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LITO PIRO ET AL: "Allele-specific inhibitors inactivate mutant KRAS G12C by a trapping mechanism", SCIENCE, vol. 351, no. 6273, 5 February 2016 (2016-02-05), US, pages 604 - 608, DOI: 10.1126/science.aad6204

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(54) Title: COMBINATION THERAPIES

(57) Abstract: 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 mTOR inhibitor and a KRAS G12C inhibitor of Formula (I), Formula I-A or Formula I-B, pharmaceutical compositions comprising a therapeutically effective amounts of the inhibitors, kits comprising the compositions and methods of use therefor.

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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 mTOR 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 dis+rupt 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.

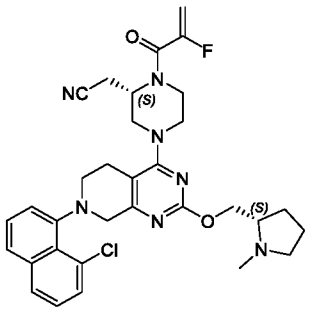
[0007] The combination therapy of the present invention, in one aspect, synergistically increases the potency of KRas G12C inhibitors resulting in improved efficacy and therapeutic index of KRas G12C inhibitors disclosed herein. The combination therapy of the present invention, in another aspect, provides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

[0007a] Any reference to any prior art in this specification is not, and should not be taken as an acknowledgement or any form of suggestion that the prior art forms part of the common general knowledge.

SUMMARY OF THE INVENTION

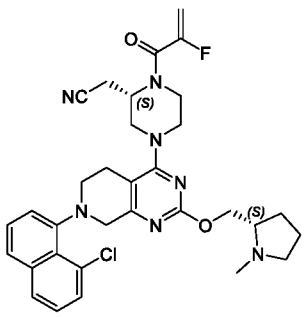
[0007b] In a first aspect of the invention, there is provided a method of treating cancer in a subject in need thereof, comprising administering to the subject a therapeutically effective

amount of a combination of a mTOR inhibitor selected from the group consisting of everolimus, rapamycin, zotarolimus, ridaforolimus, sapanisertib, Torin-1, dactolisib, BEZ235, buparlisib, GDC-0941, GDC-0349, VS-5584 or vistusertib and a KRas G12C inhibitor of formula



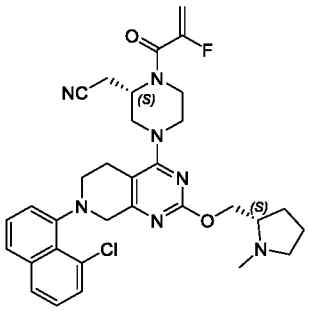
, or a pharmaceutically acceptable salt thereof.

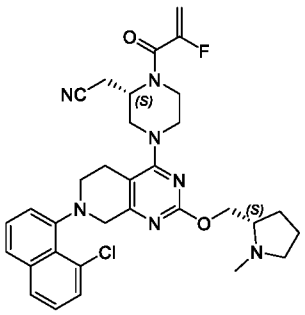
[0007c] In a second aspect of the invention, there is provided the use of an mTOR inhibitor selected from the group consisting of everolimus, rapamycin, zotarolimus, ridaforolimus, sapanisertib, Torin-1, dactolisib, BEZ235, buparlisib, GDC-0941, GDC-0349, VS-5584 or vistusertib and a KRas G12C inhibitor of formula

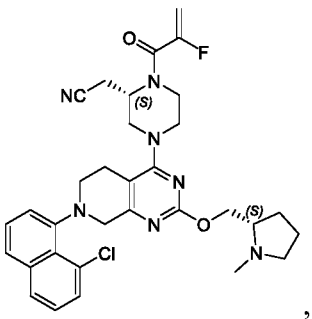


, or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating cancer.

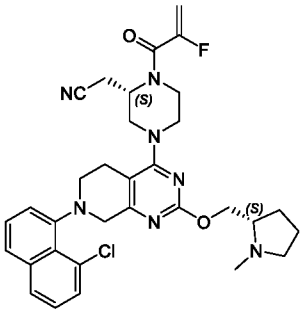
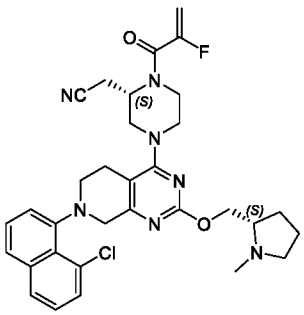
[0007d] In a third aspect of the invention, there is provided a pharmaceutical composition, comprising a therapeutically effective amount of a combination of a mTOR inhibitor selected from the group consisting of everolimus, rapamycin, zotarolimus, ridaforolimus, sapanisertib, Torin-1, dactolisib, BEZ235, buparlisib, GDC-0941, GDC-0349, VS-5584 or vistusertib and a

KRas G12 inhibitor of formula  , or a pharmaceutically acceptable salt thereof , and a pharmaceutically acceptable excipient.

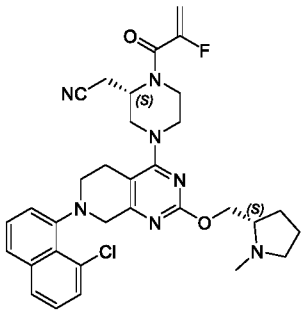
[0007e] In a fourth aspect of the invention, there is provided a method for inhibiting KRas G12C activity in a cell, comprising contacting the cell expressing the KRas G12C mutation with an effective amount of a mTOR inhibitor selected from the group consisting of everolimus, rapamycin, zotarolimus, ridaforolimus, sapanisertib, Torin-1, dactolisib, BEZ235, buparlisib, GDC-0941, GDC-0349, VS-5584 or vistusertib and a KRas G12C inhibitor compound of formula  , or pharmaceutically acceptable salts thereof, wherein the mTOR inhibitor synergistically increases the sensitivity of the cancer cells to the KRas G12C inhibitor.

[0007f] In a fifth aspect of the invention, there is provided the use of an mTOR inhibitor selected from the group consisting of everolimus, rapamycin, zotarolimus, ridaforolimus, sapanisertib, Torin-1, dactolisib, BEZ235, buparlisib, GDC-0941, GDC-0349, VS-5584 or vistusertib and a KRas G12C inhibitor compound of formula  , or a pharmaceutically

acceptable salt thereof in the manufacture of a medicament for inhibiting KRas G12C activity in a cell expressing the KRas G12C mutation, wherein the mTOR inhibitor synergistically increases the sensitivity of the cancer cells to the KRas G12C inhibitor.

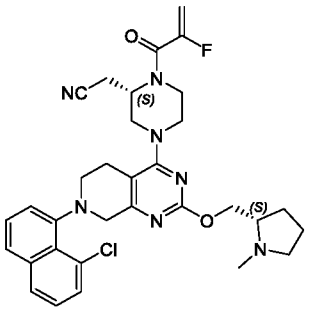
[0007g] In a sixth aspect of the invention, there is provided a method for increasing the sensitivity of a cancer cell expressing the KRas G12C mutation to a KRas G12C inhibitor compound of formula  , or a pharmaceutically acceptable salt thereof comprising administering to a subject undergoing KRas G12C treatment with a compound of formula  , or a pharmaceutically acceptable salt thereof, alone or combined with a pharmaceutically acceptable carrier, excipient or diluents, a therapeutically effective amount of a mTOR inhibitor selected from the group consisting of everolimus, rapamycin, zotarolimus, ridaforolimus, sapanisertib, Torin-1, dactolisib, BEZ235, buparlisib, GDC-0941, GDC-0349, VS-5584 or vistusertib, wherein the mTOR inhibitor synergistically increases the sensitivity of the cancer cell expressing the KRas G12C mutation to the KRas G12C inhibitor.

[0007h] In a seventh aspect of the invention, there is provided the use of an mTOR inhibitor selected from the group consisting of everolimus, rapamycin, zotarolimus, ridaforolimus, sapanisertib, Torin-1, dactolisib, BEZ235, buparlisib, GDC-0941, GDC-0349, VS-5584 or vistusertib in the manufacture of a medicament for increasing the sensitivity of a cancer cell expressing the KRas G12C mutation to a KRas G12C inhibitor compound of formula



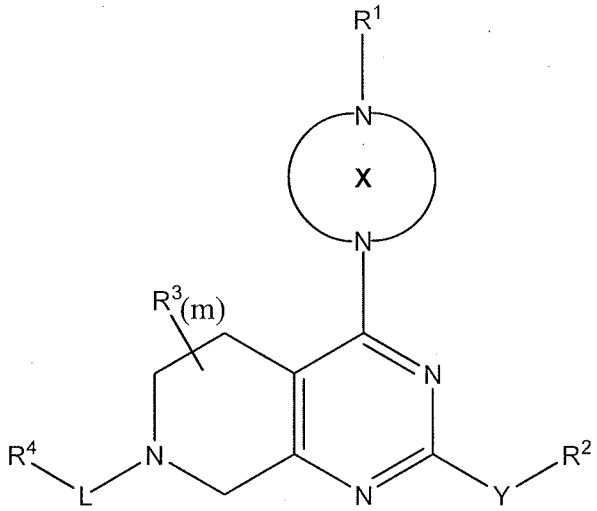
, or a pharmaceutically acceptable salt thereof, wherein the mTOR inhibitor synergistically increases the sensitivity of the cancer cell expressing the KRas G12C mutation to the KRas G12C inhibitor.

[0007i] In an eighth aspect of the invention, there is provided a kit comprising the pharmaceutical composition of the second aspect when used in treating cancer in a subject.

[0007j] In a ninth aspect of the invention, there is provided a kit comprising: a) a pharmaceutical composition comprising a mTOR inhibitor selected from the group consisting of everolimus, rapamycin, zotarolimus, ridaforolimus, sapanisertib, Torin-1, dactolisib, BEZ235, buparlisib, GDC-0941, GDC-0349, VS-5584 or vistusertib and b) a pharmaceutical composition comprising a KRas G12C inhibitor of formula  , or a pharmaceutically acceptable salt thereof,
when used in treating cancer in a subject.

[0007k] The term "comprise" and variants of the term such as "comprises" or "comprising" are used herein to denote the inclusion of a stated integer or stated integers but not to exclude any other integer or any other integers, unless in the context or usage an exclusive interpretation of the term is required.

[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 mTOR 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;

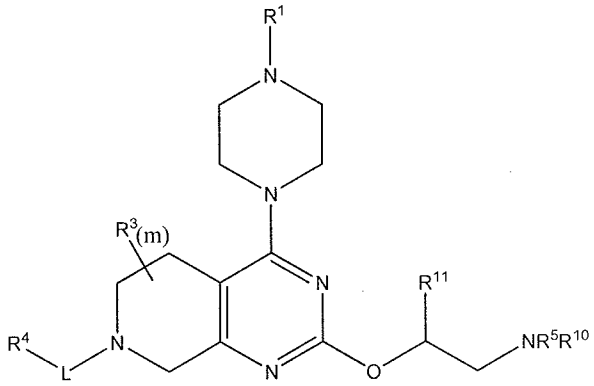
[0027] m is zero or an integer between 1 and 2;

[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.

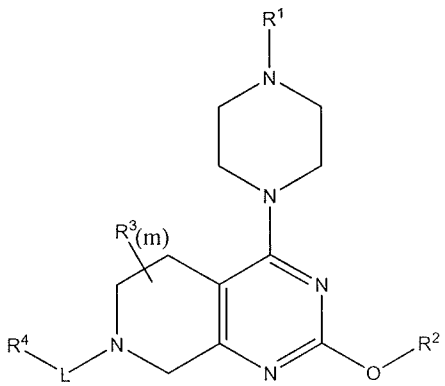
[0031] Also included for use in the methods provided herein are KRas G12C inhibitor compounds of Formula I having the Formula I-A:



Formula I-A

[0032] and pharmaceutically acceptable salts 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 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.

[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 mTOR inhibitor, or a pharmaceutically acceptable salt thereof and a KRas G12C inhibitor compound Formula I, Formula I-A, or Formula 1-B, or a pharmaceutically acceptable salt 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 mTOR inhibitor, or a pharmaceutically acceptable salt or pharmaceutical composition thereof and a KRAS G12C inhibitor of Formula (I), Formula I-A or Formula I-B, or a pharmaceutically acceptable salt or 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 mTOR inhibitors are the only active agents in the provided combinations and methods.

[0038] Examples of mTOR inhibitors suitable for the provided compositions and methods include, but are not limited to, everolimus, rapamycin, zotarolimus (ABT-578), ridaforolimus (Deforolimus; MK-8669), sapanisertib (INK128; 5-(4-amino-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-3-yl)benzo[d]oxazol-2-amine), Torin-1; 1-(4-(4-propionylpiperazin-1-yl)-3-(trifluoromethyl)cyclohexyl)-9-(quinolin-3-yl)benzo[h][1,6]naphthyridin-2(1H)-one, dactolisib (BEZ235); 2-methyl-2-(4-(3-methyl-2-oxo-8-(quinolin-3-yl)-2,3-dihydro-1H-imidazo[4,5-c]quinolin-1-yl)phenyl)propanenitrile, buparlisib (5-(2,6-dimorpholin-4-ylpyrimidin-4-yl)-4-(trifluoromethyl)pyridin-2-amine); GDC-0941 (pictilisib); 4-[2-(1H-indazol-4-yl)-6-[(4-methylsulfonylpiperazin-1-yl)methyl]thieno[3,2-d]pyrimidin-4-yl]morpholine); GDC-0349 ((S)-1-ethyl-3-(4-(4-(3-methylmorpholino)-7-(oxetan-3-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-2-yl)phenyl)urea), VS-5584 (SB2343) (5-(8-methyl-2-morpholin-4-yl-9-propan-2-

ylpurin-6-yl)pyrimidin-2-amine) and vistusertib (AZD-2014; 3-(2,4-bis((S)-3-methylmorpholino)pyrido[2,3-d]pyrimidin-7-yl)-N-methylbenzamide).

[0039] 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 mTOR inhibitor, or a pharmaceutically acceptable salt or a pharmaceutical composition thereof, wherein the mTOR 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.

[0040] 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 mTOR 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 mTOR inhibitor synergistically increases the sensitivity of the KRas G12C-associated cancer to the KRas G12C inhibitor.

[0041] Also provided herein are kits comprising a mTOR 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 mTOR 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.

[0042] In a related aspect, the invention provides a kit containing a dose of a mTOR 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 mTOR 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 mTOR 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.

[0043] 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

[0044] 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 mTOR 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 comprising therapeutically effective amounts of the inhibitors, kits comprising the compositions and methods of use therefor.

[0045] Combinations of an mTOR inhibitor, or a pharmaceutically acceptable salt or a pharmaceutical composition thereof, 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 synergistically increase the potency of KRas G12C inhibitor compounds of Formula (I), Formula I-A or Formula I-B, or a pharmaceutically acceptable salt or a pharmaceutical composition thereof against cancer cells that express KRas G12C thereby increasing the efficacy and therapeutic index of the KRas G12C inhibitor compounds of Formula (I), Formula I-A or Formula I-B, or a pharmaceutically acceptable salt or a pharmaceutical composition thereof.

DEFINITIONS

[0046] 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.

[0047] 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.

[0048] 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, or a pharmaceutically acceptable salt or a pharmaceutical composition 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 salt thereof (e.g., Example Nos 234, 359, 478 or 507, or a pharmaceutically acceptable salt thereof).

[0049] 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.

[0050] As used herein, "mTOR" or "mTOR kinase" refers to mammalian Target Of Rapamycin (mTOR) kinase, a large serine/threonine kinase that acts as the catalytic subunit of two functionally independent complexes called mTORC1 and mTORC2.

[0051] As used herein, a "mTOR 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 mTOR kinase. The modulation or inhibition of one or more family members may occur through modulating or inhibiting kinase enzymatic activity of mTOR kinase directly or allosterically.

[0052] 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).

[0053] 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.

[0054] 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.

[0055] 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).

[0056] The term "amino" refers to $-NH_2$;

[0057] The term "acyl" refers to $-C(O)CH_3$.

[0058] 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.

[0059] 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.

[0060] The term "haloalkyloxy" refers to -O-haloalkyl.

[0061] 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.

[0062] The term "alkoxy" refers to –OC1 – C6 alkyl.

[0063] 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.

[0064] 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.

[0065] As used herein, the term "hydroxyalkyl" refers to –alkyl-OH.

[0066] The term "dihydroxyalkyl" refers to an alkyl group as defined herein wherein two carbon atoms are each substituted with a hydroxyl group.

[0067] The term "alkylaminyl" refers to $-NR^x$-alkyl, wherein R^x is hydrogen. In one embodiment, R^x is hydrogen.

[0068] The term "dialkylaminyl" refers to $-N(R^y)_2$, wherein each R^y is C1 – C3 alkyl.

[0069] The term "alkylaminylalkyl" refers to –alkyl-NR^x-alkyl, wherein R^x is hydrogen. In one embodiment, R^x is hydrogen.

[0070] 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.

[0071] 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.

[0072] 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.

[0073] 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.

[0074] 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.

[0075] 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.

[0076] 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.

[0077] 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., mTOR 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.

[0078] 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 mTOR 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.

[0079] 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 mTOR 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 G12 inhibitor. In one embodiment, the therapeutically effective amount of the combination of a mTOR 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 G12 inhibitor. In one embodiment, the therapeutically effective amount of the combination of a mTOR 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 mTOR 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 mTOR 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 improvement in the duration of stable disease in subjects compared to treatment with only the KRas G12 inhibitor. Such amounts may be administered, for example, as a single dosage or may be administered according to a regimen, whereby it is effective.

[0080] 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.

[0081] 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.

[0082] As used herein, the term "about" when used to modify a numerically defined parameter (e.g., the dose of a KRAS inhibitor or a mTOR 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

[0083] 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 mTOR 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. mTOR Kinase

[0084] The mammalian Target Of Rapamycin (mTOR) kinase is a large serine/threonine kinase that acts as the catalytic subunit of two functionally independent complexes called mTORC1 and mTORC2, and is considered a key regulator of cell growth. The mTORC1 complex also contains the proteins Raptor and mLST8. The mTORC2 complex also contains mTOR and mLST8, but includes the proteins Rictor and mSIN1 instead of Raptor. Like mTORC1, mTORC2 is activated by insulin and other growth factors that activate the PI3K/PTEN pathway.

[0085] Rapamycin acts through an unusual allosteric mechanism that requires binding to its intracellular receptor, FKBP12, for inhibition of its target. Under acute treatment, rapamycin is thought to selectively inhibit mTORC1, which is often referred to as the rapamycin-sensitive complex. Conversely, mTORC2 is considered rapamycin-insensitive, although its assembly can be inhibited by prolonged rapamycin treatment in some cell types.

[0086] Over-activation of mTOR signaling significantly contributes to the initiation and development of tumors and mTOR activity was found to be deregulated in many types of cancer including breast, prostate, lung, melanoma, bladder, brain, and renal carcinomas. Constitutive activation of mTOR can occur via multiple mechanisms. Among the most common are mutations in tumor suppressor *PTEN* gene. PTEN phosphatase negatively affects mTOR signaling through interfering with the effect of PI3K, an upstream effector of mTOR. Additionally, mTOR activity is deregulated in many cancers as a result of increased activity of PI3K or Akt. Similarly, overexpression of downstream mTOR effectors 4E-BP1, S6K and eIF4E leads to poor cancer prognosis.

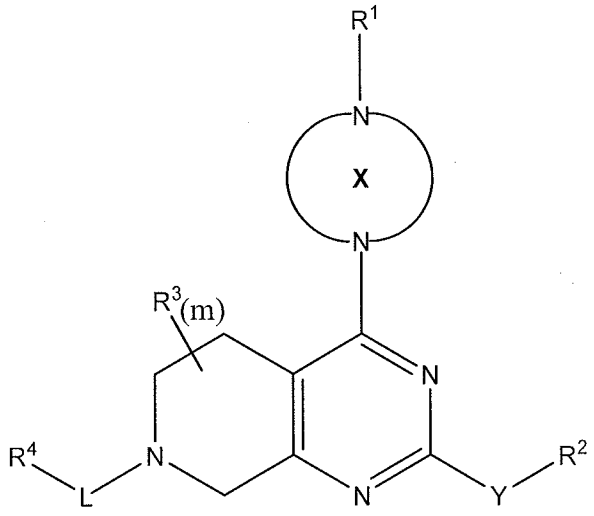
2. mTOR Inhibitors

[0087] Several inhibitors exhibiting activity against mTOR have been developed and a number have received marketing approval. Exemplary mTOR inhibitors that are useful in the methods and compositions of the present invention include, but are not limited to, everolimus, rapamycin, zotarolimus (ABT-578), ridaforolimus (Deforolimus; MK-8669), sapanisertib (INK128; 5-(4-amino-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-3-yl)benzo[d]oxazol-2-amine), Torin-1; 1-(4-(4-propionylpiperazin-1-yl)-3-(trifluoromethyl)cyclohexyl)-9-(quinolin-3-yl)benzo[h][1,6]naphthyridin-2(1H)-one, dactolisib (BEZ235); 2-methyl-2-(4-(3-methyl-2-oxo-8-(quinolin-3-yl)-2,3-dihydro-1H-imidazo[4,5-c]quinolin-1-yl)phenyl)propanenitrile, buparlisib (5-(2,6-dimorpholin-4-ylpyrimidin-4-yl)-4-(trifluoromethyl)pyridin-2-amine); GDC-0941 (pictilisib; 4-[2-(1H-indazol-4-yl)-6-[(4-methylsulfonylpiperazin-1-yl)methyl]thieno[3,2-d]pyrimidin-4-yl]morpholine); GDC-0349 ((S)-1-ethyl-3-(4-(4-(3-methylmorpholino)-7-(oxetan-3-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-2-yl)phenyl)urea), VS-5584 (SB2343) (5-(8-methyl-2-morpholin-4-yl-9-propan-2-ylpurin-6-yl)pyrimidin-2-amine) and vistusertib (AZD-2014; 3-(2,4-bis((S)-3-methylmorpholino)pyrido[2,3-d]pyrimidin-7-yl)-N-methylbenzamide).

[0088] Methods for manufacturing mTOR inhibitors that target mTOR kinase are well known to those skilled in the art and mTOR inhibitors may be obtained from a wide-variety of commercial suppliers, in forms suitable for both research or human use. In addition, suitable mTOR inhibitors for use in the compositions and methods disclosed herein, and methods for preparing such inhibitors are disclosed in US Patent Application Publication Nos: US20190077806; US20180369370; US20180193320; US20180140620; US20170369435; US20170281637; US20160000789; US20150361120; US20150166477; US20140378438; US20140378433; US20140296234; US20140288066; US20140287031; US20140171456; US20140163023; US20140135315; US20140018347; US20130165661; US20130150362; US20130072481; US20120322791; US20120114739; and US20110218183.

2. KRas G12C Inhibitors

[0089] In one embodiment, the KRas G12C inhibitors used in the methods are compounds of Formula (I):



Formula (I)

[0090] or a pharmaceutically acceptable salt thereof, wherein:

[0091] 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;

[0100] Y is a bond, O, S or NR^5;

[0101] R^1 is $-C(O)C(R^A)=C(R^B)_p$ or $-SO_2C(R^A)=C(R^B)_p$;

[0102] 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;

[0103] Z is C1 – C4 alkylene;

[0104] each R^3 is independently C1 – C3 alkyl, oxo, or haloalkyl;

[0105] L is a bond, -C(O)-, or C1 – C3 alkylene;

[0106] 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;

[0107] each R^5 is independently hydrogen or C1 – C3 alkyl;

[0108] 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;

[0109] 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;

[0110] 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;

[0111] 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;

[0112] each R^{10} is independently hydrogen, acyl, C1 – C3 alkyl, heteroalkyl or hydroxyalkyl;

[0113] R^{11} is haloalkyl;

[0114] R^A is absent, hydrogen, deuterium, cyano, halogen, C1 - C-3 alkyl, haloalkyl, heteroalkyl, $-C(O)N(R^5)_2$, or hydroxyalkyl;

[0115] 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;

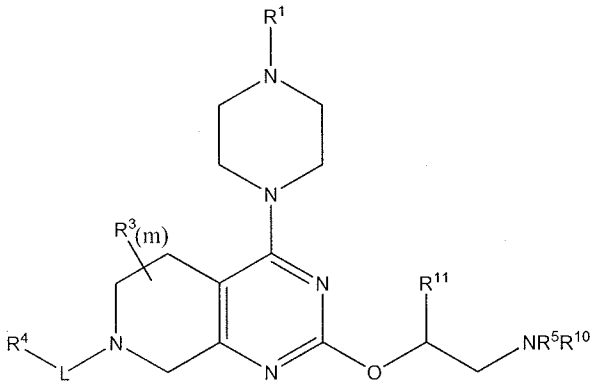
[0116] m is zero or an integer between 1 and 2;

[0117] p is one or two; and wherein,

[0118] when  is a triple bond then R^A is absent, R^B is present and p equals one;

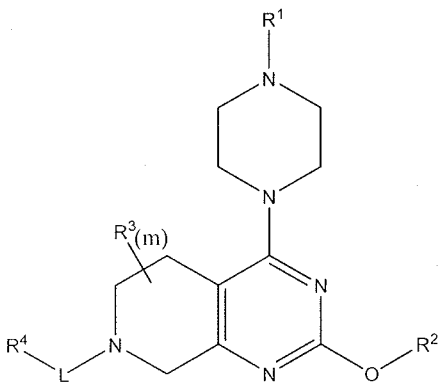
[0119] or when ------ is a double bond then R^A is present, R^B is present and p equals two, or R^A, R^B and the carbon atoms to which they are attached form a 5-8 membered partially saturated cycloalkyl optionally substituted with one or more R^7.

[0120] In one embodiment, KRas G12C inhibitors used in the methods herein includes compounds having the Formula I-A:



[0121] 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.

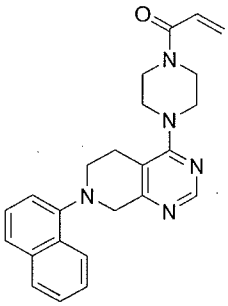
[0122] In one embodiment, KRas G12C inhibitors used in the methods herein include compounds having the Formula I-B:



Formula I-B

[0123] and pharmaceutically acceptable salts thereof, wherein R^1, R^3, R^4, R^9, R^{11}, L and m are as defined for Formula I.

[0124] 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 a compound from Example Nos. 1-678 (as numbered in WO2019099524), having the following structures, respectively: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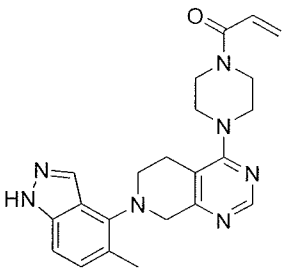
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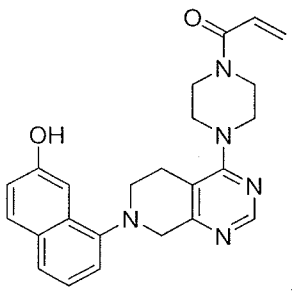
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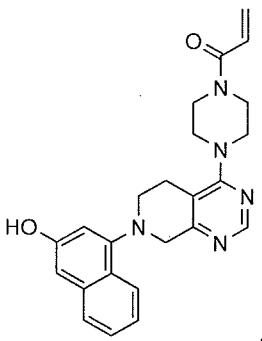
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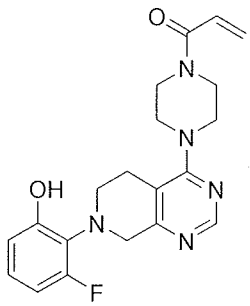
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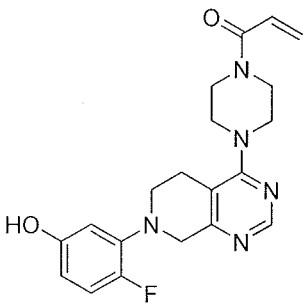
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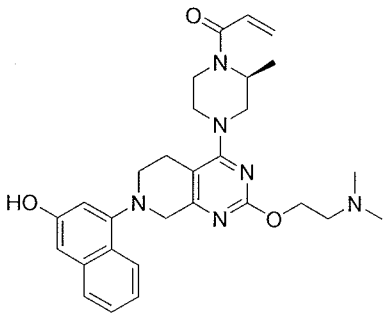
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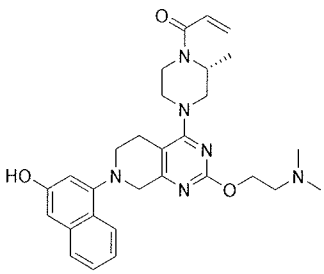
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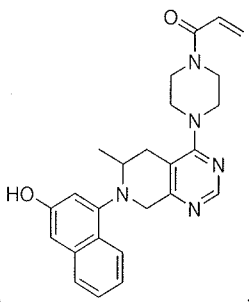
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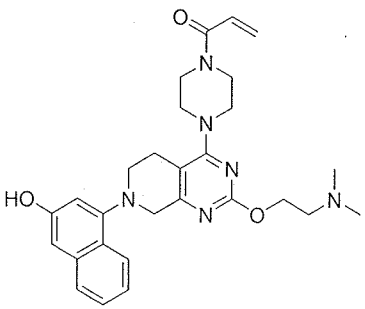
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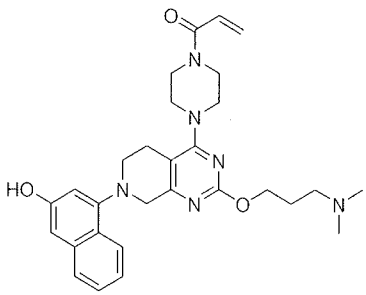
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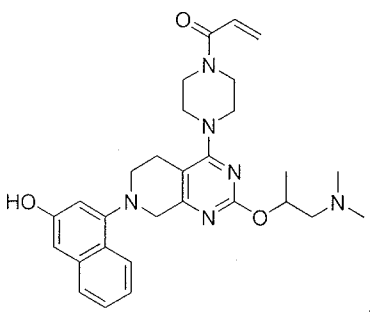
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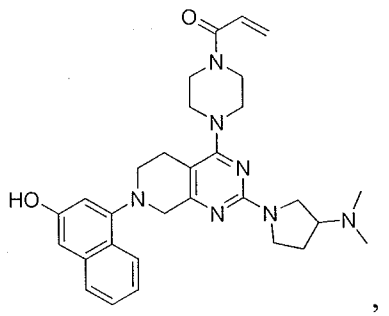
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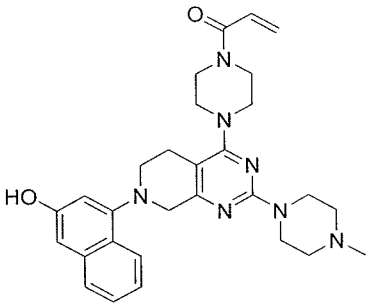
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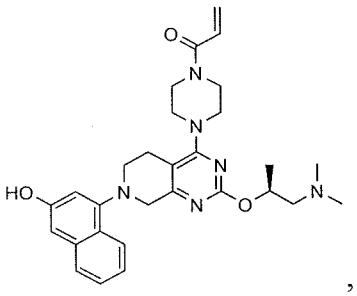
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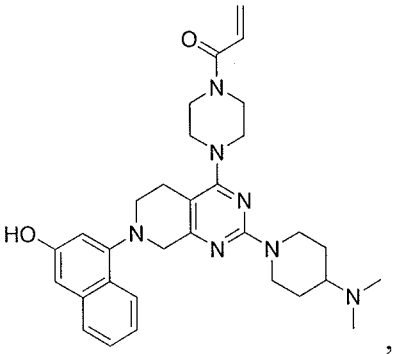
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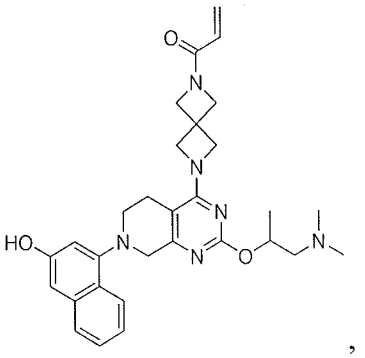
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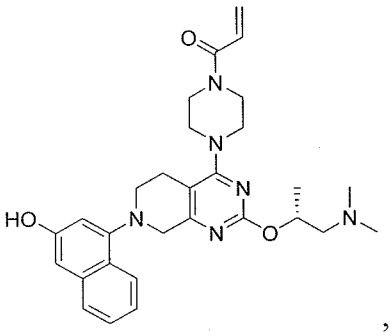
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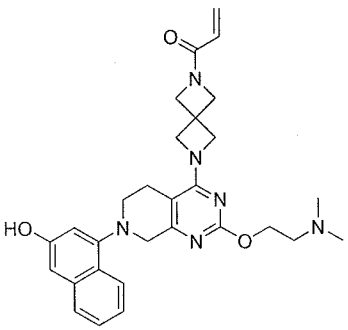
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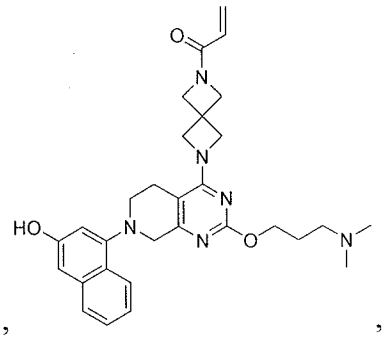
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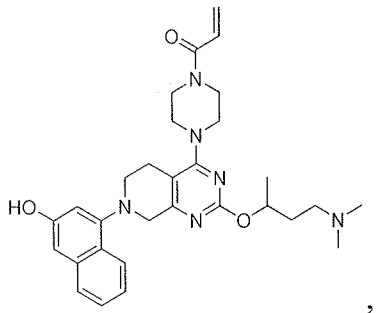
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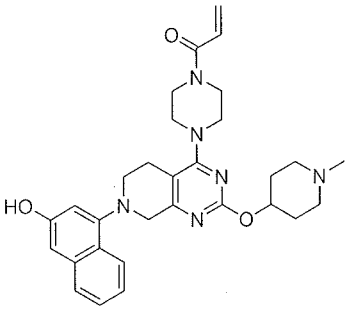
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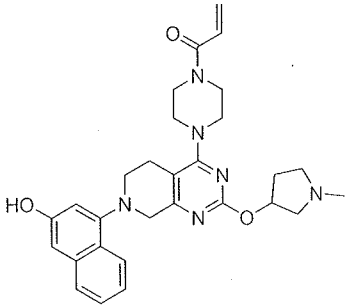
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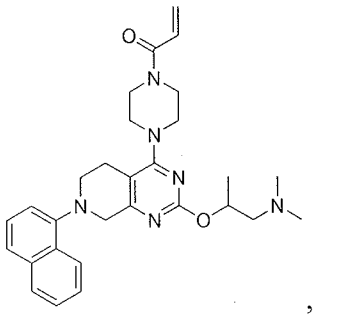
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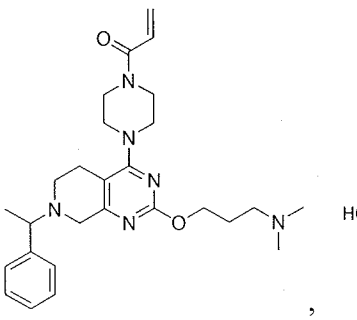
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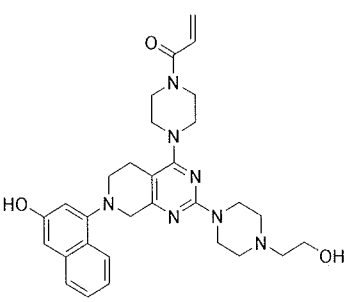
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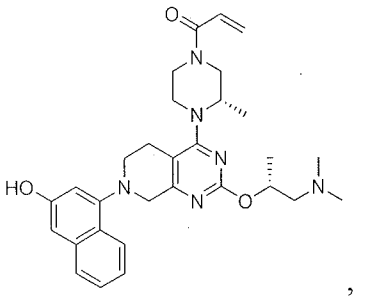
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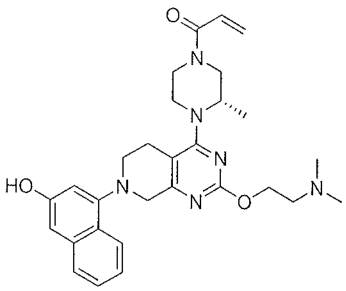
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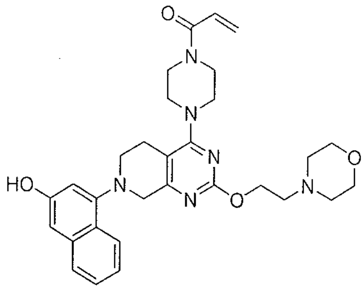
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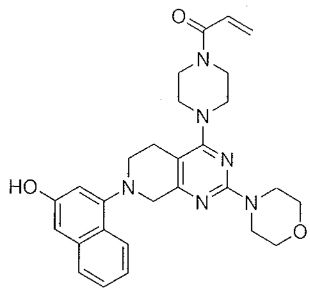
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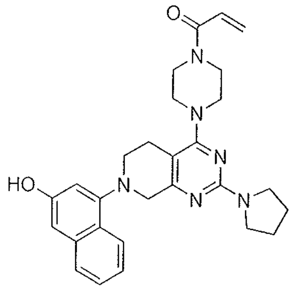
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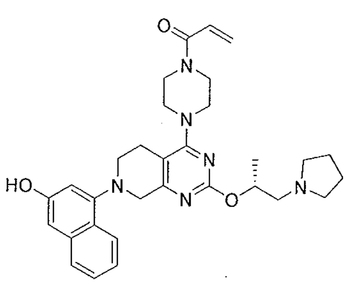
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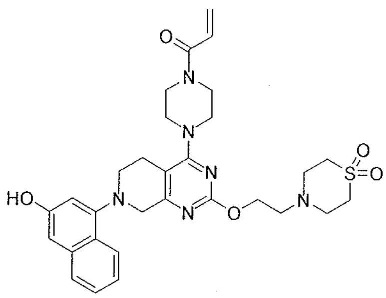
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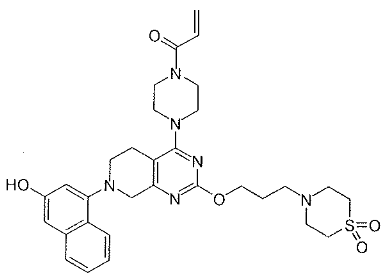
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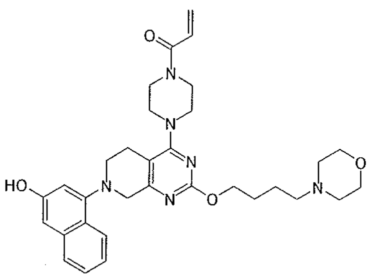
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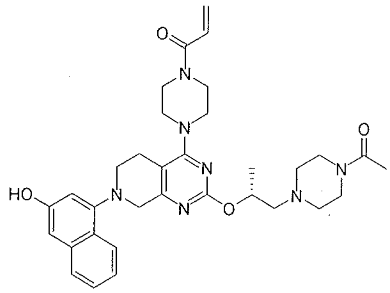
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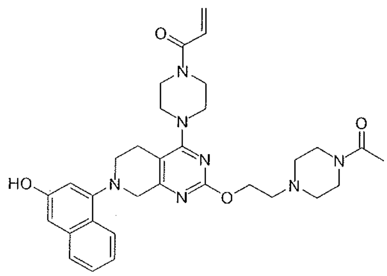
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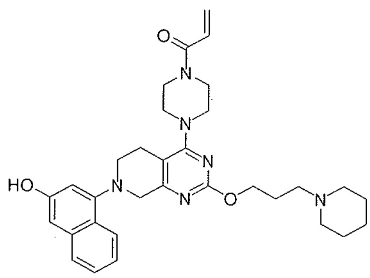
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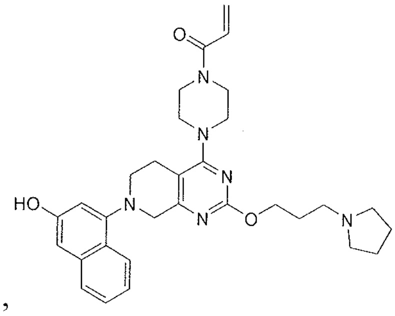
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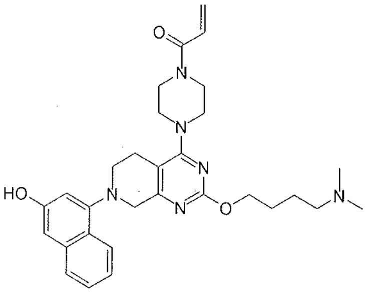
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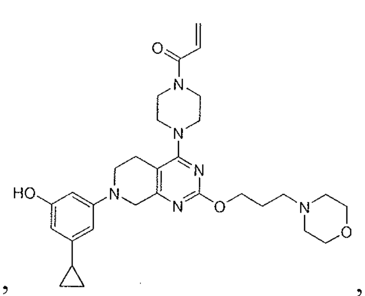
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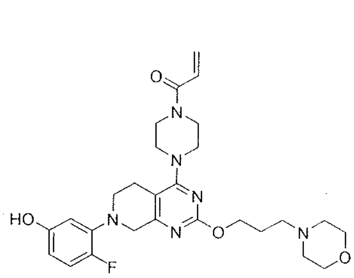
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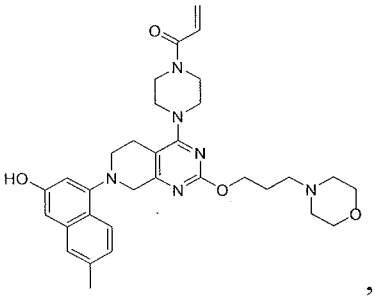
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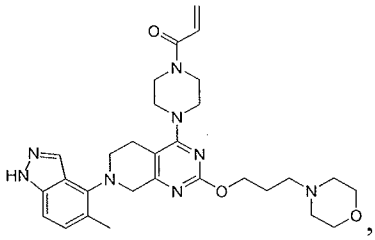
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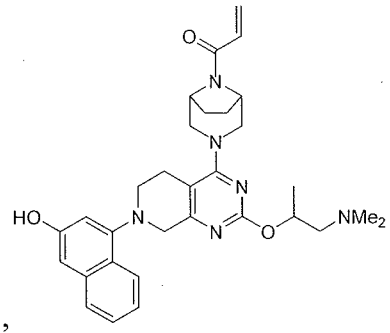
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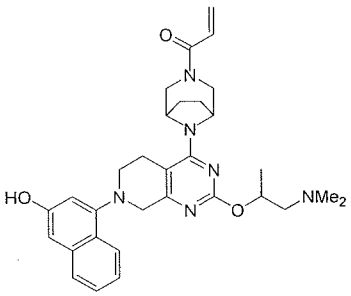
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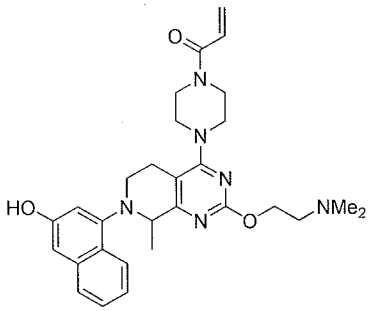
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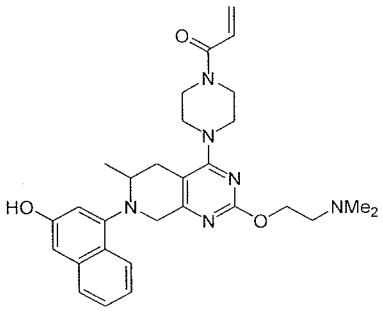
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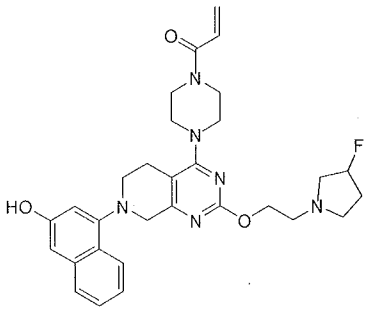
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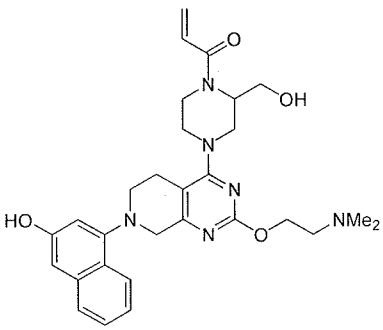
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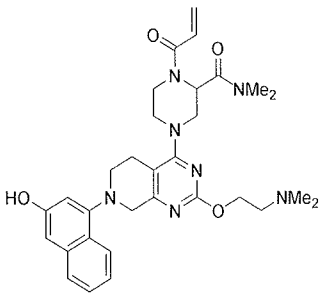
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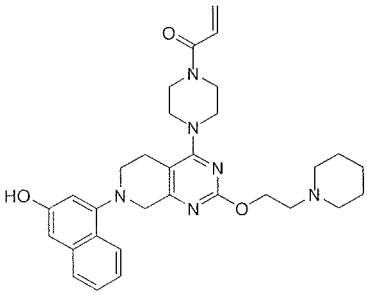
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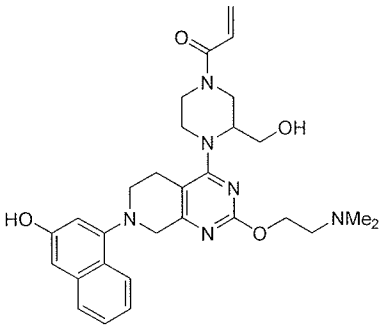
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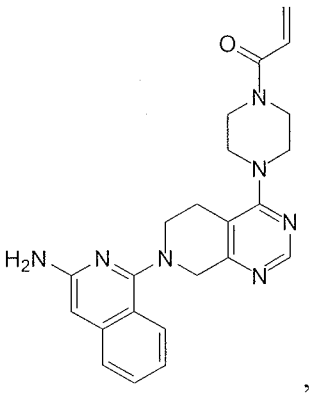

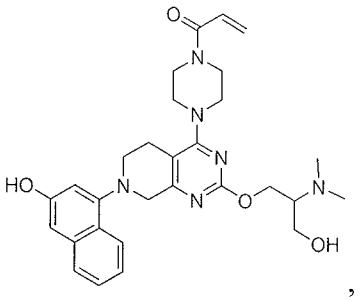
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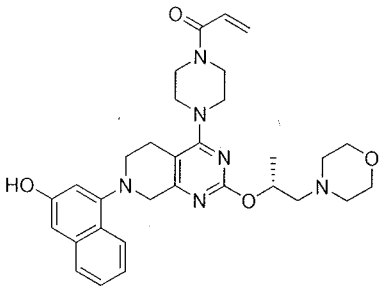
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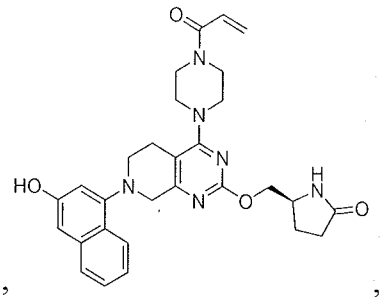
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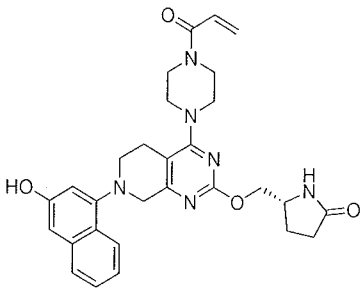
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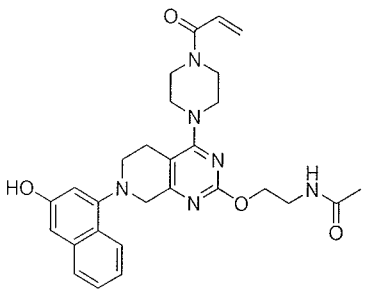
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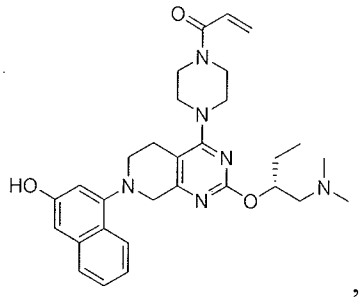
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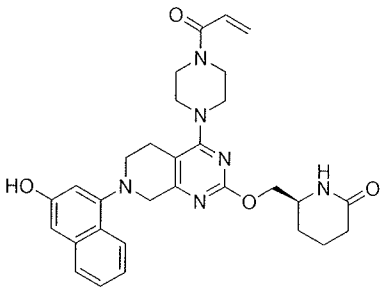
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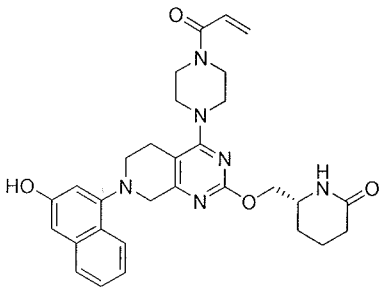
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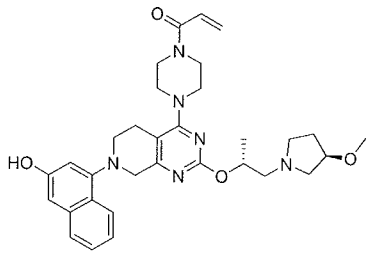
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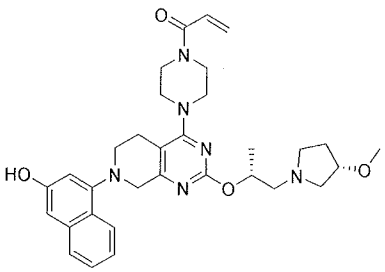
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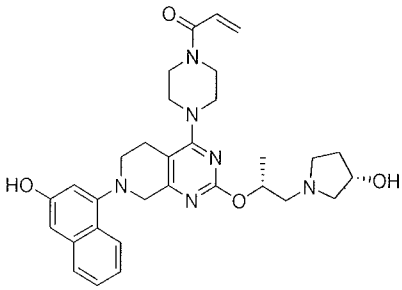
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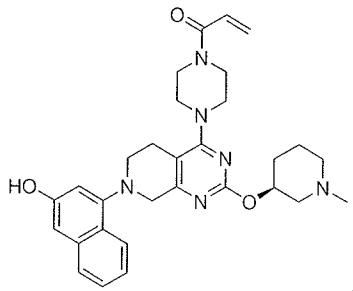
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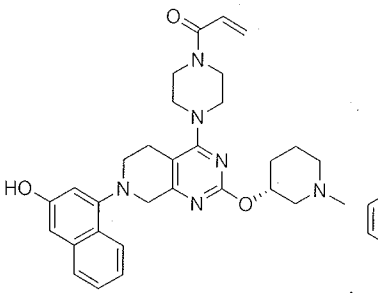
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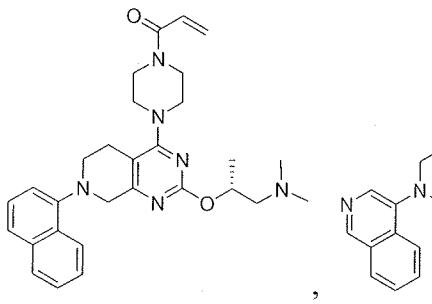
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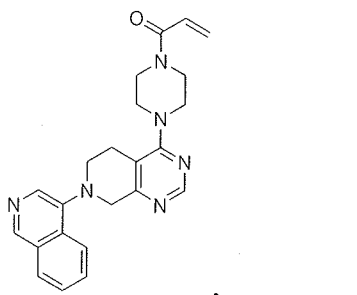
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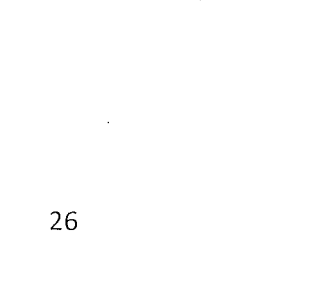
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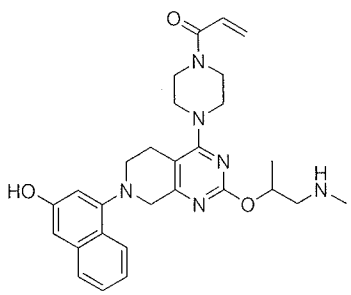
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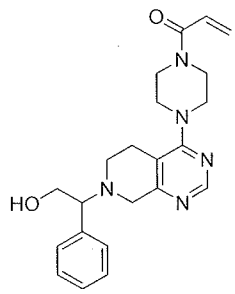
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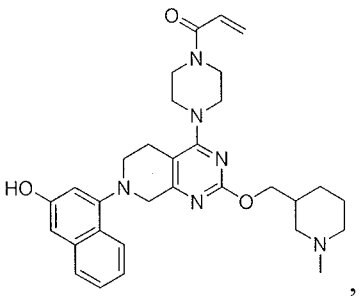
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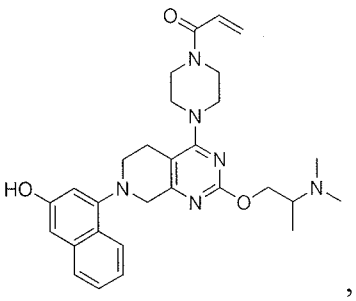
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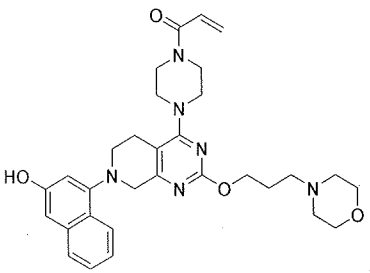
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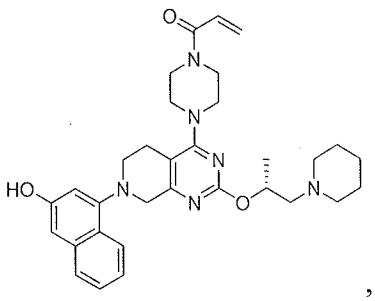
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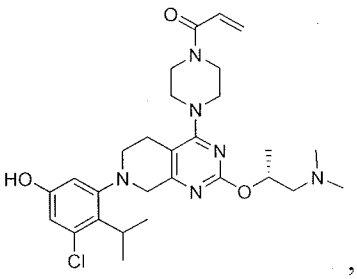
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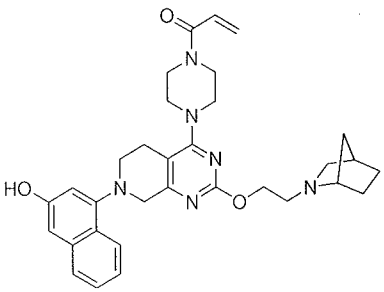
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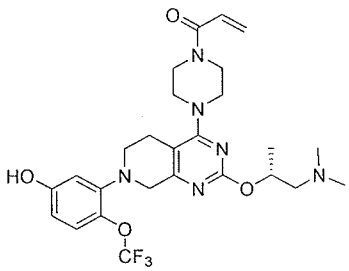
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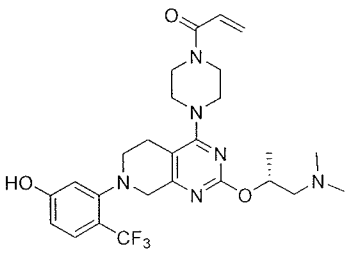
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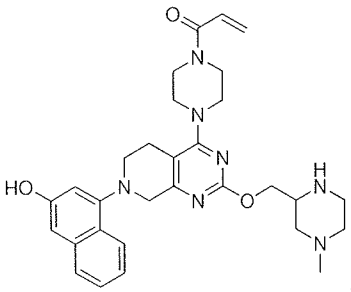
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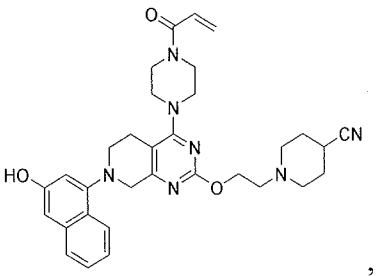
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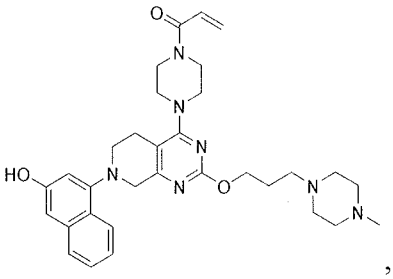
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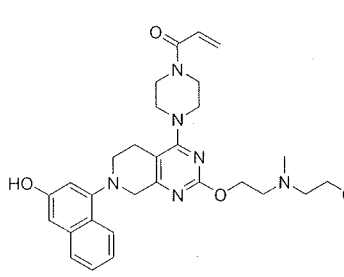
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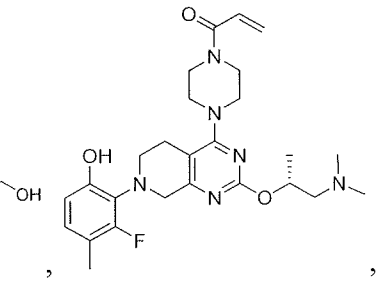
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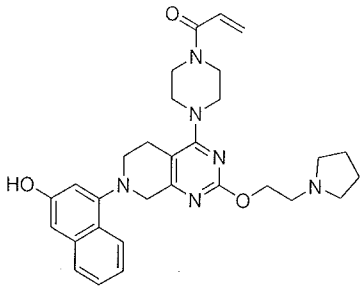
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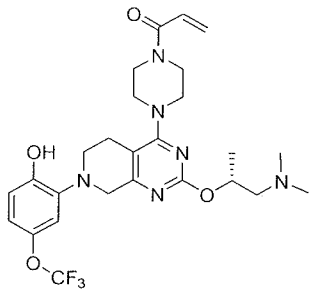
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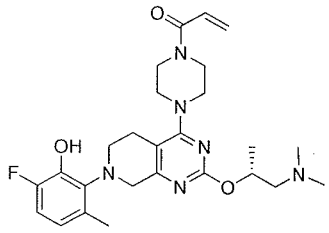
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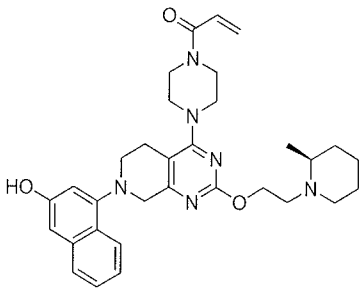
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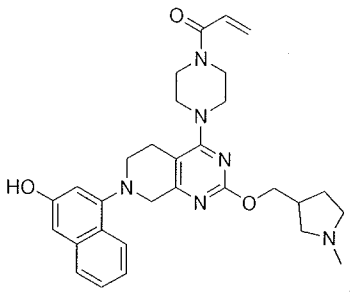
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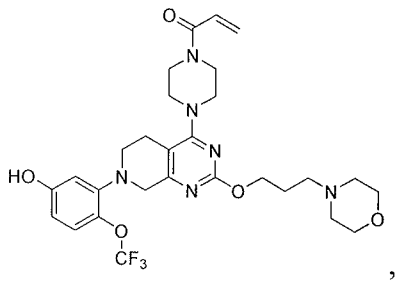
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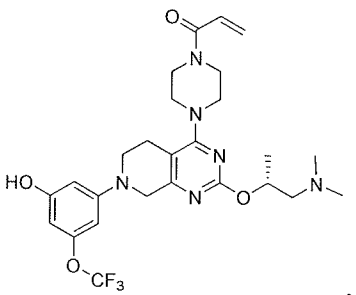
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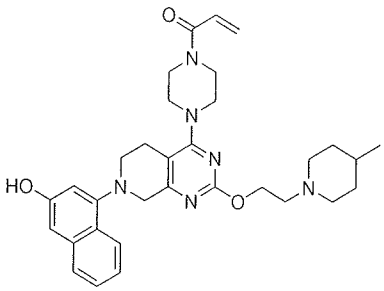
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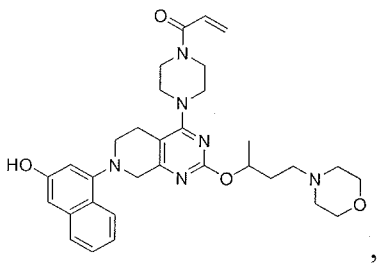
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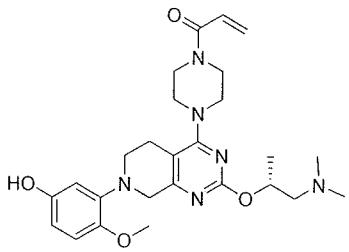
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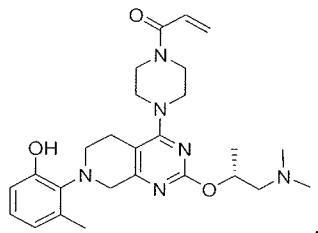
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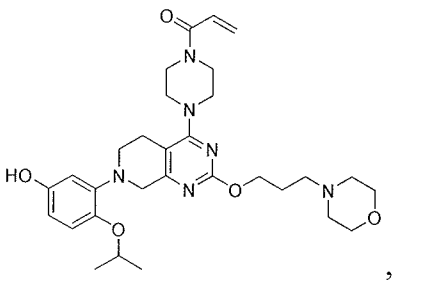
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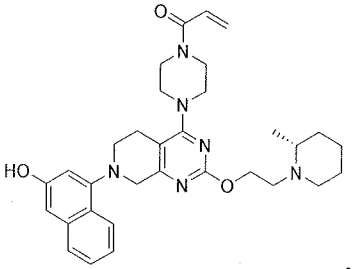
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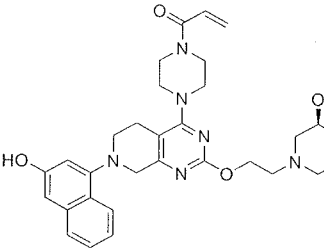
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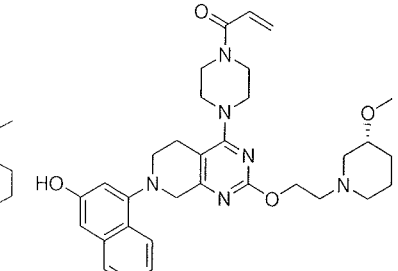
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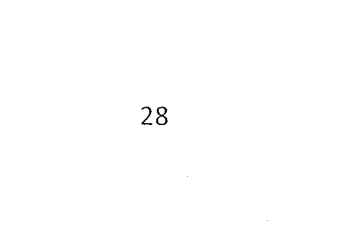
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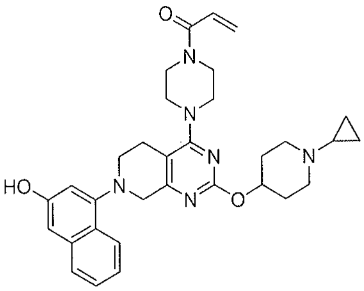
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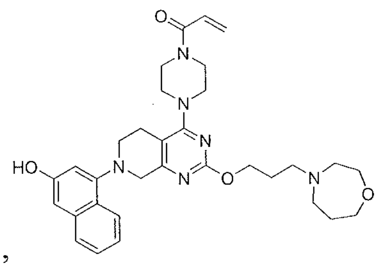
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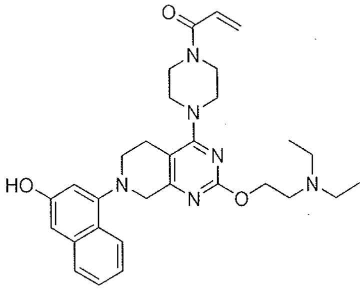
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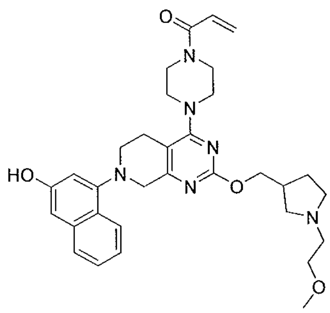
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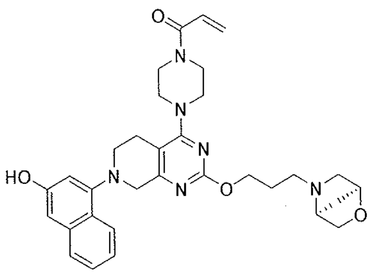
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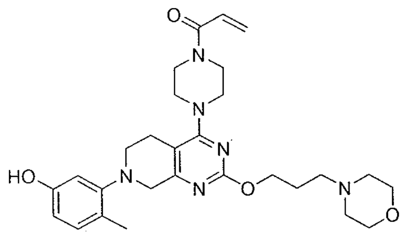
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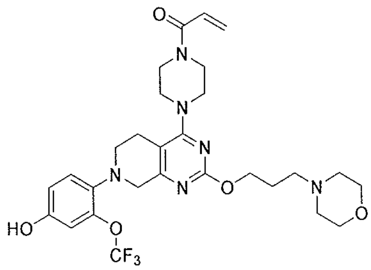
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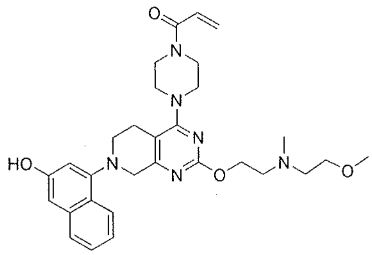
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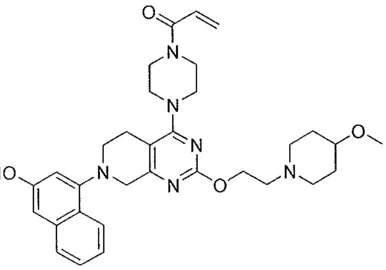
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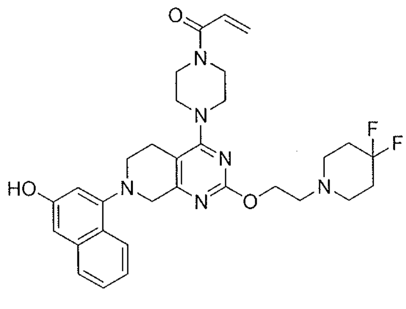
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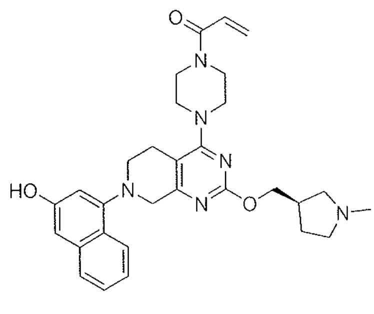
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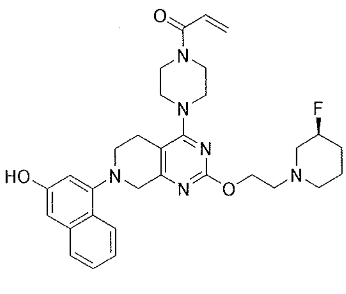
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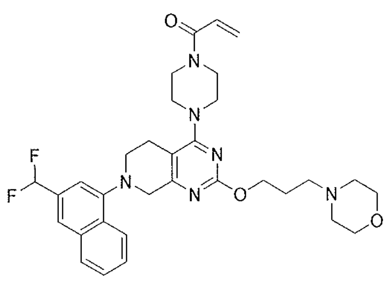
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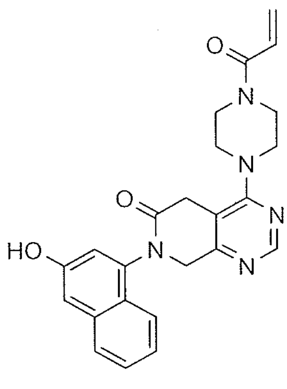
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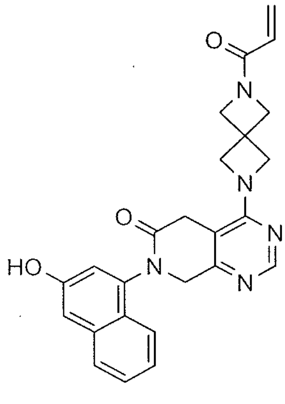
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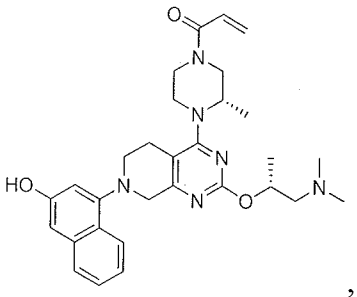
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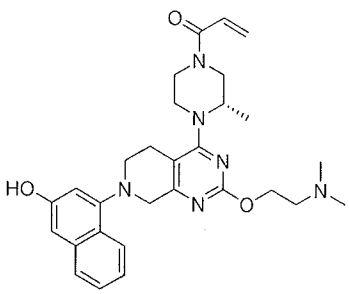
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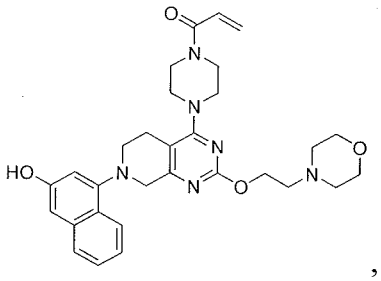
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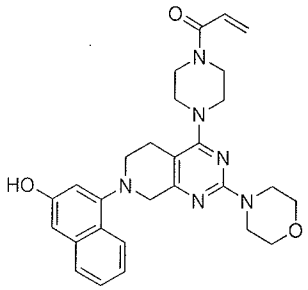
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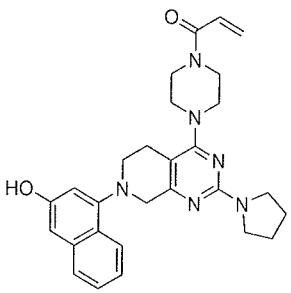
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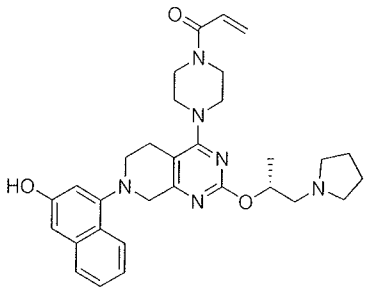
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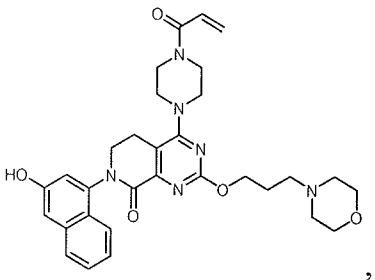
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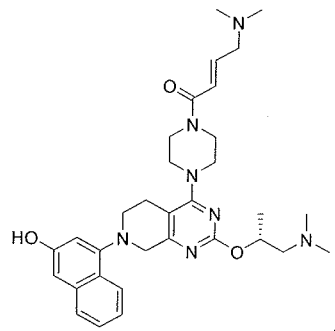
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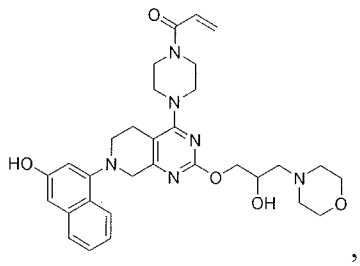
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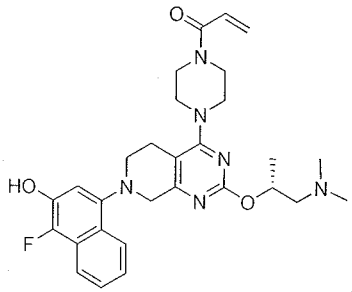
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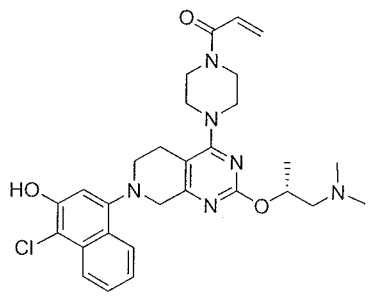
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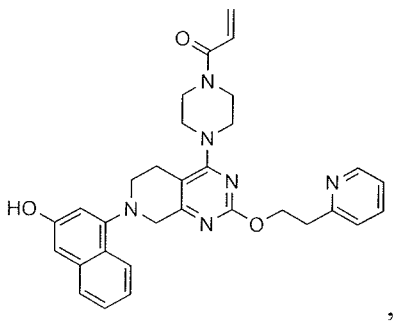
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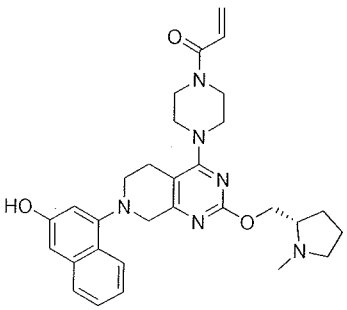
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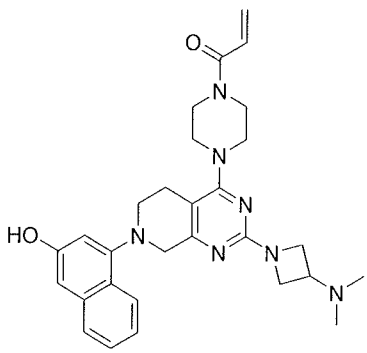
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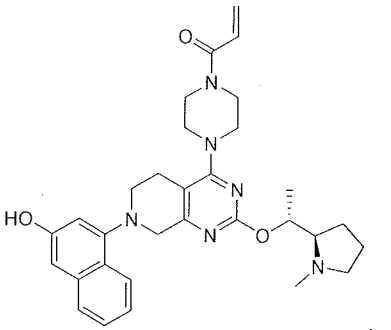
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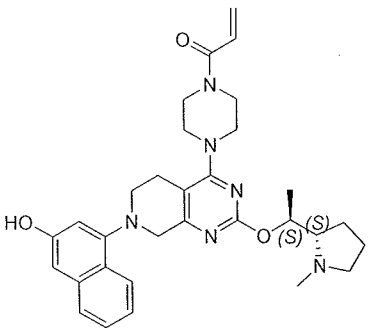
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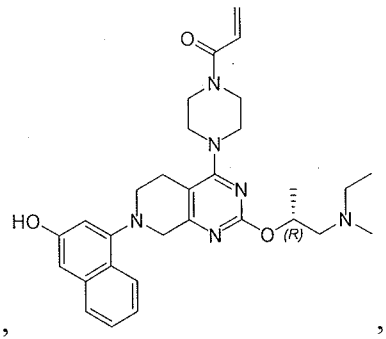
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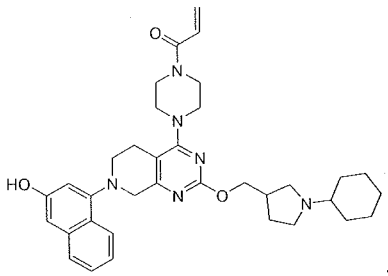
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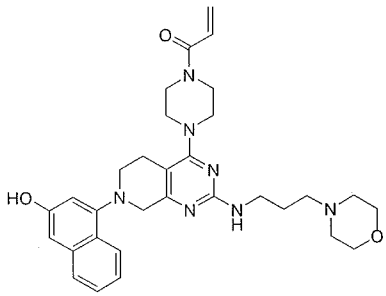
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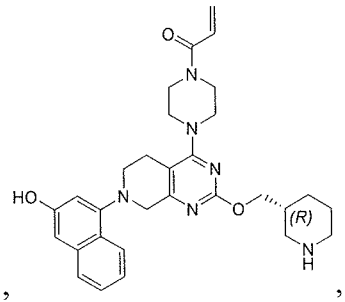
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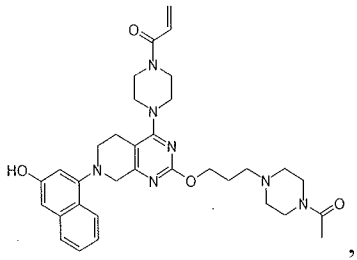
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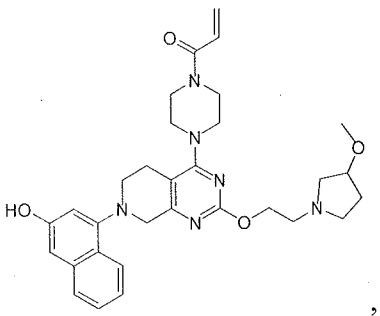
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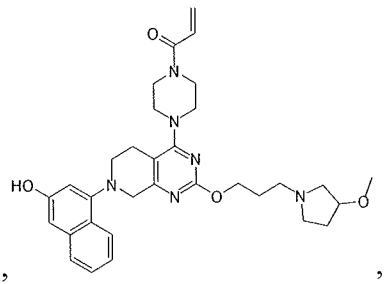
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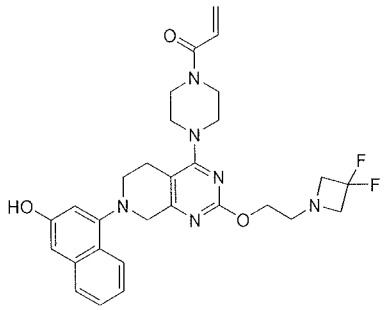
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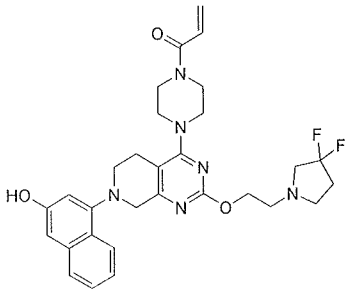
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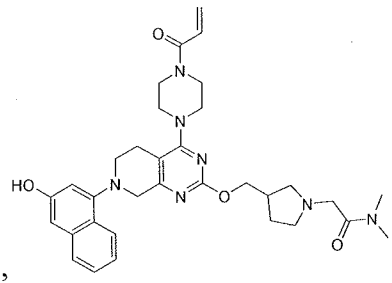
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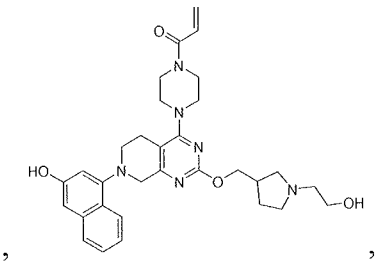
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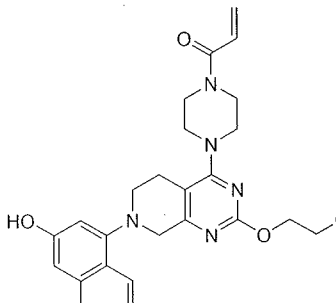
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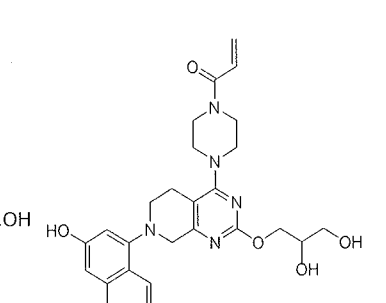
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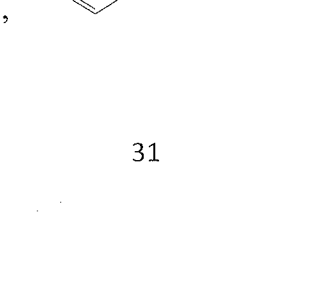
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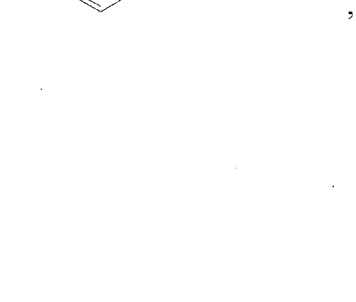
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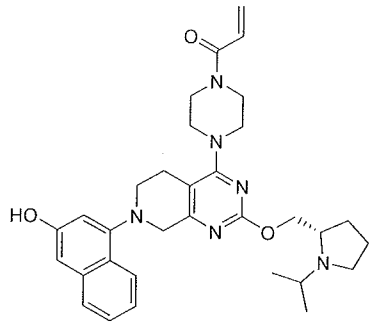
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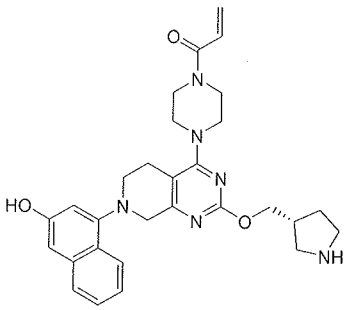
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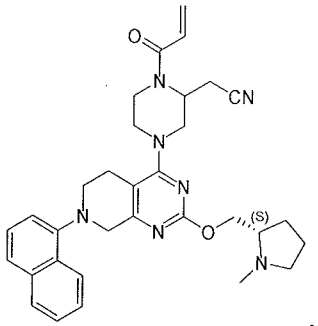
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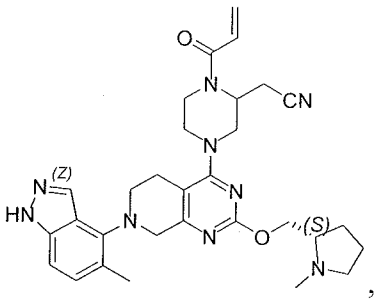
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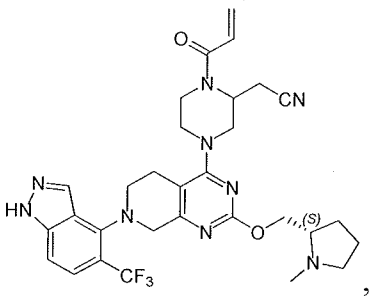
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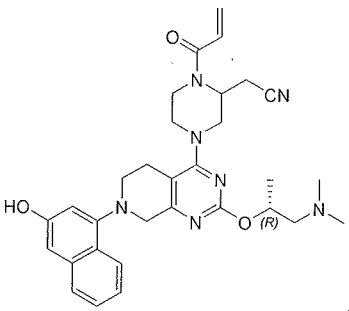
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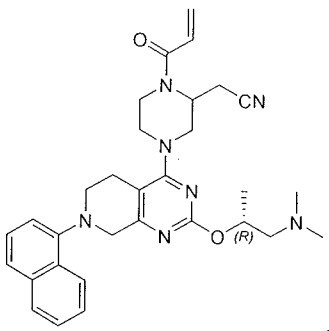
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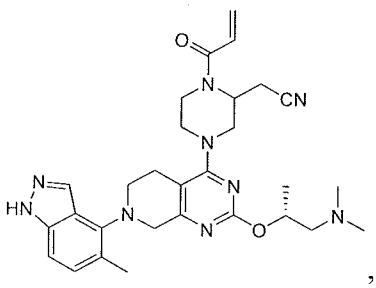
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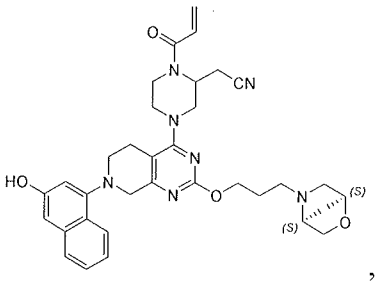
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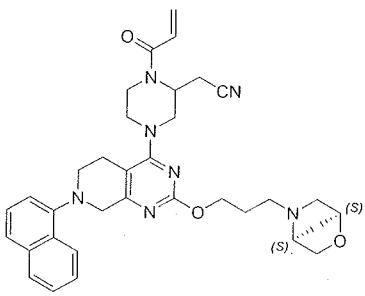
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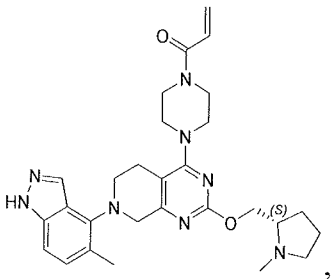
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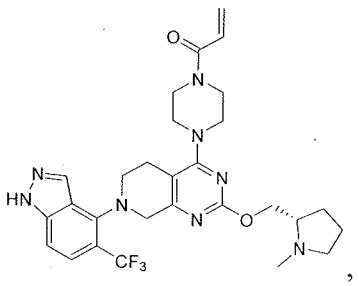
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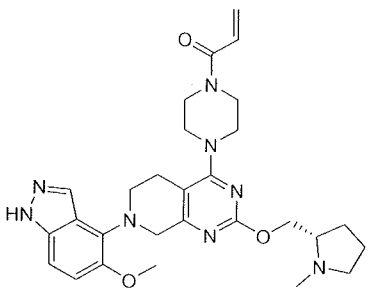
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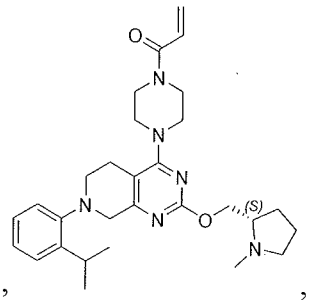
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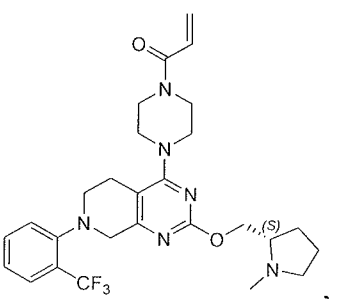
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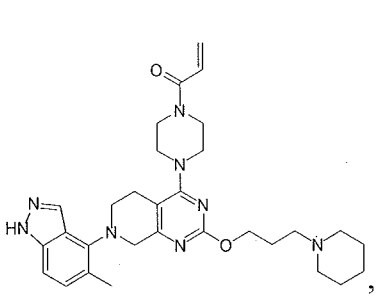
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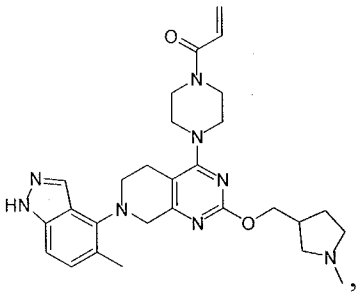
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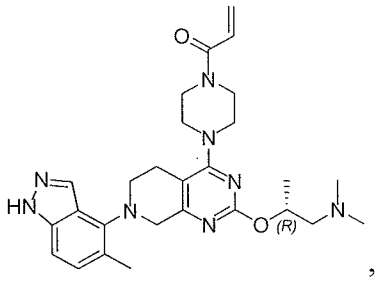
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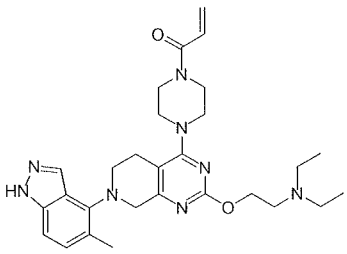
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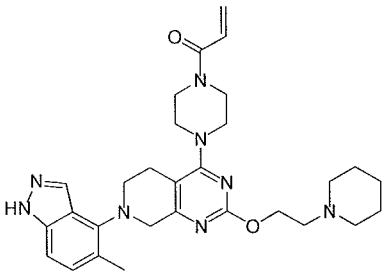
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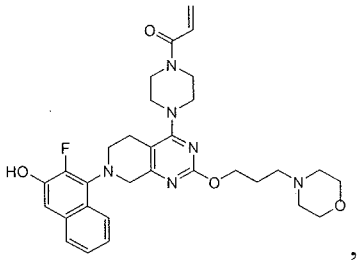
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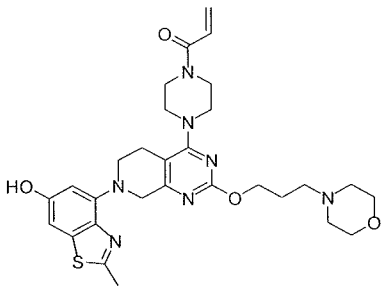
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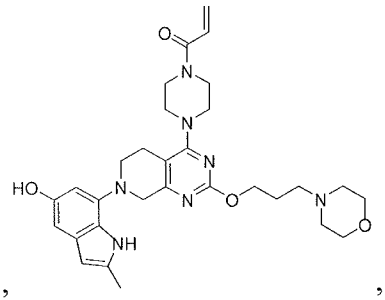
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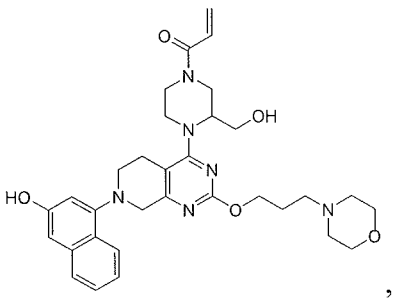
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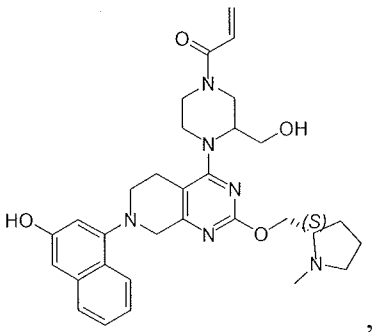
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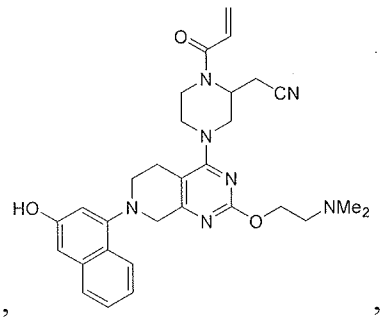
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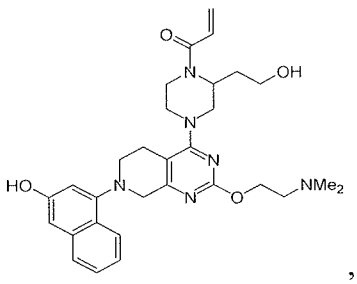
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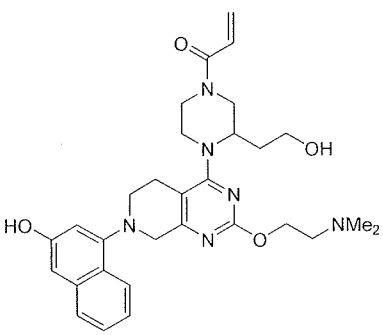
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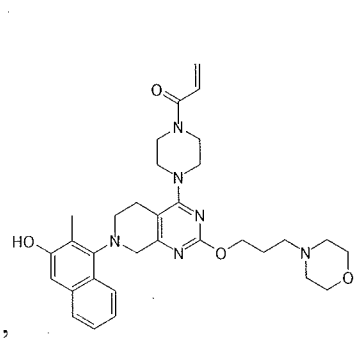
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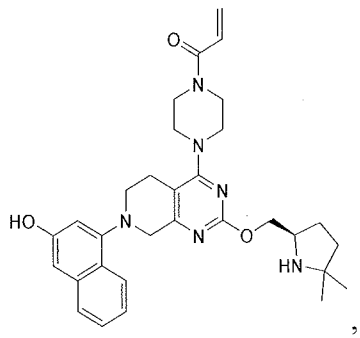
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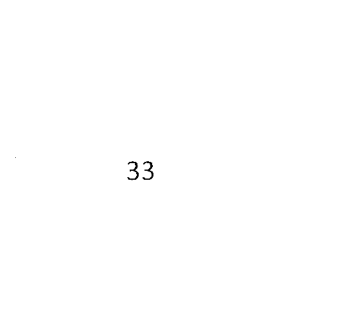
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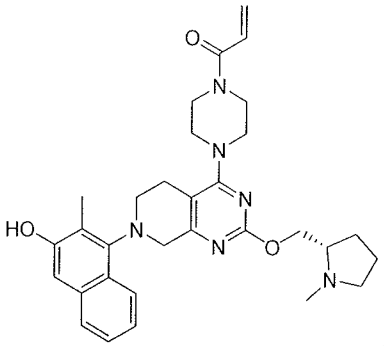
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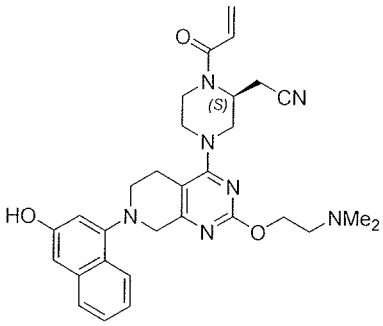
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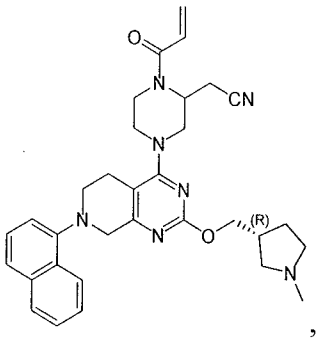
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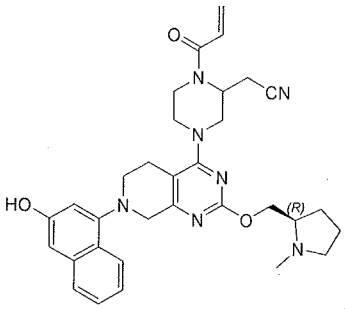
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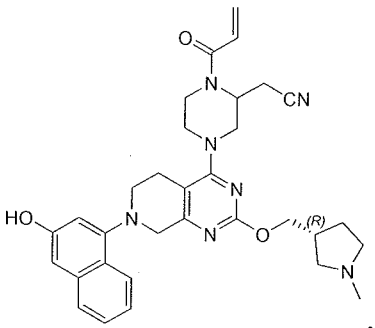
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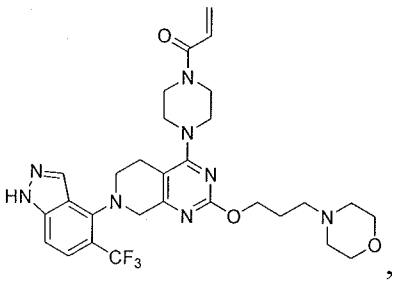
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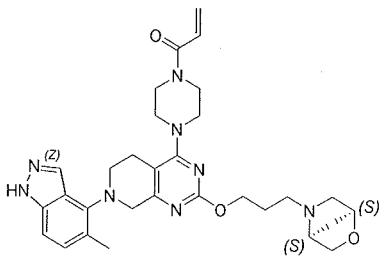
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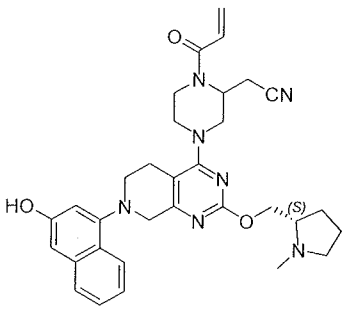
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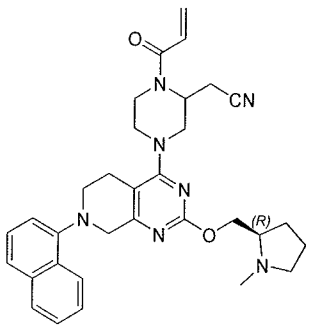
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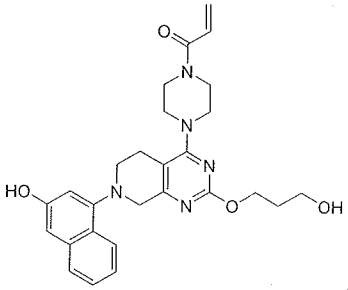
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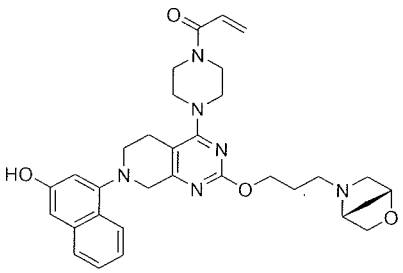
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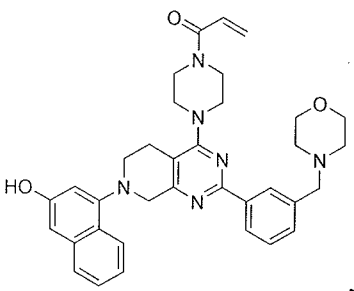
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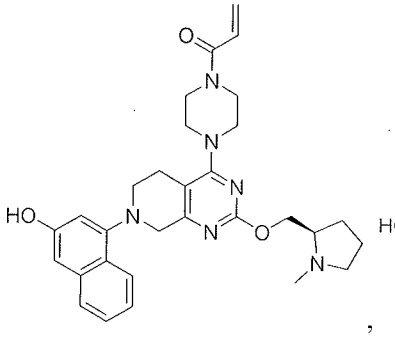
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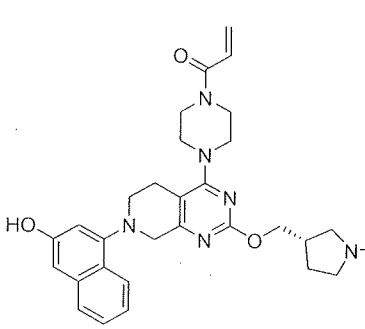
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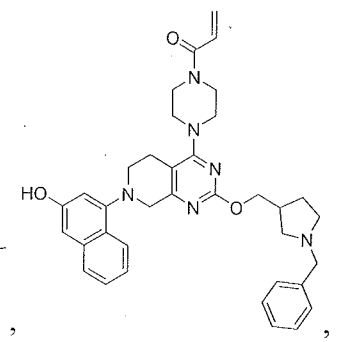
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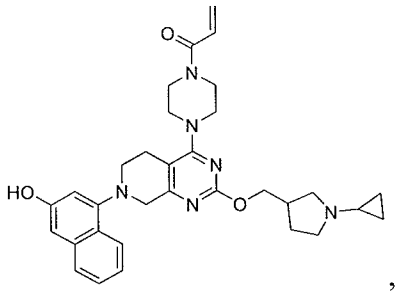
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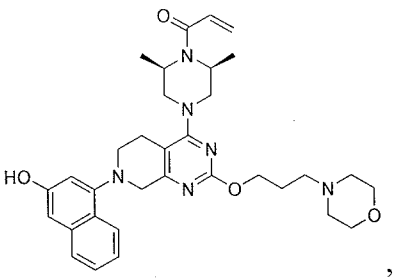
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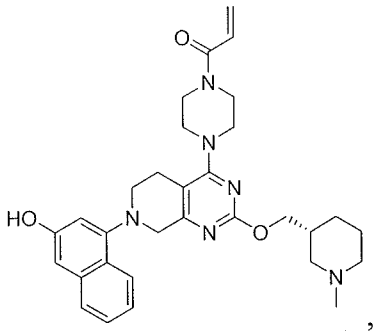
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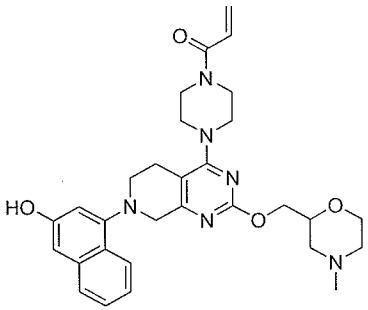
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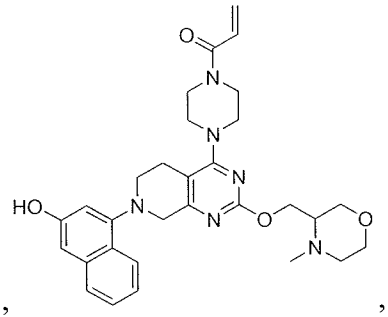
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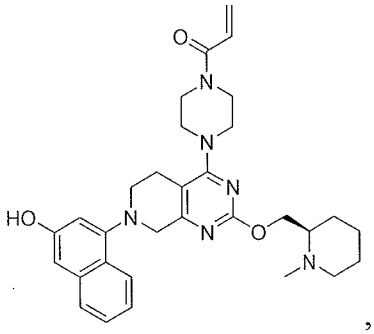
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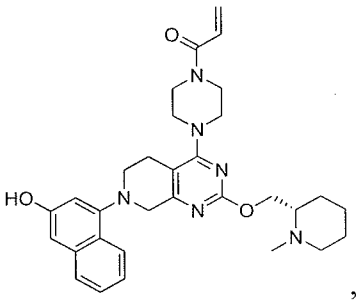
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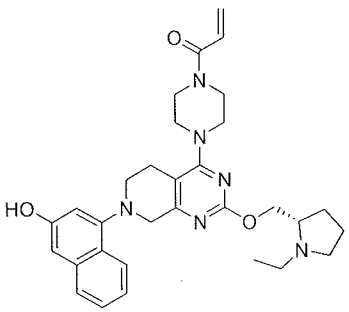
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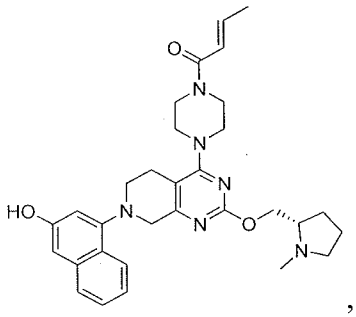
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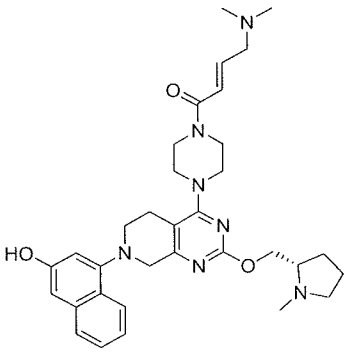
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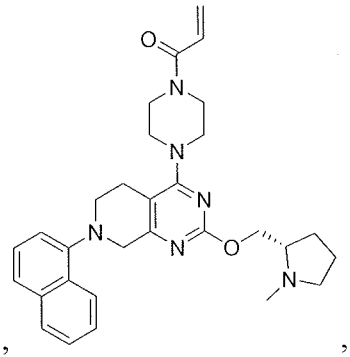
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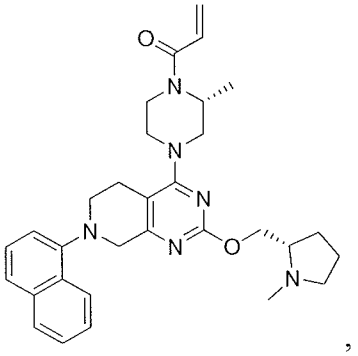
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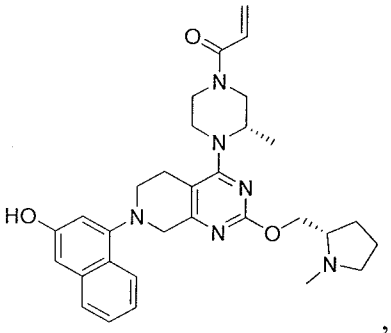
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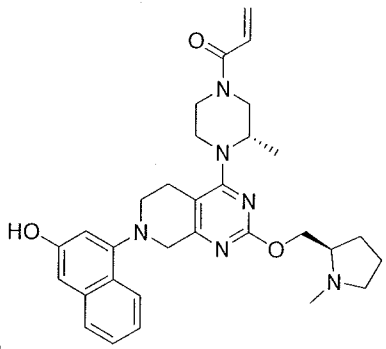
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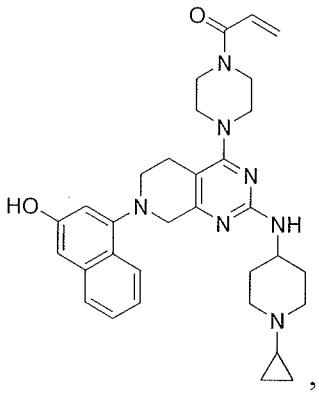
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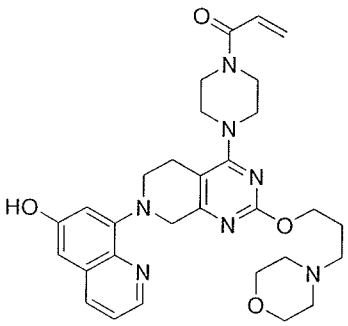
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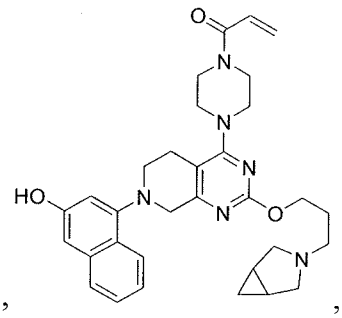
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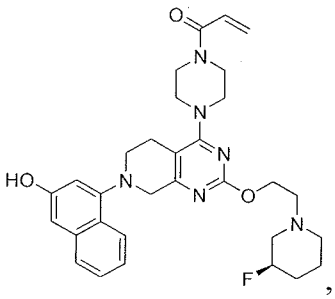
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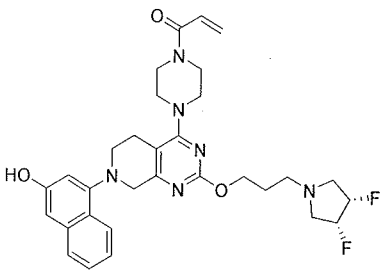
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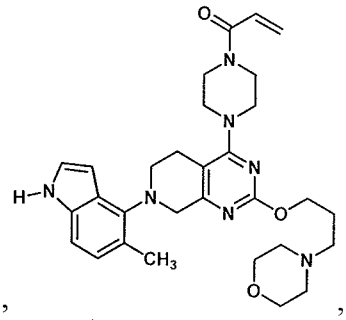
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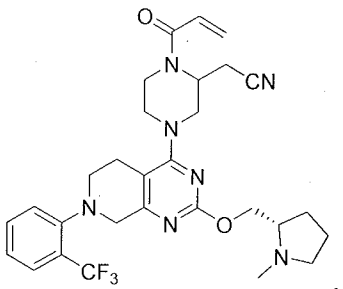
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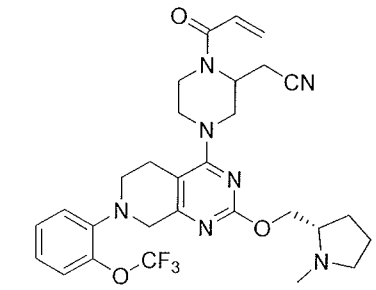
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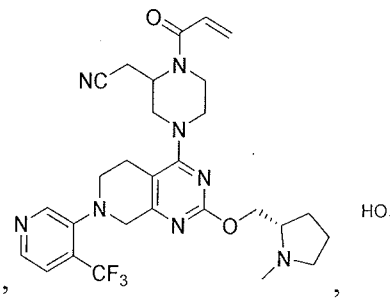
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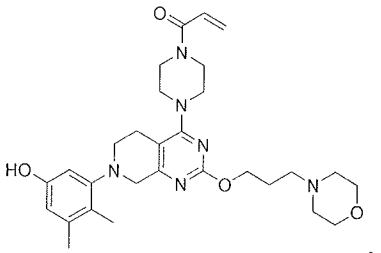
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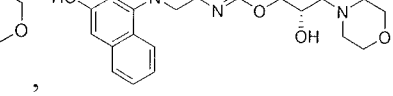

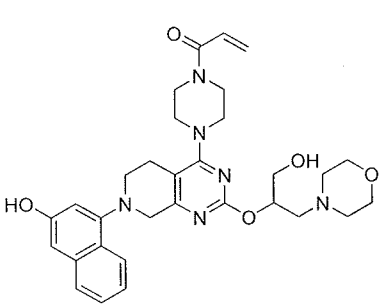
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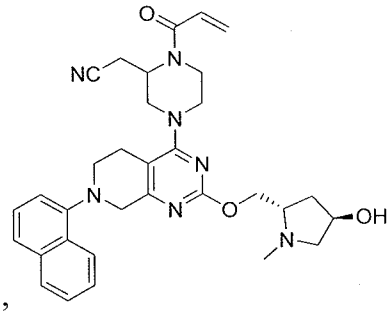
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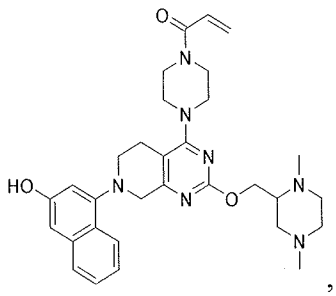
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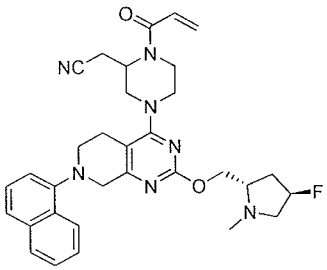
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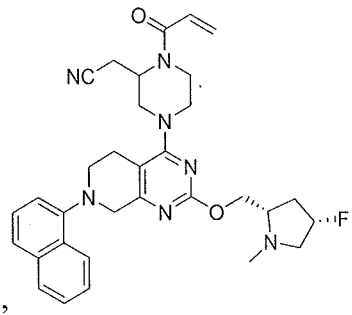
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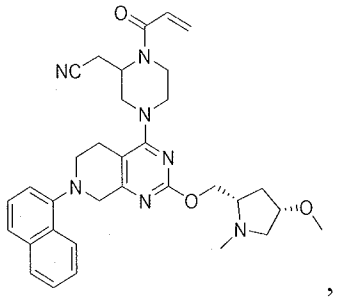
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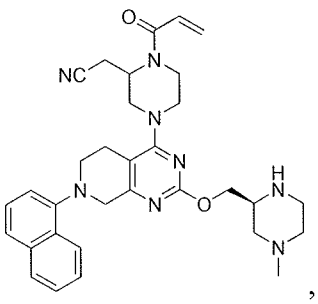
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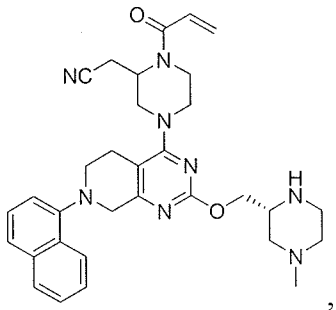
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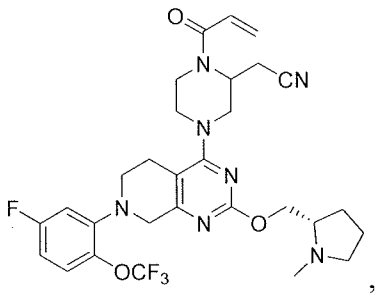
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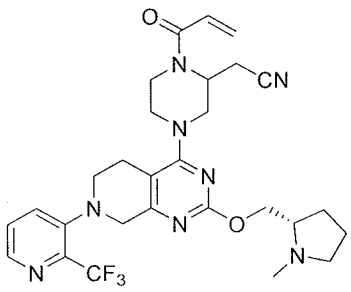
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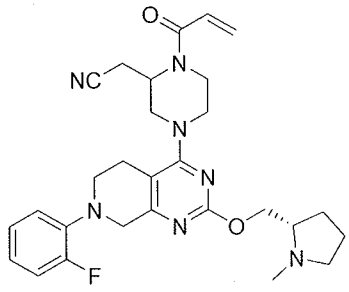
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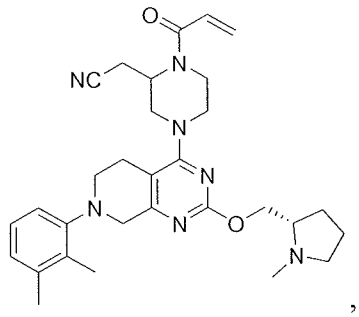
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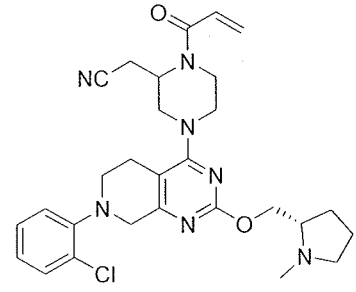
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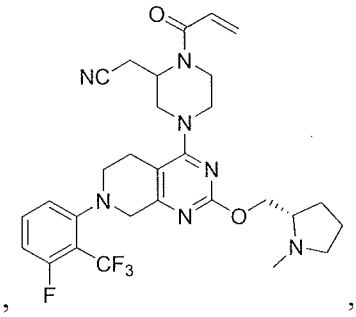
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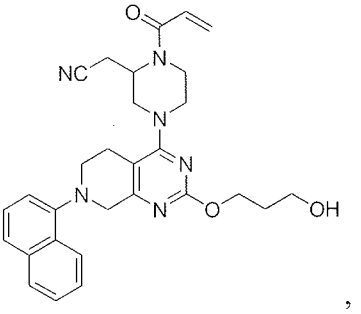
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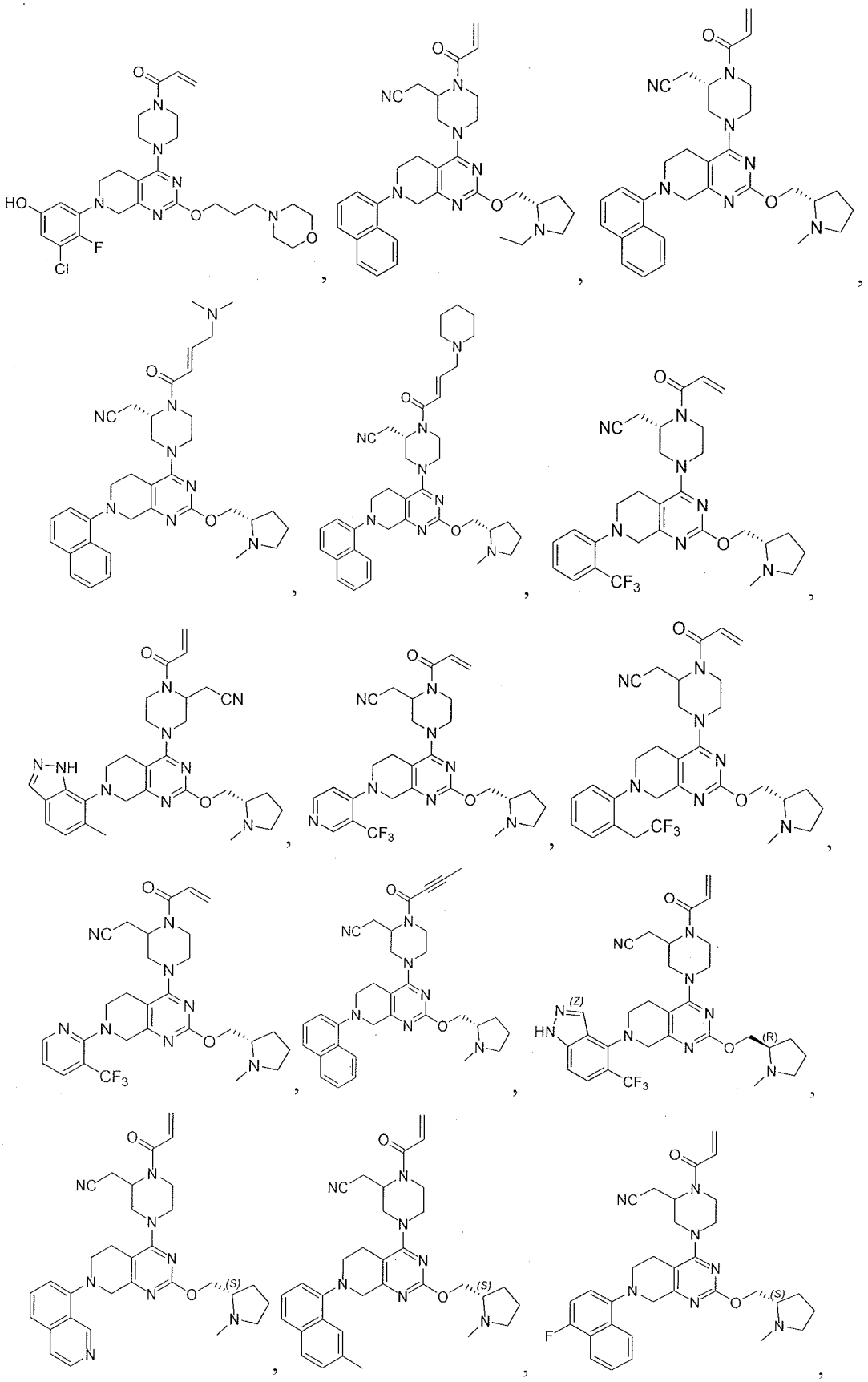

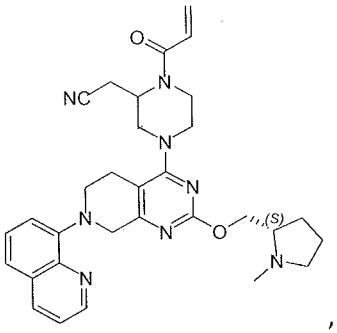
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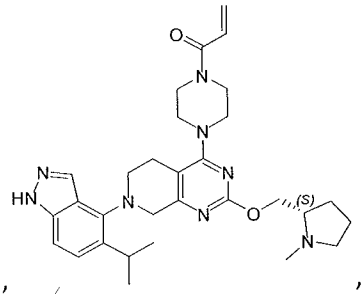
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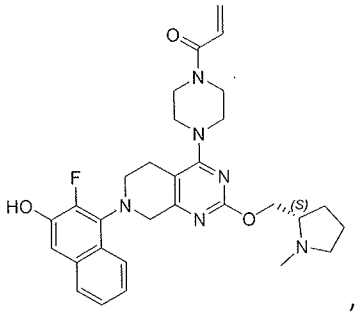
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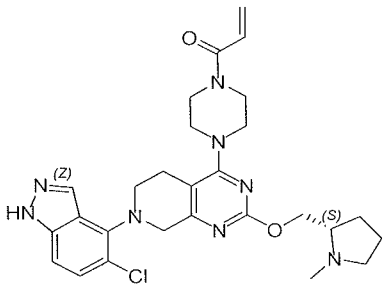
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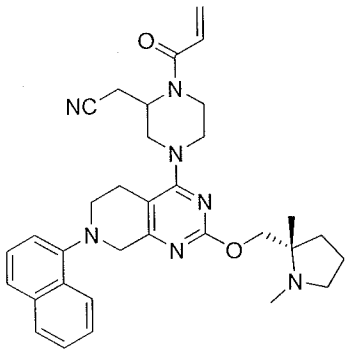
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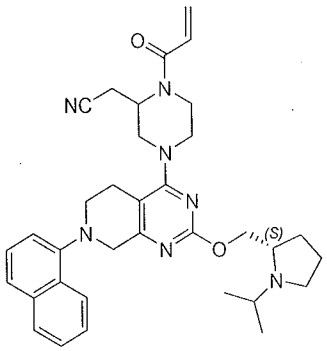
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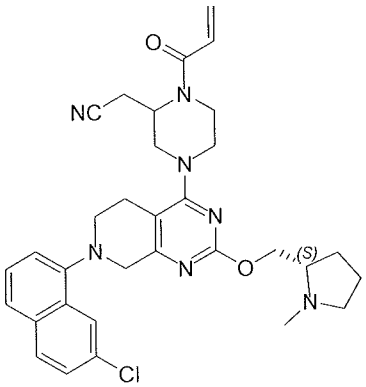
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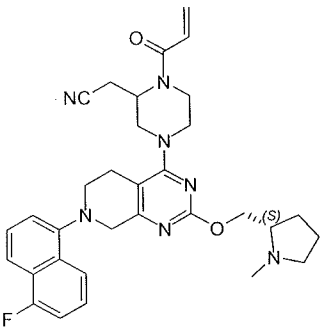
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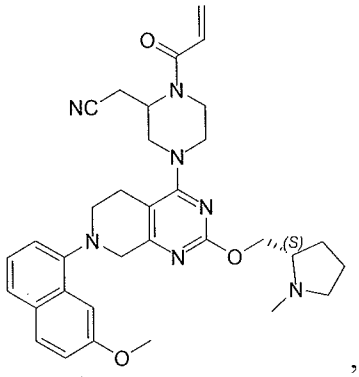
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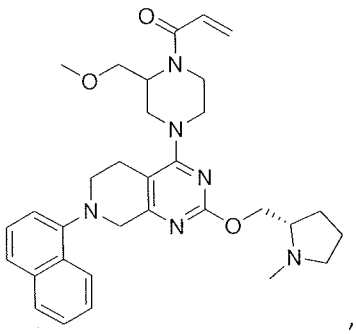
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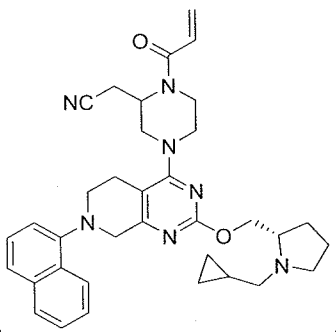
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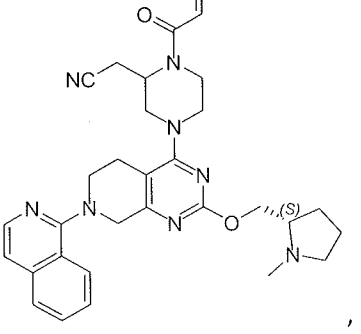
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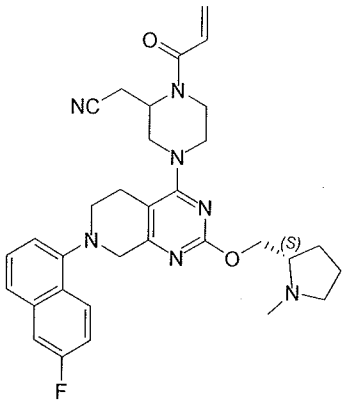
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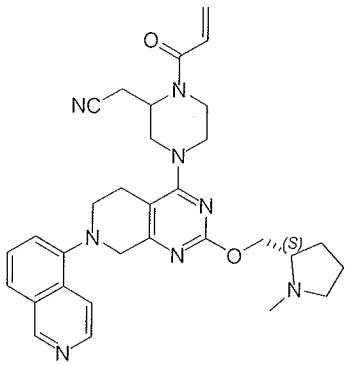
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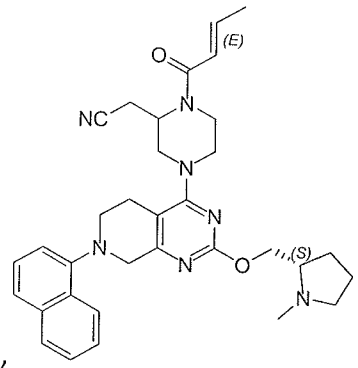
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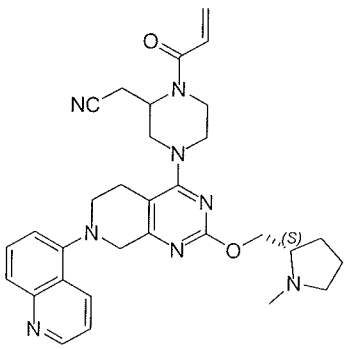
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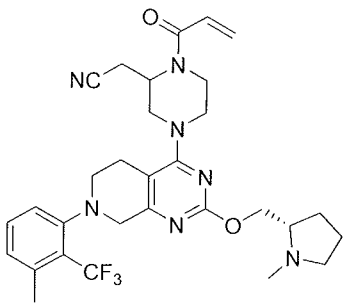
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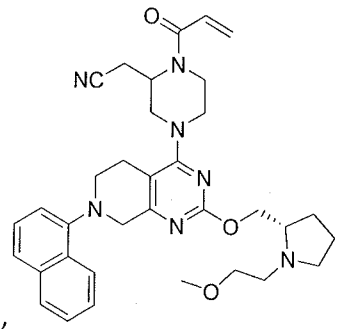
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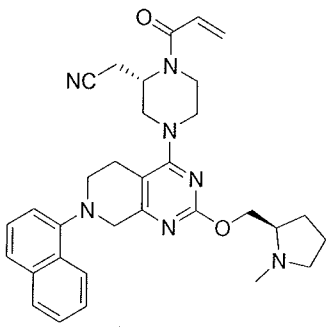
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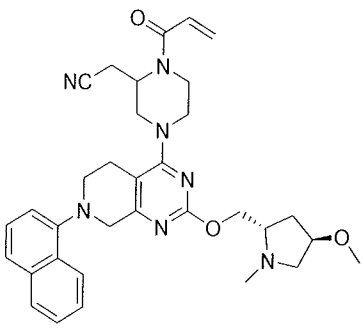
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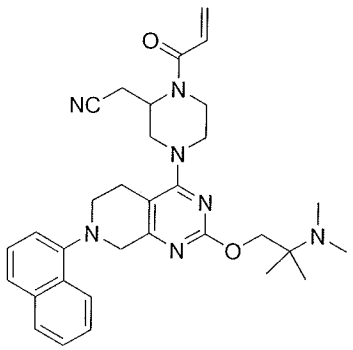
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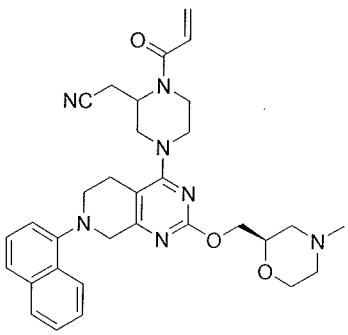
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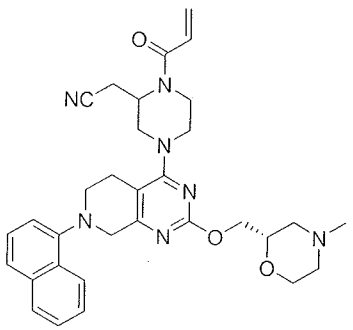
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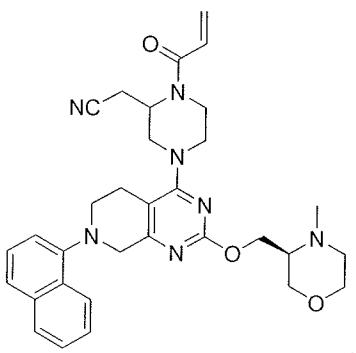
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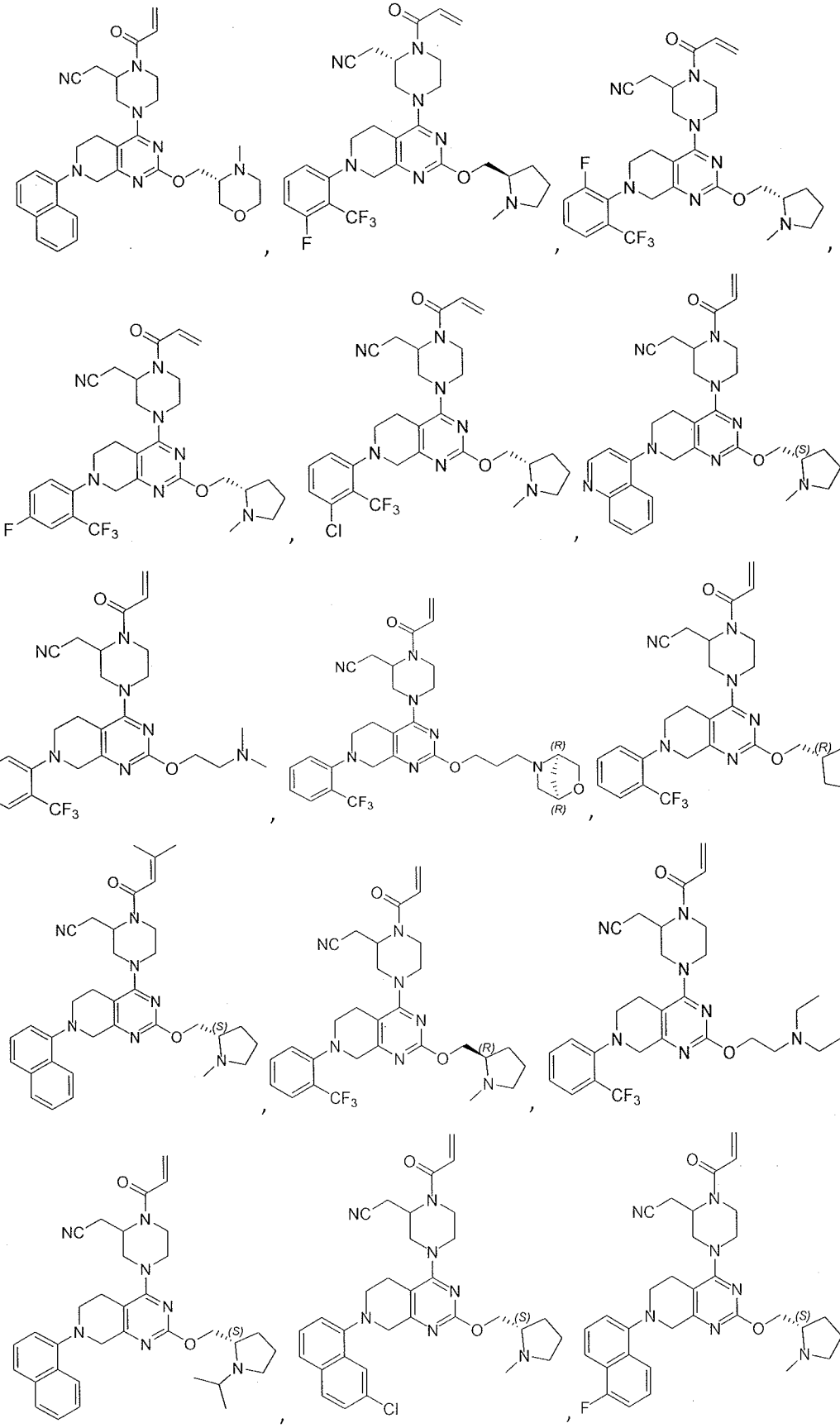

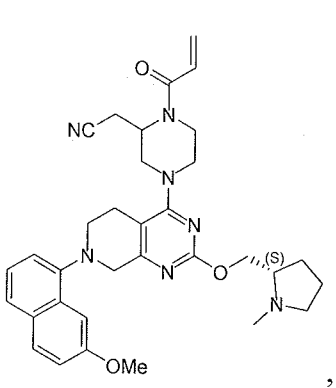
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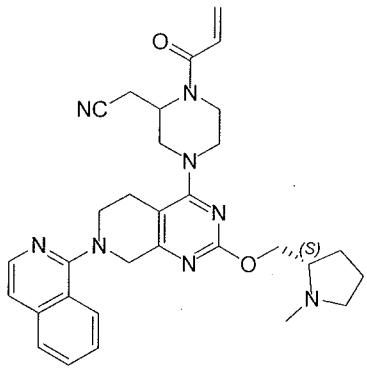
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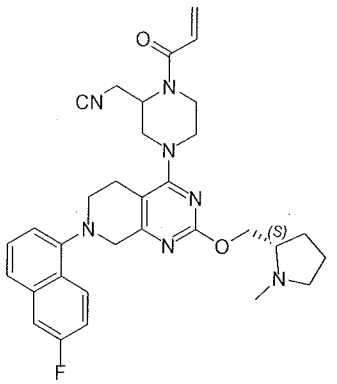
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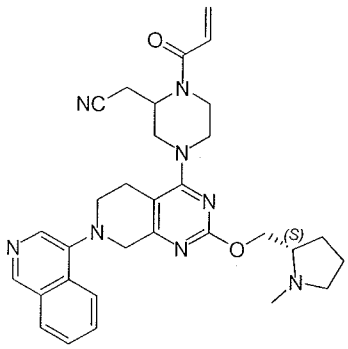
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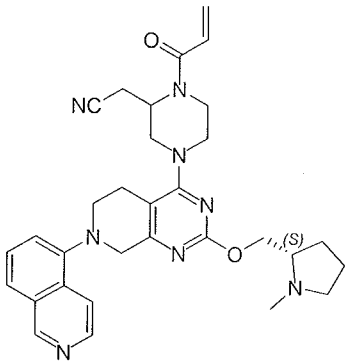
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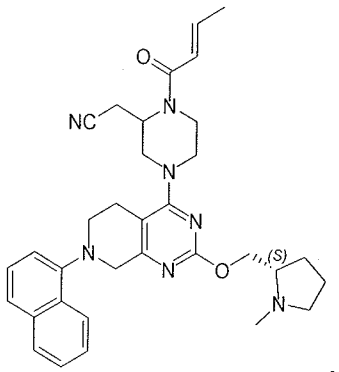
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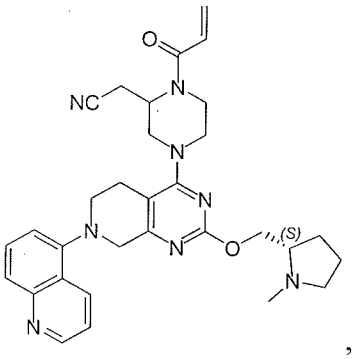
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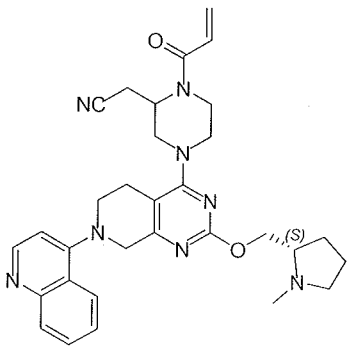
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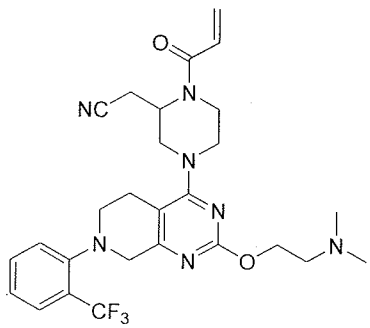
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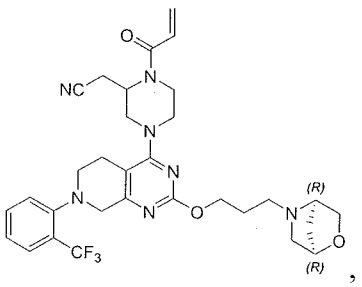
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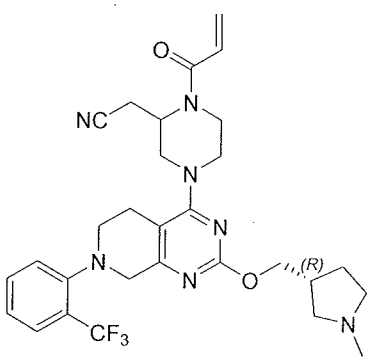
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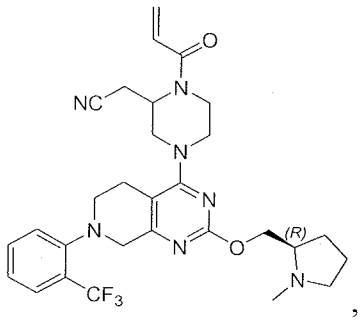
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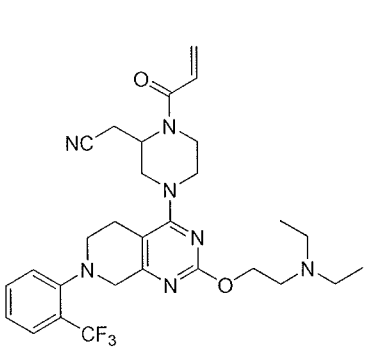
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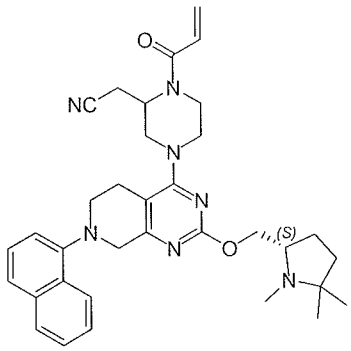
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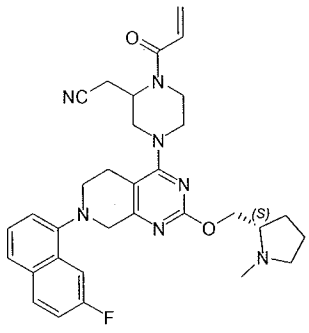
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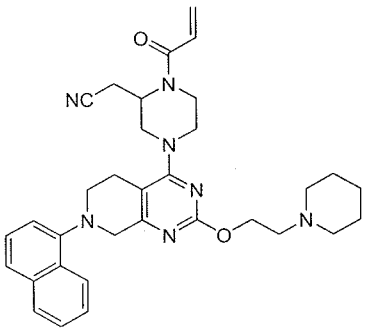
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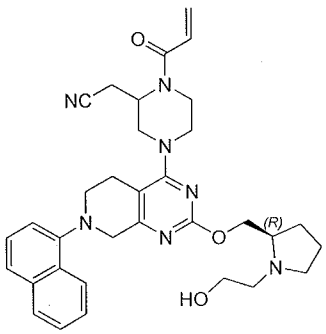
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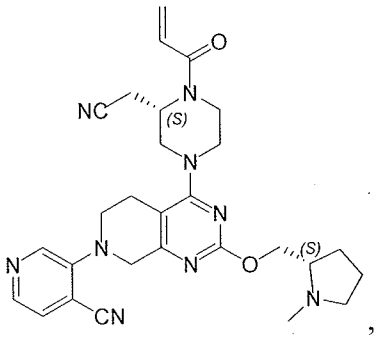
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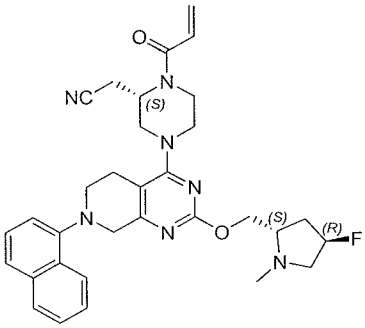
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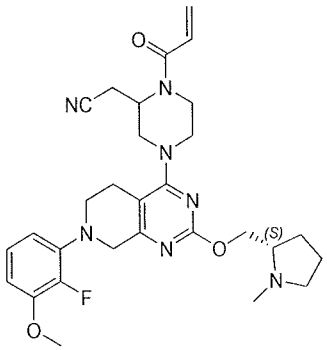
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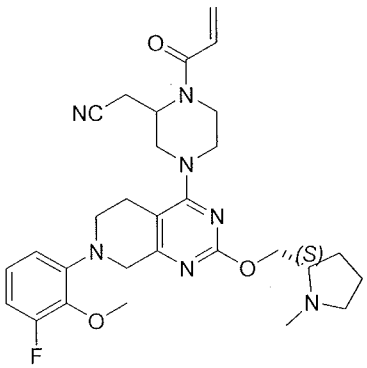
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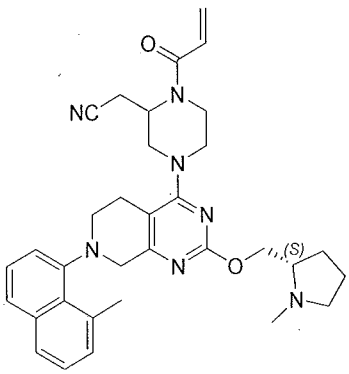
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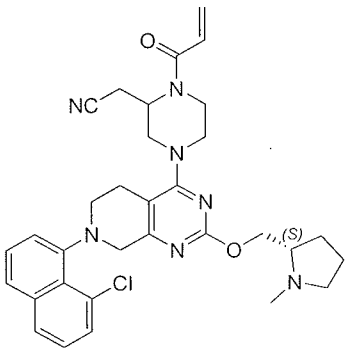
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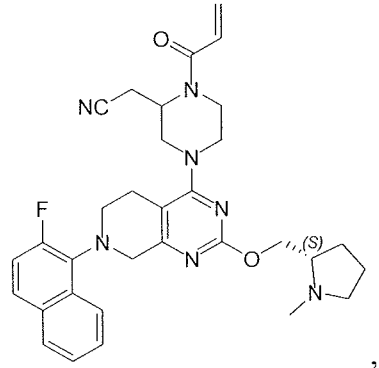
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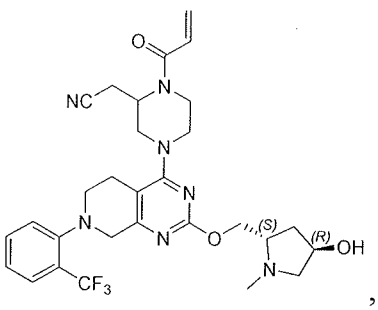
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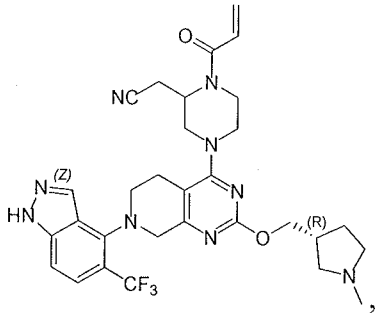
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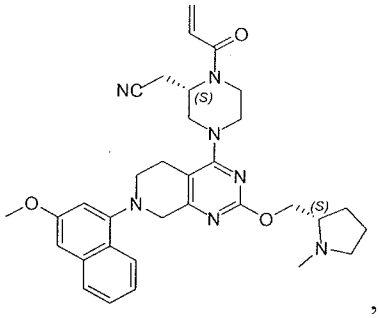
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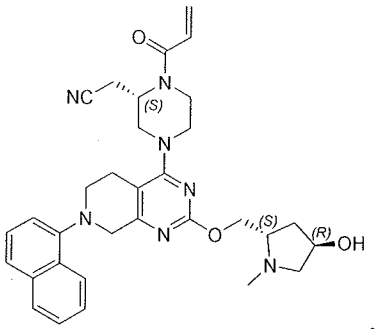
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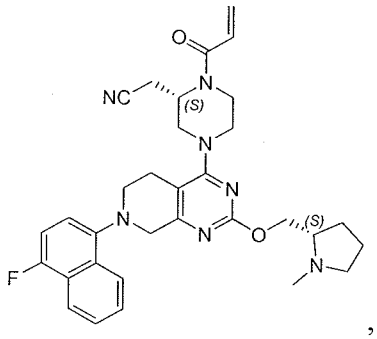
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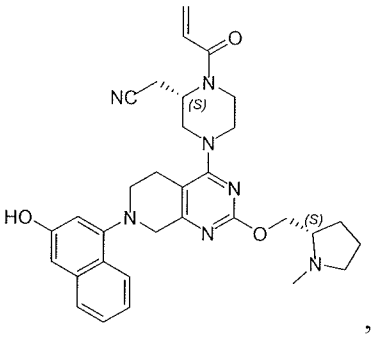
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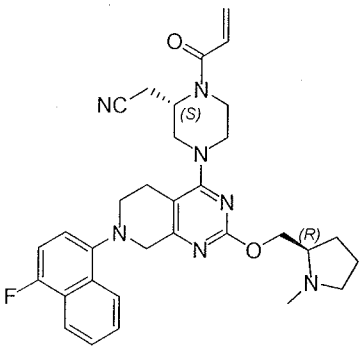
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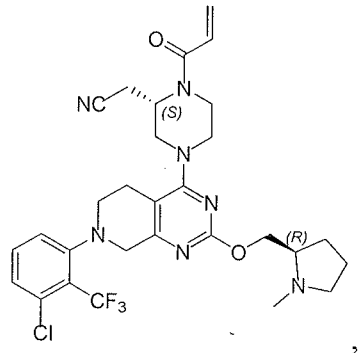
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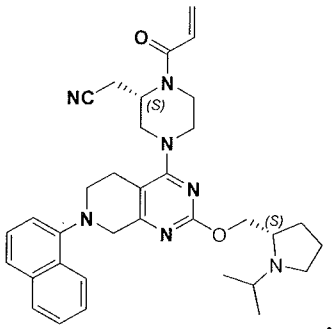
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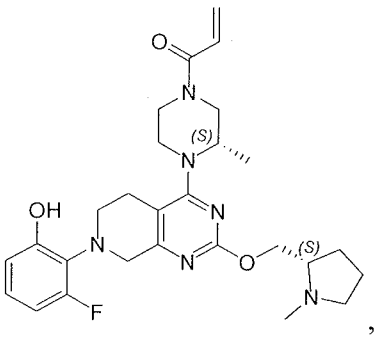
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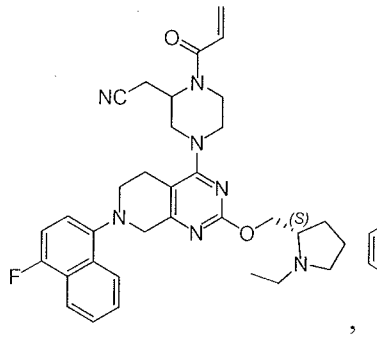
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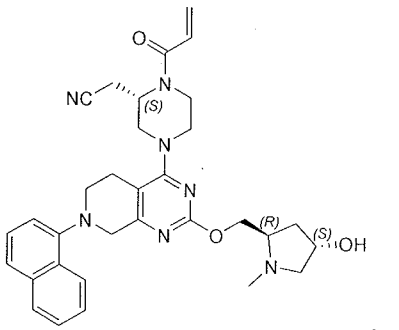
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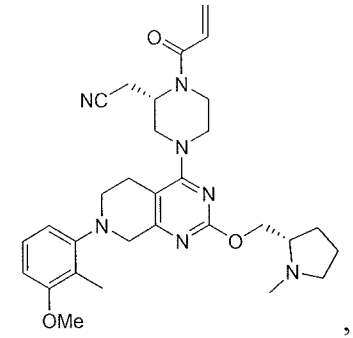
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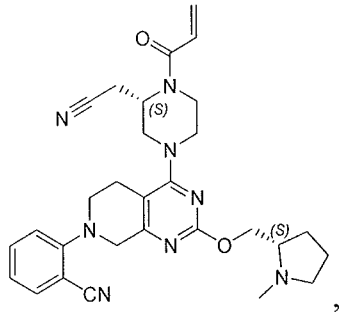
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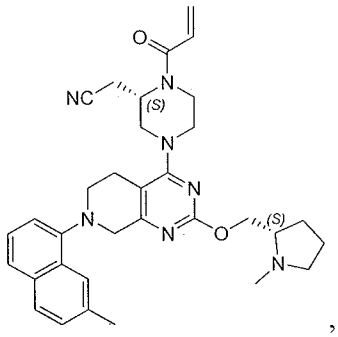
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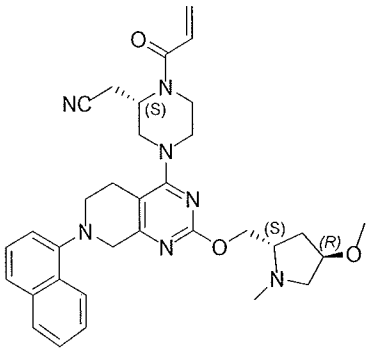
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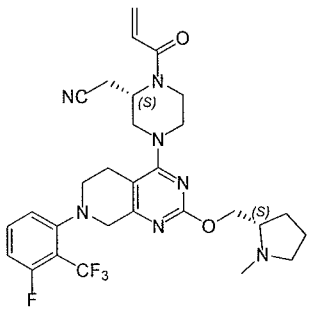
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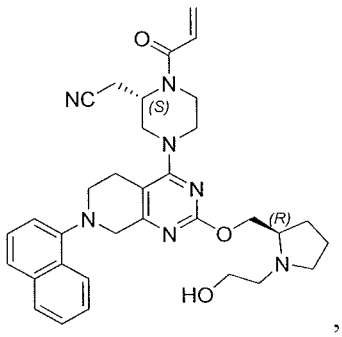
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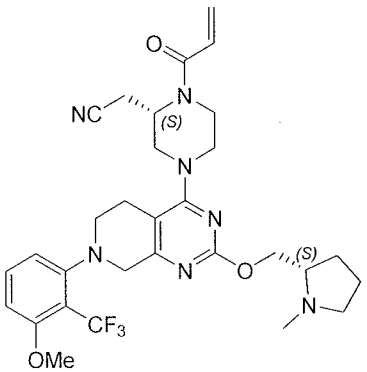
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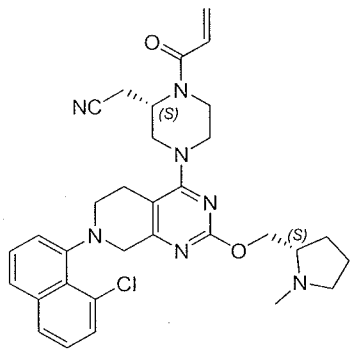
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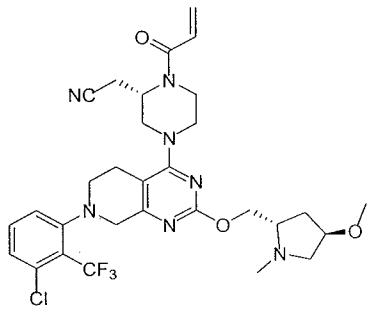
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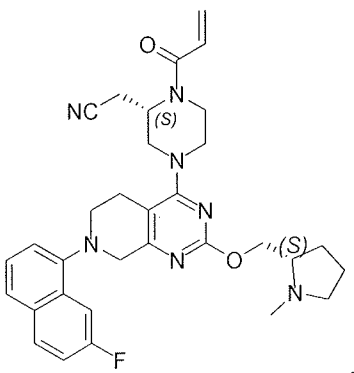
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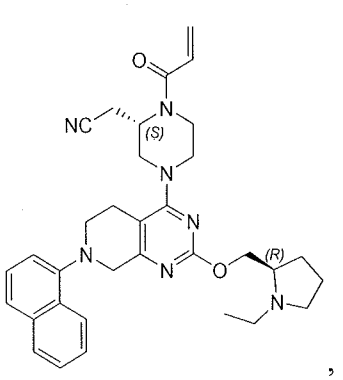
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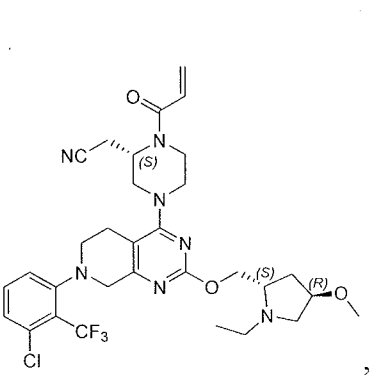
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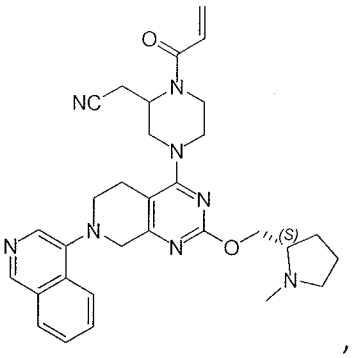
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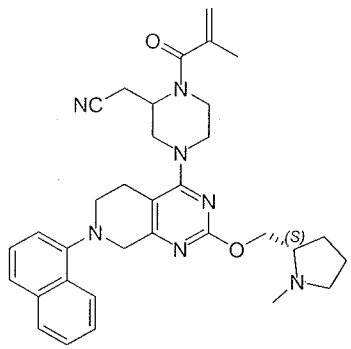
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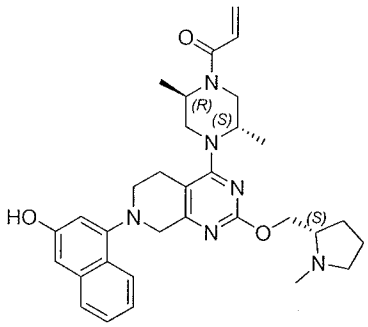
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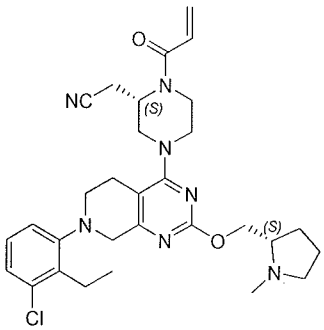
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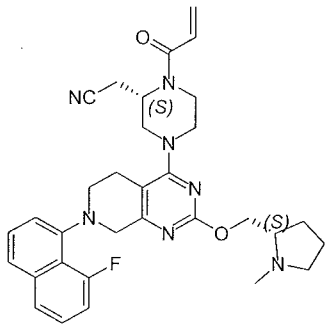
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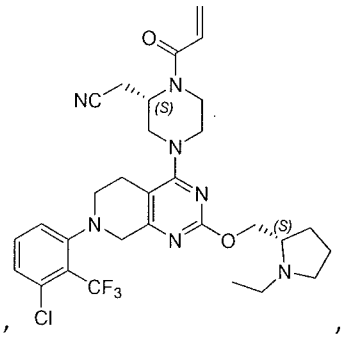
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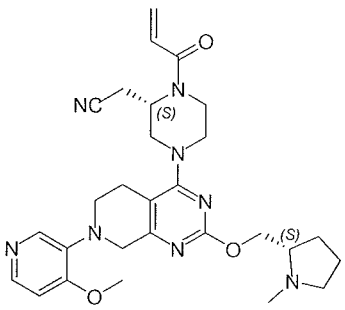
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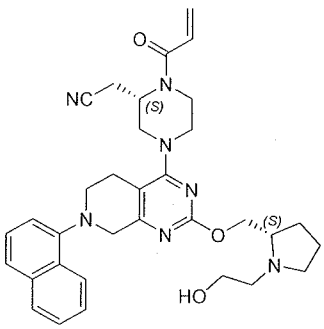
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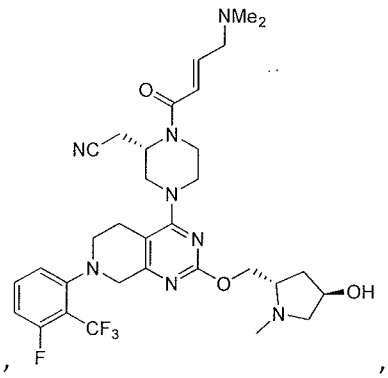
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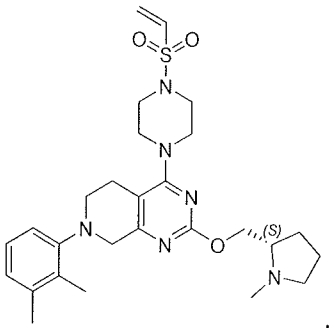
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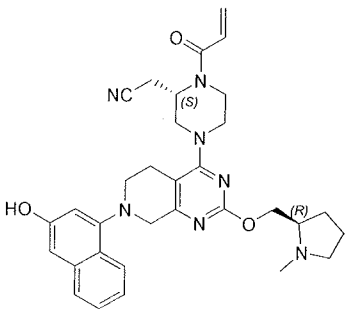
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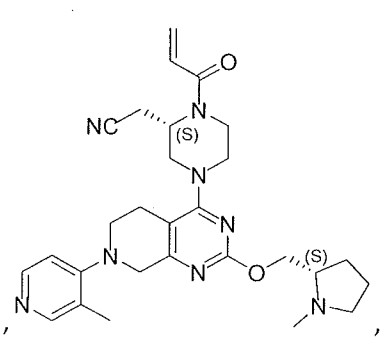
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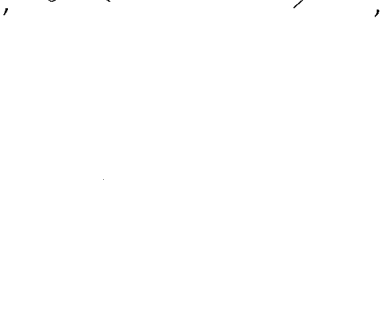
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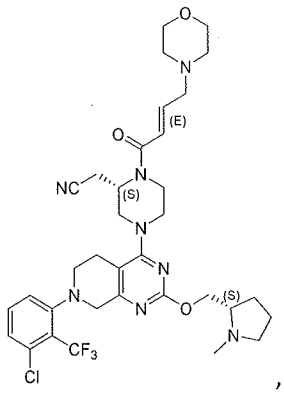
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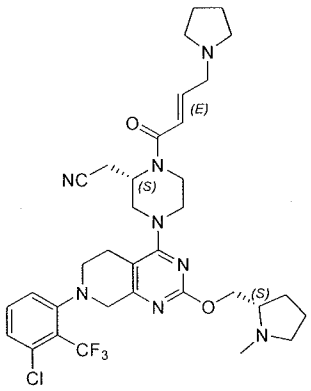
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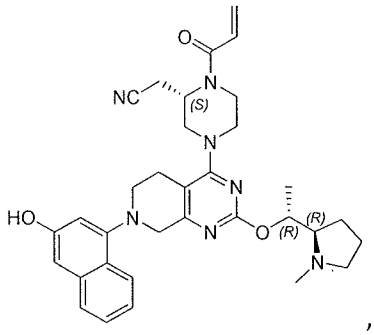
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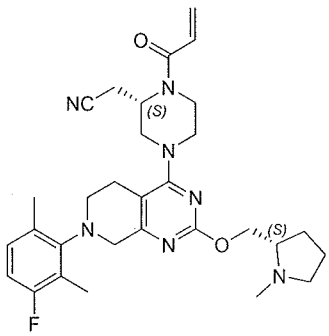
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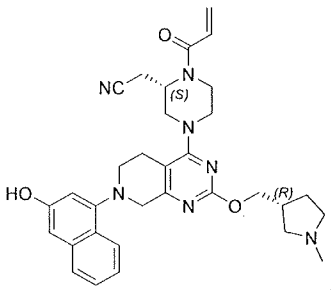
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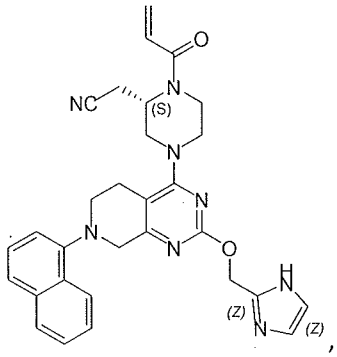
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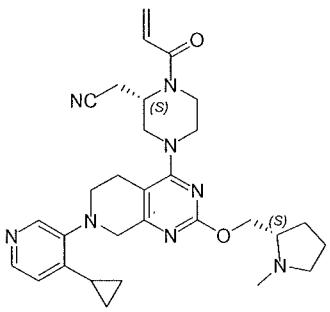
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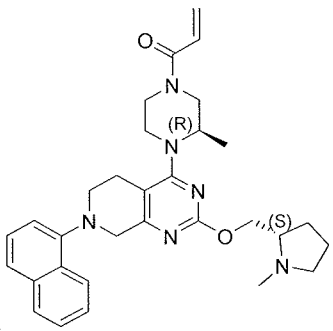
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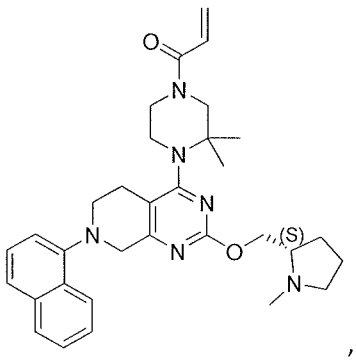
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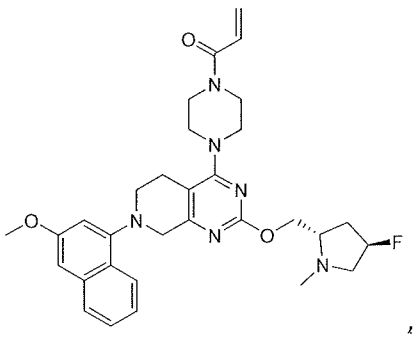
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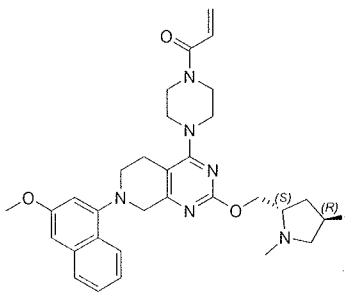
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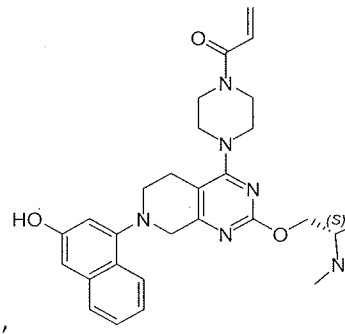
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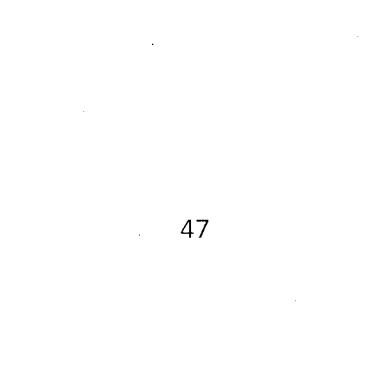
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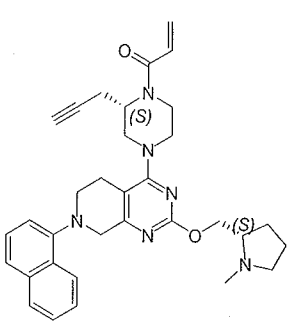
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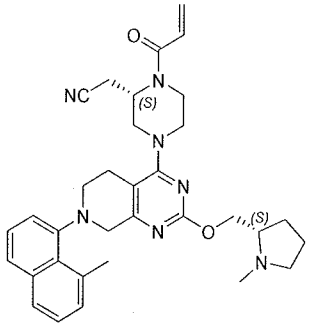
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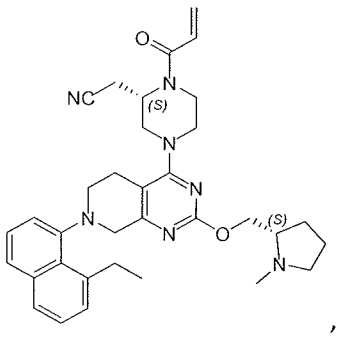
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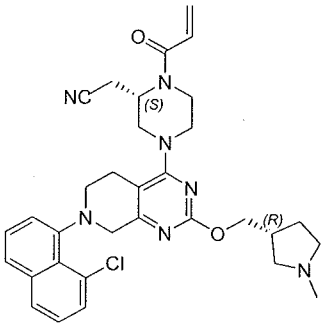
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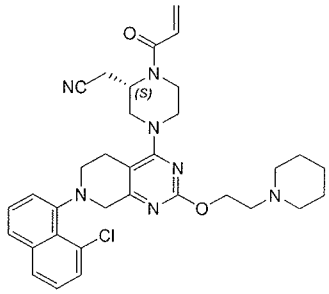
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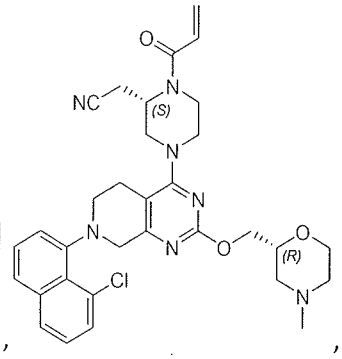
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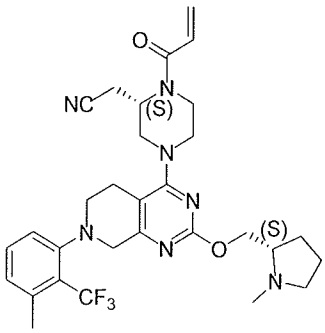
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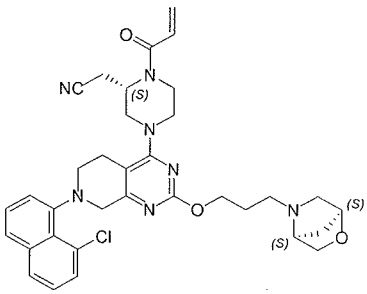
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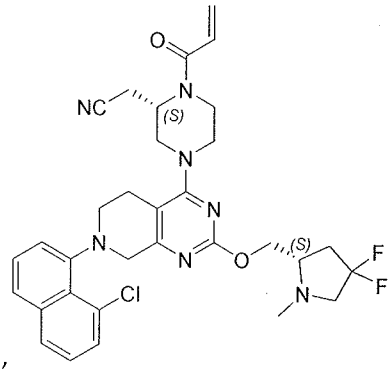
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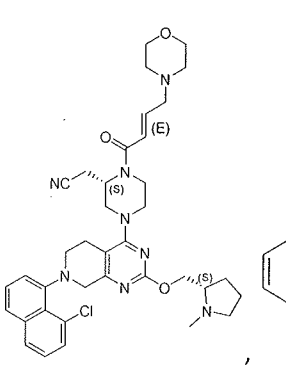
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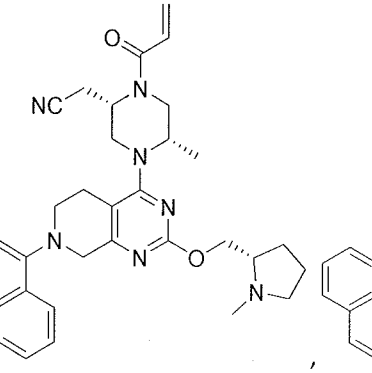
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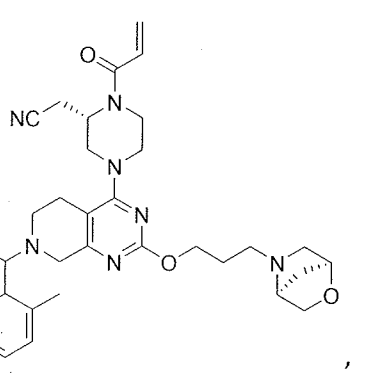
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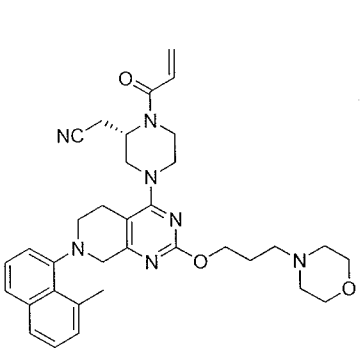
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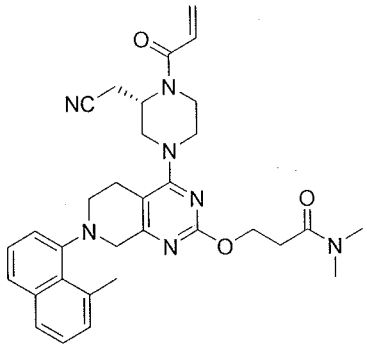
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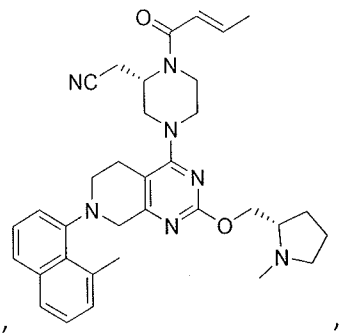
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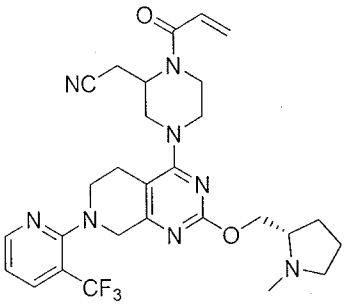
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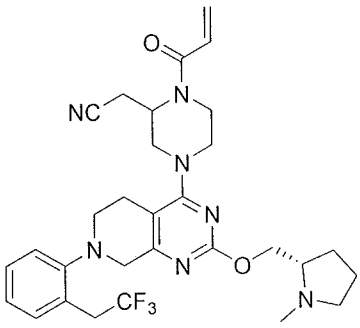
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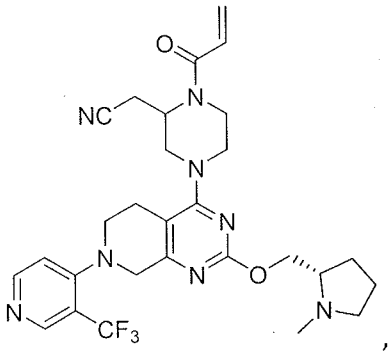
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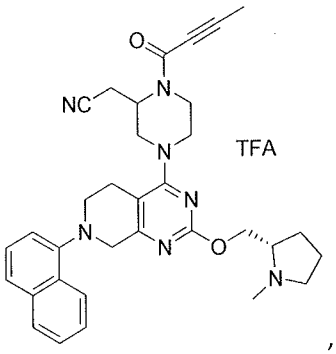
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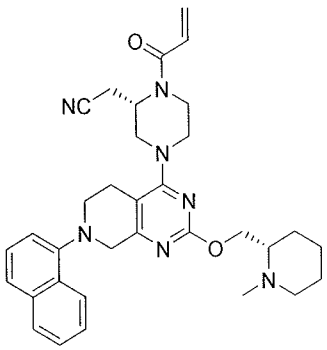
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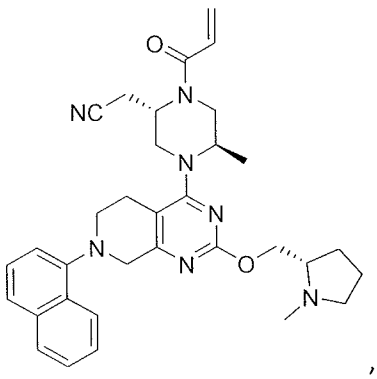
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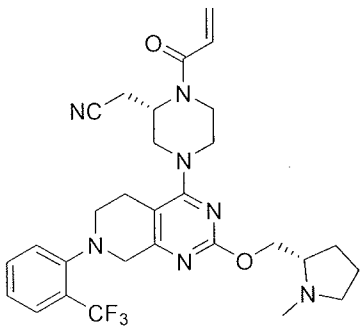
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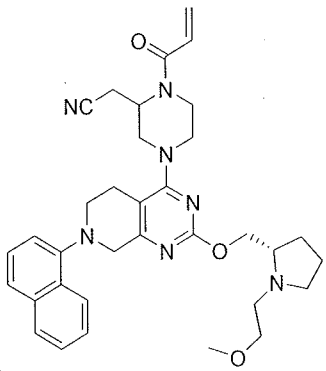
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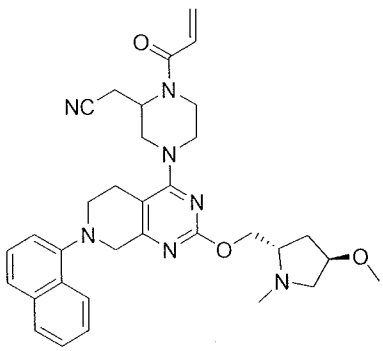
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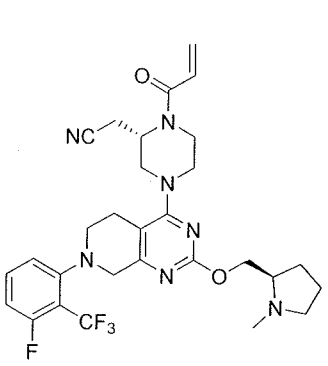
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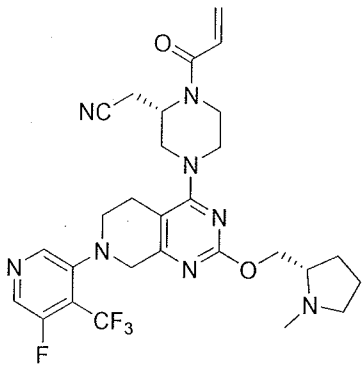
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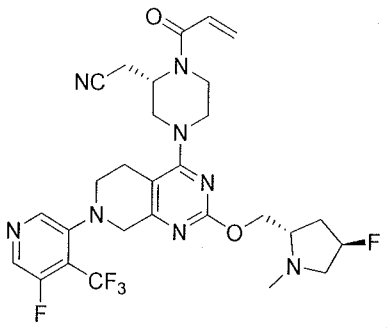
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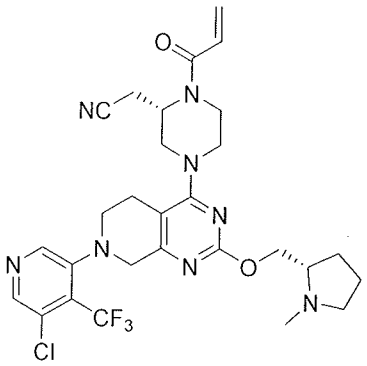
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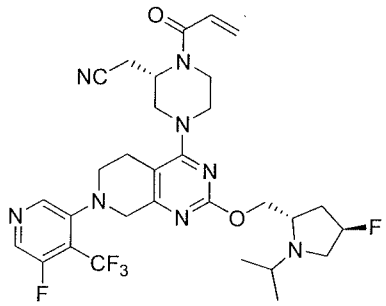
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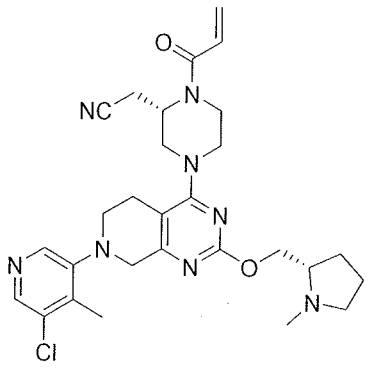
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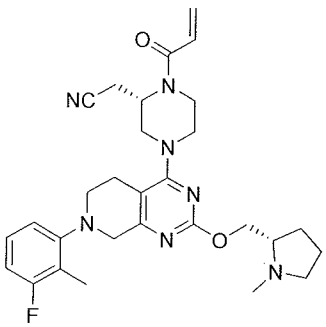
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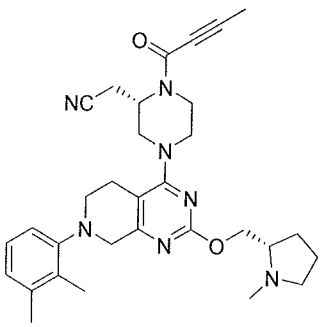
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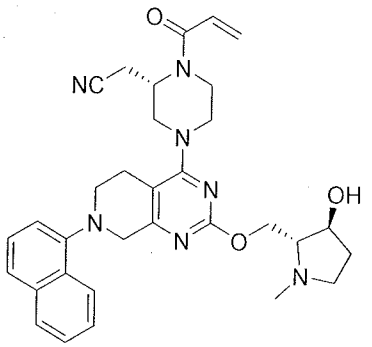
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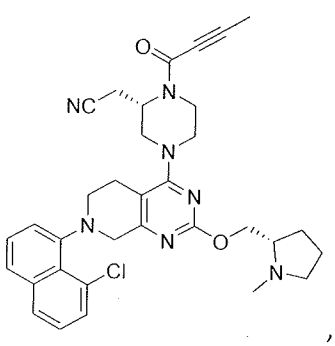
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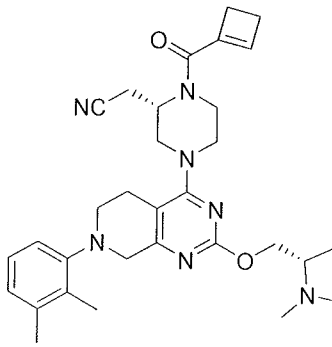
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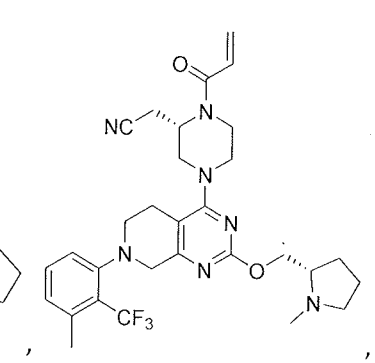
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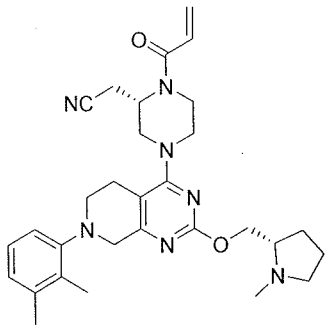
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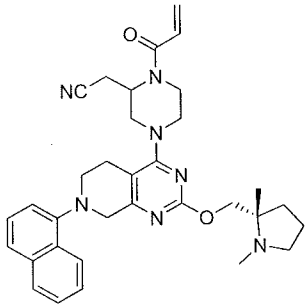
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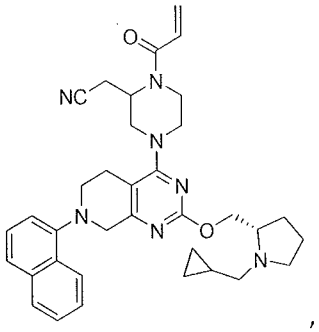
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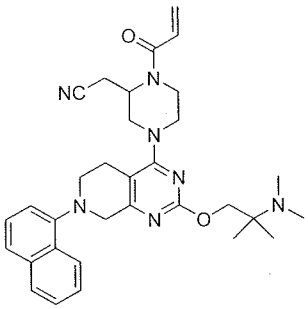
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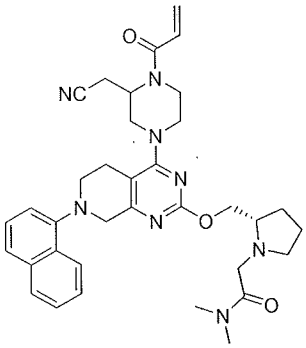
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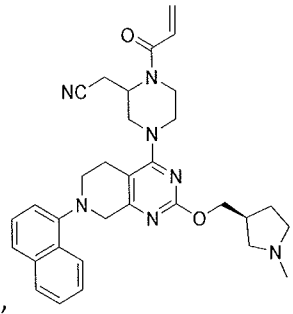
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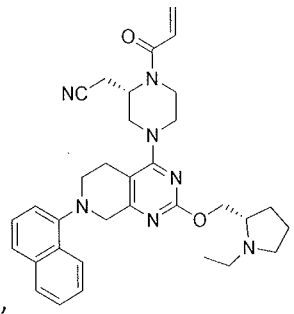
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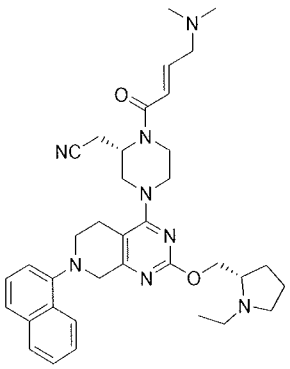
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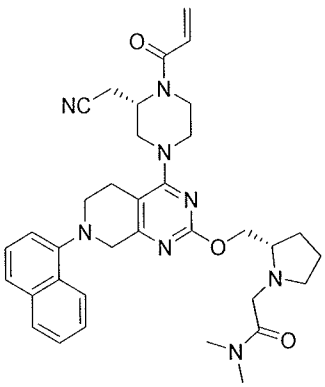
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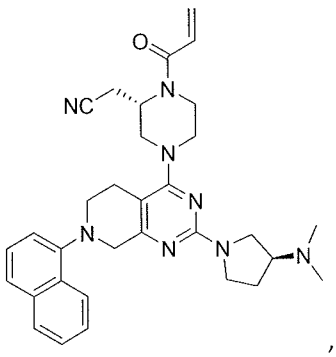
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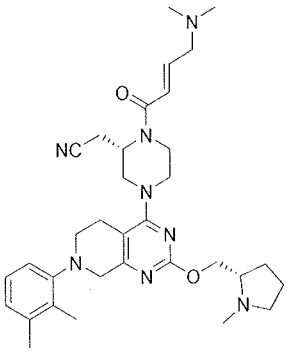
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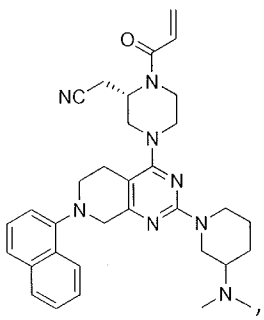
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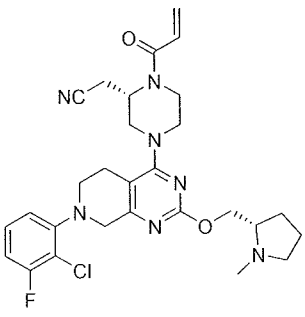
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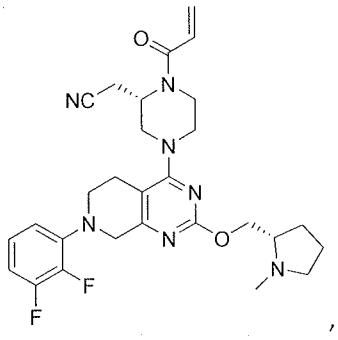
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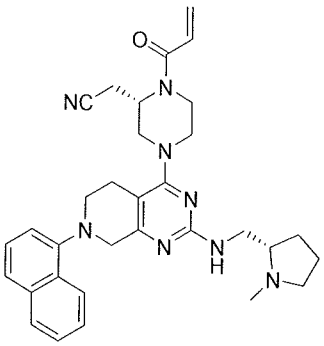
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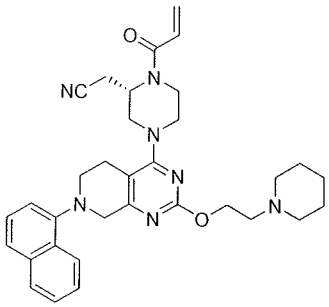
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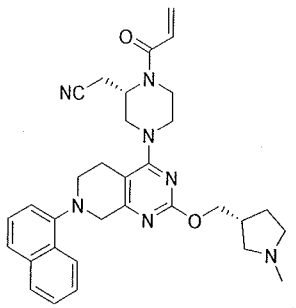
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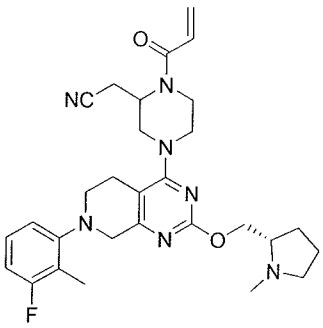
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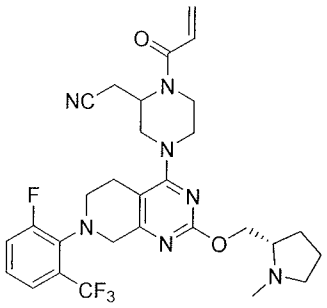
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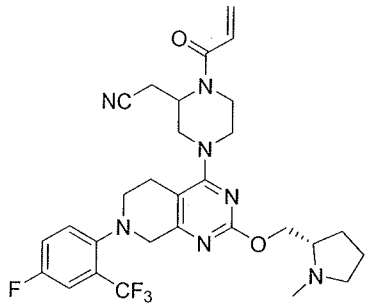
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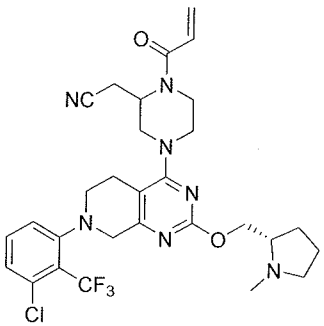
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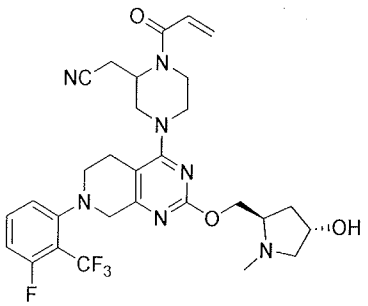
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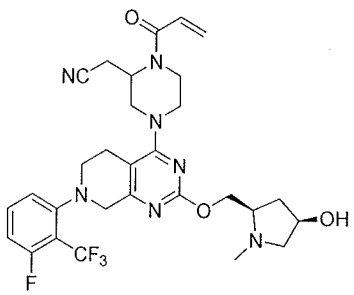
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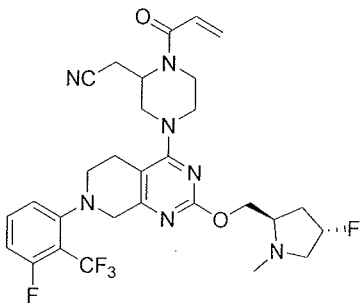
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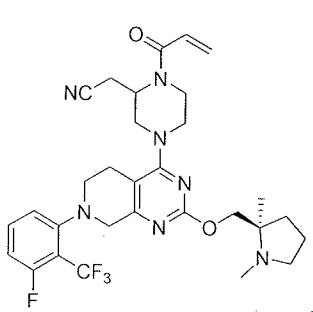
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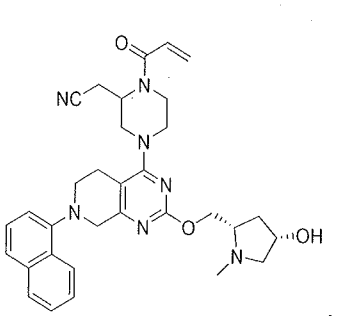
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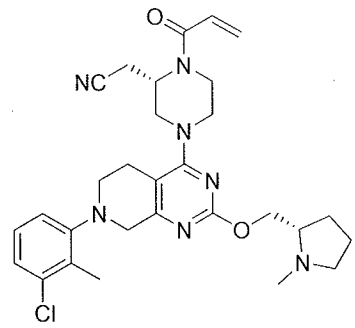
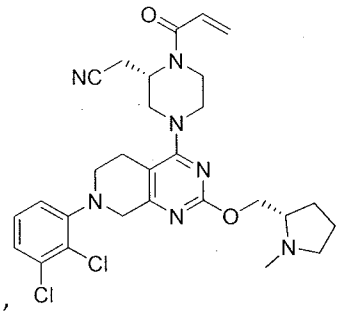
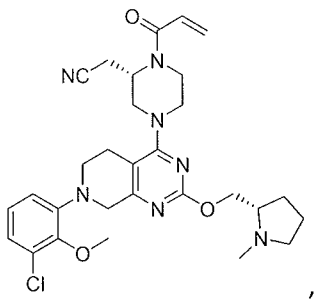
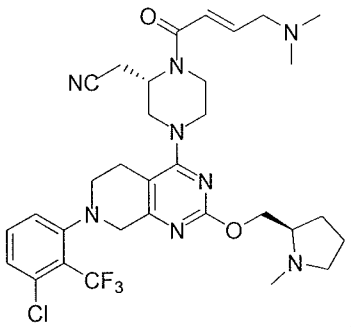
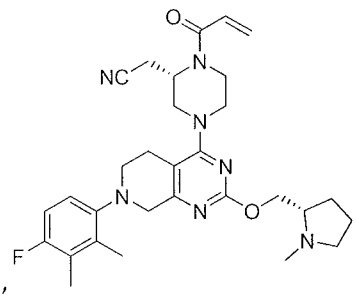
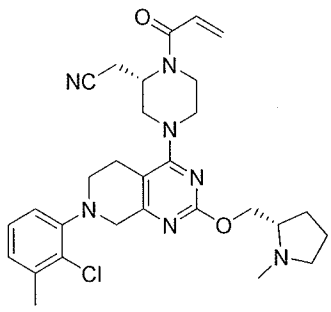
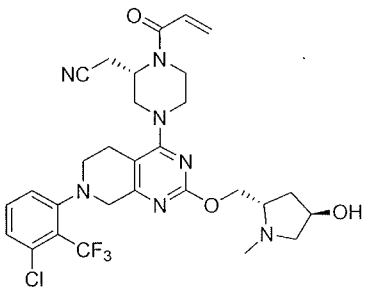
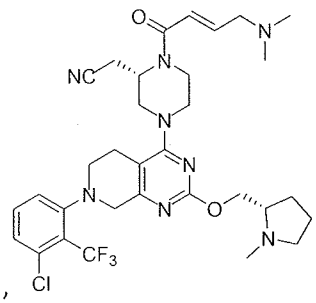
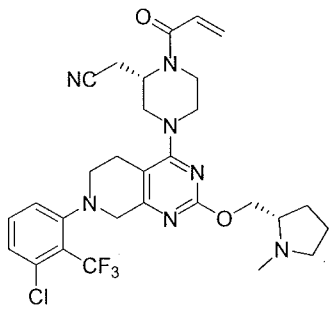
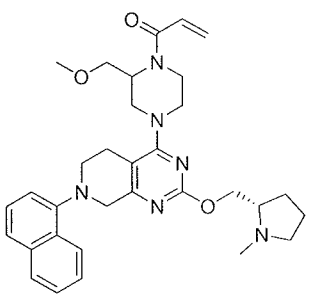
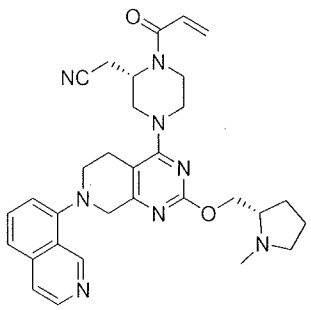
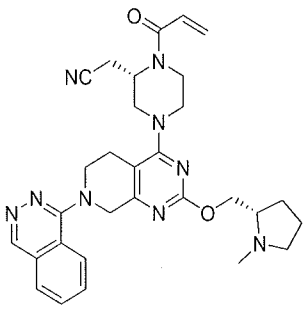
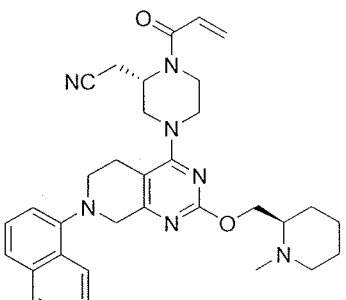
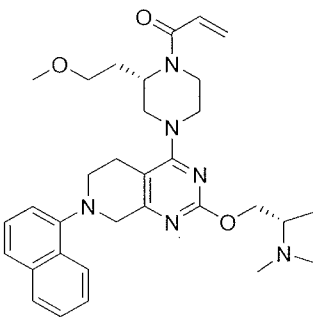
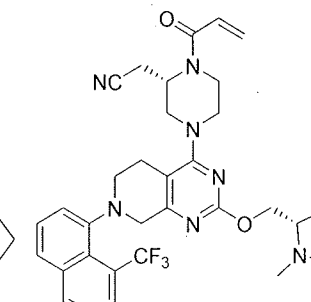

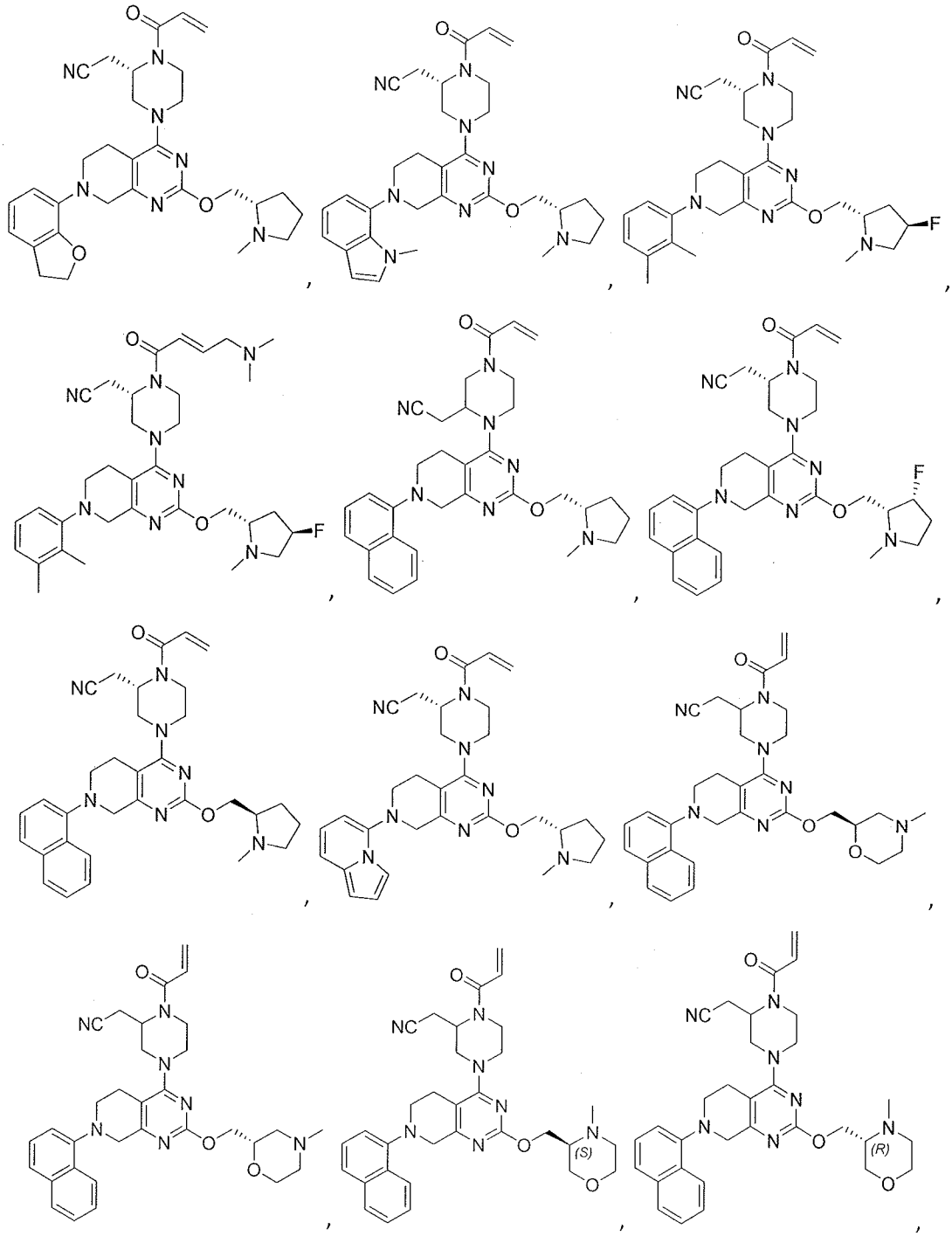

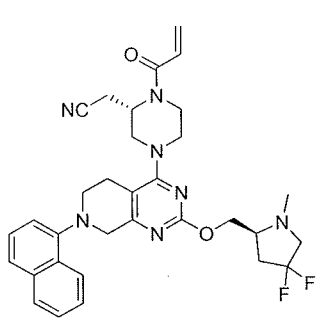
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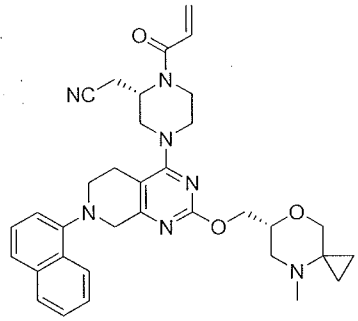
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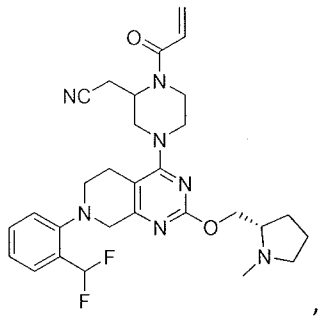
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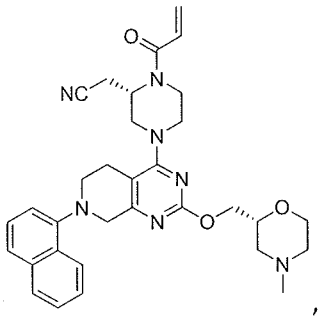
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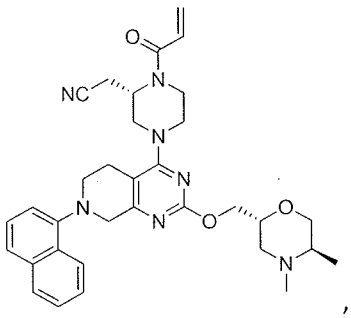
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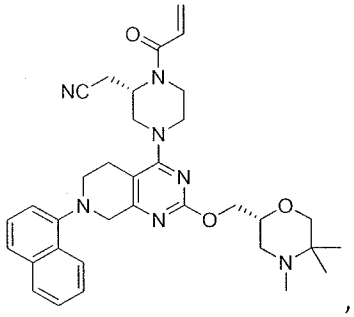
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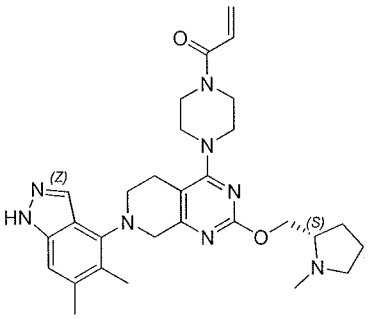
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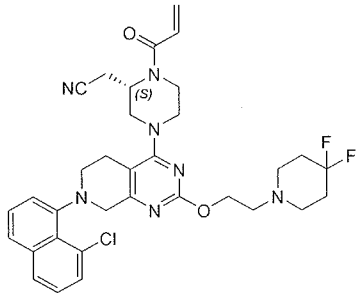
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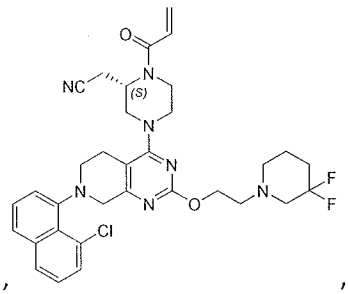
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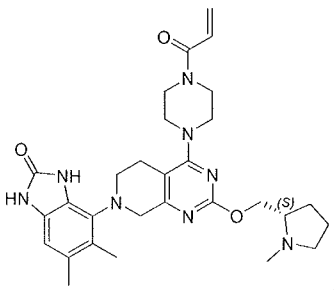
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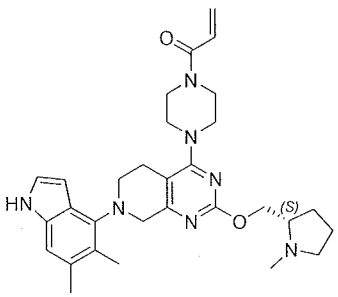
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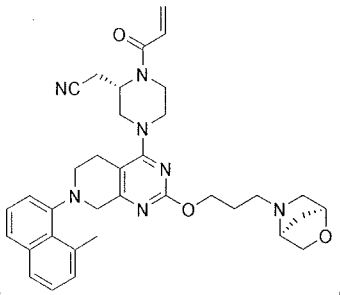
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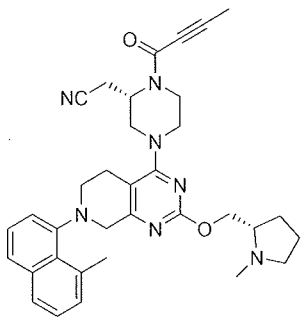
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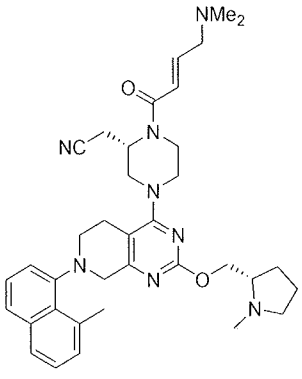
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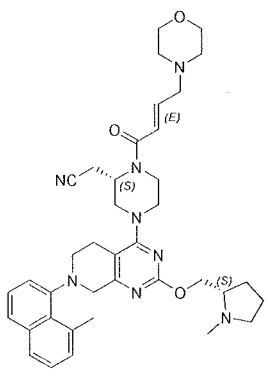
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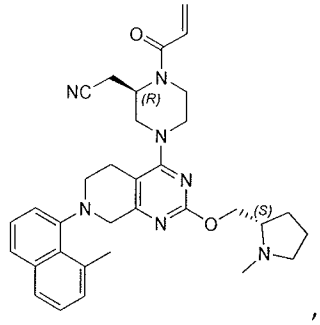
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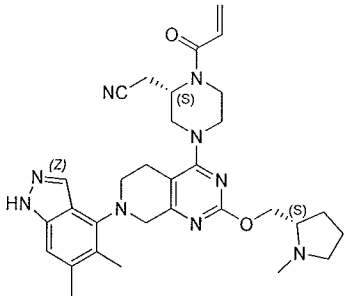
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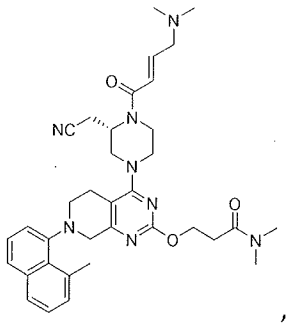
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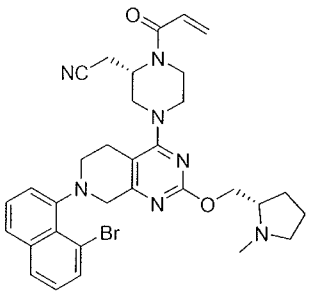
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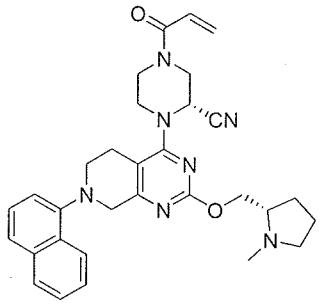
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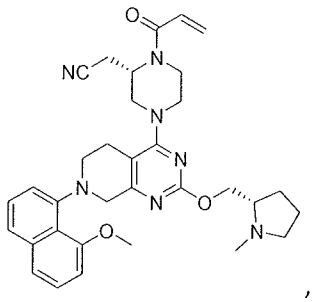
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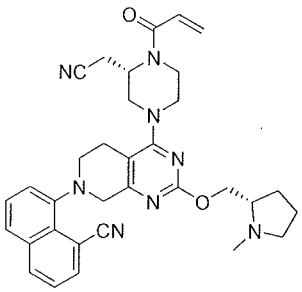
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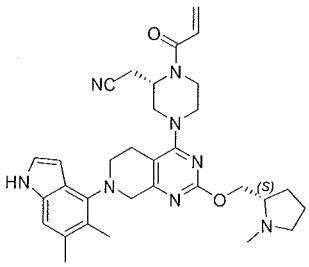
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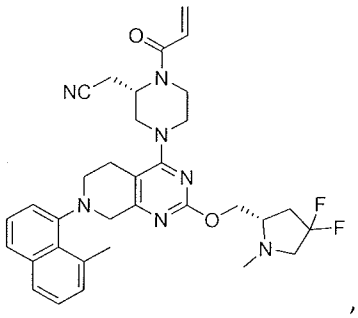
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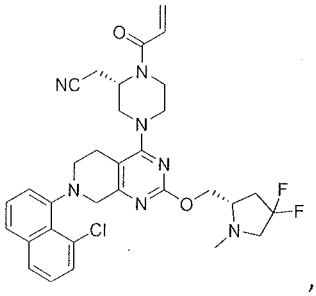
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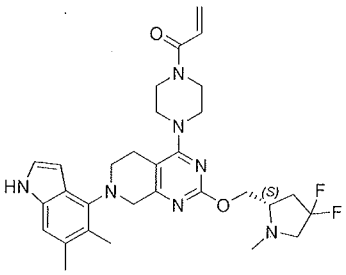
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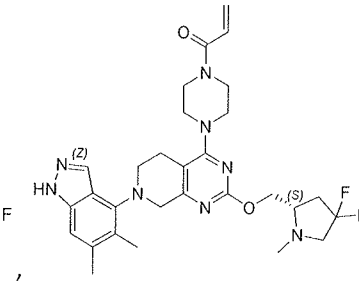
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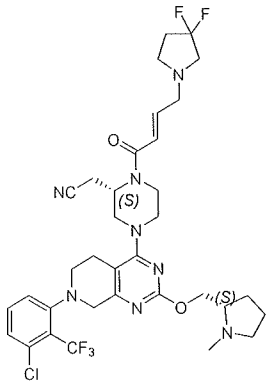
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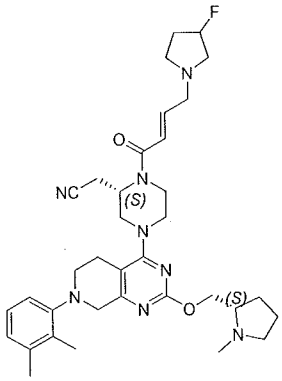
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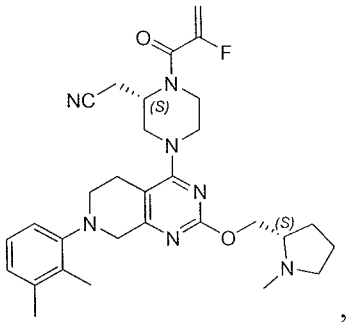
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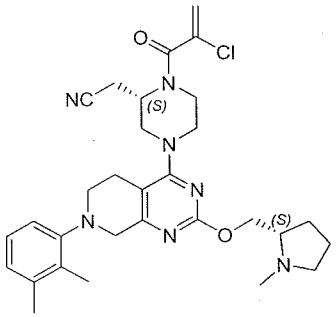
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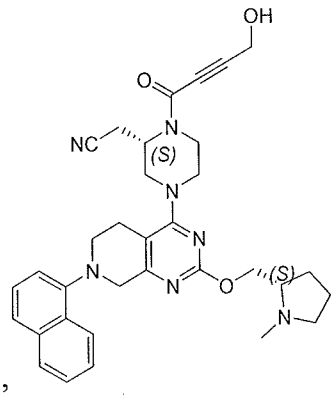
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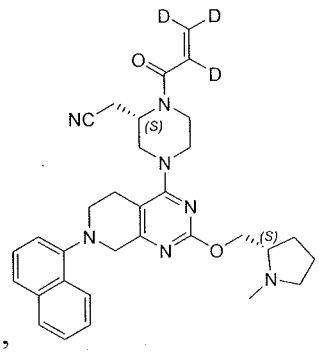
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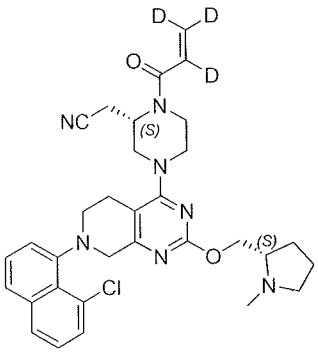
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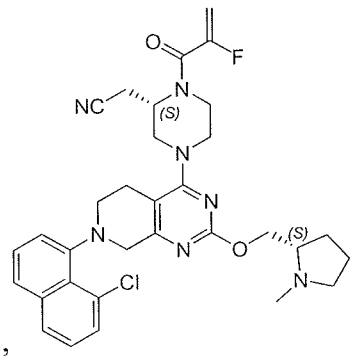
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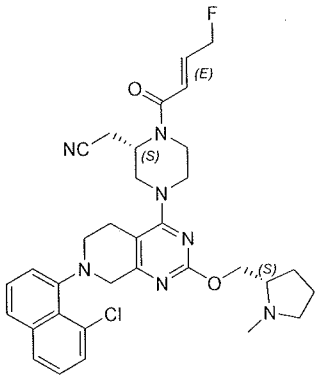
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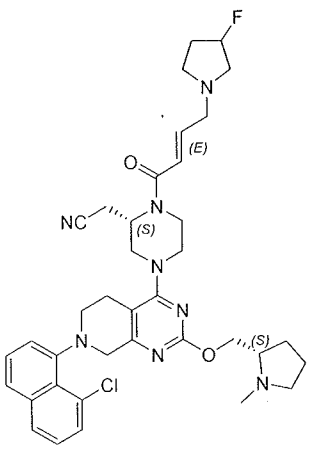
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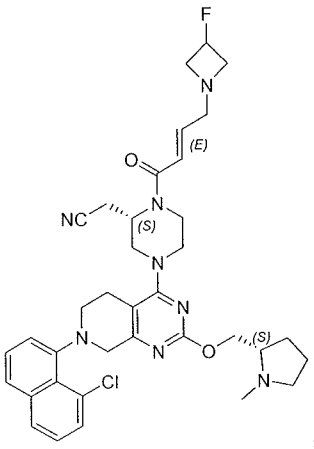
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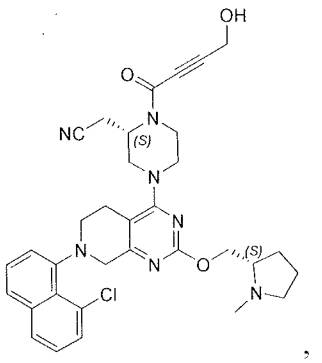
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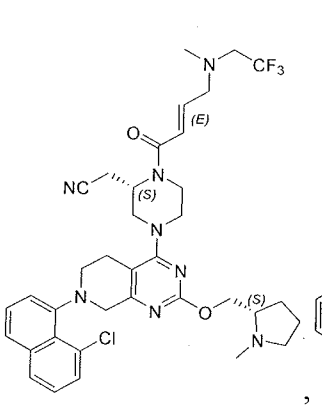
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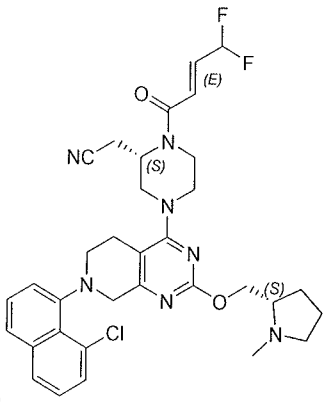
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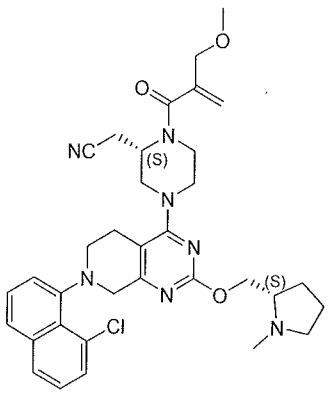
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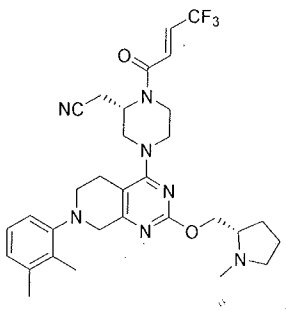
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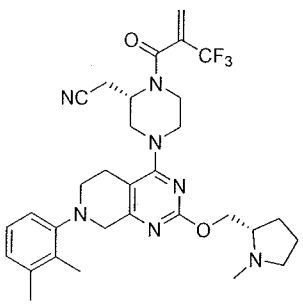
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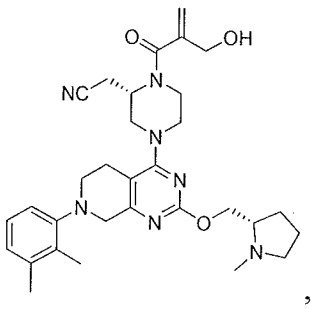
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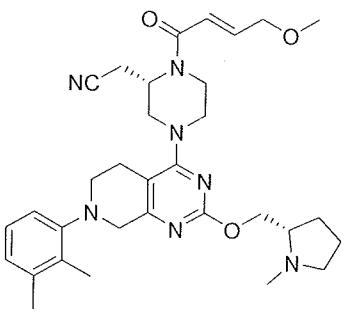
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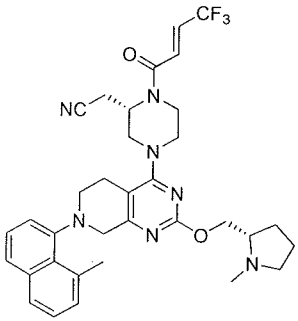
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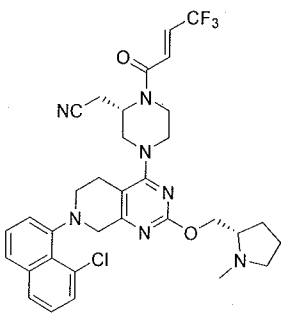
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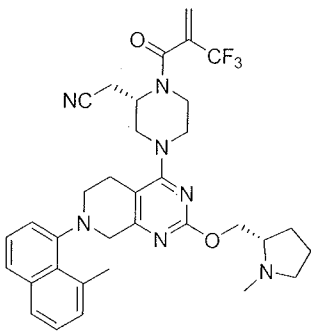
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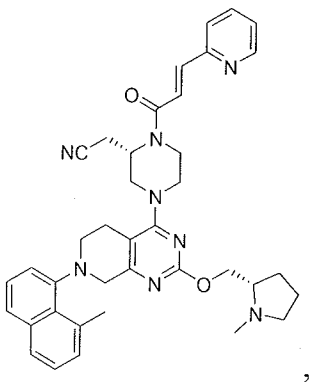
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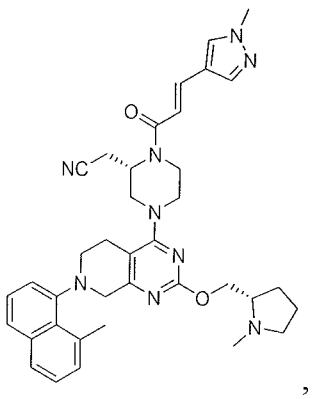
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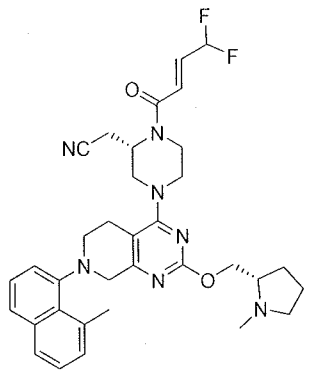
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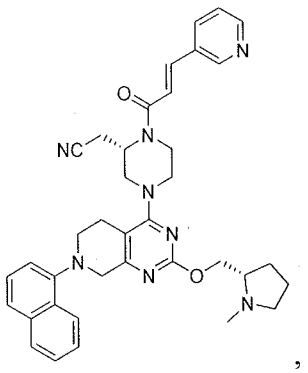
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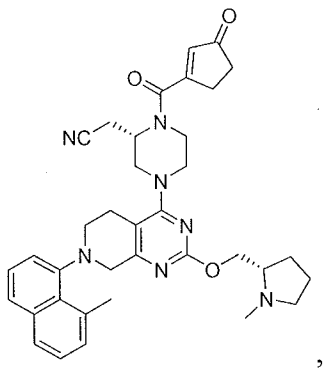
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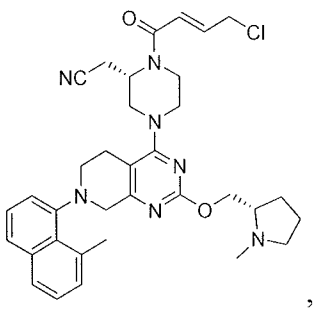
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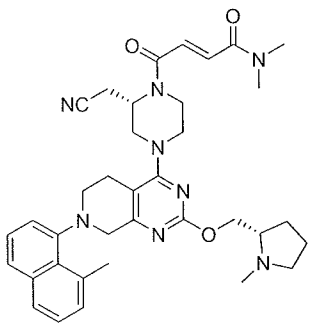
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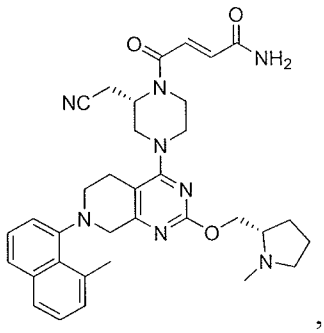
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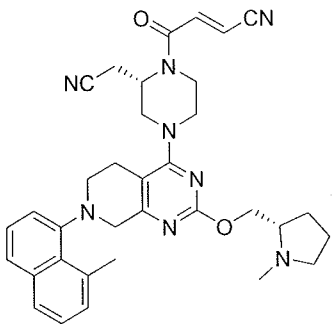
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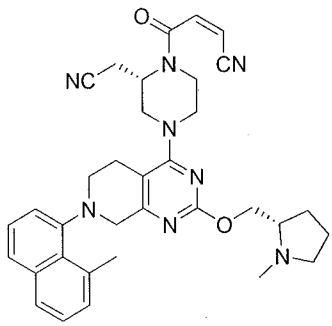
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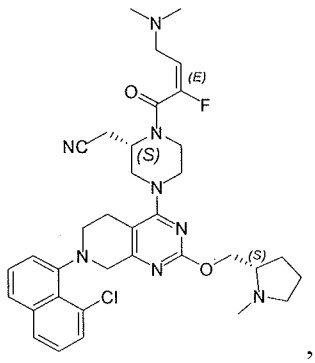
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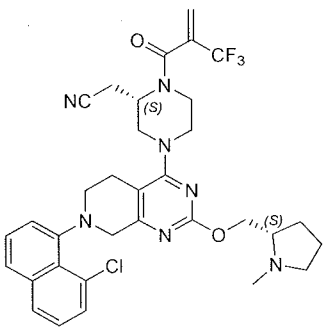
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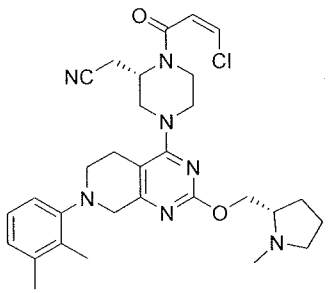
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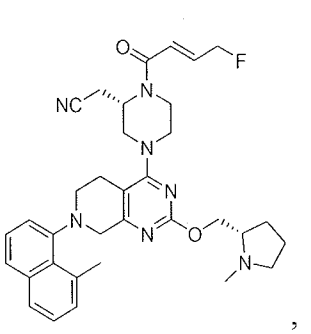
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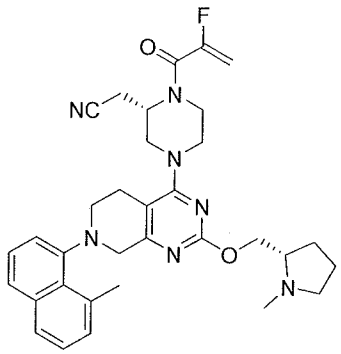
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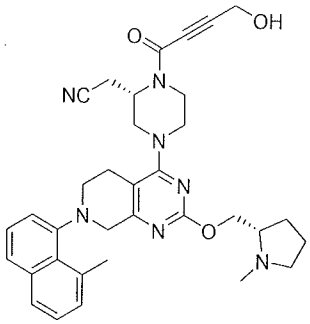
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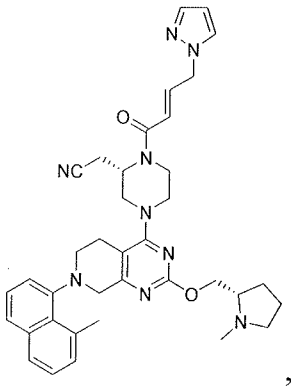
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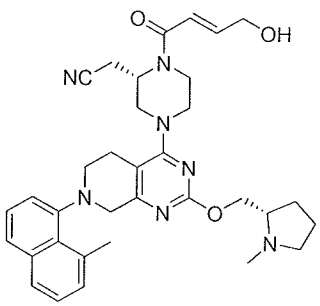
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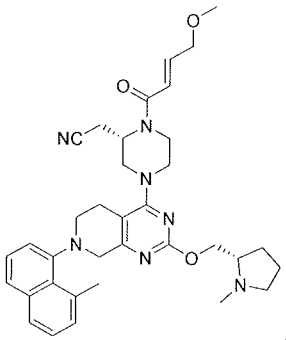
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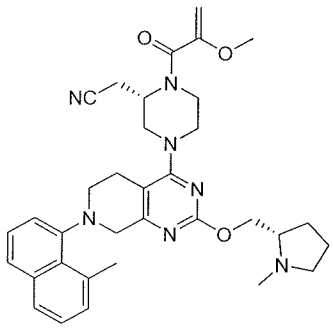
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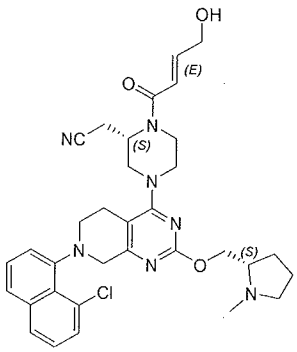
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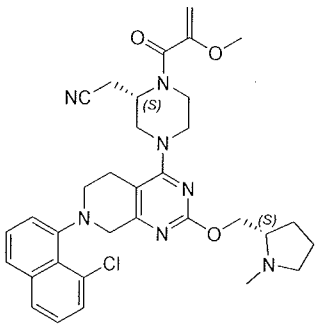
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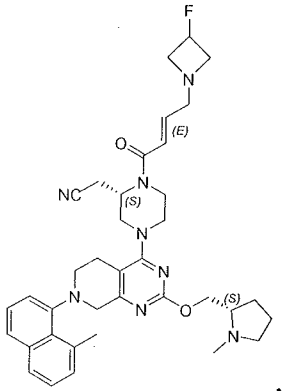
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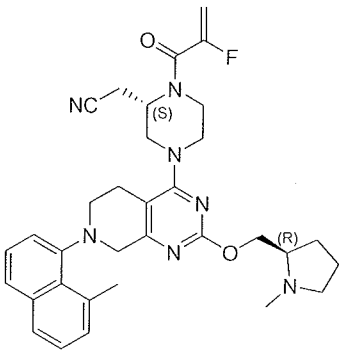
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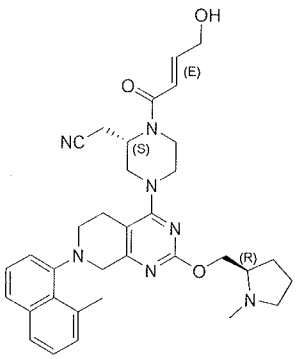
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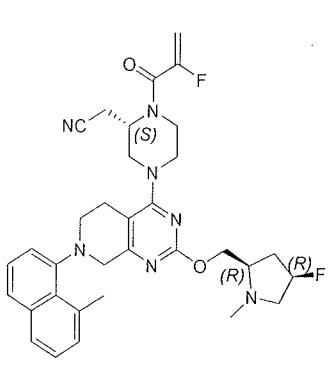
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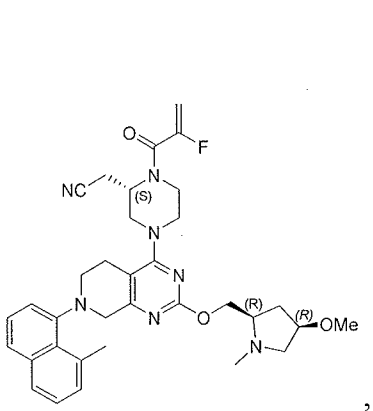
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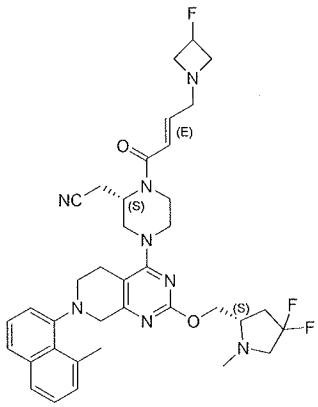
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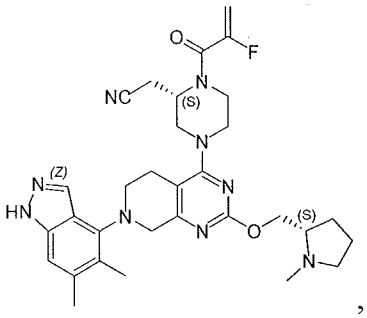
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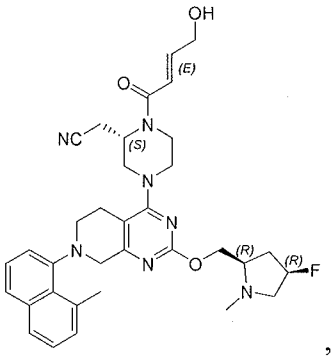
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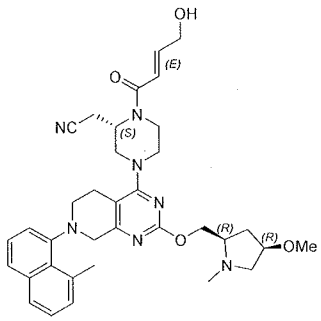
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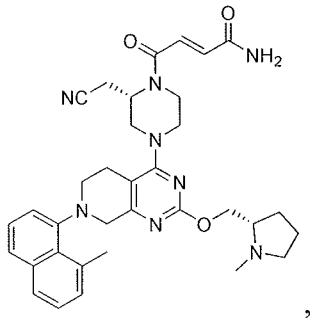
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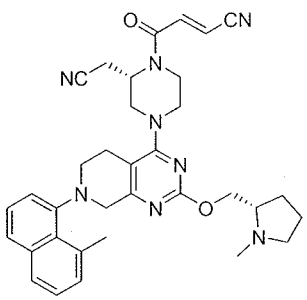
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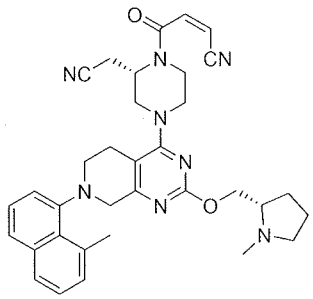
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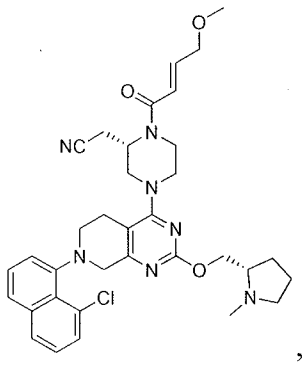
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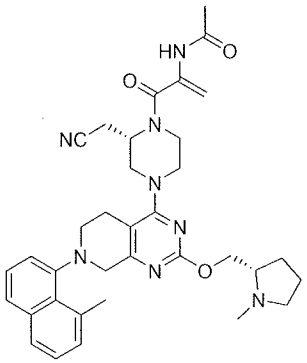
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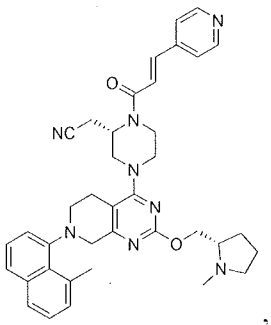
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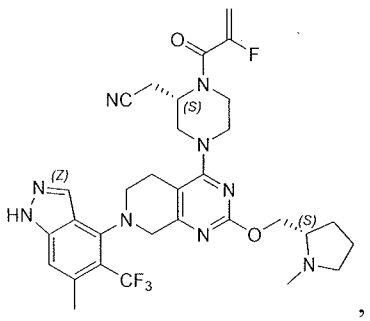
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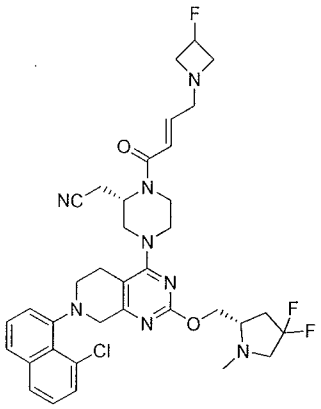
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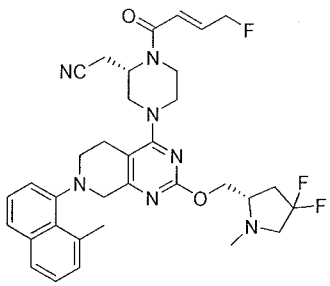
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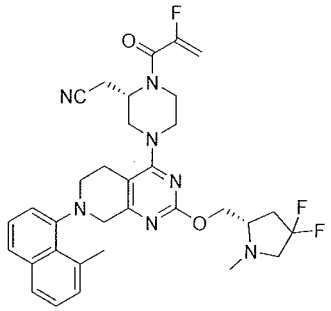
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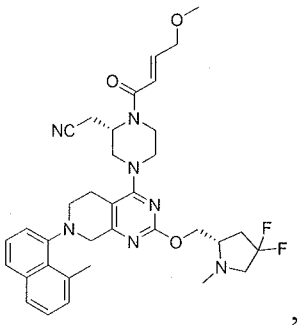
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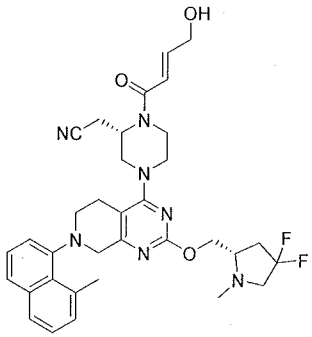
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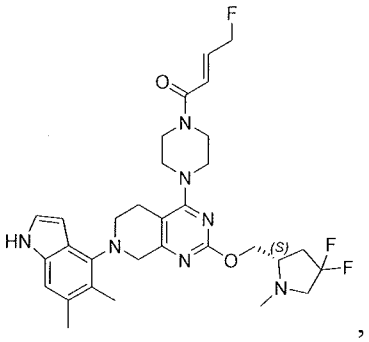
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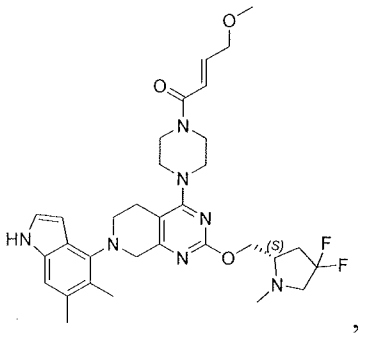
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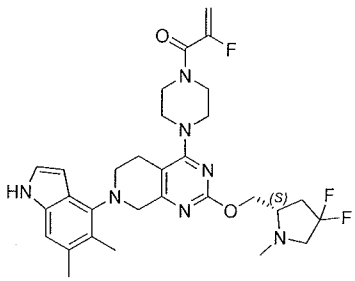
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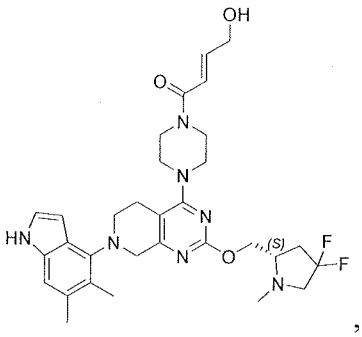
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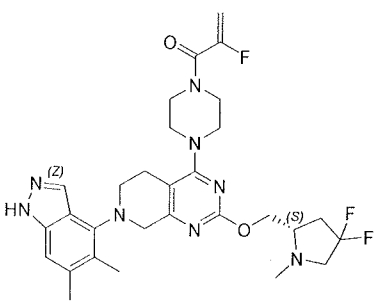
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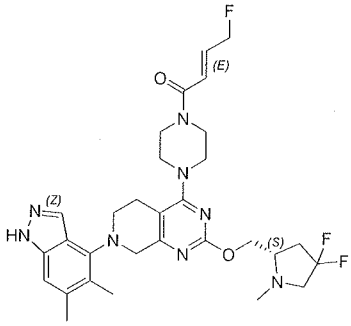
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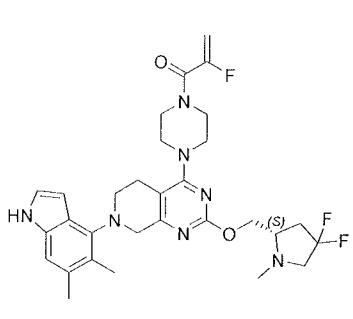
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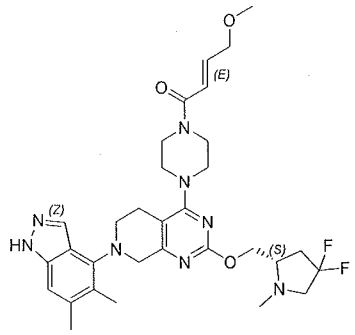
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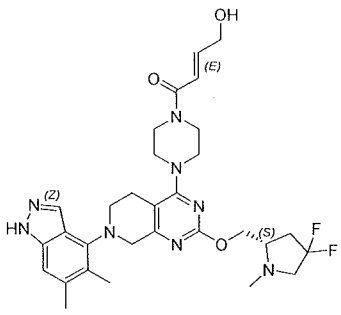
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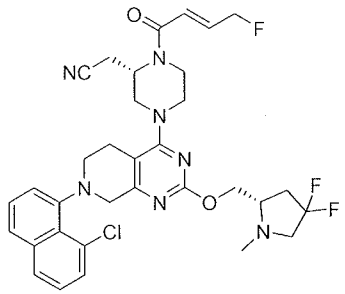
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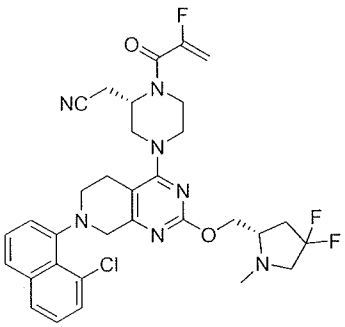
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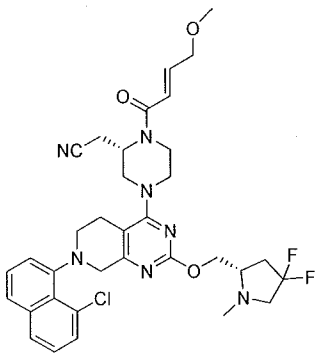
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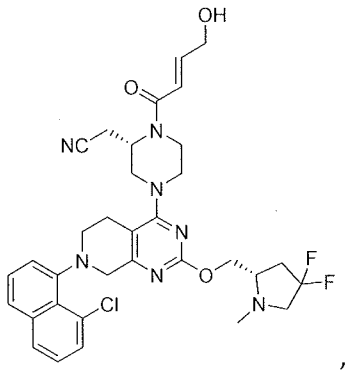
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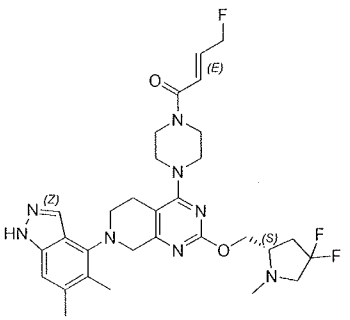
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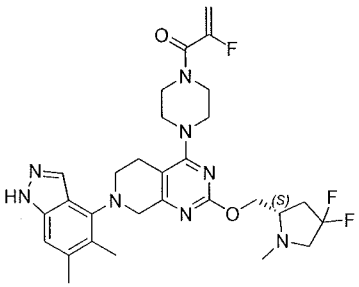
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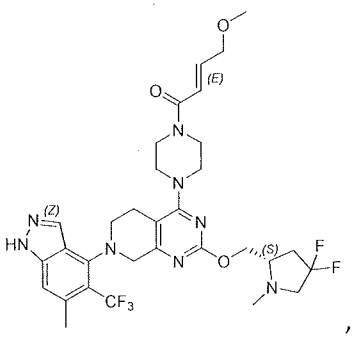
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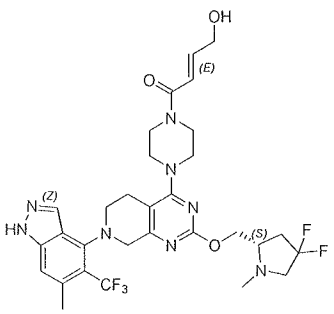
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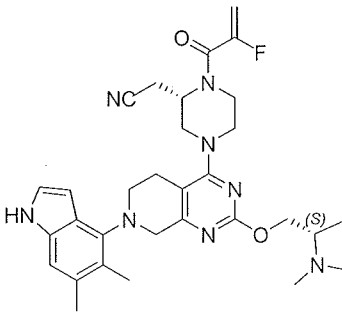
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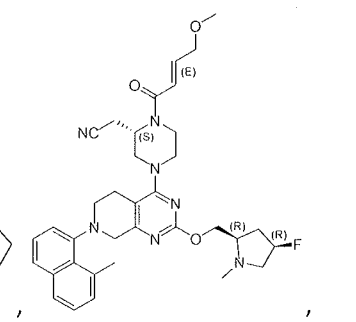
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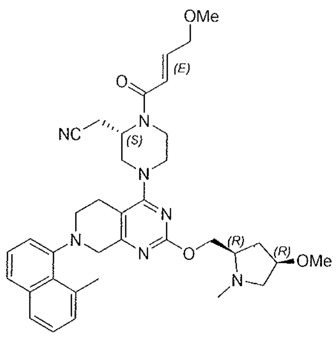
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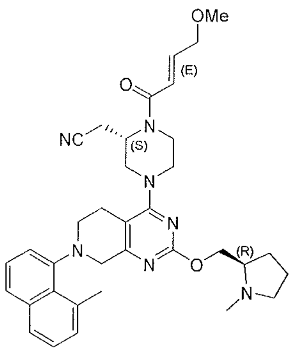
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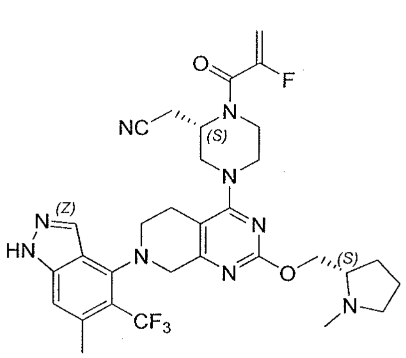
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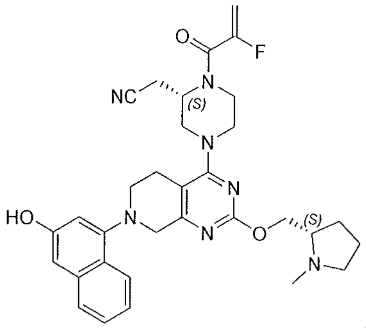
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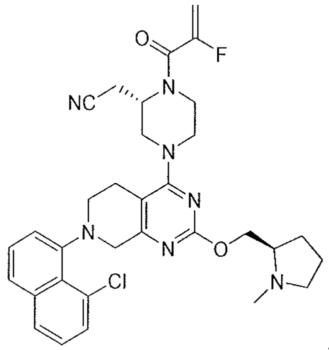
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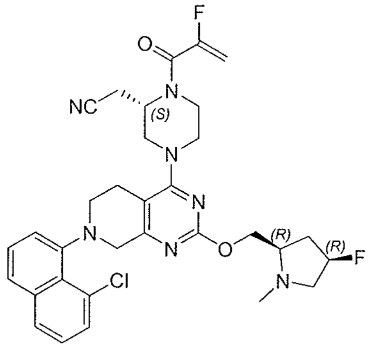
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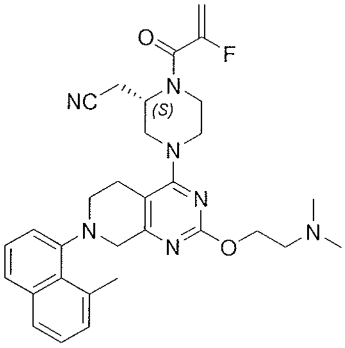
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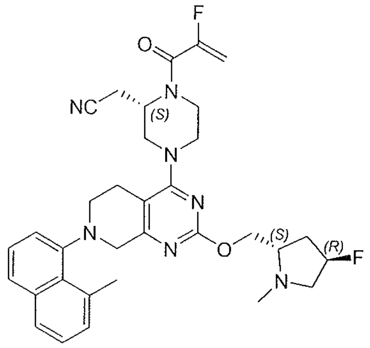
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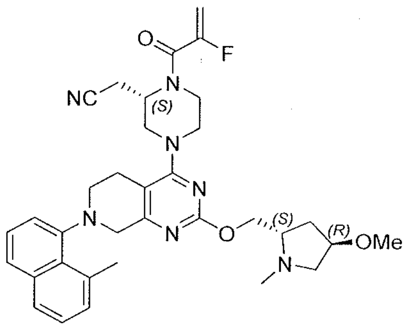
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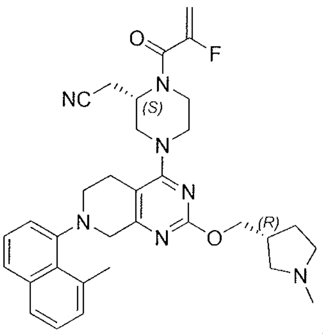
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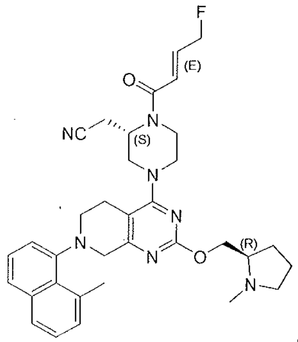
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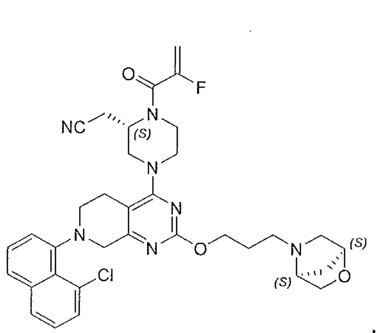
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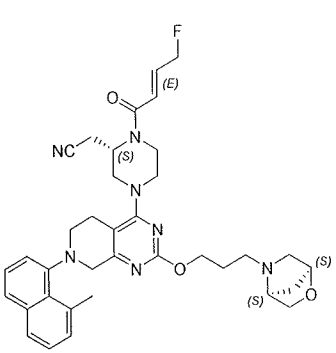
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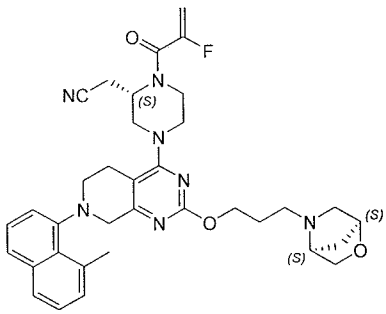
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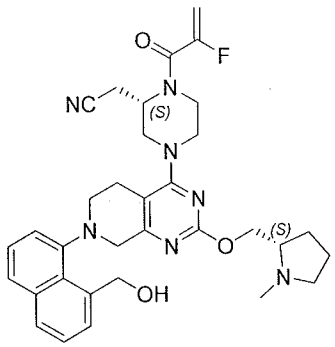
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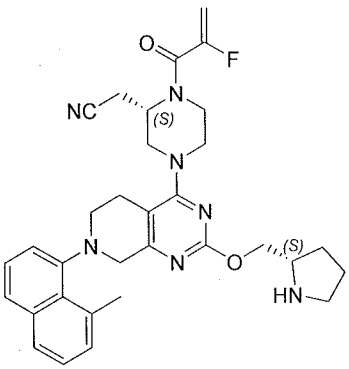
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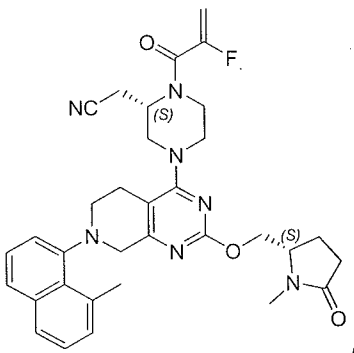
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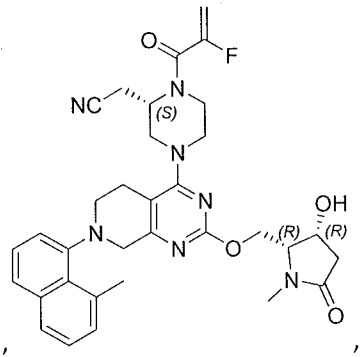
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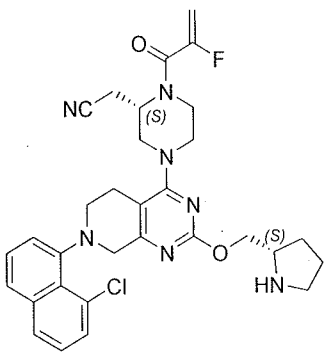
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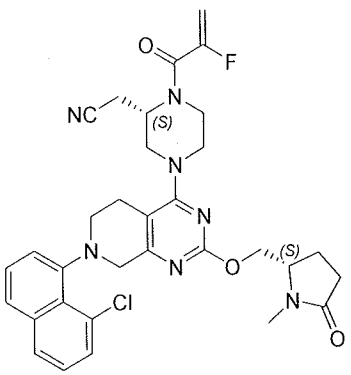
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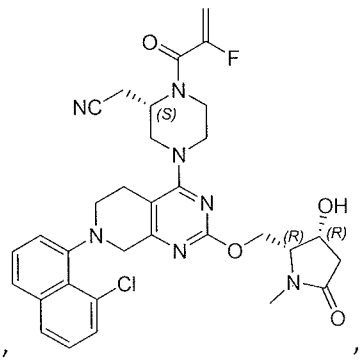
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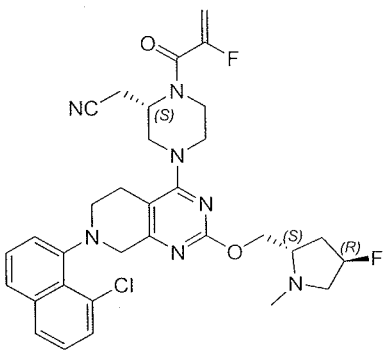
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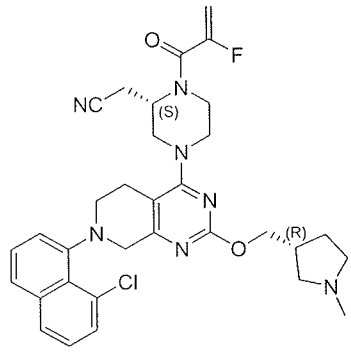
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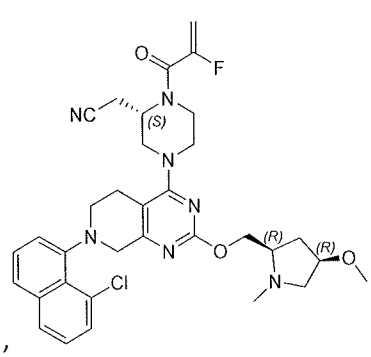
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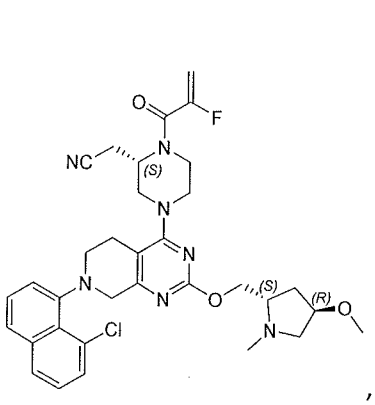
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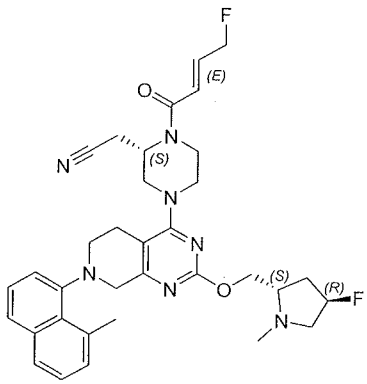
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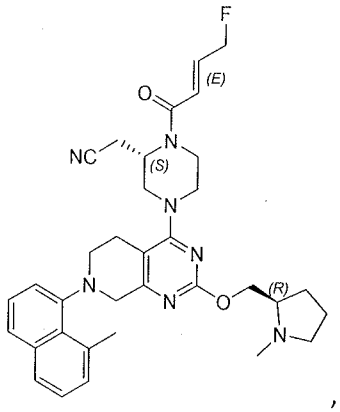
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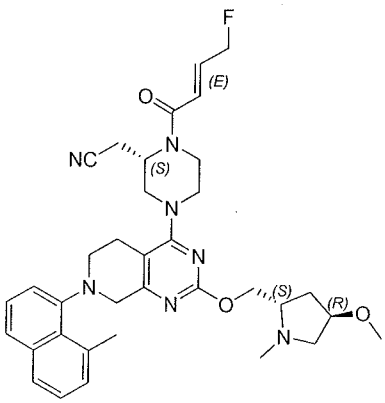
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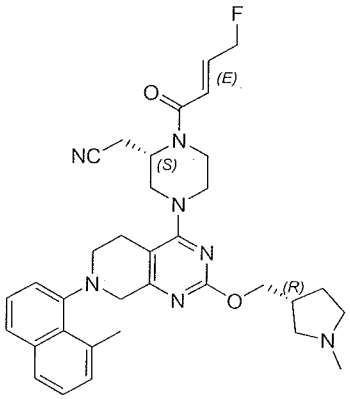
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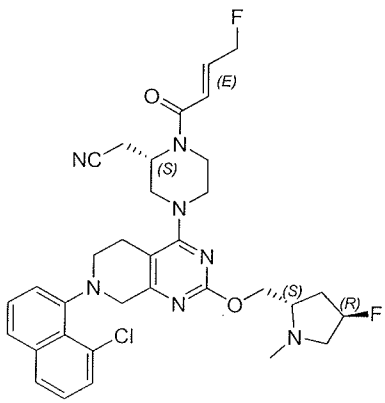
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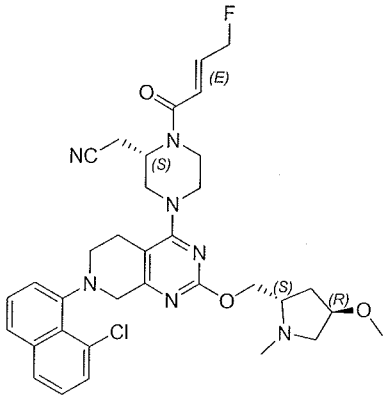
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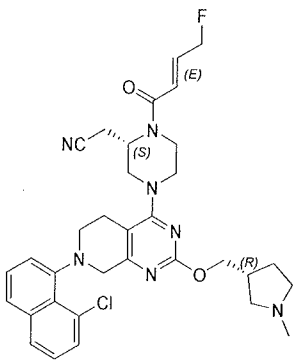
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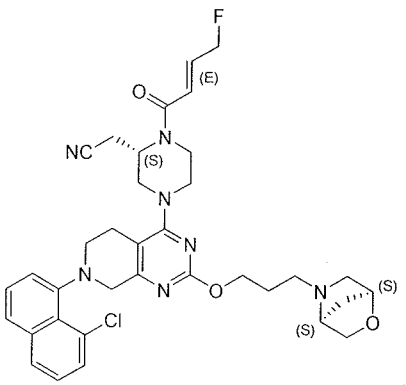
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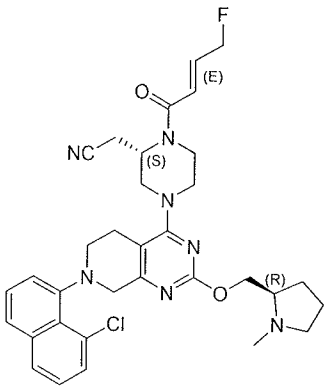
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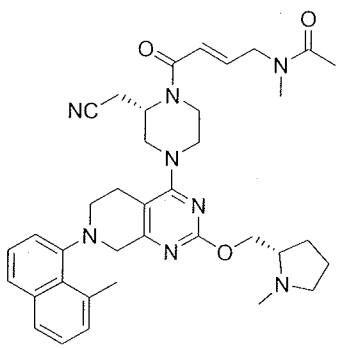
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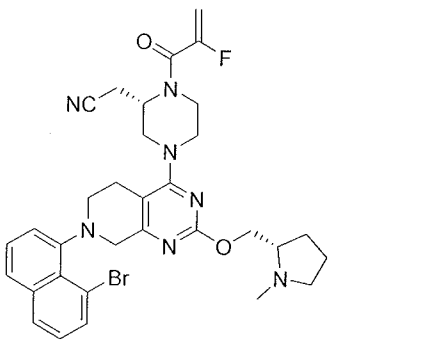
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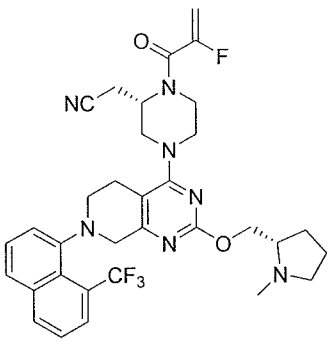
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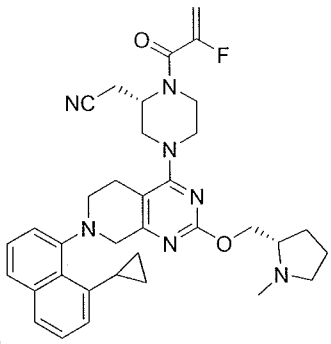
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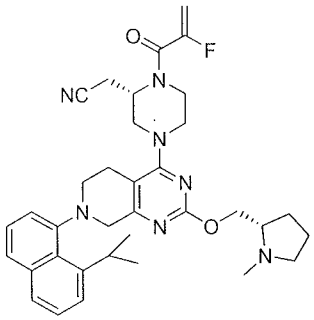
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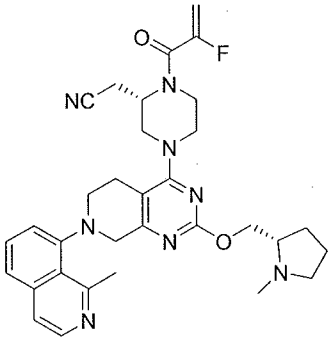
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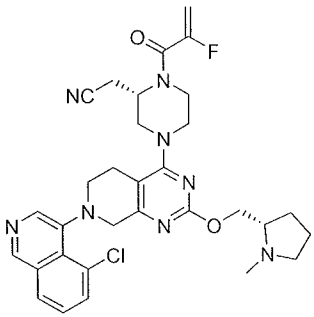
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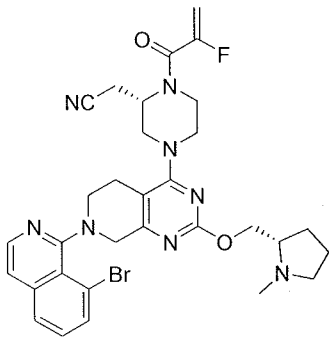
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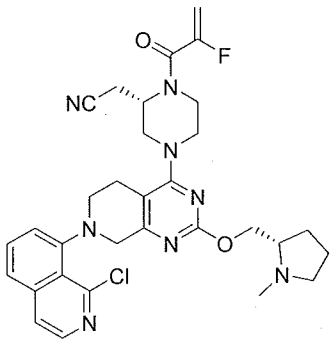
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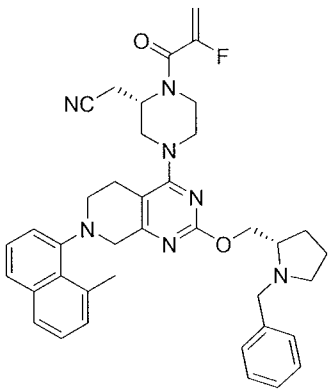
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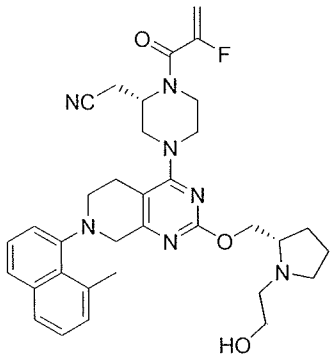
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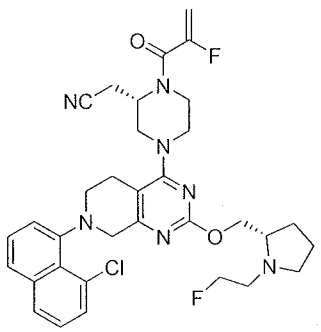
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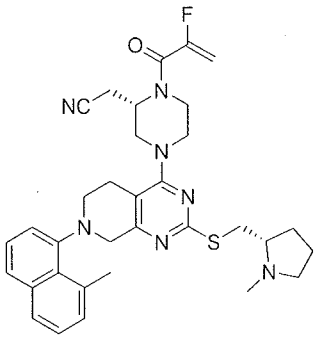
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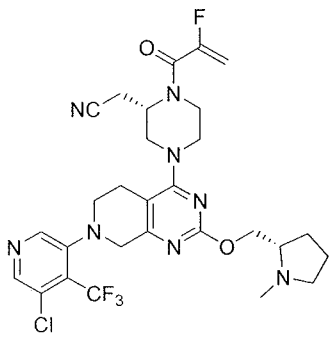
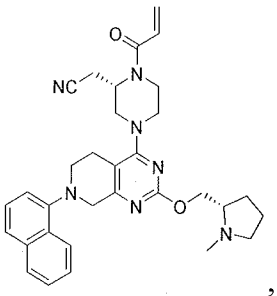


[0125] and pharmaceutically acceptable salts thereof.

[0126] In one embodiment, the KRas G12C inhibitor is selected from: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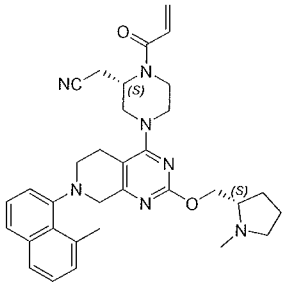
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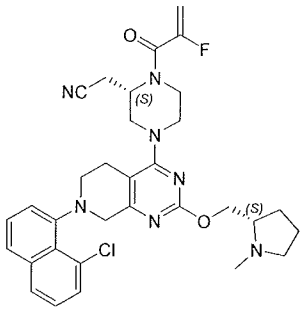
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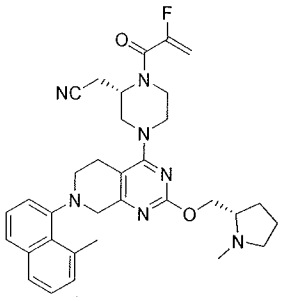
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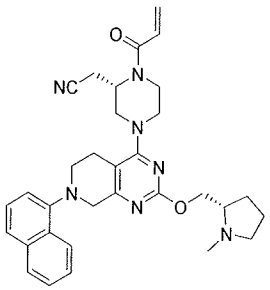
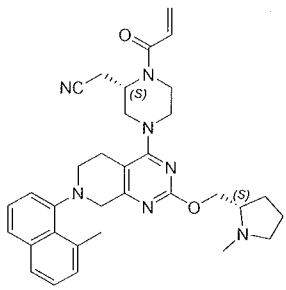
[0127] and pharmaceutically acceptable salts thereof.

[0128] In one embodiment, the KRas G12C inhibitor is:



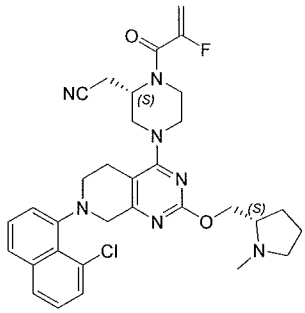
[0129] (also referred to as Example 234) or a pharmaceutically acceptable salt thereof.

[0130] In one embodiment, the KRas G12C inhibitor is:



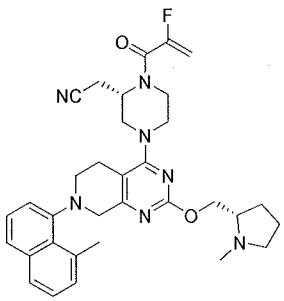
[0131] (also referred to as Example 359) or a pharmaceutically acceptable salt thereof.

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



[0133] (also referred to as Example 478) or a pharmaceutically acceptable salt thereof.

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



[0135] (also referred to as Example 507) or a pharmaceutically acceptable salt thereof.

[0136] 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.

[0137] 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.

[0138] Methods for manufacturing the KRas G12C inhibitors disclosed herein are known. For example, commonly owned published international PCT application numbers WO2017201161 and WO2019099524 describe general reaction schemes for preparing compounds of Formula I, Formula I-A, or Formula I-B and also provide detailed synthetic routes for the preparation of each KRas G12C inhibitor disclosed herein.

[0139] The mTOR inhibitors, or pharmaceutically acceptable salts thereof 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

[0140] In another aspect, the invention provides pharmaceutical compositions comprising a mTOR 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 mTOR 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, mTOR inhibitor and KRas G12C inhibitor are administered intravenously in a hospital setting. In one embodiment, administration may be by the oral route.

[0141] 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.

[0142] 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).

[0143] 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.

[0144] The pharmaceutical compositions comprising a mTOR inhibitor and a KRas G12C inhibitor may be used in the methods of use described herein.

CO-ADMINSTRATION

[0145] The mTOR inhibitor, or a pharmaceutically acceptable salt or pharmaceutical composition thereof, and the KRas G12C inhibitor, or a pharmaceutically acceptable salt or pharmaceutical composition thereof, can be formulated into separate or individual dosage forms

which can be co-administered one after the other. Another option is that if the route of administration is the same (e.g. oral) two active compounds can be formulated into a single form for co-administration, both methods of co-administration, however, being part of the same therapeutic treatment or regimen.

[0146] The pharmaceutical compositions comprising a mTOR inhibitor, or a pharmaceutically acceptable salt or pharmaceutical composition thereof, and/or a KRas G12C inhibitor, or a pharmaceutically acceptable salt or pharmaceutical composition thereof, for use in the methods may be for simultaneous, separate or sequential use. In one embodiment, the mTOR inhibitor, or a pharmaceutically acceptable salt or pharmaceutical composition thereof, is administered prior to administration of the KRas G12C inhibitor compound of Formula (I), Formula I-A or Formula I-B, or a pharmaceutically acceptable salt or pharmaceutical composition thereof. In another embodiment, the mTOR inhibitor, or a pharmaceutically acceptable salt or pharmaceutical composition thereof is administered after administration of the KRas G12C inhibitor compound of Formula (I), Formula I-A or Formula I-B, or a pharmaceutically acceptable salt or pharmaceutical composition thereof. In another embodiment, the mTOR inhibitor, or a pharmaceutically acceptable salt or pharmaceutical composition thereof 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, or a pharmaceutically acceptable salt or pharmaceutical composition thereof.

[0147] 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 or pharmaceutical composition thereof, and the mTOR inhibitor, or a pharmaceutically acceptable salt or pharmaceutical composition thereof, need not be necessarily administered at essentially the same time or in any order.

[0148] 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 and the mTOR inhibitor are each dosed at their respective MTDs. In one embodiment, the KRas G12C inhibitor is dosed at its MTD and the mTOR inhibitor is dosed in an amount less than its MTD. In one embodiment, the KRas G12C

inhibitor is dosed at an amount less than its MTD and the mTOR inhibitor is dosed at its MTD. In one embodiment, the KRas G12C inhibitor and the mTOR inhibitor 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.

[0149] 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 pharmaceutical composition thereof is administered per day (i.e., in about 24 hour intervals) (i.e., QD). In another embodiment, two doses of the KRas G12C inhibitor compound of Formula (I), Formula I-A or Formula I-B, or a pharmaceutically acceptable salt or pharmaceutical composition thereof are administered per day (i.e., BID). In another embodiment, three doses of the KRas G12C inhibitor compound of Formula (I), Formula I-A or Formula I-B, or a pharmaceutically acceptable salt or pharmaceutical composition thereof are administered per day (i.e., TID).

[0150] In one embodiment, the mTOR inhibitor, or a pharmaceutically acceptable salt or pharmaceutical composition thereof is administered QD. In another embodiment, the mTOR inhibitor, or a pharmaceutically acceptable salt or pharmaceutical composition thereof are administered BID. In another embodiment, the mTOR inhibitor, or a pharmaceutically acceptable salt or pharmaceutical composition thereof of the invention are administered TID.

[0151] 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 pharmaceutical composition thereof, and mTOR inhibitor, or a pharmaceutically acceptable salt or pharmaceutical composition thereof, are each administered once daily.

[0152] In one embodiment, the mTOR inhibitor and the KRAS G12C inhibitor are administered on the same day.

[0153] In one embodiment, the mTOR inhibitor and the KRAS G12C inhibitor are administered on different days.

[0154] . A number of suitable mTOR inhibitors may be used in the compositions and methods disclosed herein. Exemplary irreversible mTOR inhibitors for use in the methods include, but are not limited to, everolimus, rapamycin, zotarolimus (ABT-578), ridaforolimus (Deforolimus;

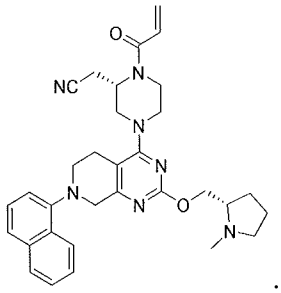
MK-8669), sapanisertib (INK128; 5-(4-amino-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-3-yl)benzo[d]oxazol-2-amine, Torin-1; 1-(4-(4-propionylpiperazin-1-yl)-3-(trifluoromethyl)cyclohexyl)-9-(quinolin-3-yl)benzo[h][1,6]naphthyridin-2(1H)-one), dactolisib (BEZ235); 2-methyl-2-(4-(3-methyl-2-oxo-8-(quinolin-3-yl)-2,3-dihydro-1H-imidazo[4,5-c]quinolin-1-yl)phenyl)propanenitrile, GDC-0349 ((S)-1-ethyl-3-(4-(4-(3-methylmorpholino)-7-(oxetan-3-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-2-yl)phenyl)urea), VS-5584 (SB2343) (5-(8-methyl-2-morpholin-4-yl-9-propan-2-ylpurin-6-yl)pyrimidin-2-amine) and vistusertib (AZD-2014; 3-(2,4-bis((S)-3-methylmorpholino)pyrido[2,3-d]pyrimidin-7-yl)-N-methylbenzamide).

COMBINATION THERAPIES

[0155] 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 mTOR inhibitor, or a pharmaceutically acceptable salt or pharmaceutical composition thereof, and a KRAS G12C inhibitor of Formula (I), Formula I-A or Formula I-B, or a pharmaceutically acceptable salt or 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.

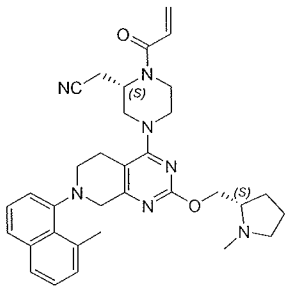
[0156] In yet another aspect, the invention provides for methods for increasing the sensitivity of a cancer cell to a KRas G12C inhibitor, comprising contacting the cancer cell with an effective amount of a combination of a KRas G12C inhibitor compound of Formula (I), Formula I-A, or Formula I-B, or a pharmaceutically acceptable salt or pharmaceutical composition thereof, and a mTOR inhibitor, or a pharmaceutically acceptable salt or a pharmaceutical composition thereof, wherein the mTOR 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.

[0157] In one embodiment, the combination therapy comprises a combination of a compound having the formula:



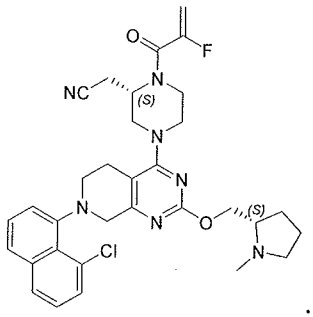
[0158] or a pharmaceutically acceptable salt thereof, and an mTOR inhibitor. In one embodiment, the mTOR inhibitor is everolimus. In one embodiment, the mTOR inhibitor is rapamycin. In one embodiment, the mTOR inhibitor is sapanisertib. In one embodiment, the mTOR inhibitor is Torin-1. In one embodiment, the mTOR inhibitor is dactolisib. In one embodiment, the mTOR inhibitor is BEZ235. In one embodiment, the mTOR inhibitor is buparlisib. In one embodiment, the mTOR inhibitor is GDC-0941. In one embodiment, the mTOR inhibitor is vistusertib.

[0159] In one embodiment, the combination therapy comprises a combination of a compound having the formula:



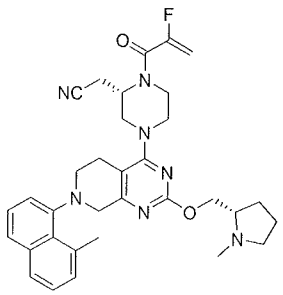
[0160] or a pharmaceutically acceptable salt thereof, and an mTOR inhibitor. In one embodiment, the mTOR inhibitor is everolimus. In one embodiment, the mTOR inhibitor is rapamycin. In one embodiment, the mTOR inhibitor is sapanisertib. In one embodiment, the mTOR inhibitor is Torin-1. In one embodiment, the mTOR inhibitor is dactolisib. In one embodiment, the mTOR inhibitor is BEZ235. In one embodiment, the mTOR inhibitor is buparlisib. In one embodiment, the mTOR inhibitor is GDC-0941. In one embodiment, the mTOR inhibitor is vistusertib.

[0161] In one embodiment, the combination therapy comprises a combination of a compound having the formula:



[0162] or a pharmaceutically acceptable salt thereof, and an mTOR inhibitor. In one embodiment, the mTOR inhibitor is everolimus. In one embodiment, the mTOR inhibitor is rapamycin. In one embodiment, the mTOR inhibitor is sapanisertib. In one embodiment, the mTOR inhibitor is Torin-1. In one embodiment, the mTOR inhibitor is dactolisib. In one embodiment, the mTOR inhibitor is BEZ235. In one embodiment, the mTOR inhibitor is buparlisib. In one embodiment, the mTOR inhibitor is GDC-0941. In one embodiment, the mTOR inhibitor is vistusertib.

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



[0164] or a pharmaceutically acceptable salt thereof, and an mTOR inhibitor. In one embodiment, the mTOR inhibitor is everolimus. In one embodiment, the mTOR inhibitor is rapamycin. In one embodiment, the mTOR inhibitor is sapanisertib. In one embodiment, the mTOR inhibitor is Torin-1. In one embodiment, the mTOR inhibitor is dactolisib. In one embodiment, the mTOR inhibitor is BEZ235. In one embodiment, the mTOR inhibitor is

buparlisib. In one embodiment, the mTOR inhibitor is GDC-0941. In one embodiment, the mTOR inhibitor is vistusertib.

[0165] 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.

[0166] 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.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 mTOR inhibitor, or a pharmaceutically acceptable salt or 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, wherein the mTOR 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.

[0167] In one embodiment, the therapeutically effective amount of the combination of a mTOR inhibitor, or a pharmaceutically acceptable salt or 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 G12 inhibitor. In one embodiment, the therapeutically effective amount of the combination of a mTOR inhibitor, or a pharmaceutically acceptable salt or 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 mTOR inhibitor, or a pharmaceutically acceptable salt or 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 mTOR inhibitor, or a pharmaceutically acceptable salt or 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 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 mTOR inhibitor is selected from everolimus, rapamycin, sapanisertib, Torin-1, dactolisib, BEZ235, buparlisib, GDC-0941 and vistusertib. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 234 and everolimus. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 234 and rapamycin. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 234 and sapanisertib. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 234 and Torin-1. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 234 and dactolisib. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 234 and BEZ235. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 234 and buparlisib. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 234 and GDC-0941. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 234 and

vistusertib. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 359 and everolimus. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 359 and rapamycin. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 359 and sapanisertib. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 359 and Torin-1. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 359 and dactolisib. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 359 and BEZ235. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 359 and buparlisib. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 359 and GDC-0941. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 359 and vistusertib. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 478 and everolimus. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 478 and rapamycin. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 478 and sapanisertib. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 478 and Torin-1. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 478 and dactolisib. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 478 and BEZ235. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 478 and buparlisib. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 478 and GDC-0941. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 478 and vistusertib. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 507 and everolimus. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 507 and rapamycin. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 507 and sapanisertib. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 507 and Torin-1. In

one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 507 and dactolisib. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 507 and BEZ235. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 507 and buparlisib. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 507 and GDC-0941. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 507 and vistusertib.

[0168] In another embodiment, the mTOR 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 mTOR inhibitor is selected from everolimus, rapamycin, sapanisertib, Torin-1, dactolisib and vistusertib. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 234 and everolimus. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 234 and rapamycin. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 234 and sapanisertib. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 234 and Torin-1. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 234 and dactolisib. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 234 and BEZ235. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 234 and buparlisib. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 234 and GDC-0941. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 234 and vistusertib. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of

Example No. 359 and everolimus. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 359 and rapamycin. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 359 and sapanisertib. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 359 and Torin-1. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 359 and dactolisib. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 359 and BEZ235. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 359 and buparlisib. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 359 and GDC-0941. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 359 and vistusertib. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 478 and everolimus. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 478 and rapamycin. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 478 and sapanisertib. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 478 and Torin-1. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 478 and dactolisib. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 478 and vistusertib. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 507 and everolimus. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 507 and rapamycin. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 507 and sapanisertib. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 507 and Torin-1. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 507 and dactolisib. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 507 and BEZ235. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 507 and buparlisib. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 507 and

GDC-0941. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 507 and vistusertib.

[0169] 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.

[0170] 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 mTOR inhibitor, or a pharmaceutically acceptable salt or 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 mTOR 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 mTOR inhibitor is selected from everolimus, rapamycin, sapanisertib, Torin-1, dactolisib, BEZ235, buparlisib, GDC-0941 and vistusertib. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 234 and everolimus. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of

Example No. 234 and rapamycin. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 234 and sapanisertib. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 234 and Torin-1. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 234 and dactolisib. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 234 and BEZ235. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 234 and buparlisib. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 234 and GDC-0941. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 234 and vistusertib. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 359 and everolimus. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 359 and rapamycin. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 359 and sapanisertib. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 359 and Torin-1. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 359 and dactolisib. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 359 and BEZ235. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 359 and buparlisib. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 359 and GDC-0941. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 359 and vistusertib. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 478 and everolimus. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 478 and rapamycin. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 478 and sapanisertib. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 478 and Torin-1. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 478 and dactolisib. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 478 and

BEZ235. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 478 and buparlisib. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 478 and GDC-0941. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 478 and vistusertib. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 507 and everolimus. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 507 and rapamycin. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 507 and sapanisertib. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 507 and Torin-1. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 507 and dactolisib. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 507 and BEZ235. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 507 and buparlisib. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 507 and GDC-0941. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 507 and vistusertib.

[0171] In one embodiment, a compound of Formula I is administered as a capsule during the period of time. In one embodiment, a tablet or capsule formulation of a compound of Formula I comprises about 10 mg to about 100 mg (e.g., about 10 mg to about 95 mg, about 10 mg to about 90 mg, about 10 mg to about 85 mg, about 10 mg to about 80 mg, about 10 mg to about 75 mg, about 10 mg to about 70 mg, about 10 mg to about 65 mg, about 10 mg to about 60 mg, about 10 mg to about 55 mg, about 10 mg to about 50 mg, about 10 mg to about 45 mg, about 10 mg to about 40 mg, about 10 mg to about 35 mg, about 10 mg to about 30 mg, about 10 mg to about 25 mg, about 10 mg to about 20 mg, about 10 mg to about 15 mg, about 15 mg to about 100 mg, about 15 mg to about 95 mg, about 15 mg to about 90 mg, about 15 mg to about 85 mg, about 15 mg to about 80 mg, about 15 mg to about 75 mg, about 15 mg to about 70 mg, about 15 mg to about 65 mg, about 15 mg to about 60 mg, about 15 mg to about 55 mg, about 15 mg to about 50 mg, about 15 mg to about 45 mg, about 15 mg to about 40 mg, about 15 mg to about 35 mg, about 15 mg to about 30 mg, about 15 mg to about 25 mg, about 15 mg to about 20 mg, about 20 mg to about 100 mg, about 20 mg to about 95 mg, about 20 mg to about 90 mg, about

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

about 85 mg, about 60 mg to about 80 mg, about 60 mg to about 75 mg, about 60 mg to about 70 mg, about 60 mg to about 65 mg, about 65 mg to about 100 mg, about 65 mg to about 95 mg, about 65 mg to about 90 mg, about 65 mg to about 85 mg, about 65 mg to about 80 mg, about 65 mg to about 75 mg, about 65 mg to about 70 mg, about 70 mg to about 100 mg, about 70 mg to about 95 mg, about 70 mg to about 90 mg, about 70 mg to about 85 mg, about 70 mg to about 80 mg, about 70 mg to about 75 mg, about 75 mg to about 100 mg, about 75 mg to about 95 mg, about 75 mg to about 90 mg, about 75 mg to about 85 mg, about 75 mg to about 80 mg, about 80 mg to about 100 mg, about 80 mg to about 95 mg, about 80 mg to about 90 mg, about 80 mg to about 85 mg, about 85 mg to about 100 mg, about 85 mg to about 95 mg, about 85 mg to about 90 mg, about 90 mg to about 100 mg, about 90 mg to about 95 mg, about 95 mg to about 100 mg, about 10 mg, about 15 mg, about 20 mg, about 25 mg, about 30 mg, about 35 mg, about 40 mg, about 45 mg, about 50 mg, about 55 mg, about 60 mg, about 65 mg, about 70 mg, about 75 mg, about 80 mg, about 85 mg, about 90 mg, about 95 mg, or about 100 mg) of a compound of Formula I (e.g., a compound selected from compound Nos 1-678 (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, about 160 mg to about 240 mg, about 160 mg to about 220 mg, about 160 mg to about 200 mg, about 160 mg to about 180 mg, about 180 mg to about 500 mg, about 180 mg to about 480 mg, about 180 mg to about 460 mg, about 180 mg to about 440 mg, about 180 mg to about 420 mg, about 180 mg to about 400 mg, about 180 mg to about 380 mg, about 180 mg to about 360 mg, about 180 mg to about 340 mg, about 180 mg to about 320 mg, about 180 mg to about 300 mg, about 180 mg to about 280 mg, about 180 mg to about 260 mg, about 180 mg to about 240 mg, about 180 mg to about 220 mg, about 180 mg to about 200 mg, about 200 mg to about 500 mg, about 200 mg to about 480 mg, about 200 mg to about 460 mg, about 200 mg to about 440 mg, about 200 mg to about 420 mg, about 200 mg to about 400 mg, about 200 mg to about 380 mg, about 200 mg to about 360 mg, about 200 mg to about 340 mg, about 200 mg to about 320 mg, about 200 mg to about 300 mg, about 200 mg to about 280 mg, about 200 mg to about 260 mg, about 200 mg to about 240 mg, about 200 mg to about 220 mg, about 220 mg to about 500 mg, about 220 mg to about 480 mg, about 220 mg to about 460 mg, about 220 mg to about 440 mg, about 220 mg to about 420 mg, about 220 mg to about 400 mg, about 220 mg to about 380 mg, about 220 mg to about 360 mg, about 220 mg to about 340 mg, about 220 mg to about 320 mg, about 220 mg to about 300 mg, about 220 mg to about 280 mg, about 220 mg to about 260 mg, about 220 mg to about 240 mg, about 240 mg to about 500 mg, about 240 mg to about 480 mg, about 240 mg to about 460 mg, about 240 mg to about 440 mg, about 240 mg to about 420 mg, about 240 mg to about 400 mg, about 240 mg to about 380 mg, about 240 mg to about 360 mg, about 240 mg to about 340 mg, about 240 mg to about 320 mg, about 240 mg to about 300 mg, about 240 mg to about 280 mg, about 240 mg to about 260 mg, about 260 mg to

about 500 mg, about 260 mg to about 480 mg, about 260 mg to about 460 mg, about 260 mg to about 440 mg, about 260 mg to about 420 mg, about 260 mg to about 400 mg, about 260 mg to about 380 mg, about 260 mg to about 360 mg, about 260 mg to about 340 mg, about 260 mg to about 320 mg, about 260 mg to about 300 mg, about 260 mg to about 280 mg, about 280 mg to about 500 mg, about 280 mg to about 480 mg, about 280 mg to about 460 mg, about 280 mg to about 440 mg, about 280 mg to about 420 mg, about 280 mg to about 400 mg, about 280 mg to about 380 mg, about 280 mg to about 360 mg, about 280 mg to about 340 mg, about 280 mg to about 320 mg, about 280 mg to about 300 mg, about 300 mg to about 500 mg, about 300 mg to about 480 mg, about 300 mg to about 460 mg, about 300 mg to about 440 mg, about 300 mg to about 420 mg, about 300 mg to about 400 mg, about 300 mg to about 380 mg, about 300 mg to about 360 mg, about 300 mg to about 340 mg, about 300 mg to about 320 mg, about 320 mg to about 500 mg, about 320 mg to about 480 mg, about 320 mg to about 460 mg, about 320 mg to about 440 mg, about 320 mg to about 420 mg, about 320 mg to about 400 mg, about 320 mg to about 380 mg, about 320 mg to about 360 mg, about 320 mg to about 340 mg, about 340 mg to about 500 mg, about 340 mg to about 480 mg, about 340 mg to about 460 mg, about 340 mg to about 440 mg, about 340 mg to about 420 mg, about 340 mg to about 400 mg, about 340 mg to about 380 mg, about 340 mg to about 360 mg, about 360 mg to about 500 mg, about 360 mg to about 480 mg, about 360 mg to about 460 mg, about 360 mg to about 440 mg, about 360 mg to about 420 mg, about 360 mg to about 400 mg, about 360 mg to about 380 mg, about 380 mg to about 500 mg, about 380 mg to about 480 mg, about 380 mg to about 460 mg, about 380 mg to about 440 mg, about 380 mg to about 420 mg, about 380 mg to about 400 mg, about 400 mg to about 500 mg, about 400 mg to about 480 mg, about 400 mg to about 460 mg, about 400 mg to about 440 mg, about 400 mg to about 420 mg, about 420 mg to about 500 mg, about 420 mg to about 480 mg, about 420 mg to about 460 mg, about 420 mg to about 440 mg, about 440 mg to about 500 mg, about 440 mg to about 480 mg, about 440 mg to about 460 mg, about 460 mg to about 500 mg, about 460 mg to about 480 mg, about 480 mg to about 500 mg, about 25, about 50, about 75, about 100, about 150, about 200, about 250, about 300, about 350, about 400, about 450, or about 500 mg), during a period of time.

[0172] In one embodiment, the combination therapy comprises oral administration of a compound of Formula I, or a pharmaceutically acceptable salt or pharmaceutical composition thereof, 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 mTOR 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.

[0173] 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.

[0174] 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

[0175] In one embodiment, the addition of a mTOR inhibitor, or a pharmaceutically acceptable salt or pharmaceutical composition thereof, synergistically increases the activity of KRas G12C inhibitor compound of Formula (I), Formula I-A or Formula I-B, or a pharmaceutically acceptable salt or pharmaceutical composition thereof, 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.

[0176] 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 mTOR inhibitor.

[0177] 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.

[0178] In some embodiments, "synergistic effect" as used herein refers to combination of a KRAS inhibitor or a pharmaceutically acceptable salt thereof, and a mTOR inhibitor or a pharmaceutically acceptable salt thereof producing an effect, for example, any of the beneficial or desired results including clinical results or endpoints as described herein, which is greater than the sum of the effect observed when a compound of Formula I or a pharmaceutically acceptable salt thereof (e.g., a compound selected from compound Nos 1-678 (as numbered in WO2019099524), or pharmaceutically acceptable salts thereof (e.g., Example Nos 234, 359, 478 or 507, or a pharmaceutically acceptable salt thereof) and a mTOR 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 mTOR inhibitor is selected from everolimus, rapamycin, sapanisertib, Torin-1, dactolisib and vistusertib. In one embodiment, the therapeutic combination comprises therapeutically effective

amounts of Example No. 234 and everolimus. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 234 and rapamycin. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 234 and sapanisertib. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 234 and Torin-1. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 234 and dactolisib. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 234 and BEZ235. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 234 and buparlisib. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 234 and GDC-0941. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 234 and vistusertib. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 359 and everolimus. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 359 and rapamycin. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 359 and sapanisertib. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 359 and Torin-1. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 359 and dactolisib. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 359 and BEZ235. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 359 and buparlisib. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 359 and GDC-0941. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 359 and vistusertib. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 478 and everolimus. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 478 and rapamycin. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 478 and sapanisertib. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 478 and Torin-1. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of

Example No. 478 and dactolisib. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 478 and BEZ235. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 478 and buparlisib. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 478 and GDC-0941. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 478 and vistusertib. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 507 and everolimus. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 507 and rapamycin. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 507 and sapanisertib. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 507 and Torin-1. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 507 and dactolisib. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 507 and BEZ235. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 507 and buparlisib. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 507 and GDC-0941. In one embodiment, the therapeutic combination comprises therapeutically effective amounts of Example No. 507 and vistusertib.

[0179] 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).

[0180] 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

[0181] The present invention also relates to a kit comprising a mTOR 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 mTOR 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.

[0182] In a related aspect, the invention provides a kit containing a dose of a mTOR inhibitor, or a pharmaceutically acceptable salt thereof, 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 a mTOR 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. The insert may provide a user with one set of instructions for using a mTOR inhibitor, or a pharmaceutically acceptable salt thereof in combination with a KRas G12C inhibitor compound of Formula (I), Formula I-A or Formula I-B, or a pharmaceutically acceptable salt thereof.

EXAMPLE A

mTOR Inhibitors Synergistically Increase the Activity of KRas G12C Inhibitors Against Cell Lines Expressing KRas G12C

[0183] 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 mTOR inhibitor synergistically inhibits the growth of tumor cell lines that express KRas G12C.

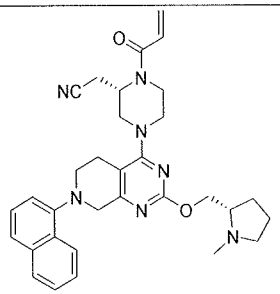
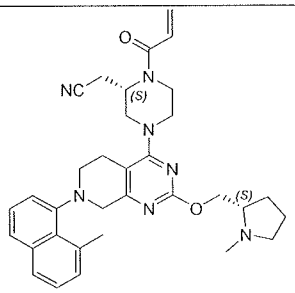
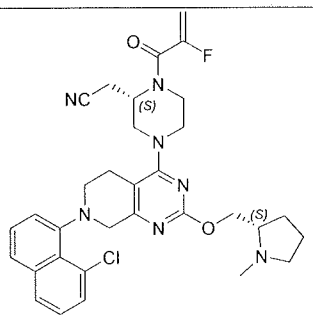
[0184] A panel of 9 lung cancer and 1 colorectal cell lines harboring KRas G12C mutations was assembled to determine whether combining mTOR inhibitors with exemplary KRas G12C inhibitors disclosed herein results in synergistic activity. The collection included NCI-H1373 (ATCC CRL-5866); NCI-H1792 (ATCC CRL-5895); NCI-H2030 (ATCC CRL-5985); NCI-H2122 (ATCC CRL-5985); NCI-HCC1171 (KCLB 71171); HCC44 (DSMZ ACC-534); LU99 (RCB1900); SW1573 (ATCC CRL-2170), SW837 (ATCC CCL-235) and KYSE-410 (ECACC 94072023).

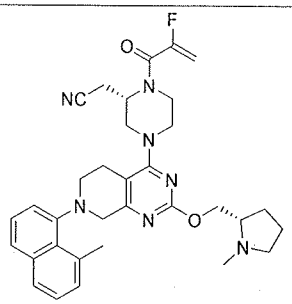
[0185] Assays for determining the synergy score for the pairwise combinations for each cell line were performed in triplicate. Three 96-well plates plus an additional 4 wells of a separate 96-well control plate for determining baseline luminescence were seeded with 2000 cells/well of a particular cell 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.

[0186] 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.

[0187] 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 mTOR inhibitor. The dilutions used for the KRas G12C inhibitor and the mTOR inhibitor varied for each individual compound but were in the range of 3- to 6-fold/serial dilution.

[0188] 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 pending published International PCT application WO2019099524.

[0189] 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 mTOR 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 mTOR inhibitor was prepared as test samples.

[0190] 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.

[0191] 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.

[0192] 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 mTOR Inhibitors Combined with Exemplary KRas G12C Inhibitors of Formula (I) Against KRas G12C Cell Lines

mTOR Inhibitor	**BEZ235**	**BKM120**	**Dactolisib**	**Everolimus**		**GDC-0941**	**Rapamycin**		**Sapanisertib**	**Torin-1**	**Vistusertib**			
KRas G12C Example #	**478**	**478**	**234**	**234**	**478**	**478**	**507**	**478**	**507**	**507**	**234**	**507**	**478**	**478**
Cell Line														
H1373	21.5	22.1	21.0	27.3	24.4	37.5	9.2	-3.1	45.1	35.6	22.3	21.8	21.6	24.5
H1792	15.4	-23.9	N.D.	7.9	6.5	31.3	30.0	5.9	15.6	5.1	7.9	-3.8	12.1	2.2
H2030	19.6	28.9	16.9	34.1	29.3	40.6	23.9	12.8	7.6	17.1	4.8	14.2	20.4	22.3
H2122	22.8	18.5	-5.2	38.8	66.3	51.2	13.1	23.8	19.4	-2.9	-7.7	2.2	9.4	-4.8
HCC1171	11.3	-13.0	-6.9	N.D.	-12.2	11.7	38.9	1.6	12.6	32.0	N.D.	10.5	13.8	0.8
HCC44	14.5	33.7	11.4	22.7	22.7	35.0	25.1	12.9	20.4	42.9	9.9	-0.2	27.6	9.6
LU99	6.2	28.4	33.7	42.1	41.0	33.7	27.9	14.6	16.8	36.1	27.7	23.0	18.2	31.7
SW1573	18.4	-11.4	0.4	-1.4	-41.2	0.0	4.7	-1.2	27.7	16.7	11.9	-0.4	-8.6	-8.8

mTOR Inhibitor	BEZ235	BKM120	Dactolisib	Everolimus		GDC-0941	Rapamycin		Sapanisertib	Torin-1	Vistusertib		
SW837	18.6	26.7	1.6	8.8	19.7	18.4	-8.4	1.3	19.0	23.1	25.4	0.2	N.D.	16.2

[0193] 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 mTOR inhibitors with exemplary KRas G12C inhibitor compounds of Formula (I) in several 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-mutant cell line to the KRas G12C inhibitor.

EXAMPLE B

In Vivo Models for Examining KRas G12C inhibitor Plus mTOR Inhibitor Combinations

[0194] 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 mTOR 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 mTOR inhibitor. The treatment period varies from cell line to cell line but typically is between 21-35 days. Tumor volumes were measured using a caliper every two – three days and tumor volumes are calculated by the formula: 0.5 x (Length x Width)^2. A greater degree of tumor 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.

A. Vistusertib

1. NCI-H2122 Cell Line

[0195] For example, on Day 1, 20 nude/nude mice were inoculated in the right hind limb with 5 x 10^6 NCI-H2122 cells. When tumor volume reached ~350 mm^3 (Day 13 post implant; Study Day 0), 5 mice in each of the four groups were administered p.o. daily for 21 days: vehicle only (10% Captisol in 50mM citrate buffer, pH 5.0), 100 mg/kg of KRas G12C inhibitor Compound 478 (10% Captisol in 50 mM citrate buffer, pH 5.0), 15.0 mg/kg of the mTOR inhibitor vistusertib (0.5% methylcellulose/0.4% Tween-80), 100 mg/kg of KRas G12C inhibitor Compound 478 and 15.0 mg/kg of vistusertib, or 100 mg/kg of KRas G12C inhibitor Compound 478 for thirteen days (Study Days 0 – 13) followed by twenty one days of treatment 100 mg/kg of KRas G12C inhibitor Compound 478 in combination with 15.0 mg/kg of the mTOR inhibitor vistusertib (Study Days 14 – 34). 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 4.

Table 4

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

Study Day	Day Post Implant	Vehicle	Compound 478	Vistusertib	Compound 478 + Vistusertib	Compound 478 (13 Days) 478 + Vistusertib (21 Days)
0	13	346	347	351	354	354
4	17	567	369	451	223	371
6	19	659	379	497	197	376
8	21	842	387	548	190	356
11	24	1053	382	640	169	363
13	26	1298	391	667	174	366
15	28	1429	396	694	170	365
18	31	1618	405	791	190	304
20	33	1685	430	870	179	270
22	35	1781	427	1036	177	236
25	38	1854	444	1156	182	222
27	40	1894	455	1242	172	215
29	42	1937	463	1364	173	218
32	45	1955	476	1526	194	221
34	47	1959	506	1611	202	228
36	49	1962	543			
39	52	1974	536			

[0196] As shown in Table 4, the administration of Compound 478 or vistusertib as a single agent exhibited 94.4% and 51.9% tumor growth inhibition at Study Day 22 and 90.1% and 21.6% tumor growth inhibition at Study Day 34, respectively. The combination of the mTOR inhibitor vistusertib and Compound 478 resulted in 50% tumor growth regression at Study Day 22 and a 43% tumor growth regression at Day 34. The administration of Compound 478 for 13 days followed by 21 days of combination therapy of Compound 478 and vistusertib resulted in a 35.5% tumor regression at Day 34.

2. NCI-H2030 Cell Line

[0197] Analogously, on Day 1, 20 nude/nude mice were inoculated in the right hind limb with 5 x 10^6 NCI-H2030 cells. When tumor volume reached ~350 mm^3 (Day 22 post implant; Study Day 0), 5 mice in each of the four groups were administered p.o. daily for 21 days: vehicle only (10% Captisol in 50mM citrate buffer, pH 5.0), 100 mg/kg of KRas G12C inhibitor Compound 478 (10% Captisol in 50 mM citrate buffer, pH 5.0), 15.0 mg/kg of the mTOR inhibitor vistusertib (0.5% methylcellulose/0.4% Tween-80), or 100 mg/kg of KRas G12C inhibitor Compound 478 and 15.0 mg/kg of vistusertib. 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 5.

Table 5

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

Study Day	Day Post Implant	Vehicle	Compound 478	Vistusertib	Compound 478 + Vistusertib
0	22	341	340	338	340
4	26	748	450	513	332
6	28	961	457	590	324
7	29	1014	450	615	297
12	34	1303	396	670	258
15	37	1408	324	676	189

[0198] As shown in Table 5, the administration of Compound 478 or vistusertib as a single agent exhibited 5% tumor regression and 100% tumor growth inhibition at Study Day 15,

respectively. The combination of the mTOR inhibitor vistusertib and Compound 478 resulted in 44% tumor regression at Study Day 15.

3. LU11692 PDX Model

[0199] Similarly, on Day 1, 20 nude/nude mice were inoculated in the right hind limb with 5 x 10^6 LU11692 cells. When tumor volume reached ~250 mm^3 (Day 22 post implant; Study Day 1), 5 mice in each of the four groups were administered p.o. daily for 21 days: vehicle only (10% Captisol in 50mM citrate buffer, pH 5.0), 100 mg/kg of KRas G12C inhibitor Compound 478 (10% Captisol in 50 mM citrate buffer, pH 5.0), 15.0 mg/kg of the mTOR inhibitor vistusertib (0.5% methylcellulose/0.4% Tween-80), or 100 mg/kg of KRas G12C inhibitor Compound 478 and 15.0 mg/kg of vistusertib. 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 6.

Table 6

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

Study Day	Vehicle	Compound 478	Vistusertib	Compound 478 + Vistusertib
1	250.58	282.92	243.08	276.95
4	353.66	321.02	321.00	342.61
8	507.29	278.62	410.15	259.70
11	594.10	228.93	377.07	165.06
15	727.24	244.87	479.17	154.62
18	859.17	223.62	510.91	131.11
22	1013.75	180.12	578.25	119.45
25	1186.76	148.50	622.88	96.61
29	1311.68	196.81	691.51	93.36
32	1330.97	176.34	782.13	95.62
36	1570.88	226.63	943.28	79.27
39	1536.80	308.21	1079.96	83.76
43	1594.44	315.42	1227.29	78.85

[0200] As shown in Table 6, the administration of Compound 478 as a single agent exhibited 95% tumor growth inhibition at Study Day 43. The combination of the mTOR inhibitor vistusertib and Compound 478 resulted in 73% tumor regression at Study Day 43.

B. Everolimus

1. NCI-H2122 Cell Line

[0201] On Day 1, 20 nude/nude mice were inoculated in the right hind limb with 5 x 10^6 NCI-H2122 cells. When tumor volume reached ~300 mm^3 (Day 13 post implant; Study Day 0), 5 mice in each of the four groups were administered p.o. daily for 21 days: vehicle only (10% Captisol in 50mM citrate buffer, pH 5.0), 100 mg/kg of KRas G12C inhibitor Compound 478 (10% Captisol in 50 mM citrate buffer, pH 5.0), 10.0 mg/kg of the mTOR inhibitor everolimus (30% PEG-400, 5% Tween-20, 65% Saline), 100 mg/kg of KRas G12C inhibitor Compound 478 and 10.0 mg/kg of everolimus. 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 7.

Table 7

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

Study Day	Vehicle	Compound 478	Everolimus	Compound 478 + Everolimus
0	313.60	314.62	301.14	292.90
3	395.56	281.54	291.60	204.92
7	494.74	233.12	312.44	129.18
10	650.72	277.28	297.94	113.83
15	749.66	252.14	274.34	91.33
17	887.98	277.48	304.42	95.60
21	1027.62	269.90	274.28	93.13
24	1151.30	254.30	294.36	86.25
28	1202.5	276	296.3	69.925

[0202] As shown in Table 7, the administration of Compound 478 as a single agent exhibited 12% tumor regression at Study Day 28. The combination of the mTOR inhibitor everolimus and Compound 478 resulted in 76% tumor regression at Study Day 28.

2. NCI-H2030 Cell Line

[0203] On Day 1, 20 nude/nude mice were inoculated in the right hind limb with 5 x 10^6 NCI-H2030 cells. When tumor volume reached ~250 mm^3 (Day 13 post implant; Study Day 0), 5 mice in each of the four groups were administered p.o. daily for 21 days: vehicle only (10% Captisol in 50mM citrate buffer, pH 5.0), 100 mg/kg of KRas G12C inhibitor Compound 478 (10% Captisol in 50 mM citrate buffer, pH 5.0), 10.0 mg/kg of the mTOR inhibitor everolimus (10% Captisol in 50 mM citrate buffer, pH 5.0), 100 mg/kg of KRas G12C inhibitor Compound 478 and 10.0 mg/kg of everolimus. 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 8.

Table 8

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

Study Day	Vehicle	Compound 478	Everolimus	Compound 478 + Everolimus
1	257.63	257.87	271.36	275.31
5	444.96	360.49	462.74	313.23
8	661.84	414.32	586.89	295.69
12	912.64	538.32	712.44	243.42
16	1273.57	710.20	805.72	250.74
18	1423.73	762.38	891.56	266.84
23	1768.70	1162.01	1141.85	278.05
25	1861.77	1240.90	1501.46	294.24
30	1932.836	1418.196	1694.328	363.344
33		1477.62	1728.0675	338.754
37		1866.77	2076.73	388.144

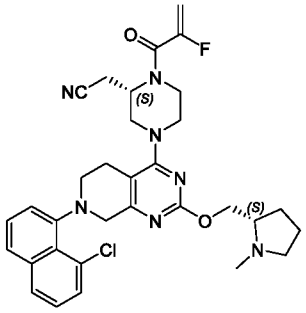
[0204] As shown in Table 8, the administration of Compound 478 as a single agent exhibited 31% tumor growth inhibition at Study Day 28. The combination of the mTOR inhibitor everolimus and Compound 478 resulted in 94% tumor growth inhibition at Study Day 28.

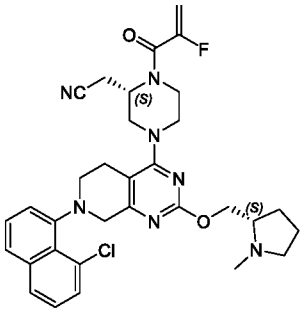
[0205] These results demonstrate that the combination therapies resulted in greater amount of tumor growth inhibition, i.e., tumor growth regression, compared to either single agent alone demonstrating enhanced in vivo anti-tumor efficacy of the combination, and that the addition of the mTOR inhibitor vistusertib or everolimus to ongoing KRas G12C inhibitor treatment further sensitized the KRas G12C expressing cells to the combination therapy.

[0206] 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 herein before 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 mTOR inhibitor selected from the group consisting of everolimus, rapamycin, zotarolimus, ridaforolimus, sapanisertib, Torin-1, dactolisib, BEZ235, buparlisib, GDC-0941, GDC-0349, VS-5584 or vistusertib and a KRas G12C inhibitor of formula  , or a pharmaceutically acceptable salt thereof.

2. Use of an mTOR inhibitor selected from the group consisting of everolimus, rapamycin, zotarolimus, ridaforolimus, sapanisertib, Torin-1, dactolisib, BEZ235, buparlisib, GDC-0941, GDC-0349, VS-5584 or vistusertib and a KRas G12C inhibitor of formula  , or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating cancer.

3. The method of claim 1 or the use of claim 2, wherein the mTOR inhibitor is everolimus.

4. The method of claim 1 or the use of claim 2, wherein the mTOR inhibitor is rapamycin.

5. The method of claim 1 or the use of claim 2, wherein the mTOR inhibitor is sapanisertib.

6. The method of claim 1 or the use of claim 2, wherein the mTOR inhibitor is Torin-1.

7. The method of claim 1 or the use of claim 2, wherein the mTOR inhibitor is dactolisib.

8. The method of claim 1 or the use of claim 2, wherein the mTOR inhibitor is vistusertib.

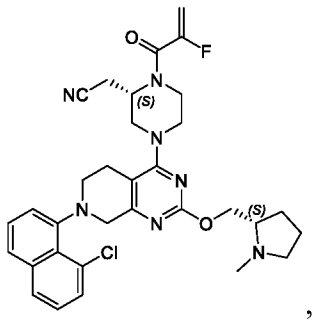
9. The method of claim 1 or the use of claim 2, wherein the mTOR inhibitor is BEZ235.

10. The method of claim 1 or the use of claim 2, wherein the mTOR inhibitor is buparlisib.

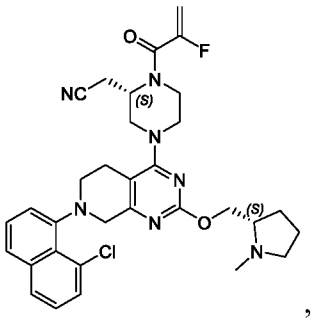
11. The method of claim 1 or the use of claim 2, wherein the mTOR inhibitor is GDC-0941.

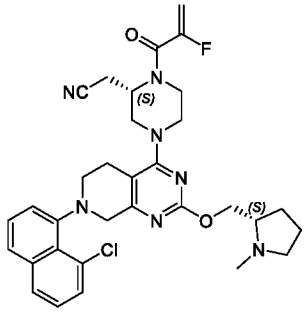
12. The method according to any one of claims 1 and 3-11 or the use according to any one of claims 2-11, wherein the mTOR inhibitor and the KRas G12C inhibitor are administered on the same day.

13. The method according to any one of claims 1-10, wherein the mTOR inhibitor and the KRas G12C inhibitor are administered on different days.

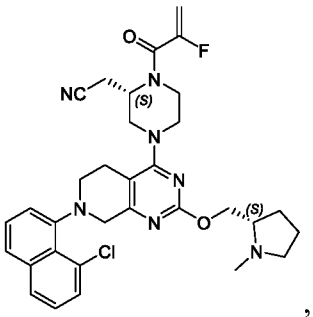
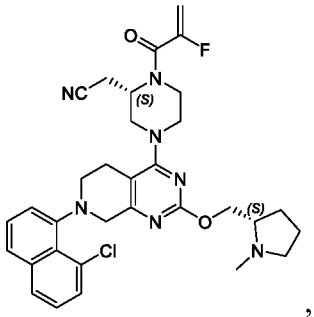
14. A pharmaceutical composition, comprising a therapeutically effective amount of a combination of a mTOR inhibitor selected from the group consisting of everolimus, rapamycin, zotarolimus, ridaforolimus, sapanisertib, Torin-1, dactolisib, BEZ235, buparlisib, GDC-0941, GDC-0349, VS-5584 or vistusertib and a KRas G12 inhibitor of formula  , or a pharmaceutically acceptable salt thereof , and a pharmaceutically acceptable excipient.

15. A method for inhibiting KRas G12C activity in a cell, comprising contacting the cell expressing the KRas G12C mutation with an effective amount of a mTOR inhibitor selected from the group consisting of everolimus, rapamycin, zotarolimus, ridaforolimus, sapanisertib, Torin-1, dactolisib, BEZ235, buparlisib, GDC-0941, GDC-0349, VS-5584

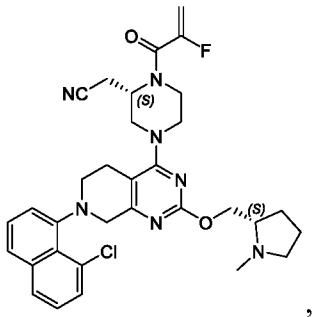
or vistusertib and a KRas G12C inhibitor compound of formula  , or pharmaceutically acceptable salts thereof, wherein the mTOR inhibitor synergistically increases the sensitivity of the cancer cells to the KRas G12C inhibitor.

16. Use of an mTOR inhibitor selected from the group consisting of everolimus, rapamycin, zotarolimus, ridaforolimus, sapanisertib, Torin-1, dactolisib, BEZ235, buparlisib, GDC-0941, GDC-0349, VS-5584 or vistusertib and a KRas G12C inhibitor compound of formula  , or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for inhibiting KRas G12C activity in a cell expressing the KRas G12C mutation, wherein the mTOR inhibitor synergistically increases the sensitivity of the cancer cells to the KRas G12C inhibitor.

17. The method according to any one of claims 1 and 3-13 or the use according to any one of claims 2-13, wherein the mTOR inhibitor synergistically increases the sensitivity of the cancer cells to the KRas G12C inhibitor.

18. A method for increasing the sensitivity of a cancer cell expressing the KRas G12C mutation to a KRas G12C inhibitor compound of formula  , or a pharmaceutically acceptable salt thereof comprising administering to a subject undergoing KRas G12C treatment with a compound of formula  , or a pharmaceutically acceptable salt thereof, alone or combined with a pharmaceutically acceptable carrier, excipient or diluents, a therapeutically effective amount of a mTOR inhibitor selected from the group consisting of everolimus, rapamycin, zotarolimus, ridaforolimus, sapanisertib, Torin-1, dactolisib, BEZ235, buparlisib, GDC-0941, GDC-0349, VS-5584 or vistusertib, wherein the mTOR inhibitor synergistically increases the sensitivity of the cancer cell expressing the KRas G12C mutation to the KRas G12C inhibitor.

19. Use of an mTOR inhibitor selected from the group consisting of everolimus, rapamycin, zotarolimus, ridaforolimus, sapanisertib, Torin-1, dactolisib, BEZ235, buparlisib, GDC-0941, GDC-0349, VS-5584 or vistusertib in the manufacture of a medicament for increasing the sensitivity of a cancer cell expressing the KRas G12C mutation to a KRas

G12C inhibitor compound of formula  , or a pharmaceutically acceptable salt thereof, wherein the mTOR inhibitor synergistically increases the sensitivity of the cancer cell expressing the KRas G12C mutation to the KRas G12C inhibitor.

20. The method according to any one of claims 1, 3-13, 15, or 17-18, or the use according to any one of claims 2-13, 16, 17 or 19, wherein the therapeutically effective amount of the compound is between about 0.01 to 100 mg/kg per day.

21. The method of claim 20 or the use of claim 20, wherein the therapeutically effective amount of the compound is between about 0.1 to 50 mg/kg per day.

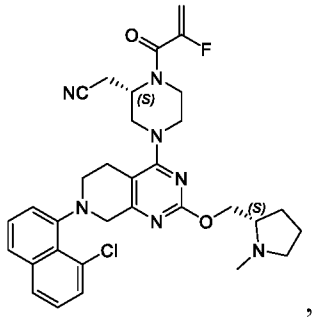
22. The method according to any one of claims 1, 3-13, 15, 17-18, or 20-21, or the use according to any one of claims 2-13, 16, 17 or 19-21, wherein the cancer is selected from the group consisting of Cardiac: sarcoma (angiosarcoma, fibrosarcoma, rhabdomyosarcoma, liposarcoma), myxoma, rhabdomyoma, fibroma, 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.

23. The method according to any one of claims 1, 3-13, 15, 17-18, or 20-22, or the use according to any one of claims 2-13, 16, 17 or 19-22, wherein the cancer wherein the cancer is a KRas G12C-associated cancer.

24. The method of claim 23 or the use of claim 23, wherein the KRas G12C-associated cancer is non-small cell lung cancer.

25. A kit comprising the pharmaceutical composition of claim 14 when used in treating cancer in a subject.

26. A kit comprising: a) a pharmaceutical composition comprising a mTOR inhibitor selected from the group consisting of everolimus, rapamycin, zotarolimus, ridaforolimus, sapanisertib, Torin-1, dactolisib, BEZ235, buparlisib, GDC-0941, GDC-0349, VS-5584 or vistusertib and b) a pharmaceutical composition comprising a KRas G12C inhibitor of formula  , or a pharmaceutically acceptable salt thereof

,
when used in treating cancer in a subject.

27. The kit according to claim 25 or 26, further comprising an insert with instructions for administration of the pharmaceutical composition(s).