10b) and the KRAS G12C inhibitor. In some embodiments, the compound of formula (I) or (10b) and the KRAS G12C inhibitor are administered sequentially. In some embodiments, the compound of formula (I) or (10b) is administered prior to the administration of the KRAS G12C inhibitor. In some embodiments, the the compound of formula (I) or (10b) is administered after the administration of the KRAS G12C inhibitor.

[0183] The therapeutically effective amount of the compound of formula (I) or (10b) can be a total daily dosage of no more than about 2000 mg, on a salt-free and anhydrous basis. In some embodiments, the therapeutically effective amount of the compound of formula (I) or (10b) is a total daily dosage of no more than about 2000 mg, on a salt-free and anhydrous basis. In some embodiments, the therapeutically effective amount is a total daily dosage of from about 100 mg to about 2000 mg, from about 150 mg to about 1000 mg, from about 200 mg to about 1000 mg, from about 250 mg to about 1000 mg, from about 300 mg to about 1000 mg, from about 350 mg to about 1000 mg, from about 400 mg to about 1000 mg, from about 450 mg to about 1000 mg, from about 500 mg to about 1000 mg, from about 550 mg to about 1000 mg, from about 600 mg to about 1000 mg, from about 650 mg to about 1000 mg, from about 700 mg to about 1000 mg, from about 100 mg to about 700 mg, from about 150 mg to about 700 mg, from about 200 mg to

about 700 mg, from about 250 mg to about 700 mg, from about 300 mg to about 700 mg, from about 350 mg to about 700 mg, from about 400 mg to about 700 mg, from about 450 mg to about 700 mg, from about 500 mg to about 700 mg, from about 550 mg to about 700 mg, from about 100 mg to about 550 mg, from about 150 mg to about 550 mg, from about 200 mg to about 550 mg, from about 250 mg to about 550 mg, from about 300 mg to about 550 mg, from about 350 mg to about 550 mg, from about 400 mg to about 550 mg, from about 450 mg to about 550 mg, from about 100 mg to about 400 mg, from about 150 mg to about 400 mg, from about 200 mg to about 400 mg, from about 250 mg to about 400 mg, or from about 300 mg to about 400 mg of the compound of formula (I) or (10b), on a salt-free and anhydrous basis, or any useful range therein. In some embodiments, the therapeutically effective amount is a total daily dosage of from about 250 mg to about 400 mg, from about 400 mg to about 550 mg, or from about 550 mg to about 700 mg of the compound of formula (I) or (10b), on a salt-free and anhydrous basis, or any useful range therein. In some embodiments, the therapeutically effective amount is a total daily dosage of from about 80 mg to about 700 mg, from about 80 mg to about 550 mg, from about 80 mg to about 400 mg, from about 80 mg to about 250 mg, or from about 80 mg to about 150 mg of the compound of formula (I) or (10b), on a salt-free and anhydrous basis, or any useful range therein.

[0184] In some embodiments, the therapeutically effective amount of the compound of formula (I) or (10b) is a total daily dosage of about 100 mg to about 2000 mg, from about 150 mg to about 1000 mg, from about 250 mg to about 1000 mg, from about 400 mg to about 1000 mg, from about 250 mg to about 700 mg, from about 250 mg to about 550 mg, from about 250 mg to about 400 mg, from about 400 mg to about 550 mg, or from about 550 mg to about 700 mg, on a salt-free and anhydrous basis, or any useful range therein. In some embodiments, the therapeutically effective amount is a total daily dosage of from about 250 mg to about 400 mg, from about 400 mg to about 550 mg, or from about 550 mg to about 700 mg of the compound of formula (I) or (10b), on a salt-free and anhydrous basis, or any useful range therein.

[0185] The therapeutically effective amount of the compound of formula (10b) can be a total daily dosage of no more than about 2000 mg, on a salt-free and anhydrous basis. In some embodiments, the therapeutically effective amount of the compound of formula (10b) is a total daily dosage of no more than about 2000 mg, on a salt-free and anhydrous basis. In some

embodiments, the therapeutically effective amount is a total daily dosage of from about 10 mg to about 2000 mg, from about 50 mg to about 2000 mg, from about 80 mg to about 2000 mg, from about 80 mg to about 1000 mg, from about 80 mg to about 700 mg, from about 80 mg to about 550 mg, from about 80 mg to about 400 mg, from about 80 mg to about 250 mg, or from about 80 mg to about 150 mg of the compound of formula (10b), on a salt-free and anhydrous basis, or any useful range therein. In some embodiments, the therapeutically effective amount is a total daily dosage of from about 80 mg to about 700 mg, from about 80 mg to about 550 mg, from about 80 mg to about 400 mg, from about 80 mg to about 250 mg, or from about 80 mg to about 150 mg of the compound of formula (10b), on a salt-free and anhydrous basis, or any useful range therein.

[0186] In some embodiments, the therapeutically effective amount of the compound of formula (10b) is a total daily dosage of about 100 mg to about 2000 mg, from about 150 mg to about 1000 mg, from about 250 mg to about 1000 mg, from about 400 mg to about 1000 mg, from about 250 mg to about 700 mg, from about 250 mg to about 550 mg, from about 250 mg to about 400 mg, from about 400 mg to about 550 mg, or from about 550 mg to about 700 mg of the compound of formula (10b), on a salt-free and anhydrous basis, or any useful range therein. In some embodiments, the therapeutically effective amount is a total daily dosage of from about 250 mg to about 400 mg, from about 400 mg to about 550 mg, or from about 550 mg to about 700 mg, on a salt-free and anhydrous basis, or any useful range therein.

[0187] In some embodiments, the therapeutically effective amount of the compound of formula (10b) is a total daily dosage of about 100 mg, about 150 mg, about 200 mg, about 250 mg, about 300 mg, about 350 mg, about 400 mg, about 450 mg, about 500 mg, about 550 mg, about 600 mg, about 650 mg, about 700 mg, about 750 mg, about 800 mg, about 850 mg, about 900 mg, about 950 mg, or about 1000 mg of the compound of formula (10b), on a salt-free and anhydrous basis. In some embodiments, the therapeutically effective amount is a total daily dosage of about 80 mg, about 150 mg, about 250 mg, about 400 mg, about 550 mg, or about 700 mg of the compound of formula (10b), on a salt-free and anhydrous basis. In some embodiments, the therapeutically effective amount of the compound of formula (10b) is a total daily dosage of about 250 mg, about 400 mg, or about 550 mg of the compound of formula (10b), on a salt-free and anhydrous basis. In some embodiments, the therapeutically effective

amount is a total daily dosage of about 80 mg of the compound of formula (10b), on a salt-free and anhydrous basis. In some embodiments, the therapeutically effective amount is a total daily dosage of about 150 mg of the compound of formula (10b), on a salt-free and anhydrous basis. In some embodiments, the therapeutically effective amount is a total daily dosage of about 250 mg of the compound of formula (10b), on a salt-free and anhydrous basis. In some embodiments, the therapeutically effective amount is a total daily dosage of about 400 mg of the compound of formula (10b), on a salt-free and anhydrous basis. In some embodiments, the therapeutically effective amount is a total daily dosage of about 550 mg of the compound of formula (10b), on a salt-free and anhydrous basis. In some embodiments, the therapeutically effective amount is a total daily dosage of about 700 mg of the compound of formula (10b), on a salt-free and anhydrous basis.

[0188] In some embodiments, the therapeutically effective amount of the KRAS G12C inhibitor is a total daily dosage of no more than about 2000 mg. In some embodiments, the therapeutically effective amount of the KRAS G12C inhibitor is a total daily dosage of from about 10 mg to about 2000 mg, from about 10 mg to about 1500 mg, from about 10 mg to about 1200 mg, from about 10 mg to about 1000 mg, from about 10 mg to about 960 mg, from about 10 mg to about 840 mg, from about 10 mg to about 800 mg, from about 10 mg to about 720 mg, from about 10 mg to about 600 mg, from about 10 mg to about 480 mg, from about 10 mg to about 360 mg, from about 10 mg to about 300 mg, from about 10 mg to about 240 mg, from about 10 mg to about 150 mg, from about 100 mg to about 2000 mg, from about 100 mg to about 1500 mg, from about 100 mg to about 1200 mg, from about 100 mg to about 1000 mg, from about 100 mg to about 960 mg, from about 100 mg to about 840 mg, from about 100 mg to about 800 mg, from about 100 mg to about 720 mg, from about 100 mg to about 600 mg, from about 100 mg to about 480 mg, from about 100 mg to about 360 mg, from about 100 mg to about 300 mg, from about 100 mg to about 240 mg, from about 100 mg to about 150 mg, from about 200 mg to about 2000 mg, from about 200 mg to about 1500 mg, from about 200 mg to about 1200 mg, from about 200 mg to about 1000 mg, from about 200 mg to about 960 mg, from about 200 mg to about 840 mg, from about 200 mg to about 800 mg, from about 200 mg to about 720 mg, from about 200 mg to about 600 mg, from about 200 mg to about 480 mg, from about 200 mg to about 360 mg, from about 200 mg to about 300 mg, from about 200 mg to about 240 mg, from about 300 mg to about 2000 mg, from about 300 mg to about 1500 mg, from about 300 mg to

about 1200 mg, from about 300 mg to about 960 mg, from about 300 mg to about 840 mg, from about 300 mg to about 720 mg, from about 300 mg to about 600 mg, from about 300 mg to about 480 mg, from about 300 mg to about 360 mg, from about 400 mg to about 2000 mg, from about 400 mg to about 1500 mg, from about 400 mg to about 1200 mg, from about 400 mg to about 960 mg, from about 400 mg to about 840 mg, from about 400 mg to about 720 mg, from about 400 mg to about 600 mg, from about 400 mg to about 480 mg, from about 500 mg to about 2000 mg, from about 500 mg to about 1500 mg, from about 500 mg to about 1200 mg, from about 500 mg to about 960 mg, from about 500 mg to about 840 mg, from about 500 mg to about 720 mg, from about 500 mg to about 600 mg, from about 600 mg to about 2000 mg, from about 600 mg to about 1500 mg, from about 600 mg to about 1200 mg, from about 600 mg to about 960 mg, from about 600 mg to about 840 mg, from about 600 mg to about 720 mg, or from about 600 mg to about 1200 mg, or any useful range therein. In some embodiments, the therapeutically effective amount of the KRAS G12C inhibitor is a total daily dosage of about 100 mg, 120 mg, about 150 mg, about 180 mg, about 200 mg, about 240 mg, about 250 mg, about 300 mg, about 350 mg, about 360 mg, about 400 mg, about 450 mg, about 480 mg, about 500 mg, about 550 mg, about 600 mg, about 650 mg, about 700 mg, about 720 mg, about 750 mg, about 800 mg, about 840 mg, about 850 mg, about 900 mg, about 950 mg, about 960 mg, about 1000 mg, about 1050 mg, about 1100 mg, about 1150 mg, or about 1200 mg.

[0189] In some embodiments, the therapeutically effective amount of the compound of formula (10b) is a total daily dosage of no more than about 2000 mg, on a salt-free and anhydrous basis; and the therapeutically effective amount of the KRAS G12C inhibitor is a total daily dosage of from about 10 mg to about 2000 mg. In some embodiments, the therapeutically effective amount of the compound of formula (10b) is a total daily dosage of about 100 mg to about 2000 mg, from about 150 mg to about 1000 mg, from about 250 mg to about 1000 mg, from about 400 mg to about 1000 mg, from about 250 mg to about 700 mg, from about 250 mg to about 550 mg, from about 250 mg to about 400 mg, from about 400 mg to about 550 mg, from about 550 mg to about 700 mg, or any useful range therein, on a salt-free and anhydrous basis; and the therapeutically effective amount of the KRAS G12C inhibitor is a total daily dosage of from about 100 mg to about 2000 mg, from about 100 mg to about 1000 mg, from about 120 mg to about 960 mg, from about 240 mg to about 960 mg, from about 360 mg to about 960 mg, from about 480 mg to about 960 mg, from about 600 mg to about 960 mg, from about 720 mg to about

960 mg, from about 840 mg to about 960 mg, about 10 mg to about 2000 mg, from about 10 mg to about 2000 mg, from about 10 mg to about 1200 mg, from about 10 mg to about 960 mg, from about 10 mg to about 840 mg, from about 10 mg to about 720 mg, from about 10 mg to about 600 mg, from about 10 mg to about 480 mg, from about 10 mg to about 360 mg, from about 10 mg to about 300 mg, from about 10 mg to about 240 mg, or from about 10 mg to about 150 mg, from about 600 mg to about 1200 mg, or any useful range therein. In some embodiments, the therapeutically effective amount of the compound of formula (10b) is a total daily dosage of from about 250 mg to about 400 mg, from about 400 mg to about 550 mg, from about 550 mg to about 700 mg, or any useful range therein, on a salt-free and anhydrous basis; and the therapeutically effective amount of the KRAS G12C inhibitor is a total daily dosage of from about 480 mg to about 1200 mg.

[0190] In some embodiments, the therapeutically effective amount of the compound of formula (10b) is a total daily dosage of about 250 mg, about 400 mg, or about 550 mg, on a salt-free and anhydrous basis; and the therapeutically effective amount of the KRAS G12C inhibitor is a total daily dosage of about 120 mg, about 150 mg, about 240 mg, about 300 mg, about 360 mg, about 480 mg, about 600 mg, about 720 mg, about 840 mg, about 960 mg, or about 1200 mg. In some embodiments, the therapeutically effective amount is a total daily dosage of about 250 mg of the compound of formula (10b), on a salt-free and anhydrous basis; and the therapeutically effective amount of the KRAS G12C inhibitor is a total daily dosage of about 960 mg. In some embodiments, the therapeutically effective amount is a total daily dosage of about 400 mg of the compound of formula (10b), on a salt-free and anhydrous basis; and the therapeutically effective amount of the KRAS G12C inhibitor is a total daily dosage of about 960 mg. In some embodiments, the therapeutically effective amount is a total daily dosage of about 550 mg of the compound of formula (10b), on a salt-free and anhydrous basis; and the therapeutically effective amount of the KRAS G12C inhibitor is a total daily dosage of about 960 mg. In some embodiments, the therapeutically effective amount is a total daily dosage of about 250 mg of the compound of formula (10b), on a salt-free and anhydrous basis; and the therapeutically effective amount of the KRAS G12C inhibitor is a total daily dosage of about 1200 mg. In some embodiments, the therapeutically effective amount is a total daily dosage of about 400 mg of the compound of formula (10b), on a salt-free and anhydrous basis; and the therapeutically effective amount of the KRAS G12C inhibitor is a total daily dosage of about

1200 mg. In some embodiments, the therapeutically effective amount is a total daily dosage of about 550 mg of the compound of formula (10b), on a salt-free and anhydrous basis; and the therapeutically effective amount of the KRAS G12C inhibitor is a total daily dosage of about 1200 mg. In some embodiments, the therapeutically effective amount is a total daily dosage of about 250 mg of the compound of formula (10b), on a salt-free and anhydrous basis; and the therapeutically effective amount of the KRAS G12C inhibitor is a total daily dosage of about 600 mg. In some embodiments, the therapeutically effective amount is a total daily dosage of about 400 mg of the compound of formula (10b), on a salt-free and anhydrous basis; and the therapeutically effective amount of the KRAS G12C inhibitor is a total daily dosage of about 600 mg. In some embodiments, the therapeutically effective amount is a total daily dosage of about 550 mg of the compound of formula (10b), on a salt-free and anhydrous basis; and the therapeutically effective amount of the KRAS G12C inhibitor is a total daily dosage of about 600 mg.

[0191] In general, the compound of formula (I) or (10b) can be administered orally. In some embodiments, the compound of formula (I) or (10b) is administered orally. In some embodiments, the compound of formula (10b) is administered orally. In some embodiments, the compound of formula (10b) in a tablet formulation is administered orally.

[0192] In general, the KRAS G12C inhibitor can be administered orally. In some embodiments, the KRAS G12C inhibitor is administered orally.

[0193] In general, the compound of formula (I) or (10b) can be administered once or multiple times (e.g., 2, 3, 4, or more times) daily. In some embodiments, the compound of formula (I) or (10b) is administered once, twice, three times, or four times daily. In some embodiments, the compound of formula (10b) is administered once, twice, three times, or four times daily. In some embodiments, the compound of formula (10b) is administered once daily. In some embodiments, the compound of formula (10b) is administered twice daily. In some embodiments, the compound of formula (10b) is administered every other day. In some embodiments, the compound of formula (10b) is administered with four days on and three days off (e.g., compound is administered for four consecutive days and then not administered for three consecutive days), five days on and two days off, two days on and five days off, one week on

and one week off, two weeks on and one week off, three weeks on and one week off, or a similar schedule.

[0194] In general, the KRAS G12C inhibitor can be administered once, twice, or multiple times (e.g., 2, 3, 4, or more times) daily. In some embodiments, the KRAS G12C inhibitor is administered once daily. In some embodiments, the KRAS G12C inhibitor is administered twice daily.

[0195] In some embodiments, the compound of formula (I) or (10b) and the KRAS G12C inhibitor are each administered orally. In some embodiments, the compound of formula (10b) and the KRAS G12C inhibitor are each administered orally. In some embodiments, the compound of formula (I) or (10b) is administered once daily; and the KRAS G12C inhibitor is administered once daily. In some embodiments, the compound of formula (10b) is administered once daily; and the KRAS G12C inhibitor is administered once daily. In some embodiments, the compound of formula (10b) is administered once daily; and the KRAS G12C inhibitor is administered twice daily.

[0196] The compound of formula (I) or (10b) can be in an oral dosage form in one or more dosage strengths, where the compound of formula (I) or (10b) is present in an amount of at least about 1 mg, 5 mg, 10 mg, 20 mg, 30 mg, 50 mg, 90 mg, 100 mg, 120 mg, 180 mg, 200 mg, 300 mg, 400 mg, or 500 mg, on a salt-free and anhydrous basis. In some embodiments, the oral dosage form is a tablet formulation in one or more dosage strengths. In some embodiments of the tablet formulation, the compound of formula (I) or (10b) is present in an amount of from 1 to 1000 mg, from 1 to 750 mg, from 1 to 500 mg, from 1 to 250 mg, from 30 to 1000 mg, from 30 to 750 mg, from 30 to 500 mg, from 30 to 200 mg, from 30 to 180 mg, from 30 to 120 mg, from 30 to 90 mg, from 50 to 1000 mg, from 50 to 750 mg, from 50 to 500 mg, from 50 to 250 mg, from 100 to 1000 mg, from 100 to 750 mg, from 100 to 500 mg, from 100 to 250 mg, from 200 to 1000 mg, from 200 to 750 mg, from 200 to 500 mg, from 300 to 1000 mg, from 300 to 750 mg, from 300 to 500 mg, from 400 to 1000 mg, from 400 to 750 mg, from 500 to 1000 mg, from 500 to 750 mg, from 600 to 1000 mg, from 5 to 250 mg, or from 5 to 100 mg in each tablet, on a salt-free and anhydrous basis. In some embodiments of the tablet formulation, the compound of formula (I) or (10b) is present in an amount of about 5 mg, 10 mg, 30 mg, 50 mg, 100 mg, 150 mg, 200 mg, 250 mg, 300 mg, 400 mg, 500 mg, 600 mg, 700 mg, 800 mg, 900 mg, or 1000 mg

in each tablet, on a salt-free and anhydrous basis. In some embodiments of the tablet formulation, the compound of formula (I) or (10b) is present in an amount of about 30 mg, 50 mg, or 100 mg in each tablet, on a salt-free and anhydrous basis.

[0197] The compound of formula (10b) can be in an oral dosage form in one or more dosage strengths, where the compound of formula (10b) is present in an amount of at least about 1 mg, 5 mg, 10 mg, 20 mg, 30 mg, 50 mg, 90 mg, 100 mg, 120 mg, 180 mg, 200 mg, 300 mg, 400 mg, or 500 mg, on a salt-free and anhydrous basis. In some embodiments, the oral dosage form is a tablet formulation in one or more dosage strengths. In some embodiments of the tablet formulation, the compound of formula (10b) is present in an amount of from 1 to 1000 mg, from 1 to 750 mg, from 1 to 500 mg, from 1 to 250 mg, from 30 to 1000 mg, from 30 to 750 mg, from 30 to 500 mg, from 30 to 200 mg, from 30 to 180 mg, from 30 to 120 mg, from 30 to 90 mg, from 50 to 1000 mg, from 50 to 750 mg, from 50 to 500 mg, from 50 to 250 mg, from 100 to 1000 mg, from 100 to 750 mg, from 100 to 500 mg, from 100 to 250 mg, from 200 to 1000 mg, from 200 to 750 mg, from 200 to 500 mg, from 300 to 1000 mg, from 300 to 750 mg, from 300 to 500 mg, from 400 to 1000 mg, from 400 to 750 mg, from 500 to 1000 mg, from 500 to 750 mg, from 600 to 1000 mg, from 5 to 250 mg, or from 5 to 100 mg in each tablet, on a salt-free and anhydrous basis. In some embodiments of the tablet formulation, the compound of formula (10b) is present in an amount of about 5 mg, 10 mg, 30 mg, 50 mg, 100 mg, 150 mg, 200 mg, 250 mg, 300 mg, 400 mg, 500 mg, 600 mg, 700 mg, 800 mg, 900 mg, or 1000 mg in each tablet, on a salt-free and anhydrous basis. In some embodiments of the tablet formulation, the compound of formula (10b) is present in an amount of about 30 mg, 50 mg, or 100 mg in each tablet, on a salt-free and anhydrous basis. In some embodiments of the tablet formulation, the compound of formula (10b) is present in an amount of about 30 mg in each tablet, on a salt-free and anhydrous basis. In some embodiments of the tablet formulation, the compound of formula (10b) is present in an amount of about 50 mg in each tablet, on a salt-free and anhydrous basis. In some embodiments of the tablet formulation, the compound of formula (10b) is present in an amount of about 100 mg in each tablet, on a salt-free and anhydrous basis.

[0198] In some embodiments, the compound of formula (10b) is administered once daily to provide a total daily dosage of no more than about 2000 mg of the compound of formula (10b). In some embodiments, the compound of formula (10b) is administered once daily to provide a

total daily dosage of from about 100 mg to about 2000 mg, from about 150 mg to about 1000 mg, from about 200 mg to about 1000 mg, from about 250 mg to about 1000 mg, from about 300 mg to about 1000 mg, from about 350 mg to about 1000 mg, from about 400 mg to about 1000 mg, from about 450 mg to about 1000 mg, from about 500 mg to about 1000 mg, from about 550 mg to about 1000 mg, from about 600 mg to about 1000 mg, from about 650 mg to about 1000 mg, from about 700 mg to about 1000 mg, from about 100 mg to about 700 mg, from about 150 mg to about 700 mg, from about 200 mg to about 700 mg, from about 250 mg to about 700 mg, from about 300 mg to about 700 mg, from about 350 mg to about 700 mg, from about 400 mg to about 700 mg, from about 450 mg to about 700 mg, from about 500 mg to about 700 mg, from about 550 mg to about 700 mg, from about 100 mg to about 550 mg, from about 150 mg to about 550 mg, from about 200 mg to about 550 mg, from about 250 mg to about 550 mg, from about 300 mg to about 550 mg, from about 350 mg to about 550 mg, from about 250 mg to about 400 mg, from about 400 mg to about 550 mg, from about 450 mg to about 550 mg, from about 100 mg to about 400 mg, from about 150 mg to about 400 mg, from about 200 mg to about 400 mg, from about 250 mg to about 400 mg, from about 300 mg to about 400 mg, or from about 550 mg to about 700 mg of the compound of formula (10b), on a salt-free and anhydrous basis. In some embodiments, the compound of formula (10b) is administered once daily to provide a total daily dosage of from about 250 mg to about 400 mg, from about 400 mg to about 550 mg, or from about 550 mg to about 700 mg of the compound of formula (10b), on a salt-free and anhydrous basis. In some embodiments, the compound of formula (10b) is administered once daily to provide a total daily dosage of about 250 mg, about 400 mg, about 550 mg of the compound of formula (10b), on a salt-free and anhydrous basis.

[0199] In some embodiments, the compound of formula (10b) is administered once daily to provide a total daily dosage of no more than about 2000 mg of the compound of formula (10b); and the KRAS G12C inhibitor is administered once daily to provide a total daily dosage of from about 10 mg to about 2000 mg. In some embodiments, the compound of formula (10b) is administered once daily to provide a total daily dosage of from about 100 mg to about 2000 mg, from about 150 mg to about 1000 mg, from about 250 mg to about 1000 mg, from about 400 mg to about 1000 mg, from about 250 mg to about 700 mg, from about 250 mg to about 550 mg, from about 250 mg to about 400 mg, from about 400 mg to about 550 mg, or from about 550 mg to about 700 mg of the compound of formula (10b), on a salt-free and anhydrous basis; and the

KRAS G12C inhibitor is administered once daily to provide a total daily dosage of from about 100 mg to about 2000 mg, from about 100 mg to about 1000 mg, from about 120 mg to about 960 mg, from about 240 mg to about 960 mg, from about 360 mg to about 960 mg, from about 480 mg to about 960 mg, from about 600 mg to about 960 mg, from about 720 mg to about 960 mg, or from about 840 mg to about 960 mg. In some embodiments, the compound of formula (10b) is administered once daily to provide a total daily dosage of from about 250 mg to about 400 mg, from about 400 mg to about 550 mg, or from about 550 mg to about 700 mg of the compound of formula (10b), on a salt-free and anhydrous basis; and the KRAS G12C inhibitor is administered once daily to provide a total daily dosage of from about 480 mg to about 960 mg. In some embodiments, the compound of formula (10b) is administered once daily to provide a total daily dosage of about 250 mg, about 400 mg, about 550 mg of the compound of formula (10b), on a salt-free and anhydrous basis; and the KRAS G12C inhibitor is administered once daily to provide a total daily dosage of about 960 mg.

[0200] In some embodiments, the compound of formula (10b) is administered once daily to provide a total daily dosage of no more than about 2000 mg of the compound of formula (10b); and the KRAS G12C inhibitor is administered twice daily to provide a total daily dosage of from about 10 mg to about 2000 mg. In some embodiments, the compound of formula (10b) is administered once daily to provide a total daily dosage of from about 100 mg to about 2000 mg, from about 150 mg to about 1000 mg, from about 250 mg to about 1000 mg, from about 400 mg to about 1000 mg, from about 250 mg to about 700 mg, from about 250 mg to about 550 mg, from about 250 mg to about 400 mg, from about 400 mg to about 550 mg, or from about 550 mg to about 700 mg of the compound of formula (10b), on a salt-free and anhydrous basis; and the KRAS G12C inhibitor is administered twice daily to provide a total daily dosage of from about from about 100 mg to about 2000 mg, from about 100 mg to about 1000 mg, from about 120 mg to about 960 mg, from about 240 mg to about 960 mg, from about 360 mg to about 960 mg, from about 480 mg to about 960 mg, from about 600 mg to about 960 mg, from about 720 mg to about 960 mg, from about 840 mg to about 960 mg, about 10 mg to about 2000 mg, from about 10 mg to about 2000 mg, from about 10 mg to about 1200 mg, from about 10 mg to about 960 mg, from about 10 mg to about 840 mg, from about 10 mg to about 720 mg, from about 10 mg to about 600 mg, from about 10 mg to about 480 mg, from about 10 mg to about 360 mg, from about 10 mg to about 300 mg, from about 10 mg to about 240 mg, or from about 10 mg to about 150 mg,

or from about 600 mg to about 1200 mg. In some embodiments, the compound of formula (10b) is administered once daily to provide a total daily dosage of from about 250 mg to about 400 mg, from about 400 mg to about 550 mg, or from about 550 mg to about 700 mg of the compound of formula (10b), on a salt-free and anhydrous basis; and the KRAS G12C inhibitor is administered twice daily to provide a total daily dosage of from about 120 mg to about 2000 mg, or from about 600 mg to about 1200 mg (e.g., as described herein). In some embodiments, the compound of formula (10b) is administered once daily to provide a total daily dosage of about 250 mg, about 400 mg, about 550 mg of the compound of formula (10b), on a salt-free and anhydrous basis; and the KRAS G12C inhibitor is administered twice daily to provide a total daily dosage of about 1200 mg. In some embodiments, the compound of formula (10b) is administered once daily to provide a total daily dosage of about 250 mg, about 400 mg, about 550 mg of the compound of formula (10b), on a salt-free and anhydrous basis; and the KRAS G12C inhibitor is administered twice daily to provide a total daily dosage of about 600 mg.

[0201] In some embodiments, the compound of formula (10b) is administered once daily during each of one or more treatment cycles, as described herein. In some embodiments, the KRAS G12C inhibitor is administered once daily during each of one or more treatment cycles, as described herein. In some embodiments, the compound of formula (10b) and the KRAS G12C inhibitor are each administered once daily during each of one or more treatment cycles, as described herein. In some embodiments, the compound of formula (10b) is administered once daily during each of one or more treatment cycles, as described herein. In some embodiments, the KRAS G12C inhibitor is administered twice daily during each of one or more treatment cycles, as described herein. In some embodiments, the compound of formula (10b) is administered once daily and the KRAS G12C inhibitor is administered twice daily during each of one or more treatment cycles, as described herein.

[0202] In general, the compound of formula (10b) is recommended to be administered to a subject without food (e.g., after an overnight fast (minimum 8 hours) followed by 2 hours of fasting after the dose is taken). The subject is allowed to have water except for one (1) hour before and after the administration and the subject is given with water (e.g., 240 mL) at the administration. In some embodiments, the compound of formula (10b) is administered to the

subject without food, at least about 8 hours prior to the administration and at least about 2 hours post the administration.

[0203] In some embodiments, the KRAS G12C inhibitor is administered once daily, in about 5 minutes after administration of the compound of formula (10b).

III-6: Efficacy

[0204] A clinical study of a PTPN inhibitor (e.g., a compound represented by formula (10b)) in combination with a KRAS G12C inhibitor can be performed to evaluate the safety, tolerability, and efficacy of the combination to reduce or stabilize cancers (e.g., cancers comprising solid tumors) in subjects. In some embodiments, the subjects have a solid tumor including non-small cell lung cancer (NSCLC). In some embodiments, the subjects have non-small cell lung cancer (NSCLC). In some embodiments, the subjects have NSCLC characterized by a KRAS mutation.

[0205] In various embodiments, the subject is administered the therapy for at least 1 month, at least 2 months, at least 3 months, at least 4 months, at least 5 months, at least 6 months, at least 7 months, at least 8 months, at least 9 months, at least 10 months, at least 11 months, at least 12 months, at least 15 months, at least 18 months, at least 21 months, or at least 23 months, e.g., for 1 month, 2 months, 3 months, 4 months, 5 months, 6 months, 7 months, 8 months, 9 months, 10 months, 11 months, 12 months, 15 months, 18 months, 21 months, or 24 months. In various embodiments, the subject is administered the therapy for at least 1 month. In various embodiments, the subject is administered the therapy for at least 3 months. In various embodiments, the subject is administered the therapy for at least 6 months. In various embodiments, the subject is administered the therapy for at least 8 months.

[0206] The subject can respond to the therapy as measured by at least a stable disease (SD), as determined by Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 protocol (Eisenhauer, et al., *Eur J Cancer*; 2009; 45(2):228-247). RECIST v1.1 is discussed in detail in the examples below. An at least stable disease is one that is a stable disease, has shown a partial response (PR) or has shown a complete response (CR) (i.e., "at least SD" = SD+PR+CR, often referred to as disease control). In various embodiments, the stable disease has neither sufficient shrinkage to qualify for partial response (PR) nor sufficient increase to qualify for progressive

disease (PD). In various embodiments, the subject exhibits at least a partial response (i.e., "at least PR" = PR+CR, often referred to as objective response).

[0207] Response can be measured by one or more of decrease in tumor size, suppression or decrease of tumor growth, decrease in target or tumor lesions, delayed time to progression, no new tumor or lesion, a decrease in new tumor formation, an increase in survival or progression-free survival (PFS), and no metastases. In various embodiments, the progression of a subject's disease can be assessed by measuring tumor size, tumor lesions, or formation of new tumors or lesions, by assessing the subject using a computerized tomography (CT) scan, a positron emission tomography (PET) scan, a magnetic resonance imaging (MRI) scan, an X-ray, ultrasound, or some combination thereof.

[0208] Progression free survival (PFS) can be assessed as described in the RECIST 1.1 protocol. In various embodiments, the subject exhibits a PFS of at least 1 month. In various embodiments, the subject exhibits a PFS of at least 3 months. In some embodiments, the subject exhibits a PFS of at least 6 months.

[0209] Administration of a therapeutically effective amount of the compound of formula (I) or (10b) in combination with a therapeutically effective amount of the KRAS G12C inhibitor can reduce or substantially eliminate cancers or solid tumors in subjects. In some embodiments, the therapeutically effective amount of formula (I) or (10b) in combination with the KRAS G12C inhibitor substantially eliminates the solid tumor. In some embodiments, the therapeutically effective amount of formula (I) or (10b) in combination with the KRAS G12C inhibitor reduces a volume of the solid tumor at least about 10%, about 20%, about 30%, about 40%, about 50%, about 60%, about 70%, about 80%, about 90%, or more. In some embodiments, the therapeutically effective amount of formula (I) or (10b) in combination with the KRAS G12C inhibitor reduces a volume of the solid tumor in a size of from about 10% to about 90%, from about 10% to about 80%, from about 10% to about 70%, from about 10% to about 60%, from about 10% to about 50%, from about 10% to about 40%, from about 10% to about 30%, from about 10% to about 20%, from about 20% to about 90%, from about 20% to about 80%, from about 20% to about 70%, from about 20% to about 60%, from about 20% to about 50%, from about 20% to about 40%, from about 20% to about 30%, from about 30% to about 90%, from about 30% to about 80%, from about 30% to about 70%, from about 30% to about 60%, from

about 30% to about 50%, from about 30% to about 40%, from about 40% to about 90%, from about 40% to about 80%, from about 40% to about 70%, from about 40% to about 60%, from about 40% to about 50%, from about 50% to about 90%, from about 50% to about 80%, from about 50% to about 70%, from about 50% to about 60%, from about 60% to about 90%, from about 60% to about 80%, from about 60% to about 70%, from about 70% to about 90%, from about 70% to about 80%, from about 80% to about 90%, or any range therein. In some embodiments, the therapeutically effective amount of formula (I) or (10b) in combination with the KRAS G12C inhibitor reduces a volume of the solid tumor about 10%, about 20%, about 30%, about 40%, about 50%, about 60%, about 70%, about 80%, or about 90%.

[0210] Administration of a therapeutically effective amount of the compound of formula (I) or (10b) in combination with a therapeutically effective amount of the KRAS G12C inhibitor can stabilize cancers or solid tumors in subjects. In some embodiments, the therapeutically effective amount of formula (I) or (10b) in combination with the KRAS G12C inhibitor stabilize the solid tumor.

[0211] Administration of a therapeutically effective amount of the compound of formula (I) or (10b) in combination with a therapeutically effective amount of the KRAS G12C inhibitor can maintain a reduction or stabilization of cancers or solid tumors in subjects for a period of time (e.g., 1 to 12 months). In some embodiments, the solid tumor is reduced or stabilized for a period of at least about one month with the therapeutically effective amount of the compound of formula (I) or (10b) in combination with the KRAS G12C inhibitor. In some embodiments, the solid tumor is reduced or stabilized for a period of at least about 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 months with the therapeutically effective amount of the compound of formula (10b) in combination with the KRAS G12C inhibitor. In some embodiments, the solid tumor is reduced or stabilized for a period of from about 1 to about 12 months, from about 1 to about 6 months, from about 1 to about 3 months, or from about 1 to about 2 months.

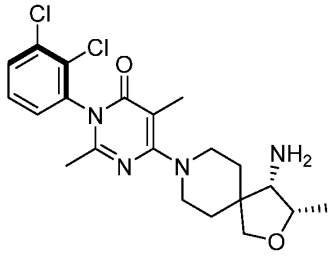
[0212] In some embodiments, the subject is further evaluated to by one or more tests to provide overall assessments including plasma pharmacokinetic and/or pharmacodynamic profiles.

[0213] In some embodiments, the subject is further evaluated for one or more biomarkers to determine a correlation of the one or more biomarkers to an antitumor response.

III-7: Combination Therapy of Formula (10b) and Adagrasib

[0214] In one aspect, the present disclosure provides a method of treating cancer in a subject. The method includes administering to the subject:

a) a therapeutically effective amount of a compound represented by formula (10b):



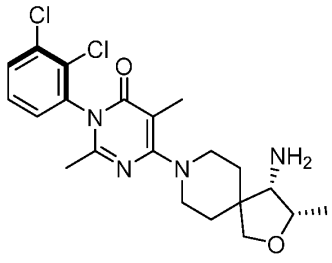
(10b),

or a pharmaceutically acceptable salt, hydrate, solvate, stereoisomer, conformational isomer, tautomer, or a combination thereof; and

b) a therapeutically effective amount of adagrasib (MRTX-849).

[0215] In another aspect, the present disclosure provides a method of treating NSCLC. The method includes administering to the subject:

a) a therapeutically effective amount of a compound represented by formula (10b):



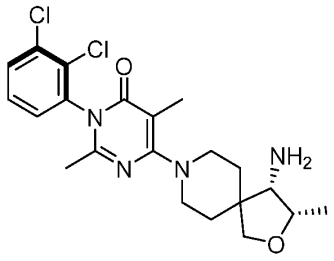
(10b),

or a pharmaceutically acceptable salt, hydrate, solvate, stereoisomer, conformational isomer, tautomer, or a combination thereof; and

b) a therapeutically effective amount of adagrasib (MRTX-849).

[0216] In another aspect, the present disclosure provides a method of treating colorectal cancer. The method includes administering to the subject:

a) a therapeutically effective amount of a compound represented by formula (10b):


(10b),

or a pharmaceutically acceptable salt, hydrate, solvate, stereoisomer, conformational isomer, tautomer, or a combination thereof; and

b) a therapeutically effective amount of adagrasib (MRTX-849).

[0217] The compound of formula (10b) is described according to **Section III-1: PTPN11 Inhibitors and/or KRAS G12C Inhibitors** and **Section IV. Compounds**. In some embodiments, the compound of formula (10) is any one of embodiments as described in **Section III-1**.

[0218] The cancer and/or solid tumor are described according to **Section III-2: Cancer/Solid Tumor**. In some embodiments, the cancer and/or solid tumor are any one of embodiments as described in **Section III-2: Cancer/Solid Tumor**.

[0219] In some embodiments, the cancer or solid tumor is non-small cell lung cancer (NSCLC) or colorectal cancer. In some embodiments, the cancer is non-small cell lung cancer (NSCLC). In some embodiments, the cancer is colorectal cancer. In some embodiments, the solid tumor is an advanced or metastatic KRASG12C-positive non-small cell lung cancer (NSCLC). In some embodiments, the cancer is a KRAS G12C-positive cancer resistant to sotorasib (AMG 510) or adagrasib (MRTX-849). In some embodiments, the cancer is a KRAS G12C-positive cancer resistant to sotorasib (AMG 510). In some embodiments, the cancer is a KRAS G12C-positive cancer resistant to adagrasib (MRTX-849). In some embodiments, the cancer is non-small cell lung cancer (NSCLC) resistant to the treatment of sotorasib (AMG 510) or adagrasib (MRTX-849). In some embodiments, the cancer is non-small cell lung cancer (NSCLC) resistant to the treatment of sotorasib (AMG 510). In some embodiments, the cancer is non-small cell lung cancer (NSCLC) resistant to the treatment of adagrasib (MRTX-849). In some embodiments, the cancer is colorectal cancer resistant to the treatment of sotorasib (AMG 510) or adagrasib (MRTX-849). In some embodiments, the cancer is colorectal cancer resistant to the treatment of

sotorasib (AMG 510). In some embodiments, the cancer is colorectal cancer resistant to the treatment of adagrasib (MRTX-849).

[0220] The subject is described according to **Section III-3: Subject**. In some embodiments, the subject is any one of embodiments as described in **Section III-3: Subject**. In some embodiments, the subject is any one of embodiments as described in **Section III-3: Subject**, wherein the KRAS G12C inhibitor, when applicable, is adagrasib (MRTX-849).

[0221] In some embodiments, the subject does not have a history of hypersensitivity to adagrasib (MRTX-849) or the compound of formula (I) or (10b), active or inactive excipients of adagrasib (MRTX-849) or the compound of formula (I) or (10b) or drugs with a similar chemical structure or class to either adagrasib (MRTX-849) or the compound of formula (I) or (10b).

[0222] In some embodiments, the subject is not previously treated with adagrasib (MRTX-849). In some embodiments, the subject has previously been treated with adagrasib (MRTX-849). In some embodiments, the subject has previously been treated with a KRAS G12C inhibitor other than adagrasib (MRTX-849). In some embodiments, the subject is not previously treated with a PTPN11 inhibitor (e.g., SHP2 inhibitor), provided that the PTPN11 inhibitor is other than the compound of formula (10b). In some embodiments, the subject is not previously treated with a PTPN11 inhibitor selected from the group consisting of TNO-155, RMC-4630, RLY-1971, JAB-3068, JAB-3312, PF-07284892, and ERAS601. In some embodiments, the subject is not previously treated with the compound of formula (10b). In some embodiments, the subject has previously been treated with a SHP2 inhibitor including any one of TNO-155, RMC-4630, RLY-1971, JAB-3068, JAB-3312, PF-07284892, ERAS601, and the compound of formula (10b). In some embodiments, the subject has previously been treated with the compound of formula (I) or (10b). In some embodiments, the subject has previously been treated with a PTPN11 inhibitor other than the compound of formula (I) or (10b).

[0223] The treatment cycle and dose adjustment are described according to **Section III-4: Treatment Cycle and Dose Adjustment**. In some embodiments, the treatment cycle and dose adjustment are any one of embodiments as described in **Section III-4: Treatment Cycle and Dose Adjustment**. In some embodiments, the treatment cycle and dose adjustment are any one

of embodiments as described in **Section III-4: Treatment Cycle and Dose Adjustment**, wherein the KRAS G12C inhibitor, when applicable, is adagrasib (MRTX-849).

[0224] The therapeutically effective amount and/or administration are described according to **Section III-5: Therapeutically Effective Amount/Administration**. In some embodiments, he therapeutically effective amount and/or administration are any one of embodiments as described in **Section III-5: Therapeutically Effective Amount/Administration**. In some embodiments, he therapeutically effective amount and/or administration are any one of embodiments as described in **Section III-5: Therapeutically Effective Amount/Administration**, wherein the KRAS G12C inhibitor, when applicable, is adagrasib (MRTX-849).

[0225] In some embodiments, the compound of formula (10b) and the adagrasib (MRTX-849) are provided in jointly therapeutically effective amounts. In some embodiments, the compound of formula (10b) and adagrasib (MRTX-849) are provided in synergistically effective amounts. In some embodiments, the compound of formula (10b) and/or adagrasib (MRTX-849) are each used at a dose lower than when each is used alone.

[0226] In some embodiments, the compound of formula (10b) and adagrasib (MRTX-849) are administered concomitantly (as described herein). In some embodiments, the compound of formula (10b) and adagrasib (MRTX-849) are administered sequentially (as described herein).

[0227] In some embodiments, the therapeutically effective amount of adagrasib (MRTX-849) is a total daily dosage of no more than about 2000 mg. In some embodiments, the therapeutically effective amount of adagrasib is a total daily dosage of from about 100 mg to about 2000 mg, from about 200 mg to about 2000 mg, from about 300 mg to about 2000 mg, from about 400 mg to about 2000 mg, from about 500 mg to about 2000 mg, from about 600 mg to about 2000 mg, from about 700 mg to about 2000 mg, from about 800 mg to about 2000 mg, from about 900 mg to about 2000 mg, from about 1000 mg to about 2000 mg, from about 1100 mg to about 2000 mg, from about 1200 mg to about 2000 mg, or any useful range therein. In some embodiments, the therapeutically effective amount of adagrasib is a total daily dosage of from about 100 mg to about 1500 mg, from about 200 mg to about 1500 mg, from about 300 mg to about 1500 mg, from about 400 mg to about 1500 mg, from about 500 mg to about 1500 mg, from about 600 mg to about 1500 mg, from about 700 mg to about 1500 mg, from about 800 mg

to about 1500 mg, from about 900 mg to about 1500 mg, from about 1000 mg to about 1500 mg, from about 1100 mg to about 1500 mg, from about 1200 mg to about 1500 mg, or any useful range therein. In some embodiments, the therapeutically effective amount of adagrasib is a total daily dosage of from about 100 mg to about 1200 mg, from about 200 mg to about 1200 mg, from about 300 mg to about 1200 mg, from about 400 mg to about 1200 mg, from about 500 mg to about 1200 mg, from about 600 mg to about 1200 mg, from about 700 mg to about 1200 mg, from about 800 mg to about 1200 mg, from about 900 mg to about 1200 mg, from about 1000 mg to about 1200 mg, from about 1100 mg to about 1200 mg, or any useful range therein. In some embodiments, the therapeutically effective amount of adagrasib is a total daily dosage of from about 600 mg to about 1200 mg, from about 700 mg to about 1200 mg, from about 800 mg to about 1200 mg, from about 900 mg to about 1200 mg, from about 1000 mg to about 1200 mg, from about 1100 mg to about 1200 mg, or any useful range therein. In some embodiments, the therapeutically effective amount of adagrasib is a total daily dosage of about 100 mg, 120 mg, about 150 mg, about 180 mg, about 200 mg, about 240 mg, about 250 mg, about 300 mg, about 350 mg, about 360 mg, about 400 mg, about 450 mg, about 480 mg, about 500 mg, about 550 mg, about 600 mg, about 650 mg, about 700 mg, about 720 mg, about 750 mg, about 800 mg, about 840 mg, about 850 mg, about 900 mg, about 950 mg, about 960 mg, about 1000 mg, about 1050 mg, about 1100 mg, about 1150 mg, or about 1200 mg.

[0228] In some embodiments, the therapeutically effective amount of adagrasib is a total daily dosage of about 150 mg, about 300 mg, about 600 mg, or about 1200 mg of adagrasib. In some embodiments, the therapeutically effective amount of adagrasib is a total daily dosage of about 600 mg of adagrasib. In some embodiments, the therapeutically effective amount of adagrasib is a total daily dosage of about 1200 mg of adagrasib.

[0229] In some embodiments, the therapeutically effective amount of the compound of formula (10b) is a total daily dosage of about 250 mg, about 400 mg, or about 550 mg, on a salt-free and anhydrous basis; and the therapeutically effective amount of adagrasib is a total daily dosage of about 120 mg, about 150 mg, about 240 mg, about 300 mg, about 360 mg, about 480 mg, about 600 mg, about 720 mg, about 840 mg, about 960 mg, or about 1200 mg. In some embodiments, the therapeutically effective amount is a total daily dosage of about 250 mg of the compound of formula (10b), on a salt-free and anhydrous basis; and the therapeutically effective

amount of adagrasib is a total daily dosage of about 1200 mg. In some embodiments, the therapeutically effective amount is a total daily dosage of about 400 mg of the compound of formula (10b), on a salt-free and anhydrous basis; and the therapeutically effective amount of adagrasib is a total daily dosage of about 1200 mg. In some embodiments, the therapeutically effective amount is a total daily dosage of about 550 mg of the compound of formula (10b), on a salt-free and anhydrous basis; and the therapeutically effective amount of adagrasib is a total daily dosage of about 1200 mg.

[0230] In some embodiments, adagrasib is administered orally.

[0231] In some embodiments, adagrasib is administered once daily. In some embodiments, adagrasib is administered twice daily.

[0232] In some embodiments, the compound of formula (10b) and adagrasib are each administered orally. In some embodiments, the compound of formula (10b) is administered once daily; and adagrasib is administered once daily. In some embodiments, the compound of formula (10b) is administered once daily; and adagrasib is administered twice daily.

[0233] In some embodiments, adagrasib is administered once or twice daily to provide a total daily dosage of no more than about 2000 mg of sotorasib. In some embodiments, adagrasib is administered twice daily to provide a total daily dosage of no more than about 1500 mg. In some embodiments, adagrasib is administered twice daily to provide a total daily dosage of about 1200 mg.

[0234] In some embodiments, the compound of formula (10b) is administered once daily during each of one or more treatment cycles, as described herein. In some embodiments, adagrasib is administered twice daily during each of one or more treatment cycles, as described herein. In some embodiments, the compound of formula (10b) is administered once daily and adagrasib is administered twice daily during each of one or more treatment cycles, as described herein.

[0235] Efficay is described according to **Section III-6: Efficacy**. In some embodiments, he therapeutically effective amount and/or administration are any one of embodiments as described in **Section III-6: Efficacy**. In some embodiments, he therapeutically effective amount and/or

administration are any one of embodiments as described in **Section III-6: Efficacy**, wherein the KRAS G12C inhibitor, when applicable, is adagrasib (MRTX-849).

[0236] A clinical study of the compound of formula (10b) in combination with adagrasib (MRTX-849) can be performed to evaluate the safety, tolerability, and efficacy of the combination to reduce or stabilize cancers (e.g., cancers comprising solid tumors) in subjects (e.g., similar to the clinical protocol of Example 5). In some embodiments, the subjects have a solid tumor including non-small cell lung cancer (NSCLC) or colorectal cancer. In some embodiments, the subjects have non-small cell lung cancer (NSCLC). In some embodiments, the subjects have NSCLC characterized by a KRAS mutation. In some embodiments, the subjects have colorectal cancer.

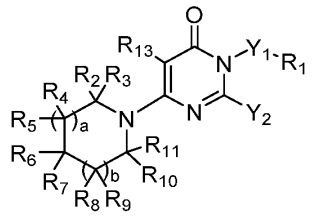
[0237] In some embodiments, the therapeutically effective amount of formula (10b) in combination with adagrasib reduces a volume of the solid tumor about 10%, about 20%, about 30%, about 40%, about 50%, about 60%, about 70%, about 80%, or about 90%.

[0238] In some embodiments, the therapeutically effective amount of formula (10b) in combination with adagrasib stabilize the solid tumor.

IV. COMPOUNDS

[0239] The present disclosure provides a PTPN11 inhibitor represent by formula (I) for use in a method of treating a disease or disorder (e.g., cancer) in a subject as described in **Section III: Combination Therapy**, a pharmaceutical composition for treating a disease or disorder (e.g., cancer) in a subject as described in **Section V: Composition**; and a kit for treating a disease or disorder (e.g., cancer) in a subject as described in **Section VI: Kits**. The PTPN11 inhibitor is as defined and described in WO 2020/033828, the entirety of which is hereby incorporated for all purpose.

[0240] The PTPN11 inhibitor is represent by formula (I):



(I),

or a pharmaceutically acceptable salt, hydrate, solvate, stereoisomer, conformational isomer, tautomer, or a combination thereof,

wherein:

subscript a is 0 or 1;

subscript b is 0 or 1;

Y_1 is a direct bond or $CR_{17}R_{18}$;

Y_2 is selected from the group consisting of C_{1-4}alkyl, amino, C_{1-4}alkylC(O)O-, C_{1-4}alkylamino and C_{1-4}aminoalkyl;

R_1 is selected from the group consisting of C_{6-10}aryl, C_{3-8}cycloalkyl, C_{3-8}cycloalkenyl, and a 5-10 membered heteroaryl group having 1 to 4 heteroatoms or groups as ring vertices independently selected from N, C(O), O, and S; said aryl or heteroaryl of R_1 is unsubstituted or substituted with 1 to 5 R_{12} groups independently selected from the group consisting of halo, hydroxy, amino, C_{1-4}alkylamino, di(C_{1-4}alkyl)amino, cyano, C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}hydroxyalkyl, C_{1-4}haloalkyl, C_{1-4}aminoalkyl, C_{3-8}cycloalkyl, C_{3-8}cycloalkenyl, $NR_{15}C(O)R_{14}$, $NR_{15}C(O)OR_{14}$, $NR_{14}C(O)NR_{15}R_{16}$, $NR_{15}S(O)R_{14}$, $NR_{15}S(O)_2R_{14}$, $C(O)NR_{15}R_{16}$, $S(O)NR_{15}R_{16}$, $S(O)_2NR_{15}R_{16}$, $C(O)R_{14}$, $C(O)OR_{14}$, OR_{14}, SR_{14}, $S(O)R_{14}$, and $S(O)_2R_{14}$;

R_2, R_3, R_{10}, and R_{11} are each independently selected from the group consisting of hydrogen, C_{1-4}alkyl, and C_{3-8}cycloalkyl;

R_4, R_5, R_8, and R_9 are each independently selected from the group consisting of hydrogen, cyano, C_{1-4}alkyl, C_{1-4}alkoxy, amino, hydroxy, C_{3-8}cycloalkyl, halo, and C_{1-4}alkylamino;

R_6 is selected from the group consisting of amino, C_{1-4}aminoalkyl, and C_{1-4}alkylamino;

R_7 is selected from the group consisting of hydrogen, amido, cyano, halo, and hydroxy, or is selected from the group consisting of C_{1-4}alkyl, C_{1-4}hydroxyalkyl, C_{3-6}cycloalkyl, phenyl, and 5- or 6- membered heteroaryl, any of which is unsubstituted or substituted with 1 to 5 groups independently selected from the group consisting of amino, halo, hydroxy, cyano, C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}haloalkyl, C_{1-4}haloalkoxy, C_{1-4}alkylamino, and C_{1-4}aminoalkyl;

or R_6 and R_7 together with the carbon atom to which they are both attached form a 3- to 7-membered saturated or unsaturated ring, having 0 to 3 heteroatoms or groups as ring

vertices independently selected from N, C(O), O, and $S(O)_m$; subscript m is 0, 1, or 2; and said saturated or unsaturated ring formed by R_6 and R_7 is unsubstituted or substituted with 1 to 3 groups independently selected from the group consisting of amino, halo, hydroxy, cyano, C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}haloalkyl, C_{1-4}haloalkoxy, C_{1-4}alkylamino and C_{1-4}aminoalkyl;

any two groups of R_2, R_3, R_4, R_5, R_7, R_8, R_9, R_{10} and R_{11} can form a 5 to 6 membered ring, having 0 to 2 heteroatoms as ring vertices elected from N, O and S;

any two groups of R_2, R_4, R_6, R_8 and R_{10} can form a direct bond, or a 1 or 2 atom carbon bridge;

R_{13} is selected from the group consisting of hydrogen, halo, cyano, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}hydroxyalkyl, C_{1-6} dihydroxyalkyl, -NH-NHR_{19}, -NHR_{19}, -OR_{19}, -$NHC(O)R_{19}$, -$NHC(O)NHR_{19}$, -$NHS(O)_2NHR_{19}$, -$NHS(O)_2R_{19}$, -$C(O)OR_{19}$, -$C(O)NR_{19}R_{20}$, -$C(O)NH(CH_2)_qOH$, -$C(O)NH(CH_2)_qR_{21}$, -$C(O)R_{21}$, -NH_2, -OH, -$S(O)_2NR_{19}R_{20}$, C_{3-8}cycloalkyl, aryl, heterocyclyl having 1-5 heteroatoms as ring vertices selected from N, O, S and P, and heteroaryl having 1-5 heteroatoms as ring vertices selected from N, O, S and P; subscript q is an integer of from 0 to 6; and each of aryl, heteroaryl, heterocyclyl and cycloalkyl of R_{13} is unsubstituted or substituted with 1 to 3 groups independently selected from the group consisting of C_{1-4}alkyl, –OH, -NH_2, -OR_{21}, halo, cyano, and oxo;

R_{14}, R_{15} and R_{16} are each independently selected from the group consisting of hydrogen, C_{1-4}alkyl, C_{3-8}cycloalkyl, C_{6-10}aryl and 5-10 membered heteroaryl, any of which is unsubstituted or substituted with one or more groups independently selected from the group consisting of amido, amino, halo, hydroxy, cyano, C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}haloalkyl, C_{1-4}haloalkoxy, C_{1-4}alkylamino and C_{1-4}aminoalkyl;

R_{17} and R_{18} are each independently selected from the group consisting of hydrogen, C_{1-4}alkyl, and CF_3;

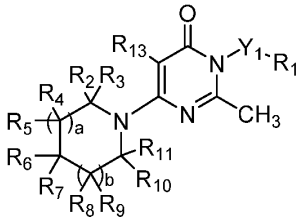
R_{19} and R_{20} are each independently selected from the group consisting of hydrogen, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}hydroxyalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl and C_{3-6}cycloalkyl; and

each R_{21} is independently selected from the group consisting of hydrogen, -OH, C_{1-6} alkyl, C_{1-6}haloalkyl, C_{1-6}hydroxyalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl and C_{3-6}cycloalkyl.

[0241] In some embodiments of formula (I), Y_1 is a direct bond. In some ebodiments, Y_1 is $CR_{17}R_{18}$. In some embodiments, R_{17} and R_{18} are each independently selected from the group consisting of hydrogen, $C_{1\text{-}4}$alkyl, and CF_3. In some embodiments, R_{17} and R_{18} are each independently hydrogen or $C_{1\text{-}4}$alkyl. In some embodimetns, Y_1 is $-CH_2$.

[0242] In some embodiments of formula (I), Y_2 is $C_{1\text{-}4}$alkyl. In some embodiments, Y_2 is methyl.

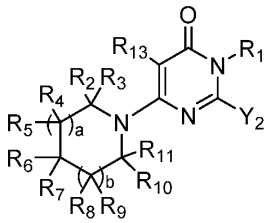
[0243] In some embodiments, the compound is represented by formula (Ia):



(Ia),

wherein the subscripts a and b, Y_1, R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_9, R_{10}, R_{11}, and R_{13} are as defined and described herein.

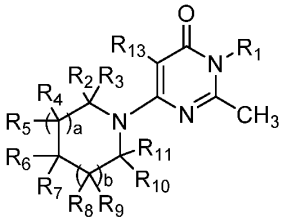
[0244] In some embodiments, the compound is represented by formula (Ib):



(Ib),

wherein the subscripts a and b, Y_2, R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_9, R_{10}, R_{11}, and R_{13} are as defined and described herein.

[0245] In some embodiments, the compound is represented by formula (Ic):



(Ic),

wherein the subscripts a and b, R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_9, R_{10}, R_{11}, and R_{13} are as defined and described herein.

[0246] In some embodiments of any one of formulae (I), (Ia), (Ib), and (Ic), subscripts a and b are each 1.

[0247] In some embodiments of any one of formulae (I), (Ia), (Ib), and (Ic), R_{13} is selected from the group consisting of hydrogen, halo, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}hydroxyalkyl, C_{1-6}dihydroxyalkyl, C_{3-8}cycloalkyl, 3- or 6-membered heterocyclyl having 1-3 heteroatoms as ring vertices selected from N, O and S; wherein heterocyclyl and cycloalkyl are substituted with 0 to 3 groups independently selected from the group consisting of C_{1-4}alkyl, –OH, -NH_2, -OR_{21}, halo, cyano and oxo. In some embodiments, R_{13} is selected from the group consisting of hydrogen, halo, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}hydroxyalkyl, C_{1-6}dihydroxyalkyl, and C_{3-8}cycloalkyl. In some embodiments, R_{13} is selected from the group consisting of hydrogen, halo, C_{1-6}alkyl, and C_{1-6}haloalkyl. In some embodiments, R_{13} is selected from the group consisting of hydrogen, halo, C_{1-4}alkyl, and C_{1-4}haloalkyl. In some embodiments, R_{13} is selected from the group consisting of -CH_2OH, CF_2OH, and –CHFOH. In some embodiments, R_{13} is selected from the group consisting of hydrogen, Cl, Br, methyl, and CF_3. In some embodiments, R_{13} is hydrogen. In some embodiments, R_{13} is Cl. In some embodiments, R_{13} is Br. In some embodiments, R_{13} is methyl. In some embodiments, R_{13} is CF_3.

[0248] In some embodiments of any one of formulae (I), (Ia), (Ib), and (Ic), R_1 is selected from the group consisting of C_{6-10}aryl and a 5- to 9- membered heteroaryl group having 1 to 4 heteroatoms groups as ring vertices independently selected from N, C(O), O, and S; and is unsubstituted or substituted with 1 to 5 R_{12} groups independently selected from the group consisting of halo, hydroxy, amino, C_{1-4}alkylamino, di(C_{1-4}alkyl)amino, cyano, C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}hydroxyalkyl, C_{1-4}haloalkyl, C_{1-4}aminoalkyl, C_{3-8}cycloalkyl, C_{3-8}cycloalkenyl, $NR_{15}C(O)R_{14}$, $NR_{15}C(O)OR_{14}$, $NR_{14}C(O)NR_{15}R_{16}$, $NR_{15}S(O)R_{14}$, $NR_{15}S(O)_2R_{14}$, $C(O)NR_{15}R_{16}$, $S(O)NR_{15}R_{16}$, $S(O)_2NR_{15}R_{16}$, $C(O)R_{14}$, $C(O)OR_{14}$, OR_{14}, SR_{14}, $S(O)R_{14}$, and $S(O)_2R_{14}$.

[0249] In some embodiments of any one of formulae (I), (Ia), (Ib), and (Ic), R_1 is selected from the group consisting of C_{6-10}aryl and a 5- to 9- membered heteroaryl group having 1 to 4 heteroatoms groups as ring vertices independently selected from N, C(O), O, and S; and is

unsubstituted or substituted with 1 to 5 R_{12} groups independently selected from the group consisting of halo, hydroxy, amino, C_{1-4}alkylamino, di(C_{1-4}alkyl)amino, cyano, C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}hydroxyalkyl, C_{1-4}haloalkyl, C_{1-4}aminoalkyl, C_{3-8}cycloalkyl, C_{3-8}cycloalkenyl, $NR_{15}C(O)R_{14}$, $NR_{15}C(O)OR_{14}$, $NR_{14}C(O)NR_{15}R_{16}$, $NR_{15}S(O)R_{14}$, $NR_{15}S(O)_2R_{14}$, $C(O)NR_{15}R_{16}$, $S(O)NR_{15}R_{16}$, $S(O)_2NR_{15}R_{16}$, $C(O)R_{14}$, $C(O)OR_{14}$, OR_{14}, SR_{14}, $S(O)R_{14}$, and $S(O)_2R_{14}$; and R_{14}, R_{15} and R_{16} are each independently selected from the group consisting of hydrogen, C_{1-4}alkyl, C_{3-8}cycloalkyl, C_{6-10}aryl and 5-10 membered heteroaryl, each of which is unsubstituted or substituted by one or more groups independently selected from the group consisting of amido, amino, halo, hydroxy, cyano, C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}haloalkyl, C_{1-4}haloalkoxy, C_{1-4}alkylamino and C_{1-4}aminoalkyl.

[0250] In some embodiments of any one of formulae (I), (Ia), (Ib), and (Ic), R_1 is selected from the group consisting of C_{6-10}aryl and a 5- to 9- membered heteroaryl group having 1 to 4 heteroatoms groups as ring vertices independently selected from N, C(O), O, and S; and is unsubstituted or substituted with 1 to 5 R_{12} groups independently selected from the group consisting of halo, hydroxy, amino, C_{1-4}alkylamino, di(C_{1-4}alkyl)amino, cyano, C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}hydroxyalkyl, C_{1-4}haloalkyl, C_{1-4}aminoalkyl, C_{3-8}cycloalkyl, C_{3-8}cycloalkenyl, $NR_{15}C(O)R_{14}$, $NR_{15}C(O)OR_{14}$, $NR_{14}C(O)NR_{15}R_{16}$, $NR_{15}S(O)R_{14}$, $NR_{15}S(O)_2R_{14}$, $C(O)NR_{15}R_{16}$, $S(O)NR_{15}R_{16}$, $S(O)_2NR_{15}R_{16}$, $C(O)R_{14}$, $C(O)OR_{14}$, OR_{14}, SR_{14}, $S(O)R_{14}$, and $S(O)_2R_{14}$; and R_{14}, R_{15} and R_{16} are each independently selected from the group consisting of hydrogen, C_{1-4}alkyl, C_{3-8}cycloalkyl, C_{6-10}aryl and 5-10 membered heteroaryl, each of which is unsubstituted or substituted by one or more groups independently selected from the group consisting of halo, hydroxy, cyano, and C_{1-4}alkyl.

[0251] In some embodiments of any one of formulae (I), (Ia), (Ib), and (Ic), R_1 is phenyl or a 5- to 6-member heteroaryl group having 1 to 4 heteroatoms as ring vertices independently selected from N, O, and S; and is unsubstituted or substituted with 1, 2 or 3 R_{12} groups independently selected from the group consisting of halo, hydroxy, amino, C_{1-4}alkylamino, di(C_{1-4}alkyl)amino, C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}haloalkyl, C_{1-4}aminoalkyl, and OR_{14}.

[0252] In some embodiments of any one of formulae (I), (Ia), (Ib), and (Ic), R_1 is phenyl or a 5- to 6-member heteroaryl group having 1 to 4 heteroatoms as ring vertices independently selected from N, O, and S; and is unsubstituted or substituted with 1, 2 or 3 R_{12} groups

independently selected from the group consisting of halo, hydroxy, amino, C_{1-4}alkylamino, di(C_{1-4}alkyl)amino, C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}haloalkyl, C_{1-4}aminoalkyl, and OR_{14}; and R_{14} is selected from the group consisting of hydrogen, C_{1-4}alkyl, C_{3-8}cycloalkyl, C_{6-10}aryl and 5-10 membered heteroaryl, each of which is unsubstituted or substituted by one or more groups independently selected from the group consisting of amido, amino, halo, hydroxy, cyano, C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}haloalkyl, C_{1-4}haloalkoxy, C_{1-4}alkylamino and C_{1-4}aminoalkyl.

[0253] In some embodiments of any one of formulae (I), (Ia), (Ib), and (Ic), R_1 is phenyl or a 5- to 6-member heteroaryl group having 1 to 4 heteroatoms as ring vertices independently selected from N, O, and S; and is unsubstituted or substituted with 1, 2 or 3 R_{12} groups independently selected from the group consisting of halo, hydroxy, amino, C_{1-4}alkylamino, di(C_{1-4}alkyl)amino, C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}haloalkyl, C_{1-4}aminoalkyl, and OR_{14}; and R_{14} is selected from the group consisting of hydrogen, C_{1-4}alkyl, C_{3-8}cycloalkyl, C_{6-10}aryl and 5-10 membered heteroaryl, each of which is unsubstituted or substituted by one or more groups independently selected from the group consisting of halo, hydroxy, cyano, and C_{1-4}alkyl.

[0254] In some embodiments of any one of formulae (I), (Ia), (Ib), and (Ic), R_1 is phenyl or a 5- to 6-member heteroaryl group having 1 to 4 heteroatoms as ring vertices independently selected from N, O, and S; and is unsubstituted or substituted with 1, 2 or 3 R_{12} groups independently selected from the group consisting of halo, hydroxy, amino, C_{1-4}alkylamino, di(C_{1-4}alkyl)amino, C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}haloalkyl, C_{1-4}aminoalkyl, and OR_{14}; and R_{14} is selected from the group consisting of C_{6-10}aryl and a 5-10 membered heteroaryl, each of which is unsubstituted or substituted by one or more groups independently selected from the group consisting of C_{1-4}alkylamido, amino, halo, hydroxy, cyano, C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}haloalkyl, C_{1-4}haloalkoxy, C_{1-4}alkylamino and C_{1-4}aminoalkyl.

[0255] In some embodiments of any one of formulae (I), (Ia), (Ib), and (Ic), R_1 is phenyl or a 5- to 6-member heteroaryl group having 1 to 4 heteroatoms as ring vertices independently selected from N, O, and S; and is unsubstituted or substituted with 1, 2 or 3 R_{12} groups independently selected from the group consisting of halo, hydroxy, amino, C_{1-4}alkylamino, di(C_{1-4}alkyl)amino, C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}haloalkyl, C_{1-4}aminoalkyl, and OR_{14}; and R_{14} is selected from the group consisting of C_{6-10}aryl and a 5-10 membered heteroaryl, each of which is

unsubstituted or substituted by one or more groups independently selected from the group consisting of halo, hydroxy, cyano, and C_{1-4}alkyl.

[0256] In some embodiments of any one of formulae (I), (Ia), (Ib), and (Ic), R_1 is phenyl or a 5- to 6-member heteroaryl group having 1 to 4 heteroatoms as ring vertices independently selected from N, O, and S; and is unsubstituted or substituted with 1, 2 or 3 R_{12} groups independently selected from the group consisting of halo, hydroxy, amino, C_{1-4}alkylamino, di(C_{1-4}alkyl)amino, C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}haloalkyl, C_{1-4}aminoalkyl, and OR_{14}; and R_{14} is phenyl or a 5-6 membered heteroaryl having 1 to 4 heteroatoms as ring vertices independently selected from N, O, and S, each of which is unsubstituted or substituted by one or two groups independently selected from the group consisting of C_{1-4}alkylamido, amino, halo, hydroxy, cyano, C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}haloalkyl, C_{1-4}haloalkoxy, C_{1-4}alkylamino and C_{1-4}aminoalkyl.

[0257] In some embodiments of any one of formulae (I), (Ia), (Ib), and (Ic), R_1 is phenyl or a 5- to 6-member heteroaryl group having 1 to 4 heteroatoms as ring vertices independently selected from N, O, and S; and is unsubstituted or substituted with 1, 2 or 3 R_{12} groups independently selected from the group consisting of halo, hydroxy, amino, C_{1-4}alkylamino, di(C_{1-4}alkyl)amino, C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}haloalkyl, C_{1-4}aminoalkyl, and OR_{14}; and R_{14} is phenyl or a 5-6 membered heteroaryl having 1 to 4 heteroatoms as ring vertices independently selected from N, O, and S, each of which is unsubstituted or substituted by one or more groups independently selected from the group consisting of halo, hydroxy, cyano, and C_{1-4}alkyl.

[0258] In some embodiments of any one of formulae (I), (Ia), (Ib), and (Ic), R_1 is phenyl or a 5- to 6-member heteroaryl group having 1 to 4 heteroatoms as ring vertices independently selected from N, O, and S; and is unsubstituted or substituted with 1, 2 or 3 R_{12} groups independently selected from the group consisting of halo, hydroxy, amino, C_{1-4}alkylamino, di(C_{1-4}alkyl)amino, C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}haloalkyl, C_{1-4}aminoalkyl, and OR_{14}; and R_{14} is phenyl or a 5-6 membered heteroaryl having 1 to 4 heteroatoms as ring vertices independently selected from N, O, and S, each of which is unsubstituted or substituted by one or more groups independently selected from the group consisting of C_{1-4}alkylamido, halo, hydroxy, cyano, and C_{1-4}alkyl.

[0259] In some embodiments of any one of formulae (I), (Ia), (Ib), and (Ic), R_1 is phenyl or a 5- to 6-member heteroaryl group having 1 to 4 heteroatoms as ring vertices independently selected from N, O, and S; and is unsubstituted or substituted with 1, 2 or 3 R_{12} groups independently selected from the group consisting of halo, hydroxy, amino, C_{1-4}alkylamino, di(C_{1-4}alkyl)amino, C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}haloalkyl, C_{1-4}aminoalkyl, and OR_{14}; and R_{14} is phenyl or a 5-6 membered heteroaryl having 1 to 4 heteroatoms as ring vertices independently selected from N, O, and S, each of which is unsubstituted or substituted by one or more groups independently selected from the group consisting of C_{1-4}alkylamido and C_{1-4}alkyl.

[0260] In some embodiments of any one of formulae (I), (Ia), (Ib), and (Ic), R_1 is phenyl or a 5- to 6-member heteroaryl group having 1 to 4 heteroatoms or groups as ring vertices independently selected from N, C(O), O, and S; and is unsubstituted or substituted with 1, 2 or 3 R_{12} groups independently selected from the group consisting of halo, hydroxy, amino, C_{1-4}alkylamino, di(C_{1-4}alkyl)amino, C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}haloalkyl, and C_{1-4}aminoalkyl.

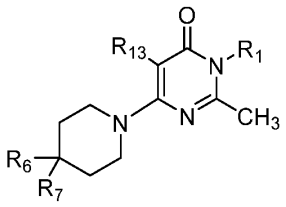
[0261] In some embodiments of any one of formulae (I), (Ia), (Ib), and (Ic), R_2, R_3, R_{10}, and R_{11} are independently hydrogen or C_{1-4}alkyl. In certain embodiments, R_2, R_3, R_{10}, and R_{11} are each hydrogen.

[0262] In some embodiments of any one of formulae (I), (Ia), (Ib), and (Ic), R_4, R_5, R_8, and R_9 are independently selected from the group consisting of hydrogen, C_{1-4}alkyl, C_{1-4}alkoxy, amino, hydroxy, C_{3-8}cycloalkyl, and C_{1-4}alkylamino. In certain embodiments, R_4, R_5, R_8, and R_9 are independently hydrogen or C_{1-4}alkyl. In certain embodiments, R_4, R_5, R_8, and R_9 are each hydrogen.

[0263] In some embodiments of any one of formulae (I), (Ia), (Ib), and (Ic), R_1 is phenyl or a 5- to 6-member heteroaryl group having 1 to 4 heteroatoms or groups as ring vertices independently selected from N, C(O), O, and S; and is unsubstituted or substituted with 1, 2 or 3 R_{12} groups independently selected from the group consisting of halo, hydroxy, amino, C_{1-4}alkylamino, di(C_{1-4}alkyl)amino, C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}haloalkyl, and C_{1-4}aminoalkyl; and R_4, R_5, R_8, and R_9 are independently selected from the group consisting of hydrogen, C_{1-4}alkyl, C_{1-4}alkoxy, amino, hydroxy, C_{3-6}cycloalkyl, and C_{1-4}alkylamino.

[0264] In some embodiments of any one of formulae (I), (Ia), (Ib), and (Ic), R_2, R_3, R_4, R_5, R_8, R_9, R_{10} and R_{11} are each hydrogen.

[0265] In some embodiments, the compound is represented by formula (II):



(II),

wherein R_1, R_6, R_7, and R_{13} are as defined and described herein.

[0266] In some embodiments of any one of formulae (I), (Ia)-(Ic), and (II), R_6 is selected from the group consisting of amino, C_{1-4}aminoalkyl, and C_{1-4}alkylamino; and R_7 is selected from the group consisting of hydrogen, amido, cyano, halo, and hydroxy, or is selected from the group consisting of C_{1-4}alkyl, C_{1-4}hydroxyalkyl, C_{3-6}cycloalkyl, phenyl, and 5- or 6- membered heteroaryl, any of which is unsubstituted or substituted with one to three substituents selected from the group consisting of amino, halo, hydroxy, cyano, trifluoromethyl, trifluoromethoxy, C_{1-4}alkyl, and C_{1-4}alkoxy. In some embodiments, R_6 is selected from the group consisting of amino, C_{1-4}aminoalkyl, and C_{1-4}alkylamino; and R_7 is selected from the group consisting of hydrogen, amido, halo, and hydroxy, or is selected from the group consisting of C_{1-4}alkyl, C_{1-4}hydroxyalkyl, C_{3-6}cycloalkyl, phenyl, and 5- or 6- membered heteroaryl, any of which is unsubstituted or substituted with one or two substituents selected from the group consisting of amino, halo, hydroxy, cyano, trifluoromethyl, trifluoromethoxy, C_{1-4}alkyl, and C_{1-4}alkoxy.

[0267] In some embodiments of any one of formulae (I), (Ia)-(Ic), and (II), R_6 is selected from the group consisting of amino, C_{1-4}aminoalkyl, and methylamino. In some embodiments, R_6 is amino or C_{1-4}aminoalkyl. In certain embodiments, R_6 is amino, aminomethyl, or methylamino. In certain embodiments, R_6 is amino or aminomethyl. In certain embodiments, R_6 is amino. In certain embodiments, R_6 is aminomethyl.

[0268] In some embodiments of any one of formulae (I), (Ia)-(Ic), and (II), R_7 is selected from the group consisting of hydroxy, C_{1-4}alkyl, C_{1-4}hydroxyalkyl, C_{3-6}cycloalkyl, phenyl, and 5- or 6-membered heteroaryl, any of which is unsubstituted or substituted with one or two groups

selected from the group consisting of amino, halo, hydroxy, cyano, trifluoromethyl, trifluoromethoxy, C_{1-4}alkyl, and C_{1-4}alkoxy. In some embodiments, R_7 is selected from the group consisting of hydroxy, C_{1-4}alkyl, C_{1-4}hydroxyalkyl, C_{3-6}cycloalkyl, phenyl, and 5- or 6-membered heteroaryl. In some embodiments, R_7 is hydroxy, C_{1-4}alkyl, or C_{1-4}hydroxyalkyl. In certain embodiments, R_7 is C_{1-4}alkyl. In certain embodiments, R_7 is methyl. In certain embodiments, R_7 is ethyl.

[0269] In some embodiments of any one of formulae (I), (Ia)-(Ic), and (II), R_6 is C_{1-4}aminoalkyl; and R_7 is selected from the group consisting of hydroxy, C_{1-4}alkyl, C_{1-4}hydroxyalkyl, C_{3-6}cycloalkyl, phenyl, and 5- or 6- membered heteroaryl, any of which is unsubstituted or substituted with one to three groups independently selected from the group consisting of amino, halo, hydroxy, cyano, trifluoromethyl, trifluoromethoxy, C_{1-4}alkyl, and C_{1-4}alkoxy.

[0270] In some embodiments of any one of formulae (I), (Ia)-(Ic), and (II), R_6 is aminomethyl; and R_7 is selected from the group consisting of hydroxy, C_{1-4}alkyl, C_{1-4}hydroxyalkyl, C_{3-6}cycloalkyl, phenyl, and 5- or 6- membered heteroaryl.

[0271] In some embodiments of any one of formulae (I), (Ia)-(Ic), and (II), R_6 is amino; and R_7 is selected from the group consisting of hydroxy, C_{1-4}alkyl, C_{1-4}hydroxyalkyl, C_{3-6}cycloalkyl, phenyl, and 5- or 6- membered heteroaryl, any of which is unsubstituted or substituted with one to three groups independently selected from the group consisting of amino, halo, hydroxy, cyano, trifluoromethyl, trifluoromethoxy, C_{1-4}alkyl, and C_{1-4}alkoxy.

[0272] In some embodiments of any one of formulae (I), (Ia)-(Ic), and (II), R_6 is amino; and R_7 is selected from the group consisting of hydroxy, C_{1-4}alkyl, C_{1-4}hydroxyalkyl, C_{3-6}cycloalkyl, phenyl, and 5- or 6- membered heteroaryl.

[0273] In some embodiments of any one of formulae (I), (Ia)-(Ic), and (II), R_6 is amino; and R_7 is C_{1-4}hydroxyalkyl. In some embodiments, R_6 is amino; and R_7 is hydroxymethyl. In some embodiments, R_6 is amino; and R_7 is C_{1-4}alkyl. In certain embodiments, R_6 is amino; and R_7 is methyl. In some embodiments, R_6 is amino; and R_7 is ethyl. In some embodiments, R_6 is aminomethyl; and R_7 is C_{1-4}alkyl. In certain embodiments, R_6 is aminomethyl; and R_7 is methyl. In some embodiments, R_6 is aminomethyl; and R_7 is ethyl.

[0274] In any of the above embodiments, the amido of R_7 may specifically be $-C(O)NH_2$.

[0275] In some embodiments of any one of formulae (I), (Ia)-(Ic), and (II), R_6 and R_7 together with the carbon atom to which they are both attached form a 3- to 7-membered saturated or unsaturated ring having 1 to 3 heteroatoms or groups as ring vertices independently selected from N, C(O), O, and $S(O)_m$, and that is unsubstituted or substituted with one or two groups independently selected from the group consisting of amino, halo, hydroxy, C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}alkylamino and C_{1-4}aminoalkyl.

[0276] In some embodiments of any one of formulae (I), (Ia)-(Ic), and (II), R_6 and R_7 together with the carbon atom to which they are both attached form a 4- to 6-membered saturated or unsaturated ring having 1 to 3 heteroatoms or groups as ring vertices independently selected from N, C(O), and O, and that is unsubstituted or substituted with one or two groups independently selected from the group consisting of amino, halo, hydroxy, C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}alkylamino and C_{1-4}aminoalkyl.

[0277] In some embodiments of any one of formulae (I), (Ia)-(Ic), and (II), R_6 and R_7 together with the carbon atom to which they are both attached form a 3- to 7-membered saturated ring having 1 to 3 heteroatoms or groups as ring vertices independently selected from N, C(O), O, and $S(O)_m$, and that is unsubstituted or substituted with one or two groups independently selected from the group consisting of amino, halo, hydroxy, C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}alkylamino and C_{1-4}aminoalkyl.

[0278] In some embodiments of any one of formulae (I), (Ia)-(Ic), and (II), R_6 and R_7 together with the carbon atom to which they are both attached form a 4- to 6-membered saturated ring having 1 to 3 heteroatoms or groups as ring vertices independently selected from N, C(O), and O, and that is unsubstituted or substituted with one or two groups independently selected from the group consisting of amino, halo, hydroxy, C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}alkylamino and C_{1-4}aminoalkyl.

[0279] In some embodiments of any one of formulae (I), (Ia)-(Ic), and (II), R_6 and R_7 together with the carbon atom to which they are both attached form a 4- to 6-membered saturated ring having 1 to 3 heteroatoms or groups as ring vertices independently selected from N and O, and

that is unsubstituted or substituted with one or two groups independently selected from the group consisting of amino, halo, hydroxy, C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}alkylamino and C_{1-4}aminoalkyl.

[0280] In some embodiments of any one of formulae (I), (Ia)-(Ic), and (II), R_6 and R_7 together with the carbon atom to which they are both attached form a 3- to 7- membered cycloalkyl ring that is unsubstituted or substituted with one or two groups independently selected from the group consisting of amino, halo, hydroxy, C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}alkylamino and C_{1-4}aminoalkyl.

[0281] In some embodiments of any one of formulae (I), (Ia)-(Ic), and (II), R_6 and R_7 together with the carbon atom to which they are both attached form a 4- to 6- membered cycloalkyl ring that is unsubstituted or substituted with one or two groups independently selected from the group consisting of amino, halo, hydroxy, C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}alkylamino and C_{1-4}aminoalkyl.

[0282] In some embodiments of any one of formulae (I), (Ia)-(Ic), and (II), R_1 is phenyl or a 5- to 6-member heteroaryl group having 1 to 4 heteroatoms as ring vertices independently selected from N, O, and S; and is unsubstituted or substituted with 1, 2 or 3 R_{12} groups independently selected from the group consisting of halo, hydroxy, amino, C_{1-4}alkylamino, di(C_{1-4}alkyl)amino, C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}haloalkyl, C_{1-4}aminoalkyl, and OR_{14}; R_{14} is phenyl or a 5-6 membered heteroaryl having 1 to 4 heteroatoms as ring vertices independently selected from N, O, and S, each of which is unsubstituted or substituted by one or two groups independently selected from the group consisting of C_{1-4}alkylamido, amino, halo, hydroxy, cyano, C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}haloalkyl, C_{1-4}haloalkoxy, C_{1-4}alkylamino and C_{1-4}aminoalkyl; R_6 is selected from the group consisting of amino, C_{1-4}aminoalkyl, and C_{1-4}alkylamino; and R_7 is selected from the group consisting of hydrogen, halo, and hydroxy, or is selected from the group consisting of amido, C_{1-4}alkyl, C_{1-4}hydroxyalkyl, C_{3-6}cycloalkyl, phenyl, and 5- or 6- membered heteroaryl, any of which is unsubstituted or substituted with one or two substituents selected from the group consisting of amino, halo, hydroxy, cyano, trifluoromethyl, trifluoromethoxy, C_{1-4}alkyl, and C_{1-4}alkoxy.

[0283] In some embodiments of any one of formulae (I), (Ia)-(Ic), and (II), R_1 is phenyl or a 5- to 6-member heteroaryl group having 1 to 4 heteroatoms as ring vertices independently selected from N, O, and S; and is unsubstituted or substituted with 1, 2 or 3 R_{12} groups independently selected from the group consisting of halo, hydroxy, amino, C_{1-4}alkylamino, di(C_{1-4}alkyl)amino,

C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}haloalkyl, C_{1-4}aminoalkyl, and OR_{14}; R_{14} is phenyl or a 5-6 membered heteroaryl having 1 to 4 heteroatoms as ring vertices independently selected from N, O, and S, each of which is unsubstituted or substituted by one or two groups independently selected from the group consisting of C_{1-4}alkylamido, amino, halo, hydroxy, cyano, C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}haloalkyl, C_{1-4}haloalkoxy, C_{1-4}alkylamino and C_{1-4}aminoalkyl; R_6 is amino or aminomethyl; and R_7 is selected from the group consisting of hydroxy, C_{1-4}alkyl, and C_{1-4}hydroxyalkyl.

[0284] In some embodiments of any one of formulae (I), (Ia)-(Ic), and (II), R_1 is phenyl or a 5- to 6-member heteroaryl group having 1 to 4 heteroatoms as ring vertices independently selected from N, O, and S; and is unsubstituted or substituted with 1, 2 or 3 R_{12} groups independently selected from the group consisting of halo, hydroxy, amino, C_{1-4}alkylamino, di(C_{1-4}alkyl)amino, C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}haloalkyl, C_{1-4}aminoalkyl, and OR_{14}; R_{14} is phenyl or a 5-6 membered heteroaryl having 1 to 4 heteroatoms as ring vertices independently selected from N, O, and S, each of which is unsubstituted or substituted by one or two groups independently selected from the group consisting of C_{1-4}alkylamido, amino, halo, hydroxy, cyano, C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}haloalkyl, C_{1-4}haloalkoxy, C_{1-4}alkylamino and C_{1-4}aminoalkyl; and R_6 and R_7 together with the carbon atom to which they are both attached form a 3- to 7-membered saturated or unsaturated ring having 1 to 3 heteroatoms or groups as ring vertices independently selected from N, C(O), O, and $S(O)_m$, and that is unsubstituted or substituted with one or two groups independently selected from the group consisting of amino, halo, hydroxy, C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}alkylamino and C_{1-4}aminoalkyl.

[0285] In some embodiments of any one of formulae (I), (Ia)-(Ic), and (II), R_1 is phenyl or a 5- to 6-member heteroaryl group having 1 to 4 heteroatoms as ring vertices independently selected from N, O, and S; and is unsubstituted or substituted with 1, 2 or 3 R_{12} groups independently selected from the group consisting of halo, hydroxy, amino, C_{1-4}alkylamino, di(C_{1-4}alkyl)amino, C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}haloalkyl, C_{1-4}aminoalkyl, and OR_{14}; R_{14} is phenyl or a 5-6 membered heteroaryl having 1 to 4 heteroatoms as ring vertices independently selected from N, O, and S, each of which is unsubstituted or substituted by one or two groups independently selected from the group consisting of C_{1-4}alkylamido, amino, halo, hydroxy, cyano, C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}haloalkyl, C_{1-4}haloalkoxy, C_{1-4}alkylamino and C_{1-4}aminoalkyl; and R_6 and R_7 together with the carbon atom to which they are both attached form a 4- to 6-membered saturated or

unsaturated ring having 1 to 3 heteroatoms or groups as ring vertices independently selected from N, C(O), and O, and that is unsubstituted or substituted with one or two groups independently selected from the group consisting of amino, halo, hydroxy, C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}alkylamino and C_{1-4}aminoalkyl.

[0286] In some embodiments of any one of formulae (I), (Ia)-(Ic), and (II), R_1 is phenyl or a 5- to 6-member heteroaryl group having 1 to 4 heteroatoms as ring vertices independently selected from N, O, and S; and is unsubstituted or substituted with 1, 2 or 3 R_{12} groups independently selected from the group consisting of halo, hydroxy, amino, C_{1-4}alkylamino, di(C_{1-4}alkyl)amino, C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}haloalkyl, C_{1-4}aminoalkyl, and OR_{14}; R_{14} is phenyl or a 5-6 membered heteroaryl having 1 to 4 heteroatoms as ring vertices independently selected from N, O, and S, each of which is unsubstituted or substituted by one or two groups independently selected from the group consisting of C_{1-4}alkylamido, amino, halo, hydroxy, cyano, C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}haloalkyl, C_{1-4}haloalkoxy, C_{1-4}alkylamino and C_{1-4}aminoalkyl; and R_6 and R_7 together with the carbon atom to which they are both attached form a 3- to 7-membered cycloalkyl ring that is unsubstituted or substituted with one or two groups independently selected from the group consisting of amino, halo, hydroxy, C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}alkylamino and C_{1-4}aminoalkyl.

[0287] In some embodiments of any one of formulae (I), (Ia)-(Ic), and (II), R_1 is phenyl or a 5- to 6-member heteroaryl group having 1 to 4 heteroatoms as ring vertices independently selected from N, O, and S; and is unsubstituted or substituted with 1, 2 or 3 R_{12} groups independently selected from the group consisting of halo, hydroxy, amino, C_{1-4}alkylamino, di(C_{1-4}alkyl)amino, C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}haloalkyl, and C_{1-4}aminoalkyl; R_6 is selected from the group consisting of amino, C_{1-4}aminoalkyl, and C_{1-4}alkylamino; and R_7 is selected from the group consisting of hydrogen, halo, and hydroxy, or is selected from the group consisting of amido, C_{1-4}alkyl, C_{1-4}hydroxyalkyl, C_{3-6}cycloalkyl, phenyl, and 5- or 6- membered heteroaryl, any of which is unsubstituted or substituted with one or two substituents selected from the group consisting of amino, halo, hydroxy, cyano, trifluoromethyl, trifluoromethoxy, C_{1-4}alkyl, and C_{1-4}alkoxy.

[0288] In some embodiments of any one of formulae (I), (Ia)-(Ic), and (II), R_1 is phenyl or a 5- to 6-member heteroaryl group having 1 to 4 heteroatoms as ring vertices independently

selected from N, O, and S; and is unsubstituted or substituted with 1, 2 or 3 R_{12} groups independently selected from the group consisting of halo, hydroxy, amino, C_{1-4}alkylamino, di(C_{1-4}alkyl)amino, C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}haloalkyl, and C_{1-4}aminoalkyl; R_6 is amino or aminomethyl; and R_7 is selected from the group consisting of hydroxy, C_{1-4}alkyl, and C_{1-4}hydroxyalkyl.

[0289] In some embodiments of any one of formulae (I), (Ia)-(Ic), and (II), R_1 is phenyl or a 5- to 6-member heteroaryl group having 1 to 4 heteroatoms as ring vertices independently selected from N, O, and S; and is unsubstituted or substituted with 1, 2 or 3 R_{12} groups independently selected from the group consisting of halo, hydroxy, amino, C_{1-4}alkylamino, di(C_{1-4}alkyl)amino, C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}haloalkyl, and C_{1-4}aminoalkyl; and R_6 and R_7 together with the carbon atom to which they are both attached form a 3- to 7-membered saturated or unsaturated ring having 1 to 3 heteroatoms or groups as ring vertices independently selected from N, C(O), O, and $S(O)_m$, and that is unsubstituted or substituted with one or two groups independently selected from the group consisting of amino, halo, hydroxy, C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}alkylamino and C_{1-4}aminoalkyl.

[0290] In some embodiments of any one of formulae (I), (Ia)-(Ic), and (II), R_1 is phenyl or a 5- to 6-member heteroaryl group having 1 to 4 heteroatoms as ring vertices independently selected from N, O, and S; and is unsubstituted or substituted with 1, 2 or 3 R_{12} groups independently selected from the group consisting of halo, hydroxy, amino, C_{1-4}alkylamino, di(C_{1-4}alkyl)amino, C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}haloalkyl, and C_{1-4}aminoalkyl; and R_6 and R_7 together with the carbon atom to which they are both attached form a 4- to 6-membered saturated or unsaturated ring having 1 to 3 heteroatoms or groups as ring vertices independently selected from N, C(O), and O, and that is unsubstituted or substituted with one or two groups independently selected from the group consisting of amino, halo, hydroxy, C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}alkylamino and C_{1-4}aminoalkyl.

[0291] In some embodiments of any one of formulae (I), (Ia)-(Ic), and (II), R_1 is phenyl or a 5- to 6-member heteroaryl group having 1 to 4 heteroatoms as ring vertices independently selected from N, O, and S; and is unsubstituted or substituted with 1, 2 or 3 R_{12} groups independently selected from the group consisting of halo, hydroxy, amino, C_{1-4}alkylamino, di(C_{1-4}alkyl)amino, C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}haloalkyl, and C_{1-4}aminoalkyl; and R_6 and R_7 together with the carbon

atom to which they are both attached form a 3- to 7- membered cycloalkyl ring that is unsubstituted or substituted with one or two groups independently selected from the group consisting of amino, halo, hydroxy, C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}alkylamino and C_{1-4}aminoalkyl.

[0292] In some embodiments of any one of formulae (I), (Ia)-(Ic), and (II), R_1 is selected from the group consisiting of phenyl, pyridyl, pyrimidinyl, pyrazolyl, pyrazinyl, pyridazinyl, and 1,2,4-triazinyl; and is unsubstituted or substituted with 1, 2, or 3 R_{12}, wherein each R_{12} is as defined and described herein, In some embodiments, R_1 is selected from the group consisiting of phenyl, pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, and 1,2,4-triazinyl; and is unsubstituted or substituted with 1, 2, or 3 R_{12}, wherein each R_{12} is as defined and described herein. In some embodiments, R_1 is phenyl or pyridyl; and is unsubstituted or substituted with 1, 2, or 3 R_{12}, wherein each R_{12} is as defined and described herein.

[0293] In some embodiments of any one of formulae (I), (Ia)-(Ic), and (II), R_1 is selected from the group consisting of phenyl, pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, and 1,2,4-triazinyl; and is unsubstituted or substituted with 1, 2, or 3 R_{12} independently selected from the group consisting of halo, hydroxy, amino, C_{1-4}alkylamino, di(C_{1-4}alkyl)amino, C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}haloalkyl, C_{1-4}aminoalkyl, and OR_{14}.

[0294] In some embodiments of any one of formulae (I), (Ia)-(Ic), and (II), R_1 is selected from the group consisting of phenyl, pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, and 1,2,4-triazinyl; and is unsubstituted or substituted with 1, 2, or 3 R_{12} independently selected from the group consisting of halo, hydroxy, amino, C_{1-4}alkylamino, di(C_{1-4}alkyl)amino, C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}haloalkyl, and C_{1-4}aminoalkyl.

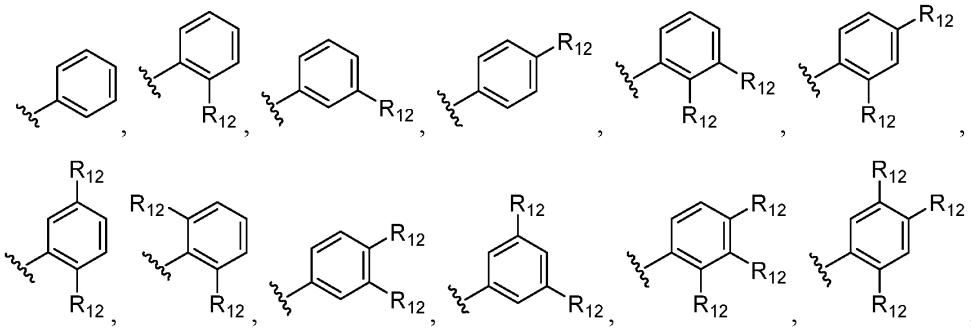
[0295] In some embodiments of any one of formulae (I), (Ia)-(Ic), and (II), R_1 is phenyl or pyridyl, each of which is unsubstituted or substituted with 1, 2, or 3 R_{12} independently selected from the group consisting of halo, hydroxy, amino, C_{1-4}alkylamino, di(C_{1-4}alkyl)amino, C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}haloalkyl, C_{1-4}aminoalkyl, and OR_{14}.

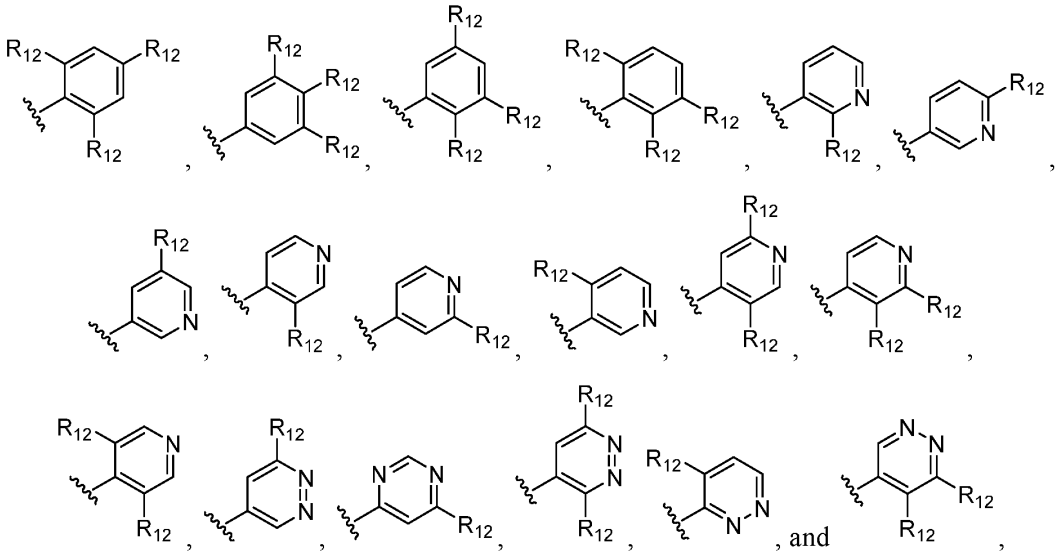
[0296] In some embodiments of any one of formulae (I), (Ia)-(Ic), and (II), R_1 is phenyl or pyridyl, each of which is unsubstituted or substituted with 1, 2, or 3 R_{12} independently selected from the group consisting of halo, hydroxy, amino, C_{1-4}alkylamino, di(C_{1-4}alkyl)amino, C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}haloalkyl, and C_{1-4}aminoalkyl.

[0297] In some embodiments of any one of formulae (I), (Ia)-(Ic), and (II), R_1 is phenyl and is unsubstituted or substituted with 1-3 R_{12}, each of which is independently selected from the group consisting of halo, hydroxy, amino, C_{1-4}alkylamino, di(C_{1-4}alkyl)amino, C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}haloalkyl, C_{1-4}aminoalkyl, and OR_{14}. In some embodiments, R_1 is phenyl and is unsubstituted or substituted with 1-3 R_{12}, each of which is independently selected from the group consisting of halo, hydroxy, amino, methylamino, dimethylamino, cyano, C_{1-4}alkyl, C_{1-4}haloalkyl, and C_{1-4}alkoxy. In some embodiments, R_1 is phenyl and is unsubstituted or substituted with 1-3 R_{12}, each of which is independently selected from the group consisting of halo, hydroxy, C_{1-4}alkyl, and C_{1-4}alkoxy.

[0298] In some embodiments of any one of formulae (I), (Ia)-(Ic), and (II), R_1 is pyridyl and is unsubstituted or substituted with 1-3 R_{12}, each of which is independently selected from the group consisting of halo, hydroxy, amino, C_{1-4}alkylamino, di(C_{1-4}alkyl)amino, C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}haloalkyl, C_{1-4}aminoalkyl, and OR_{14}. In some embodiments, R_1 is pyridyl and is unsubstituted or substituted with 1-3 R_{12}, each of which is independently selected from the group consisting of halo, hydroxy, amino, methylamino, dimethylamino, cyano, C_{1-4}alkyl, C_{1-4}haloalkyl, and C_{1-4}alkoxy. In some embodiments, R_1 is pyridyl and is unsubstituted or substituted with 1-3 R_{12}, each of which is independently selected from the group consisting of halo, hydroxy, C_{1-4}alkyl, and C_{1-4}alkoxy.

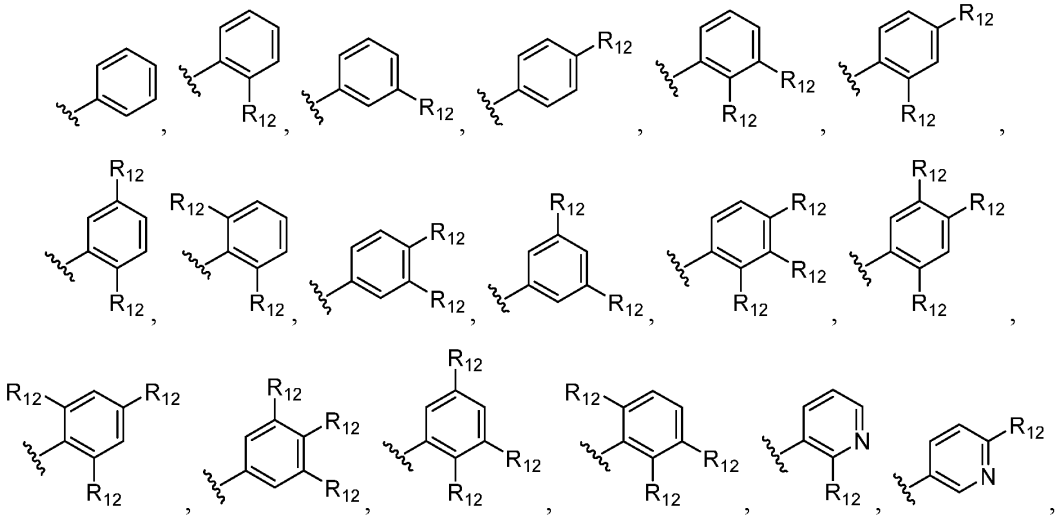
[0299] In some embodiments of any one of formulae (I), (Ia)-(Ic), and (II), R_1 is selected from the group consisting of:

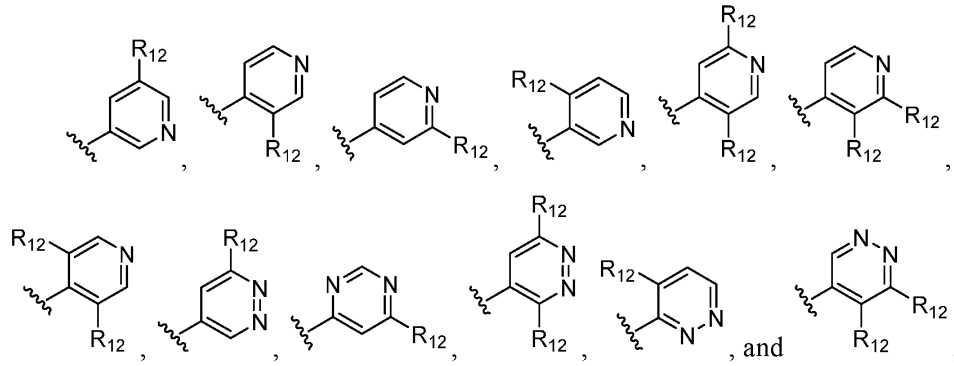




wherein each R_{12} is as defined and described herein.

[0300] In some embodiments of any one of formulae (I), (Ia)-(Ic), and (II), R_1 is selected from the group consisting of:

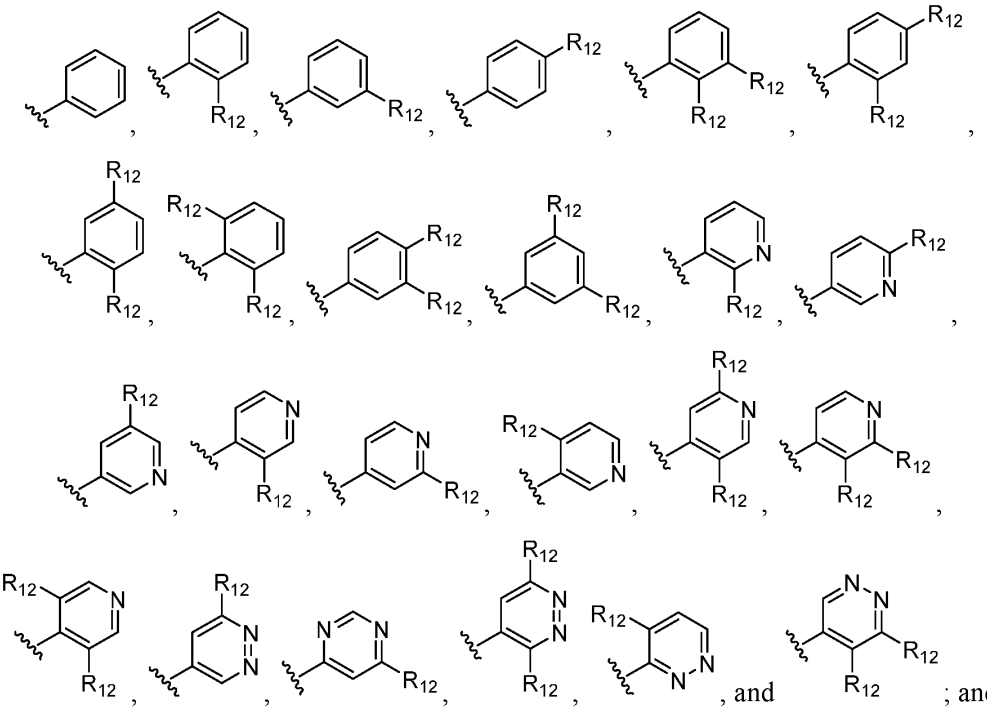




; and

each R_{12} is independently selected from the group consisting of halo, hydroxy, amino, C_{1-4}alkylamino, di(C_{1-4}alkyl)amino, C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}haloalkyl, C_{1-4}aminoalkyl, and OR_{14}, wherein R_{14} is as defined and described herein.

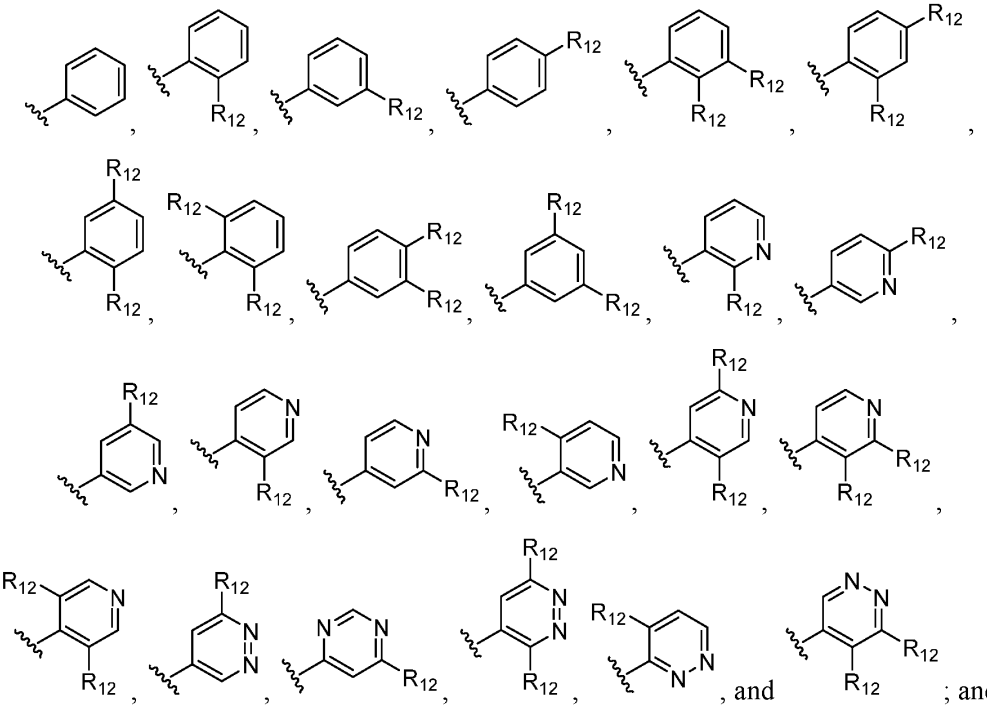
[0301] In some embodiments of any one of formulae (I), (Ia)-(Ic), and (II), R_1 is selected from the group consisting of:



; and

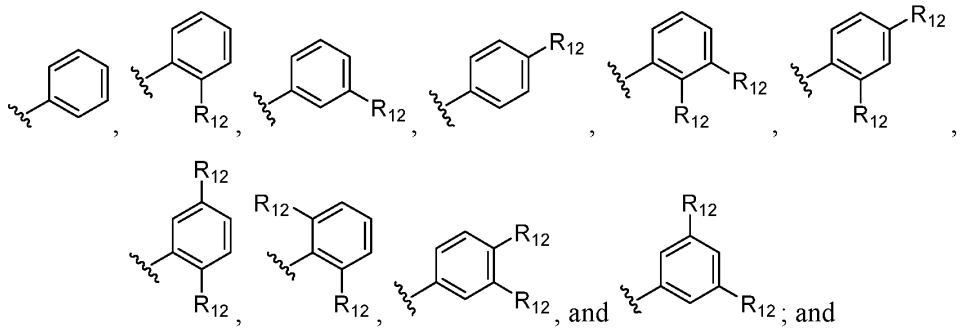
each R_{12} is independently selected from the group consisting of halo, hydroxy, amino, C_{1-4}alkylamino, di(C_{1-4}alkyl)amino, C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}haloalkyl, and C_{1-4}aminoalkyl.

[0302] In some embodiments of any one of formulae (I), (Ia)-(Ic), and (II), R_1 is selected from the group consisting of:



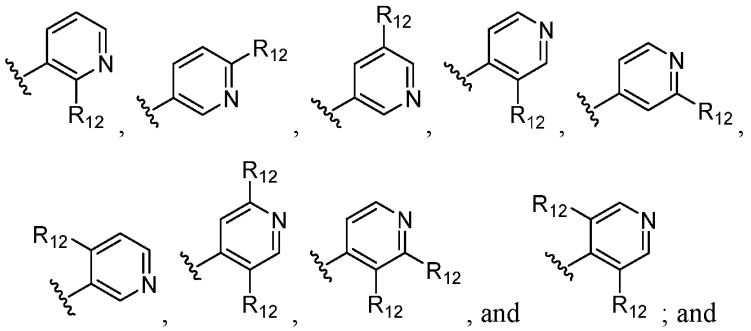
; and each R_{12} is independently selected from the group consisting of halo, hydroxy, amino, methylamino, dimethylamino, cyano, C_{1-4}alkyl, C_{1-4}haloalkyl, and C_{1-4}alkoxy.

[0303] In some embodiments of any one of formulae (I), (Ia)-(Ic), and (II), R_1 is selected from the group consisting of:



; and each R_{12} is independently selected from the group consisting of halo, hydroxy, amino, methylamino, dimethylamino, cyano, C_{1-4}alkyl, C_{1-4}haloalkyl, and C_{1-4}alkoxy.

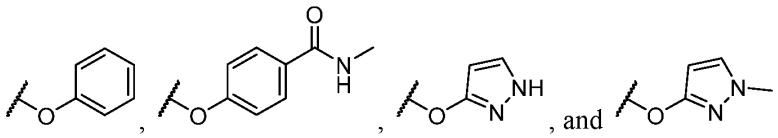
[0304] In some embodiments of any one of formulae (I), (Ia)-(Ic), and (II), R_1 is selected from the group consisting of:



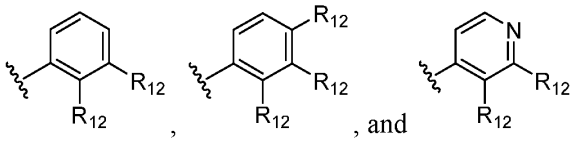
each R_{12} is independently selected from the group consisting of halo, hydroxy, amino, methylamino, dimethylamino, cyano, C_{1-4}alkyl, C_{1-4}haloalkyl, and C_{1-4}alkoxy.

[0305] In some embodiments of any one of formulae (I), (Ia)-(Ic), and (II), each R_{12} is independently selected from the group consisting of halo, hydroxy, amino, C_{1-4}alkylamino, di(C_{1-4}alkyl)amino, C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}haloalkyl, C_{1-4}aminoalkyl, and OR_{14}. In some embodiments, each R_{12} is independently selected from the group consisting of halo, C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}haloalkyl, and OR_{14}. In some embodiments, each R_{12} is independently selected from the group consisting of halo, hydroxy, amino, methylamino, dimethylamino, cyano, C_{1-4}alkyl, C_{1-4}haloalkyl, and C_{1-4}alkoxy. In some embodiments, each R_{12} is independently selected from the group consisting of halo, C_{1-4}alkyl, C_{1-4}alkoxy, and C_{1-4}haloalkyl. In some embodiments, each R_{12} is independently selected from the group consisting of F, Cl, Br, CH_3, OCH_3, and CF_3.

[0306] In some embodiments of any one of formulae (I), (Ia)-(Ic), and (II), each R_{12} is independently selected from the group consisting of F, Cl, Br, CH_3, OCH_3, CF_3,



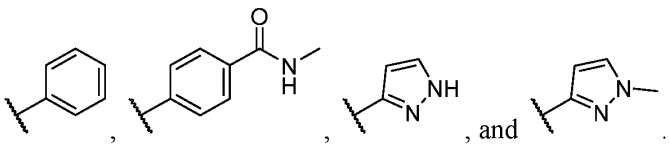
[0307] In some embodiments of any one of formulae (I), (Ia)-(Ic), and (II), R_1 is selected from the group consisting of:



, , and ; and

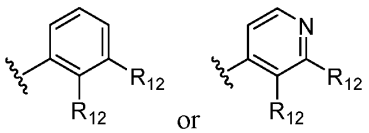
each R_{12} is independently selected from the group consisting of halo, hydroxy, amino, C_{1-4}alkylamino, di(C_{1-4}alkyl)amino, C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}haloalkyl, C_{1-4}aminoalkyl, and OR_{14}, wherein R_{14} is as defined and described herein.

[0308] In some embodiments of any one of formulae (I), (Ia)-(Ic), and (II), each R_{12} is independently selected from the group consisting of F, Cl, Br, CH_3, OCH_3, CF_3, and OR_{14}; and R_{14} is selected from the group consisting of:



, , , and .

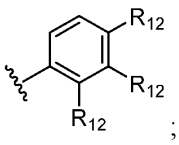
[0309] In some embodiments of any one of formulae (I), (Ia)-(Ic), and (II), R_1 is represented by:



or ; and

each R_{12} is independently selected from the group consisting of halo, C_{1-4}alkyl, C_{1-4}alkoxy, and C_{1-4}haloalkyl. In some embodiments, each R_{12} is independently selected from the group consisting of F, Cl, Br, CH_3, OCH_3, and CF_3. In some embodiments, each R_{12} is Cl.

[0310] In some embodiments of any one of formulae (I), (Ia)-(Ic), and (II), R_1 is represented by:



; and

each R_{12} is independently selected from the group consisting of halo, C_{1-4}alkyl, C_{1-4}alkoxy, and C_{1-4}haloalkyl. In some embodiments, each R_{12} is independently selected from the group

consisting of F, Cl, Br, CH_3, OCH_3, and CF_3. In some embodiments, each R_{12} is independently Cl or Br.

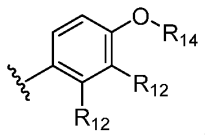
[0311] In some embodiments of any one of formulae (I), (Ia)-(Ic), and (II), R_{14} is independently selected from the group consisting of C_{6-10}aryl and a 5-10 membered heteroaryl, each of which is unsubstituted or substituted by one or more groups independently selected from the group consisting of C_{1-4}alkylamido, amino, halo, hydroxy, cyano, C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}haloalkyl, C_{1-4}haloalkoxy, C_{1-4}alkylamino and C_{1-4}aminoalkyl. In some embodiments, R_{14} is independently selected from the group consisting of C_{6-10}aryl and a 5-10 membered heteroaryl, each of which is unsubstituted or substituted by one or two groups independently selected from the group consisting of C_{1-4}alkylamido, halo, hydroxy, cyano, and C_{1-4}alkyl. In some embodiments, R_{14} is independently selected from the group consisting of C_{6-10}aryl and a 5-10 membered heteroaryl, each of which is unsubstituted or substituted by one or two groups independently selected from the group consisting of halo, hydroxy, cyano, and C_{1-4}alkyl.

[0312] In some embodiments of any one of formulae (I), (Ia)-(Ic), and (II), R_{14} is independently phenyl or a 5-6 membered heteroaryl having 1 to 4 heteroatoms as ring vertices independently selected from N, O, and S, each of which is unsubstituted or substituted by one or more groups independently selected from the group consisting of C_{1-4}alkylamido, amino, halo, hydroxy, cyano, C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}haloalkyl, C_{1-4}haloalkoxy, C_{1-4}alkylamino and C_{1-4}aminoalkyl. In some embodiments, R_{14} is independently phenyl or a 5-6 membered heteroaryl having 1 to 4 heteroatoms as ring vertices independently selected from N, O, and S, each of which is unsubstituted or substituted by one or two groups independently selected from the group consisting of C_{1-4}alkylamido, halo, hydroxy, cyano, and C_{1-4}alkyl. In some embodiments, R_{14} is independently phenyl or a 5-6 membered heteroaryl having 1 to 4 heteroatoms as ring vertices independently selected from N, O, and S, each of which is unsubstituted or substituted by one or two groups independently selected from the group consisting of halo, hydroxy, cyano, and C_{1-4}alkyl.

[0313] In some embodiments of any one of formulae (I), (Ia)-(Ic), and (II), R_{14} is phenyl or pyrazolyl, each of which is unsubstituted or substituted by one or two groups independently selected from the group consisting of C_{1-4}alkylamido, halo, hydroxy, cyano, and C_{1-4}alkyl. In some embodiments, R_{14} is phenyl, unsubstituted or substituted by one or two groups

independently selected from the group consisting of C_{1-4}alkylamido, halo, hydroxy, cyano, and C_{1-4}alkyl. In some embodiments, R_{14} is phenyl, substituted with C_{1-4}alkylamido. In some embodiments, R_{14} is phenyl substituted with -C(O)NHMe. In some embodiments, R_{14} is phenyl. In some embodiments, R_{14} is pyrazolyl, unsubstituted or substituted by one or two groups independently selected from the group consisting of C_{1-4}alkylamido, halo, hydroxy, cyano, and C_{1-4}alkyl. In some embodiments, R_{14} is pyrazolyl substituted with C_{1-4}alkyl. In some embodiments, R_{14} is pyrazolyl substituted with methyl. In some embodiments, R_{14} is *N*-methylpyrazolyl. In some embodiments, R_{14} is pyrazolyl.

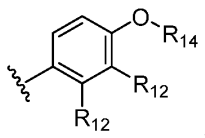
[0314] In some embodiments of any one of formulae (I), (Ia)-(Ic), and (II), R_1 is represented by:



;

each R_{12} is independently selected from the group consisting of halo, hydroxy, amino, C_{1-4}alkylamino, di(C_{1-4}alkyl)amino, C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}haloalkyl, and C_{1-4}aminoalkyl; and R_{14} is phenyl or a 5-6 membered heteroaryl having 1 to 4 heteroatoms as ring vertices independently selected from N, O, and S, each of which is unsubstituted or substituted by one or two groups independently selected from the group consisting of C_{1-4}alkylamido, halo, hydroxy, cyano, and C_{1-4}alkyl.

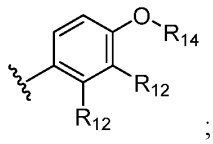
[0315] In some embodiments of any one of formulae (I), (Ia)-(Ic), and (II), R_1 is represented by:



;

each R_{12} is independently selected from the group consisting of halo, C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}haloalkyl, and OR_{14}; and R_{14} is phenyl or a 5-6 membered heteroaryl having 1 to 4 heteroatoms as ring vertices independently selected from N, O, and S, each of which is unsubstituted or substituted by one or two groups independently selected from the group consisting of C_{1-4}alkylamido, halo, hydroxy, cyano, and C_{1-4}alkyl.

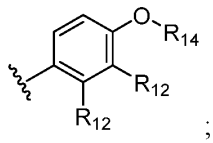
[0316] In some embodiments of any one of formulae (I), (Ia)-(Ic), and (II), R_1 is represented by:



;

each R_{12} is independently selected from the group consisting of halo, C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}haloalkyl, and OR_{14}; and R_{14} is selected from the group consisting of phenyl or pyrazolyl, each of which is unsubstituted or substituted by one or two groups independently selected from the group consisting of C_{1-4}alkylamido, halo, hydroxy, cyano, and C_{1-4}alkyl.

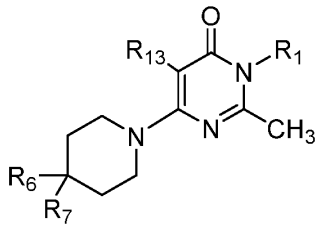
[0317] In some embodiments of any one of formulae (I), (Ia)-(Ic), and (II), R_1 is represented by:



;

each R_{12} is independently selected from the group consisting of halo, C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}haloalkyl, and OR_{14}; and R_{14} is selected from the group consisting of phenyl, phenyl substituted with C_{1-4}alkylamido, pyrazolyl, and pyrazolyl substituted with C_{1-4}alkyl. In some embodiments, each R_{12} is independently selected from the group consisting of F, Cl, Br, CH_3, OCH_3, and CF_3; and R_{14} is selected from the group consisting of phenyl, MeNHC(O)-phenyl, pyrazolyl, and *N*-methylpyrazolyl. In some embodiments, each R_{12} is Cl; and R_{14} is selected from the group consisting of phenyl, MeNHC(O)-phenyl, pyrazolyl, and *N*-methylpyrazolyl.

[0318] In certain embodiments, the compound is represented by formula (II):



(II)

or a salt, ester or prodrug thereof, wherein:

R_1 is phenyl or pyridyl, each of which is substituted with 0 to 3 R_{12};

each R_{12} is independently selected from the group consisting of halo, hydroxy, C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}haloalkyl, and OR_{14};

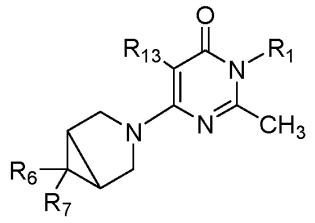
R_6 is selected from the group consisting of amino, C_{1-4}aminoalkyl, and C_{1-4}alkylamino;

R_7 is selected from the group consisting of hydrogen, cyano, amido, halo, and hydroxy, or is selected from the group consisting of C_{1-4}alkyl, C_{1-4}hydroxyalkyl, C_{3-6}cycloalkyl, phenyl, and 5- or 6- membered heteroaryl, any of which is unsubstituted or substituted with one to three substituents independently selected from the group consisting of amino, halo, hydroxy, cyano, trifluoromethyl, trifluoromethoxy, C_{1-4}alkyl, and C_{1-4}alkoxy;

R_{13} is selected from the group consisting of hydrogen, halo, cyano, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}hydroxyalkyl, C_{1-6}dihydroxyalkyl, and C_{3-8}cycloalkyl; and

R_{14} is phenyl or pyrazolyl, each of which is unsubstituted or substituted by one or two groups independently selected from the group consisting of C_{1-4}alkylamido, halo, hydroxy, cyano, and C_{1-4}alkyl.

[0319] In certain embodiments, the compound is represented by formula (III):



(III)

or a salt, ester or prodrug thereof, wherein:

R_1 is phenyl or pyridyl, each of which is substituted with 0 to 3 R_{12};

each R_{12} is independently selected from the group consisting of halo, hydroxy, C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}haloalkyl, and OR_{14};

R_6 is selected from the group consisting of amino, C_{1-4}aminoalkyl, and C_{1-4}alkylamino;

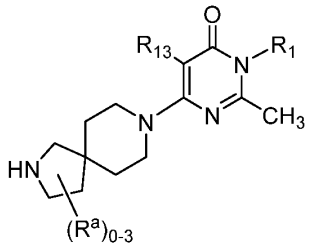
R_7 is selected from the group consisting of hydrogen, cyano, amido, halo, and hydroxy, or is selected from the group consisting of C_{1-4}alkyl, C_{1-4}hydroxyalkyl, C_{3-6}cycloalkyl, phenyl, and 5- or 6- membered heteroaryl, any of which is unsubstituted or substituted with one to three substituents independently selected from the group

consisting of amino, halo, hydroxy, cyano, trifluoromethyl, trifluoromethoxy, C_{1-4}alkyl, and C_{1-4}alkoxy;

R_{13} is selected from the group consisting of hydrogen, halo, cyano, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}hydroxyalkyl, C_{1-6} dihydroxyalkyl, and C_{3-8}cycloalkyl; and

R_{14} is phenyl or pyrazolyl, each of which is unsubstituted or substituted by one or two groups independently selected from the group consisting of C_{1-4}alkylamido, halo, hydroxy, cyano, and C_{1-4}alkyl.

[0320] In certain embodiments, the compound is represented by formula (IV):



(IV)

or a salt, ester or prodrug thereof, wherein:

R_1 is phenyl or pyridyl, each of which is substituted with 0 to 3 R_{12};

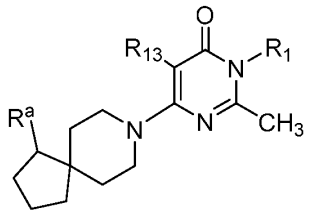
each R_{12} is independently selected from the group consisting of halo, hydroxy, C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}haloalkyl, and OR_{14};

R_{13} is selected from the group consisting of hydrogen, halo, cyano, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}hydroxyalkyl, C_{1-6}dihydroxyalkyl, and C_{3-8}cycloalkyl;

R_{14} is phenyl or pyrazolyl, each of which is unsubstituted or substituted by one or two groups independently selected from the group consisting of C_{1-4}alkylamido, halo, hydroxy, cyano, and C_{1-4}alkyl; and

each R^a is independently selected from the group consisting of amino, halo, hydroxy, cyano, C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}haloalkyl, C_{1-4}haloalkoxy, C_{1-4}alkylamino and C_{1-4}aminoalkyl.

[0321] In certain embodiments, the compound is represented by formula (V):



(V)

or a salt, ester or prodrug thereof, wherein:

R_1 is phenyl or pyridyl, each of which is substituted with 0 to 3 R_{12};

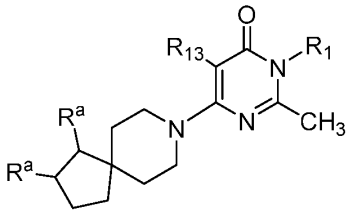
each R_{12} is independently selected from the group consisting of halo, hydroxy, C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}haloalkyl, and OR_{14}; and

R_{13} is selected from the group consisting of hydrogen, halo, cyano, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}hydroxyalkyl, C_{1-6}dihydroxyalkyl, and C_{3-8}cycloalkyl;

R_{14} is phenyl or pyrazolyl, each of which is unsubstituted or substituted by one or two groups independently selected from the group consisting of C_{1-4}alkylamido, halo, hydroxy, cyano, and C_{1-4}alkyl; and

R^a is selected from the group consisting of amino, halo, hydroxy, cyano, trifluoromethyl, trifluoromethoxy, C_{1-4}alkyl, and C_{1-4}alkoxy.

[0322] In certain embodiments, the compound is represented by formula (VI):



(VI)

or a salt, ester or prodrug thereof, wherein:

R_1 is phenyl or pyridyl, each of which is substituted with 0 to 3 R_{12};

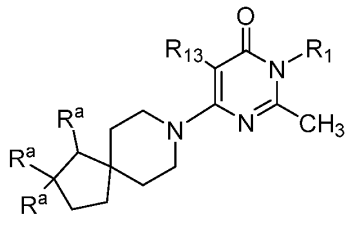
each R_{12} is independently selected from the group consisting of halo, hydroxy, C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}haloalkyl, and OR_{14}; and

R_{13} is selected from the group consisting of hydrogen, halo, cyano, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}hydroxyalkyl, C_{1-6}dihydroxyalkyl, and C_{3-8}cycloalkyl;

R_{14} is phenyl or pyrazolyl, each of which is unsubstituted or substituted by one or two groups independently selected from the group consisting of C_{1-4}alkylamido, halo, hydroxy, cyano, and C_{1-4}alkyl; and

each R^a is independently selected from the group consisting of amino, halo, hydroxy, cyano, trifluoromethyl, trifluoromethoxy, C_{1-4}alkyl, and C_{1-4}alkoxy.

[0323] In certain embodiments, the compound is represented by formula (VII):



(VII)

or a salt, ester or prodrug thereof, wherein:

R_1 is phenyl or pyridyl, each of which is substituted with 0 to 3 R_{12};

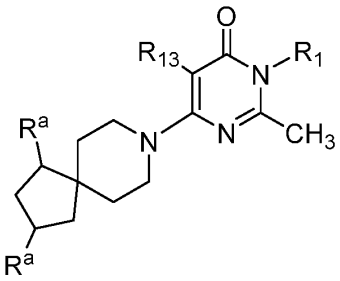
each R_{12} is independently selected from the group consisting of halo, hydroxy, C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}haloalkyl, and OR_{14}; and

R_{13} is selected from the group consisting of hydrogen, halo, cyano, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}hydroxyalkyl, C_{1-6}dihydroxyalkyl, and C_{3-8}cycloalkyl;

R_{14} is phenyl or pyrazolyl, each of which is unsubstituted or substituted by one or two groups independently selected from the group consisting of C_{1-4}alkylamido, halo, hydroxy, cyano, and C_{1-4}alkyl; and

each R^a is independently selected from the group consisting of amino, halo, hydroxy, cyano, trifluoromethyl, trifluoromethoxy, C_{1-4}alkyl, and C_{1-4}alkoxy.

[0324] In certain embodiments, the compound is represented by formula (VIII):



(VIII)

or a salt, ester or prodrug thereof, wherein:

R_1 is phenyl or pyridyl, each of which is substituted with 0 to 3 R_{12};

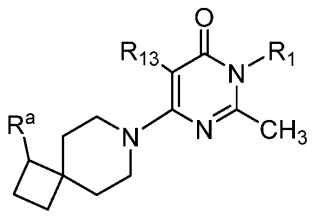
each R_1 is independently selected from the group consisting of halo, hydroxy, C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}haloalkyl, and OR_{14}; and

R_{13} is selected from the group consisting of hydrogen, halo, cyano, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}hydroxyalkyl, C_{1-6}dihydroxyalkyl, and C_{3-8}cycloalkyl;

R_{14} is phenyl or pyrazolyl, each of which is unsubstituted or substituted by one or two groups independently selected from the group consisting of C_{1-4}alkylamido, halo, hydroxy, cyano, and C_{1-4}alkyl; and

each R^a is independently selected from the group consisting of amino, halo, hydroxy, cyano, trifluoromethyl, trifluoromethoxy, C_{1-4}alkyl, and C_{1-4}alkoxy.

[0325] In certain embodiments, the compound is represented by formula (IX):



(IX)

or a salt, ester or prodrug thereof, wherein:

R_1 is phenyl or pyridyl, each of which is substituted with 0 to 3 R_{12};

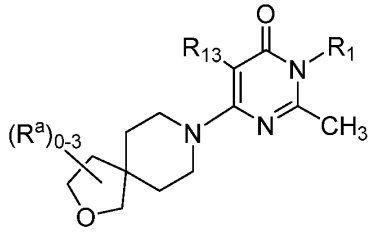
each R_{12} is independently selected from the group consisting of halo, hydroxy, C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}haloalkyl, and OR_{14}; and

R_{13} is selected from the group consisting of hydrogen, halo, cyano, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}hydroxyalkyl, C_{1-6}dihydroxyalkyl, and C_{3-8}cycloalkyl;

R_{14} is phenyl or pyrazolyl, each of which is unsubstituted or substituted by one or two groups independently selected from the group consisting of C_{1-4}alkylamido, halo, hydroxy, cyano, and C_{1-4}alkyl; and

R^a is selected from the group consisting of amino, halo, hydroxy, cyano, trifluoromethyl, trifluoromethoxy, C_{1-4}alkyl, and C_{1-4}alkoxy.

[0326] In certain embodiments, the compound is represented by formula (X):



(X)

or a salt, ester or prodrug thereof, wherein:

R_1 is phenyl or pyridyl, each of which is substituted with 0 to 3 R_{12};

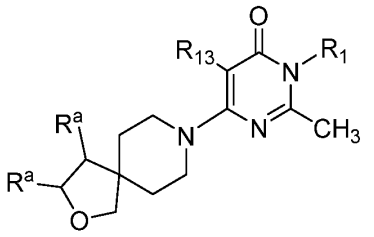
each R_{12} is independently selected from the group consisting of halo, hydroxy, C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}haloalkyl, and OR_{14}; and

R_{13} is selected from the group consisting of hydrogen, halo, cyano, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}hydroxyalkyl, C_{1-6}dihydroxyalkyl, and C_{3-8}cycloalkyl;

R_{14} is phenyl or pyrazolyl, each of which is unsubstituted or substituted by one or two groups independently selected from the group consisting of C_{1-4}alkylamido, halo, hydroxy, cyano, and C_{1-4}alkyl; and

each R^a is independently selected from the group consisting of amino, halo, hydroxy, cyano, C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}haloalkyl, C_{1-4}haloalkoxy, C_{1-4}alkylamino and C_{1-4}aminoalkyl.

[0327] In certain embodiments, the compound is represented by formula (XI):



(XI)

or a salt, ester or prodrug thereof, wherein:

R_1 is phenyl or pyridyl, each of which is substituted with 0 to 3 R_{12};

each R_{12} is independently selected from the group consisting of halo, hydroxy, C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}haloalkyl, and OR_{14}; and

R_{13} is selected from the group consisting of hydrogen, halo, cyano, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}hydroxyalkyl, C_{1-6}dihydroxyalkyl, and C_{3-8}cycloalkyl;

R_{14} is phenyl or pyrazolyl, each of which is unsubstituted or substituted by one or two groups independently selected from the group consisting of C_{1-4}alkylamido, halo, hydroxy, cyano, and C_{1-4}alkyl; and

each R^a is independently selected from the group consisting of amino, halo, hydroxy, cyano, C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}haloalkyl, C_{1-4}haloalkoxy, C_{1-4}alkylamino and C_{1-4}aminoalkyl.

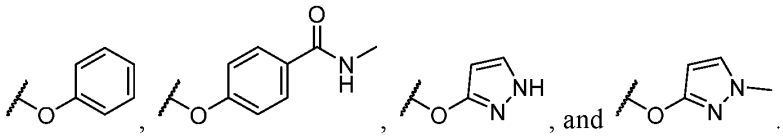
[0328] In some embodiement of any one of formulae (II)-(XI), R_1, R_6, R_7, R_{12}, R_{13}, and R_{14} may have the meanings set forth in any one or more of the selected embodiments noted above.

[0329] In some embodiments of any one of formulae (II)-(XI), R_{13} is selected from the group consisting of hydrogen, halo, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}hydroxyalkyl, C_{1-6}dihydroxyalkyl, and C_{3-8}cycloalkyl. In some embodiments, R_{13} is selected from the group consisting of hydrogen, halo, C_{1-6}alkyl, and C_{1-6}haloalkyl. In some embodiments, R_{13} is selected from the group consisting of hydrogen, halo, C_{1-4}alkyl, and C_{1-4}haloalkyl. In some embodiments, R_{13} is selected from the group consisting of hydrogen, Cl, Br, methyl, and CF_3. In some embodiments, R_{13} is hydrogen. In some embodiments, R_{13} is Cl. In some embodiments, R_{13} is Br. In some embodiments, R_{13} is methyl. In some embodiments, R_{13} is CF_3.

[0330] In some embodiments of any one of formulae (II)-(XI), R_1 is phenyl or pyridyl, each of which is substituted with 1 to 3 R_{12}. In some embodiments, R_1 is phenyl or pyridyl, each of which is substituted with 2 or 3 R_{12}. In some embodiments, R_1 is phenyl substituted with 2 or 3 R_{12}. In some embodiments, R_1 is phenyl substituted with 2 R_{12}. In some embodiments, R_1 is phenyl substituted with 3 R_{12}. In some embodiments, R_1 is pyridyl substituted with 2 R_{12}.

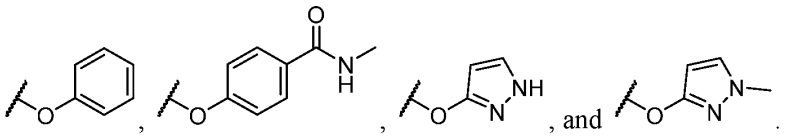
[0331] In some embodiments of any one of formulae (II)-(XI), each R_{12} is independently selected from the group consisting of halo, C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}haloalkyl, and OR_{14}. In some embodiments, each R_{12} is independently selected from the group consisting of halo, hydroxy, amino, methylamino, dimethylamino, cyano, C_{1-4}alkyl, C_{1-4}haloalkyl, and C_{1-4}alkoxy. In some embodiments, each R_{12} is independently selected from the group consisting of halo, C_{1-4}alkyl, C_{1-4}alkoxy, and C_{1-4}haloalkyl. In some embodiments, each R_{12} is independently selected from the group consisting of F, Cl, Br, CH_3, OCH_3, and CF_3.

[0332] In some embodiments of any one of formulae (II)-(XI), each R_{12} is independently selected from the group consisting of F, Cl, Br, CH_3, OCH_3, CF_3,

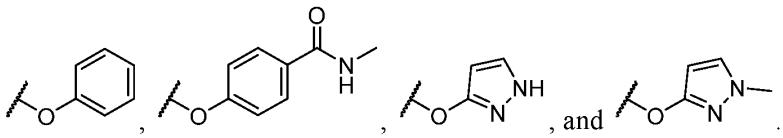


[0333] In some embodiments of any one of formulae (II)-(XI), R_1 is phenyl substituted with 2 R_{12}; and each R_{12} is independently selected from the group consisting of F, Cl, Br, CH_3, OCH_3, and CF_3. In some embodiments, R_1 is phenyl substituted with 2 R_{12}; and each R_{12} is Cl.

[0334] In some embodiments of any one of formulae (II)-(XI), R_1 is phenyl substituted with 3 R_{12}; and each R_{12} is independently selected from the group consisting of F, Cl, Br, CH_3, OCH_3, CF_3,



[0335] In some embodiments of any one of formulae (II)-(XI), R_1 is phenyl substituted with 3 R_{12}; the first and second R_{12} are each Cl; and the third R_{12} is Br. In some embodiments, R_1 is phenyl substituted with 3 R_{12}; the first and second R_{12} are each Cl; and the third R_{12} is selected from the group consisting of:



[0336] In some embodiments of any one of formulae (II)-(XI), In some embodiments, R_{14} is phenyl, unsubstituted or substituted by one or two groups independently selected from the group consisting of C_{1-4}alkylamido, halo, hydroxy, cyano, and C_{1-4}alkyl. In some embodiments, R_{14} is phenyl, substituted with C_{1-4}alkylamido. In some embodiments, R_{14} is phenyl substituted with -C(O)NHMe. In some embodiments, R_{14} is phenyl. In some embodiments, R_{14} is pyrazolyl, unsubstituted or substituted by one or two groups independently selected from the group consisting of C_{1-4}alkylamido, halo, hydroxy, cyano, and C_{1-4}alkyl. In some embodiments, R_{14} is pyrazolyl substituted with C_{1-4}alkyl. In some embodiments, R_{14} is pyrazolyl substituted with

methyl. In some embodiments, R_{14} is *N*-methylpyrazolyl. In some embodiments, R_{14} is pyrazolyl.

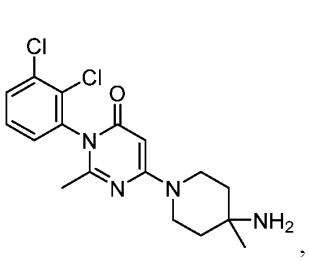
[0337] In some embodiments of formula (II) or (III), R_6 is amino or C_{1-4}aminoalkyl. In certain embodiments, R_6 is amino or aminomethyl. In certain embodiments, R_6 is amino. In certain embodiments, R_6 is aminomethyl.

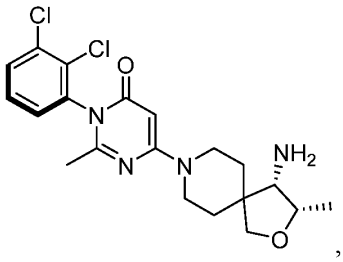
[0338] In some embodiments of formula (II) or (III), R_7 is hydroxy, C_{1-4}alkyl, or C_{1-4}hydroxyalkyl. In certain embodiments, R_7 is C_{1-4}alkyl. In certain embodiments, R_7 is methyl. In certain embodiments, R_7 is ethyl.

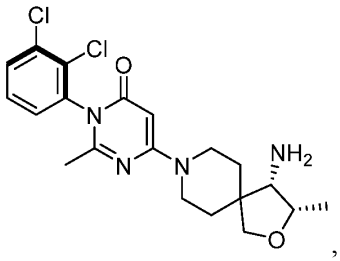
[0339] In some embodiments of formula (II) or (III), R_6 is amino; and R_7 is C_{1-4}alkyl. In certain embodiments, R_6 is amino; and R_7 is methyl. In some embodiments, R_6 is amino; and R_7 is ethyl. In some embodiments, R_6 is aminomethyl; and R_7 is C_{1-4}alkyl. In certain embodiments, R_6 is aminomethyl; and R_7 is methyl.

[0340] In some embodiments of any one of formulae (IV)-(XI), each R^a is independently selected from the group consisting of amino, halo, hydroxy, cyano, C_{1-4}alkyl, C_{1-4}alkoxy, and C_{1-4}haloalkyl. In some embodiments, each R^a is independently amino or C_{1-4}alkyl. In some embodiments, each R^a is independently amino or methyl.

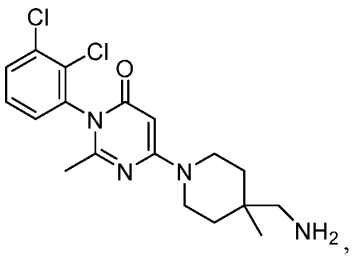
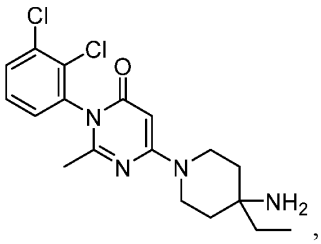
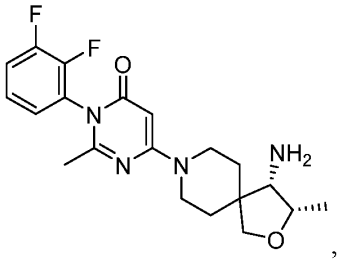
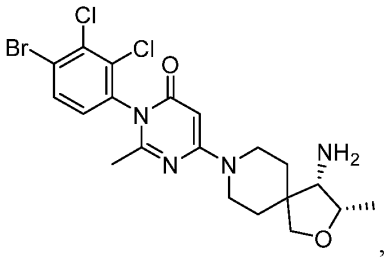
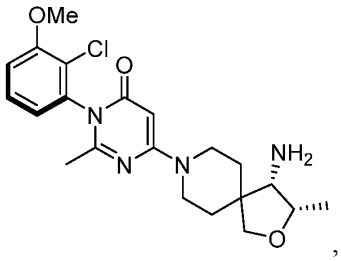
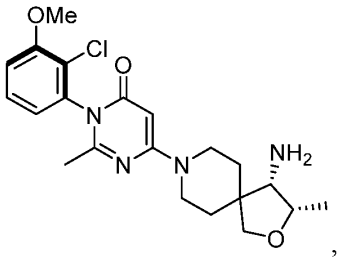
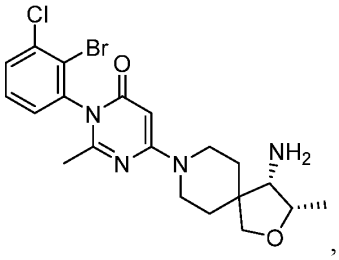
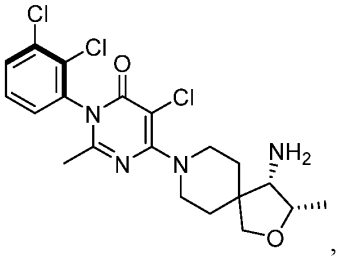
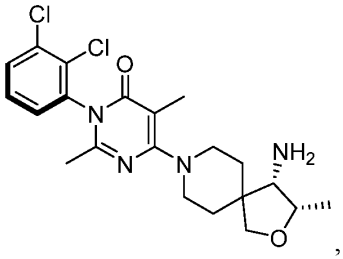
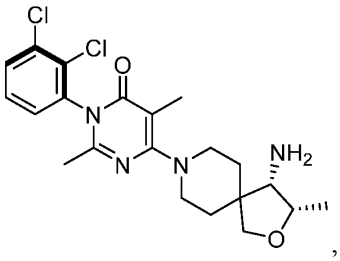
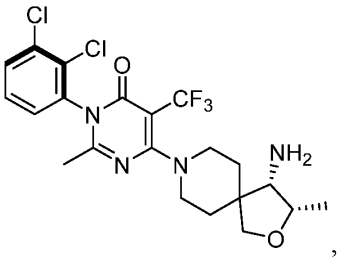
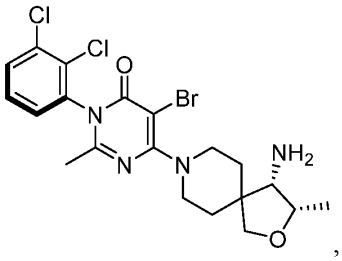
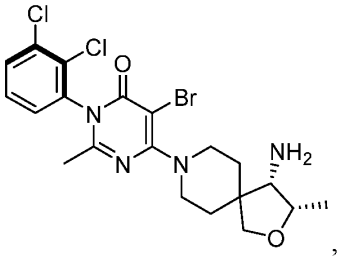
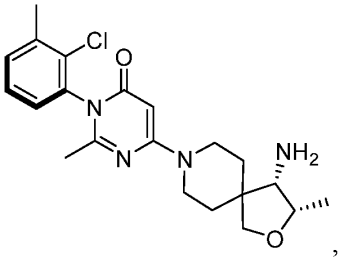
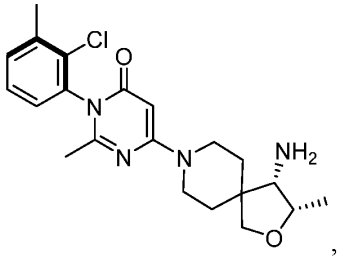
[0341] In some embodiments, the compound is represented by the formula selected from the group consisting of:

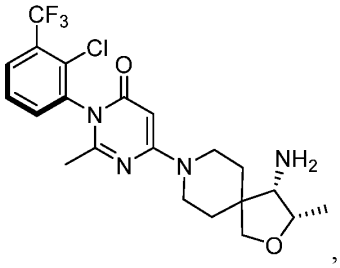
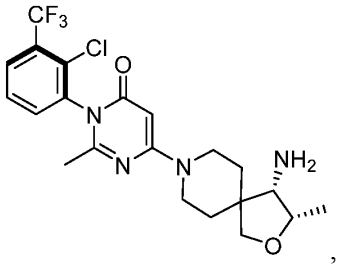
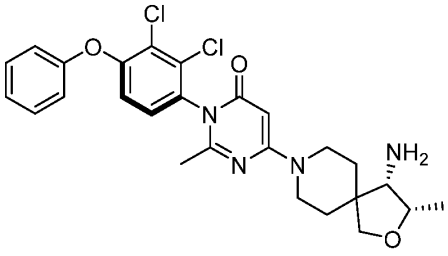
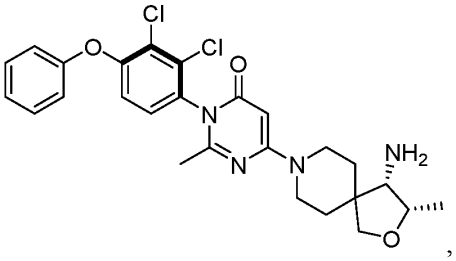
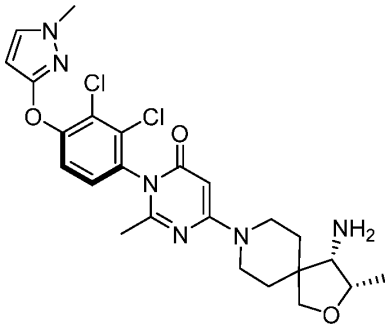
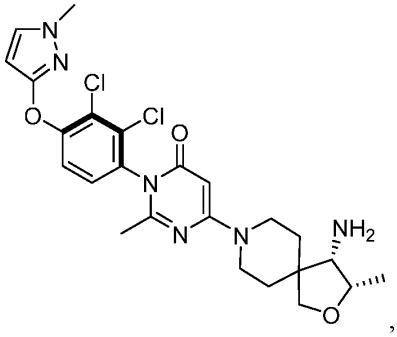
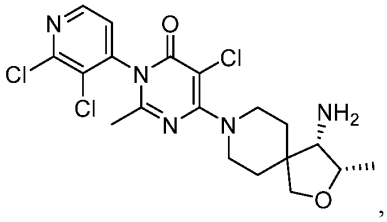
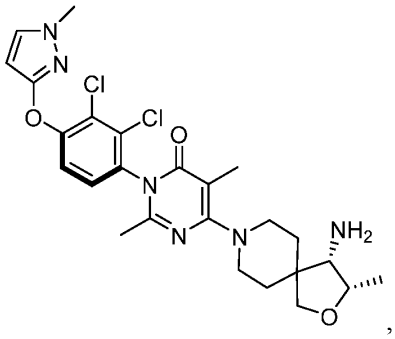


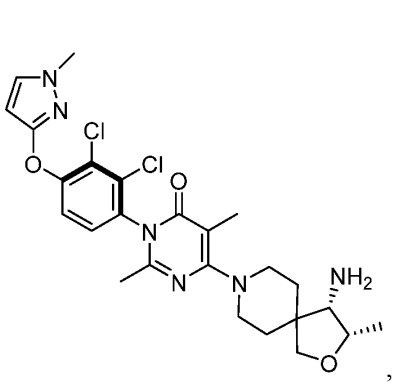
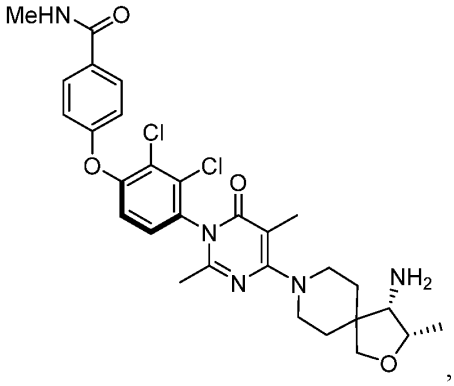
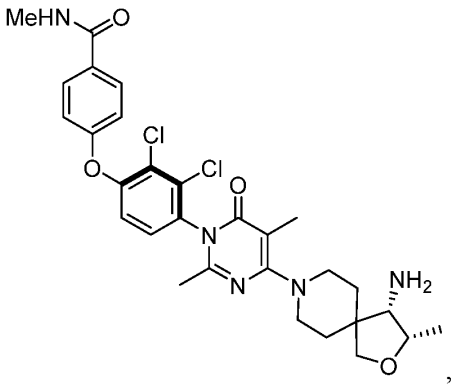
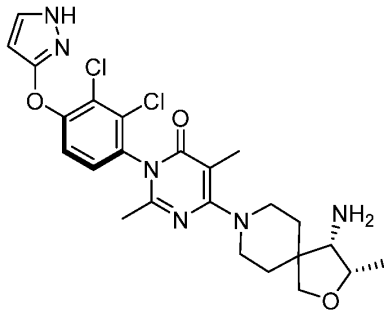
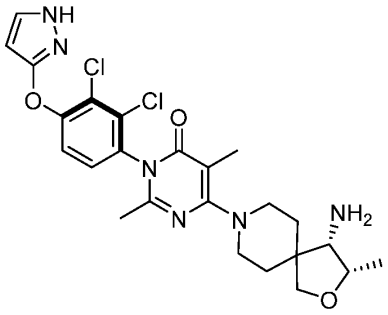
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[0342] Also provided are embodiments wherein any embodiment above may be combined with any one or more of these embodiments, provided the combination is not mutually exclusive.

[0343] As used herein, two embodiments are "mutually exclusive" when one is defined to be something which is different than the other. For example, an embodiment wherein two groups combine to form a cycloalkyl is mutually exclusive with an embodiment in which one group is ethyl the other group is hydrogen. Similarly, an embodiment wherein one group is CH_2 is mutually exclusive with an embodiment wherein the same group is NH.

[0344] The compounds disclosed herein can exist as pharmaceutically acceptable salts. The present disclosure includes compounds listed above in the form of salts, including acid addition salts. Suitable salts include those formed with both organic and inorganic acids. Such acid addition salts will normally be pharmaceutically acceptable. However, salts of non-pharmaceutically acceptable salts may be of utility in the preparation and purification of the compound in question. Basic addition salts may also be formed and be pharmaceutically acceptable.

[0345] The term "pharmaceutically acceptable" refers to those compounds (or salts, tautomers, zwitterionic forms, etc.) which are suitable for use in contact with the tissues of patients without undue toxicity, irritation, and allergic response, are commensurate with a reasonable benefit/risk ratio, and are effective for their intended use.

[0346] The term "pharmaceutically acceptable salt," as used herein, represents salts or zwitterionic forms of the compounds disclosed herein which are water or oil-soluble or dispersible and pharmaceutically acceptable as defined herein. The salts can be prepared during the final isolation and purification of the compounds or separately by reacting the appropriate compound in the form of the free base with a suitable acid. Representative acid addition salts include acetate, adipate, alginate, L-ascorbate, aspartate, benzoate, benzenesulfonate (besylate), bisulfate, butyrate, camphorate, camphorsulfonate, citrate, digluconate, formate, fumarate, gentisate, glutarate, glycerophosphate, glycolate, hemisulfate, heptanoate, hexanoate, hippurate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxyethansulfonate (isethionate), lactate, maleate, malonate, DL-mandelate, mesitylenesulfonate, methanesulfonate, naphthylenesulfonate, nicotinate, 2-naphthalenesulfonate, oxalate, pamoate, pectinate, persulfate, 3-phenylproprionate, phosphonate, picrate, pivalate, propionate, pyroglutamate, succinate, sulfonate, tartrate, L-tartrate, trichloroacetate, trifluoroacetate, phosphate, glutamate, bicarbonate, para-toluenesulfonate (p-tosylate), and undecanoate. Also, basic groups in the compounds disclosed herein can be quaternized with methyl, ethyl, propyl, and butyl chlorides, bromides, and iodides; dimethyl, diethyl, dibutyl, and diamyl sulfates; decyl, lauryl, myristyl, and steryl chlorides, bromides, and iodides; and benzyl and phenethyl bromides. Examples of acids which can be employed to form pharmaceutically acceptable addition salts include inorganic acids such as hydrochloric, hydrobromic, sulfuric, and phosphoric, and organic acids such as oxalic, maleic,

succinic, and citric. Salts can also be formed by coordination of the compounds with an alkali metal or alkaline earth ion. Hence, the present disclosure contemplates sodium, potassium, magnesium, and calcium salts of the compounds disclosed herein, and the like.

[0347] Basic addition salts can be prepared during the final isolation and purification of the compounds by reacting a carboxy group with a suitable base such as the hydroxide, carbonate, or bicarbonate of a metal cation or with ammonia or an organic primary, secondary, or tertiary amine. The cations of pharmaceutically acceptable salts include lithium, sodium, potassium, calcium, magnesium, and aluminum, as well as nontoxic quaternary amine cations such as ammonium, tetramethylammonium, tetraethylammonium, methylamine, dimethylamine, trimethylamine, triethylamine, diethylamine, ethylamine, tributylamine, pyridine, *N,N*-dimethylaniline, *N*-methylpiperidine, *N*-methylmorpholine, dicyclohexylamine, procaine, dibenzylamine, *N,N*-dibenzylphenethylamine, 1-ephenamine, and *N,N'*-dibenzylethylenediamine. Other representative organic amines useful for the formation of base addition salts include ethylenediamine, ethanolamine, diethanolamine, piperidine, and piperazine.

[0348] A salt of a compound can be made by reacting the appropriate compound in the form of the free base with the appropriate acid.

V. COMPOSITION

[0349] The oral dosage form including the compound of formula (I) or (10b) can be in any oral dosage forms including one or more pharmaceutically acceptable carriers and/or excipients. Oral preparations include tablets, pills, powder, dragees, capsules, liquids, lozenges, cachets, gels, syrups, slurries, suspensions, etc., suitable for ingestion by the patient.

[0350] For preparing oral dosage forms including the compound of formula (I) or (10b), pharmaceutically acceptable carriers can be either solid or liquid. Solid form preparations include powders, tablets, pills, capsules, cachets, suppositories, and dispersible granules. A solid carrier can be one or more substances, which may also act as diluents, flavoring agents, binders, preservatives, tablet disintegrating agents, or an encapsulating material. Details on techniques for formulation and administration are well described in the scientific and patent literature, see, e.g., the latest edition of Remington's Pharmaceutical Sciences, Maack Publishing Co, Easton PA ("Remington's").

[0351] In powders, the carrier is a finely divided solid, which is in a mixture with the finely divided active component. In tablets, the active component is mixed with the carrier having the necessary binding properties in suitable proportions and compacted in the shape and size desired.

[0352] The powders, capsules and tablets preferably contain from 5% to 70% of the compound of formula (I) or (10b), or from about 10% to about 70% of the compound of formula (I) or (10b). Suitable carriers are magnesium carbonate, magnesium stearate, talc, sugar, lactose, pectin, dextrin, starch, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose, a low melting wax, cocoa butter, and the like. The term "preparation" is intended to include the formulation of the active compound with encapsulating material as a carrier providing a capsule in which the active component with or without other excipients, is surrounded by a carrier, which is thus in association with it. Similarly, cachets and lozenges are included. Tablets, powders, capsules, pills, cachets, and lozenges can be used as solid dosage forms suitable for oral administration.

[0353] Suitable solid excipients include, but are not limited to, magnesium carbonate; magnesium stearate; talc; pectin; dextrin; starch; tragacanth; a low melting wax; cocoa butter; carbohydrates; sugars including, but not limited to, lactose, sucrose, mannitol, or sorbitol, starch from corn, wheat, rice, potato, or other plants; cellulose such as methyl cellulose, hydroxypropylmethyl-cellulose, or sodium carboxymethylcellulose; and gums including arabic and tragacanth; as well as proteins including, but not limited to, gelatin and collagen. If desired, disintegrating or solubilizing agents may be added, such as the cross-linked polyvinyl pyrrolidone, agar, alginic acid, or a salt thereof, such as sodium alginate.

[0354] Dragee cores are provided with suitable coatings such as concentrated sugar solutions, which may also contain gum arabic, talc, polyvinylpyrrolidone, carbopol gel, polyethylene glycol, and/or titanium dioxide, lacquer solutions, and suitable organic solvents or solvent mixtures. Dyestuffs or pigments may be added to the tablets or dragee coatings for product identification or to characterize the quantity of active compound (i.e., dosage). Pharmaceutical preparations of the dosage forms can also be used orally using, for example, push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a coating such as glycerol or sorbitol. Push-fit capsules can contain the compound of formula (I) or (10b) mixed with a filler or binders such as lactose or starches, lubricants such as talc or magnesium stearate, and,

optionally, stabilizers. In soft capsules, the compound of formula (I) or (10b) may be dissolved or suspended in suitable liquids, such as fatty oils, liquid paraffin, or liquid polyethylene glycol with or without stabilizers.

[0355] For preparing suppositories, a low melting wax, such as a mixture of fatty acid glycerides or cocoa butter, is first melted and the compound of formula (I) or (10b) are dispersed homogeneously therein, as by stirring. The molten homogeneous mixture is then poured into convenient sized molds, allowed to cool, and thereby to solidify.

[0356] Liquid form preparations include solutions, suspensions, and emulsions, for example, water or water/propylene glycol solutions.

[0357] Aqueous solutions suitable for oral use can be prepared by dissolving the compound of formula (I) or (10b) in water and adding suitable colorants, flavors, stabilizers, and thickening agents as desired. Aqueous suspensions suitable for oral use can be made by dispersing the finely divided active component in water with viscous material, such as natural or synthetic gums, resins, methylcellulose, sodium carboxymethylcellulose, hydroxypropylmethylcellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia, and dispersing or wetting agents such as a naturally occurring phosphatide (e.g., lecithin), a condensation product of an alkylene oxide with a fatty acid (e.g., polyoxyethylene stearate), a condensation product of ethylene oxide with a long chain aliphatic alcohol (e.g., heptadecaethylene oxycetanol), a condensation product of ethylene oxide with a partial ester derived from a fatty acid and a hexitol (e.g., polyoxyethylene sorbitol mono-oleate), or a condensation product of ethylene oxide with a partial ester derived from fatty acid and a hexitol anhydride (e.g., polyoxyethylene sorbitan mono-oleate). The aqueous suspension can also contain one or more preservatives such as ethyl or n-propyl p-hydroxybenzoate, one or more coloring agents, one or more flavoring agents and one or more sweetening agents, such as sucrose, aspartame or saccharin. Formulations can be adjusted for osmolarity.

[0358] Also included are solid form preparations, which are intended to be converted, shortly before use, to liquid form preparations for oral administration. Such liquid forms include solutions, suspensions, and emulsions. These preparations may contain, in addition to the active

component, colorants, flavors, stabilizers, buffers, artificial and natural sweeteners, dispersants, thickeners, solubilizing agents, and the like.

[0359] Oil suspensions can be formulated by suspending the compound of formula (I) or (10b) in a vegetable oil, such as arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin; or a mixture of these. The oil suspensions can contain a thickening agent, such as beeswax, hard paraffin or cetyl alcohol. Sweetening agents can be added to provide a palatable oral preparation, such as glycerol, sorbitol or sucrose. These formulations can be preserved by the addition of an antioxidant such as ascorbic acid. As an example of an injectable oil vehicle, see Minto, *J. Pharmacol. Exp. Ther.* 281:93-102, 1997. The pharmaceutical formulations including the compound of formula (I) or (10b) can also be in the form of oil-in-water emulsions. The oily phase can be a vegetable oil or a mineral oil, described above, or a mixture of these. Suitable emulsifying agents include naturally-occurring gums, such as gum acacia and gum tragacanth, naturally occurring phosphatides, such as soybean lecithin, esters or partial esters derived from fatty acids and hexitol anhydrides, such as sorbitan mono-oleate, and condensation products of these partial esters with ethylene oxide, such as polyoxyethylene sorbitan mono-oleate. The emulsion can also contain sweetening agents and flavoring agents, as in the formulation of syrups and elixirs. Such formulations can also contain a demulcent, a preservative, or a coloring agent.

[0360] In another aspect, the present disclosure provides a pharmaceutical composition for treating cancer in a subject, the composition including:

a) a therapeutically effective amount of a PTPN11 inhibitor; and

b) a therapeutically effective amount of a KRAS G12C inhibitor,

together with a pharmaceutically acceptable carrier or excipient,

wherein the PTPN11 inhibitor is represented by formula (I) as defined and described herein.

[0361] The cancer and/or solid tumor are described according to **Section III-2: Cancer/Solid Tumor**. In some embodiments, the cancer and/or solid tumor are any one of embodiments as described in **Section III-2: Cancer/Solid Tumor**.

[0362] The subject is described according to **Section III-3: Subject**. In some embodiments, the subject is any one of embodiments as described in **Section III-3: Subject**.

[0363] The PTPN11 inhibitor represented by formula (I) is described according to **Section III-1: PTPN11 Inhibitors and/or KRAS G12C Inhibitors**. In some embodiments, the PTPN11 inhibitor of formula (I) is any of embodiments as described in **Section III-1: PTPN11 Inhibitors and/or KRAS G12C Inhibitors**. In some embodiments, the PTPN11 inhibitor of formula (I) is the compound of formula (10b).

[0364] The PTPN11 inhibitor of formula (I) is further described according to **Section IV. Compounds**. In some embodiments, the PTPN11 inhibitor of formula (I) is any of embodiments as described in **Section IV. Compounds**.

[0365] The KRAS G12C inhibitor is described according to **Section III-1: PTPN11 Inhibitors and/or KRAS G12C Inhibitors**. In some embodiments, the KRAS G12C inhibitor is any of embodiments as described in **Section III-1: PTPN11 Inhibitors and/or KRAS G12C Inhibitors**.

[0366] In some embodiments, the KRAS G12C inhibitor is sotorasib (AMG 510), adagrasib (MRTX-849), MRTX1257, ARS-853, ARS-1620, JNJ-74699157 (ARS-3248), JDQ443, GDC-6036, JAB-21822, BI 1823911, MK-1084, LY3537982, or LY3499446. In some embodiments, the KRAS G12C inhibitor is adagrasib (MRTX-849). In some embodiments, when the PTPN11 inhibitor is represented by formula (10b), the KRAS G12C inhibitor is other than sotorasib.

[0367] The compositions of the present disclosure (including the compound of formula (I) and the KRAS G12C inhibitor) can be prepared in a wide variety of oral, parenteral and topical dosage forms. Oral preparations include tablets, pills, powder, dragees, capsules, liquids, lozenges, cachets, gels, syrups, slurries, suspensions, etc., suitable for ingestion by the patient. The compositions of the present disclosure can also be administered by injection, that is, intravenously, intramuscularly, intracutaneously, subcutaneously, intraduodenally, or intraperitoneally. Also, the compositions described herein can be administered by inhalation, for example, intranasally. Additionally, the compositions of the present disclosure can be administered transdermally. The compositions of this disclosure can also be administered by intraocular, intravaginal, and intrarectal routes including suppositories, insufflation, powders and aerosol formulations (for examples of steroid inhalants, see Rohatagi, *J. Clin. Pharmacol.* 35:1187-1193, 1995; Tjwa, *Ann. Allergy Asthma Immunol.* 75:107-111, 1995).

[0368] For preparing pharmaceutical compositions of the present disclosure (including the compound of formula (I) and the KRAS G12C inhibitor), pharmaceutically acceptable carriers can be either solid or liquid. Solid form preparations include powders, tablets, pills, capsules, cachets, suppositories, and dispersible granules. A solid carrier can be one or more substances, which may also act as diluents, flavoring agents, binders, preservatives, tablet disintegrating agents, or an encapsulating material. Details on techniques for formulation and administration are well described in the scientific and patent literature, see, e.g., the latest edition of Remington's Pharmaceutical Sciences, Maack Publishing Co, Easton PA ("Remington's").

[0369] In powders, the carrier is a finely divided solid, which is in a mixture with the finely divided active component. In tablets, the active components are mixed with the carrier having the necessary binding properties in suitable proportions and compacted in a particular shape and size.

[0370] The powders, capsules and tablets preferably contain from about 5% to about 70% of the active compounds, such as from about 10% to about 70% of the active compounds (e.g., the compound of formula (I) and the KRAS G12C inhibitor). Suitable carriers are magnesium carbonate, magnesium stearate, talc, sugar, lactose, pectin, dextrin, starch, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose, a low melting wax, cocoa butter, and the like. The term "preparation" is intended to include the formulation of the active compound with encapsulating material as a carrier providing a capsule in which the active component with or without other excipients, is surrounded by a carrier, which is thus in association with it. Similarly, cachets and lozenges are included. Tablets, powders, capsules, pills, cachets, and lozenges can be used as solid dosage forms suitable for oral administration.

[0371] Suitable solid excipients include, but are not limited to, magnesium carbonate; magnesium stearate; talc; pectin; dextrin; starch; tragacanth; a low melting wax; cocoa butter; carbohydrates; sugars including, but not limited to, lactose, sucrose, mannitol, or sorbitol, starch from corn, wheat, rice, potato, or other plants; cellulose such as methyl cellulose, hydroxypropylmethyl-cellulose, or sodium carboxymethylcellulose; and gums including arabic and tragacanth; as well as proteins including, but not limited to, gelatin and collagen. Disintegrating or solubilizing agents may be added, such as the cross-linked polyvinyl pyrrolidone, agar, alginic acid, or a salt thereof, such as sodium alginate.

[0372] Dragee cores are provided with suitable coatings such as concentrated sugar solutions, which may also contain gum arabic, talc, polyvinylpyrrolidone, carbopol gel, polyethylene glycol, and/or titanium dioxide, lacquer solutions, and suitable organic solvents or solvent mixtures. Dyestuffs or pigments may be added to the tablets or dragee coatings for product identification or to characterize the quantity of active compound (i.e., dosage). Pharmaceutical preparations of the present disclosure can also be used orally using, for example, push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a coating such as glycerol or sorbitol. Push-fit capsules can contain the active compounds (e.g., the compound of formula (I) and the KRAS G12C inhibitor) mixed with a filler or binders such as lactose or starches, lubricants such as talc or magnesium stearate, and, optionally, stabilizers. In soft capsules, the active compounds (e.g., the compound of formula (I) and the KRAS G12C inhibitor) may be dissolved or suspended in suitable liquids, such as fatty oils, liquid paraffin, or liquid polyethylene glycol with or without stabilizers.

[0373] For preparing suppositories, a low melting wax, such as a mixture of fatty acid glycerides or cocoa butter, is first melted and the active compounds (e.g., the compound of formula (I) and the KRAS G12C inhibitor) are dispersed homogeneously therein, as by stirring. The molten homogeneous mixture is then poured into convenient sized molds, allowed to cool, and thereby to solidify.

[0374] Liquid form preparations include solutions, suspensions, and emulsions, for example, water or water/propylene glycol solutions. For parenteral injection, liquid preparations can be formulated in solution in aqueous polyethylene glycol solution.

[0375] Aqueous solutions suitable for oral use can be prepared by dissolving the active compounds (e.g., the compound of formula (I) and the KRAS G12C inhibitor), as defined and described herein, in water and adding optional suitable colorants, flavors, stabilizers, and thickening agents. Aqueous suspensions suitable for oral use can be made by dispersing the finely divided active component in water with viscous material, such as natural or synthetic gums, resins, methylcellulose, sodium carboxymethylcellulose, hydroxypropylmethylcellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia, and dispersing or wetting agents such as a naturally occurring phosphatide (e.g., lecithin), a condensation product of an alkylene oxide with a fatty acid (e.g., polyoxyethylene stearate), a condensation product of

ethylene oxide with a long chain aliphatic alcohol (e.g., heptadecaethylene oxycetanol), a condensation product of ethylene oxide with a partial ester derived from a fatty acid and a hexitol (e.g., polyoxyethylene sorbitol mono-oleate), or a condensation product of ethylene oxide with a partial ester derived from fatty acid and a hexitol anhydride (e.g., polyoxyethylene sorbitan mono-oleate). The aqueous suspension can also contain one or more preservatives such as ethyl or n-propyl p-hydroxybenzoate, one or more coloring agents, one or more flavoring agents and one or more sweetening agents, such as sucrose, aspartame or saccharin. Formulations can be adjusted for osmolarity.

[0376] Also included are solid form preparations, which are intended to be converted, shortly before use, to liquid form preparations for oral administration. Such liquid forms include solutions, suspensions, and emulsions. These preparations may contain, in addition to the active component, colorants, flavors, stabilizers, buffers, artificial and natural sweeteners, dispersants, thickeners, solubilizing agents, and the like.

[0377] Oil suspensions can be formulated by suspending the active compounds (e.g., the compound of formula (I) and the KRAS G12C inhibitor) in a vegetable oil, such as arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin; or a mixture of these. The oil suspensions can contain a thickening agent, such as beeswax, hard paraffin or cetyl alcohol. Sweetening agents can be added to provide a palatable oral preparation, such as glycerol, sorbitol or sucrose. These formulations can be preserved by the addition of an antioxidant such as ascorbic acid. As an example of an injectable oil vehicle, see Minto, *J. Pharmacol. Exp. Ther.* 281:93-102, 1997. The pharmaceutical formulations of the present disclosure can also be in the form of oil-in-water emulsions. The oily phase can be a vegetable oil or a mineral oil, described above, or a mixture of these. Suitable emulsifying agents include naturally-occurring gums, such as gum acacia and gum tragacanth, naturally occurring phosphatides, such as soybean lecithin, esters or partial esters derived from fatty acids and hexitol anhydrides, such as sorbitan mono-oleate, and condensation products of these partial esters with ethylene oxide, such as polyoxyethylene sorbitan mono-oleate. The emulsion can also contain sweetening agents and flavoring agents, as in the formulation of syrups and elixirs. Such formulations can also contain a demulcent, a preservative, or a coloring agent.

[0378] The compositions of the present disclosure (including the compound of formula (I) and the KRAS G12C inhibitor) can be delivered by any suitable means, including oral, parenteral and topical methods. Transdermal administration methods, by a topical route, can be formulated as applicator sticks, solutions, suspensions, emulsions, gels, creams, ointments, pastes, jellies, paints, powders, and aerosols.

[0379] The compositions of the present disclosure (including the compound of formula (I) and the KRAS G12C inhibitor) can also be delivered as microspheres for slow release in the body. For example, microspheres can be formulated for administration via intradermal injection of drug-containing microspheres, which slowly release subcutaneously (see Rao, *J. Biomater Sci. Polym. Ed.* 7:623-645, 1995; as biodegradable and injectable gel formulations (see, e.g., Gao *Pharm. Res.* 12:857-863, 1995); or, as microspheres for oral administration (see, e.g., Eyles, *J. Pharm. Pharmacol.* 49:669-674, 1997). Both transdermal and intradermal routes afford constant delivery for weeks or months.

[0380] In another embodiment, the compositions of the present disclosure can be formulated for parenteral administration, such as intravenous (IV) administration or administration into a body cavity or lumen of an organ. The formulations for administration will commonly comprise a solution of the compositions of the present disclosure dissolved in a pharmaceutically acceptable carrier. Among the acceptable vehicles and solvents that can be employed are water and Ringer's solution, an isotonic sodium chloride. In addition, sterile fixed oils can be employed as a solvent or suspending medium. For this purpose any bland fixed oil can be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid can likewise be used in the preparation of injectables. These solutions are sterile and generally free of undesirable matter. These formulations may be sterilized by various sterilization techniques. The formulations may contain pharmaceutically acceptable auxiliary substances as required to approximate physiological conditions such as pH adjusting and buffering agents, toxicity adjusting agents, e.g., sodium acetate, sodium chloride, potassium chloride, calcium chloride, sodium lactate and the like. The concentration of the compositions of the present disclosure in these formulations can vary widely, and will be selected primarily based on fluid volumes, viscosities, body weight, and the like, in accordance with the particular mode of administration selected and the patient's needs. For IV administration, the formulation can be a

sterile injectable preparation, such as a sterile injectable aqueous or oleaginous suspension. This suspension can be formulated using those suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation can also be a sterile injectable solution or suspension in a nontoxic parenterally-acceptable diluent or solvent, such as a solution of 1,3-butanediol.

[0381] In another embodiment, the formulations of the compositions of the present disclosure can be delivered by the use of liposomes which fuse with the cellular membrane or are endocytosed, i.e., by employing ligands attached to the liposome, or attached directly to the oligonucleotide, that bind to surface membrane protein receptors of the cell resulting in endocytosis. By using liposomes, particularly where the liposome surface carries ligands specific for target cells, or are otherwise preferentially directed to a specific organ, one can focus the delivery of the compositions of the present disclosure into the target cells in vivo. (See, e.g., Al-Muhammed, *J. Microencapsul.* 13:293-306, 1996; Chonn, *Curr. Opin. Biotechnol.* 6:698-708, 1995; Ostro, *Am. J. Hosp. Pharm.* 46:1576-1587, 1989).

[0382] Lipid-based drug delivery systems include lipid solutions, lipid emulsions, lipid dispersions, self-emulsifying drug delivery systems (SEDDS) and self-microemulsifying drug delivery systems (SMEDDS). In particular, SEDDS and SMEDDS are isotropic mixtures of lipids, surfactants and co-surfactants that can disperse spontaneously in aqueous media and form fine emulsions (SEDDS) or microemulsions (SMEDDS). Lipids useful in the formulations of the present disclosure include any natural or synthetic lipids including, but not limited to, sesame seed oil, olive oil, castor oil, peanut oil, fatty acid esters, glycerol esters, Labrafil®, Labrasol®, Cremophor®, Solutol®, Tween®, Capryol®, Capmul®, Captex®, and Peceol®.

[0383] The pharmaceutical formulations of the present disclosure can be provided as a salt and can be formed with many acids, including but not limited to hydrochloric, sulfuric, acetic, lactic, tartaric, malic, succinic, etc. Salts tend to be more soluble in aqueous or other protonic solvents that are the corresponding free base forms. In other cases, the preparation may be a lyophilized powder in, e.g., 1 mM-50 mM histidine, 0.1%-2% sucrose, 2%-7% mannitol at a pH range of 4.5 to 5.5, that is combined with buffer prior to use.

[0384] The pharmaceutical formulations of the present disclosure can be provided as a salt and can be formed with bases, namely cationic salts such as alkali and alkaline earth metal salts, such

as sodium, lithium, potassium, calcium, magnesium, as well as ammonium salts, such as ammonium, trimethyl-ammonium, diethylammonium, and tris-(hydroxymethyl)-methyl-ammonium salts.

VI. KITS

[0385] In another aspect, the present disclosure provides a kit for treating a disease or disorder (e.g., cancer) in a subject, the kit including:

a) a therapeutically effective amount of a PTPN11 inhibitor; and

b) a therapeutically effective amount of a KRAS G12C inhibitor,

together with instruction for effective administration,

wherein the PTPN11 inhibitor is represented by formula (I) as defined and described herein.

[0386] The cancer and/or solid tumor are described according to **Section III-2: Cancer/Solid Tumor**. In some embodiments, the cancer and/or solid tumor are any of embodiments as described in **Section III-2: Cancer/Solid Tumor**.

[0387] The subject is described according to **Section III-3: Subject**. In some embodiments, the subject is any of embodiments as described in **Section III-3: Subject**.

[0388] The PTPN11 inhibitor represented by formula (I) is described according to **Section III-1: PTPN11 Inhibitors and/or KRAS G12C Inhibitors**. In some embodiments, the PTPN11 inhibitor of formula (I) is any of embodiments as described in **Section III-1: PTPN11 Inhibitors and/or KRAS G12C Inhibitors**. In some embodiments, the PTPN11 inhibitor of formula (I) is the compound of formula (10b).

[0389] The PTPN11 inhibitor of formula (I) is further described according to **Section IV. Compounds**. In some embodiments, the PTPN11 inhibitor of formula (I) is any of embodiments as described in **Section IV. Compounds**.

[0390] The KRAS G12C inhibitor is described according to **Section III-1: PTPN11 Inhibitors and/or KRAS G12C Inhibitors**. In some embodiments, the KRAS G12C inhibitor is any of embodiments as described in **Section III-1: PTPN11 Inhibitors and/or KRAS G12C Inhibitors**.

[0391] In some embodiments, the KRAS G12C inhibitor is sotorasib (AMG 510), adagrasib (MRTX-849), MRTX1257, ARS-853, ARS-1620, JNJ-74699157 (ARS-3248), JDQ443, GDC-6036, JAB-21822, BI 1823911, MK-1084, LY3537982, or LY3499446. In some embodiments, the KRAS G12C inhibitor is adagrasib (MRTX-849). In some embodiments, when the PTPN11 inhibitor is represented by formula (10b), the KRAS G12C inhibitor is other than sotorasib.

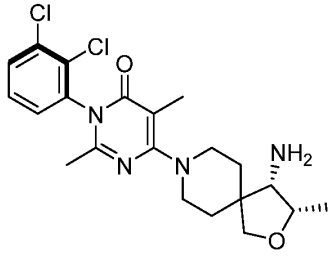
[0392] In some embodiments, the kit includes instructions for administration of the compound of formula (I) or (10b) and the KRAS G12C inhibitor. In some embodiments, the kit includes instructions for administration of the compound of formula (10b) and the KRAS G12C inhibitor. In some embodiments, such instructions include directions relating to safety provisions as well as timing and amounts of administration of the compound of formula (I) or (10b) and the KRAS G12C inhibitor. In some embodiments, such instructions include directions relating to safety provisions as well as timing and amounts of administration of the compound of formula (10b) and the KRAS G12C inhibitor. In some embodiments, such instructions include directions relating to safety provisions as well as timing and amounts of administration of the compound of formula (10b) and adagrasib (MRTX-849).

[0393] The PTPN11 inhibitor represented by formula (I) or (10b) as described herein and the KRAS G12C inhibitor as described herein can be are formulated for concomitant administration or sequential administration. In some embodiments, the PTPN11 inhibitor of formula (I) or (10b) and the KRAS G12C inhibitor are formulated for concomitant administration. In some embodiments, the PTPN11 inhibitor of formula (I) or (10b) and the KRAS G12C inhibitor are formulated for sequential administration. In some embodiments, the PTPN11 inhibitor of formula (I) or (10b) is administered prior to the administration of the KRAS G12C inhibitor. In some embodiments, the PTPN11 inhibitor of formula (I) or (10b) is administered after the administration of the KRAS G12C inhibitor.

VII. EMBODIMENTS

[0394] Embodiment 1. A method of treating cancer in a subject, comprising administering to the subject:

a) a therapeutically effective amount of a compound represented by formula (10b):

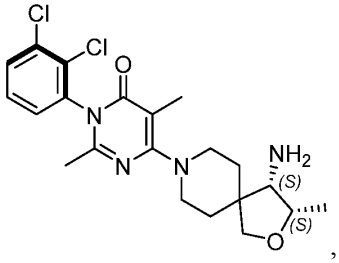


(I),

or a pharmaceutically acceptable salt, hydrate, solvate, stereoisomer, conformational isomer, tautomer, or a combination thereof; and

b) a therapeutically effective amount of adagrasib (MRTX-849).

[0395] Embodiment 2. The method of embodiment 1, wherein the compound of formula (10b) is represented by:



,

having the name of 6-((3S,4S)-4-amino-3-methyl-2-oxa-8-azaspiro[4.5]decan-8-yl)-3-(Ra)-(2,3-dichlorophenyl)-2,5-dimethylpyrimidin-4(3H)-one.

[0396] Embodiment 3. The method of embodiment 1 or 2, wherein the cancer is characterized by a KRAS mutation.

[0397] Embodiment 4. The method of embodiment 3, wherein the cancer is characterized by a KRAS G12C mutation.

[0398] Embodiment 5. The method of any one of embodiments 1 to 4, wherein the cancer comprises a solid tumor.

[0399] Embodiment 6. The method of any one of embodiments 1 to 5, wherein the cancer is lung cancer, colorectal cancer, pancreatic cancer, urothelial carcinoma, stomach cancer, mesothelioma, or a combination thereof.

[0400] Embodiment 7. The method of embodiment 6, wherein the cancer is non-small cell lung cancer (NSCLC).

[0401] Embodiment 8. The method of embodiment 6, wherein the cancer is colorectal cancer.

[0402] Embodiment 9. The method of any one of embodiments 1 to 8, wherein the cancer is a KRAS G12C-positive cancer resistant to a KRAS G12C inhibitor.

[0403] Embodiment 10. The method of any one of embodiments 1 to 9, wherein the cancer is a KRAS G12C-positive cancer characterized by intrinsic and/or acquired resistance to a KRAS G12C inhibitor.

[0404] Embodiment 11. The method of any one of embodiments 1 to10, wherein the cancer is a KRAS G12C-positive cancer resistant to adagrasib.

[0405] Embodiment 12. The method of any one of embodiments 1 to 11, wherein the cancer has progressed or recurred on or after at least one prior line of a systemic therapy comprising a platinum-based doublet chemotherapy and/or an anti-PD-1/PD-L1 therapy, each of which is given in monotherapy or both of which are given in combination therapy.

[0406] Embodiment 13. The method of any one of embodiments 1 to 12, wherein the subject does not have an activating mutation in BRAF V600X, PTPN11 (SHP2), or KRAS Q61X.

[0407] Embodiment 14. The method of any one of embodiments 1 to 13, wherein the subject is not previously treated with a PTPN11 inhibitor.

[0408] Embodiment 15. The method of any one of embodiments 1 to 13, wherein the subject is previously treated with a PTPN11 inhibitor other than a compound of formula (10b).

[0409] Embodiment 16. The method of any one of embodiments 1 to 13, wherein the subject is previously treated with a compound of formula (10b).

[0410] Embodiment 17. The method of any one of embodiments 1 to 9 and 11 to 16, wherein the subject is not previously treated with a KRAS G12C inhibitor.

[0411] Embodiment 18. The method of any one of embodiments 1 to 16, wherein the subject is previously treated with a KRAS G12C inhibitor.

[0412] Embodiment 19. The method of any one of embodiments 1 to 16, wherein the subject is previously treated with adagrasib.

[0413] Embodiment 20. The method of any one of embodiments 1 to 19, wherein the subject meets all of inclusion criteria of 1) to 11) according to Example 5, provided that the subject does not meet any one of exclusion criteria of 1) to 17) according to Example 5.

[0414] Embodiment 21. The method of any one of embodiments 1 to 20, wherein the subject is human.

[0415] Embodiment 22. The method of any one of embodiments 1 to 21, wherein the compound of formula (10b) and adagrasib are administered concomitantly.

[0416] Embodiment 23. The method of any one of embodiments 1 to 21, wherein the compound of formula (10b) and adagrasib are administered sequentially.

[0417] Embodiment 24. The method of embodiment 23, wherein the compound of formula (10b) is administered prior to the administration of adagrasib.

[0418] Embodiment 25. The method of embodiment 23, wherein the compound of formula (10b) is administered after the administration of adagrasib.

[0419] Embodiment 26. The method of any one of embodiments 1 to 25, wherein the compound of formula (10b) or adagrasib is administered orally, or each of adagrasib and the compound of formula (10b) are administered orally.

[0420] Embodiment 27. The method of any one of embodiments 1 to 26, wherein the compound of formula (10b) is administered orally.

[0421] Embodiment 28. The method of any one of embodiments 1 to 27, wherein adagrasib is administered orally.

[0422] Embodiment 29. The method of any one of embodiments 1 to 28, wherein the compound of formula (10b) and adagrasib are provided in jointly therapeutically effective amounts.

[0423] Embodiment 30. The method of any one of embodiments 1 to 28, wherein the compound of formula (10b) and adagrasib are provided in synergistically effective amounts.

[0424] Embodiment 31. The method of any one of embodiments 1 to 30, wherein the compound of formula (10b) and/or adagrasib is used at a dose different than when it is used alone.

[0425] Embodiment 32. The method of embodiment 31, wherein the compound of formula (10b) is used at a dose lower than when it is used alone.

[0426] Embodiment 33. The method of embodiment 31, wherein the compound of formula (10b) is used at a dose higher than when it is used alone.

[0427] Embodiment 34. The method of any one of embodiments 31-33, wherein adagrasib is used at a dose lower than when it is used alone.

[0428] Embodiment 35. The method of any one of embodiments 31-33, wherein adagrasib is used at a dose higher than when it is used alone.

[0429] Embodiment 36. The method of any one of embodiments 1 to 35, wherein the treating comprises one or more treatment cycles; each of one or more treatment cycles has a duration of about 28 days; and the compound of formula (10b) and/or adagrasib are administered daily.

[0430] Embodiment 37. The method of any one of embodiments 1 to 36, wherein the administration of the compound of formula (10b) and adagrasib comprises one or more dose escalations, dose retentions, or dose de-escalations of the compound of formula (10b) and/or adagrasib.

[0431] Embodiment 38. The method of embodiment 37, wherein the administration of the compound of formula (10b) and adagrasib comprises one or more dose escalations, dose retentions, or dose de-escalations of the compound of formula (10b).

[0432] Embodiment 39. The method of embodiment 38, wherein the one or more dose escalations, dose retentions, or dose de-escalations of the compound of formula (10b) are determined by a dose-limiting toxicity (DLT) assessment.

[0433] Embodiment 40. The method of embodiment 39, wherein the administration of the compound of formula (10b) comprises a dose escalation after a previous treatment cycle, when a dose-limiting toxicity (DLT) rate is less than about 19.7% as determined by a DLT assessment.

[0434] Embodiment 41. The method of embodiment 39, wherein the administration of the compound of formula (10b) comprises a dose de-escalation after a previous treatment cycle, when a dose-limiting toxicity rate is more than about 29.8% as determined by a DLT assessment.

[0435] Embodiment 42. The method of embodiment 39, wherein the administration of the compound of formula (10b) comprises a dose retention after a previous treatment cycle, when a dose-limiting toxicity rate is in a range of from about 21.9% to about 29.8% as determined by a DLT assessment.

[0436] Embodiment 43. The method of any one of embodiments 36 to 42, wherein the treating comprises a dose escalation period, and wherein, after the dose escalation period, the treating further comprises a dose expansion/optimization period; and the compound of formula (10b) is administered at a dose regimen determined during the dose escalation period.

[0437] Embodiment 44. The method of embodiment 43, wherein, during the dose expansion/optimization period, the administration of the compound of formula (10b) comprises one or more dose adjustments.

[0438] Embodiment 45. The method of any one of embodiments 1 to 44, wherein the therapeutically effective amount of adagrasib is a total daily dosage of about 600 mg, about 720 mg, about 840 mg, about 960 mg, or about 1200 mg.

[0439] Embodiment 46. The method of embodiment 45, wherein the therapeutically effective amount of adagrasib is a total daily dosage of about 1200 mg.

[0440] Embodiment 47. The method of any one of embodiments 1 to 46, wherein the therapeutically effective amount of the compound of formula (10b) is a total daily dosage of from about 100 mg to about 2000 mg, from about 150 mg to about 1000 mg, from about 200 mg to about 1000 mg, from about 250 mg to about 1000 mg, from about 300 mg to about 1000 mg, from about 350 mg to about 1000 mg, from about 400 mg to about 1000 mg, from about 450 mg to about 1000 mg, from about 500 mg to about 1000 mg, from about 550 mg to about 1000 mg,

from about 600 mg to about 1000 mg, from about 650 mg to about 1000 mg, from about 700 mg to about 1000 mg, from about 100 mg to about 700 mg, from about 150 mg to about 700 mg, from about 200 mg to about 700 mg, from about 250 mg to about 700 mg, from about 300 mg to about 700 mg, from about 3 mg to about 700 mg, from about 400 mg to about 700 mg, from about 450 mg to about 700 mg, from about 500 mg to about 700 mg, from about 550 mg to about 700 mg, from about 100 mg to about 550 mg, from about 150 mg to about 550 mg, from about 200 mg to about 550 mg, from about 250 mg to about 550 mg, from about 300 mg to about 550 mg, from about 350 mg to about 550 mg, from about 400 mg to about 550 mg, from about 450 mg to about 550 mg, from about 100 mg to about 400 mg, from about 150 mg to about 400 mg, from about 200 mg to about 400 mg, from about 250 mg to about 400 mg, or from about 300 mg to about 400 mg, on a salt-free and anhydrous basis.

[0441] Embodiment 48. The method of embodiment 47, wherein the therapeutically effective amount is a total daily dosage of from about 250 mg to about 400 mg, from about 400 mg to about 550 mg, or from about 550 mg to about 700 mg of the compound of formula (10b), on a salt-free and anhydrous basis.

[0442] Embodiment 49. The method of embodiment 48, wherein the therapeutically effective amount is a total daily dosage of about 250 mg, about 400 mg, or about 550 mg of the compound of formula (10b), on a salt-free and anhydrous basis.

[0443] Embodiment 50. The method of any one of embodiments 47 to 49, wherein the therapeutically effective amount is a total daily dosage of about 250 mg of the compound of formula (10b), on a salt-free and anhydrous basis.

[0444] Embodiment 51. The method of any one of embodiments 47 to 49, wherein the therapeutically effective amount is a total daily dosage of about 400 mg of the compound of formula (10b), on a salt-free and anhydrous basis.

[0445] Embodiment 52. The method of any one of embodiments 47 to 49, wherein the therapeutically effective amount is a total daily dosage of about 550 mg of the compound of formula (10b), on a salt-free and anhydrous basis.

[0446] Embodiment 53. The method of any one of embodiments 1 to 52, wherein the compound of formula (10b) and adagrasib are each administered orally.

[0447] Embodiment 54. The method of any one of embodiments 1 to 53, wherein the compound of formula (10b) is administered once, twice, three times, or four times daily.

[0448] Embodiment 55. The method of embodiment 54, wherein the compound of formula (10b) is administered once daily; and adagrasib is administered twice daily.

[0449] Embodiment 56. The method of any one of embodiments 1 to 55, wherein the compound of formula (10b) is provided in a tablet formulation.

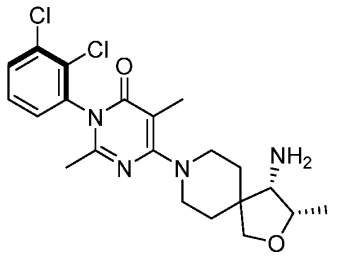
[0450] Embodiment 57. The method of any one of embodiments 1 to 56, wherein the treating reduces a volume of the cancer or a solid tumor at least about 10%, about 20%, about 30%, about 40%, about 50%, about 60%, about 70%, about 80%, or about 90%.

[0451] Embodiment 58. The method of any one of embodiments 1 to 56, wherein the treating stabilizes the cancer or a solid tumor.

[0452] Embodiment 59. The method of any one of embodiments 1 to 58, wherein the subject is further evaluated for one or more biomarkers that correlate to an antitumor response.

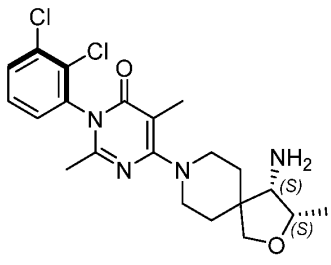
[0453] Embodiment 60. A kit for treating cancer in a subject, comprising:

a) a therapeutically effective amount of a compound represented by formula (10b):



(10b),

or a pharmaceutically acceptable salt, hydrate, solvate, stereoisomer, conformational isomer, tautomer, or a combination thereof, or a compound represented by formula:



; and

b) a therapeutically effective amount of adagrasib,

together with instruction for effective administration.

[0454] Embodiment 61. The kit of embodiment 60, wherein the compound of formula (10b) and adagrasib are formulated for concomitant administration.

[0455] Embodiment 62. The kit of embodiment 60, wherein the compound of formula (10b) and adagrasib are formulated for sequential administration.

VIII. LIST OF ABBREVIATIONS

Abbreviation	Definition
(e)CRF	(electronic) case report form
(p)ERK	(phosphorylated) extracellular signal-regulated kinase
AAALAC	Association for the Assessment and Accreditation for Laboratory Animal Care
AE	adverse event
ALK	anaplastic lymphoma kinase
ALT	alanine aminotransferase (or transaminase)
ANC	absolute neutrophil count
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase (or transaminase)
ATCC	American Type Culture Collection
AUC	area under the plasma concentration-time curve
BBP	BridgeBio Pharma
BCRP	breast cancer resistance protein
BICR	blinded independent central review
BOIN	Bayesian optimal interval
BQL	Below Quantitation Limit
BW	Body Weight
BWL	Body Weight Loss
CI	confidence interval
CLIA	Clinical Laboratory Improvement Amendments
C_{max}	maximum plasma drug concentration
CNS	central nervous system
CR	complete response(s)

Abbreviation	Definition
CRO	contract research organization
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	circulating tumor deoxyribonucleic acid
CYP	cytochrome P450
DLT	dose-limiting toxicity
DNA	deoxyribonucleic acid
DOR	duration of response
DUSP6	dual specificity phosphatase 6
ECG	electrocardiogram
ECHO	echocardiogram
ECOG	Eastern Cooperative Oncology Group
EDC	electronic data capture (system)
EDTA	Ethylenediaminetetraacetic acid
EGFR	epidermal growth factor receptor
EORTC	European Organization for Research and Treatment of Cancer
EOS	end of study
EOT	end of treatment
FBS	fetal bovine serum
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
G12C	Glycine 12 to cysteine mutation
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
GTP	guanosine triphosphate
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HNSTD	highest non-severely toxic dose
HPMC	Hydroxypropyl methylcellulose
IACS	Institute for Applied Cancer Science
IACUC	Institutional Animal Care and Use Committee
IB	Investigator's Brochure

Abbreviation	Definition
ICF	informed consent form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
INR	international normalized ratio
IRB	Institutional Review Board
IV	intravenous
KRAS	Kirsten rat sarcoma viral oncogene homolog
LC-MS/MS	liquid chromatography with tandem mass spectrometry
LD (or LDi)	longest diameter
LVEF	left ventricular ejection fraction
MAPK	mitogen-activated protein kinase
MATE	multidrug and toxin extrusion protein
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
MUGA	multiple-gated acquisition scan (radionuclide angiography)
NCI	National Cancer Institute
NGS	next generation sequencing
NOD/SCID	Nonobese Diabetic/Severe Combined Immunodeficiency
NSCLC	non-small cell lung cancer
OATP	organic anion transporter polypeptide
ORR	objective response rate
OS	overall survival
PBS	Phosphate-buffered saline
PD	progressive disease
PD-1	programmed cell death-1
PD-L1	programmed cell death ligand-1
PET	positron emission tomography
PFS	progression free survival
P-gp	P-glycoprotein
PI	package insert
PK	pharmacokinetic
PO	*Per os* (oral administration, by mouth)
PR	partial response
PS	performance status

Abbreviation	Definition
PT	prothrombin time
PTPN11	*protein tyrosine phosphatase non-receptor type 11*, the gene encoding SHP2
QD	once daily
RAF	rapidly accelerated fibrosarcoma
RAS	any of a family of genes that undergo mutation to oncogenes and especially to some commonly linked to human cancers (as of the colon, lung, and pancreas)
REB	Research Ethics Board
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	ribonucleic acid
RP1bD	recommended phase 1b dose
RP2D	recommended phase 2 dose
RPM	Round per minute
RPMI	Roswell Park Memorial Institute
RTK	receptor tyrosine kinase
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD (Example 1)	Standard Deviation
SD	stable disease
SEM	Standard error of the mean
SGOT	serum glutamic-oxaloacetic transaminase
SGPT	serum glutamic-pyruvic transaminase
SHP2	Src homology-2-containing protein tyrosine phosphatase 2
SRC	Safety Review Committee
STD10	severely toxic dose in 10% of animals
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
TGI	Tumor Growth Inhibition
T_{max}	time to reach maximum drug concentration following drug administration
UHPLC	Ultra High Performance Liquid Chromatography
ULN	upper limit of normal
US	United States

IX. EXAMPLES

Example 1: *In vivo* Efficacy of Formula (10b) and Compound A

A. MATERIALS

[0456] **Test article #1** – formula (10b):

[0457] Chemical name: 6-[(3S,4S)-4-amino-3-methyl-2-oxa-8-azaspiro [4.5] decan-8-yl]-3-(2,3-dichlorophenyl)-2,5-dimethyl-3,4-dihydropyrimidin-4-one

[0458] Molecular formula: $C_{21}H_{26}Cl_2N_4O_2$

[0459] Molecular weight: 437.37

[0460] **Test article #2** – Compound A:

[0461] Chemical name: 6-fluoro-7-(2-fluoro-6-hydroxyphenyl)-1-[4-methyl-2-(propan-2-yl)pyridin-3-yl]-4-[(2S)-2- methyl-4-(prop-2-enoyl)piperazin-1-yl]pyrido[2,3-d]pyrimidin-2(1H)-one

[0462] CAS #: 252403-56-6

[0463] Molecular formula: $C_{30}H_{30}F_2N_6O_3$

[0464] Molecular weight: 560.6

[0465] **Cell lines**. The NCI-H358 cell line was purchased from ATCC. It is a human NSCLC cell line, harboring heterozygous mutation of KRAS G12C. The cells were cultured in RPMI 1640 containing glutamine (Thermo Fisher #22400-089) +10% fetal bovine serum (FBS, Thermo Fisher # 10099-141) in 37 °C tissue culture incubator (Thermo Fisher) with 5% CO_2.

[0466] **Test animals.** Female NOD/SCID mice (Beijing Anikeeper Biotech Co., Ltd) were utilized in this experiment. Animals were 6~8 weeks of age at the time of xenograft implantation. The protocol and any amendment(s) or procedures involving the care and use of animals in this study was reviewed and approved by the Institutional Animal Care and Use Committee (IACUC) of Crown Bioscience Ltd. prior to execution. During the study, the care and use of animals was conducted in accordance with the regulations of the Association for Assessment and Accreditation of Laboratory Animal Care (AAALAC).

[0467] All mice were housed in AAALAC accredited animal research facilities at the Crown Bioscience Beijing, at Light Muller Building, Changping Sector of Zhongguancun Scientific Park, No.21 Huoju Road, Changping District, Beijing, China. All animals were maintained under the supervision and care of Veterinary of the Animal Facilities, who oversee a comprehensive and well-executed health surveillance program.

[0468] Mice were housed in polysulfone IVC cage (325mm × 210mm × 180mm), with a maximum of five animals and had free access to food and water with light 12-hour on/12-hour off. All animals received irradiated Standard rodent chow - Rats & Mice Growing and Breeding Feed diet (Beijing Keao Xieli Feed Co., LTD) *ad libitum*. Mice were monitored daily and cages changed once every second week.

B. EXPERIMENTAL PROCEDURES

[0469] **Formulation.** Formula (10b) was prepared in 0.5% methylcellulose. To prepare 0.5% methylcellulose solution, methylcellulose powder (400 cP, Sigma # M0262) was added to heated 80 °C sterile water. The solution was incubated at 80 °C with stirring for 3~4 hours, then incubated at 4 °C with continuous stirring for 18 hours. After adjusting the final volume with sterile H_2O, the solution was stirred for another 30 min at 4 °C, then filtered using 0.45 μM sterile filter. The prepared 0.5% methylcellulose solution was stored at 4 °C for future use.

[0470] To prepare formula (10b) dosing suspension in 0.5% methylcellulose, the weighed compound was placed in a glass vial and 0.5% methylcellulose solution was added to the vial with a syringe. After vortexing for 30 seconds, the vial was sonicated in a water bath sonicator (Shanghai Kudos Ultrasonic Instrument Co., LTD, Model SK2510HP) on "High" setting at room temperature for ~ 20 min until an off-white suspension without visible solids was obtained. The prepared dosing suspension was stored at 4 °C with gentle continuous stirring. Fresh dosing suspension was prepared once a week.

[0471] Compound A was prepared in Labrasol (Gattefosse #3074). To prepare Compound A dosing solution, the weighed compound was placed in a glass vial and Labrasol was added to the vial. The mixture was vortexed for 30 sec, sonicated in a water bath sonicator (Shanghai Kudos Ultrasonic Instrument Co., LTD, Model SK2510HP) for ~ 5 min until a pale yellow solution was obtained. The dosing solution was stored at 4 °C with gentle continuous stirring. Fresh dosing

solution was prepared once a week. Immediately before dosing the animals with Compound A, the dosing solution was mixed with an equal volume of sterile ddH_2O, vortexed, and then incubated at room temperature for 10 min, at which time a uniform solution was formed and was used to dose the mice. The diluted dosing solution was used within one hour following addition of water.

[0472] ***In vivo*** **modeling, treatment and data analysis.** For xenograft studies with the NCI-H358 cells, 5 million cells with 50% Matrigel (BD bioscience #356234) in sterile PBS (Hyclone Laboratories #SH30256.01) in a volume of 100 µL were injected subcutaneously into the right flank of female 6~8 weeks old NOD/SCID mice (Beijing Anikeeper Biotech Co.,Ltd). Tumor size measurement was performed with caliper and calculated using a standard formula: length x width^2/2, where length and width were the long and short diameters of the tumor, respectively.

[0473] When the average tumor volume reached 250 mm^3, mice were randomized into groups of 8 based on both tumor volume and body weight. Randomization was performed based on the "Matched distribution" method/ "Stratified" method in the StudyDirector software version 3.1.399.19 (StudyLog). The mice were then treated with vehicle, Compound A alone at one of three dosing levels (100 mg/kg QD, 30 mg/kg QD and 10 mg/kg QD), formula (10b) alone at one of two dosing levels (100 mg/kg QD and 50 mg/kg QD), or the combination of the two compounds, through oral gavage (PO), as shown below. Formula (10b) was administered in the morning, and Compound A was administered in the afternoon, with the morning and afternoon dosing separated by 6 hours.

Group	Treatment
A	0.5% methylcellulose QD AM + 50% Labrasol QD PM
B	0.5% methylcellulose AM + Compound A 100 mg/kg QD PM
C	0.5% methylcellulose AM + Compound A 30 mg/kg QD PM
D	0.5% methylcellulose AM + Compound A 10 mg/kg QD PM
E	Formula (10b) 100 mg/kg QD AM+50% Labrasol QD PM
F	Formula (10b) 50 mg/kg QD AM+50% Labrasol QD PM
G	Formula (10b) 100 mg/kg QD AM + Compound A 100 mg/kg QD PM
H	Formula (10b) 50 mg/kg QD AM + Compound A 100 mg/kg QD PM
I	Formula (10b) 100 mg/kg QD AM + Compound A 30 mg/kg QD PM

Group	Treatment
J	Formula (10b) 100 mg/kg QD AM + Compound A 10 mg/kg QD PM

[0474] Dosing started ~2 weeks post the subcutaneous implantation of the tumor cells. Dosing volume for formula (10b) was 5 mL/kg, for Compound A was 6 mL/kg, and was adjusted based on individual mouse weight from the biweekly measurements. Tumor volume was measured twice a week. The body weight and tumor volume were captured in the StudyDirector software version 3.1.399.19 (StudyLog). After dosing for 21 days (all dosing levels but 10 mg/kg formula (10b)) or 29 days (10 mg/kg formula (10b)), plasma samples were harvested 2 hours after the final dose of Compound A (8 hours after the final dose of formula (10b)), following the blood collection method described below.

[0475] Data were analyzed using Microsoft Excel and GraphPad Prism 8.0. Day 0 was the day before treatment started. Body weight change and tumor growth inhibition (TGI) were calculated based on the following formulas.

$$\text{Body Weight Change \%} = (BW_i\text{-}BW_0)/BW_0*100\%$$

BW_i and BW_0 are the body weight of an individual mouse on measurement day I and on day 0, respectively.

$$TGI\% = (C_i\text{-}T_i)/(C_i\text{-}C_0)*100\%$$

T_i and C_i are the mean tumor volumes of the treatment and vehicle groups on the measurement day, respectively; C_0 is the mean tumor volume of the vehicle group on day 0.

[0476] **Blood collection for pharmacokinetic analysis.** Blood from live animals for pharmacokinetic (PK) analyses was obtained via the retro-orbital sinus. The mouse was grasped firmly behind the ears and rotated slightly to one side so that a disposable, sterile microcapillary tube could be inserted behind the eyeball and gently rotated to break the sinus cavity. Blood flowed through the capillary tube, directly into a K_2 EDTA tube (Jiangsu KangJian Medical Apparatus Corporation #044022) to a volume of 100 μL. Blood in the tube was inverted several times to distribute the EDTA evenly. To separate plasma, tubes were centrifuged in a bench top centrifuge (Eppendorf, Model 5424R) for 5 minutes at 8000 rpm without braking. The

supernatant (plasma) was carefully transferred to a microcentrifuge tube and placed onto dry ice prior to storage at -80 °C.

[0477] LC-MS/MS quantitation of formula (10b) and Compound A in mouse plasma. Concentrations of formula (10b) and Compound A in mouse plasma were quantitated using a validated LC-MS/MS method. For plasma sample analysis, 20 µL of each sample was precipitated with 200 µL of acetonitrile containing Glipizide (100 ng/mL) as an internal standard. This suspension was vortexed for 1 min and centrifuged at 4,000 rpm for 10 min, after which 80 µL of the extract was aliquoted for LC-MS/MS analysis. LC-MS/MS analysis was conducted on a Shimadzu Nexera UHPLC system coupled with a Sciex 6500 TQ-S triple quadrupole mass spectrometer (MS/MS) operated at the positive mode (ESI^+). The mass spec source conditions were set as the following: Ion spray voltage (5500 volts), CAD (8), CUR (35), TEM (450), GS1 (60), GS2 (60), EP (10), CXP (12), CEM (2000) and for formula (10b): DP (40), CE (65), for Compound A: DP (40), CE (47), for the internal standard: DP (35), CE (20). formula (10b) and Compound A were separated using a Waters X-Bridge BEH C18 column (2.1×50 mm, 1.7 µm) and detected by a multiple reaction monitoring transition (m/z 437.10>186.10 for formula (10b), m/z 561.20>134.20 for Compound A and m/z 446.20>321.10 for the internal standard). The injection volume was 2 µL. The LC mobile phase A was 0.025% formic acid-water containing 1 mM ammonium acetate and B was 100% methanol containing 5 mM ammonium acetate. The gradient (%B) was 2% (0-0.4 min), 2-65% (0.4-1.7 min), 65-90% (0.7 to 1.3 min), 90% (1.3-1.9 min), 90-2% (1.9 to 1.91 min), 2% (1.91-2.5min). The flow rate was 0.6 mL/min. The column temperature was 60 °C. Under these conditions, the retention time was 1.42 min for formula (10b), 1.44 min for Compound A and the internal standard. The method was validated with the analytical range of 3 – 3,000 nM for both formula (10b) and Compound A in untreated CD-1 mouse plasma.

C. RESULTS

[0478] Sotorasib (AMG 510) is a KRAS covalent inhibitor that specifically targets the KRAS G12C mutant. It has demonstrated single agent response in patients with solid tumors, including NSCLC, harboring KRAS G12C mutation. Specifically, in the CodeBreaK 100 study, the subgroup with NSCLC had a confirmed objective response rate (complete or partial response) of 32.2% and a disease control rate (objective response or stable disease) of 88.1%; the median

progression-free survival was 6.3 months. Hong et al., *N. Engl. J. Med.* 2020; 383:1207-1217. Unbiased functional genomics approaches have also identified SHP2 as a vulnerability under KRAS G12C inhibition. Inhibition of KRAS G12C induces adaptive feedback activation of the MAPK pathway through multiple RTKs, which signal through SHP2. This study was designed to assess the effect of the SHP2 inhibitor formula (10b) in combination with the KRAS G12C inhibitor Compound A in a human NSCLC tumor model harboring KRAS G12C *in vivo*.

[0479] Treatment with the combination of formula (10b) and Compound A resulted in tumor growth inhibition in a subcutaneous model of NSCLC harboring KRAS G12C. A mouse tumor xenograft model was developed by subcutaneous implantation of the NCI-H358 cells which harbor KRAS G12C, and was used to test the anti-tumor response of formula (10b) in combination with Compound A *in vivo*. Mice harboring established NCI-H358 subcutaneous tumors were were randomized and treated with vehicle, Compound A alone, formula (10b) alone, or the combination of the two compounds, delivered orally for 21 days. Formula (10b) was administered every day in the morning, and Compound A was administered every day in the afternoon, with the morning and afternoon dosing separated by 6 hours. Tumor volume was monitored bi-weekly by caliper and body weights were recorded. Data presented in **FIGs. 1A-1E** represent mean±SEM, and N=8 mice/group for **FIGs. 1B-1E** and 10 for **FIG. 1A**.

[0480] FIG. 1A shows mean (+/- SEM) tumor volume (mm^3) of NCI-H358 tumor-bearing female NOD/SCID mice following daily oral dosing of either formula (10b), Compound A, or the combination of both test articles at the indicated dose levels from day 1 to 28.

[0481] As shown in **FIGs. 1A**, **1B**, and **1D** and **Tables 1 and 2**, treatment with formula (10b) alone suppressed the growth of the NCI-H358 tumors in a dose-dependent manner, leading to tumor growth inhibition (TGI) of 89% and 46% on study day 21 at 100 mg/kg QD and 50 mg/kg QD, respectively. Treatment with Compound A alone also suppressed the growth of the NCI-H358 tumors in a dose-dependent manner, with tumor regression observed at 100 mg/kg QD, 30 mg/kg QD, and 10 mg/kg QD. Notably, the combination of Compound A 10 mg/kg QD and formula (10b) 100 mg/kg QD more potently suppressed tumor growth as compared to either agent alone, causing tumor regression (**FIG. 1A**). Notable enhancement of anti-tumor activity was observed when formula (10b) 100 mg/kg QD was combined with Compound A at either 30 mg/kg and 100 mg/kg QD (**FIGs. 1B** and **1D**), likely due to the robust single agent response

from Compound A. All dosing conditions were considered well-tolerated, as shown by the maintenance of body weight of the mice during the study (**FIGs. 1C** and **1E**). Although random mouse loss was observed in this study, the mouse loss was not considered treatment related due to lack of dose dependency (**Table 3**).

Table 1: Overview of combination study of formula (10b) at 100 mg/kg and Compound A at 10 mg/kg.

Group (n=10)	Day 29		
	Mean tumor regression	Number of regressions	Mean body weight change
Vehicle	-	0/10	+5.1%
Formula (10b) 100 mg/kg QD	14%	8/10	-6.5%
Compound A 10 mg/kg QD	13%	9/10	-0.3%
Compound A 10 mg/kg QD + Formula (10b) 100 mg/kg QD	83%	10/10	-2.4%

Table 2: Endpoint TGI and plasma concentration at 2 hours after the final dose of Compound A (8 hours after the final dose of formula (10b)) from the study shown in FIGs. 1B-1E.

Treatments	Day 21 TGI (%)	Compound A Plasma concentration (μM)	Formula (10b) Plasma concentration (μM)
Vehicle	0%	BQL	BQL
Compound A 100 mg/kg QD	137%	8.77 ± 7.25	BQL
Compound A 30 mg/kg QD	126%	2.02 ± 0.31	BQL
Formula (10b) 100 mg/kg QD	89%	BQL	7.54 ± 1.60
Formula (10b) 50 mg/kg QD	46%	BQL	4.44 ± 1.05
Compound A 100 mg/kg QD+ Formula (10b) 100 mg/kg QD	136%	7.79 ± 3.40	5.41 ± 3.43
Compound A 100 mg/kg QD+ Formula (10b) 50 mg/kg QD	131%	9.20 ± 5.29	5.52 ± 1.46
Compound A 30 mg/kg QD+ Formula (10b) 100 mg/kg QD	133%	2.70 ± 0.92	8.27 ± 1.18

TGI%=(Ci-Ti)/(Ci-C_0) *100%. Ti and Ci are the mean tumor volumes of the treatment and vehicle groups on the measurement day, respectively; C_0 denotes the mean tumor volume of the vehicle group on Day 0. For plasma concentrations, data represent mean ± SD. N=4 mice/group. BQL, below quantitation limit (3 nM).

[0482] Pharmacokinetic analysis (**Table 2**) was conducted 2 hours after the final dose of Compound A, which was 8 hours after the final dose of formula (10b). Significant concentrations of Compound A in the plasma were detected, with 30 mg/kg giving rise to 2.0 μM, and 100 mg/kg giving rise to 8.8 μM at 2 hours after the final dose. Compound A plasma concentration was not impacted by treatment with formula (10b). Formula (10b) 100 mg/kg gave rise to similar significant plasma concentration when administered as a single agent (7.5 μM) and in combination with Compound A (5-10 μM), 8 hours after dosing. Formula (10b) 50 mg/kg dosing also resulted in similar significant plasma concentration when administered as a single agent (4.4 μM) and in combination with Compound A (5.5 μM), 8 hours after dosing. The data suggest no drug-drug interactions between Compound A and formula (10b) in mice.

Table 3: Summary of mouse morbidity in the efficacy study presented in FIGs. 1B-1E.

Treatment Groups	Mouse loss and observations (n=8 mice/group)
Vehicle	None
Compound A 100 mg/kg QD	None
Compound A 30 mg/kg QD	None
Formula (10b) 100 mg/kg QD	Day 18 (Found dead) Day 21 (Found dead)
Formula (10b) 50 mg/kg QD	Day 3 (BWL) Day 12 (BWL) Day 19 (BWL)
Compound A 100 mg/kg QD+ Formula (10b) 100 mg/kg QD	Day 8 (Found dead) Day 15 (Found dead) Day 16 (Found dead)
Compound A 100 mg/kg QD+ Formula (10b) 50 mg/kg QD	Day 15 (BWL) Day 17 (Found dead)
Compound A 30 mg/kg QD+ Formula (10b) 100 mg/kg QD	Day 10 (BWL)

Each event (mouse loss) indicates loss of one mouse, with the day indicating the dosing day on which the mouse was removed from the study. BWL, body weight loss; QD, dosed once every day.

D. CONCLUSIONS

[0483] In the NCI-H358 NSCLC xenograft model, which harbors a KRAS G12C mutation, treatment with formula (10b) in combination with Compound A robustly inhibited tumor growth. In detail, treatment with Compound A 10 mg/kg QD as a single agent resulted in tumor growth inhibition, and combination with formula (10b) resulted in tumor regression. Treatment with higher doses of Compound A (30 mg/kg QD or 100 mg/kg QD) as a single agent caused robust tumor regression; combination with formula (10b) did not notably further suppress tumor volume. Treatment with formula (10b) monotherapy at 100 mg/kg QD causes approximately tumor stasis. All treatment conditions tested are well tolerated in the mouse model.

Example 2: *In Vivo* Efficacy of the Combination of Formula (10b) and Sotorasib

A. MATERIALS

[0484] **Test article #1** - formula (10b):

[0485] Chemical name: 6-[(3S,4S)-4-amino-3-methyl-2-oxa-8-azaspiro [4.5] decan-8-yl]-3-(2,3-dichlorophenyl)-2,5-dimethyl-3,4-dihydropyrimidin-4-one

[0486] Molecular formula: $C_{21}H_{26}Cl_2N_4O_2$

[0487] Molecular weight: 437.37

[0488] **Test article #2** – Sotorasib:

[0489] CAS #: 2296729-00-3

[0490] Molecular formula: $C_{30}H_{30}F_2N_6O_3$

[0491] Molecular weight: 560.6

B. EXPERIMENTAL PROCEDURES

[0492] **Tumor Cell Line Culture.** The human NSCLC NCI-H358 cell line (Shanghai Institutes for Biological Sciences of Chinese Academy of Sciences) was maintained *in vitro* with RPMI-1640 medium (Gibco, catalog C22400500BT) supplemented with 10% heat inactivated fetal bovine serum (Gibco, catalog 10099-141C) in a 37°C chamber with 5% CO_2. Passage 9

NCI-H358 cells were thawed and expanded, and passage 13 cells were harvested for inoculations. The human NSCLC NCI-H2122 cell line (American Type Culture Collection) was maintained *in vitro* with RPMI-1640 medium (Gibco, catalog C22400500BT) supplemented with 10% heat inactivated fetal bovine serum (Gibco, catalog 10091-148) in a 37°C chamber with 5% CO_2. Passage 6 NCI-H2122 cells were thawed and expanded, and passage 14 cells were harvested for inoculations.

[0493] Animal Inoculations and Randomization. All experiments were reviewed and approved by the Crown Bioscience, Inc., Institutional Animal Care and Use Committee (IACUC) prior to execution and performed in accordance with the regulations of the Association for Assessment and Accreditation of Laboratory Animal Care (AAALAC). For the NCI-H358 study, 75 NOD/SCID female mice (Beijing Anikeeper Biotech Co., Ltd) at 6 to 8 weeks of age were inoculated subcutaneously in the right front flank region with NCI-H358 tumor cells ($5x10^6$ cells per mouse), suspended in a 1:1 ratio of PBS to Matrigel (Corning, catalog 354234) in a volume of 0.1 mL per mouse. Mice were randomized into four groups (10 mice/group) by tumor volume (size mm^3) 13 days post cell inoculation when the mean tumor volume was 160 mm^3. For the NCI-H2122 study, 80 BALB/c nude female mice (GemPharmatech Co., Ltd) at 6 to 8 weeks of age were inoculated subcutaneously in the right front flank region with NCI-H2122 tumor cells ($1x10^7$ cells per mouse), suspended in a 1:1 ratio of PBS to Matrigel (Corning, catalog 356234) in a volume of 0.1 mL per mouse. Mice were randomized into four groups (10 mice/group) by tumor volume (size mm^3) 9 days post cell inoculation when the mean tumor volume was 180 mm^3.

[0494] Dosing. Four groups of NCI-H358 tumor-bearing female NOD/SCID mice (10 animals/group) were administered one of the following treatment regimens 1) vehicle, 2) formula (10b) (100 mg/kg), 3) sotorasib (10 mg/kg), or 4) a combination of formula (10b) (100 mg/kg) and sotorasib (10 mg/kg) once daily by oral gavage for a period of 28 days. Four groups of NCI-H2122 tumor-bearing female BALB/c nude mice (10 animals/group) were administered one of the following treatment regimens 1) vehicle, 2) formula (10b) (100 mg/kg), 3) sotorasib (100 mg/kg), or 4) a combination of formula (10b) (100 mg/kg) and sotorasib (100 mg/kg) once daily by oral gavage for a period of 21 days.

[0495] Formula (10b) Formulation. Formula (10b) formulation buffer (0.5% v/v methyl cellulose in sterile deionized water) was prepared by weighing the desired amount of methyl cellulose (Sigma-Aldrich, catalog M0262, viscosity 400 cP) into a glass bottle. Sterile deionized water equivalent to 75% v/v of the intended final volume was added under continuous magnetic stirring with a stir bar and stirred at room temperature until complete dissolution. The buffer was then brought to the final volume with sterile deionized water. A correction factor of 1.025 was applied to the formula (10b) formulation to accommodate for the purity (97.7%).

[0496] Formula (10b) working suspensions of 10 mg/mL (10.25 mg/mL with correction factor) were prepared and administered at a 10 mL/kg dose volume by oral gavage to mice for the 100 mg/kg doses. To prepare formula (10b) formulations, compound was accurately weighed into a glass vial. Formula (10b) formulation buffer equivalent to 70% v/v of the intended final volume was added to the glass vial containing drug substance and mixed well using a 1/4-inch probe for 4 to 9 minutes until a homogeneous suspension was achieved with no large visible agglomerates/particles. The rest of the suspending vehicle was added to reach the intended final volume to the dispersion containing drug substance. The suspension was mixed well for 30 minutes, stored at 4°C for one week, and well mixed prior to and throughout dosing each day.

[0497] Sotorasib Formulation. Sotorasib formulation buffer (2% v/v HPMC / 1% v/v Tween 80 in sterile deionized water) was prepared by weighing the desired amount of HPMC (Sigma-Aldrich, catalog H3785) and Tween 80 (Sigma-Aldrich, catalog P4780) into a glass bottle. Sterile deionized water equivalent to 80% v/v of the intended final volume was added under continuous magnetic stirring with a stir bar and stirred at room temperature until complete dissolution. The buffer was then brought to the final volume with sterile deionized water.

[0498] Sotorasib working suspensions of 1 mg/mL and 10 mg/mL were prepared and administered at a 10 mL/kg dose volume by oral gavage to mice for the 10 mg/kg and 100 mg/kg doses, respectively. To prepare sotorasib formulations, compound was accurately weighed into a glass vial. Sotorasib formulation buffer equivalent to 100% v/v of the intended final volume was added to the glass vial containing drug substance and mixed well until a homogeneous suspension was achieved with no large visible agglomerates/particles. The suspension was mixed well and the working suspension was dosed as soon as possible. The suspension was prepared daily and well mixed prior to and throughout dosing.

[0499] Tumor and Body Weight Measurements. Tumor volumes were measured two times per week after randomization in two dimensions using a caliper, and the volume was expressed in mm^3 using the formula: Tumor volume = (length x width x width)/2, where length was defined as the longest tumor dimension and width was defined as the longest tumor dimension perpendicular to the length. Dosing as well as tumor and body weight measurements were conducted in a Laminar flow cabinet. Individual mouse tumor volumes (and mean tumor volumes (± standard error of the mean (SEM)) for each group were recorded. Tumor growth inhibition (TGI), an indicator of anti-tumor effectiveness, was calculated for each treatment (T) versus control (C) group using the day 1 (0) and indicated measurement day (i) mean tumor volume measurements with the formula: TGI (%) = (1 - (Ti-T0) / (Ci-C0)) x 100. TGI was calculated on the day after the last continuous daily dose (day 29) and only reported if ≤ 100%. Tumor regression (REG) was also assessed and defined as a tumor with a smaller tumor volume on the indicated day of the study compared to the first day of dosing on day 1. If the TGI was >100%, mean tumor regression was reported instead and calculated by determining the mean percentage of tumor regression on the day after the last continuous daily dose as indicated compared to the first dose on day 1.

[0500] Body weights (BW) were also recorded twice weekly. Individual mouse body weights and body weight change, expressed in percentage, were calculated for each animal using the day 1 (0) body weight on the first day of dosing and the body weight on the indicated (i) day after dosing using the following formula: BW change (%) = ((BWi/BW0) × 100) – 100. Mean body weight changes (± SEM) were recorded for group. Treatments were not considered tolerated if >20% of the mice in the group had ≥20% body weight loss or >20% of the mice in group spontaneously died or had any clinical signs of distress that required euthanasia.

[0501] Animal tumor and body weight measurement data were recorded and stored using Study Director™ software (version 3.1.399.19). All analyses were performed using GraphPad Prism software (version 9) or calculated from the raw data in Microsoft Excel.

[0502] Statistical analyses. Statistical analyses were performed with GraphPad Prism software (version 9). For statistical analyses comparing the vehicle group to all other groups, two-way repeated-measures analysis of variance (ANOVA) followed by post hoc Tukey's multiple comparisons test of the means was applied over the indicated number of days. For

statistical analyses comparing the monotherapy and combination groups, two-way repeated-measures ANOVA was performed between each monotherapy group mean and combination group mean over the number of indicated days. A p value of less than 0.05 was considered statistically significant.

[0503] Experimental Endpoints. Animal health was monitored at least twice weekly through behavioral observations and weight checks. After tumor inoculation, the animals were checked daily for morbidity and mortality. During routine monitoring, the animals were checked for any effects of tumor growth and treatments on behavior such as mobility, food and water consumption, body weight gain/loss, eye/hair matting, and any other abnormalities.

Study endpoint was defined when animals reached one of the following criteria for euthanasia: ≥20% body weight loss at any time versus day 1, ≥15% body weight loss for 72 hours versus day 1, individual tumor volume of ≥3000 mm^3, or all mice in each group were euthanized when the mean tumor volume reached ≥2000 mm^3. In the NCI-H358 study, animals in all groups were euthanized on day 34 or day 35 and in the NCI-H2122 study, animals in all groups were euthanized on day 21 or day 22.

C. RESULTS

[0504] Sotorasib (AMG 510) is a KRAS covalent inhibitor that specifically targets the KRAS G12C mutant. It has demonstrated single agent response in patients with solid tumors, including NSCLC, harboring KRAS G12C mutation. Specifically, in the CodeBreaK 100 study, the subgroup with NSCLC had a confirmed objective response rate (complete or partial response) of 32.2% and a disease control rate (objective response or stable disease) of 88.1%; the median progression-free survival was 6.3 months. Hong et al., *N. Engl. J. Med.* 2020; 383:1207-1217. Cell line studies have shown that SHP2 inhibitors increased KRAS-GDP occupancy and enhanced KRAS G12C inhibitor efficacy as the current generation of KRAS G12C inhibitors only inhibit the GDP-bound form of KRAS G12C. Unbiased functional genomics approaches have identified SHP2 as a vulnerability under KRAS G12C inhibition. The addition of SHP2 inhibition to therapeutics that target mutant KRAS G12C may improve efficacy in several ways. Because mutant KRAS G12C retains some level of cycling between these two states, the GTP-bound form of KRAS G12C can still activate ERK signaling in the presence of sotorasib. SHP2

inhibition decreases SOS1-dependent GTP loading of RAS, which leads to elevated RAS-GDP levels and may therefore enhance the efficacy of sotorasib. In addition, compensatory bypass signaling feedback activation of either upstream or downstream mediators of the RTK/MAPK pathway has been demonstrated to reduce effectiveness of KRAS G12C inhibitors both preclinically and clinically, and SHP2 inhibition may inhibit this feedback activation.

[0505] SHP2 inhibition may also enhance anti-tumor activity of KRAS G12C inhibitors in patients with molecular subtypes where outcomes have been particularly poor. For example, mutations in the tumor suppressor Kelch-like ECH-associated protein 1 (KEAP1) are found in approximately 20% of KRAS mutant NSCLC, and co-mutation of KRAS and KEAP1 is associated with poorer prognosis and clinical outcomes.

[0506] Two studies were performed to determine if the combination of the SHP2 inhibitor formula (10b) and sotorasib enhanced anti-tumor activity over either agent alone. Studies were performed with the NSCLC NCI-H358 cell line-derived xenograft model, which bears a KRAS G12C mutation and the NSCLC NCI-H2122 cell line-derived xenograft model, which bears KRAS G12C, KEAP1, and STK11 co-mutations.

[0507] **Treatment with the combination of formula (10b) and sotorasib resulted in tumor regressions in the NSCLC NCI-H358 subcutaneous xenograft model harboring a KRAS G12C mutation.** An *in vivo* study was conducted to evaluate the impact of formula (10b) in combination with the KRAS G12C inhibitor, sotorasib, on tumor volume in female NOD/SCID mice bearing the cell line-derived NCI-H358 NSCLC xenograft model, which harbors a KRAS G12C mutation. Female NOD/SCID mice were implanted subcutaneously with NSCLC NCI-H358 tumor cells. When tumors reached a mean size of 160 mm^3, mice were randomized into treatment groups (n=10 per group) and dosed by oral gavage once each day with the indicated levels of vehicle, 100 mg/kg formula (10b), 10 mg/kg sotorasib, or the combination of 100 mg/kg formula (10b) and 100 mg/kg sotorasib from day 1 to day 28. Mouse tumor volumes were measured twice weekly until day 34 and results are shown through day 29.

[0508] As shown in **FIG. 2A** and **Table 4**, the combination of formula (10b) and sotorasib showed significantly greater anti-tumor activity than treatment with either test article as monotherapy. Following once daily oral administration of formula (10b) (100 mg/kg) and

sotorasib (10 mg/kg) in combination, a statistically significant tumor volume reduction was observed in the combination group compared to both monotherapy groups (**FIG. 2A** and **Table 4**) and the day 29 mean tumor regression was significantly increased to 83% (**Table 4**). The results also showed that both formula (10b) and sotorasib had monotherapy anti-tumor activity at the tested dose levels. Following once daily oral administration of formula (10b) (100 mg/kg) or sotorasib (10 mg/kg), a statistically significant reduction in tumor volume compared to the vehicle group was observed for both treatment groups (**FIG. 2A** and **Table 4**), with day 29 mean tumor regressions of 14% and 13% for the formula (10b) and sotorasib monotherapy groups, respectively.

Table 4: Summary of Anti-tumor Activity of Formula (10b) and Sotorasib as Monotherapy and in Combination in NOD/SCID Mice Bearing NCI-H358 Subcutaneous Cell Line-Derived Tumors

Group (n=10)	Treatment	Dose Level (mg/kg)	Day 29				
			Mean Tumor Volume (mm^3) (± SEM)	Mean Tumor REG	p value vs Vehicle*	p value vs Formula (10b)**	p value vs Sotorasib**
1	Vehicle	-	574 (± 64)	-	-	-	-
2	Formula (10b)	100	138 (± 17)	14%	<0.0001	-	-
3	Sotorasib	10	139 (± 27)	13%	<0.0001	-	-
4	Formula (10b)	100	27 (± 3)	83%	<0.0001	<0.0001	0.0004
	Sotorasib	10					

Abbreviations: ANOVA=analysis of variance; NOD/SCID=non-obese diabetic/severe combined immunodeficiency; n=number; REG=regression; SEM=standard error of the mean.

Note: Daily oral dosing was performed from day 1 to day 28 and the last tumor measurement was performed on day 34. For the statistical analyses, 2-way repeated-measures ANOVA of group means from day 5 to 29 followed by post hoc Tukey's multiple comparisons test was performed for the vehicle group comparisons* and 2-way repeated-measures ANOVA of the monotherapy and combination group means from day 5 to 29 were performed for the combination group comparisons**.

[0509] As shown in **FIG. 2B**, there was no impact of the treatments on body weights and all treatments were well tolerated in the mouse model.

[0510] Treatment with the combination of formula (10b) and sotorasib results in tumor growth inhibition in the NSCLC NCI-H2122 subcutaneous xenograft model harboring KRAS G12C, KEAP1, and STK11 co-mutations. An *in vivo* study was conducted to evaluate

the impact of formula (10b) in combination with the KRAS G12C inhibitor, sotorasib, on tumor volume in BALB/c nude mice bearing the cell line-derived NCI-H2122 NSCLC xenograft model, which harbors a KRAS G12C mutation. The model also has several co-occurring mutations including a frameshift insertion in KEAP1 (KEAP1 A203fs), and a frameshift deletion in STK11 (STK11 G279fs), which cause loss of function of KEAP1 and STK11. When tumors reached a mean size of 180 mm^3, mice were randomized into treatment groups (n=10 per group) and dosed by oral gavage once each day with the indicated levels of vehicle, 100 mg/kg formula (10b), 100 mg/kg sotorasib, or the combination of 100 mg/kg formula (10b) and 100 mg/kg sotorasib from day 1 to day 21. Mouse tumor volumes and body weights were measured twice weekly until day 21.

[0511] As shown in **FIG. 3A** and **Table 5**, the combination of formula (10b) and sotorasib showed significantly greater anti-tumor activity than treatment with either test article as monotherapy. Following once daily oral administration of formula (10b) (100 mg/kg) and sotorasib (100 mg/kg) in combination, a statistically significant tumor volume reduction was observed in the combination group compared to both monotherapy groups (**FIG. 3A** and **Table 5**) and the day 21 tumor growth inhibition was significantly increased to 96% (**Table 5**). The results also showed that both formula (10b) and sotorasib had monotherapy anti-tumor activity at the tested dose levels. Following once daily oral administration of formula (10b) (100 mg/kg) or sotorasib (100 mg/kg), a statistically significant reduction in tumor volume compared to the vehicle group was observed for both treatment groups (**FIG. 3A** and **Table 5**), with day 21 tumor growth inhibition of 58% and 72% for the formula (10b) and sotorasib monotherapy groups, respectively (**Table 5**).

Table 5: Summary of Anti-tumor Activity of Formula (10b) and Sotorasib as Monotherapy and in Combination in BALB/c Nude Mice Bearing NCI-H2122 Subcutaneous Cell Line-Derived Tumors

Group (n=10)	Treatment	Dose Level (mg/kg)	Day 21				
			Mean Tumor Volume (mm^3) (± SEM)	TGI	p value vs Vehicle*	p value vs formula (10b)**	p value vs Sotorasib**
1	Vehicle	-	1149 (± 98)	-	-	-	-
2	Formula (10b)	100	590 (± 48)	58%	p<0.0001	-	-

3	Sotorasib	100	449 (± 47)	72%	p<0.0001	-	-
4	Formula (10b)	100	221 (± 12)	96%	p<0.0001	p<0.0001	p<0.0001
	Sotorasib	100					

Abbreviations: ANOVA=analysis of variance; BALB= Bagg Albino; n=number; SEM=standard error of the mean; TGI=tumor growth inhibition.

Note: Daily oral dosing was performed from day 1 to day 21 and the last tumor measurement was performed on day 21. For the statistical analyses, 2-way repeated-measures ANOVA of group means from day 3 to 21 followed by post hoc Tukey's multiple comparisons test was performed for the vehicle group comparisons* and 2-way repeated-measures ANOVA of the monotherapy and combination group means from day 3 to 21 were performed for the combination group comparisons**.

[0512] As shown in **FIG. 3B**, there was no impact of the sotorasib monotherapy or combination treatments on body weights and these treatments were well tolerated in the mouse model. Unexpectedly, several mice in the formula (10b) monotherapy group had body weight loss over 10%, therefore, the animals in this group were placed on diet gel from day 11 to day 21 (**FIG. 3B**). The cause of this weight loss is unknown and has not been observed in previous studies at this dose level (100 mg/kg). Importantly, formula (10b) was administered at the same dose level (100 mg/kg) in the combination group of formula (10b) and sotorasib, and the combination was well tolerated (**FIG. 3B**).

D. CONCLUSIONS

[0513] The results from these two *in vivo* studies demonstrate that formula (10b) in combination with sotorasib was well tolerated and showed a significant anti-tumor benefit in the mutant KRAS G12C NSCLC NCI-H358 cell line-derived xenograft model and the mutant KRAS G12C and KEAP1 A203fs NSCLC NCI-H2122 cell line-derived xenograft model. These *in vivo* studies support the clinical evaluation of the combination and show that SHP2 inhibition may potentiate the response of KRAS G12C inhibitors and increase the number of patients, with mutant KRAS G12C with or without co-mutations such as KEAP1 or STK11, that may benefit from formula (10b) as a potential treatment in combination with sotorasib.

Example 3: Efficacy of the Combination of Formula (10b) and Adagrasib (*In Vitro*)

A. METHODS

[0514] **Tumor Cell Line Culture.** The human Pancreatic Cancer MIA PaCa-2 cell line was maintained *in vitro* with DMEM medium (Gibco, catalog 11995065) supplemented with 10%

heat inactivated fetal bovine serum (Gibco, catalog 16140071) in a 37°C chamber with 5% CO_2. Passage 5 MIA PaCa-2 cells were harvested for inoculations. The human NSCLC NCI-H358 cell line was maintained *in vitro* with RPMI-1640 medium (Gibco, catalog 21875034) supplemented with 10% heat inactivated fetal bovine serum (Gibco, catalog 16140071) in a 37°C chamber with 5% CO_2. Passage 14 NCI-H358 cells were harvested for inoculations. Three-dimensional (3D) cancer organoid structures with extracellular matrix have been demonstrated to be physiologically relevant models. Therefore, the 3D cell viability assay was used to test a combination of Adagrasib (MRTX849) and formula (10b) with diverse KRAS G12C mutant cancer cell lines, including MIA PaCa-2 and NCI-H358. For 3D proliferation assays, 1,500 cells per well were mixed with 100% CULTREX (R&D systems, catalog 3700-100-01) and seeded into 96-well plates supplemented with Organoid Growth Medium to mimic the tumor microenvironment. The complete Organoid Growth Medium of Mia PaCa-2 was prepared by adding the following components to advanced DMEM/F-12: R-Spondin-1 (100 ng/ml), Noggin (100 ng/ml), Gastrin (10 nM), FGF 10 (100 ng/ml), EGF (50 ng/ml), A83-01 (500 nM), B27 supplement (1x), N-Acetylcysteine (1 mM), Nicotinamide (10 mM), GlutaMax (1x), HEPES (10 mM), Penicillin-Streptomycin (100 U/ml - 100 µg/ml), and Primocin (100µg/ml). The complete organoid culture medium of NCI H358 was prepared by adding the following components to advanced DMEM/F-12: R-Spondin-1 (100 ng/ml), Noggin (100 ng/ml), FGF 7 (25 ng/ml), FGF 10 (100 ng/ml), A83-01 (500 nM), Y-27632 (5 µM), SB202190 (1 µM), B27 supplement (1x), N-Acetylcysteine (1.25 mM), Nicotinamide (10 mM), GlutaMax (1x), HEPES (10 mM), Penicillin-Streptomycin (100 U/ml - 100 µg/ml), and Primocin (100 µg/ml). Twenty-four hours after seeding, cells were treated with Adagrasib (MRTX849) and formula (10b) at different final concentrations with serial dilution as shown in **Table 6**.

Table 6: Various Concentrations of Adagrasib (MRTX849) and Formula (10b)

Dilution	Concentration (µM)	
	Adagrasib (MRTX849)	**Formula (10b)**
1	2.00	10
2	0.40	2.5
3	0.080	0.625
4	0.016	0.15625

5	0.0032	0.03906
6	0.00064	0.00977
7	0.000128	0.00244

[0515] After 5 days of incubation, 3D Cell Titer-Glo (Promega, catalog G9683) assay was performed to determine cell viability and the IC50 values, data were fitted using the dose response algorithm in GraphPad Prism 9.4.0. Synergistic effects were evaluated using HSA response matrix and Loewe model analysis.

[0516] **Patient-derived organoid establishment, culture, and characterization**. Surgically resected tumor tissue was obtained from previously untreated CRC patient under informed consent (MT Group). After pathologist review, normal adjacent tissue was removed. CRC tumor cells were isolated through a combination of mechanical disruption and enzymatic digestion. Genomic DNA was isolated from tumor organoids for whole-exome sequencing to identify tumor-specific somatic mutations. CRC S002375 organoids were established, expanded, and maintained in the complete organoid culture medium with Matrigel/CULTREX. The complete organoid culture medium was prepared by adding the following components to advanced DMEM/F-12: R-Spondin-1 (200 ng/ml), Noggin (100 ng/ml), Gastrin (10 nM), EGF (50 ng/ml), A83-01 (500 nM), SB202190 (1 μM), B27 supplement (1x), N-Acetylcysteine (1.25 mM), Nicotinamide (10 mM), GlutaMax (1x), HEPES (10 mM), Penicillin-Streptomycin (100 U/ml - 100 μg/ml), and Primocin (100 μg/ml). For 3D proliferation assays, 1,000 cells per well were mixed with 10% CULTREX (R&D systems, catalog 3700-100-01) and seeded into 384-well ULA plates supplemented with Organoid Growth Medium. Twenty-four hours after seeding, cells were treated with Adagrasib (MRTX849) and formula (10b) at different final concentrations with serial dilution as shown in **Table 6**. After 5 days of incubation, 3D Cell Titer-Glo (Promega, catalog G9683) assay was performed to determine cell viability and the IC50 values, data were fitted using the dose response algorithm in GraphPad Prism 9.4.0. Synergistic effects were evaluated using HSA response matrix and Loewe model analysis.

B. RESULTS

[0517] **A combination therapy of KRAS G12C and SHP2 inhibition exerts stronger anti-tumor activity in KRAS G12C mutant cancer cells than monotherapy**. KRAS G12C mutant cell lines showed good sensitivity to Adagrasib and formula (10b) inhibition as shown in **Table**

7, **FIG. 5A**, and **FIG. 6A**. The combination treatment conferred stronger cytotoxic effects than KRAS G12C inhibition monotherapy or the SHP2 inhibition monotherapy as shown in **FIGs. 5B-5E** and **FIGs. 6B-6E**. The ability of patient-derived organoids (PDOs) to recapitulate morphological, genetic and phenotypic characteristics of the original tumor and resemble tumor heterogeneity makes them a powerful tool for deepen our understanding of disease biology, investigating the function of driver genes for cancer modeling, assessing specimens from individual patient for ex vivo personalized drug screening. As shown in **Table 7** and **FIGs. 7A-7E**, the synergistic effect of Adagrasib and formula (10b) was further confirmed in CRC PDOs. In summary, the *in vitro* and *ex vivo* data demonstrated the combination therapy of Adagrasib and formula (10b) inhibition induces stronger anti-tumor response than each monotherapy in Pancreatic Cancer, NSCLC and CRC.

Table 7: Summary of anti-tumor Activity of Adagrasib and Formula (10b) as Monotherapy and in Combination in MIA PaCa-2 and NCI-H358 Cell Lines, and S002375 CRC Patient-Derived Organoid Model

Model (n = 3)	Adagrasib IC50 (uM)	Formula 10b IC50 (uM)	Loewe Synergy Volume
MIA PaCa-2	0.003	1.645	5.763
H358	0.001	0.699	3.401
S002375	0.017	294.700	8.398

Example 4: Efficacy of the Combination of Formula (10b) and Adagrasib (*In Vivo*)

A. MATERIALS

[0518] **Test article #1** - formula (10b):

[0519] Chemical name: 6-[(3S,4S)-4-amino-3-methyl-2-oxa-8-azaspiro [4.5] decan-8-yl]-3-(2,3-dichlorophenyl)-2,5-dimethyl-3,4-dihydropyrimidin-4-one

[0520] Molecular formula: $C_{21}H_{26}Cl_2N_4O_2$

[0521] Molecular weight: 437.37

[0522] **Test article #2** – adagrasib (MRTX849):

[0523] CAS No. 2326521-71-3

[0524] Molecular formula: $C_{33}H_{35}ClFN_7O_2$

[0525] Molecular weight: 604.13

[0526] **Cell lines**. KRAS G12C MiaPaCa (pancreatic cancer), NCI-H2122 (lung cancer), and SW837 (colorectal cancer) cell lines are used. SW837 cells are cultured in RPMI 1640 +10% fetal bovine serum, MIAPaCa-2 cells are cultured in DMEM + 10% fetal bovine serum, and NCI-H2122 cells are cultured in RPMI-1640 + 10% fetal bovine serum. All three cell lines are cultured in 37°C tissue culture incubator with 5% CO_2.

[0527] **Test animals.** Female immunocompromised mice are utilized in these experiments. Animals are 5 to 12 weeks of age at the time of xenograft implantation. The protocol and any procedures involving the care and use of animals in this study is reviewed and approved by the Institutional Animal Care and Use Committee prior to study start.

[0528] All animals are maintained under the supervision and care of veterinary staff. Monitoring takes place daily. Mice have free access to standard chow and water with light 12-hour on/12-hour off.

B. EXPERIMENTAL PROCEDURES

[0529] **Formulation.** Formula (10b) is prepared in 0.5% methylcellulose and is stored at 4 °C for future use.

[0530] Adagrasib (MRTX849) is formulated as previously described, for example as a free base and resuspended as a solution in 10% Captisol and 50 mmol/L citrate buffer, pH 5.0.

[0531] ***In vivo* growth, treatment and data analysis.** For xenograft studies, sterile cells are suspended in sterile media or PBS that may contain 50% Matrigel. A volume of 50-200 µL is injected subcutaneously into the flank of female mice 5~12 weeks of age. Tumor size measurement is performed with caliper and calculated using a standard formula, for example: length x width^2/2, where length and width are the long and short diameters of the tumor, respectively.

[0532] When the average tumor volume reaches approximately 100 to 300 mm^3, mice are randomized into groups on both tumor volume and body weight. The mice are then assigned to one of the following treatments in the table below. The adagrasib dose in the range of 1 to 100 mg/kg PO QD that yields tumor stasis is selected for combinations.

Group	Treatment
A	Control
B	Formula (10b) 1-100 mg/kg QD
C	Adagrasib 1-100 mg/kg QD
D	Formula (10b) (1-100 mg/kg QD) + Adagrasib (1-100 mg/kg QD)

[0533] Dosing starts once tumor volumes reach between approximately 100 and 300 mm^3. Amount of compound administered is based on individual mouse body weight to achieve the planned mg/kg dose. Tumor volume is measured twice a week. The body weight and tumor volume are captured in study records. Dosing and body weight and tumor volume data collection continues until the vehicle control group tumor volume is at least 1,000 mm^3.

[0534] Data are analyzed using commercial graphing and statistical analysis software packages. Body weight change and tumor growth inhibition (TGI) are reported.

Example 5: A Clinical Study of the SHP2 Inhibitor Compound (10b) in Combination with a KRAS G12C inhibitor in Patients with Solid Tumors

[0535] A clinical study of the SHP2 inhibitor Compound (10b) in combination with a KRAS G12C inhibitor (e.g., a KRAS G12C inhibitor other than sotorasib) can be performed. Subjects of the study have a solid tumor such as non-small cell lung cancer (NSCLC), optionally the NSCLC is characterized by a KRAS mutation (e.g., a KRAS mutation other than a Q61 mutation, such as a mutation at codon 12 or 13). The subject may have previously completed a standard of care treatment.

[0536] The clinical study may include a dose escalation phase to evaluate the safety, tolerability, and recommended phase 2 dose (RP2D) of Compound (10b) when used in combination with the KRAS G12C inhibitor. Additional objectives for the dose escalation study may include assessment of preliminary antitumor activity of Compound (10b) in combination

with the KRAS G12C inhibitor (as defined by objective response rate [ORR, complete response (CR) + partial response (PR) rate], duration of response [DOR], and progression free survival [PFS] according to Response Evaluation Criteria in Solid Tumors (RECIST) v1.1, and as assessed by investigator, and overall survival [OS]); characterization of the pharmacokinetics (PK) of Compound (10b) and the KRAS G12C inhibitor given in combination (e.g., area under the curve [AUC], maximum drug concentration [C_{max}], time to C_{max} [T_{max}], half-life) of Compound (10b) and the KRAS G12C inhibitor from plasma or serum concentration-time data); characterization of circulating and intratumoral target engagement (pharmacodynamic activity) of Compound (10b) in combination with the KRAS G12C inhibitor (e.g., raw, normalized, and/or baseline adjusted analyte signal in circulating and intratumoral target engagement biomarkers of Compound (10b) activity in combination with the KRAS G12C inhibitor); and characterization of the immunogenicity of the KRAS G12C inhibitor when given in combination with Compound (10b). Peripheral and intratumoral biomarkers may also be assessed. The dose escalation phase may include, e.g., 5-10 patients.

[0537] The clinical study may also include a dose expansion/optimization period to evaluate the antitumor activity of Compound (10b), as defined by the ORR (per investigator) according to RECIST v1.1, when used in combination with the KRAS G12C inhibitor in subjects (e.g., subjects with advanced NSCLC with a KRAS mutation who have failed standard of care treatment). Additional objectives for the dose expansion/optimization study may include assessment of additional measures of antitumor activity of Compound (10b) in combination with the KRAS G12C inhibitor, including ORR (per blinded independent central review [BICR]) and DOR and PFS (per investigator and BICR), as defined by RECIST v1.1, and OS; assessment of safety and tolerability of Compound (10b) at the RP2D, in combination with the KRAS G12C inhibitor; characterization of the PK of Compound (10b) and the KRAS G12C inhibitor given in combination; characterization of circulating and intratumoral target engagement (pharmacodynamic activity) of Compound (10b) in combination with the KRAS G12C inhibitor; and characterization of the immunogenicity of the KRAS G12C inhibitor when given in combination with Compound (10b). Peripheral and intratumoral biomarkers may also be assessed. The dose expansion/optimization phase may include, e.g., 10-30 patients.

[0538] The KRAS G12C inhibitor used in the clinical study may be, for example, adagrasib (MRTX-849), MRTX1257, ARS-853, ARS-1620, JNJ-74699157(ARS-3248), LY3537982, or LY3499446. The KRAS G12C inhibitor may be administered orally.

[0539] Compound (10b) is as described herein. Compound (10b) may be administered as oral capsules of, e.g., 50 and 100 mg.

[0540] Subjects in the study may have had had at least one previous line of treatment which included platinum-based doublet chemotherapy and anti-PD-(L)1 therapy, either given as one line or individual lines of therapy. Subjects in the study may have a solid tumor, such as a solid tumor characterized by a KRAS mutation (e.g., a mutation in codon 12 or 13, as described herein). For examples, subjects in the study may have NSCLC with a KRAS mutation.

Inclusion Criteria

[0541] Patients participating in the clinical study will meet the inclusion criteria listed below (as applicable):

1. Individuals ≥18 years old and be willing and able to provide signed informed consent at the Screening visit as well as comply with all study visits and requirements through the end of the study.
2. Have documentation of a KRAS-G12C mutation from local or central laboratory testing in tumor or liquid biopsy samples, collected within 2 years prior to screening, and have no other previously identified targetable driver mutations (i.e., epidermal growth factor receptor [EGFR], anaplastic lymphoma kinase [ALK], ROS1).
3. Have measurable disease by RECIST v1.1.
4. Have a minimum life expectancy of >12 weeks after the start of study treatment according to the investigator's judgement.
5. Women of childbearing potential MUST have a negative serum human chorionic gonadotropin test during screening and within 48 hours of initiating dosing or have had a hysterectomy, bilateral salpingectomy or bilateral oophorectomy, or have had menopause (defined as 12 consecutive months of amenorrhea and confirmed by follow up hormone level assessment).

6. Patients of childbearing potential must use 2 methods of contraception for the duration of the study and for at least 90 days after the last dose of study treatment for female patients or 105 days after the last dose of study treatment for male patients, whichever is later for the individual patient. Female patients should not become pregnant or breastfeed while on this study. Female and male patients must also agree not to donate eggs (ova, oocytes) or sperm for the purpose of reproduction for at least 90 days or 105 days after the last dose of study treatment, respectively. Acceptable methods of contraception are fully described in Appendix 2.
7. Patients must have an Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0-1 (see Appendix 1) with no deterioration over the previous 2 weeks.

Phase 1a Dose Escalation Only

8. Have histologically documented, locally advanced and unresectable, or metastatic solid tumor with KRAS-G12C mutation whether naïve to KRAS-G12C inhibitor treatment or not.
9. Have progression or disease recurrence on or after all available standard of care treatments.

Phase 1b Dose Expansion/Optimization Only

10. Have histologically documented, locally advanced and unresectable, or metastatic NSCLC, naïve to treatment with KRAS-G12C inhibitor.
11. Have progression or disease recurrence on or after at least one prior line of systemic therapy, which must include platinum-based doublet chemotherapy OR anti-PD-(L)1 therapy, OR both given together as one line or as individual lines of therapy.

Exclusion Criteria

[0542] Patients who meet any of the exclusion criteria listed below will not be eligible for participation in the study.

1. Have participated in an interventional clinical study within the last 4 weeks OR, if applicable, be within 5 times the half-life of the investigational study drug(s), whichever is lesser, prior to the Cycle 1 Day 1 visit. Patients should always adhere to other eligibility criteria that apply to specified concomitant medication regarding washout periods as specified below.

2. Have received radiotherapy or proton therapy with a limited field of radiation for palliation within 1 week of the start of study treatment, OR radiation to more than 30% of the bone marrow or with a wide field of radiation within 4 weeks of the start of study treatment.
3. Have taken any of the following:
    a. Strong or moderate inducers or inhibitors of cytochrome P450 (CYP) 3A4 or P-glycoprotein (P-gp) inducers (including herbal supplements or food products containing grapefruit juice, star fruit, or Seville oranges) within 14 days or 5 half-lives (whichever is longer) of Cycle 1 Day 1, and/or
    b. Use of known cytochrome P450 (CYP) 3A4 and P-glycoprotein (P-gp) sensitive substrates (with a narrow therapeutic window), within 14 days or 5 half lives of the drug or its major active metabolite, whichever is longer, prior to study day 1, and/or
    c. Acid reducing agents, such as proton pump inhibitors (PPIs) or H2 receptor antagonists within 14 days or 5 half-lives (whichever is longer) of Cycle 1 Day 1.
4. Have inadequate organ function as defined below:

    <u>Hematological</u>
    a. Absolute neutrophil count <1,500/μL
    b. Platelets <100,000/μL
    c. Hemoglobin <9 g/dL without transfusion for ≤2 weeks or erythropoiesis-stimulating agents (e.g., Epo, Procrit) for ≤6 weeks

    <u>Renal</u>
    d. Serum creatinine > 1.5 × ULN, unless creatinine clearance ≥ 40 mL /min (measured or calculated using the Cockcroft-Gault formula)

    <u>Hepatic</u>
    e. Serum total bilirubin ≥2× institutional upper limit of normal (ULN) or ≥3.0× institutional ULN if the patient has a diagnosis of Gilbert syndrome or hemolytic anemia as confirmed by the investigator
    f. Aspartate aminotransferase/serum glutamic-oxaloacetic transaminase (AST/SGOT) and/or alanine aminotransferase/serum glutamic-pyruvic transaminase (ALT/SGPT) >2.5×ULN

    <u>Coagulation</u>

g. International normalized ratio (INR) or prothrombin time (PT) >1.5×ULN unless the patient is receiving anticoagulant therapy and as long as PT or activated partial thromboplastin time (aPTT) is within the therapeutic range of intended use of anticoagulants.

h. Activated partial thromboplastin time >1.5×ULN unless the patient is receiving anticoagulant therapy and as long as PT or aPTT is within the therapeutic range of intended use of anticoagulants.

5. Have active Hepatitis B infection (defined by the presence of hepatitis B surface antigen [HBsAg] or the presence of hepatitis B virus [HBV] DNA), hepatitis C infection (defined by the presence of hepatitis C virus [HCV] antibody and positive HCV RNA), or human immunodeficiency virus (HIV) infection with measurable viral load.

6. Have a life-threatening illness, medical condition, active uncontrolled infection, or organ system dysfunction (such as ascites, coagulopathy, or encephalopathy), or other reasons which, in the investigator's opinion, could compromise the participating patient's safety, or interfere with or compromise the integrity of the study outcomes.

7. Have any of the following cardiac-related issues or findings:

a. History of significant cardiovascular disease, such as cerebrovascular accident, myocardial infarction or unstable angina, within the last 6 months before starting study treatment.

b. Clinically significant cardiac disease, including New York Heart Association Class II or higher heart failure.

c. History of left ventricular ejection fraction (LVEF) <50% within the previous 12 months before starting study treatment.

d. Resting corrected QT interval Fridericia (QTcF) >470 msec, derived as the averaged from three electrocardiograms (ECGs), using the ECG machines provided by the sponsor for study purposes.

e. Any clinically significant abnormalities in rhythm, conduction, or morphology of resting ECG (e.g., third degree heart block, Mobitz Type II heart block, ventricular arrhythmias, uncontrolled atrial fibrillation).

8. Have a diagnosis of another invasive malignancy within the previous 3 years from time of informed consent other than curatively treated non-melanomatous skin cancer, superficial urothelial carcinoma, in situ cervical cancer, or any other curatively treated or closely monitored malignancy that is not expected to require treatment for recurrence or progress during the course of the study.
9. Have untreated brain metastases from non-brain tumors. Patients who have had brain metastases resected or have received radiation therapy ending at least 4 weeks prior to Cycle 1, Day 1 are eligible if they meet all of the following criteria prior to first dose of study medication: a) residual neurological symptoms related to the CNS treatment Grade ≤2; b) on a stable or decreasing dose of ≤ 10 mg daily prednisone (or equivalent) for at least 2 weeks prior to Cycle 1, Day 1; and c) follow-up magnetic resonance imaging (MRI) within 4 weeks prior to Cycle 1, Day 1 shows no new lesions appearing.
10. Have undergone major surgery within 4 weeks prior to study enrollment.

    Note: This does not include patients who have had procedures such as peripherally inserted central catheter line placement, thoracentesis, paracentesis, biopsies, or abscess drainage.
11. Have a history of hypersensitivity to a KRAS G12C inhibitor or Compound (10b), active or inactive excipients of a KRAS G12C inhibitor or Compound (10b) or drugs with a similar chemical structure or class to either a KRAS G12C inhibitor or Compound (10b), dependent on which combination the patient could receive.
12. Have tumors harboring known activating mutations in BRAF V600X, PTPN11 (SHP2), or KRAS Q61X.
13. Have previously received a SHP2 inhibitor (e.g., TNO-155, RMC-4630, RLY-1971, JAB-3068, JAB-3312 or PF-07284892).
14. Have gastrointestinal illness that, in the opinion of the investigator, would preclude absorption of Compound (10b) and/or the KRAS G12C inhibitor (e.g., post gastrectomy, short bowel syndrome, uncontrolled Crohn's disease, celiac disease with villous atrophy, or chronic gastritis).
15. Are on dialysis.
16. Have a history of allogenic bone marrow transplant.

17. Are unable to swallow oral medications (capsules, tablets) without chewing, breaking, crushing, opening, or otherwise altering the product dosage form.

Study Design

[0543] A study may include an initial screening period (e.g., a 30 day screening period), followed by a treatment period including multiple consecutive treatment cycles and a subsequent post-treatment follow up period. Dosing may continue for 1 or more years unless a patient is discontinued from study treatment or withdrawn from the study.

[0544] A dose escalation phase of a clinical study may follow a Bayesian optimal interval (BOIN) design. Three dose levels of Compound (10b) may be used in the dose escalation study, such as 250 mg, 400 mg, and 550 mg. The KRAS G12C inhibitor will be administered in combination with Compound (10b) at appropriate dosing, such as dosing approved by the Food and Drug Administration. Such dosing may be, e.g., between about 10-2000 mg daily. The dose escalation phase will be used to determine an RP2D that will be used in the dose escalation phase of the study.

[0545] In a dose expansion/optimization phase of a clinical study, subjects will receive compound (10b) at the RP2D from the dose escalation phase in combination with the KRAS G12C inhibitor. Depending on the results of the expansion/optimization phase, one or more additional cohorts including dosing of Compound (10b) at different dosing levels may be used.

[0546] Dosing of compound (10b) or the KRAS G12C inhibitor may be adjusted, e.g., in the event of drug-related adverse events.

[0547] **FIG. 8** shows a clinical study of the SHP2 Inhibitor Compound (10b) in combination with a KRAS G12C inhibitor in patients with solid tumors. The study design includes a dose escalation and a dose expansion/optimization.

[0548] **FIG. 9** shows a flowchart for a trial conducted using the BOIN Design. Abbreviations: BOIN=Bayesian optimal interval design; DLT=dose limiting toxicity; MTD=maximum tolerated dose. Note: $\lambda e = 19.7\%$ and $\lambda d = 29.8\%$. In practice, with 6 patients/cohort, if the DLT rate is $\leq 1/6$ then escalate the dose, if the DLT rate is $\geq 2/6$ then de-escalate the dose.

[0549] Although the foregoing disclosure has been described in some detail by way of illustration and example for purposes of clarity of understanding, one of skill in the art will appreciate that certain changes and modifications may be practiced within the scope of the appended claims. In addition, each reference provided herein is incorporated by reference in its entirety to the same extent as if each reference was individually incorporated by reference. Where a conflict exists between the instant application and a reference provided herein, the instant application shall dominate.

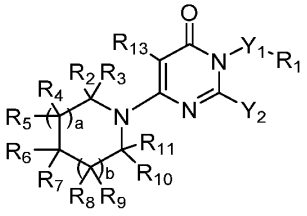
WHAT IS CLAIMED IS:

1. A method of treating cancer in a subject, comprising administering to the subject:

a) a therapeutically effective amount of a PTPN11 inhibitor; and

b) a therapeutically effective amount of a KRAS G12C inhibitor,

wherein the PTPN11 inhibitor is represent by formula (I):



(I),

or a pharmaceutically acceptable salt, hydrate, solvate, stereoisomer, conformational isomer, tautomer, or a combination thereof,

wherein:

subscript a is 0 or 1;

subscript b is 0 or 1;

Y_1 is a direct bond or $CR_{17}R_{18}$;

Y_2 is selected from the group consisting of C_{1-4}alkyl, amino, C_{1-4}alkylC(O)O-, C_{1-4}alkylamino and C_{1-4}aminoalkyl;

R_1 is selected from the group consisting of C_{6-10}aryl, C_{3-8}cycloalkyl, C_{3-8}cycloalkenyl, and a 5-10 membered heteroaryl group having 1 to 4 heteroatoms or groups as ring vertices independently selected from N, C(O), O, and S; said aryl or heteroaryl of R_1 is unsubstituted or substituted with 1 to 5 R_{12} groups independently selected from the group consisting of halo, hydroxy, amino, C_{1-4}alkylamino, di(C_{1-4}alkyl)amino, cyano, C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}hydroxyalkyl, C_{1-4}haloalkyl, C_{1-4}aminoalkyl, C_{3-8}cycloalkyl, C_{3-8}cycloalkenyl, $NR_{15}C(O)R_{14}$, $NR_{15}C(O)OR_{14}$, $NR_{14}C(O)NR_{15}R_{16}$, $NR_{15}S(O)R_{14}$, $NR_{15}S(O)_2R_{14}$, $C(O)NR_{15}R_{16}$, $S(O)NR_{15}R_{16}$, $S(O)_2NR_{15}R_{16}$, $C(O)R_{14}$, $C(O)OR_{14}$, OR_{14}, SR_{14}, $S(O)R_{14}$, and $S(O)_2R_{14}$;

R_2, R_3, R_{10}, and R_{11} are each independently selected from the group consisting of hydrogen, C_{1-4}alkyl, and C_{3-8}cycloalkyl;

R_4, R_5, R_8, and R_9 are each independently selected from the group consisting of hydrogen, cyano, C_{1-4}alkyl, C_{1-4}alkoxy, amino, hydroxy, C_{3-8}cycloalkyl, halo, and C_{1-4}alkylamino;

R_6 is selected from the group consisting of amino, C_{1-4}aminoalkyl, and C_{1-4}alkylamino;

R_7 is selected from the group consisting of hydrogen, amido, cyano, halo, and hydroxy, or is selected from the group consisting of C_{1-4}alkyl, C_{1-4}hydroxyalkyl, C_{3-6}cycloalkyl, phenyl, and 5- or 6- membered heteroaryl, any of which is unsubstituted or substituted with 1 to 5 groups independently selected from the group consisting of amino, halo, hydroxy, cyano, C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}haloalkyl, C_{1-4}haloalkoxy, C_{1-4}alkylamino, and C_{1-4}aminoalkyl;

or R_6 and R_7 together with the carbon atom to which they are both attached form a 3- to 7-membered saturated or unsaturated ring, having 0 to 3 heteroatoms or groups as ring vertices independently selected from N, C(O), O, and $S(O)_m$; subscript m is 0, 1, or 2; and said saturated or unsaturated ring formed by R_6 and R_7 is unsubstituted or substituted with 1 to 3 groups independently selected from the group consisting of amino, halo, hydroxy, cyano, C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}haloalkyl, C_{1-4}haloalkoxy, C_{1-4}alkylamino and C_{1-4}aminoalkyl;

any two groups of R_2, R_3, R_4, R_5, R_7, R_8, R_9, R_{10} and R_{11} can form a 5 to 6 membered ring, having 0 to 2 heteroatoms as ring vertices elected from N, O and S;

any two groups of R_2, R_4, R_6, R_8 and R_{10} can form a direct bond, or a 1 or 2 atom carbon bridge;

R_{13} is selected from the group consisting of hydrogen, halo, cyano, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}hydroxyalkyl, C_{1-6} dihydroxyalkyl, -NH-NHR_{19}, -NHR_{19}, -OR_{19}, -$NHC(O)R_{19}$, -$NHC(O)NHR_{19}$, -$NHS(O)_2NHR_{19}$, -$NHS(O)_2R_{19}$, -$C(O)OR_{19}$, -$C(O)NR_{19}R_{20}$, -$C(O)NH(CH_2)_qOH$, -$C(O)NH(CH_2)_qR_{21}$, -$C(O)R_{21}$, -NH_2, -OH, -$S(O)_2NR_{19}R_{20}$, C_{3-8}cycloalkyl, aryl, heterocyclyl having 1-5 heteroatoms as ring vertices selected from N, O, S and P, and heteroaryl having 1-5 heteroatoms as ring vertices selected from N, O, S and P; subscript q is an integer of from 0 to 6; and each of aryl, heteroaryl, heterocyclyl and cycloalkyl of R_{13} is unsubstituted or substituted with 1 to 3 groups independently selected from the group consisting of C_{1-4}alkyl, –OH, -NH_2, -OR_{21}, halo, cyano, and oxo;

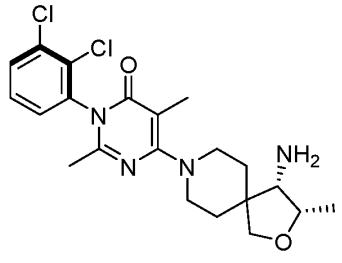
R_{14}, R_{15} and R_{16} are each independently selected from the group consisting of hydrogen, C_{1-4}alkyl, C_{3-8}cycloalkyl, C_{6-10}aryl and 5-10 membered heteroaryl, any of which is unsubstituted or substituted with one or more groups independently selected from the group consisting of amido, amino, halo, hydroxy, cyano, C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}haloalkyl, C_{1-4}haloalkoxy, C_{1-4}alkylamino and C_{1-4}aminoalkyl;

R_{17} and R_{18} are each independently selected from the group consisting of hydrogen, C_{1-4}alkyl, and CF_3;

R_{19} and R_{20} are each independently selected from the group consisting of hydrogen, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}hydroxyalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl and C_{3-6}cycloalkyl; and

each R_{21} is independently selected from the group consisting of hydrogen, -OH, C_{1-6} alkyl, C_{1-6}haloalkyl, C_{1-6}hydroxyalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl and C_{3-6}cycloalkyl,

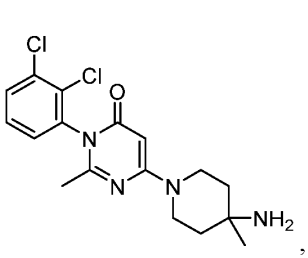
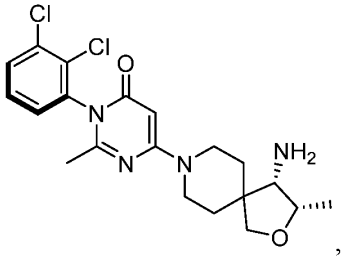
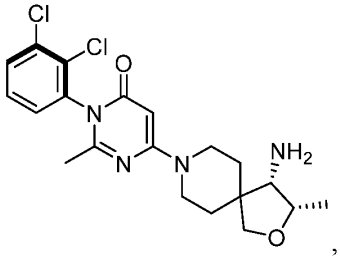
provided that when the PTPN11 inhibitor is represented by formula (10b):

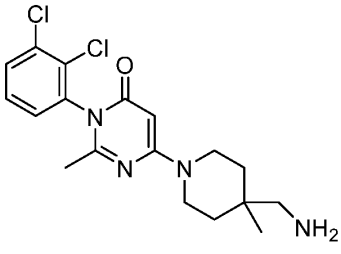
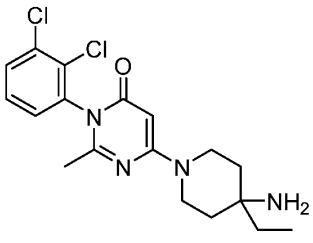
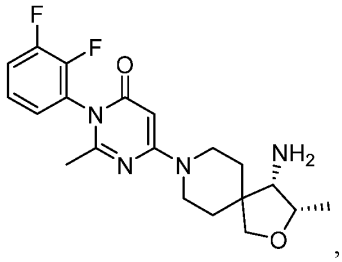


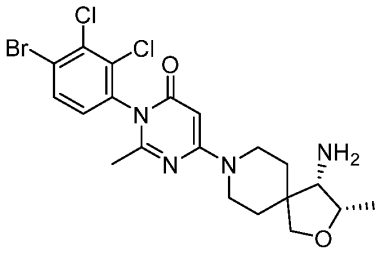
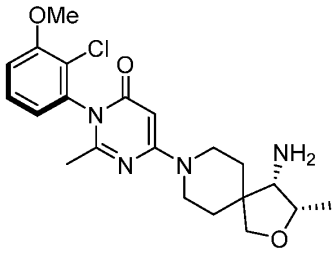
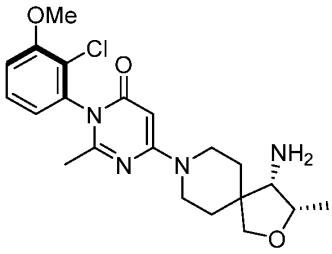
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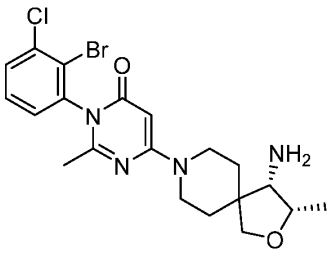
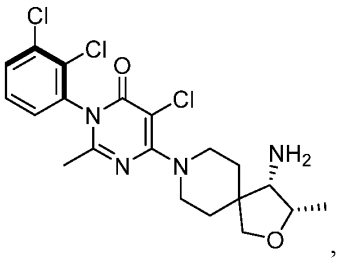
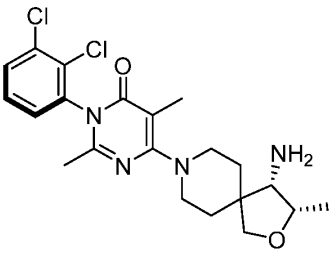
the KRAS G12C inhibitor is not sotorasib.

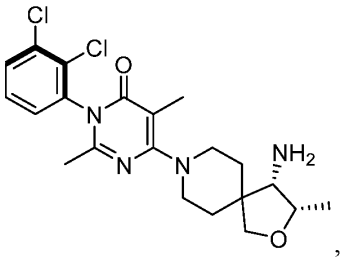
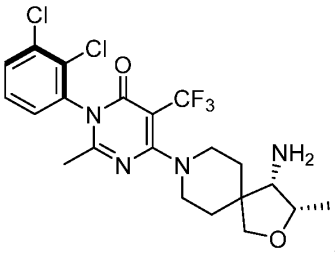
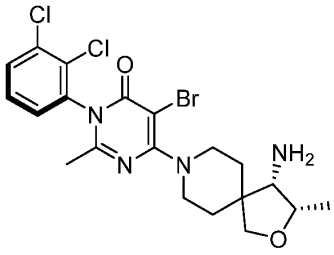
2. The method of claim **1**, wherein the PTPN11 inhibitor is selected from the group consisting of:

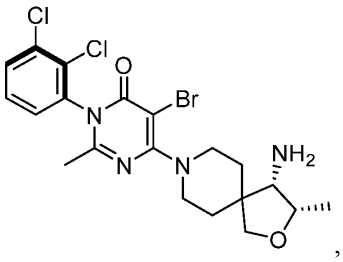
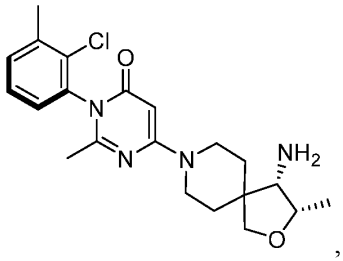
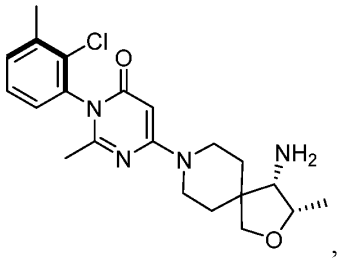
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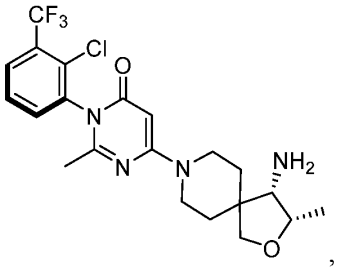
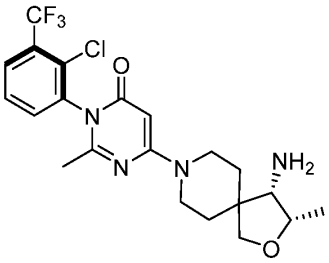
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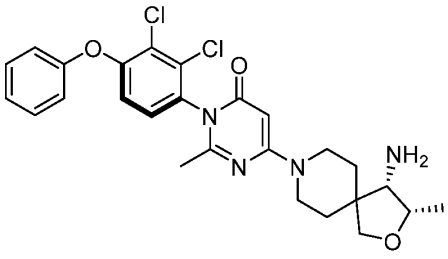
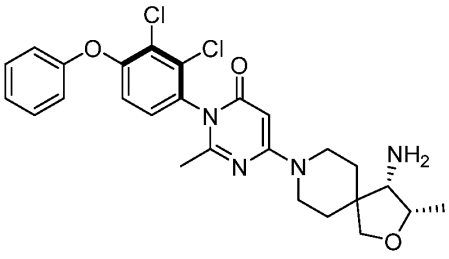
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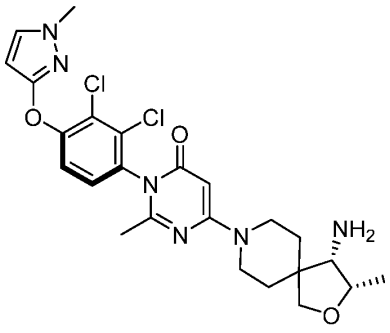
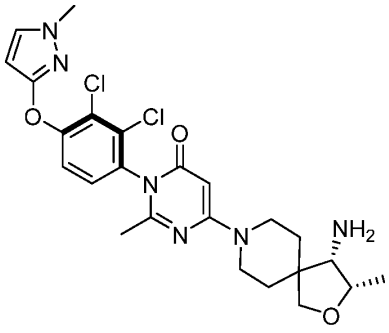
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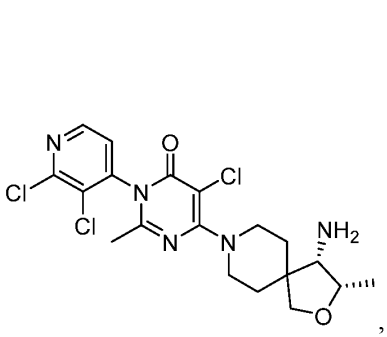
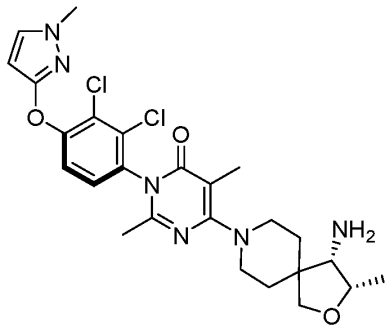
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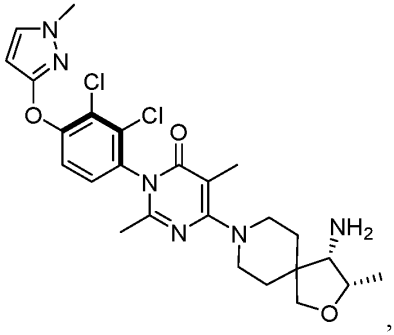
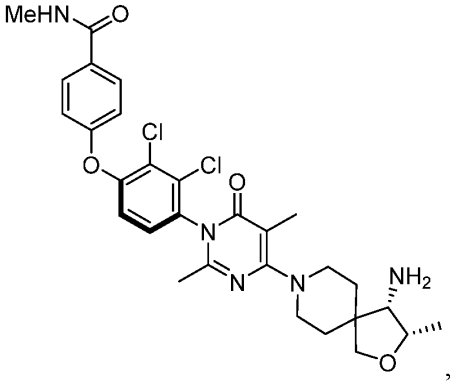
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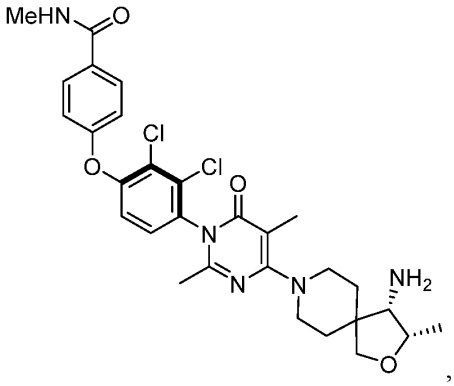
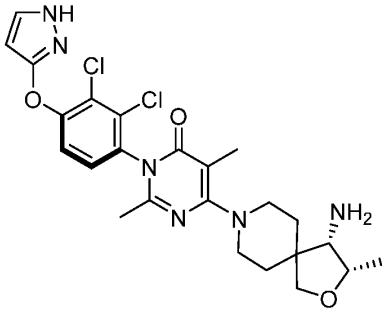
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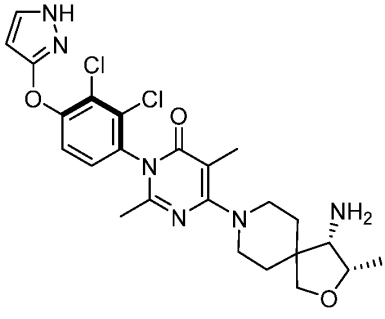
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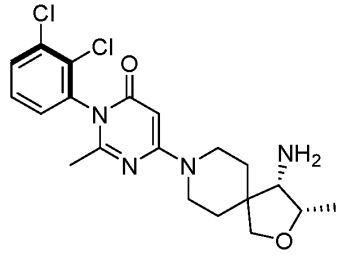
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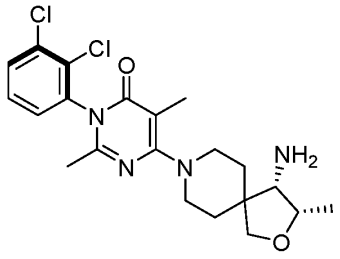
3. The method of claim **1** or **2**, wherein the PTPN11 inhibitor is represented by formula (2b):



(2b),

having the name of 6-((3*S*,4*S*)-4-amino-3-methyl-2-oxa-8-azaspiro[4.5]decan-8-yl)-3-(R_a)-(2,3-dichlorophenyl)-2-methylpyrimidin-4(3*H*)-one.

4. The method of claim **1** or **2**, wherein the PTPN11 inhibitor is represented by formula (10b):



(10b),

having the name of 6-((3*S*,4*S*)-4-amino-3-methyl-2-oxa-8-azaspiro[4.5]decan-8-yl)-3-(R_a)-(2,3-dichlorophenyl)-2,5-dimethylpyrimidin-4(3*H*)-one.

5. The method of any one of claims **1** to **4**, wherein the KRAS G12C inhibitor is sotorasib (AMG 510), adagrasib (MRTX-849), MRTX1257, ARS-853, ARS-1620, JNJ-74699157 (ARS-3248), JDQ443, GDC-6036, JAB-21822, BI 1823911, MK-1084, LY3537982, or LY3499446, provided that, when the PTPN11 inhibitor is represented by formula (10b), the KRAS G12C inhibitor is other than sotorasib.

6. The method of claim **5**, wherein the KRAS G12C inhibitor is adagrasib (MRTX-849).

7. The method of any one of claims **1** to **6**, wherein the cancer is characterized by a KRAS G12C mutation.

8. The method of any one of claims **1** to **7**, wherein the cancer comprises a solid tumor.

9. The method of any one of claims **1** to **8**, wherein the cancer is lung cancer, colorectal cancer, pancreatic cancer, urothelial carcinoma, stomach cancer, mesothelioma, or a combination thereof.

10. The method of claim **9**, wherein the cancer is non-small cell lung cancer (NSCLC).

11. The method of claim **9**, wherein the cancer is colorectal cancer.

12. The method of any one of claims **1** to **11**, wherein the cancer is a KRAS G12C-positive cancer resistant to a KRAS G12C inhibitor.

13. The method of any one of claims **1** to **12**, wherein the cancer is a KRAS G12C-positive cancer characterized by intrinsic and/or acquired resistance to a KRAS G12C inhibitor.

14. The method of any one of claims **1** to **13**, wherein the cancer is a KRAS G12C-positive cancer resistant to sotorasib (AMG 510), adagrasib (MRTX-849), MRTX1257, ARS-853, ARS-1620, JNJ-74699157 (ARS-3248), JDQ443, GDC-6036, JAB-21822, BI 1823911, MK-1084, LY3537982, or LY3499446.

15. The method of claim **14**, wherein the cancer is a KRAS G12C-positive cancer resistant to sotorasib (AMG 510).

16. The method of claim **14**, wherein the cancer is a KRAS G12C-positive cancer resistant to adagrasib (MRTX-849).

17. The method of any one of claims **1** to **16**, wherein the cancer has progressed or recurred on or after at least one prior line of a systemic therapy comprising a platinum-based doublet chemotherapy and/or an anti-PD-1/PD-L1 therapy, each of which is given in monotherapy or both of which are given in combination therapy.

18. The method of any one of claims **1** to **17**, wherein the subject does not have an activating mutation in BRAF V600X, PTPN11 (SHP2), or KRAS Q61X.

19. The method of any one of claims **1** to **18**, wherein the subject is not previously treated with a PTPN inhibitor.

20. The method of any one of claims **1** to **18**, wherein the subject is previously treated with a PTPN11 inhibitor other than a compound of formula (I).

21. The method of any one of claims **1** to **18**, wherein the subject is previously treated with a PTPN11 inhibitor of formula (I).

22. The method of any one of claims **1** to **20**, wherein the subject is not previously treated with a KRAS G12C inhibitor.

23. The method of any one of claims **1** to **20**, wherein the subject is previously treated with a KRAS G12C inhibitor.

24. The method of any one of claims **1** to **23**, wherein the subject is human.

25. The method of any one of claims **1** to **24**, wherein the PTPN11 inhibitor and the KRAS G12C inhibitor are administered concomitantly.

26. The method of claim **25**, wherein the PTPN11 inhibitor and the KRAS G12C inhibitor are administered in a pharmaceutical composition comprising the PTPN11 inhibitor and the KRAS G12C inhibitor.

27. The method of any one of claims **1** to **24**, wherein the PTPN11 inhibitor and the KRAS G12C inhibitor are administered sequentially.

28. The method of claim **27**, wherein the PTPN11 inhibitor is administered prior to the administration of the KRAS G12C inhibitor.

29. The method of claim **27**, wherein the PTPN11 inhibitor is administered after the administration of the KRAS G12C inhibitor.

30. The method of any one of claims **1** to **29**, wherein the PTPN11 inhibitor and/or the KRAS G12C inhibitor are administered orally.

31. The method of any one of claims **1** to **30**, wherein the PTPN11 inhibitor and the KRAS G12C inhibitor are provided in jointly therapeutically effective amounts.

32. The method of any one of claims **1** to **30**, wherein the PTPN11 inhibitor and the KRAS G12C inhibitor are provided in synergistically effective amounts.

33. The method of any one of claims **1** to **30**, wherein the PTPN11 inhibitor and the KRAS G12C inhibitor is used at a dose different than when it is used alone.

34. The method of claim **33**, wherein the PTPN11 inhibitor is used at a dose lower than when it is used alone.

35. The method of claim **33**, wherein the PTPN11 inhibitor is used at a dose higher than when it is used alone.

36. The method of any one of claims **33** to **35**, wherein the KRAS G12C inhibitor is used at a dose lower than when it is used alone.

37. The method of any one of claims **33** to **35**, wherein the KRAS G12C inhibitor is used at a dose higher than when it is used alone.

38. The method of any one of claims **1** to **37**, wherein the treating comprises one or more treatment cycles; each of one or more treatment cycles has a duration of about 28 days; and the PTPN11 inhibitor and/or the KRAS G12C inhibitor are administered daily.

39. The method of any one of claim **1** to **38**, wherein the administration of the compound of formula (I) or (10b) and the KRAS G12C inhibitor comprises one or more dose escalations, dose retentions, or dose de-escalations of the compound of formula (I) or (10b) and/or the KRAS G12C inhibitor.

40. The method of any one of claim **1** to **38**, wherein the administration of the compound of formula (I) or (10b) and the KRAS G12C inhibitor comprises one or more dose escalations, dose retentions, or dose de-escalations of the compound of formula (I) or (10b).

41. The method of claim **40**, wherein the administration of the compound of formula (I) or (10b) comprises a dose escalation after a previous treatment cycle, when a dose-limiting toxicity (DLT) rate is less than about 19.7% as determined by a DLT assessment.

42. The method of claim **40**, wherein the administration of the compound of formula (I) or (10b) comprises a dose de-escalation after a previous treatment cycle, when a dose-limiting toxicity rate is more than about 29.8% as determined by a DLT assessment.

43. The method of claim **40**, wherein the administration of the compound of formula (I) or (10b) comprises a dose retention after a previous treatment cycle, when a dose-limiting toxicity rate is in a range of from about 21.9% to about 29.8% as determined by a DLT assessment.

44. The method of any one of claims **39** to **43**, wherein the treating comprises a dose escalation period, and wherein, after the dose escalation period, the treating further comprises a dose expansion/optimization period; and the compound of formula (I) or (10b) is administered at a dose regimen determined during the dose escalation period.

45. The method of claim **44**, wherein, during the dose expansion/optimization period, the administration of the compound of formula (I) or (10b) comprises one or more dose adjustments.

46. The method of any one of claims **4** to **45**, wherein the therapeutically effective amount of the compound of formula (I) or (10b) is a total daily dosage of from about 10 mg to about 2000 mg, from about 50 mg to about 2000 mg, from about 80 mg to about 2000 mg, from about 80 mg to about 1000 mg, from about 80 mg to about 700 mg, from about 80 mg to about 550 mg, from about 80 mg to about 400 mg, from about 80 mg to about 250 mg, from about 80 mg to about 150 mg, 100 mg to about 2000 mg, from about 150 mg to about 1000 mg, from about 200 mg to about 1000 mg, from about 250 mg to about 1000 mg, from about 300 mg

to about 1000 mg, from about 350 mg to about 1000 mg, from about 400 mg to about 1000 mg, from about 450 mg to about 1000 mg, from about 500 mg to about 1000 mg, from about 550 mg to about 1000 mg, from about 600 mg to about 1000 mg, from about 650 mg to about 1000 mg, from about 700 mg to about 1000 mg, from about 100 mg to about 700 mg, from about 150 mg to about 700 mg, from about 200 mg to about 700 mg, from about 250 mg to about 700 mg, from about 300 mg to about 700 mg, from about3 mg to about 700 mg, from about 400 mg to about 700 mg, from about 450 mg to about 700 mg, from about 500 mg to about 700 mg, from about 550 mg to about 700 mg, from about 100 mg to about 550 mg, from about 150 mg to about 550 mg, from about 200 mg to about 550 mg, from about 250 mg to about 550 mg, from about 300 mg to about 550 mg, from about 350 mg to about 550 mg, from about 400 mg to about 550 mg, from about 450 mg to about 550 mg, from about 100 mg to about 400 mg, from about 150 mg to about 400 mg, from about 200 mg to about 400 mg, from about 250 mg to about 400 mg, or from about 300 mg to about 400 mg, on a salt-free and anhydrous basis.

47. The method of claim **46**, wherein the therapeutically effective amount is a total daily dosage of from about 250 mg to about 400 mg, from about 400 mg to about 550 mg, or from about 550 mg to about 700 mg of the compound of formula (I) or (10b), on a salt-free and anhydrous basis.

48. The method of claim **46**, wherein the therapeutically effective amount of the compound of formula (10b) is a total daily dosage of about 80 mg, about 150 mg, about 250 mg, about 400 mg, about 550 mg, or about 700 mg, on a salt-free and anhydrous basis.

49. The method of any one of claims **1** to **48**, wherein the therapeutically effective amount of the KRAS G12C inhibitor is a total daily dosage of from about 10 mg to about 2000 mg.

50. The method of claim **49**, wherein the therapeutically effective amount of the KRAS G12C inhibitor is a total daily dosage of about 120 mg, about 150 mg, about 240 mg, about 300 mg, about 360 mg, about 480 mg, about 600 mg, about 720 mg, about 840 mg, about 960 mg, or about 1200 mg.

51. The method of any one of claims **4** to **50**, wherein the compound of formula (10b) and the KRAS G12C inhibitor are each administered orally.

52. The method of any one of claims **1** to **51**, wherein the PTPN11 inhibitor and/or the KRAS G12C inhibitor is administered once, twice, three times, or four times daily.

53. The method of claim **52**, wherein the PTPN11 inhibitor and/or the KRAS G12C inhibitor is administered once daily.

54. The method of any one of claims **1** to **53**, wherein the treating with the PTPN11 inhibitor and the KRAS G12C inhibitor reduces a volume of the cancer or a solid tumor at least about 10%, about 20%, about 30%, about 40%, about 50%, about 60%, about 70%, about 80%, or about 90%.

55. The method of any one of claims **1** to **53**, wherein the treating with the PTPN11 inhibitor and the KRAS G12C inhibitor stabilizes the cancer or a solid tumor.

56. A pharmaceutical composition for treating cancer in a subject, comprising:

a) a therapeutically effective amount of a PTPN11 inhibitor according to any one of claims **1** to **4**; and

b) a therapeutically effective amount of a KRAS G12C inhibitor,

together with a pharmaceutically acceptable carrier or excipient.

57. The pharmaceutical composition of claim **56**, wherein the KRAS G12C inhibitor is sotorasib (AMG 510), adagrasib (MRTX-849), MRTX1257, ARS-853, ARS-1620, JNJ-74699157 (ARS-3248), JDQ443, GDC-6036, JAB-21822, BI 1823911, MK-1084, LY3537982, or LY3499446, provided that, when the PTPN11 inhibitor is represented by formula (10b), the KRAS G12C inhibitor is other than sotorasib.

58. A kit for treating cancer in a subject, comprising:

a) a therapeutically effective amount of a PTPN11 inhibitor according to any one of claims **1** to **4**; and

b) a therapeutically effective amount of a KRAS G12C inhibitor,

together with instruction for effective administration.

59. The kit of claim **58**, wherein the KRAS G12C inhibitor is sotorasib (AMG 510), adagrasib (MRTX-849), MRTX1257, ARS-853, ARS-1620, JNJ-74699157 (ARS-3248), JDQ443, GDC-6036, JAB-21822, BI 1823911, MK-1084, LY3537982, or LY3499446, provided that, when the PTPN11 inhibitor is represented by formula (10b), the KRAS G12C inhibitor is other than sotorasib.

60. The kit of claim **58** or **59**, wherein the PTPN11 inhibitor and the KRAS G12C inhibitor are formulated for concomitant administration.

61. The kit of any one of claims **58** to **59**, wherein the PTPN11 inhibitor and the KRAS G12C inhibitor are formulated for sequential administration.