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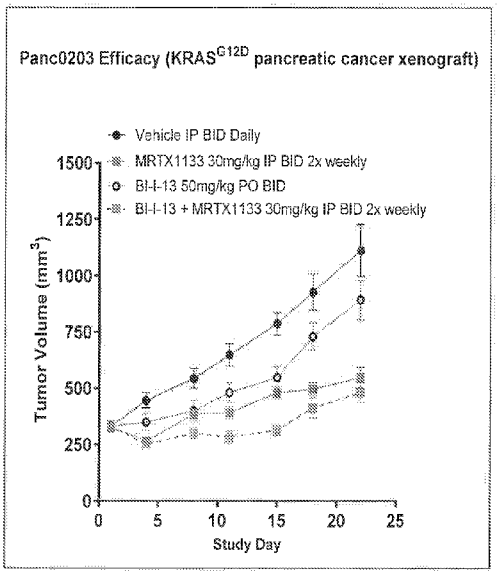
(54) Title: COMBINATION THERAPIES OF KRAS G12D INHIBITORS WITH SOS1 INHIBITORS

(57) Abstract: The present invention relates to combination therapies for treating KRas G12D cancers, In particular, the present invention relates to methods of treating cancer in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a combination of a SOS1 inhibitor and a KRAS G12D inhibitor of Formula (I), pharmaceutical compositions comprising a therapeutical ly effective amounts of the inhibitors, kits comprising the compositions and methods of use thereof.

FIGURE 1



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COMBINATION THERAPIES OF KRAS G12D INHIBITORS WITH SOS1 INHIBITORS

FIELD OF THE INVENTION

[0001] The present invention relates to combination therapies useful for treating cancer. In particular, the present invention relates to therapeutically effective combinations of compounds that inhibit Son of sevenless homolog 1 (SOS1) GTP-mediated nucleotide exchange (SOS1 inhibitors) and a KRas G12D inhibitor, pharmaceutical compositions comprising the inhibitors, kits comprising the compositions and methods of use thereof.

BACKGROUND OF THE INVENTION

[0002] Kirsten Rat Sarcoma 2 Viral Oncogene Homolog ("KRas") is a small GTPase and a member of the Ras family of oncogenes. KRas serves as a molecular switch cycling between inactive (GDP-bound) and active (GTP-bound) states to transduce upstream cellular signals received from multiple tyrosine kinases to downstream effectors regulating a wide variety of processes, including cellular proliferation (e.g., see Alamgeer et al., (2013) Current Opin Pharmcol. 13:394-401).

[0003] The role of activated KRas in malignancy was observed over thirty years ago (e.g., see Der et al., (1982) Proc. Natl Acad. Sci. USA 79(11):3637-3640). Aberrant expression of KRas accounts for up to 20% of all cancers and oncogenic KRas mutations that stabilize GTP binding and lead to constitutive activation of KRas and downstream signaling have been reported in 25 - 30% of lung adenocarcinomas. (e.g., see Samatar and Poulikakos (2014) Nat Rev Drug Disc 13(12): 928-942 doi: 10.1038/nrd428). Single nucleotide substitutions that result in missense mutations at codons 12 and 13 of the KRas primary amino acid sequence comprise approximately 33% of these KRas driver mutations in lung adenocarcinoma, with a G12D mutation being a common activating mutation (e.g., see Li, Balmain and Counter, (2018) Nat Rev Cancer Dec; 18(12):767-777; Sanchez-Vega, et al, (2018) Cell; 173, 321-337).

[0004] The well-known role of KRas in malignancy and the discovery of these frequent mutations in KRas in various tumor types made KRas a highly attractable target of the pharmaceutical industry for cancer therapy. Notwithstanding thirty years of large scale discovery efforts to develop inhibitors of KRas for treating cancer, only a single KRas G12C inhibitor (the KRas G12C inhibitor sotorasib) has demonstrated sufficient safety and/or efficacy to obtain regulatory approval (e.g., see: FDA Approves First KRAS Inhibitor: Sotorasib. [No authors listed] Cancer Discov. 2021 Aug;11(8):OF4. doi: 10.1158/2159-8290.CD-NB2021-0362. Epub 2021 Jun 22). To date, no KRas G12D inhibitors have demonstrated sufficient safety and/or efficacy to obtain regulatory approval.

[0005] Compounds that inhibit KRas activity are still highly desirable and under investigation, including those that disrupt effectors such as guanine nucleotide exchange factors (e.g., see Sun et al., (2012) Agnew Chem Int Ed Engl. 51(25):6140-6143 doi: 10.1002/anie201201358) as well as those that target KRas G12D (e.g., see K-Ras(G12D) Has a Potential Allosteric Small Molecule Binding Site, Feng H, Zhang Y, Bos PH, Chambers JM, Dupont MM, Stockwell BR, Biochemistry, 2019 May 28;58(21):2542-2554. doi: 10.1021/acs.biochem.8b01300. Epub 2019 May 14; and Second harmonic generation detection of Ras conformational changes and discovery of a small molecule binder, Donohue E, Khorsand S, Mercado G, Varney KM, Wilder PT, Yu W, MacKerell AD Jr, Alexander P, Van QN, Moree B, Stephen AG, Weber DJ, Salafsky J, McCormick F., Proc Natl Acad Sci USA 2019 Aug 27;116(35):17290-17297, doi: 10.1073/pnas.1905516116. Epub 2019 Aug 9)…). Clearly there remains a continued interest and effort to develop inhibitors of KRas, particularly inhibitors of activating KRas mutants, including KRas G12D.

[0006] While the KRas G12D inhibitors disclosed herein are potent inhibitors of KRas G12D signaling and exhibit single agent activity inhibiting the in vitro proliferation of cell lines harboring a KRas G12D mutation, the relative potency and/or observed maximal effect of any given KRas G12D inhibitor can vary between KRAS mutant cell lines. The reason or reasons for the range of potencies and observed maximal effect is not fully understood but certain cell lines appear to possess differing intrinsic resistance. Thus, there is a need to develop alternative approaches to maximize the potency, efficacy, therapeutic index and/or clinical benefit of KRas G12D inhibitors *in vitro* and *in vivo*.

[0007] The combination therapy of the present invention, in one aspect, synergistically increases the potency of KRas G12D inhibitors resulting in improved efficacy of KRas G12D inhibitors disclosed herein. The combination therapy of the present invention, in another aspect, provides improved clinical benefit to patients compared to treatment with KRas G12D inhibitors disclosed herein as a single agent.

SOS-1 Inhibitors

[0008] The Ras family comprises v-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog (KRAS), neuroblastoma RAS viral oncogene homolog (NRAS), and Harvey murine sarcoma virus oncogene (HRAS) and critically regulates cellular division, growth and function in normal and altered states including cancer (see e.g., Simanshu et al. Cell, 2017. 170(1): p. 17-33; Matikas et al., Crit Rev Oncol Hematol, 2017. 110: p. 1-12). RAS proteins are activated by upstream signals, including receptor tyrosine kinases (RTKs), and transduce signals to several downstream signaling pathways such as the mitogen-activated protein kinase (MAPK)/extracellular signal-regulated kinases (ERK) pathway. Hyperactivation of RAS signaling is frequently observed in cancer as a result of mutations or alterations in RAS genes or other genes in the RAS pathway. The identification of strategies to inhibit RAS and RAS signaling are predicted to be useful for the treatment of cancer and RAS-regulated disease states.

[0009] RAS proteins are guanosine triphosphatases (GTPases) that cycle between an inactive, guanosine diphosphate (GDP)-bound state and an active guanosine triphosphate (GTP)-bound state. Son of sevenless homolog 1 (SOS1) is a guanine nucleotide exchange factor (GEF) that mediates the exchange of GDP for GTP, thereby activating RAS proteins. RAS proteins hydrolyze GTP to GDP through their intrinsic GTPase activity which is greatly enhanced by GTPase-activating proteins (GAPs). This regulation through GAPs and GEFs is the mechanism whereby activation and deactivation are tightly regulated under normal conditions. Mutations at several residues in all three RAS proteins are frequently observed in cancer and result in RAS remaining predominantly in the activated state (Sanchez-Vega et al., Cell, 2018. 173: p. 321-337 Li et al., Nature Reviews Cancer, 2018. 18: p. 767-777). Mutations at codon 12 and 13 are the most frequently mutated RAS residues and prevent GAP-stimulated GTP hydrolysis by blocking the interaction of GAP proteins and RAS. Recent biochemical analyses however, demonstrated these mutated proteins still require nucleotide cycling for activation based on their intrinsic GTPase

activity and/or partial sensitivity to extrinsic GTPases. As such, mutant RAS proteins are sensitive to inhibition of upstream factors such as SOS1 or SHP2, another upstream signaling molecule required for RAS activation (Hillig, 2019; Patricelli, 2016; Lito, 2016; Nichols, 2018).

[00010] The three main RAS-GEF families that have been identified in mammalian cells are SOS, RAS-GRF and RAS-GRP (Rojas, 2011). RAS-GRF and RAS-GRP are expressed in the cells of the central nervous system and hematopoietic cells, respectively, while the SOS family is ubiquitously expressed and is responsible for transducing RTK signaling. The SOS family comprises SOS1 and SOS2 and these proteins share approximately 70% sequence identity. SOS1 appears to be much more active than SOS2 due to the rapid degradation of SOS2. The mouse SOS2 knockout is viable whereas the SOS1 knockout is embryonic lethal. A tamoxifen-inducible SOS1 knockout mouse model was used to interrogate the role of SOS1 and SOS2 in adult mice and demonstrated the SOS1 knockout was viable but the SOS1/2 double knockout was not viable (Baltanas, 2013) suggesting functional redundancy and that selective inhibition of SOS1 may have a sufficient therapeutic index for the treatment of SOS1 – RAS activated diseases.

[00011] SOS proteins are recruited to phosphorylated RTKs through an interaction with growth factor receptor bound protein 2 (GRB2). Recruitment to the plasma membrane places SOS in close proximity to RAS and enables SOS-mediated RAS activation. SOS proteins bind to RAS through a binding site that promotes nucleotide exchange as well as through an allosteric site that binds GTP-bound RAS-family proteins and increases the function of SOS (Freedman et al., Proc. Natl. Acad. Sci, USA 2006. 103(45): p. 16692-97). Binding to the allosteric site relieves steric occlusion of the RAS substrate binding site and is therefore required for nucleotide exchange. Retention of the active conformation at the catalytic site following interaction with the allosteric site is maintained in isolation due to strengthened interactions of key domains in the activated state. SOS1 mutations are found in Noonan syndrome and several cancers including lung adenocarcinoma, embryonal rhabdomyosarcoma, Sertoli cell testis tumor and granular cell tumors of the skin (see e.g., Denayer, E., et al, Genes Chromosomes Cancer, 2010. 49(3): p. 242-52).

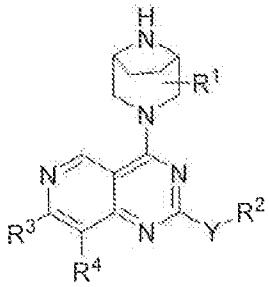
[00012] GTPase-activating proteins (GAPs) are proteins that stimulate the low intrinsic GTPase activity of RAS family members and therefore converts active GTP-bound RAS proteins into inactive, GDP-bound RAS proteins (e.g., see Simanshu, D.K., Cell, 2017, Ras Proteins and their Regulators in Human Disease). While activating alterations in the GEF SOS1 occur in

cancers, inactivating mutations and loss-of-function alterations in the GAPs neurofibromin 1 (NF-1) or neurofibromin 2 (NF-2) also occur creating a state where SOS1 activity is unopposed and activity downstream of the pathway through RAS proteins is elevated.

[00013] BI-I-13 (also known as BI-3406) is a SOS1::pan-KRAS inhibitor blocking KRAS independent of mutation type. It structure is described in CAS No. 2230836-55-0. See BI-3406, a Potent and Selective SOS1-KRAS Interaction Inhibitor, Is Effective in KRAS-Driven Cancers through Combined MEK Inhibition, Hofman M, Gmachl M, Ramharter J, Savarese F, et al, Cancer Discovery, 2021 January doi: 10.1158/2159-8290. CD-20-0142.

SUMMARY OF THE INVENTION

[00014] In one aspect of the invention, provided herein are methods of treating cancer in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a combination of a SOS1 inhibitor and a KRAS G12D inhibitor of formula (I):



Formula (I)

[00015] or a pharmaceutically acceptable salt thereof:

[00016] wherein:

[00017] R^1 is hydrogen, hydroxy, halogen, C1 – C3 alkyl, C1 - C3 cyanoalkyl, C1 - C3 hydroxyalkyl, HC(=O)-, $-CO_2R^5$, $-CO_2N(R^5)_2$ or a 5-6 membered heteroaryl;

[00018] Y is a bond, O or NR^5;

[00019] R^2 is hydrogen, -$N(R^5)_2$, heterocyclyl, C1 – C6 alkyl, -L-heterocyclyl, -L-aryl, -L-heteroaryl, -L-cycloalkyl, -L-$N(R^5)_2$, -L-$NHC(=NH)NH_2$, -L-$C(O)N(R^5)_2$, -L-C1-C6 haloalkyl, -L-OR^5, -L-$(CH_2OR^5)(CH_2)_nOR^5$, -L-$NR^5C(O)$-aryl, -L-COOH, or -LC(=O)OC1-C6 alkyl, wherein the heterocyclyl and the aryl portion of -L-$NR^5C(O)$-aryl and the heterocyclyl portion of -L-heterocyclyl and the cycloalkyl portion of the -L-cycloalkyl may be optionally substituted with one or more R^6, and wherein the aryl or heteroaryl of the -L-aryl and the -L-heteroaryl may be optionally substituted with one or more R^7;

[00020] each L is independently a C1 – C4 alkylene optionally substituted with hydroxy, C1 – C4 hydroxyalkyl or heteroaryl;

[00021] R^3 is aryl or heteroaryl, wherein the aryl or the heteroaryl is optionally substituted with one or more R^8;

[00022] R^4 is hydrogen, halogen or C1 – C3 alkyl;

[00023] each R^5 is independently hydrogen or C1 – C3 alkyl;

[00024] each R^6 is independently halogen, hydroxy, C1 - C3 hydroxyalkyl, C1 – C3 alkyl, C1 - C3 haloalkyl, C1-C3 alkoxy, cyano, -Q-phenyl, -Q-phenylSO_2F, -NHC(O)phenyl, -NHC(O)phenylSO_2F, C1-C3 alkyl substituted pyrazolyl, araC1-C3 alkyl-, tert-butyldimethylsilyloxyCH_2- , -$N(R^5)_2$, (C1-C3 alkoxy)C1-C3 alkyl-, (C1-C3 alkyl)C(=O), oxo, (C1-C3 haloalkyl)C(=O)-, -SO_2F, (C1-C3 alkoxy)C1-C3 alkoxy, -$CH_2OC(O)N(R^5)_2$, -$CH_2NHC(O)OC1$-C6 alkyl, -$CH_2NHC(O)N(R^5)_2$, -$CH_2NHC(O)$C1-C6 alkyl, -CH_2(pyrazolyl), -CH_2NHSO_2C1-C6 alkyl, -$CH_2OC(O)$heterocyclyl, -$OC(O)N(R^5)_2$, -OC(O)NH(C1-C3 alkyl)O(C1-C3 alkyl), -OC(O)NH(C1-C3 alkyl)O(C1-C3 alkyl)phenyl(C1-C3 alkyl)$N(CH_3)_2$, -OC(O)NH(C1-C3 alkyl)O(C1-C3 alkyl)phenyl or OC(O)heterocyclyl, -CH_2heterocyclyl, wherein the phenyl of -NHC(O)phenyl or -OC(O)NH(C1-C3 alkyl)O(C1-C3 alkyl)phenyl is optionally substituted with -C(O)H or OH and wherein the heterocyclyl of -CH_2heterocyclyl is optionally substituted with oxo;

[00025] Q is a bond or O;

[00026] each R^7 is independently halogen, hydroxy, HC(=O)-, C1 – C4 alkyl, C1 – C4 alkoxy, C1 – C4 haloalkyl, C1 – C4 hydroxyalkyl, or -$N(R^5)_2$; and

[00027] each R^8 is independently halogen, cyano, hydroxy, C1 - C4 alkyl, -S-C1 - C3 alkyl, C2 – C4 alkenyl, C2 – C4 alkynyl, C2 – C4 hydroxyalkynyl, C1-C3 cyanoalkyl , triazolyl, C1 - C3 haloalkyl, -O- C1 - C3 haloalkyl, -S- C1 - C3 haloalkyl, C1-C3 alkoxy, hydroxyC1-C3 alkyl, $-CH_2C(=O)N(R^5)_2$, -C3-C4 alkynyl$(NR^5)_2$, $-N(R^5)_2$, deuteroC2-C4 alkynyl, (C1-C3 alkoxy)haloC1-C3 alkyl-, or C3-C6 cycloalkyl wherein said C3-C6 cycloalkyl is optionally substituted with halogen or C1-C3 alkyl.

[00028] In one aspect of the invention, KRas G12D inhibitors comprise compound MRTX1133 or MRTX1133 analogs and related compounds such as any of the compounds disclosed and described in WIPO publication WO2021/041671, including but not limited to: Ex. 252 (MRTX1133), 4-(4-((1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)-5-ethynyl-6-fluoronaphthalen-2-ol; Ex. 243, 4-(4-((1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)-5-ethynylnaphthalen-2-ol; Ex. 246, 4-(4-((1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)-5,6-difluoronaphthalen-2-ol; Ex. 251, 4-(4-((1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)-5-chloronaphthalen-2-ol; Ex. 253, 4-(4-((1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)-5-ethyl-6-fluoronaphthalen-2-ol; Ex. 259, 4-(4-((1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)-5-ethylnaphthalen-2-ol; and Ex. 282, 4-(4-((1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)-5-fluoronaphthalen-2-ol; or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable excipient.

[00029] In another aspect of the invention, pharmaceutical compositions are provided for use in the methods comprising a therapeutically effective amount of a combination of a SOS-1 inhibitor and a KRas G12D inhibitor compound Formula I, or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable excipient.

[00030] In one aspect of the invention, provided herein are methods of treating cancer in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a combination of a SOS-1 inhibitor or a pharmaceutically acceptable salt or a pharmaceutical composition thereof and a KRAS G12D inhibitor of Formula (I), or a pharmaceutically acceptable salt or a pharmaceutical composition thereof. In one embodiment, the cancer is a KRas G12D-associated cancer. In one embodiment, the KRas G12D-associated cancer is pancreatic, colorectal, endometrial, and non-small cell lung cancer.

[00031] In some aspects of the invention, KRas G12D inhibitor compounds and SOS-1 inhibitors are the only active agents in the provided compositions and methods.

[00032] Examples of SOS-1 inhibitors suitable for the provided compositions and methods include, but are not limited to BI-3406 (aka BI-I-13) (Boehringer Ingelheim) and related compounds such as BI-170963 (Boehringer Ingelheim).

[00033] In yet another aspect, the invention provides for methods for increasing the sensitivity of a cancer cell to a KRas G12D inhibitor, comprising contacting the cancer cell with a therapeutically effective amount of a combination of a KRas G12D inhibitor compound of Formula (I), or a pharmaceutically acceptable salt or a pharmaceutical composition thereof, and a SOS-1 inhibitor, or a pharmaceutically acceptable salt or a pharmaceutical composition thereof, wherein the SOS-1 inhibitor synergistically increases the sensitivity of the cancer cell to the KRas G12D inhibitor. In one embodiment, the contacting is in vitro. In one embodiment, the contacting is in vivo.

[00034] Also provided herein are methods for treating cancer in a subject in need thereof, the method comprising (a) determining that cancer is associated with a KRas G12D mutation (e.g., a KRas G12D-associated cancer) (e.g., as determined using a regulatory agency-approved, e.g., FDA-approved, assay or kit); and (b) administering to the patient a therapeutically effective amount of a combination of a SOS1 inhibitor, or a pharmaceutically acceptable salt or a pharmaceutical composition thereof, and a KRas G12D inhibitor compound of Formula I, or a pharmaceutically acceptable salt or a pharmaceutical composition thereof, wherein the SOS1 inhibitor synergistically increases the sensitivity of the KRas G12D-associated cancer to the KRas G12D inhibitor.

[00035] Also provided herein are kits comprising a SOS1 inhibitor, or a pharmaceutically acceptable salt or a pharmaceutical composition thereof and a KRas G12D inhibitor compound of Formula (I), or a pharmaceutically acceptable salt or a pharmaceutical composition thereof. Also provided is a kit comprising a SOS1 inhibitor, or a pharmaceutically acceptable salt or a pharmaceutical composition thereof, and a KRas G12D inhibitor compound of Formula (I), or a pharmaceutically acceptable salt or a pharmaceutical composition thereof, for use in treating a KRas G12D cancer.

[00036] In a related aspect, the invention provides a kit containing a dose of a SOS1 inhibitor, or a pharmaceutically acceptable salt or a pharmaceutical composition thereof and a KRas G12D inhibitor compound of Formula (I), or a pharmaceutically acceptable salt or a pharmaceutical composition thereof in an amount effective to inhibit proliferation of cancer cells in a subject. The kit in some cases includes an insert with instructions for administration of a SOS1 inhibitor, or a pharmaceutically acceptable salt or a pharmaceutical composition thereof and a KRas G12D inhibitor compound of Formula (I), or a pharmaceutically acceptable salt or a pharmaceutical composition thereof. The insert may provide a user with one set of instructions for using the a SOS1 inhibitor, or a pharmaceutically acceptable salt or a pharmaceutical composition thereof in combination with a KRas G12D inhibitor compound of Formula (I), or a pharmaceutically acceptable salt or a pharmaceutical composition thereof.

[00037] In some embodiments of any of the methods described herein, before treatment with the compositions or methods of the invention, the patient was treated with one or more of a chemotherapy, a targeted anticancer agent, radiation therapy, and surgery, and optionally, the prior treatment was unsuccessful; and/or the patient has been administered surgery and optionally, the surgery was unsuccessful; and/or the patient has been treated with a platinum-based chemotherapeutic agent, and optionally, the patient has been previously determined to be non-responsive to treatment with the platinum-based chemotherapeutic agent; and/or the patient has been treated with a kinase inhibitor, and optionally, the prior treatment with the kinase inhibitor was unsuccessful; and/or the patient was treated with one or more other therapeutic agent(s).

BRIEF DESCRIPTION OF THE DRAWINGS

[00038] Figure 1 depicts the average tumor volumes in mouse xenografts for MRTX1133, alone and in combination with BI-I-13 (aka BI-3406) (Panc0203 pancreatic cancer cell line).

DETAILED DESCRIPTION OF THE INVENTION

[00039] The present invention relates to combination therapies for treating KRas G12D cancers. In particular, the present invention relates to methods of treating cancer in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a combination of a SOS1 inhibitor, or a pharmaceutically acceptable salt or a pharmaceutical composition thereof, and a KRAS G12D inhibitor of Formula (I), or a pharmaceutically acceptable salt or a pharmaceutical composition thereof, pharmaceutical compositions comprising therapeutically effective amounts of the inhibitors, kits comprising the compositions and methods of use thereof.

[00040] Combinations of the SOS1 inhibitor, or a pharmaceutically acceptable salt or a pharmaceutical composition thereof, with a KRas G12D inhibitor, or a pharmaceutically acceptable salt or a pharmaceutical composition thereof, synergistically increase the potency of KRas G12D inhibitor compounds of Formula (I), against cancer cells that express KRas G12D thereby increasing the efficacy and therapeutic index of KRas G12D inhibitor compounds of Formula (I), or pharmaceutically acceptable salts thereof.

[00041] DEFINITIONS

[00042] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood by one of skill in the art to which this invention belongs. All patents, patent applications, and publications referred to herein are incorporated by reference.

[00043] As used herein, "KRas G12D" refers to a mutant form of a mammalian KRas protein that contains an amino acid substitution of an aspartic acid for a glycine at amino acid

position 12. The assignment of amino acid codon and residue positions for human KRas is based on the amino acid sequence identified by UniProtKB/Swiss-Prot P01116: Variant p.Gly12Asp.

[00044] As used herein, a "KRas G12D inhibitor" refers to compounds of the present invention that are represented by Formula (I), as described herein. These compounds are capable of negatively modulating or inhibiting all or a portion of the enzymatic activity of KRas G12D. In one embodiment, the KRas G12D inhibitor is a compound selected from compound Nos 1-458 (as numbered in WO2021/041671), or pharmaceutically acceptable salts thereof.

[00045] A "KRas G12D-associated disease or disorder" as used herein refers to diseases or disorders associated with or mediated by or having a KRas G12D mutation. A non-limiting example of a KRas G12D-associated disease or disorder is a KRas G12D-associated cancer.

[00046] As used herein, "SOS1" refers to a mammalian Son of sevenless homolog 1 (SOS1) enzyme.

[00047] As used herein, a "SOS1 inhibitor" refers to a compound that is capable of negatively modulating or inhibiting all or a portion of the interaction of SOS1 with Ras family mutant or SOS1 activating mutation thereby reducing and/or modulating the nucleotide exchange activity of Ras family member - SOS1 complex.

[00048] As used herein, the term "subject," "individual," or "patient," used interchangeably, refers to any animal, including mammals such as mice, rats, other rodents, rabbits, dogs, cats, swine, cattle, sheep, horses, primates, and humans. In some embodiments, the patient is a human. In some embodiments, the subject has experienced and/or exhibited at least one symptom of the disease or disorder to be treated and/or prevented. In some embodiments, the subject has been identified or diagnosed as having a cancer having a KRas G12D mutation (e.g., as determined using a regulatory agency-approved, e.g., FDA-approved, assay or kit). In some embodiments, the subject has a tumor that is positive for a KRas G12D mutation (e.g., as determined using a regulatory agency-approved assay or kit). The subject can be a subject with a tumor(s) that is positive for a KRas G12D mutation (e.g., identified as positive using a regulatory agency-approved, e.g., FDA-approved, assay or kit). The subject can be a subject whose tumors have a KRas G12D mutation (e.g., where the tumor is identified as such using a regulatory agency-approved, e.g., FDA-approved, kit or assay). In some embodiments, the subject is

suspected of having a KRas G12D gene-associated cancer. In some embodiments, the subject has a clinical record indicating that the subject has a tumor that has a KRas G12D mutation (and optionally the clinical record indicates that the subject should be treated with any of the compositions provided herein).

[00049] The term "pediatric patient" as used herein refers to a patient under the age of 16 years at the time of diagnosis or treatment. The term "pediatric" can be further be divided into various subpopulations including: neonates (from birth through the first month of life); infants (1 month up to two years of age); children (two years of age up to 12 years of age); and adolescents (12 years of age through 21 years of age (up to, but not including, the twenty-second birthday)). Berhman RE, Kliegman R, Arvin AM, Nelson WE. Nelson Textbook of Pediatrics, 15th Ed. Philadelphia: W.B. Saunders Company, 1996; Rudolph AM, et al. Rudolph's Pediatrics, 21st Ed. New York: McGraw-Hill, 2002; and Avery MD, First LR. Pediatric Medicine, 2nd Ed. Baltimore: Williams & Wilkins; 1994.

[00050] In some embodiments of any of the methods or uses described herein, an assay is used to determine whether the patient has KRas G12D mutation using a sample (e.g., a biological sample or a biopsy sample such as a paraffin-embedded biopsy sample) from a patient (e.g., a patient suspected of having a KRas G12D-associated cancer, a patient having one or more symptoms of a KRas G12D-associated cancer, and/or a patient that has an increased risk of developing a KRas G12D-associated cancer) can include, for example, next generation sequencing, immunohistochemistry, fluorescence microscopy, break apart FISH analysis, Southern blotting, Western blotting, FACS analysis, Northern blotting, and PCR-based amplification (e.g., RT-PCR, quantitative real-time RT-PCR, allele-specific genotyping or ddPCR). As is well-known in the art, the assays are typically performed, e.g., with at least one labelled nucleic acid probe or at least one labelled antibody or antigen-binding fragment thereof.

[00051] The term "regulatory agency" is a country's agency for the approval of the medical use of pharmaceutical agents with the country. For example, a non-limiting example of a regulatory agency is the U.S. Food and Drug Administration (FDA).

[00052] The term "amino" refers to $-NH_2$;

[00053] The term "acyl" refers to $-C(O)CH_3$.

[00054] The term "alkyl" as employed herein refers to straight and branched chain aliphatic groups having from 1 to 12 carbon atoms, 1-8 carbon atoms 1-6 carbon atoms, or 1-3 carbon atoms which is optionally substituted with one, two or three substituents. Examples of alkyl groups include, without limitation, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, and hexyl.

[00055] The term "haloalkyl" refers to an alkyl chain in which one or more hydrogen has been replaced by a halogen. Examples of haloalkyls are trifluoromethyl, difluoromethyl and fluoromethyl.

[00056] The term "haloalkyloxy" refers to -O-haloalkyl.

[00057] An "alkylene," group is an alkyl group, as defined hereinabove, that is positioned between and serves to connect two other chemical groups. Exemplary alkylene groups include, without limitation, methylene, ethylene, propylene, and butylene.

[00058] The term "alkoxy" refers to $-OC_1 - C_6$ alkyl.

[00059] The term "cycloalkyl" as employed herein includes saturated and partially unsaturated cyclic hydrocarbon groups having 3 to 12 carbons, for example 3 to 8 carbons, and as a further example 3 to 6 carbons, wherein the cycloalkyl group additionally is optionally substituted. Examples of cycloalkyl groups include, without limitation, cyclopropyl, cyclobutyl, cyclopentyl, cyclopentenyl, cyclohexyl, cyclohexenyl, cycloheptyl, and cyclooctyl.

[00060] The term "heteroalkyl" refers to an alkyl group, as defined hereinabove, wherein one or more carbon atoms in the chain are replaced by a heteroatom selected from the group consisting of O, S, and N.

[00061] As used herein, the term "hydroxyalkyl" refers to –alkyl-OH.

[00062] The term "dihydroxyalkyl" refers to an alkyl group as defined herein wherein two carbon atoms are each substituted with a hydroxyl group.

[00063] The term "alkylaminyl" refers to $-NR^x$-alkyl, wherein R^x is hydrogen. In one embodiment, R^x is hydrogen.

[00064] The term "dialkylaminyl" refers to $-N(R^y)_2$, wherein each R^y is $C_1 - C_3$ alkyl.

[00065] The term "alkylaminylalkyl" refers to -alkyl-NR^x-alkyl, wherein R^x is hydrogen. In one embodiment, R^x is hydrogen.

[00066] The term "dialkylaminylalkyl" refers to -alkyl-$N(R^y)_2$, wherein each R^y is $C_1 - C_4$ alkyl, wherein the alkyl of the—alkyl-$N(R^y)_2$ may be optionally substituted with hydroxy or hydroxyalkyl.

[00067] An "aryl" group is a C_6-C_{14} aromatic moiety comprising one to three aromatic rings, which is optionally substituted. As one embodiment, the aryl group is a C_6-C_{10} aryl group. Examples of aryl groups include, without limitation, phenyl, naphthyl, anthracenyl, fluorenyl, and dihydrobenzofuranyl.

[00068] An "aralkyl" or "arylalkyl" group comprises an aryl group covalently linked to an alkyl group, either of which may independently be optionally substituted or unsubstituted. An example of an aralkyl group is (C_1- C_6)alkyl(C_6-C_{10})aryl, including, without limitation, benzyl, phenethyl, and naphthylmethyl. An example of a substituted aralkyl is wherein the alkyl group is substituted with hydroxyalkyl.

[00069] A "heterocyclyl" or "heterocyclic" group is a ring structure having from about 3 to about 12 atoms, for example 4 to 8 atoms, wherein one or more atoms are selected from the group consisting of N, O, and S, the remainder of the ring atoms being carbon. The heterocyclyl may be a monocyclic, a bicyclic, a spirocyclic or a bridged ring system. The heterocyclic group is optionally substituted with R^7 on carbon or nitrogen at one or more positions, wherein R^7 is as defined for Formula I. The heterocyclic group is also independently optionally substituted on nitrogen with alkyl, aryl, aralkyl, alkylcarbonyl, alkylsulfonyl, arylcarbonyl, arylsulfonyl, alkoxycarbonyl, aralkoxycarbonyl, or on sulfur with oxo or lower alkyl. Examples of heterocyclic groups include, without limitation, epoxy, azetidinyl, aziridinyl, tetrahydrofuranyl, tetrahydropyranyl, pyrrolidinyl, pyrrolidinonyl, piperidinyl, piperazinyl, imidazolidinyl, thiazolidinyl, dithianyl, trithianyl, dioxolanyl, oxazolidinyl, oxazolidinonyl, decahydroquinolinyl, piperidonyl, 4-piperidinonyl, thiomorpholinyl, thiomorpholinyl 1,1 dioxide, morpholinyl, oxazepanyl, azabicyclohexanes, azabicycloheptanes and oxa

azabiocycloheptanes. Specifically excluded from the scope of this term are compounds having adjacent annular O and/or S atoms.

[00070] The term "heterocyclylalkyl" refers to a heterocyclyl group as defined herein linked to the remaining portion of the molecule via an alkyl linker, wherein the alkyl linker of the heterocyclylalkyl may be optionally substituted with hydroxy or hydroxyalkyl.

[00071] As used herein, the term "heteroaryl" refers to groups having 5 to 14 ring atoms, preferably 5, 6, 9, or 10 ring atoms; having 6, 10, or 14 π electrons shared in a cyclic array; and having, in addition to carbon atoms, from one to three heteroatoms per ring selected from the group consisting of N, O, and S. Examples of heteroaryl groups include acridinyl, azocinyl, benzimidazolyl, benzofuranyl, benzothiofuranyl, benzothiophenyl, benzoxazolyl, benzthiazolyl, benztriazolyl, benztetrazolyl, benzisoxazolyl, benzisothiazolyl, benzimidazolinyl, carbazolyl, 4aH-carbazolyl, carbolinyl, chromanyl, chromenyl, cinnolinyl, furanyl, furazanyl, imidazolinyl, imidazolyl, 1H-indazolyl, indolenyl, indolinyl, indolizinyl, indolyl, 3H-indolyl, isobenzofuranyl, isochromanyl, isoindazolyl, isoindolinyl, isoindolyl, isoquinolinyl, isothiazolyl, isoxazolyl, methylenedioxyphenyl, naphthyridinyl, octahydroisoquinolinyl, oxadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, oxazolidinyl, oxazolyl, oxazolidinyl, pyrimidinyl, phenanthridinyl, phenanthrolinyl, phenazinyl, phenothiazinyl, phenoxathiinyl, phenoxazinyl, phthalazinyl, piperonyl, pteridinyl, purinyl, pyranyl, pyrazinyl, pyrazolidinyl, pyrazolinyl, pyrazolyl, pyridazinyl, pyridooxazole, pyridoimidazole, pyridothiazole, pyridinyl, pyridyl, pyrimidinyl, pyrrolinyl, 2H-pyrrolyl, pyrrolyl, quinazolinyl, quinolinyl, 4H-quinolizinyl, quinoxalinyl, quinuclidinyl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, tetrazolyl, 6H-1,2,5-thiadiazinyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, thianthrenyl, thiazolyl, thienyl, thienothiazolyl, thienooxazolyl, thienoimidazolyl, thiophenyl, triazinyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,5-triazolyl, 1,3,4-triazolyl, and xanthenyl.

[00072] A "heteroarylalkyl" group comprises a heteroaryl group covalently linked to an alkyl group, wherein the radical is on the alkyl group, either of which is independently optionally substituted or unsubstituted. Examples of heteroarylalkyl groups include a heteroaryl group having 5, 6, 9, or 10 ring atoms bonded to a C_1-C_6 alkyl group. Examples of heteroaralkyl groups include pyridylmethyl, pyridylethyl, pyrrolylmethyl, pyrrolylethyl, imidazolylmethyl, imidazolylethyl, thiazolylmethyl, thiazolylethyl, benzimidazolylmethyl, benzimidazolylethyl

quinazolinylmethyl, quinolinylmethyl, quinolinylethyl, benzofuranylmethyl, indolinylethyl isoquinolinylmethyl, isoinodylmethyl, cinnolinylmethyl, and benzothiophenylethyl. Specifically excluded from the scope of this term are compounds having adjacent annular O and/or S atoms.

[00073] As used herein, "an effective amount" of a compound is an amount that is sufficient to negatively modulate or inhibit the activity of the desired target, i.e., a SOS1 or KRas G12D. Such amount may be administered as a single dosage or may be administered according to a regimen, whereby it is effective.

[00074] As used herein, a "therapeutically effective amount" of a compound is an amount that is sufficient to ameliorate, or in some manner reduce a symptom or stop or reverse progression of a condition, or negatively modulate or inhibit the activity of SOS1 or KRas G12D. Such amount may be administered as a single dosage or may be administered according to a regimen, whereby it is effective.

[00075] As used herein, a "therapeutically effective amount of a combination" of two compounds is an amount that together synergistically increases the activity of the combination in comparison to the therapeutically effective amount of each compound in the combination, i.e., more than merely additive. Alternatively, in vivo, the therapeutically effective amount of the combination of a SOS1 inhibitor, or a pharmaceutically acceptable salt or a pharmaceutical composition thereof, and a KRas G12D inhibitor compound of Formula (I), or a pharmaceutically acceptable salt or a pharmaceutical composition thereof, results in an increased duration of overall survival ("OS") in subjects relative to treatment with only the KRas G12D inhibitor. In one embodiment, the therapeutically effective amount of the combination of a SOS1 inhibitor, or a pharmaceutically acceptable salt or a pharmaceutical composition thereof, and a KRas G12D inhibitor compound of Formula (I), or a pharmaceutically acceptable salt or a pharmaceutical composition thereof, results in an increased duration of progression-free survival ("PFS") in subjects relative to treatment with only the KRas G12D inhibitor. In one embodiment, the therapeutically effective amount of the combination of a SOS1 inhibitor, or a pharmaceutically acceptable salt or a pharmaceutical composition thereof, and a KRas G12D inhibitor compound of Formula (I), or a pharmaceutically acceptable salt or a pharmaceutical composition thereof, results in increased tumor regression in subjects relative to treatment with only the KRas G12D inhibitor. In one embodiment, the therapeutically effective amount of the

combination of a SOS1 inhibitor, or a pharmaceutically acceptable salt or a pharmaceutical composition thereof, and a KRas G12D inhibitor compound of Formula (I), or a pharmaceutically acceptable salt or a pharmaceutical composition thereof, results in increased tumor growth inhibition in subjects relative to treatment with only the KRas G12D inhibitor. In one embodiment, the therapeutically effective amount of the combination of a SOS1 inhibitor, or a pharmaceutically acceptable salt or a pharmaceutical composition thereof, and a KRas G12D inhibitor compound of Formula (I), or a pharmaceutically acceptable salt or a pharmaceutical composition thereof, results in an improvement in the duration of stable disease in subjects compared to treatment with only the KRas G12D inhibitor. The amount of each compound in the combination may be the same or different than the therapeutically effective amount of each compound when administered alone as a monotherapy as long as the combination is synergistic. Such amounts may be administered as a single dosage or may be administered according to a regimen, whereby it is effective.

[00076] As used herein, treatment means any manner in which the symptoms or pathology of a condition, disorder or disease are ameliorated or otherwise beneficially altered. Treatment also encompasses any pharmaceutical use of the compositions herein.

[00077] As used herein, amelioration of the symptoms of a particular disorder by administration of a particular pharmaceutical composition refers to any lessening, whether permanent or temporary, lasting or transient that can be attributed to or associated with administration of the composition.

[00078] As used herein, the term "about" when used to modify a numerically defined parameter (e.g., the dose of a KRAS inhibitor or a SOS1 inhibitor or a pharmaceutically acceptable salt thereof, or the length of treatment time with a combination therapy described herein) means that the parameter may vary by as much as 10% below or above the stated numerical value for that parameter. For example, a dose of about 5 mg/kg may vary between 4.5 mg/kg and 5.5 mg/kg. "About" when used at the beginning of a listing of parameters is meant to modify each parameter. For example, about 0.5 mg, 0.75 mg or 1.0 mg means about 0.5 mg, about 0.75 mg or about 1.0 mg. Likewise, about 5% or more, 10% or more, 15% or more, 20% or more, and 25% or more means about 5% or more, about 10% or more, about 15% or more, about 20% or more, and about 25% or more.

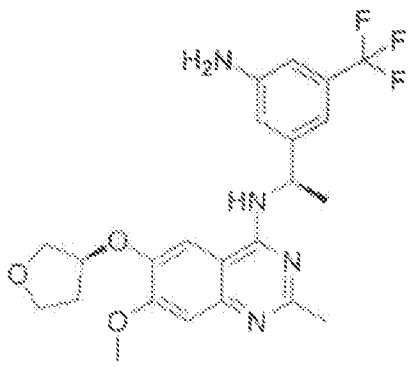
[00079] INHIBITOR COMPOUNDS

[00080] In one aspect of the invention, provided herein are methods of treating cancer in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a combination of a SOS1 inhibitor, or a pharmaceutically acceptable salt or a pharmaceutical composition thereof, and a KRAS G12D inhibitor of Formula (I), or a pharmaceutically acceptable salt or a pharmaceutical composition thereof.

[00081] 1. SOS1 Inhibitors

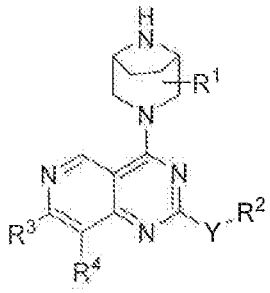
[00082] SOS-1 inhibitors block the interaction between SOS1 and Ras-family members and prevent the recycling of KRas in to the active GTP-bound form and, therefore, may provide therapeutic benefit for a wide range of cancers, particularly Ras family member-associated cancers. These compounds negatively modulate the activity of KRas through blocking SOS1-KRas interaction in a cell for treating various forms of cancer, including Ras-associated cancer, SOS1-associated cancer and NF1/NF2-associated cancer.

[00083] One SOS1 inhibitor that can be used for the purposes of the present invention is BI-I-13 (aka BI-3406). Its structure can be found at https://cancerdiscovery.aacrjournals.org/content/11/1/142. It has the following structure:



[00084] 2. KRas G12D Inhibitors

[00085] In one embodiment, the KRas G12D inhibitors used in the methods are compounds of Formula (I):



Formula (I)

[00086] or a pharmaceutically acceptable salt thereof:

[00087] wherein:

[00088] R^1 is hydrogen, hydroxy, halogen, C1 – C3 alkyl, C1 - C3 cyanoalkyl, C1 - C3 hydroxyalkyl, HC(=O)-, $-CO_2R^5$, $-CO_2N(R^5)_2$ or a 5-6 membered heteroaryl;

[00089] Y is a bond, O or NR^5;

[00090] R^2 is hydrogen, $-N(R^5)_2$, heterocyclyl, C1 – C6 alkyl, -L-heterocyclyl, -L-aryl, -L-heteroaryl, -L-cycloalkyl, $-L-N(R^5)_2$, -L-NHC(=NH)NH_2, $-L-C(O)N(R^5)_2$, -L-C1-C6 haloalkyl, $-L-OR^5$, $-L-(CH_2OR^5)(CH_2)_nOR^5$, $-L-NR^5C(O)$-aryl, -L-COOH, or -LC(=O)OC1-C6 alkyl, wherein the heterocyclyl and the aryl portion of $-L-NR^5C(O)$-aryl and the heterocyclyl portion of -L-heterocyclyl and the cycloalkyl portion of the -L-cycloalkyl may be optionally substituted with one or more R^6, and wherein the aryl or heteroaryl of the -L-aryl and the -L-heteroaryl may be optionally substituted with one or more R^7;

[00091] each L is independently a C1 – C4 alkylene optionally substituted with hydroxy, C1 – C4 hydroxyalkyl or heteroaryl;

[00092] R^3 is aryl or heteroaryl, wherein the aryl or the heteroaryl is optionally substituted with one or more R^8;

[00093] R^4 is hydrogen, halogen or C1 – C3 alkyl;

[00094] each R^5 is independently hydrogen or C1 – C3 alkyl;

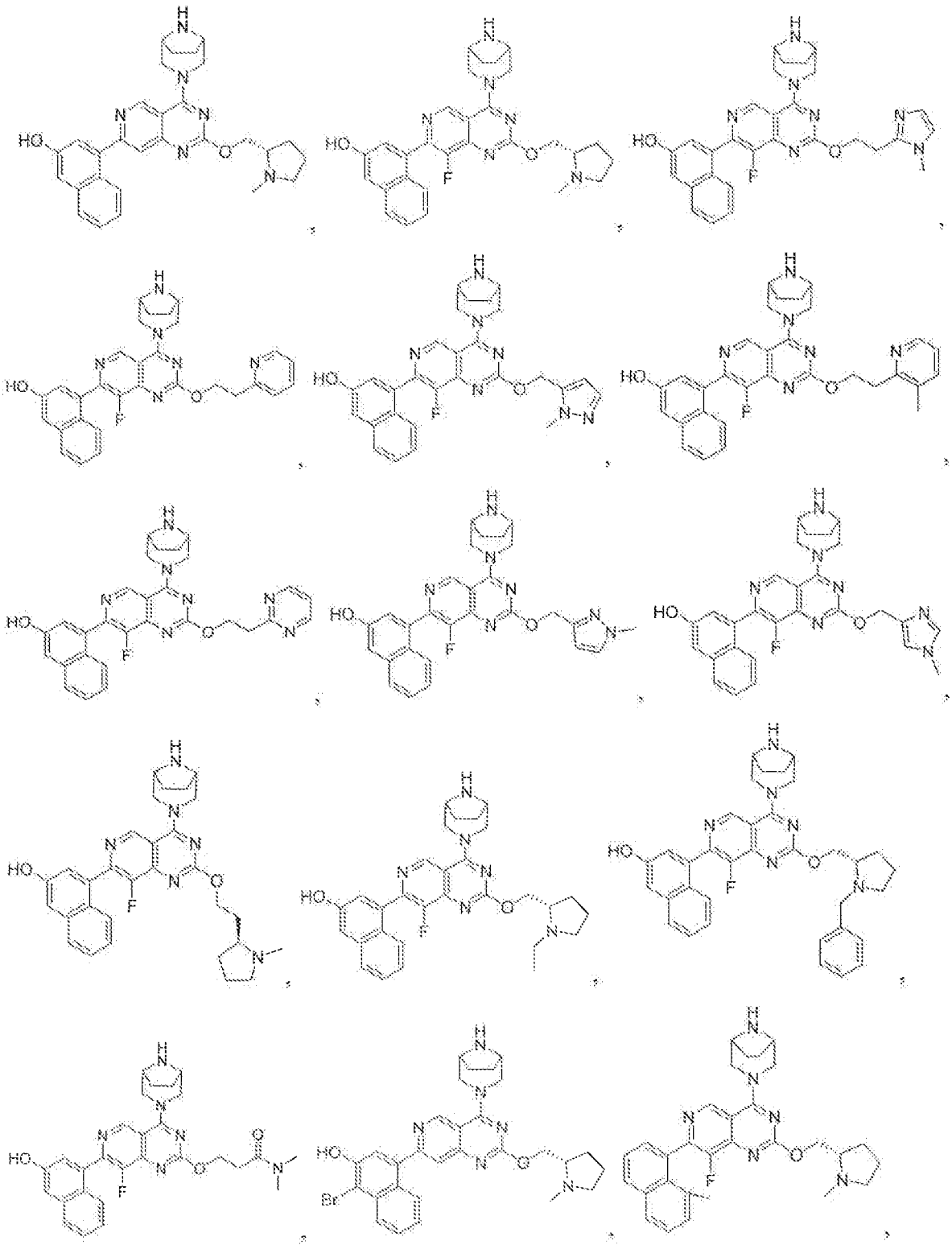
[00095] each R^6 is independently halogen, hydroxy, C1 - C3 hydroxyalkyl, C1 – C3 alkyl, C1 - C3 haloalkyl, C1-C3 alkoxy, cyano, -Q-phenyl, -Q-phenylSO_2F, -NHC(O)phenyl, -NHC(O)phenylSO_2F, C1-C3 alkyl substituted pyrazolyl, araC1-C3 alkyl-, tert-butyldimethylsilyloxyCH_2- , -N(R^5)$_2$, (C1-C3 alkoxy)C1-C3 alkyl-, (C1-C3 alkyl)C(=O), oxo, (C1-C3 haloalkyl)C(=O)-, -SO_2F, (C1-C3 alkoxy)C1-C3 alkoxy, -$CH_2OC(O)N(R^5)_2$, -$CH_2NHC(O)OC1$-C6 alkyl, -$CH_2NHC(O)N(R^5)_2$, -$CH_2NHC(O)C1$-C6 alkyl, -CH_2(pyrazolyl), -CH_2NHSO_2C1-C6 alkyl, -$CH_2OC(O)$heterocyclyl, -$OC(O)N(R^5)_2$, -OC(O)NH(C1-C3 alkyl)O(C1-C3 alkyl), -OC(O)NH(C1-C3 alkyl)O(C1-C3 alkyl)phenyl(C1-C3 alkyl)N(CH_3)$_2$, -OC(O)NH(C1-C3 alkyl)O(C1-C3 alkyl)phenyl or -OC(O)heterocyclyl, -CH_2heterocyclyl, wherein the phenyl of -NHC(O)phenyl or -OC(O)NH(C1-C3 alkyl)O(C1-C3 alkyl)phenyl is optionally substituted with -C(O)H or OH and wherein the heterocyclyl of -CH_2heterocyclyl is optionally substituted with oxo;

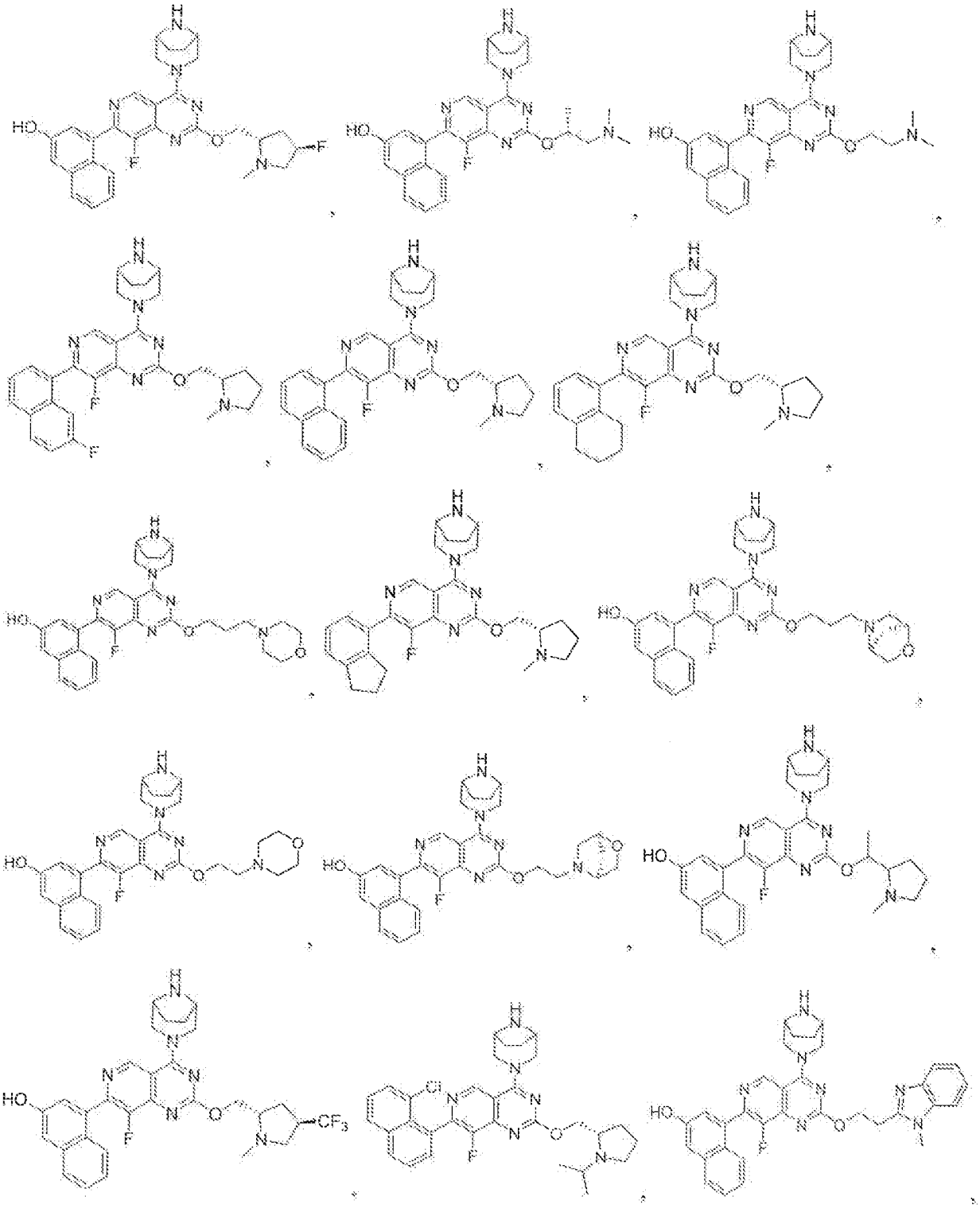
[00096] Q is a bond or O;

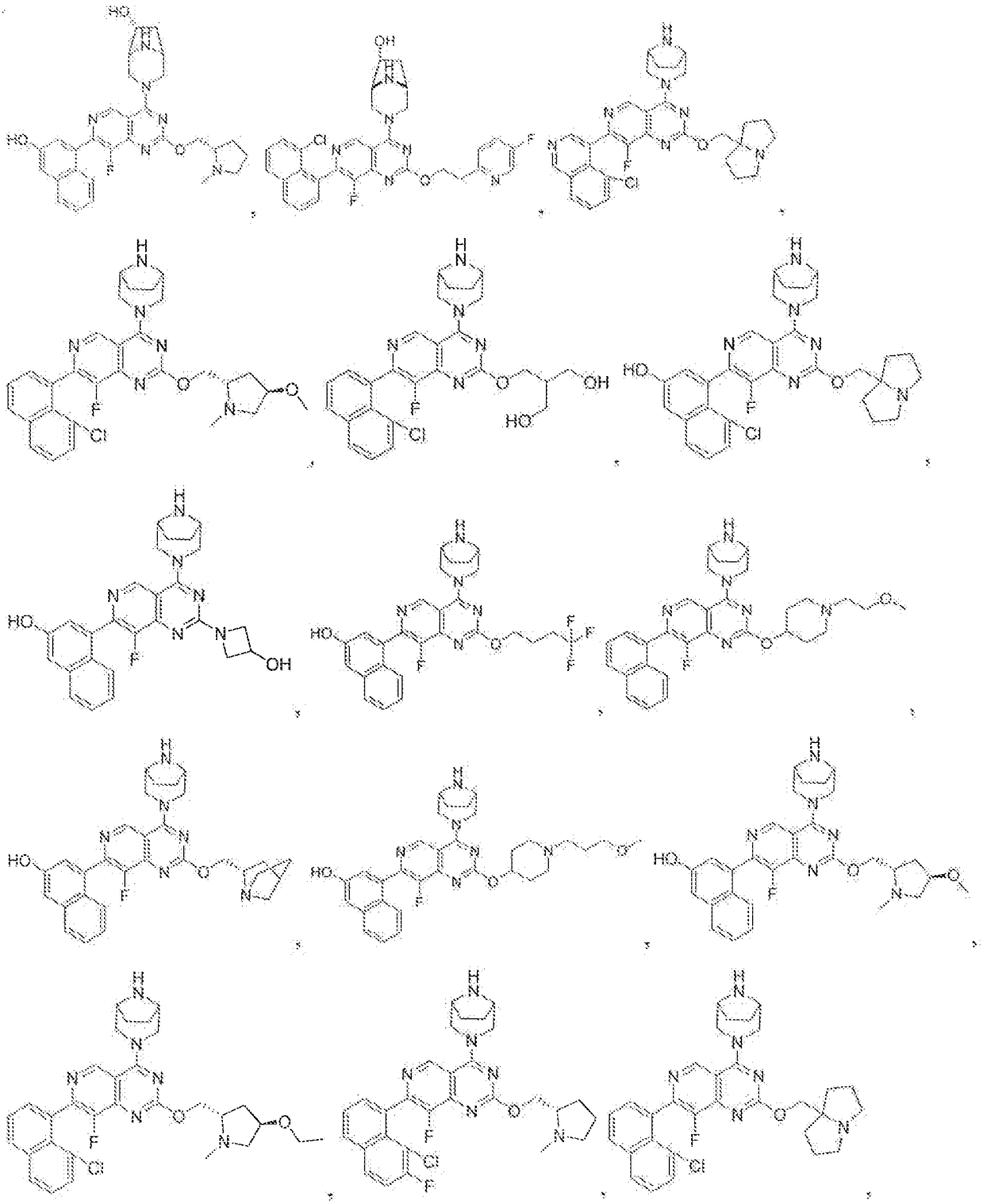
[00097] each R^7 is independently halogen, hydroxy, HC(=O)-, C1 – C4 alkyl, C1 – C4 alkoxy, C1 – C4 haloalkyl, C1 – C4 hydroxyalkyl, or -N(R^5)$_2$; and

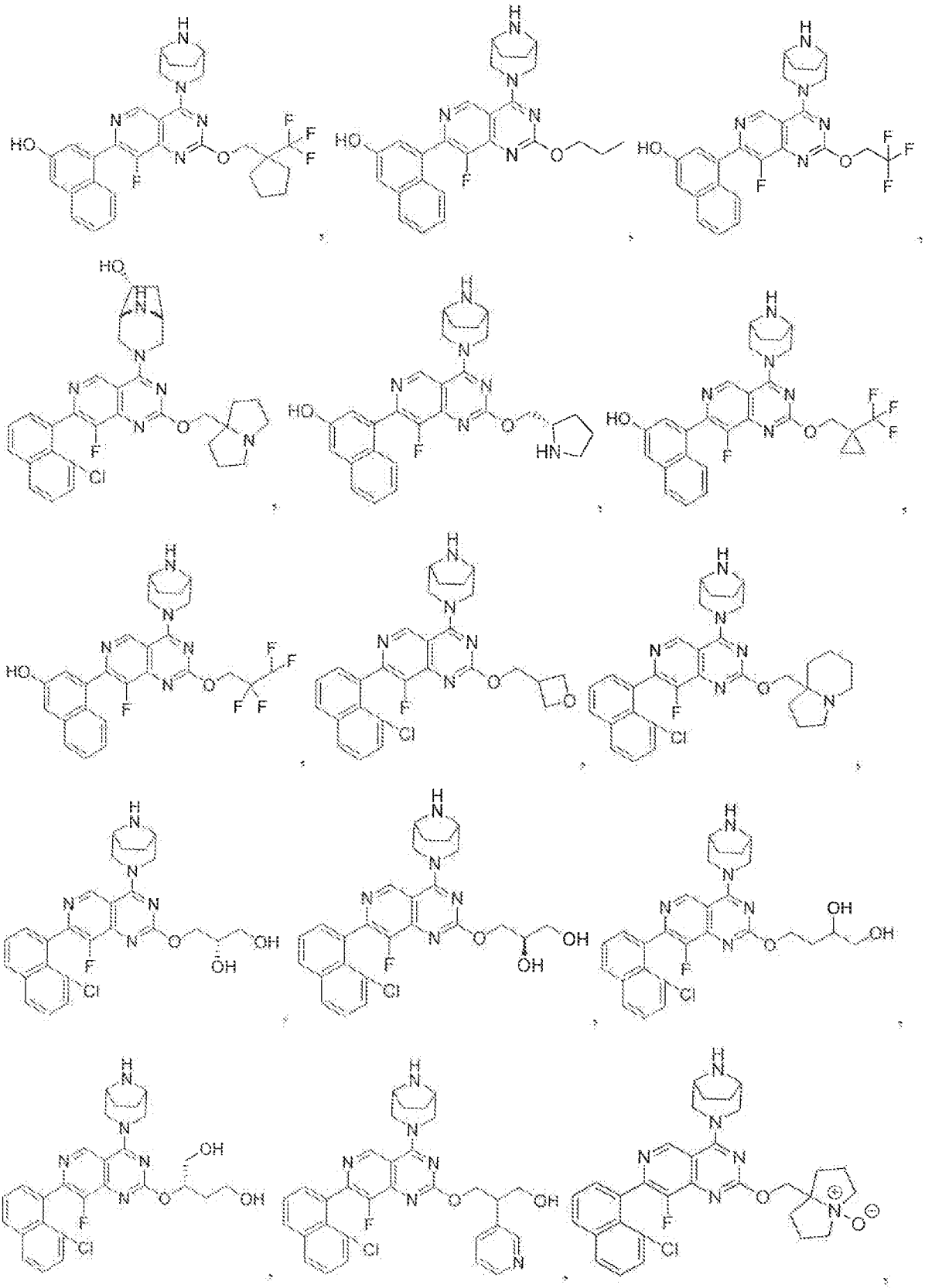
[00098] each R^8 is independently halogen, cyano, hydroxy, C1 - C4 alkyl, -S-C1 - C3 alkyl, C2 – C4 alkenyl, C2 – C4 alkynyl, C2 – C4 hydroxyalkynyl, C1-C3 cyanoalkyl , triazolyl, C1 - C3 haloalkyl, -O- C1 - C3 haloalkyl, -S- C1 - C3 haloalkyl, C1-C3 alkoxy, hydroxyC1-C3 alkyl, -$CH_2C(=O)N(R^5)_2$, -C3-C4 alkynyl(NR^5)$_2$, -N(R^5)$_2$, deuteroC2-C4 alkynyl, (C1-C3 alkoxy)haloC1-C3 alkyl-, or C3-C6 cycloalkyl wherein said C3-C6 cycloalkyl is optionally substituted with halogen or C1-C3 alkyl.

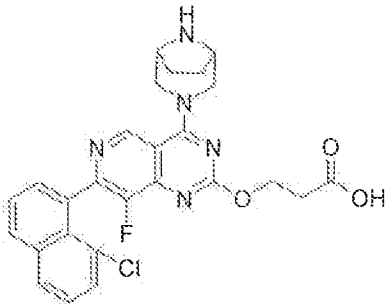
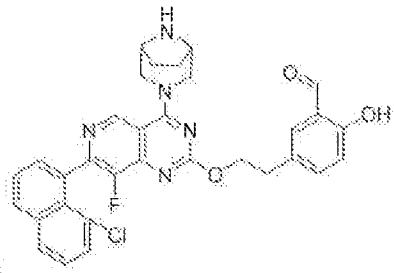
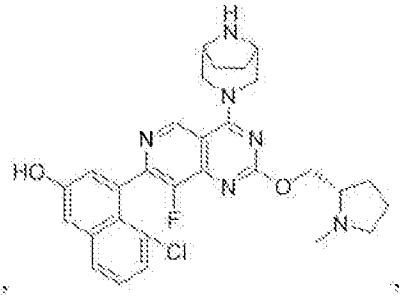
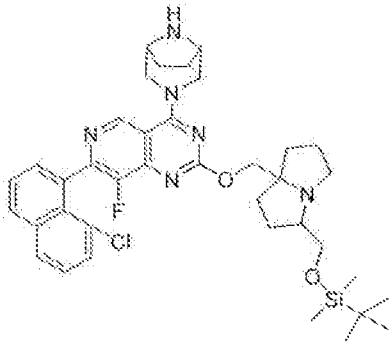
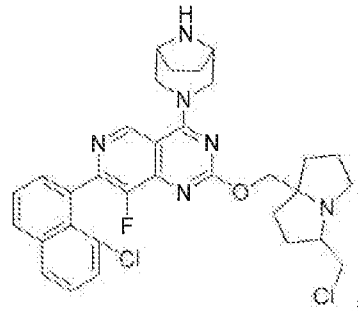
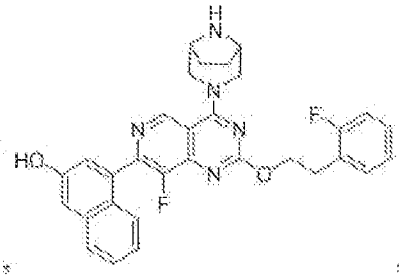
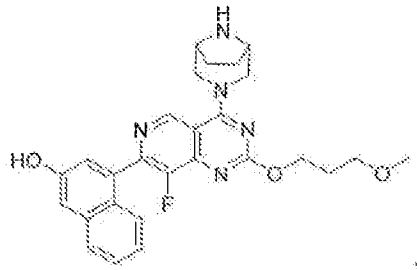
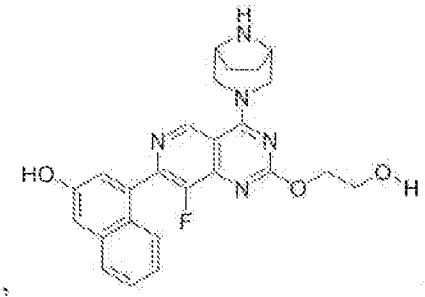
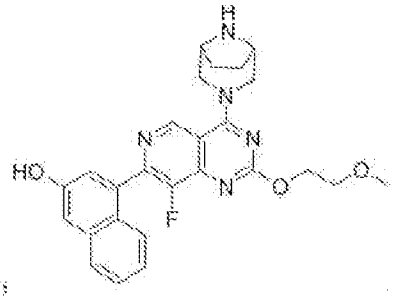
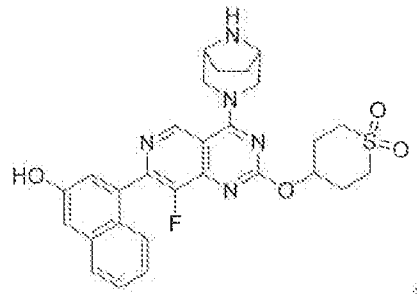
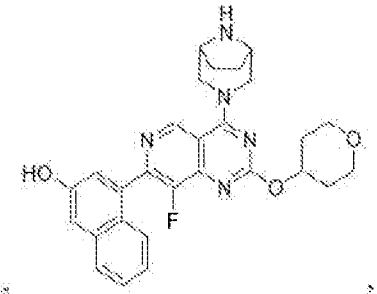
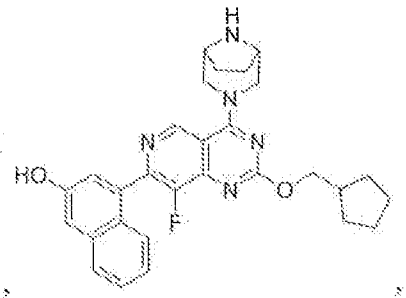
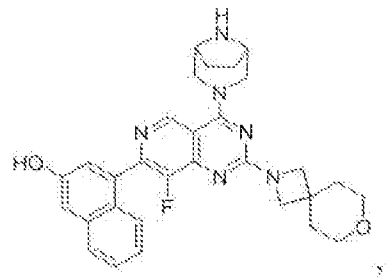
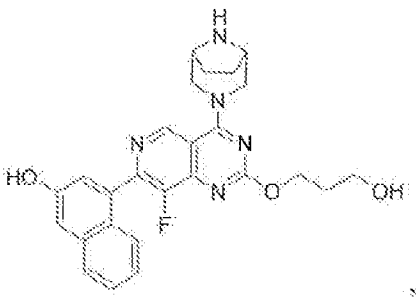
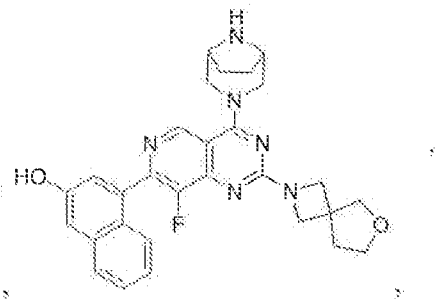
[00099] Nonlimiting examples of KRas G12D inhibitor compounds of Formula (I), useful in the methods disclosed herein are are selected from the group consisting of compound Nos 1-458 (as numbered in WO2021/041671), or pharmaceutically acceptable salts thereof, including the following structures:In one embodiment, the KRas G12D inhibitor is selected from:

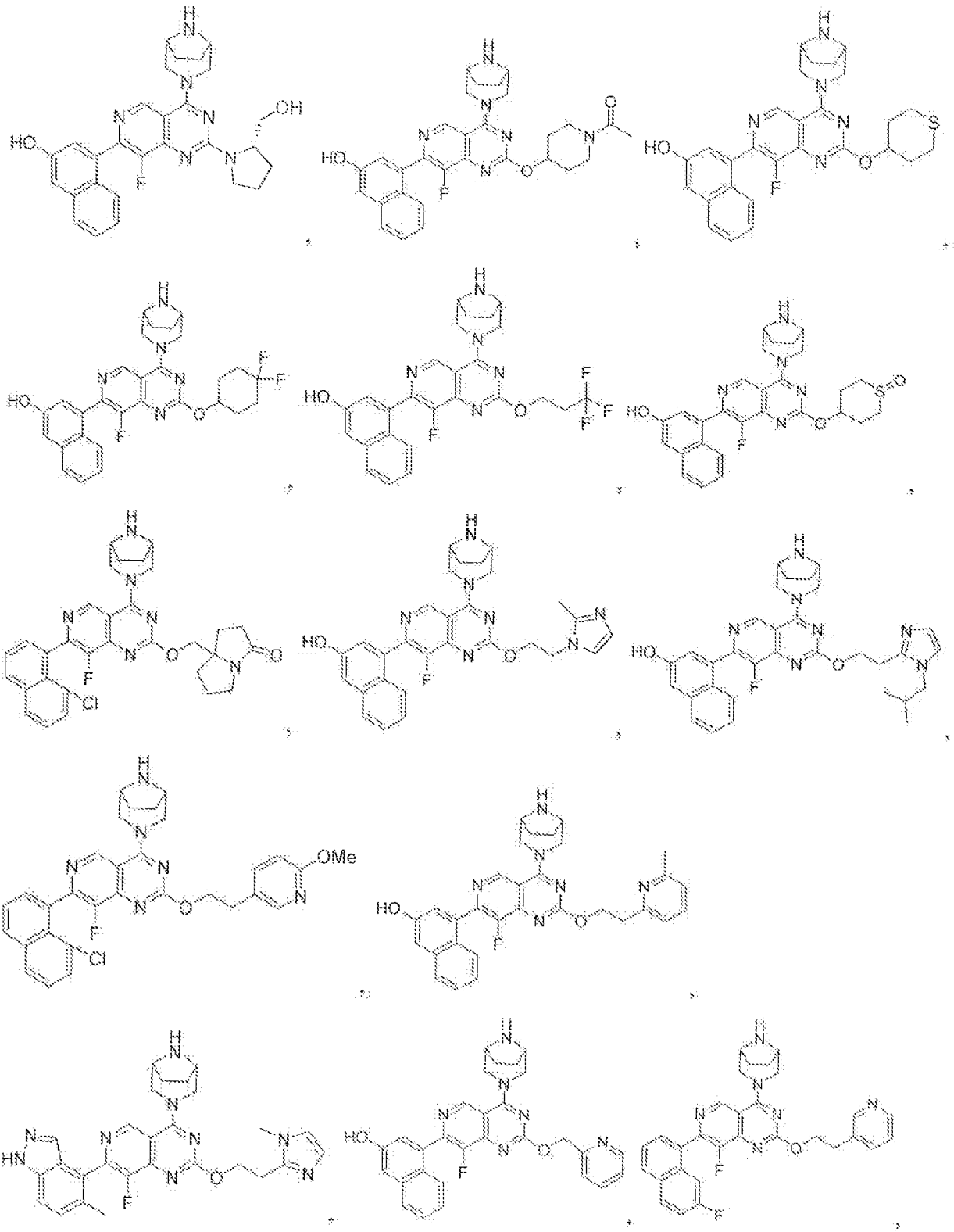


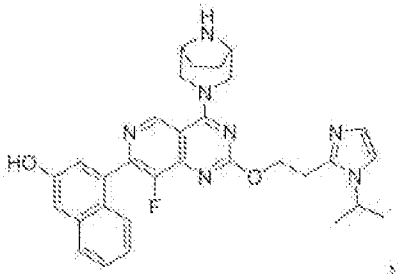






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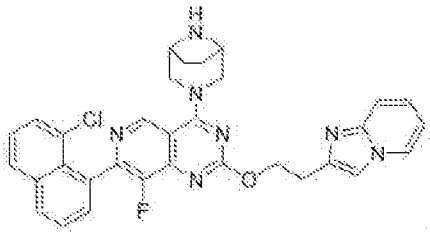
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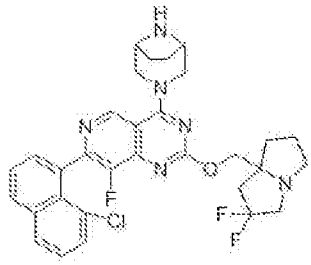
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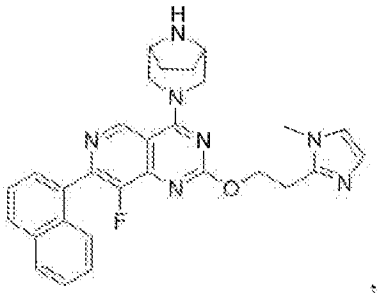
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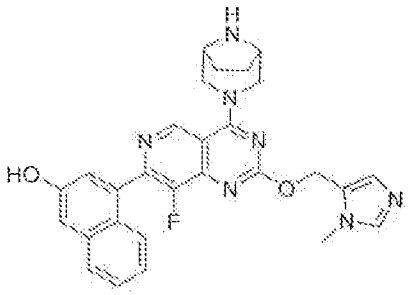
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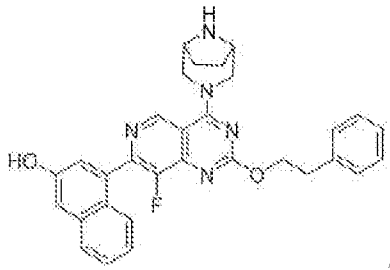
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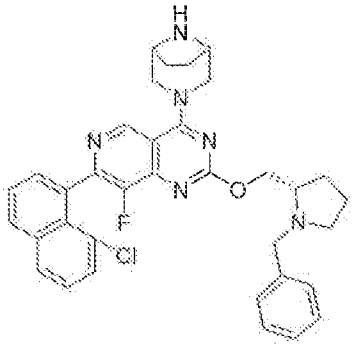
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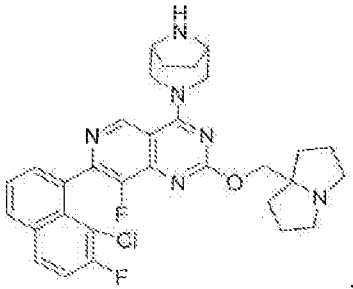
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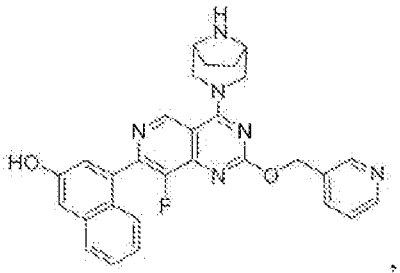
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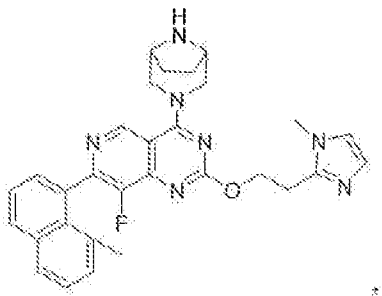
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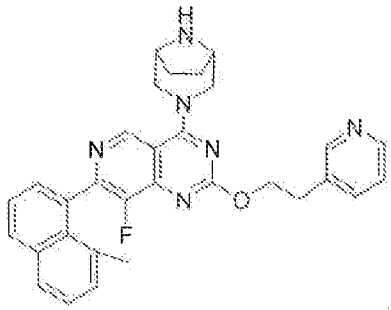
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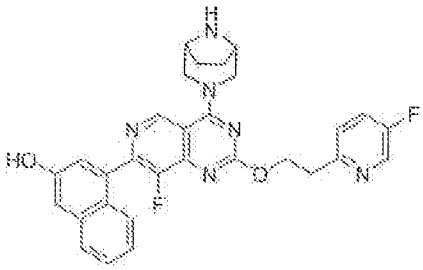
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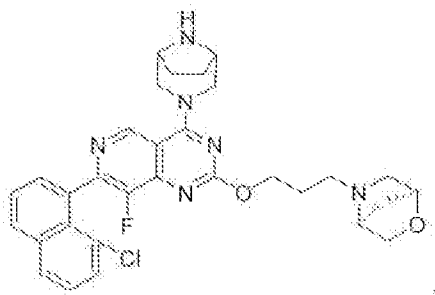
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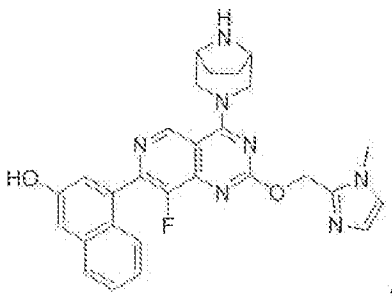
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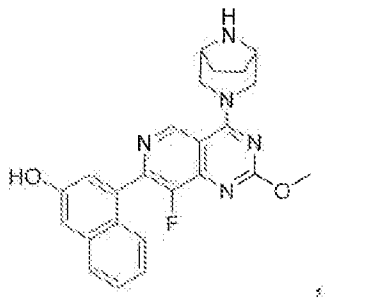
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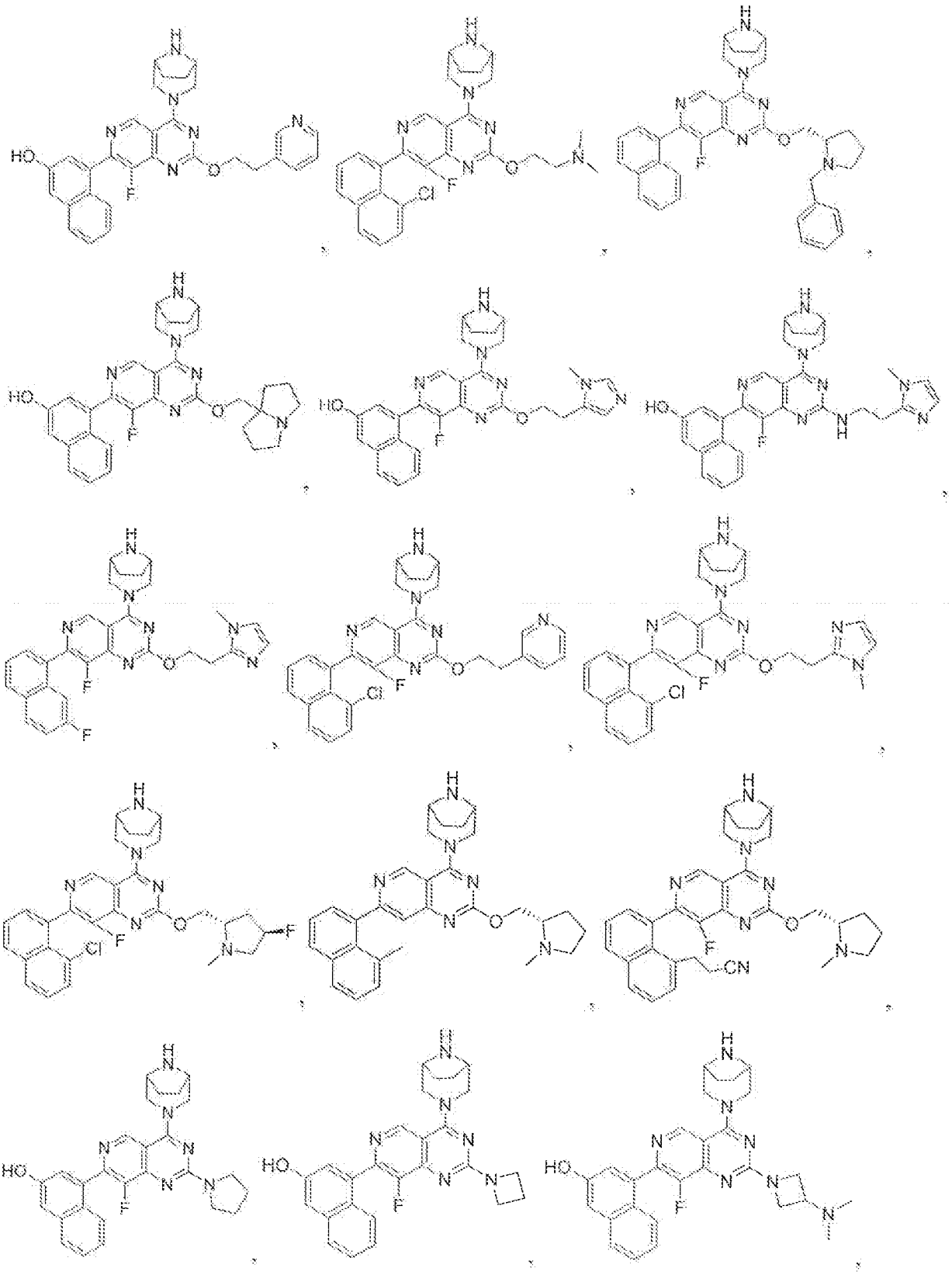

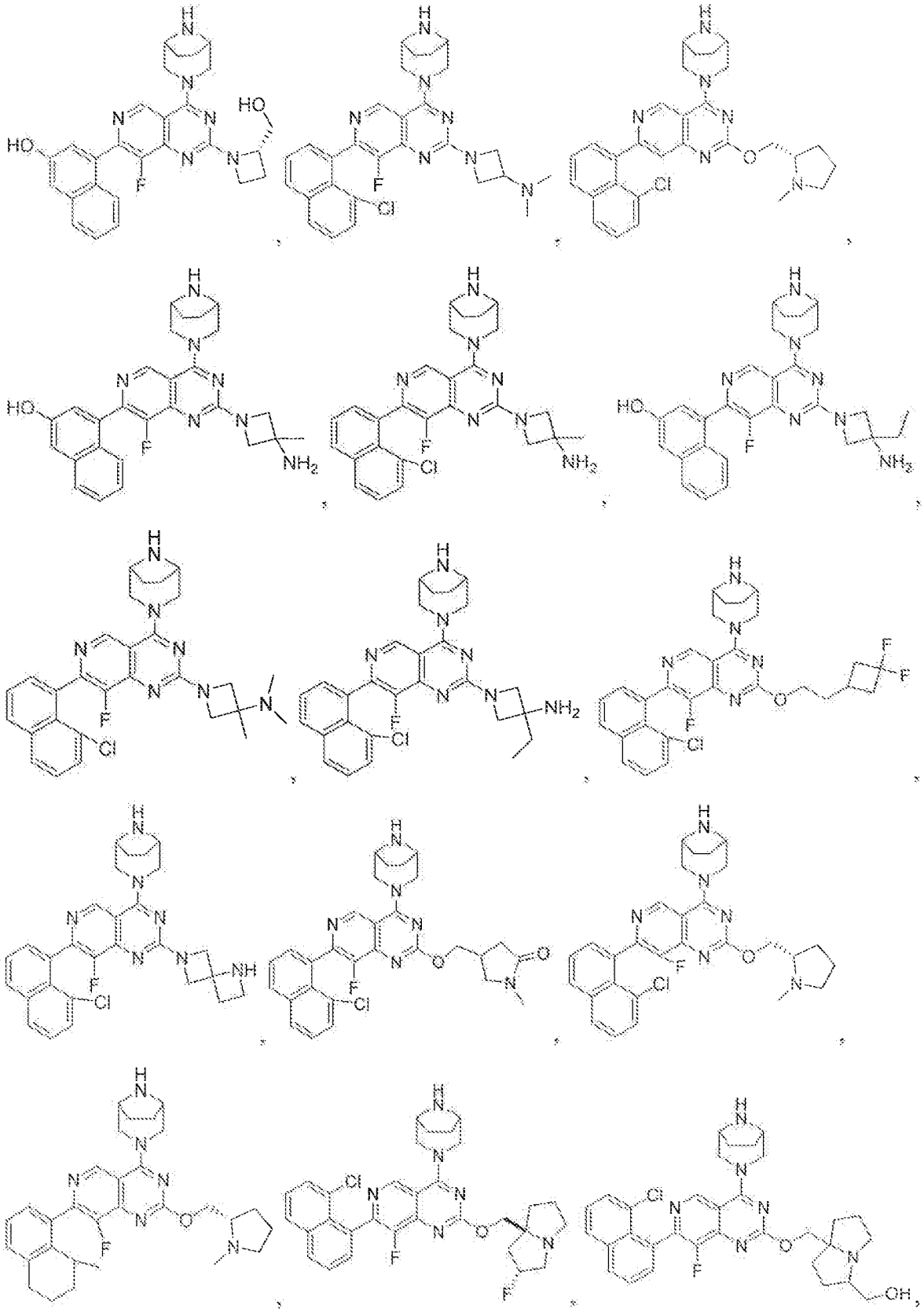

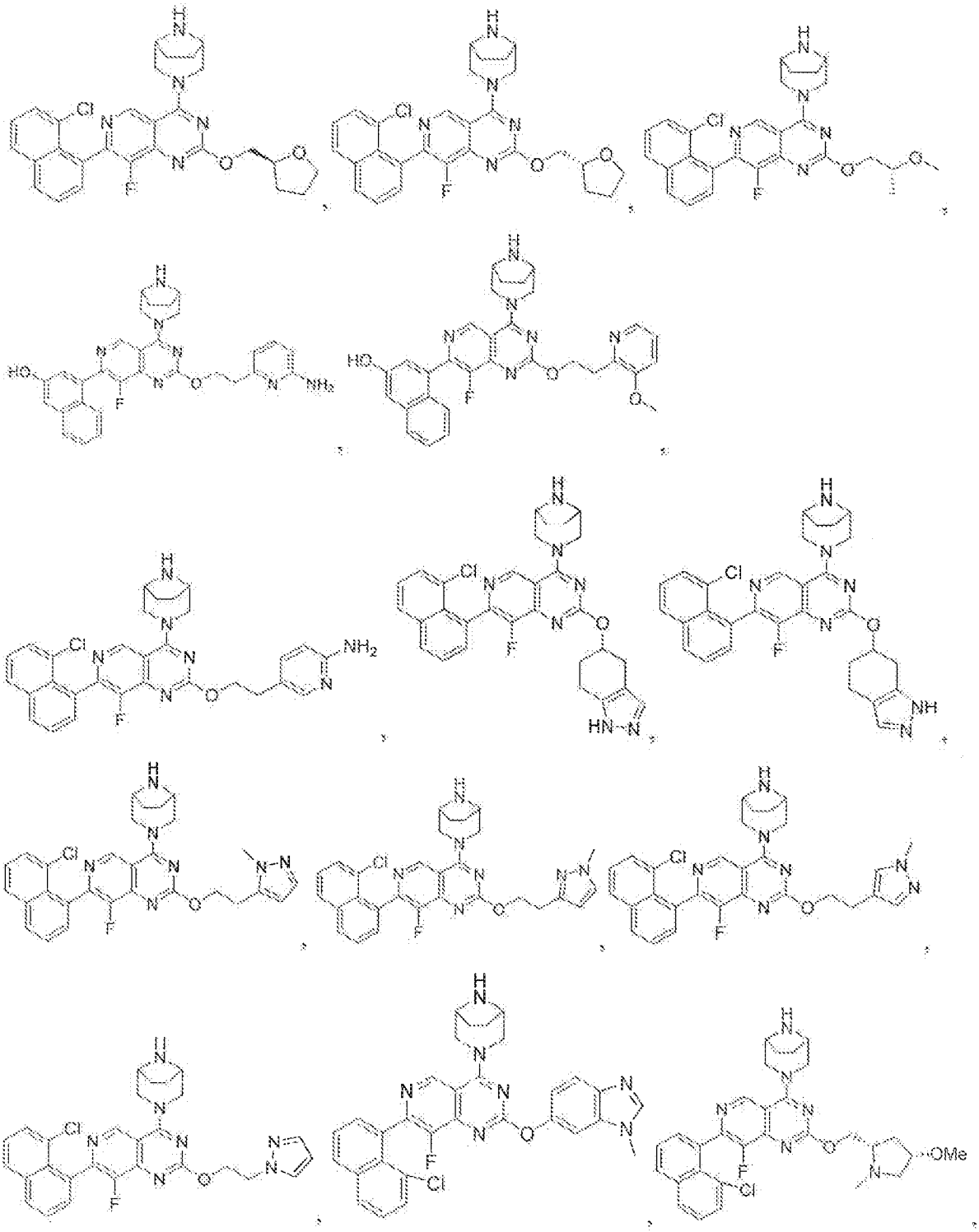

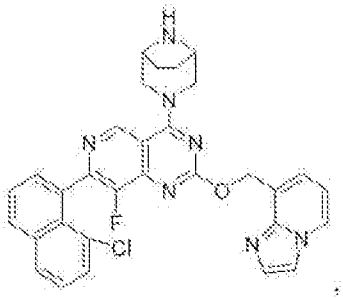

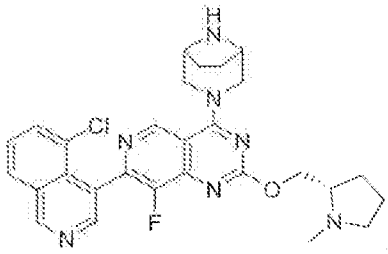

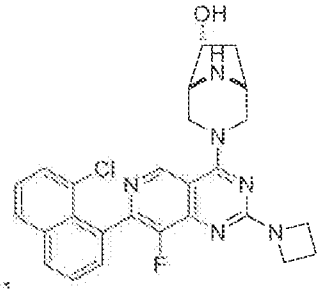

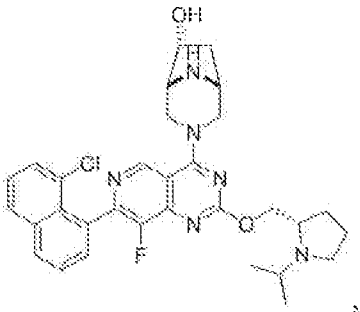

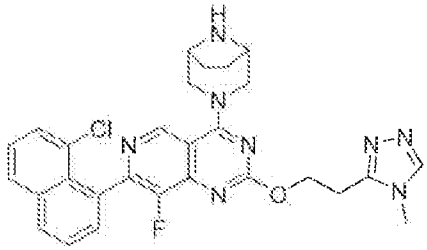

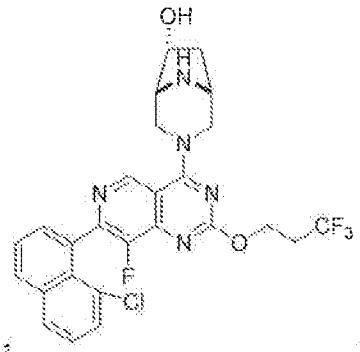

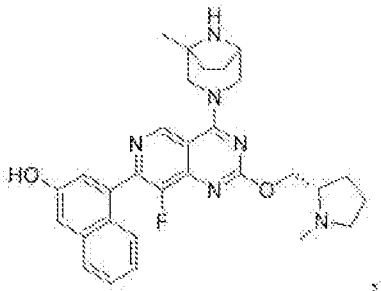

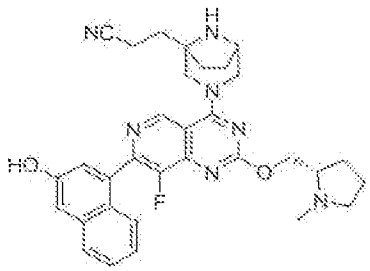

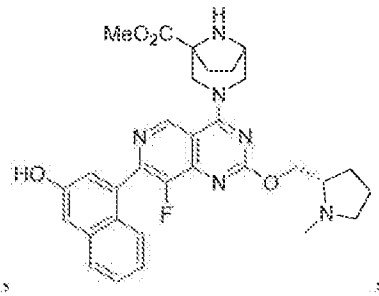

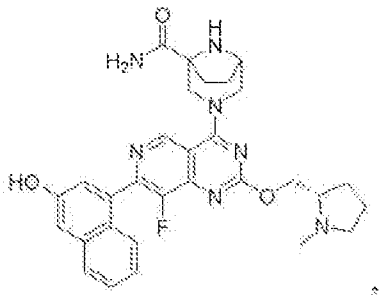

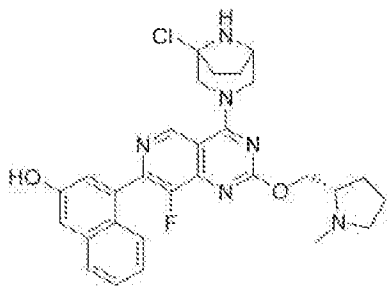

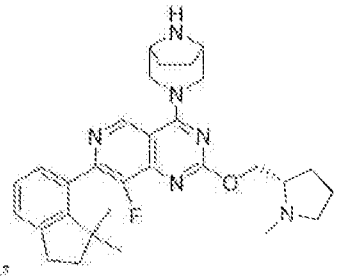

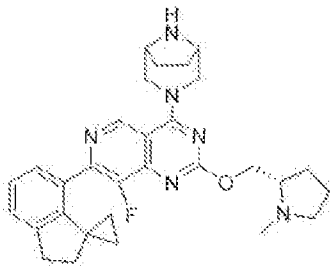

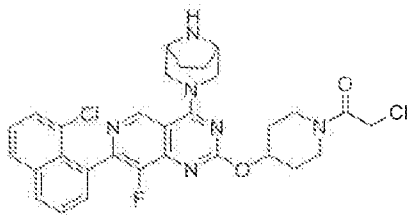

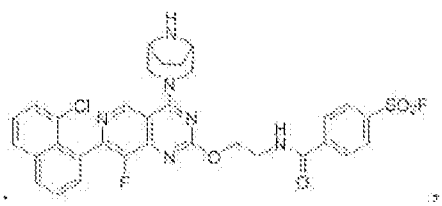

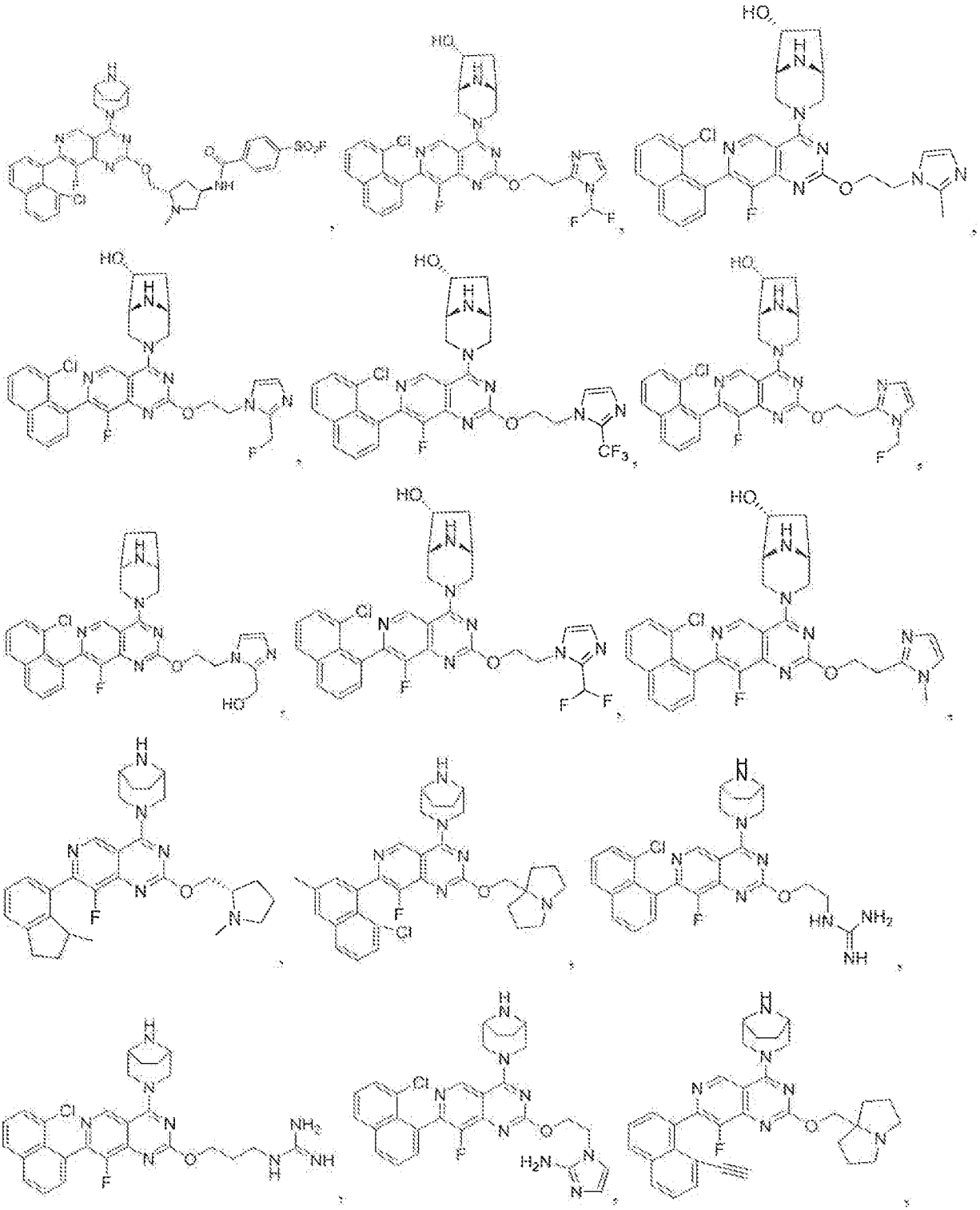

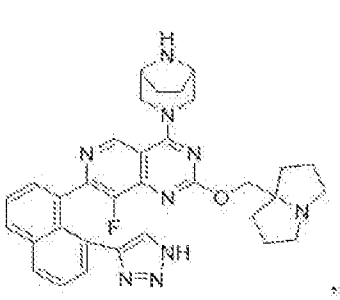
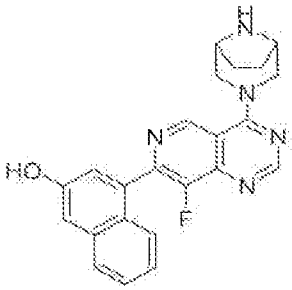
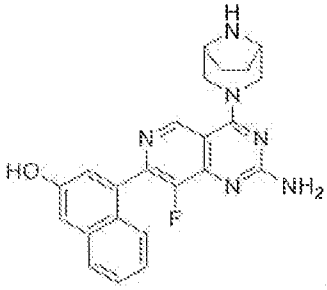
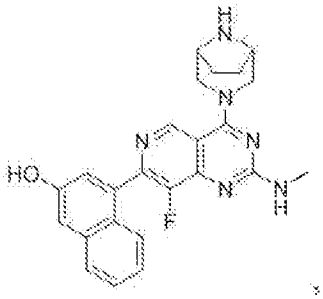
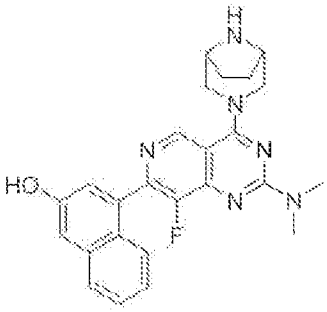
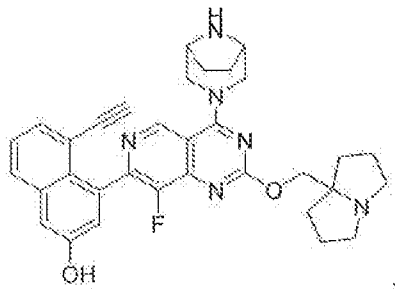
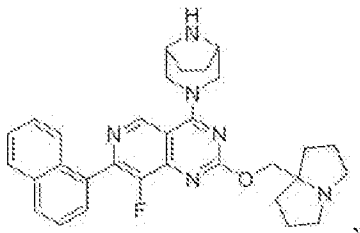
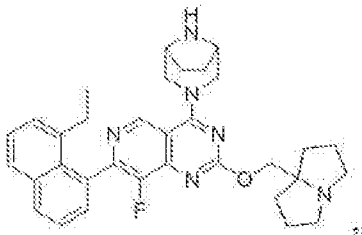
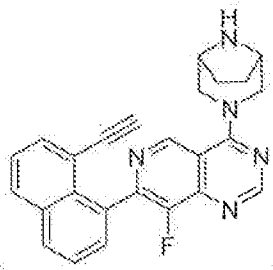
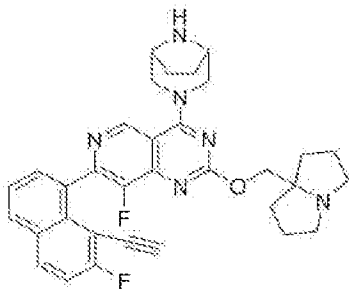
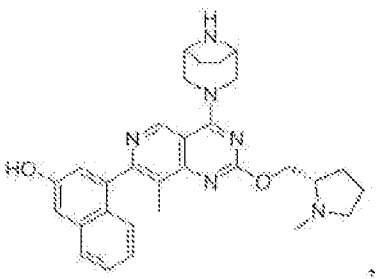
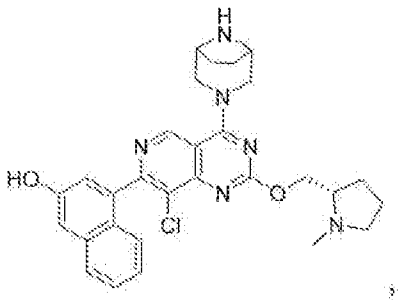
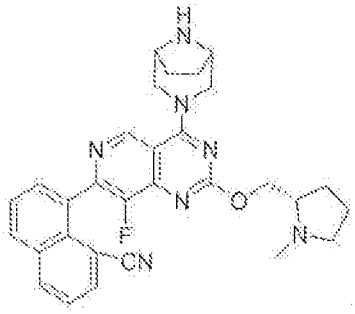
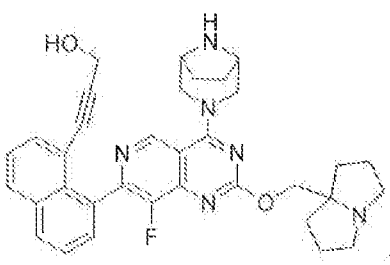
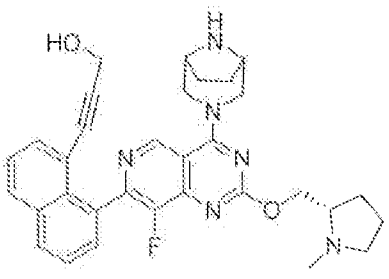

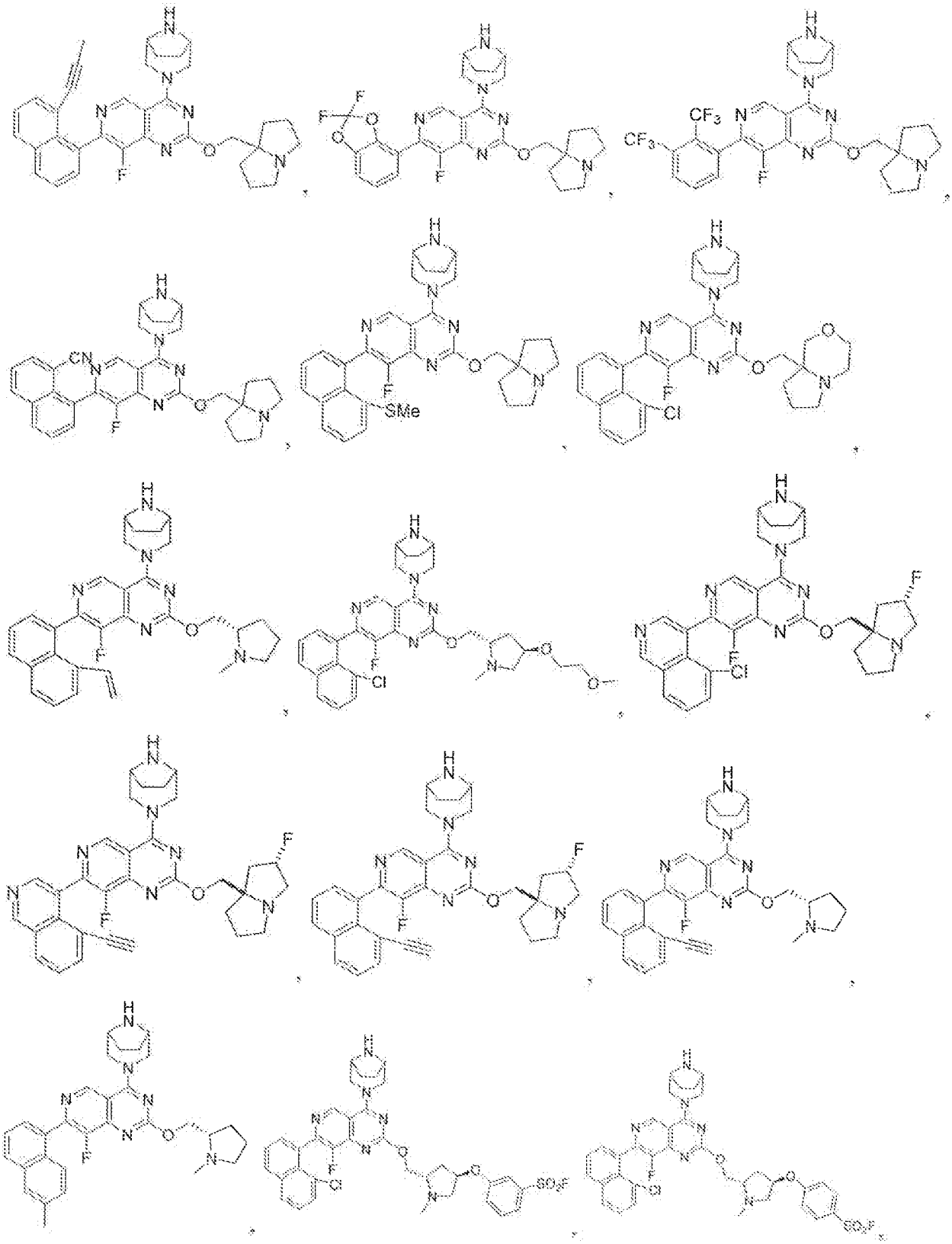

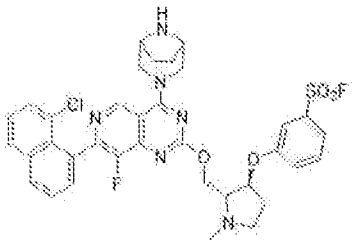
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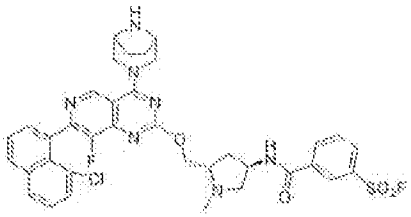
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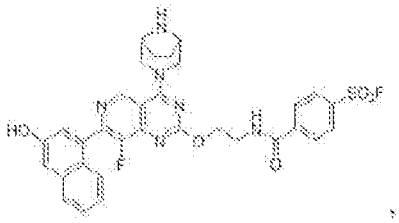
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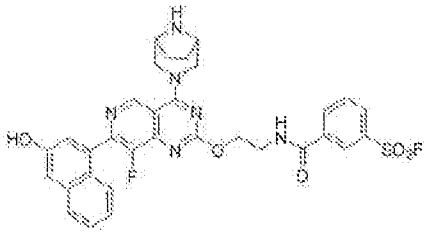
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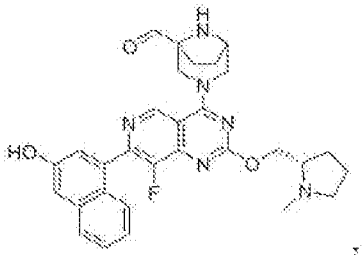
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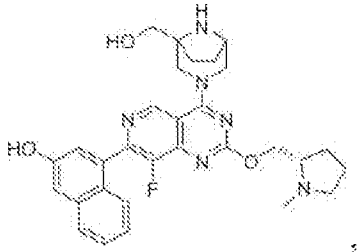
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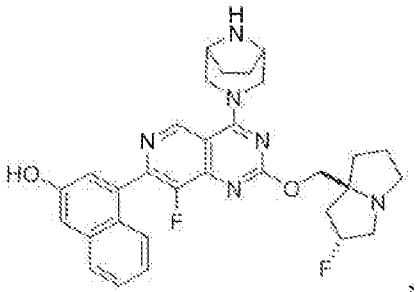
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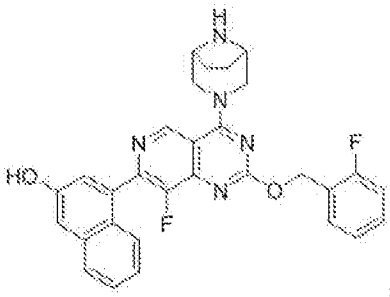
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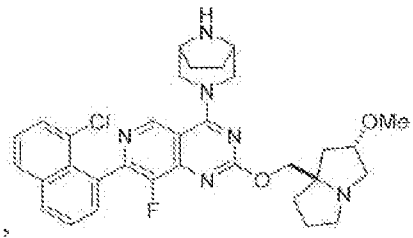
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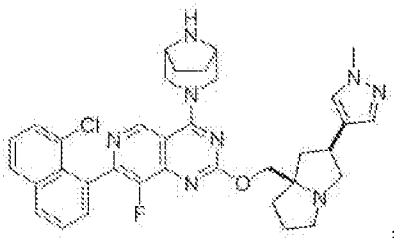
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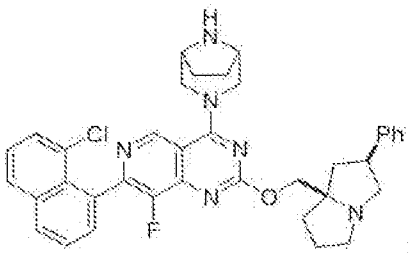
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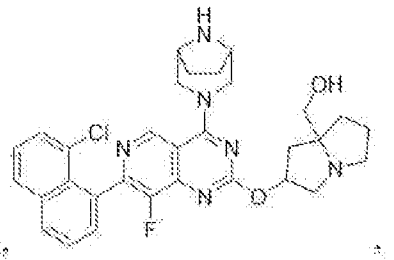
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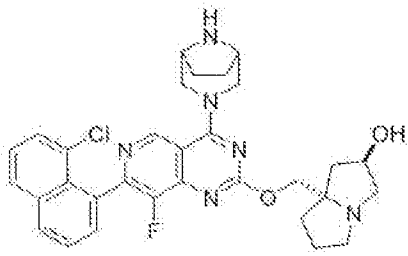
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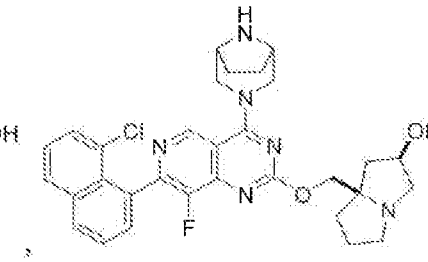
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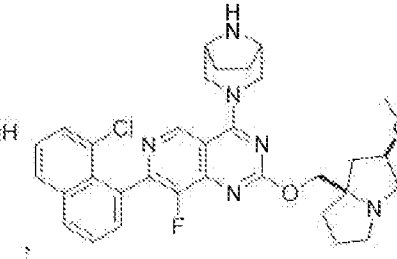
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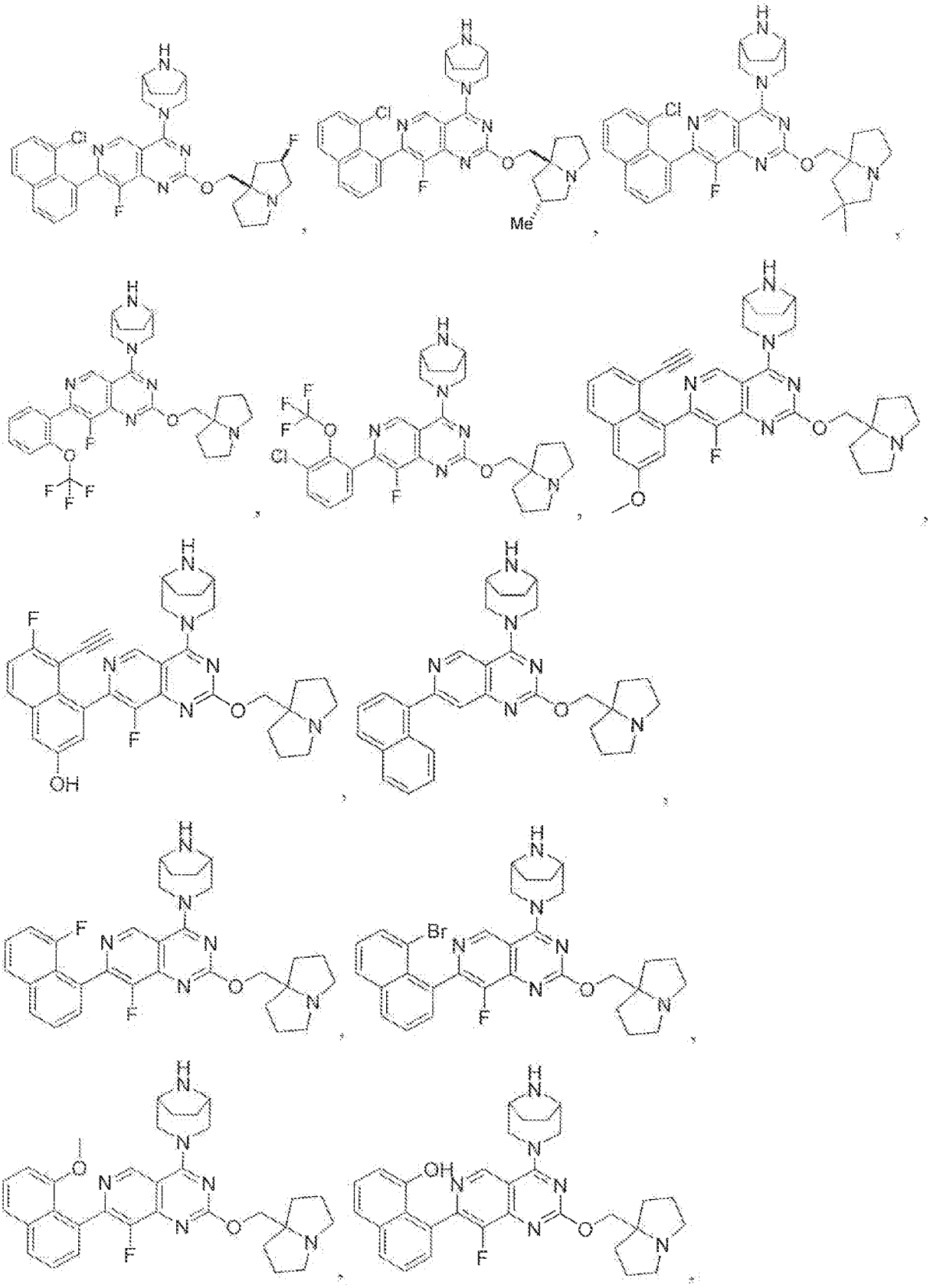

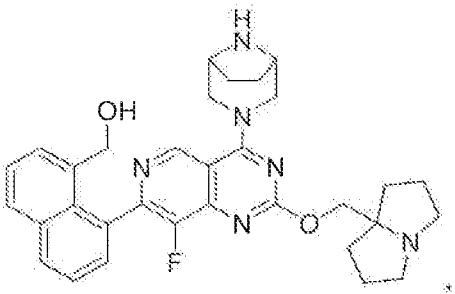
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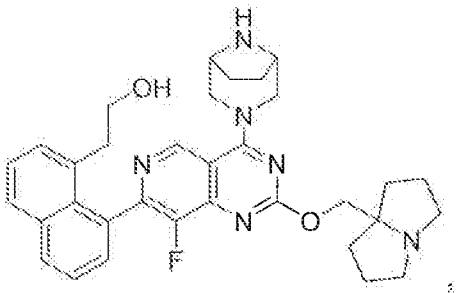
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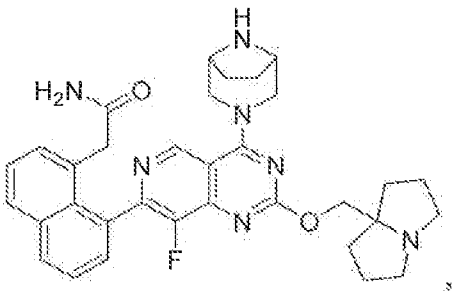
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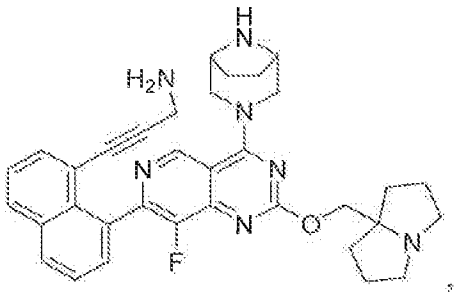
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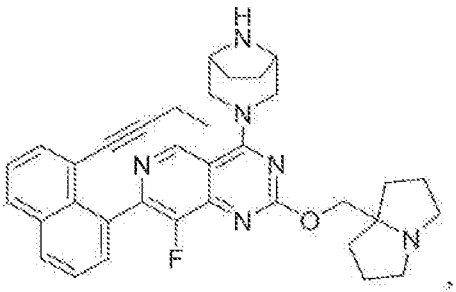
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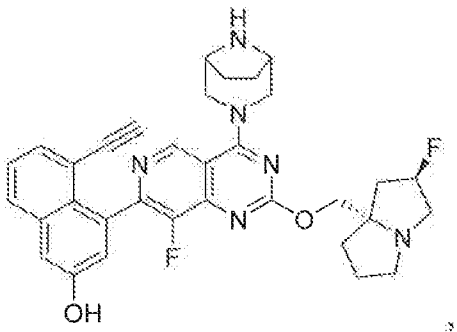
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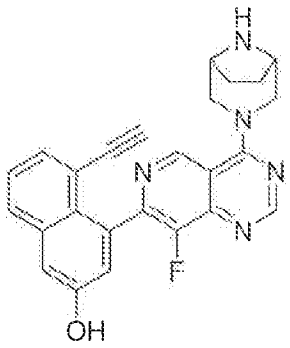
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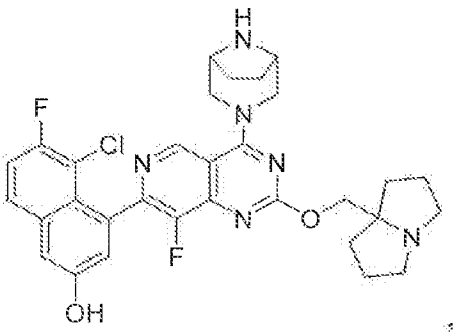
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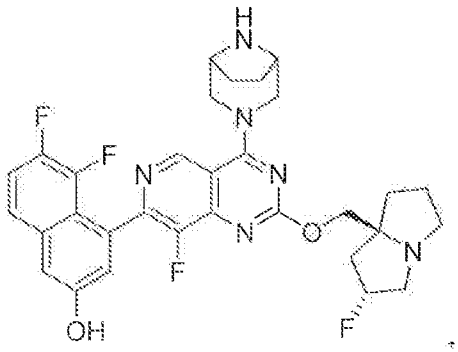
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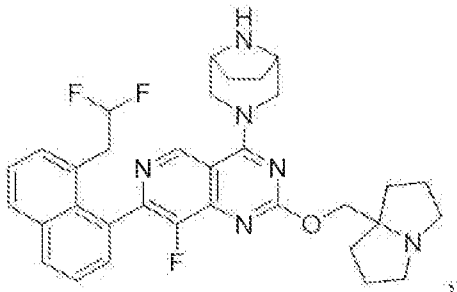
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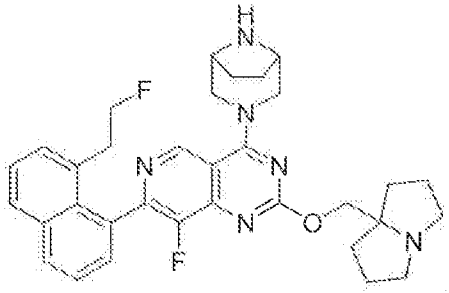
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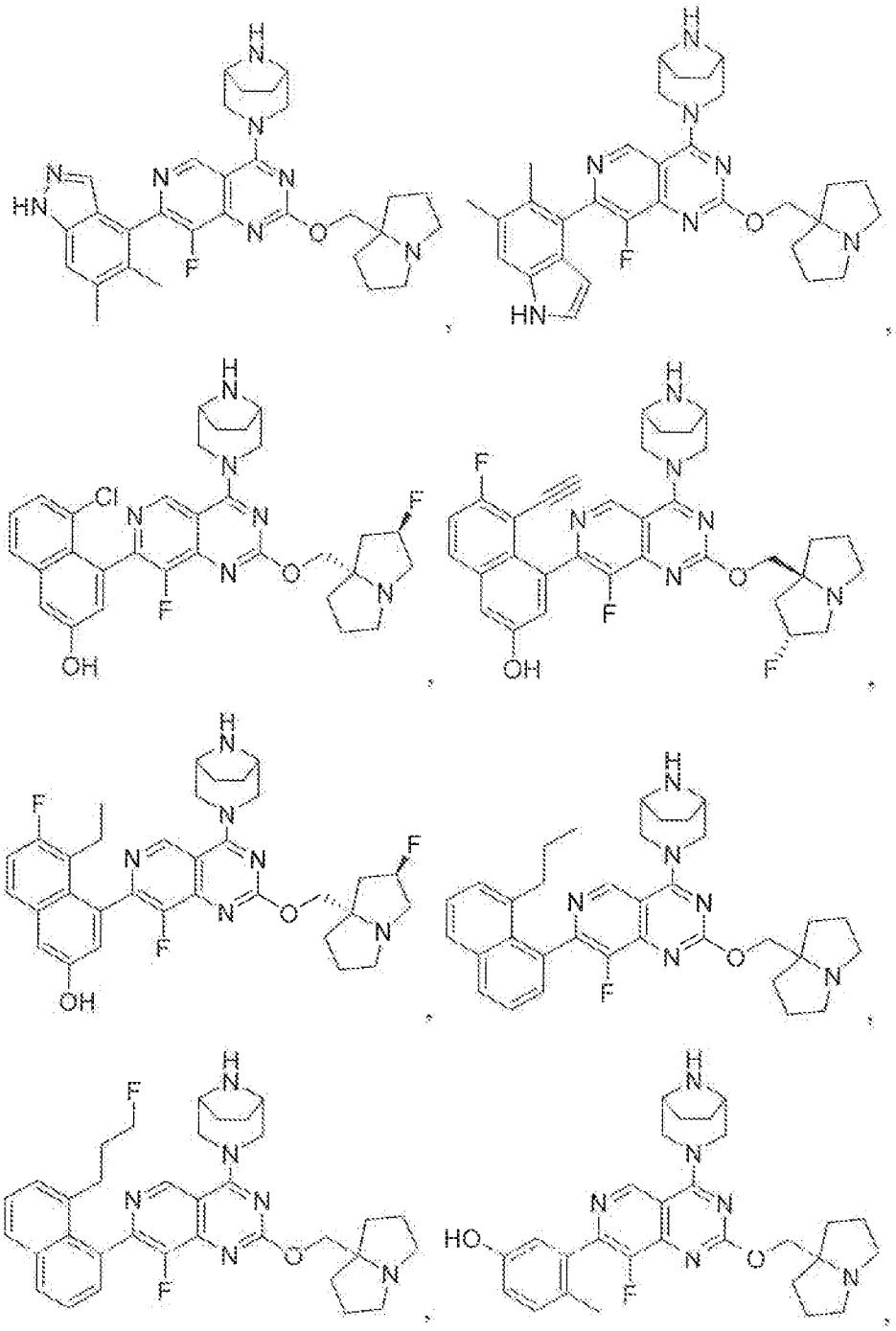
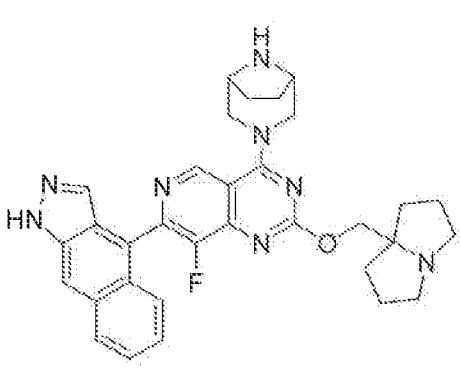
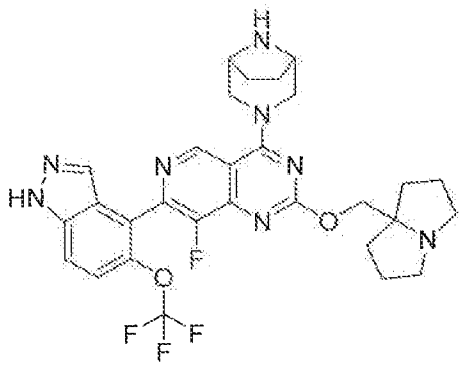
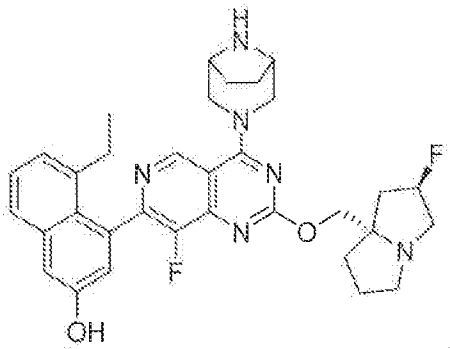
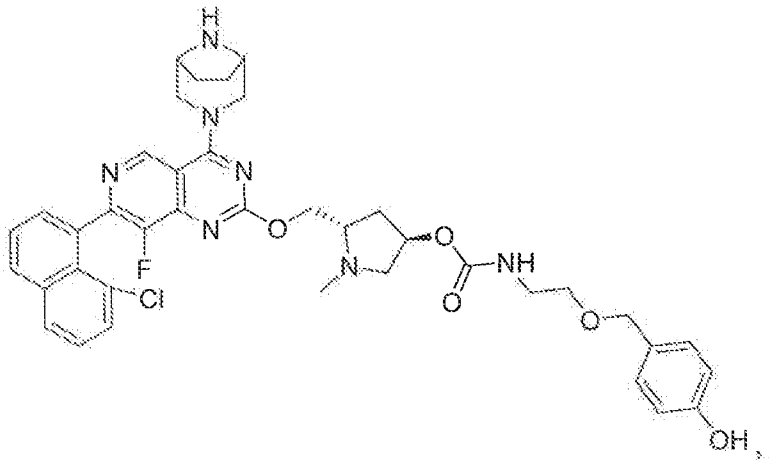
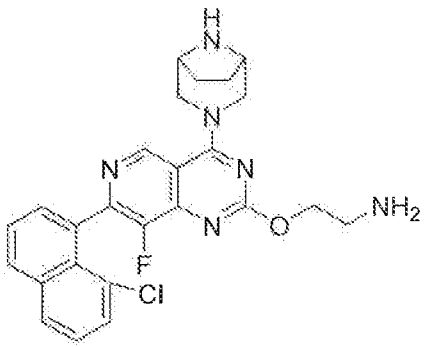


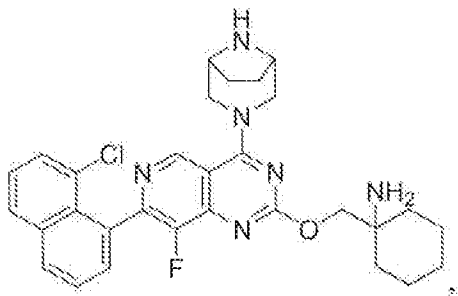


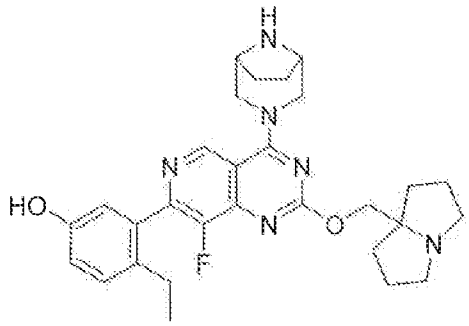


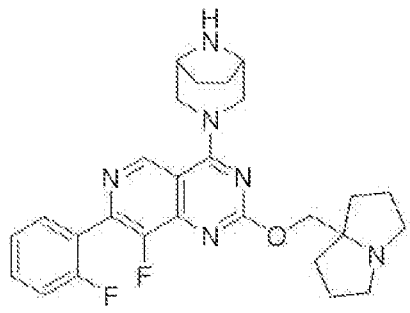


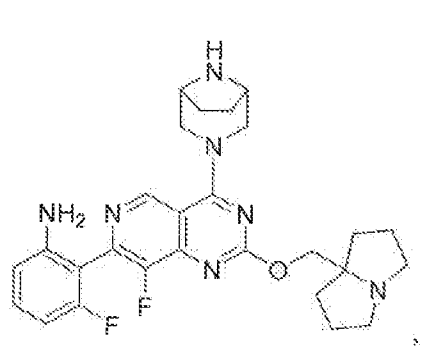


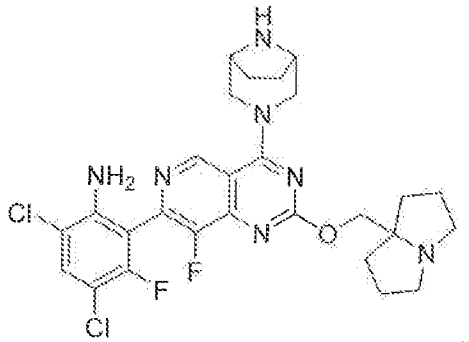


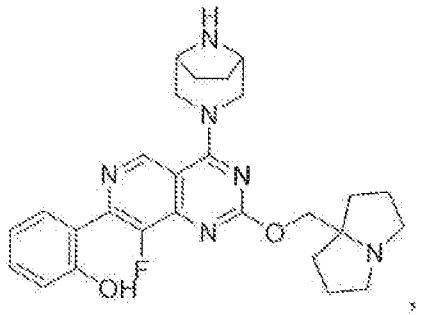


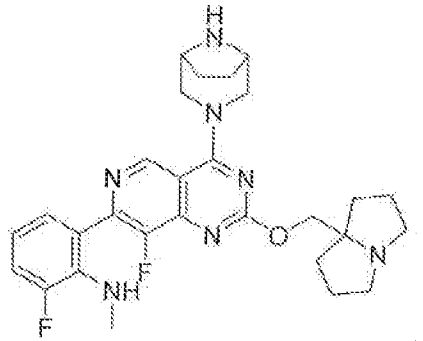


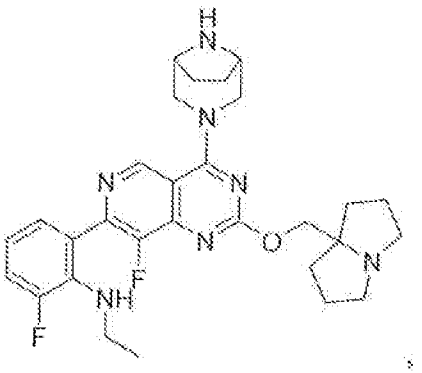


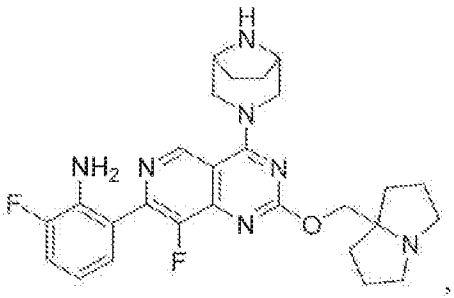


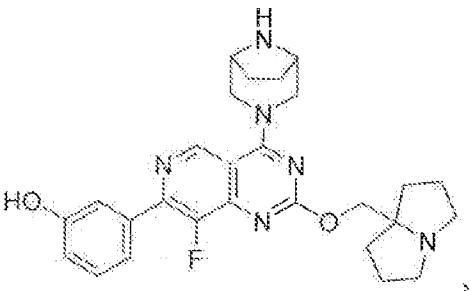


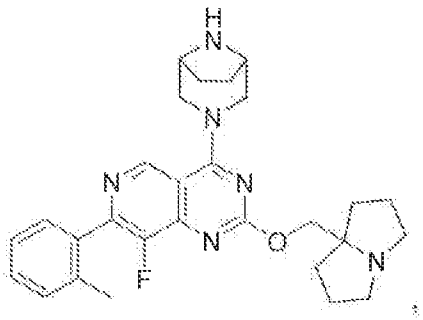


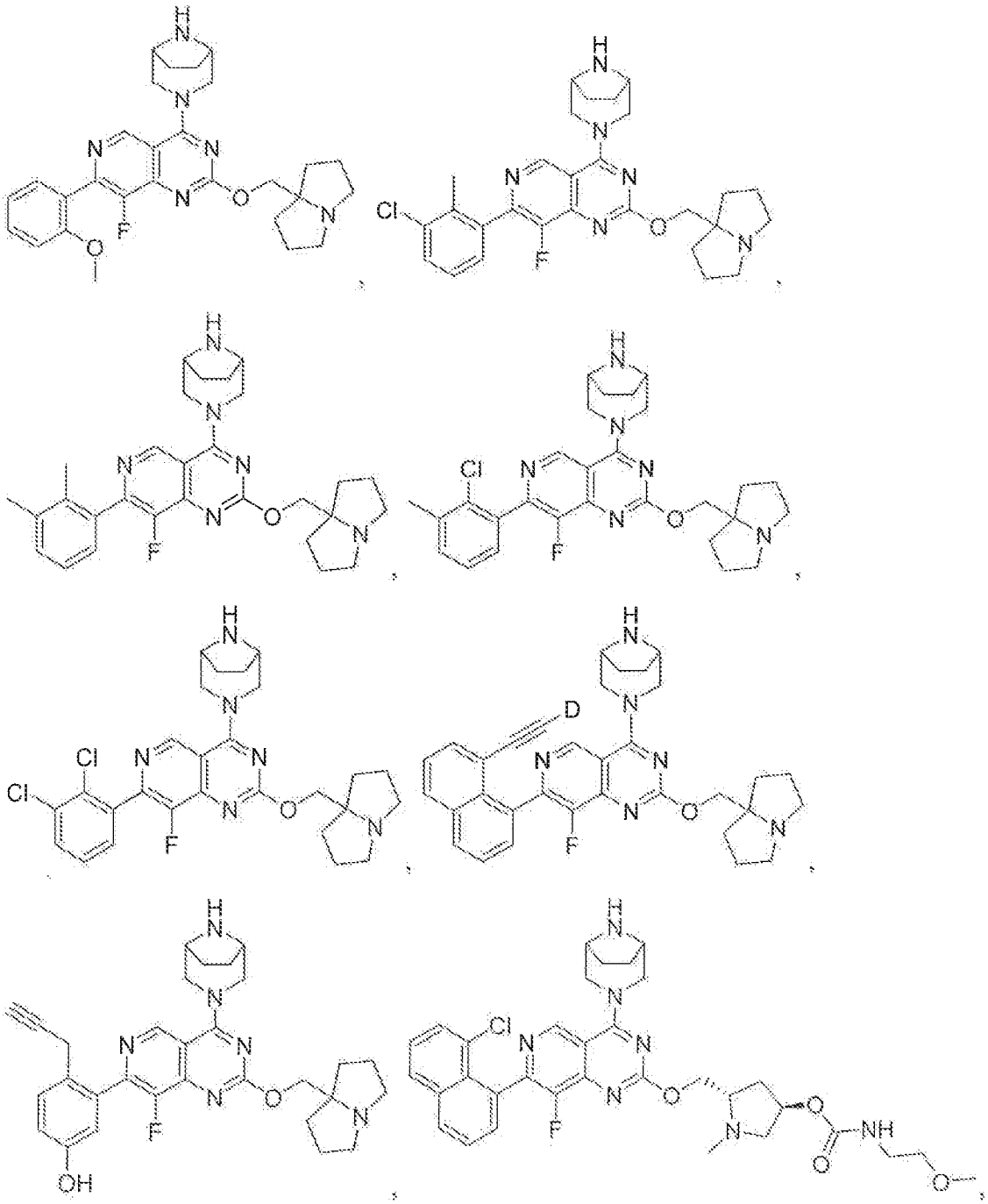


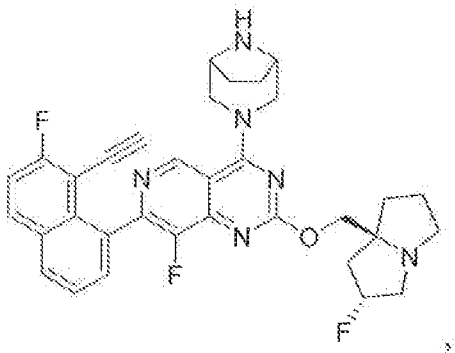


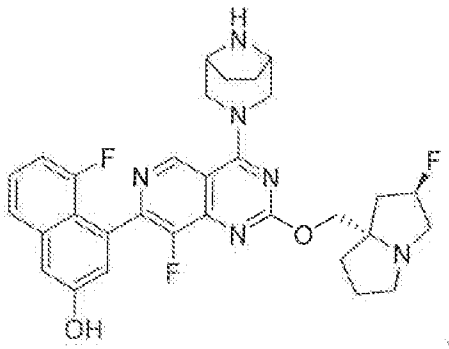


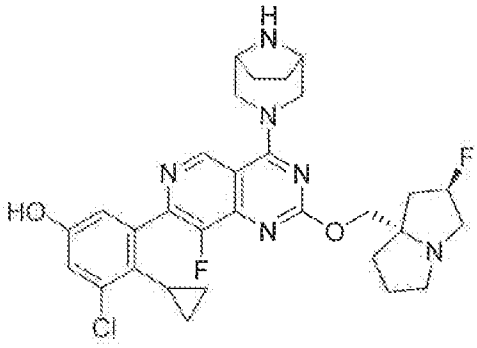


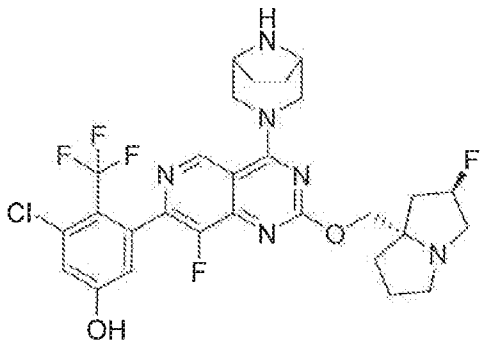


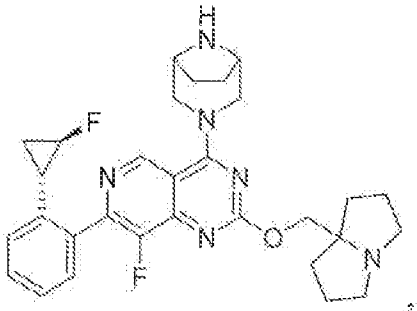


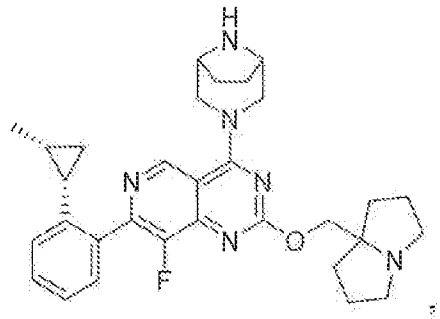


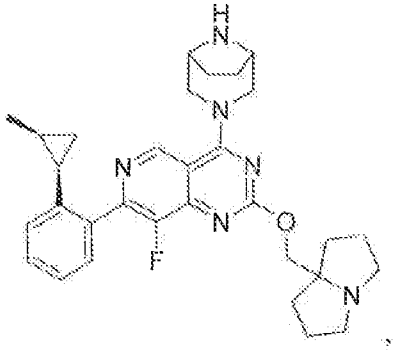


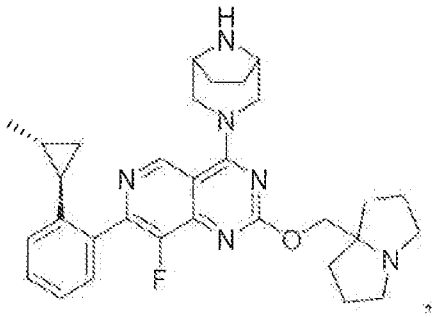


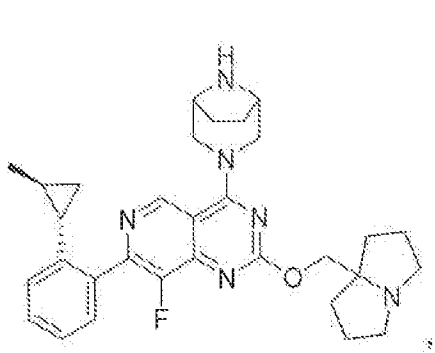


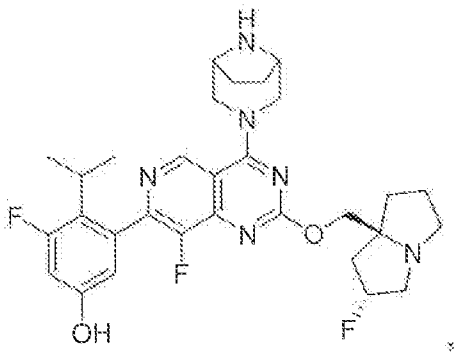


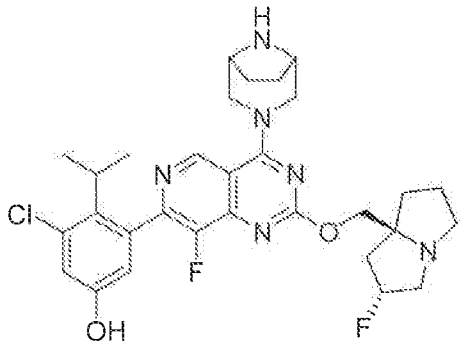


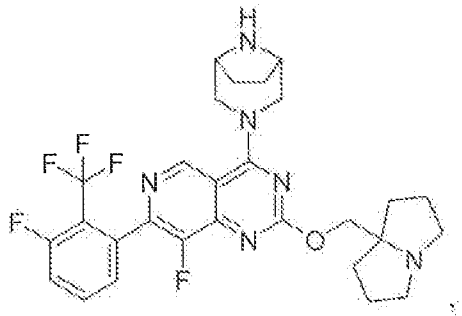


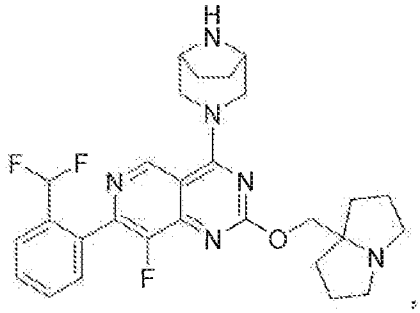


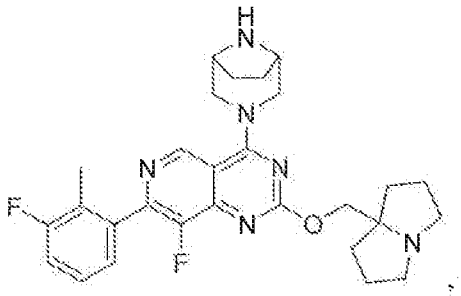


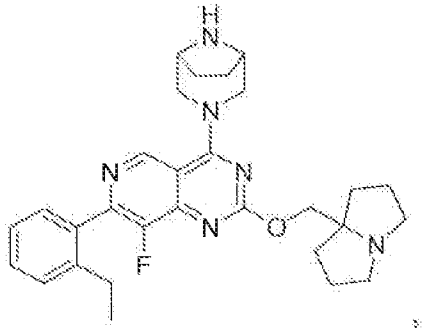


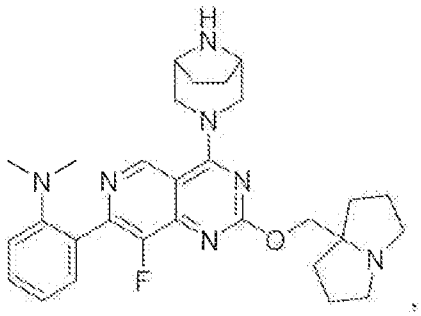


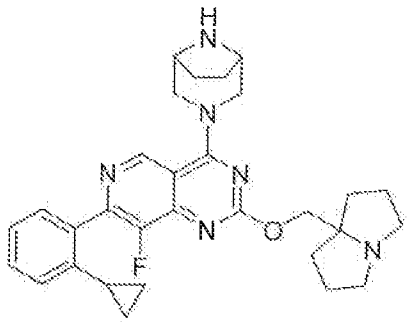


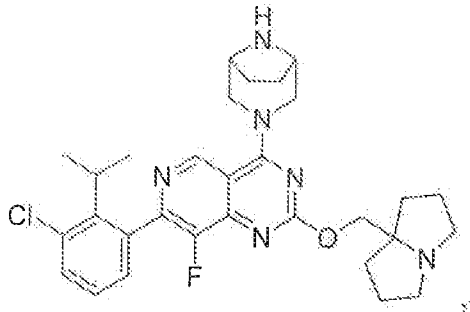


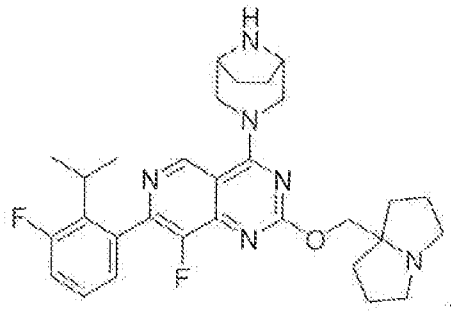


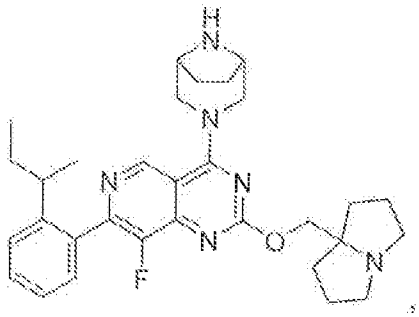


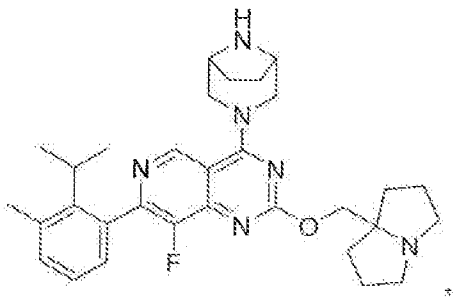


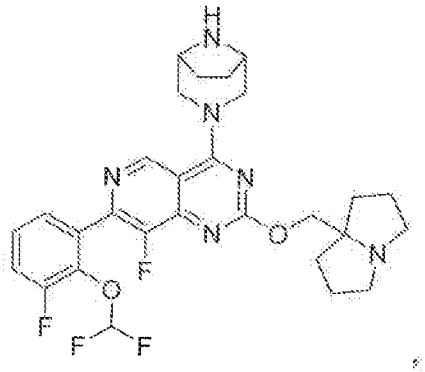


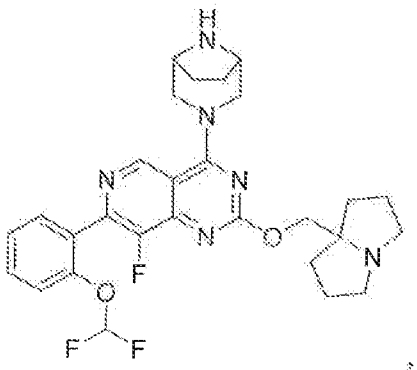


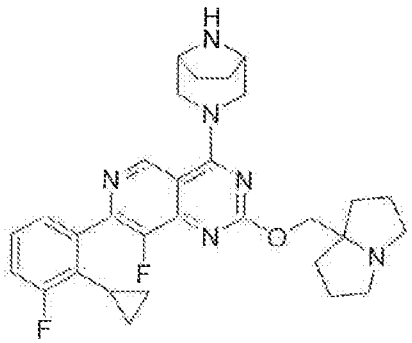


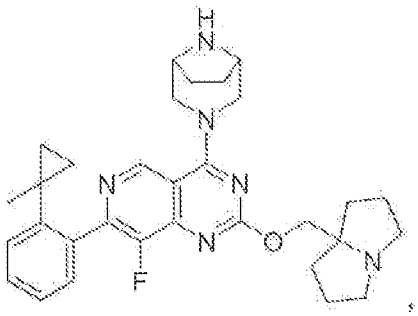


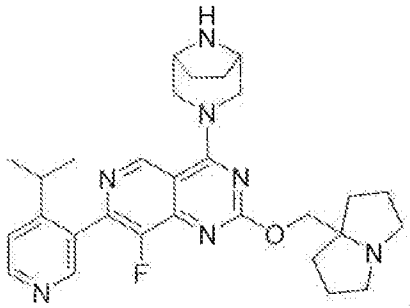


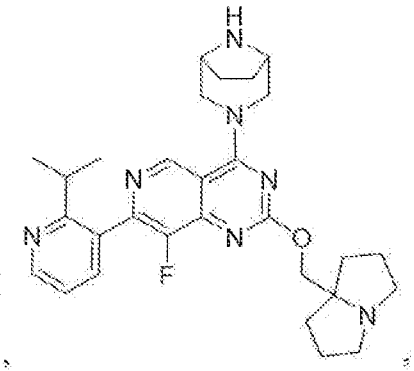


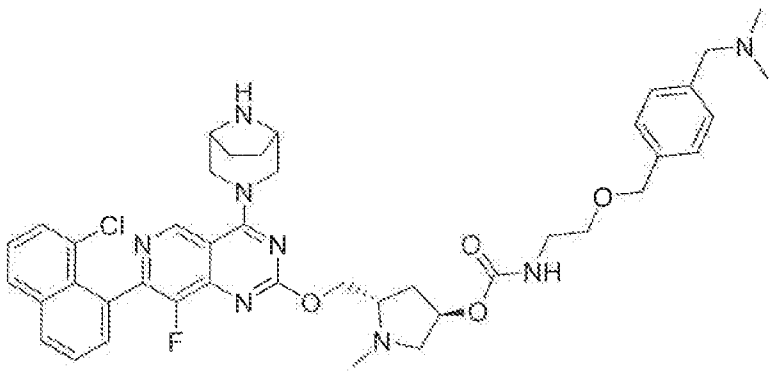


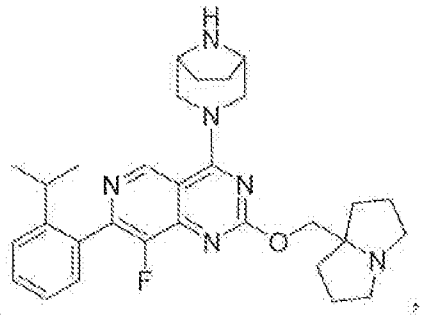


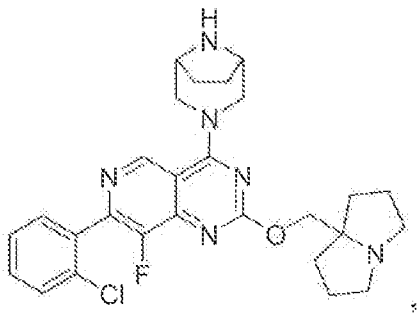


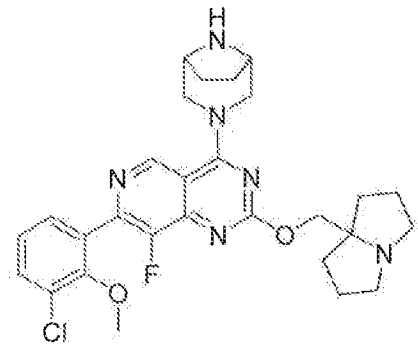


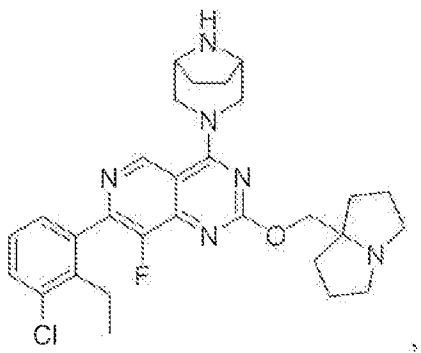


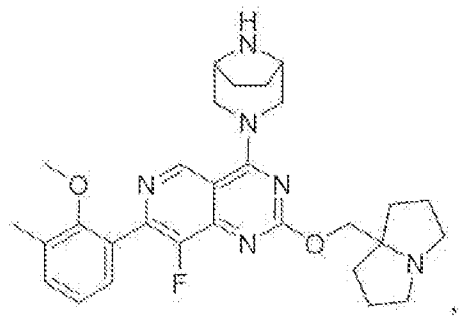


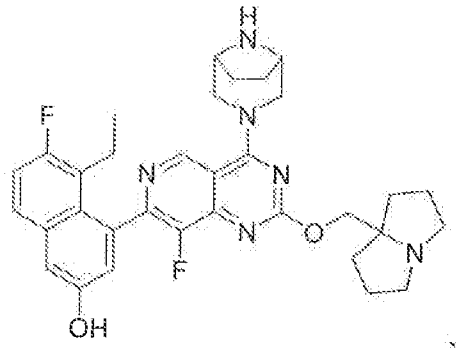


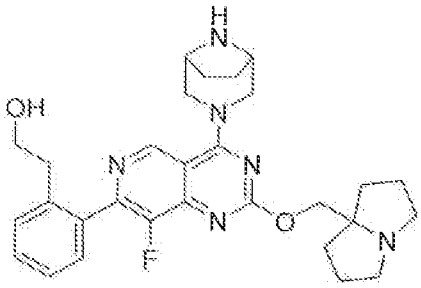


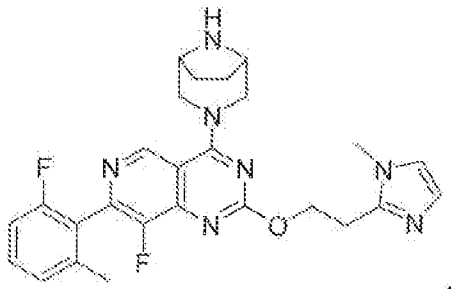


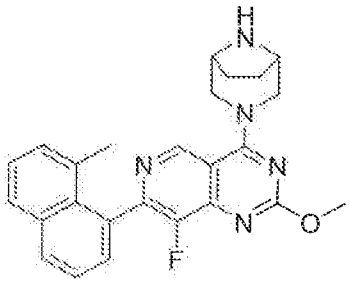


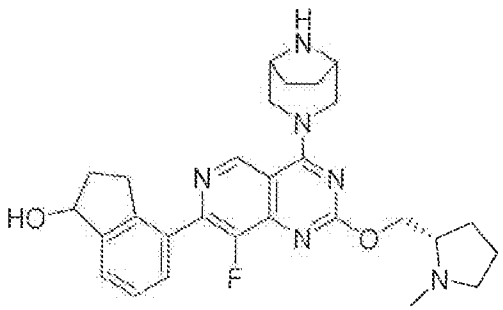


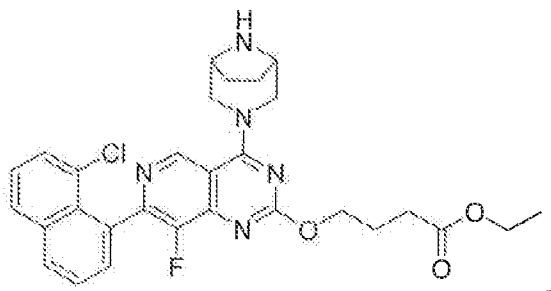


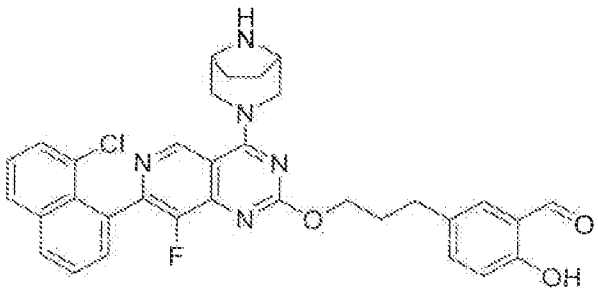


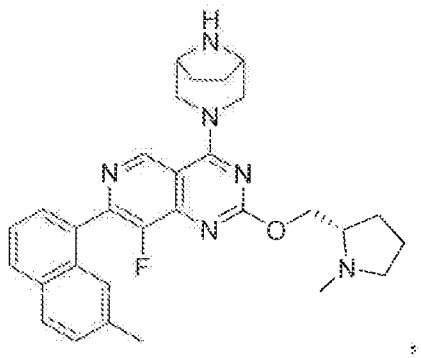


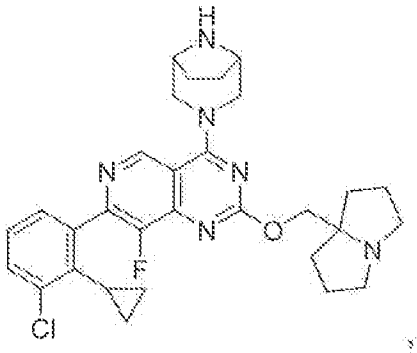


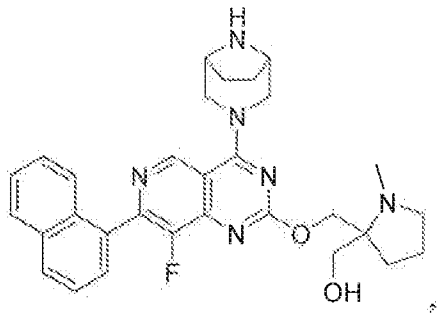


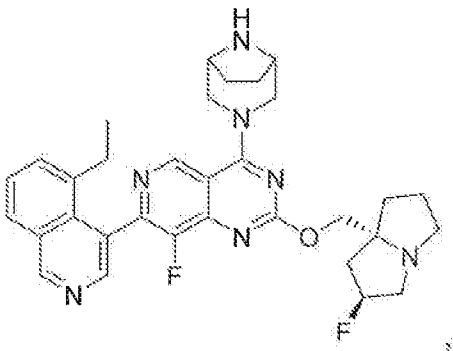


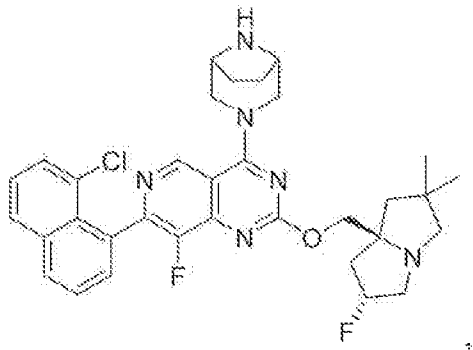


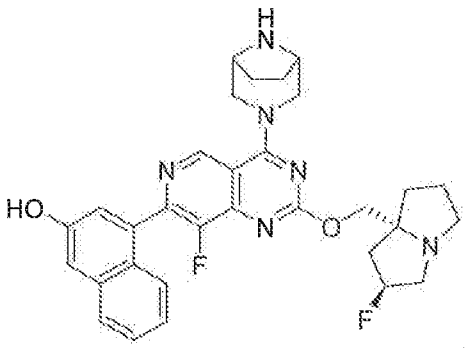


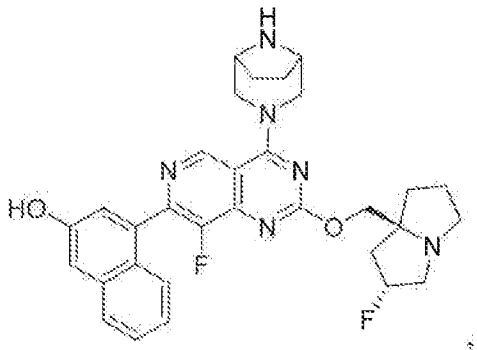


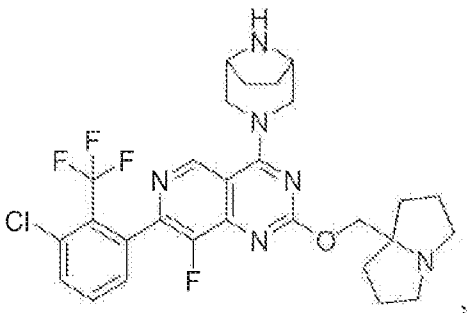


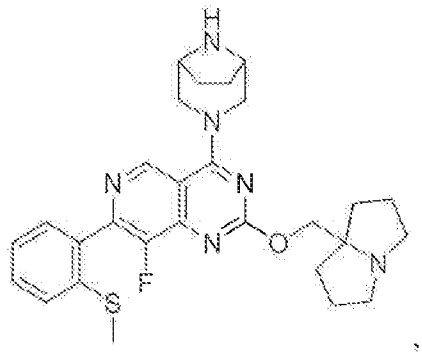


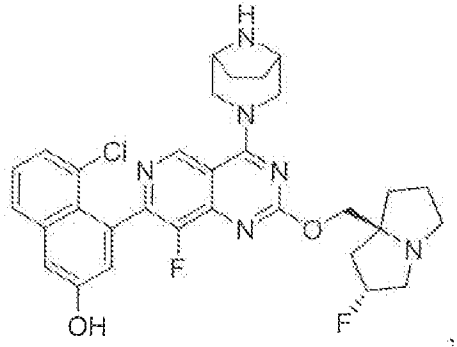


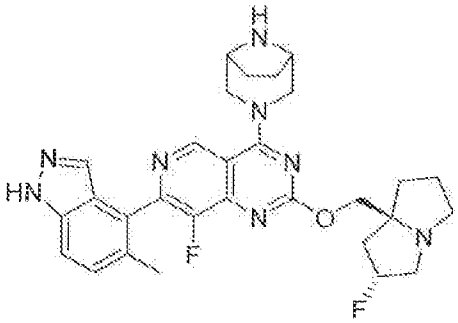


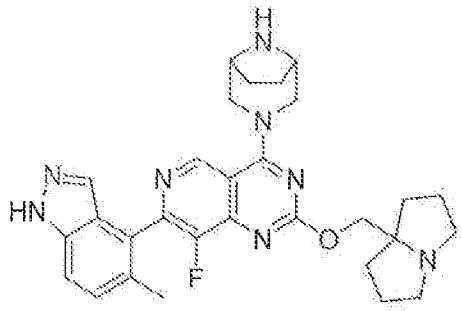


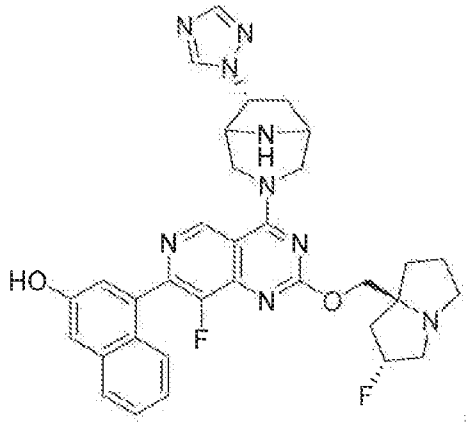


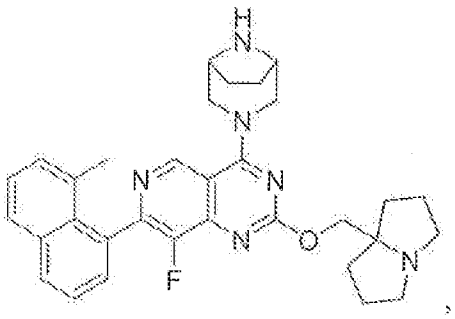


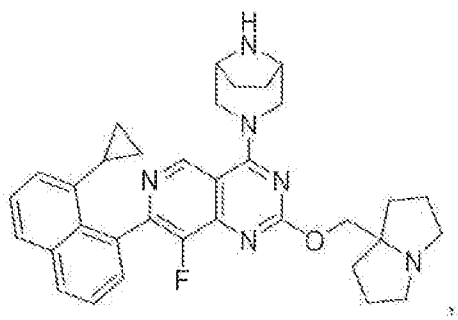


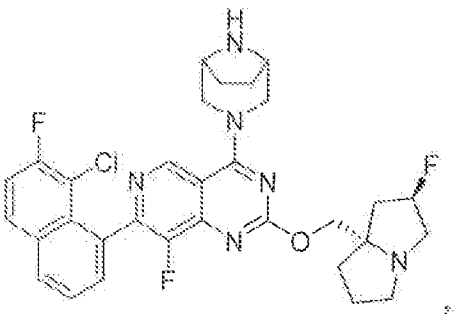


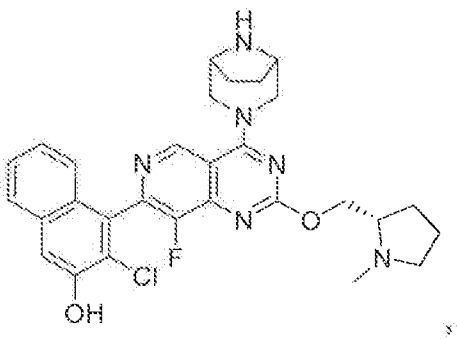


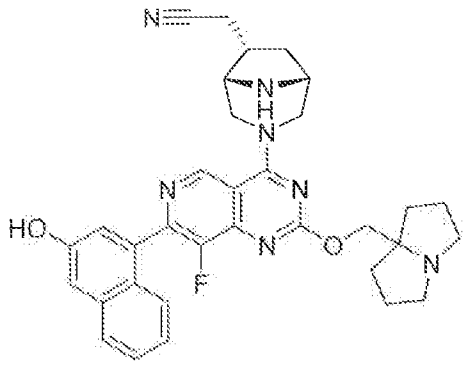


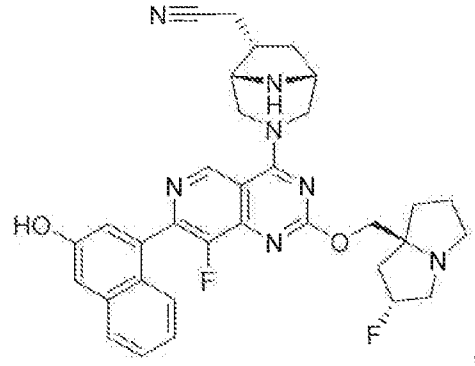


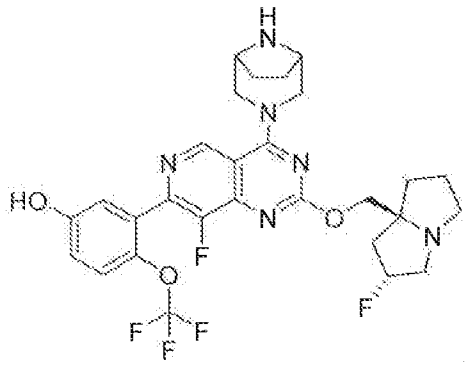


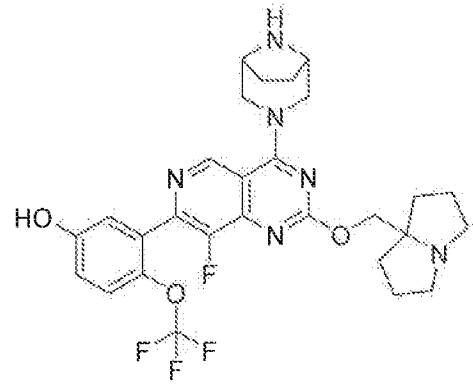


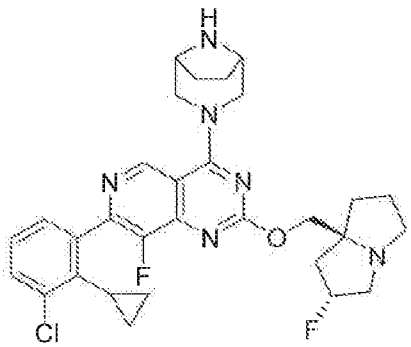


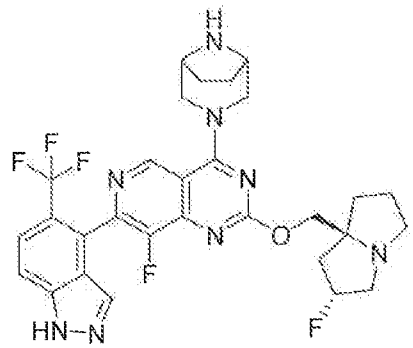


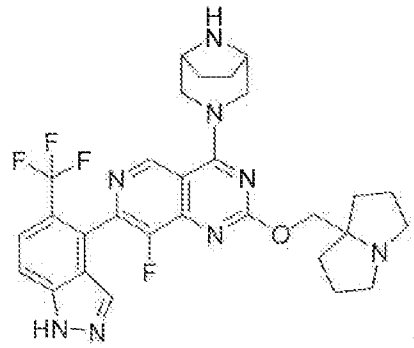


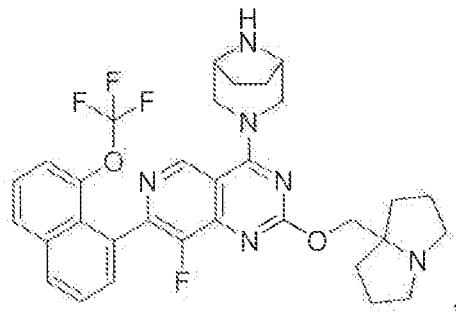


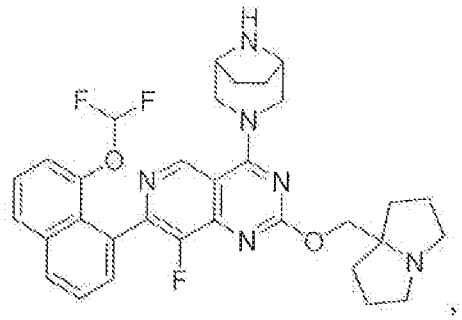


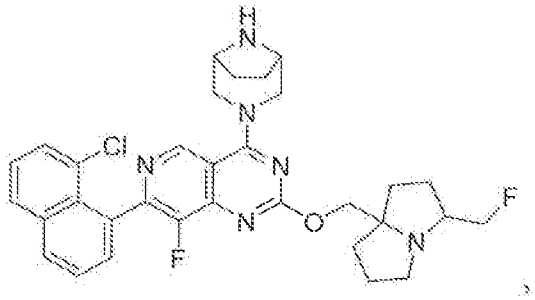


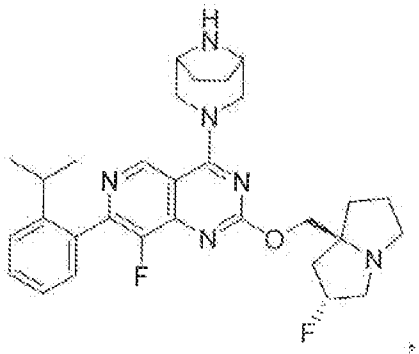


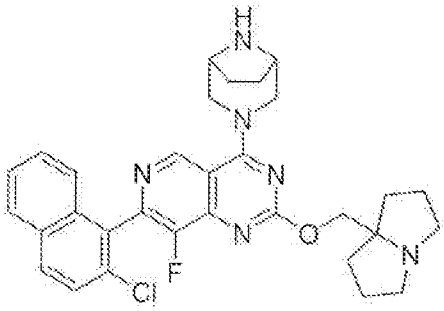


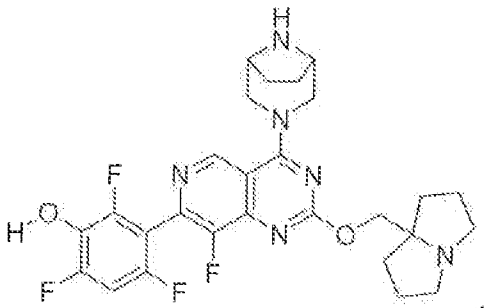


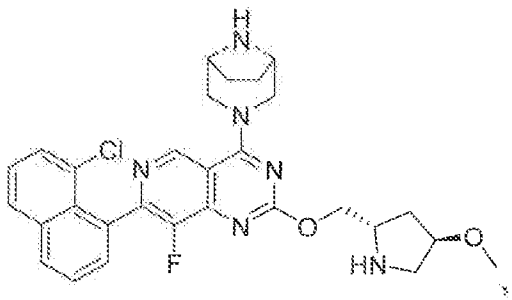


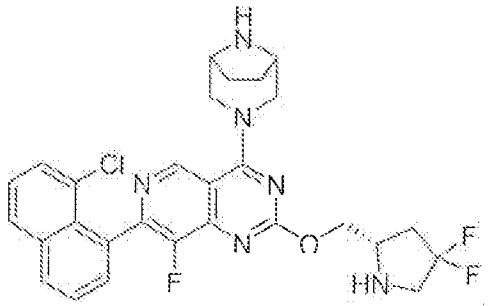


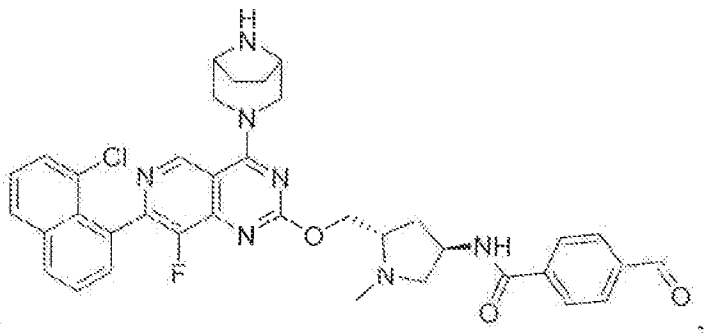


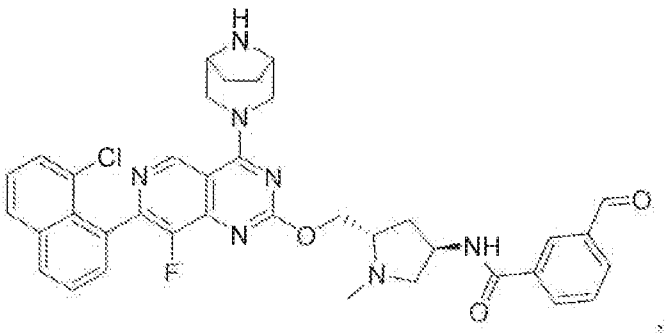


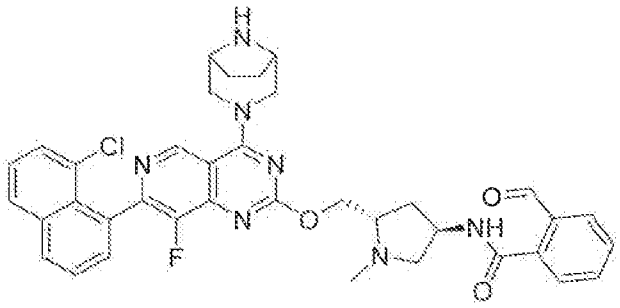


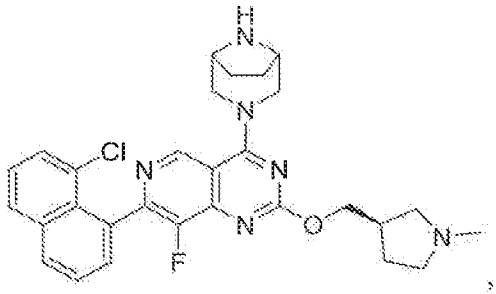


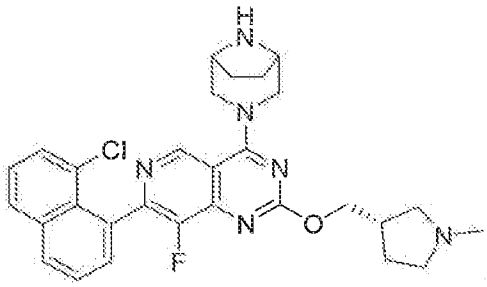


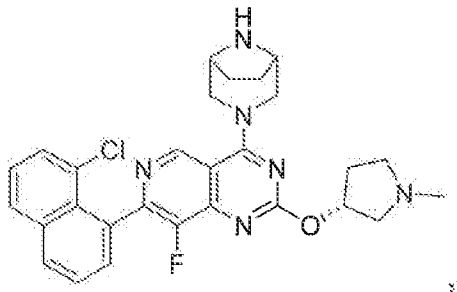


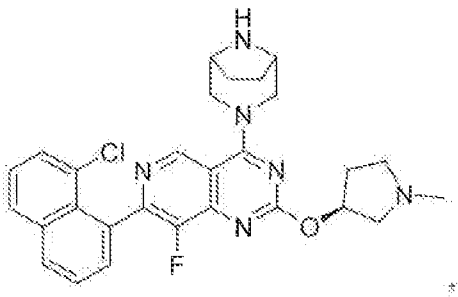


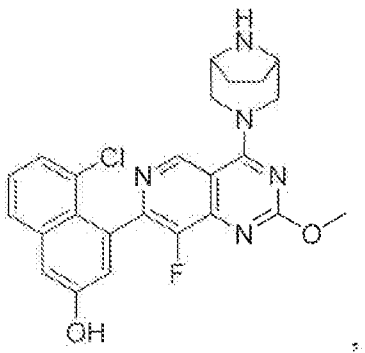


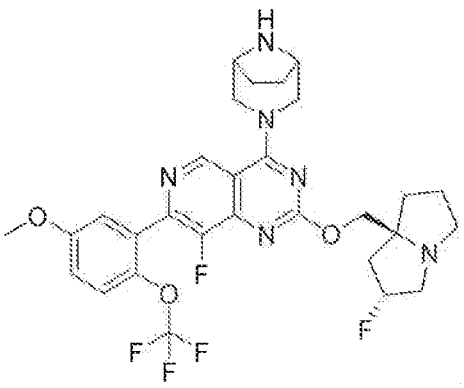


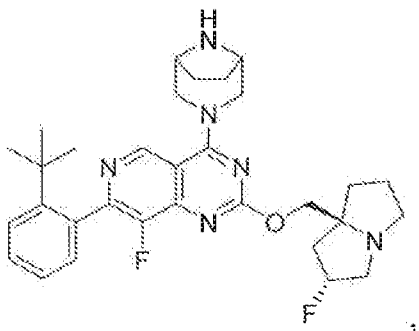


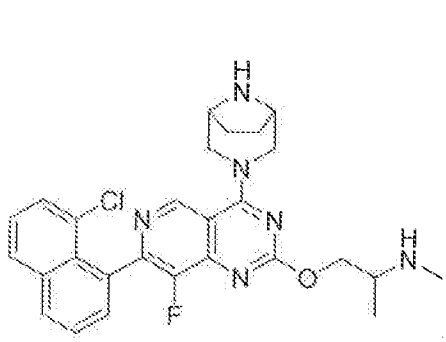


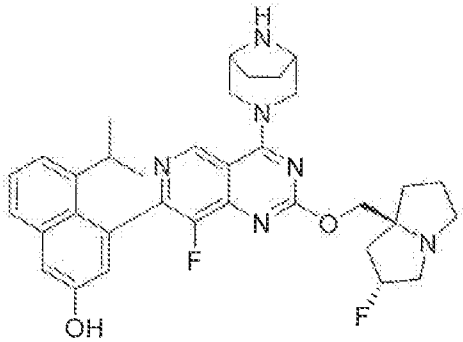


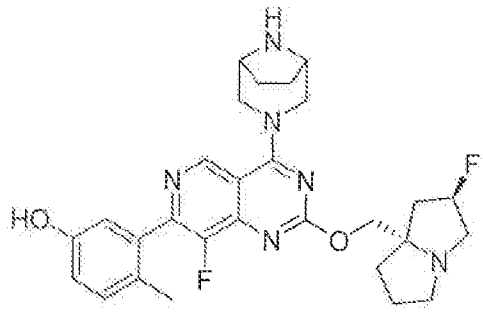


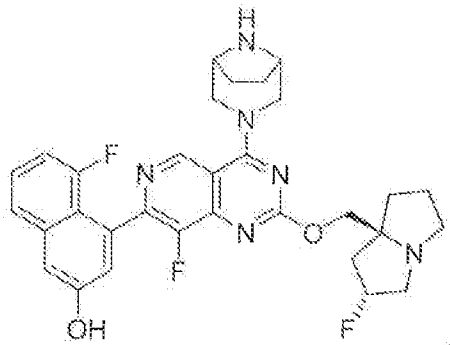


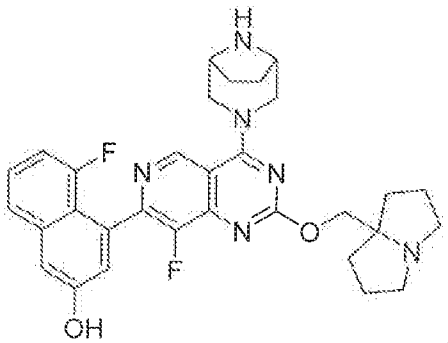


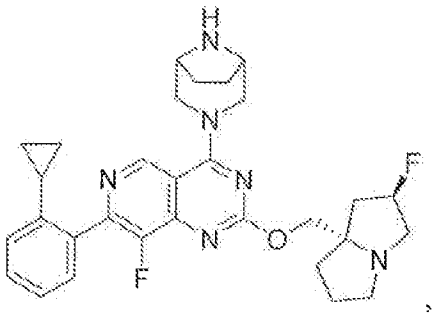


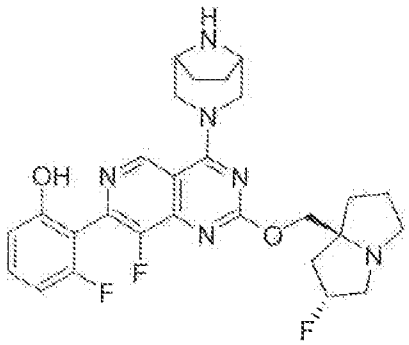


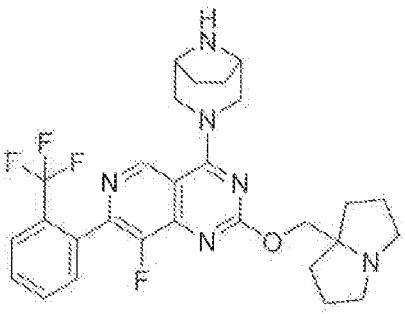


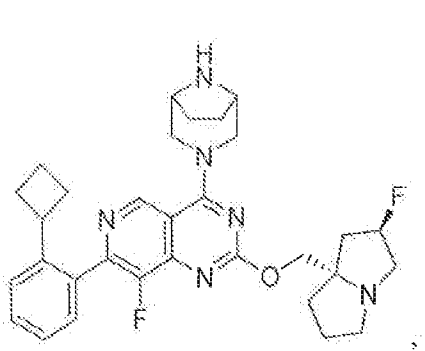


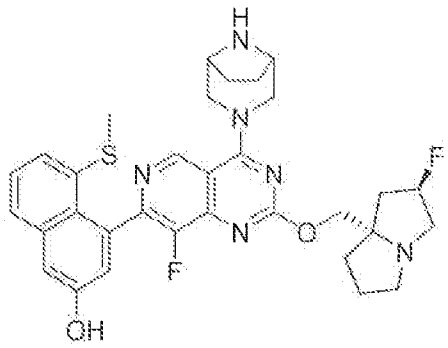


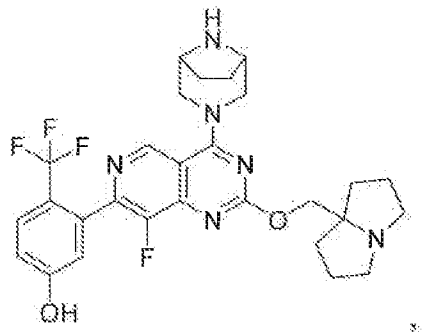


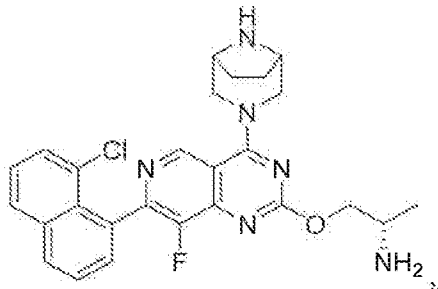


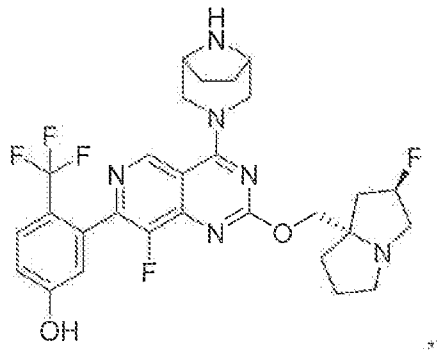


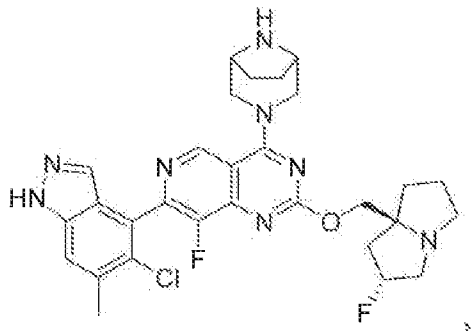


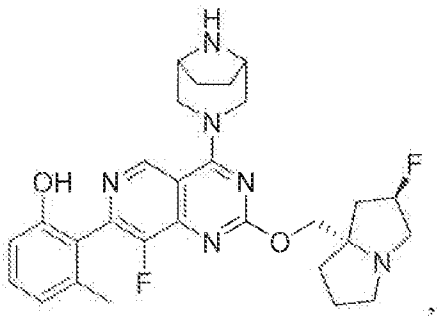


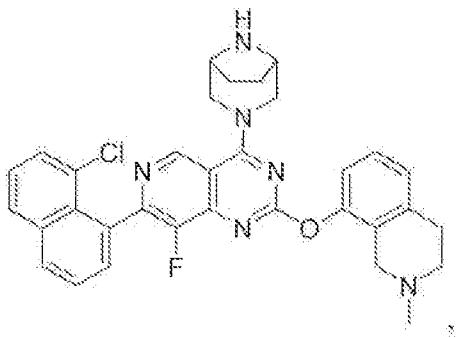


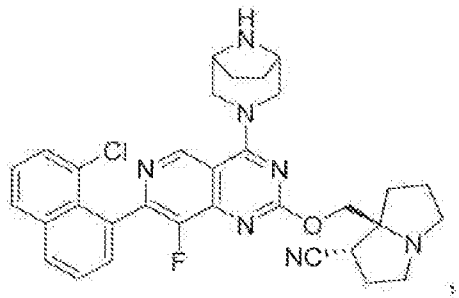


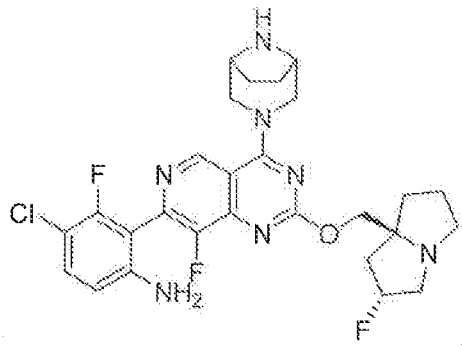


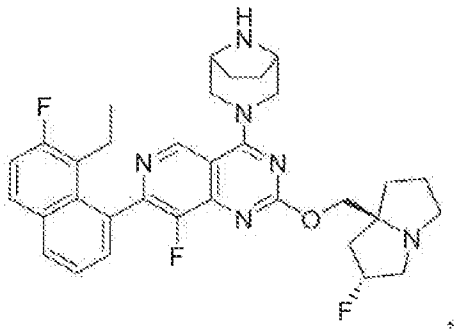


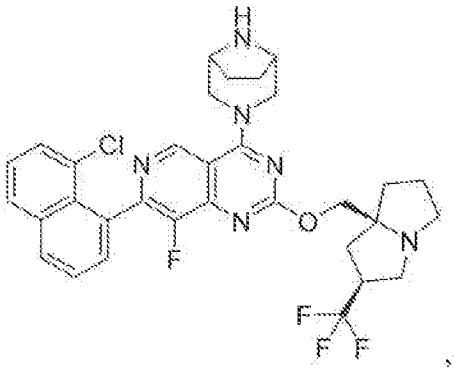


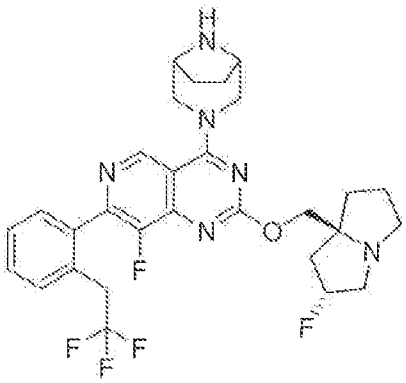


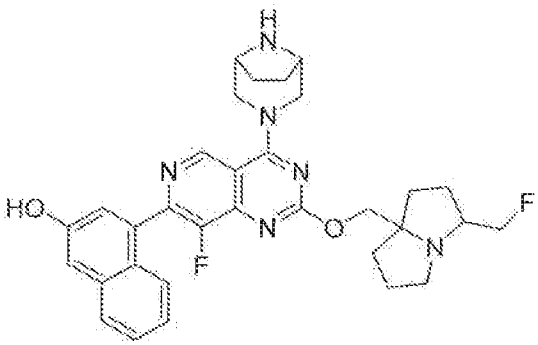


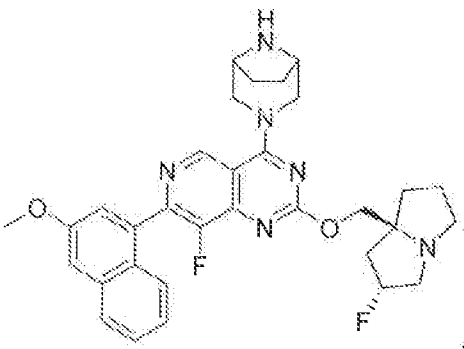


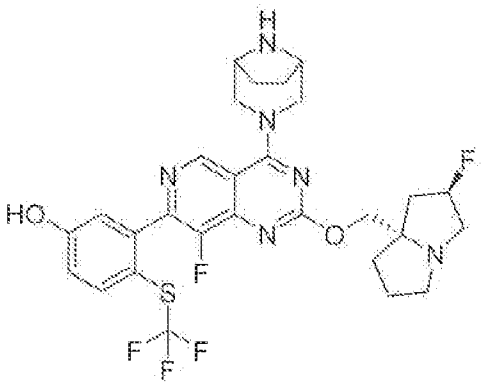


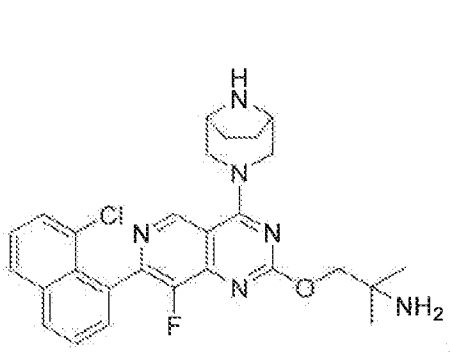


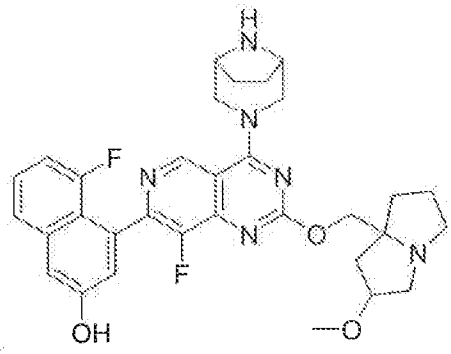


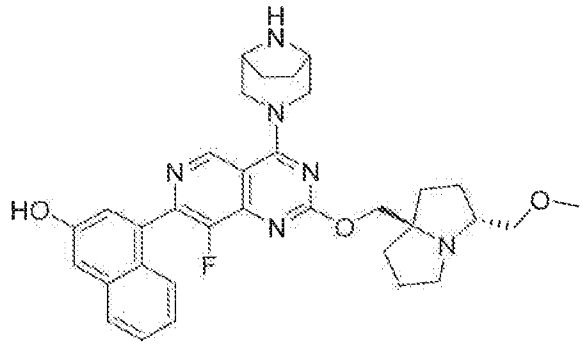


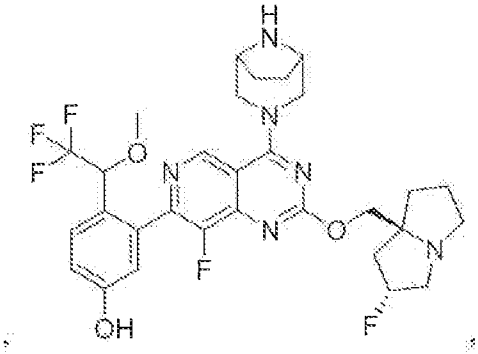


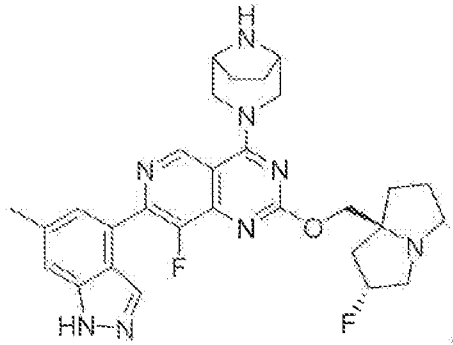


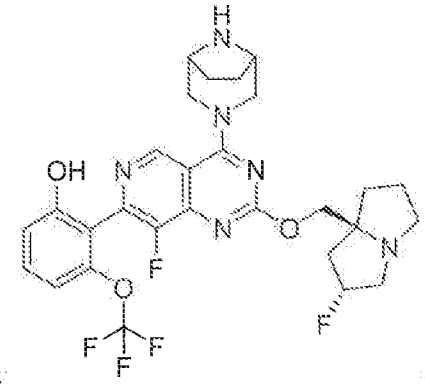


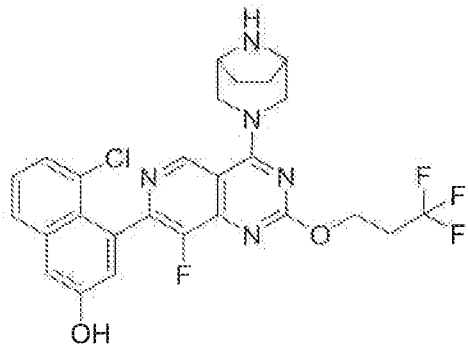


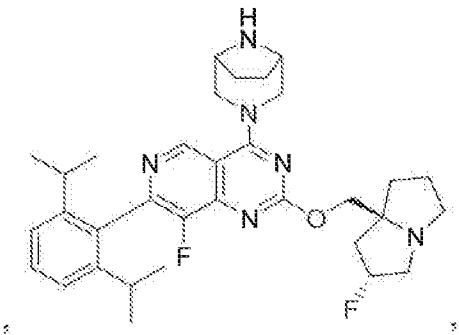


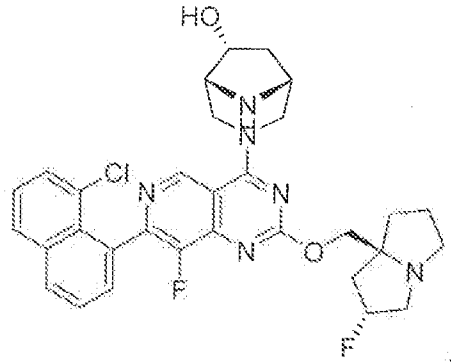


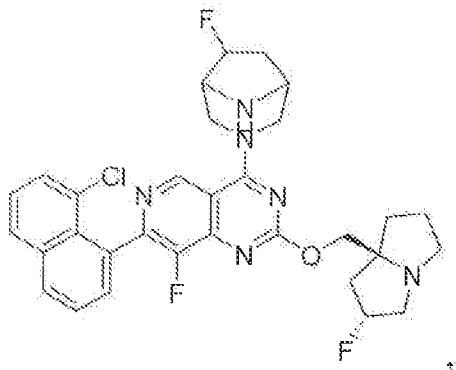


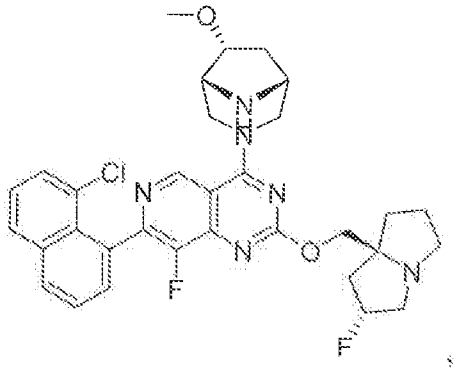


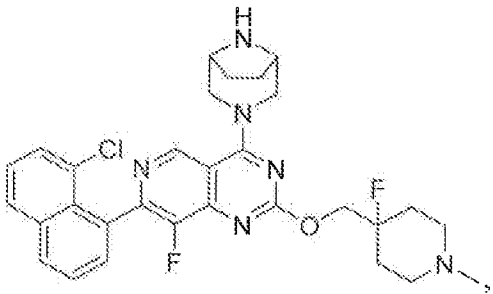


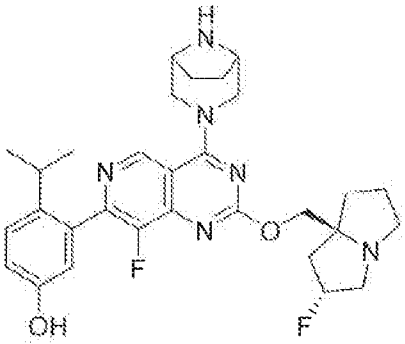


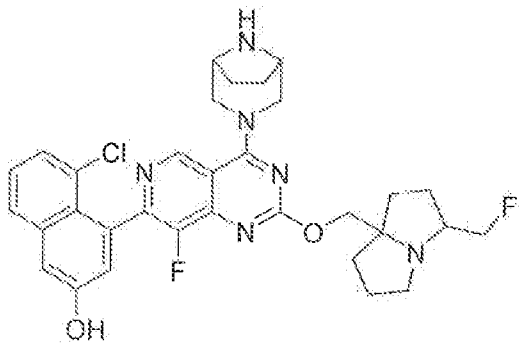


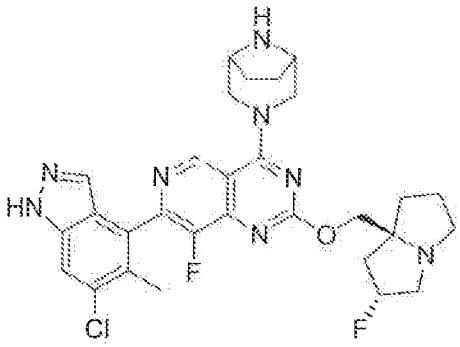


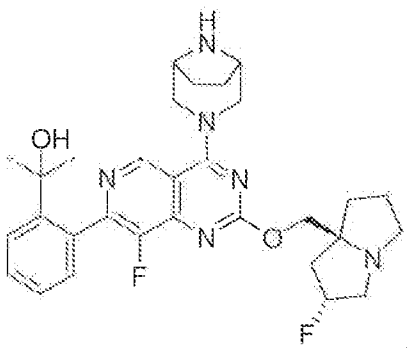


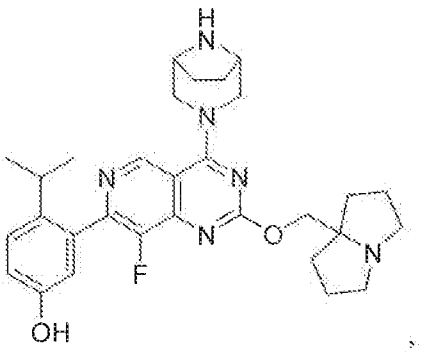


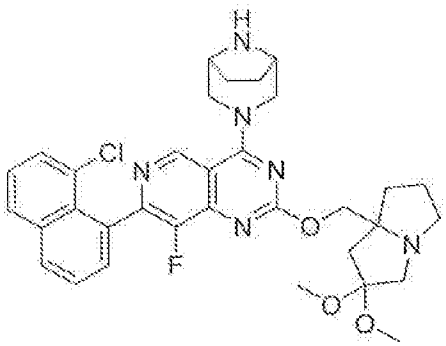


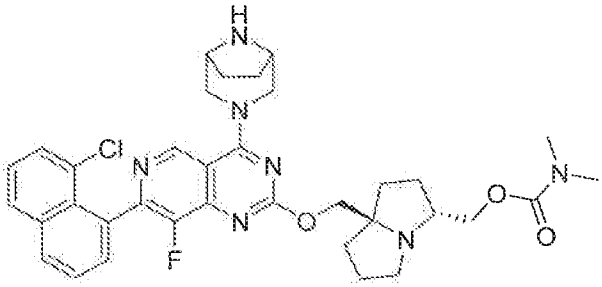


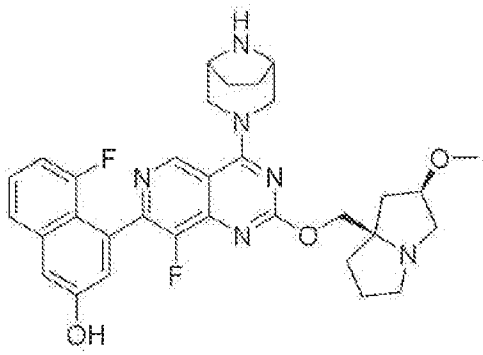


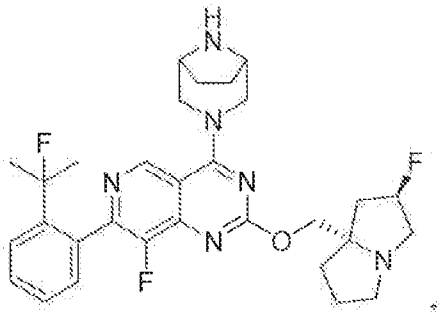


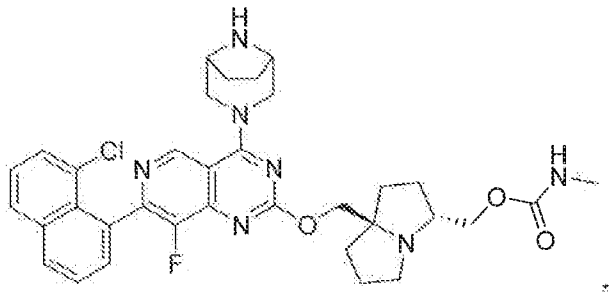


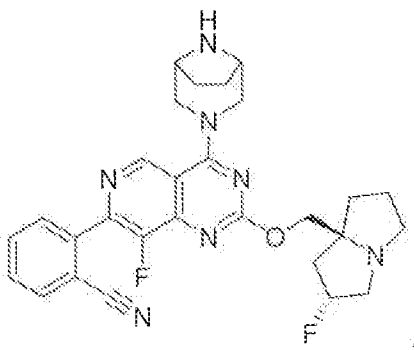


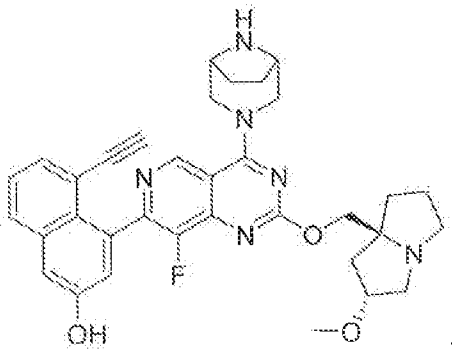


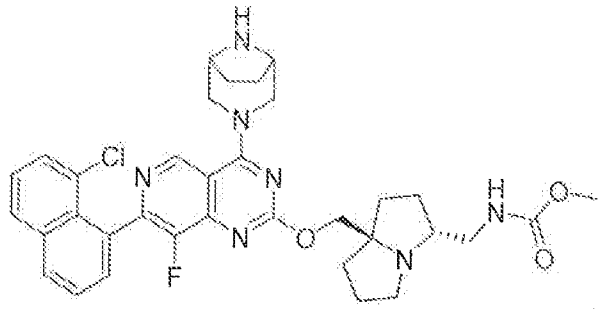


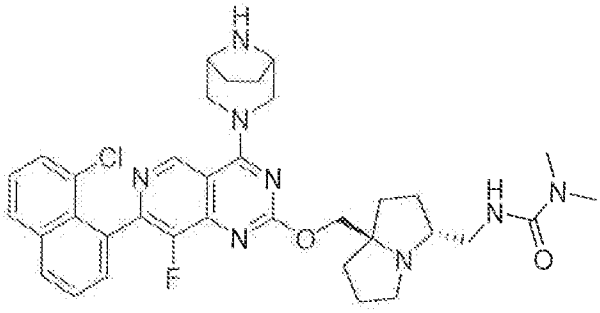


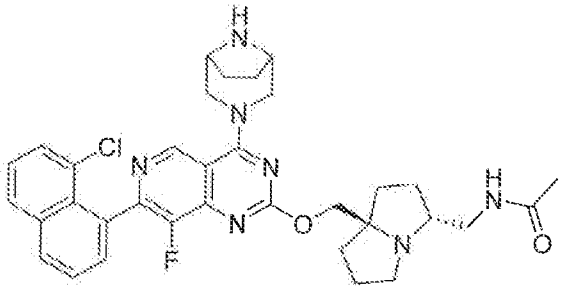


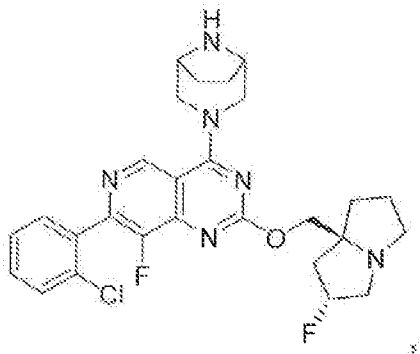


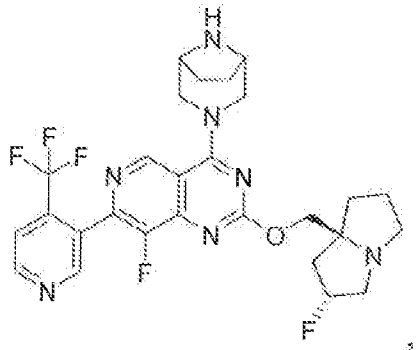


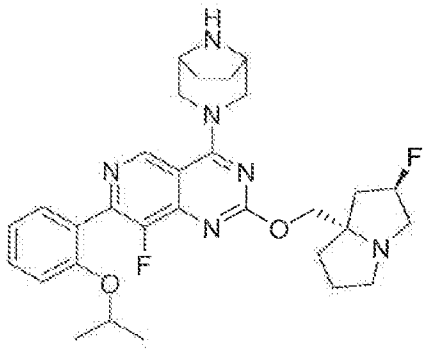


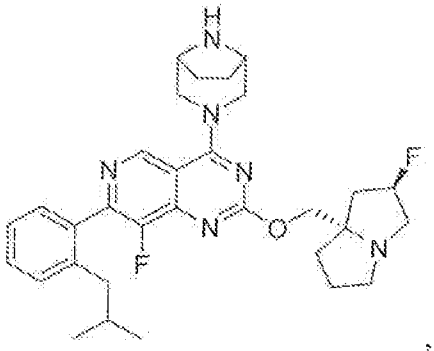


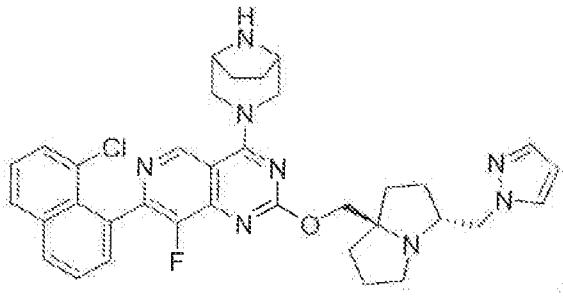


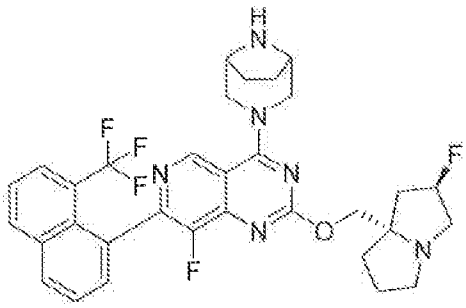


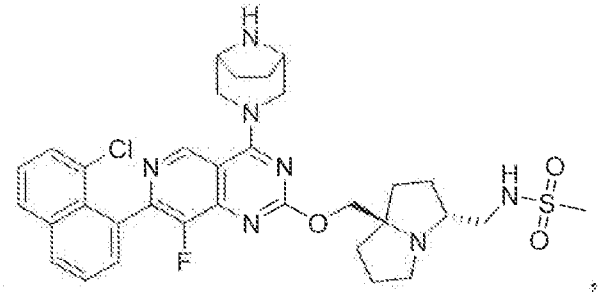


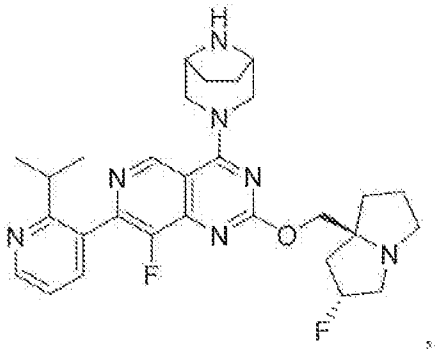


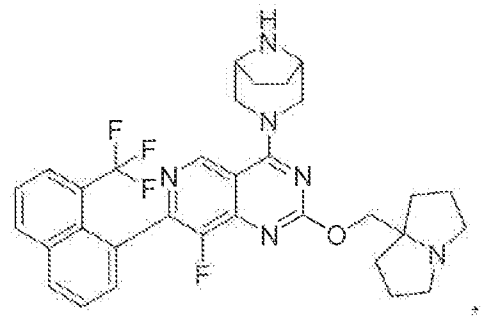


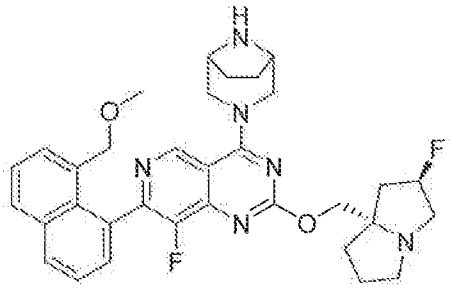


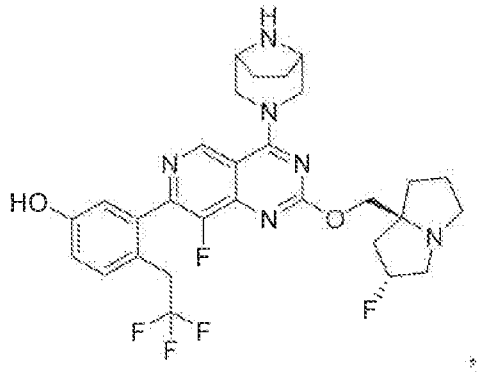


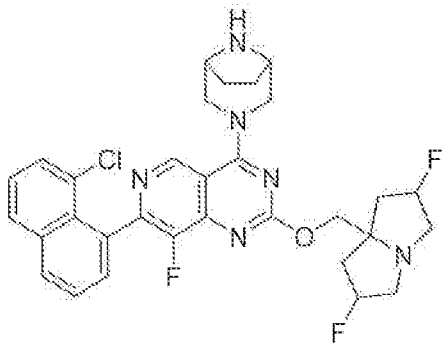


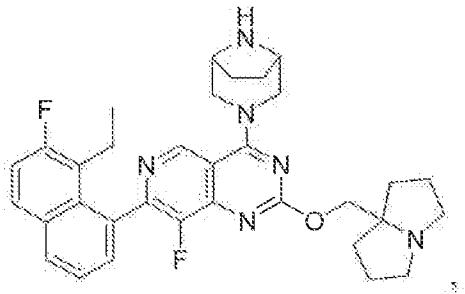


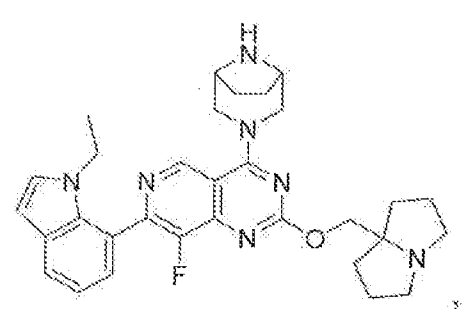


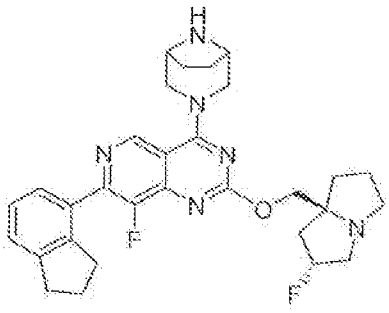


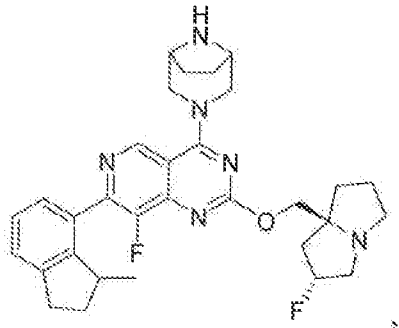


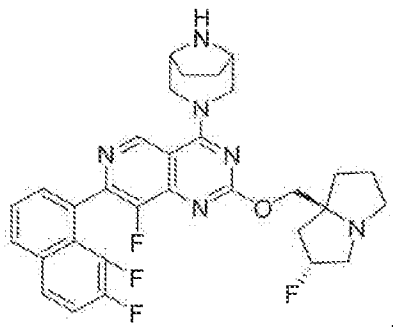


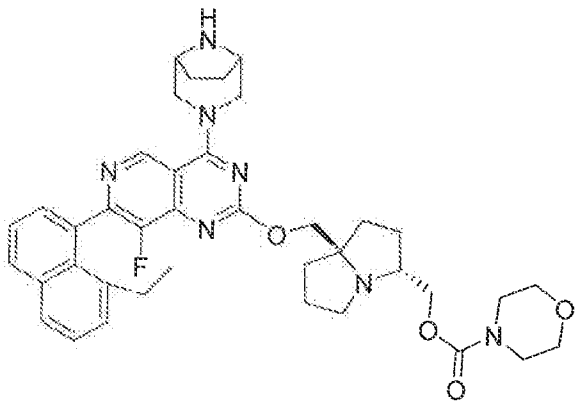


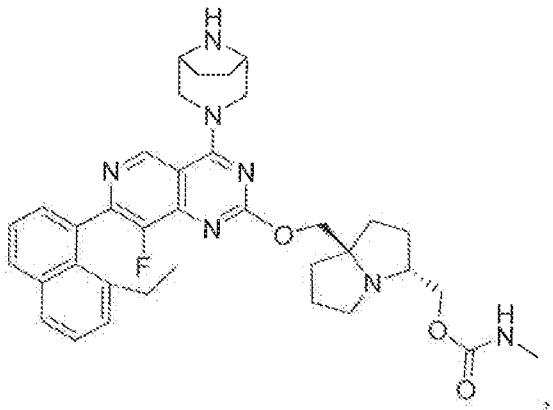


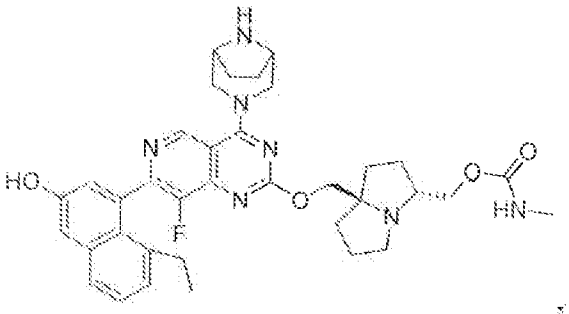


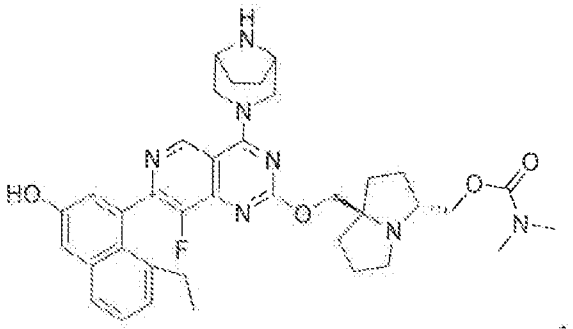


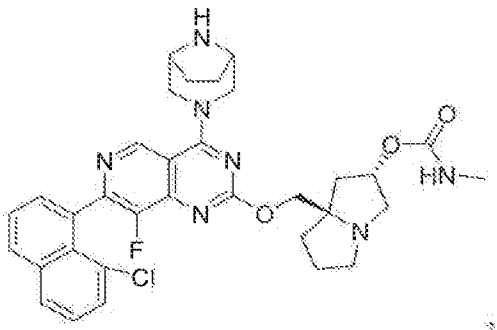


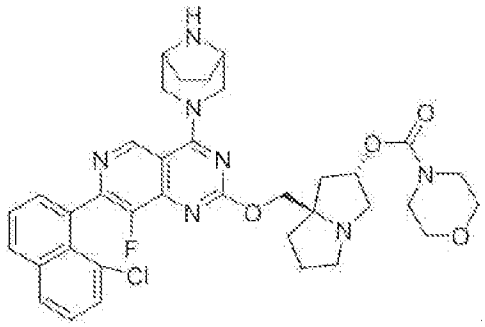


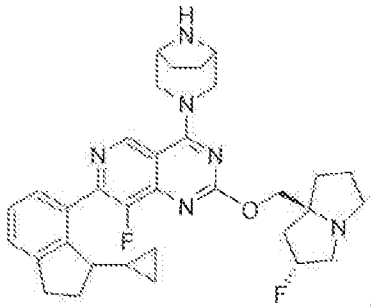


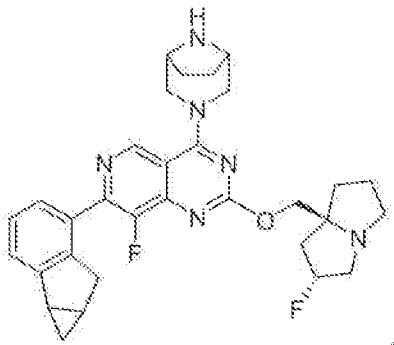


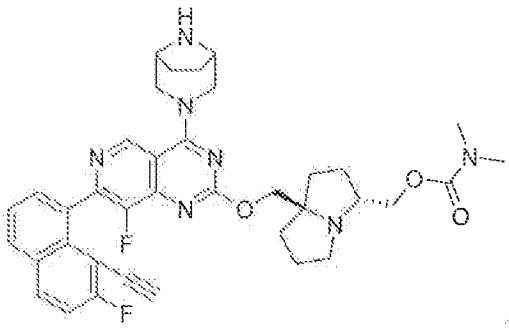


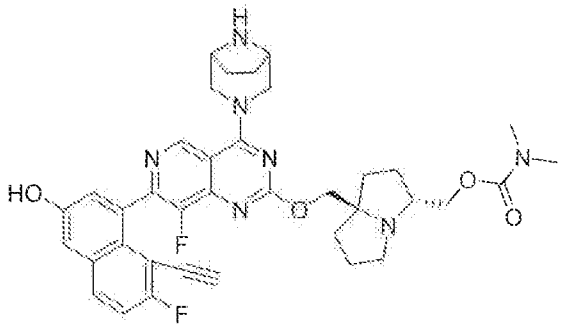


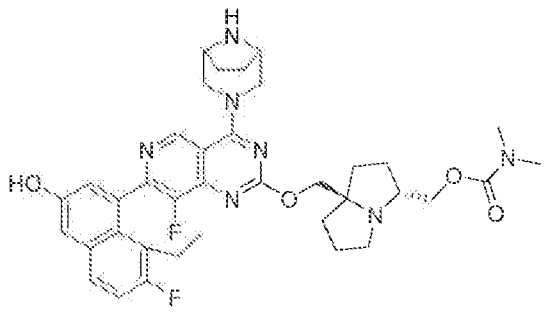


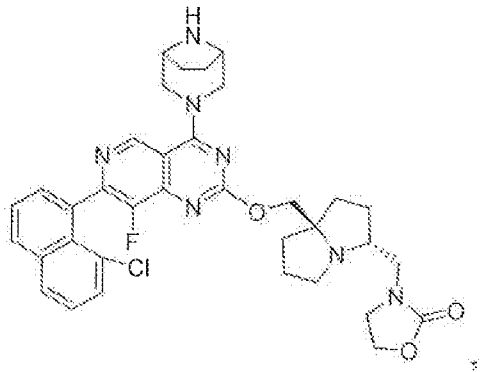


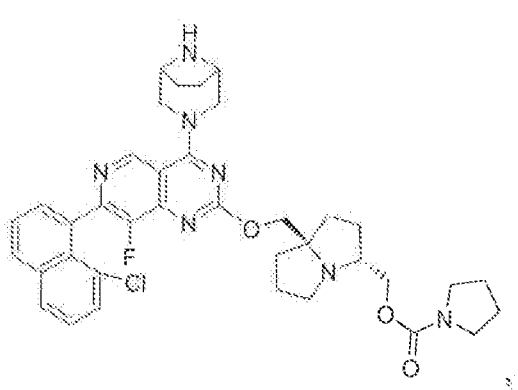


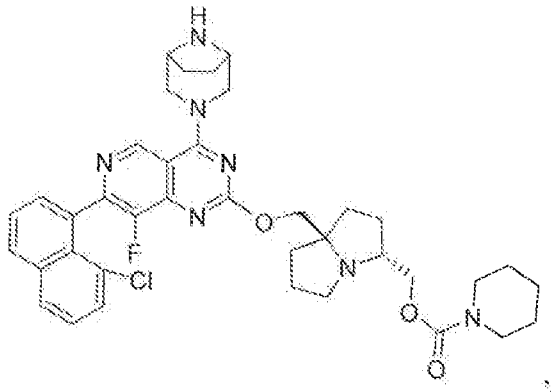


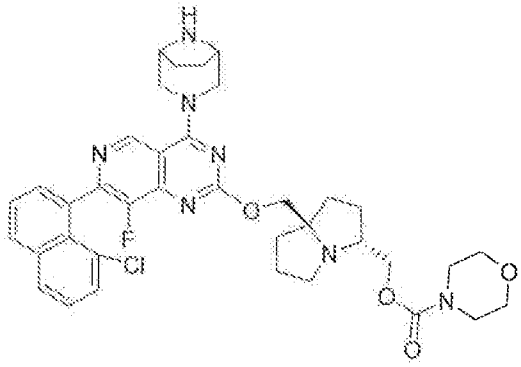


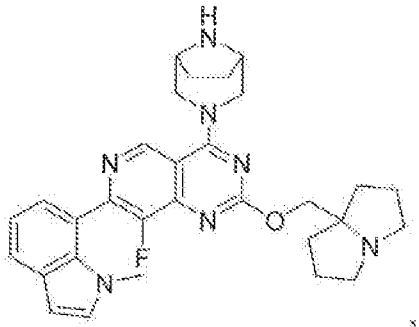


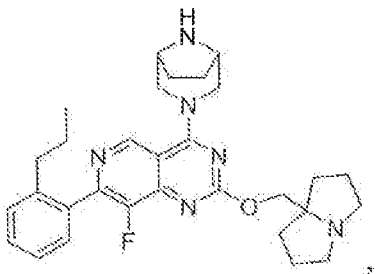


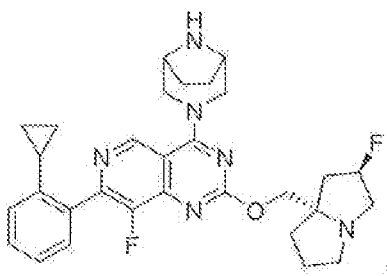


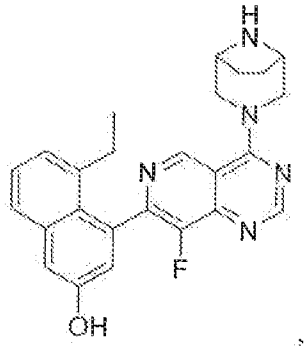


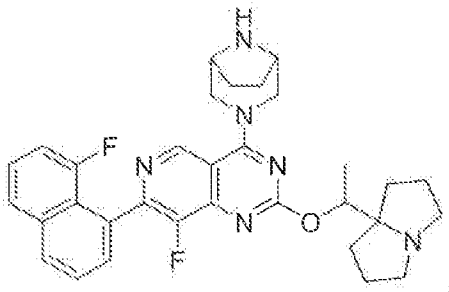


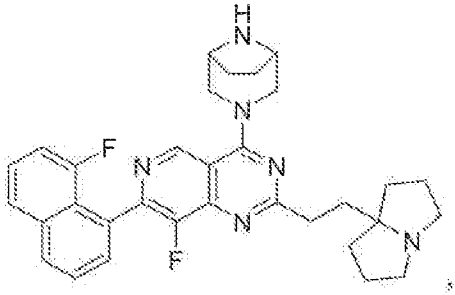


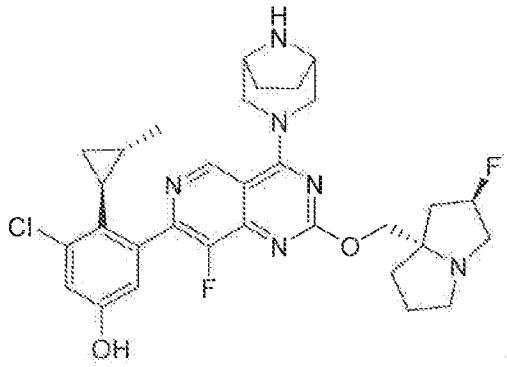


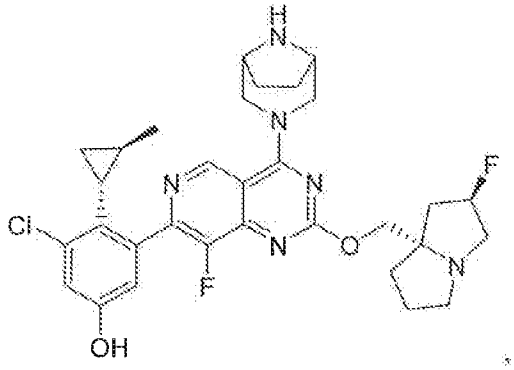


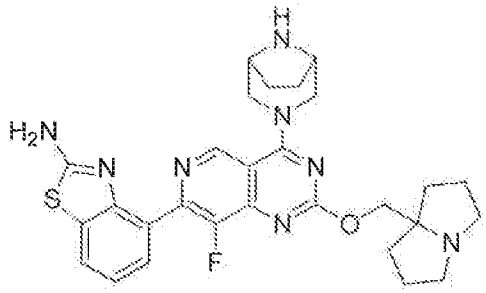


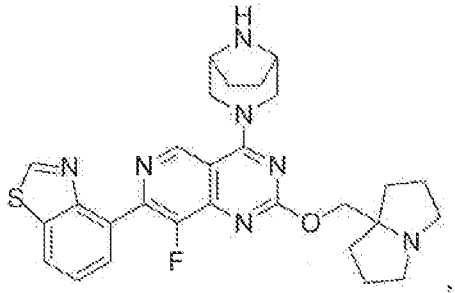


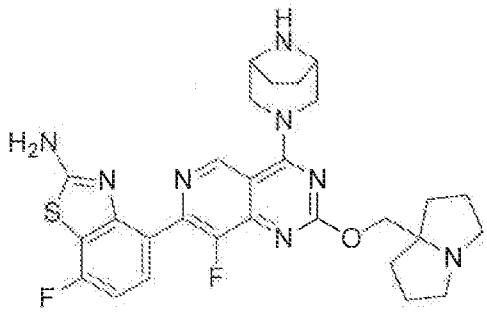


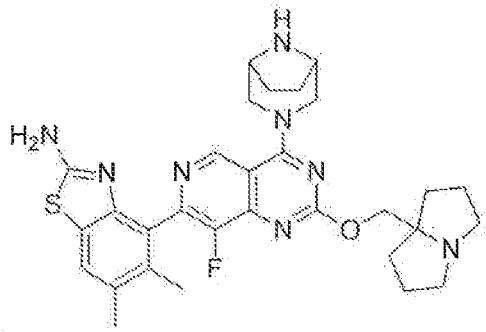


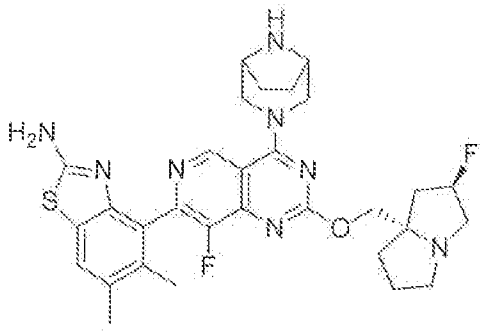
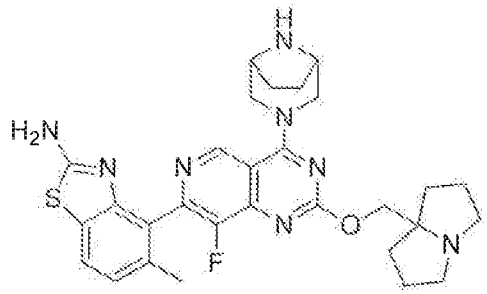








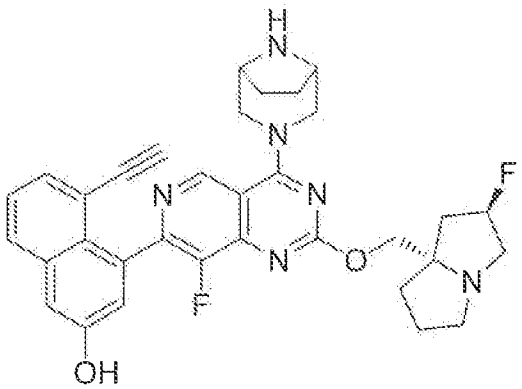


or pharmaceutically acceptable salts thereof.

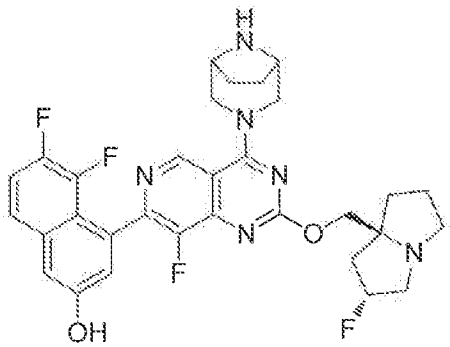
[0100] In one aspect of the invention, KRas G12D inhibitors comprise compound MRTX1133 or MRTX1133 analogs and related compounds such as any of the compounds disclosed and described in WIPO publication WO2021/041671, including but not limited to: Ex. 252 (MRTX1133), 4-(4-((1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)-5-ethynyl-6-fluoronaphthalen-2-ol; Ex. 243, 4-(4-((1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)-5-ethynylnaphthalen-2-ol; Ex. 246, 4-(4-((1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)-5,6-difluoronaphthalen-2-ol; Ex. 251, 4-(4-((1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)-5-chloronaphthalen-2-ol; Ex. 253, 4-(4-((1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)-5-ethyl-6-fluoronaphthalen-2-ol; Ex. 259, 4-(4-((1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)-5-ethylnaphthalen-2-ol; and Ex. 282, 4-(4-((1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)-5-fluoronaphthalen-2-ol; or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable excipient

[0101] In one embodiment, the KRas G12D inhibitor is:



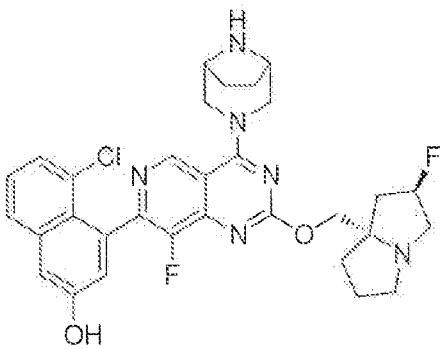
(also referred to as Example 243 in WO 2021/041671) or a pharmaceutically acceptable salt thereof.

[0102] In one embodiment, the KRas G12D inhibitor is:



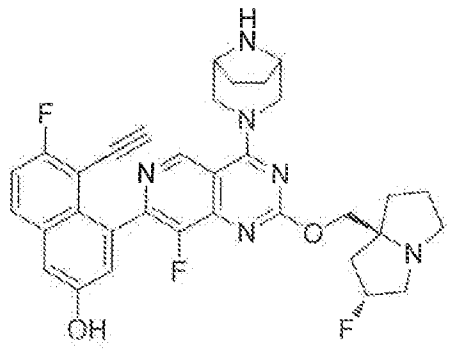
[0103] (also referred to as Example 246 in WO 2021/041671) or a pharmaceutically acceptable salt thereof.

[0104] In one embodiment, the KRas G12D inhibitor is:



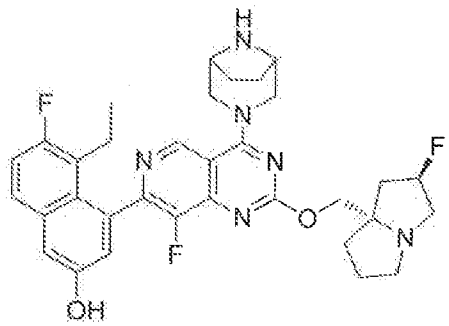
[0105] (also referred to as Example 251 in WO 2021/041671) or a pharmaceutically acceptable salt thereof.

[0106] In one embodiment, the KRas G12D inhibitor is:



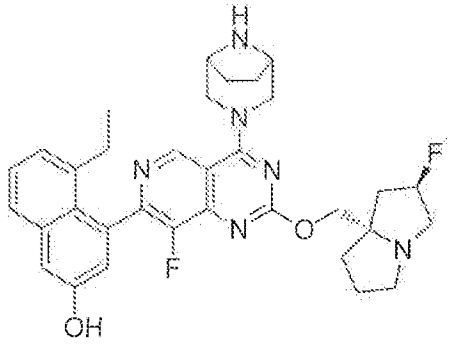
[0107] (also referred to as Example 252 in WO 2021/041671) or a pharmaceutically acceptable salt thereof. This compound is also known as MRTX1133 and may be referred to as "MRTX1133" in this application.

[0108] In one embodiment, the KRas G12D inhibitor is:



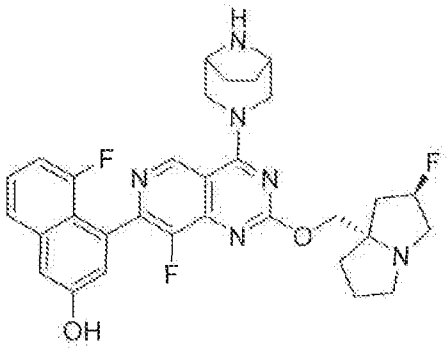
[0109] (also referred to as Example 253 in WO 2021/041671) or a pharmaceutically acceptable salt thereof.

[0110] In one embodiment, the KRas G12D inhibitor is:



[0111] (also referred to as Example 259 in WO 2021/041671) or a pharmaceutically acceptable salt thereof.

[0112] In one embodiment, the KRas G12D inhibitor is:



[0113] (also referred to as Example 282 in WO 2021/041671) or a pharmaceutically acceptable salt thereof.

[0114] The KRas G12D inhibitors used in the methods of the present invention may have one or more chiral center and may be synthesized as stereoisomeric mixtures, isomers of identical constitution that differ in the arrangement of their atoms in space. The compounds may be used as mixtures or the individual components/isomers may be separated using commercially available reagents and conventional methods for isolation of stereoisomers and enantiomers well-known to those skilled in the art, e.g., using CHIRALPAK® (Sigma-Aldrich) or CHIRALCEL® (Diacel Corp) chiral chromatographic HPLC columns according to the manufacturer's instructions. Alternatively, compounds of the present invention may be synthesized using optically pure, chiral reagents and intermediates to prepare individual isomers or enantiomers. Unless otherwise indicated, all chiral (enantiomeric and diastereomeric) and racemic forms are within the scope of the invention. Unless otherwise indicated, whenever the specification, including the claims, refers

to compounds of the invention, the term "compound" is to be understood to encompass all chiral (enantiomeric and diastereomeric) and racemic forms.

[0115] In one embodiment, the KRas G12D inhibitor compounds of Formula I used in the methods include trifluoroacetic acid salts of the above compounds.

[0116] Methods for manufacturing the KRas G12D inhibitors disclosed herein are known. For example, commonly owned published international PCT application number WO2021/041671 describes general reaction schemes for preparing compounds of Formula I and also provides detailed synthetic routes for the preparation of each KRas G12D inhibitor disclosed herein.

[0117] The SOS1 inhibitors and the KRas G12D compounds of Formula (I) or pharmaceutically acceptable salts thereof may be formulated into pharmaceutical compositions.

PHARMACEUTICAL COMPOSITIONS

[0118] In another aspect, the invention provides pharmaceutical compositions comprising a SOS1 inhibitor, or a pharmaceutically acceptable salt thereof, and KRas G12D inhibitor, or a pharmaceutically acceptable salt thereof according to the invention and a pharmaceutically acceptable carrier, excipient, or diluent that may be used in the methods disclosed herein. The SOS1 inhibitor, or a pharmaceutically acceptable salt thereof, and KRas G12D inhibitor, or a pharmaceutically acceptable salt thereof may be independently formulated by any method well known in the art and may be prepared for administration by any route, including, without limitation, parenteral, oral, sublingual, transdermal, topical, intranasal, intratracheal, or intrarectal. In certain embodiments, SOS1 inhibitor, or a pharmaceutically acceptable salt thereof, and KRas G12D inhibitor, or a pharmaceutically acceptable salt thereof, are administered intravenously in a hospital setting. In one embodiment, administration may be by the oral route.

[0119] The characteristics of the carrier will depend on the route of administration. As used herein, the term "pharmaceutically acceptable" means a non-toxic material that is compatible with a biological system such as a cell, cell culture, tissue, or organism, and that does not interfere with the effectiveness of the biological activity of the active ingredient(s). Thus, compositions may contain, in addition to the inhibitor, diluents, fillers, salts, buffers, stabilizers, solubilizers, and other materials well known in the art. The preparation of pharmaceutically acceptable formulations

is described in, e.g., Remington's Pharmaceutical Sciences, 18th Edition, ed. A. Gennaro, Mack Publishing Co., Easton, Pa., 1990.

[0120] As used herein, the term pharmaceutically acceptable salt refers to salts that retain the desired biological activity of the above-identified compounds and exhibit minimal or no undesired toxicological effects. Examples of such salts include, but are not limited to acid addition salts formed with inorganic acids (for example, hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, nitric acid, and the like), and salts formed with organic acids such as acetic acid, oxalic acid, tartaric acid, succinic acid, malic acid, ascorbic acid, benzoic acid, tannic acid, pamoic acid, alginic acid, polyglutamic acid, naphthalenesulfonic acid, naphthalenedisulfonic acid, and polygalacturonic acid. The compounds can also be administered as pharmaceutically acceptable quaternary salts known by those skilled in the art, which specifically include the quaternary ammonium salt of the formula --NR+Z-, wherein R is hydrogen, alkyl, or benzyl, and Z is a counterion, including chloride, bromide, iodide, --O-alkyl, toluenesulfonate, methylsulfonate, sulfonate, phosphate, or carboxylate (such as benzoate, succinate, acetate, glycolate, maleate, malate, citrate, tartrate, ascorbate, benzoate, cinnamoate, mandeloate, benzyloate, and diphenylacetate).

[0121] The active compound is included in the pharmaceutically acceptable carrier or diluent in an amount sufficient to deliver to a patient a therapeutically effective amount without causing serious toxic effects in the patient treated. In one embodiment, a dose of the active compound for all of the above-mentioned conditions is in the range from about 0.01 to 300 mg/kg, for example 0.1 to 100 mg/kg per day, and as a further example 0.5 to about 25 mg per kilogram body weight of the recipient per day. A typical topical dosage will range from 0.01-3% wt/wt in a suitable carrier. The effective dosage range of the pharmaceutically acceptable derivatives can be calculated based on the weight of the parent compound to be delivered. If the derivative exhibits activity in itself, the effective dosage can be estimated as above using the weight of the derivative, or by other means known to those skilled in the art.

[0122] The pharmaceutical compositions comprising a SOS1 inhibitor, or a pharmaceutically acceptable salt or a pharmaceutical composition thereof and a KRas G12D inhibitor, or a pharmaceutically acceptable salt or a pharmaceutical composition thereof, may be used in the methods of use described herein.

CO-ADMINSTRATION

[0123] The SOS1 inhibitor, or a pharmaceutically acceptable salt thereof, and the KRas G12D inhibitor, or a pharmaceutically acceptable salt thereof, can be formulated into separate or individual dosage forms which can be co-administered one after the other. Another option is that if the route of administration is the same (e.g. oral) two active compounds can be formulated into a single form for co-administration, both methods of co-administration, however, being part of the same therapeutic treatment or regimen.

[0124] The pharmaceutical compositions comprising a SOS1 inhibitor, or a pharmaceutically acceptable salt thereof, and/or a KRas G12D inhibitor, or a pharmaceutically acceptable salt thereof, for use in the methods may be for simultaneous, separate or sequential use. In one embodiment, the SOS1 inhibitor, or a pharmaceutically acceptable salt thereof, is administered prior to administration of the KRas G12D inhibitor compound of Formula (I), or a pharmaceutically acceptable salt thereof. In another embodiment, the SOS1 inhibitor, or a pharmaceutically acceptable salt thereof, is administered after administration of the KRas G12D inhibitor compound of Formula (I), or a pharmaceutically acceptable salt thereof. In another embodiment, the SOS1 inhibitor, or a pharmaceutically acceptable salt thereof, is administered at about the same time as administration of the KRas G12D inhibitor compound of Formula (I), or a pharmaceutically acceptable salt thereof.

[0125] Separate administration of each inhibitor, at different times and by different routes, in some cases would be advantageous. Thus, the components in the combination i.e. the KRas G12D inhibitor compound of Formula (I), or a pharmaceutically acceptable salt thereof and the SOS1 inhibitor, or a pharmaceutically acceptable salt thereof, need not be necessarily administered at essentially the same time or in any order.

[0126] Oncology drugs are typically administered at the maximum tolerated dose ("MTD"), which is the highest dose of drug that does not cause unacceptable side effects. In one embodiment, the KRas G12D inhibitor, or a pharmaceutically acceptable salt or a pharmaceutical composition thereof and the SOS1 inhibitor, or a pharmaceutically acceptable salt or a pharmaceutical composition thereof, are each dosed at their respective MTDs. In one embodiment, the KRas G12D inhibitor, or a pharmaceutically acceptable salt or a pharmaceutical composition thereof, is

dosed at its MTD and the SOS1 inhibitor, or a pharmaceutically acceptable salt or a pharmaceutical composition thereof, is dosed in an amount less than its MTD. In one embodiment, the KRas G12D inhibitor, or a pharmaceutically acceptable salt or a pharmaceutical composition thereof, is dosed at an amount less than its MTD and the SOS1 inhibitor, or a pharmaceutically acceptable salt or a pharmaceutical composition thereof, is dosed at its MTD. In one embodiment, the KRas G12D inhibitor, or a pharmaceutically acceptable salt or a pharmaceutical composition thereof and the SOS1 inhibitor, or a pharmaceutically acceptable salt or a pharmaceutical composition thereof are each dosed at less than their respective MTDs. The administration can be so timed that the peak pharmacokinetic effect of one compound coincides with the peak pharmacokinetic effect of the other.

[0127] In one embodiment, a single dose of KRas G12D inhibitor compound of Formula (I), or a pharmaceutically acceptable salt or a pharmaceutical composition thereof, is administered per day (i.e., in about 24 hour intervals) (i.e., QD). In another embodiment, two doses of the KRas G12D inhibitor compound of Formula (I), or a pharmaceutically acceptable salt or a pharmaceutical composition thereof, are administered per day (i.e., BID). In another embodiment, three doses of the KRas G12D inhibitor compound of Formula (I), or a pharmaceutically acceptable salt or a pharmaceutical composition thereof, are administered per day (i.e., TID).

[0128] In one embodiment, the SOS1 inhibitor, or a pharmaceutically acceptable salt or a pharmaceutical composition thereof, is administered QD. In another embodiment the SOS1 inhibitor, or a pharmaceutically acceptable salt or a pharmaceutical composition thereof, are administered BID. In another embodiment, the SOS1 inhibitor, or a pharmaceutically acceptable salt or a pharmaceutical composition thereof, of the invention are administered TID.

[0129] In one embodiment, a single dose of KRas G12D inhibitor compound of Formula (I), or a pharmaceutically acceptable salt or a pharmaceutical composition thereof, and SOS1 inhibitor, or a pharmaceutically acceptable salt or a pharmaceutical composition thereof are each administered once daily.

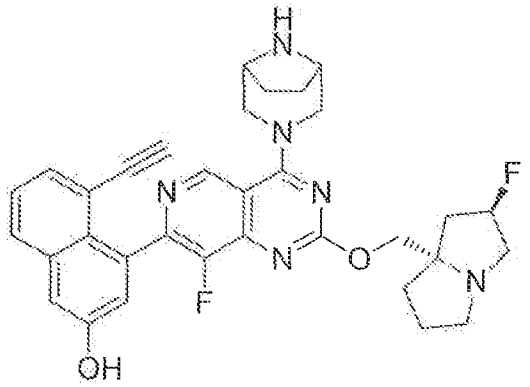
[0130] Examples of SOS1 inhibitors suitable for the provided compositions and methods include, but are not limited to, BI-1701963 (Boehringer Ingelheim) and BI-3406 (Boehringer Ingelheim).

COMBINATION THERAPIES

[0131] In one aspect of the invention, provided herein are methods of treating cancer in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a combination of a SOS1 inhibitor, or a pharmaceutically acceptable salt or a pharmaceutical composition thereof, and a KRAS G12D inhibitor of Formula (I), or a pharmaceutically acceptable salt or a pharmaceutical composition thereof. In one embodiment, the cancer is a KRas G12D-associated cancer. In one embodiment, the KRas G12D-associated cancer is pancreatic, colorectal, endometrial, and non-small cell lung cancer.

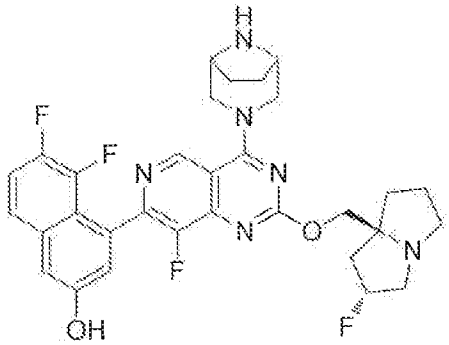
[0132] In yet another aspect, the invention provides for methods for increasing the sensitivity of a cancer cell to a KRas G12D inhibitor, comprising contacting the cancer cell with an effective amount of a combination of a KRas G12D inhibitor compound of Formula (I), or a pharmaceutically acceptable salt or a pharmaceutical composition thereof, and a SOS1 inhibitor, or a pharmaceutically acceptable salt or a pharmaceutical composition thereof, wherein the SOS1 inhibitor synergistically increases the sensitivity of the cancer cell to the KRas G12D inhibitor. In one embodiment, the contacting is in vitro. In one embodiment, the contacting is in vivo.

[0133] In one embodiment, the combination therapy comprises a combination of a compound having the formula:



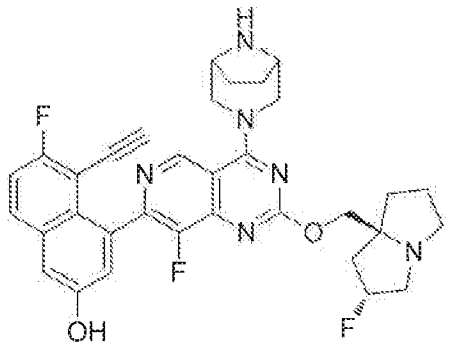
or a pharmaceutically acceptable salt thereof, and a SOS1 inhibitor. In one embodiment, the SOS1 inhibitor is BI-3406.

[0134] In one embodiment, the combination therapy comprises a combination of a compound having the formula:



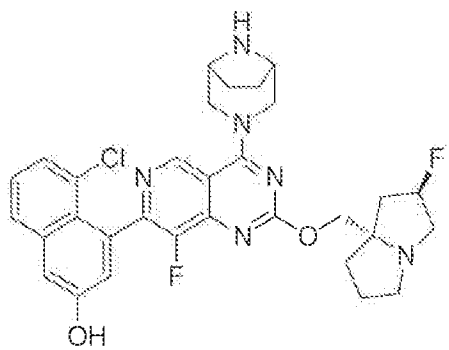
or a pharmaceutically acceptable salt thereof, and a SOS1 inhibitor. In one embodiment, the SOS1 inhibitor is BI-3406.

[0135] In one embodiment, the combination therapy comprises a combination of a compound having the formula:



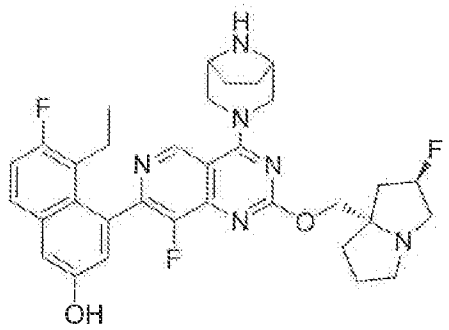
or a pharmaceutically acceptable salt thereof, and a SOS1 inhibitor. In one embodiment, the SOS1 inhibitor is BI-3406.

[0136] In one embodiment, the combination therapy comprises a combination of a compound having the formula:



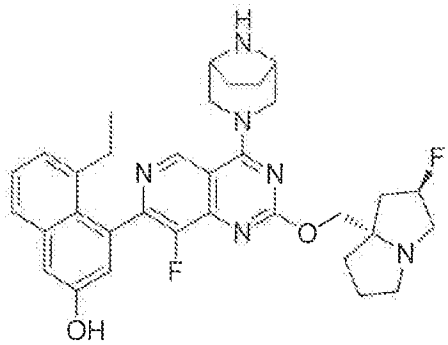
or a pharmaceutically acceptable salt thereof, and a SOS1 inhibitor. In one embodiment, the SOS1 inhibitor is BI-3406.

[0137] In one embodiment, the combination therapy comprises a combination of a compound having the formula:



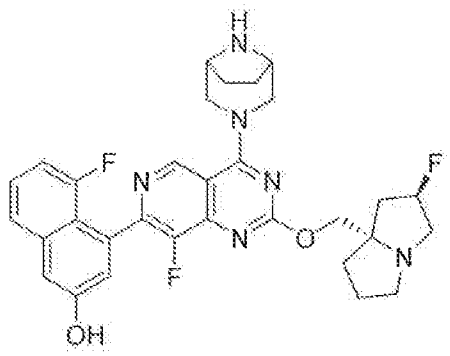
or a pharmaceutically acceptable salt thereof, and a SOS1 inhibitor. In one embodiment, the SOS1 inhibitor is BI-3406.

[0138] In one embodiment, the combination therapy comprises a combination of a compound having the formula:



or a pharmaceutically acceptable salt thereof, and a SOS1 inhibitor. In one embodiment, the SOS1 inhibitor is BI-3406.

[0139] In one embodiment, the combination therapy comprises a combination of a compound having the formula:



or a pharmaceutically acceptable salt thereof, and a SOS1 inhibitor. In one embodiment, the SOS1 inhibitor is BI-3406.

[0140] As used herein, the term "contacting" refers to the bringing together of indicated moieties in an in vitro system or an in vivo system. For example, "contacting" a cancer cell includes the administration of a combination provided herein to an individual or subject, such as a human, having KRas G12D, as well as, for example, introducing a combination provided herein into a sample containing a cellular or purified preparation containing KRas G12D.

[0141] By negatively modulating the activity of KRas G12D, the methods described herein are designed to inhibit undesired cellular proliferation resulting from enhanced KRas G12D activity within the cell. The ability of a compound to inhibit KRas G12D may be monitored in vitro using well known methods, including those described in published international PCT application number WO 2021/041671. Likewise, the inhibitory activity of combination in cells may be monitored, for example, by measuring the inhibition of KRas G12D activity of the amount of phosphorylated ERK to assess the effectiveness of treatment and dosages may be adjusted accordingly by the attending medical practitioner.

[0142] The compositions and methods provided herein may be used for the treatment of a KRas G12D-associated cancer in a subject in need thereof, comprising administering to said subject a therapeutically effective amount of a combination of a SOS1 inhibitor, or a pharmaceutically acceptable salt or a pharmaceutical composition thereof, and a KRas G12D inhibitor compound of Formula (I), or a pharmaceutically acceptable salt or a pharmaceutical composition thereof, wherein the SOS1 inhibitor synergistically increases the sensitivity of the KRas G12D-associated cancer to the KRas G12D inhibitor. In one embodiment, the KRas G12D-associated cancer is pancreatic, colorectal, endometrial, and non-small cell lung cancer.

[0143] In one embodiment, the therapeutically effective amount of the combination of a SOS1 inhibitor, or a pharmaceutically acceptable salt or a pharmaceutical composition thereof, and a KRas G12D inhibitor compound of Formula (I), or a pharmaceutically acceptable salt or a pharmaceutical composition thereof, results in an increased duration of overall survival ("OS") in subjects relative to treatment with only the KRas G12D inhibitor. In one embodiment, the therapeutically effective amount of the combination of a SOS1 inhibitor, or a pharmaceutically acceptable salt or a pharmaceutical composition thereof, and a KRas G12D inhibitor compound of Formula (I), or a pharmaceutically acceptable salt or a pharmaceutical composition thereof, results in an increased duration of progression-free survival ("PFS") in subjects relative to treatment with only the KRas G12D inhibitor. In one embodiment, the therapeutically effective amount of the combination of a SOS1 inhibitor, or a pharmaceutically acceptable salt or a pharmaceutical composition thereof, and a KRas G12D inhibitor compound of Formula (I), or a pharmaceutically acceptable salt or a pharmaceutical composition thereof, results in increased tumor regression in subjects relative to treatment with only the KRas G12D inhibitor. In one embodiment, the therapeutically effective amount of the combination of a SOS1 inhibitor, or a pharmaceutically acceptable salt or a pharmaceutical composition thereof, and a KRas G12D inhibitor compound of Formula (I), or a pharmaceutically acceptable salt or a pharmaceutical composition thereof, results in increased tumor growth inhibition in subjects relative to treatment with only the KRas G12D inhibitor. In one embodiment, the therapeutically effective amount of the combination of a SOS1 inhibitor, or a pharmaceutically acceptable salt or a pharmaceutical composition thereof, and a KRas G12D inhibitor compound of Formula (I), or a pharmaceutically acceptable salt or a pharmaceutical composition thereof, results in an improvement in the duration of stable disease in subjects compared to treatment with only the KRas G12D inhibitor. In one embodiment, the KRas G12D inhibitor is a compound selected from compound Nos. 1-458 (as numbered in WO2021/041671), or a pharmaceutically acceptable salt thereof (e.g., Example Nos. 252, 243, 246, 251, 253, 259 or 282 or a pharmaceutically acceptable salt thereof). In one embodiment, the SOS1 inhibitor is BI-3406. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 252 and BI-3406. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 243 and BI-3406. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 246 and BI-3406. In one embodiment, the therapeutic combination

comprises therapeutically effective amounts of Example No. 251 and BI-3406. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 253 and BI-3406. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 259 and BI-3406. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 282 and BI-3406.

[0144] In another embodiment, the SOS1 inhibitor, or a pharmaceutically acceptable salt or a pharmaceutical composition thereof, is administered in combination with the KRas G12D inhibitor, or a pharmaceutically acceptable salt or a pharmaceutical composition thereof, once disease progression has been observed for KRas G12D monotherapy, in which the combination therapy results in enhanced clinical benefit for the patient by increasing OS, PFS, tumor regression, tumor growth inhibition or the duration of stable disease in the patient. In one embodiment, the KRas G12D inhibitor is a compound selected from compound Nos. 1-458 (as numbered in WO2021/041671), or a pharmaceutically acceptable salt thereof (e.g., Example Nos. 252, 243, 246, 251, 253, 259 or 282 or a pharmaceutically acceptable salt thereof). In one embodiment, the SOS1 inhibitor is BI-3406. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 252 and BI-3406. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 243 and BI-3406. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 246 and BI-3406. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 251 and BI-3406. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 253 and BI-3406. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 259 and BI-3406. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 282 and BI-3406.

[0145] The compositions and methods provided herein may be used for the treatment of a wide variety of cancers including tumors such as lung, colorectal, pancreas, prostate, breast, brain, skin, cervical carcinomas, testicular carcinomas, etc. More particularly, cancers that may be treated by the compositions and methods of the invention include, but are not limited to, tumor types such as astrocytic, breast, cervical, colorectal, endometrial, esophageal, gastric, head and neck, hepatocellular, laryngeal, lung, oral, ovarian, prostate and thyroid carcinomas and sarcomas. More

specifically, these compounds can be used to treat: Cardiac: sarcoma (angiosarcoma, fibrosarcoma, rhabdomyosarcoma, liposarcoma), myxoma, rhabdomyoma, fibroma, lipoma and teratoma; Lung: bronchogenic carcinoma (squamous cell, undifferentiated small cell, undifferentiated large cell, adenocarcinoma), alveolar (bronchiolar) carcinoma, bronchial adenoma, sarcoma, lymphoma, chondromatous hamartoma, mesothelioma; Gastrointestinal: esophagus (squamous cell carcinoma, adenocarcinoma, leiomyosarcoma, lymphoma), stomach (carcinoma, lymphoma, leiomyosarcoma), pancreas (ductal adenocarcinoma, insulinoma, glucagonoma, gastrinoma, carcinoid tumors, vipoma), small bowel (adenocarcinoma, lymphoma, carcinoid tumors, Kaposi's sarcoma, leiomyoma, hemangioma, lipoma, neurofibroma, fibroma), large bowel (adenocarcinoma, tubular adenoma, villous adenoma, hamartoma, leiomyoma); Genitourinary tract: kidney (adenocarcinoma, Wilm's tumor (nephroblastoma), lymphoma, leukemia), bladder and urethra (squamous cell carcinoma, transitional cell carcinoma, adenocarcinoma), prostate (adenocarcinoma, sarcoma), testis (seminoma, teratoma, embryonal carcinoma, teratocarcinoma, choriocarcinoma, sarcoma, interstitial cell carcinoma, fibroma, fibroadenoma, adenomatoid tumors, lipoma); Liver: hepatoma (hepatocellular carcinoma), cholangiocarcinoma, hepatoblastoma, angiosarcoma, hepatocellular adenoma, hemangioma; Biliary tract: gall bladder carcinoma, ampullary carcinoma, cholangiocarcinoma; Bone: osteogenic sarcoma (osteosarcoma), fibrosarcoma, malignant fibrous histiocytoma, chondrosarcoma, Ewing's sarcoma, malignant lymphoma (reticulum cell sarcoma), multiple myeloma, malignant giant cell tumor chordoma, osteochronfroma (osteocartilaginous exostoses), benign chondroma, chondroblastoma, chondromyxofibroma, osteoid osteoma and giant cell tumors; Nervous system: skull (osteoma, hemangioma, granuloma, xanthoma, osteitis deformans), meninges (meningioma, meningiosarcoma, gliomatosis), brain (astrocytoma, medulloblastoma, glioma, ependymoma, germinoma (pinealoma), glioblastoma multiform, oligodendroglioma, schwannoma, retinoblastoma, congenital tumors), spinal cord neurofibroma, meningioma, glioma, sarcoma); Gynecological: uterus (endometrial carcinoma), cervix (cervical carcinoma, pre-tumor cervical dysplasia), ovaries (ovarian carcinoma (serous cystadenocarcinoma, mucinous cystadenocarcinoma, unclassified carcinoma), granulosa-thecal cell tumors, Sertoli-Leydig cell tumors, dysgerminoma, malignant teratoma), vulva (squamous cell carcinoma, intraepithelial carcinoma, adenocarcinoma, fibrosarcoma, melanoma), vagina (clear cell carcinoma, squamous cell carcinoma, botryoid sarcoma (embryonal rhabdomyosarcoma), fallopian tubes (carcinoma);

Hematologic: blood (myeloid leukemia (acute and chronic), acute lymphoblastic leukemia, chronic lymphocytic leukemia, myeloproliferative diseases, multiple myeloma, myelodysplastic syndrome), Hodgkin's disease, non-Hodgkin's lymphoma (malignant lymphoma); Skin: malignant melanoma, basal cell carcinoma, squamous cell carcinoma, Kaposi's sarcoma, moles dysplastic nevi, lipoma, angioma, dermatofibroma, keloids, psoriasis; and Adrenal glands: neuroblastoma. In certain embodiments, the cancer is non-small cell lung cancer.

[0146] Also provided herein is a method for treating cancer in a subject in need thereof, the method comprising (a) determining that cancer is associated with a KRas G12D mutation (e.g., a KRas G12D-associated cancer) (e.g., as determined using a regulatory agency-approved, e.g., FDA-approved, assay or kit); and (b) administering to the patient a therapeutically effective amount of a combination of a SOS1 inhibitor, or a pharmaceutically acceptable salt or a pharmaceutical composition thereof, and a KRas G12D inhibitor compound of Formula I, or a pharmaceutically acceptable salt or a pharmaceutical composition thereof, wherein the SOS1 inhibitor synergistically increases the sensitivity of the KRas G12D-associated cancer to the KRas G12D inhibitor. In one embodiment, the KRas G12D inhibitor is a compound selected from compound Nos. 1-458 (as numbered in WO2021/041671), or a pharmaceutically acceptable salt thereof (e.g., Example Nos. 252, 243, 246, 251, 253, 259 or 282 or a pharmaceutically acceptable salt thereof). In one embodiment, the SOS1 inhibitor is selected BI-3406. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 252 and BI-3406. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 243 and BI-3406. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 246 and BI-3406. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 251 and BI-3406. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 253 and BI-3406. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 259 and BI-3406. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 282 and BI-3406.

[0147] In one embodiment, a compound of Formula I is administered as a capsule during the period of time. In one embodiment, a tablet or capsule formulation of a compound of Formula I comprises about 10 mg to about 100 mg (e.g., about 10 mg to about 95 mg, about 10 mg to about

90 mg, about 10 mg to about 85 mg, about 10 mg to about 80 mg, about 10 mg to about 75 mg, about 10 mg to about 70 mg, about 10 mg to about 65 mg, about 10 mg to about 60 mg, about 10 mg to about 55 mg, about 10 mg to about 50 mg, about 10 mg to about 45 mg, about 10 mg to about 40 mg, about 10 mg to about 35 mg, about 10 mg to about 30 mg, about 10 mg to about 25 mg, about 10 mg to about 20 mg, about 10 mg to about 15 mg, about 15 mg to about 100 mg, about 15 mg to about 95 mg, about 15 mg to about 90 mg, about 15 mg to about 85 mg, about 15 mg to about 80 mg, about 15 mg to about 75 mg, about 15 mg to about 70 mg, about 15 mg to about 65 mg, about 15 mg to about 60 mg, about 15 mg to about 55 mg, about 15 mg to about 50 mg, about 15 mg to about 45 mg, about 15 mg to about 40 mg, about 15 mg to about 35 mg, about 15 mg to about 30 mg, about 15 mg to about 25 mg, about 15 mg to about 20 mg, about 20 mg to about 100 mg, about 20 mg to about 95 mg, about 20 mg to about 90 mg, about 20 mg to about 85 mg, about 20 mg to about 80 mg, about 20 mg to about 75 mg, about 20 mg to about 70 mg, about 20 mg to about 65 mg, about 20 mg to about 60 mg, about 20 mg to about 55 mg, about 20 mg to about 50 mg, about 20 mg to about 45 mg, about 20 mg to about 40 mg, about 20 mg to about 35 mg, about 20 mg to about 30 mg, about 20 mg to about 25 mg, about 25 mg to about 100 mg, about 25 mg to about 95 mg, about 25 mg to about 90 mg, about 25 mg to about 85 mg, about 25 mg to about 80 mg, about 25 mg to about 75 mg, about 25 mg to about 70 mg, about 25 mg to about 65 mg, about 25 mg to about 60 mg, about 25 mg to about 55 mg, about 25 mg to about 50 mg, about 25 mg to about 45 mg, about 25 mg to about 40 mg, about 25 mg to about 35 mg, about 25 mg to about 30 mg, about 30 mg to about 100 mg, about 30 mg to about 95 mg, about 30 mg to about 90 mg, about 30 mg to about 85 mg, about 30 mg to about 80 mg, about 30 mg to about 75 mg, about 30 mg to about 70 mg, about 30 mg to about 65 mg, about 30 mg to about 60 mg, about 30 mg to about 55 mg, about 30 mg to about 50 mg, about 30 mg to about 45 mg, about 30 mg to about 40 mg, about 30 mg to about 35 mg, about 35 mg to about 100 mg, about 35 mg to about 95 mg, about 35 mg to about 90 mg, about 35 mg to about 85 mg, about 35 mg to about 80 mg, about 35 mg to about 75 mg, about 35 mg to about 70 mg, about 35 mg to about 65 mg, about 35 mg to about 60 mg, about 35 mg to about 55 mg, about 35 mg to about 50 mg, about 35 mg to about 45 mg, about 35 mg to about 40 mg, about 40 mg to about 100 mg, about 40 mg to about 95 mg, about 40 mg to about 90 mg, about 40 mg to about 85 mg, about 40 mg to about 80 mg, about 40 mg to about 75 mg, about 40 mg to about 70 mg, about 40 mg to about 65 mg, about 40 mg to about 60 mg, about 40 mg to about 55 mg, about 40 mg to about 50 mg, about 40 mg to about 45 mg, about 45

mg to about 100 mg, about 45 mg to about 95 mg, about 45 mg to about 90 mg, about 45 mg to about 85 mg, about 45 mg to about 80 mg, about 45 mg to about 75 mg, about 45 mg to about 70 mg, about 45 mg to about 65 mg, about 45 mg to about 60 mg, about 45 mg to about 55 mg, about 45 mg to about 50 mg, about 50 mg to about 100 mg, about 50 mg to about 95 mg, about 50 mg to about 90 mg, about 50 mg to about 85 mg, about 50 mg to about 80 mg, about 50 mg to about 75 mg, about 50 mg to about 70 mg, about 50 mg to about 65 mg, about 50 mg to about 60 mg, about 50 mg to about 55 mg, about 55 mg to about 100 mg, about 55 mg to about 95 mg, about 55 mg to about 90 mg, about 55 mg to about 85 mg, about 55 mg to about 80 mg, about 55 mg to about 75 mg, about 55 mg to about 70 mg, about 55 mg to about 65 mg, about 55 mg to about 60 mg, about 60 mg to about 100 mg, about 60 mg to about 95 mg, about 60 mg to about 90 mg, about 60 mg to about 85 mg, about 60 mg to about 80 mg, about 60 mg to about 75 mg, about 60 mg to about 70 mg, about 60 mg to about 65 mg, about 65 mg to about 100 mg, about 65 mg to about 95 mg, about 65 mg to about 90 mg, about 65 mg to about 85 mg, about 65 mg to about 80 mg, about 65 mg to about 75 mg, about 65 mg to about 70 mg, about 70 mg to about 100 mg, about 70 mg to about 95 mg, about 70 mg to about 90 mg, about 70 mg to about 85 mg, about 70 mg to about 80 mg, about 70 mg to about 75 mg, about 75 mg to about 100 mg, about 75 mg to about 95 mg, about 75 mg to about 90 mg, about 75 mg to about 85 mg, about 75 mg to about 80 mg, about 80 mg to about 100 mg, about 80 mg to about 95 mg, about 80 mg to about 90 mg, about 80 mg to about 85 mg, about 85 mg to about 100 mg, about 85 mg to about 95 mg, about 85 mg to about 90 mg, about 90 mg to about 100 mg, about 90 mg to about 95 mg, about 95 mg to about 100 mg, about 10 mg, about 15 mg, about 20 mg, about 25 mg, about 30 mg, about 35 mg, about 40 mg, about 45 mg, about 50 mg, about 55 mg, about 60 mg, about 65 mg, about 70 mg, about 75 mg, about 80 mg, about 85 mg, about 90 mg, about 95 mg, or about 100 mg) of a compound of Formula I (e.g., a compound selected from compound Nos. 1-553, e.g., compound No. 234, 359, 478 or 507). In one embodiment, a compound of Formula I is orally administered once a day (QD) on a daily basis during a period of time. In one embodiment, a compound of Formula I is orally administered twice a day (BID) on a daily basis during a period of time. In one embodiment, a compound of Formula I is orally administered in the amount of about 20 mg to about 500 mg (e.g., about 20 mg to about 480 mg, about 20 mg to about 460 mg, about 20 mg to about 440 mg, about 20 mg to about 420 mg, about 20 mg to about 400 mg, about 20 mg to about 380 mg, about 20 mg to about 360 mg, about 20 mg to about 340 mg, about 20 mg to about 320 mg, about 20 mg to

about 300 mg, about 20 mg to about 280 mg, about 20 mg to about 260 mg, about 20 mg to about 240 mg, about 20 mg to about 220 mg, about 20 mg to about 200 mg, about 20 mg to about 180 mg, about 20 mg to about 160 mg, about 20 mg to about 140 mg, about 20 mg to about 120 mg, about 20 mg to about 100 mg, about 20 mg to about 80 mg, about 20 mg to about 60 mg, about 20 mg to about 40 mg, about 40 mg to about 500 mg, about 40 mg to about 480 mg, about 40 mg to about 460 mg, about 40 mg to about 440 mg, about 40 mg to about 420 mg, about 40 mg to about 400 mg, about 40 mg to about 380 mg, about 40 mg to about 360 mg, about 40 mg to about 340 mg, about 40 mg to about 320 mg, about 40 mg to about 300 mg, about 40 mg to about 280 mg, about 40 mg to about 260 mg, about 40 mg to about 240 mg, about 40 mg to about 220 mg, about 40 mg to about 200 mg, about 40 mg to about 180 mg, about 40 mg to about 160 mg, about 40 mg to about 140 mg, about 40 mg to about 120 mg, about 40 mg to about 100 mg, about 40 mg to about 80 mg, about 40 mg to about 60 mg, about 60 mg to about 500 mg, about 60 mg to about 480 mg, about 60 mg to about 460 mg, about 60 mg to about 440 mg, about 60 mg to about 420 mg, about 60 mg to about 400 mg, about 60 mg to about 380 mg, about 60 mg to about 360 mg, about 60 mg to about 340 mg, about 60 mg to about 320 mg, about 60 mg to about 300 mg, about 60 mg to about 280 mg, about 60 mg to about 260 mg, about 60 mg to about 240 mg, about 60 mg to about 220 mg, about 60 mg to about 200 mg, about 60 mg to about 180 mg, about 60 mg to about 160 mg, about 60 mg to about 140 mg, about 60 mg to about 120 mg, about 60 mg to about 100 mg, about 60 mg to about 80 mg, about 80 mg to about 500 mg, about 80 mg to about 480 mg, about 80 mg to about 460 mg, about 80 mg to about 440 mg, about 80 mg to about 420 mg, about 80 mg to about 400 mg, about 80 mg to about 380 mg, about 80 mg to about 360 mg, about 80 mg to about 340 mg, about 80 mg to about 320 mg, about 80 mg to about 300 mg, about 80 mg to about 280 mg, about 80 mg to about 260 mg, about 80 mg to about 240 mg, about 80 mg to about 220 mg, about 80 mg to about 200 mg, about 80 mg to about 180 mg, about 80 mg to about 160 mg, about 80 mg to about 140 mg, about 80 mg to about 120 mg, about 80 mg to about 100 mg, about 100 mg to about 500 mg, about 100 mg to about 480 mg, about 100 mg to about 460 mg, about 100 mg to about 440 mg, about 100 mg to about 420 mg, about 100 mg to about 400 mg, about 100 mg to about 380 mg, about 100 mg to about 360 mg, about 100 mg to about 340 mg, about 100 mg to about 320 mg, about 100 mg to about 300 mg, about 100 mg to about 280 mg, about 100 mg to about 260 mg, about 100 mg to about 240 mg, about 100 mg to about 220 mg, about 100 mg to about 200 mg, about 100 mg to about 180 mg, about 100 mg to about 160 mg,

about 100 mg to about 140 mg, about 100 mg to about 120 mg, about 120 mg to about 500 mg, about 120 mg to about 480 mg, about 120 mg to about 460 mg, about 120 mg to about 440 mg, about 120 mg to about 420 mg, about 120 mg to about 400 mg, about 120 mg to about 380 mg, about 120 mg to about 360 mg, about 120 mg to about 340 mg, about 120 mg to about 320 mg, about 120 mg to about 300 mg, about 120 mg to about 280 mg, about 120 mg to about 260 mg, about 120 mg to about 240 mg, about 120 mg to about 220 mg, about 120 mg to about 200 mg, about 120 mg to about 180 mg, about 120 mg to about 160 mg, about 120 mg to about 140 mg, about 140 mg to about 500 mg, about 140 mg to about 480 mg, about 140 mg to about 460 mg, about 140 mg to about 440 mg, about 140 mg to about 420 mg, about 140 mg to about 400 mg, about 140 mg to about 380 mg, about 140 mg to about 360 mg, about 140 mg to about 340 mg, about 140 mg to about 320 mg, about 140 mg to about 300 mg, about 140 mg to about 280 mg, about 140 mg to about 260 mg, about 140 mg to about 240 mg, about 140 mg to about 220 mg, about 140 mg to about 200 mg, about 140 mg to about 180 mg, about 140 mg to about 160 mg, about 160 mg to about 500 mg, about 160 mg to about 480 mg, about 160 mg to about 460 mg, about 160 mg to about 440 mg, about 160 mg to about 420 mg, about 160 mg to about 400 mg, about 160 mg to about 380 mg, about 160 mg to about 360 mg, about 160 mg to about 340 mg, about 160 mg to about 320 mg, about 160 mg to about 300 mg, about 160 mg to about 280 mg, about 160 mg to about 260 mg, about 160 mg to about 240 mg, about 160 mg to about 220 mg, about 160 mg to about 200 mg, about 160 mg to about 180 mg, about 180 mg to about 500 mg, about 180 mg to about 480 mg, about 180 mg to about 460 mg, about 180 mg to about 440 mg, about 180 mg to about 420 mg, about 180 mg to about 400 mg, about 180 mg to about 380 mg, about 180 mg to about 360 mg, about 180 mg to about 340 mg, about 180 mg to about 320 mg, about 180 mg to about 300 mg, about 180 mg to about 280 mg, about 180 mg to about 260 mg, about 180 mg to about 240 mg, about 180 mg to about 220 mg, about 180 mg to about 200 mg, about 200 mg to about 500 mg, about 200 mg to about 480 mg, about 200 mg to about 460 mg, about 200 mg to about 440 mg, about 200 mg to about 420 mg, about 200 mg to about 400 mg, about 200 mg to about 380 mg, about 200 mg to about 360 mg, about 200 mg to about 340 mg, about 200 mg to about 320 mg, about 200 mg to about 300 mg, about 200 mg to about 280 mg, about 200 mg to about 260 mg, about 200 mg to about 240 mg, about 200 mg to about 220 mg, about 220 mg to about 500 mg, about 220 mg to about 480 mg, about 220 mg to about 460 mg, about 220 mg to about 440 mg, about 220 mg to about 420 mg, about 220 mg to about 400 mg,

about 220 mg to about 380 mg, about 220 mg to about 360 mg, about 220 mg to about 340 mg, about 220 mg to about 320 mg, about 220 mg to about 300 mg, about 220 mg to about 280 mg, about 220 mg to about 260 mg, about 220 mg to about 240 mg, about 240 mg to about 500 mg, about 240 mg to about 480 mg, about 240 mg to about 460 mg, about 240 mg to about 440 mg, about 240 mg to about 420 mg, about 240 mg to about 400 mg, about 240 mg to about 380 mg, about 240 mg to about 360 mg, about 240 mg to about 340 mg, about 240 mg to about 320 mg, about 240 mg to about 300 mg, about 240 mg to about 280 mg, about 240 mg to about 260 mg, about 260 mg to about 500 mg, about 260 mg to about 480 mg, about 260 mg to about 460 mg, about 260 mg to about 440 mg, about 260 mg to about 420 mg, about 260 mg to about 400 mg, about 260 mg to about 380 mg, about 260 mg to about 360 mg, about 260 mg to about 340 mg, about 260 mg to about 320 mg, about 260 mg to about 300 mg, about 260 mg to about 280 mg, about 280 mg to about 500 mg, about 280 mg to about 480 mg, about 280 mg to about 460 mg, about 280 mg to about 440 mg, about 280 mg to about 420 mg, about 280 mg to about 400 mg, about 280 mg to about 380 mg, about 280 mg to about 360 mg, about 280 mg to about 340 mg, about 280 mg to about 320 mg, about 280 mg to about 300 mg, about 300 mg to about 500 mg, about 300 mg to about 480 mg, about 300 mg to about 460 mg, about 300 mg to about 440 mg, about 300 mg to about 420 mg, about 300 mg to about 400 mg, about 300 mg to about 380 mg, about 300 mg to about 360 mg, about 300 mg to about 340 mg, about 300 mg to about 320 mg, about 320 mg to about 500 mg, about 320 mg to about 480 mg, about 320 mg to about 460 mg, about 320 mg to about 440 mg, about 320 mg to about 420 mg, about 320 mg to about 400 mg, about 320 mg to about 380 mg, about 320 mg to about 360 mg, about 320 mg to about 340 mg, about 340 mg to about 500 mg, about 340 mg to about 480 mg, about 340 mg to about 460 mg, about 340 mg to about 440 mg, about 340 mg to about 420 mg, about 340 mg to about 400 mg, about 340 mg to about 380 mg, about 340 mg to about 360 mg, about 360 mg to about 500 mg, about 360 mg to about 480 mg, about 360 mg to about 460 mg, about 360 mg to about 440 mg, about 360 mg to about 420 mg, about 360 mg to about 400 mg, about 360 mg to about 380 mg, about 380 mg to about 500 mg, about 380 mg to about 480 mg, about 380 mg to about 460 mg, about 380 mg to about 440 mg, about 380 mg to about 420 mg, about 380 mg to about 400 mg, about 400 mg to about 500 mg, about 400 mg to about 480 mg, about 400 mg to about 460 mg, about 400 mg to about 440 mg, about 400 mg to about 420 mg, about 420 mg to about 500 mg, about 420 mg to about 480 mg, about 420 mg to about 460 mg, about 420 mg to about 440 mg,

about 440 mg to about 500 mg, about 440 mg to about 480 mg, about 440 mg to about 460 mg, about 460 mg to about 500 mg, about 460 mg to about 480 mg, about 480 mg to about 500 mg, about 25, about 50, about 75, about 100, about 150, about 200, about 250, about 300, about 350, about 400, about 450, or about 500 mg), during a period of time.

[0148] In one embodiment, the combination therapy comprises oral administration of a compound of Formula I once or twice a day on a daily basis (during a period of time), e.g., in an amount of about 10 mg to about 400 mg (e.g., about 10 mg to about 380 mg, about 10 mg to about 360 mg, about 10 mg to about 340 mg, about 10 mg to about 320 mg, about 10 mg to about 300 mg, about 10 mg to about 280 mg, about 10 mg to about 260 mg, about 10 mg to about 240 mg, about 10 mg to about 220 mg, about 10 mg to about 200 mg, about 10 mg to about 180 mg, about 10 mg to about 160 mg, about 10 mg to about 140 mg, about 10 mg to about 120 mg, about 10 mg to about 100 mg, about 10 mg to about 80 mg, about 10 mg to about 60 mg, about 10 mg to about 40 mg, about 10 mg to about 20 mg, about 20 mg to about 400 mg, about 20 mg to about 380 mg, about 20 mg to about 360 mg, about 20 mg to about 340 mg, about 20 mg to about 320 mg, about 20 mg to about 300 mg, about 20 mg to about 280 mg, about 20 mg to about 260 mg, about 20 mg to about 240 mg, about 20 mg to about 220 mg, about 20 mg to about 200 mg, about 20 mg to about 180 mg, about 20 mg to about 160 mg, about 20 mg to about 140 mg, about 20 mg to about 120 mg, about 20 mg to about 100 mg, about 20 mg to about 80 mg, about 20 mg to about 60 mg, about 20 mg to about 40 mg, about 40 mg to about 400 mg, about 40 mg to about 380 mg, about 40 mg to about 360 mg, about 40 mg to about 340 mg, about 40 mg to about 320 mg, about 40 mg to about 300 mg, about 40 mg to about 280 mg, about 40 mg to about 260 mg, about 40 mg to about 240 mg, about 40 mg to about 220 mg, about 40 mg to about 200 mg, about 40 mg to about 180 mg, about 40 mg to about 160 mg, about 40 mg to about 140 mg, about 40 mg to about 120 mg, about 40 mg to about 100 mg, about 40 mg to about 80 mg, about 40 mg to about 60 mg, about 60 mg to about 400 mg, about 60 mg to about 380 mg, about 60 mg to about 360 mg, about 60 mg to about 340 mg, about 60 mg to about 320 mg, about 60 mg to about 300 mg, about 60 mg to about 280 mg, about 60 mg to about 260 mg, about 60 mg to about 240 mg, about 60 mg to about 220 mg, about 60 mg to about 200 mg, about 60 mg to about 180 mg, about 60 mg to about 160 mg, about 60 mg to about 140 mg, about 60 mg to about 120 mg, about 60 mg to about 100 mg, about 60 mg to about 80 mg, about 80 mg to about 400 mg, about 80 mg to about 380 mg, about 80 mg to about 360 mg, about 80 mg to about 340 mg, about 80 mg to about 320 mg, about 80 mg to

about 300 mg, about 80 mg to about 280 mg, about 80 mg to about 260 mg, about 80 mg to about 240 mg, about 80 mg to about 220 mg, about 80 mg to about 200 mg, about 80 mg to about 180 mg, about 80 mg to about 160 mg, about 80 mg to about 140 mg, about 80 mg to about 120 mg, about 80 mg to about 100 mg, about 100 mg to about 400 mg, about 100 mg to about 380 mg, about 100 mg to about 360 mg, about 100 mg to about 340 mg, about 100 mg to about 320 mg, about 100 mg to about 300 mg, about 100 mg to about 280 mg, about 100 mg to about 260 mg, about 100 mg to about 240 mg, about 100 mg to about 220 mg, about 100 mg to about 200 mg, about 100 mg to about 180 mg, about 100 mg to about 160 mg, about 100 mg to about 140 mg, about 100 mg to about 120 mg, about 120 mg to about 400 mg, about 120 mg to about 380 mg, about 120 mg to about 360 mg, about 120 mg to about 340 mg, about 120 mg to about 320 mg, about 120 mg to about 300 mg, about 120 mg to about 280 mg, about 120 mg to about 260 mg, about 120 mg to about 240 mg, about 120 mg to about 220 mg, about 120 mg to about 200 mg, about 120 mg to about 180 mg, about 120 mg to about 160 mg, about 120 mg to about 140 mg, about 140 mg to about 400 mg, about 140 mg to about 380 mg, about 140 mg to about 360 mg, about 140 mg to about 340 mg, about 140 mg to about 320 mg, about 140 mg to about 300 mg, about 140 mg to about 280 mg, about 140 mg to about 260 mg, about 140 mg to about 240 mg, about 140 mg to about 220 mg, about 140 mg to about 200 mg, about 140 mg to about 180 mg, about 140 mg to about 160 mg, about 160 mg to about 400 mg, about 160 mg to about 380 mg, about 160 mg to about 360 mg, about 160 mg to about 360 mg, about 160 mg to about 340 mg, about 160 mg to about 320 mg, about 160 mg to about 300 mg, about 160 mg to about 280 mg, about 160 mg to about 260 mg, about 160 mg to about 240 mg, about 160 mg to about 220 mg, about 160 mg to about 200 mg, about 160 mg to about 180 mg, about 180 mg to about 400 mg, about 180 mg to about 380 mg, about 180 mg to about 360 mg, about 180 mg to about 340 mg, about 180 mg to about 320 mg, about 180 mg to about 300 mg, about 180 mg to about 280 mg, about 180 mg to about 260 mg, about 180 mg to about 240 mg, about 180 mg to about 220 mg, about 180 mg to about 200 mg, about 200 mg to about 400 mg, about 200 mg to about 380 mg, about 200 mg to about 360 mg, about 200 mg to about 340 mg, about 200 mg to about 320 mg, about 200 mg to about 300 mg, about 200 mg to about 280 mg, about 200 mg to about 260 mg, about 200 mg to about 240 mg, about 200 mg to about 220 mg, about 220 mg to about 400 mg, about 220 mg to about 380 mg, about 220 mg to about 360 mg, about 220 mg to about 340 mg, about 220 mg to about 320 mg, about 220 mg to about 300 mg, about 220 mg to about 280 mg,

about 220 mg to about 260 mg, about 220 mg to about 240 mg, about 240 mg to about 400 mg, about 240 mg to about 380 mg, about 240 mg to about 360 mg, about 240 mg to about 340 mg, about 240 mg to about 320 mg, about 240 mg to about 300 mg, about 240 mg to about 280 mg, about 240 mg to about 260 mg, about 260 mg to about 400 mg, about 260 mg to about 380 mg, about 260 mg to about 360 mg, about 260 mg to about 340 mg, about 260 mg to about 320 mg, about 260 mg to about 300 mg, about 260 mg to about 280 mg, about 280 mg to about 400 mg, about 280 mg to about 380 mg, about 280 mg to about 360 mg, about 280 mg to about 340 mg, about 280 mg to about 320 mg, about 280 mg to about 300 mg, about 300 mg to about 400 mg, about 300 mg to about 380 mg, about 300 mg to about 360 mg, about 300 mg to about 340 mg, about 300 mg to about 320 mg, about 320 mg to about 400 mg, about 320 mg to about 380 mg, about 320 mg to about 360 mg, about 340 mg to about 360 mg, about 340 mg to about 400 mg, about 340 mg to about 380 mg, about 340 mg to about 360 mg, about 360 mg to about 400 mg, about 360 mg to about 380 mg, about 380 mg to about 400 mg, about 100 mg, about 200 mg, about 300 mg, or about 400 mg), and oral administration of a SOS1 inhibitor, or a pharmaceutically acceptable salt or a pharmaceutical composition thereof which is administered, for example once a day on a daily basis (during a period of time). In one embodiment, the KRAS G12D inhibitor, or a pharmaceutically acceptable salt or a pharmaceutical composition thereof, is orally administered once daily. In one embodiment, the KRAS G12D inhibitor, or a pharmaceutically acceptable salt or a pharmaceutical composition thereof, is orally administered twice daily.

[0149] One skilled in the art will recognize that, both in vivo and in vitro trials using suitable, known and generally accepted cell and/or animal models are predictive of the ability of a test compound of the combination or the combination to treat or prevent a given disorder.

[0150] One skilled in the art will further recognize that human clinical trials including first-in-human, dose ranging and efficacy trials, in healthy patients and/or those suffering from a given disorder, may be completed according to methods well known in the clinical and medical arts.

SYNERGY

[0151] In one embodiment, the addition of a SOS1 inhibitor, or a pharmaceutically acceptable salt or a pharmaceutical composition thereof, synergistically increases the activity of KRas G12D inhibitor compound of Formula (I), or a pharmaceutically acceptable salt or a pharmaceutical

composition thereof against cancer or cancer cell lines expressing KRas G12D. Any method for determining whether two compounds exhibit synergy may be used for determining the synergistic effect of the combination.

[0152] Several mathematical models have been developed to determine whether two compounds act synergistically, i.e., beyond a mere additive effect. For instance, Loewe Additivity (Loewe (1928) Physiol. 27: 47-187), Bliss Independence (Bliss (1939) Ann. Appl. Biol. 26: 585-615), Highest Single Agent, ZIP (Yadav et al (2015) Comput Struct Biotech J 13: 504-513) and other models (Chou & Talalay (1984) Adv Enzyme Regul 22: 27-55. #6382953; and Greco et al. (1995) Pharmacol Rev 47(2): 331-85. #7568331) are well known models in the pharmaceutical industry and may be used to calculate a "synergy score" that indicates whether synergy was detected and the magnitude of such synergy. Combining these synergy scores produces a composite synergy score which may be used to evaluate and characterize the KRas G12D inhibitor compounds of Formula (I) in combination with a SOS1 inhibitor.

[0153] In general, the mathematical models use data obtained from single agent values to determine the predicted additive effect of the combination which is compared to the observed effect for the combination. If the observed effect is greater than the predicted effect, the combination is deemed to be synergistic. For example, the Bliss independence model compares the observed combination response (Y_O) with the predicted combination response (Y_P), which was obtained based on the assumption that there is no effect from drug-drug interactions. Typically, the combination effect is declared synergistic if Y_O is greater than Y_P.

[0154] In some embodiments, "synergistic effect" as used herein refers to combination of a KRAS inhibitor or a pharmaceutically acceptable salt thereof, and a SOS1 inhibitor or a pharmaceutically acceptable salt thereof producing an effect, for example, any of the beneficial or desired results including clinical results or endpoints as described herein, which is greater than the sum of the effect observed when a compound of Formula I or a pharmaceutically acceptable salt thereof (e.g., a compound selected from compound Nos. 1-458 as numbered in WO2021/041671) and a SOS1 inhibitor or a pharmaceutically acceptable salt thereof are administered alone. In one embodiment, the KRas G12D inhibitor is a compound selected from compound Nos. 1-458 (as numbered in WO2021/041671), or a pharmaceutically acceptable salt thereof (e.g., Example Nos. 252, 243, 246, 251, 253, 259 or 282 or a pharmaceutically acceptable salt thereof). In one embodiment, the

SOS1 inhibitor is BI-3406. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 252 and BI-3406. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 243 and BI-3406. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 246 and BI-3406. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 251 and BI-3406. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 253 and BI-3406. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 259 and BI-3406. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 282 and BI-3406.

[0155] In some embodiments, the methods provided herein can result in a 1% to 99% (e.g., 1% to 98%, 1% to 95%, 1% to 90%, 1 to 85%, 1 to 80%, 1% to 75%, 1% to 70%, 1% to 65%, 1% to 60%, 1% to 55%, 1% to 50%, 1% to 45%, 1% to 40%, 1% to 35%, 1% to 30%, 1% to 25%, 1% to 20%, 1% to 15%, 1% to 10%, 1% to 5%, 2% to 99%, 2% to 90%, 2% to 85%, 2% to 80%, 2% to 75%, 2% to 70%, 2% to 65%, 2% to 60%, 2% to 55%, 2% to 50%, 2% to 45%, 2% to 40%, 2% to 35%, 2% to 30%, 2% to 25%, 2% to 20%, 2% to 15%, 2% to 10%, 2% to 5%, 4% to 99%, 4% to 95%, 4% to 90%, 4% to 85%, 4% to 80%, 4% to 75%, 4% to 70%, 4% to 65%, 4% to 60%, 4% to 55%, 4% to 50%, 4% to 45%, 4% to 40%, 4% to 35%, 4% to 30%, 4% to 25%, 4% to 20%, 4% to 15%, 4% to 10%, 6% to 99%, 6% to 95%, 6% to 90%, 6% to 85%, 6% to 80%, 6% to 75%, 6% to 70%, 6% to 65%, 6% to 60%, 6% to 55%, 6% to 50%, 6% to 45%, 6% to 40%, 6% to 35%, 6% to 30%, 6% to 25%, 6% to 20%, 6% to 15%, 6% to 10%, 8% to 99%, 8% to 95%, 8% to 90%, 8% to 85%, 8% to 80%, 8% to 75%, 8% to 70%, 8% to 65%, 8% to 60%, 8% to 55%, 8% to 50%, 8% to 45%, 8% to 40%, 8% to 35%, 8% to 30%, 8% to 25%, 8% to 20%, 8% to 15%, 10% to 99%, 10% to 95%, 10% to 90%, 10% to 85%, 10% to 80%, 10% to 75%, 10% to 70%, 10% to 65%, 10% to 60%, 10% to 55%, 10% to 50%, 10% to 45%, 10% to 40%, 10% to 35%, 10% to 30%, 10% to 25%, 10% to 20%, 10% to 15%, 15% to 99%, 15% to 95%, 15% to 90%, 15% to 85%, 15% to 80%, 15% to 75%, 15% to 70%, 15% to 65%, 15% to 60%, 15% to 55%, 15% to 50%, 15% to 55%, 15% to 50%, 15% to 45%, 15% to 40%, 15% to 35%, 15% to 30%, 15% to 25%, 15% to 20%, 20% to 99%, 20% to 95%, 20% to 90%, 20% to 85%, 20% to 80%, 20% to 75%, 20% to 70%, 20% to 65%, 20% to 60%, 20% to 55%, 20% to 50%, 20% to 45%, 20% to 40%, 20% to 35%, 20% to 30%, 20% to 25%, 25% to 99%, 25% to 95%, 25% to 90%, 25% to 85%, 25% to

80%, 25% to 75%, 25% to 70%, 25% to 65%, 25% to 60%, 25% to 55%, 25% to 50%, 25% to 45%, 25% to 40%, 25% to 35%, 25% to 30%, 30% to 99%, 30% to 95%, 30% to 90%, 30% to 85%, 30% to 80%, 30% to 75%, 30% to 70%, 30% to 65%, 30% to 60%, 30% to 55%, 30% to 50%, 30% to 45%, 30% to 40%, 30% to 35%, 35% to 99%, 35% to 95%, 35% to 90%, 35% to 85%, 35% to 80%, 35% to 75%, 35% to 70%, 35% to 65%, 35% to 60%, 35% to 55%, 35% to 50%, 35% to 45%, 35% to 40%, 40% to 99%, 40% to 95%, 40% to 90%, 40% to 85%, 40% to 80%, 40% to 75%, 40% to 70%, 40% to 65%, 40% to 60%, 40% to 55%, 40% to 60%, 40% to 55%, 40% to 50%, 40% to 45%, 45% to 99%, 45% to 95%, 45% to 95%, 45% to 90%, 45% to 85%, 45% to 80%, 45% to 75%, 45% to 70%, 45% to 65%, 45% to 60%, 45% to 55%, 45% to 50%, 50% to 99%, 50% to 95%, 50% to 90%, 50% to 85%, 50% to 80%, 50% to 75%, 50% to 70%, 50% to 65%, 50% to 60%, 50% to 55%, 55% to 99%, 55% to 95%, 55% to 90%, 55% to 85%, 55% to 80%, 55% to 75%, 55% to 70%, 55% to 65%, 55% to 60%, 60% to 99%, 60% to 95%, 60% to 90%, 60% to 85%, 60% to 80%, 60% to 75%, 60% to 70%, 60% to 65%, 65% to 99%, 60% to 95%, 60% to 90%, 60% to 85%, 60% to 80%, 60% to 75%, 60% to 70%, 60% to 65%, 70% to 99%, 70% to 95%, 70% to 90%, 70% to 85%, 70% to 80%, 70% to 75%, 75% to 99%, 75% to 95%, 75% to 90%, 75% to 85%, 75% to 80%, 80% to 99%, 80% to 95%, 80% to 90%, 80% to 85%, 85% to 99%, 85% to 95%, 85% to 90%, 90% to 99%, 90% to 95%, or 95% to 100%) reduction in the volume of one or more solid tumors in a patient following treatment with the combination therapy for a period of time between 1 day and 2 years (e.g., between 1 day and 22 months, between 1 day and 20 months, between 1 day and 18 months, between 1 day and 16 months, between 1 day and 14 months, between 1 day and 12 months, between 1 day and 10 months, between 1 day and 9 months, between 1 day and 8 months, between 1 day and 7 months, between 1 day and 6 months, between 1 day and 5 months, between 1 day and 4 months, between 1 day and 3 months, between 1 day and 2 months, between 1 day and 1 month, between one week and 2 years, between 1 week and 22 months, between 1 week and 20 months, between 1 week and 18 months, between 1 week and 16 months, between 1 week and 14 months, between 1 week and 12 months, between 1 week and 10 months, between 1 week and 9 months, between 1 week and 8 months, between 1 week and 7 months, between 1 week and 6 months, between 1 week and 5 months, between 1 week and 4 months, between 1 week and 3 months, between 1 week and 2 months, between 1 week and 1 month, between 2 weeks and 2 years, between 2 weeks and 22 months, between 2 weeks and 20 months, between 2 weeks and 18 months, between 2 weeks and

16 months, between 2 weeks and 14 months, between 2 weeks and 12 months, between 2 weeks and 10 months, between 2 weeks and 9 months, between 2 weeks and 8 months, between 2 weeks and 7 months, between 2 weeks and 6 months, between 2 weeks and 5 months, between 2 weeks and 4 months, between 2 weeks and 3 months, between 2 weeks and 2 months, between 2 weeks and 1 month, between 1 month and 2 years, between 1 month and 22 months, between 1 month and 20 months, between 1 month and 18 months, between 1 month and 16 months, between 1 month and 14 months, between 1 month and 12 months, between 1 month and 10 months, between 1 month and 9 months, between 1 month and 8 months, between 1 month and 7 months, between 1 month and 6 months, between 1 month and 6 months, between 1 month and 5 months, between 1 month and 4 months, between 1 month and 3 months, between 1 month and 2 months, between 2 months and 2 years, between 2 months and 22 months, between 2 months and 20 months, between 2 months and 18 months, between 2 months and 16 months, between 2 months and 14 months, between 2 months and 12 months, between 2 months and 10 months, between 2 months and 9 months, between 2 months and 8 months, between 2 months and 7 months, between 2 months and 6 months, or between 2 months and 5 months, between 2 months and 4 months, between 3 months and 2 years, between 3 months and 22 months, between 3 months and 20 months, between 3 months and 18 months, between 3 months and 16 months, between 3 months and 14 months, between 3 months and 12 months, between 3 months and 10 months, between 3 months and 8 months, between 3 months and 6 months, between 4 months and 2 years, between 4 months and 22 months, between 4 months and 20 months, between 4 months and 18 months, between 4 months and 16 months, between 4 months and 14 months, between 4 months and 12 months, between 4 months and 10 months, between 4 months and 8 months, between 4 months and 6 months, between 6 months and 2 years, between 6 months and 22 months, between 6 months and 20 months, between 6 months and 18 months, between 6 months and 16 months, between 6 months and 14 months, between 6 months and 12 months, between 6 months and 10 months, or between 6 months and 8 months) (e.g., as compared to the size of the one or more solid tumors in the patient prior to treatment).

[0156] The phrase "time of survival" means the length of time between the identification or diagnosis of cancer (e.g., any of the cancers described herein) in a mammal by a medical professional and the time of death of the mammal (caused by the cancer). Methods of increasing the time of survival in a mammal having a cancer are described herein.

[0157] In some embodiments, any of the methods described herein can result in an increase (e.g., a 1% to 400%, 1% to 380%, 1% to 360%, 1% to 340%, 1% to 320%, 1% to 300%, 1% to 280%, 1% to 260%, 1% to 240%, 1% to 220%, 1% to 200%, 1% to 180%, 1% to 160%, 1% to 140%, 1% to 120%, 1% to 100%, 1% to 95%, 1% to 90%, 1% to 85%, 1% to 80%, 1% to 75%, 1% to 70%, 1% to 65%, 1% to 60%, 1% to 55%, 1% to 50%, 1% to 45%, 1% to 40%, 1% to 35%, 1% to 30%, 1% to 25%, 1% to 20%, 1% to 15%, 1% to 10%, 1% to 5%, 5% to 400%, 5% to 380%, 5% to 360%, 5% to 340%, 5% to 320%, 5% to 300%, 5% to 280%, 5% to 260%, 5% to 240%, 5% to 220%, 5% to 200%, 5% to 180%, 5% to 160%, 5% to 140%, 5% to 120%, 5% to 100%, 5% to 90%, 5% to 80%, 5% to 70%, 5% to 60%, 5% to 50%, 5% to 40%, 5% to 30%, 5% to 20%, 5% to 10%, 10% to 400%, 10% to 380%, 10% to 360%, 10% to 340%, 10% to 320%, 10% to 300%, 10% to 280%, 10% to 260%, 10% to 240%, 10% to 220%, 10% to 200%, 10% to 180%, 10% to 160%, 10% to 140%, 10% to 120%, 10% to 100%, 10% to 90%, 10% to 80%, 10% to 70%, 10% to 60%, 10% to 50%, 10% to 40%, 10% to 30%, 10% to 20%, 20% to 400%, 20% to 380%, 20% to 360%, 20% to 340%, 20% to 320%, 20% to 300%, 20% to 280%, 20% to 260%, 20% to 240%, 20% to 220%, 20% to 200%, 20% to 180%, 20% to 160%, 20% to 140%, 20% to 120%, 20% to 100%, 20% to 90%, 20% to 80%, 20% to 70%, 20% to 60%, 20% to 50%, 20% to 40%, 20% to 30%, 30% to 400%, 30% to 380%, 30% to 360%, 30% to 340%, 30% to 320%, 30% to 300%, 30% to 280%, 30% to 260%, 30% to 240%, 30% to 220%, 30% to 200%, 30% to 180%, 30% to 160%, 30% to 140%, 30% to 120%, 30% to 100%, 30% to 90%, 30% to 80%, 30% to 70%, 30% to 60%, 30% to 50%, 30% to 40%, 40% to 400%, 40% to 380%, 40% to 360%, 40% to 340%, 40% to 320%, 40% to 300%, 40% to 280%, 40% to 260%, 40% to 240%, 40% to 220%, 40% to 200%, 40% to 180%, 40% to 160%, 40% to 140%, 40% to 120%, 40% to 100%, 40% to 90%, 40% to 80%, 40% to 70%, 40% to 60%, 40% to 50%, 50% to 400%, 50% to 380%, 50% to 360%, 50% to 340%, 50% to 320%, 50% to 300%, 50% to 280%, 50% to 260%, 50% to 240%, 50% to 220%, 50% to 200%, 50% to 180%, 50% to 160%, 50% to 140%, 50% to 140%, 50% to 120%, 50% to 100%, 50% to 90%, 50% to 80%, 50% to 70%, 50% to 60%, 60% to 400%, 60% to 380%, 60% to 360%, 60% to 340%, 60% to 320%, 60% to 300%, 60% to 280%, 60% to 260%, 60% to 240%, 60% to 220%, 60% to 200%, 60% to 180%, 60% to 160%, 60% to 140%, 60% to 120%, 60% to 100%, 60% to 90%, 60% to 80%, 60% to 70%, 70% to 400%, 70% to 380%, 70% to 360%, 70% to 340%, 70% to 320%, 70% to 300%, 70% to 280%, 70% to 260%, 70% to 240%, 70% to 220%, 70% to 200%, 70% to 180%, 70% to 160%, 70% to 140%, 70% to 120%, to 100%, 70% to

90%, 70% to 80%, 80% to 400%, 80% to 380%, 80% to 360%, 80% to 340%, 80% to 320%, 80% to 300%, 80% to 280%, 80% to 260%, 80% to 240%, 80% to 220%, 80% to 200%, 80% to 180%, 80% to 160%, 80% to 140%, 80% to 120%, 80% to 100%, 80% to 90%, 90% to 400%, 90% to 380%, 90% to 360%, 90% to 340%, 90% to 320%, 90% to 300%, 90% to 280%, 90% to 260%, 90% to 240%, 90% to 220%, 90% to 200%, 90% to 180%, 90% to 160%, 90% to 140%, 90% to 120%, 90% to 100%, 100% to 400%, 100% to 380%, 100% to 360%, 100% to 340%, 100% to 320%, 100% to 300%, 100% to 280%, 100% to 260%, 100% to 240%, 100% to 220%, 100% to 200%, 100% to 180%, 100% to 160%, 100% to 140%, 100% to 120%, 120% to 400%, 120% to 380%, 120% to 360%, 120% to 340%, 120% to 320%, 120% to 300%, 120% to 280%, 120% to 260%, 120% to 240%, 120% to 220%, 120% to 200%, 120% to 180%, 120% to 160%, 120% to 140%, 140% to 400%, 140% to 380%, 140% to 360%, 140% to 340%, 140% to 320%, 140% to 300%, 140% to 280%, 140% to 260%, 140% to 240%, 140% to 220%, 140% to 200%, 140% to 180%, 140% to 160%, 160% to 400%, 160% to 380%, 160% to 360%, 160% to 340%, 160% to 320%, 160% to 300%, 160% to 280%, 160% to 260%, 160% to 240%, 160% to 220%, 160% to 200%, 160% to 180%, 180% to 400%, 180% to 380%, 180% to 360%, 180% to 340%, 180% to 320%, 180% to 300%, 180% to 280%, 180% to 260%, 180% to 240%, 180% to 220%, 180% to 200%, 200% to 400%, 200% to 380%, 200% to 360%, 200% to 340%, 200% to 320%, 200% to 300%, 200% to 280%, 200% to 260%, 200% to 240%, 200% to 220%, 220% to 400%, 220% to 380%, 220% to 360%, 220% to 340%, 220% to 320%, 220% to 300%, 220% to 280%, 220% to 260%, 220% to 240%, 240% to 400%, 240% to 380%, 240% to 360%, 240% to 340%, 240% to 320%, 240% to 300%, 240% to 280%, 240% to 260%, 260% to 400%, 260% to 380%, 260% to 360%, 260% to 340%, 260% to 320%, 260% to 300%, 260% to 280%, 280% to 400%, 280% to 380%, 280% to 360%, 280% to 340%, 280% to 320%, 280% to 300%, 300% to 400%, 300% to 380%, 300% to 360%, 300% to 340%, or 300% to 320%) in the time of survival of the patient (e.g., as compared to a patient having a similar cancer and administered a different treatment or not receiving a treatment).

[0158] In some embodiments of any of the methods described herein, before treatment with the compositions or methods of the invention, the patient was treated with one or more of a chemotherapy, a targeted anticancer agent, radiation therapy, and surgery, and optionally, the prior treatment was unsuccessful; and/or the patient has been administered surgery and optionally, the surgery was unsuccessful; and/or the patient has been treated with a platinum-based

chemotherapeutic agent, and optionally, the patient has been previously determined to be non-responsive to treatment with the platinum-based chemotherapeutic agent; and/or the patient has been treated with a kinase inhibitor, and optionally, the prior treatment with the kinase inhibitor was unsuccessful; and/or the patient was treated with one or more other therapeutic agent(s).

KITS

[0159] The present invention also relates to a kit comprising a SOS1 inhibitor, or a pharmaceutically acceptable salt or a pharmaceutical composition thereof, and a KRas G12D inhibitor compound of Formula (I), or a pharmaceutically acceptable salt or a pharmaceutical composition thereof. Also provided is a kit comprising a SOS1 inhibitor, or a pharmaceutically acceptable salt or a pharmaceutical composition thereof, and a KRas G12D inhibitor compound of Formula (I), or a pharmaceutically acceptable salt or a pharmaceutical composition thereof, for use in treating a hematological cancer.

[0160] In a related aspect, the invention provides a kit containing a dose of a SOS1 inhibitor, or a pharmaceutically acceptable salt or a pharmaceutical composition thereof, and dose of a KRas G12D inhibitor compound of Formula (I), or a pharmaceutically acceptable salt or a pharmaceutical composition thereof, in an amount effective to inhibit proliferation of cancer cells, particularly KRas G12D-expressing cancer cells, in a subject. The kit in some cases includes an insert with instructions for administration of the a SOS1 inhibitor, or a pharmaceutically acceptable salt or a pharmaceutical composition thereof, and a KRas G12D inhibitor compound of Formula (I), or a pharmaceutically acceptable salt or a pharmaceutical composition thereof. The insert may provide a user with one set of instructions for using the a SOS1 inhibitor, or a pharmaceutically acceptable salt or a pharmaceutical composition thereof, in combination with a KRas G12D inhibitor compound of Formula (I), or a pharmaceutically acceptable salt or a pharmaceutical composition thereof.

EXAMPLE A

SOS1 Inhibitors Synergistically Increase the Activity of KRas G12D Inhibitors Against Cell Lines Expressing KRas G12D

[0161] This Example illustrates that the combination of exemplary KRas G12D inhibitor compound of Formula I (i.e., MRTX1133) and a SOS1 inhibitor synergistically inhibits the growth of tumor cell lines that express KRas G12D.

[0162] A panel of colon, pancreatic, lung, gastric, and endometrial cell lines harboring KRas G12D mutations was assembled to determine whether combining SOS1 inhibitors with exemplary KRas G12D inhibitors disclosed herein results in synergistic activity. The collection included SNU61 (colon, KCLB #00061), LS180 (colon, ATCC #CL-187), Panc 05.04 (pancreas, ATCC #CRL-2557), Panc 02.03 (pancreas ATCC #CRL-2553) , SNU-407 (colon, AddexBio # C0009016), LS513 (colon, ATCC #CRL-2134), A427 (lung, ATCC #HTB-53), HPAC (pancreas, ATCC #CRL-2119), AGS (gastric, ATCC #CRL-1739), SNU-1197 (colon, KCLB #01197.1) , SNU-1033 (colon, KCLB #01033), SNU-410 (pancreas, KCLB #00410), HEC-1-B (endometrial, ATCC #HTB-113), SU.86.86 (pancreas, ATCC #CRL-1837), SNU-C2B (colon, ATCC #CCL-250), Panc 08.13 (pancreas, ATCC #CRL-2551), SUIT-2 (pancreas, JCRB #JCRB1094), HPAF-II (pancreas, ATCC #CRL-1997), Panc 04.03 (pancreas, ATCC #CRL-2555),Panc 1005 (pancreas, ATCC #CRL-2547), HCC-1588 (lung, KCLB #71588), GP2D (colon, SigmaAldrich #95090714), AsPC-1 (pancreas, ATCC CRL-1682), and SW 1990 (pancreas, ATCC CRL-2172)

[0163] Assays for determining the synergy score for the pairwise combinations for each cell line were performed in triplicate. Three 96-well plates plus an additional 4 wells of a separate 96-well control plate for determining baseline luminescence were seeded with 2000 cells/well of a particular cell line in a total volume of 90µl of a suitable growth medium for that cell line, e.g., RPMI 1640 medium supplemented with 10% FBS and any cell line specific reagents need for growth. The plates were incubated overnight at 37°C in a 5% CO_2 atmosphere.

[0164] To each of the designated baseline wells, 30µl of Cell-Titer Glo reagent (CTG; Promega Corporation) was added to each well and the plates were incubated for 20 min with shaking at room temperature. Baseline luminescence was quantitated using a BMG ClarioStar multimode plate reader according to the manufacturer's instructions.

[0165] A series of working stock 1000X drug dilutions in 100% DMSO was prepared that includes an 8 point single agent dilution of MRTX 1133 and a 5-point single agent dilution of the SOS1

inhibitor. The dilutions used for MRTX1133 and the SOS1 inhibitor varied for each individual compound but were in the range of 3- to 6-fold/serial dilution.

[0166] A 10X intermediate dosing plate was prepared in serum free RPMI medium that contains arrayed single agent dilutions MRTX1133 or the SOS1 inhibitor. In addition, a matrix of 40 dilution combinations of MRTX1133 and the SOS1 inhibitor was prepared as test samples.

[0167] To each corresponding well of the three 96-well plates seeded with the appropriate cell line above, 10µl of each 10X single agent and the 40 combinations of the dose matrix was added and the plates were incubated for 72 hours at 37C in 5% CO_2 atmosphere. A 30µl aliquot of Cell-Titer Glo reagent (CTG) was added to each test well, the plates were inclubated for 20 min with shaking at room temperature, and luminescence was quantitated using a BMG ClarioStar multimode plate reader according to the manufacturer's instructions.

[0168] The raw data and metadata files were used as input files to calculate percent effect for each treatment condition and analyzed using four independent mathematical reference models designed to determine whether the two test compounds demonstrate synergy: Loewe additivity, Bliss independence, Highest Single Agent and ZIP.

[0169] The output of the data from each mathematical model is the assignment of a relative synergy score. The data reported in Table 1 are the aggregate sum of the Loewe additivity, Bliss independence, Highest Single Agent and ZIP scores ("Composite Synergy Score").

Table 1

Composite Synergy Scores for Exemplary SOS1 Inhibitors Combined with MRTX1133 Against KRas G12D Cell Lines

SOS1 Inhibitor combined with MRTX1133	**BI-3406**
Cell Line	

SNU61	14
LS180	42
Panc0504	41
Panc0203	34
SNU407	34
LS513	29
A427	27
HPAC	25
AGS	25
SNU1197	24
SNU1033	19
SNU410	13
Hec1B	13
SU8684	12
SNUC2B	12
Panc0813	10
SUIT2	6
HPAFII	6
Panc0403	2
Panc1005	2
HCC1588	1
GP2D	1
ASPC1	-10
SW1990	-17

[0170] A custom R-script was created, integrating open source Bioconductor packages, to batch process metadata files containing experimental parameters and raw data files. Various numerical and graphical outputs were generated to summarize the data. Single agent parameters were generated using GRmetrics Clark N, Hafner M, Kouril M, Muhlich J, Niepel M, Williams E,

Sorger P, Medvedovic M (2016). "GRcalculator: an online tool for calculating and mining drug response data." doi: 10.6084/m9.figshare.4244408.v1, http://www.grcalculator.org/.

[0171] The synergyfinder package was used to determine whether the two test compounds demonstrate synergy using four independent mathematical reference models (Loewe additivity, Bliss independence, Highest Single Agent and ZIP) (He L et al) https://bioconductor.statistik.tu-dortmund.de/packages/3.6/bioc/vignettes/synergyfinder/inst/doc/synergyfinder.pdf

[0172] A composite score of 22 to 80 was interpreted as a synergistic hit whereas a composite score of 11 to 21 indicates additive effect and score of <0 to 10 indicates no benefit. These results demonstrate that certain members of the panel of KRas G12D cell lines exhibited a synergistic effect for the combination of a SOS1 inhibitor with MRTX1133 warranting further interrogation of the combine efficacy studies in in vivo models.

EXAMPLE B

In Vivo Models for Examining KRas G12D inhibitor – SOS1 Inhibitor Combinations

[0173] Immunocompromised nude/nude mice are inoculated in the right hind flank with Panc 02.03 cells harboring a KRas G12D mutation. When tumor volumes reached ~ 300 mm^3 in size, the mice were divided into four groups of 5 mice each. The first group is administered vehicle dosed twice daily. The second group was administered twice daily for 2 consecutive days followed by 5 days off the single agent dose of the KRas G12D inhibitor at a concentration that yields a maximal biological effect or a less than maximal biological effect, depending on the cell line and the single agent activity, that does not result in complete tumor regression. The third group was administered twice daily a single agent dose of the SOS1 inhibitor at a concentration that yields a maximal biological effect or a less than maximal biological effect, depending on the cell line and the single agent activity, that also does not result in complete tumor regression. The fourth group is administered the single agent dose of the KRas G12D inhibitor using the twice daily for 2 sequential days followed by 5 days off schedule in combination with the single agent dose of the SOS1 inhibitor. The treatment period was 22 days. Tumor volumes are measured using a caliper every two – three days and tumor volumes are calculated by the formula: 0.5 x (Length x Width)^2. A greater degree of tumor growth inhibition for the combination in this model demonstrates that the combination therapy is likely to have a clinically meaningful benefit to treated subjects relative

to treatment with only a KRas G12D inhibitor.20 nude/nude mice per study were inoculated in the right hind limb with 5 x 106 Panc 02.03 cells.

[0174] When tumor volumes reached ~ 300mm^3 (study day 0) 5 mice in each of the groups were administered i.p. vehicle only (10% captisol in 50mM citrate buffer pH 5.0), 30mg/kg of Kras G12D inhibitor MRTX-'1133 (10% captisol in 50mM citrate buffer, pH 5.0) twice daily for 2 consecutive days followed by 5 days off schedule, 50mg/kg twice daily of the BI-3406 (also known as BI-I-13) (5% DMSO 45% PEG400 50% saline) SOS1 inhibitor or 30mg/kg of Kras G12D inhibitor and BI-3406. Tumor volumes, measured at pre-specified days, for the five mice per group were averaged and are reported for Panc 02.03 in Table 2.

EXAMPLE C

KRas G12D inhibitor MRTX-1133 in Combination with SOS1 Inhibitor (Panc0203 TGI-43 Pancreatic Cancer Cell Line)

[0175] Experimental Procedures. 20 nude/nude mice were inoculated with Panc 02.03 cells in the right hind flank. When the tumors reached ~ 300mm^3 four treatment groups were established with five mice per group. The results of this study are provided in Table 2.

Table 2

Average Tumor Volumes (mm^3) of Panc0203 TGI-43Tumor Bearing Mice Treated with Single Agents and in Combination

Study Day	Vehicle BID daily	MRTX1133 30 mg/kg BID 2x /week	BI-3406 50mg/kg BID Daily	BI-3406 BID Daily +MRTX1133 BID 2x/week
1	328.896	329.18	331.672	329.902
4	446.116	265.246	349.632	252.158
8	544.424	386.354	400.406	299.716
11	647.874	392.042	481.264	283.624
15	786.634	480.434	547.852	313.954

18	927.746	496.496	730.884	413.236
22	1113.464	549.618	892.786	482.426

[0176] As shown in Table 2, the administration of MRTX1133 at 30 mg/kg BID (twice per day) as a single agent exhibited 72% tumor growth inhibition at Day 22 (twice per week administration). The administration of SOS1 inhibitor BI-3406 (aka BI-I-13) at 50 mg/kg BID dailyas a single agent exhibited 28% tumor growth inhibition at Day 22. The combination of SOS1 inhibitor BI-3406 and MRTX1133 administered twice per week resulted in 80% tumor growth inhibition at Day 22.

[0177] The results are also shown in Figure 1.

EXAMPLE D

KRas G12D inhibitor MRTX-1133 in Combination with SOS1 Inhibitor (AsPC-1 Pancreatic Cancer Cell Line)

[0178] Experimental Procedures. 20 nude/nude mice were inoculated with AsPC-1 cells in the right hind flank. When the tumors reached ~ 200mm^3 four treatment groups were established with five mice per group. The results of this study are provided in Table 3.

Table 3

Average Tumor Volumes (mm^3) of AsPC-1 TGI-70 Tumor Bearing Mice Treated with Single Agents and in Combination

Study Day	Vehicle BID daily	MRTX1133 30 mg/kg BID Daily	MRTX0902 50mg/kg BID Daily	MRTX0902 BID Daily +MRTX1133 BID Daily
1	192.666	193.378	194.8	193.332
6	224.804	168.124	215.066	169.77
9	258.39	146.75	220.892	140.022
13	287.39	143.612	262.374	120.766

16	326.492	120.916	316.164	114.264
20	353.452	119.264	387.59	131.784
23	381.112	139.296	480.782	163.792

[0179] As shown in Table 2, the administration of MRTX1133 at 30 mg/kg BID daily as a single agent exhibited 26% tumor regression at Day 13. The administration of SOS1 inhibitor MRTX0902 at 50 mg/kg BID daily as a single agent exhibited 26% tumor growth inhibition at Day 13. The combination of SOS1 inhibitor MRTX0902 and MRTX1133 each administered twice daily resulted in 38% tumor regression at Day 13.

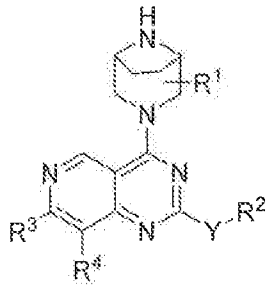
[0180] The results are also shown in Figure 2.

[0181] While the invention has been described in connection with specific embodiments thereof, it will be understood that it is capable of further modifications and this application is intended to cover any variations, uses, or adaptations of the invention following, in general, the principles of the invention and including such departures from the present disclosure as come within known or customary practice within the art to which the invention pertains and as may be applied to the essential features hereinbefore set forth, and as follows in the scope of the appended claims.

CLAIMS

WHAT IS CLAIMED IS:

1. A method of treating cancer in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a combination of a SOS1 inhibitor and a KRAS G12D inhibitor of formula (I):



Formula (I)

or a pharmaceutically acceptable salt thereof:

wherein:

R^1 is hydrogen, hydroxy, halogen, C1 – C3 alkyl, C1 - C3 cyanoalkyl, C1 - C3 hydroxyalkyl, HC(=O)-, $-CO_2R^5$, $-CO_2N(R^5)_2$ or a 5-6 membered heteroaryl;

Y is a bond, O or NR^5;

R^2 is hydrogen, $-N(R^5)_2$, heterocyclyl, C1 – C6 alkyl, -L-heterocyclyl, -L-aryl, -L-heteroaryl, -L-cycloalkyl, $-L-N(R^5)_2$, $-L-NHC(=NH)NH_2$, $-L-C(O)N(R^5)_2$, -L-C1-C6 haloalkyl, $-L-OR^5$, $-L-(CH_2OR^5)(CH_2)_nOR^5$, $-L-NR^5C(O)$-aryl, -L-COOH, or -LC(=O)OC1-C6 alkyl, wherein the heterocyclyl and the aryl portion of $-L-NR^5C(O)$-aryl and the heterocyclyl portion of -L-heterocyclyl and the cycloalkyl portion of the -L-cycloalkyl may be optionally substituted with one or more R^6, and wherein the aryl or heteroaryl of the -L-aryl and the -L-heteroaryl may be optionally substituted with one or more R^7;

each L is independently a C1 – C4 alkylene optionally substituted with hydroxy, C1 – C4 hydroxyalkyl or heteroaryl;

R^3 is aryl or heteroaryl, wherein the aryl or the heteroaryl is optionally substituted with one or more R^8;

R^4 is hydrogen, halogen or C1 – C3 alkyl;

each R^5 is independently hydrogen or C1 – C3 alkyl;

each R^6 is independently halogen, hydroxy, C1 - C3 hydroxyalkyl, C1 – C3 alkyl, C1 - C3 haloalkyl, C1-C3 alkoxy, cyano, -Q-phenyl, -Q-phenylSO_2F, -NHC(O)phenyl, -NHC(O)phenylSO_2F, C1-C3 alkyl substituted pyrazolyl, araC1-C3 alkyl-, tert-butyldimethylsilyloxyCH_2- , -N(R^5)$_2$, (C1-C3 alkoxy)C1-C3 alkyl-, (C1-C3 alkyl)C(=O), oxo, (C1-C3 haloalkyl)C(=O)-, -SO_2F, (C1-C3 alkoxy)C1-C3 alkoxy, -$CH_2OC(O)N(R^5)_2$, -$CH_2NHC(O)OC1$-C6 alkyl, -$CH_2NHC(O)N(R^5)_2$, -$CH_2NHC(O)C1$-C6 alkyl, -CH_2(pyrazolyl), -CH_2NHSO_2C1-C6 alkyl, -$CH_2OC(O)$heterocyclyl, -$OC(O)N(R^5)_2$, -OC(O)NH(C1-C3 alkyl)O(C1-C3 alkyl), -OC(O)NH(C1-C3 alkyl)O(C1-C3 alkyl)phenyl(C1-C3 alkyl)N(CH_3)$_2$, -OC(O)NH(C1-C3 alkyl)O(C1-C3 alkyl)phenyl or -OC(O)heterocyclyl, -CH_2heterocyclyl, wherein the phenyl of -NHC(O)phenyl or -OC(O)NH(C1-C3 alkyl)O(C1-C3 alkyl)phenyl is optionally substituted with -C(O)H or OH and wherein the heterocyclyl of -CH_2heterocyclyl is optionally substituted with oxo;

Q is a bond or O;

each R^7 is independently halogen, hydroxy, HC(=O)-, C1 – C4 alkyl, C1 – C4 alkoxy, C1 – C4 haloalkyl, C1 – C4 hydroxyalkyl, or -N(R^5)$_2$; and

each R^8 is independently halogen, cyano, hydroxy, C1 - C4 alkyl, -S-C1 - C3 alkyl, C2 – C4 alkenyl, C2 – C4 alkynyl, C2 – C4 hydroxyalkynyl, C1-C3 cyanoalkyl , triazolyl, C1 - C3 haloalkyl, -O- C1 - C3 haloalkyl, -S- C1 - C3 haloalkyl, C1-C3 alkoxy, hydroxyC1-C3 alkyl, -$CH_2C(=O)N(R^5)_2$, -C3-C4 alkynyl(NR^5)$_2$, -N(R^5)$_2$, deuteroC2-C4 alkynyl, (C1-C3 alkoxy)haloC1-C3 alkyl-, or C3-C6 cycloalkyl wherein said C3-C6 cycloalkyl is optionally substituted with halogen or C1-C3 alkyl.

2. The method of claim 1, wherein R^1 is hydrogen, halogen, hydroxy, C1 – C3 alkyl, C1-C3 cyanoalkyl, hydroxyalkyl, HC(=O)-, -CO_2R^5, or -$CO_2N(R^5)_2$.

3. The method of claim 2, wherein R^5 is hydrogen, C1 – C3 alkyl or C1 - C3 cyanoalkyl.

4. The method of claim 2, wherein Y is O and R^2 is C1 – C6 alkyl or -L-heterocyclyl optionally substituted with one or more R^6.

5. The method of claim 4, wherein the C1 – C6 alkyl is methyl, ethyl, isopropyl or isobutyl.

6. The method of claim 4, wherein L is methylene and the heterocyclyl is hexahydro-1*H*-pyrrolizinyl, hexahydro-3H-pyrrolizin-3-one, hexahydro-1H-pyrrolo[2,1-c][1,4]oxazinyl, octahydroindolizinyl, hexahydropyrrolizine 4(1H)-oxide, azetidinyl, pyrrolidinyl, pyrrolidin-2-one, oxetanyl, piperidinyl, 1-azabicyclo[2.2.1]heptanyl, morpholinyl, oxa-5-azabicyclo[2.2.1]heptan-5-yl, thiopyranyl, 6-oxa-2λ^2-azaspiro[3.4]octanyl, 7-oxa-2λ^2-azaspiro[3.5]nonanyl, 2',3'-dihydrospiro[cyclopropane-1,1'-indenyl], (2S)-1-azabicyclo[2.2.1]heptan-2-yl, or tetrahydrofuranyl, each optionally substituted with one or more R^6.

7. The method of claim 4, wherein L is methylene and the heterocyclyl is hexahydro-1*H*-pyrrolizinyl.

8. The method of claim 7, wherein heterocyclyl is hexahydro-1*H*-pyrrolizinyl substituted with one R^6, wherein R^6 is halogen, hydroxy, C1 - C3 hydroxyalkyl, C1 - C3 haloalkyl, C1 – C3 alkyl, C1 - C3 alkoxy, phenyl or pyrazolyl.

9. The method of claim 8, wherein the halogen is fluorine.

10. The method of claim 6, wherein the heterocyclyl is hexahydro-1*H*-pyrrolizinyl further substituted with two additional R^6 groups, wherein the two additional R^6 groups are independently C1 – C3 alkyl.

11. The method of claim 6, wherein the heterocyclyl is azetidinyl substituted with one R^6, wherein R^6 is C1 – C3 alkyl.

12. The method of claim 6, wherein the heterocyclyl is pyrrolidinyl substituted with one R^6, wherein R^6 is hydroxalkyl, haloalkyl, C1 – C3 alkyl, alkoxy, araC1-C3 alkyl, -Q-phenyl and -NHC(O)phenyl, and wherein the aryl portion of the araC1-C3 alkyl or the phenyl portion of the -Q-phenyl and -NHC(O)phenyl are each optionally substituted with one or more R^6.

13. The method of claim 12, wherein the phenyl group of the -Q-phenyl or the -NHC(O)phenyl is substituted with SO_2F.

14. The method of claim 6, wherein the heterocyclyl is pyrrolidinyl substituted with two R^6 groups wherein one R^6 is C1 – C3 alkyl and the other R^6 is C1-C3 alkoxy or halogen.

15. The method of claim 6, wherein the heterocyclyl is pyrrolidin-2-one substituted with one R^6, wherein R^6 is C1 – C3 alkyl.

16. The compound or salt of claim 6, wherein the heterocyclyl is piperidinyl substituted with one R^6, wherein R^6 is acetyl, (C1-C3 alkoxy)C1-C3 alkoxy, or $-C(O)CH_2Cl$.

17. The method of claim 6, wherein Y is O, L is ethylene or propylene and the heterocyclyl is morpholinyl or oxa-5-azabicyclo[2.2.1]heptan-5-yl.

18. The method of claim 2, wherein Y is O and R^2 is -L-heteroaryl, wherein the heteroaryl portion is optionally substituted with one or more R^7.

19. The method of claim 18, wherein L is methylene or ethylene and the heteroaryl is pyridyl, pyrazolyl, imidazolyl, triazolyl, 4,5,6,7-tetrahydro-1*H*-indazolyl, benzimidazolyl, imidazo[1,2-a]pyridinyl, or pyrimidinyl, each optionally substituted with one or more R^7.

20. The method of claim 19, wherein the heteroaryl is pyridyl substituted with one R^7, wherein R^7 is halogen, C1 – C4 alkyl, -$N(R^5)_2$, or C1-C4 alkoxy.

21. The method of claim 19, wherein the heteroaryl is pyrazolyl substituted with one R^7, wherein R^7 is C1 – C4 alkyl or -$N(R^5)_2$.

22. The method of claim 19, wherein the heteroaryl is imidazolyl substituted with one R^7, wherein R^7 is C1 – C4 alkyl, C1 – C4 haloalkyl, or C1 – C4 hydroxyalkyl.

23. The method of claim 19, wherein the heteroaryl is triazolyl substituted with one R^7, wherein R^7 is C1 – C4 alkyl.

24. The method of claim 2, wherein Y is O and R^2 is -L-aryl, wherein the aryl portion is optionally substituted with one or more R^7.

25. The method of claim 2, wherein Y is O and R^2 is -L-cycloalkyl, wherein the cycloalkyl portion is optionally substituted with one or more R^7.

26. The method of claim 2, wherein Y is O, and R^2 is -L-$N(R^5)_2$.

27. The method of claim 26, wherein L is ethylene and each R^5 is an independently selected C1 – C3 alkyl.

28. The method of claim 2, wherein Y is O, and R^2 is -L-NC(=NH)-NH_2.

29. The method of claim 28, wherein L is ethylene or propylene.

30. The method of claim 2, wherein Y is O, and R^2 is -L-C1-C6 haloalkyl.

31. The method of claim 2, wherein Y is O, and R^2 is -L-OR^5.

32. The method of claim 2, wherein Y is O, and R^2 is -L-$(CH_2OR^5)(CH_2)_nOR^5$.

33. The method of claim 2, wherein Y is O, and R^2 is -L-$NR^5C(O)$-aryl.

34. The method of claim 2, wherein R^3 is aryl optionally substituted with one or more R^8.

35. The method of claim 34, wherein the aryl is phenyl, naphthyl, 1,2,3,4-tetrahydronaphthalenyl and 2,3-dihydro-1H-indenyl, each optionally substituted with one or more R^8.

36. The method of claim 2, wherein R^3 is heteroaryl optionally substituted with one or more R^8.

37. The method of claim 36, wherein the heteroaryl is isoquinolinyl, indazolyl, or benzo[d][1,3]dioxolyl optionally substituted with one or more R^8.

38. The method of claim 37, wherein the heteroaryl is isoquinolinyl substituted with one R^8, wherein R^8 is halogen or C2 - C4 alkynyl.

39. The method of claim 37, wherein the heteroaryl is indazolyl substituted with one R^8, wherein R^8 is C1 - C3 alkyl.

40. The method of claim 37, wherein the heteroaryl is benzo[d][1,3]dioxolyl substituted with two R^8 groups, wherein the R^8 groups are independently selected halogens.

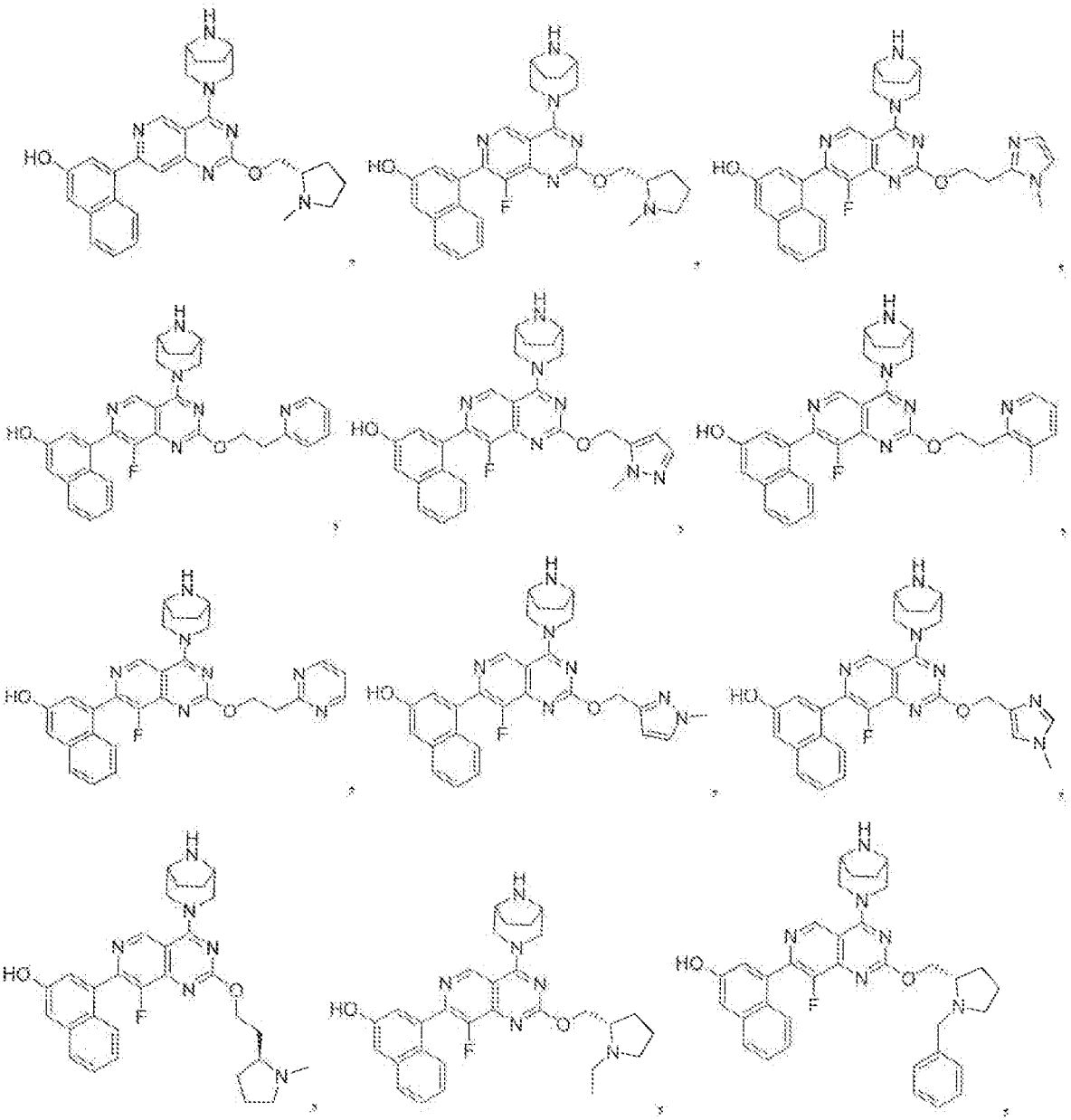
41. The method of claim 2, wherein R^4 is halogen, or C1 – C3 alkyl.

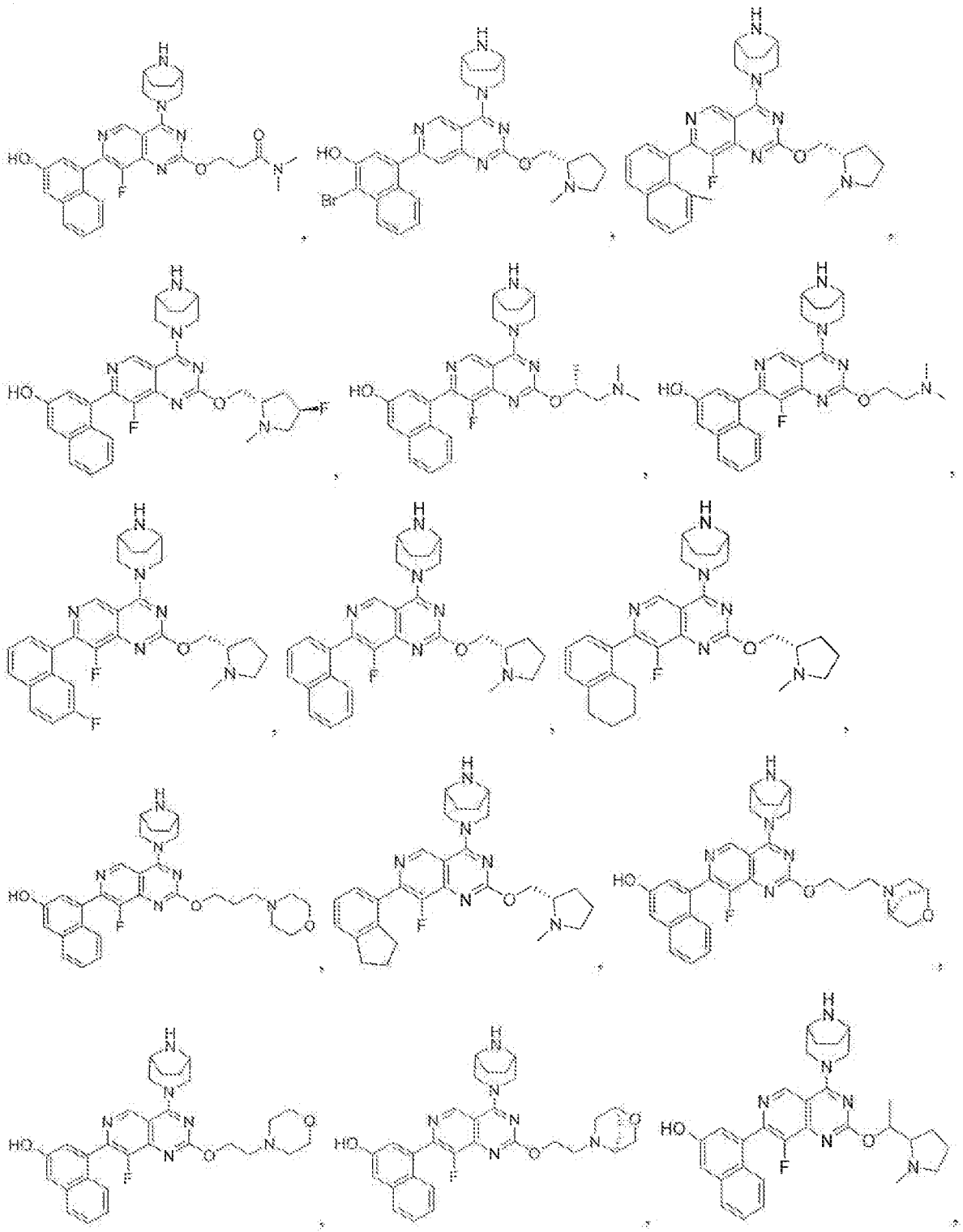
42. The method of claim 41, wherein the halogen is fluorine.

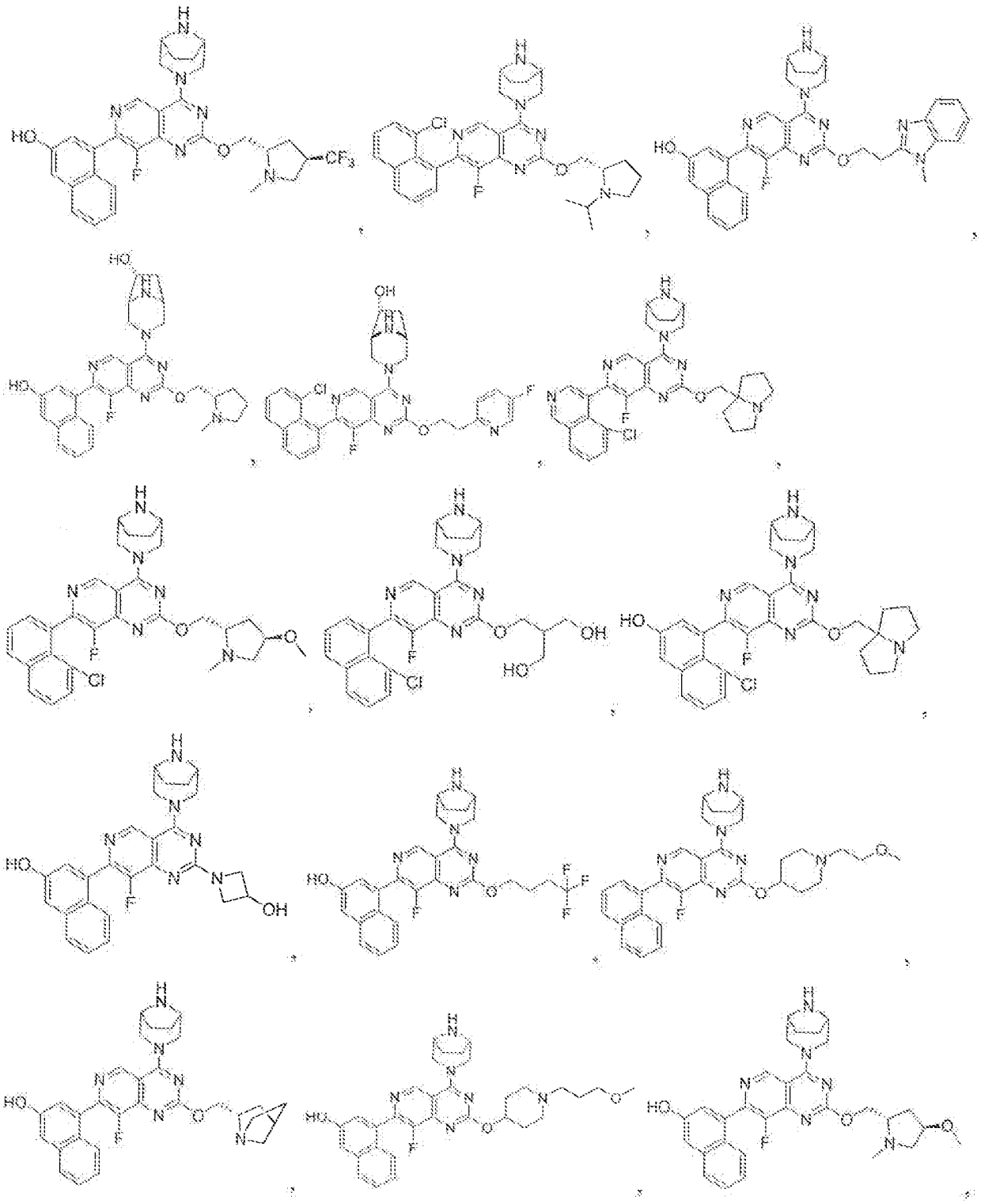
43. The method of claim 41, wherein the C1 – C3 alkyl is methyl.

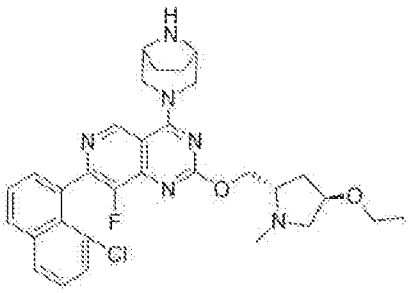
44. The method of claim 1, wherein R^1 is hydrogen.

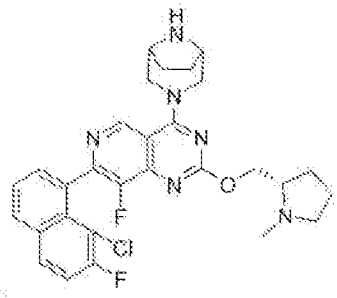
45. The method of claim 1, wherein the KRas G12D inhibitor is selected from the group consisting of:

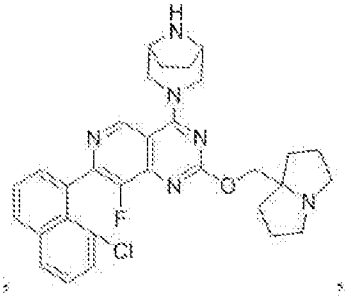


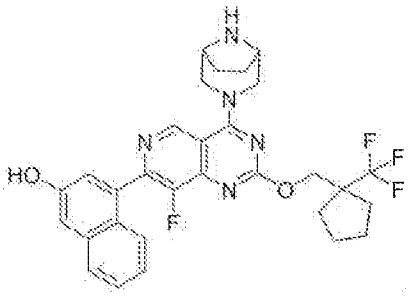


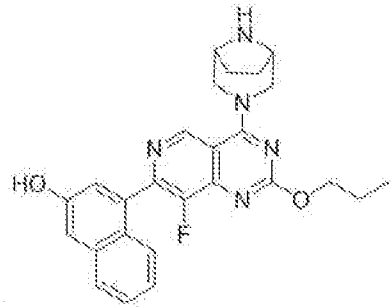


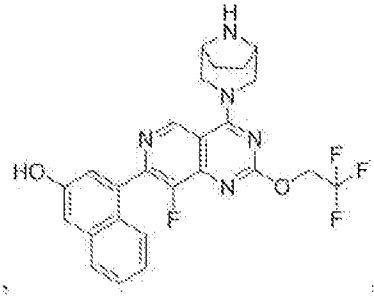


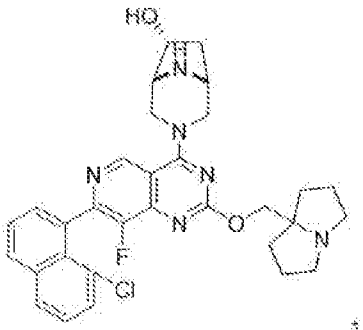


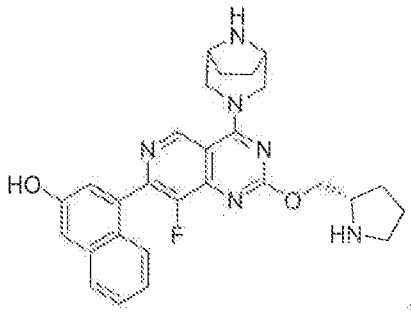


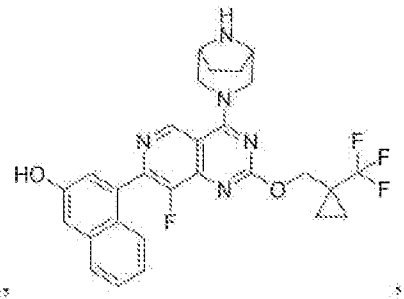


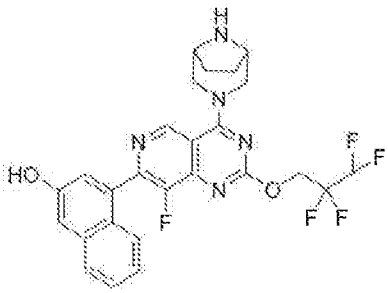


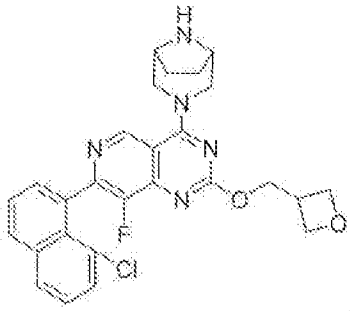


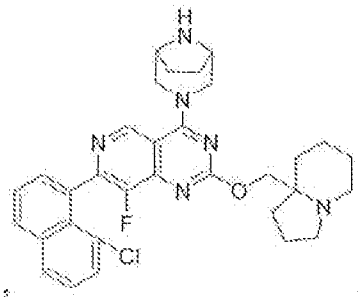


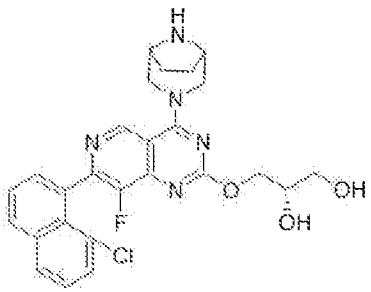


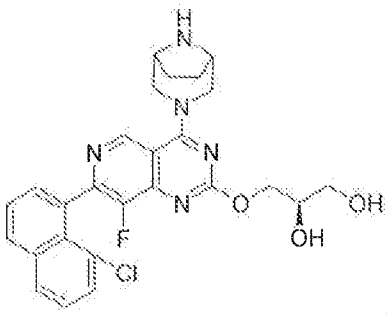


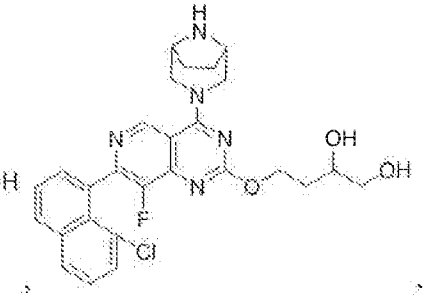


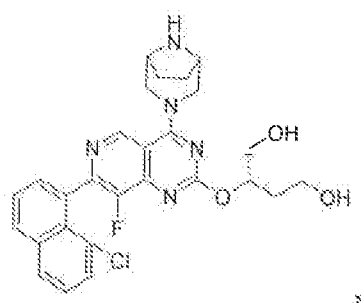
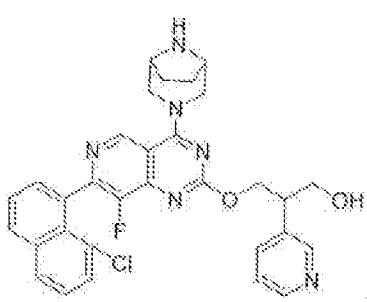
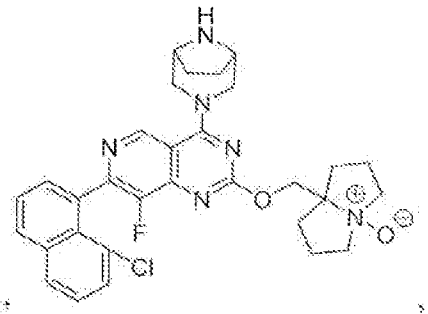
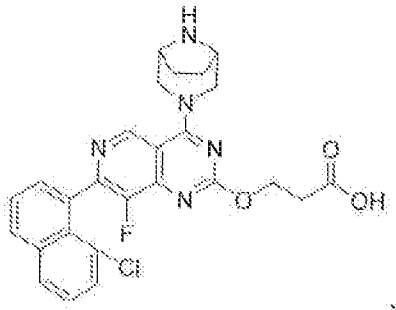
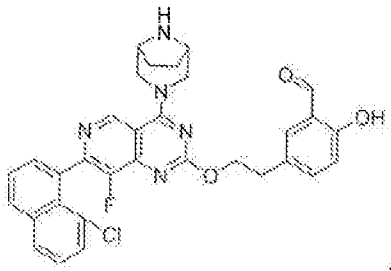
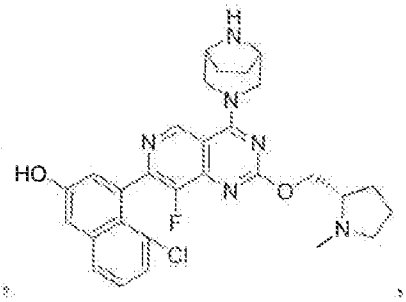
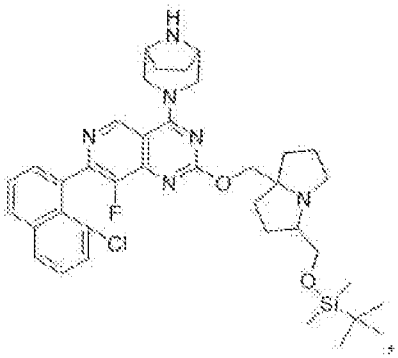
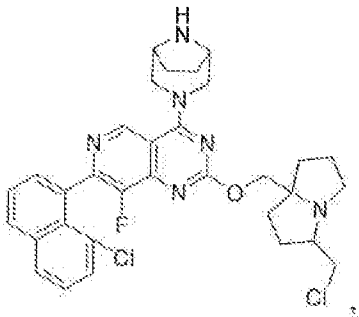
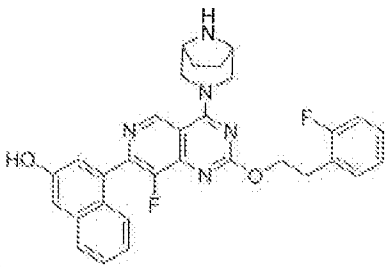
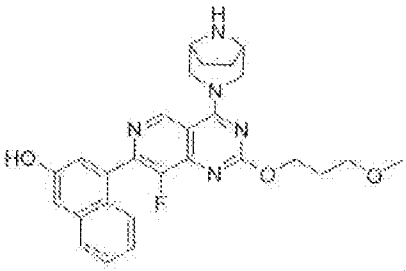
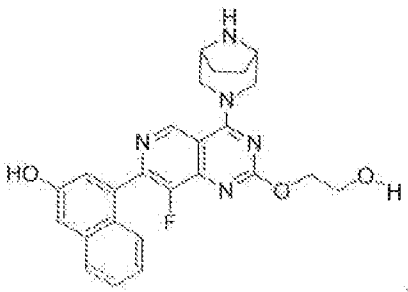
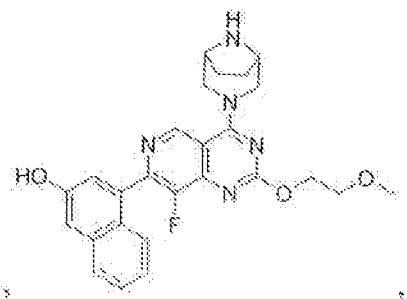
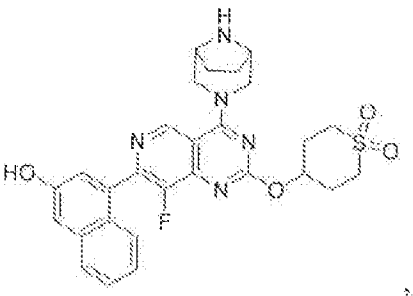
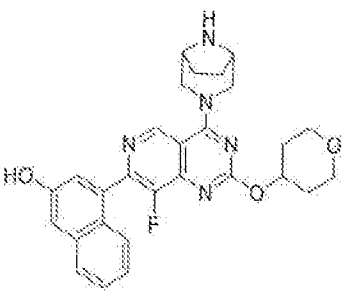
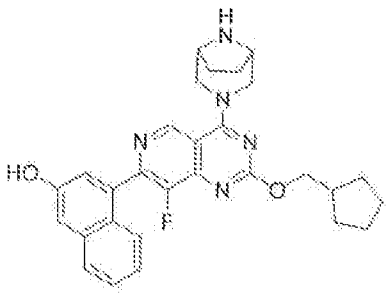


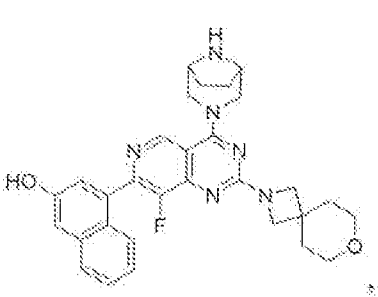


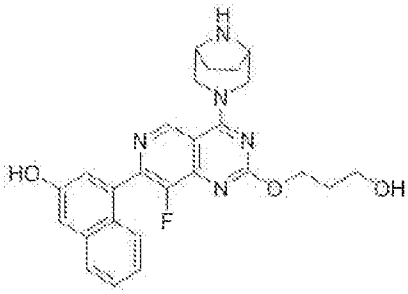


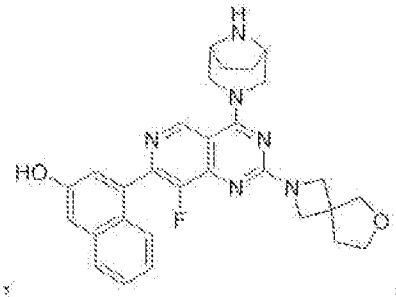


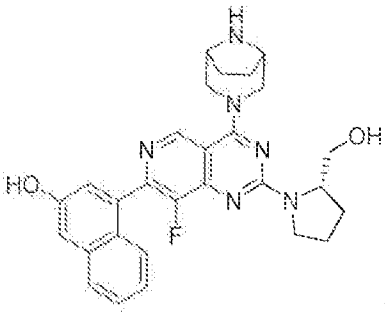


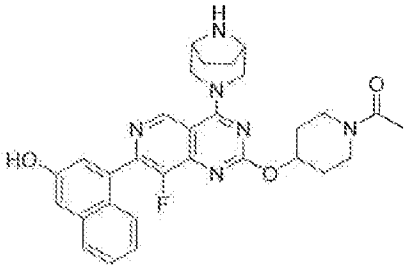
















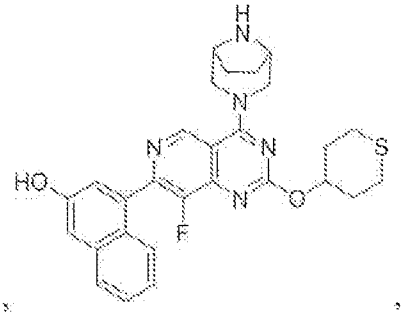


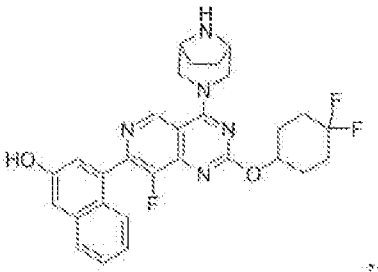


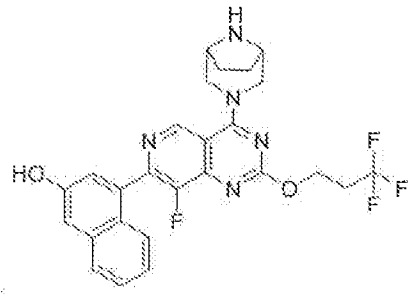


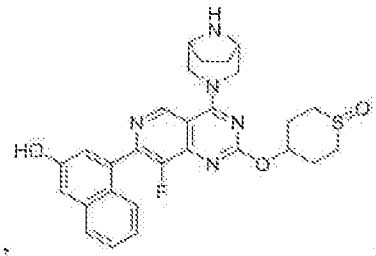


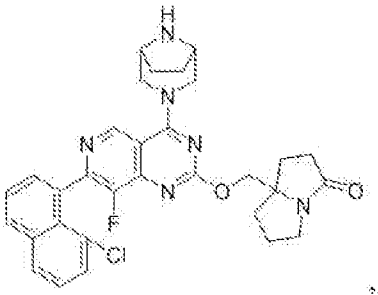


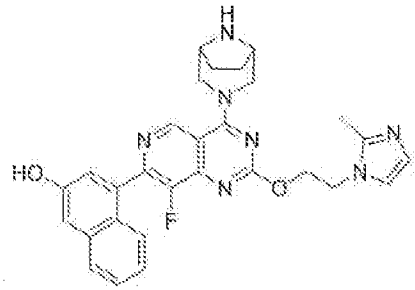


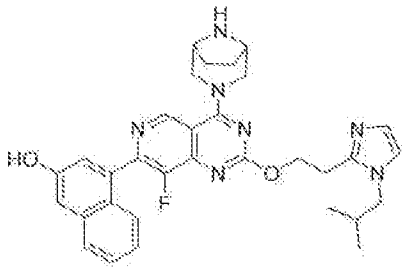


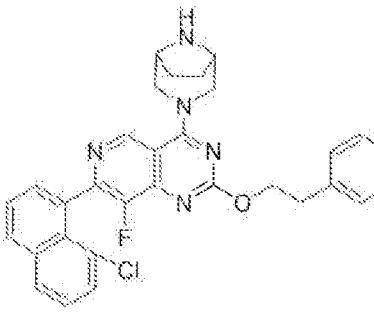


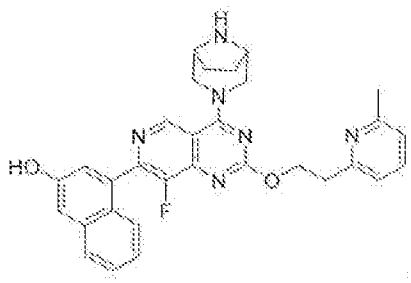


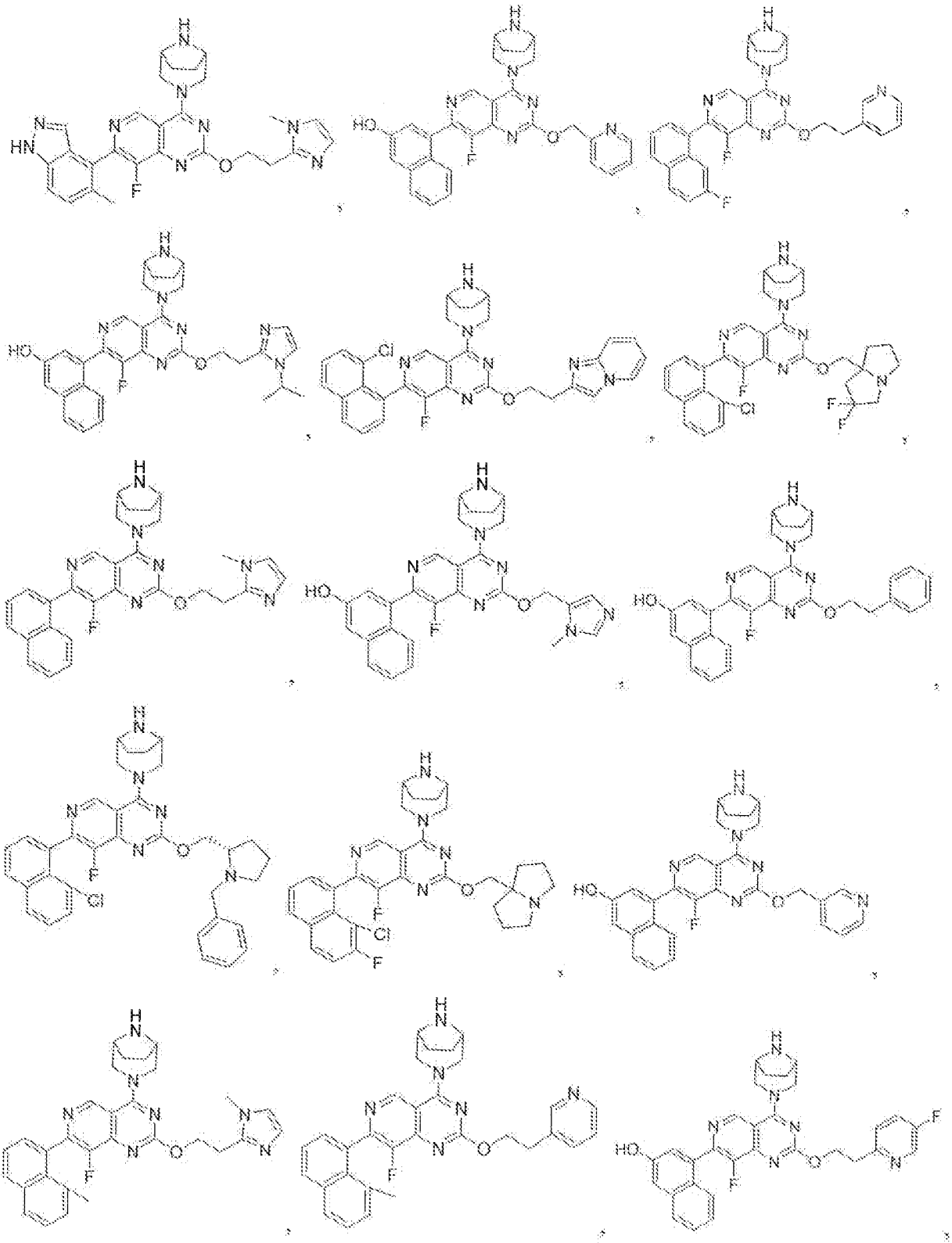


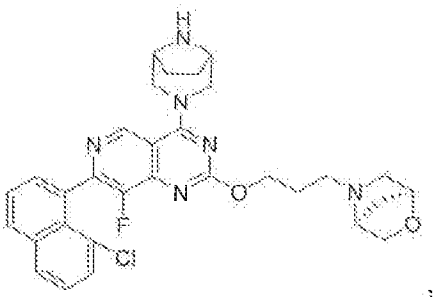


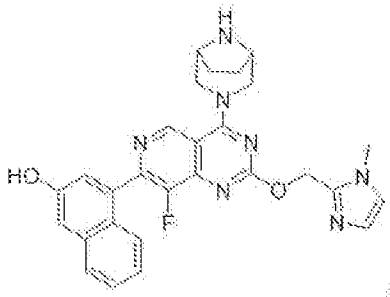


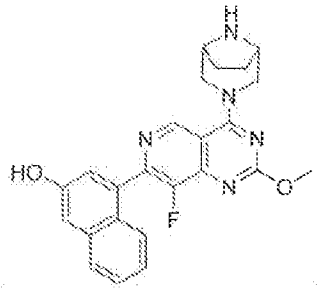


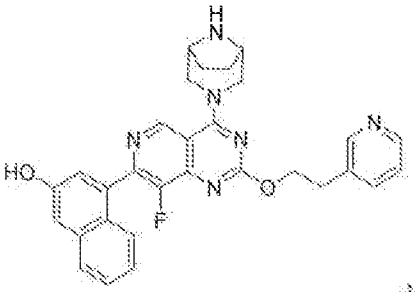


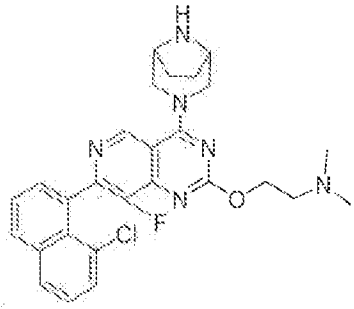


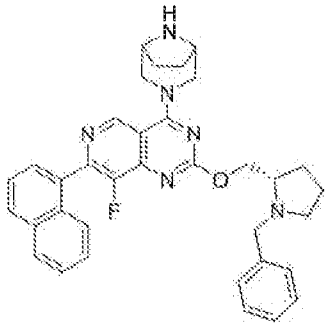


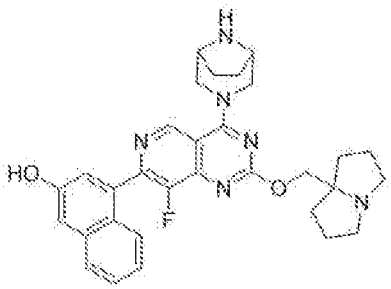


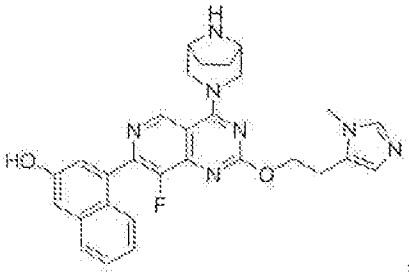


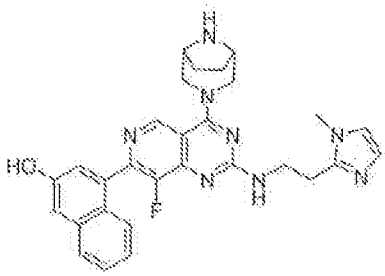


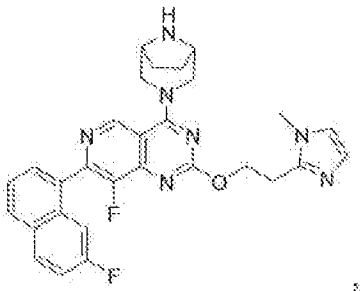


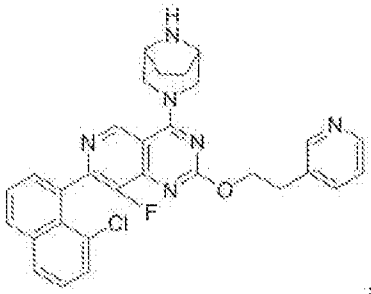


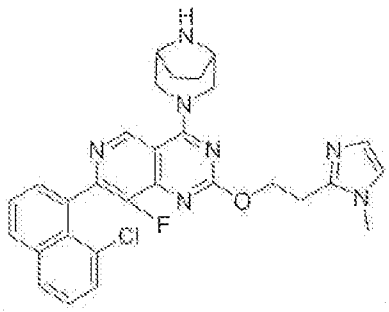


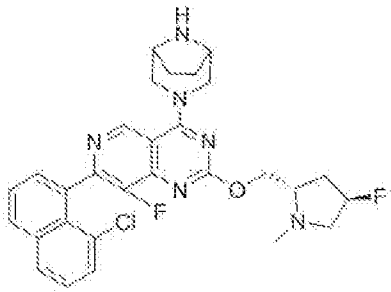


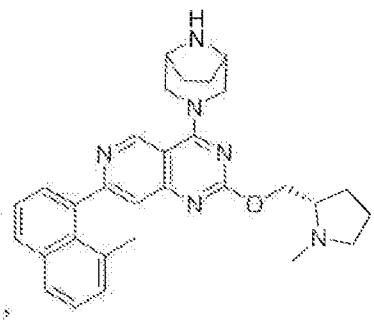


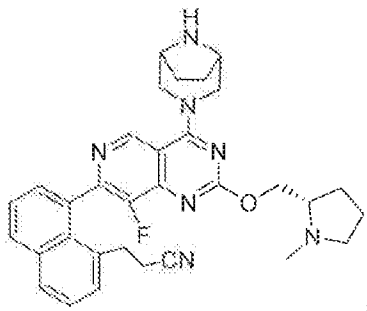


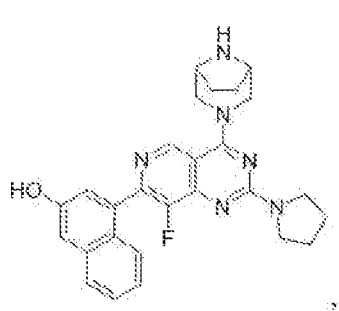


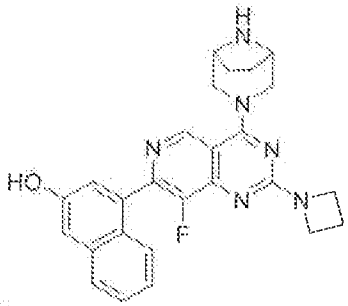


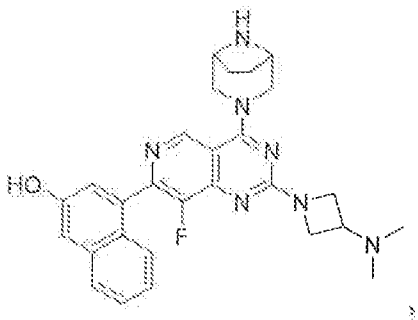


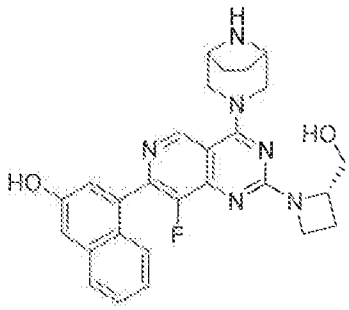


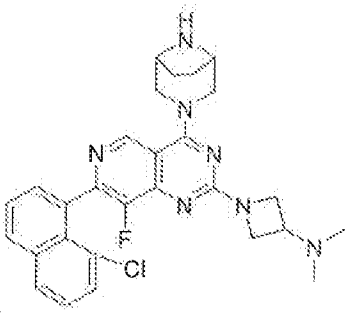


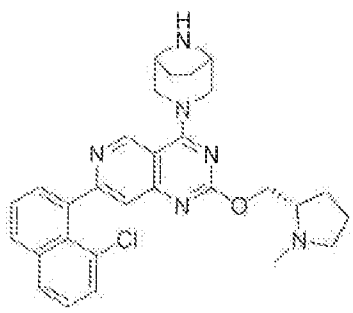


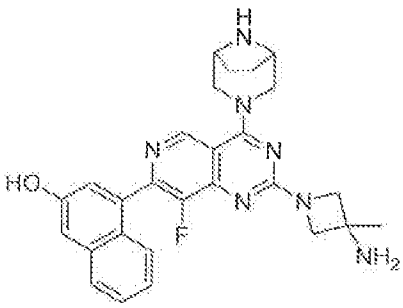


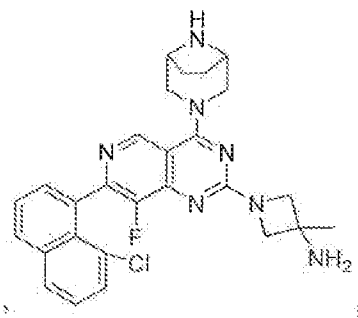


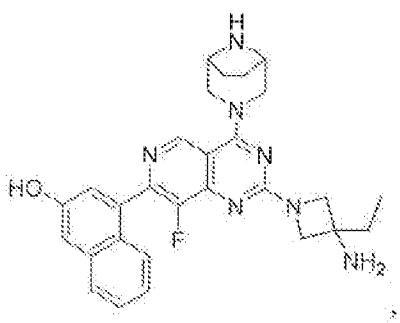


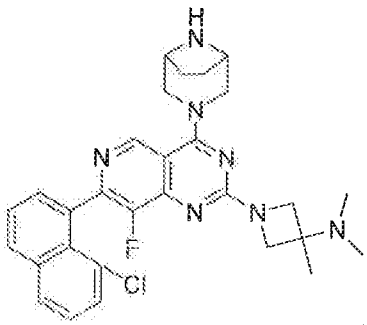


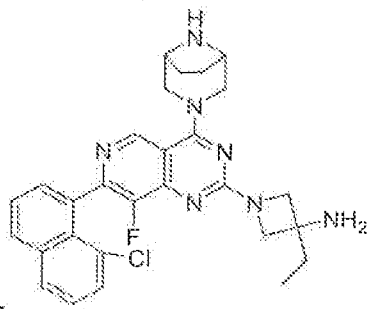


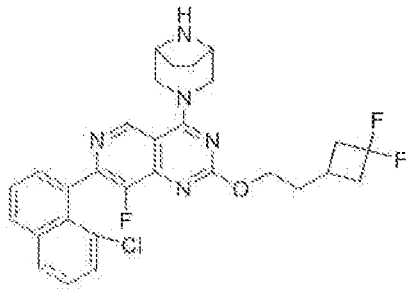


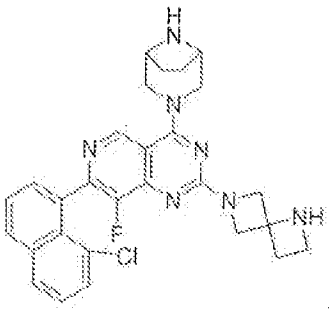


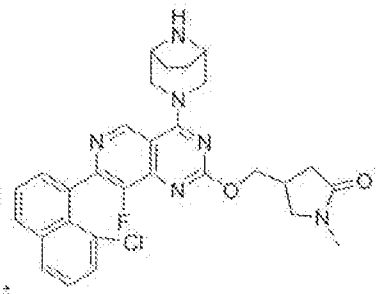


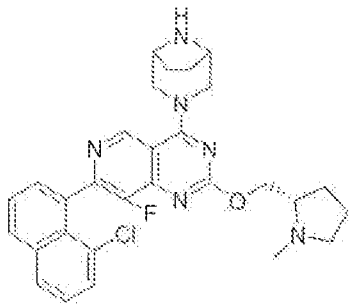


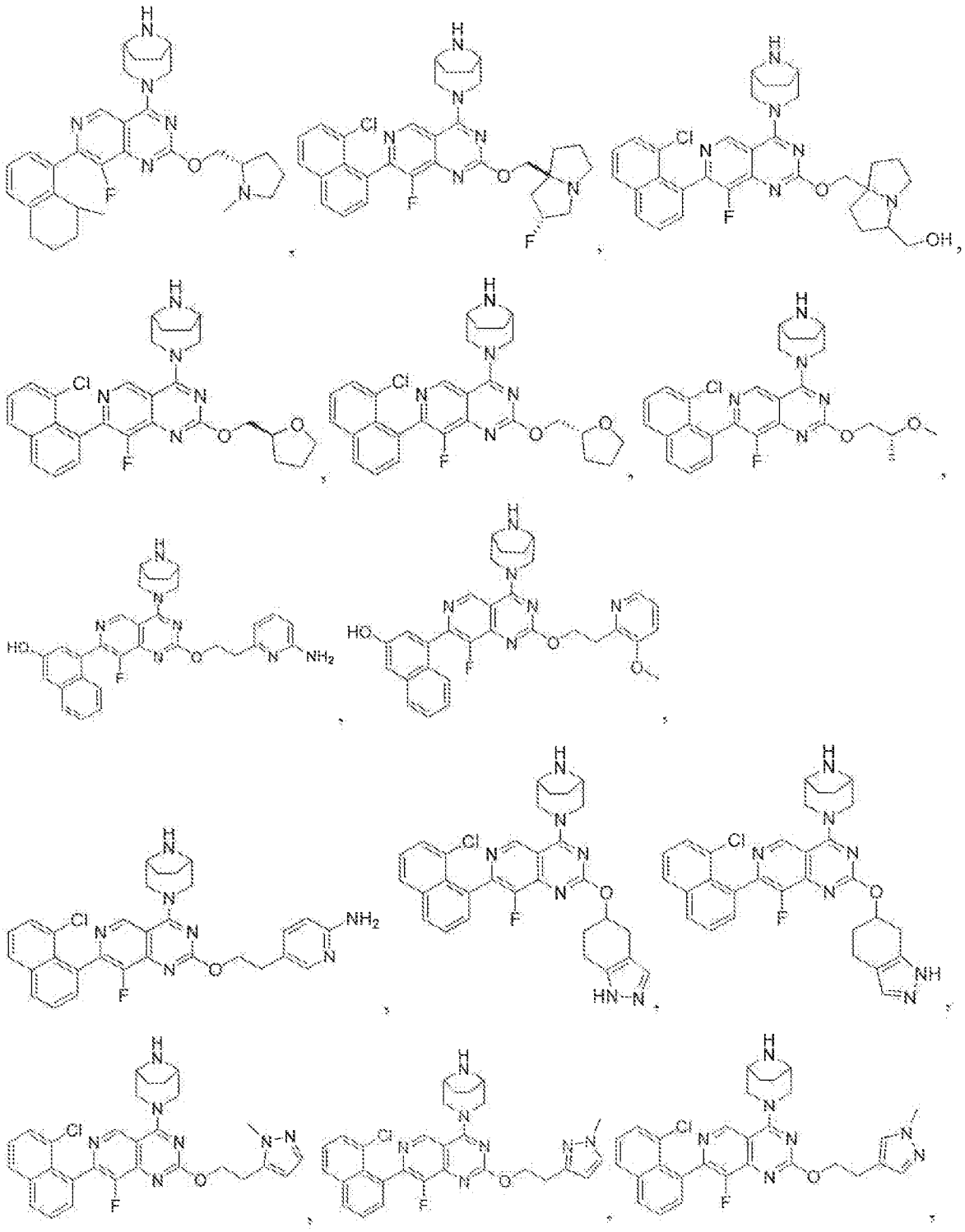


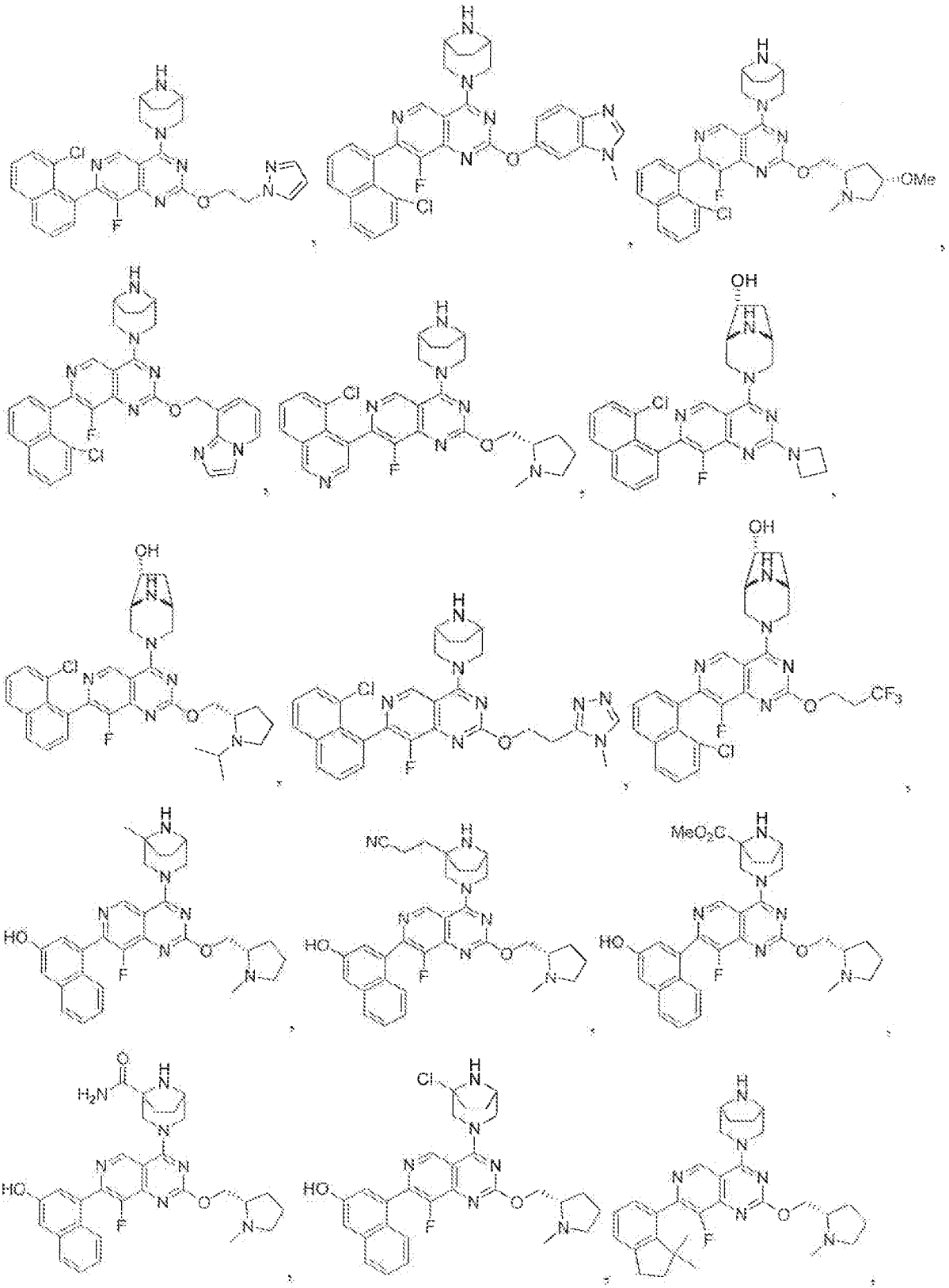


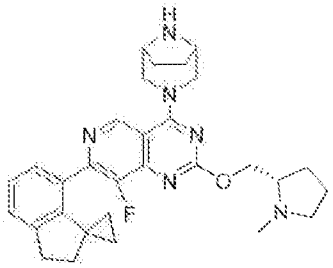


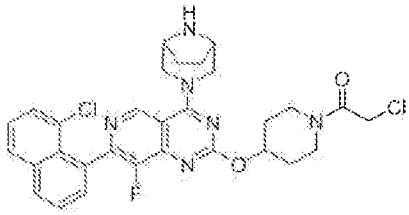


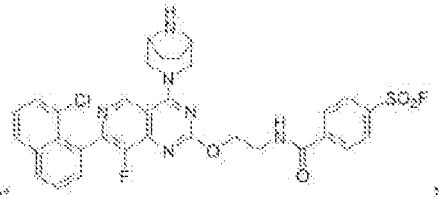


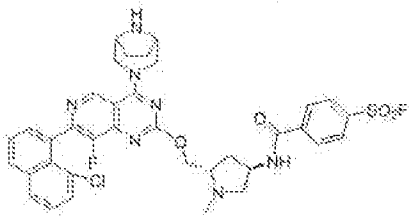


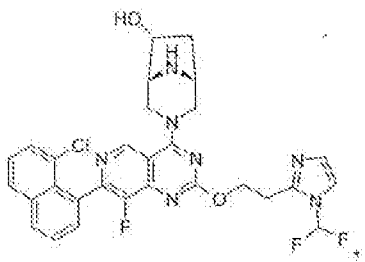


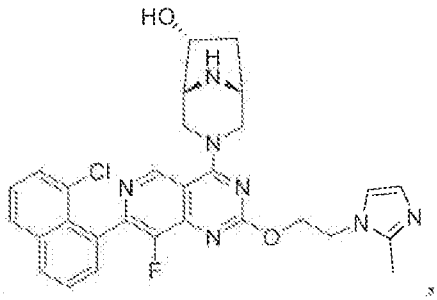


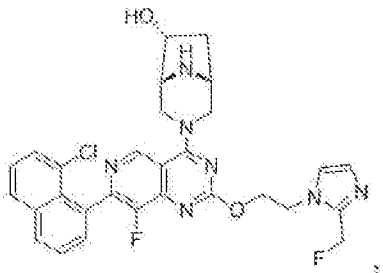


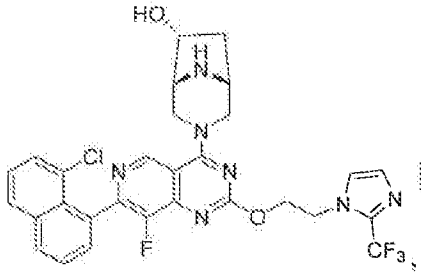


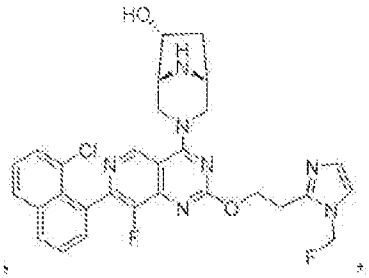


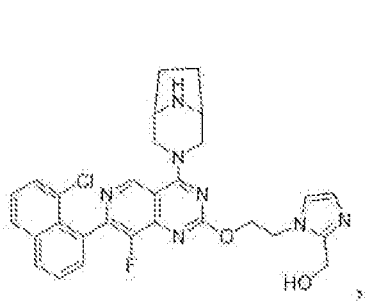


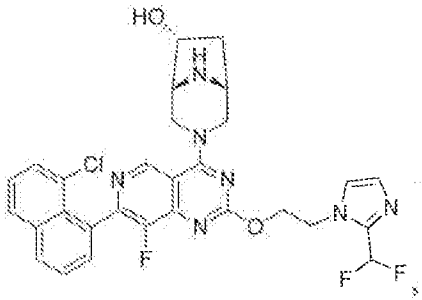


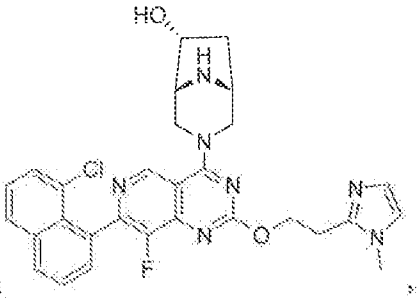


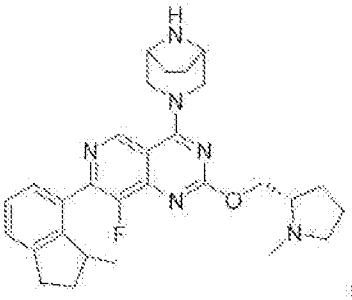


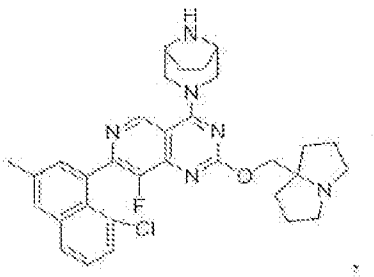


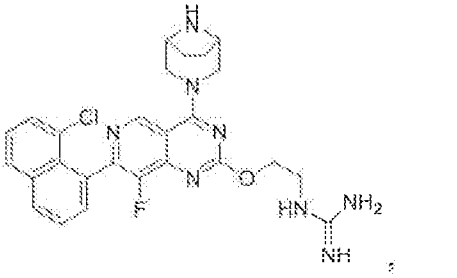


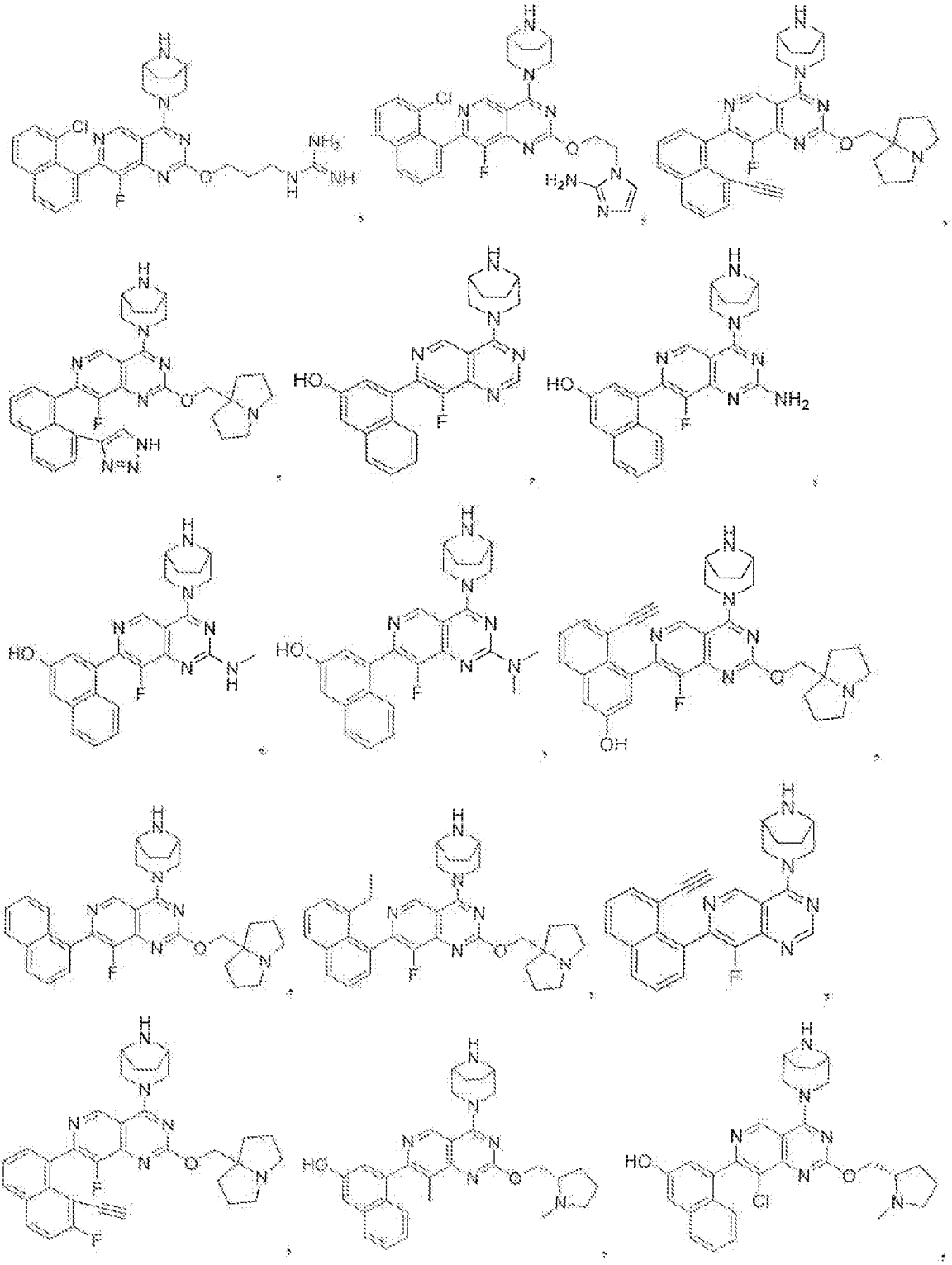


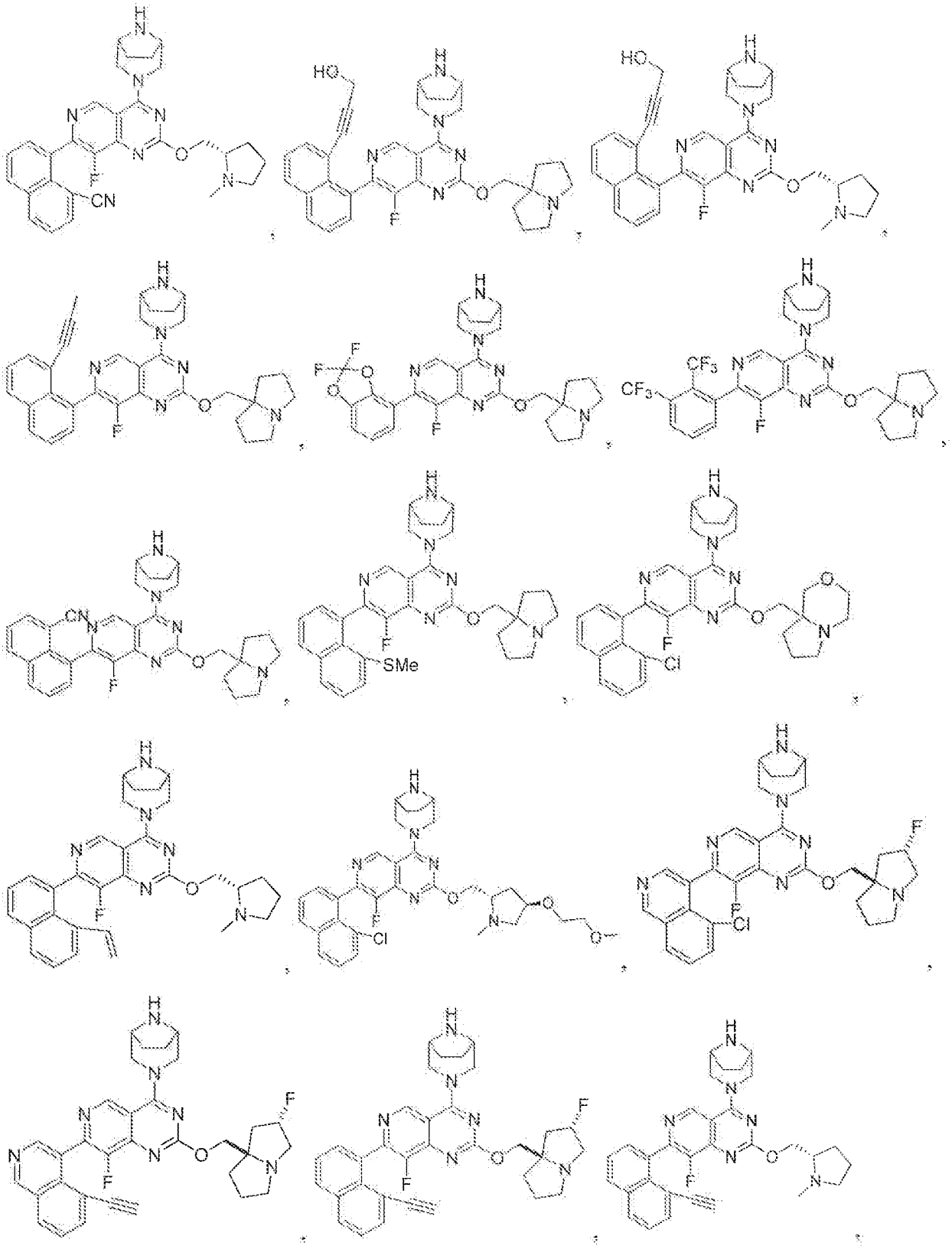


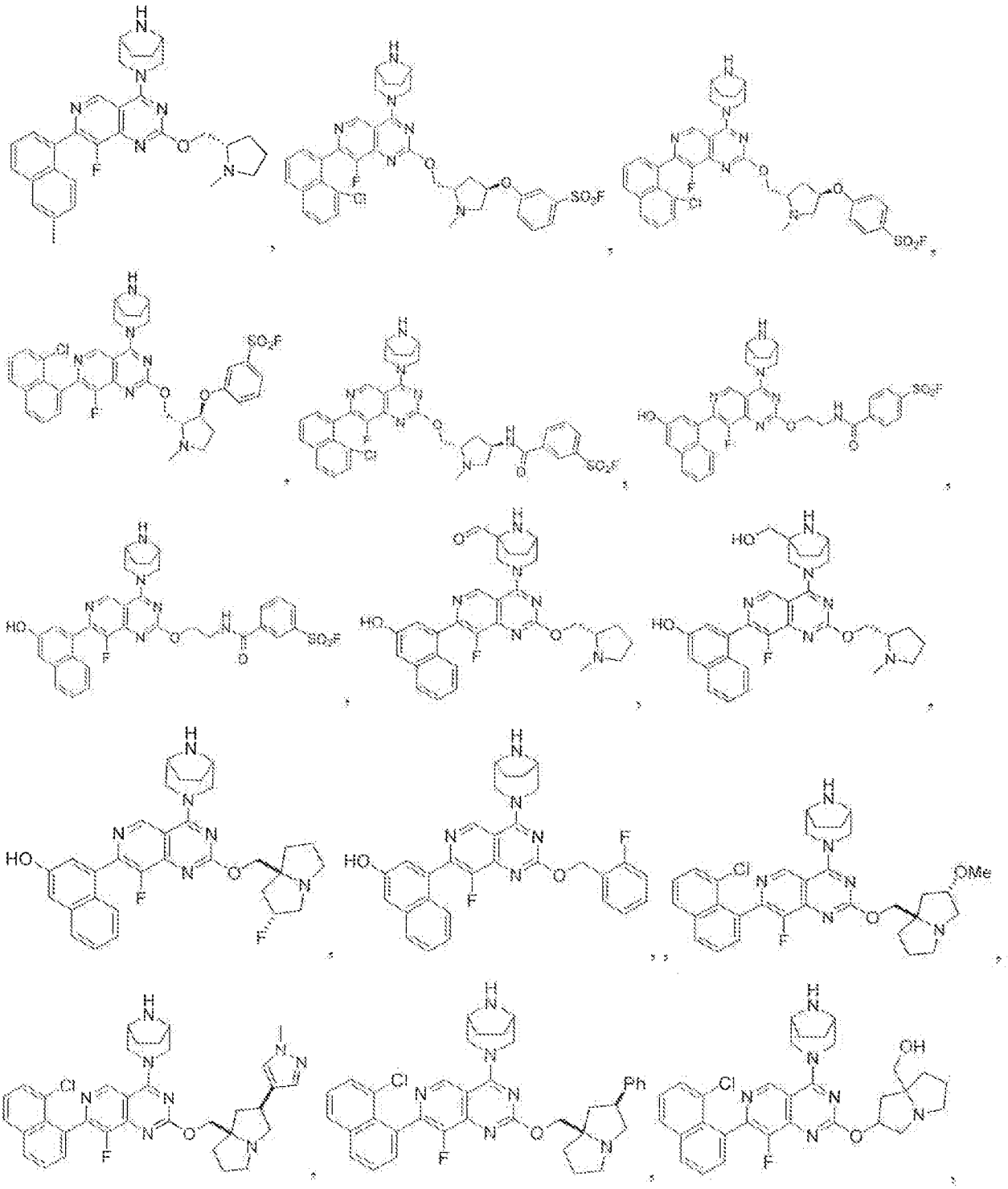


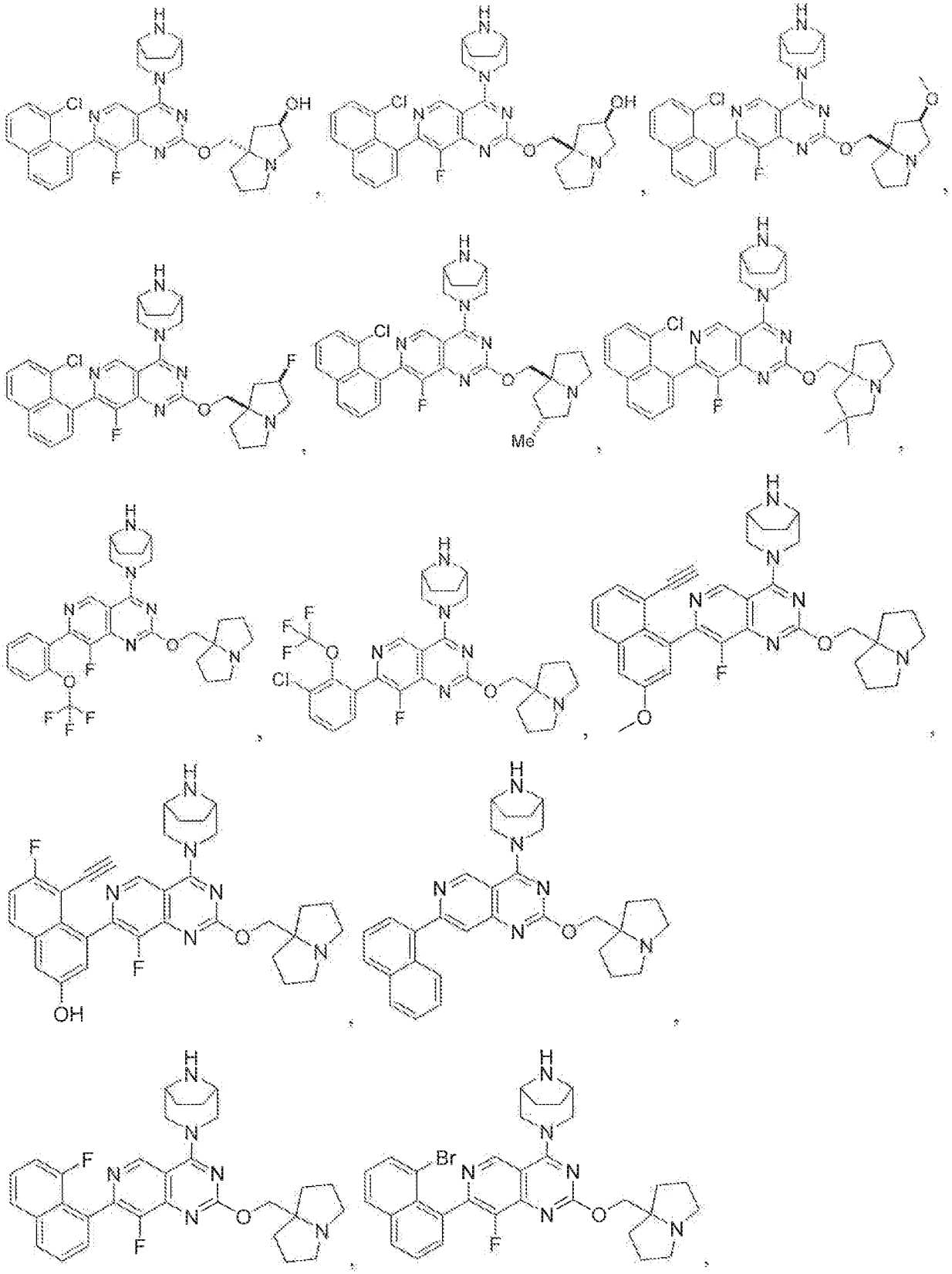


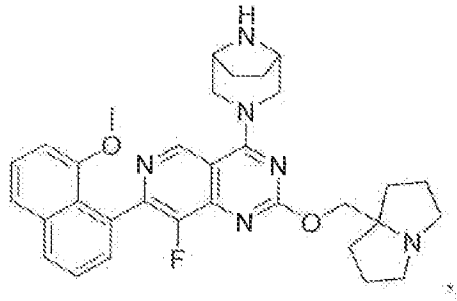


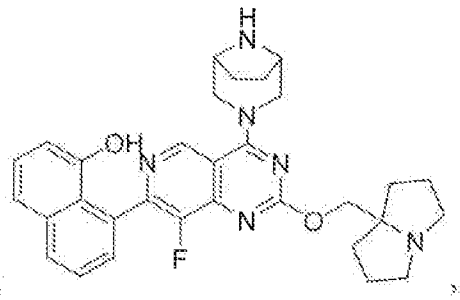


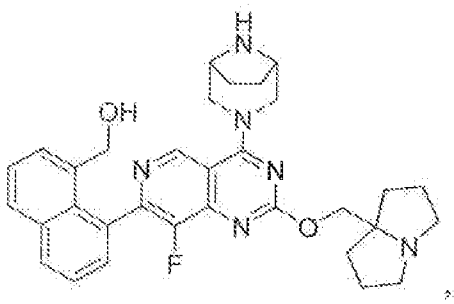


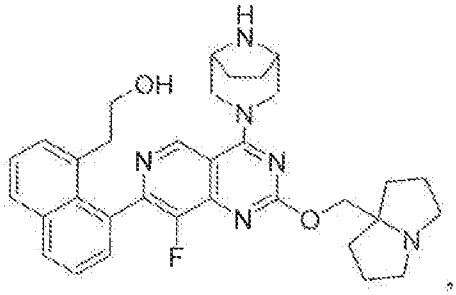


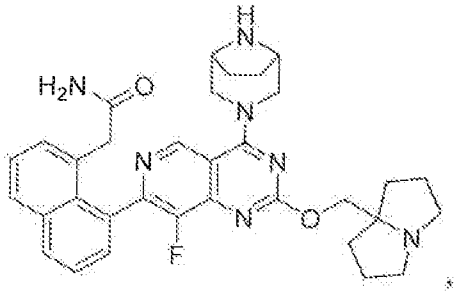


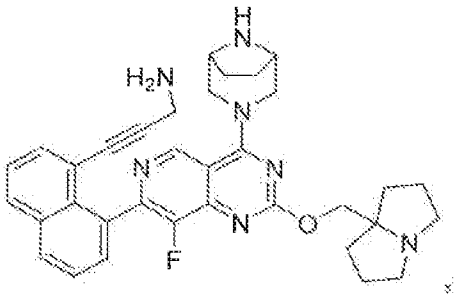


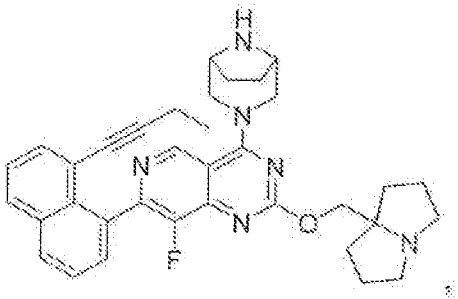


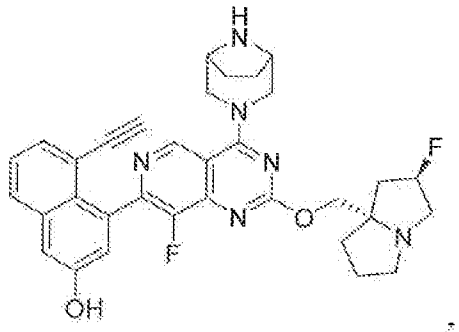


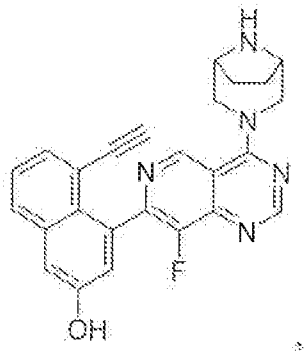


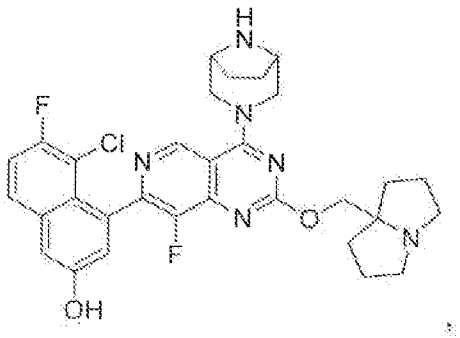


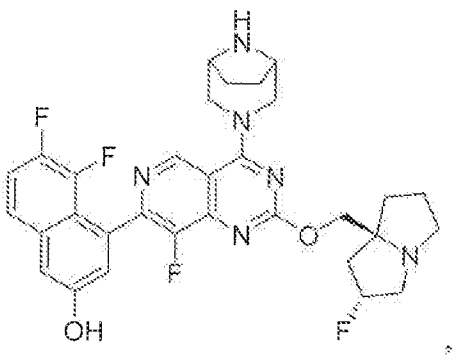


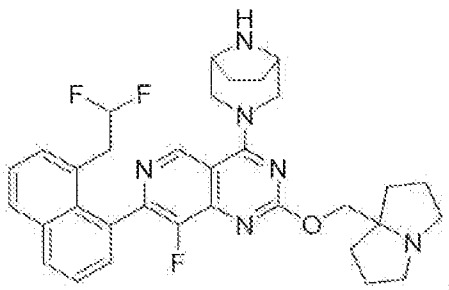


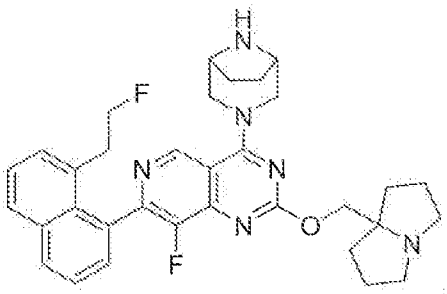


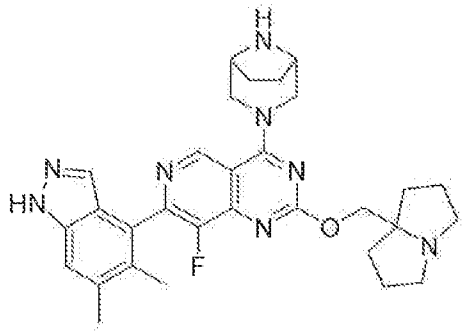


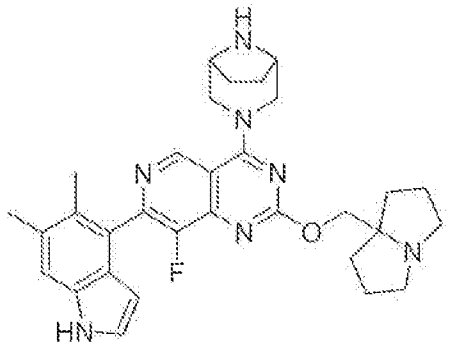


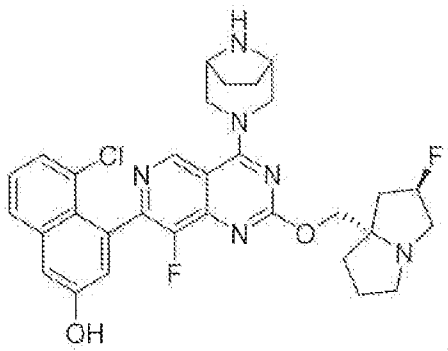


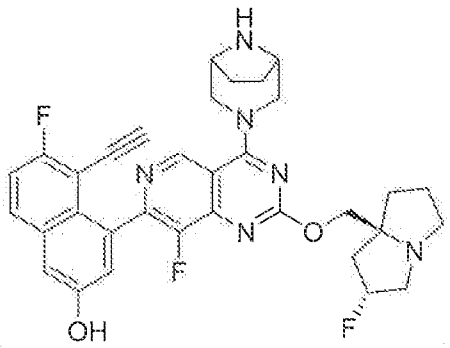


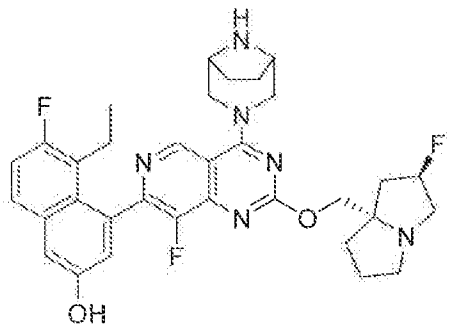


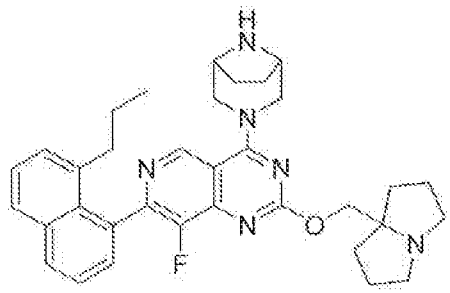


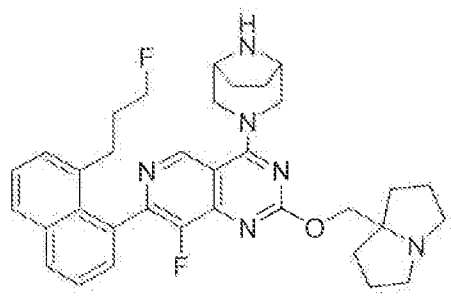


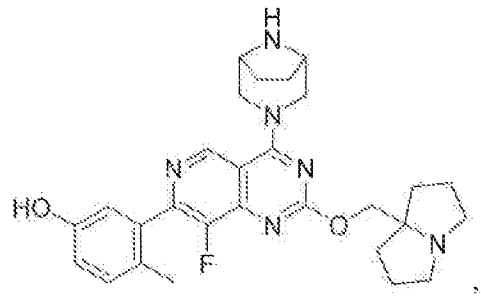


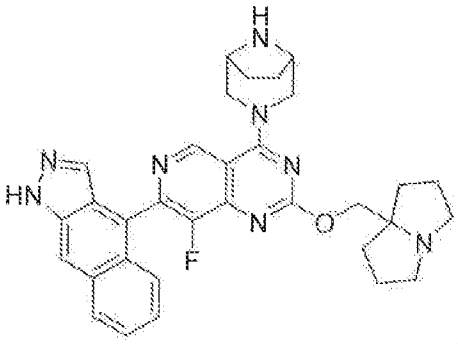


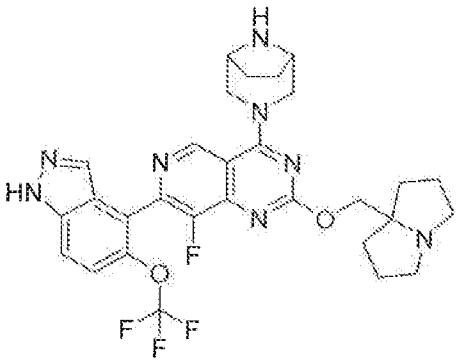


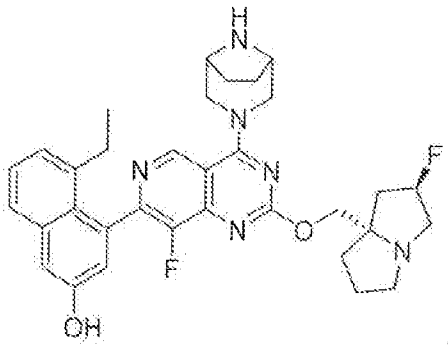


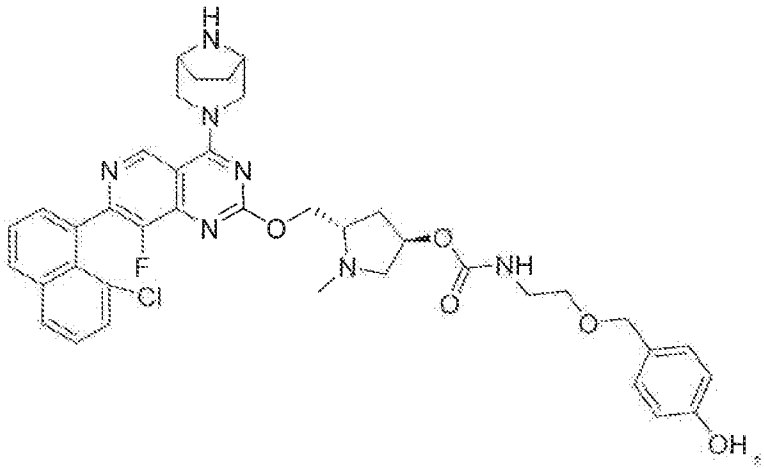


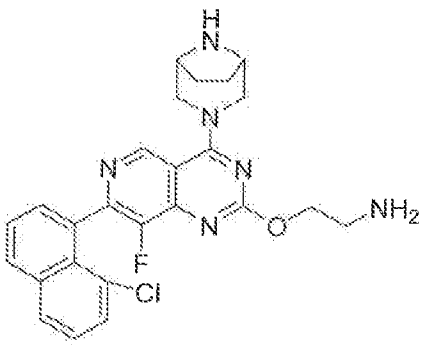


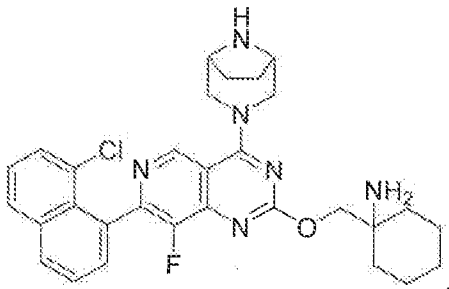


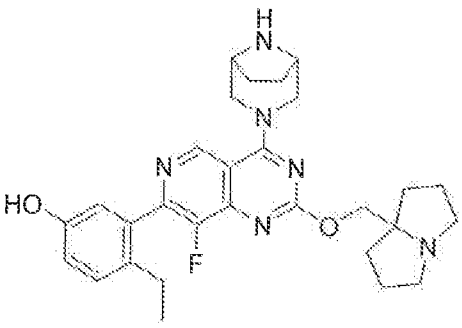


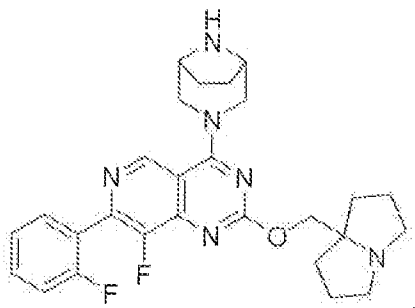


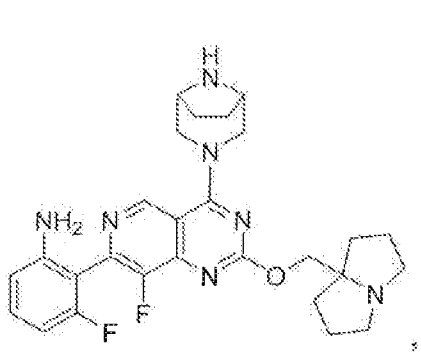


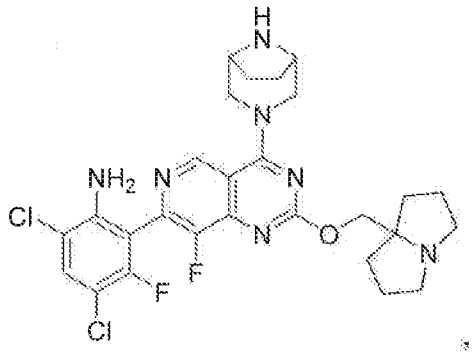


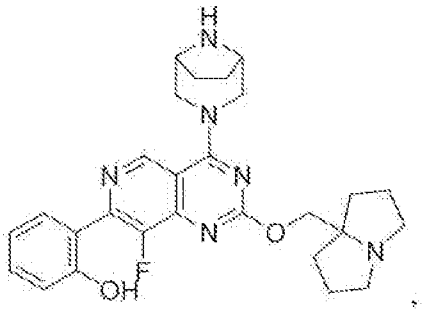


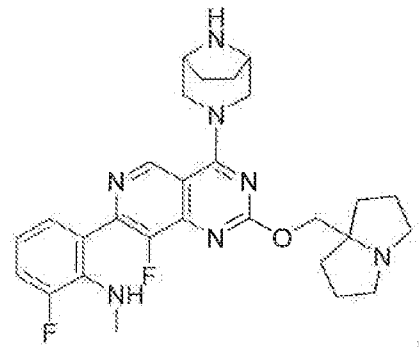


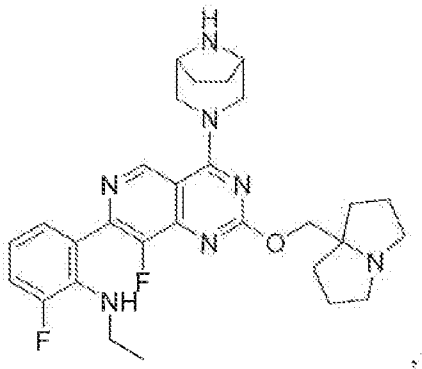


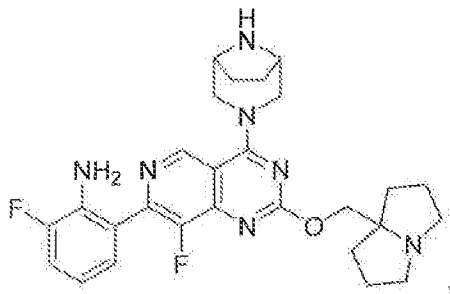


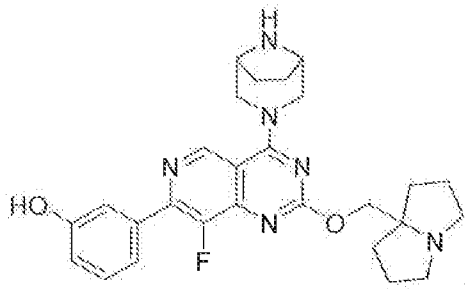


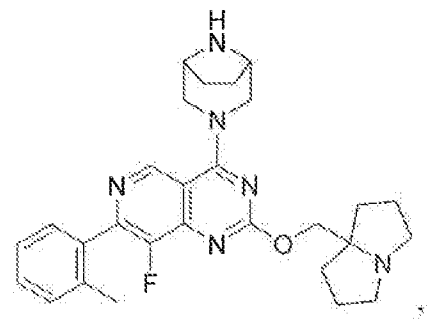


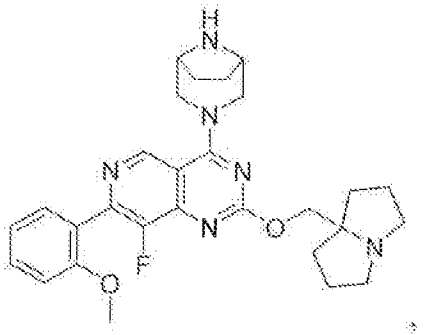


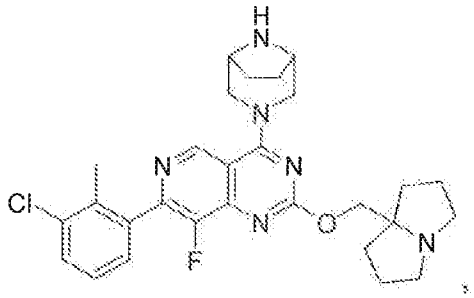


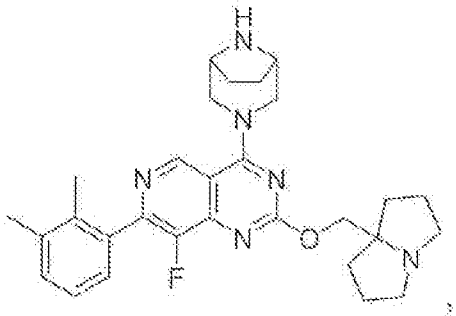


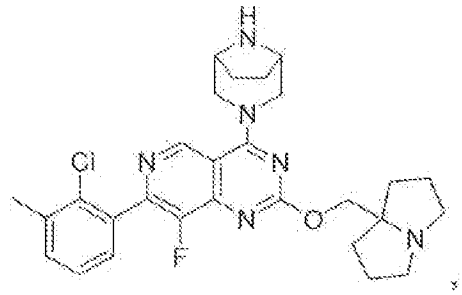


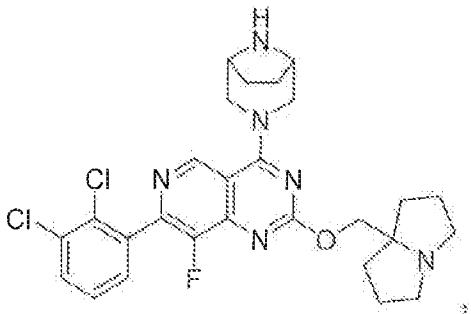


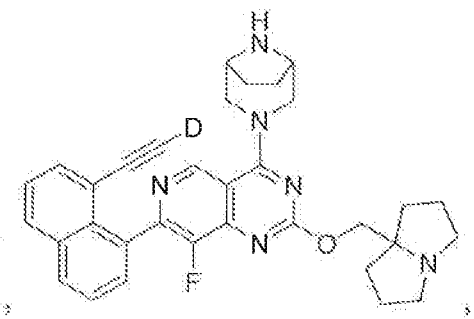


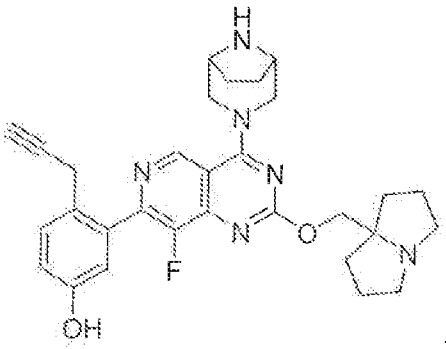


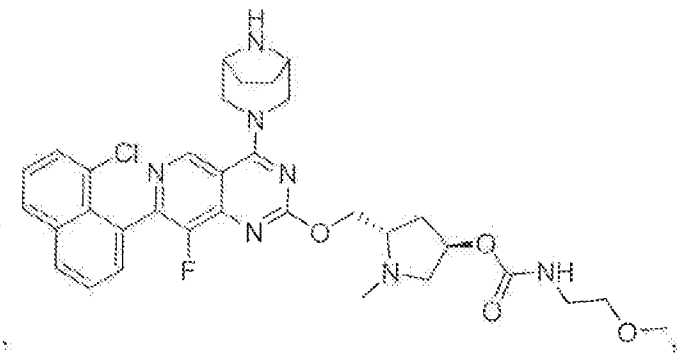


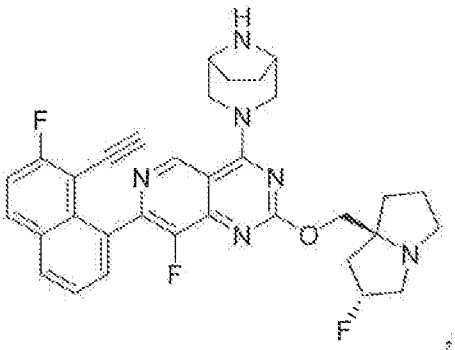


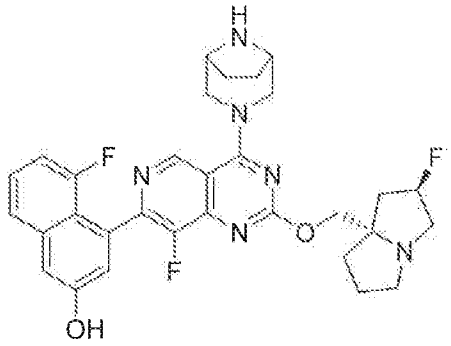


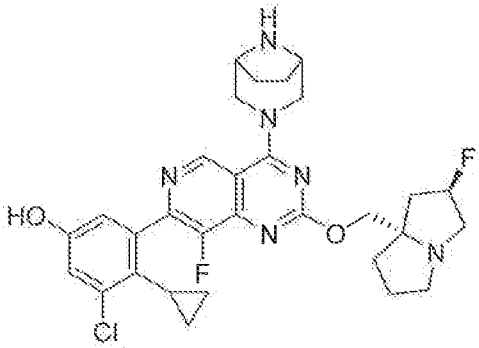


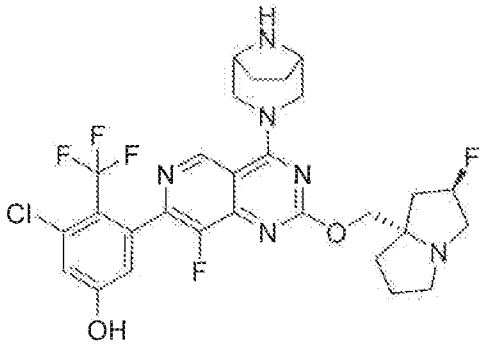


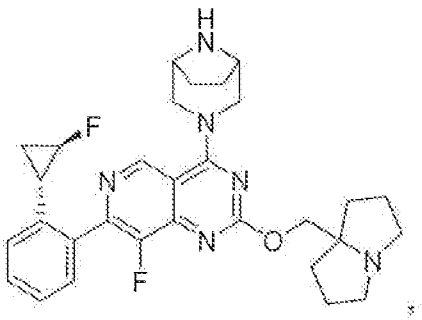


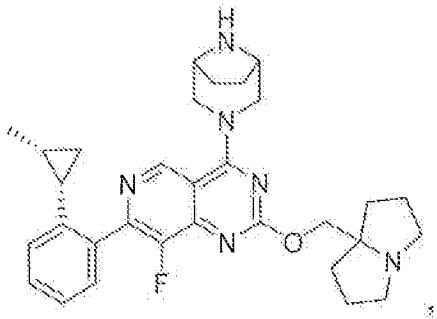


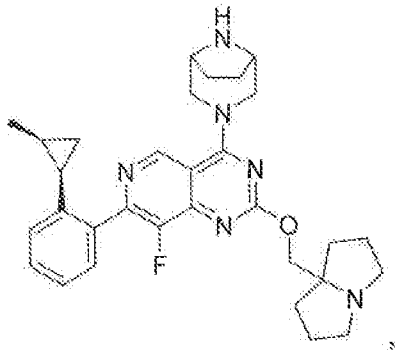


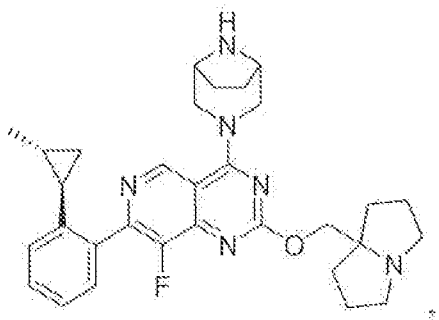


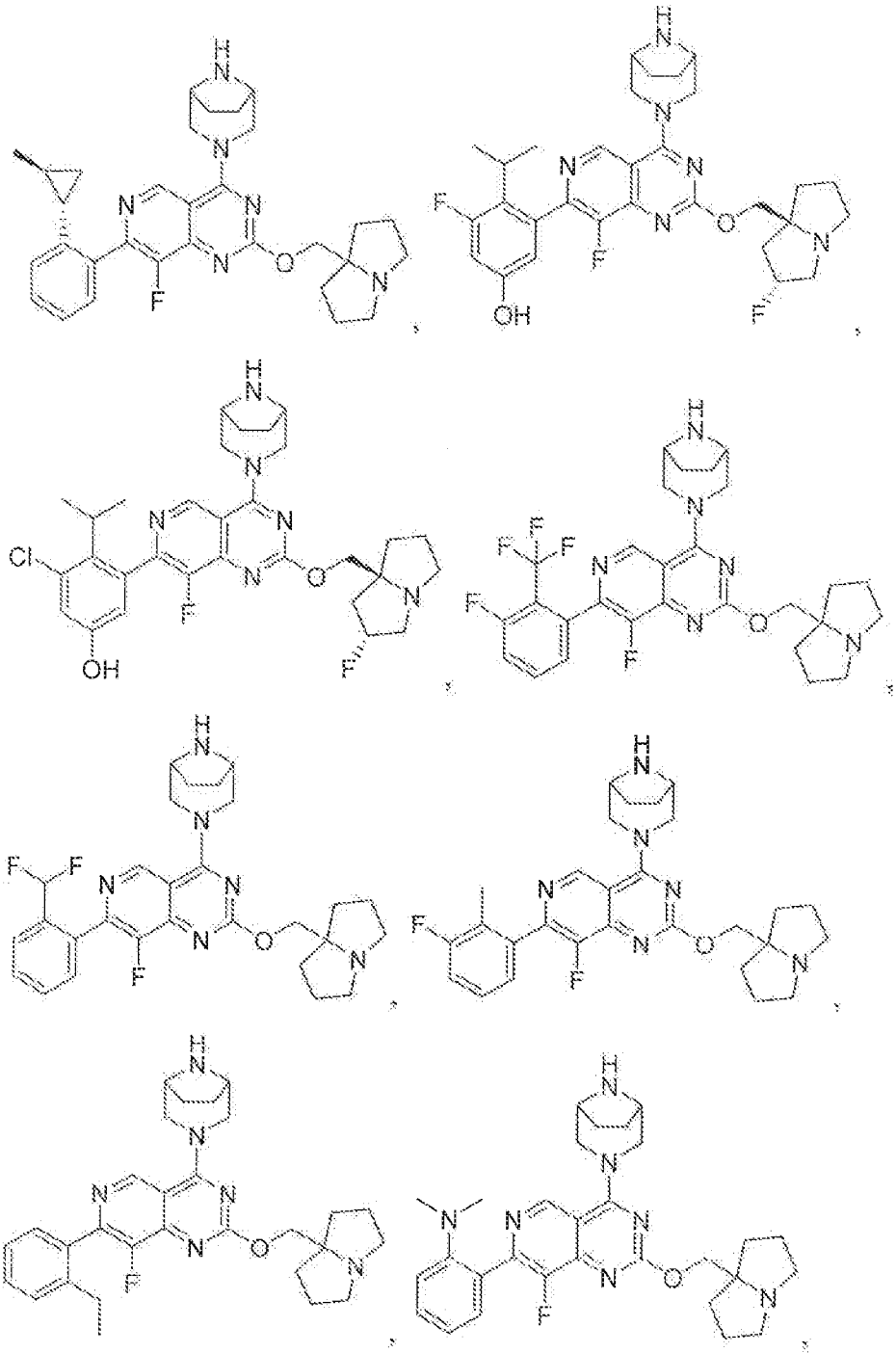


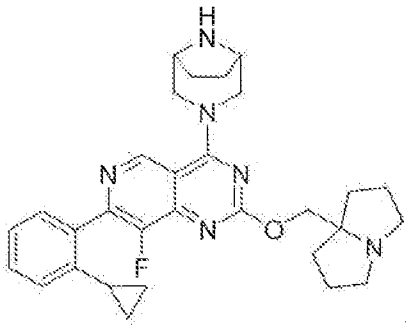


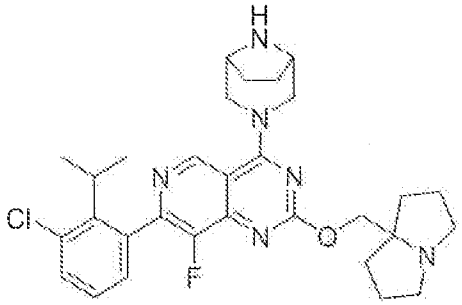


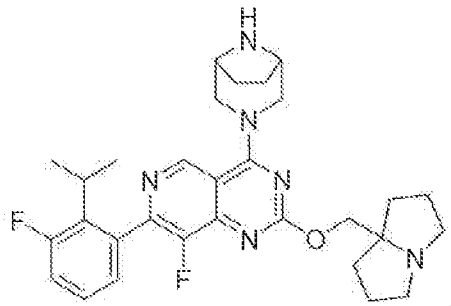


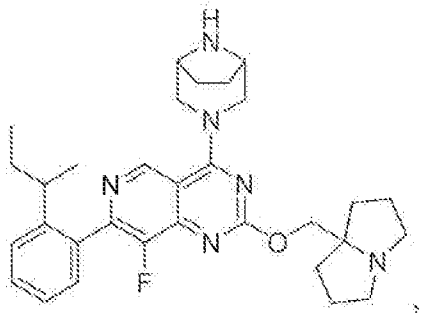


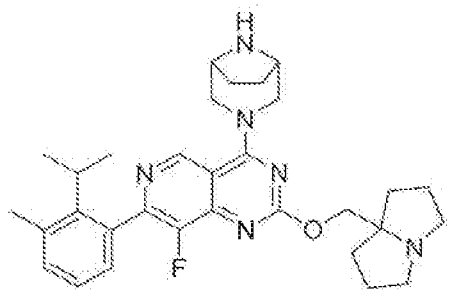


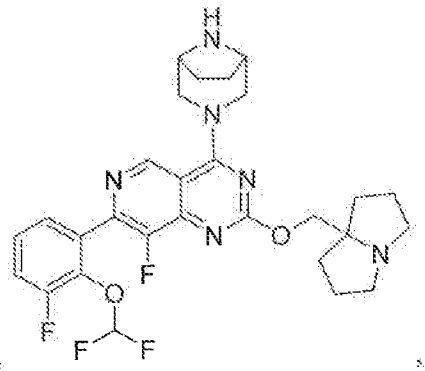


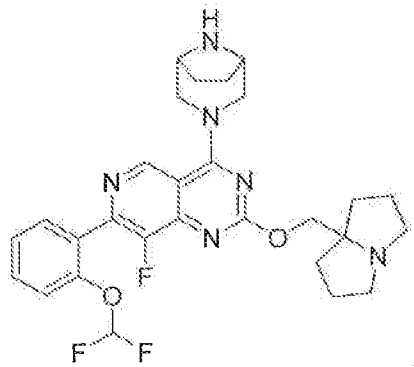


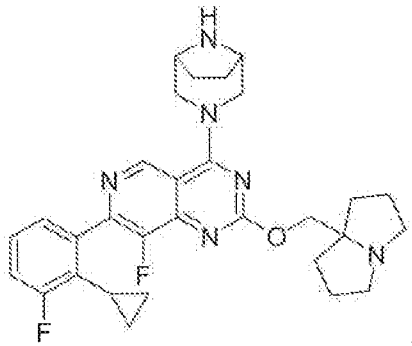


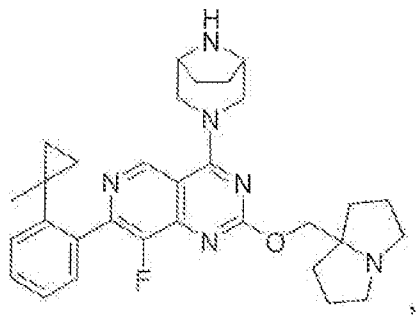








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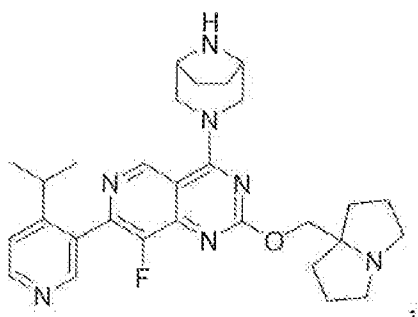
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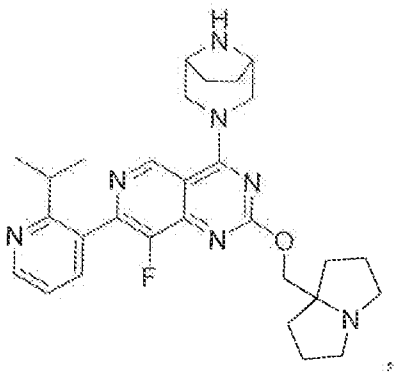
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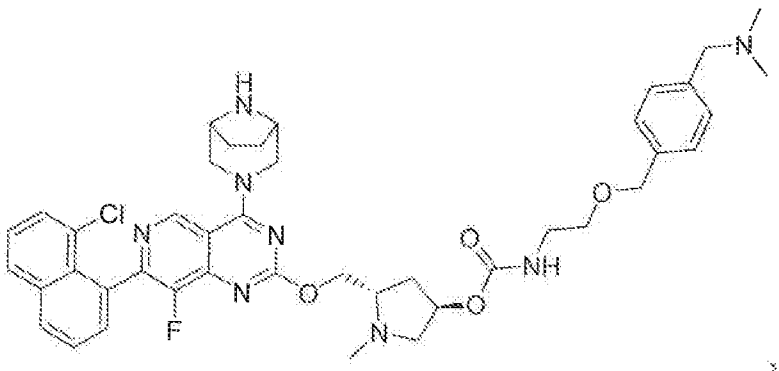
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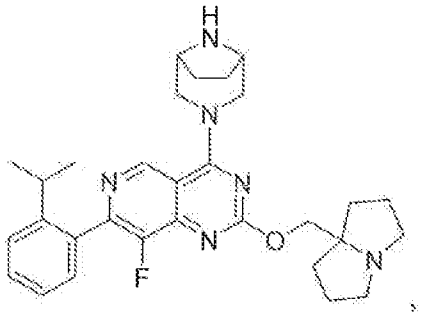
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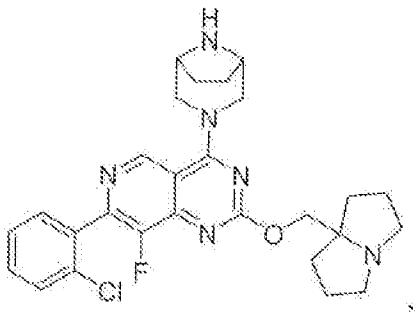
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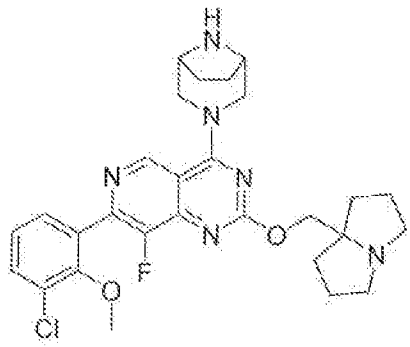
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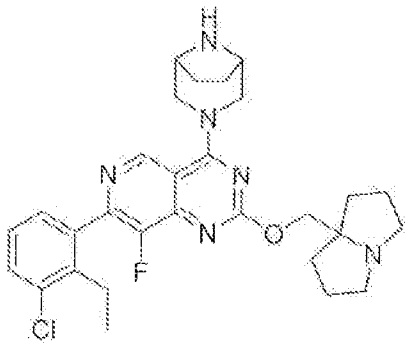
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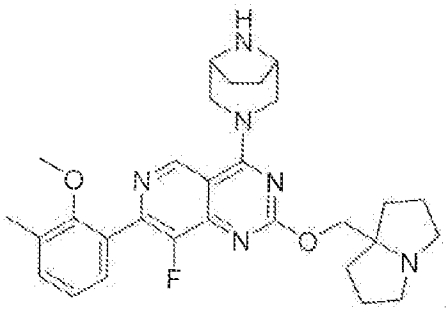
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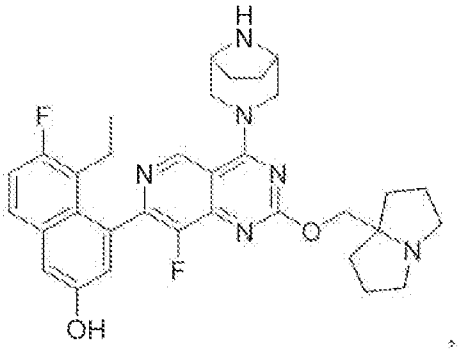
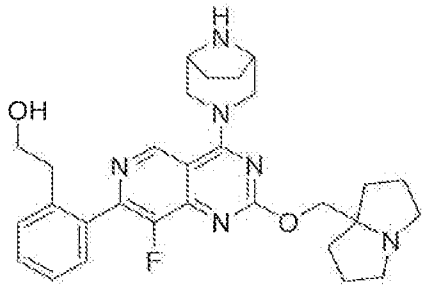
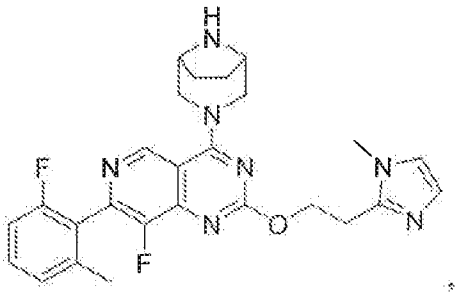
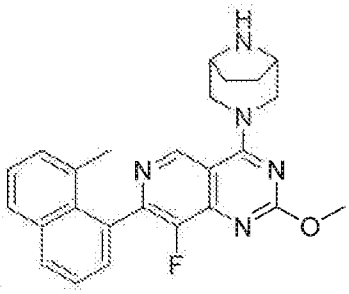
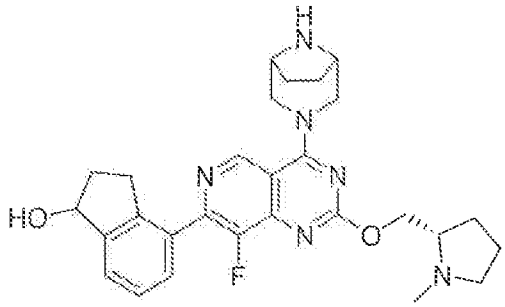
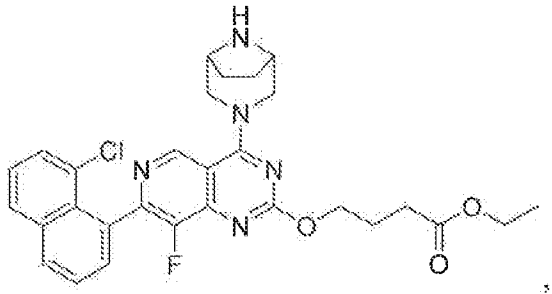


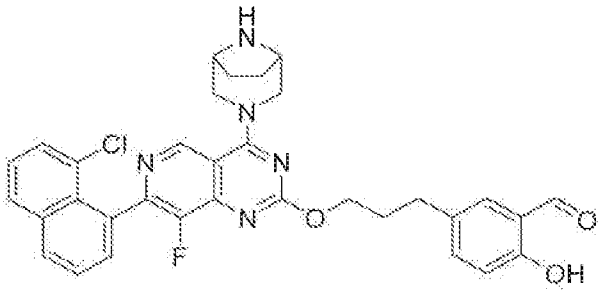


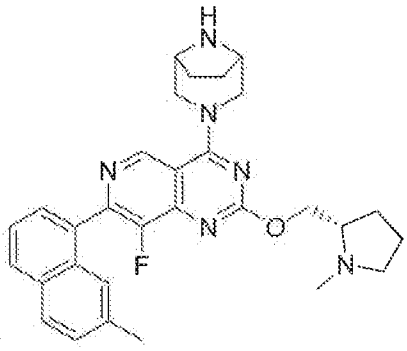


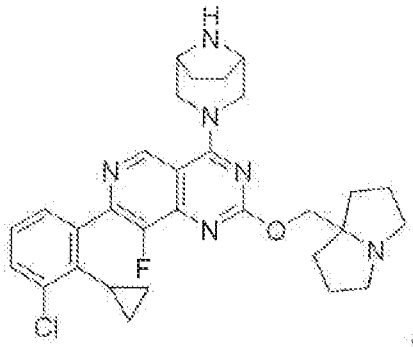


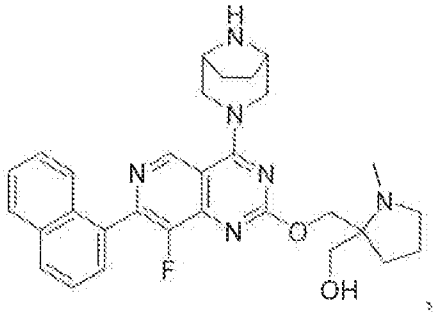


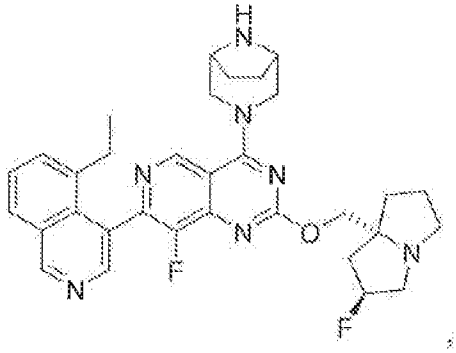


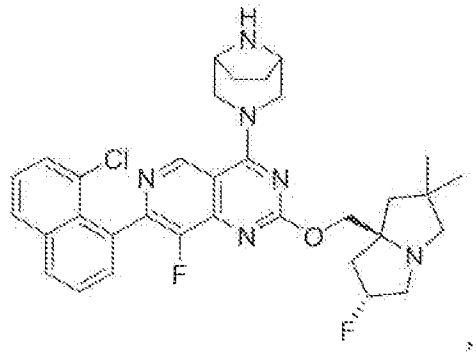


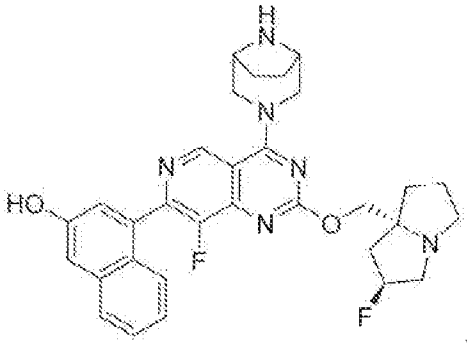


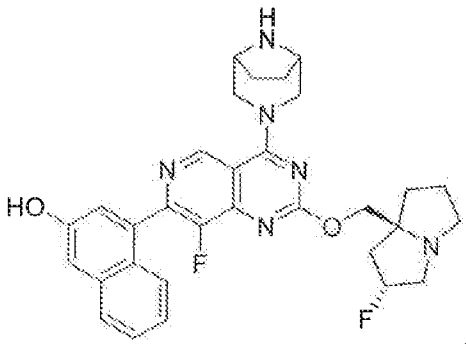


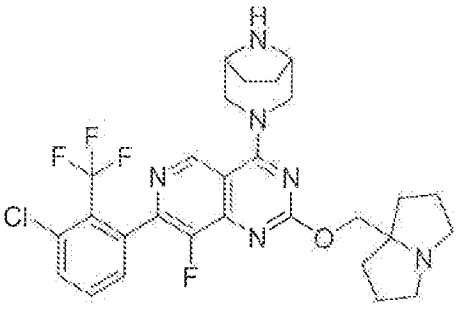


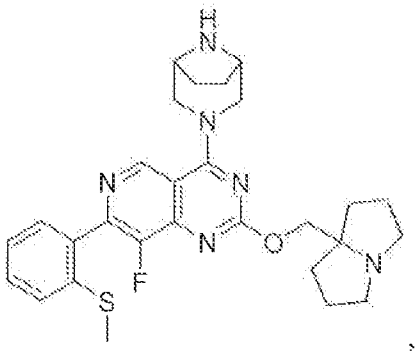


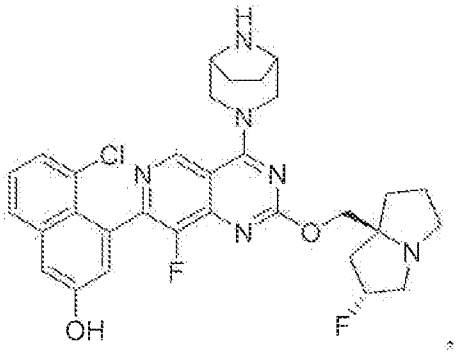


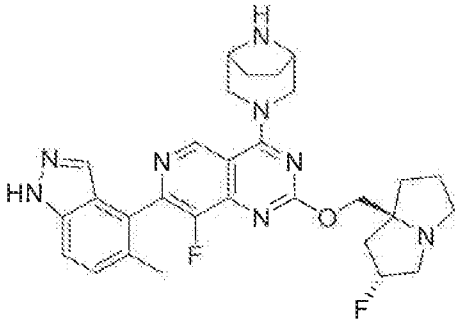


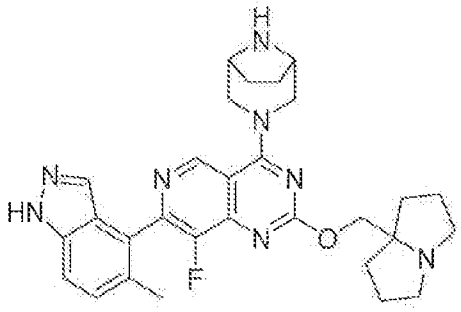


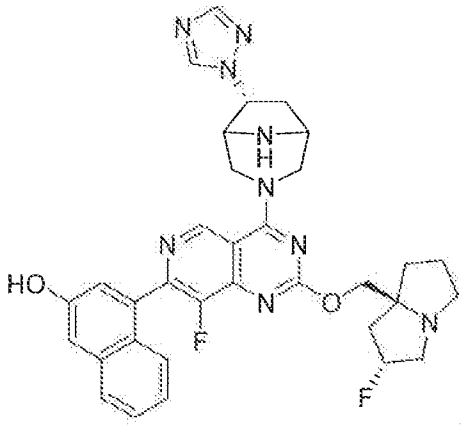


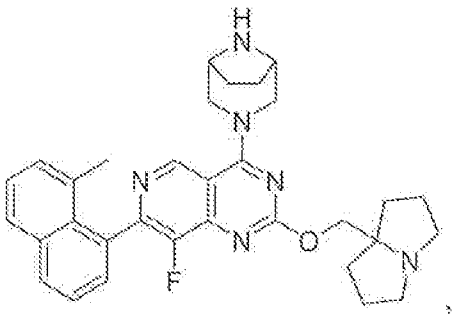


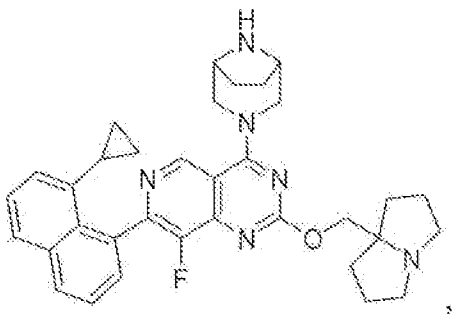


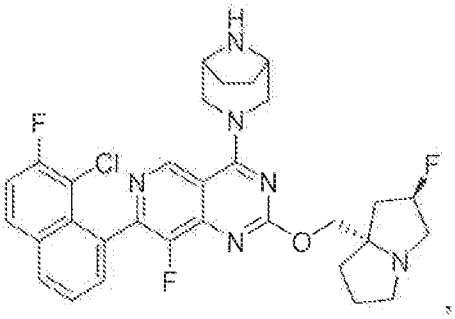


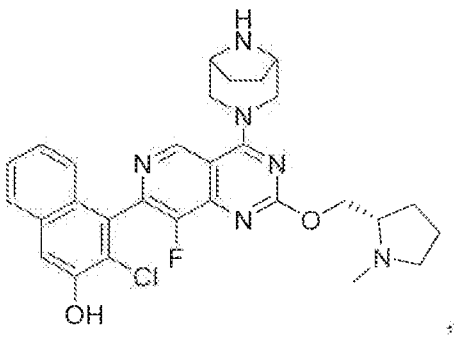


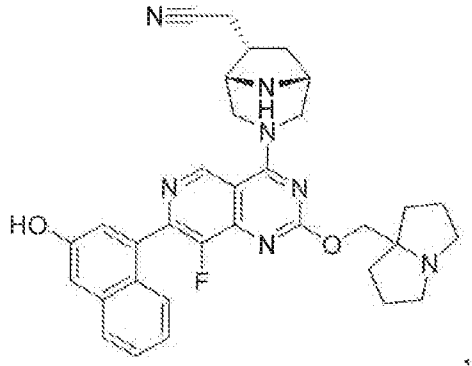


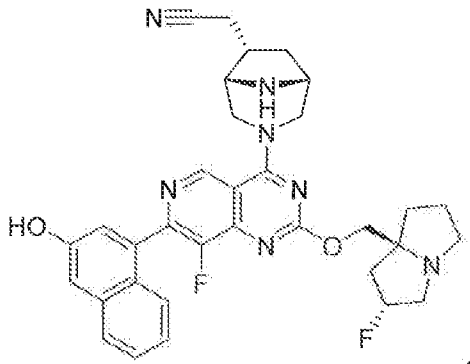


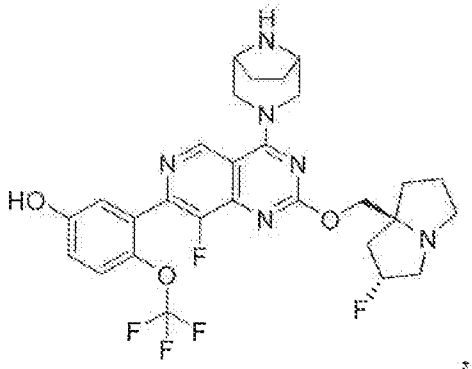


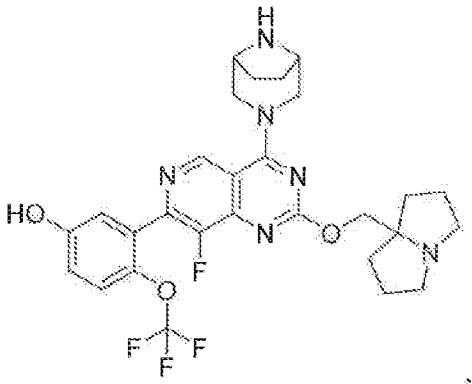


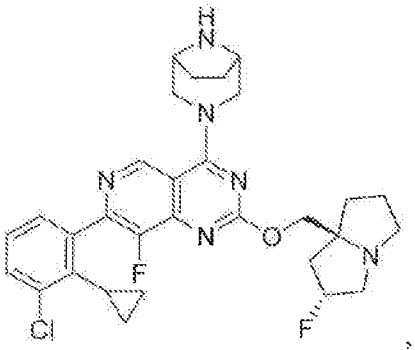


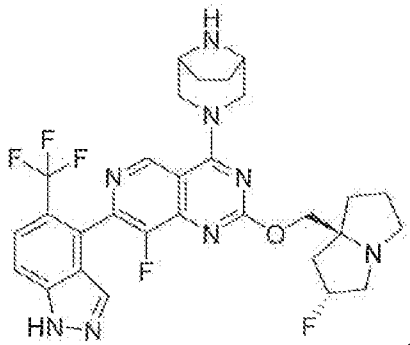


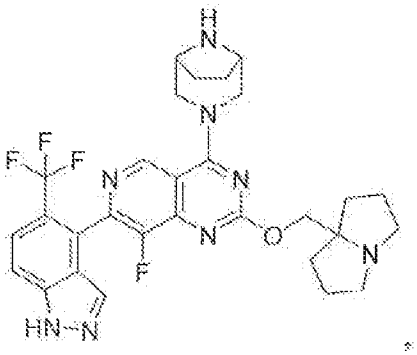


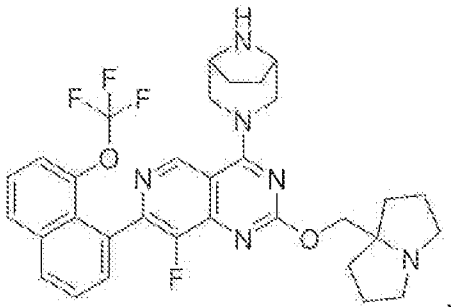


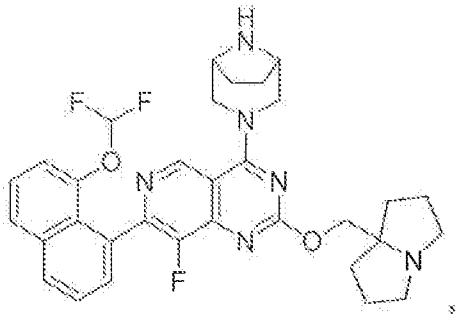


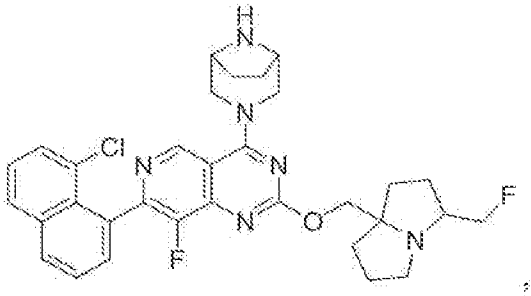


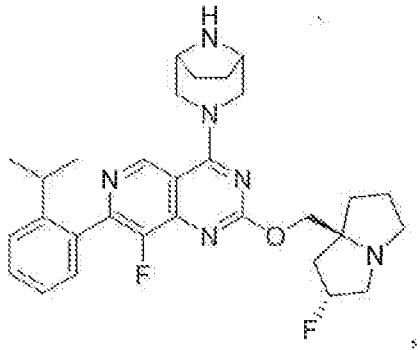


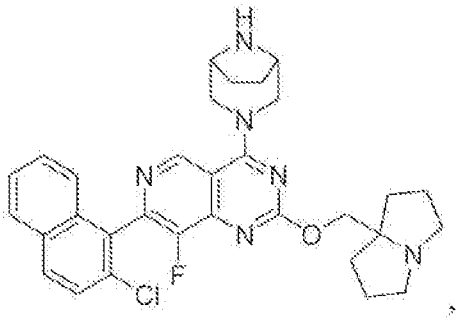


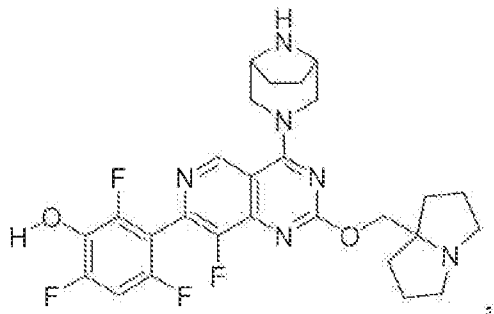


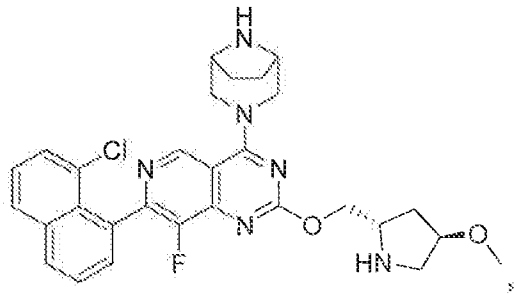


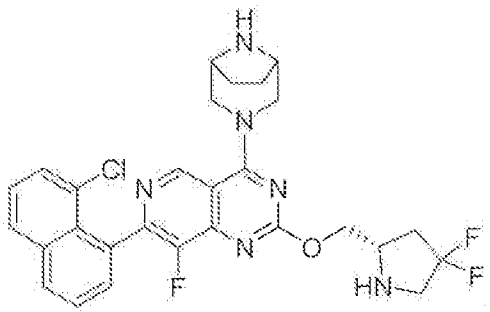


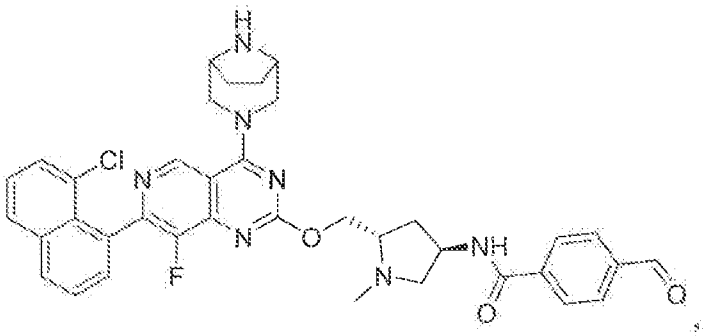


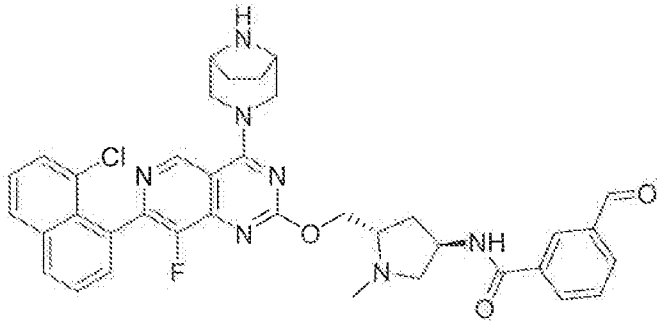


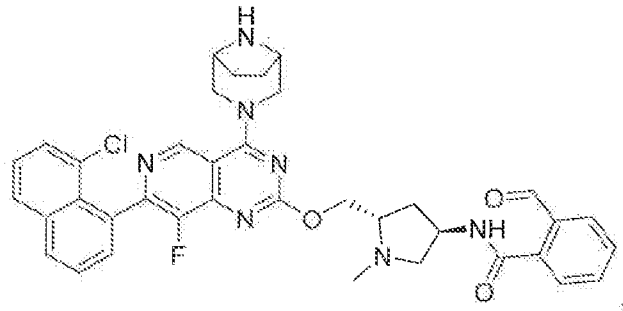


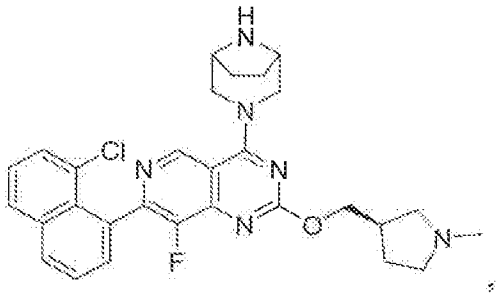


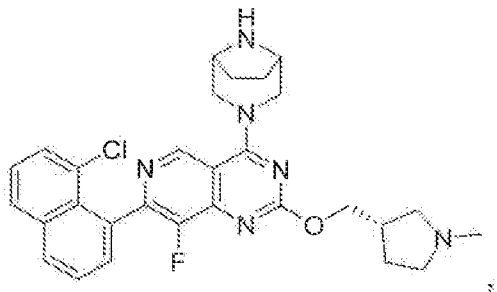


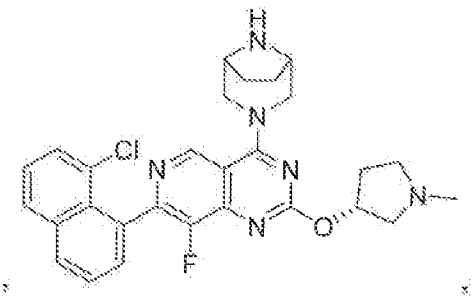


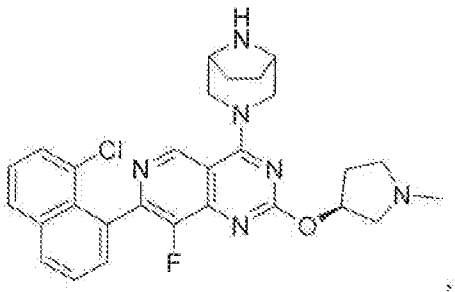


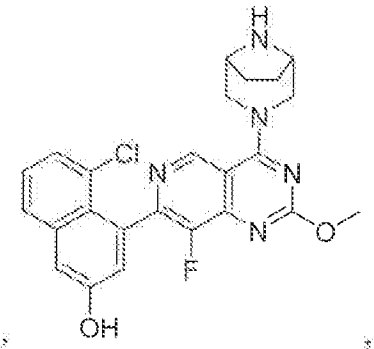


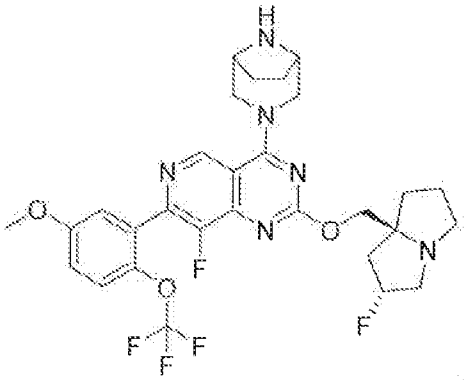


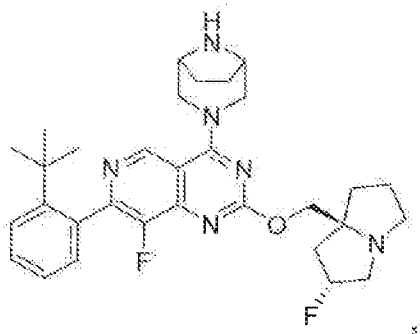


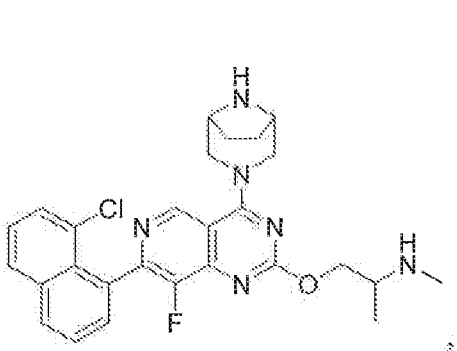


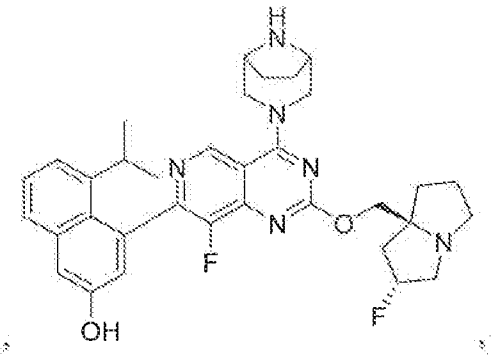


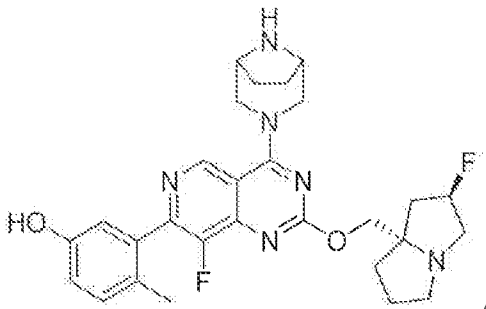


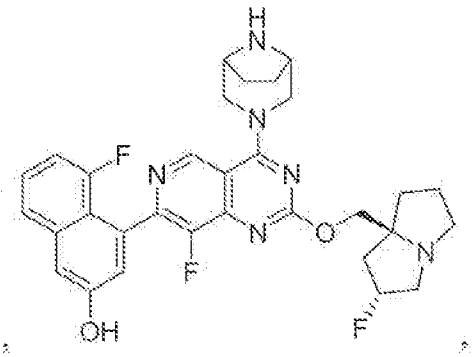


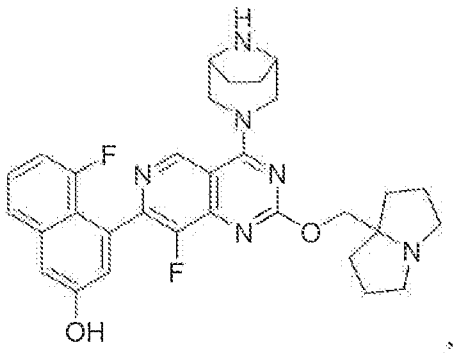


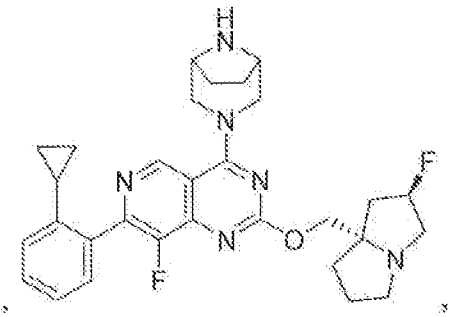


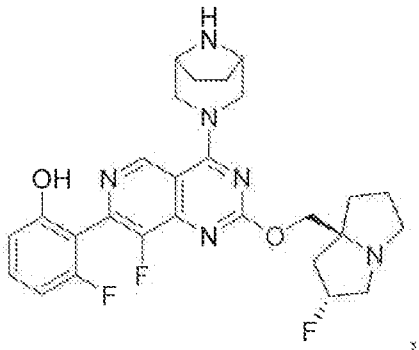


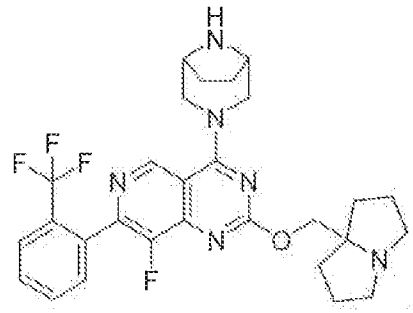


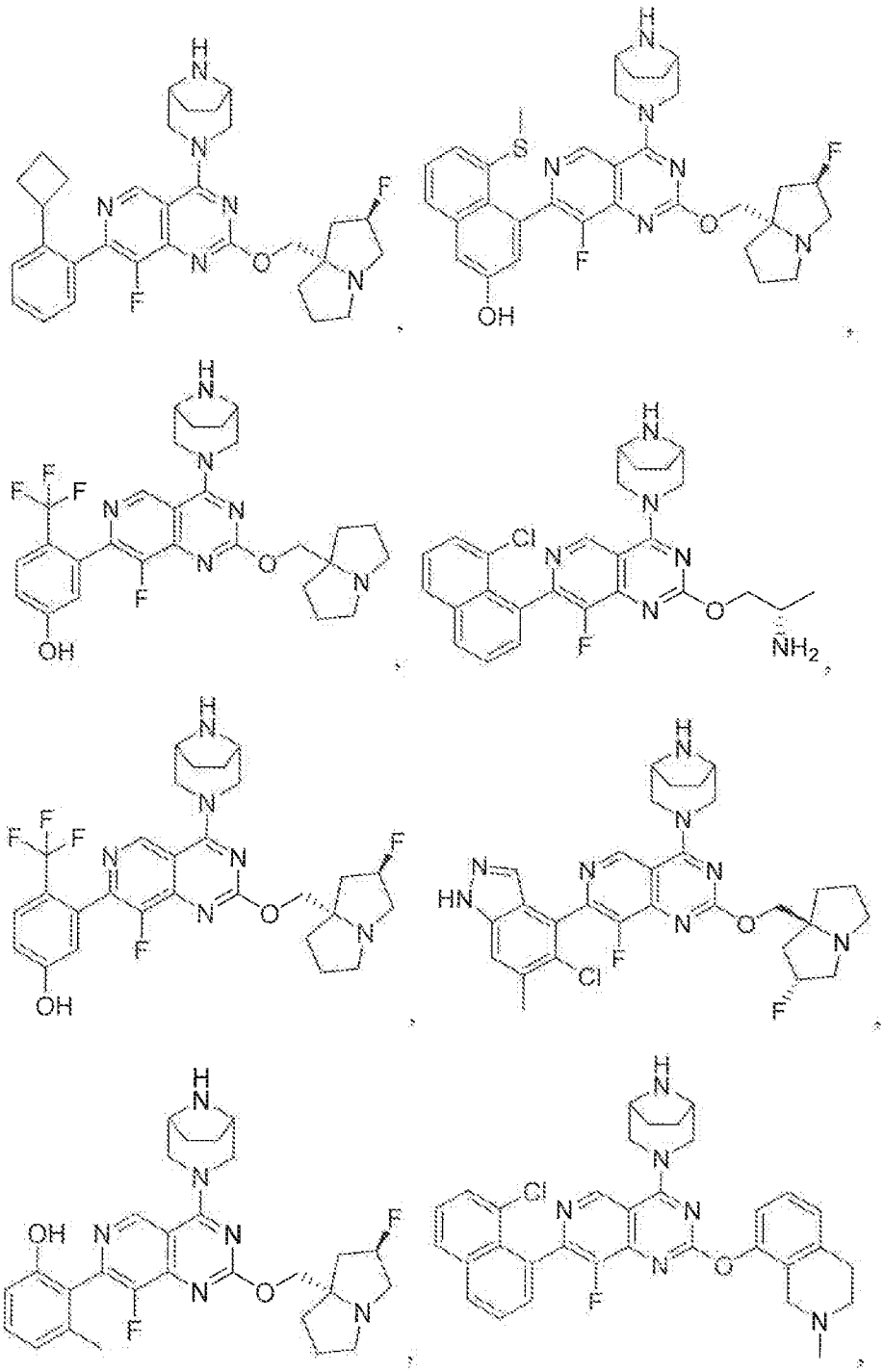


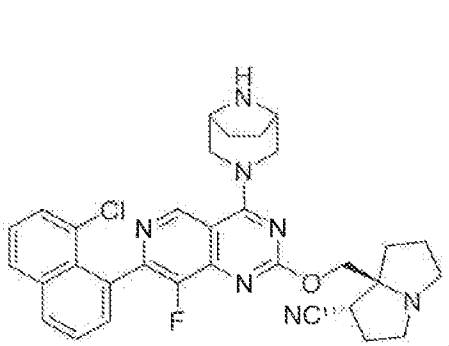


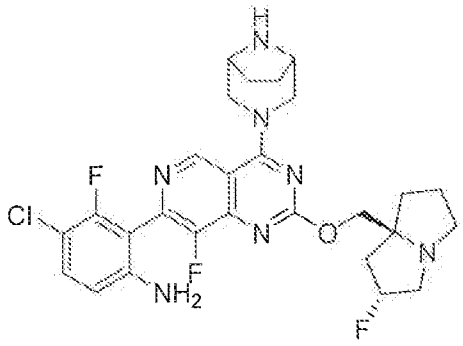


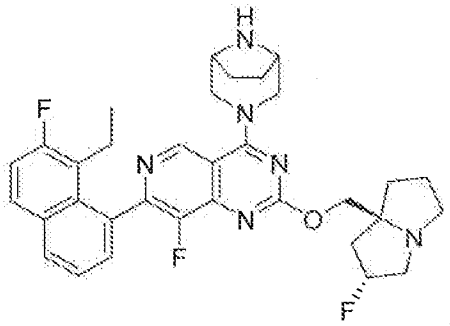


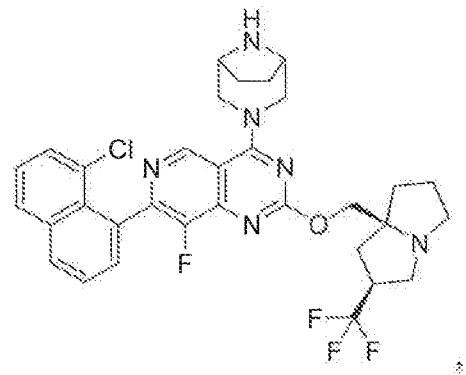


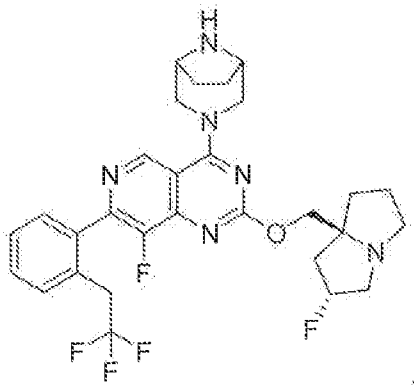


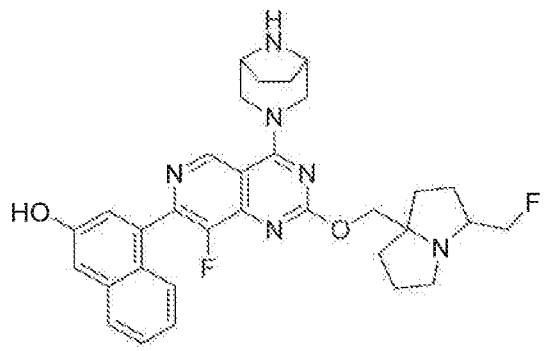


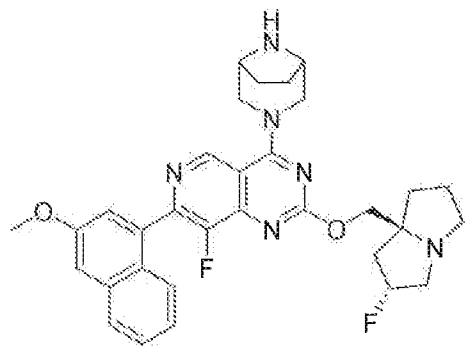


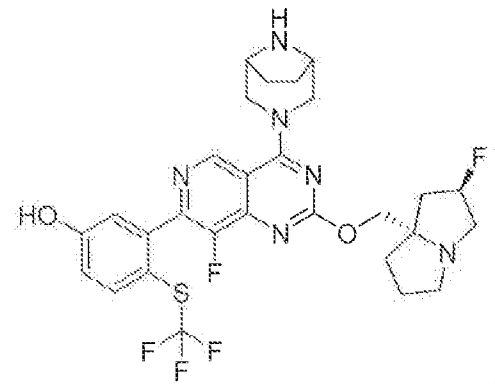


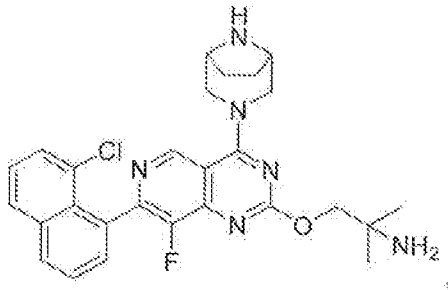


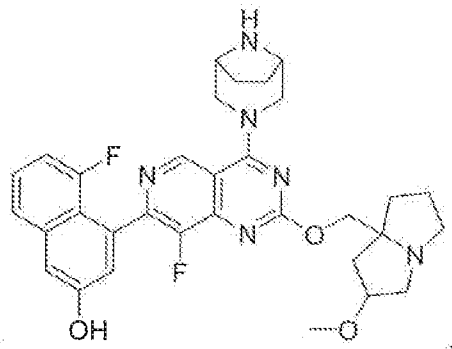


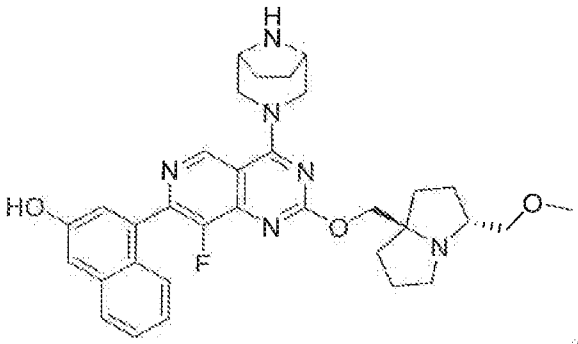


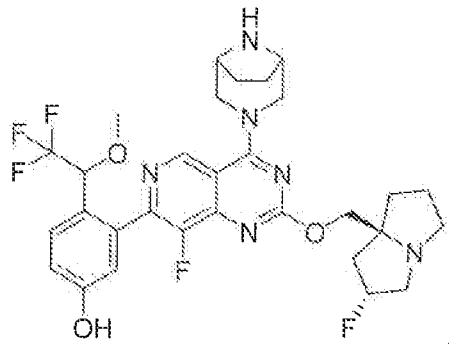


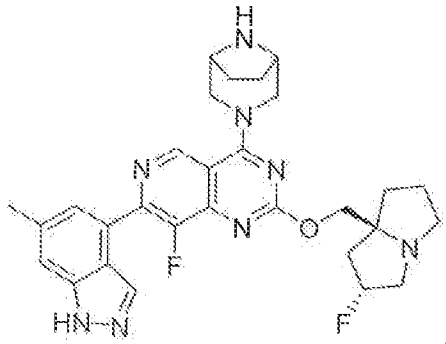


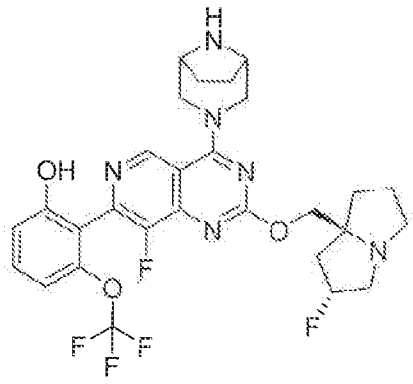


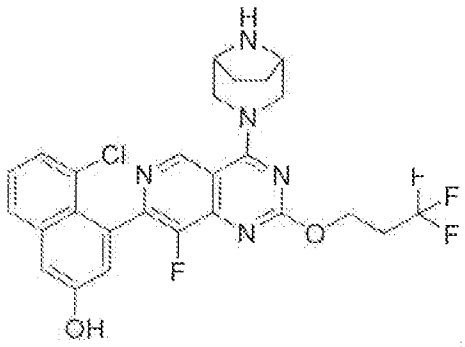


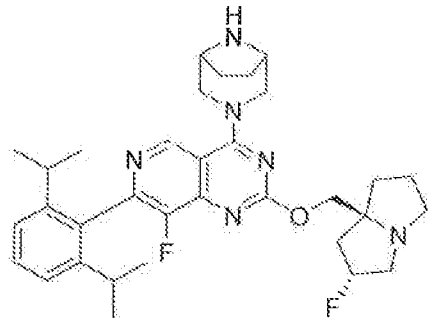


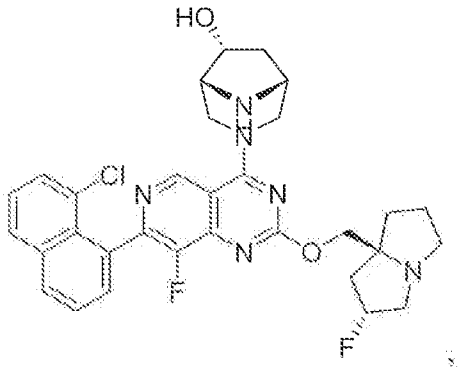


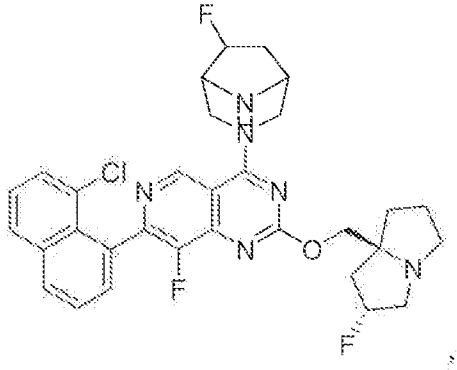


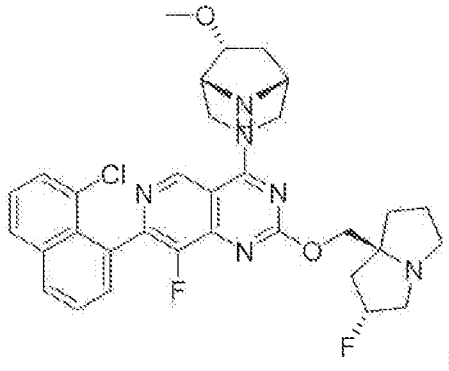


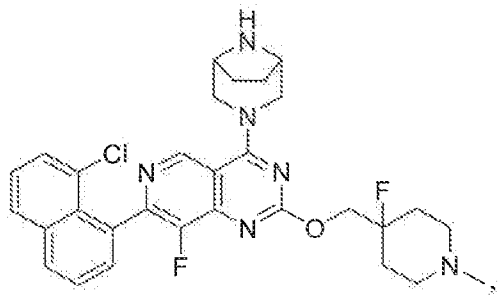


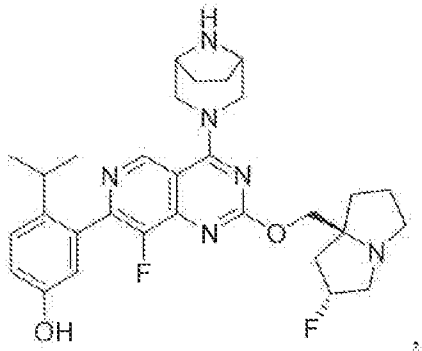


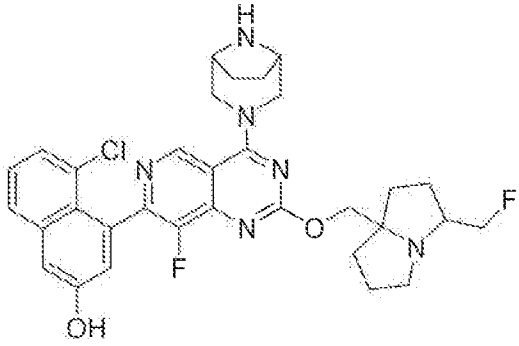


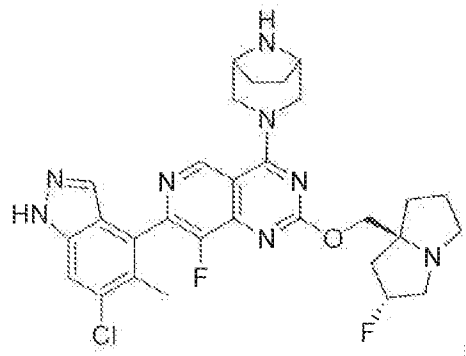


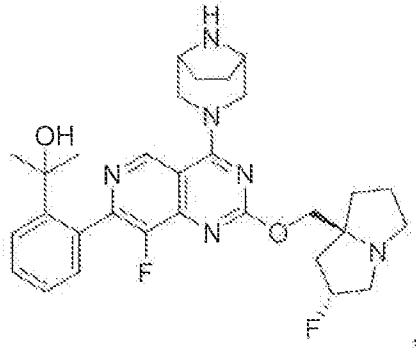


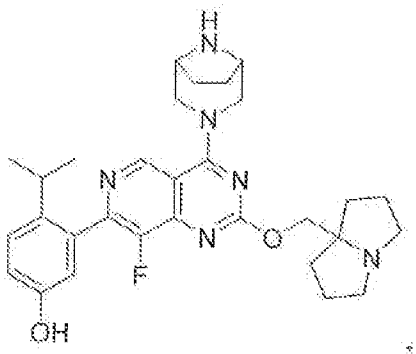


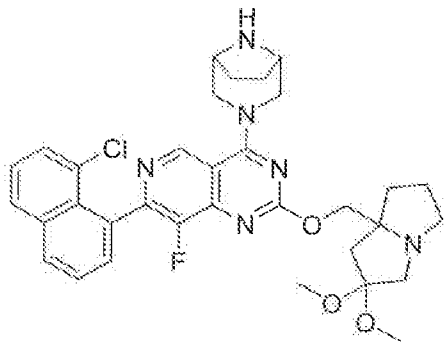


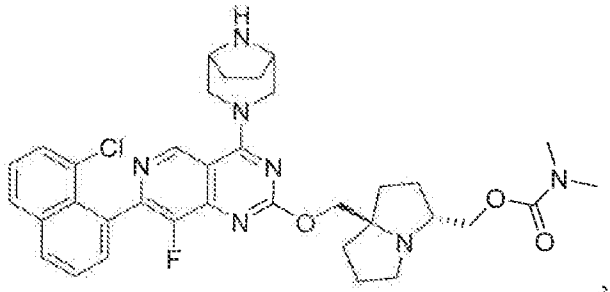


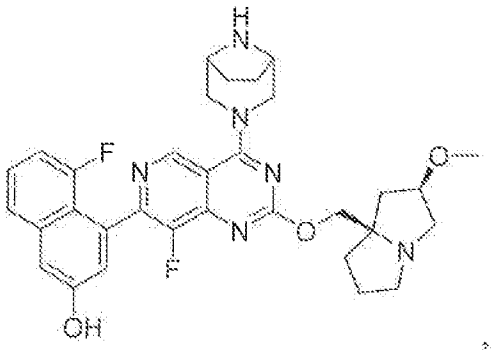


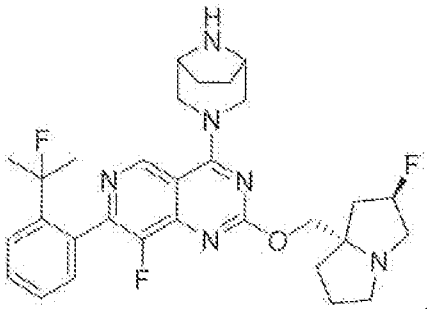


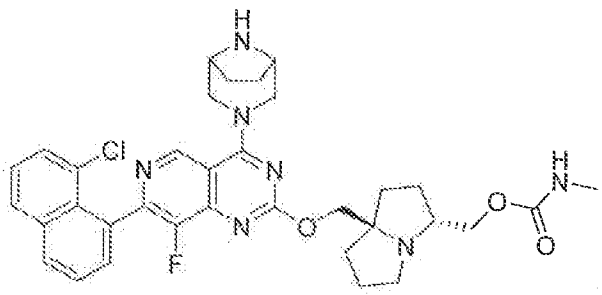


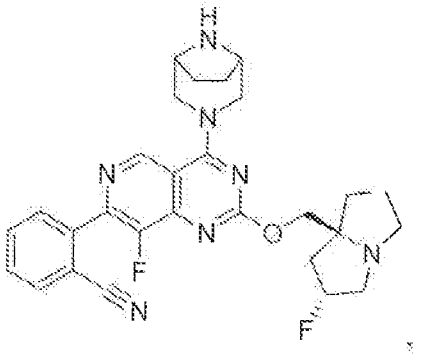


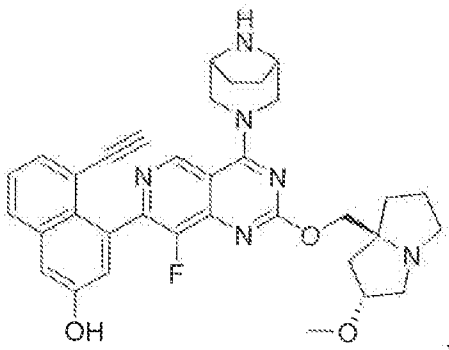


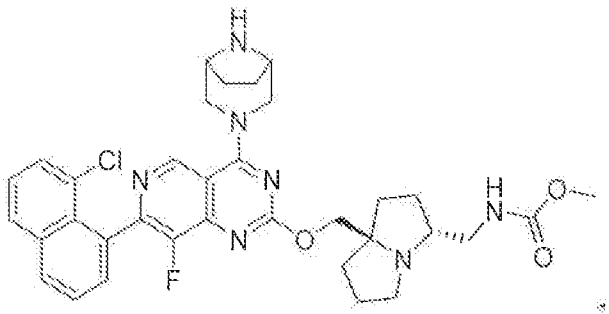


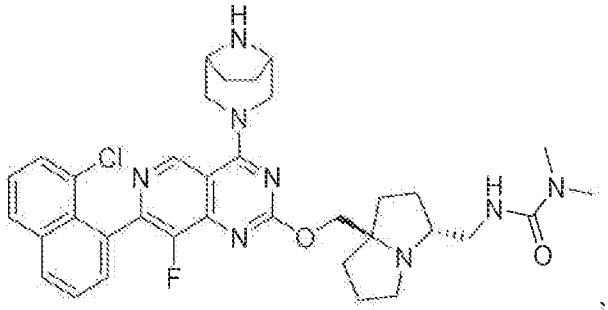


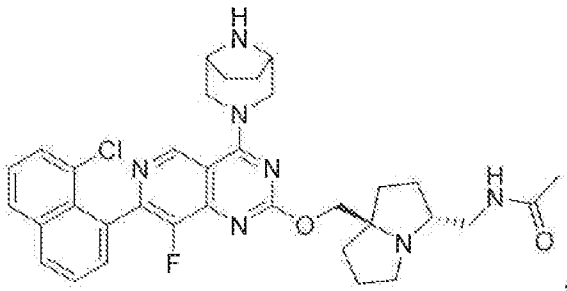


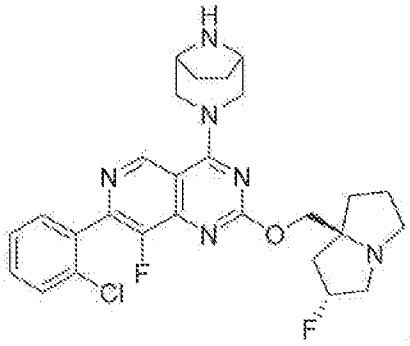


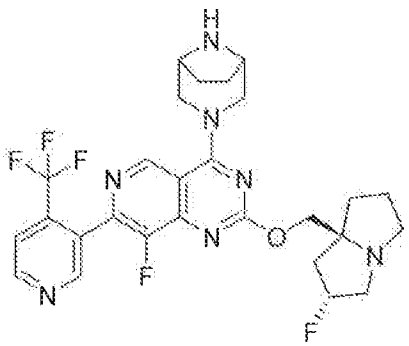


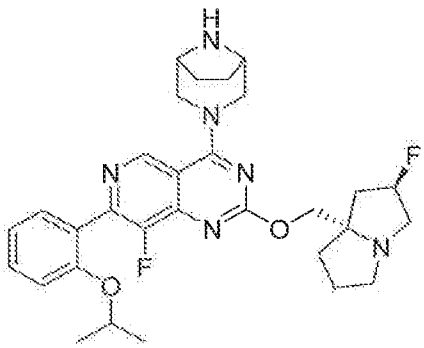


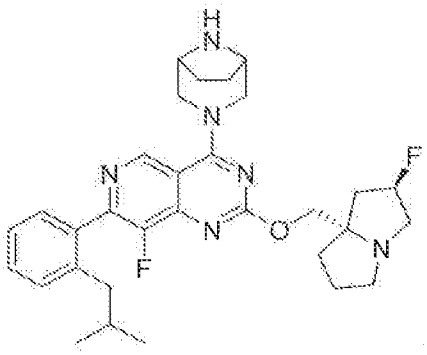


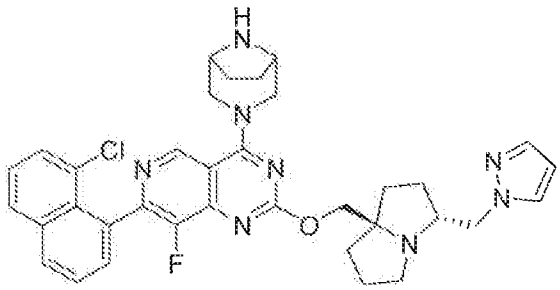


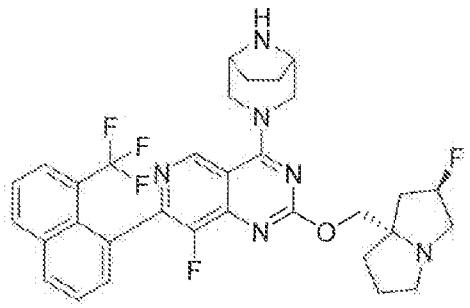


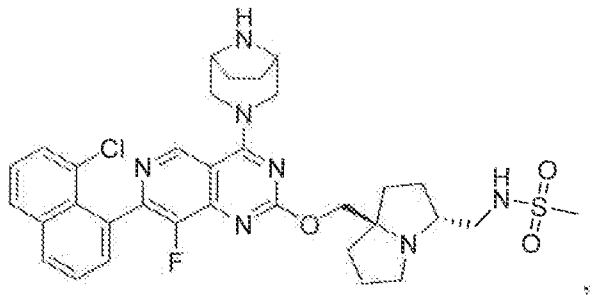


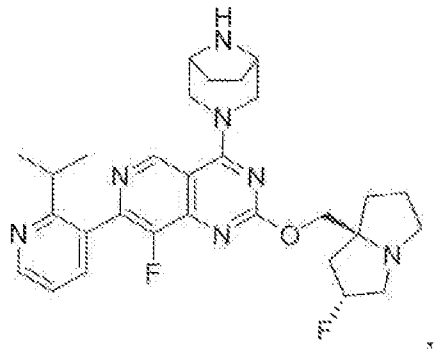


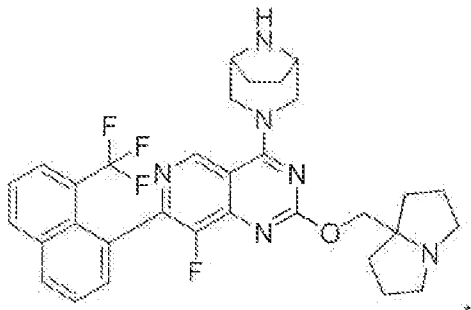


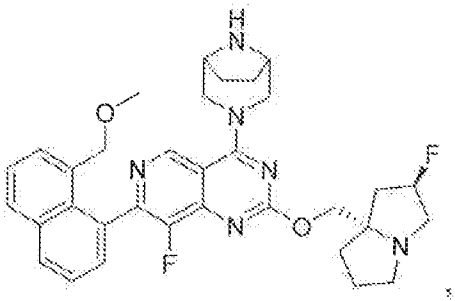


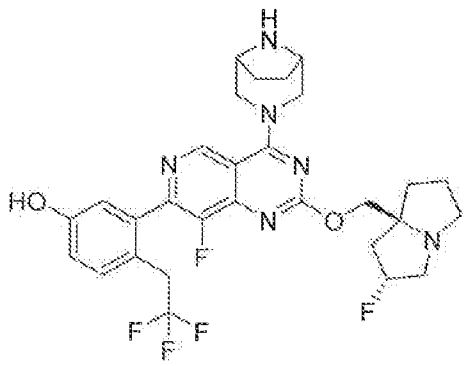


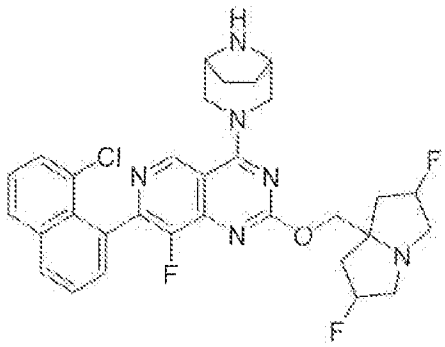


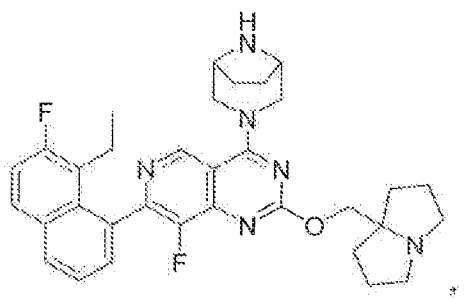


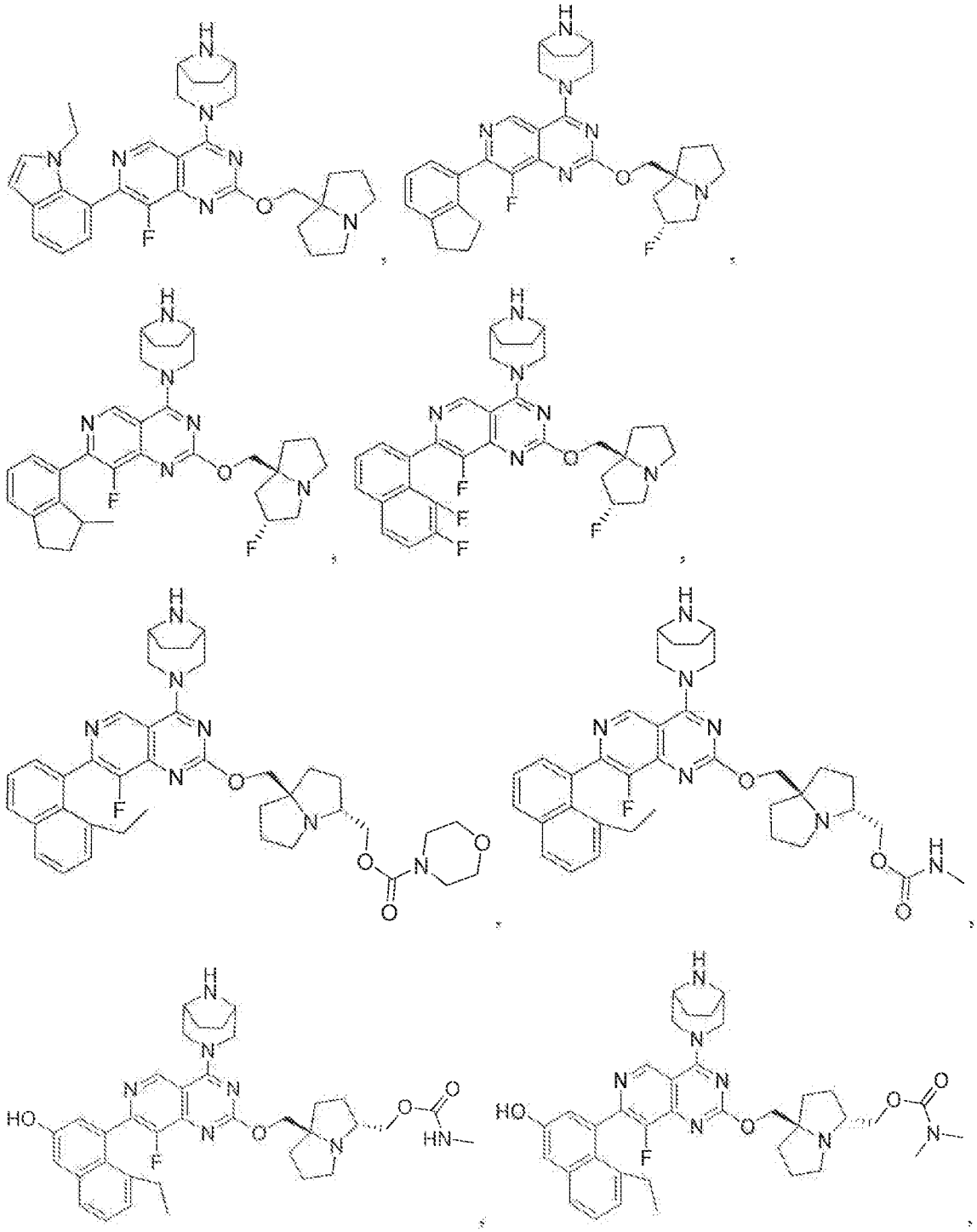


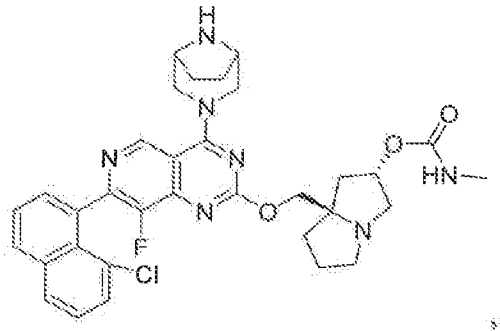


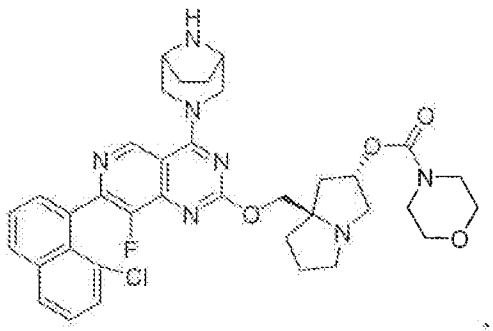


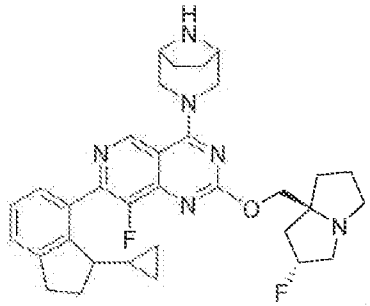


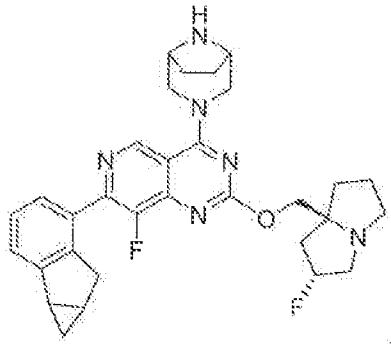


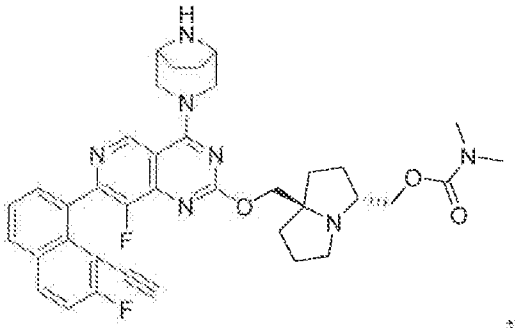


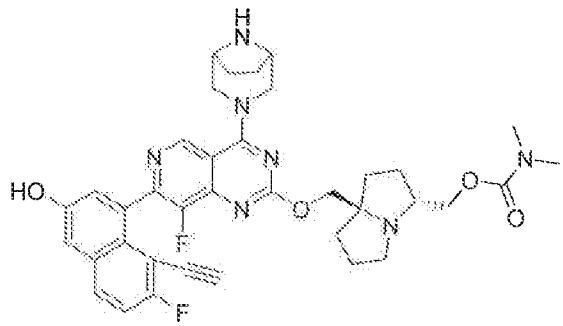


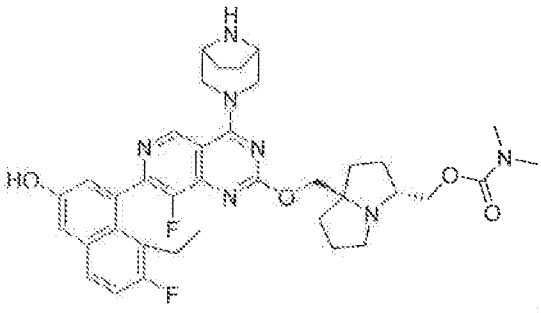


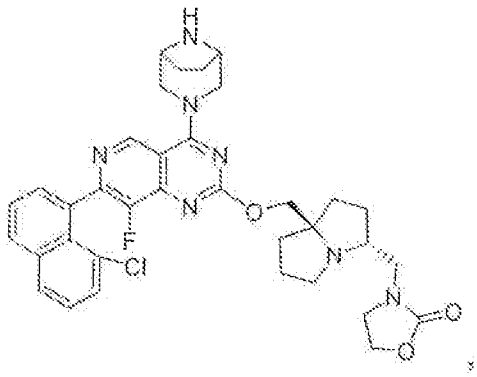


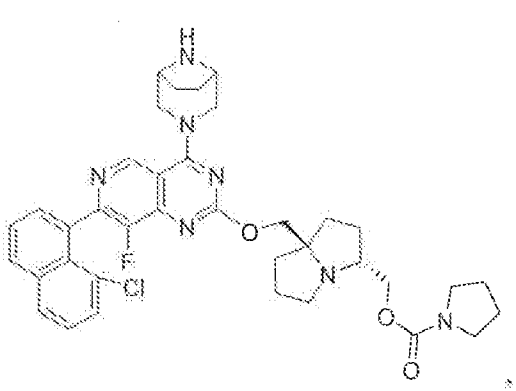


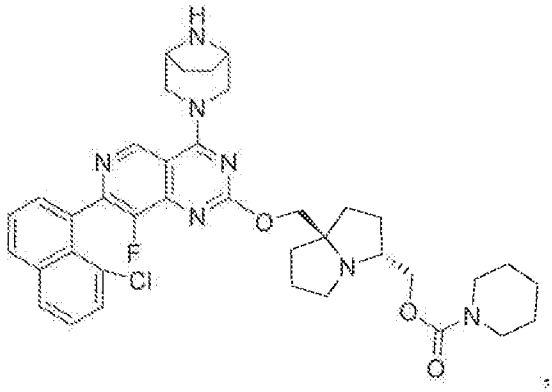


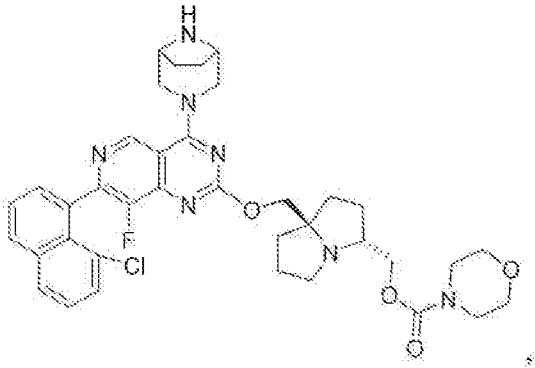


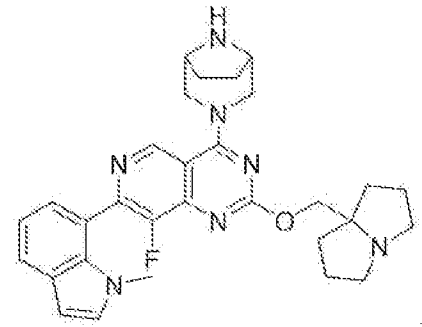


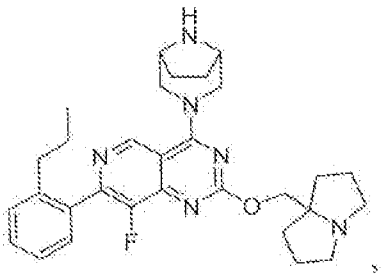


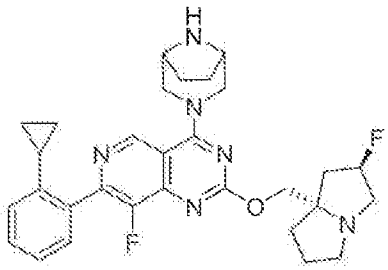


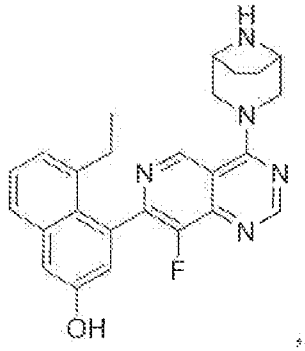


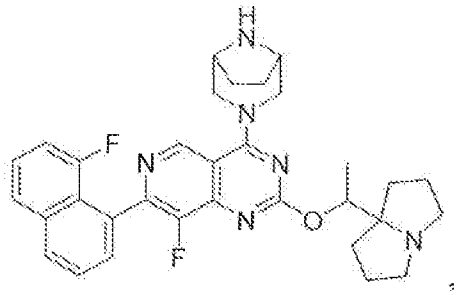


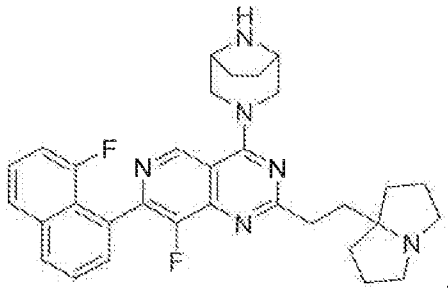


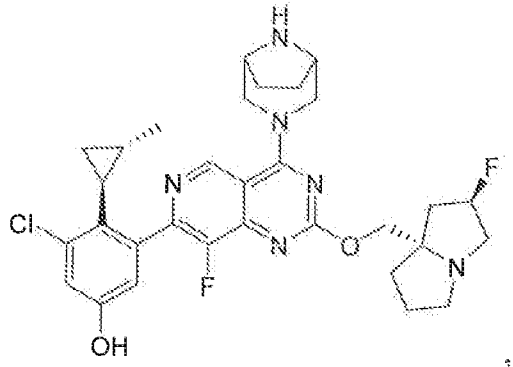


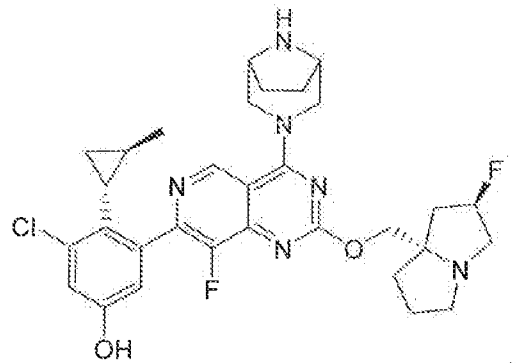


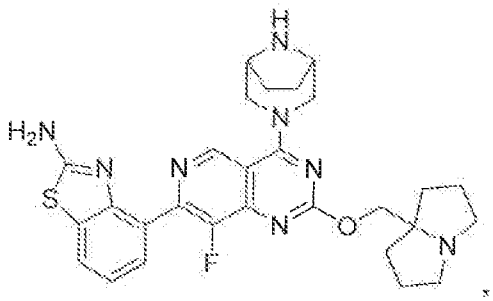


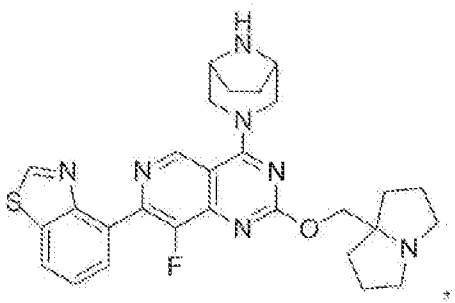


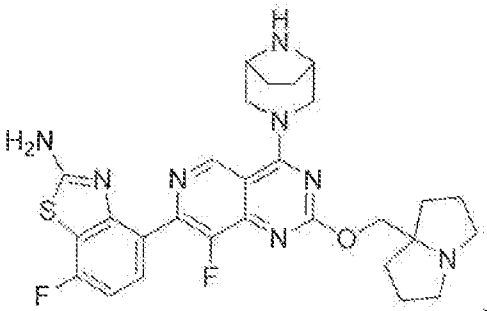


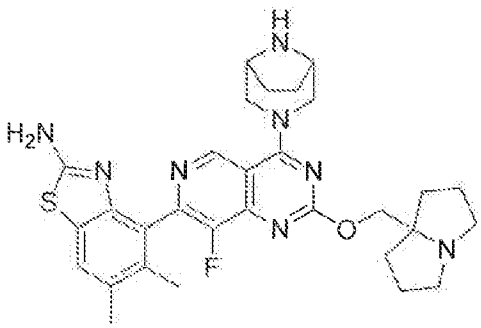


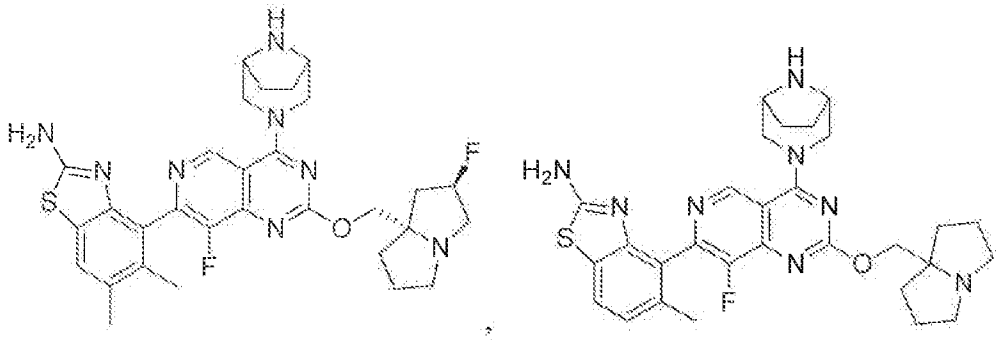






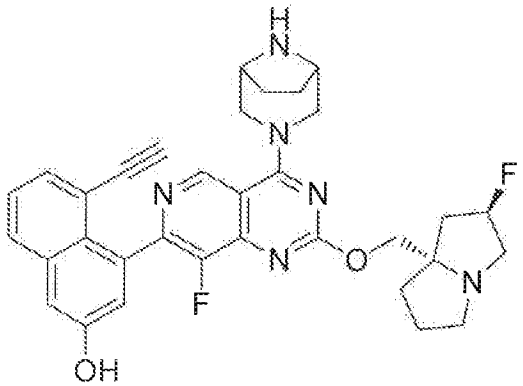






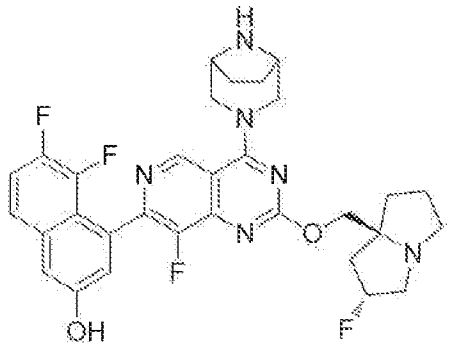
and pharmaceutically acceptable salts thereof.

46. The method of claim 1, wherein the KRas G12D inhibitor is:



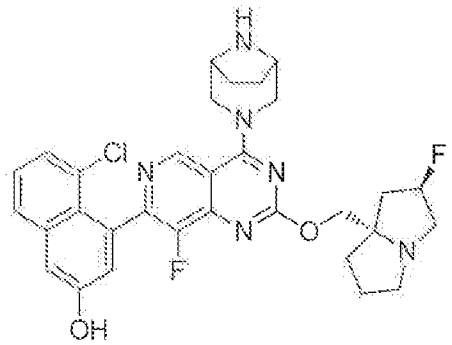
or a pharmaceutically acceptable salt thereof.

47. The method of claim 1, wherein the KRas G12D inhibitor is:



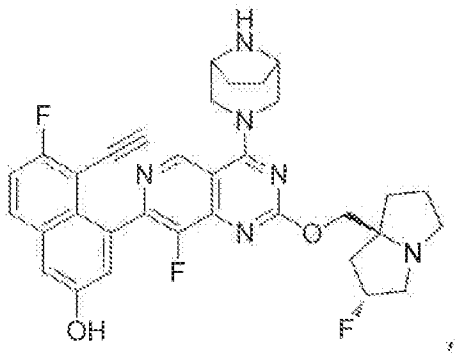
or a pharmaceutically acceptable salt thereof.

48. The method of claim 1, wherein the KRas G12D inhibitor is:



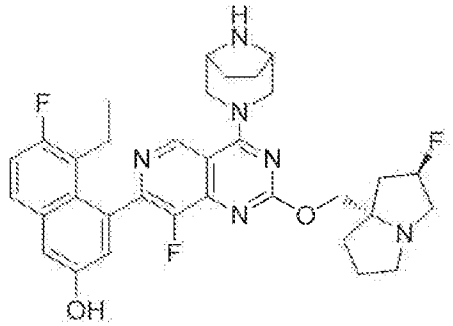
or a pharmaceutically acceptable salt thereof.

49. The method of claim 1, wherein he KRas G12D inhibitor is:



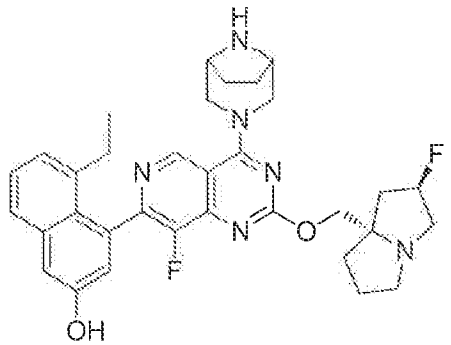
or a pharmaceutically acceptable salt thereof.

51. The method of claim 1, wherein the KRas G12D inhibitor is:



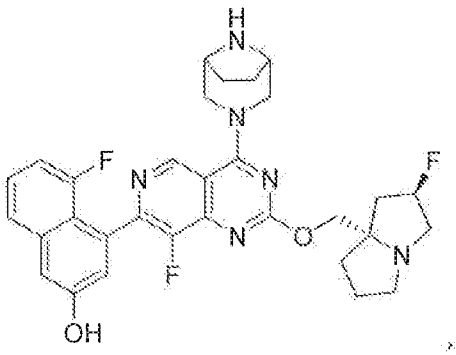
or a pharmaceutically acceptable salt thereof.

52. The method of claim 1, wherein the KRas G12D inhibitor is:



or a pharmaceutically acceptable salt thereof.

53. The method of claim 1, wherein he KRas G12D inhibitor is:



or a pharmaceutically acceptable salt thereof.

54. The method according to any one of claims 1-52, wherein the SOS1 inhibitor is BI-3406.

55. The method of claim 53, wherein the SOS1 inhibitor is BI-3406.

56. The method of claim 46, wherein the SOS1 inhibitor is BI-3406.

57. The method of claim 47, wherein the SOS1 inhibitor is BI-3406.

58. The method of claim 48, wherein the SOS1 inhibitor is BI-3406.

59. The method of claim 49, wherein the SOS1 inhibitor is BI-3406.

60. The method of claim 50, wherein the SOS1 inhibitor is BI-3406.

61. The method of claim 51, wherein the SOS1 inhibitor is BI-3406.

62. The method of claim 52, wherein the SOS1 inhibitor is BI-3406.

63. The method of according to any one of claims 1-61, wherein the SOS1 inhibitor and the KRAS G12D inhibitor are administered on the same day.

64. The method of according to any one of claims 1-61, wherein the SOS1 inhibitor and the KRAS G12D inhibitor are administered on different days.

65. The method of according to any one of claims 1-63, wherein the KRas G12D inhibitor is administered at a maximum tolerated dose.

66. The method according to any one of claims 1-63, wherein the SOS1 inhibitor and the KRAS G12D inhibitor are each administered at a maximum tolerated dose.

67. The method according to any one of claims 1-65, wherein the therapeutically effective amount of the combination of the SOS1 inhibitor and the KRAS G12D inhibitor results in an increased duration of overall survival, an increased duration of progression free survival, an

increase in tumor growth regression, an increase in tumor growth inhibition or an increased duration of stable diseasein the subjects relative to treatment with only the KRas G12D inhibitor.

68. A pharmaceutical composition, comprising a therapeutically effective amount of a combination of a SOS1 inhibitor and a KRas G12D inhibitor according to any one of claims 1-52, and a pharmaceutically acceptable excipient.

69. A method for inhibiting KRas G12D activity in a cancer cell, comprising contacting the cancer cell in which inhibition of KRas G12D activity is desired with an effective amount of a SOS1 inhibitor and a KRas G12D inhibitor compound according to any one of claims 1-52, pharmaceutical compositions or pharmaceutically acceptable salts thereof, wherein the SOS1 inhibitor synergistically increases the sensitivity of the cancer cells to the KRas G12D inhibitor.

70. The method according to any one of claims 1-66 and 68, wherein the SOS1 inhibitor synergistically increases the sensitivity of the cancer cells to the KRas G12D inhibitor.

71. A method for increasing the sensitivity of a cancer cell to a KRas G12D inhibitor compound of Formula (I), comprising administering to a subject undergoing KRas G12D treatment with a compound according to any one of claims 1-52, alone or combined with a pharmaceutically acceptable carrier, excipient or diluents, a therapeutically effective amount of a SOS1 inhibitor, wherein the SOS1 inhibitor synergistically increases the sensitivity of the cancer cell to the KRas G12D inhibitor.

72. The method according to claim 70, wherein the therapeutically effective amount of the KRas G12D inhibitor in the combination is between about 0.01 to 100 mg/kg per day.

73. The method of claim 71, wherein the therapeutically effective amount of the KRas G12D inhibitor in the combination is between about 0.1 to 50 mg/kg per day.

74. The method according to claim 70, wherein the therapeutically effective amount of the SOS1 inhibitor in the combination is between about 0.01 to 100 mg/kg per day.

75. The method of claim 73, wherein the therapeutically effective amount of the SOS1 inhibitor in the combination is between about 0.1 to 50 mg/kg per day.

76. The method according to any one of claims 1-66 and 68-74, wherein the cancer is selected from the group consisting of Cardiac: sarcoma (angiosarcoma, fibrosarcoma, rhabdomyosarcoma, liposarcoma), myxoma, rhabdomyoma, fibroma, lipoma and teratoma; Lung: bronchogenic carcinoma (squamous cell, undifferentiated small cell, undifferentiated large cell, adenocarcinoma), alveolar (bronchiolar) carcinoma, bronchial adenoma, sarcoma, lymphoma, chondromatous hamartoma, mesothelioma; Gastrointestinal: esophagus (squamous cell carcinoma, adenocarcinoma, leiomyosarcoma, lymphoma), stomach (carcinoma, lymphoma, leiomyosarcoma), pancreas (ductal adenocarcinoma, insulinoma, glucagonoma, gastrinoma, carcinoid tumors, vipoma), small bowel (adenocarcinoma, lymphoma, carcinoid tumors, Kaposi's sarcoma, leiomyoma, hemangioma, lipoma, neurofibroma, fibroma), large bowel (adenocarcinoma, tubular adenoma, villous adenoma, hamartoma, leiomyoma); Genitourinary tract: kidney (adenocarcinoma, Wilm's tumor (nephroblastoma), lymphoma, leukemia), bladder and urethra (squamous cell carcinoma, transitional cell carcinoma, adenocarcinoma), prostate (adenocarcinoma, sarcoma), testis (seminoma, teratoma, embryonal carcinoma, teratocarcinoma, choriocarcinoma, sarcoma, interstitial cell carcinoma, fibroma, fibroadenoma, adenomatoid tumors, lipoma); Liver: hepatoma (hepatocellular carcinoma), cholangiocarcinoma, hepatoblastoma, angiosarcoma, hepatocellular adenoma, hemangioma; Biliary tract: gall bladder carcinoma, ampullary carcinoma, cholangiocarcinoma; Bone: osteogenic sarcoma (osteosarcoma), fibrosarcoma, malignant fibrous histiocytoma, chondrosarcoma, Ewing's sarcoma, malignant lymphoma (reticulum cell sarcoma), multiple myeloma, malignant giant cell tumor chordoma, osteochronfroma (osteocartilaginous exostoses), benign chondroma, chondroblastoma, chondromyxofibroma, osteoid osteoma and giant cell tumors; Nervous system: skull (osteoma, hemangioma, granuloma, xanthoma, osteitis deformans), meninges (meningioma, meningiosarcoma, gliomatosis), brain (astrocytoma, medulloblastoma, glioma, ependymoma, germinoma (pinealoma), glioblastoma multiform, oligodendroglioma, schwannoma, retinoblastoma, congenital tumors), spinal cord neurofibroma, meningioma, glioma, sarcoma); Gynecological: uterus (endometrial `carcinoma (serous cystadenocarcinoma,

mucinous cystadenocarcinoma, unclassified carcinoma), granulosa-thecal cell tumors, Sertoli-Leydig cell tumors, dysgerminoma, malignant teratoma), vulva (squamous cell carcinoma, intraepithelial carcinoma, adenocarcinoma, fibrosarcoma, melanoma), vagina (clear cell carcinoma, squamous cell carcinoma, botryoid sarcoma (embryonal rhabdomyosarcoma), fallopian tubes (carcinoma); Hematologic: blood (myeloid leukemia (acute and chronic), acute lymphoblastic leukemia, chronic lymphocytic leukemia, myeloproliferative diseases, multiple myeloma, myelodysplastic syndrome), Hodgkin's disease, non-Hodgkin's lymphoma (malignant lymphoma); Skin: malignant melanoma, basal cell carcinoma, squamous cell carcinoma, Kaposi's sarcoma, moles dysplastic nevi, lipoma, angioma, dermatofibroma, keloids, psoriasis; and Adrenal glands: neuroblastoma.

77. The method of claim 75, wherein the cancer wherein the cancer is a KRas G12D-associated cancer.

78. The method of claim 75, wherein the cancer is non-small cell lung cancer.

79. A kit comprising the pharmaceutical composition of claim 67 for treating KRas G12D cancer in a subject.

80. A kit comprising: a) a pharmaceutical composition comprising a SOS1 inhibitor and b) a pharmaceutical composition comprising a KRas G12D inhibitor of claim 1, for treating a KRas G12D cancer in a subject.

81. The kit according to claim 78 or 79, further comprising an insert with instructions for administration of the pharmaceutical composition(s).

FIGURE 1

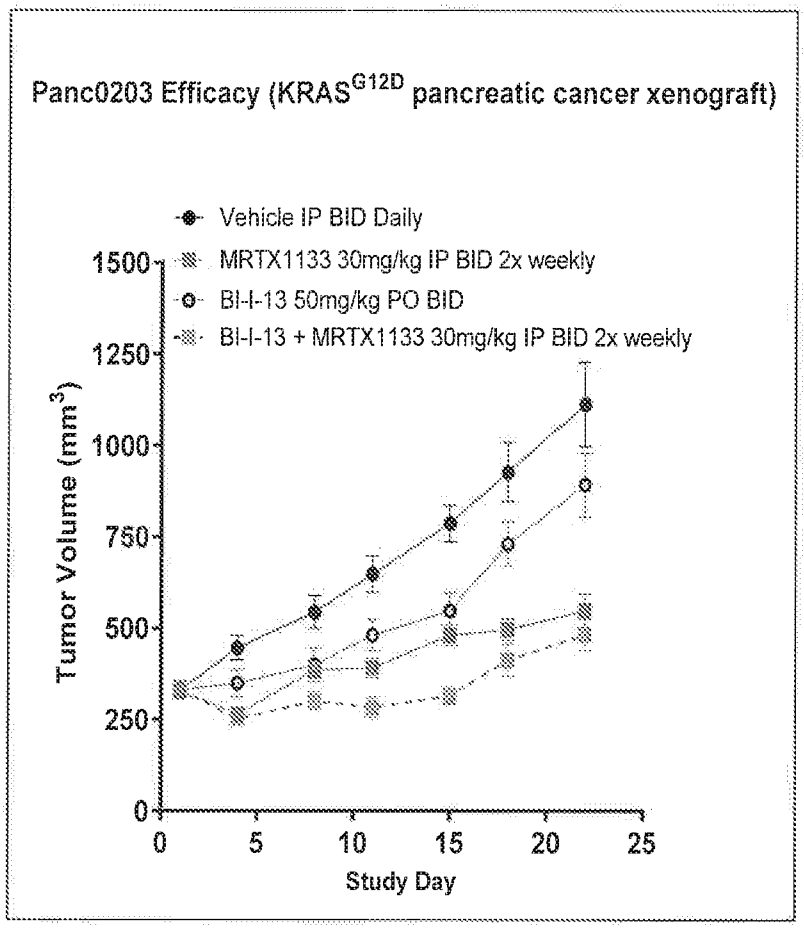
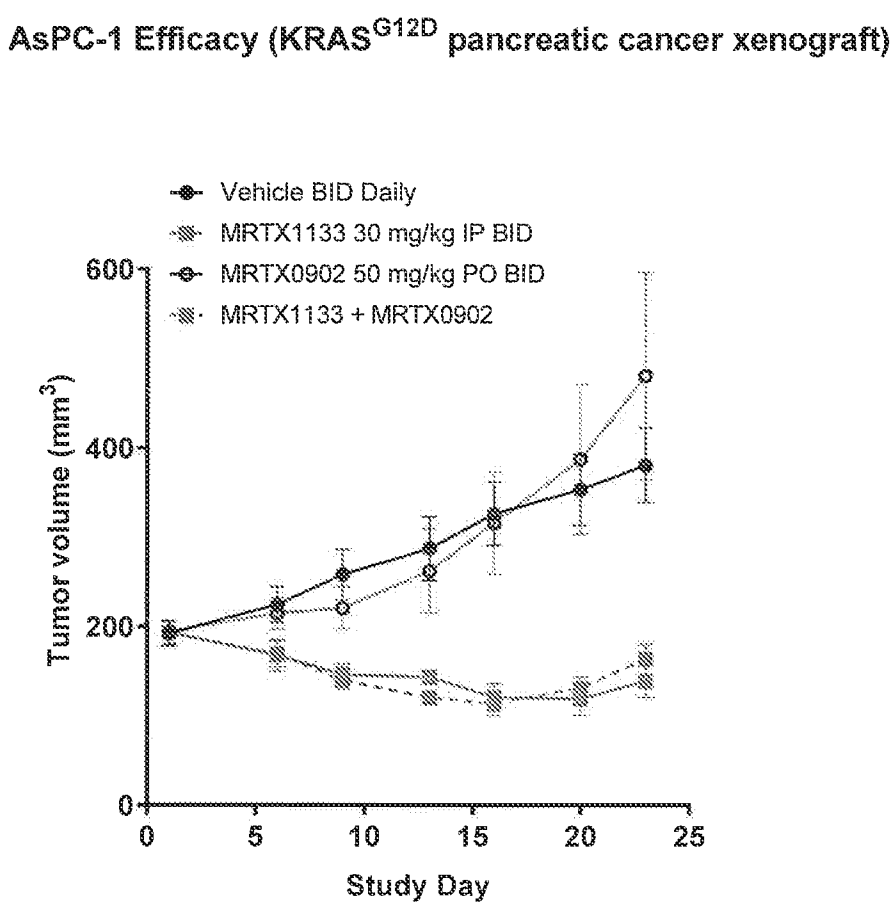

Panc0203 Efficacy (KRAS^{G12D} pancreatic cancer xenograft)
Vehicle IP BID Daily
MRTX1133 30mg/kg IP BID 2x weekly
BI-I-13 50mg/kg PO BID
BI-I-13 + MRTX1133 30mg/kg IP BID 2x weekly
Tumor Volume (mm^3)
1500
1250
1000
750
500
250
0
0
5
10
15
20
25
Study Day

FIGURE 2


AsPC-1 Efficacy (KRASG12D pancreatic cancer xenograft)
Vehicle BID Daily
MRTX1133 30 mg/kg IP BID
MRTX0902 50 mg/kg PO BID
MRTX1133 + MRTX0902
Tumor volume (mm3)
600
400
200
0
0
5
10
15
20
25
Study Day

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2022/045622

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - INV. - A61P 35/00 (2022.01)
ADD. - A61K 31/4375; C07D 471/06 (2022.01)

CPC - INV. - A61P 35/00 (2022.08)

ADD. - C07D 471/06; A61K 31/4375 (2022.08)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
See Search History document

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
See Search History document

Electronic database consulted during the international search (name of database and, where practicable, search terms used)
See Search History document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2021/041671 A1 (MIRATI THERAPEUTICS INC. et al) 04 March 2021 (04.03.2021) entire document	1, 2, 34, 35, 44, 54, 68, 69, 71, 73, 75, 77, 78, 80
A	US 2021/0139517 A1 (REVOLUTION MEDICINES INC.) 13 May 2021 (13.05.2021) entire document	1, 2, 34, 35, 44, 54, 68, 69, 71, 73, 75, 77, 78, 80
A	WO 2020/146613 A1 (MIRATI THERAPEUTICS INC. et al) 16 July 2020 (16.07.2020) entire document	1, 2, 34, 35, 44, 54, 68, 69, 71, 73, 75, 77, 78, 80

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"D" document cited by the applicant in the international application
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"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
27 December 2022	JAN 25 2023
Name and mailing address of the ISA/ Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, VA 22313-1450 Facsimile No. 571-273-8300	Authorized officer Taina Matos Telephone No. PCT Helpdesk: 571-272-4300

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2022/045622

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☒ Claims Nos.: 63-67, 70, 72, 74, 76, 79, 81
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

See extra sheet(s).

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1, 2, 34, 35, 44, 54, 68, 69, 71, 73, 75, 77, 78, 80

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

Continued from Box No. III Observations where unity of invention is lacking

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees need to be paid.

Group I+: claims 1-62, 68, 69, 71, 73, 75, 77, 78, and 80 are drawn to KRAS G12D inhibitors of formula (I), or a pharmaceutically acceptable salt thereof, methods of treating cancer in a subject in need thereof, pharmaceutical compositions thereof, methods for inhibiting KRas G12D activity in a cancer cell thereof, methods for increasing the sensitivity of a cancer cell to a KRas G12D inhibitor compound of Formula (I) thereof, and kits thereof.

The first invention of Group I+ is restricted to a KRAS G12D inhibitor of formula (I), or a pharmaceutically acceptable salt thereof, wherein R1 is hydrogen; Y is a bond; R2 is hydrogen; R3 is aryl, specifically unsubstituted phenyl; and R4 is hydrogen, methods of treating cancer in a subject in need thereof, pharmaceutical compositions thereof, methods for inhibiting KRas G12D activity in a cancer cell thereof, methods for increasing the sensitivity of a cancer cell to a KRas G12D inhibitor compound of Formula (I) thereof, and kits thereof. It is believed that claims 1, 2, 34, 35, 44, 54, 68, 69, 71, 73, 75, 77, 78, and 80 read on this first named invention and thus these claims will be searched without fee to the extent that they read on the above embodiment.

Applicant is invited to elect additional formula(e) for each additional compound to be searched in a specific combination by paying an additional fee for each set of election. Each additional elected formula(e) requires the selection of a single definition for each compound variable. An exemplary election would be a KRAS G12D inhibitor of formula (I), or a pharmaceutically acceptable salt thereof, wherein R1 is hydroxy; Y is a bond; R2 is hydrogen; R3 is aryl, specifically unsubstituted phenyl; and R4 is hydrogen, methods of treating cancer in a subject in need thereof, pharmaceutical compositions thereof, methods for inhibiting KRas G12D activity in a cancer cell thereof, methods for increasing the sensitivity of a cancer cell to a KRas G12D inhibitor compound of Formula (I) thereof, and kits thereof. Additional formula(e) will be searched upon the payment of additional fees. Applicants must specify the claims that read on any additional elected inventions. Applicants must further indicate, if applicable, the claims which read on the first named invention if different than what was indicated above for this group. Failure to clearly identify how any paid additional invention fees are to be applied to the "+" group(s) will result in only the first claimed invention to be searched/examined.

The inventions listed in Groups I+ do not relate to a single general inventive concept under PCT Rule 13.1, because under PCT Rule 13.2 they lack the same or corresponding special technical features for the following reasons:

The Groups I+ formulae do not share a significant structural element requiring the selection of alternatives for the compound variables, R1, Y, R2, R3, R4, and accordingly these groups lack unity a priori.

Additionally, even if Groups I+ were considered to share the technical features of a compound having the core structure of a KRAS G12D inhibitor of formula (I), or a pharmaceutically acceptable salt thereof; a method of treating cancer in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a combination of a SOS1 inhibitor and a KRAS G12D inhibitor; a pharmaceutical composition comprising a therapeutically effective amount of a combination of a SOS1 inhibitor and a KRas G12D inhibitor, and a pharmaceutically acceptable excipient; a method for inhibiting KRas G12D activity in a cancer cell, comprising contacting the cancer cell in which inhibition of KRas G12D activity is desired with an effective amount of a SOS1 inhibitor and a KRas G12D inhibitor, wherein the SOS1 inhibitor synergistically increases the sensitivity of the cancer cells to the KRas G12D inhibitor; a method for increasing the sensitivity of a cancer cell to a KRas G12D inhibitor comprising administering to a subject undergoing KRas G12D treatment with a compound, alone or combined with a pharmaceutically acceptable carrier, excipient or diluents, a therapeutically effective amount of a SOS1 inhibitor, wherein the SOS1 inhibitor synergistically increases the sensitivity of the cancer cell to the KRas G12D inhibitor; a kit comprising a pharmaceutical composition for treating KRas G12D cancer in a subject; and a kit comprising a pharmaceutical composition comprising a SOS1 inhibitor and a pharmaceutical composition comprising a KRas G12D inhibitor, for treating a KRas G12D cancer in a subject, these shared technical features do not represent a contribution over the prior art as disclosed by WO 2021/041671 A1 to Mirati Therapeutics Inc. et al. (hereinafter, "Mirati") and US 2021/0139517 A1 to Revolution Medicines, Inc. (hereinafter, "Revolution").

Mirati teaches a compound having the core structure of a KRAS G12D inhibitor of formula (I), or a pharmaceutically acceptable salt thereof (Para. [0007], compounds are provided that inhibit KRas G12D activity. In certain embodiments, the compounds are represented by Formula (I)); a method of treating cancer in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a KRAS G12D inhibitor (Claim 49, method for treating a KRas G12D-associated cancer comprising administering to a patient in need thereof a therapeutically effective amount of a compound according to claim 1 or a pharmaceutically acceptable salt thereof; Abstract, present invention relates to compounds that inhibit KRas G12D); a pharmaceutical composition comprising a therapeutically effective amount of a KRas G12D inhibitor, and a pharmaceutically acceptable excipient (Claim 46, pharmaceutical composition, comprising a therapeutically effective amount of a compound of claim 1 or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient, Abstract, present invention relates to compounds that inhibit KRas G12D); a method for inhibiting KRas G12D activity in a cancer cell, comprising contacting the cancer cell in which inhibition of KRas G12D activity is desired with an effective amount of a KRas G12D inhibitor (Claim 47, method for inhibiting KRas G12D activity in a cell, comprising contacting the cell in which inhibition of KRas G12D activity is desired with an effective amount of a compound of according to claim 1 or a pharmaceutically acceptable salt thereof, Abstract, present invention relates to compounds that inhibit KRas G12D); a method for increasing the sensitivity of a cancer cell to a KRas G12D inhibitor comprising administering to a subject undergoing KRas G12D treatment with a compound, alone or combined with a pharmaceutically acceptable carrier, excipient or diluents (Para. [0184], [t]he compounds, pharmaceutically acceptable salts thereof and pharmaceutical compositions comprising such compounds and salts also may be co-administered with other anti-neoplastic compounds, e.g., chemotherapy, or used in combination with other treatments, such as radiation or surgical intervention, either as an adjuvant prior to surgery or post-operatively; Abstract, present invention relates to compounds that inhibit KRas G12D).

Revolution teaches a method comprising administering to the subject a therapeutically effective amount of a SOS1 inhibitor (Para. [0230], a method is provided of treating or preventing cancer in a subject in need thereof, comprising administering to the subject an effective amount of a compound of any formula disclosed herein); a pharmaceutical composition comprising a therapeutically effective amount of a SOS1 inhibitor (Para. [0315], kit includes (a) a pharmaceutical composition including an agent (e.g., a compound of the invention) described herein, (b) one or more additional therapies (e.g., non-drug treatment or therapeutic agent), and (c) a package insert with instructions to perform any of the methods described herein; Para. [0012], present disclosure relates to compounds capable

of inhibiting the activity of SOS1); a kit comprising a pharmaceutical composition (Para. [0315], kit includes (a) a pharmaceutical composition including an agent (e.g., a compound of the invention) described herein, (b) one or more additional therapies (e.g., non-drug treatment or therapeutic agent), and (c) a package insert with instructions to perform any of the methods described herein); and a kit comprising a pharmaceutical composition comprising a SOS1 inhibitor (Para. [0315], kit includes (a) a pharmaceutical composition including an agent (e.g., a compound of the invention) described herein, (b) one or more additional therapies (e.g., non-drug treatment or therapeutic agent), and (c) a package insert with instructions to perform any of the methods described herein; Para. [0012], present disclosure relates to compounds capable of inhibiting the activity of SOS1).

The inventions listed in Groups I+ therefore lack unity under Rule 13 because they do not share a same or corresponding special technical feature.