COMBINATION THERAPIES

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 a pan ErbB family inhibitor and a KRas G12C inhibitor, pharmaceutical compositions comprising the inhibitors, kits comprising the compositions and methods of use therefor.

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 Santos et al., (1984) Science 223:661-664). 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 40% of these KRas driver mutations in lung adenocarcinoma, with a G12C transversion being the most common activating mutation (e.g., see Dogan et al., (2012) Clin Cancer Res. 18(22):6169-6177, published online 2012 Sep 26. doi: 10.1158/1078-0432.CCR-11-3265).

[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, no KRas inhibitor has demonstrated sufficient safety and/or efficacy to obtain regulatory approval (e.g., see McCormick (2015) Clin Cancer Res. 21 (8):1797-1801).

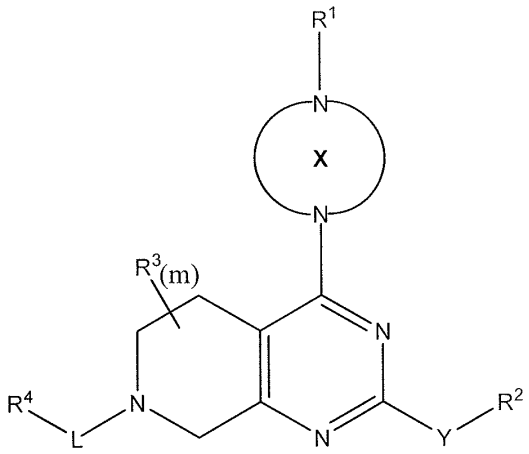
[0005] Compounds that inhibit KRas activity are still highly desirable and under investigation, including those that disrupt effectors such as guanine nucleotide exchange factors (e.g., see Sun et al., (2012) Agnew Chem Int Ed Engl. 51(25):6140-6143 doi: 10.1002/anie201201358) as well as those that target KRas G12C (e.g., see Ostrem et al., (2013) Nature 503:548-551). Clearly there remains a continued interest and effort to develop inhibitors of KRas, particularly inhibitors of activating KRas mutants, including KRas G12C.

[0006] While the KRas G12C inhibitors disclosed herein are potent inhibitors of KRas G12C enzymatic activity and exhibit single agent activity inhibiting the in vitro proliferation of cell lines harboring a KRas G12C mutation, the relative potency and or observed maximal effect of any given KRas G12C 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 G12C inhibitors in vitro and in vivo.

[0007] The combination therapy of the present invention, in one aspect, synergistically increases the potency of KRas G12C inhibitors resulting in improved efficacy of KRas G12C inhibitors disclosed herein. The combination therapy of the present invention, in another aspect, provides improved clinical benefit to patients compared to treatment with KRas G12C inhibitors disclosed herein as a single agent.

SUMMARY OF THE INVENTION

[0008] 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 pan ErbB family inhibitor and a KRAS G12C inhibitor of formula (I):



Formula (I)

[0009] or a pharmaceutically acceptable salt thereof, wherein:

[0010] X is a 4-12 membered saturated or partially saturated monocyclic, bridged or spirocyclic ring, wherein the saturated or partially saturated monocyclic ring is optionally substituted with one or more R^8;

[0011] Y is a bond, O, S or NR^5;

[0012] R^1 is $-C(O)C(R^A)$ ------ $C(R^B)_p$ or $-SO_2C(R^A)$ ------ $C(R^B)_p$;

[0013] R^2 is hydrogen, alkyl, hydroxyalkyl, dihydroxyalkyl, alkylaminylalkyl, dialkylaminylalkyl, -Z-NR^5R^{10}, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, or heteroarylalkyl, wherein each of the Z, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl may be optionally substituted with one or more R^9;

[0014] Z is C1 – C4 alkylene;

[0015] each R^3 is independently C1 – C3 alkyl, oxo, or haloalkyl;

[0016] L is a bond, -C(O)-, or C1 – C3 alkylene;

[0017] R^4 is hydrogen, cycloalkyl, heterocyclyl, aryl, aralkyl or heteroaryl, wherein each of the cycloalkyl, heterocyclyl, aryl, aralkyl and heteroaryl may be optionally substituted with one or more R^6 or R^7;

[0018] each R^5 is independently hydrogen or C1 – C3 alkyl;

[0019] R^6 is cycloalkyl, heterocyclyl, heterocyclylalkyl, aryl, or heteroaryl, wherein each of the cycloalkyl, heterocyclyl, aryl, or heteroaryl may be optionally substituted with one or more R^7;

[0020] each R^7 is independently halogen, hydroxyl, C1 – C6 alkyl, cycloalkyl, alkoxy, haloalkyl, amino, cyano, heteroalkyl, hydroxyalkyl or Q-haloalkyl, wherein Q is O or S;

[0021] R^8 is oxo, C1 – C3 alkyl, C2 – C4 alkynyl, heteroalkyl, cyano, $-C(O)OR^5$, $-C(O)N(R^5)_2$, $-N(R^5)_2$, wherein the C1 – C3 alkyl may be optionally substituted with cyano, halogen, $-OR^5$, $-N(R^5)_2$, or heteroaryl

[0022] each R^9 is independently hydrogen, oxo, acyl, hydroxyl, hydroxyalkyl, cyano, halogen, C1 – C6 alkyl, aralkyl, haloalkyl, heteroalkyl, cycloalkyl, heterocyclylalkyl, alkoxy, dialkylaminyl, dialkylamidoalkyl, or dialkylaminylalkyl, wherein the C1 – C6 alkyl may be optionally substituted with cycloalkyl;

[0023] each R^{10} is independently hydrogen, acyl, C1 – C3 alkyl, heteroalkyl or hydroxyalkyl;

[0024] R^{11} is haloalkyl;

[0025] R^A is absent, hydrogen, deuterium, cyano, halogen, C1 - C-3 alkyl, haloalkyl, heteroalkyl, $-C(O)N(R^5)_2$, or hydroxyalkyl;

[0026] each R^B is independently hydrogen, deuterium, cyano, C1 – C3 alkyl, hydroxyalkyl, heteroalkyl, C1 – C3 alkoxy, halogen, haloalkyl, $-ZNR^5R^{11}$, $-C(O)N(R^5)_2$, -NHC(O)C1 – C3 alkyl, $-CH_2NHC(O)$C1 – C3 alkyl, heteroaryl, heteroarylalkyl, dialkylaminylalkyl, or heterocyclylalkyl wherein the heterocyclyl portion is substituted with one or more substituents independently selected from halogen, hydroxyl, alkoxy and C1 – C3 alkyl, wherein the heteroaryl or the heteroaryl portion of the heteroarylalkyl is optionally substituted with one or more R^7;

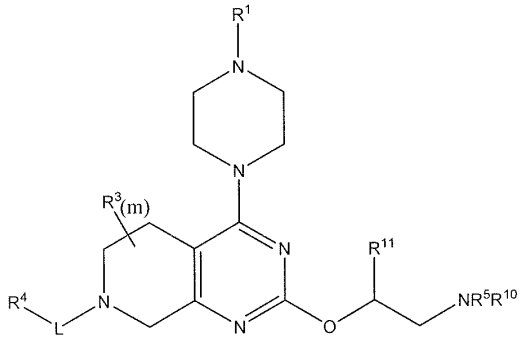
[0027] m is zero or an integer between 1 and 2;

[0028] p is one or two; and wherein,

[0029] when ------ is a triple bond then R^A is absent, R^B is present and p equals one,

[0030] or when ------ is a double bond then R^A is present, R^B is present and p equals two, or R^A, R^B and the carbon atoms to which they are attached form a 5-8 membered partially saturated cycloalkyl optionally substituted with one or more R^7.

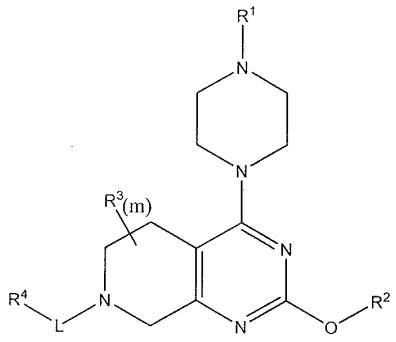
[0031] Also included for use in the methods provided herein are KRas G12C inhibitor compounds of Formula I having the Formula I-A:



Formula I-A

[0032] or a pharmaceutically acceptable salt thereof, wherein R^1, R^3, R^4, R^5, R^{10}, R^{11}, L and m are as defined for Formula I, and the piperazinyl ring is optionally substituted with R^8 wherein R^8 is as defined for Formula I.

[0033] Also included for use in the methods provided herein are KRas G12C inhibitor compounds of Formula I having the Formula I-B:



Formula I-B

[0034] or a pharmaceutically acceptable salt thereof, wherein R^1, R^3, R^4, L and m are as defined for Formula I, R^2 is heterocyclylalkyl optionally substituted with one or more R^9 where R^9 is as defined for Formula I, and the piperazinyl ring is optionally substituted with R^8, where R^8 is as defined for Formula I.

[0035] 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 pan ErbB family inhibitor and a KRas G12C inhibitor compound Formula I, Formula I-A, or Formula 1-B, or a pharmaceutically acceptable salts thereof and a pharmaceutically acceptable excipient.

[0036] 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 pan ErbB family inhibitor, or a pharmaceutically acceptable salt or a pharmaceutical composition thereof and a KRAS G12C inhibitor of Formula (I), Formula I-A or Formula I-B, or a pharmaceutically acceptable salt or a pharmaceutical composition thereof. In one embodiment, the cancer is a KRas G12C-associated cancer. In one embodiment, the KRas G12C-associated cancer is lung cancer.

[0037] In some aspects of the invention, KRas G12C inhibitor compounds and pan ErbB family inhibitors are the only active agents in the provided compositions and methods.

[0038] In one embodiment, the pan ErbB family inhibitor is an irreversible inhibitor. Examples of irreversible pan ErbB family inhibitors suitable for the provided compositions and methods

include, but are not limited to, Afatinib; Dacomitinib; Canertinib; Poziotinib, AV 412; PF 6274484 and HKI 357.

[0039] In one embodiment, the pan ErbB family inhibitor is a reversible inhibitor. Examples of reversible pan ErbB family inhibitors suitable for the provided compositions and methods include, but are not limited to erlotinib, gefitinib, sapitinib; varlitinib; TAK-285 (N-[2-[4-[3-chloro-4-[3-(trifluoromethyl)phenoxy]phenylamino]-5H-pyrrolo[3,2-d]pyrimidin-5-yl]ethyl]-3-hydroxy-3-methylbutyramide); AEE788 (6-[4-(4-Ethylpiperazin-1-ylmethyl)phenyl]-N-[1(R)-phenylethyl]-7H-pyrrolo[2,3-d]pyrimidin-4-amine);tarloxotinib 3-[N-[4-(3-Bromo-4-chlorophenylamino)pyrido[3,4-d]pyrimidin-6-yl]carbamoyl]-N,N-dimethyl-N-(1-methyl-4-nitro-1H-imidazol-5-ylmethyl)-2(E)-propen-1-aminium bromide); BMS 599626/AC-480 (N-[4-[1-(3-Fluorobenzyl)-1H-indazol-5-ylamino]-5-methylpyrrolo[2,1-f][1,2,4]triazin-6-yl]carbamic acid morpholin-3(S)-ylmethyl ester hydrochloride); and GW 583340 HCl (N-[3-chloro-4-(3-fluorobenzyloxy)phenyl]-6-[2-[2-(methylsulfonyl)ethylaminomethyl]thiazol-4-yl]quinazolin-4-amine).

[0040] In one embodiment, the pan ErbB family inhibitor is a combination of an EGFR inhibitor and a HER2 inhibitor, wherein the EGFR inhibitor and the HER2 inhibitor are a combination of two of: AG 1478 (N-(3-chlorophenyl)-6-methoxy-7-[11C]methoxyquinazolin-4-amine); AG 555 (2-cyano-3-(3,4-dihydroxyphenyl)-N-(3-phenylpropyl)-2(E)-propenamide); AG 556 ((E)-2-cyano-3-(3,4-dihydroxyphenyl)-N-(4-phenylbutyl)acrylamide; AG 825 (3-[3-(benzothiazol-2-ylsulfanylmethyl)-4-hydroxy-5-methoxyphenyl]-2-cyano-2-propenamide); CP 724714 (2-methoxy-N-[3-[4-[3-methyl-4-(6-methylpyridin-3-yloxy)phenylamino]quinazolin-6-yl]-2(E)-propenyl]acetamide; BIBU 1361 (N-(3-chloro-4-fluorophenyl)-6-[4-(diethylaminomethyl)piperidin-1-yl]pyrimido[5,4-d]pyrimidin-4-amine); BIBU 1382; JNJ 28871063 ((E)-4-amino-6-[4-(benzyloxy)-3-chlorophenylamino]pyrimidine-5-carbaldehyde O-[2-(4-morpholinyl)ethyl]oxime); PD 153035 (4-(3-bromophenylamino)-6,7-dimethoxyquinazoline); and PD 158780 (N^4-(3-bromophenyl)-N^6-methyl-pyrido[3,4-*d*]pyrimidine-4,6-diamine).

[0041] In one embodiment, the pan ErbB family inhibitor is an anti-EGFR antibody, a anti-HER2 antibody or combination of an anti-EGFR antibody and anti-HER2 antibody. Antibodies, including monoclonal antibodies, antibody conjugates and bispecific antibodies, targeting EGFR

and/or HER2 are well known and a number of antibodies are commercially available for research and human clinical use.

[0042] Examples of anti-EGFR antibodies suitable for the provided compositions and methods include necitumumab, panitumumab and cetuximab. Examples of anti-HER2 antibodies suitable for the provided compositions and methods include, pertuzumab, trastuzumab, and trastuzumab emtansine.

[0043] In yet another aspect, the invention provides for methods for increasing the sensitivity of a cancer cell to a KRas G12C inhibitor, comprising contacting the cancer cell with a therapeutically effective amount of a combination of a KRas G12C inhibitor compound of Formula (I), Formula I-A, or Formula I-B, or a pharmaceutically acceptable salt or a pharmaceutical composition thereof and a pan ErbB family inhibitor or a pharmaceutically acceptable salt or a pharmaceutical composition thereof, wherein the pan ErbB family inhibitor synergistically increases the sensitivity of the cancer cell to the KRas G12C inhibitor. In one embodiment, the contacting is in vitro. In one embodiment, the contacting is in vivo.

[0044] 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 G12C mutation (e.g., a KRas G12C-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 pan ErbB family inhibitor, or a pharmaceutically acceptable salt or a pharmaceutical composition thereof and a KRas G12C inhibitor compound of Formula I, Formula I-A, Formula 1-B, or a pharmaceutically acceptable salt or a pharmaceutical composition thereof, wherein the pan ErbB family inhibitor synergistically increases the sensitivity of the KRas G12C-associated cancer to the KRas G12C inhibitor.

[0045] Also provided herein are kits comprising a pan ErbB inhibitor, or a pharmaceutically acceptable salt or a pharmaceutical composition thereof and a KRas G12C inhibitor compound of Formula (I), Formula I-A or Formula I-B, or a pharmaceutically acceptable salt or a pharmaceutical composition thereof. Also provided is a kit comprising a pan ErbB family inhibitor, or a pharmaceutically acceptable salt or a pharmaceutical composition thereof and a KRas G12C inhibitor compound of Formula (I), Formula I-A or Formula I-B, or a

pharmaceutically acceptable salt or a pharmaceutical composition thereof, for use in treating a KRas G12C cancer.

[0046] In a related aspect, the invention provides a kit containing a dose of a pan ErbB inhibitor, or a pharmaceutically acceptable salt or a pharmaceutical composition thereof and a KRas G12C inhibitor compound of Formula (I), Formula I-A or Formula I-B, 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 the a pan ErbB family inhibitor, or a pharmaceutically acceptable salt or a pharmaceutical composition thereof and a KRas G12C inhibitor compound of Formula (I), Formula I-A or Formula I-B, 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 pan ErbB family inhibitor, or a pharmaceutically acceptable salt or a pharmaceutical composition thereof in combination with a KRas G12C inhibitor compound of Formula (I), Formula I-A or Formula I-B, or a pharmaceutically acceptable salt or a pharmaceutical composition thereof.

[0047] 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).

DETAILED DESCRIPTION OF THE INVENTION

[0048] The present invention relates to combination therapies for treating KRas G12C 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 pan ErbB family inhibitor, or a pharmaceutically acceptable salt or a pharmaceutical composition thereof and a KRAS G12C inhibitor of Formula (I), Formula I-A or Formula I-B, or a pharmaceutically acceptable salt or a pharmaceutical composition thereof, pharmaceutical compositions each separately comprising a therapeutically effective amount of the inhibitors, kits comprising the compositions and methods of use therefor.

[0049] Combinations of a pan ErbB family inhibitor with a KRas G12C inhibitor compounds of Formula (I), Formula I-A or Formula I-B, or a pharmaceutically acceptable salt thereof synergistically increase the potency of the KRas G12C inhibitor compounds of Formula (I), Formula I-A or Formula I-B, or a pharmaceutically acceptable salt thereof against cancer cells that express KRas G12C thereby increasing the efficacy and therapeutic index of KRas G12C inhibitor compounds of Formula (I), Formula I-A or Formula I-B , and pharmaceutically acceptable salts thereof.

DEFINITIONS

[0050] 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.

[0051] As used herein, "KRas G12C" refers to a mutant form of a mammalian KRas protein that contains an amino acid substitution of a cysteine 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.Gly12Cys.

[0052] As used herein, a "KRas G12C inhibitor" refers to compounds of the present invention that are represented by Formula (I), Formula I-A and Formula I-B, and pharmaceutically acceptable salts thereof as described herein. These compounds are capable of negatively modulating or inhibiting all or a portion of the enzymatic activity of KRas G12C. The KRas G12C inhibitors of the present invention interact with and irreversibly bind to KRas G12C by forming a covalent adduct with the sulfhydryl side chain of the cysteine residue at position 12 resulting in the inhibition of the enzymatic activity of KRas G12C. In one embodiment, the KRas G12C inhibitor is a compound selected from compound Nos 1-678 (as numbered in

WO2019099524), or pharmaceutically acceptable salts thereof (e.g., Example Nos 234, 359, 478 or 507, or a pharmaceutically acceptable salt thereof).

[0053] A "KRas G12C-associated disease or disorder" as used herein refers to diseases or disorders associated with or mediated by or having a KRas G12C mutation. A non-limiting example of a KRas G12C-associated disease or disorder is a KRas G12C-associated cancer.

[0054] As used herein, an "ErbB family" or "ErbB family member" refers to a member of a mammalian transmembrane protein tyrosine kinase family including: EGFR, ErbB2 (HER2), ErbB3 (HER3), and ErbB4 (HER4).

[0055] As used herein, a "pan ErbB family inhibitor" refers to an agent, e.g., a compound or antibody, that is capable of negatively modulating or inhibiting all or a portion of the activity of at least one member of the ErbB family. The modulation or inhibition of one or more ErbB family members may occur through modulating or inhibiting kinase enzymatic activity of one or more ErbB family member or by blocking homodimerization or heterodimerization of ErbB family members. In some embodiments of the methods herein, the term "pan ErbB inhibitor" refers to the use of a single pan ErbB inhibitor. In some embodiments of the methods herein, the term "pan ErbB inhibitor" refers to the use of two pan ErbB inhibitors.

[0056] 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 G12C 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 G12C 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 G12C 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 G12C 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 G12C gene-associated cancer. In some embodiments, the subject has a clinical record indicating that the subject has a tumor that has a KRas G12C mutation (and optionally the clinical record indicates that the subject should be treated with any of the compositions provided herein).

[0057] 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.

[0058] In some embodiments of any of the methods or uses described herein, an assay is used to determine whether the patient has KRas G12C mutation using a sample (e.g., a biological sample or a biopsy sample (e.g., a paraffin-embedded biopsy sample) from a patient (e.g., a patient suspected of having a KRas G12C-associated cancer, a patient having one or more symptoms of a KRas G12C-associated cancer, and/or a patient that has an increased risk of developing a KRas G12C-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.

[0059] 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).

[0060] The term "amino" refers to $-NH_2$;

[0061] The term "acyl" refers to $-C(O)CH_3$.

[0062] 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.

[0063] 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.

[0064] The term "haloalkyloxy" refers to -O-haloalkyl.

[0065] 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.

[0066] The term "alkoxy" refers to –OC1 – C6 alkyl.

[0067] 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.

[0068] 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.

[0069] As used herein, the term "hydroxyalkyl" refers to –alkyl-OH.

[0070] The term "dihydroxyalkyl" refers to an alkyl group as defined herein wherein two carbon atoms are each substituted with a hydroxyl group.

[0071] The term "alkylaminyl" refers to $-NR^x$-alkyl, wherein R^x is hydrogen. In one embodiment, R^x is hydrogen.

[0072] The term "dialkylaminyl" refers to $-N(R^y)_2$, wherein each R^y is C1 – C3 alkyl.

[0073] The term "alkylaminylalkyl" refers to –alkyl-NR^x-alkyl, wherein R^x is hydrogen. In one embodiment, R^x is hydrogen.

[0074] The term "dialkylaminylalkyl" refers to $-alkyl-N(R^y)_2$, wherein each R^y is C1 – C4 alkyl, wherein the alkyl of the $-alkyl-N(R^y)_2$ may be optionally substituted with hydroxy or hydroxyalkyl.

[0075] 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.

[0076] 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.

[0077] 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.

[0078] 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.

[0079] 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.

[0080] 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 C1-C6 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.

[0081] 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., ErbB family member or KRas G12C. Such amount may be administered, for example, as a single dosage or may be administered according to a regimen, whereby it is effective.

[0082] 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 ErbB family member(s) or KRas G12C. Such amount may be administered, for example, as a single dosage or may be administered according to a regimen, whereby it is effective.

[0083] 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 effect. Alternatively, in vivo, the therapeutically effective amount of the combination of a pan ErbB inhibitor, or a pharmaceutically acceptable salt or a pharmaceutical composition thereof and a KRas G12C inhibitor compound of Formula (I), Formula I-A, or Formula I-B, 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 G12C inhibitor. In one embodiment, the therapeutically effective amount of the combination of a pan ErbB inhibitor, or a pharmaceutically acceptable salt or a pharmaceutical composition thereof and a KRas G12C inhibitor compound of Formula (I), Formula I-A, or Formula I-B, 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 G12C inhibitor. In one embodiment, the therapeutically effective amount of the combination of a pan ErbB inhibitor, or a pharmaceutically acceptable salt or a pharmaceutical composition thereof and a KRas G12C inhibitor compound of Formula (I), Formula I-A, or Formula I-B, or a

pharmaceutically acceptable salt or a pharmaceutical composition thereof, results in increased tumor regression in subjects relative to treatment with only the KRas G12C inhibitor. In one embodiment, the therapeutically effective amount of the combination of a pan ErbB inhibitor, or a pharmaceutically acceptable salt or a pharmaceutical composition thereof and a KRas G12C inhibitor compound of Formula (I), Formula I-A, or Formula I-B, 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 G12C inhibitor. In one embodiment, the therapeutically effective amount of the combination of a pan ErbB inhibitor, or a pharmaceutically acceptable salt or a pharmaceutical composition thereof and a KRas G12C inhibitor compound of Formula (I), Formula I-A, or Formula I-B, or a pharmaceutically acceptable salt or pharmaceutical composition thereof, results in an improvement in the duration of stable disease in subjects compared to treatment with only the KRas G12C inhibitor.. Such amounts may be administered, for example, as a single dosage or may be administered according to a regimen, whereby it is effective.

[0084] 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.

[0085] 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.

[0086] As used herein, the term "about" when used to modify a numerically defined parameter (e.g., the dose of a KRAS inhibitor or a pan ErbB family 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.

INHIBITOR COMPOUNDS

[0087] In one aspect of the invention, provided herein are methods of treating cancer, for example a KRas G12C-associated cancer, in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a combination of a pan ErbB family inhibitor, or a pharmaceutically acceptable salt or a pharmaceutical composition thereof and a KRAS G12C inhibitor of Formula (I), Formula I-A or Formula I-B, or a pharmaceutically acceptable salt or a pharmaceutical composition thereof.

1. ErbB Family

[0088] Epidermal Growth Factor Receptor (EGFR) is a transmembrane protein tyrosine kinase of the ErbB receptor family. Upon binding epidermal growth factor (EGF), the EGFR receptor can homo-dimerize with another EGFR molecule or hetero-dimerize with another family member such as ErbB2 (HER2), ErbB3 (HER3), or ErbB4 (HER4). Homo- and/or hetero-dimerization of ErbB receptors results in the phosphorylation of key tyrosine residues in the intracellular domain and leads to the stimulation of numerous intracellular signal transduction pathways involved in cell proliferation and survival.

[0089] Overexpression of the EGFR gene has been identified in a variety of cancers including bladder, brain, head and neck, pancreas, lung, breast, ovary, colon, prostate, and kidney. In addition to overexpression, EGFR activating mutations have been detected in a subset of non-small cell lung cancers (NSCLCs) tumors. These mutations tend to occur within EGFR exons 18–21, which encodes a portion of the EGFR kinase domain. Approximately 90% of these mutations are exon 19 deletions or exon 21 L858R point mutations (Ladanyi and Pao (2008) Mod Path. May;21 Suppl 2:S16-22. doi: 10.1038/modpathol.3801018). These mutations increase the kinase activity of EGFR, leading to hyperactivation of downstream pro-survival signaling pathways.

[0090] The frequency of overexpression and/or activating mutations of EGFR has made it a desired target for anticancer therapies and a number of EGFR inhibitors have been developed and are clinically available.

[0091] First generation erlotinib and gefitinib inhibit EGFR activity by competitively binding to the ATP binding site of the EGFR kinase domain; however additional mutations in the EGFR gene, e.g., the T790M mutation, produces mutant EGFR proteins to which drugs like erlotinib and gefitinib bind less well. Those mutations are associated with resistance to the drugs and to relapse in cancer patients bearing such mutation leading to the development of second generation EGFR inhibitors targeting the T790M mutant.

[0092] Furthermore, inhibition of the pathway-related enzyme MEK results in increased expression of ErbB family members, especially EGFR, that can lead to adaptive and acquired resistance to ErbB family inhibitors (Sun et al., (2014) Cell Reports 7:86-93).

2. Pan ErbB family Inhibitors

[0093] The pan ErbB family inhibitors used in the methods of the present invention may be reversible or irreversible ErbB family inhibitors. In one embodiment, the pan ErbB family inhibitor inhibits the activity of more than one ErbB family member.

[0094] In one embodiment, the pan ErbB family inhibitor is an irreversible inhibitor. Irreversible pan ErbB family inhibitors inhibit the activity of EGFR and HER2 by forming a covalent bond with the sulfhydryl group of cysteine 797 and cysteine 773, respectively, that blocks the binding of ATP to the intracellular catalytic domain. As such, these inhibitors are active against, for example, cell lines harboring EGFR exon 19 deletions/insertions, and L858R and T790M resistant mutations.

[0095] Exemplary irreversible pan ErbB family inhibitors for use in the methods include afatinib ((E)-N-(4-((3-chloro-4-fluorophenyl)amino)-7-((tetrahydrofuran-3-yl)oxy)quinazolin-6-yl)-4-(dimethylamino)but-2-enamide); dacomitinib ((2*E*)-*N*-{4-[(3-Chloro-4-fluorophenyl)amino]-7-methoxy-6-quinazolinyl}-4-(1-piperidinyl)-2-butenamide); canertinib (N-(4-((3-chloro-4-fluorophenyl)amino)-7-(3-morpholinopropoxy)quinazolin-6-yl)acrylamide); poziotinib (1-(4-((4-((3,4-dichloro-2-fluorophenyl)amino)-7-methoxyquinazolin-6-yl)oxy)piperidin-1-yl)prop-2-en-1-one); AV 412 (*N*-[4-[(3-Chloro-4-fluorophenyl)amino]-7-[3-methyl-3-(4-methyl-1-piperazinyl)-1-butyn-1-yl]-6-quinazolinyl]-2-propenamide); PF 6274484 (*N*-[4-[(3-Chloro-4-fluorophenyl)amino]-7-methoxy-6-quinazolinyl]-2-propenamide) and HKI 357 ((2*E*)-*N*-[[4-[[(3-Chloro-4-[(3-fluorophenyl)methoxy]phenyl]amino]-3-cyano-7-ethoxy-6-quinolinyl]-4-

(dimethylamino)-2-butenamide), and pharmaceutically acceptable salts or pharmaceutical compositions thereof. In one embodiment, the irreversible pan ErbB family inhibitor is afatinib. In one embodiment, the irreversible pan ErbB family inhibitor is dacomitinib.

[0096] In one embodiment, the pan ErbB family inhibitor is a reversible inhibitor. Exemplary reversible pan EGFR family inhibitors include erlotinib ([6,7-Bis-(2-methoxy-ethoxy)-quinazolin-4-yl]-(3-ethynyl-phenyl)-amine)), gefitinib (4-(3'-chloro-4'-fluoroanilino)-7-methoxy-6-(3-morpholinopropoxy)quinazoline, sapitinib (2-(4-((4-((3-chloro-2-fluorophenyl)amino)-7-methoxyquinazolin-6-yl)oxy)piperidin-1-yl)-N-methylacetamide); varlitinib ((R)-N4-(3-chloro-4-(thiazol-2-ylmethoxy)phenyl)-N6-(4-methyl-4,5-dihydrooxazol-2-yl)quinazoline-4,6-diamine); TAK-285 (N-(2-(4-((3-chloro-4-(3-(trifluoromethyl)phenoxy)phenyl)amino)-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethyl)-3-hydroxy-3-methylbutanamide); AEE788 ((S)-6-(4-((4-ethylpiperazin-1-yl)methyl)phenyl)-N-(1-phenylethyl)-7H-pyrrolo[2,3-d]pyrimidin-4-amine); tarloxotinib 3-[N-[4-(3-Bromo-4-chlorophenylamino)pyrido[3,4-d]pyrimidin-6-yl]carbamoyl]-N,N-dimethyl-N-(1-methyl-4-nitro-1H-imidazol-5-ylmethyl)-2(E)-propen-1-aminium bromide); BMS 599626 ((3*S*)-3-Morpholinylmethyl-[4-[[1-[(3-fluorophenyl)methyl]-1*H*-indazol-5-yl]amino]-5-methylpyrrolo[2,1-*f*][1,2,4]triazin-6-yl]-carbamate dihydrochloride); and GW 583340 HCl (*N*-[3-Chloro-4-[(3-fluorophenyl)methoxy]phenyl]-6-[2-[[[2-(methylsulfonyl)ethyl]amino]methyl]-4-thiazolyl]-4-quinazolinamine dihydrochloride), and pharmaceutically acceptable salts or pharmaceutical compositions thereof. In one embodiment, the reversible pan ErbB family inhibitor is sapitinib. In one embodiment, the reversible pan ErbB family inhibitor is tarloxotinib.

[0097] In one embodiment, the pan ErbB family inhibitor is a combination of an EGFR inhibitor and a HER2 inhibitor, wherein the EGFR inhibitor and the HER2 inhibitor are a combination of two of: AG 1478 HCl (*N*-(3-Chlorophenyl)-6,7-dimethoxy-4-quinazolinanine hydrochloride); AG 494 (*E*)-2-Cyano-3-(3,4-dihydroxyphenyl)-*N*-phenyl-2-propenamide; AG 555 (*E*)-2-Cyano-3-(3,4-dihydroxyphenyl)-*N*-(3-phenylpropyl)-2-propenamide; AG 556 (*E*)-2-Cyano-3-(3,4-dihydroxyphenyl)-*N*-(4-phenylbutyl)-2-propenamide; AG 825 (*E*)-3-[3-[2-Benzothiazolythio)methyl]-4-hydroxy-5-methoxyphenyl]-2-cyano-2-propenamide; CP 724714 (2-Methoxy-*N*-[(2*E*)-3-[4-[[3-methyl-4-[(6-methyl-3-pyridinyl)oxy]phenyl]amino]-6-quinazolinyl]-2-propen-1-yl]acetamide; BIBU 1361 diHCl (*N*-(3-Chloro-4-fluorophenyl)-6-[4-

[(diethylamino)methyl]-1-piperidinyl]-pyrimido[5,4-*d*]pyrimidin-4-amine dihydrochloride); BIBU 1382 (N^8-(3-Chloro-4-fluorophenyl)-N^2-(1-methyl-4-piperidinyl)-pyrimido[5,4-*d*]pyrimidine-2,8-diamine dihydrochloride); JNJ 28871063 HCl (5*E*-4-Amino-6-(4-benzyloxy-3-chlorophenylamino)pyrimidine-5-carboxaldehyde *N*-(2-morpholin-4-ylethyl) oxime hydrochloride); PD 153035 (4-[(3-Bromophenyl)amino]-6,7-dimethoxyquinazoline hydrochloride); PD 158780 (N^4-(3-Bromophenyl)-N^6-methyl-pyrido[3,4-*d*]pyrimidine-4,6-diamine), and pharmaceutically acceptable salts or a pharmaceutical compositions thereof.

[0098] Methods for manufacturing reversible and irreversible pan ErbB family inhibitors that target wild type and mutant ErbB family members are well known to those skilled in the art and pan ErbB family inhibitors may be obtained from a wide-variety of commercial suppliers, in forms suitable for both research or human use. In addition, suitable reversible and irreversible pan ErbB family inhibitors for use in the compositions and methods disclosed herein, and methods for preparing such inhibitors are disclosed in US Patent Application Publication Nos: US20180050993; US20180016268; US20180008607; US20170362204; US 20170362203; US20170355683; US20170342055; US20170267671; US20170183330; US20170174697; 20170008856; US20160375148; US20160332994; US20160257682; US 20160244469; US 20160137610; US20160102076; US20160016948; US20150284340; US20150274678; US20150250778; US 20150246047; US20150126508; US20150025055; US 20140221403; US 20140178412; US20140161722; US20140155606; US20140038981; US20140038940; US20140005391; US 20130296348; US20130209461; US20130137709; US 20120316135L US 20120094999; US 20110295004; US 20110033453; US 20100196365; US20100143295; US 20100120678; US 20100034689; US 20090209758; US 20090111772; US20090029968; US20080194578; US 20080139590; US 2000125448; US 20080051395; US 20070232607; US 20060235046 and US20040023957.

[0099] In one embodiment, the pan ErbB family inhibitor is an anti-EGFR antibody, an anti-HER2 antibody or a combination of an anti-EGFR antibody and anti-HER2 antibody, or pharmaceutical compositions thereof. Antibodies, including monoclonal antibodies, antibody drug conjugates and bispecific antibodies, targeting EGFR and/or HER-2 are well known and a number of antibodies are commercially available for research and human clinical use.

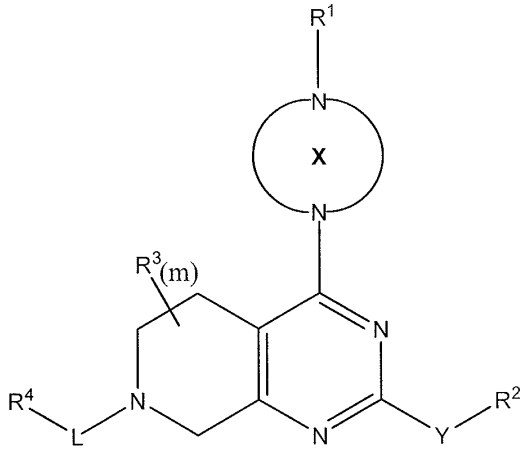
[0100] Exemplary anti-EGFR monoclonal antibodies approved for human clinical use include, but are not limited to, necitumumab (Eli Lilly), panitumumab (Amgen) and cetuximab (ImClone). Other anti-EGFR antibodies suitable for use in the methods include EP384, H11, 11.6, 225 and 199.12 (Thermo Fisher), GT133 (GeneTex) and those disclosed in United States Patent Application Publication Nos: US 20080274114; US 20100166755; US 20100117110; US 20120034211; US 20120308576; US 20130273033; US 20130344093; US 20140286969; US 20150337042; US 20170218073; US 20170267765, US 20180036405, US 20180066066, US 20180094062, US 20180155433, US 20180306049, US 20180362443, US 20190040143, US 20190151328, US 20190194347, US 20190194350, US 20190209704, US 20190216924, and US 20190263930.

[0101] In one embodiment, the anti-EGFR monoclonal antibody is cetuximab.

[0102] Exemplary anti-HER-2 monoclonal antibodies approved for human clinical use include, but are not limited to, pertuzumab (Roche), trastuzumab (Roche) and trastuzumab emtansine (Roche). Other anti-Her2 antibodies, antibody drug conjugates and bispecific antibodies suitable for use in the methods include those disclosed in United States Patent Application Publication Nos: US 20030228663; US 20060018899; US 20090187007; US 20090285837; US 20110159014; US 20110177095; US 20110313137; US 20120309942; US 20150166664; US 20150352225; US 20160051695; US 20160096893, US 20180022816, US 20180022820, US 20180057608, US 20180118837, US 20180258173, US 20190177428, and US 20190248918.

2. KRas G12C Inhibitors

[0103] In one embodiment, the KRas G12C inhibitors used in the methods are compounds of Formula (I):



Formula (I)

[0104] or a pharmaceutically acceptable salt thereof, wherein:

[0105] X is a 4-12 membered saturated or partially saturated monocyclic, bridged or spirocyclic ring, wherein the saturated or partially saturated monocyclic ring is optionally substituted with one or more R^8;

[0106] Y is a bond, O, S or NR^5;

[0107] R^1 is $-C(O)C(R^A)$ ------ $C(R^B)_p$ or $-SO_2C(R^A)$ ------ $C(R^B)_p$;

[0108] R^2 is hydrogen, alkyl, hydroxyalkyl, dihydroxyalkyl, alkylaminylalkyl, dialkylaminylalkyl, -Z-NR^5R^{10}, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, or heteroarylalkyl, wherein each of the Z, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl may be optionally substituted with one or more R^9;

[0109] Z is C1 – C4 alkylene;

[0110] each R^3 is independently C1 – C3 alkyl, oxo, or haloalkyl;

[0111] L is a bond, -C(O)-, or C1 – C3 alkylene;

[0112] R^4 is hydrogen, cycloalkyl, heterocyclyl, aryl, aralkyl or heteroaryl, wherein each of the cycloalkyl, heterocyclyl, aryl, aralkyl and heteroaryl may be optionally substituted with one or more R^6 or R^7;

[0113] each R^5 is independently hydrogen or C1 – C3 alkyl;

[0114] R^6 is cycloalkyl, heterocyclyl, heterocyclylalkyl, aryl, or heteroaryl, wherein each of the cycloalkyl, heterocyclyl, aryl, or heteroaryl may be optionally substituted with one or more R^7;

[0115] each R^7 is independently halogen, hydroxyl, C1 – C6 alkyl, cycloalkyl, alkoxy, haloalkyl, amino, cyano, heteroalkyl, hydroxyalkyl or Q-haloalkyl, wherein Q is O or S;

[0116] R^8 is oxo, C1 – C3 alkyl, C2 – C4 alkynyl, heteroalkyl, cyano, $-C(O)OR^5$, $-C(O)N(R^5)_2$, $-N(R^5)_2$, wherein the C1 – C3 alkyl may be optionally substituted with cyano, halogen, $-OR^5$, $-N(R^5)_2$, or heteroaryl;

[0117] each R^9 is independently hydrogen, oxo, acyl, hydroxyl, hydroxyalkyl, cyano, halogen, C1 – C6 alkyl, aralkyl, haloalkyl, heteroalkyl, cycloalkyl, heterocyclylalkyl, alkoxy, dialkylaminyl, dialkylamidoalkyl, or dialkylaminylalkyl, wherein the C1 – C6 alkyl may be optionally substituted with cycloalkyl;

[0118] each R^{10} is independently hydrogen, acyl, C1 – C3 alkyl, heteroalkyl or hydroxyalkyl;

[0119] R^{11} is haloalkyl;

[0120] R^A is absent, hydrogen, deuterium, cyano, halogen, C1 - C-3 alkyl, haloalkyl, heteroalkyl, $-C(O)N(R^5)_2$, or hydroxyalkyl;

[0121] each R^B is independently hydrogen, deuterium, cyano, C1 – C3 alkyl, hydroxyalkyl, heteroalkyl, C1 – C3 alkoxy, halogen, haloalkyl, $-ZNR^5R^{11}$, $-C(O)N(R^5)_2$, -NHC(O)C1 – C3 alkyl, $-CH_2NHC(O)$C1 – C3 alkyl, heteroaryl, heteroarylalkyl, dialkylaminylalkyl, or heterocyclylalkyl wherein the heterocyclyl portion is substituted with one or more substituents independently selected from halogen, hydroxyl, alkoxy and C1 – C3 alkyl, wherein the heteroaryl or the heteroaryl portion of the heteroarylalkyl is optionally substituted with one or more R^7;

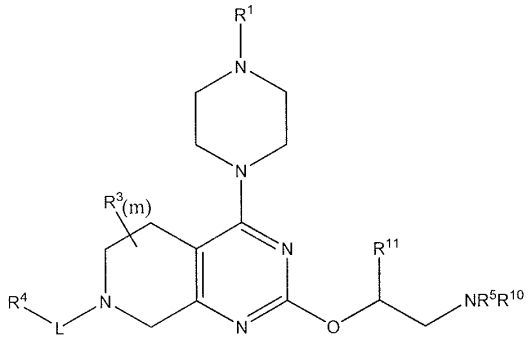
[0122] m is zero or an integer between 1 and 2;

[0123] p is one or two; and wherein,

[0124] when ------ is a triple bond then R^A is absent, R^B is present and p equals one;

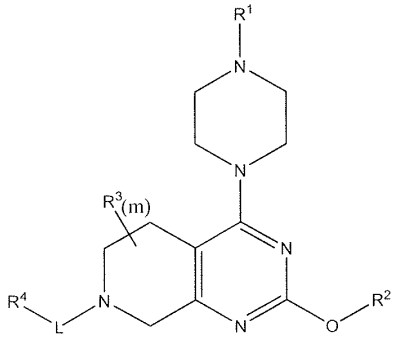
[0125] or when ------ is a double bond then R^A is present, R^B is present and p equals two, or R^A, R^B and the carbon atoms to which they are attached form a 5-8 membered partially saturated cycloalkyl optionally substituted with one or more R^7.

[0126] In one embodiment, KRas G12C inhibitors used in the methods herein include compounds having the Formula I-A:



[0127] or a pharmaceutically acceptable salt thereof, wherein R^1, R^3, R^4, R^5, R^{10}, L and m are as defined for Formula I, R^{11} is hydrogen, methyl or hydroxyalkyl, and the piperidinyl ring is optionally substituted with R^8 wherein R^8 is as defined for Formula I.

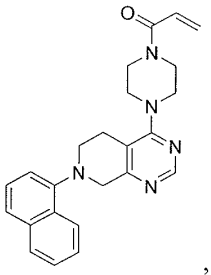
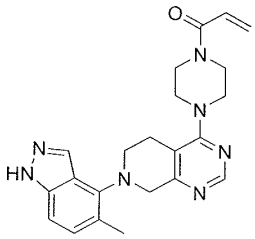
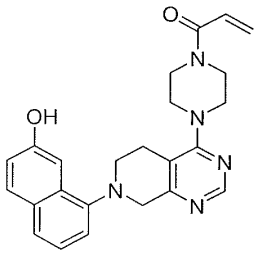
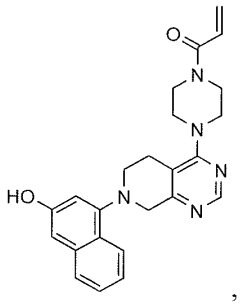
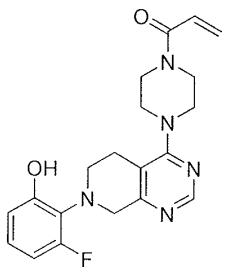
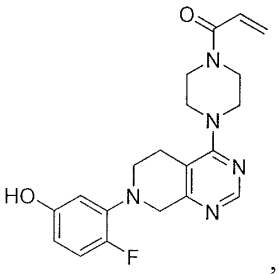
[0128] In one embodiment, KRas G12C inhibitors used in the methods herein include compounds having the Formula I-B:

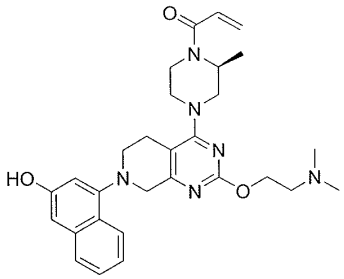
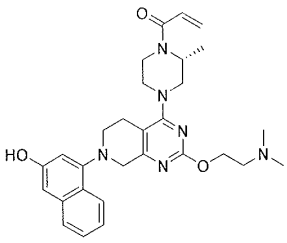
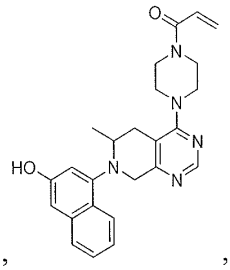
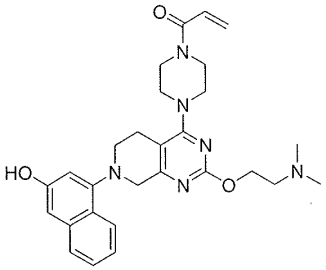
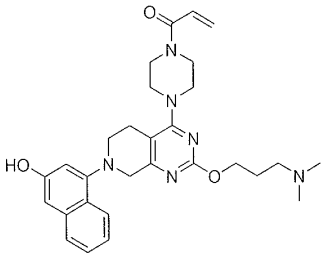
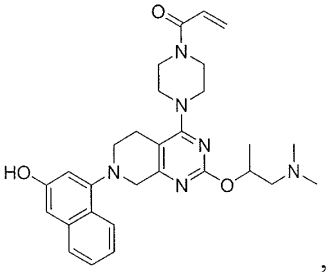
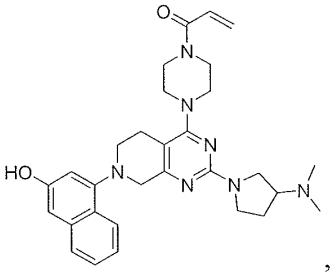
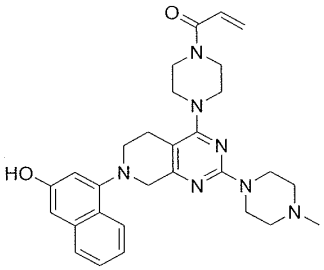
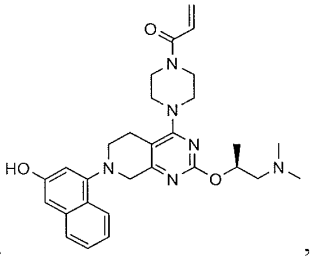
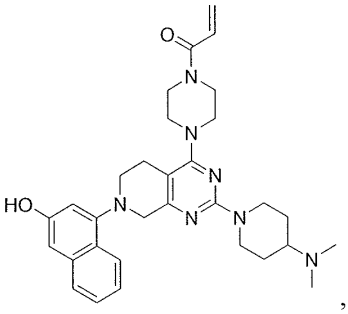
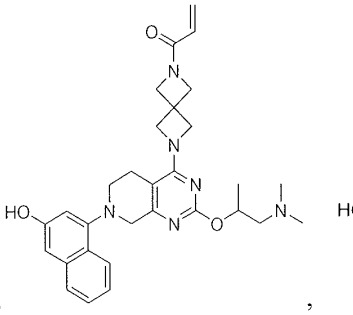
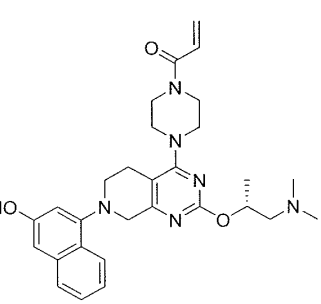


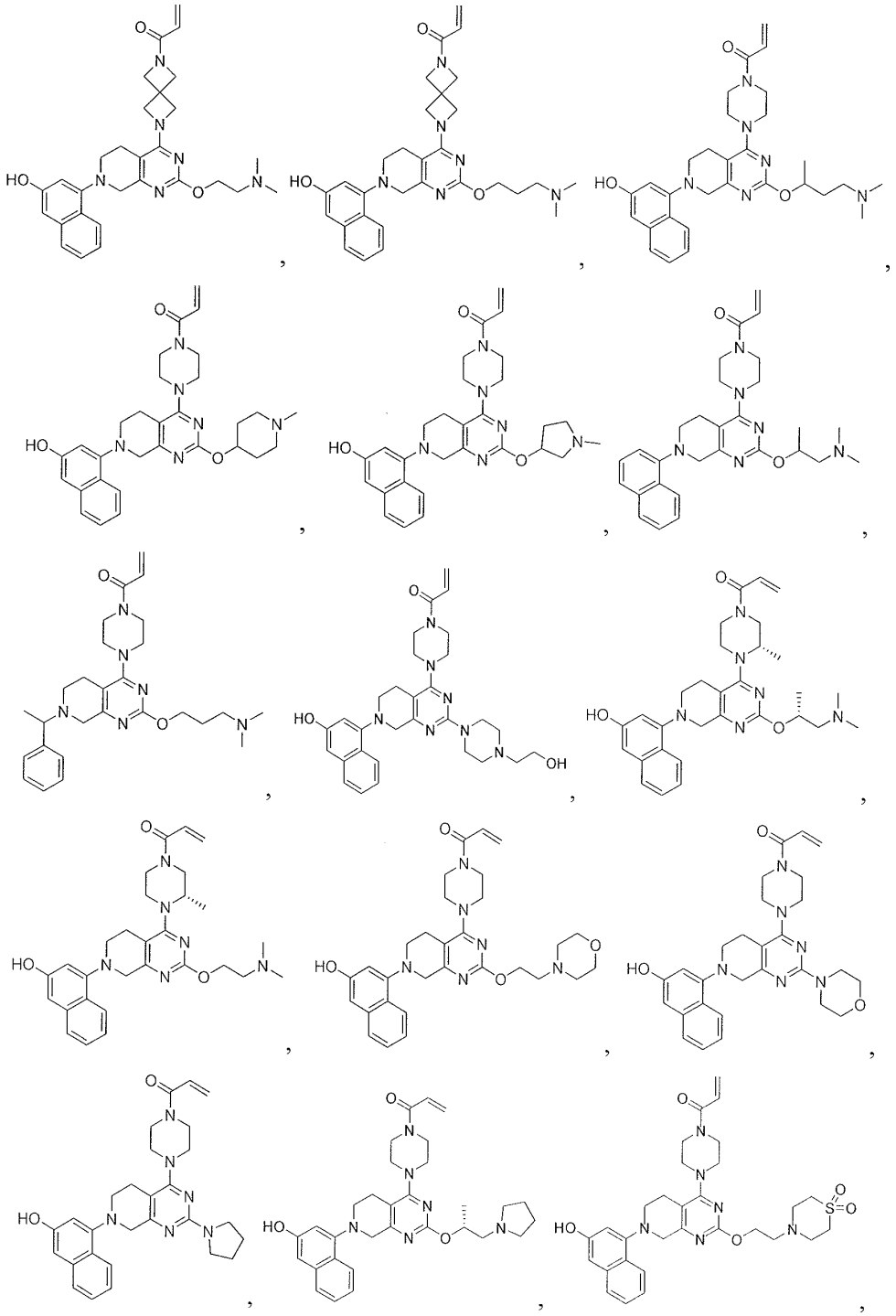
Formula I-B

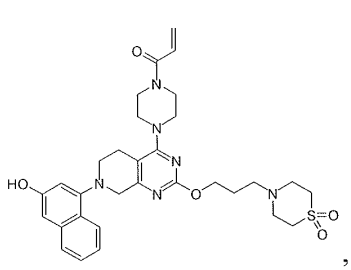
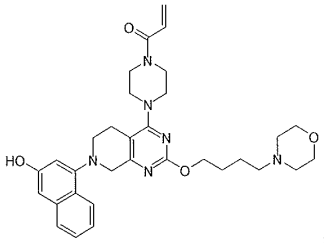
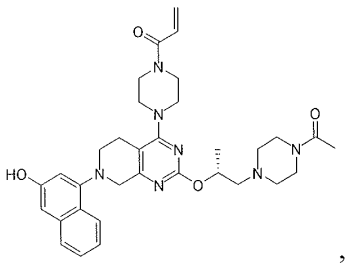
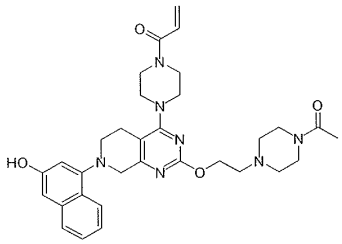
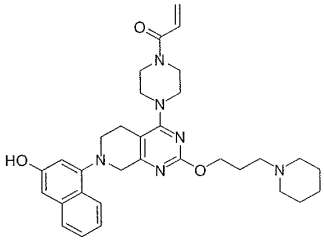
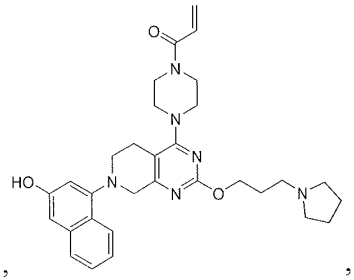
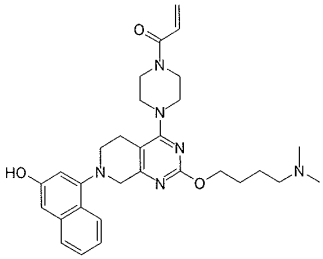
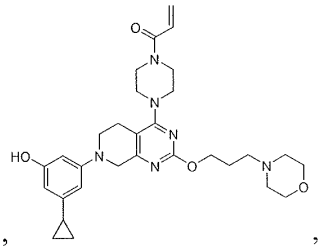
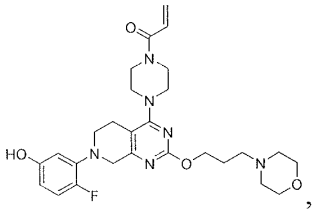
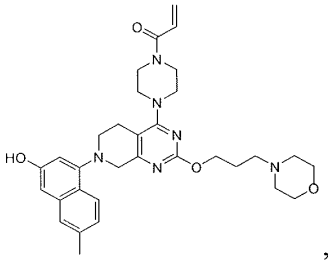
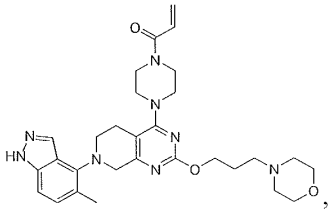
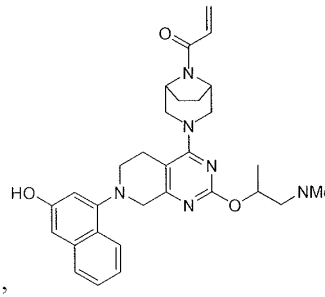
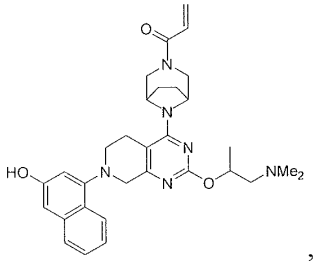
[0129] or a pharmaceutically acceptable salt thereof, wherein R^1, R^3, R^4, R^9, R^{11}, L and m are as defined for Formula I.

[0130] Nonlimiting examples of KRas G12C inhibitor compounds of Formula (I), Formula I-A and Formula I-B useful in the methods disclosed herein are selected from the group consisting of Example Nos 1-678 including the following structures:


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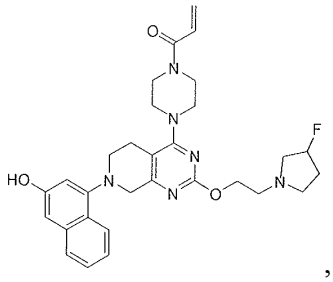
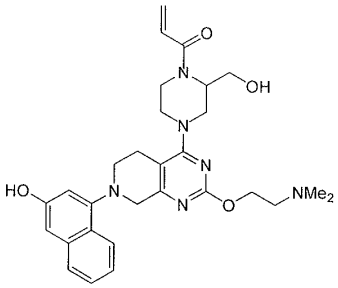
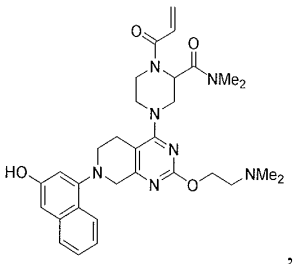
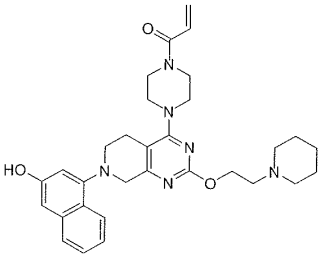
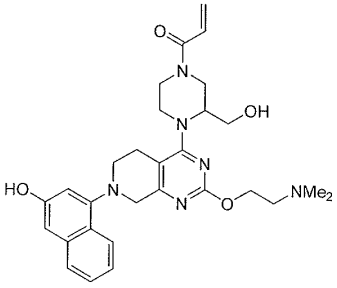
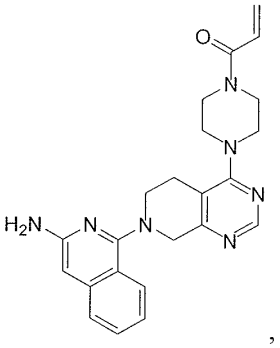
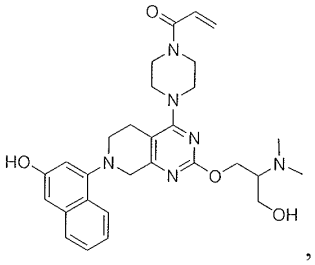
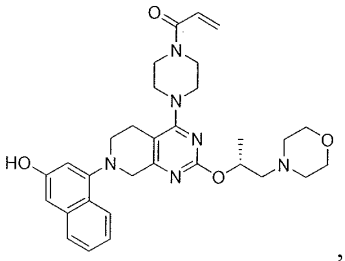
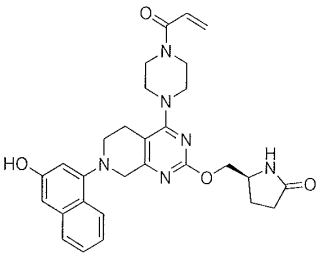
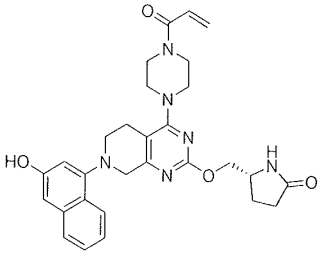
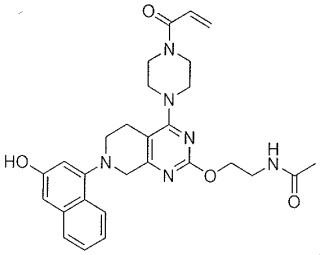
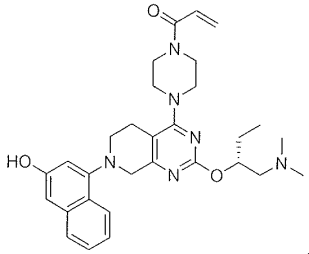
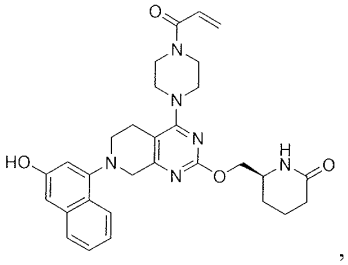
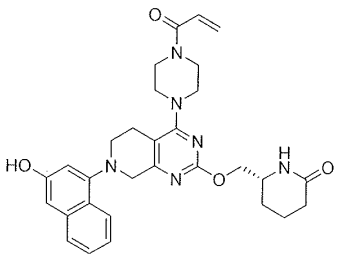
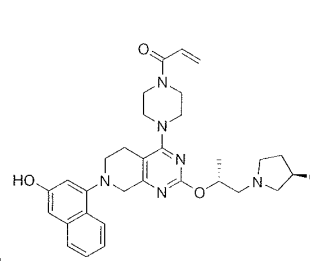
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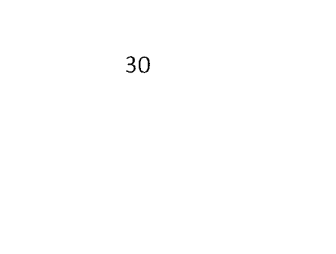
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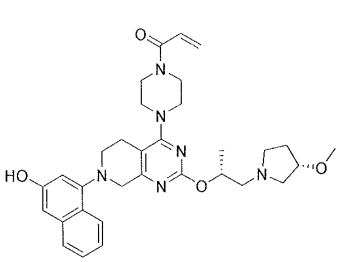
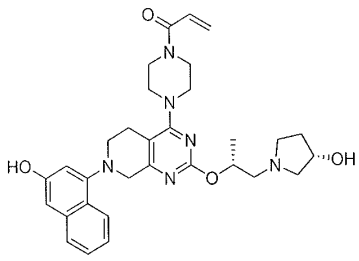
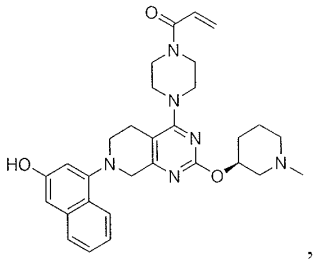
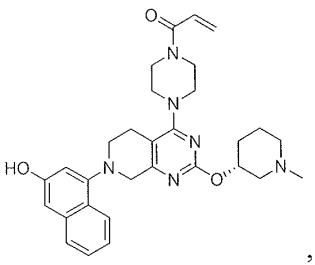
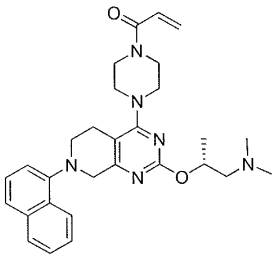
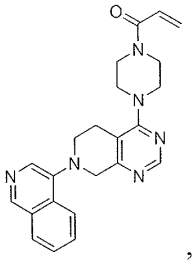
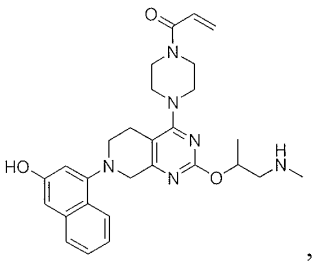
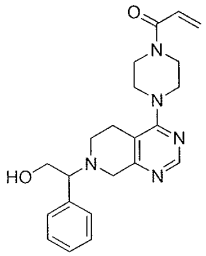
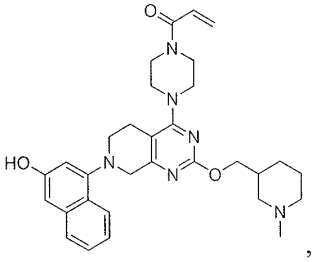
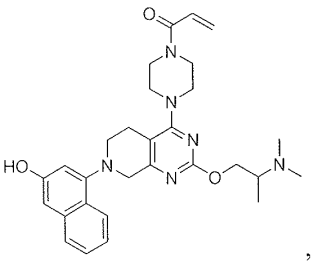
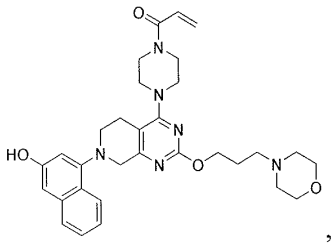
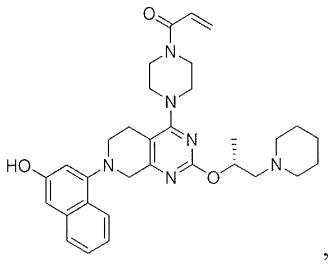
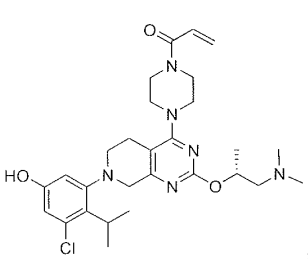
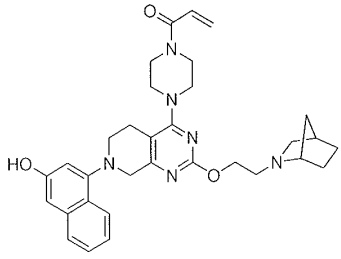
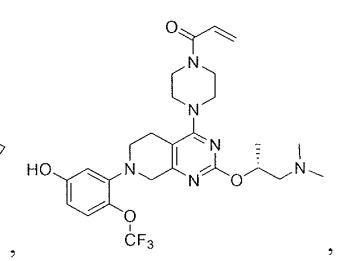
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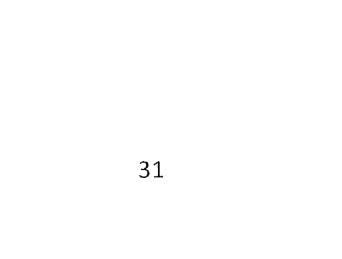
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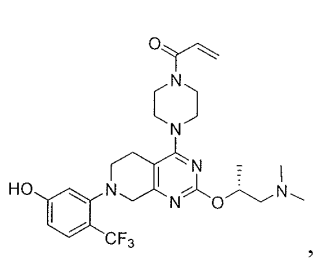
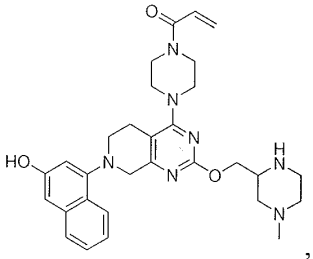
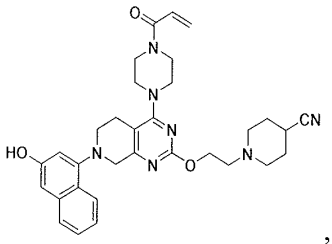
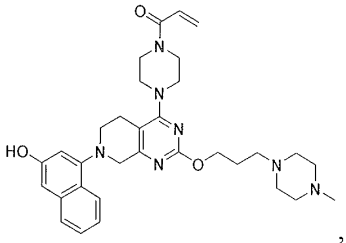
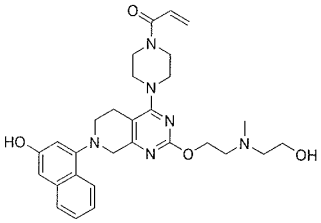
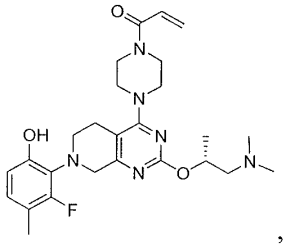
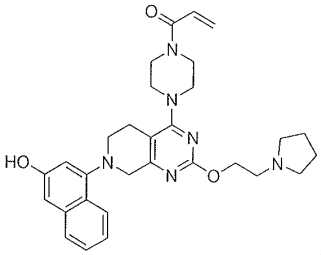
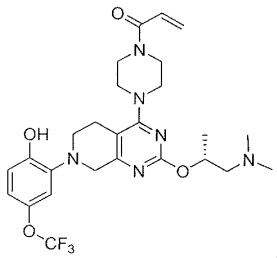
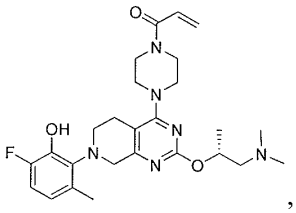
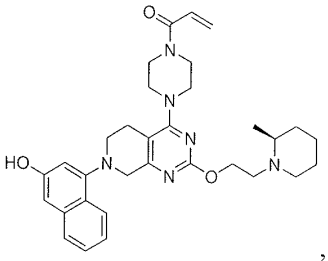
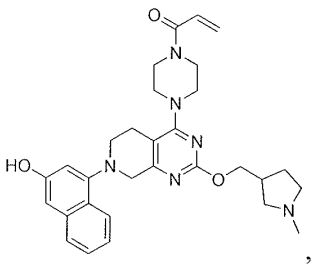
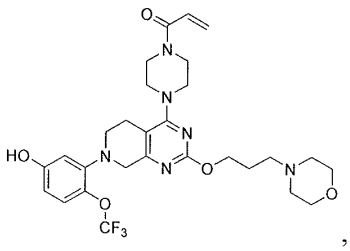
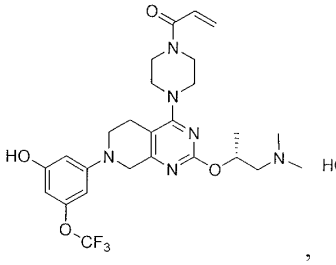
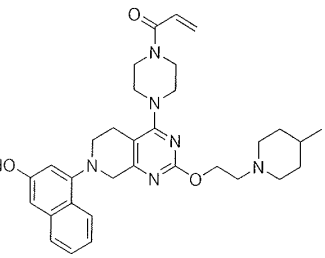
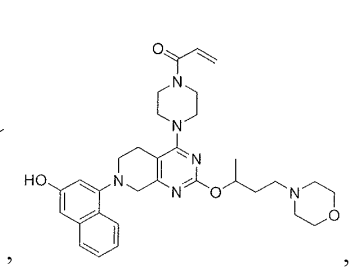
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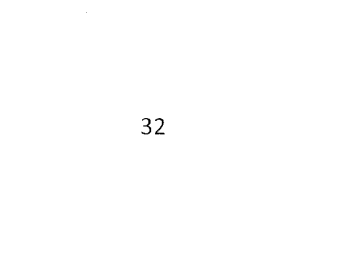
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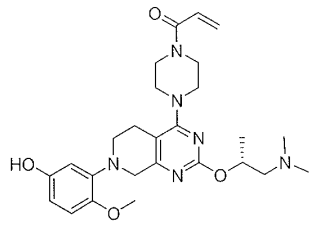
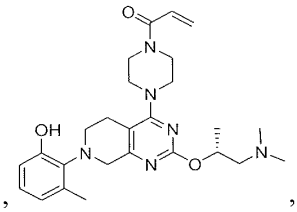
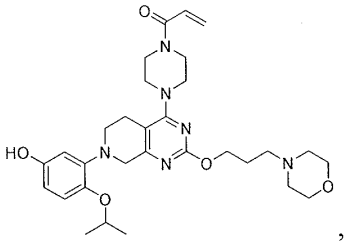
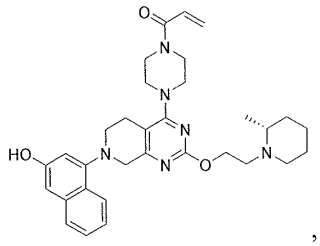
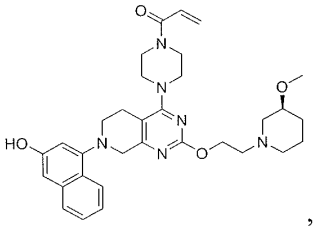
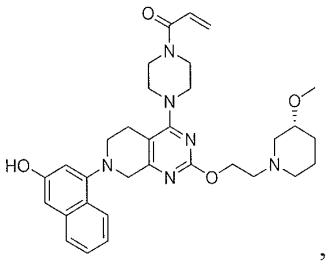
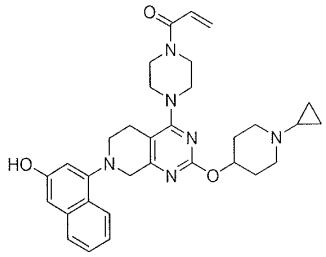
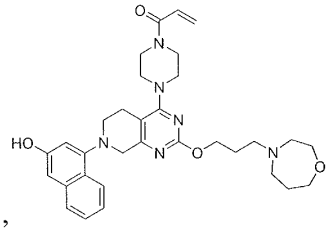
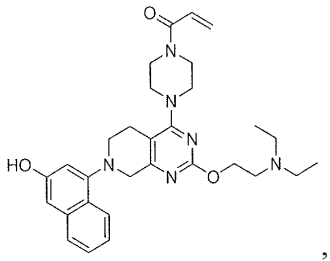
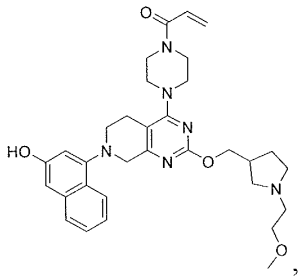
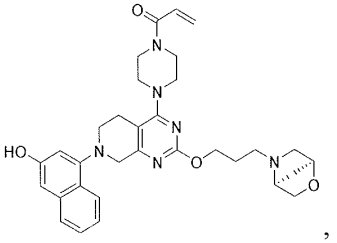
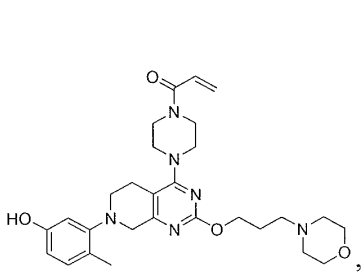
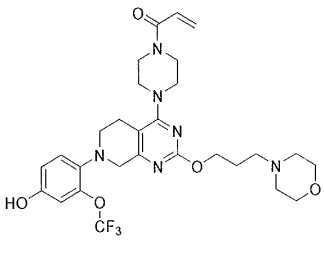
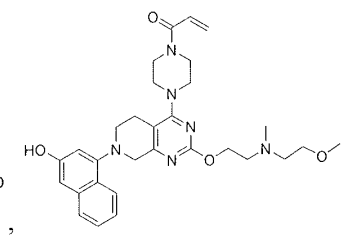
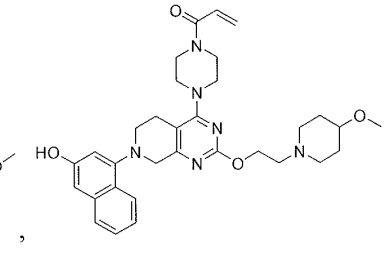
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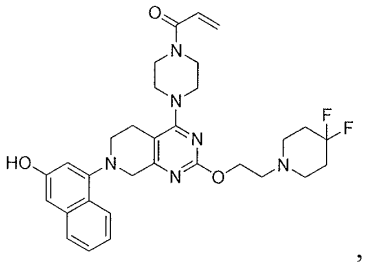
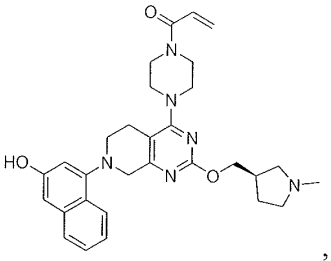
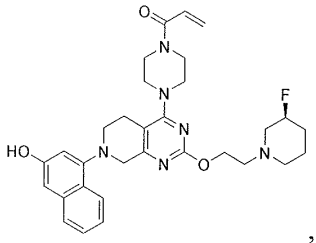
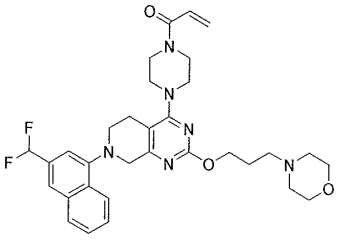
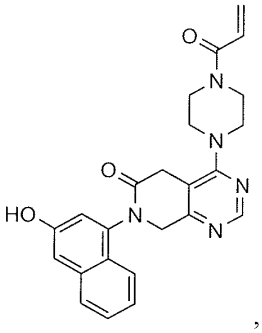
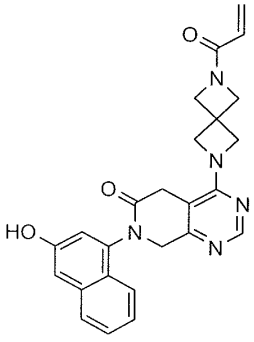
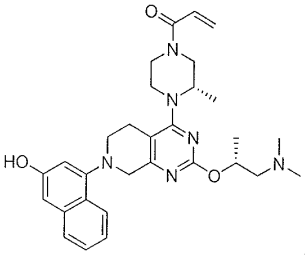
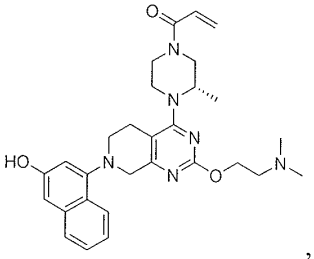
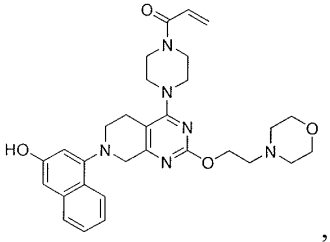
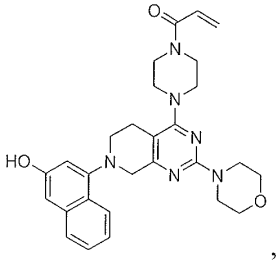
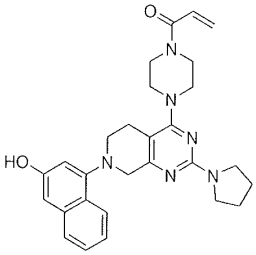
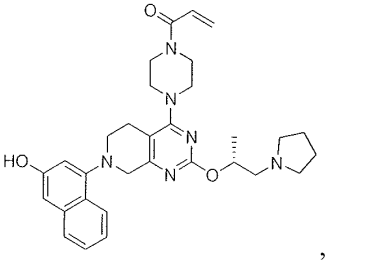
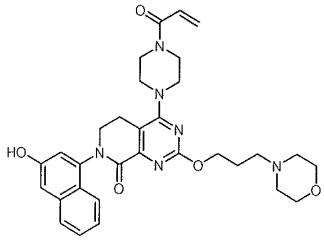
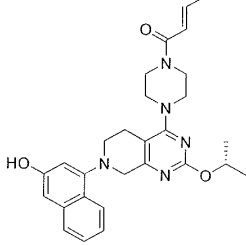
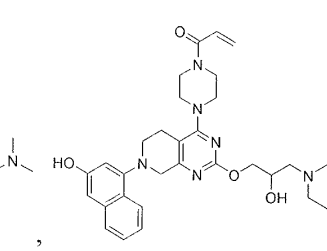
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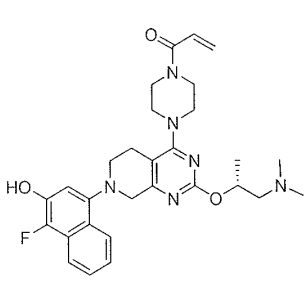
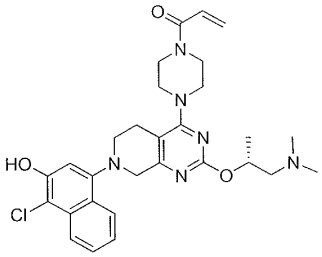
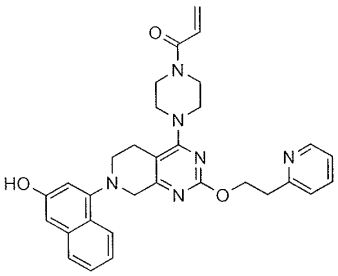
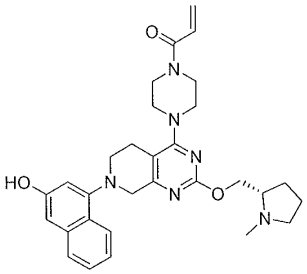
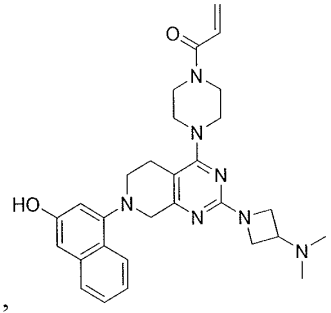
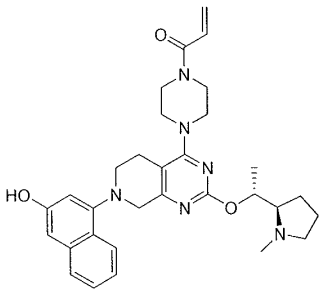
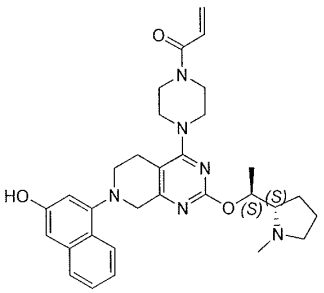
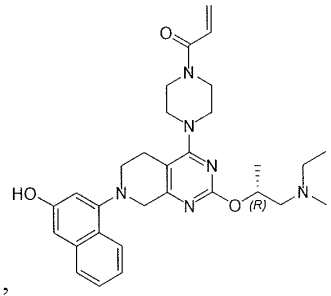
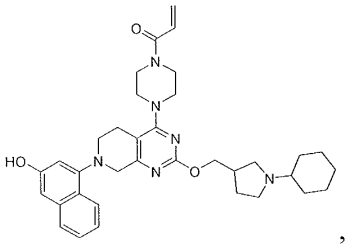
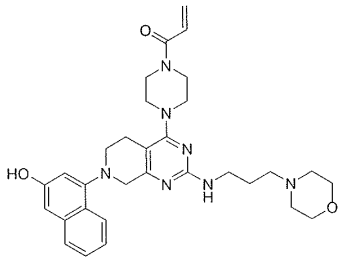
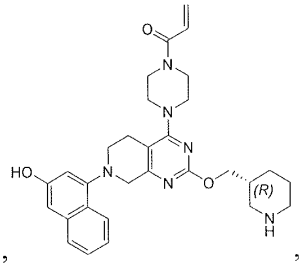
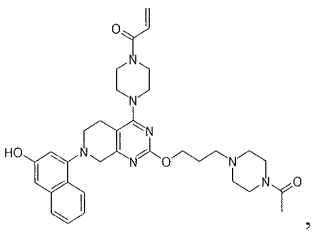
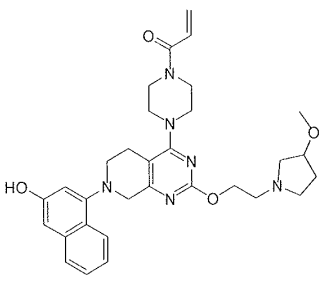
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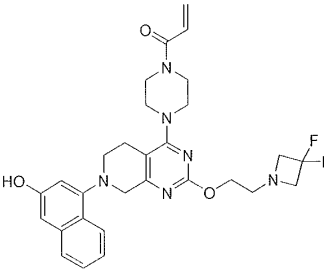
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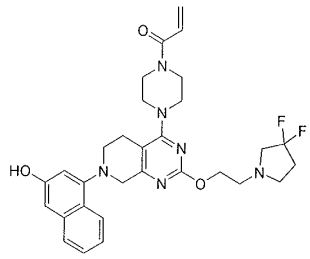
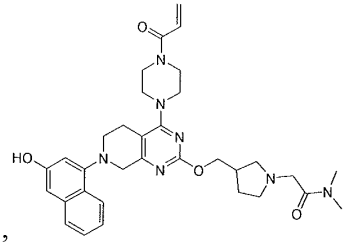
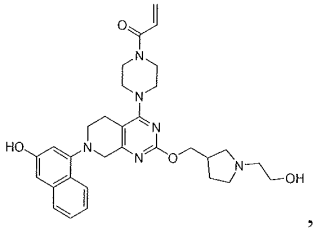
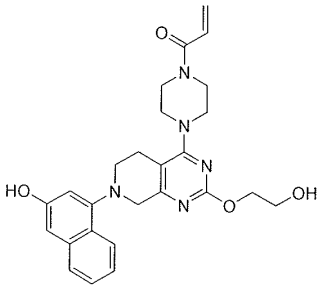
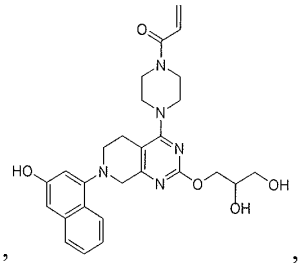
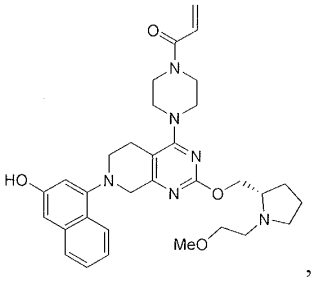
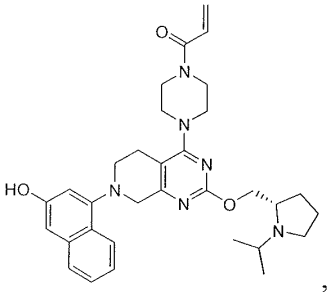
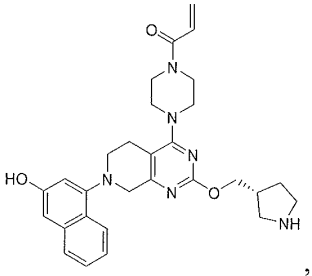
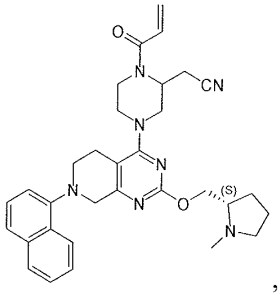
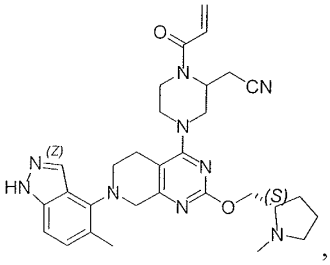
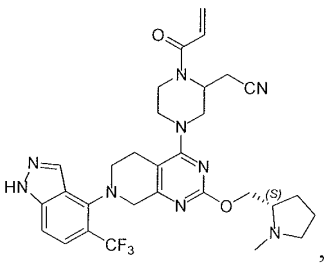
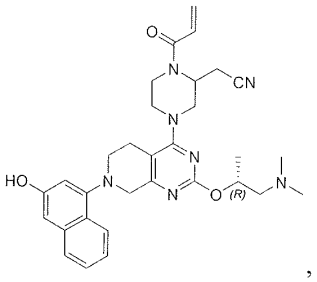
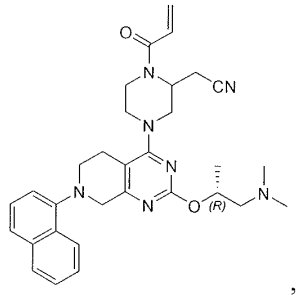

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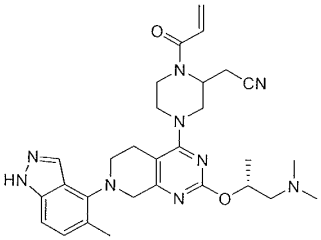
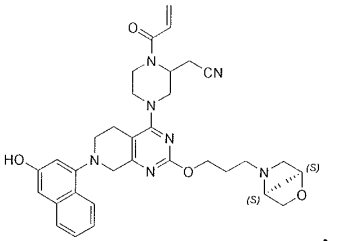
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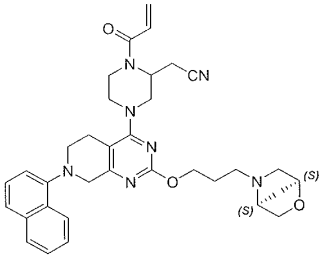
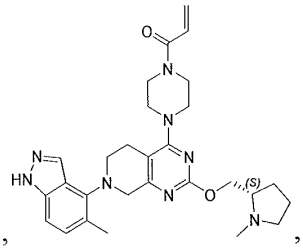
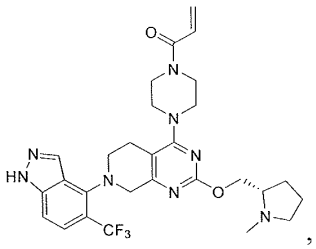
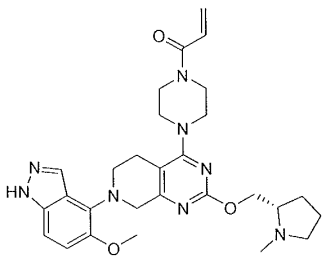
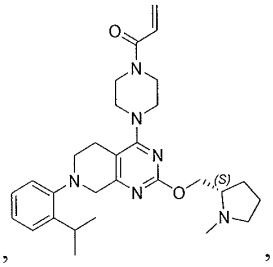
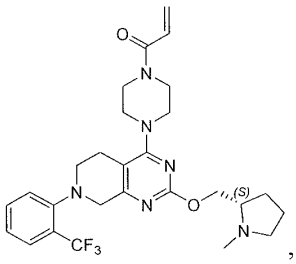
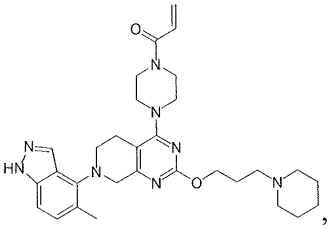
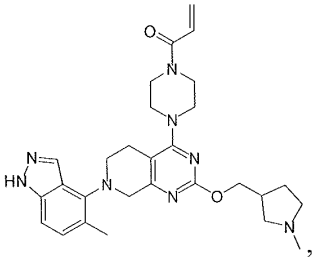
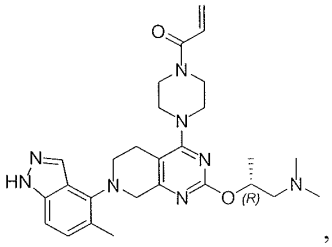
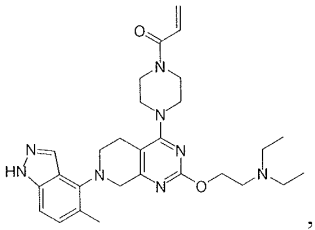
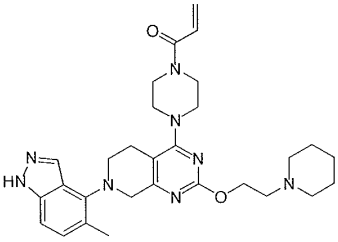
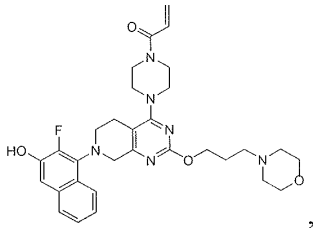
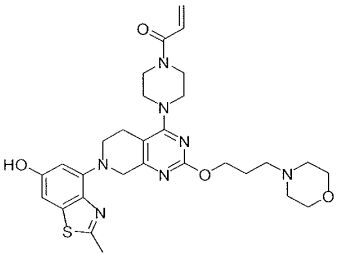
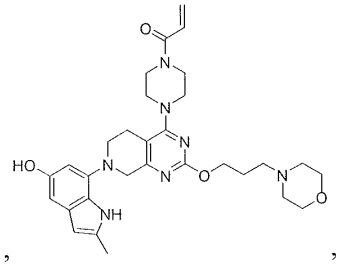
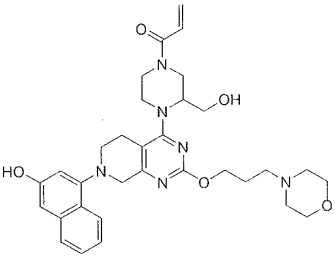

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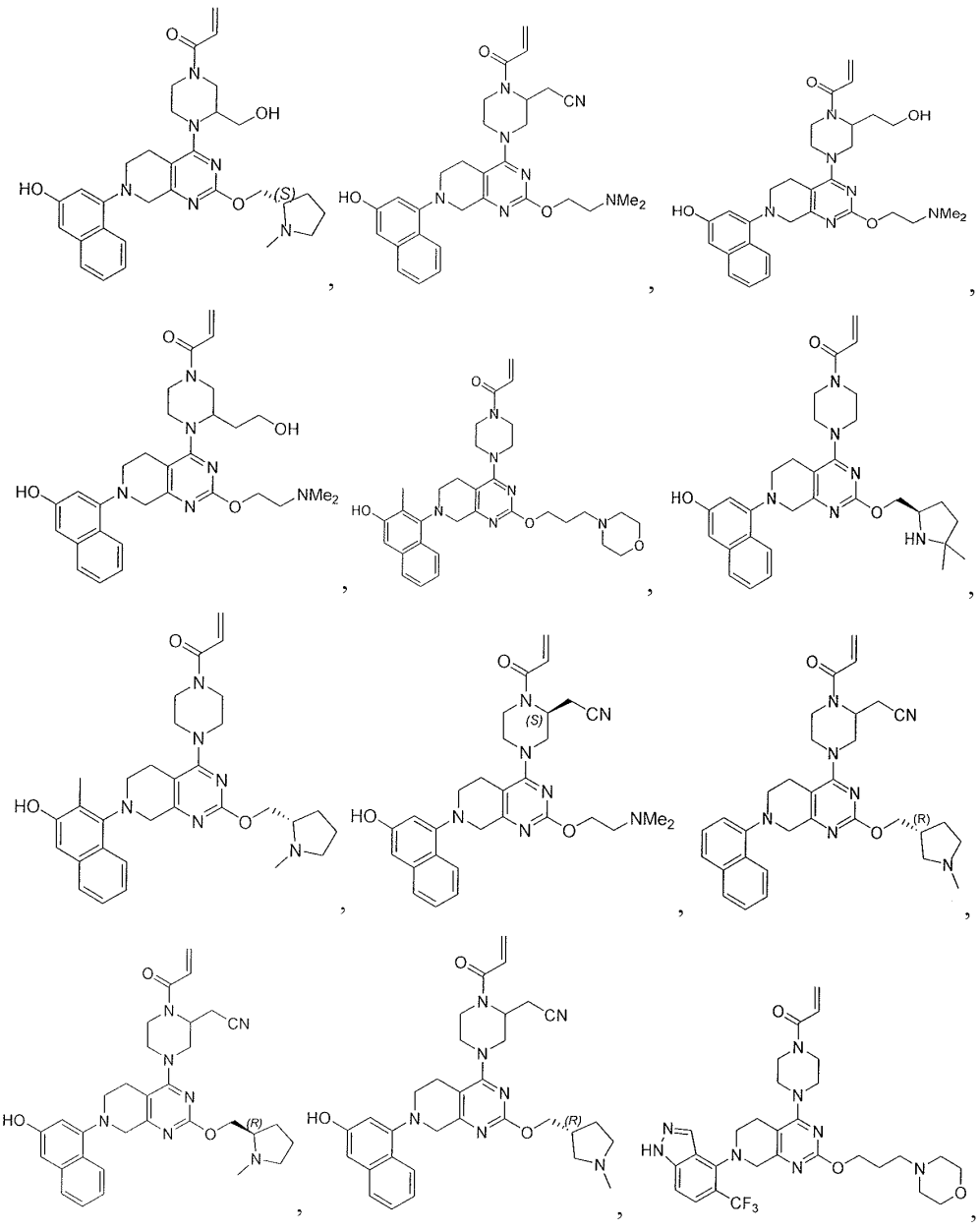
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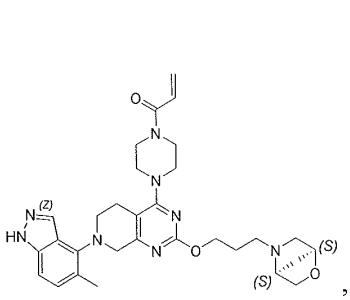
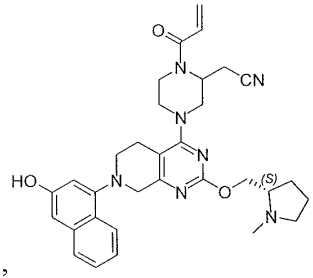
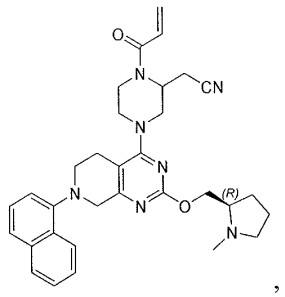
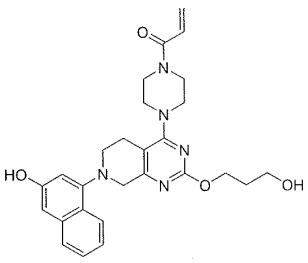
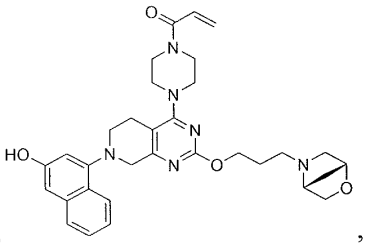
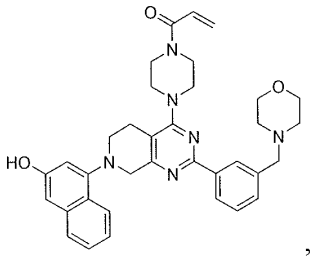
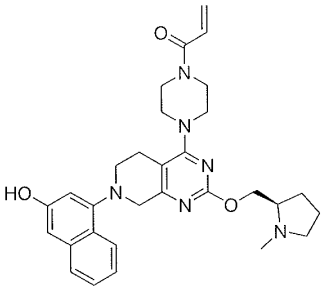
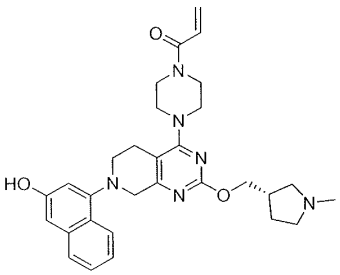
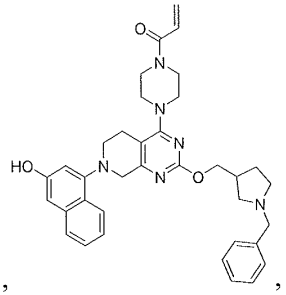
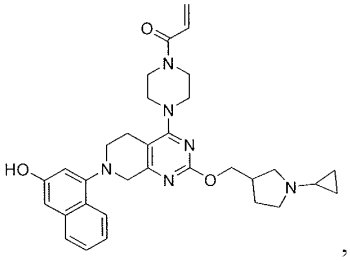
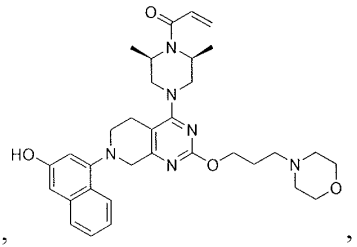
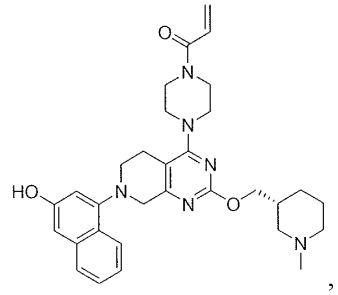
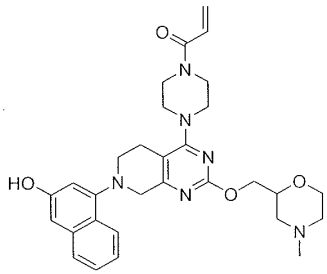
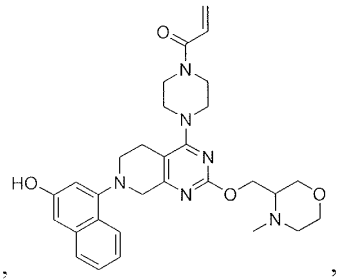
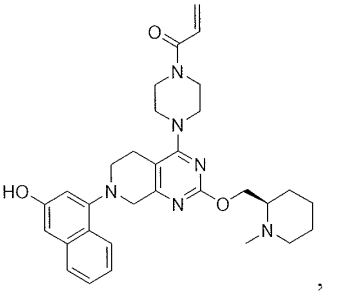
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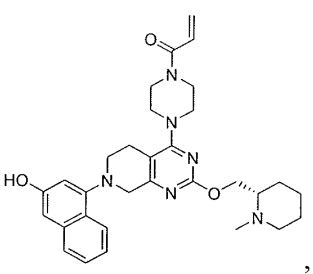
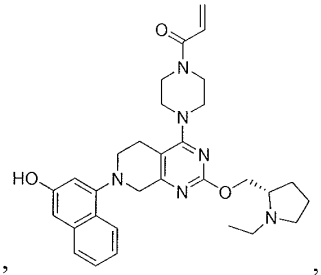
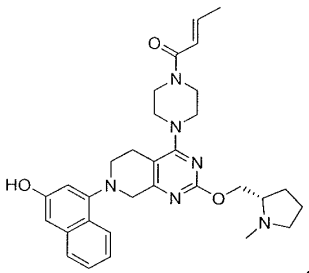
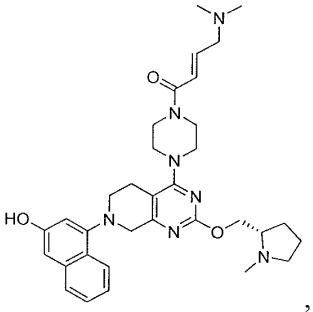
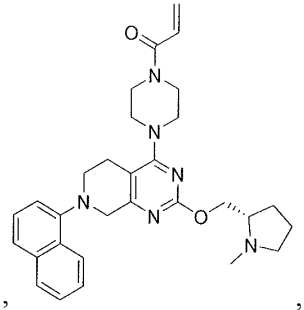
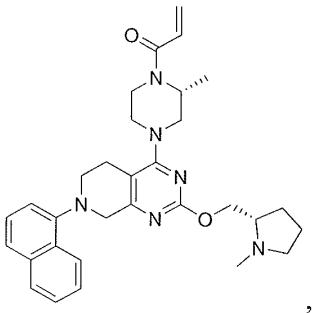
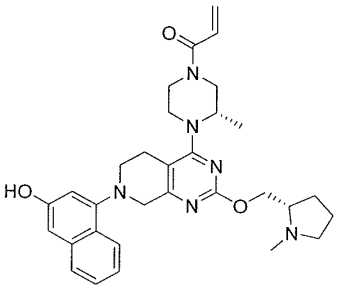
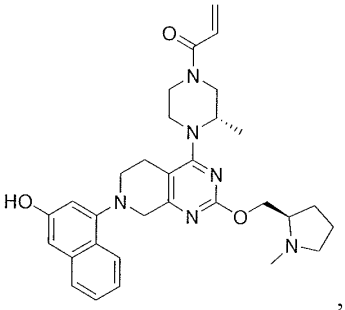
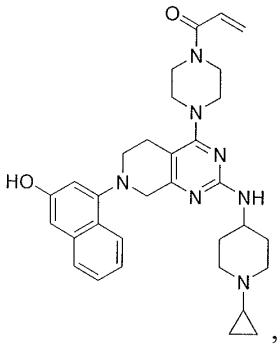
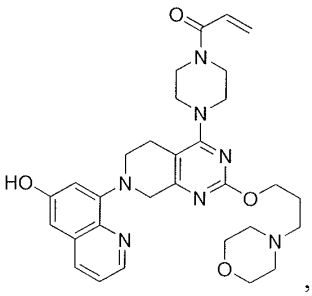
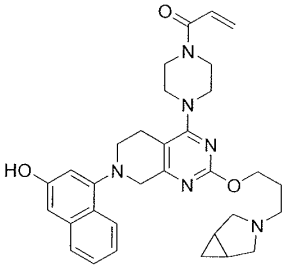
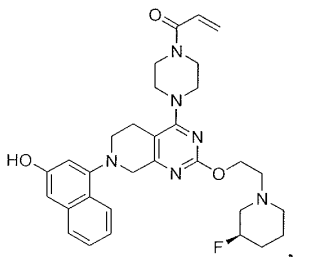


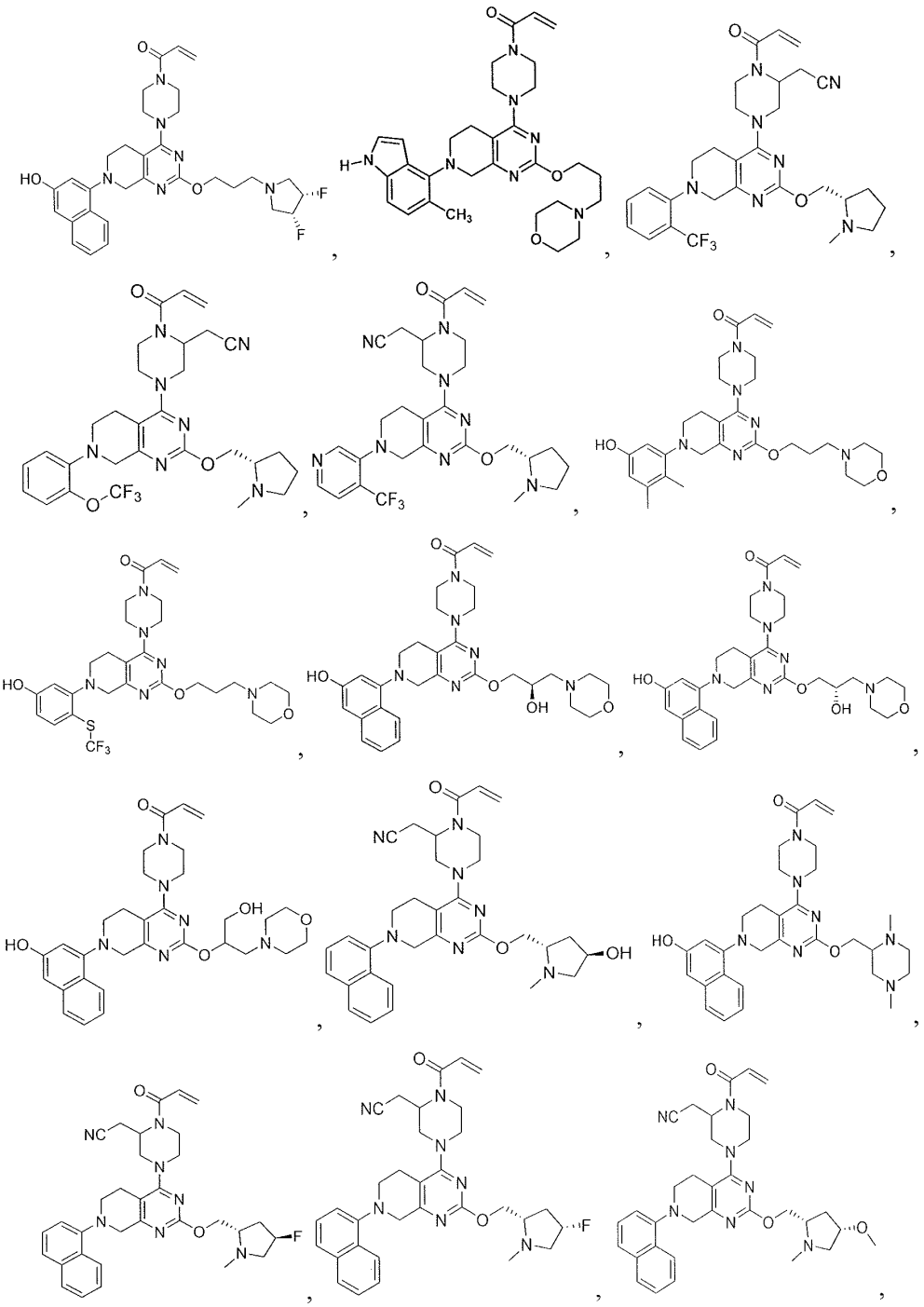

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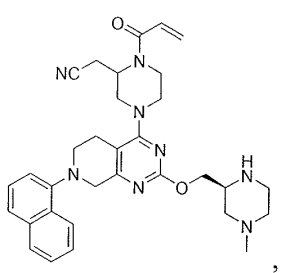
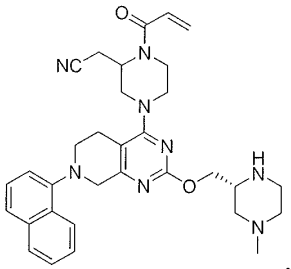
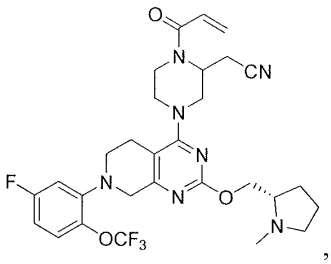
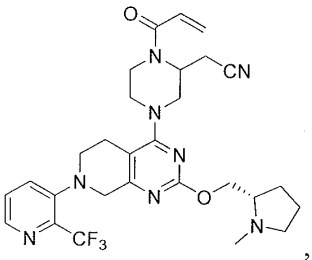
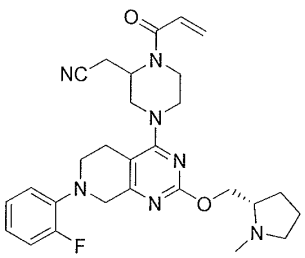
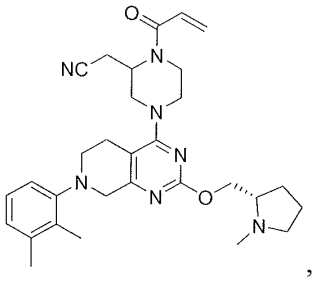
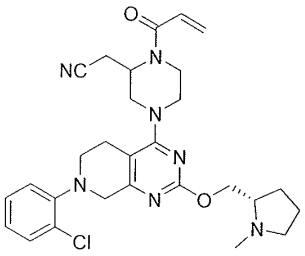
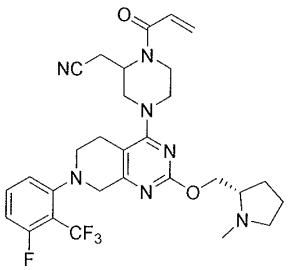
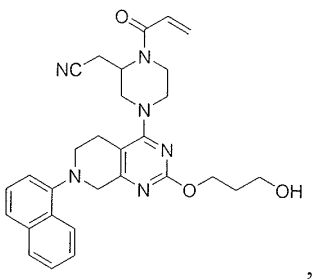
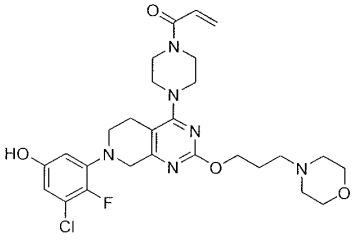
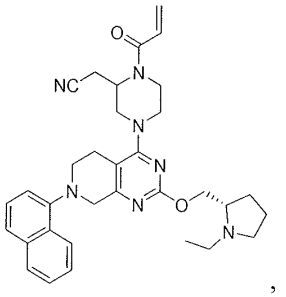
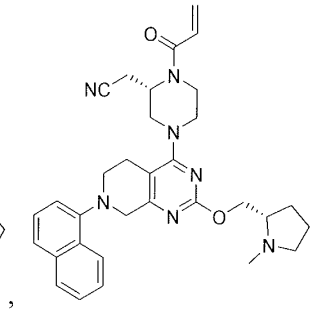
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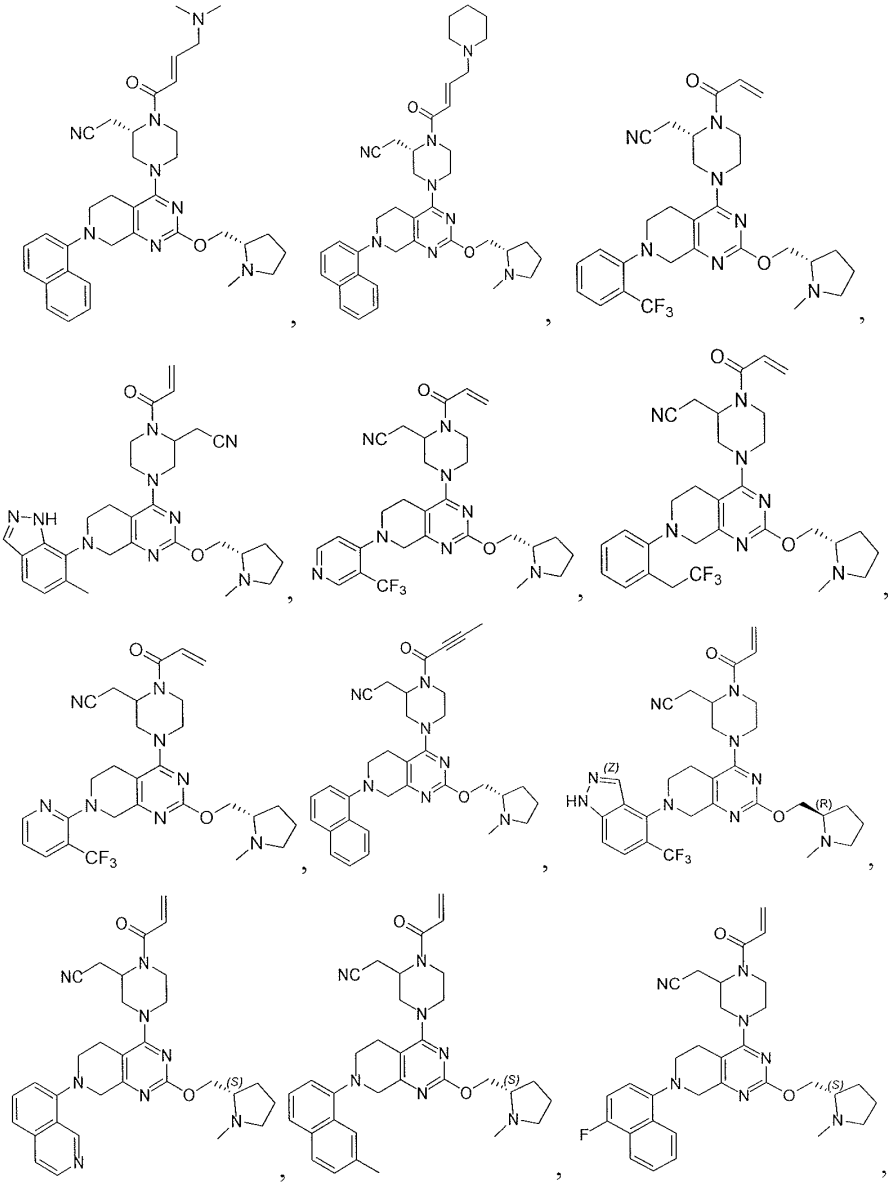
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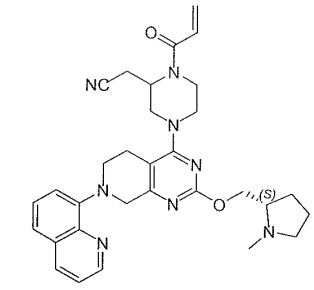
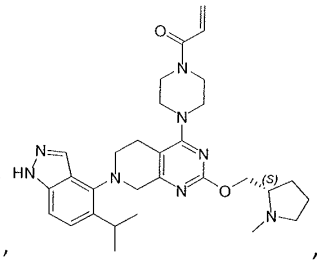
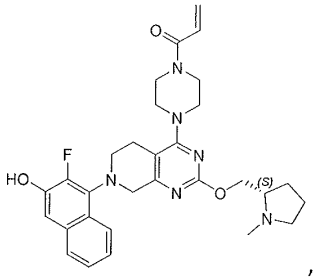
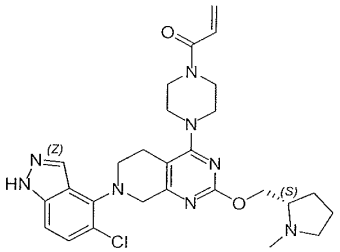
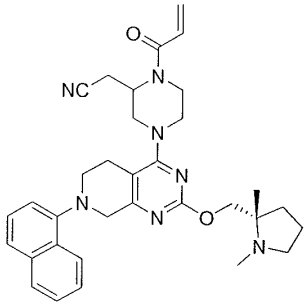
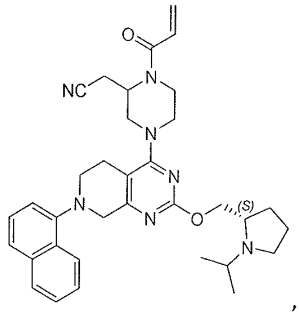
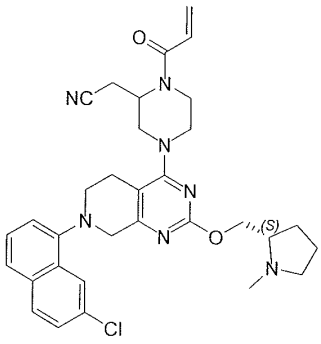
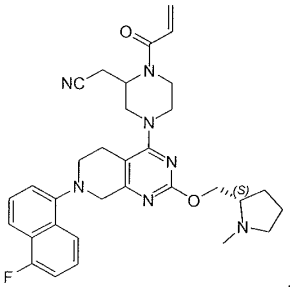
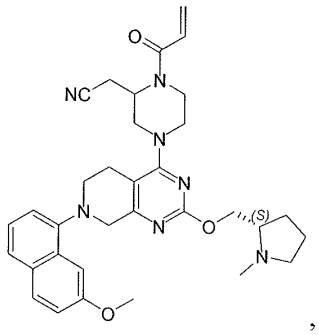
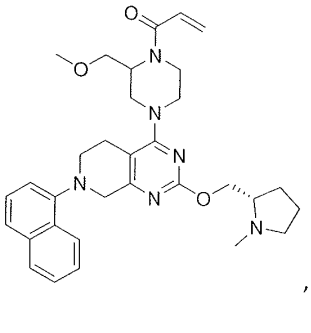
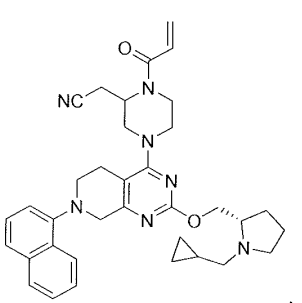
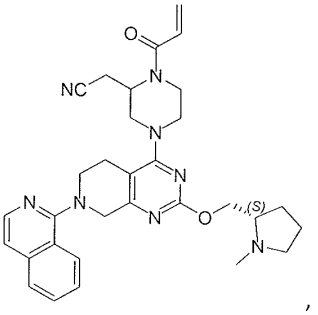
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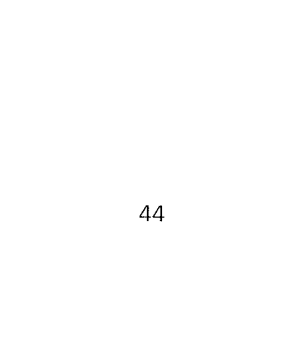
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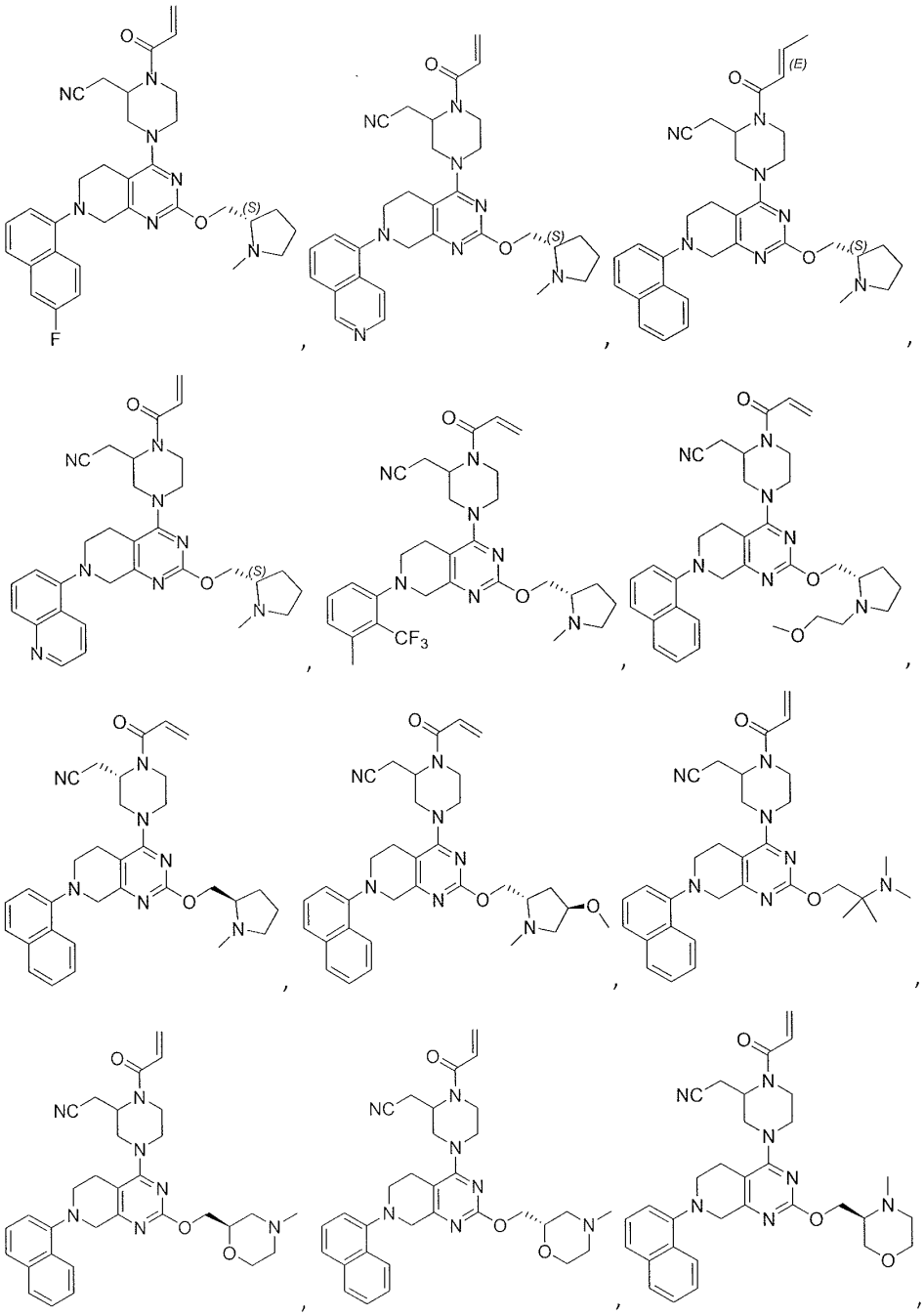
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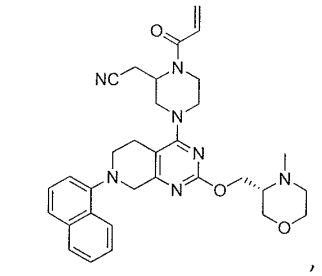
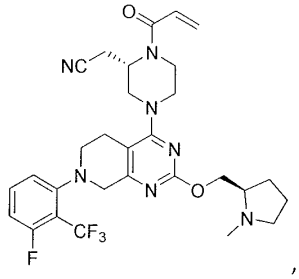
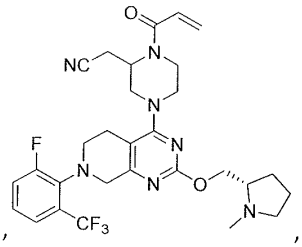
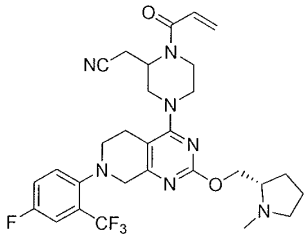
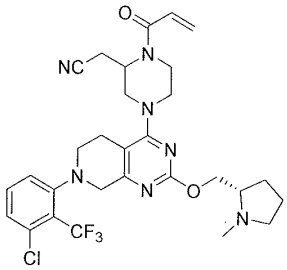
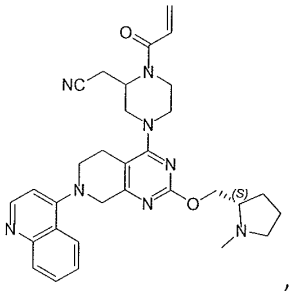
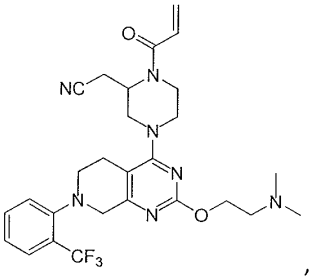
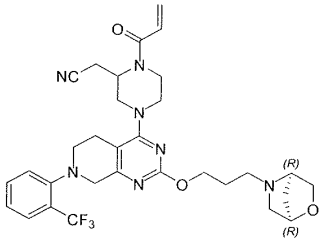
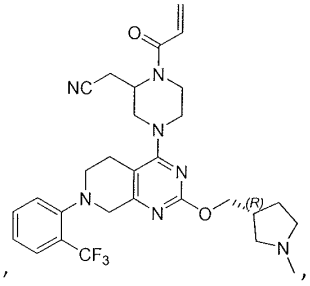
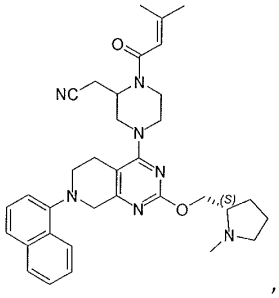
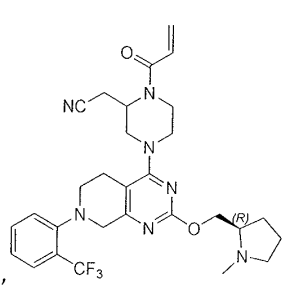
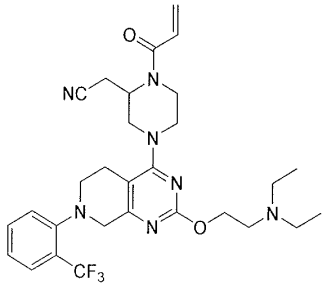
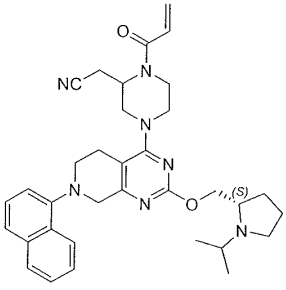
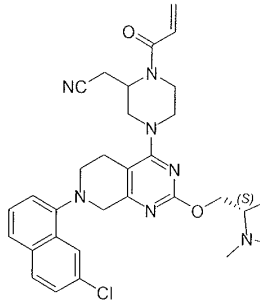
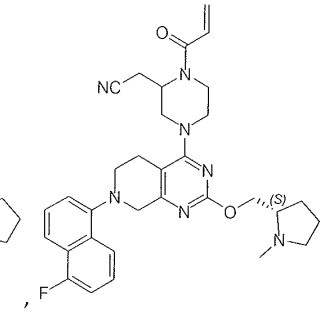


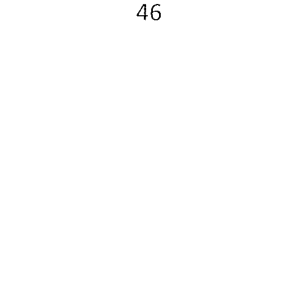

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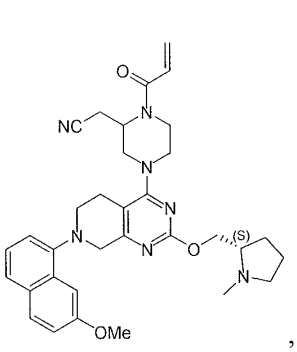
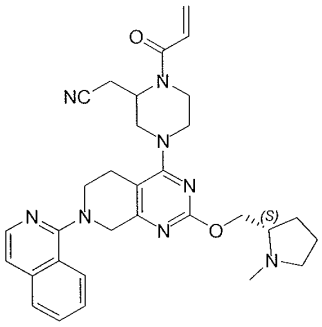
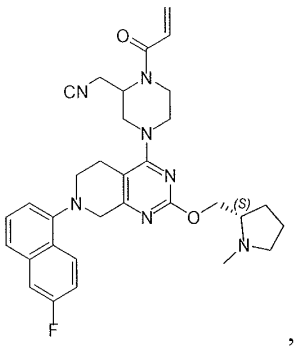
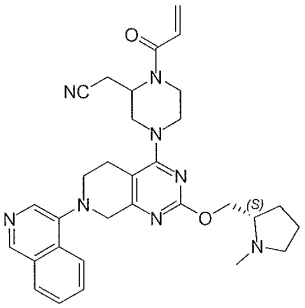
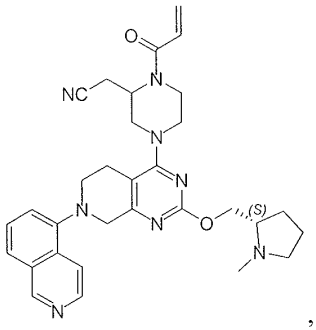
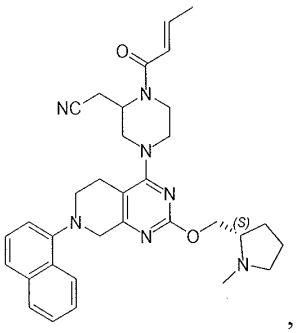
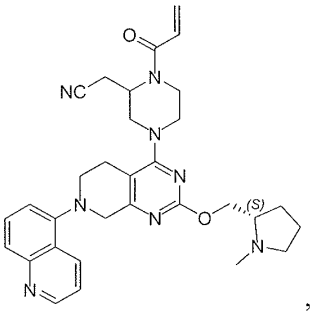
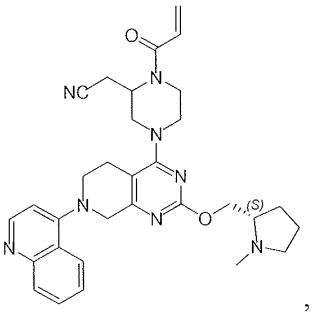
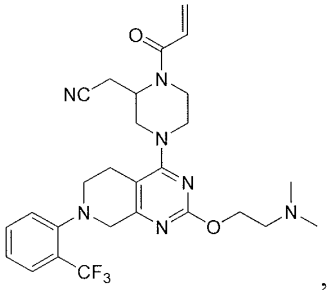
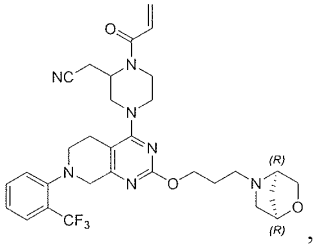
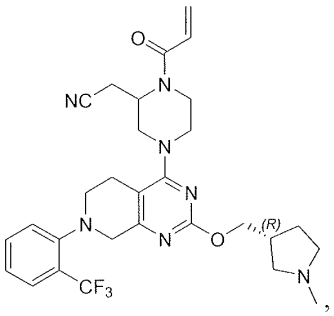
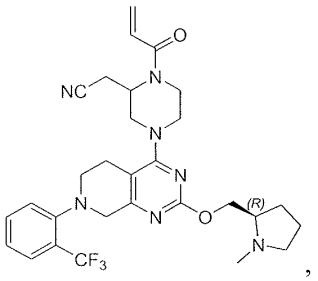
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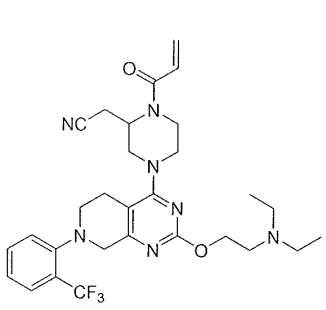
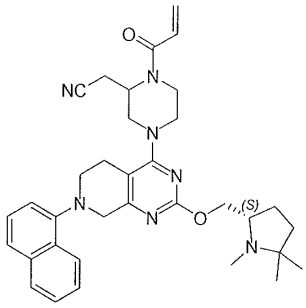
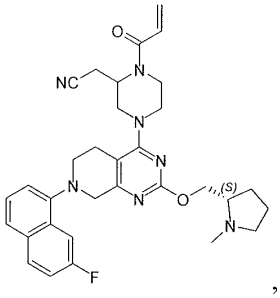
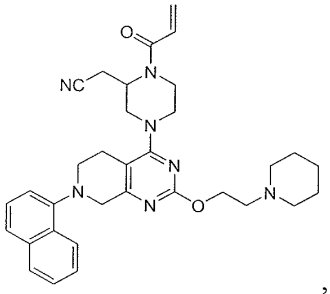
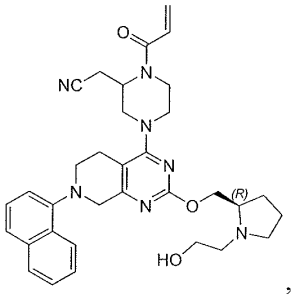
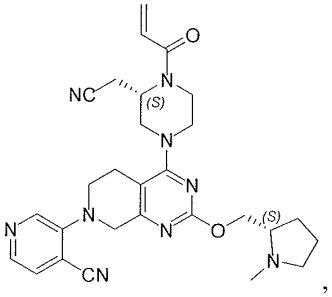
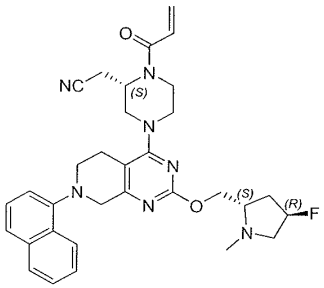
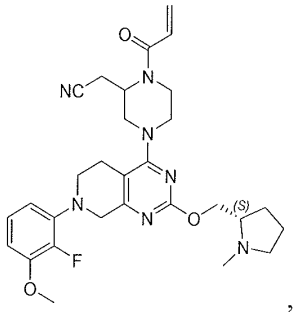
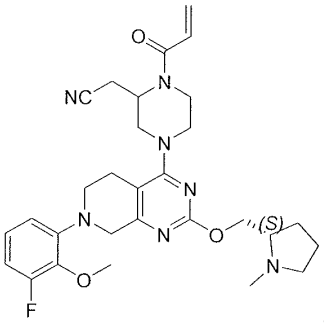
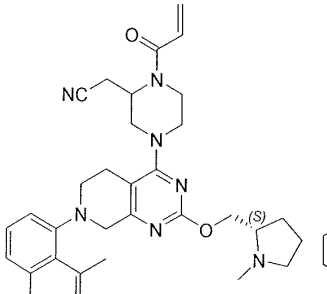
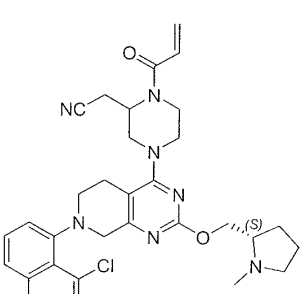
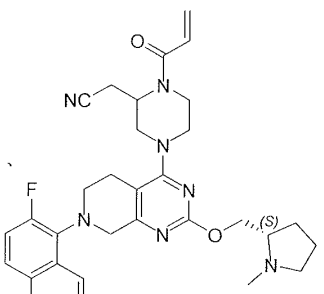


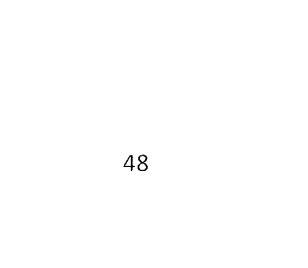

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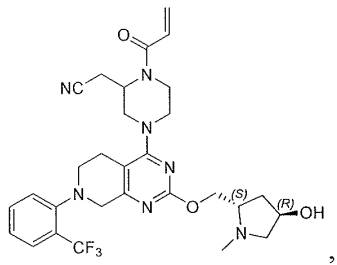
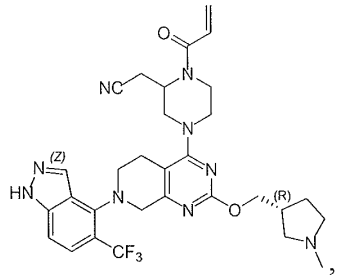
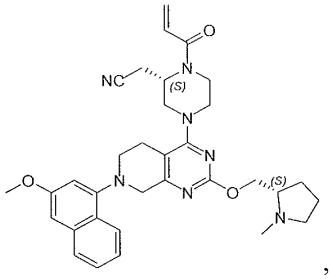
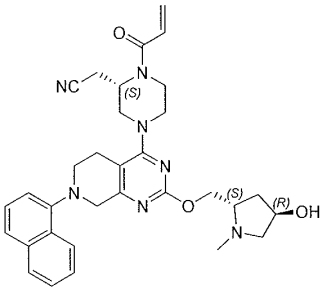
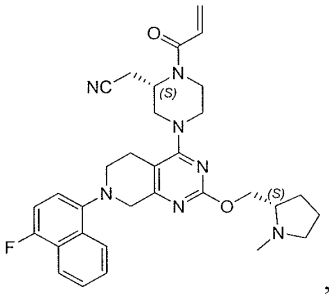
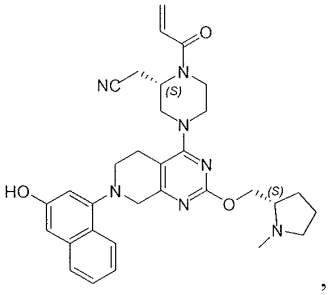
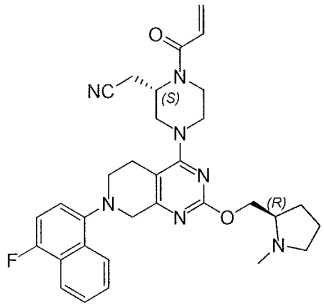
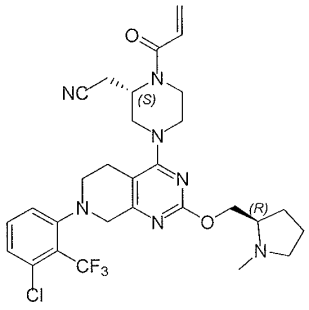
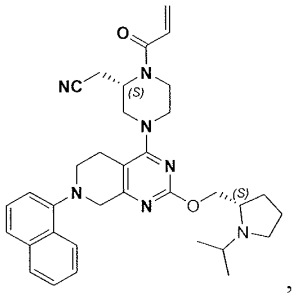
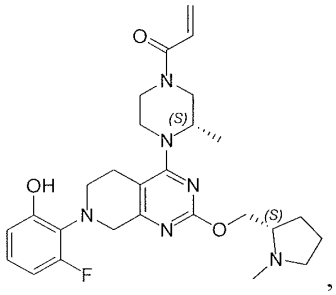
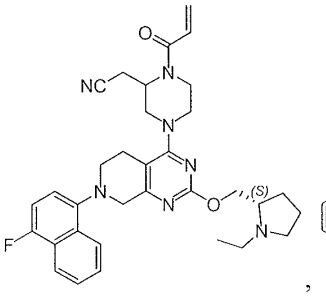
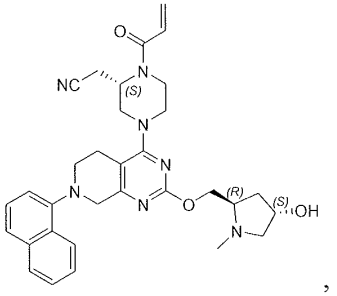
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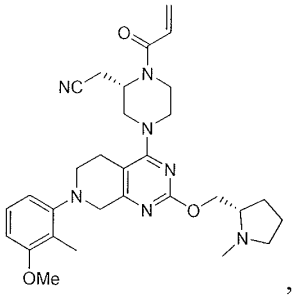
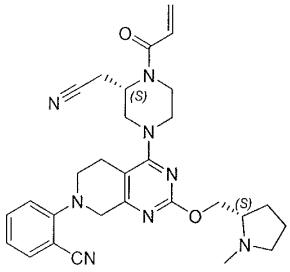
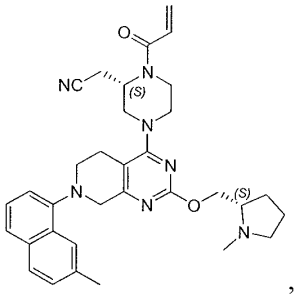
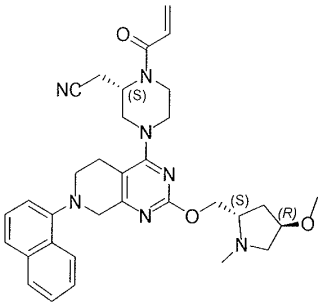
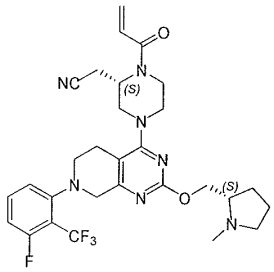
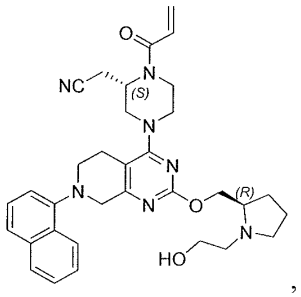
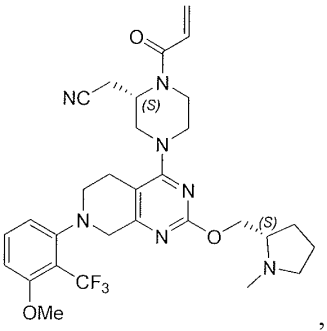
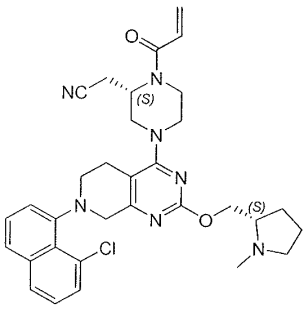
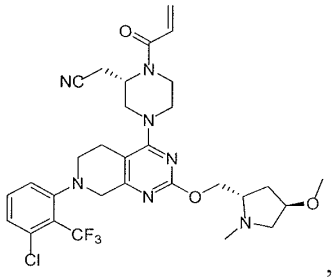
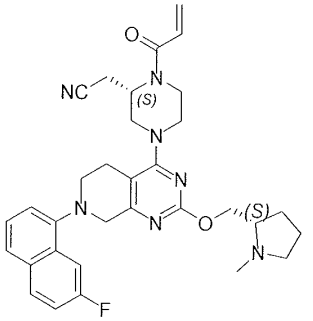
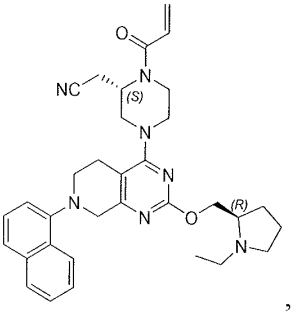
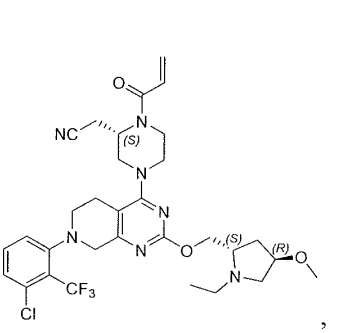

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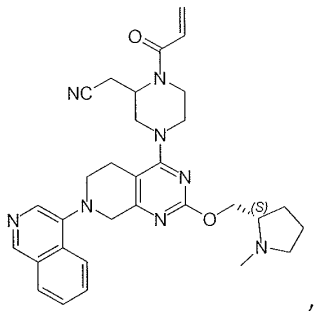
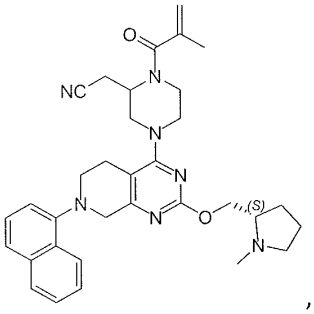
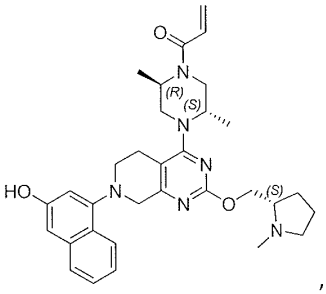
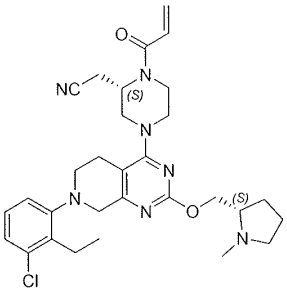
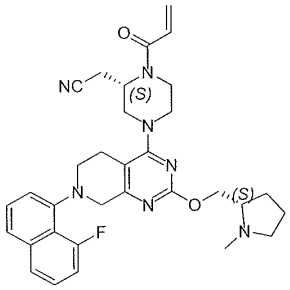
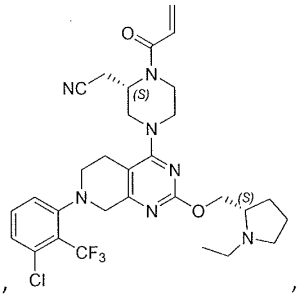
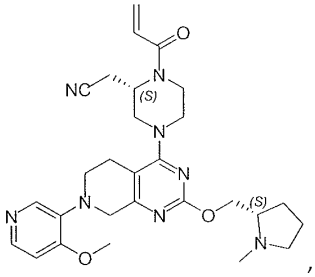
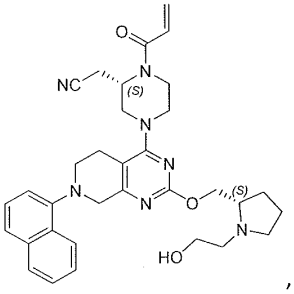
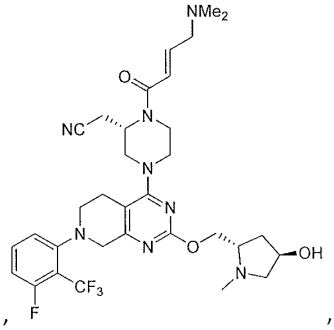
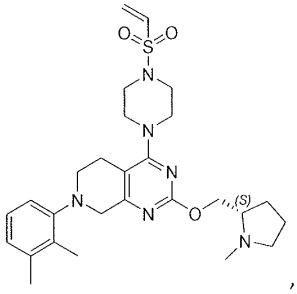
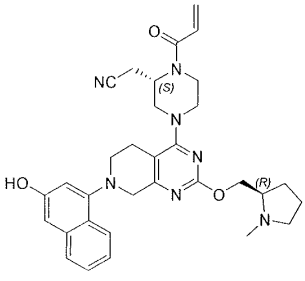
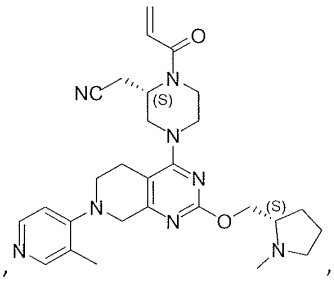

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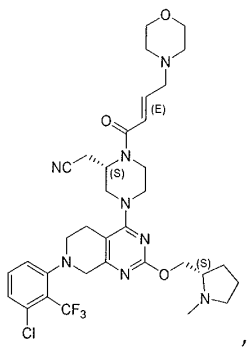
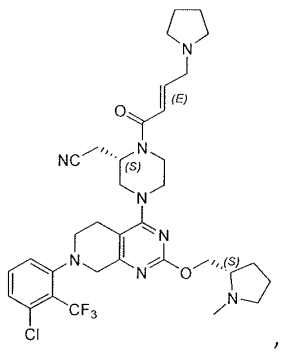
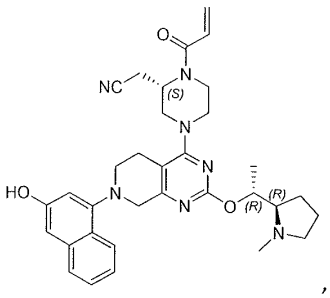
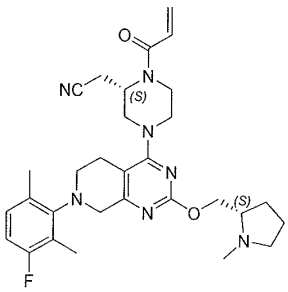
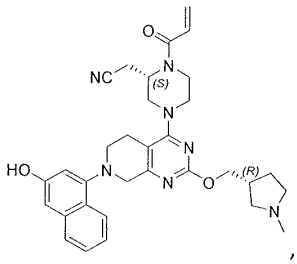
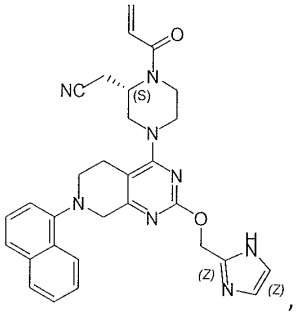
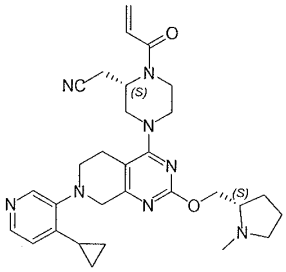
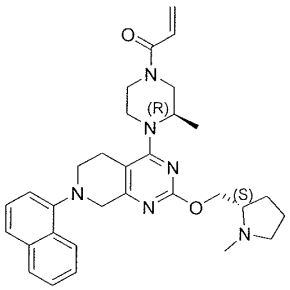
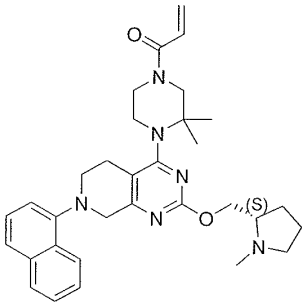
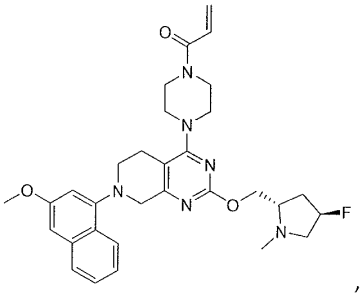
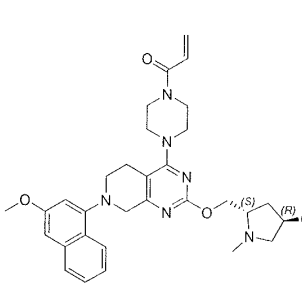
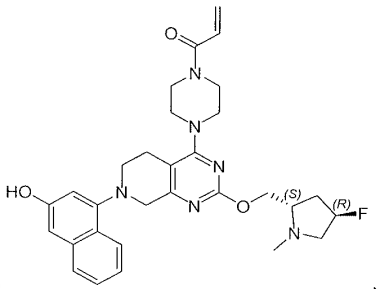
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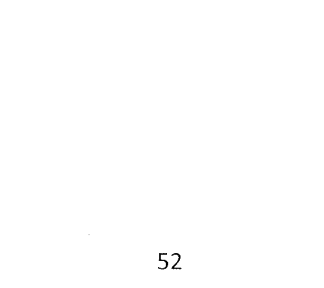
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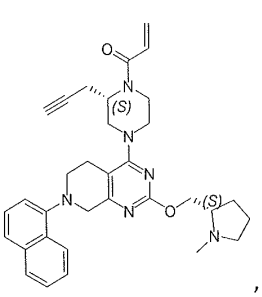
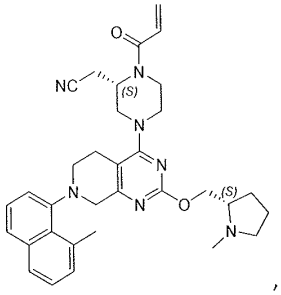
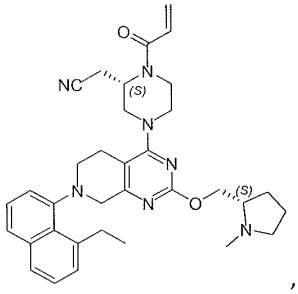
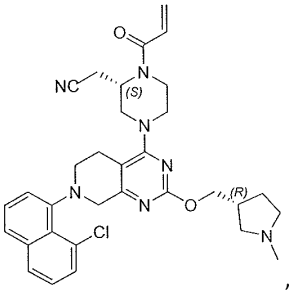
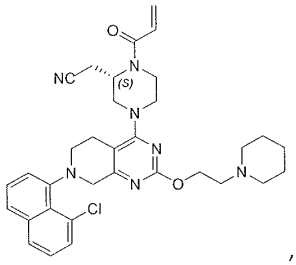
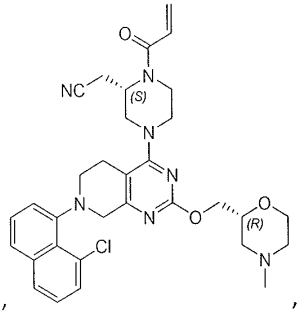
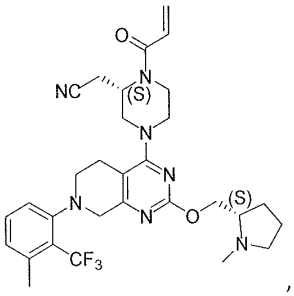
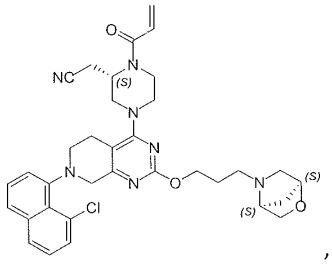
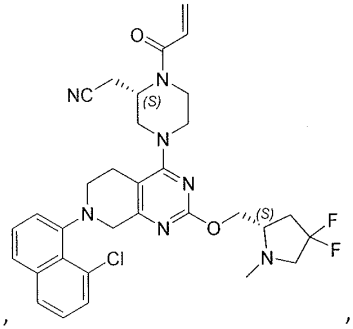
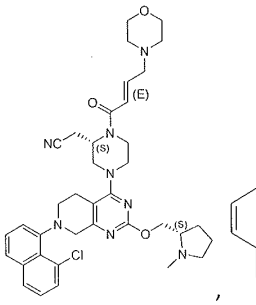
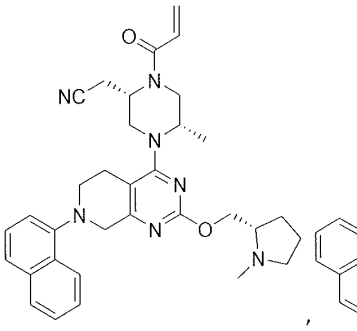
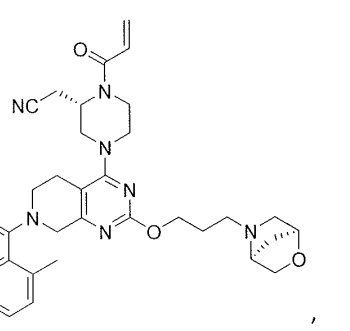













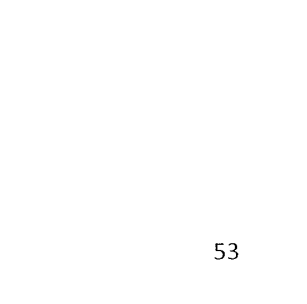

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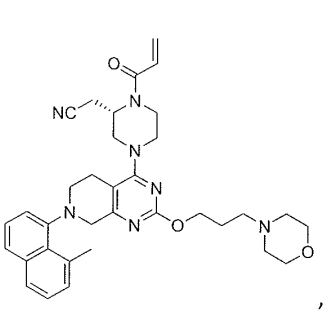
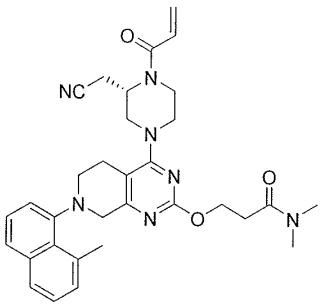
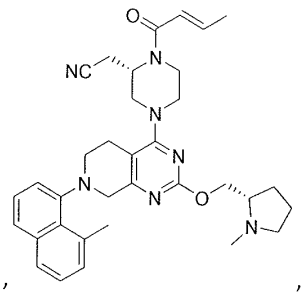
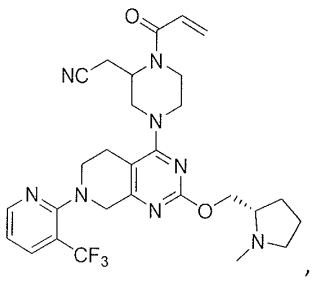
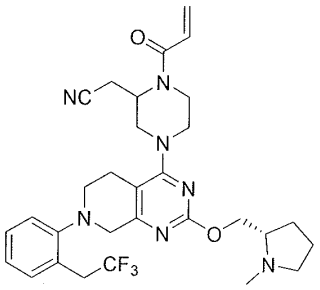
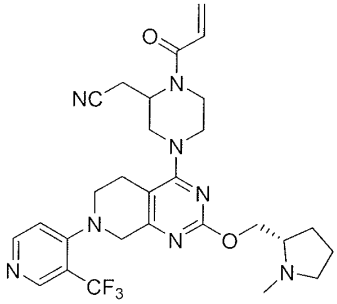
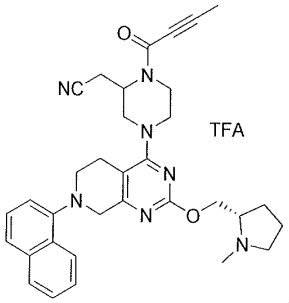
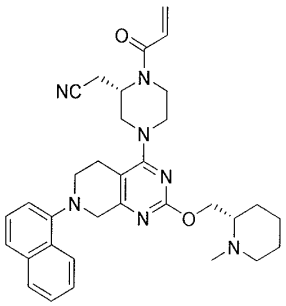
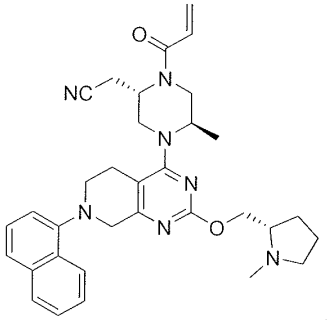
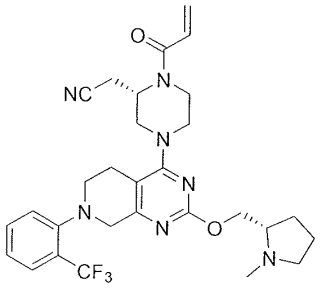
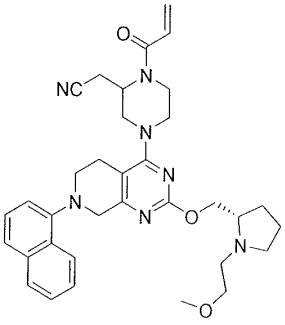
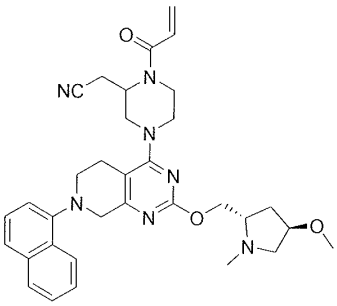
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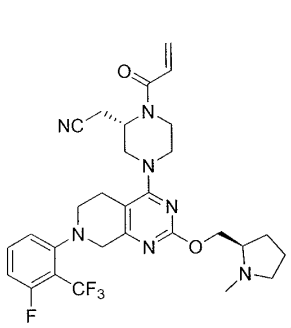
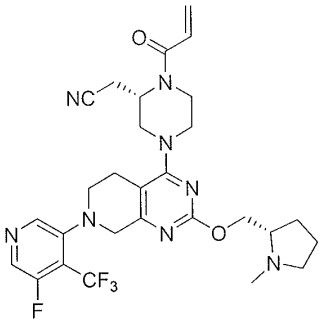
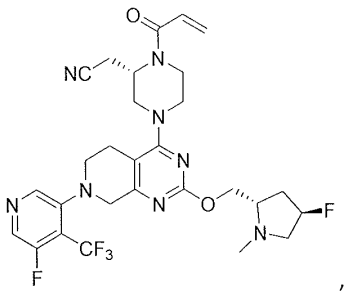
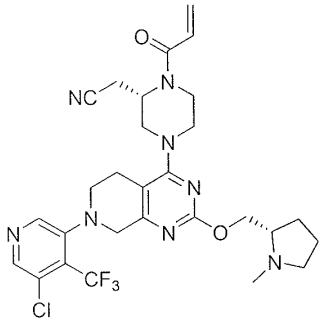
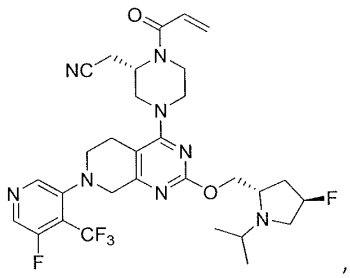
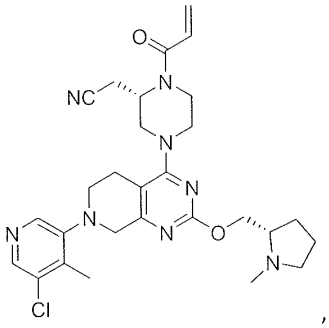
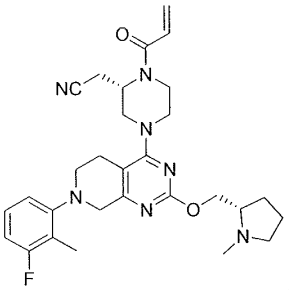
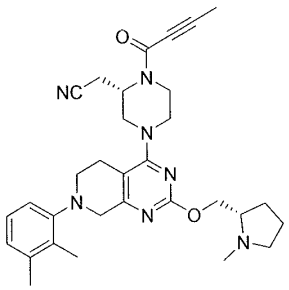
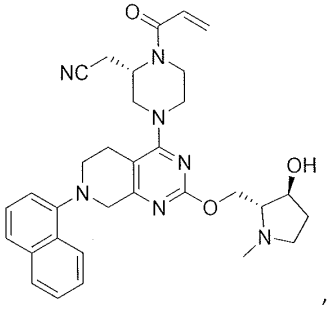
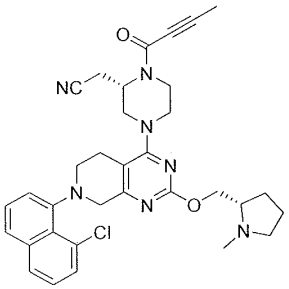
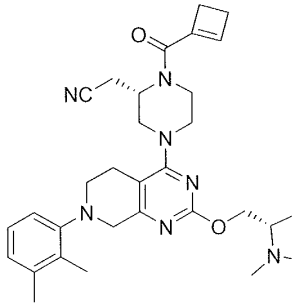
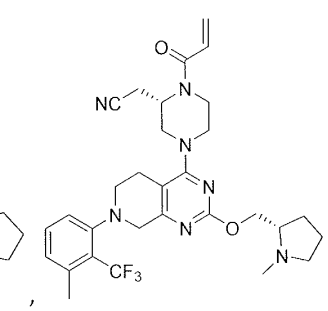
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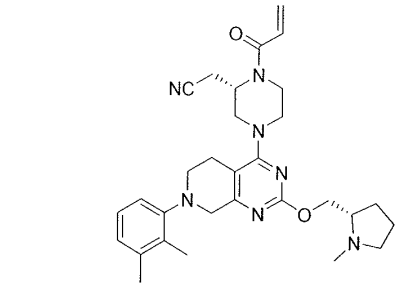
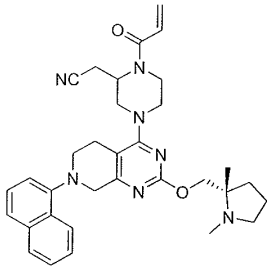
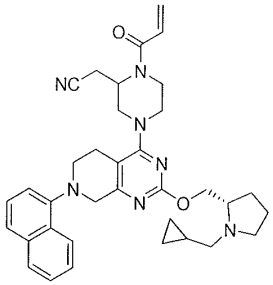
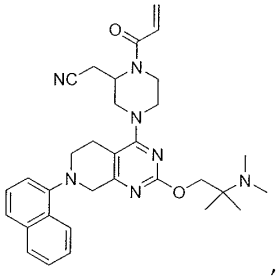
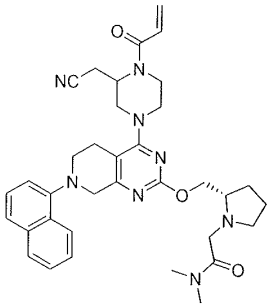
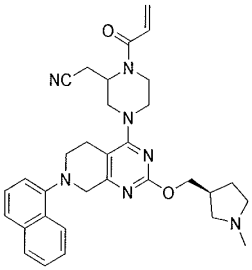
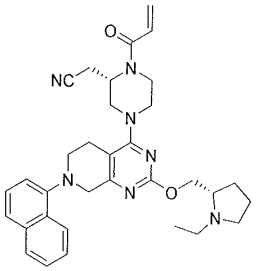
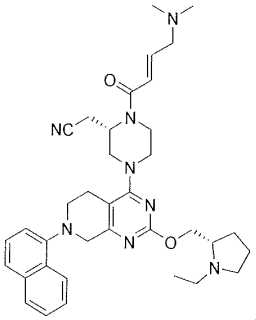
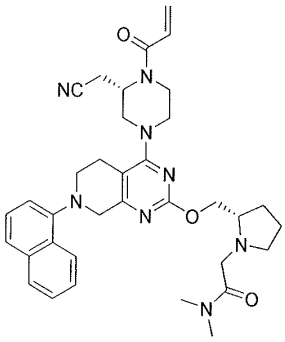
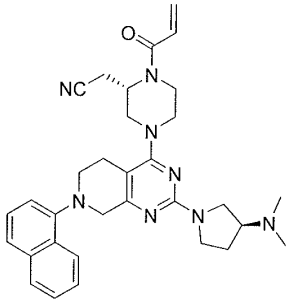
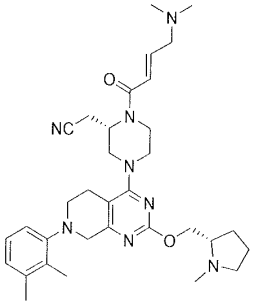
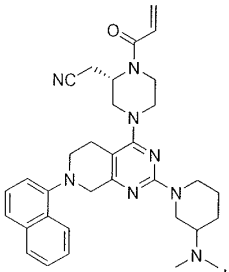
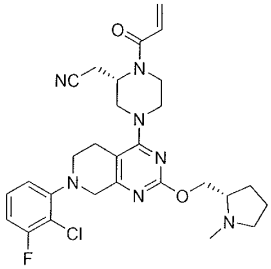
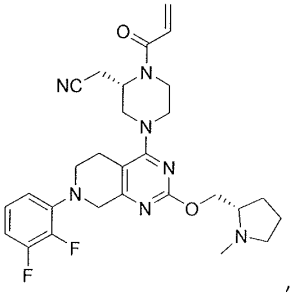

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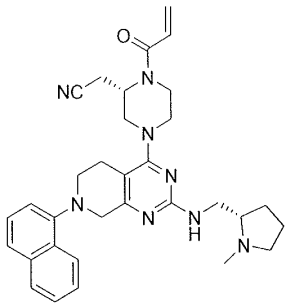
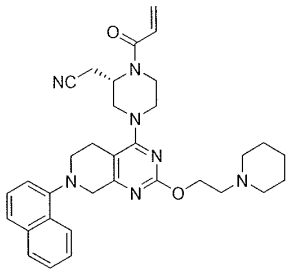
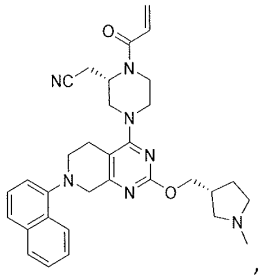
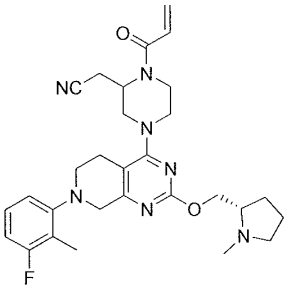
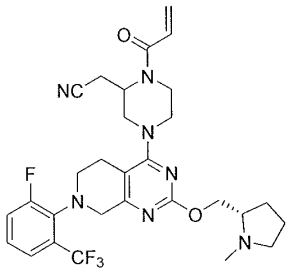
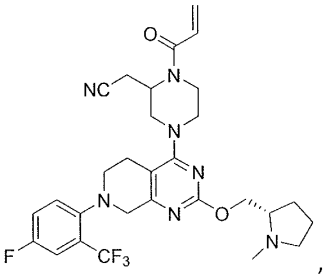
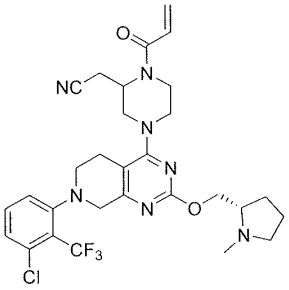
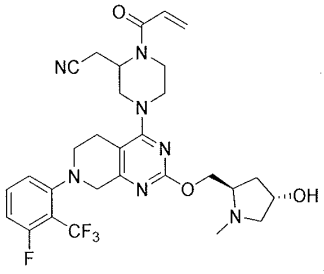
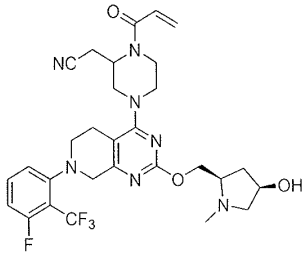
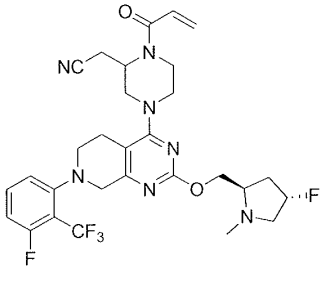
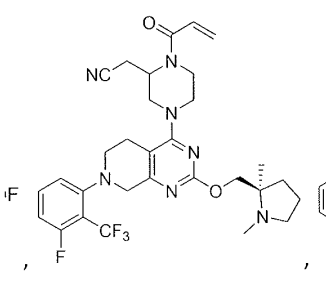
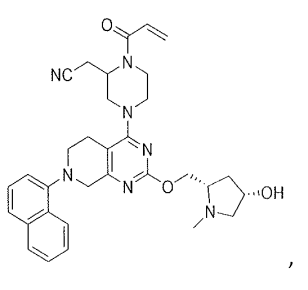

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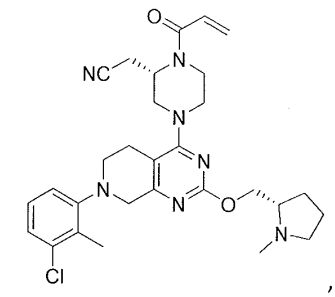
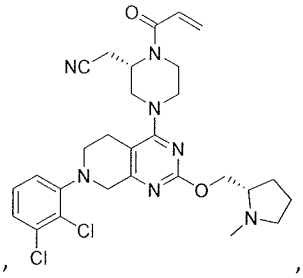
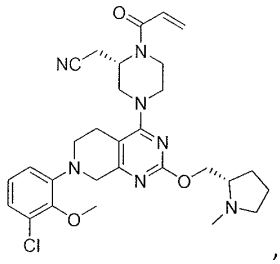
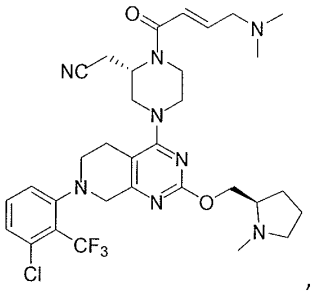
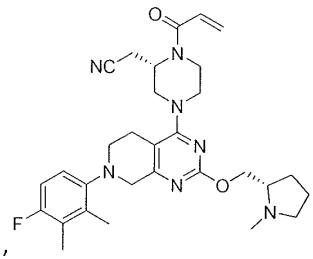
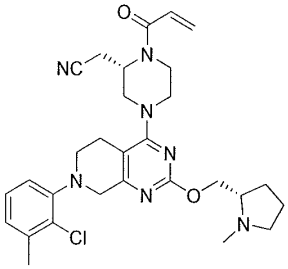
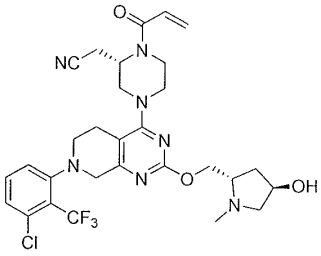
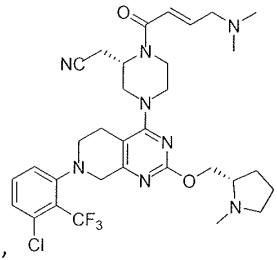
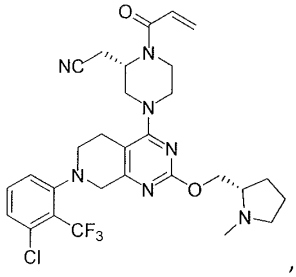
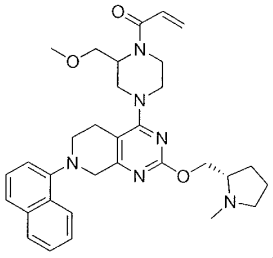
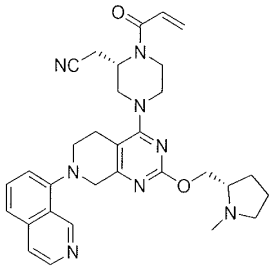
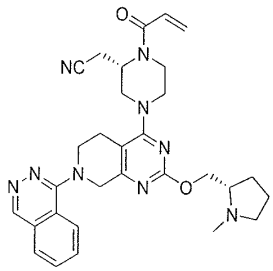
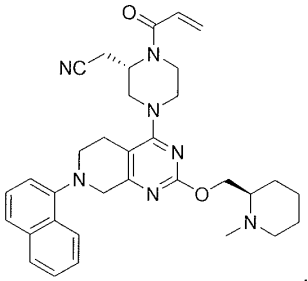
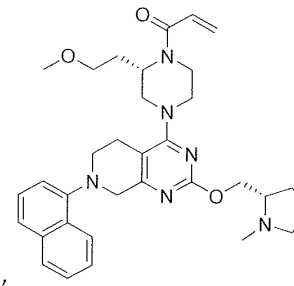
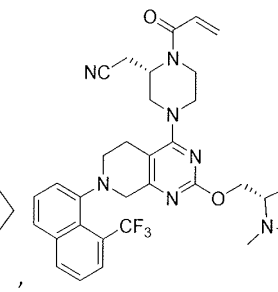
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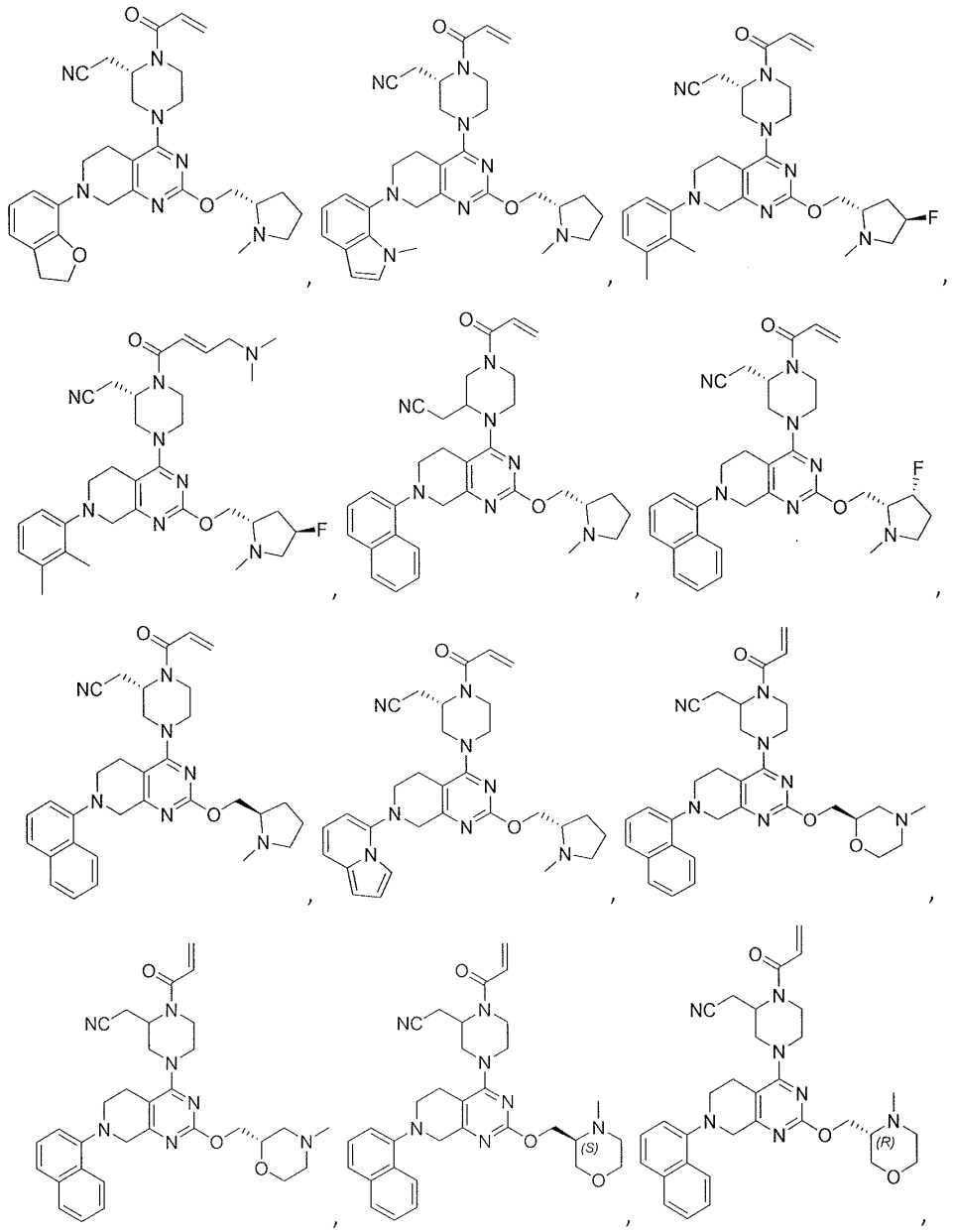

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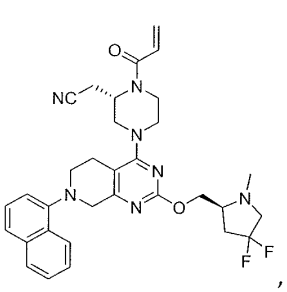
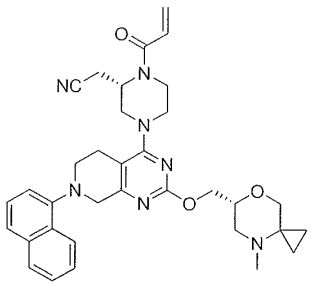
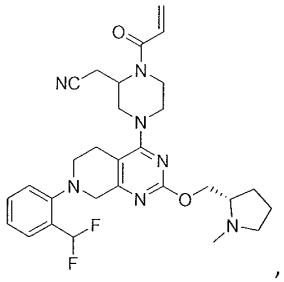
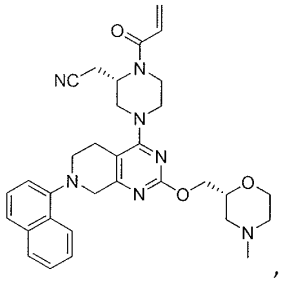
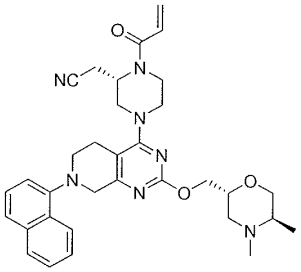
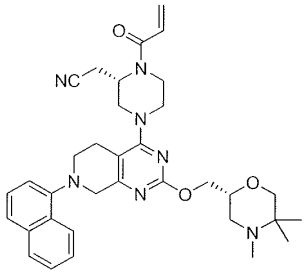
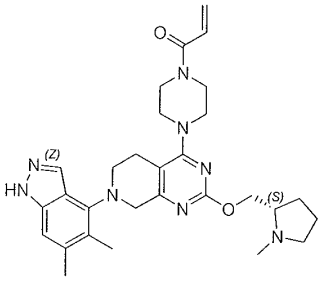
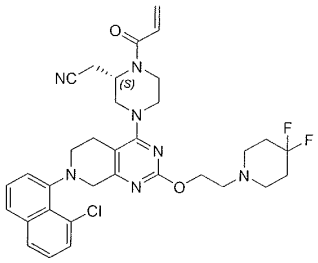
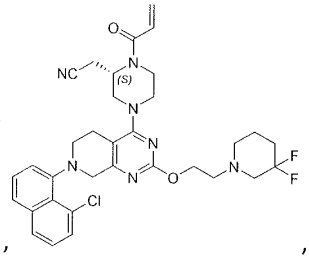
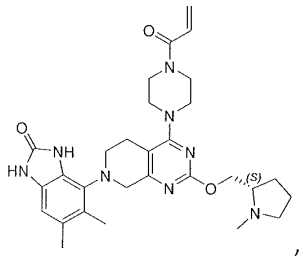
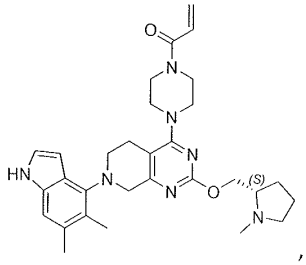
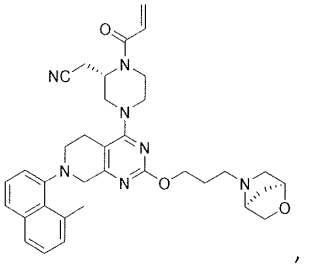
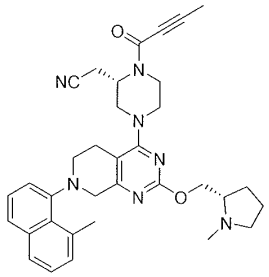
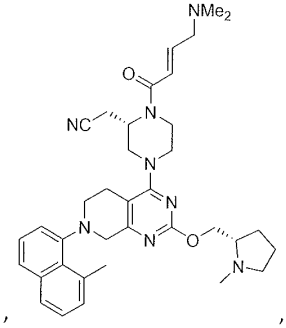
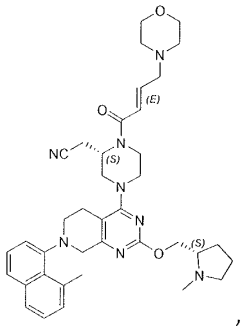
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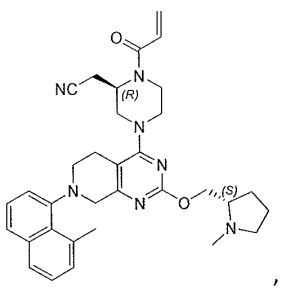
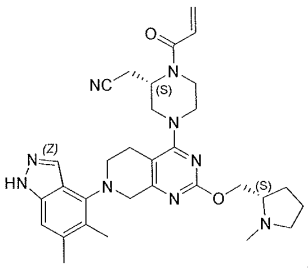
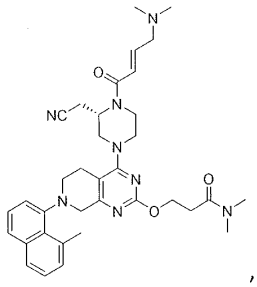
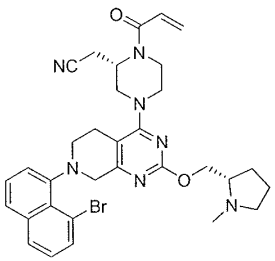
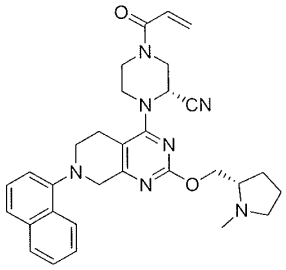
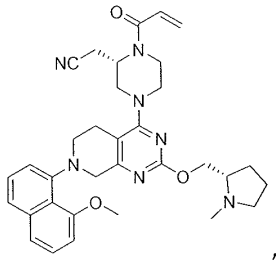
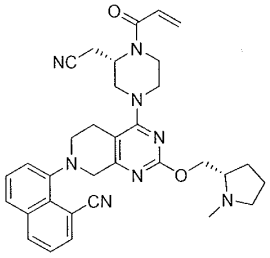
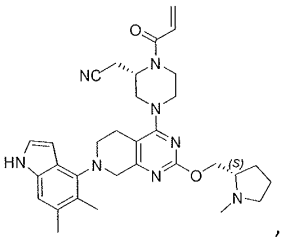
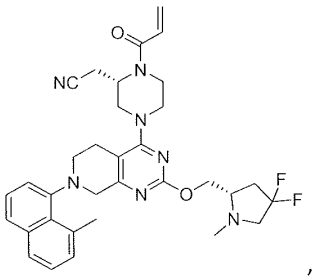
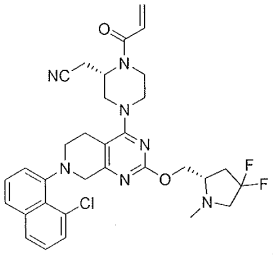
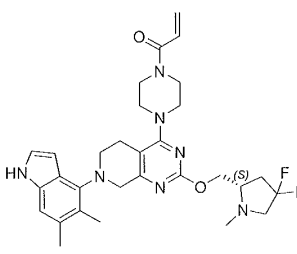
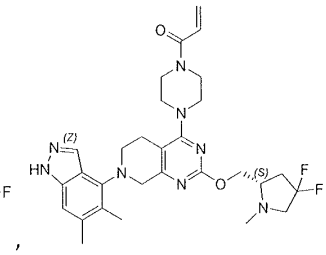


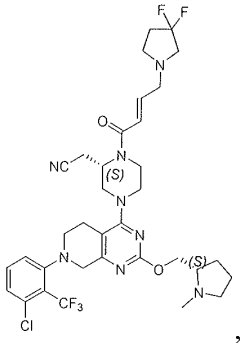
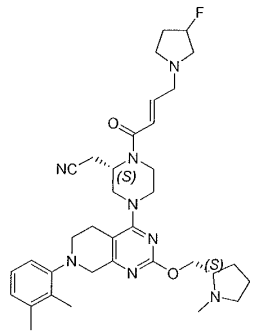
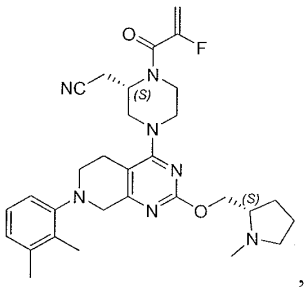
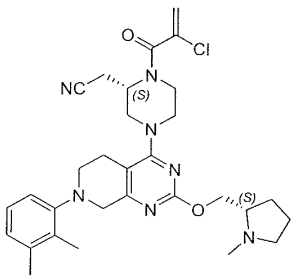
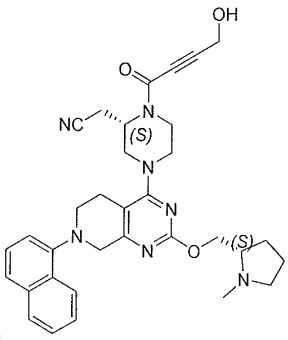
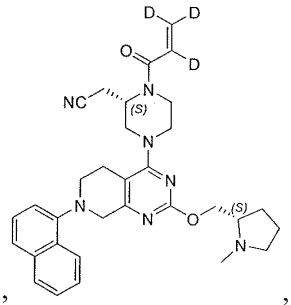
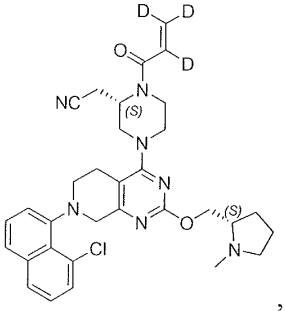
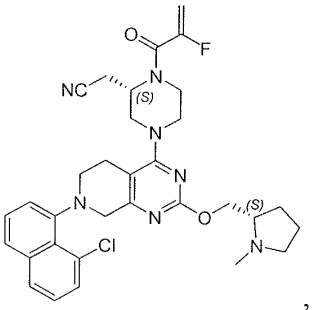
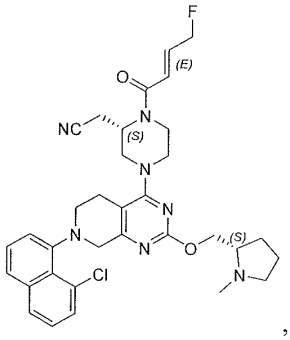
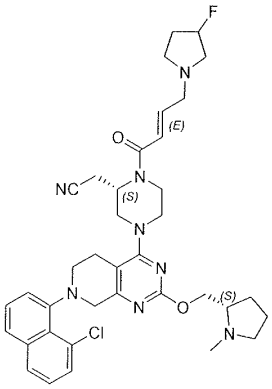
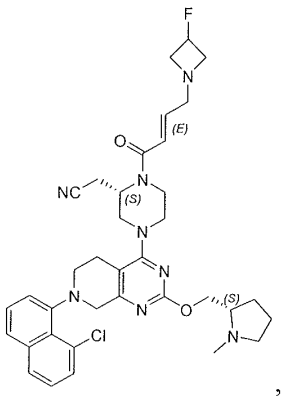
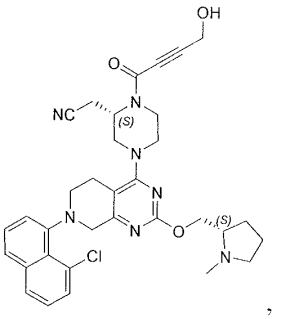

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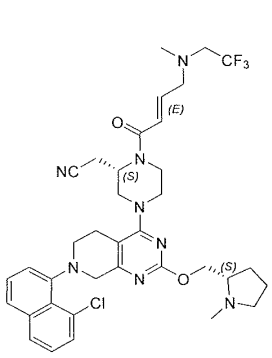
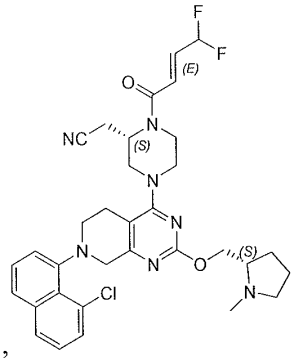
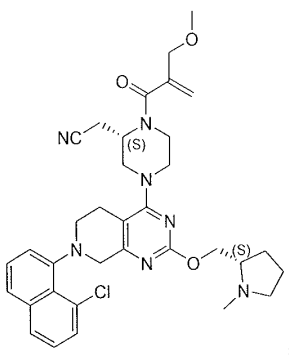
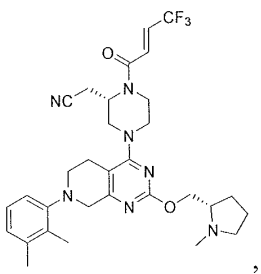
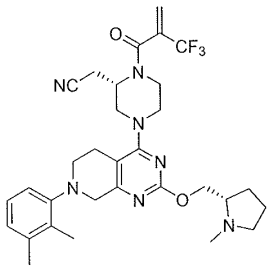
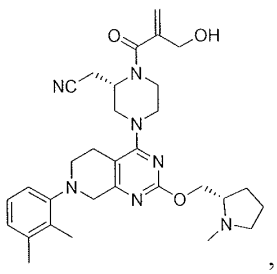
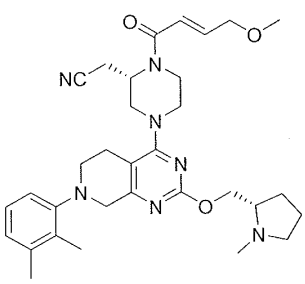
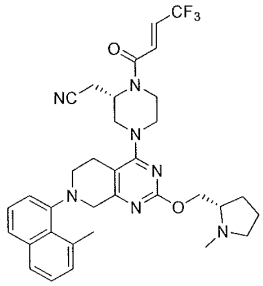
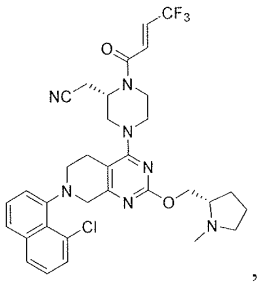
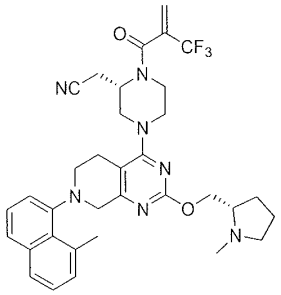
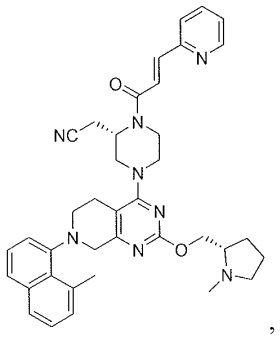
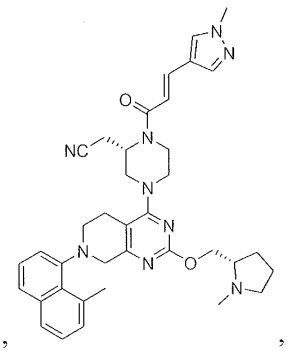
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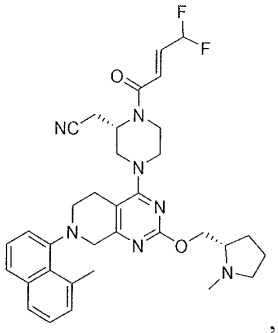
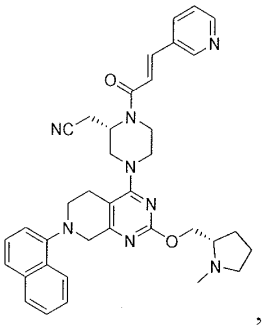
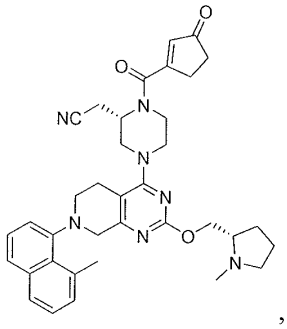
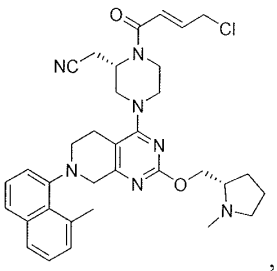
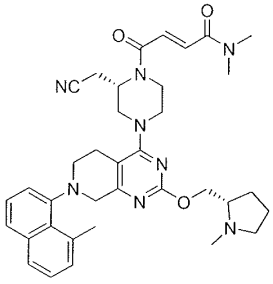
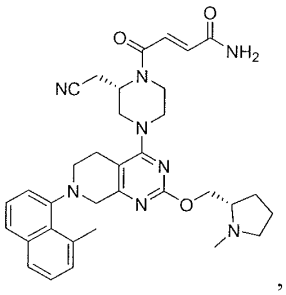
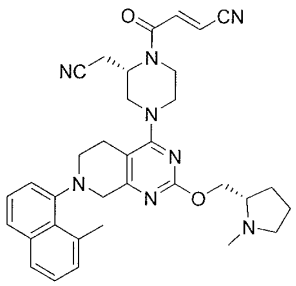
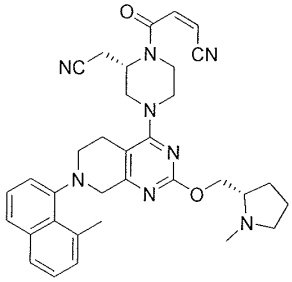
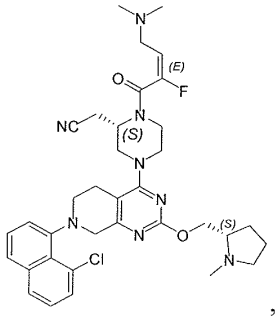
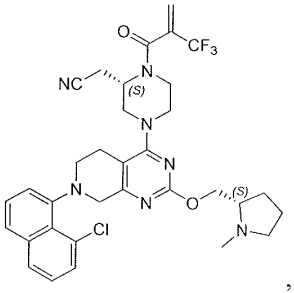
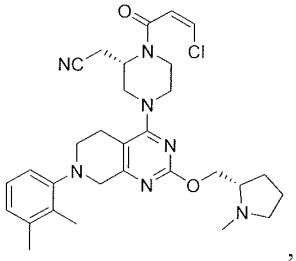
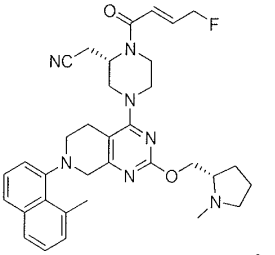
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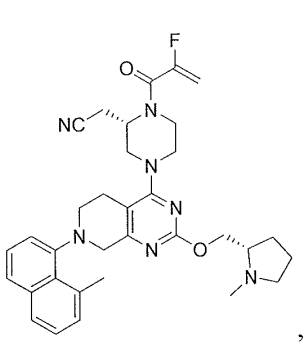
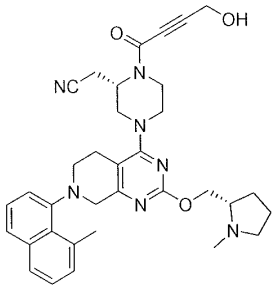
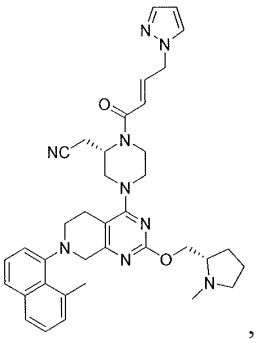
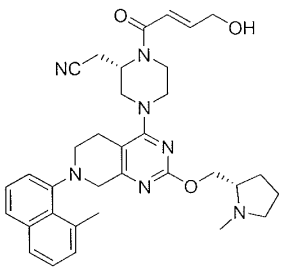
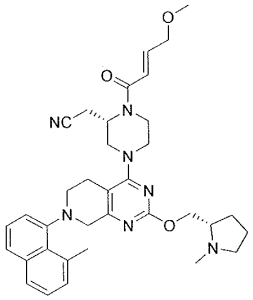
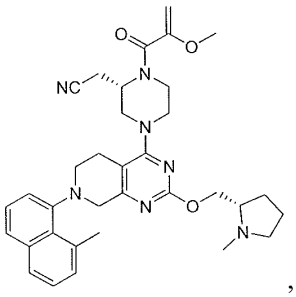
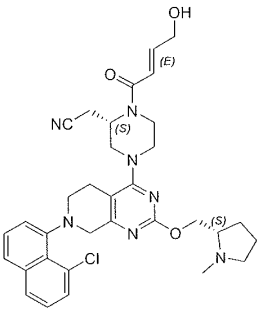
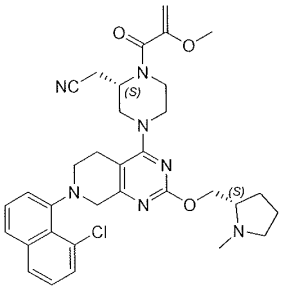
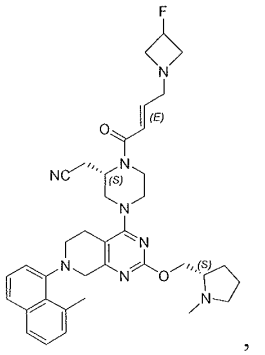
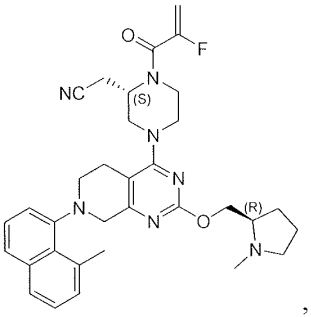
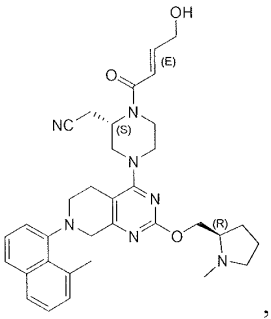
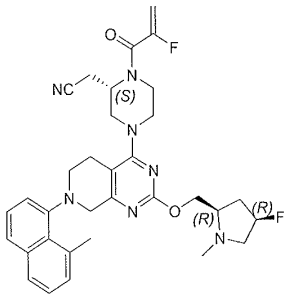
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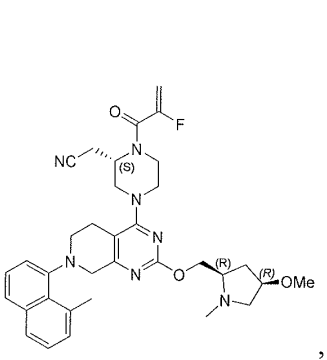
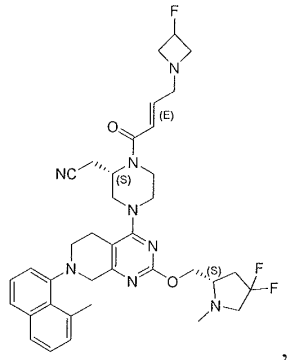
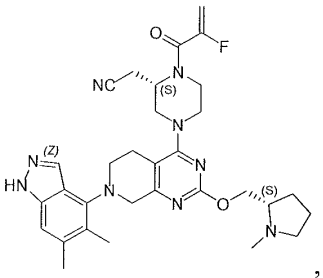
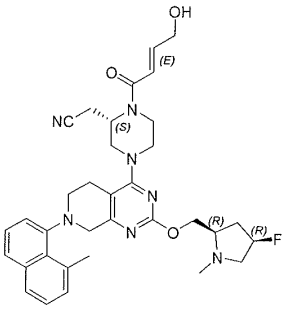
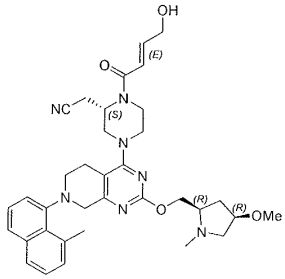
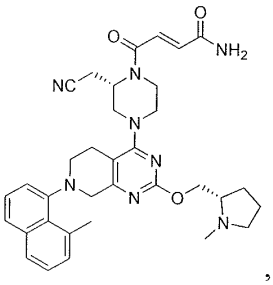
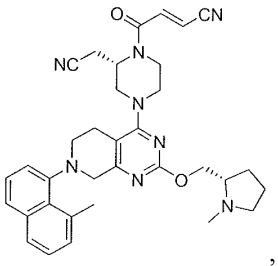
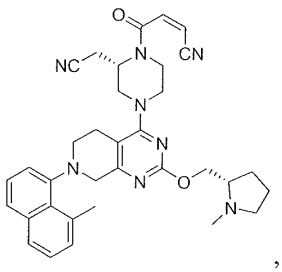
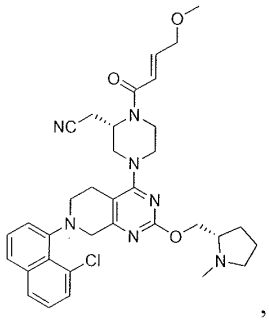
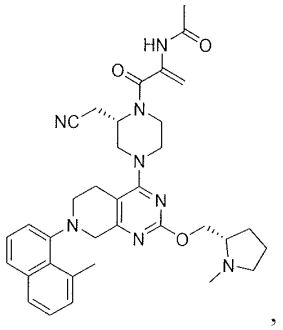
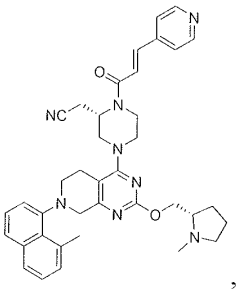
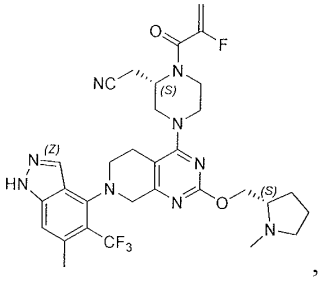

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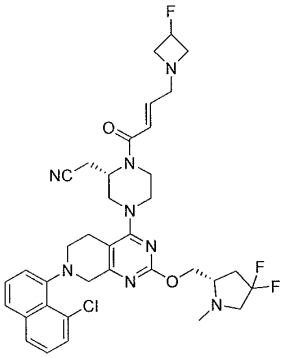
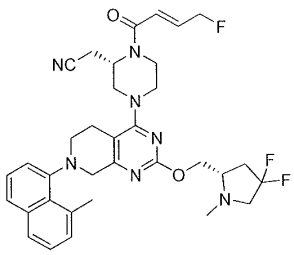
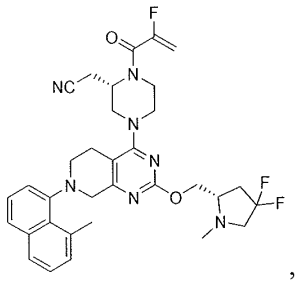
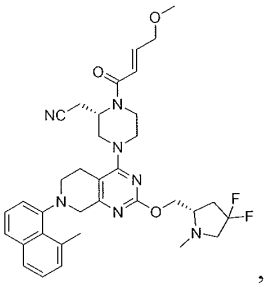
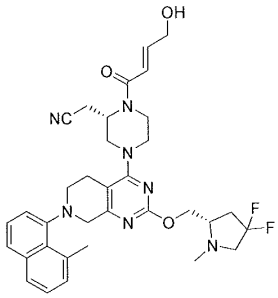
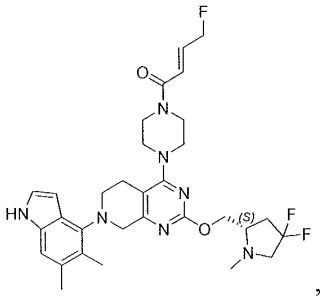
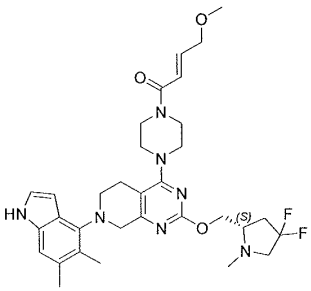
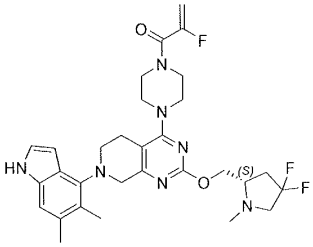
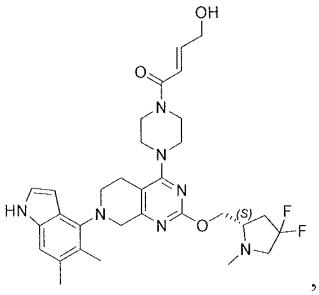
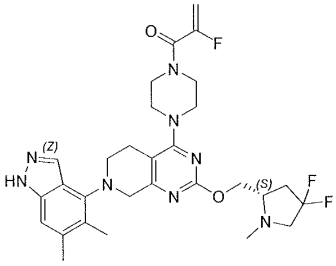
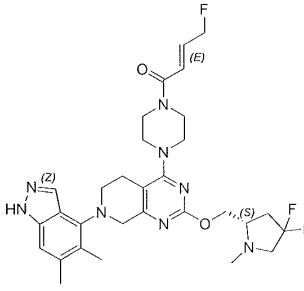
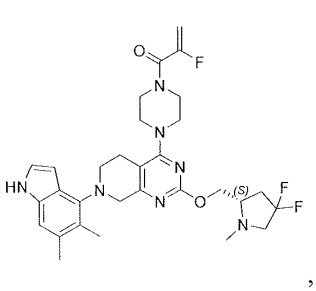

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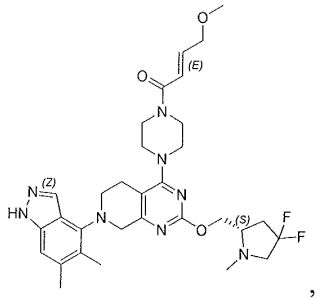
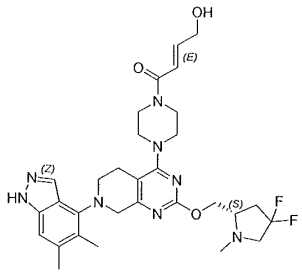
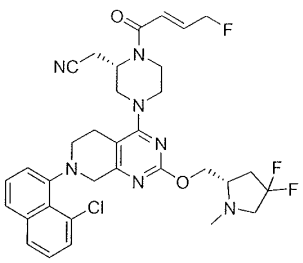
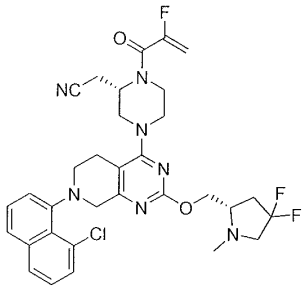
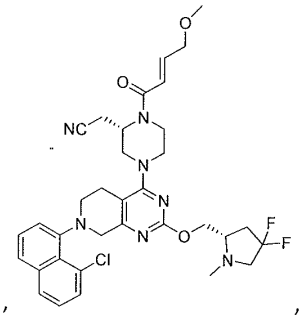
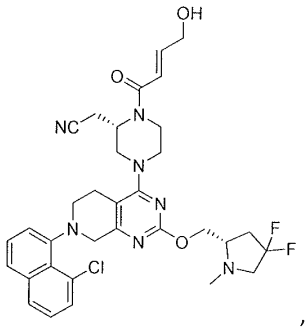
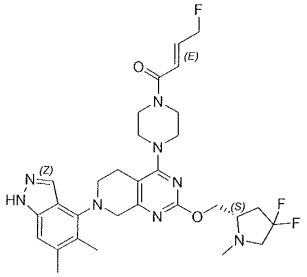
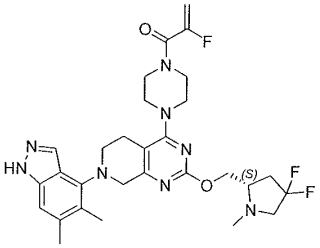
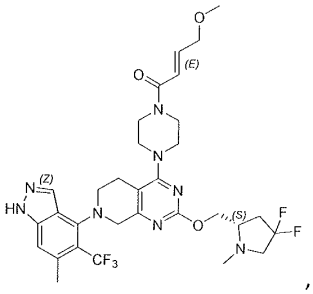
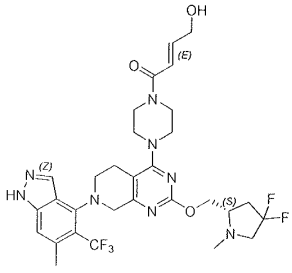
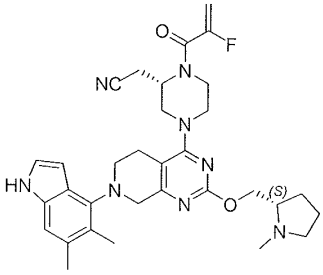
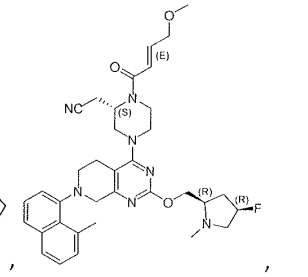

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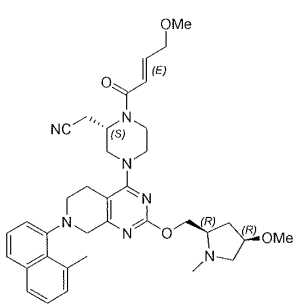
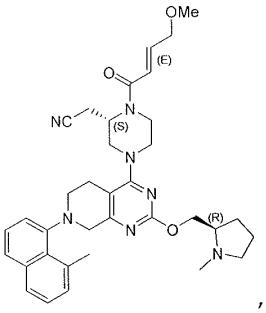
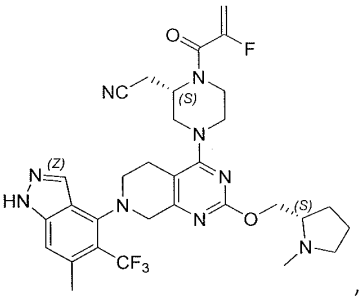
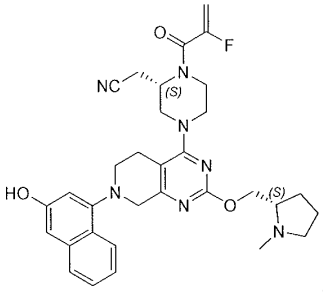
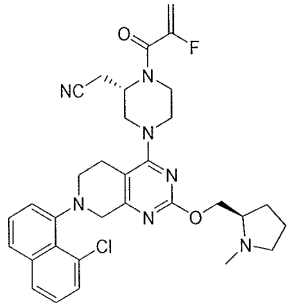
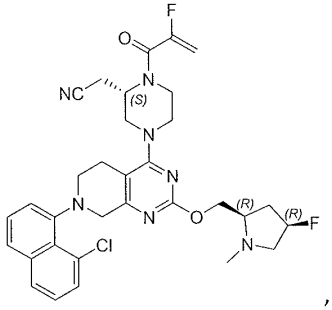
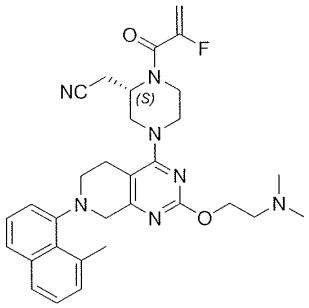
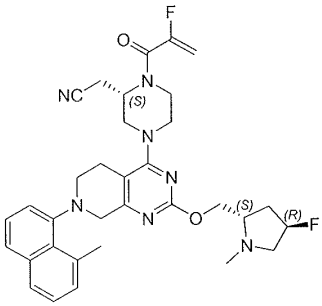
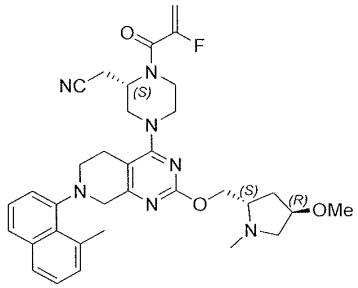
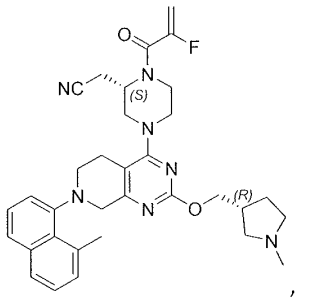
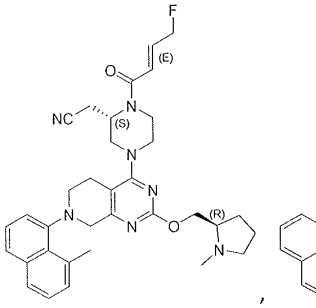
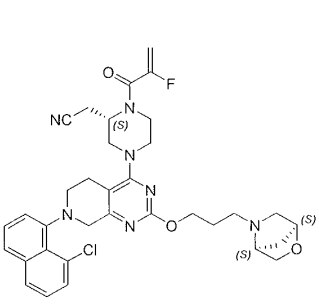
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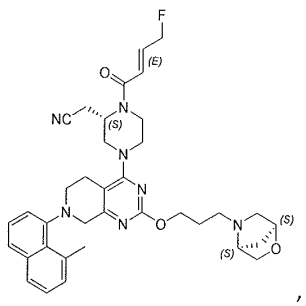
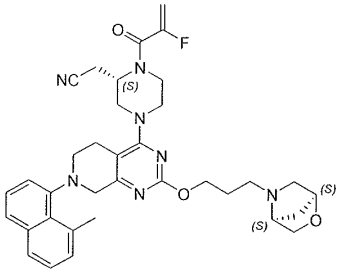
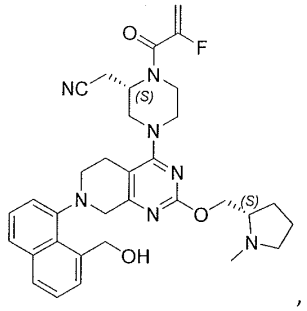
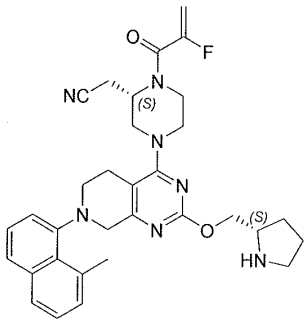
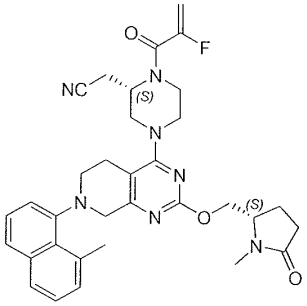
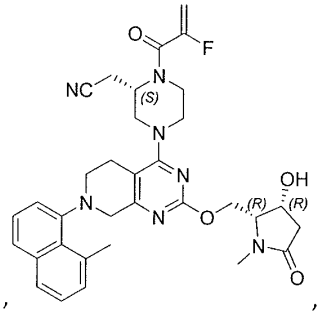
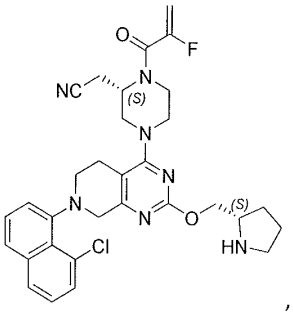
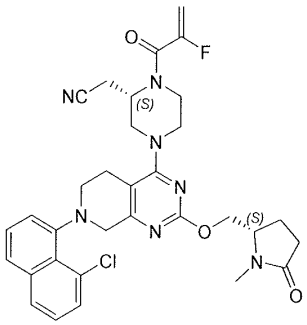
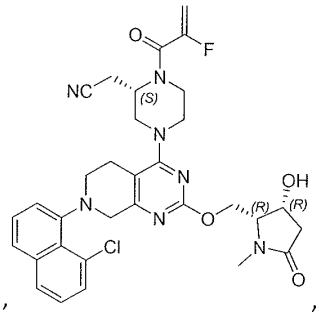
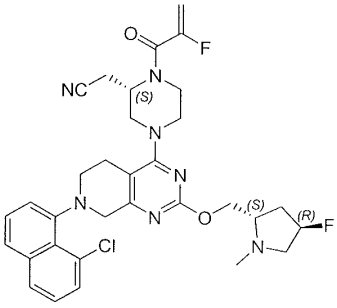
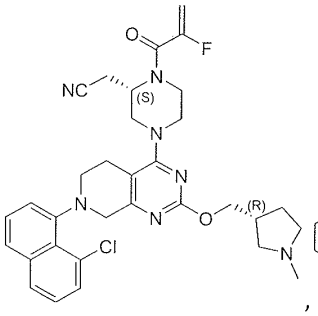
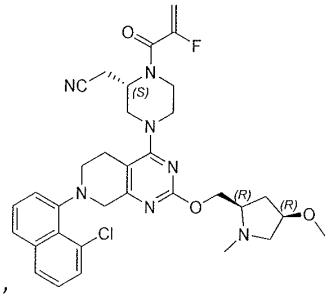
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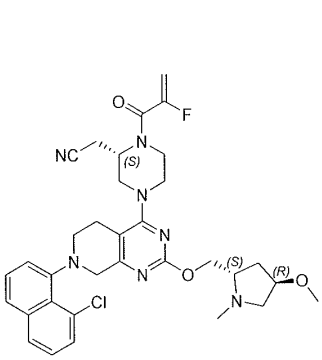
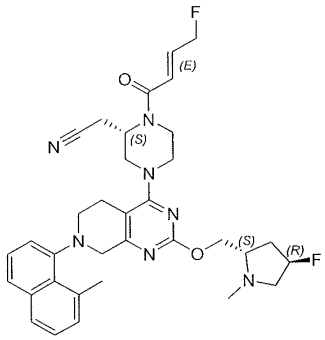
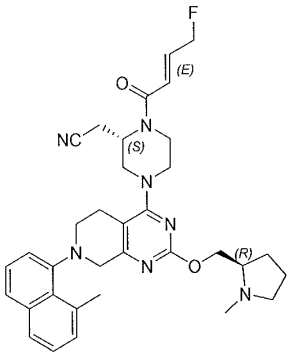
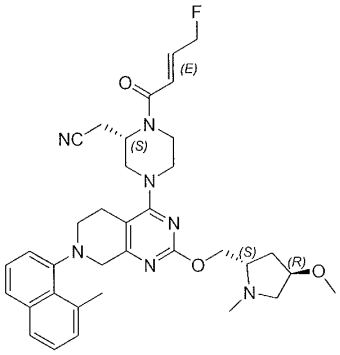
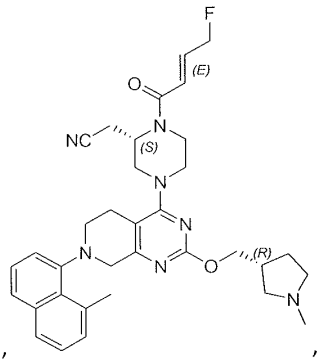
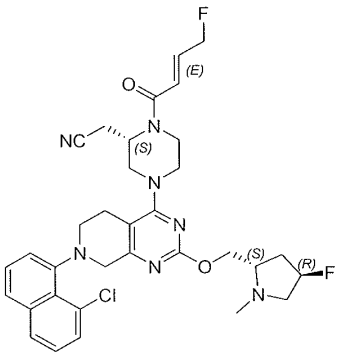
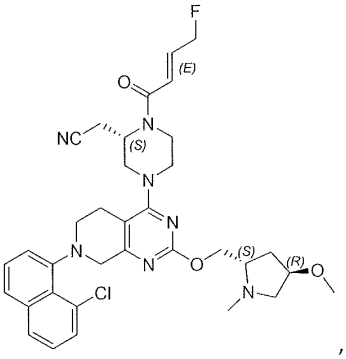
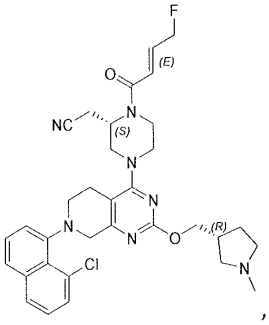
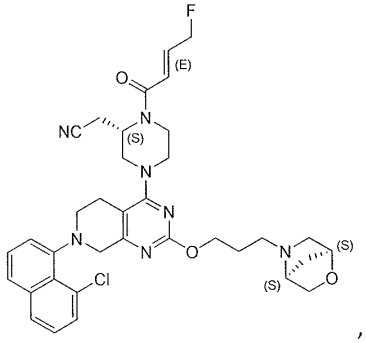
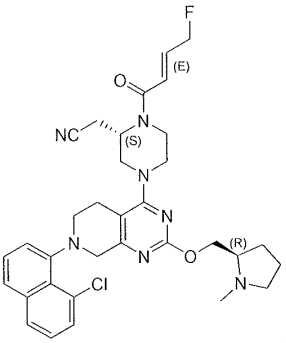
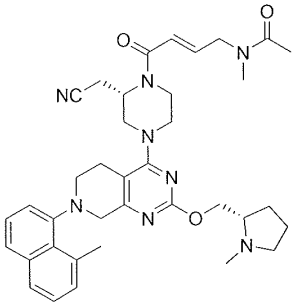
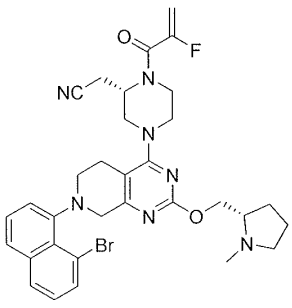
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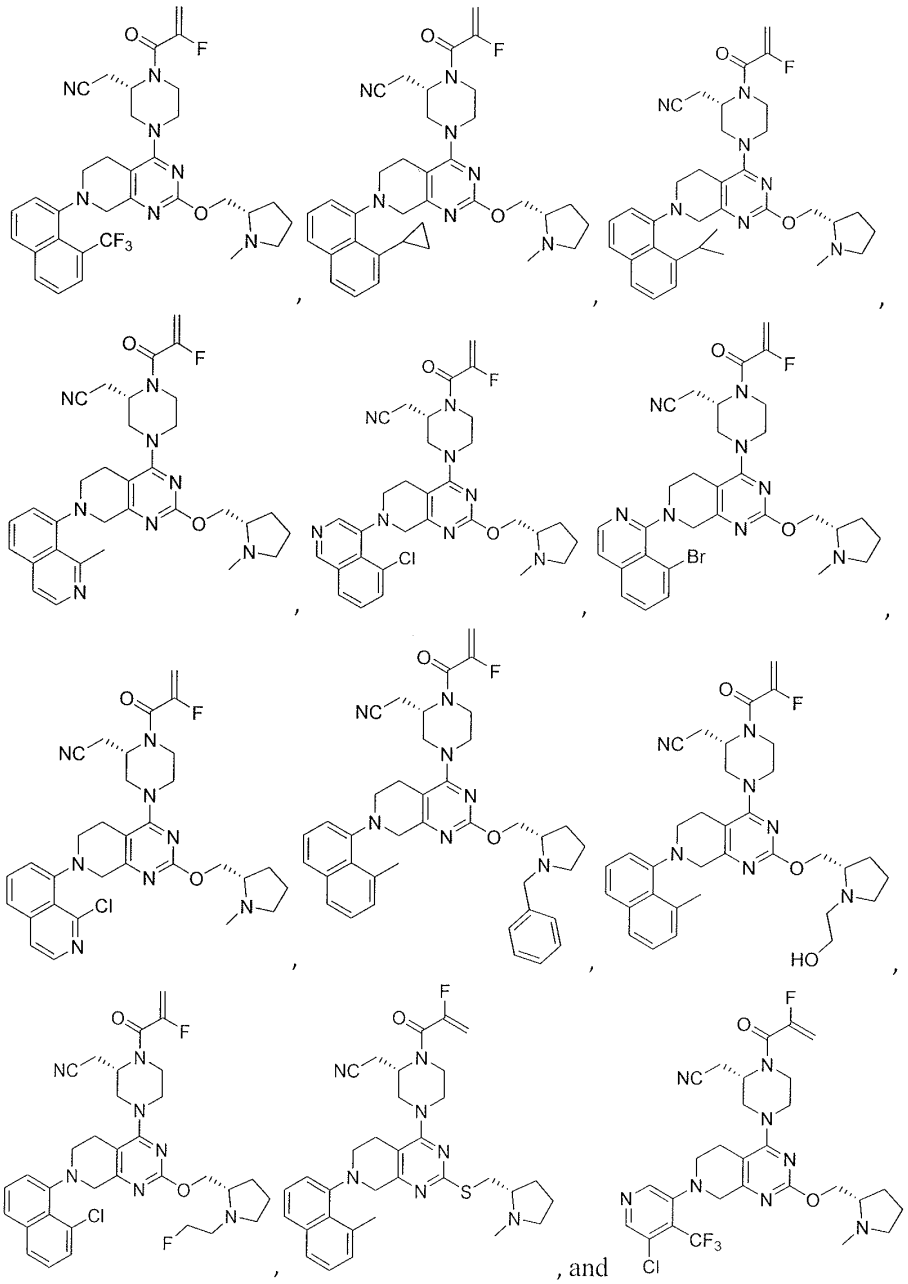
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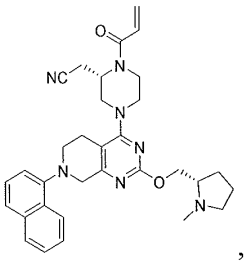
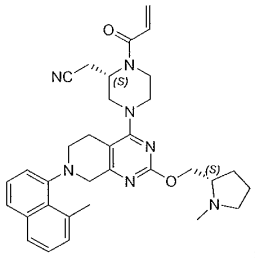
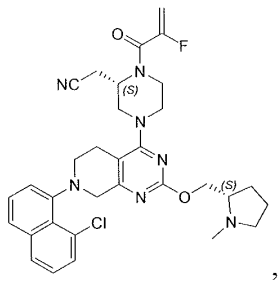
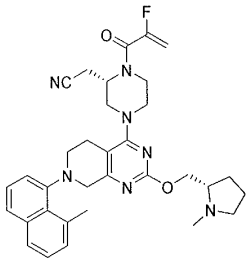

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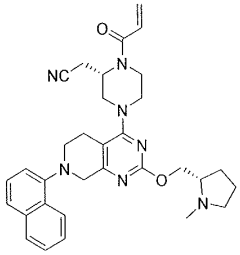
[0131] and pharmaceutically acceptable salts thereof.

[0132] In one embodiment, the KRas G12C inhibitor is selected from:


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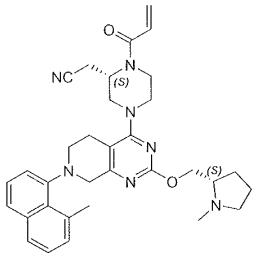
[0133] and pharmaceutically acceptable salts thereof.

[0134] In one embodiment, the KRas G12C inhibitor is:



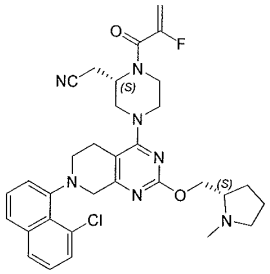
[0135] (also referred to as Example 234) or a pharmaceutically acceptable salt thereof.

[0136] In one embodiment, the KRas G12C inhibitor is:



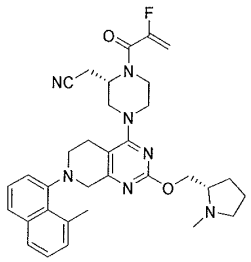
[0137] (also referred to as Example 359) or a pharmaceutically acceptable salt thereof.

[0138] In one embodiment, the KRas G12C inhibitor is:



[0139] (also referred to as Example 478) or a pharmaceutically acceptable salt thereof.

[0140] In one embodiment, the KRas G12C inhibitor is:



(also referred to as Example 507) or a pharmaceutically acceptable salt thereof.

[0141] The KRas G12C 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.

[0142] In one embodiment, the KRas G12C inhibitor compounds of Formula I, Formula I-A, or Formula I-B used in the methods include trifluoroacetic acid salts of the above compounds.

[0143] Methods for manufacturing the KRas G12C inhibitors disclosed herein are known. For example, commonly owned published international PCT application numbers WO2017201161 and WO2019099524describe general reaction schemes for preparing compounds of Formula I, Formula I-A, or Formula I-B and pharmaceutically acceptable salts thereof and also provide detailed synthetic routes for the preparation of each KRas G12C inhibitor disclosed herein.

[0144] The Pan ErbB inhibitors and the KRas G12C compounds of Formula (I), Formula I-A, or Formula I-B or pharmaceutically acceptable salts thereof may be formulated into pharmaceutical compositions.

PHARMACEUTICAL COMPOSITIONS

[0145] In another aspect, the invention provides pharmaceutical compositions comprising a pan ErbB family inhibitor and KRas G12C inhibitor according to the invention and a pharmaceutically acceptable carrier, excipient, or diluent that may be used in the methods disclosed herein. The pan ErbB family inhibitor and KRas G12C inhibitor 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, pan ErbB family inhibitor and KRas G12C inhibitor are administered intravenously in a hospital setting. In one embodiment, administration may be by the oral route.

[0146] 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.

[0147] 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).

[0148] 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.

[0149] The pharmaceutical compositions comprising a pan ErbB family inhibitor and a KRas G12C inhibitor may be used in the methods of use described herein.

CO-ADMINSTRATION

[0150] The pan ErbB family inhibitor and the KRas G12C inhibitor 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.

[0151] The pharmaceutical compositions comprising a pan ErbB family inhibitor and/or a KRas G12C inhibitor for use in the methods may be for simultaneous, separate or sequential use. In one embodiment, the pan ErbB family inhibitor is administered prior to administration of the KRas G12C inhibitor compound of Formula (I), Formula I-A or Formula I-B. In another embodiment, the pan ErbB family inhibitor is administered after administration of the KRas G12C inhibitor compound of Formula (I), Formula I-A or Formula I-B. In another embodiment, the pan ErbB family inhibitor is administered at about the same time as administration of the KRas G12C inhibitor compound of Formula (I), Formula I-A or Formula I-B.

[0152] 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 G12C inhibitor compound of Formula (I), Formula I-A or Formula I-B, or a pharmaceutically acceptable salt thereof and the pan ErbB family inhibitor or a pharmaceutically acceptable salt thereof, need not be necessarily administered at essentially the same time or in any order.

[0153] 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 G12C inhibitor or a pharmaceutically acceptable salt or a pharmaceutically composition thereof and the pan ErbB family inhibitor or a pharmaceutically acceptable salt or a pharmaceutically composition thereof are each dosed at their respective MTDs. In one embodiment, the KRas G12C inhibitor or a pharmaceutically acceptable salt or a pharmaceutically composition thereof is dosed at its MTD and the pan ErbB family inhibitor or a pharmaceutically acceptable salt or a pharmaceutically composition thereof is dosed in an amount less than its MTD. In one embodiment, the KRas G12C inhibitor or a pharmaceutically acceptable salt or a pharmaceutically composition thereof is dosed at an amount less than its MTD and the pan ErbB family inhibitor or a pharmaceutically acceptable salt or a pharmaceutically composition thereof is dosed at its MTD. In one embodiment, the KRas G12C

inhibitor or a pharmaceutically acceptable salt or a pharmaceutically composition thereof and the pan ErbB family inhibitor or a pharmaceutically acceptable salt or a pharmaceutically 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.

[0154] In one embodiment, the KRas G12C inhibitor compound of Formula (I), Formula I-A or Formula I-B or a pharmaceutically acceptable salt or a pharmaceutically composition thereof is administered per day (i.e., in about 24 hour intervals) (i.e., QD). In another embodiment, the KRas G12C inhibitor compound of Formula (I), Formula I-A or Formula I-B or a pharmaceutically acceptable salt or a pharmaceutically composition thereof is administered per day (i.e., BID). In another embodiment, the KRas G12C inhibitor compound of Formula (I), Formula I-A or Formula I-B or a pharmaceutically acceptable salt or a pharmaceutically composition thereof is administered per day (i.e., TID).

[0155] In one embodiment, the pan ErbB family inhibitor or a pharmaceutically acceptable salt or a pharmaceutically composition thereof is administered QD. In another embodiment, the pan ErbB family inhibitor or a pharmaceutically acceptable salt or a pharmaceutically composition thereof is administered BID. In another embodiment, the pan ErbB family inhibitor or a pharmaceutically acceptable salt or a pharmaceutically composition thereof of the invention are administered TID.

[0156] In one embodiment, a single dose of KRas G12C inhibitor compound of Formula (I), Formula I-A or Formula I-B or a pharmaceutically acceptable salt or a pharmaceutically composition thereof and pan ErbB family inhibitor or a pharmaceutically acceptable salt or a pharmaceutically composition thereof are each administered once daily.

[0157] In one embodiment, the pan ErbB family inhibitor is an irreversible inhibitor. Exemplary irreversible pan ErbB family inhibitors for use in the methods herein include afatinib ((E)-N-(4-((3-chloro-4-fluorophenyl)amino)-7-((tetrahydrofuran-3-yl)oxy)quinazolin-6-yl)-4-(dimethylamino)but-2-enamide); dacomitinib ((2*E*)-*N*-{4-[(3-Chloro-4-fluorophenyl)amino]-7-methoxy-6-quinazolinyl}-4-(1-piperidinyl)-2-butenamide); canertinib (N-(4-((3-chloro-4-fluorophenyl)amino)-7-(3-morpholinopropoxy)quinazolin-6-yl)acrylamide); poziotinib (1-(4-

((4-((3,4-dichloro-2-fluorophenyl)amino)-7-methoxyquinazolin-6-yl)oxy)piperidin-1-yl)prop-2-en-1-one); AV 412 (*N*-[4-[(3-Chloro-4-fluorophenyl)amino]-7-[3-methyl-3-(4-methyl-1-piperazinyl)-1-butyn-1-yl]-6-quinazolinyl]-2-propenamide); PF 6274484 (*N*-[4-[(3-Chloro-4-fluorophenyl)amino]-7-methoxy-6-quinazolinyl]-2-propenamide) and HKI 357 ((2*E*)-*N*-[[4-[[(3-Chloro-4-[(3-fluorophenyl)methoxy]phenyl]amino]-3-cyano-7-ethoxy-6-quinolinyl]-4-(dimethylamino)-2-butenamide), or pharmaceutically acceptable salts or pharmaceutically compositions thereof.

[0158] In one embodiment, the pan ErbB family inhibitor is a reversible inhibitor. Exemplary reversible pan EGFR family inhibitors include erlotinib ([6,7-Bis-(2-methoxy-ethoxy)-quinazolin-4-yl]-(3-ethynyl-phenyl)-amine)), gefitinib ((4-(3'-chloro-4'-fluoroanilino)-7-methoxy-6-(3-morpholinopropoxy)quinazoline), sapitinib (2-(4-((4-((3-chloro-2-fluorophenyl)amino)-7-methoxyquinazolin-6-yl)oxy)piperidin-1-yl)-N-methylacetamide); varlitinib ((R)-N4-(3-chloro-4-(thiazol-2-ylmethoxy)phenyl)-N6-(4-methyl-4,5-dihydrooxazol-2-yl)quinazoline-4,6-diamine); TAK-285 (N-(2-(4-((3-chloro-4-(3-(trifluoromethyl)phenoxy)phenyl)amino)-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethyl)-3-hydroxy-3-methylbutanamide); AEE788 ((S)-6-(4-((4-ethylpiperazin-1-yl)methyl)phenyl)-N-(1-phenylethyl)-7H-pyrrolo[2,3-d]pyrimidin-4-amine); tarloxotinib ([(*E*)-4-[[4-(3-bromo-4-chloroanilino)pyrido[3,4-d]pyrimidin-6-yl]amino]-4-oxobut-2-enyl]-dimethyl-[(3-methyl-5-nitroimidazol-4-yl)methyl]azanium); BMS 599626 ((3*S*)-3-Morpholinylmethyl-[4-[[1-[(3-fluorophenyl)methyl]-1*H*-indazol-5-yl]amino]-5-methylpyrrolo[2,1-*f*][1,2,4]triazin-6-yl]-carbamate dihydrochloride); and GW 583340 HCl (*N*-[3-Chloro-4-[(3-fluorophenyl)methoxy]phenyl]-6-[2-[[[2-(methylsulfonyl)ethyl]amino]methyl]-4-thiazolyl]-4-quinazolinamine dihydrochloride), or pharmaceutically acceptable salts or pharmaceutically compositions thereof.

[0159] In one embodiment, the pan ErbB family inhibitor is an anti-EGFR antibody, an anti-HER2 antibody or a combination of an anti-EGFR antibody and anti-HER2 antibody, or pharmaceutical compositions thereof. In one embodiment, the anti-EGFR antibody is necitumumab, panitumumab or cetuximab. In one embodiment, the anti-EGFR antibody is cetuximab. In one embodiment, the anti-HER2 antibodies suitable for use in the methods herein is pertuzumab, trastuzumab, or trastuzumab emtansine.

[0160] In one embodiment, the pan ErbB family inhibitor is a an EGFR inhibitor and a HER2 inhibitor, wherein the EGFR inhibitor and the HER2 inhibitor are independently selected from two agents selected from the group consisting of: AG 1478 HCl (*N*-(3-Chlorophenyl)-6,7-dimethoxy-4-quinazolinanine hydrochloride); AG 494 (*E*)-2-Cyano-3-(3,4-dihydroxyphenyl)-*N*-phenyl-2-propenamide; AG 555 (*E*)-2-Cyano-3-(3,4-dihydroxyphenyl)-*N*-(3-phenylpropyl)-2-propenamide; AG 556 (*E*)-2-Cyano-3-(3,4-dihydroxyphenyl)-*N*-(4-phenylbutyl)-2-propenamide; AG 825 (*E*)-3-[3-[2-Benzothiazolythio)methyl]-4-hydroxy-5-methoxyphenyl]-2-cyano-2-propenamide; CP 724714 (2-Methoxy-*N*-[(2*E*)-3-[4-[[3-methyl-4-[(6-methyl-3-pyridinyl)oxy]phenyl]amino]-6-quinazolinyl]-2-propen-1-yl]acetamide; BIBU 1361 diHCl (*N*-(3-Chloro-4-fluorophenyl)-6-[4-[(diethylamino)methyl]-1-piperidinyl]-pyrimido[5,4-*d*]pyrimidin-4-amine dihydrochloride); BIBU 1382 (N^8-(3-Chloro-4-fluorophenyl)-N^2-(1-methyl-4-piperidinyl)-pyrimido[5,4-*d*]pyrimidine-2,8-diamine dihydrochloride); JNJ 28871063 HCl (5*E*-4-Amino-6-(4-benzyloxy-3-chlorophenylamino)pyrimidine-5-carboxaldehyde *N*-(2-morpholin-4-ylethyl) oxime hydrochloride); PD 153035 (4-[(3-Bromophenyl)amino]-6,7-dimethoxyquinazoline hydrochloride); PD 158780 (N^4-(3-Bromophenyl)-N^6-methyl-pyrido[3,4-*d*]pyrimidine-4,6-diamine) or pharmaceutically acceptable salts or pharmaceutically compositions thereof.

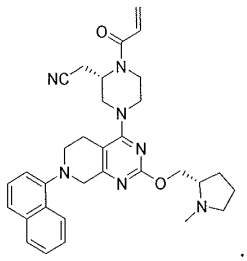
COMBINATION THERAPIES

[0161] 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 pan ErbB family inhibitor, or a pharmaceutically acceptable salt or a pharmaceutically composition thereof and a KRAS G12C inhibitor of Formula (I), Formula I-A or Formula I-B , or a pharmaceutically acceptable salt or a pharmaceutically composition thereof. In one embodiment, the cancer is a KRas G12C-associated cancer. In one embodiment, the KRas G12C-associated cancer is lung cancer.

[0162] In yet another aspect, the invention provides for methods for increasing the sensitivity of a cancer cell to a KRas G12C inhibitor, comprising contacting the cancer cell with an effective amount of a combination of a KRas G12C inhibitor compound of Formula (I), Formula I-A, or Formula I-B, or a pharmaceutically acceptable salt or a pharmaceutically composition thereof and a pan ErbB family inhibitor, or a pharmaceutically acceptable salt or a pharmaceutical

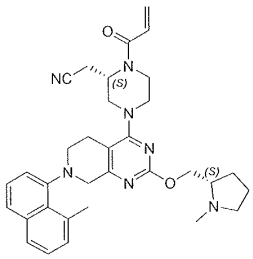
composition thereof, wherein the pan ErbB family inhibitor synergistically increases the sensitivity of the cancer cell to the KRas G12C inhibitor. In one embodiment, the contacting is in vitro. In one embodiment, the contacting is in vivo.

[0163] In one embodiment, the combination therapy comprises a combination of a compound having the formula:



[0164] or a pharmaceutically acceptable salt thereof, and a pan ErbB family inhibitor. In one embodiment, the pan ErbB family inhibitor is afatinib. In one embodiment, the pan ErbB family inhibitor is dacomitinib. In one embodiment, the pan ErbB family inhibitor is poziotinib. In one embodiment, the pan ErbB family inhibitor is erlotinib. In one embodiment, the pan ErbB family inhibitor is Gefitinib. In one embodiment, the pan ErbB family inhibitor is sapitinib. In one embodiment, the pan ErbB family inhibitor is tarloxotinib. In one embodiment, the pan ErbB family inhibitor is an anti-EGFR antibody, wherein the anti-EGFR antibody is cetuximab.

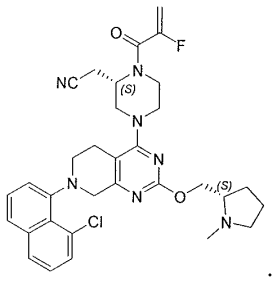
[0165] In one embodiment, the combination therapy comprises a combination of a compound having the formula:



[0166] or a pharmaceutically acceptable salt thereof, and a pan ErbB family inhibitor. In one embodiment, the pan ErbB family inhibitor is Afatinib. In one embodiment, the pan ErbB

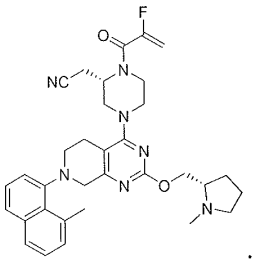
family inhibitor is dacomitinib. In one embodiment, the pan ErbB family inhibitor is poziotinib. In one embodiment, the pan ErbB family inhibitor is erlotinib. In one embodiment, the pan ErbB family inhibitor is gefitinib. In one embodiment, the pan ErbB family inhibitor is sapitinib. In one embodiment, the pan ErbB family inhibitor is tarloxotinib. In one embodiment, the pan ErbB family inhibitor is an anti-EGFR antibody, wherein the anti-EGFR antibody is cetuximab.

[0167] In one embodiment, the combination therapy comprises a combination of a compound having the formula:



[0168] or a pharmaceutically acceptable salt thereof, and a pan ErbB family inhibitor. In one embodiment, the pan ErbB family inhibitor is afatinib. In one embodiment, the pan ErbB family inhibitor is dacomitinib. In one embodiment, the pan ErbB family inhibitor is poziotinib. In one embodiment, the pan ErbB family inhibitor is erlotinib. In one embodiment, the pan ErbB family inhibitor is Gefitinib. In one embodiment, the pan ErbB family inhibitor is sapitinib. In one embodiment, the pan ErbB family inhibitor is tarloxotinib. In one embodiment, the pan ErbB family inhibitor is an anti-EGFR antibody, wherein the anti-EGFR antibody is cetuximab.

[0169] In one embodiment, the combination therapy comprises a combination of a compound having the formula:



[0170] or a pharmaceutically acceptable salt thereof, and a pan ErbB family inhibitor. In one embodiment, the pan ErbB family inhibitor is afatinib. In one embodiment, the pan ErbB family inhibitor is Dacomitinib. In one embodiment, the pan ErbB family inhibitor is poziotinib. In one embodiment, the pan ErbB family inhibitor is erlotinib. In one embodiment, the pan ErbB family inhibitor is Gefitinib. In one embodiment, the pan ErbB family inhibitor is sapitinib. In one embodiment, the pan ErbB family inhibitor is tarloxotinib. In one embodiment, the pan ErbB family inhibitor is an anti-EGFR antibody, wherein the anti-EGFR antibody is cetuximab.

[0171] 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 G12C, as well as, for example, introducing a combination provided herein into a sample containing a cellular or purified preparation containing the KRas G12C.

[0172] By negatively modulating the activity of KRas G12C, the methods described herein are designed to inhibit undesired cellular proliferation resulting from enhanced KRas G12C activity within the cell. The degree of covalent modification of KRas G12C may be monitored in vitro using well known methods, including those described in published international PCT application numbers WO2017201161 and WO2019099524. In addition, the inhibitory activity of combination in cells may be monitored, for example, by measuring the inhibition of KRas G12C activity of the amount of phosphorylated ERK to assess the effectiveness of treatment and dosages may be adjusted accordingly by the attending medical practitioner.

[0173] The compositions and methods provided herein may be used for the treatment of a KRas G12C-associated cancer in a subject in need thereof, comprising administering to said subject a

therapeutically effective amount of a combination of a pan ErbB family inhibitor, or a pharmaceutically acceptable salt or a pharmaceutically composition thereof and a KRas G12C inhibitor compound of Formula (I), Formula I-A, or Formula I-B, or a pharmaceutically acceptable salt or a pharmaceutical composition thereof, wherein the pan ErbB family inhibitor synergistically increases the sensitivity of the KRas G12C-associated cancer to the KRas G12C inhibitor. In one embodiment, the KRas G12C-associated cancer is lung cancer.

[0174] In one embodiment, the therapeutically effective amount of the combination of a pan ErbB family inhibitor or a pharmaceutically acceptable salt or a pharmaceutically composition thereof and a KRas G12C inhibitor compound of Formula (I), Formula I-A, or Formula I-B, 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 G12C inhibitor. In one embodiment, the therapeutically effective amount of the combination of a pan ErbB family inhibitor or a pharmaceutically acceptable salt or a pharmaceutically composition thereof and a KRas G12C inhibitor compound of Formula (I), Formula I-A, or Formula I-B, 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 G12C inhibitor. In one embodiment, the therapeutically effective amount of the combination of a pan ErbB family inhibitor or a pharmaceutically acceptable salt or a pharmaceutically composition thereof and a KRas G12C inhibitor compound of Formula (I), Formula I-A, or Formula I-B, 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 G12C inhibitor. In one embodiment, the therapeutically effective amount of the combination of a pan ErbB family inhibitor or a pharmaceutically acceptable salt or a pharmaceutically composition thereof and a KRas G12C inhibitor compound of Formula (I), Formula I-A, or Formula I-B, 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 G12C inhibitor. In one embodiment, the KRas G12C inhibitor is a compound selected from compound Nos. 1-678 (as numbered in WO2019099524), or a pharmaceutically acceptable salt thereof (e.g., Example No. 234, 359, 478 or 507 or a pharmaceutically acceptable salt thereof). In one embodiment, the pan ErbB family inhibitor is selected from

afatinib, dacomitinib, poziotinib, erlotinib, gefitinib, sapitinib, and tarloxotinib. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 234 and afatinib. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 234 and dacomitinib. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 234 and poziotinib. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 234 and erlotinib. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 234 and gefitinib. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 234 and Tarloxotinib. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 234 and the anti-EGFR antibody cetuximab. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 359 and afatinib. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 359 and dacomitinib. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 359 and poziotinib. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 359 and erlotinib. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 359 and gefitinib. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 359 and tarloxotinib. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 359 and the anti-EGFR antibody cetuximab. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 478 and afatinib. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 478 and dacomitinib. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 478 and poziotinib. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 478 and erlotinib. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 478 and gefitinib. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 478 and tarloxotinib. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 478 and the anti-EGFR antibody cetuximab.

In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 507 and afatinib. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 507 and dacomitinib. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 507 and poziotinib. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 507 and erlotinib. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 507 and gefitinib. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 507 and tarloxotinib. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 507 and the anti-EGFR antibody cetuximab. In one embodiment of any of said combination therapies, the combination is useful for treating a KRas G12C-associated cancer. In one embodiment, the KRas G12C-associated cancer is lung cancer.

[0175] In another embodiment, the pan ErbB family inhibitor, or a pharmaceutically acceptable salt or a pharmaceutical composition thereof is administered in combination with the KRas G12C inhibitor, or a pharmaceutically acceptable salt or a pharmaceutical composition thereof once disease progression has been observed for KRas G12C monotherapy, in which the combination therapy results in enhanced clinical benefit or time of survival 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 G12C inhibitor is a compound selected from compound Nos. 1-678 (as numbered in WO2019099524), or a pharmaceutically acceptable salt thereof (e.g., Example No. 234, 359, 478 or 507 or a pharmaceutically acceptable salt thereof). In one embodiment, the pan ErbB family inhibitor is selected from afatinib, dacomitinib, poziotinib, erlotinib, gefitinib, sapitinib, and tarloxotinib. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 234 and afatinib. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 234 and dacomitinib. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 234 and poziotinib. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 234 and erlotinib. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 234 and gefitinib. In one embodiment, the therapeutic combination

comprises therapeutically effective amounts of Example No. 234 and tarloxotinib. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 234 and the anti-EGFR antibody cetuximab. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 359 and afatinib. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 359 and dacomitinib. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 359 and poziotinib. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 359 and Erlotinib. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 359 and gefitinib. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 359 and tarloxotinib. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 359 and the anti-EGFR antibody Cetuximab. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 478 and afatinib. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 478 and dacomitinib. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 478 and poziotinib. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 478 and erlotinib. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 478 and gefitinib. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 478 and tarloxotinib. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 478 and the anti-EGFR antibody cetuximab. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 507 and afatinib. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 507 and dacomitinib. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 507 and poziotinib. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 507 and erlotinib. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 507 and gefitinib. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 507 and tarloxotinib. In one

embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 507 and the anti-EGFR antibody cetuximab. In one embodiment of any of said combination therapies, the combination is useful for treating a KRas G12C-associated cancer. In one embodiment, the KRas G12C-associated cancer is lung cancer.

[0176] In one embodiment of any of the methods herein, the pan ErbB family inhibitor and the KRAS G12C inhibitor are administered on the same day.

[0177] In one embodiment of any of the methods herein, the pan ErbB family inhibitor and the KRAS G12C inhibitor are administered on different days.

[0178] The compositions and methods provided herein may be used for the treatment of a wide variety of cancers including tumors such as lung, 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.

[0179] 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 G12C mutation (e.g., a KRas G12C-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 pan ErbB family inhibitor and a KRas G12C inhibitor compound of Formula I, Formula I-A, Formula 1-B, or pharmaceutically acceptable salts or pharmaceutical compositions thereof, wherein the pan ErbB inhibitor synergistically increases the sensitivity of the KRas G12C-associated cancer to the KRas G12C inhibitor. In one embodiment, the KRas G12C inhibitor is a compound selected from compound Nos. 1-678 (as

numbered in WO2019099524), or a pharmaceutically acceptable salt thereof (e.g., Example No. 234, 359, 478 or 507 or a pharmaceutically acceptable salt thereof). In one embodiment, the pan ErbB family inhibitor is selected from afatinib, dacomitinib, poziotinib, Erlotinib, gefitinib, sapitinib, and tarloxotinib. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 234 and afatinib. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 234 and dacomitinib. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 234 and poziotinib. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 234 and erlotinib. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 234 and gefitinib. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 234 and tarloxotinib. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 234 and the anti-EGFR antibody cetuximab. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 359 and afatinib. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 359 and dacomitinib. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 359 and poziotinib. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 359 and erlotinib. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 359 and gefitinib. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 359 and tarloxotinib. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 359 and the anti-EGFR antibody cetuximab. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 478 and afatinib. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 478 and dacomitinib. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 478 and poziotinib. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 478 and erlotinib. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 478 and gefitinib. In one embodiment, the therapeutic combination comprises

therapeutically effective amounts of Example No. 478 and tarloxotinib. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 478 and the anti-EGFR antibody cetuximab. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 507 and afatinib. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 507 and dacomitinib. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 507 and poziotinib. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 507 and erlotinib. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 507 and gefitinib. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 507 and tarloxotinib. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 507 and the anti-EGFR antibody cetuximab. In one embodiment of any of said combination therapies, the combination is useful for treating a KRas G12C-associated cancer. In one embodiment, the KRas G12C-associated cancer is lung cancer.

[0180] In another embodiment, the pan ErbB family inhibitor, or a pharmaceutically acceptable salt or a pharmaceutical composition thereof is administered in combination with the KRas G12C inhibitor, or a pharmaceutically acceptable salt or a pharmaceutical composition thereof once disease progression has been observed for KRas G12C monotherapy, in which the combination therapy results in enhanced clinical benefit or time of survival 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 G12C inhibitor is a compound selected from compound Nos. 1-678 (as numbered in WO2019099524), or a pharmaceutically acceptable salt thereof (e.g., Example No. 234, 359, 478 or 507 or a pharmaceutically acceptable salt thereof). In one embodiment, the pan ErbB family inhibitor is selected from Afatinib, dacomitinib, poziotinib, erlotinib, gefitinib, sapitinib, and tarloxotinib. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 234 and afatinib. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 234 and dacomitinib. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 234 and poziotinib. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 234 and

erlotinib. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 234 and gefitinib. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 234 and tarloxotinib. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 234 and the anti-EGFR antibody cetuximab. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 359 and afatinib. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 359 and dacomitinib. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 359 and poziotinib. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 359 and erlotinib. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 359 and gefitinib. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 359 and tarloxotinib. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 359 and the anti-EGFR antibody cetuximab. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 478 and afatinib. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 478 and dacomitinib. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 478 and poziotinib. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 478 and erlotinib. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 478 and gefitinib. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 478 and tarloxotinib. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 478 and the anti-EGFR antibody cetuximab. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 507 and afatinib. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 507 and dacomitinib. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 507 and poziotinib. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 507 and erlotinib. In one embodiment, the therapeutic combination comprises therapeutically effective

amounts of Example No. 507 and gefitinib. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 507 and tarloxotinib. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 507 and the anti-EGFR antibody cetuximab. In one embodiment of any of said combination therapies, the combination is useful for treating a KRas G12C-associated cancer. In one embodiment, the KRas G12C-associated cancer is lung cancer.

[0181] In one embodiment, a compound of Formula I, or a pharmaceutically acceptable salt or pharmaceutical composition thereof, 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 1-678 (as numbered in WO2019099524), or pharmaceutically acceptable salts thereof (e.g., Example Nos 234, 359, 478 or 507, or a pharmaceutically acceptable salt thereof). 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,

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[0182] 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 pan ErbB inhibitor which is administered, for example once a day on a daily basis (during a period of time). In one embodiment, the KRAS G12C inhibitor, or a pharmaceutically acceptable salt or

pharmaceutical composition thereof, is orally administered once daily. In one embodiment, the KRAS G12C inhibitor, or a pharmaceutically acceptable salt or pharmaceutical composition thereof, is orally administered twice daily.

[0183] 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 to treat or prevent a given disorder.

[0184] 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

[0185] In one embodiment, the addition of a pan ErbB family inhibitor synergistically increases the activity of KRas G12C inhibitor compound of Formula (I), Formula I-A or Formula I-B against cancer cell lines expressing KRas G12C. Any method for determining whether two compounds exhibit synergy may be used for determining the synergistic effect of the combination.

[0186] 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 G12C inhibitor compounds of Formula (I), Formula I-A or Formula I-B in combination with a Pan ErbB inhibitor.

[0187] 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.

[0188] In some embodiments, "synergistic effect" as used herein refers to combination of a KRAS inhibitor or a pharmaceutically acceptable salt thereof, and a pan ErbB family 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, Formula I-A or Formula I-B or a pharmaceutically acceptable salt thereof (e.g., 1-678 (as numbered in WO2019099524), or a pharmaceutically acceptable salt thereof (e.g., Example No. 234, 359, 478 or 507 or a pharmaceutically acceptable salt thereof) and a pan ErbB family inhibitor or a pharmaceutically acceptable salt thereof are administered alone. In one embodiment, the KRas G12C inhibitor is a compound selected from compound Nos. 1-678 (as numbered in WO2019099524), or a pharmaceutically acceptable salt thereof (e.g., Example No. 234, 359, 478 or 507 or a pharmaceutically acceptable salt thereof). In one embodiment, the pan ErbB family inhibitor is selected from afatinib, dacomitinib, gefitinib, sapitinib, tarloxotinib. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 234 and afatinib. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 234 and dacomitinib. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 234 and gefitinib. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 234 and tarloxotinib. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 234 and the anti-EGFR antibody cetuximab. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 359 and afatinib. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 359 and dacomitinib. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 359 and gefitinib. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 359 and tarloxotinib. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of

Example No. 359 and the anti-EGFR antibody cetuximab. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 478 and afatinib. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 478 and dacomitinib. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 478 and gefitinib. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 478 and tarloxotinib. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 478 and the anti-EGFR antibody cetuximab. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 507 and afatinib. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 507 and dacomitinib. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 507 and gefitinib. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 507 and tarloxotinib. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 507 and the anti-EGFR antibody cetuximab. In one embodiment of any of said combination therapies, the combination is useful for treating a KRas G12C-associated cancer. In one embodiment, the KRas G12C-associated cancer is lung cancer.

[0189] 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).

[0190] 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

[0191] The present invention also relates to a kit comprising a pan ErbB family inhibitor, or a pharmaceutically acceptable salt thereof and a KRas G12C inhibitor compound of Formula (I), Formula I-A or Formula I-B or a pharmaceutically acceptable salt thereof. Also provided is a kit comprising a pan ErbB family inhibitor or a pharmaceutically acceptable salt thereof and a KRas G12C inhibitor compound of Formula (I), Formula I-A or Formula I-B or a pharmaceutically acceptable salt thereof, for use in treating a KRas G12C-associated cancer.

[0192] In a related aspect, the invention provides a kit containing a dose of a pan ErbB family inhibitor and dose of a KRas G12C inhibitor compound of Formula (I), Formula I-A or Formula I-B or a pharmaceutically acceptable salt thereof in an amount effective to inhibit proliferation of cancer cells, particularly KRas G12C-expressing cancer cells, in a subject. The kit in some cases includes an insert with instructions for administration of the pan ErbB family inhibitor and a KRas G12C inhibitor compound of Formula (I), Formula I-A or Formula I-B. The insert may provide a user with one set of instructions for using a pan ErbB family inhibitor in

combination with a KRas G12C inhibitor compound of Formula (I), Formula I-A or Formula I-B.

EXAMPLE A

Pan ErbB Family Inhibitors Synergistically Increase the Activity of KRas G12C Inhibitors Against Cell Lines Expressing KRas G12C

[0193] This Example illustrates that the combination of exemplary KRas G12C inhibitor compounds of Formula I, Formula I-A and Formula 1-B or a pharmaceutically acceptable salt thereof (e.g., a compound selected from compound Example Nos 1-678, or a pharmaceutically acceptable salt thereof, e.g., Example No. 234, 359, 478 or 507, or a pharmaceutically acceptable salt thereof) and a pan ErbB family inhibitor or a pharmaceutically acceptable salt or a pharmaceutical composition thereof synergistically inhibits the growth of tumor cell lines that express KRas G12C.

[0194] A panel of 9 lung cancer and 1 colorectal cell lines harboring KRas G12C mutations was assembled to determine whether combining pan ErbB family inhibitors with exemplary KRas G12C inhibitors disclosed herein results in synergistic activity. The collection included NCI-H1373 (ATCC CRL-5866); NCI-H1792 (ATCC CRL-5895); NCI-H2030 (ATCC CRL-5985); NCI-H2122 (ATCC CRL-5985); HCC1171 (KCLB 71171); HCC44 (DSMZ ACC-534); LU99 (RCB1900); SW1573 (ATCC CRL-2170), SW837 (ATCC CCL-235) and KYSE-410 (ECACC 94072023).

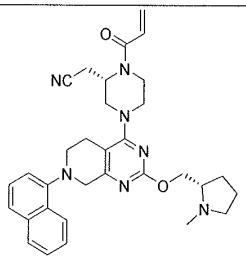
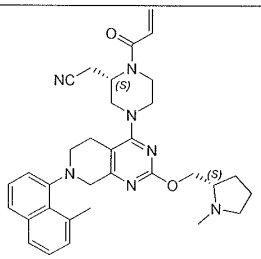
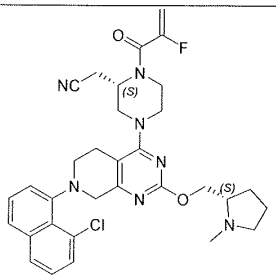
[0195] Assays for determining the synergy score for the pairwise combinations for each cell line were performed in triplicate. Three 96-well plates plus an additional 4 wells of a separate 96-well control plate for determining baseline luminescence were seeded with 2000 cells/well of a particular cell 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.

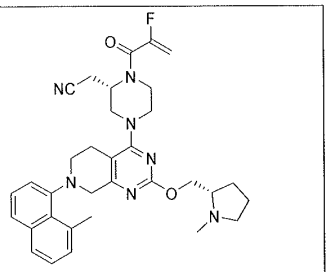
[0196] To each of the designated baseline wells, 30µl of Cell-Titer Glo reagent (CTG; Promega Corporation) was added to each well and the plates were incubated for 20 min with shaking at

room temperature. Baseline luminescence was quantitated using a BMG ClarioStar multimode plate reader according to the manufacturer's instructions.

[0197] A series of working stock 1000X drug dilutions in 100% DMSO was prepared that includes an 8 point single agent dilution of the exemplary KRas G12C inhibitor of Formula (I) and a 5-point single agent dilution of the pan ErbB family inhibitor. The dilutions used for the KRas G12C inhibitor and the pan ErbB family inhibitor varied for each individual compound but were in the range of 3- to 6-fold/serial dilution.

[0198] Exemplary KRas G12C inhibitors tested in this Example included:

Example No.*	Structure
234	
359	
478	

507	

*Example Number refers to the example number for each compound as disclosed in published International PCT application WO2019099524.

[0199] A 10X intermediate dosing plate was prepared in serum free RPMI medium that contains arrayed single agent dilutions of exemplary KRas G12C inhibitor of Formula (I) or the Pan ErbB inhibitor. In addition, a matrix of 40 dilution combinations of exemplary KRas G12C inhibitor of Formula (I), Formula I-A or Formula I-B and the pan ErbB family inhibitor was prepared as test samples.

[0200] 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 incubated 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.

[0201] 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.

[0202] The output of the data from each mathematical model is the assignment of a relative synergy score. The data reported in Table 3 are the aggregate sum of the Loewe additivity, Bliss independence, Highest Single Agent and ZIP scores ("Composite Synergy Score").

Table 3

Composite Synergy Scores for Exemplary pan ErbB Family Inhibitors Combined with Exemplary KRas G12C Inhibitors of Formula (I) Against KRas G12C Cell Lines

Pan ErbB Family Inhibitor	**Afatinib**				**Dacomitinib**		**Erlotinib**	**Gefitinib**		**Poziotinib**	**Sapitin**
KRas G12C Example #	**234**	**507**	**359**	**478**	**234**	**507**	**478**	**234**	**507**	**478**	**507**
Cell Line											
H1373	46.5	37.5	25.5	29.0	42.9	46.0	-3.5	23.4	40.2	16.1	16.5
H1792	42.5	19.6	24.8	27.2	34.7	13.5	-15.4	12.7	2.1	41.6	15.8
H2030	65.6	43.9	32.2	29.4	45.7	33.9	26.9	32.1	25.2	18.6	35.5
H2122	ND	57.3	40.2	56.8	149.3	55.2	41.2	52.6	31.5	33.8	55.8
HCC1171	98.8	66.6	91.0	65.6	97.1	73.1	49.4	62.2	51.7	42.5	39.8
HCC44	22.0	6.7	19.6	11.5	53.3	-1.5	-40.3	-18.0	-6.0	9.6	3.0
LU99	39.9	16.7	23.7	11.0	32.1	11.8	-17.0	13.3	-4.8	18.6	10.3
SW1573	33.3	31.8	16.1	17.0	-26.6	16.5	-20.9	-2.6	-2.2	10.7	
SW837	53.7	48.0	40.5	36.6	26.4	47.0	6.7	23.2	40.5	33.4	
KYSE-410	ND	ND	28.6	21.3	ND	ND	7.7	ND	ND	35.3	

[0203] A composite score of greater than or equal to 27 was interpreted as a synergistic hit whereas a composite score between 17 and 26 indicates potential synergy. These results demonstrate that a synergistic effect was observed for the combination of a variety of pan ErbB family inhibitors with exemplary KRas G12C inhibitor compounds of Formula (I) in a majority of cell line harboring a KRas G12C mutation listed in Table 1 that are less sensitive to KRas G12C single agent treatment thereby increasing the sensitivity of the KRas G12C cell line to the KRas G12C inhibitor.

EXAMPLE B

In Vivo Models for Examining KRas G12C inhibitor Plus Pan ErbB Family Inhibitor Combinations

[0204] Immunocompromised nude/nude mice were inoculated in the right hind flank with cells or patient derived tumor samples harboring a KRas G12C mutation. When tumor volumes reached between 200 – 400 mm^3 in size, the mice were divided into four groups of 5-12 mice each. The first group was administered vehicle only. The second group was administered a single agent dose of the KRas G12C 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 a single agent dose of the pan ErbB 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 was administered the single agent dose of the KRas G12C inhibitor in combination with the single agent dose of the pan ErbB family inhibitor. The treatment period varied from cell line to cell line but typically was between 21-35 days. Tumor volumes were measured using a caliper every two – three days and tumor volumes were calculated by the formula: 0.5 x (Length x Width)^2. A greater degree of tumor regression 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 G12C inhibitor.

[0205] For example, on Day 1, three sets of 20 nude/nude mice each were inoculated in the right hind limb with 5 x 10^6 H2122 cells, KYSE-410 cells or LU6405 cells (PDX model). When

tumor volume reached ~300 mm^3 (Day 11), 5 mice in each of the four groups were administered p.o. daily for 21 days: vehicle only (10% Captisol), 100 mg/kg of the KRas G12C inhibitor Compound 478 (10% Captisol in 50 mM citrate buffer, pH 5.0), 12.5 mg/kg of the pan ErbB family inhibitor Afatinib (0.5% methylcellulose/0.4% Tween-80), or 100 mg/kg of the KRas G12C inhibitor Compound 478 and 12.5 mg/kg of Afatinib. Tumor volumes were measured at pre-specified days set forth below. Tumor volumes for the five mice per group were averaged and are reported in Table 4a (H2122 cell line), 4b (KYSE-410 cell line) and 4c (LU6405 cells).

Table 4a

Average Tumor Volumes (mm^3) of H2122 Tumor Bearing Mice Treated with Single Agents and in Combination

Day Post Implant	Vehicle	Compound 478	Afatinib	Compound 478 + Afatinib
11	324.86	325.05	324.86	329.49
13	519.62	339.80	429.76	257.56
15	688.80	337.58	573.36	186.03
18	954.95	381.78	694.70	170.99
20	1126.81	462.40	850.85	174.29
22	1350.85	479.48	931.53	194.99
25	1504.56	492.76	1153.42	220.34
27	1574.31	541.06	1307.50	246.90
29	1343.95	537.14	1137.09	246.42
32	1491.71	547.06	1403.33	219.49
34	1559.70	546.96	1830.13	208.05

Table 4b

Average Tumor Volumes (mm^3) of KYSE-410 Tumor Bearing Mice Treated with Single Agents and in Combination

Day Post Implant	Vehicle	Compound 478	Afatinib	Compound 478 + Afatinib
11	308.24	307.30	311.84	313.08
14	333.98	274.64	199.20	137.64
16	388.62	311.34	135.30	77.84

18	418.14	297.62	114.40	49.02
21	420.80	338.18	114.08	34.60
23	494.66	320.42	132.92	33.40
25	519.48	358.68	141.90	27.22
28	577.98	459.20	144.36	24.60
30	673.74	441.60	166.46	21.12
32	738.70	480.62	163.92	21.92
35	889.72	543.02	181.68	18.12
37	905.00	525.86	198.34	18.57

Table 4c

Average Tumor Volumes (mm^3) of LU6405 Tumor Bearing Mice Treated with Single Agents and in Combination

Day Post Implant	Vehicle	Compound 478	Afatinib	Compound 478 + Afatinib
11	256.45	256.06	257.48	253.48
14	447.44	308.98	371.98	273.28
18	877.95	324.46	585.54	264.33
21	1215.89	329.09	775.75	199.62
25	1727.56	310.21	1056.23	168.34
28	1950.09	290.88	1197.31	144.99
32	2074.33	257.34	1540.74	82.99
34	2074.33	249.19	1655.49	53.55

[0206] As shown in Table 4a, the administration of Compound 478 or afatinib as a single agent to H2122 tumor bearing mice exhibited 85% and 41% tumor growth inhibition at Day 22 (Treatment Day 10), respectively. The combination of the pan ErbB family inhibitor afatinib and Compound 478 resulted in 41% tumor regression at Day 22,.

[0207] As shown in Table 4b, the administration of Compound 478 as a single agent to KYSE-410 tumor bearing mice resulted in 64% tumor growth inhibition at Day 37 (Treatment Day 27) whereas the combination of the pan ErbB family inhibitor afatinib and Compound 478 resulted in 93 % tumor regression at Day 37 compared to administration of Compound 478 as a single agent.

[0208] As shown in Table 4c, the administration of Compound 478 as a single agent to LU6405-implanted mice resulted in 96% tumor growth inhibition at Day 34 (Treatment Day 24) whereas the combination of the pan ErbB family inhibitor afatinib and Compound 478 resulted in 67 % tumor regression at Day 37 compared to administration of Compound 478 as a single agent.

[0209] In a related experiment, on Day 1, two sets of 20 nude/nude mice each were inoculated in the right hind limb with 5 x 10^6 CR6256 cells or CR2528 cells (PDX models). When tumor volume reached ~200 - 300 mm^3 (Day 11), 5 mice in each of the first two groups were administered p.o. daily for 21 days: vehicle only (10% Captisol) or 100 mg/kg of KRas G12C inhibitor Compound 478 (10% Captisol in 50 mM citrate buffer, pH 5.0). The third group of mice were administered every third day 0.25 mg/kg i.p of the pan ErbB family inhibitor antibody Cetuximab (PBS, pH 7.2), or 100 mg/kg of KRas G12C inhibitor Compound 478 p.o and 0.25 mg/kg of Cetuximab i.p every three days. Tumor volumes were measured at pre-specified days set forth below. Tumor volumes for the five mice per group were averaged and are reported in Table 5a (CR6256 cell line) and 5b (CR2528 cell line).

Table 5a

Average Tumor Volumes (mm^3) of CR6258 Tumor Bearing Mice Treated with Single Agents and in Combination

Day Post Implant	Vehicle	Compound 478	Cetuximab	Compound 478 + Cetuximab
11	187.38	190.54	187.77	192.96
14	330.09	253.11	258.50	270.22
18	510.20	256.91	321.93	277.94
21	773.12	252.05	390.52	257.98
25	1135.07	201.00	503.75	90.49
28	1473.99	128.77	571.30	40.33
32	1638.23	77.44	652.14	26.89
35	1775.29	56.15	678.49	0.00
39	1740.94	44.24	768.49	0.00
42	1965.90	41.80	890.83	0.00
46	1995.68	29.92	975.10	0.00
49	2469.47	19.79	1233.04	0

Table 5b

Average Tumor Volumes (mm^3) of CR2528 Tumor Bearing Mice Treated with Single Agents and in Combination

Day Post Implant	Vehicle	Compound 478	Cetuximab	Compound 478 + Cetuximab
11	264.96	265.11	266.03	265.85
14	449.44	350.48	450.64	313.82
17	671.85	434.64	616.52	347.80
20	1407.65	656.73	1208.84	352.92
24	1796.07	950.91	1924.82	353.44
27	1776.55	1252.80	2424.63	330.12
31	2215.54	1713.13	2741.36	237.44
34		2757.63		222.67
38				220.78
40				184.11

[0210] As shown in Table 5a, the administration of Compound 478 as a single agent to CR6258-implanted mice resulted in 71% tumor regression at Day 37 (Treatment Day 27) whereas the combination of the pan ErbB family inhibitor cetuximab and Compound 478 resulted in a complete response, or 100% tumor regression at Day 37 compared to administration of Compound 478 as a single agent.

[0211] As shown in Table 5b, the administration of Compound 478 as a single agent to CR2528-implanted mice resulted in no single-agent anti-tumor activity at Day 34 (Treatment Day 24) whereas the combination of the pan ErbB family inhibitor cetuximab and Compound 478 resulted in 31% tumor regression at Day 37 compared to administration of Compound 478 as a single agent.

[0212] In yet another experiment, on Day 1, two sets of 20 nude/nude mice each were inoculated in the right hind limb with 5 x 10^6 H2122 cells or KYSE-410 cells. When tumor volume reached ~300 mm^3 (Day 11), 5 mice in each of the four groups were administered p.o. daily for 21 days: vehicle only (10% Captisol) or 100 mg/kg of KRas G12C inhibitor Compound 478 (10% Captisol in 50 mM citrate buffer, pH 5.0). The third group of 5 mice were administered every seven days 48 mg/kg i.p. of the pan ErbB family inhibitor tarloxotinib (10 mg/kg Beta-

cyclodextrin), or 100 mg/kg of KRas G12C inhibitor Compound 478 p.o and 48 mg/kg of tarloxotinib i.p every seven days. Tumor volumes were measured at pre-specified days set forth below. Tumor volumes for the five mice per group were averaged and are reported in Table 6a (KYSE-410 cell line) and 6b (H2122 cell line).

Table 6a

Average Tumor Volumes (mm^3) of KYSE-410 Tumor Bearing Mice Treated with Single Agents and in Combination

Day Post Implant	Vehicle	Compound 478	Tarloxotinib	Compound 478 + Tarloxotinib
11	225.71	231.53	233.57	237.74
19	310.33	237.61	40.90	32.96
26	367.27	273.90	28.99	23.87
33	456.50	306.12	20.30	14.08
40	579.80	334.72	20.81	10.12
47	646.54	354.97	14.67	10.67
54	854.31	431.28	19.20	7.87
61	1129.53	488.08	15.55	7.73

Table 6b

Average Tumor Volumes (mm^3) of H2122 Tumor Bearing Mice Treated with Single Agents and in Combination

Day Post Implant	Vehicle	Compound 478	Tarloxotinib	Compound 478 + Tarloxotinib
11	313.60	314.62	305.56	296.06
14	395.56	281.54	287.64	163.54
18	494.74	233.12	380.02	101.60
21	650.72	277.28	374.78	91.42
26	749.66	252.14	443.76	72.12
28	887.98	277.48	450.62	50.80
32	1027.62	269.90	466.00	66.14
35	1151.30	254.30	471.26	56.78
39	1202.5	276	544.78	63.38
43	1232.14	286.56	507.6	53.46
46	1243.74	304.9	640.975	62.34

[0213] As shown in Table 6a, the administration of Compound 478 as a single agent to KYSE-410-implanted mice resulted in 71% tumor growth inhibition at Day 61 (Treatment Day 50) whereas the combination of the pan ErbB family inhibitor Cetuximab and Compound 478 resulted in 97% tumor regression at Day 61 compared to administration of Compound 478 as a single agent.

[0214] As shown in Table 6b, the administration of Compound 478 as a single agent to H2122-implanted mice resulted in 3% tumor regression at Day 46 (Treatment Day 35) whereas the combination of the pan ErbB family inhibitor cetuximab and Compound 478 resulted in 79% tumor regression at Day 37 compared to administration of Compound 478 as a single agent.

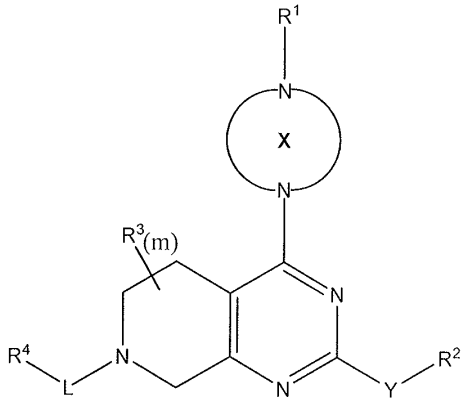
[0215] These results demonstrate that each of the combination therapies resulted in greater amount of tumor growth inhibition compared to either single agent alone demonstrating enhanced in vivo anti-tumor efficacy of the combination.

[0216] 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

WE CLAIM:

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 pan ErbB family inhibitor and a KRAS G12C inhibitor of formula (I):



Formula (I)

or a pharmaceutically acceptable salt thereof:

wherein:

X is a 4-12 membered saturated or partially saturated monocyclic, bridged or spirocyclic ring, wherein the saturated or partially saturated monocyclic ring is optionally substituted with one or more R^8;

Y is a bond, O, S or NR^5;

R^1 is $-C(O)C(R^A)$ ------ $C(R^B)_p$ or $-SO_2C(R^A)$ ------ $C(R^B)_p$;

R^2 is hydrogen, alkyl, hydroxyalkyl, dihydroxyalkyl, alkylaminylalkyl, dialkylaminylalkyl, -Z-NR^5R^{10}, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, or heteroarylalkyl, wherein each of the Z, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl may be optionally substituted with one or more R^9;

each Z is C1 – C4 alkylene;

each R^3 is independently C1 – C3 alkyl, oxo, haloalkyl, hydroxyl or halogen;

L is a bond, -C(O)-, or C1 – C3 alkylene;

R^4 is hydrogen, cycloalkyl, heterocyclyl, aryl, aralkyl or heteroaryl, wherein each of the cycloalkyl, heterocyclyl, aryl, aralkyl and heteroaryl may be optionally substituted with one or more R^6, R^7 or R^8;

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

R^6 is cycloalkyl, heterocyclyl, heterocyclylalkyl, aryl, or heteroaryl, wherein each of the cycloalkyl, heterocyclyl, aryl, or heteroaryl may be optionally substituted with one or more R^7;

each R^7 is independently halogen, hydroxyl, C1 – C6 alkyl, cycloalkyl, alkoxy, haloalkyl, amino, cyano, heteroalkyl, hydroxyalkyl or Q-haloalkyl, wherein Q is O or S;

R^8 is oxo, C1 – C3 alkyl, C2 – C4 alkynyl, heteroalkyl, cyano, $-C(O)OR^5$, $-C(O)N(R^5)_2$, $-N(R^5)_2$, wherein the C1 – C3 alkyl may be optionally substituted with cyano, halogen, $-OR^5$, $-N(R^5)_2$, or heteroaryl;

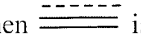
each R^9 is independently hydrogen, oxo, acyl, hydroxyl, hydroxyalkyl, cyano, halogen, C1 – C6 alkyl, aralkyl, haloalkyl, heteroalkyl, cycloalkyl, heterocyclylalkyl, alkoxy, dialkylaminyl, dialkylamidoalkyl, or dialkylaminylalkyl, wherein the C1 – C6 alkyl may be optionally substituted with cycloalkyl;

each R^{10} is independently hydrogen, acyl, C1 – C3 alkyl, heteroalkyl or hydroxyalkyl;

R^{11} is haloalkyl;

R^A is absent, hydrogen, deuterium, cyano, halogen, C1 - C-3 alkyl, haloalkyl, heteroalkyl, $-C(O)N(R^5)_2$, or hydroxyalkyl;

each R^B is independently hydrogen, deuterium, cyano, C1 – C3 alkyl, hydroxyalkyl, heteroalkyl, C1 – C3 alkoxy, halogen, haloalkyl, $-ZNR^5R^{11}$, $-C(O)N(R^5)_2$, -NHC(O)C1 – C3 alkyl, $-CH_2NHC(O)$C1 – C3 alkyl, heteroaryl, heteroarylalkyl, dialkylaminylalkyl, or heterocyclylalkyl wherein the heterocyclyl portion is substituted with one or more substituents independently selected from halogen, hydroxyl, alkoxy and C1 – C3 alkyl, wherein the heteroaryl or the heteroaryl portion of the heteroarylalkyl is optionally substituted with one or more R^7;

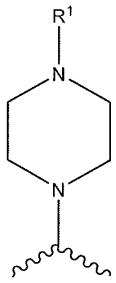
when  is a triple bond then R^A is absent, R^B is present and p equals one,

or when ------ is a double bond then R^A is present, R^B is present and p equals two, or R^A, R^B and the carbon atoms to which they are attached form a 5-8 membered partially saturated cycloalkyl optionally substituted with one or more R^7;

m is zero or an integer between 1 and 2; and

p is one or two.

2. The method of claim 1, wherein R^1-X is:



wherein the piperazinyl ring is optionally substituted with R^8.

3. The method of claim 2, wherein R^1 is $-C(O)C(R^A)$ ------ $C(R^B)_p$

4. The method of claim 3, wherein ------ is a triple bond and R^A is absent, p is one and R^B is C1 – C3 alkyl, hydroxyalkyl or C1 – C3 alkoxy.

5. The method of claim 3, wherein ------ is a double bond and R^A is hydrogen and R^B is hydrogen.

6. The method of claim 3, wherein ------ is a double bond and R^A is hydrogen, p is two and at least one R^B is independently deuterium, cyano, halogen, haloalkyl, hydroxyalkyl, heteroalkyl, heteroaryl, heteroarylalkyl, $-ZNR^5R^{11}$, $-C(O)N(R^5)_2$, -NHC(O)C1 – C3 alkyl or heterocyclylalkyl wherein the heterocyclyl portion is substituted with one or more substituents independently selected from halogen, hydroxyl, alkoxy or C1 – C3 alkyl.

7. The method of claim 6, wherein the at least one R^B is halogen.

8. The method of claim 6, wherein the at least one R^B is haloalkyl.

9. The method of claim 6, wherein the at least one R^B is $-ZNR^5R^{11}$.

10. The method of claim 9, wherein Z is methylene, R^5 is methyl and R^{11} is trifluoromethyl.

11. The method of claim 6, wherein the at least one R^B is cyano.

12. The method of claim 6, wherein the at least one R^B is hydroxyalkyl.

13. The method of claim 6, wherein the at least one R^B is heteroalkyl.

14. The method of claim 13, wherein the heteroalkyl is methoxymethyl.

15. The method of claim 6, wherein the at least one R^B is $-C(O)N(R^5)_2$, wherein each R^5 is hydrogen.

16. The method of claim 6, wherein the at least one R^B is $-C(O)N(R^5)_2$, wherein each R^5 is C1 – C3 alkyl.

17. The method of claim 6, wherein the at least one R^B is heteroaryl optionally substituted with one or more R^7.

18. The method of claim 17, wherein the heteroaryl is pyrrolyl, imidazolyl, pyrazolyl, triazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl or triazinyl, each substituted with one or more R^7.

19. The method of claim 6, wherein the at least one R^B is heteroarylalkyl optionally substituted with one or more R^7.

20. The method of claim 19, wherein the heteroaryl portion of the heteroarylalkyl is pyrrolyl, imidazolyl, pyrazolyl, triazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl or triazinyl, each optionally substituted with one or more R^7.

21. The method of claim 6, wherein the at least one R^B is heterocyclylalkyl substituted with one or more R^7.

22. The method of claim 21, wherein the heterocyclyl portion of the heterocyclylalkyl is azetindinyl, pyrrolidinyl, piperidinyl piperazinyl or morpholinyl, each substituted with one or more groups independently selected from halogen, hydroxyl, alkoxy or C1 – C3 alkyl.

23. The method according to any of claims 6-22, wherein the double bond is in the E configuration..

24. The method according to any of claims 6-22, wherein the double bond is in the Z configuration..

25. The method of claim 6, wherein  is a double bond and p is two, each R^B is hydrogen, and R^A is deuterium, cyano, halogen, haloalkyl, heteroalkyl, $-C(O)N(R^5)_2$, or hydroxyalkyl.

26. The method of claim 25, wherein R^A is halogen.

27. The method of claim 25, wherein R^A is haloalkyl.

28. The method of claim 25, wherein R^A is cyano.

29. The method of claim 25, wherein R^A is heteroalkyl.

30. The method of claim 29, wherein the heteroalkyl is methoxymethyl.

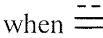
31. The method of claim 29, wherein the heteroalkyl is alkoxy.

32. The method of claim 25, wherein R^A is $-C(O)N(R^5)_2$, wherein each R^5 is hydrogen.

33. The method of claim 25, wherein R^A is hydroxyalkyl.

34. The method of claim 2, wherein  is a double bond and p is two, one R^B is hydrogen, the second R^B is dialkylaminylalkyl, and R^A is halogen.

35. The method of claim 2, wherein  is a double bond and p is two, each R^B is deuterium, and R^A is deuterium.

36. The method of claim 2, wherein when  is a double bond and p is two, one R^B is hydrogen and R^A and one R^B and the carbon atoms to which they are attached form a 5-8 membered partially saturated cycloalkyl substituted with oxo.

37. The method of according to any one of claims 2-36, wherein Y is O.

38. The method according to any one of claims 2-37, wherein R^2 is selected from the group consisting of hydroxyalkyl, alkylaminylalkyl, dialkylaminylalkyl, $-ZNR^5R^{10}$, heterocyclyl and heterocyclylalkyl, wherein each of the Z, heterocyclyl or heterocyclylalkyl are independently optionally substituted with R^9.

39. The method of claim 38, wherein R^2 is heterocyclylalkyl optionally substituted with one or more R^9.

40. The method of claim 39, wherein the heterocyclyl of the heterocyclylalkyl is independently azetidinyl, methylazetidinyl, difluoroazetidinyl, tetrahydropyran, pyrrolidinyl, methylpyrrolidinyl, diemethylpyrrolidinyl, isopropylpyrrolidinyl, cycloalkylalkylpyrrolidinyl, hydroxypyrrolindinyl, fluoropyrrolidinyl, difluoropyrrolidinyl, (N-methyl)fluoropyrrolidinyl, (N-methyl)difluoropyrrolidinyl, methoxyethylpyrrolidinyl, (N-methyl)methoxypyrrolidinyl, piperazinyl, dimethylaminylpyrrolidinyl, morpholinyl, methylmorpholinyl, 1,4-oxazepanyl, piperdinyl, methylpiperidinyl acylpiperdinyl, cyanopiperdinyl, cycloalkylpiperdinyl, halopiperdinyl, dihalopiperdinyl, fluoropiperdinyl, difluoropiperdinyl, alkoxypiperdinyl, pyrrolidonyl, piperidinonyl, thiomorpholinyl-1,1-dioxide, 3-azabicyclo[3.1.0]hexanyl, oxa-5-azabicyclo[2.2.1]heptan-5-yl, or azabicyclo[2.2.1]heptan-2-yl.

41. The method of claim 40, wherein the (N-methyl)difluoropyrrolidinyl is 3,3-difluoro-1-methylpyrrolidinyl.

42. The method of claim 40, wherein the heterocyclyl is N-methylpyrrolidinyl.

43. The method of claim 38, wherein R^2 is dialkylaminylalkyl optionally substituted with one or more R^9.

44. The method according to any one of claims 2-43, wherein R^4 is aryl optionally substituted with one or more R^7.

45. The method of claim 44, wherein the aryl is selected from the group consisting of phenyl and naphthyl optionally substituted with one or more R^7.

46. The method of claim 45, wherein the phenyl and the naphthyl are each optionally substituted with one or more R^7 selected from the group consisting of halogen, hydroxyl, cyano, C1- C6 alkyl, haloalkyl, Q-haloalkyl, and alkoxy.

47. The method of claim 46, wherein R^7 is selected from the group consisting of halogen, haloalkyl, methyl, isopropyl, methoxy, Q-haloalkyl, hydroxyl and cyano.

48. The method according to any one of claims 2-43, wherein R^4 is heteroaryl.

49. The method according to any one of claims 2-43, wherein R^4 is aralkyl optionally substituted with one or more R^7.

50. The method according to any one of claims 2-49, wherein m is zero.

51. The method according to any one of claims 2-50, wherein L is a bond.

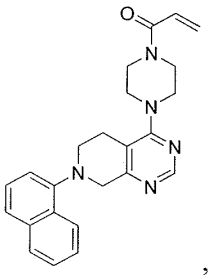
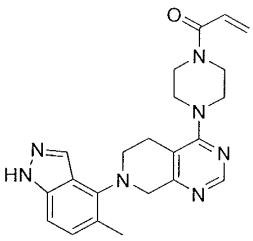
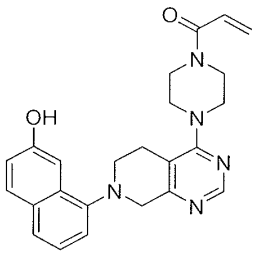
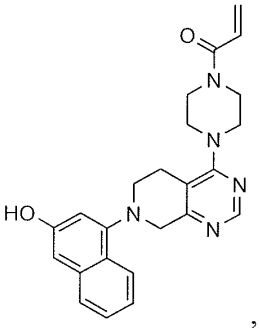
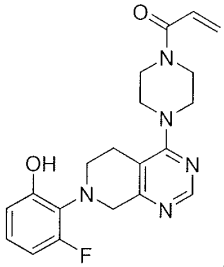
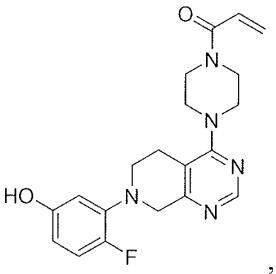
52. The method according to any one of claims 2-51, wherein R^8 is heteroalkyl, C2-C4 alkynyl, or C1 – C3alkyl optionally substituted with -OR^5, cyano or heteroaryl.

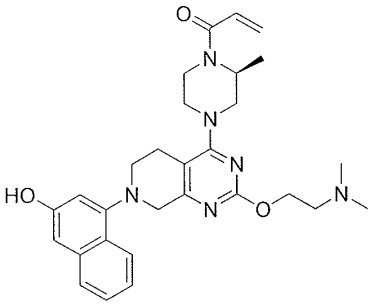
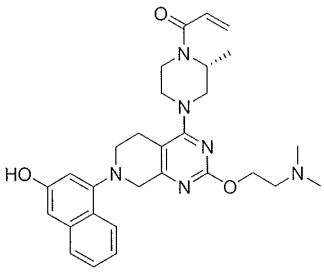
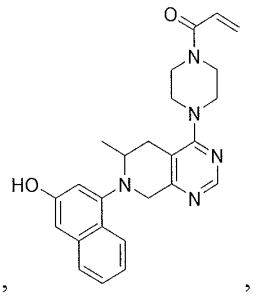
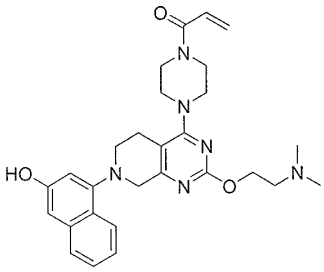
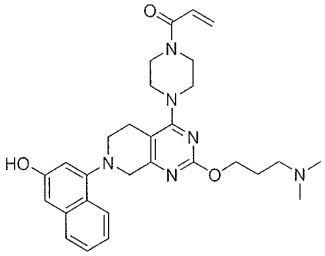
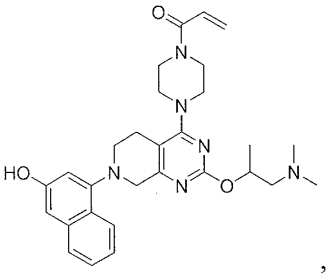
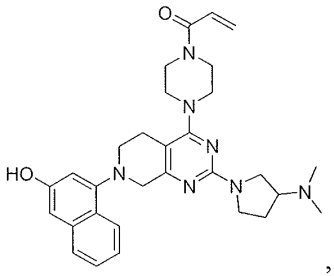
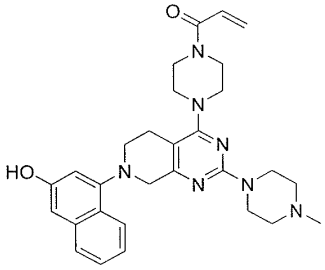
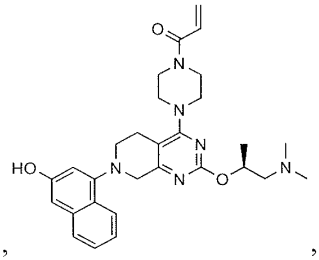
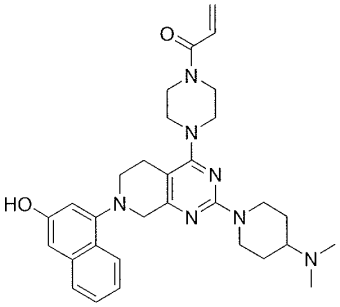
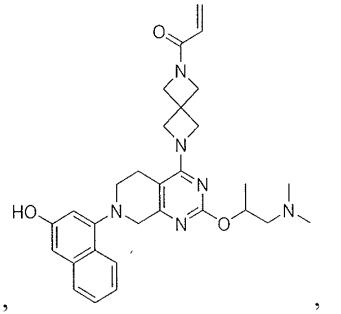
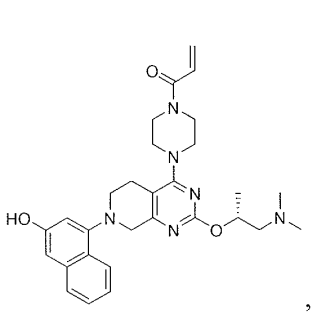
53. The method of claim 52, wherein R^8 is C1 – C3 alkyl optionally substituted with cyano.

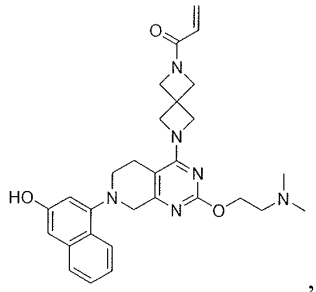
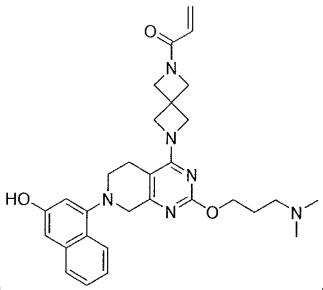
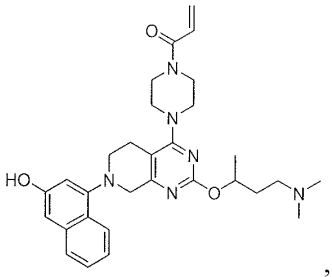
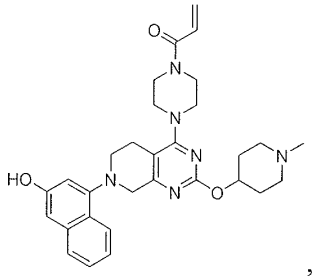
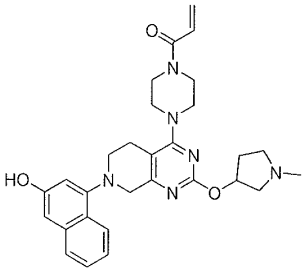
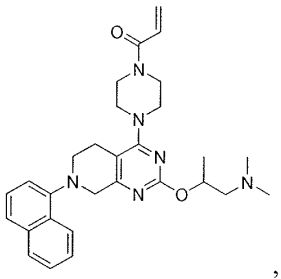
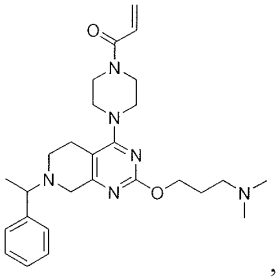
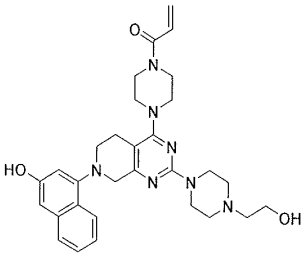
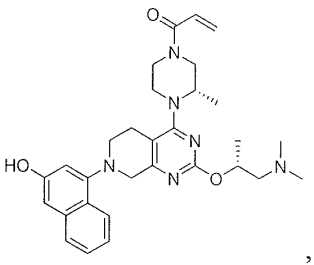
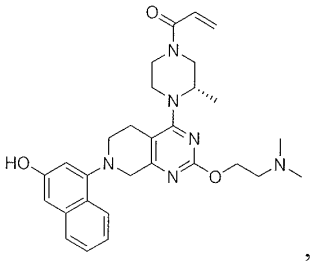
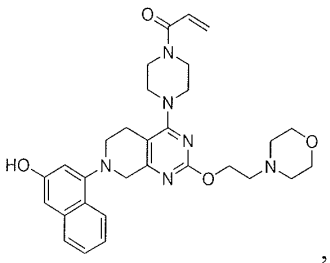
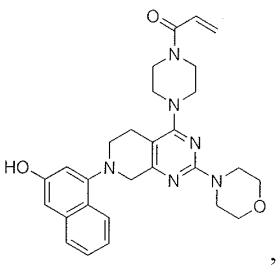
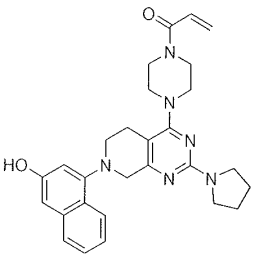
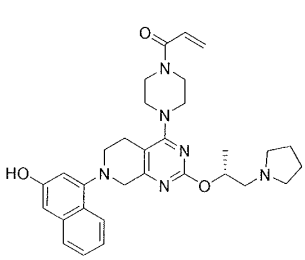
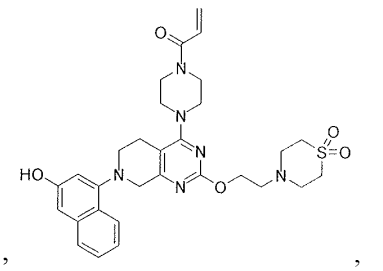
54. The method of claim 52, wherein R^8 is cyanomethyl.

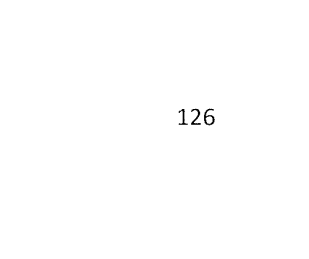
55. The method according to any one of claims 52-54, wherein X is substituted with one R^8.

56. The method of claim 1, wherein the KRas G12C inhibitor is:

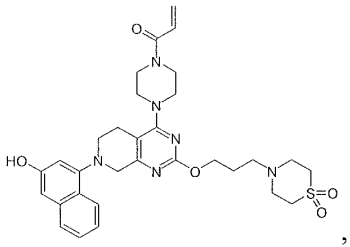
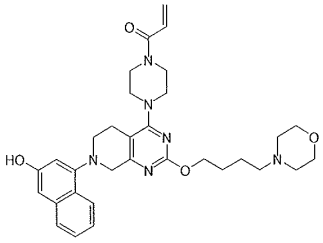
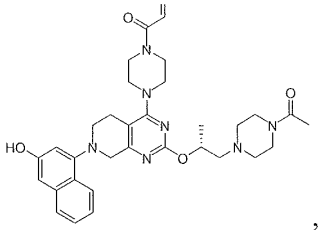
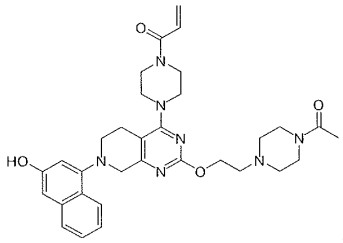
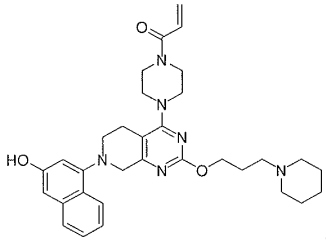
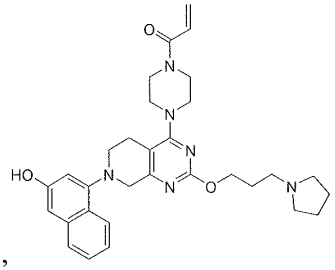
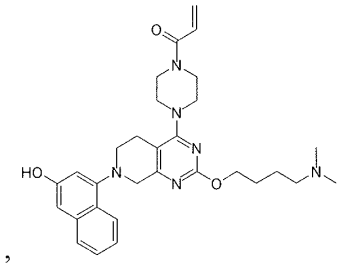
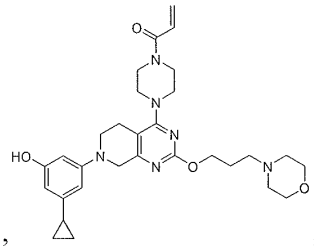
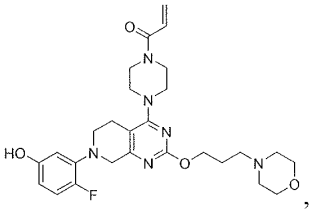
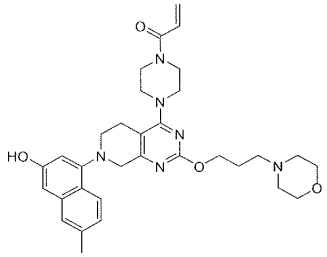
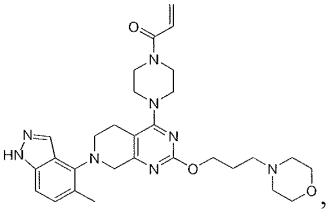
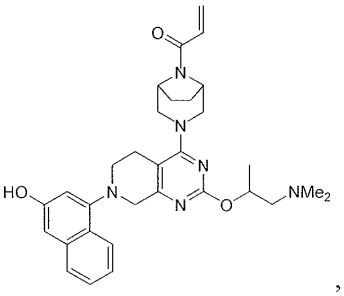
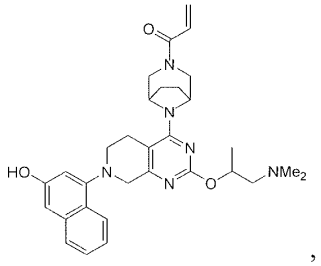
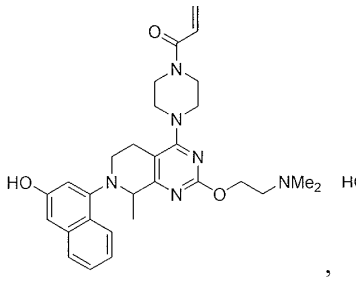

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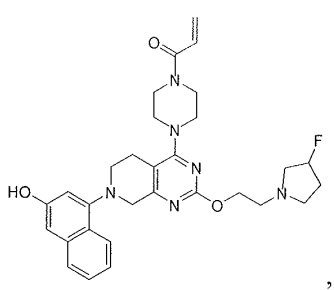
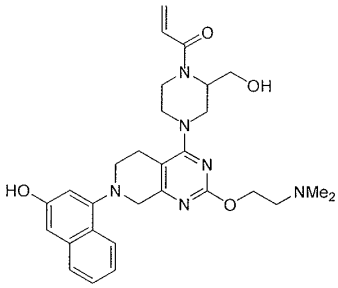
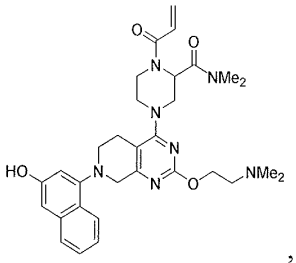
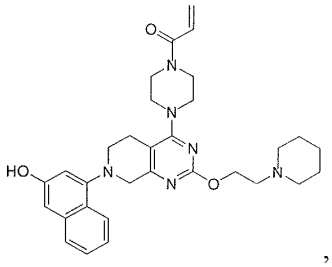
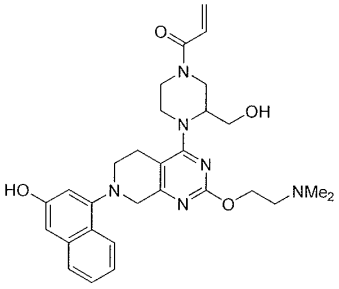
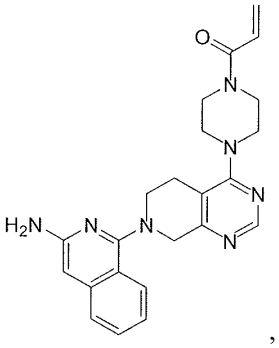
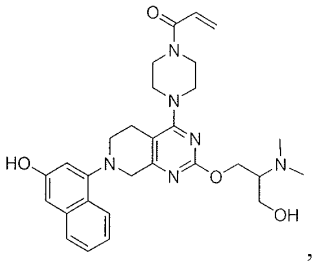
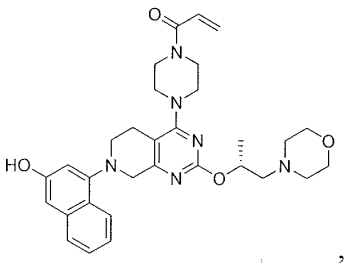
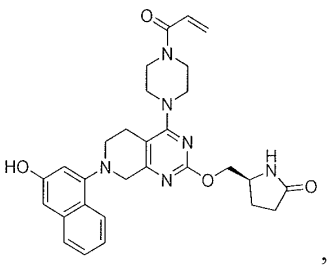
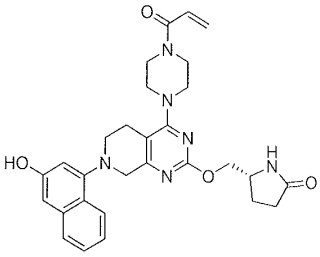
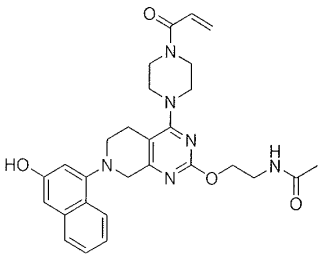
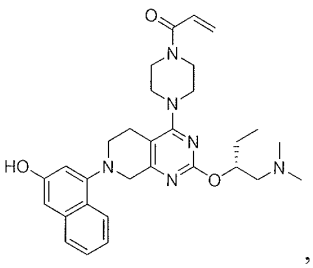
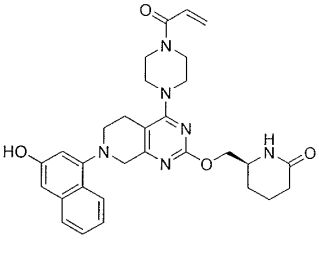
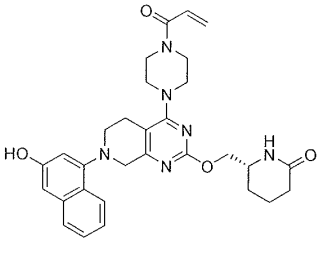
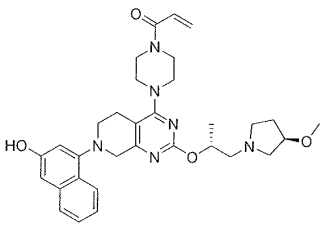
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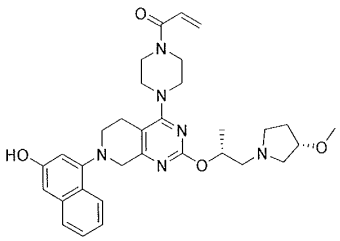
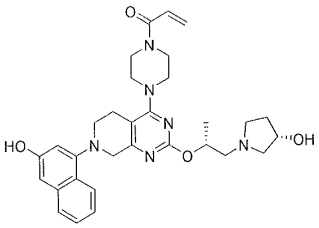
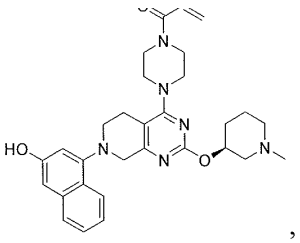
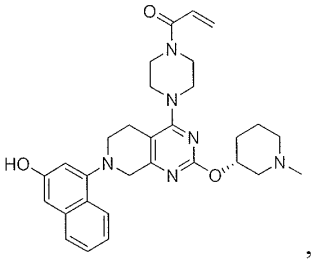
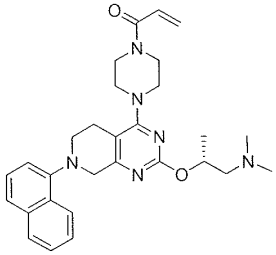
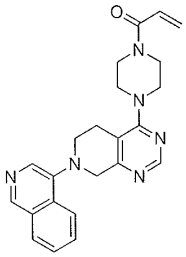
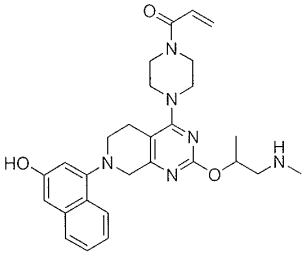
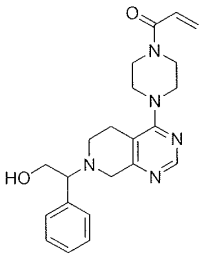
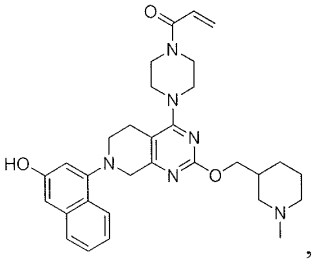
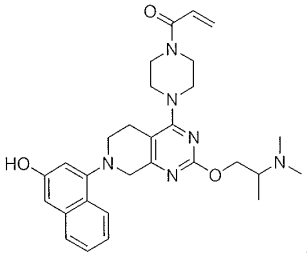
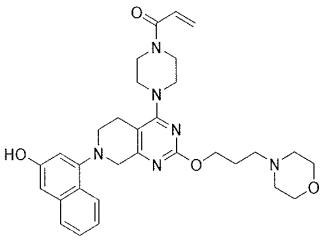
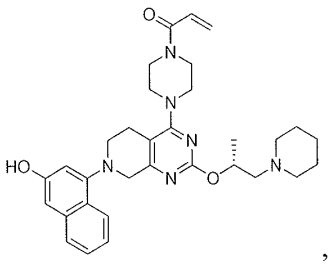
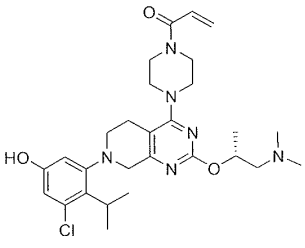
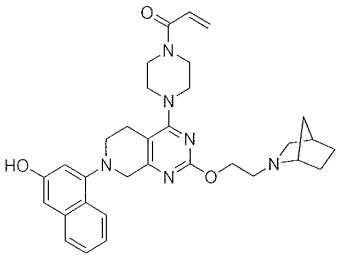
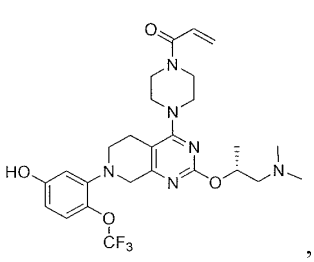
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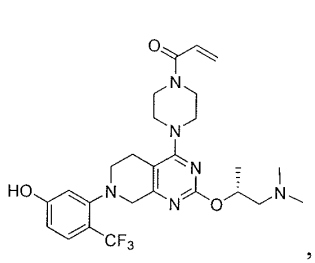
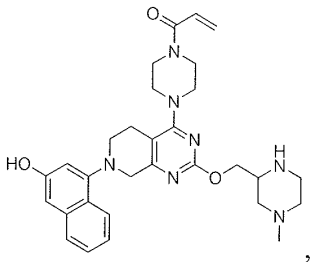
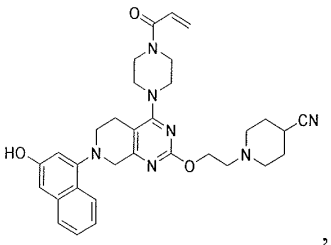
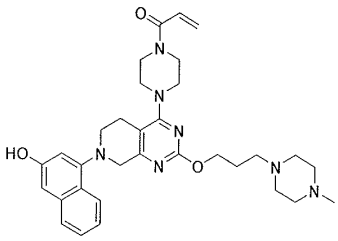
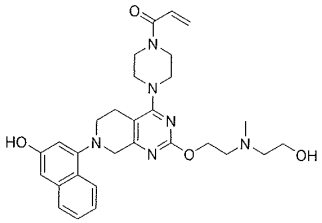
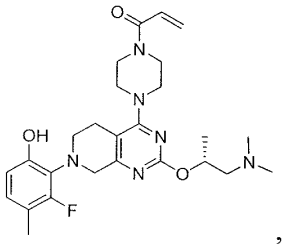
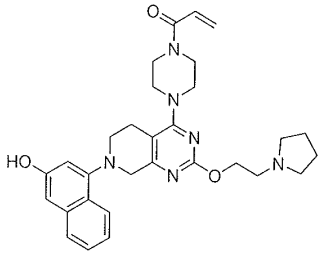
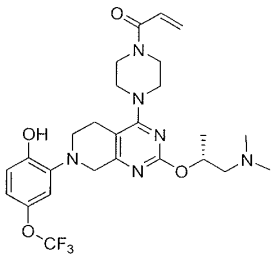
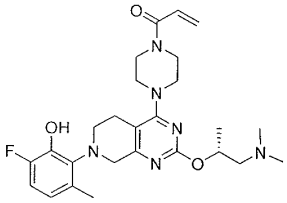
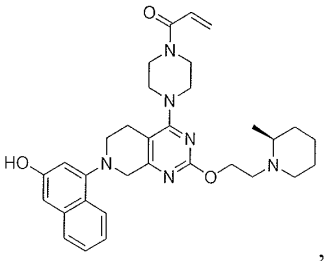
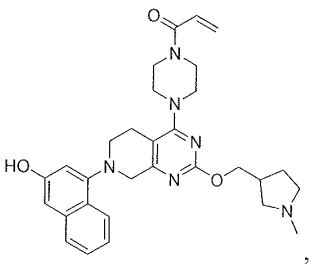
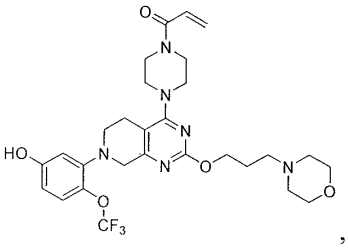
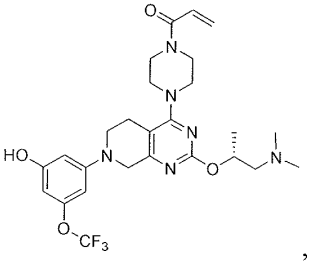
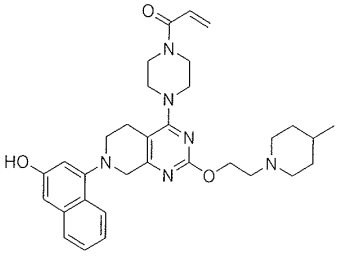
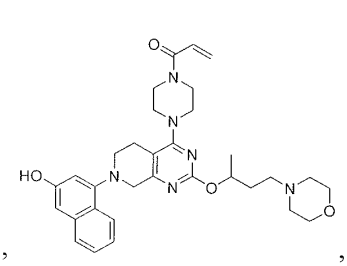
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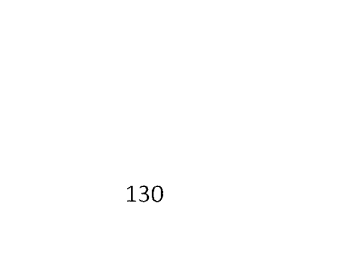
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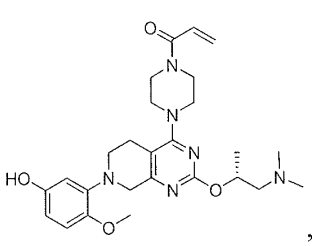
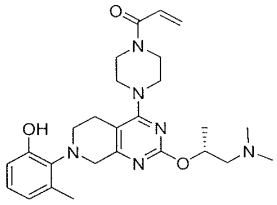
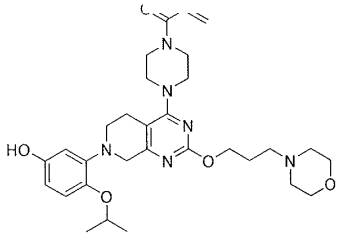
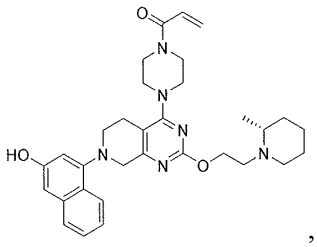
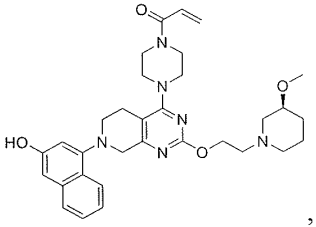
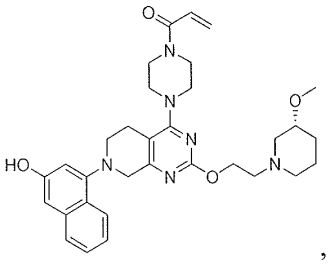
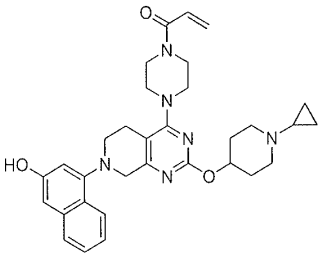
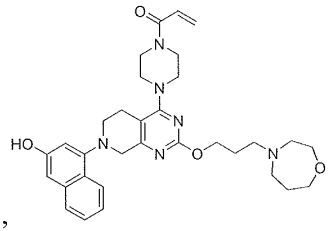
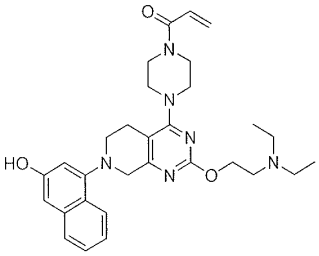
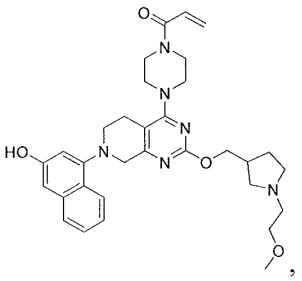
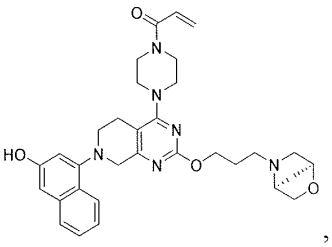
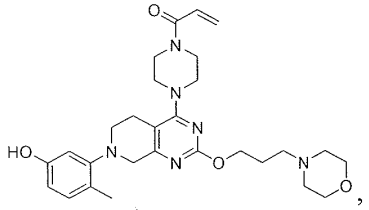
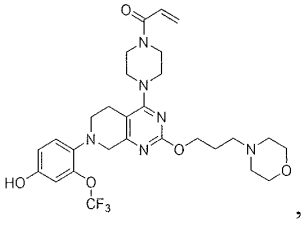
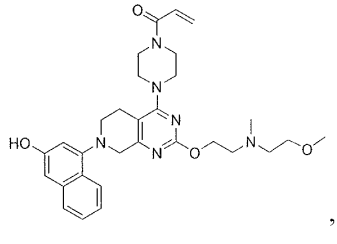
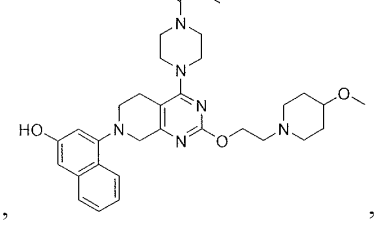

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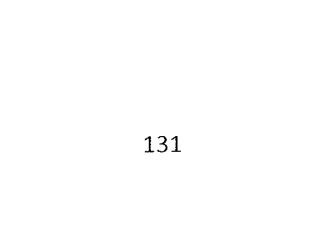

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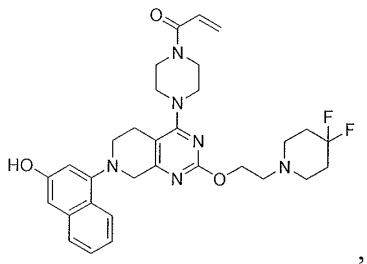
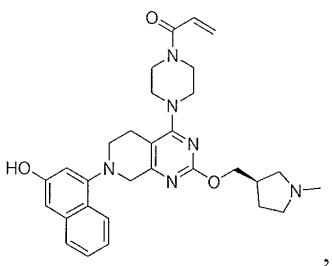
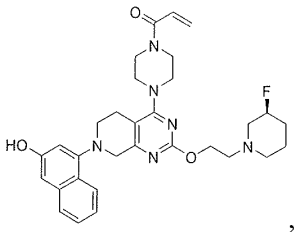
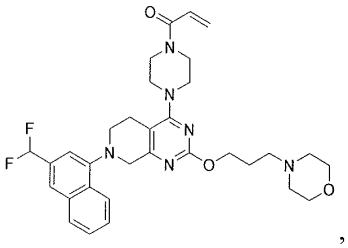
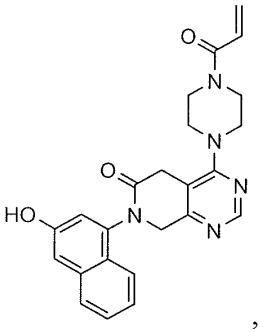
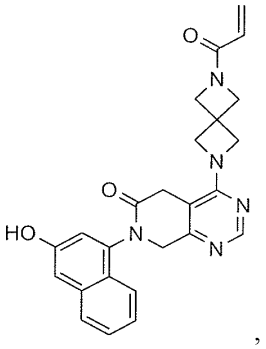
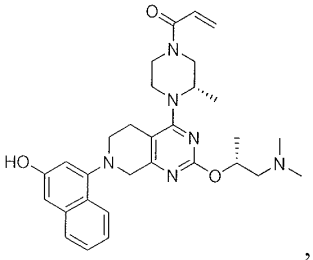
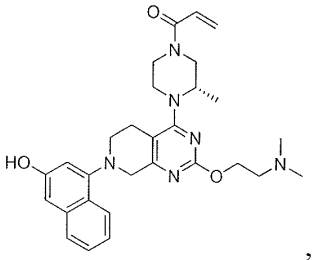
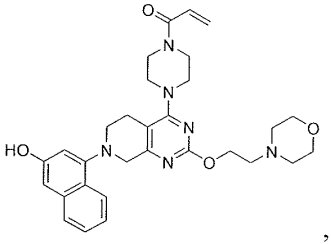
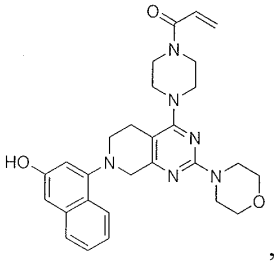
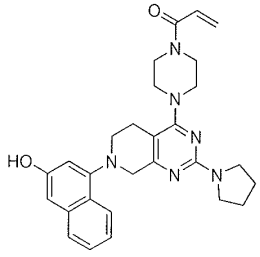
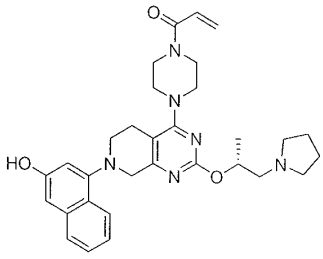
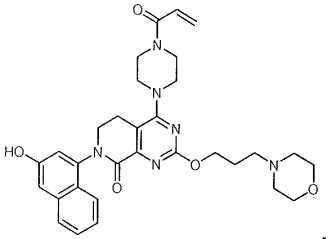
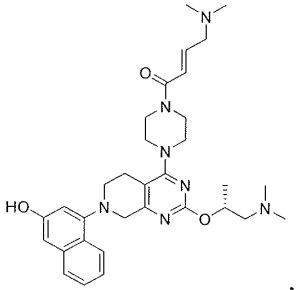
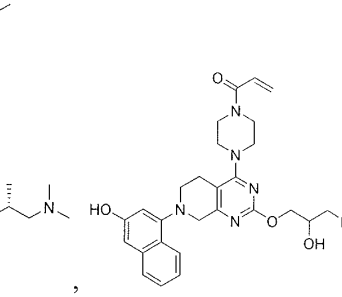
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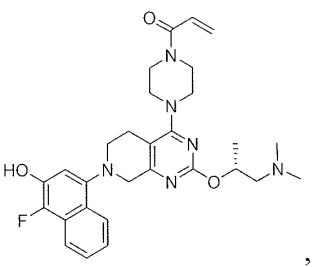
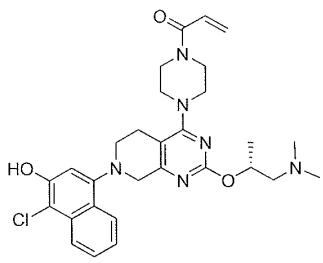
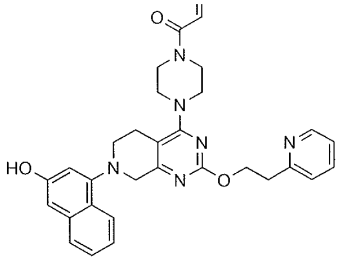
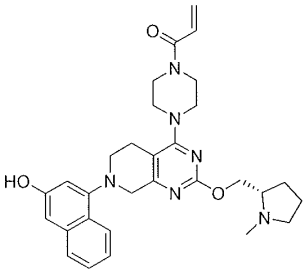
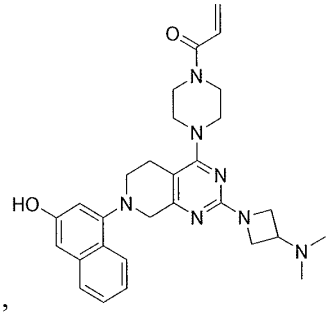
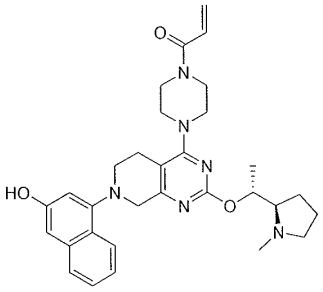
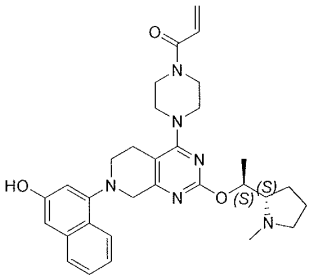
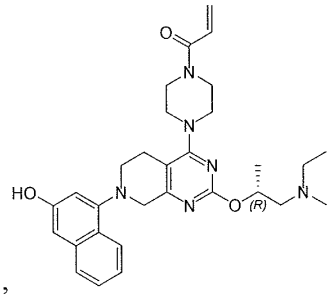
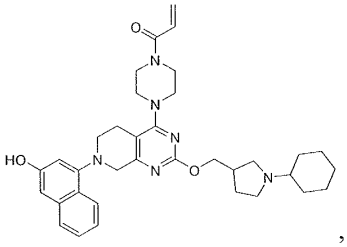
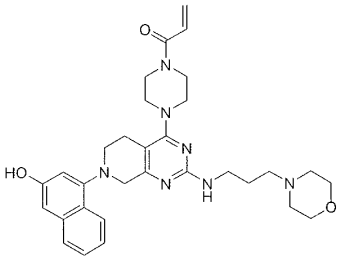
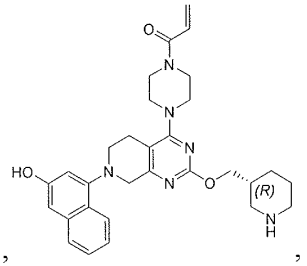
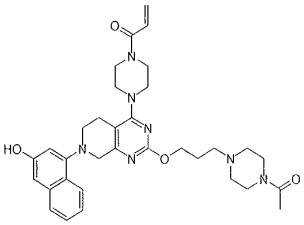
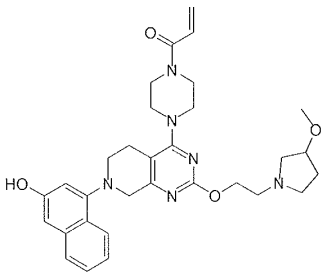
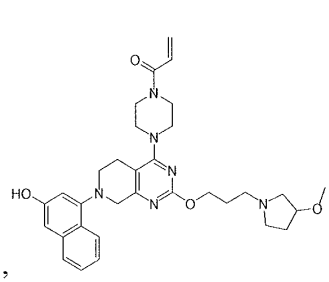
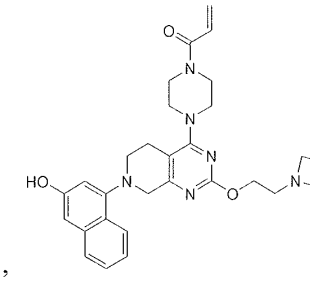
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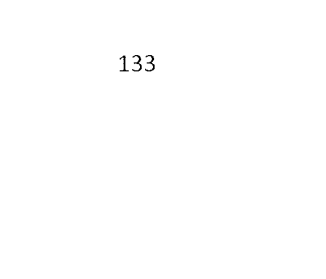
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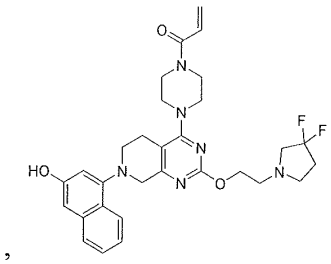
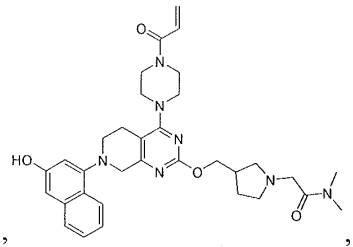
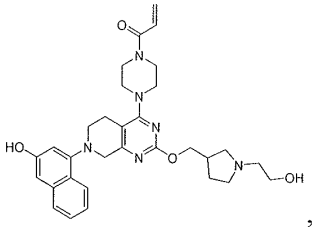
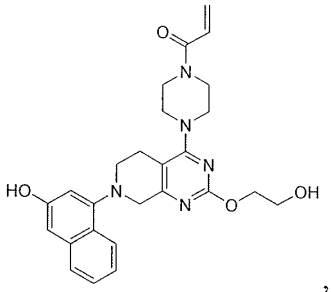
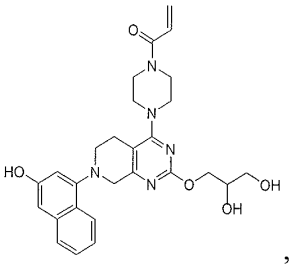
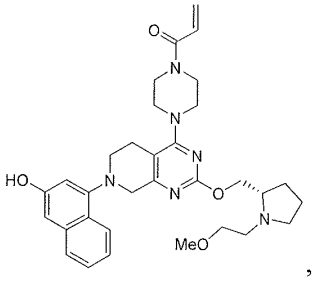
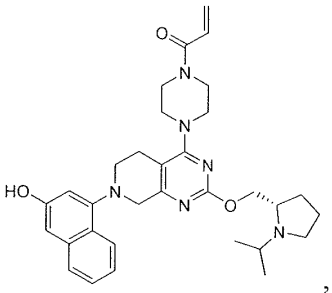
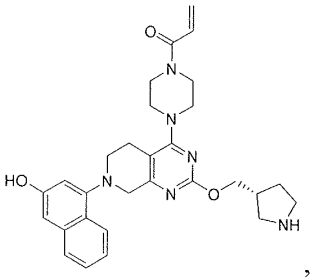
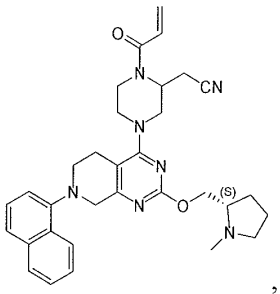
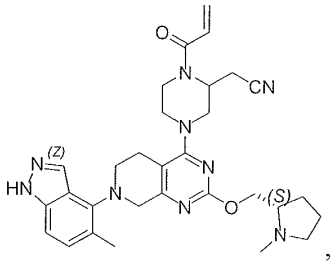
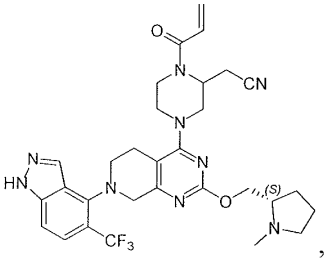
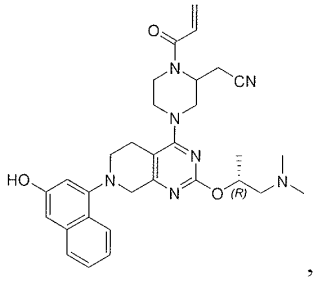
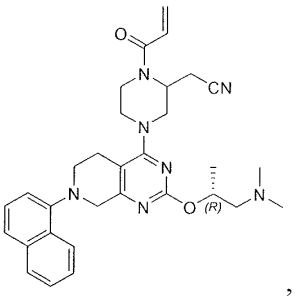
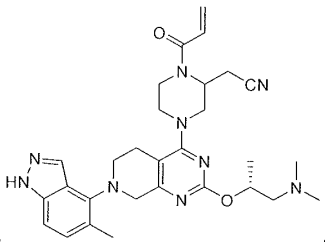
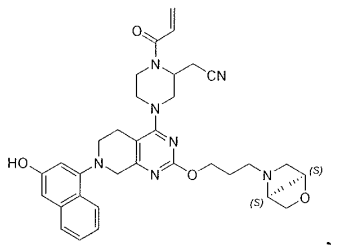
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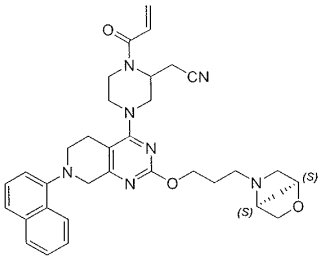
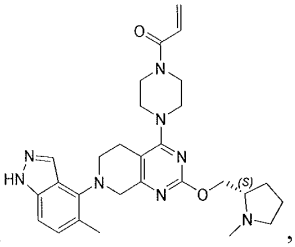
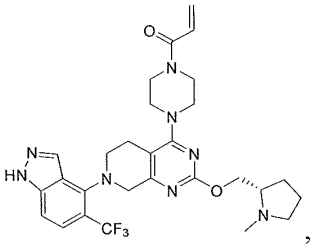
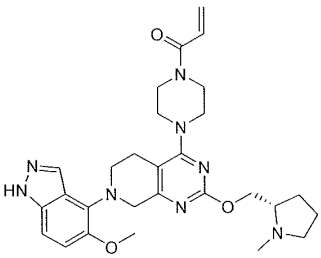
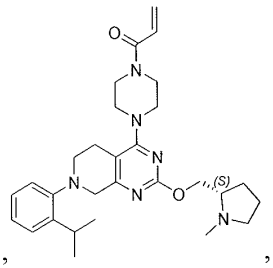
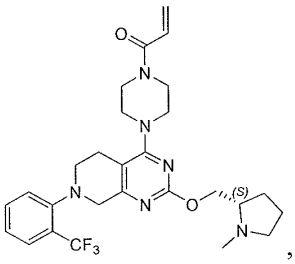
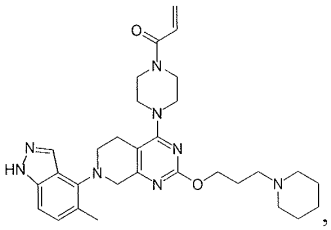
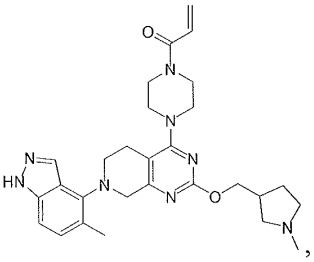
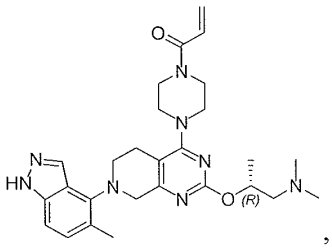
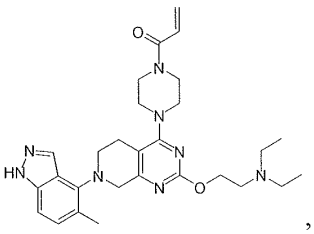
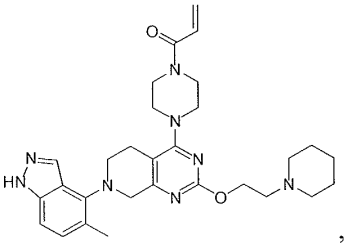
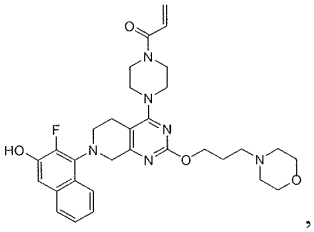
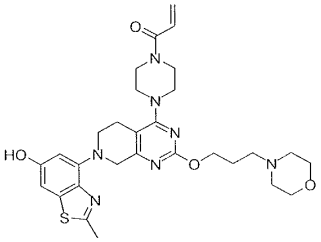
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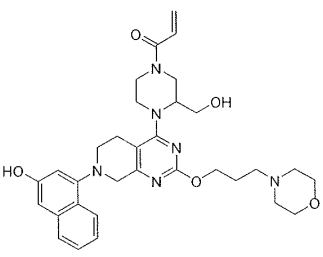

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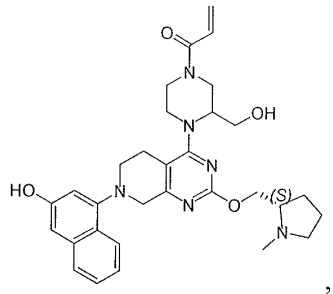
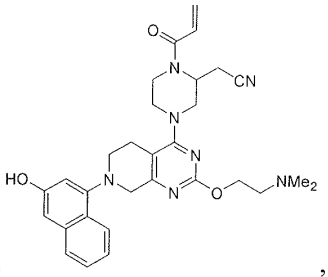
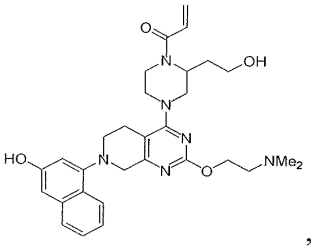
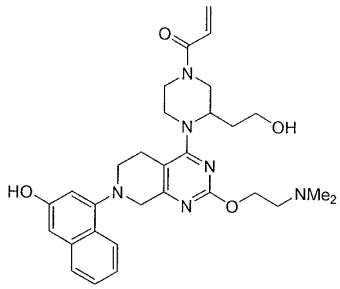
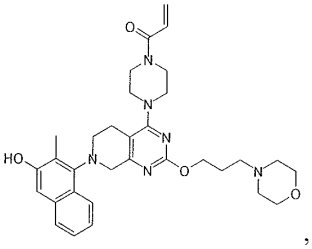
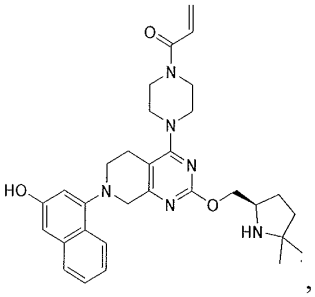
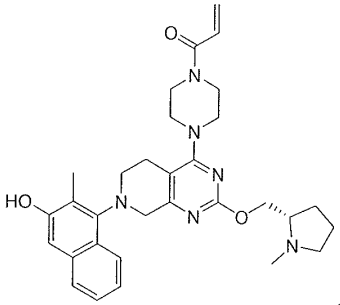
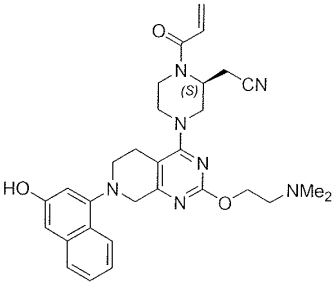
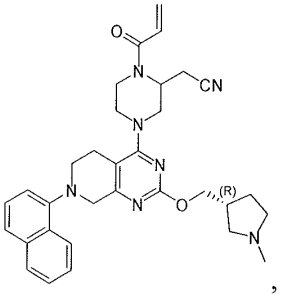
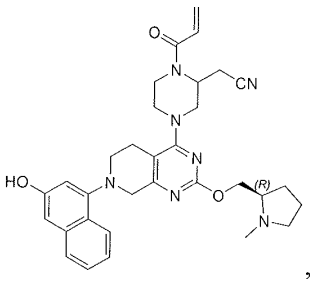
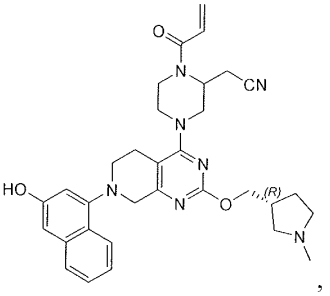
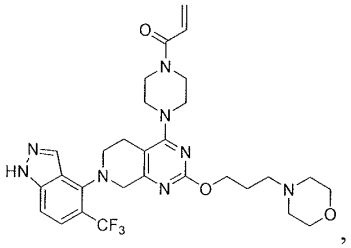

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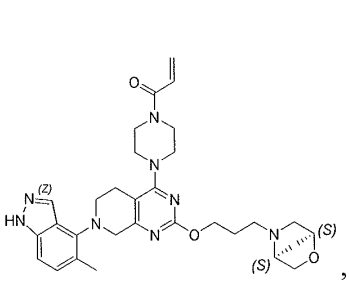
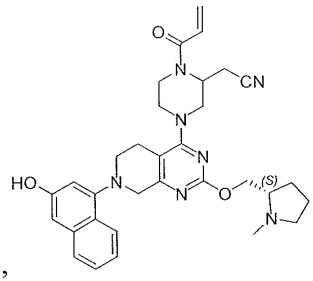
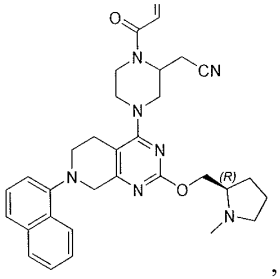
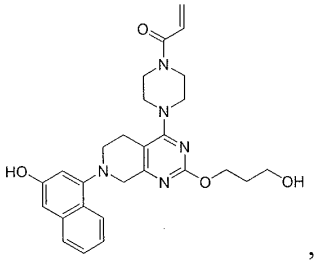
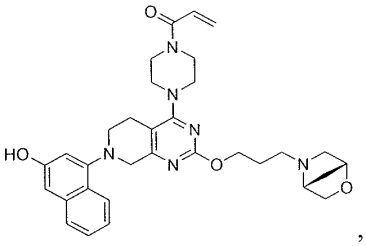
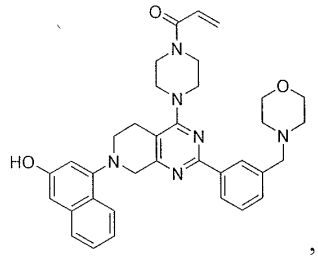
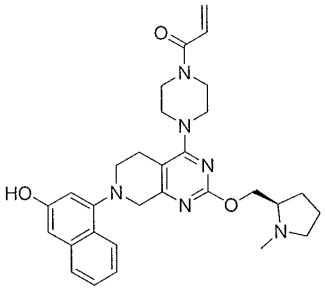
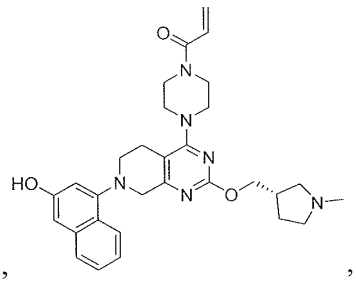
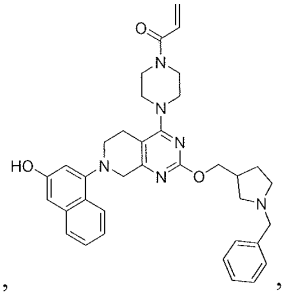
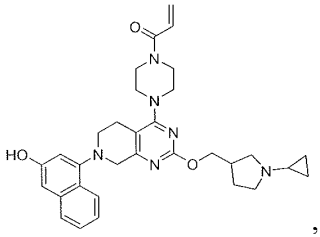
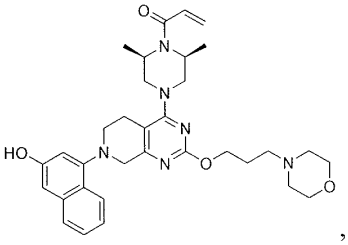
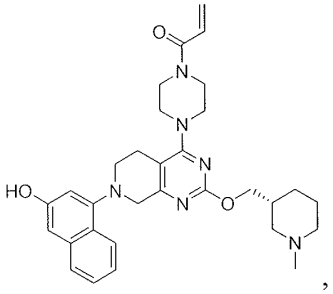
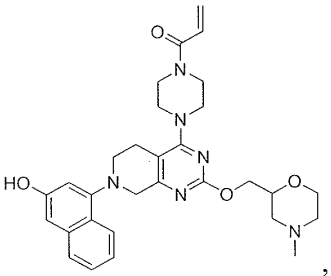
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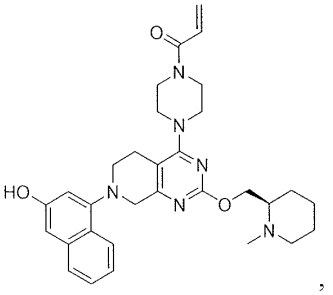
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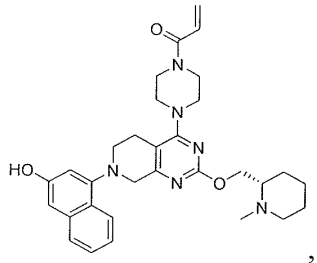
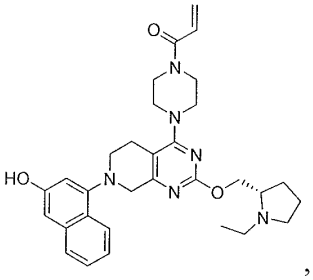
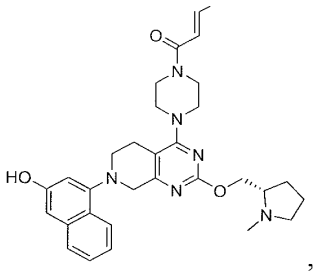
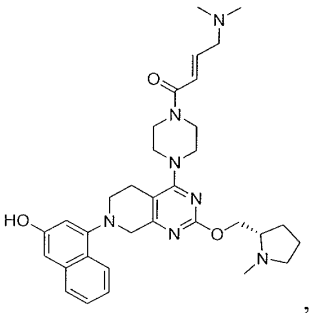
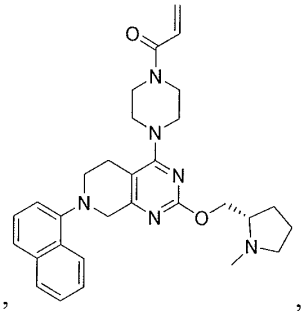
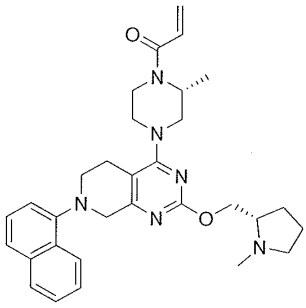
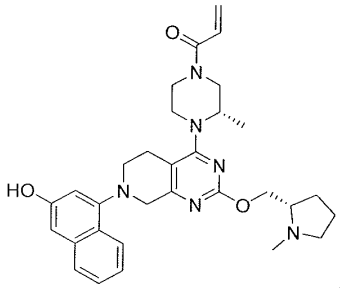
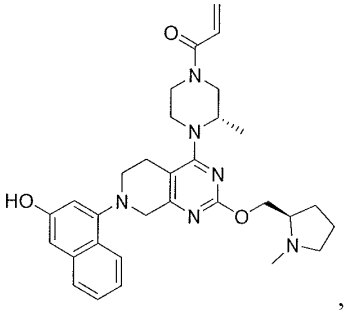
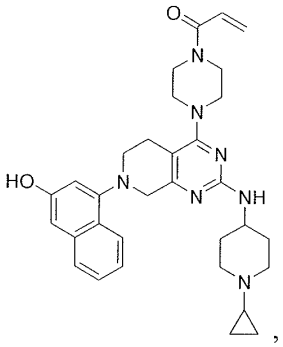
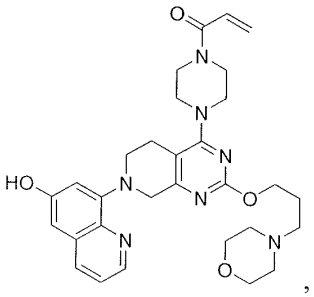
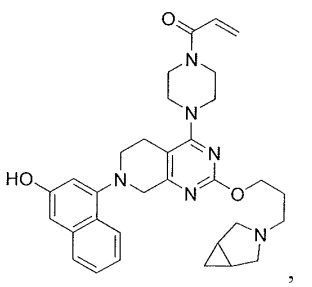
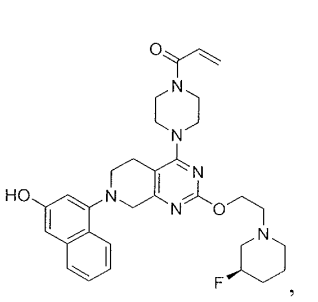

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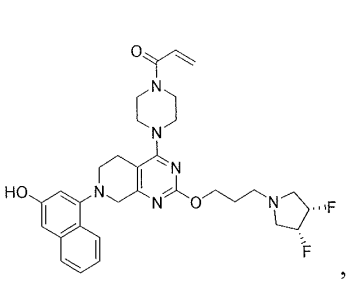
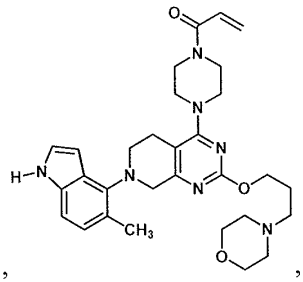
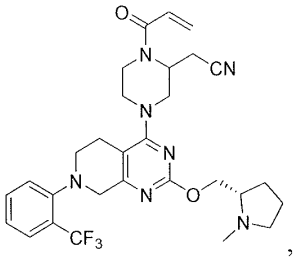
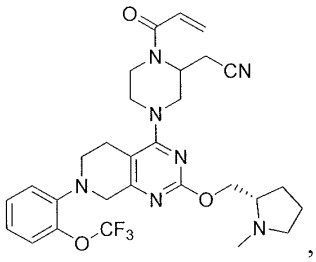
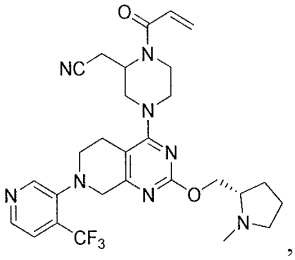
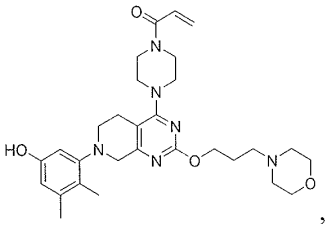
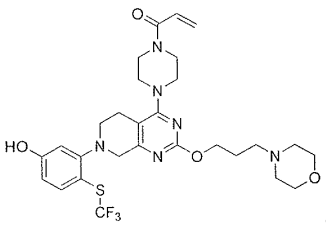
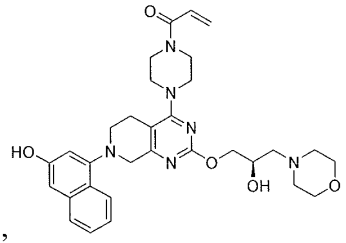
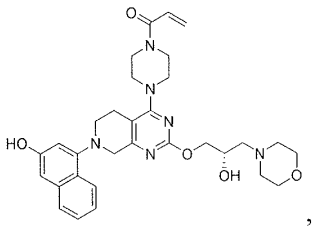
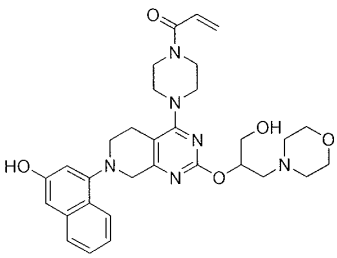
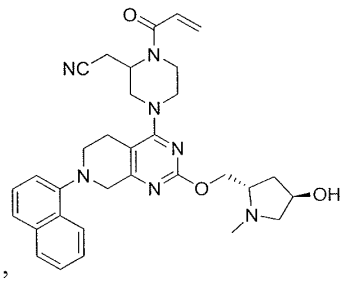
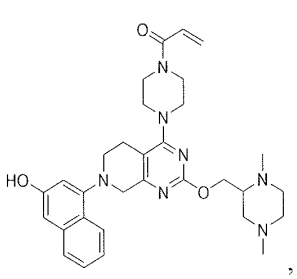
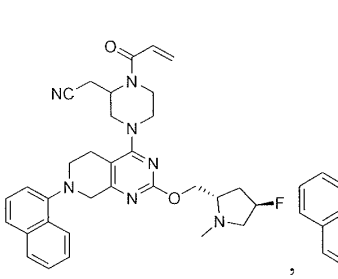
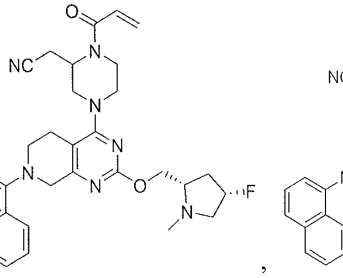
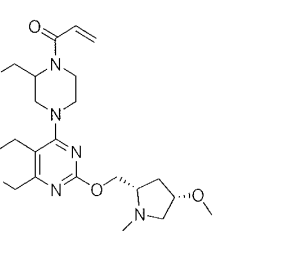
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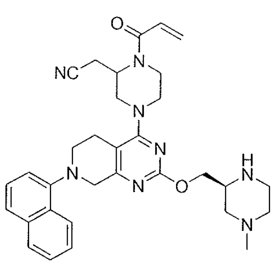
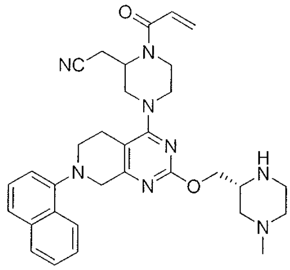
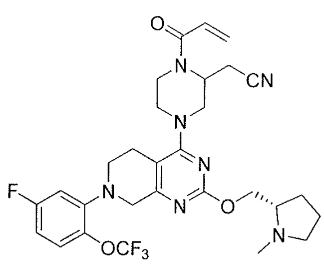
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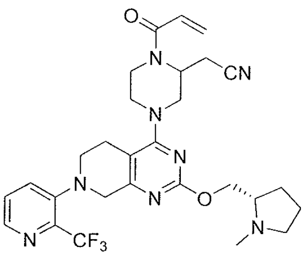
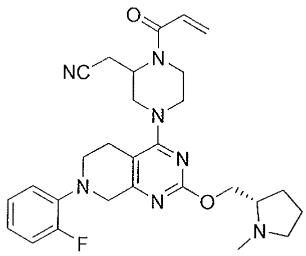
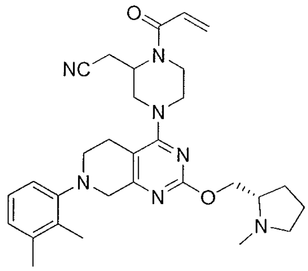

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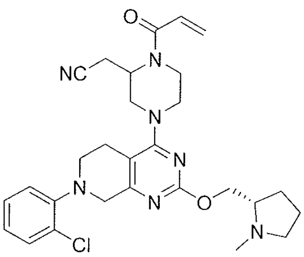
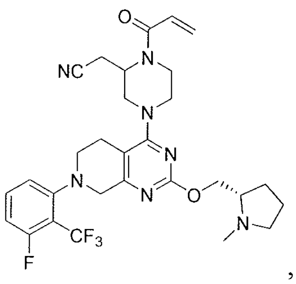
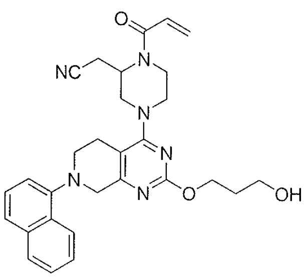
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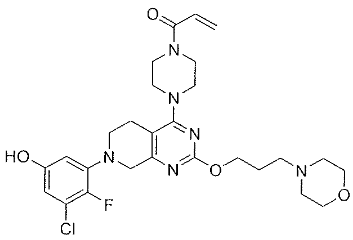
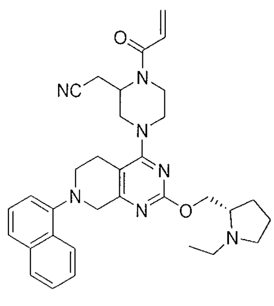
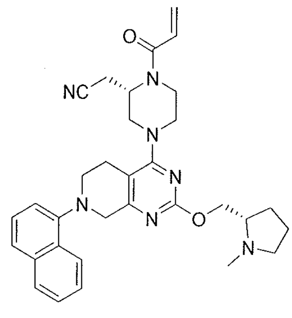
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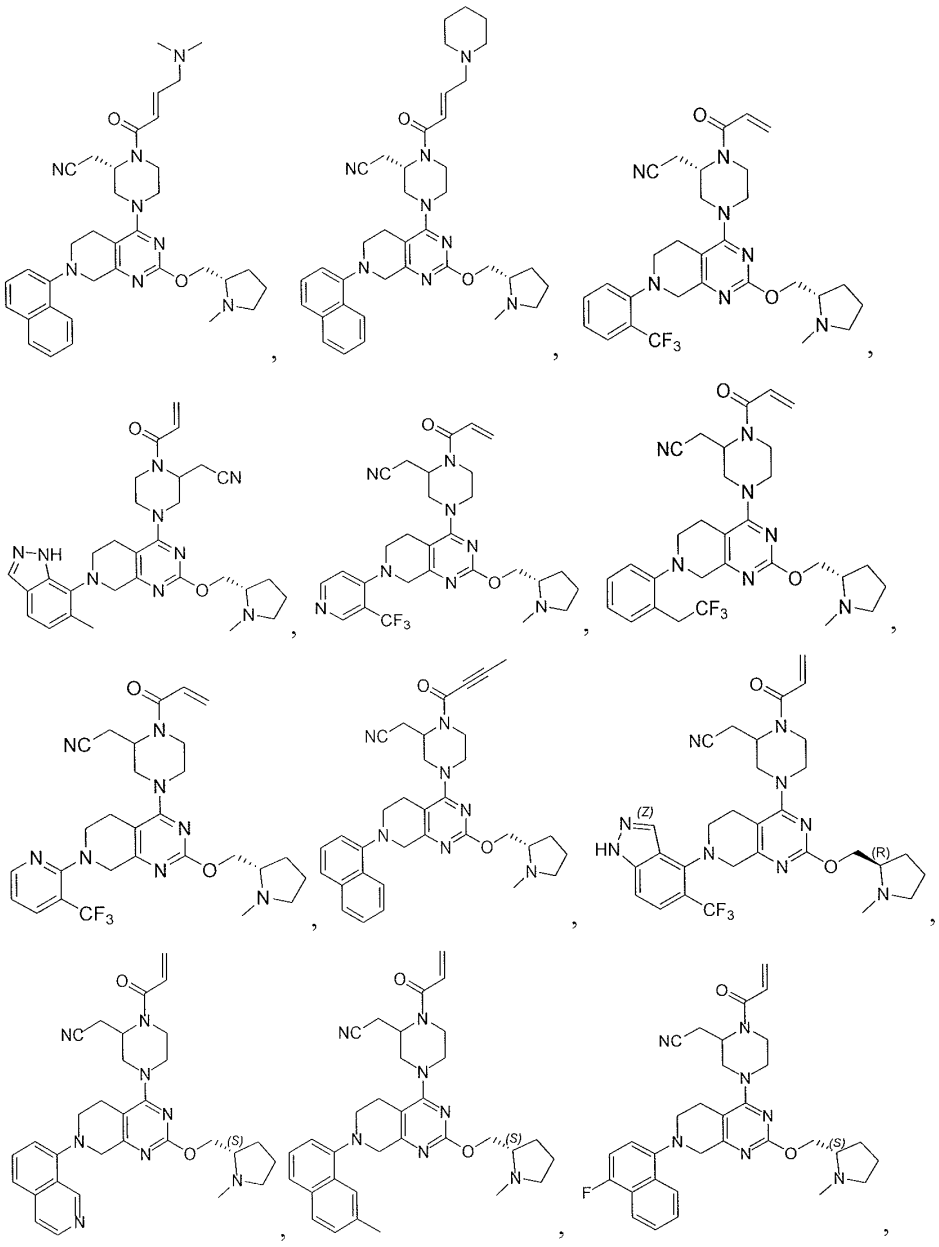
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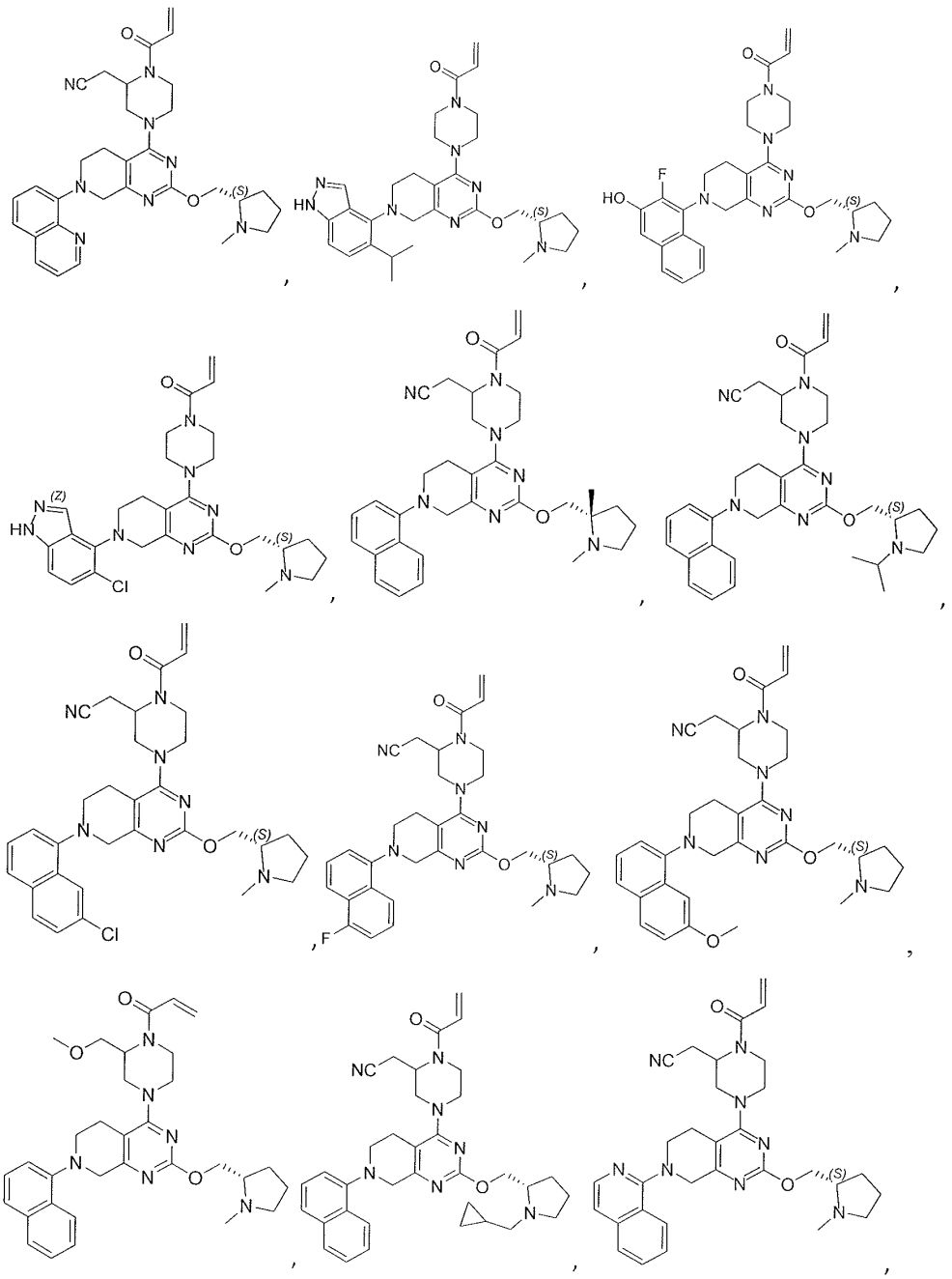
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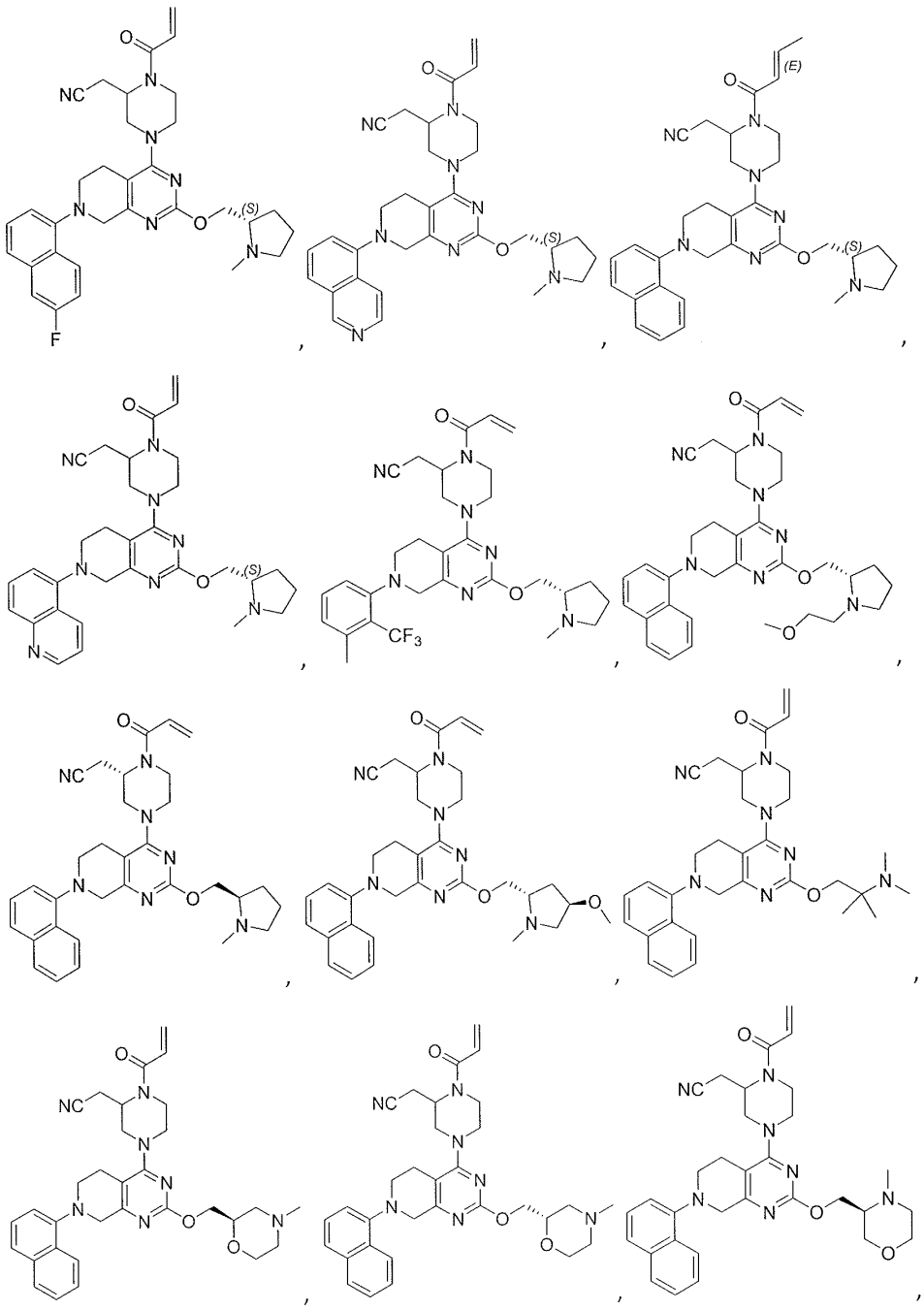
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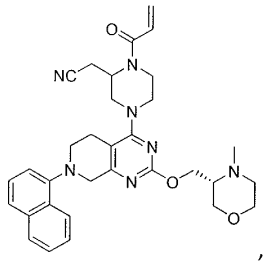
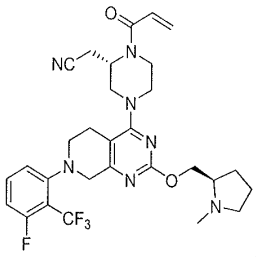
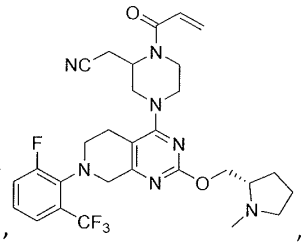
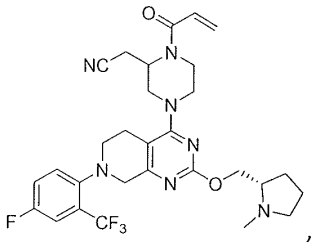
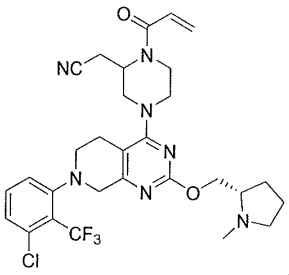
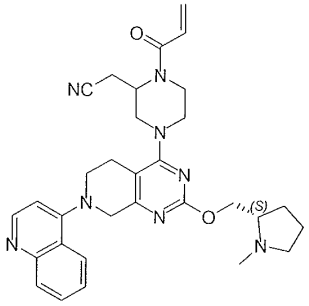
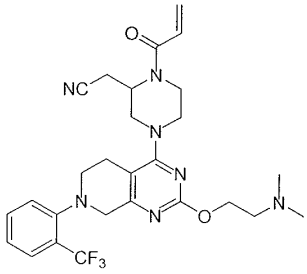
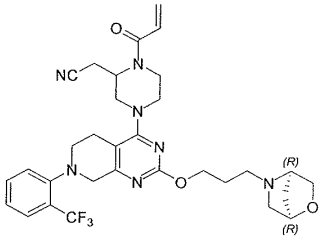
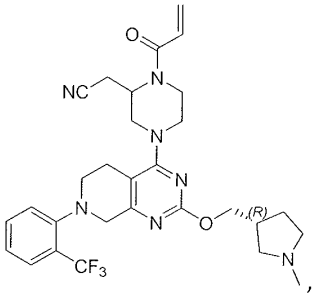
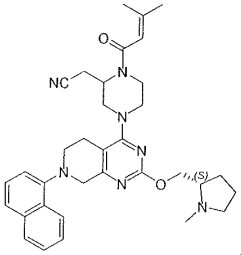
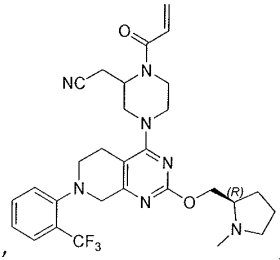
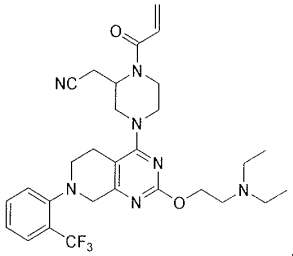
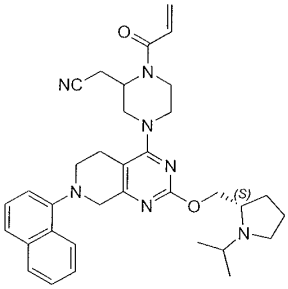
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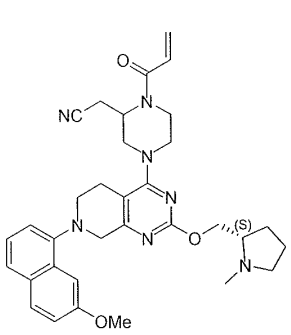
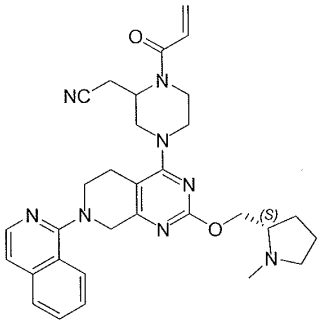
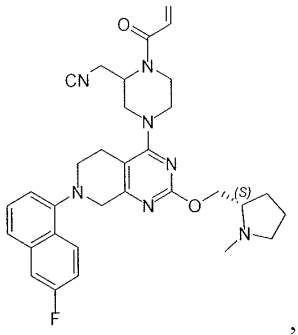
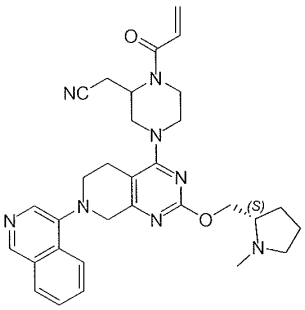
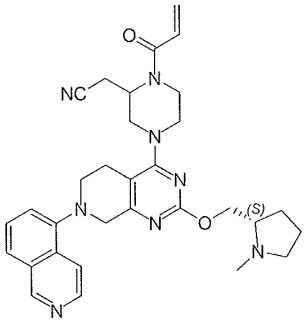
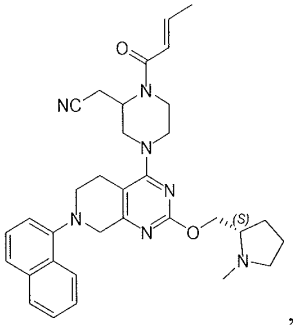
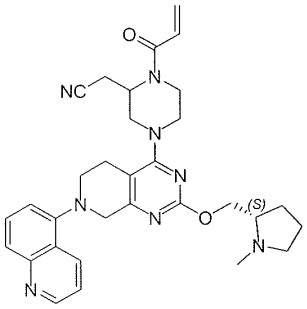
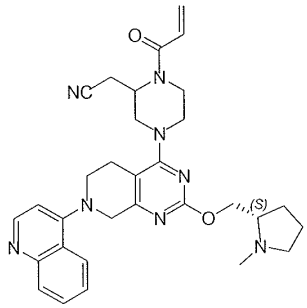
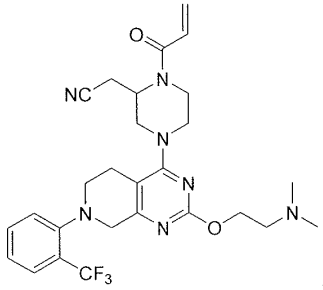
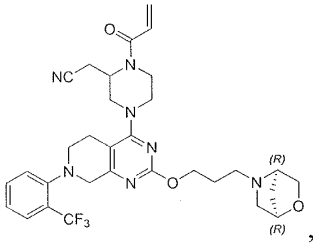
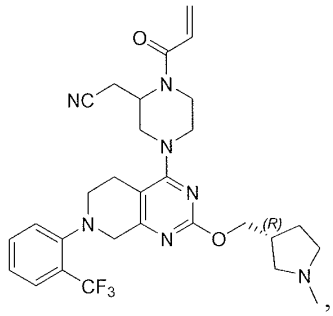
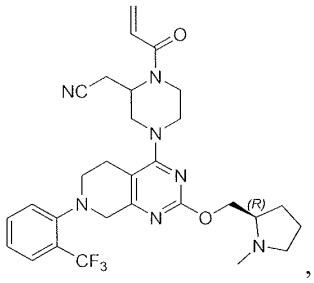
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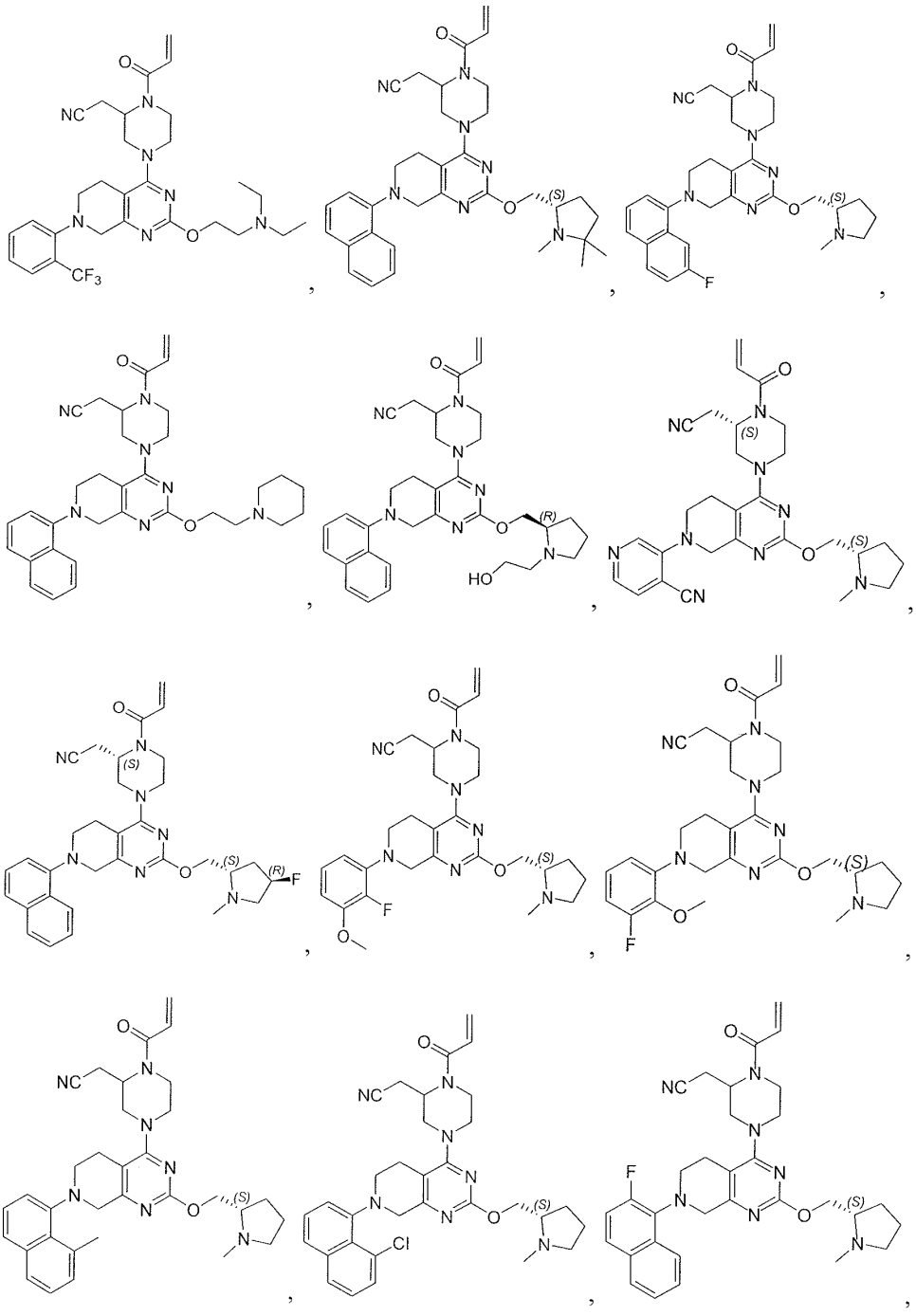


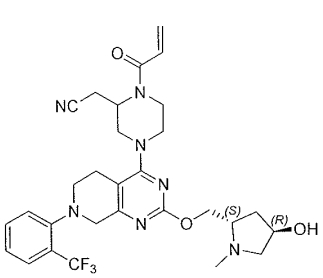
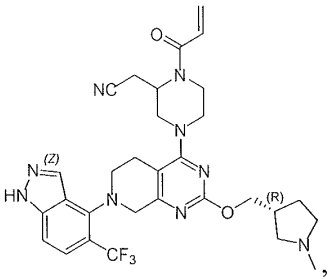
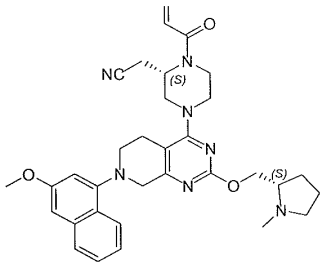
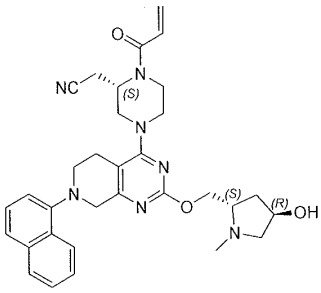
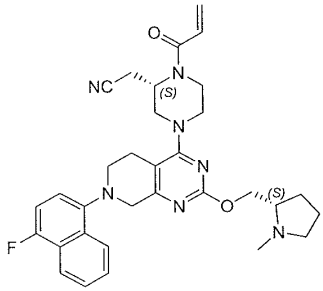
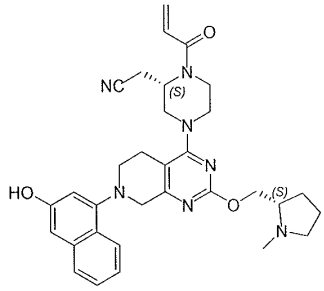
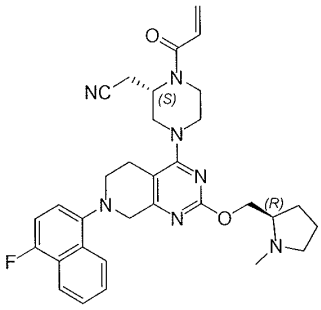
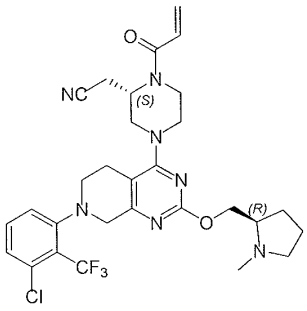
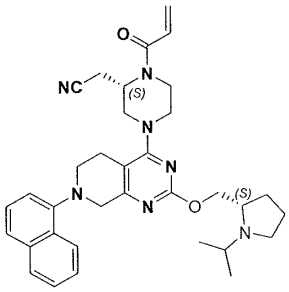
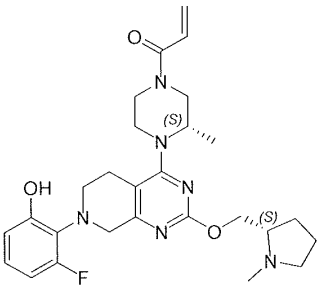
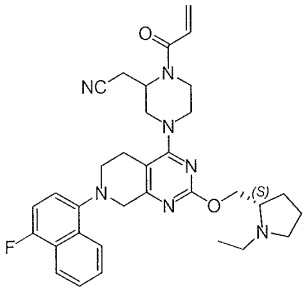
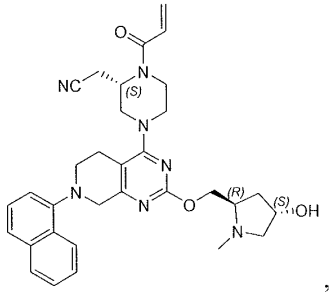


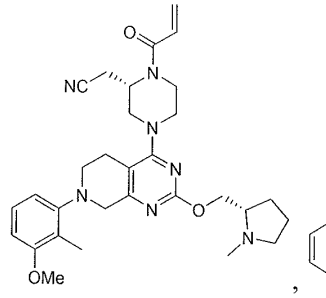
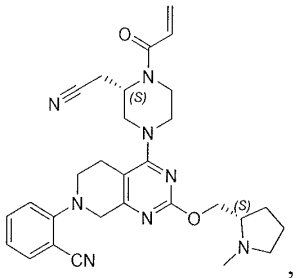
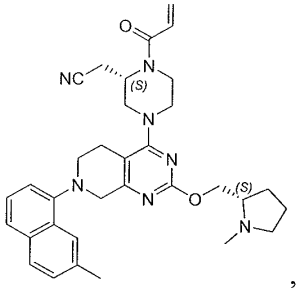
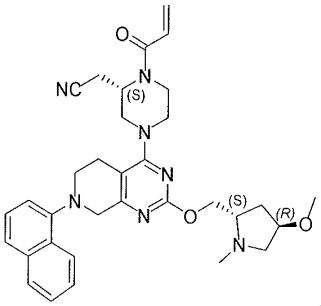
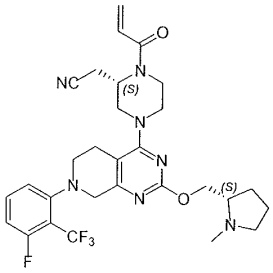
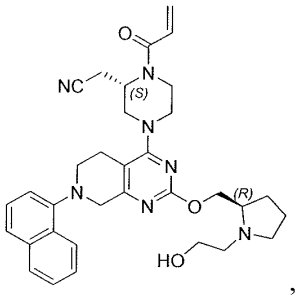
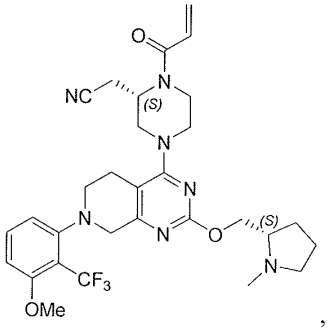
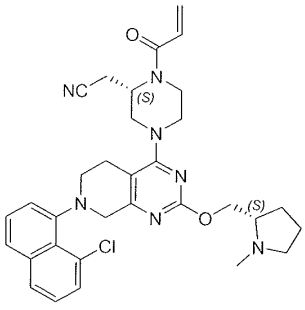
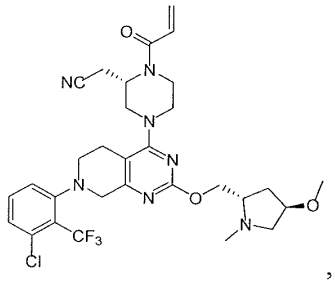
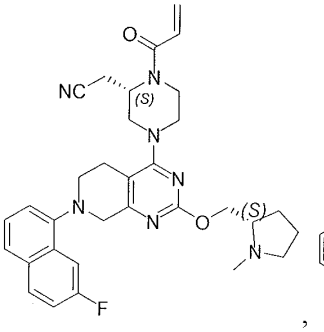
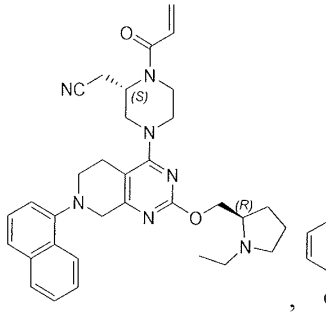
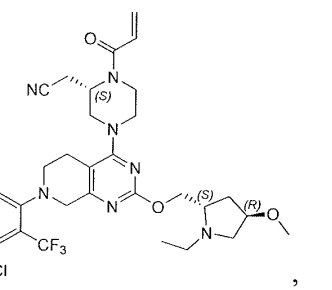


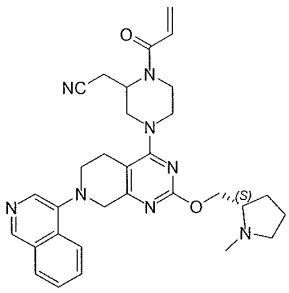
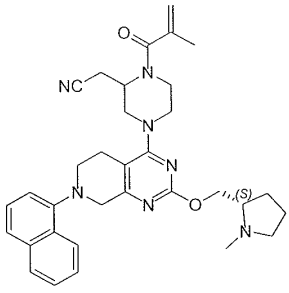
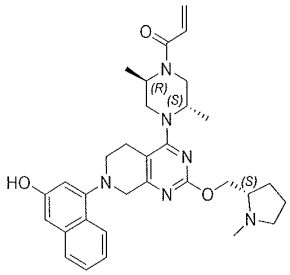
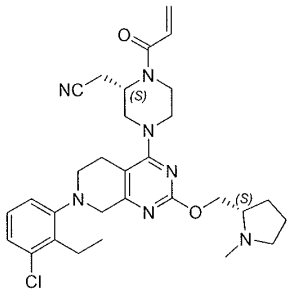
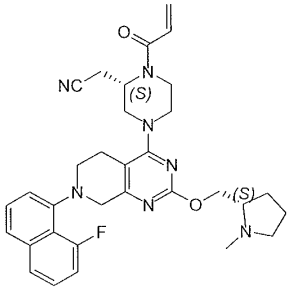
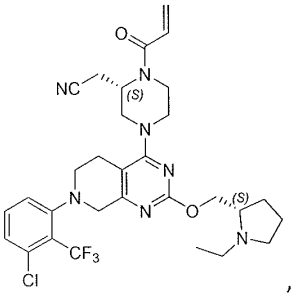
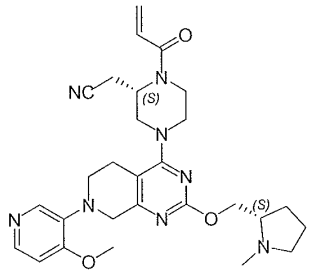
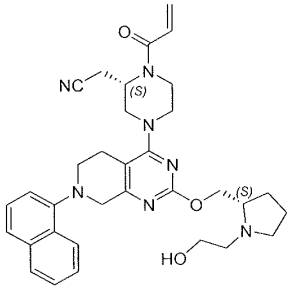
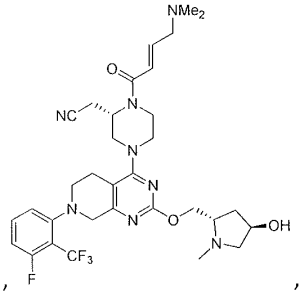
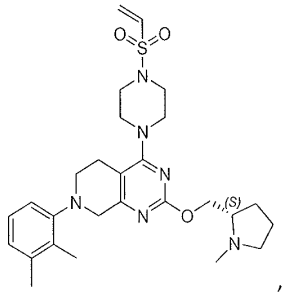
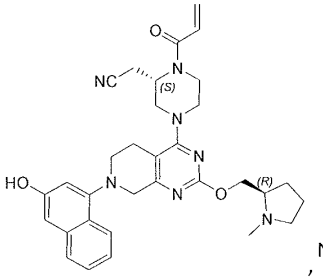
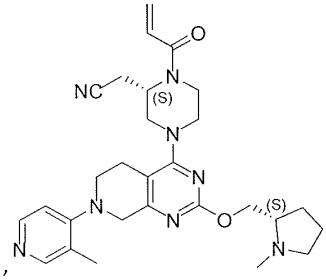















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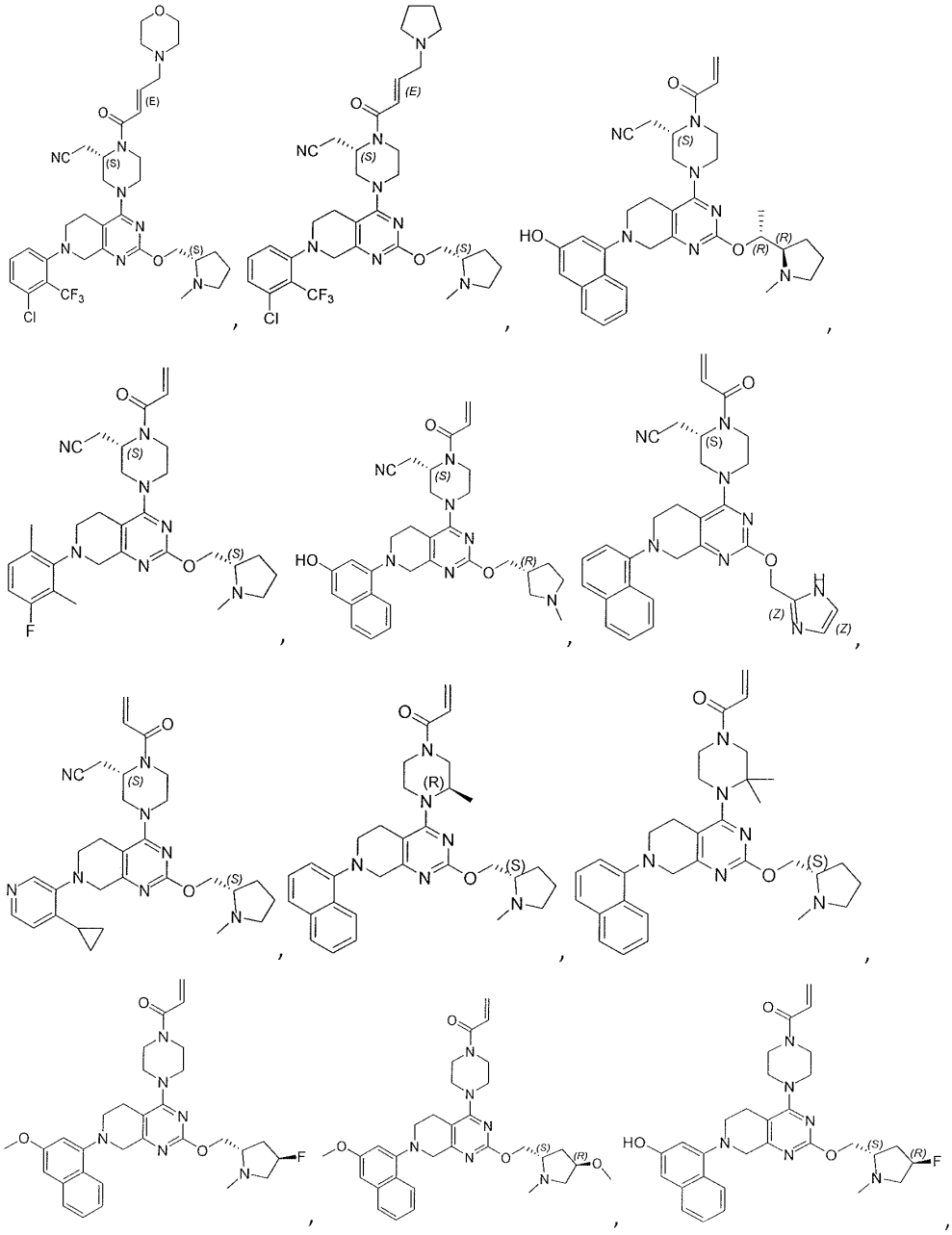













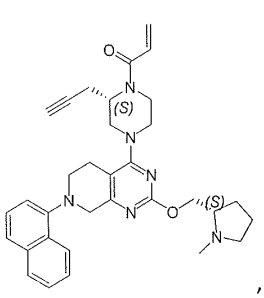
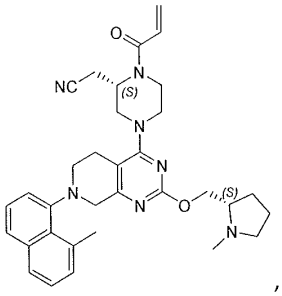
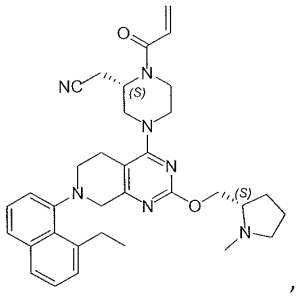
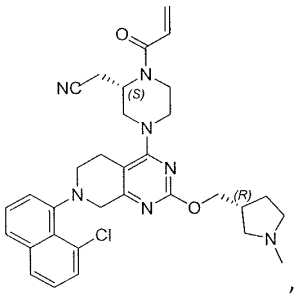
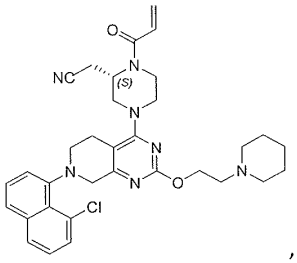
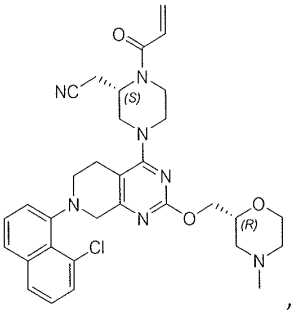
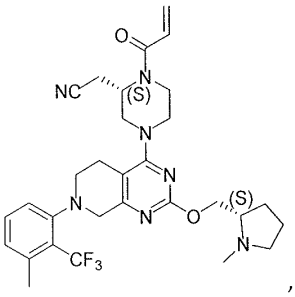
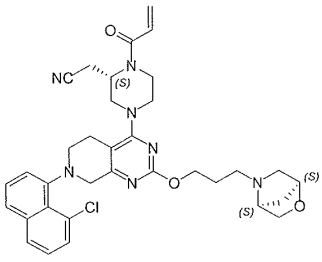
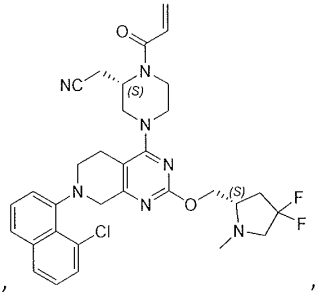
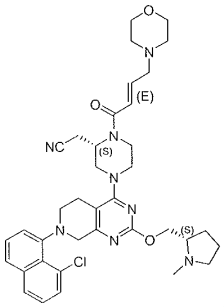

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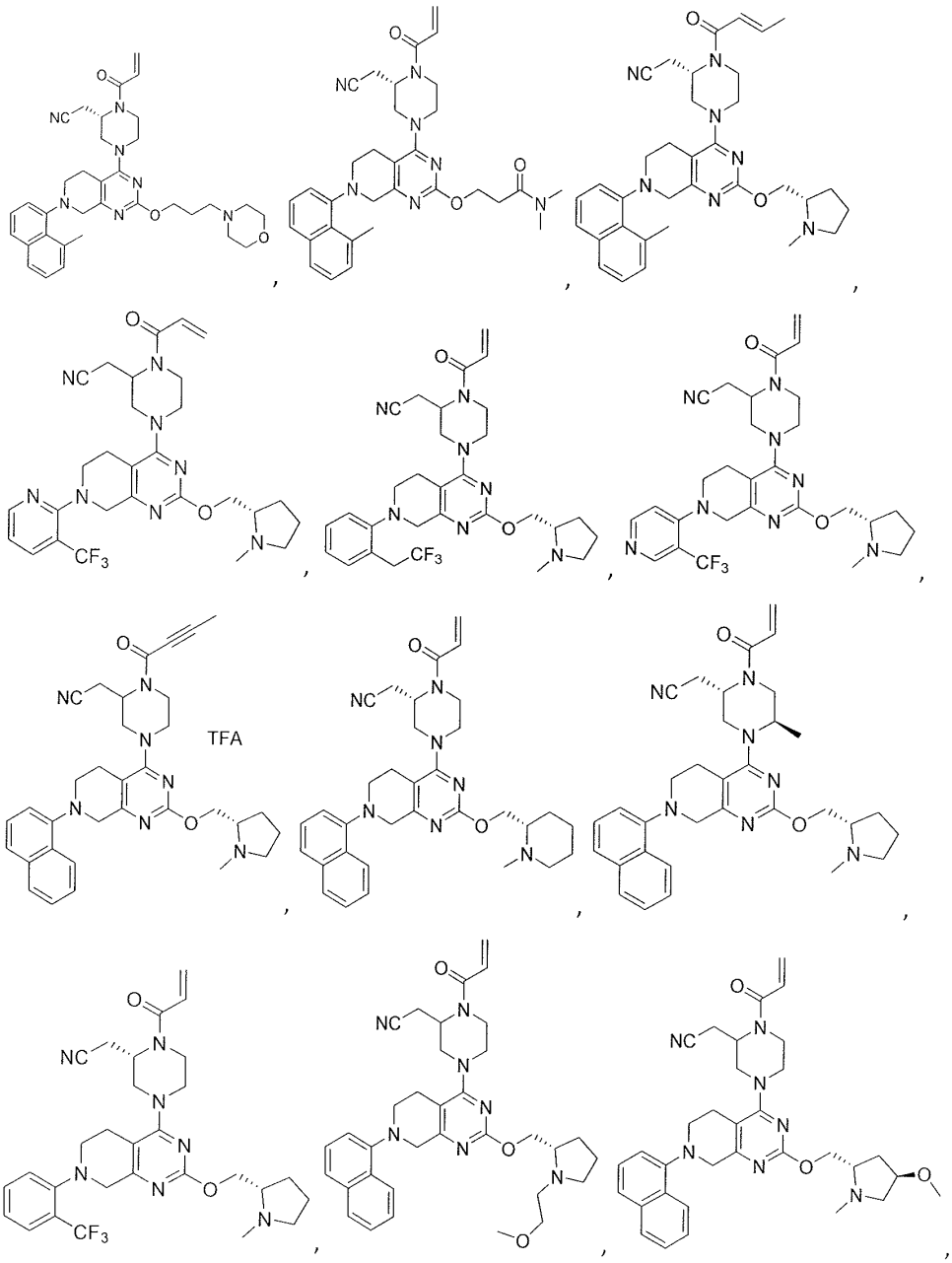
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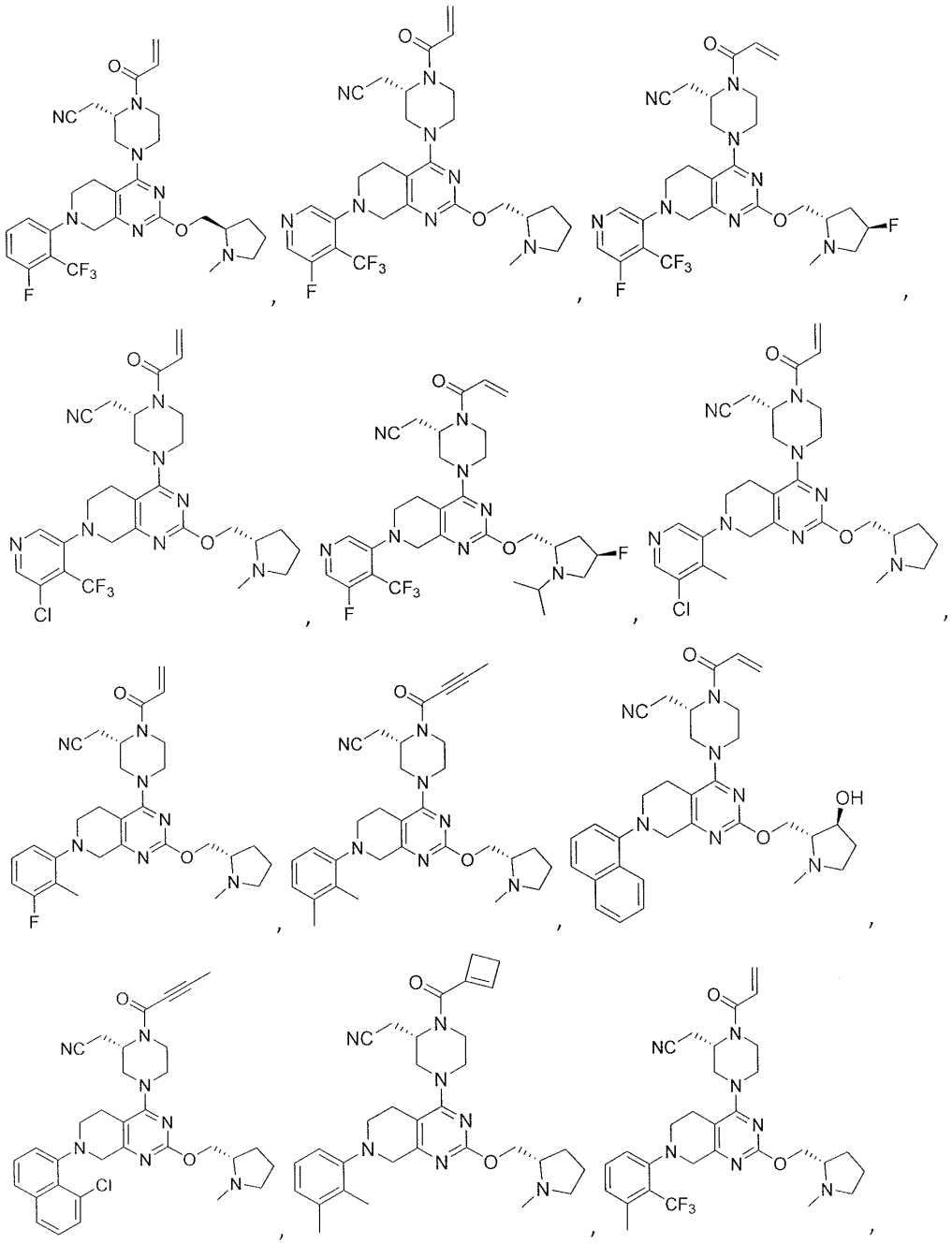
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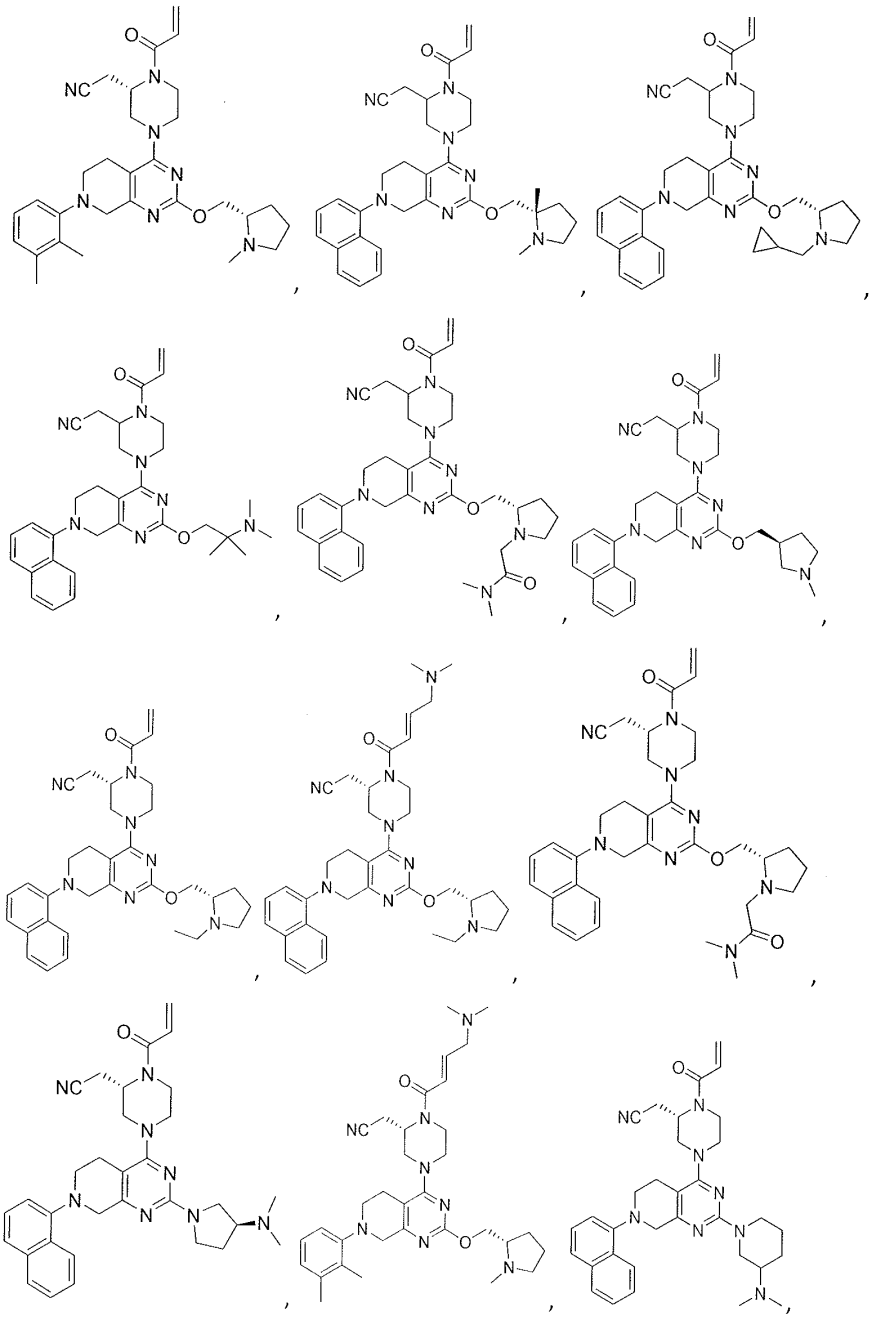
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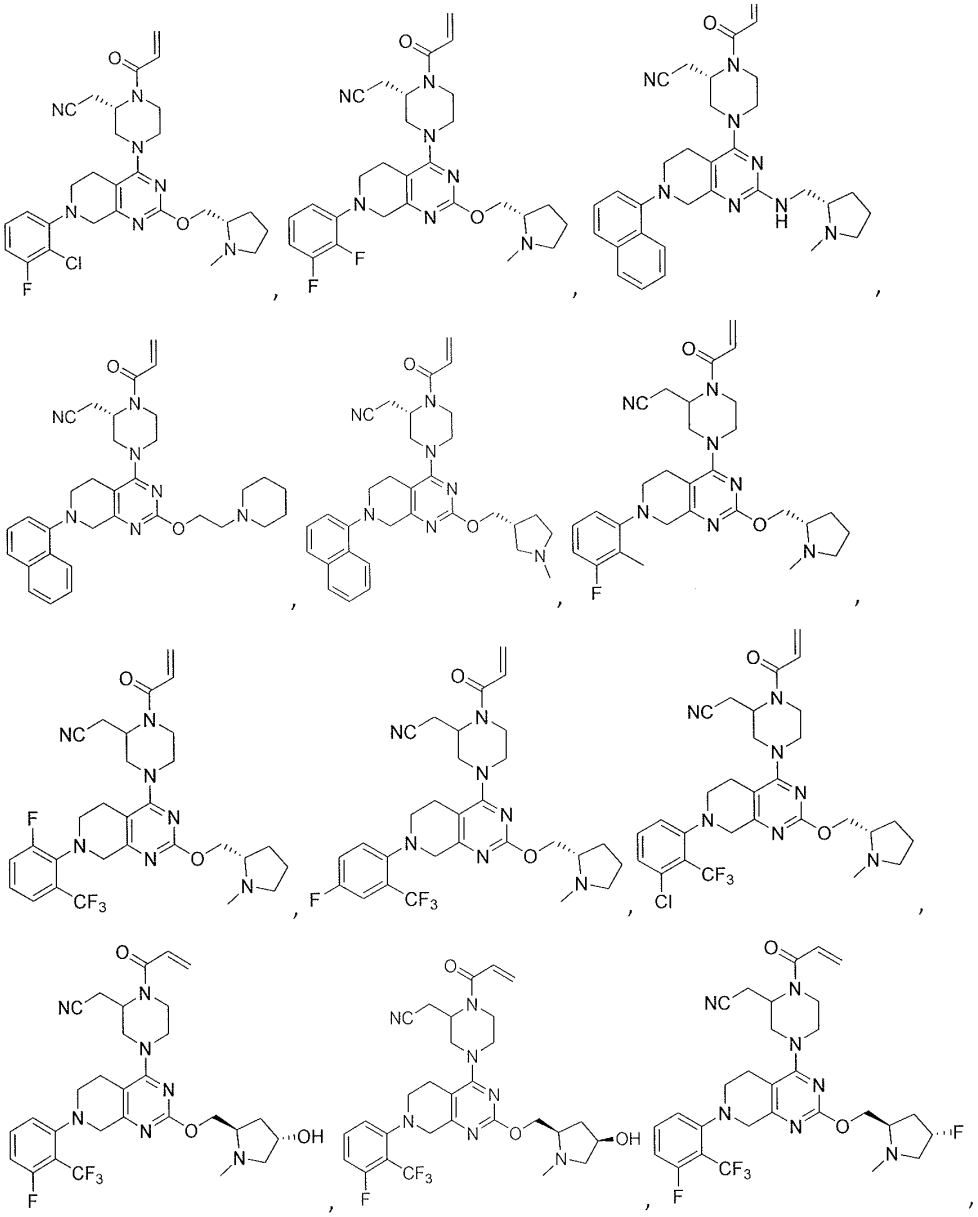
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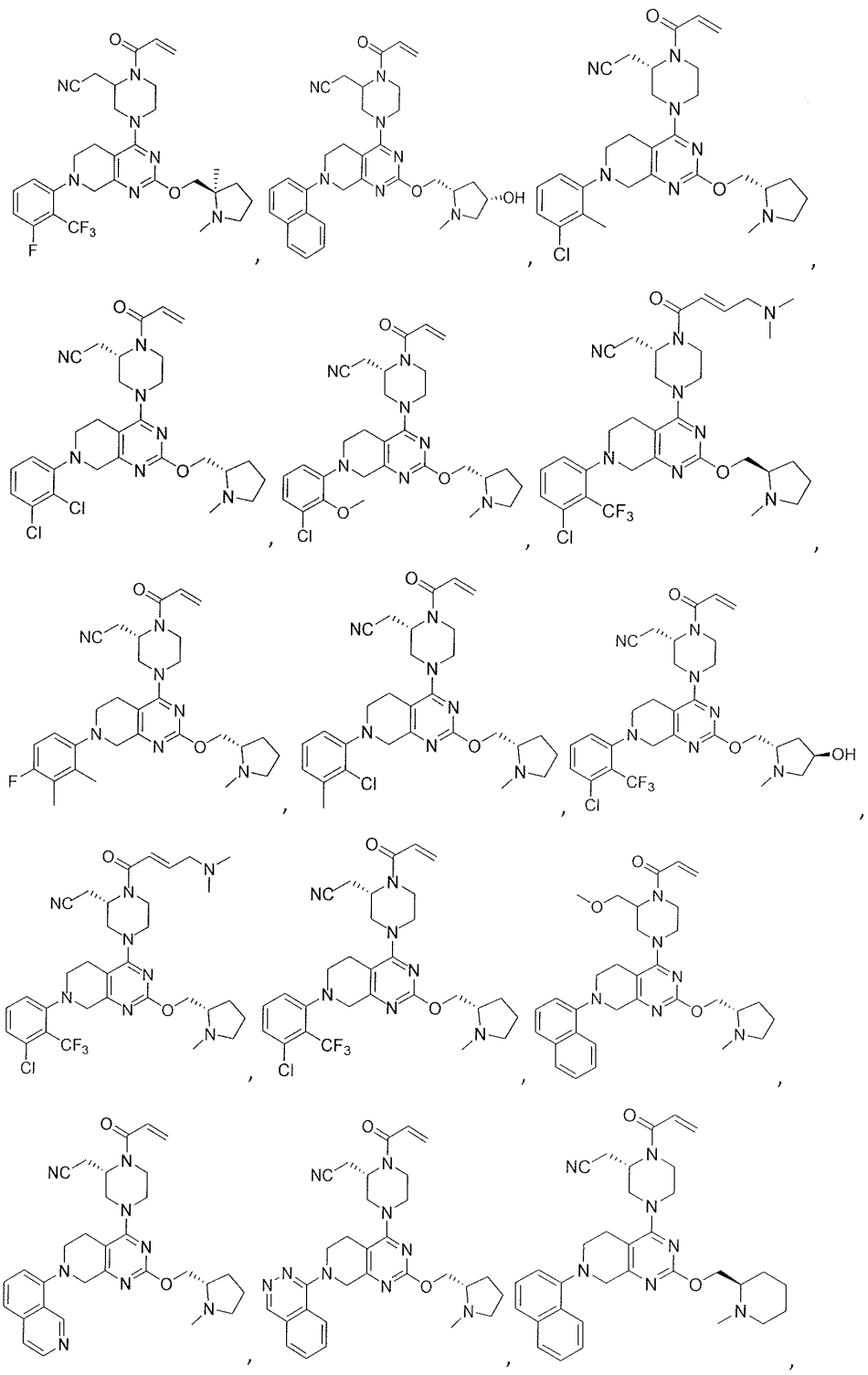
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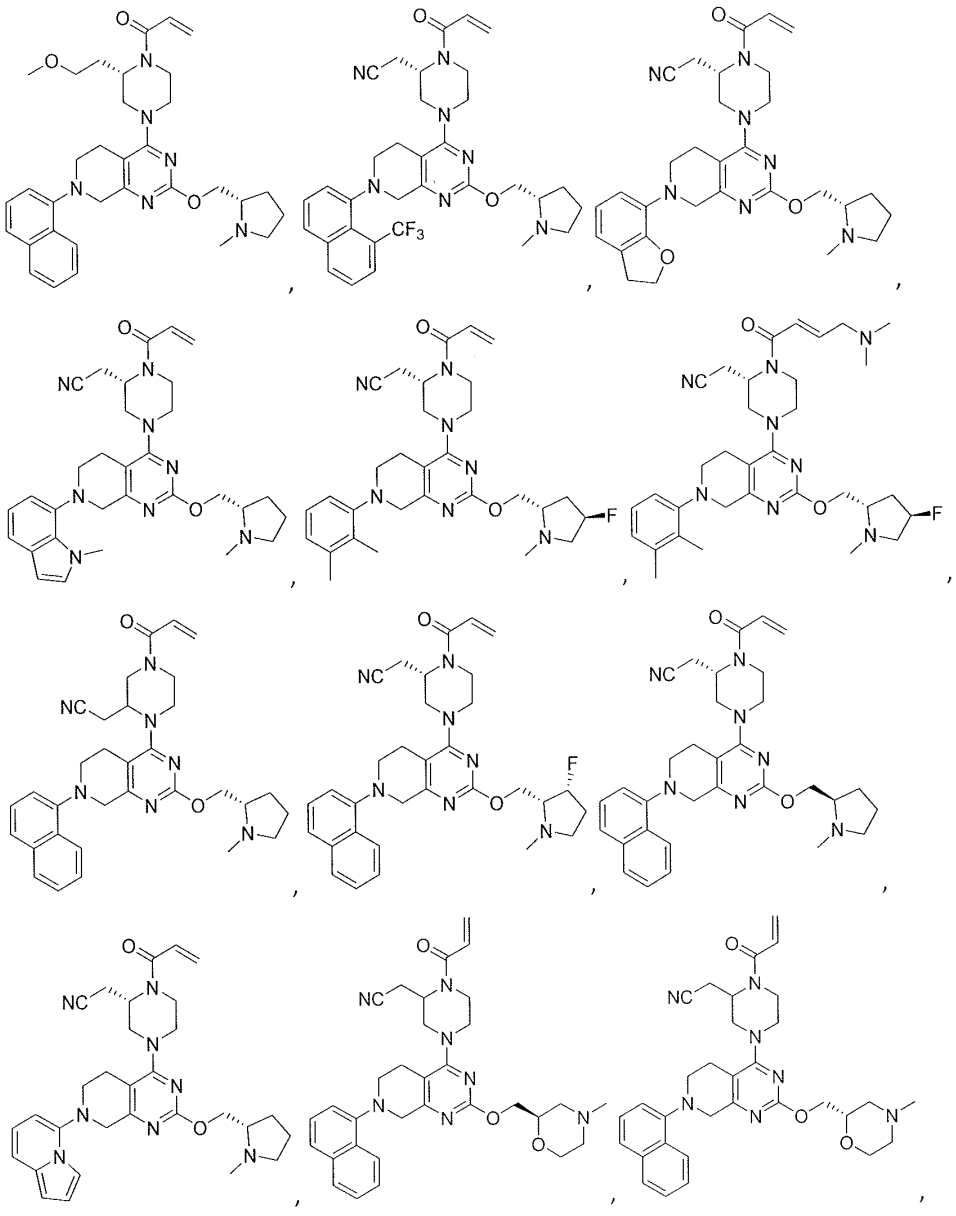


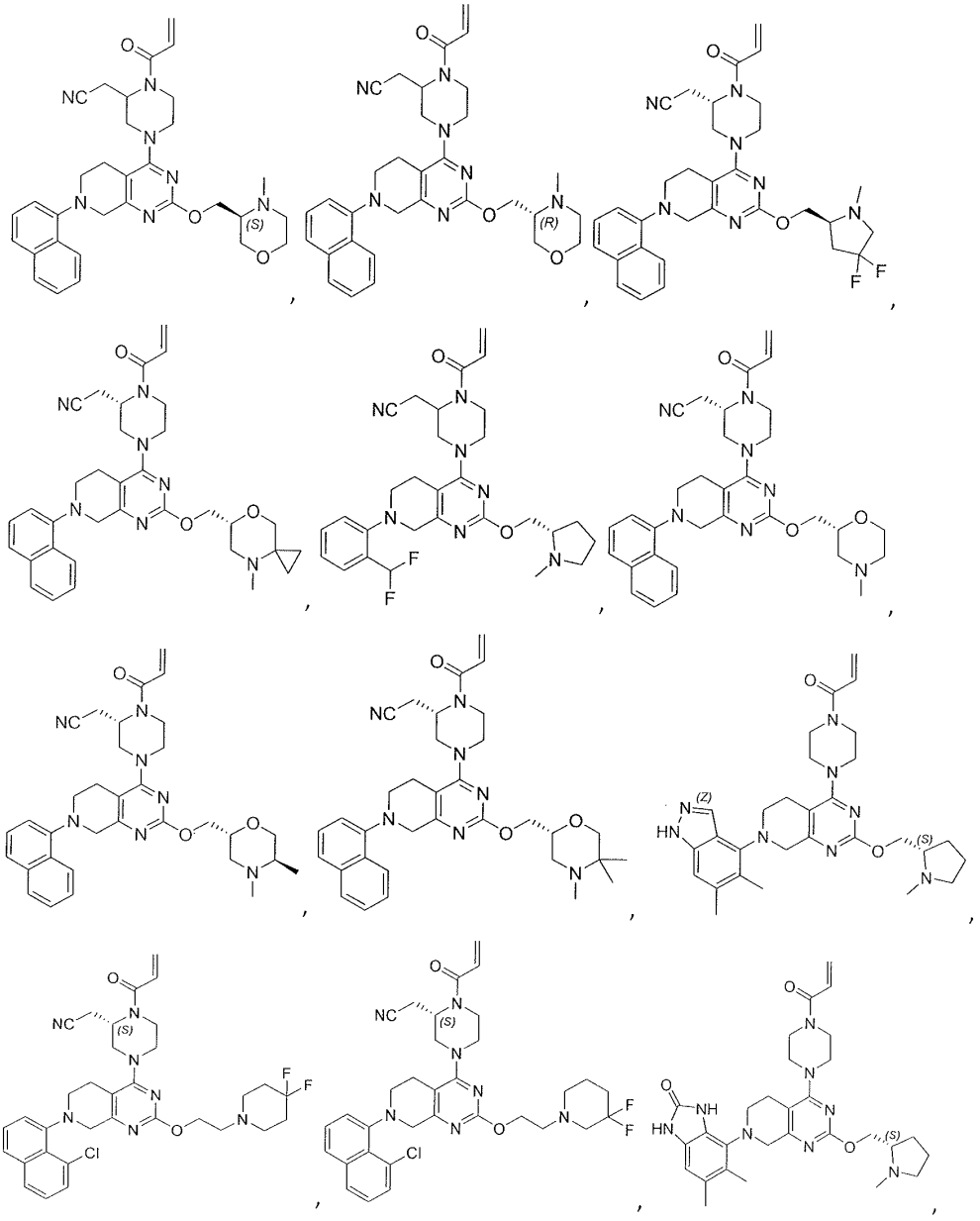


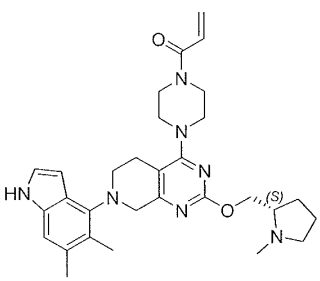
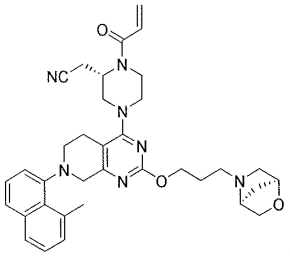
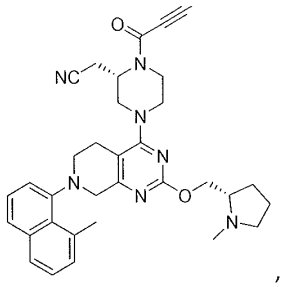
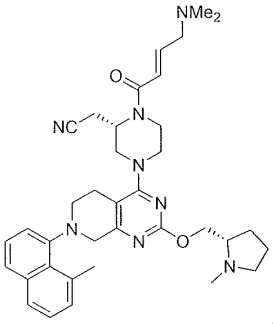
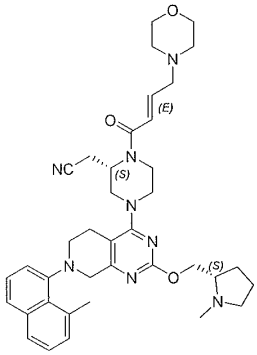
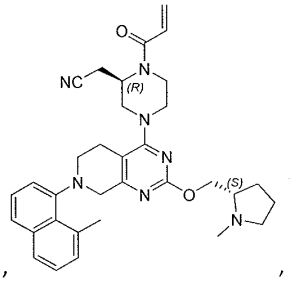
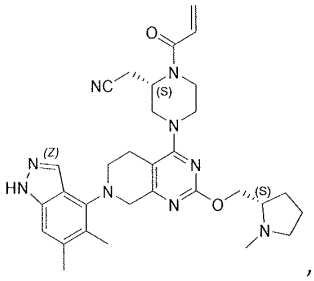
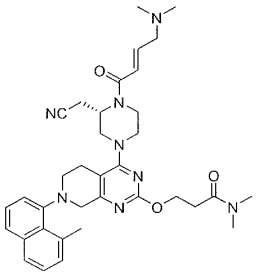
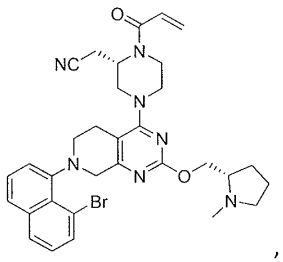
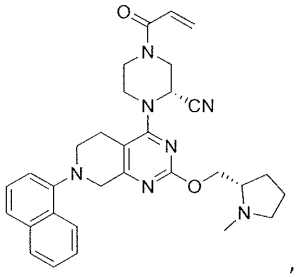
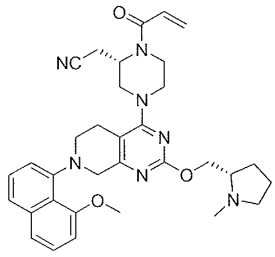
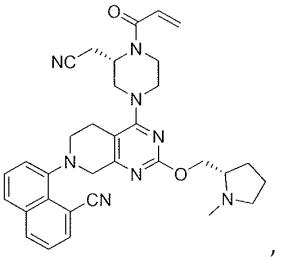


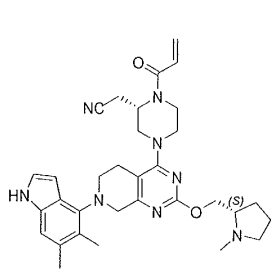
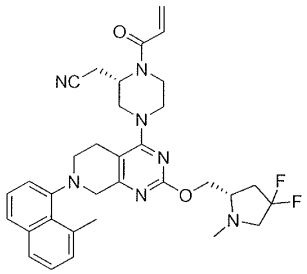
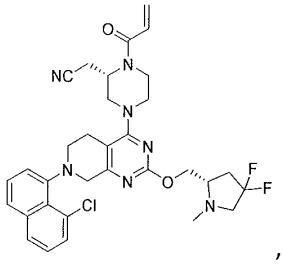
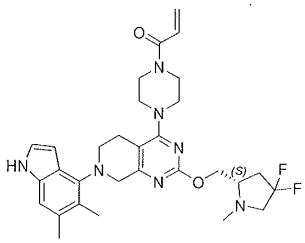
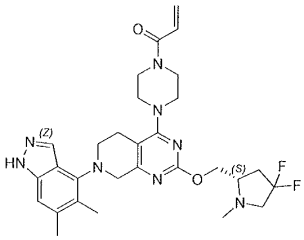
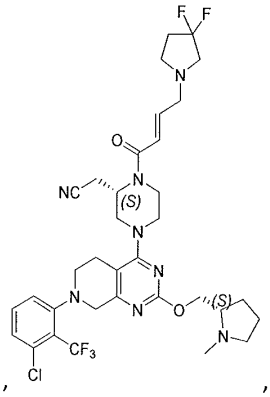
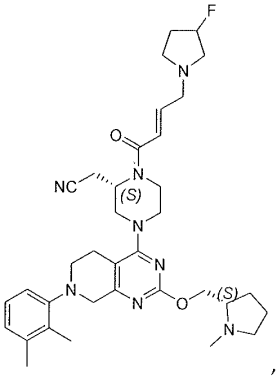
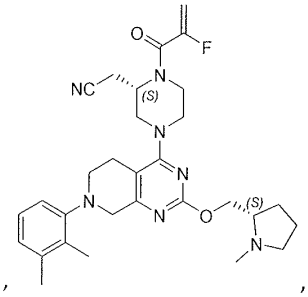
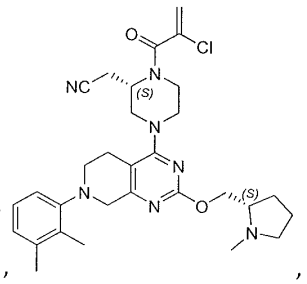
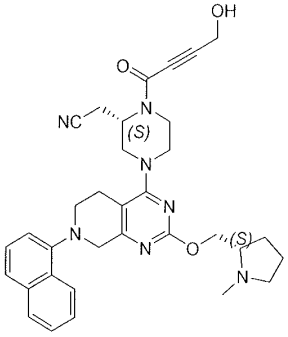
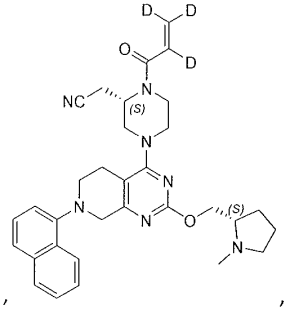
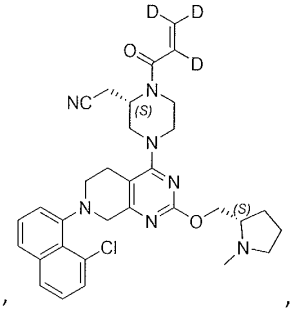


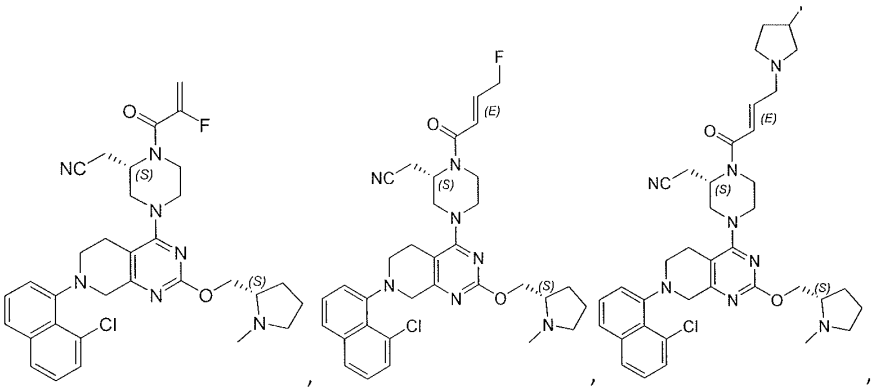


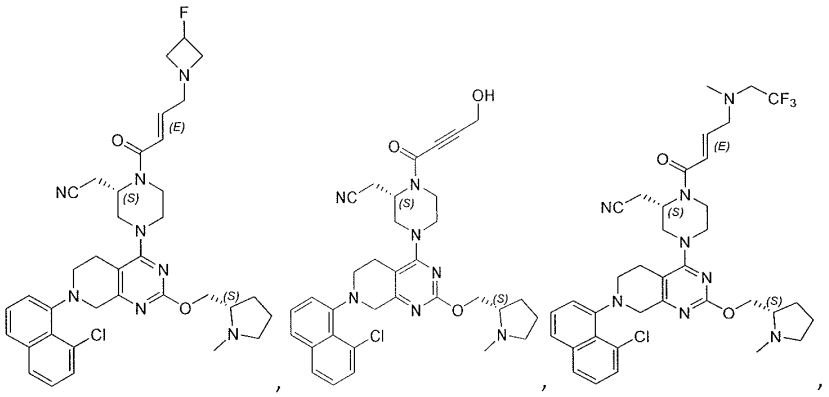


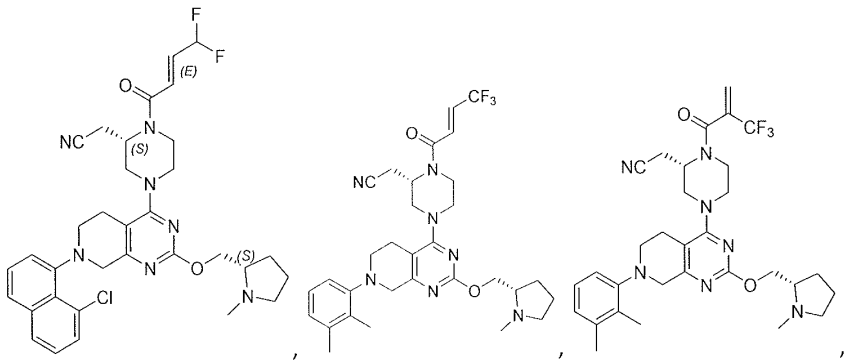


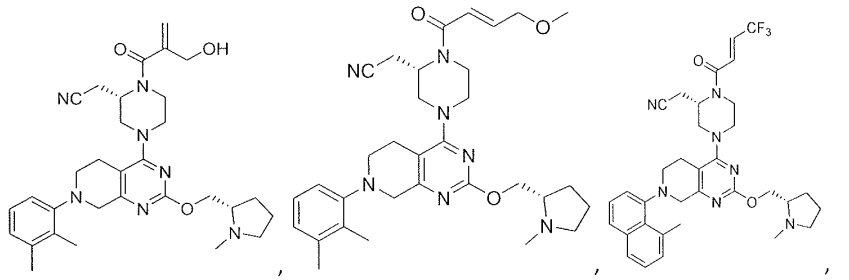

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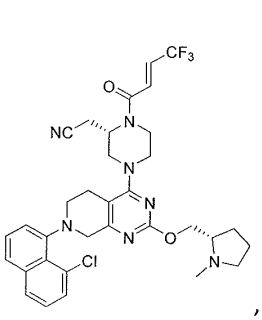
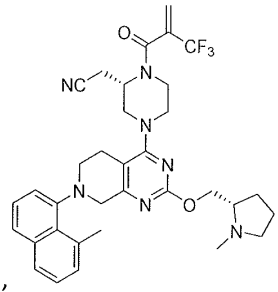
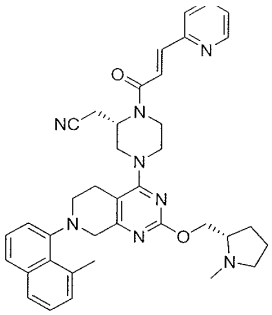
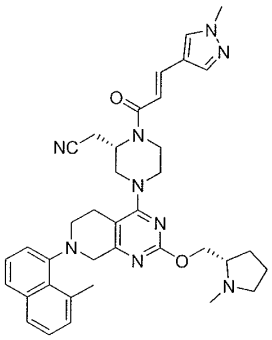
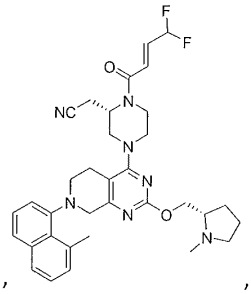
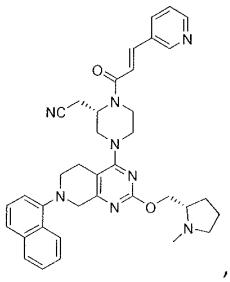
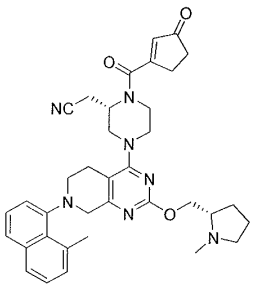
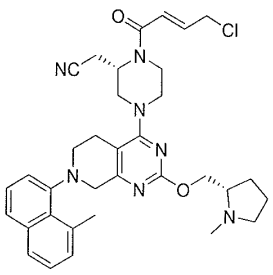
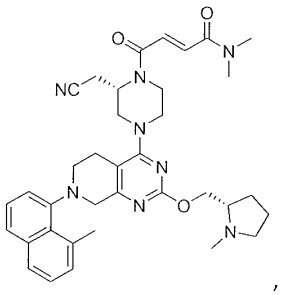
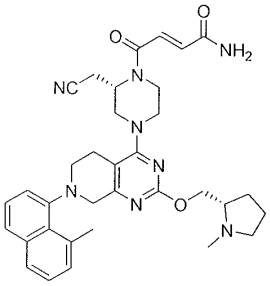
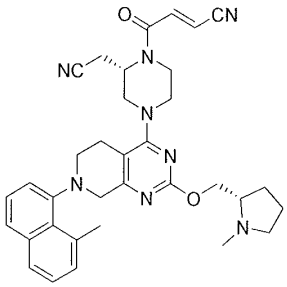
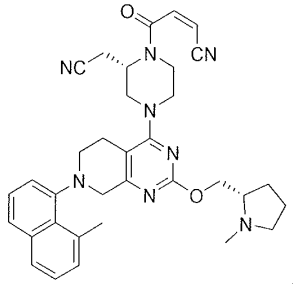

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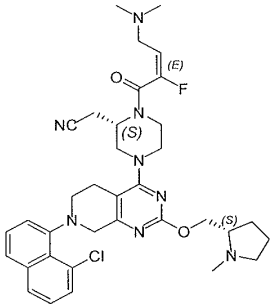
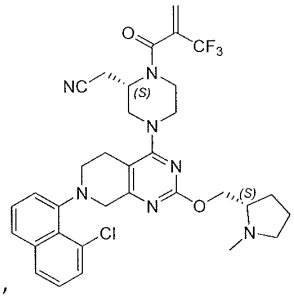
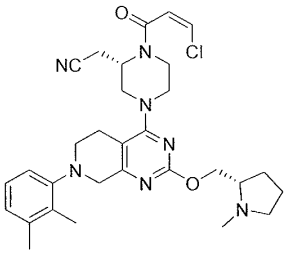
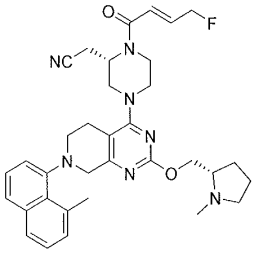
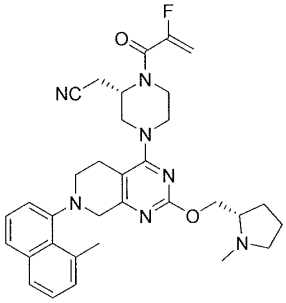
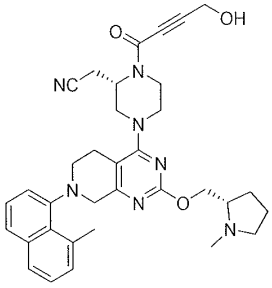
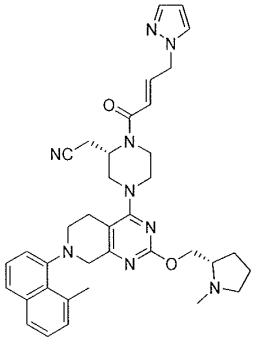
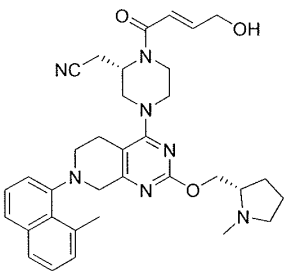
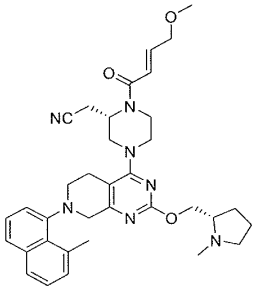
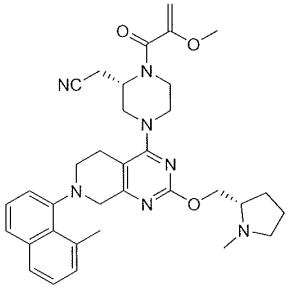
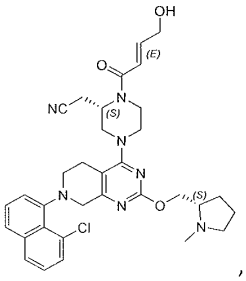
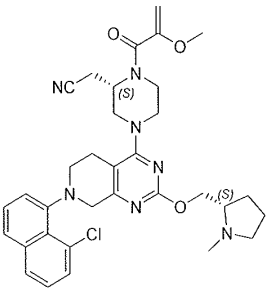
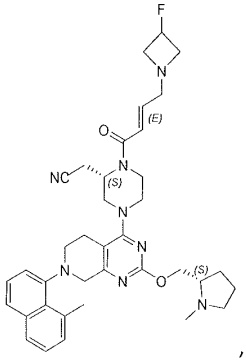
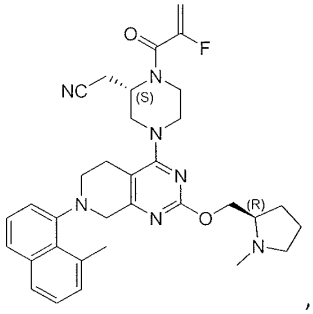


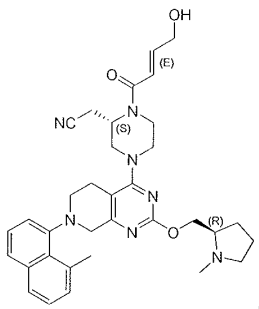
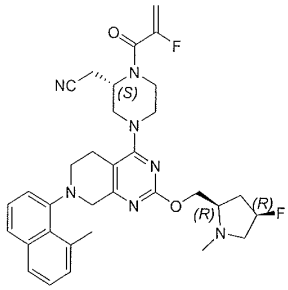
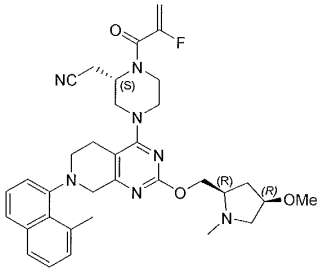
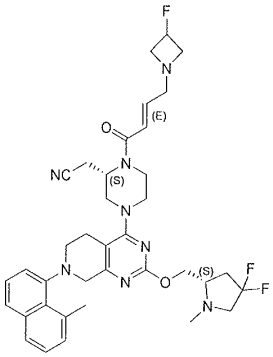
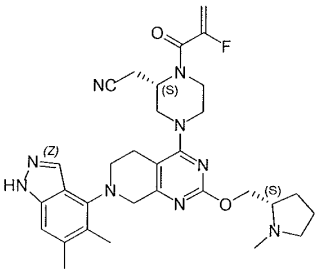
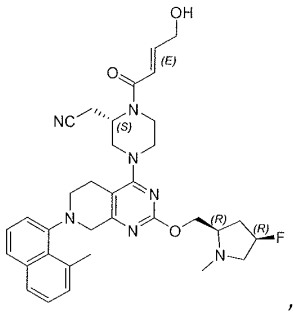
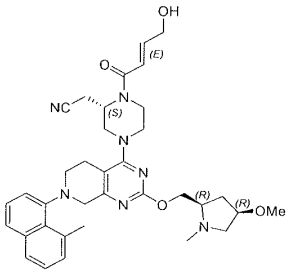
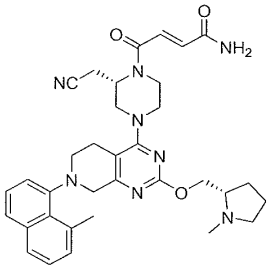
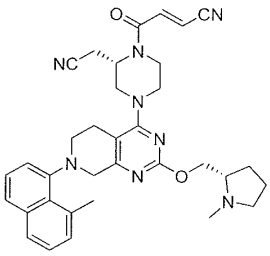
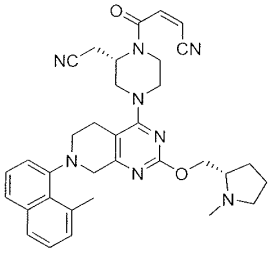
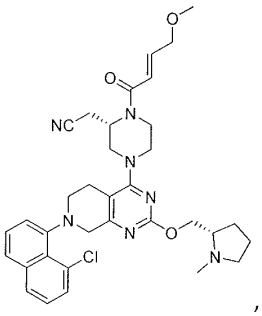
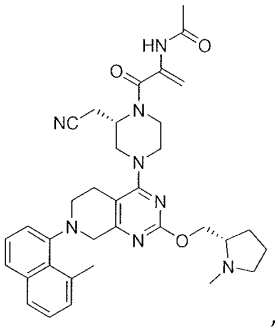
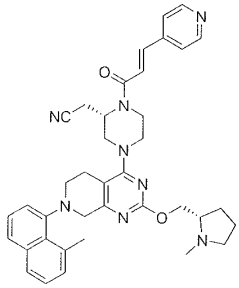


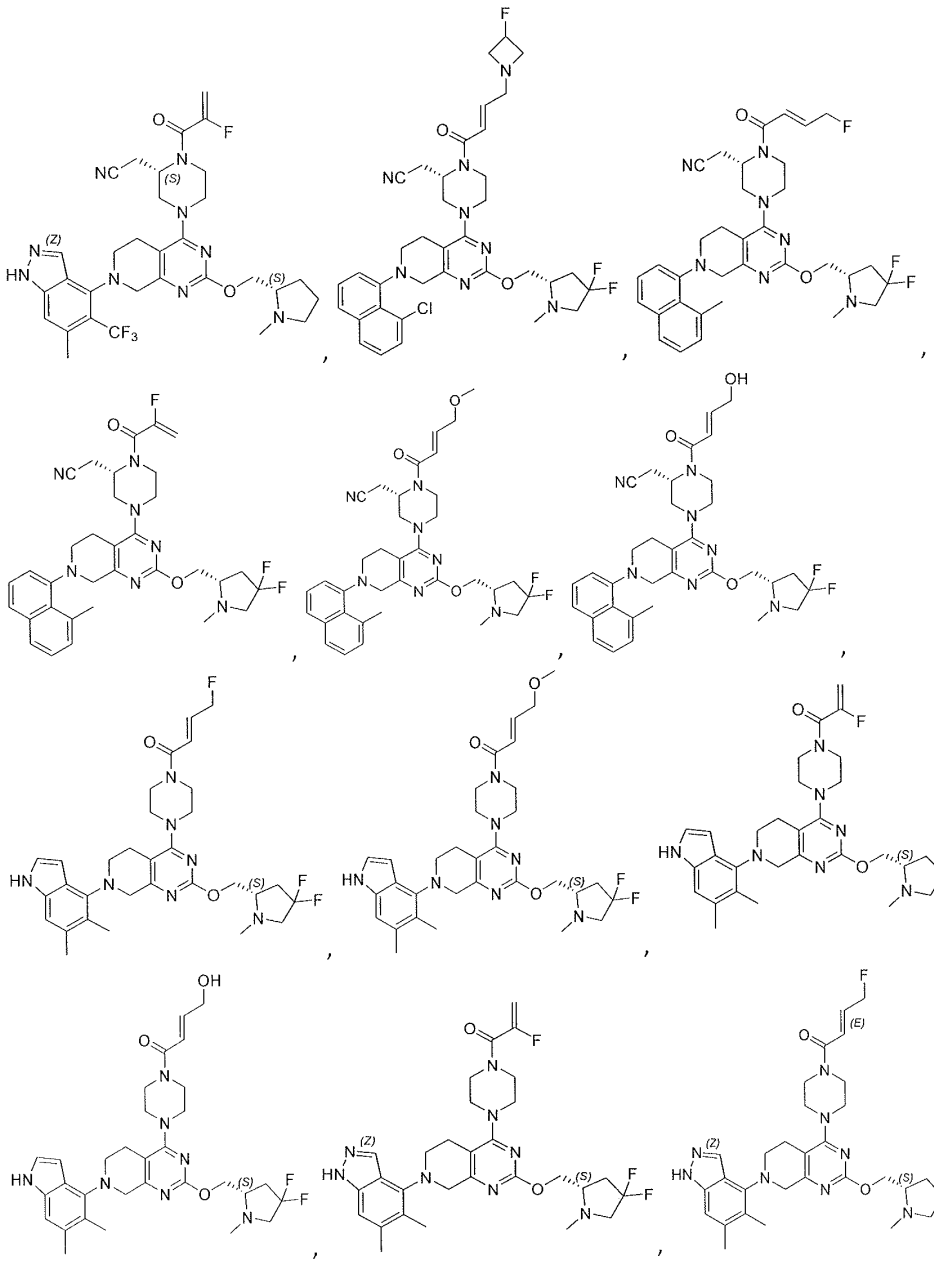


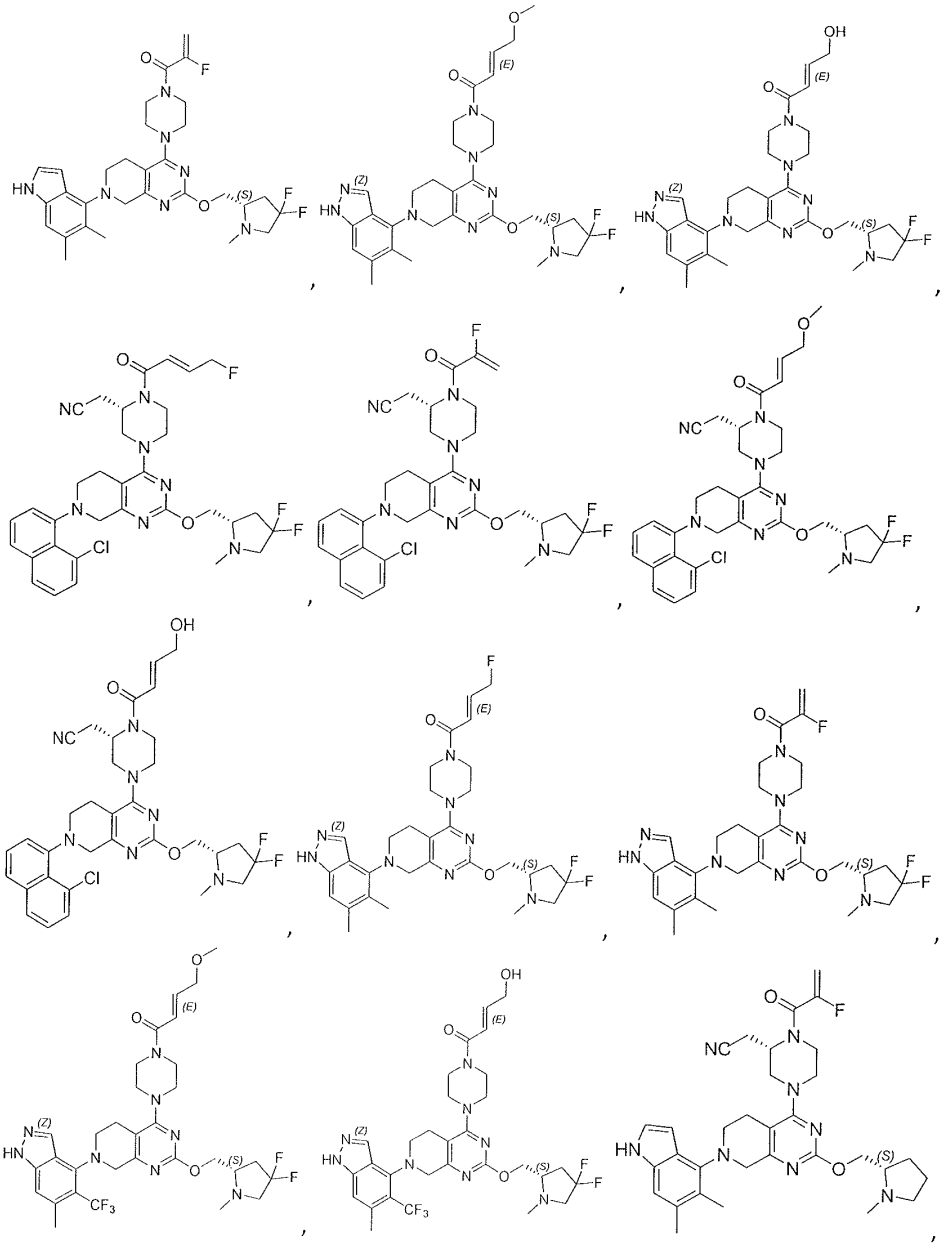


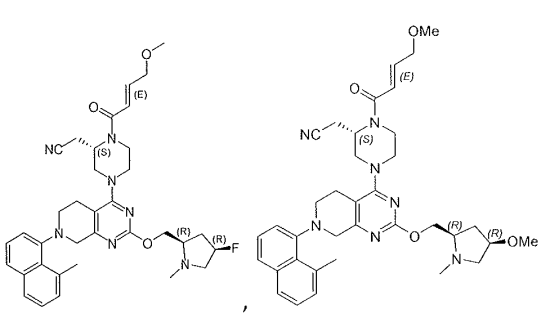

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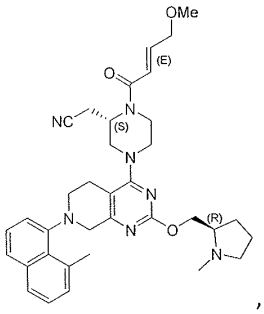
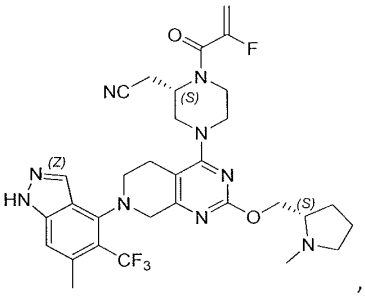
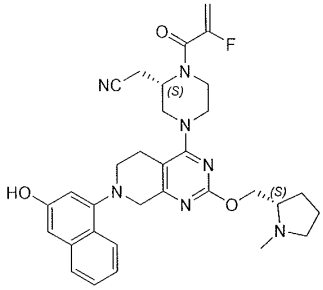
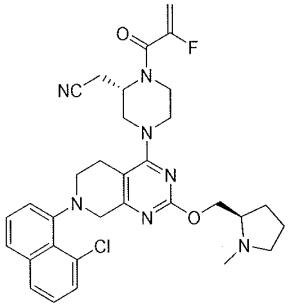
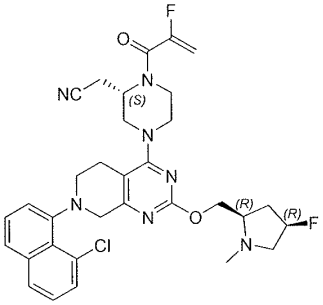
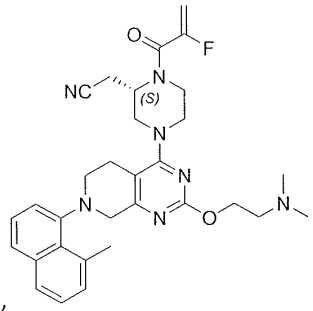
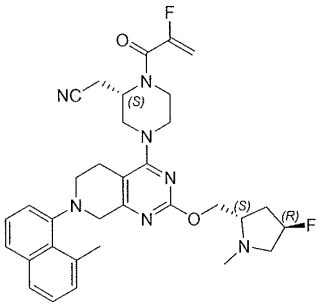
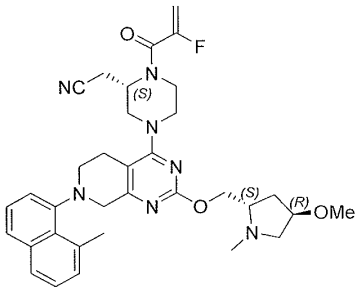
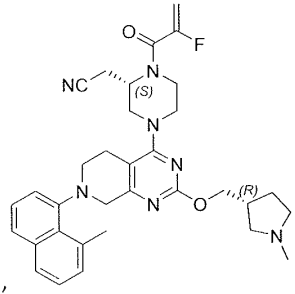
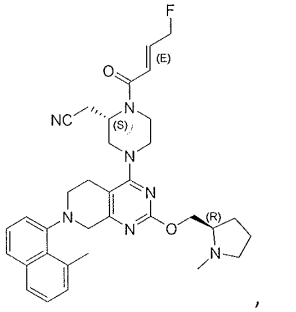

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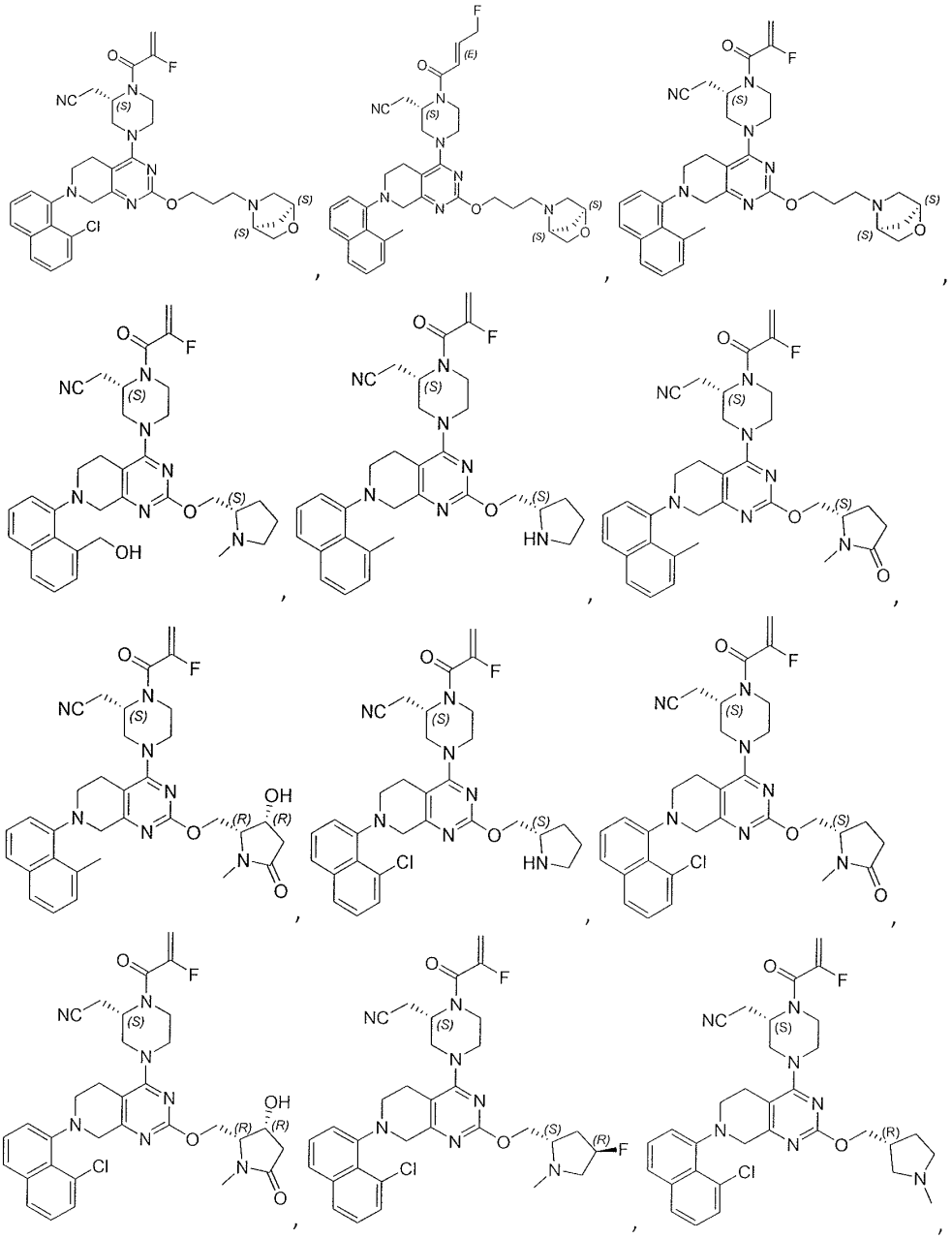

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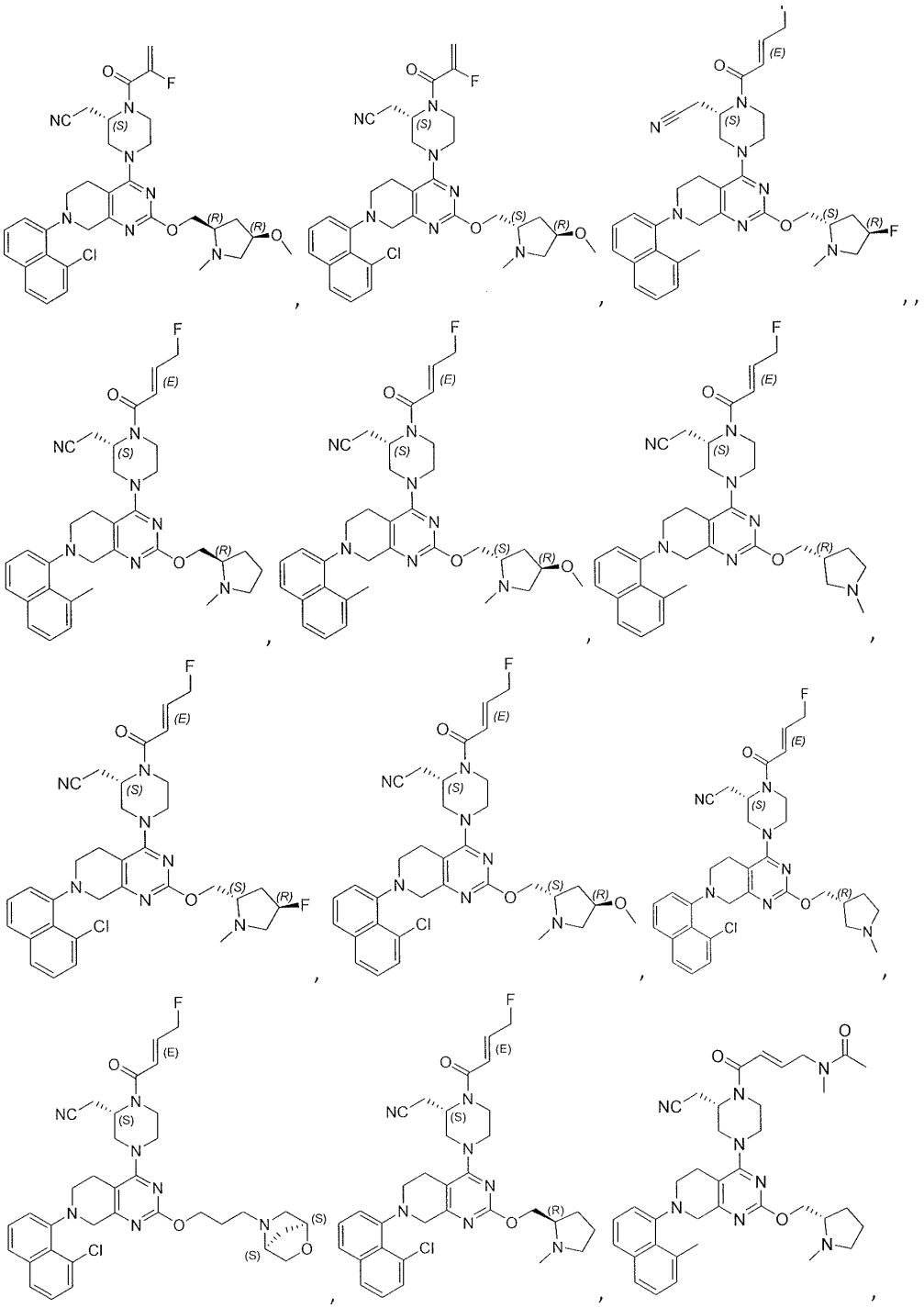


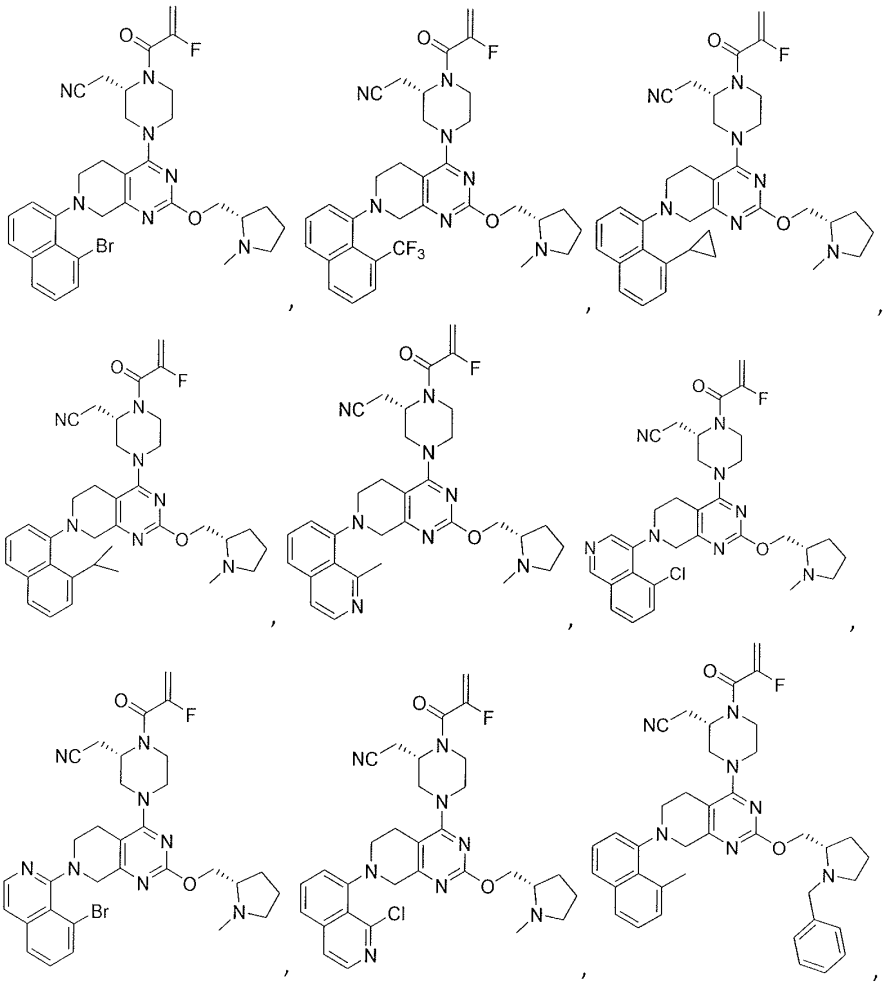


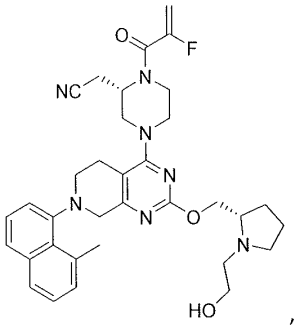
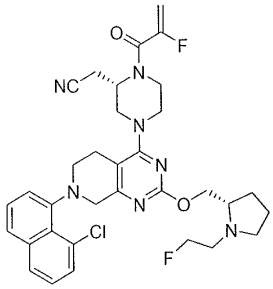
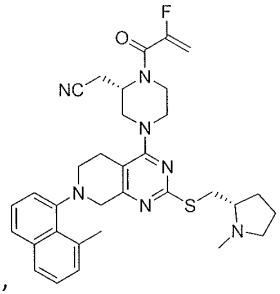
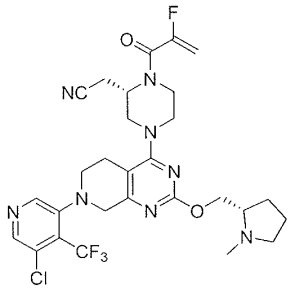

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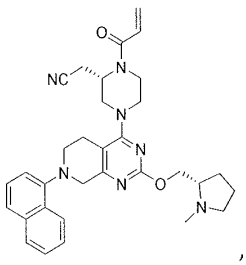
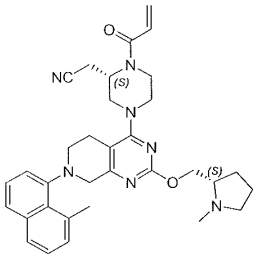
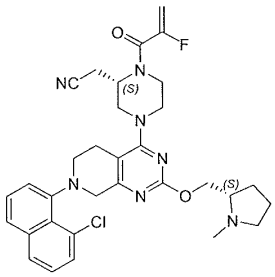
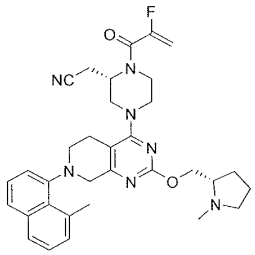







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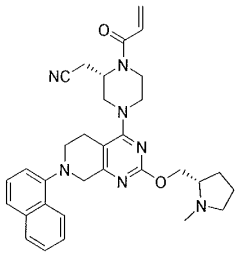
or a pharmaceutically acceptable salt thereof.

57. The method of claim 1, wherein the KRas G12C inhibitor is selected from the group consisting of:

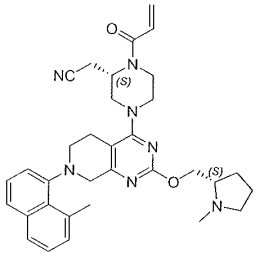
and pharmaceutically acceptable salts thereof.

58. The method of claim 1, wherein the KRas G12C inhibitor is:



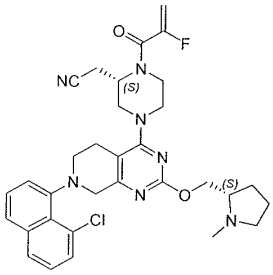
or a pharmaceutically acceptable salt thereof.

59. The method of claim 1, wherein the KRas G12C inhibitor is:



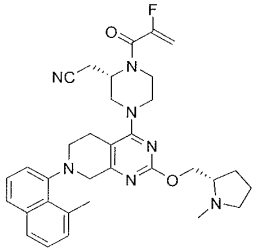
or a pharmaceutically acceptable salt thereof.

60. The method of claim 1, wherein the KRas G12C inhibitor is:



or a pharmaceutically acceptable salt thereof.

61. The method of claim 1, wherein the KRas G12C inhibitor is:



or a pharmaceutically acceptable salt thereof.

62. The method according to any one of claims 1-61, wherein the pan ErbB family inhibitor is an irreversible pan ErbB inhibitor.

63. The method of claim 62, wherein the irreversible pan ErbB family inhibitor is: Afatinib ((E)-N-(4-((3-chloro-4-fluorophenyl)amino)-7-((tetrahydrofuran-3-yl)oxy)quinazolin-6-yl)-4-(dimethylamino)but-2-enamide); dacomitinib ((2*E*)-*N*-{4-[(3-Chloro-4-fluorophenyl)amino]-7-methoxy-6-quinazolinyl}-4-(1-piperidinyl)-2-butenamide); canertinib (N-(4-((3-chloro-4-fluorophenyl)amino)-7-(3-morpholinopropoxy)quinazolin-6-yl)acrylamide); poziotinib (1-(4-((4-((3,4-dichloro-2-fluorophenyl)amino)-7-methoxyquinazolin-6-yl)oxy)piperidin-1-yl)prop-2-en-1-one); AV 412 (*N*-[4-[(3-Chloro-4-fluorophenyl)amino]-7-[3-methyl-3-(4-methyl-1-piperazinyl)-1-butyn-1-yl]-6-quinazolinyl]-2-propenamide); PF 6274484 (*N*-[4-[(3-Chloro-4-fluorophenyl)amino]-7-methoxy-6-quinazolinyl]-2-propenamide) or HKI 357 ((2*E*)-*N*-[[4-[[(3-Chloro-4-[(3-fluorophenyl)methoxy]phenyl]amino]-3-cyano-7-ethoxy-6-quinolinyl]-4-(dimethylamino)-2-butenamide).

64. The method of claim 63, wherein the irreversible pan ErbB family inhibitor is afatinib ((E)-N-(4-((3-chloro-4-fluorophenyl)amino)-7-((tetrahydrofuran-3-yl)oxy)quinazolin-6-yl)-4-(dimethylamino)but-2-enamide).

65. The method of claim 63, wherein the irreversible pan ErbB family inhibitor is dacomitinib ((2*E*)-*N*-{4-[(3-Chloro-4-fluorophenyl)amino]-7-methoxy-6-quinazolinyl}-4-(1-piperidinyl)-2-butenamide).

66. The method according to any one of claims 1-61, wherein the pan ErbB family inhibitor is a reversible pan ErbB family inhibitor.

67. The method of claim 66, wherein the reversible pan ErbB family inhibitor is: Erlotinib ([6,7-Bis-(2-methoxy-ethoxy)-quinazolin-4-yl]-(3-ethynyl-phenyl)-amine)), Gefitinib (4-(3'-chloro-4'-fluoroanilino)-7-methoxy-6-(3-morpholinopropoxy)quinazoline, sapitinib (2-(4-((4-((3-chloro-2-fluorophenyl)amino)-7-methoxyquinazolin-6-yl)oxy)piperidin-1-yl)-N-

methylacetamide); varlitinib ((R)-N4-(3-chloro-4-(thiazol-2-ylmethoxy)phenyl)-N6-(4-methyl-4,5-dihydrooxazol-2-yl)quinazoline-4,6-diamine); TAK-285 (N-(2-(4-((3-chloro-4-(3-(trifluoromethyl)phenoxy)phenyl)amino)-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethyl)-3-hydroxy-3-methylbutanamide); AEE788 ((S)-6-(4-((4-ethylpiperazin-1-yl)methyl)phenyl)-N-(1-phenylethyl)-7H-pyrrolo[2,3-d]pyrimidin-4-amine); tarloxotinib ([(*E*)-4-[[4-(3-bromo-4-chloroanilino)pyrido[3,4-d]pyrimidin-6-yl]amino]-4-oxobut-2-enyl]-dimethyl-[(3-methyl-5-nitroimidazol-4-yl)methyl]azanium); BMS 599626 ((3*S*)-3-Morpholinylmethyl-[4-[[1-[(3-fluorophenyl)methyl]-1*H*-indazol-5-yl]amino]-5-methylpyrrolo[2,1-*f*][1,2,4]triazin-6-yl]-carbamate dihydrochloride); and GW 583340 HCl (*N*-[3-Chloro-4-[(3-fluorophenyl)methoxy]phenyl]-6-[2-[[[2-(methylsulfonyl)ethyl]amino]methyl]-4-thiazolyl]-4-quinazolinamine dihydrochloride).

68. The method of claim 67, wherein the reversible pan ErbB family inhibitor is sapitinib (2-(4-((4-((3-chloro-2-fluorophenyl)amino)-7-methoxyquinazolin-6-yl)oxy)piperidin-1-yl)-N-methylacetamide) or tarloxotinib ([(*E*)-4-[[4-(3-bromo-4-chloroanilino)pyrido[3,4-d]pyrimidin-6-yl]amino]-4-oxobut-2-enyl]-dimethyl-[(3-methyl-5-nitroimidazol-4-yl)methyl]azanium).

69. The method according to any one of claims 1-61, wherein the pan ErbB family inhibitor is an anti-EGFR antibody, an anti-HER2 antibody or a combination of anti-EGFR antibody and an anti-HER2 antibody.

70. The method of claim 69, wherein the anti-EGFR antibody is necitumumab, panitumumab or cetuximab.

71. The method of claim 69, wherein the anti-HER2 antibody is trastuzumab, trastuzumab emtansine, or pertuzumab.

72. The method according to any one of claims 1-71, wherein the pan ErbB family inhibitor and the KRAS G12C inhibitor are administered on the same day.

73. The method according to any one of claims 1-71, wherein the pan ErbB family inhibitor and the KRAS G12C inhibitor are administered on different days.

74. The method according to any one of claims 1-71, wherein the KRas G12C inhibitor is administered at a maximum tolerated dose.

75. The method according to any one of claims 1-71, wherein the pan ErbB family inhibitor and the KRAS G12C inhibitor are each administered at a maximum tolerated dose.

76. The method according to any one of claims 1-75, wherein the therapeutically effective amount of the combination of the pan ErbB family inhibitor and the KRAS G12C 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 disease in the subjects relative to treatment with only the KRas G12C inhibitor.

77. A pharmaceutical composition, comprising a therapeutically effective amount of a combination of a pan ErbB family inhibitor and a KRas G12C inhibitor of Formula (I), Formula I-A or Formula I-B, and a pharmaceutically acceptable excipient.

78. A method for inhibiting KRas G12C activity in a cell, comprising contacting the cell in which inhibition of KRas G12C activity is desired with an effective amount of a pan ErbB family inhibitor and a KRas G12C inhibitor compound of a Formula (I), Formula I-A or Formula I-B, pharmaceutical compositions or pharmaceutically acceptable salts thereof, wherein the pan ErbB family inhibitor synergistically increases the sensitivity of the cancer cells to the KRas G12C inhibitor.

79. The method according to any one of claims 1-76 or 78, wherein the pan ErbB family inhibitor synergistically increases the sensitivity of the cancer cells to the KRas G12C inhibitor.

80. A method for increasing the sensitivity of a cancer cell to a KRas G12C inhibitor compound of Formula (I), Formula I-A or Formula I-B comprising administering to a subject undergoing KRas G12C treatment with a compound of Formula (I), Formula I-A or Formula I-B or a pharmaceutically acceptable salt thereof, alone or combined with a pharmaceutically

acceptable carrier, excipient or diluents, a therapeutically effective amount of a pan ErbB family inhibitor, wherein the pan ErbB family inhibitor synergistically increases the sensitivity of the cancer cell to the KRas G12C inhibitor.

81. The method according to any one of claims 1-76 and 78-80, wherein the therapeutically effective amount of the KRas G12C inhibitor is between about 0.01 to 100 mg/kg per day.

82. The method of claim 81, wherein the therapeutically effective amount of the KRas G12C inhibitor is between about 0.1 to 50 mg/kg per day.

83. The method according to any one of claims 1-76 and 78-80, wherein the therapeutically effective amount of the pan ErbB family inhibitor is between about 0.01 to 100 mg/kg per day.

84. The method of claim 83, wherein the therapeutically effective amount of the pan ErbB family inhibitor is between about 0.1 to 50 mg/kg per day.

85. The method according to any one of claims 1-76 and 78-80, 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,

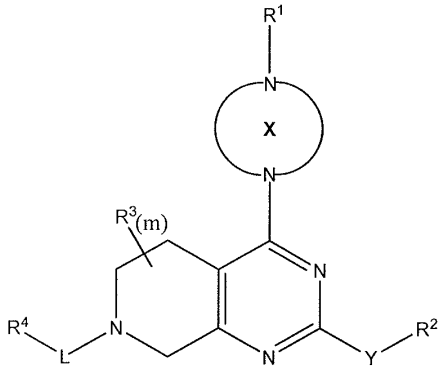
hepatoblastoma, angiosarcoma, hepatocellular adenoma, hemangioma; Biliary tract: gall bladder carcinoma, ampullary carcinoma, cholangiocarcinoma; Bone: osteogenic sarcoma (osteosarcoma), fibrosarcoma, malignant fibrous histiocytoma, chondrosarcoma, Ewing's sarcoma, malignant lymphoma (reticulum cell 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.

86. The method according to any one of claims 1-76 and 78-80, wherein the cancer wherein the cancer is a KRas G12C-associated cancer.

87. The method of claim 86, wherein the KRas G12C-associated cancer is non-small cell lung cancer.

88. A kit comprising the pharmaceutical composition of claim 77 for treating cancer in a subject.

89. A kit comprising: a) a pharmaceutical composition comprising a pan ErbB family inhibitor and b) a pharmaceutical composition comprising a KRas G12C inhibitor of:



Formula (I)

or a pharmaceutically acceptable salt thereof:
wherein:

X is a 4-12 membered saturated or partially saturated monocyclic, bridged or spirocyclic ring, wherein the saturated or partially saturated monocyclic ring is optionally substituted with one or more R^8;
Y is a bond, O, S or NR^5;

R^1 is $-C(O)C(R^A)$ ------ $C(R^B)_p$ or $-SO_2C(R^A)$ ------ $C(R^B)_p$;

R^2 is hydrogen, alkyl, hydroxyalkyl, dihydroxyalkyl, alkylaminylalkyl, dialkylaminylalkyl, $-Z-NR^5R^{10}$, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, or heteroarylalkyl, wherein each of the Z, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl may be optionally substituted with one or more R^9;

each Z is C1 – C4 alkylene;

each R^3 is independently C1 – C3 alkyl, oxo, haloalkyl, hydroxyl or halogen;

L is a bond, -C(O)-, or C1 – C3 alkylene;

R^4 is hydrogen, cycloalkyl, heterocyclyl, aryl, aralkyl or heteroaryl, wherein each of the cycloalkyl, heterocyclyl, aryl, aralkyl and heteroaryl may be optionally substituted with one or more R^6, R^7 or R^8;

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

R^6 is cycloalkyl, heterocyclyl, heterocyclylalkyl, aryl, or heteroaryl, wherein each of the cycloalkyl, heterocyclyl, aryl, or heteroaryl may be optionally substituted with one or more R^7;

each R^7 is independently halogen, hydroxyl, C1 – C6 alkyl, cycloalkyl, alkoxy, haloalkyl, amino, cyano, heteroalkyl, hydroxyalkyl or Q-haloalkyl, wherein Q is O or S;

R^8 is oxo, C1 – C3 alkyl, C2 – C4 alkynyl, heteroalkyl, cyano, $-C(O)OR^5$, $-C(O)N(R^5)_2$, $-N(R^5)_2$, wherein the C1 – C3 alkyl may be optionally substituted with cyano, halogen, $-OR^5$, $-N(R^5)_2$, or heteroaryl;

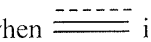
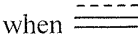
each R^9 is independently hydrogen, oxo, acyl, hydroxyl, hydroxyalkyl, cyano, halogen, C1 – C6 alkyl, aralkyl, haloalkyl, heteroalkyl, cycloalkyl, heterocyclylalkyl, alkoxy, dialkylaminyl, dialkylamidoalkyl, or dialkylaminylalkyl, wherein the C1 – C6 alkyl may be optionally substituted with cycloalkyl;

each R^{10} is independently hydrogen, acyl, C1 – C3 alkyl, heteroalkyl or hydroxyalkyl;

R^{11} is haloalkyl;

R^A is absent, hydrogen, deuterium, cyano, halogen, C1 - C-3 alkyl, haloalkyl, heteroalkyl, $-C(O)N(R^5)_2$, or hydroxyalkyl;

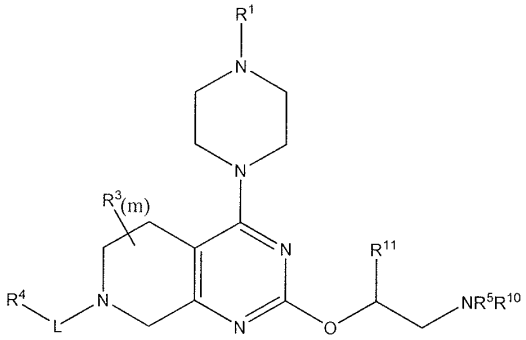
each R^B is independently hydrogen, deuterium, cyano, C1 – C3 alkyl, hydroxyalkyl, heteroalkyl, C1 – C3 alkoxy, halogen, haloalkyl, $-ZNR^5R^{11}$, $-C(O)N(R^5)_2$, -NHC(O)C1 – C3 alkyl, $-CH_2NHC(O)$C1 – C3 alkyl, heteroaryl, heteroarylalkyl, dialkylaminylalkyl, or heterocyclylalkyl wherein the heterocyclyl portion is substituted with one or more substituents independently selected from halogen, hydroxyl, alkoxy and C1 – C3 alkyl, wherein the heteroaryl or the heteroaryl portion of the heteroarylalkyl is optionally substituted with one or more R^7;

when  is a triple bond then R^A is absent, R^B is present and p equals one, or when  is a double bond then R^A is present, R^B is present and p equals two, or R^A, R^B and the carbon atoms to which they are attached form a 5-8 membered partially saturated cycloalkyl optionally substituted with one or more R^7;

m is zero or an integer between 1 and 2; and

p is one or two.

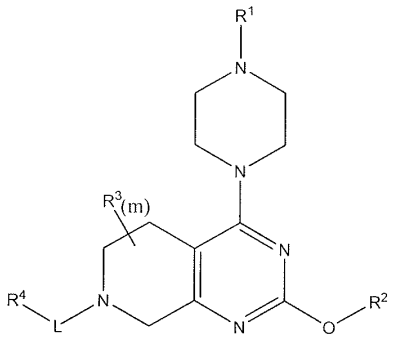
or



Formula I-A

and pharmaceutically acceptable salts thereof, wherein R^1, R^3, R^4, R^5, R^{10}, L and m are as defined for Formula I, R^{11} is hydrogen, methyl or hydroxyalkyl, and the piperidinyl ring is optionally substituted with R^8 wherein R^8 is as defined for Formula I

or



Formula I-B

and pharmaceutically acceptable salts thereof, wherein R^1, R^3, R^4, L and m are as defined for Formula I, R^2 is heterocyclylalkyl optionally substituted with one or more R^9 where R^9 is as defined for Formula I, and the piperazinyl ring is optionally substituted with R^8, where R^8 is as defined for Formula I,

for treating cancer in a subject.

90. The kit according to claim 88 or 89, further comprising an insert with instructions for administration of the pharmaceutical composition(s).