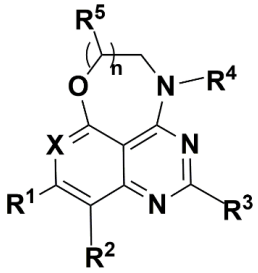
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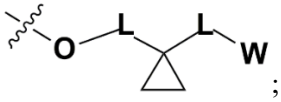
[21] In Formula 1,

[22] X is N or CR^{11};

[23] R^1 is R^{1A}-substituted or unsubstituted phenyl, R^{1A}-substituted or unsubstituted naphthyl, or R^{1A}-substituted or unsubstituted benzothiophenyl;

[24] each R^{1A} is independently selected from hydrogen, hydroxy, a halogen, C_1-C_3 haloalkyl, C_1-C_3 alkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, C_1-C_3 alkoxy, C_3-C_6 cycloalkyl, NH_2, $NH(C_1$-C_3 alkyl), $N(C_1$-C_3 alkyl)$_2$, and CN;

[25] R^2 is hydrogen or a halogen;

[26] R^3 is hydrogen, -O-L-W, or ;

[27] L is a bond or L^A-substituted or unsubstituted C_1-C_3 alkylene;

[28] L^A is hydrogen, a halogen, or C_1-C_3 alkyl;

[29] W is R^6-substituted or unsubstituted C_1-C_3 alkyl, R^6-substituted or unsubstituted 3- to 10-membered monocyclic heterocycle, or R^6-substituted or unsubstituted 6- to 14-membered bicyclic heterocycle;

[30] each R^6 is independently selected from hydrogen, a halogen, C_1-C_3 haloalkyl, C_1-C_3 alkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, C_1-C_3 alkoxy, C_3-C_6 cycloalkyl, amino, CN, $=CH_2$, oxo(=O), $S(C_1$-C_3 alkyl), SO_2NH_2, $SO_2NH(C_1$-C_3 alkyl), $SO_2(C_1$-C_3 alkyl), $SO_2(C_1$-C_3 haloalkyl), and halo C_1-C_3 alkoxy;

[31] R^4 is hydrogen, R^{4A}-substituted or unsubstituted C_1-C_6 haloalkyl, R^{4A}-substituted or unsubstituted C_1-C_6 alkyl, R^{4A}-substituted or unsubstituted C_3-C_{10} cycloalkyl, R^{4A}-substituted or unsubstituted C_5-C_8 aryl, R^{4A}-substituted or unsubstituted 3- to 10-membered heterocycle, or R^{4A}-substituted or unsubstituted 5- to 10-membered heteroaryl;

[32] each R^{4A} is independently selected from hydrogen, CN, NR^9R^{10}, =O, OR^7, SR^8, SO_2R^8, $C(O)N(R^7)_2$, $C(O)R^7$, R^{4B}-substituted or unsubstituted C_1-C_6 haloalkyl, R^{4B}-substituted or unsubstituted C_1-C_6 alkyl, R^{4B}-substituted or unsubstituted C_3-C_{10} cycloalkyl, R^{4B}-substituted or unsubstituted C_5-C_8 aryl, R^{4B}-substituted or unsubstituted 3- to 6-membered heterocycle, and R^{4B}-substituted or unsubstituted 5- to 9-membered heteroaryl;

[33] wherein two of R^{4A} together form R^{4B}-substituted or unsubstituted C_3-C_{10} cycloalkyl, R^{4B}-substituted or unsubstituted C_5-C_8 aryl, R^{4B}-substituted or unsubstituted 3- to 10-membered heterocycle, or R^{4B}-substituted or unsubstituted 5- to 10-membered heteroaryl;

[34] each R^{4B} is independently selected from hydrogen, a halogen, C_1-C_3 haloalkyl, C_1-C_3 alkyl, C_3-C_6 cycloalkyl, CN, NR^9R^{10}, =O, C_1-C_3 alkoxy, halo C_1-C_3 alkoxy, hydroxy, SCH_3, SO_2NH_2, SO_2CH_3, $C(O)NH_2$, $C(O)CH_3$, a 3- to 6-membered heterocycle, C_5-C_8 aryl, and 5- or 6-membered heteroaryl;

[35] each R^5 is independently selected from hydrogen, hydroxy, a halogen, C_1-C_3 haloalkyl, and C_1-C_3 alkyl;

[36] each R^7 is independently selected from hydrogen, amino, C_1-C_3 haloalkyl, C_1-C_3 alkyl, C_3-C_6 cycloalkyl, and a 3- or 4-membered heterocycle;

[37] each R^8 is independently selected from hydrogen, amino, and C_1-C_3 alkyl;

[38] R^9 and R^{10} are each independently selected from hydrogen, C_1-C_3 alkyl, C_3-C_6 cycloalkyl, $C(O)NH_2$, $C(O)CH_3$, and a 3- to 6-membered heterocycle;

[39] each R^{11} is independently selected from hydrogen, hydroxy, a halogen, C_1-C_3 haloalkyl, and C_1-C_3 alkyl,

[40] n is an integer selected from 0 to 2; and

[41] wherein the heterocycles or heteroaryls each comprise 1 to 3 heteroatoms independently selected from N, O, and S.

[42]

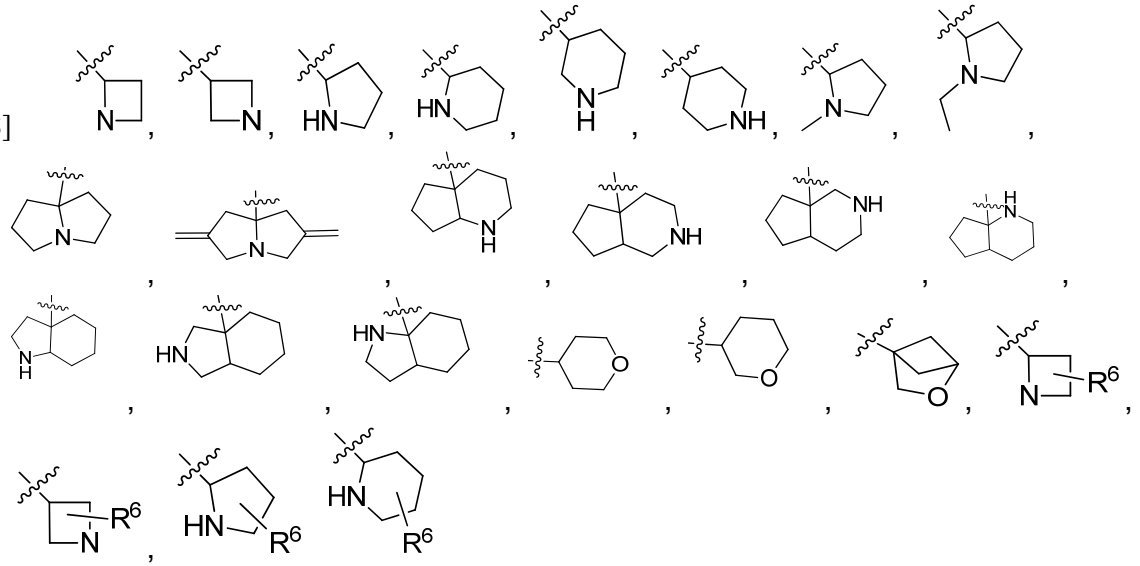
[43] In an embodiment, L is methylene;

[44] W is R^6-substituted or unsubstituted 3- to 10-membered monocyclic heterocycle or R^6-substituted or unsubstituted 6- to 14-membered bicyclic heterocycle; and

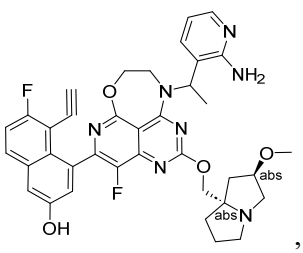
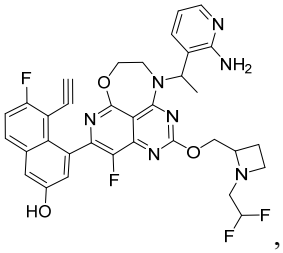
[45] each R^6 is independently selected from a halogen, C_1-C_3 haloalkyl, C_1-C_3 alkyl, C_1-C_3 alkoxy, CN, $=CH_2$, =O, SCH_3, SO_2NH_2, $SO_2NH(CH_3)$, SO_2CH_3, and SO_2CF_3.

[46]

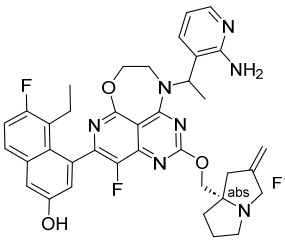
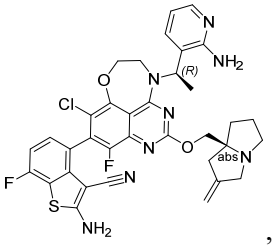
[47] In one embodiment, W may be a substituted monocyclic or bicyclic non-aromatic ring, for example, it includes, but is not limited to,

[48] 

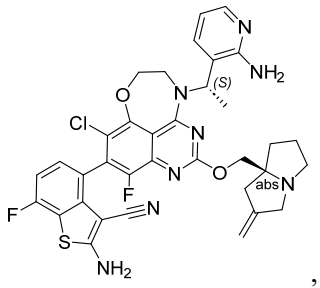
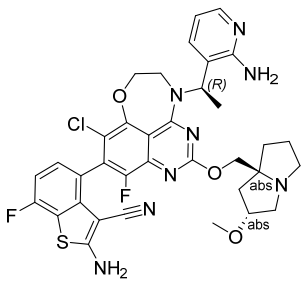
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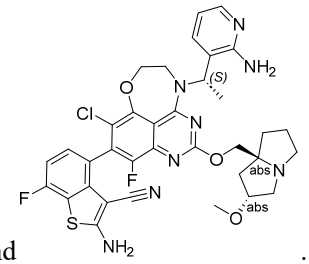

,

,

[109]


,

,

[110]


,




[111] and .

[112]

[113] According to an aspect of another embodiment, provided is a pharmaceutical composition including the compound selected from compounds of Formula 1 and stereoisomers, diastereomers, enantiomers, atropisomers, isotopic variants, tautomers, solvates, and pharmaceutically acceptable salts thereof.

[114] In an embodiment, wherein the pharmaceutical composition exhibits KRAS protein inhibitory activity.

[115]

[116] **Definitions**

[117] The term “halogen” used herein refers to fluorine, chlorine, bromine or iodine, unless stated otherwise.

[118] The term “alkyl” used herein refers to a straight-chain or branched, saturated, monovalent hydrocarbon group, unless stated otherwise.

[119] The term “alkylene” used herein refers to a divalent straight-chain or branched hy-

solvents ACN and water (4:1, 20 mL) was added Oxone (3.02 g, 9.83 mmol) at 0 °C and the reaction mixture was allowed to warm up to room temperature and stirred for 2 h. Progress of the reaction was monitored by TLC and LC-MS. After completion of the reaction, the reaction mixture was diluted with ice cold water (30 mL) and extracted with 10% methanol in DCM (2 x 30 mL), dried over *anhydrous* Na_2SO_4 and concentrated under reduced pressure to get residue. The residue was washed with 20% THF in Hexane solution to get solid, the solid was filtered and dried under high vacuum to get crude compound 1-((5-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-2-(ethylsulfonyl)-4-fluoro-8,9-dihydro-10*H*-7-oxa-1,3,6,10-tetraazacyclohepta[*de*]naphthalen-10-yl)methyl)-*N*,*N*-dimethylcyclobutan-1-amine **Example 1-Int-9** (0.30 g, crude) as a brown color solid. The crude compound was used as such in next step without further purification. MS (LC-MS): 642.44 *m/z* [M+H].

[205]

[206] **Step 6: 1-((5-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-4-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-8,9-dihydro-10*H*-7-oxa-1,3,6,10-tetraazacyclohepta[*de*]naphthalen-10-yl)methyl)-*N*,*N*-dimethylcyclobutan-1-amine (Example 1-Int-10)**

[207] To a stirred solution of ((2*R*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methanol (0.099 g, 0.62 mmol) in toluene (10 mL, 30 vol) was added NaO^tBu (0.06 g, 0.62 mmol) at 0 °C and stirred for 15 min, followed by an addition of 1-((5-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-2-(ethylsulfonyl)-4-fluoro-8,9-dihydro-10*H*-7-oxa-1,3,6,10-tetraazacyclohepta[*de*]naphthalen-10-yl)methyl)-*N*,*N*-dimethylcyclobutan-1-amine **Example 1-Int-9** (0.33 g, 0.51 mmol) at 0 °C. The reaction mixture was allowed to warm up to room temperature and stirred for 4 h. Progress of the reaction was monitored by TLC and LC-MS. After completion of the reaction, the reaction mixture was diluted with ice cold water (30 mL) and extracted with ethyl acetate (2 x 15 mL), combined organic layer was washed with brine solution (10 mL), dried over *anhydrous* Na_2SO_4, filtered and evaporated under reduced pressure to get crude compound 1-((5-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-4-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-8,9-dihydro-10*H*-7-oxa-1,3,6,10-tetraazacyclohepta[*de*]naphthalen-10-yl)methyl)-*N*,*N*-dimethylcyclobutan-1-amine **Example 1-Int-10** (0.32 g, crude) as a yellow solid. The crude compound was used as such in next step without further purification. MS (LC-MS): 707.58 *m/z* [M+H].

[208]

[209] **Step 7:**

(2-(1-((2-((7-chloro-8-fluoro-4-hydroxy-2-(methylthio)pyrido[4,3-*d*]pyrimidin-5-yl)oxy)ethyl)amino)ethyl)phenyl)carbamate (2.2g, 4.20 mmol) in DCM (20 mL) was added BOPCl (3.2 g, 12.59 mmol), DIEA (4.9 g, 37.79 mmol). The reaction mixture was stirred at 25°C for 16 h under N_2. The reaction mixture was diluted with DCM (40 mL). The organic phase was washed with brine (40 mL), dried over Na_2SO_4(s). The organic phase was concentrated under reduced pressure. The residue was concentrated was purified by silica gel chromatography eluted PE/EA = 4:1 to give *tert*-butyl (2-(1-(5-chloro-4-fluoro-2-(methylthio)-8,9-dihydro-10*H*-7-oxa-1,3,6,10-tetraazacyclohepta[*de*]naphthalen-10-yl)ethyl)phenyl)carbamate (1.4 g, 65%) as a white solid. MS: *m/z* = 506.0 ($M+H^+$, ESI+)

[656]

[657] **Step 5: *tert*-butyl (2-(1-(4-fluoro-5-(7-fluoro-3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-2-(methylthio)-8,9-dihydro-10*H*-7-oxa-1,3,6,10-tetraazacyclohepta[*de*]naphthalen-10-yl)ethyl)phenyl)carbamate (Example 20-Int-6)**

[658] To the solution of *tert*-butyl (2-(1-(5-chloro-4-fluoro-2-(methylthio)-8,9-dihydro-10*H*-7-oxa-1,3,6,10-tetraazacyclohepta[*de*]naphthalen-10-yl)ethyl)phenyl)carbamate (700 mg, 1.39 mmol) in dioxane (7 mL) / H_2O (0.7 mL) were added ((2-fluoro-6-(methoxymethoxy)-8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-1-yl)ethynyl)triisopropylsilane (709 mg, 1.39 mmol), K_3PO_4 (890 mg, 4.16 mmol) and Ruphos-Pd-G3 (116 mg, 0.14 mmol). The reaction mixture was stirred at 100°C for 2 h under N_2. The reaction mixture was concentrated under reduced pressure. The residue was purified by silica gel chromatography eluted PE/EA = 3:1 to give the desired product *tert*-butyl (2-(1-(4-fluoro-5-(7-fluoro-3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-2-(methylthio)-8,9-dihydro-10*H*-7-oxa-1,3,6,10-tetraazacyclohepta[*de*]naphthalen-10-yl)ethyl)phenyl)carbamate (750 mg, 63%) as a yellow solid. MS: *m/z* = 856.1 ($M+H^+$, ESI+)

[659]

[660] **Step 6: *tert*-butyl (2-(1-(4-fluoro-5-(7-fluoro-3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-2-(methylsulfonyl)-8,9-dihydro-10*H*-7-oxa-1,3,6,10-tetraazacyclohepta[*de*]naphthalen-10-yl)ethyl)phenyl)carbamate (Example 20-Int-7)**

[661] To a solution of *tert*-butyl (2-(1-(4-fluoro-5-(7-fluoro-3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-2-(methylthio)-8,9-dihydro-10*H*-7-oxa-1,3,6,10-tetraazacyclohepta[*de*]naphthalen-10-yl)ethyl)phenyl)carbamate (650 mg, 0.76 mmol) in THF (6 mL)/ H_2O (3 mL) was added Oxone (2.33 g, 3.79 mmol) at 0°C. The mixture was stirred at 25 °C for 2 h. The reaction mixture was quenched with con. $NaHSO_3$ (aq, 20 mL) and extracted with EA (10 mL), dried over Na_2SO_4. The

organic phase was concentrated under reduced pressure to give *tert*-butyl (2-(1-(4-fluoro-5-(7-fluoro-3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-2-(methylsulfinyl)-8,9-dihydro-10*H*-7-oxa-1,3,6,10-tetraazacyclohepta[*de*]naphthalen-10-yl)ethyl)phenyl)carbamate (670 mg, crude) as a yellow solid. MS: *m/z* = 872.3 ($M+H^+$, ESI+)

[662]

[663] **Step 7: *tert*-butyl (2-(1-(4-fluoro-5-(7-fluoro-3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-2-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-8,9-dihydro-10*H*-7-oxa-1,3,6,10-tetraazacyclohepta[*de*]naphthalen-10-yl)ethyl)phenyl)carbamate (Example 20-Int-8)**

[664] To the solution of ((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methanol (167 mg, 1.047 mmol) in THF (7 mL) was added NaH (56 mg, 1.396 mmol) at 0°C under Argon. The mixture was stirred at 0°C for 0.5 h. To the above mixture was added *tert*-butyl (2-(1-(4-fluoro-5-(7-fluoro-3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-2-(methylsulfinyl)-8,9-dihydro-10*H*-7-oxa-1,3,6,10-tetraazacyclohepta[*de*]naphthalen-10-yl)ethyl)phenyl)carbamate (620 mg, 0.698 mmol) at 0°Cunder Argon. The resulting mixture was stirred for additional 1 h at 0°C. The reaction was detected by LCMS. LCMS detected the desired product. The reaction was quenched with the solution of NH_4Cl （60 mL） at 0°C. The resulting mixture was extracted with EA (3×40 mL). The combined organic layers were washed with brine (60 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure to get the desired product *tert*-butyl (2-(1-(4-fluoro-5-(7-fluoro-3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-2-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-8,9-dihydro-10*H*-7-oxa-1,3,6,10-tetraazacyclohepta[*de*]naphthalen-10-yl)ethyl)phenyl)carbamate (600 mg, crude) as a yellow solid. MS: *m/z* = 967.6 ($M+H^+$, ESI+)

[665]

[666] **Step 8: *tert*-butyl (2-(1-(5-(8-ethynyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-4-fluoro-2-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-8,9-dihydro-10*H*-7-oxa-1,3,6,10-tetraazacyclohepta[*de*]naphthalen-10-yl)ethyl)phenyl)carbamate**

[990] 2. Adjust the density of transfected cells to 2×10^5 cells/mL in Opti-MEM without phenol red and mix 20x K-2 tracer with the cells.

[991] 3. Dispense the cell and tracer mixture into 384 wells, place in a 37°C, 5% CO_2 incubator for one hour, and then leave at room temperature for 15 minutes.

[992] 4. Substrate and test compound solutions are treated to 384 wells dispensed with cells and tracers and reacted at room temperature for 15 minutes.

[993] 5. Measurements are made at the donor emission wavelength (460 nm) and the acceptor emission wavelength (600 nm) using the Envision 2104 plate reader.

[994] 6. Calculate the BRET ratio by dividing the acceptor emission value (600 nm) by the donor emission value (460 nm), and correct the background by eliminating the BRET ratio that does not include the tracer.

[995] 7. The BRET reaction is calculated as the BRET ratio *100 when treated with a compound compared to the BRET ratio when treated with DMSO.

[996] 8. The IC_{50} value is calculated based on the sigmoidal dose-response equation in the GraphPad Prism 4 program.

[997]

[998] **<Test Example 3: Cell proliferation assay>**

[999]

[1000] Purpose

[1001] Cell viability testing of test compounds in AsPC-1 pancreatic cancer (KRAS G12D mutation) or SW480 colon cancer (KRAS G12V mutation) cells for 72 hours

[1002]

[1003] Test conditions and procedures

[1004] Materials

[1005] The reference compound Staurosporine was purchased from Sigma-Aldrich (Saint Louis, MI), and CellTiter-Glo® 2.0 Luminescent cell viability assay reagent (cat# G9243) was purchased from Promega (Madison, WI). AsPC-1 and SW480 cell lines were purchased from American Type Culture Collection (Manassas, VA). AsPC-1 cells were cultured with RPMI-1640 (ATCC, cat#30-2001) and SW480 cells were cultured with DMEM (ATCC cat#30-2002). A medium supplemented with 10% FBS (Sigma-Aldrich, cat#F2442) and 100 μg/mL of penicillin-streptomycin (Sigma-Aldrich, cat#P4333) was used. Cells were cultured at 37°C in a humidified atmosphere of 5% CO_2 and 95% air.

[1006]

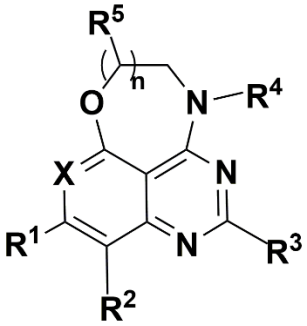
[1007] Test procedure

[1008] 1. The test compound and reference compound, Staurosporine were dissolved in DMSO solution to prepare 20mM (test compound) and 10mM (control compound, Staurosporine) in the Source Plate and diluted with DMSO to 3-fold and 10 doses.

Claims

【**Claim 1**】A compound selected from compounds of Formula 1 and stereoisomers, diastereomers, enantiomers, atropisomers, isotopic variants, tautomers, solvates, and pharmaceutically acceptable salts thereof:

[Formula 1]



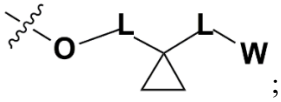
In Formula 1,

X is N or CR^{11};

R^1 is R^{1A}-substituted or unsubstituted phenyl, R^{1A}-substituted or unsubstituted naphthyl, or R^{1A}-substituted or unsubstituted benzothiophenyl;

each R^{1A} is independently selected from hydrogen, hydroxy, a halogen, C_1-C_3 haloalkyl, C_1-C_3 alkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, C_1-C_3 alkoxy, C_3-C_6 cycloalkyl, NH_2, $NH(C_1$-C_3 alkyl), $N(C_1$-C_3 alkyl)$_2$, and CN;

R^2 is hydrogen or a halogen;

R^3 is hydrogen, -O-L-W, or ;

L is a bond or L^A-substituted or unsubstituted C_1-C_3 alkylene;

L^A is hydrogen, a halogen, or C_1-C_3 alkyl;

W is R^6-substituted or unsubstituted C_1-C_3 alkyl, R^6-substituted or unsubstituted 3- to 10-membered monocyclic heterocycle, or R^6-substituted or unsubstituted 6- to 14-membered bicyclic

heterocycle;

each R^6 is independently selected from hydrogen, a halogen, C_1-C_3 haloalkyl, C_1-C_3 alkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, C_1-C_3 alkoxy, C_3-C_6 cycloalkyl, amino, CN, $=CH_2$, oxo(=O), S(C_1-C_3 alkyl), SO_2NH_2, SO_2NH(C_1-C_3 alkyl), SO_2(C_1-C_3 alkyl), SO_2(C_1-C_3 haloalkyl), and halo C_1-C_3 alkoxy;

R^4 is hydrogen, R^{4A}-substituted or unsubstituted C_1-C_6 haloalkyl, R^{4A}-substituted or unsubstituted C_1-C_6 alkyl, R^{4A}-substituted or unsubstituted C_3-C_{10} cycloalkyl, R^{4A}-substituted or unsubstituted C_5-C_8 aryl, R^{4A}-substituted or unsubstituted 3- to 10-membered heterocycle, or R^{4A}-substituted or unsubstituted 5- to 10-membered heteroaryl;

each R^{4A} is independently selected from hydrogen, CN, NR^9R^{10}, =O, OR^7, SR^8, SO_2R^8, $C(O)N(R^7)_2$, $C(O)R^7$, R^{4B}-substituted or unsubstituted C_1-C_6 haloalkyl, R^{4B}-substituted or unsubstituted C_1-C_6 alkyl, R^{4B}-substituted or unsubstituted C_3-C_{10} cycloalkyl, R^{4B}-substituted or unsubstituted C_5-C_8 aryl, R^{4B}-substituted or unsubstituted 3- to 6-membered heterocycle, and R^{4B}-substituted or unsubstituted 5- to 9-membered heteroaryl;

wherein two of R^{4A} together form R^{4B}-substituted or unsubstituted C_3-C_{10} cycloalkyl, R^{4B}-substituted or unsubstituted C_5-C_8 aryl, R^{4B}-substituted or unsubstituted 3- to 10-membered heterocycle, or R^{4B}-substituted or unsubstituted 5- to 10-membered heteroaryl;

each R^{4B} is independently selected from hydrogen, a halogen, C_1-C_3 haloalkyl, C_1-C_3 alkyl, C_3-C_6 cycloalkyl, CN, NR^9R^{10}, =O, C_1-C_3 alkoxy, halo C_1-C_3 alkoxy, hydroxy, SCH_3, SO_2NH_2, SO_2CH_3, $C(O)NH_2$, $C(O)CH_3$, a 3- to 6-membered heterocycle, C_5-C_8 aryl, and 5- or 6-membered heteroaryl;

each R^5 is independently selected from hydrogen, hydroxy, a halogen, C_1-C_3 haloalkyl, and C_1-C_3 alkyl;

each R^7 is independently selected from hydrogen, amino, C_1-C_3 haloalkyl, C_1-C_3 alkyl, C_3-C_6 cycloalkyl, and a 3- or 4-membered heterocycle;

each R^8 is independently selected from hydrogen, amino, and C_1-C_3 alkyl;

R^9 and R^{10} are each independently selected from hydrogen, C_1-C_3 alkyl, C_3-C_6 cycloalkyl, $C(O)NH_2$, $C(O)CH_3$, and a 3- to 6-membered heterocycle;

each R^{11} is independently selected from hydrogen, hydroxy, a halogen, C_1-C_3 haloalkyl, and C_1-C_3 alkyl,

n is an integer selected from 0 to 2; and

wherein the heterocycles or heteroaryls each comprise 1 to 3 heteroatoms independently selected from N, O, and S.

【Claim 2】 The compound of claim 1, wherein

L is methylene;

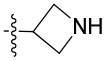
W is R^6-substituted or unsubstituted 3- to 10-membered monocyclic heterocycle or R^6-substituted or unsubstituted 6- to 14-membered bicyclic heterocycle; and

each R^6 is independently selected from a halogen, C_1-C_3 haloalkyl, C_1-C_3 alkyl, C_1-C_3 alkoxy, CN, $=CH_2$, =O, SCH_3, SO_2NH_2, $SO_2NH(CH_3)$, SO_2CH_3, and SO_2CF_3.

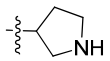
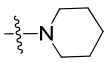
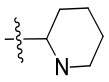
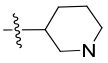
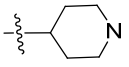
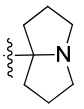
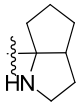
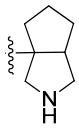
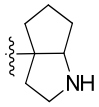
【Claim 3】 The compound of claim 1, wherein

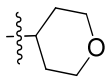
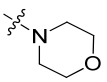
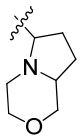
L is methylene;

each W is independently R^6-substituted or unsubstituted





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, or ; and

each R^6 is independently selected from hydrogen, a halogen, C_1-C_3 haloalkyl, C_1-C_3 alkyl, C_1-C_3 alkoxy, CN, $=CH_2$, =O, SCH_3, SO_2NH_2, $SO_2NH(CH_3)$, SO_2CH_3, and SO_2CF_3.

【Claim 4】 The compound of claim 1, wherein

R^4 is R^{4A}-substituted or unsubstituted C_1-C_3 alkyl;

each R^{4A} is independently selected from hydrogen, a halogen, CN, NH_2, $NH(C_1$-C_3 alkyl), $N(C_1$-C_3 alkyl$)_2$, =O, R^{4C}-substituted or unsubstituted C_3-C_6 cycloalkyl, R^{4C}-substituted or unsubstituted phenyl, and R^{4C}-substituted or unsubstituted pyridinyl, R^{4C}-substituted or unsubstituted pyrimidinyl, and R^{4C}-substituted or unsubstituted pyrazinyl;

or wherein two of R^{4A} together form 5- to 10-membered heteroaryl selected from saturated or partially unsaturated isoquinoline or quinoline; and

each R^{4C} is independently selected from hydrogen, a halogen, C_1-C_3 alkyl, NH_2, $NH(C_1$-C_3 alkyl), and $N(C_1$-C_3 alkyl$)_2$.

【Claim 5】 The compound of claim 1, wherein

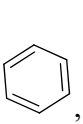
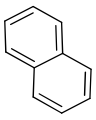
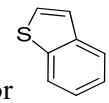
X is CR^{11},

each R^{11} is independently selected from hydrogen, a halogen, C_1-C_3 haloalkyl, and C_1-C_3 alkyl;

R^1 is R^{1A}-substituted or unsubstituted benzothiophenyl;

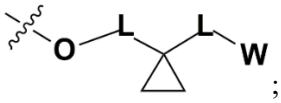
each R^{1A} is independently selected from hydrogen, a halogen, NH_2, $NH(C_1$-C_3 alkyl), $N(C_1$-C_3 alkyl$)_2$, and CN.

【Claim 6】 The compound of claim 1, wherein

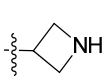
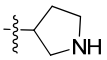
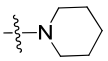
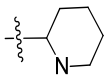
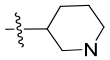
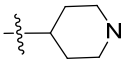
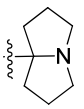
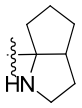
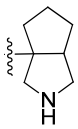
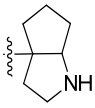
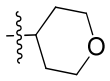
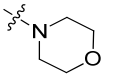
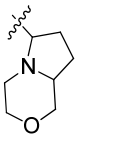
R^1 is , , or 

each substituted or unsubstituted with one or more substituents independently selected hydrogen, hydroxy, a halogen, C_1-C_3 alkyl, C_3-C_6 cycloalkyl, amino, and CN;

R^2 is F;

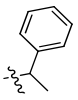
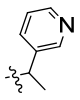
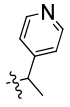
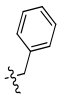
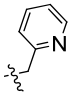
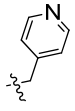
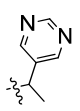
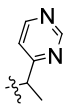
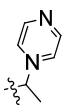
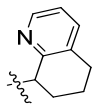
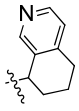
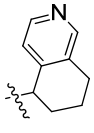
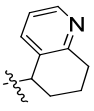
R^3 is hydrogen, -O-L-W, or ;

L is methylene;

W is , , , , , , , , , , , , , , , , , , or ,

each substituted or unsubstituted 1 to 3 times by R^6;

each R^6 is independently selected from hydrogen, a halogen, C_1-C_3 haloalkyl, C_1-C_3 alkyl, C_1-C_3 alkoxy, CN, $=CH_2$, and =O;

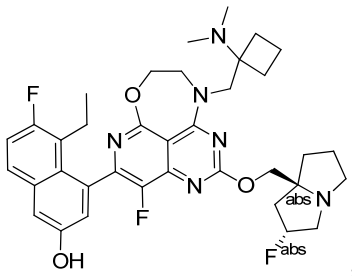
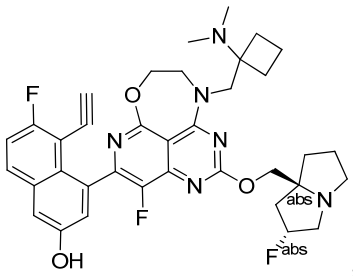
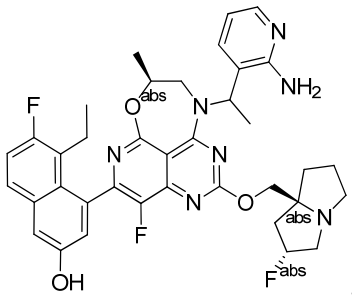
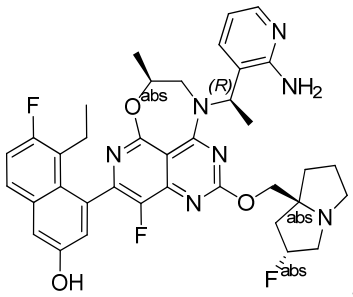
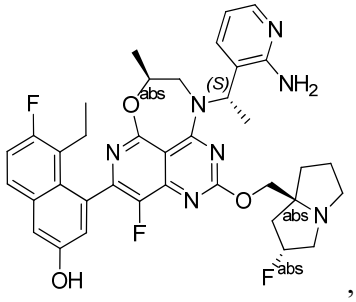
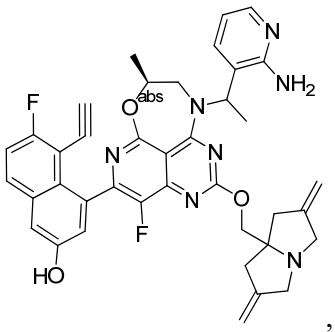
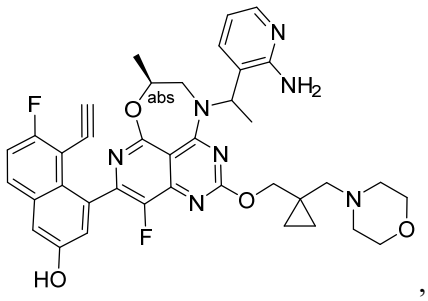
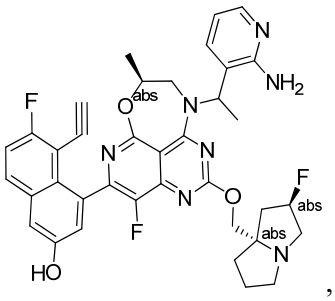
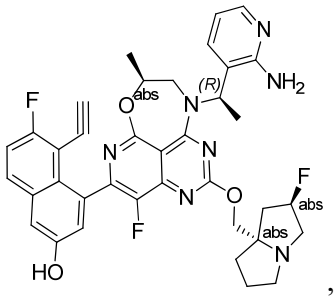
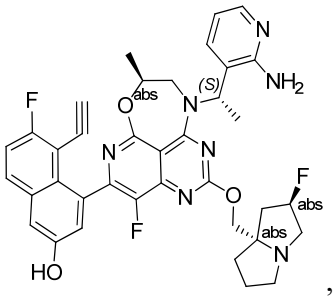
R^4 is , , , , , , , , , , , , , , , , , or ,

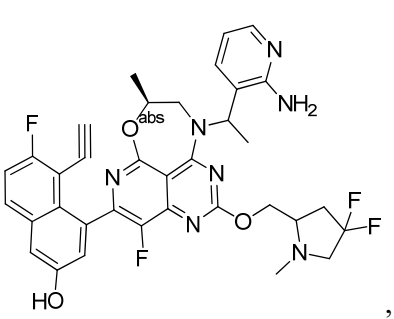
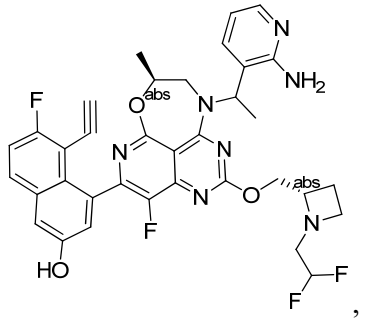
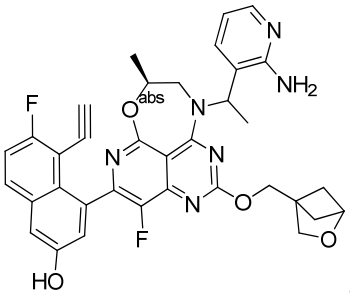
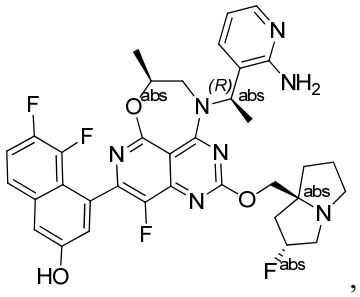
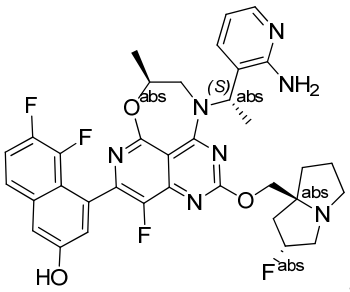
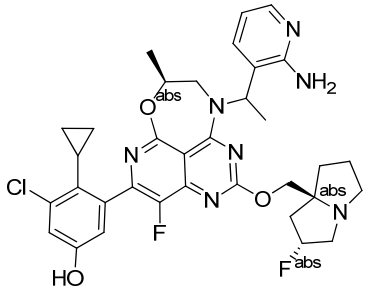
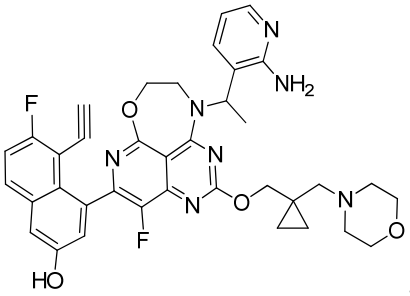
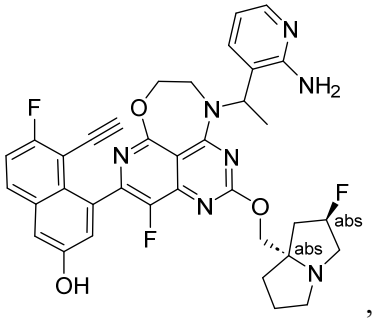
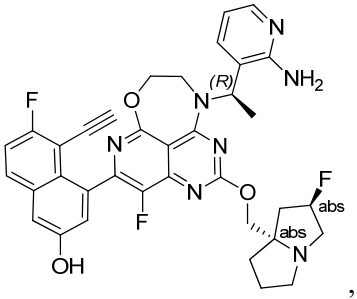
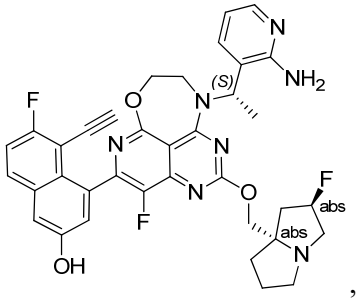
each substituted or unsubstituted with one or more substituents independently selected from hydrogen, a halogen, C_1-C_3 alkyl, NH_2, $NH(C_1$-C_3 alkyl), and $N(C_1$-C_3 alkyl)$_2$; and

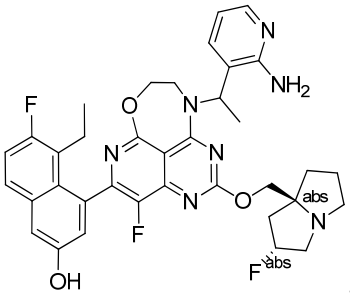
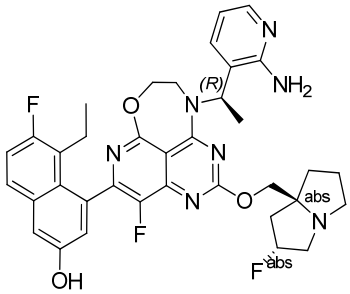
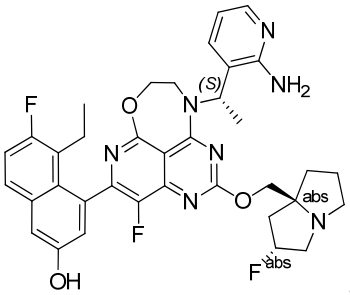
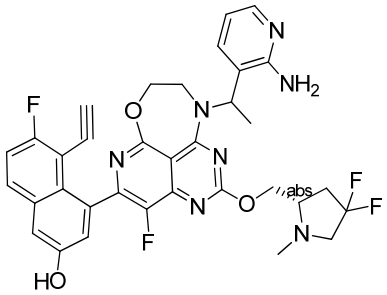
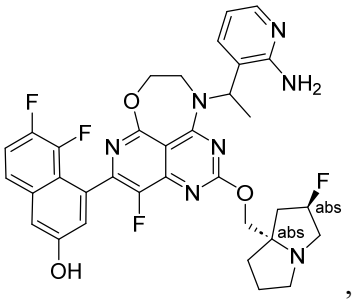
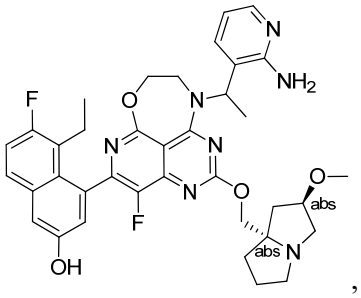
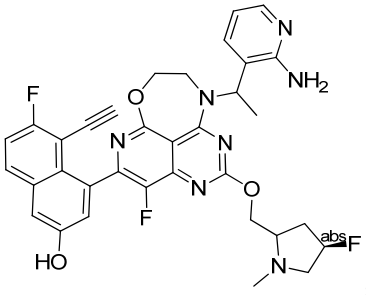
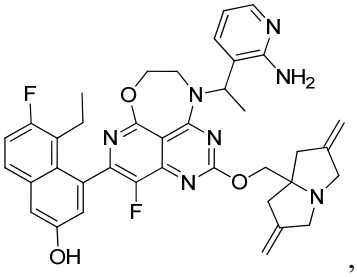
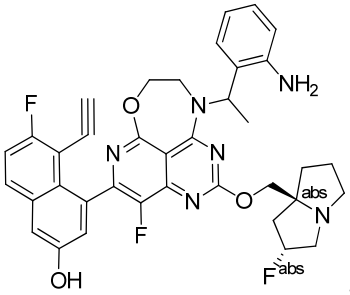
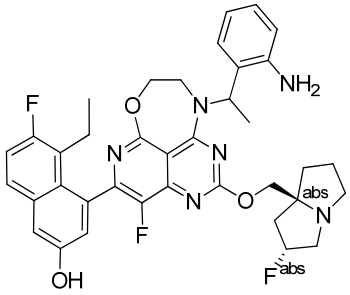
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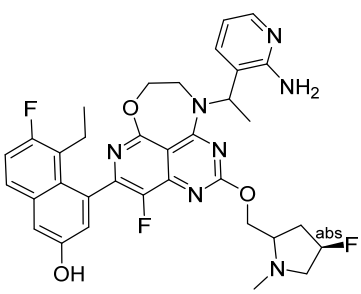
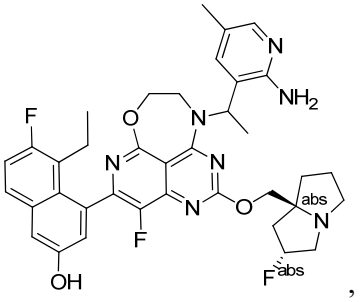
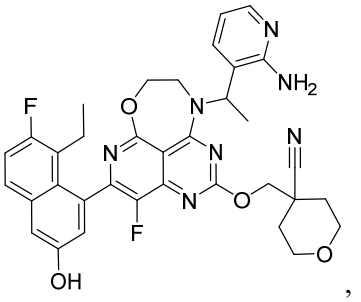
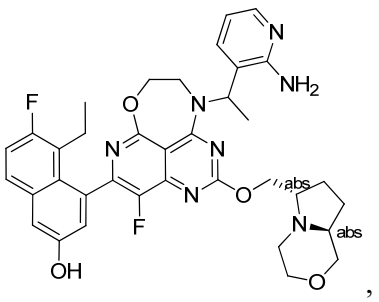
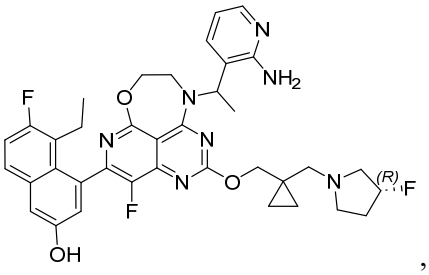
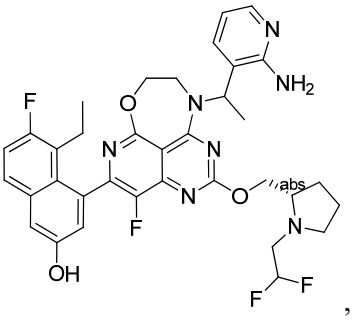
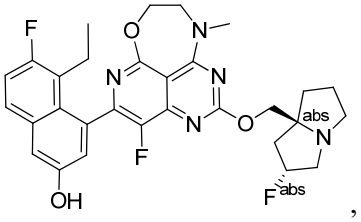
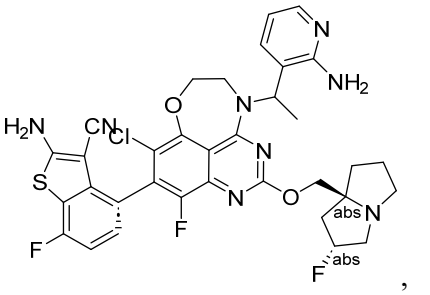
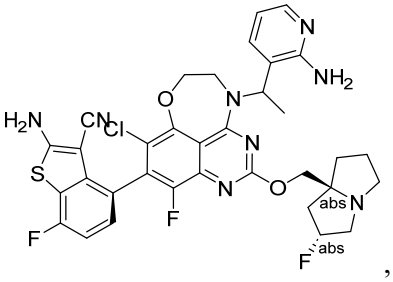
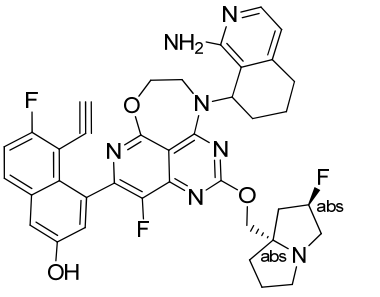
【Claim 7】 The compound of claim 1, wherein the compound is selected from the group consisting of the following compounds and stereoisomers, diastereomers, enantiomers, atropisomers, isotopic

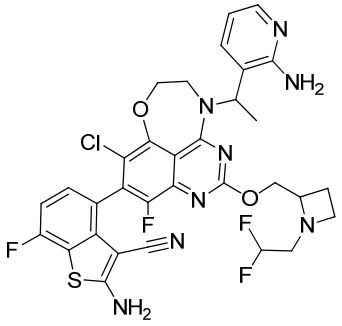
variants, tautomers, solvates, and pharmaceutically acceptable salts thereof:


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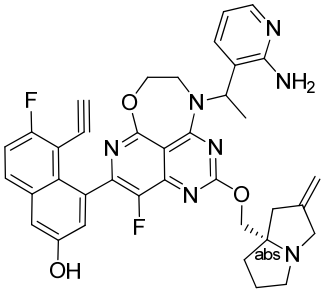

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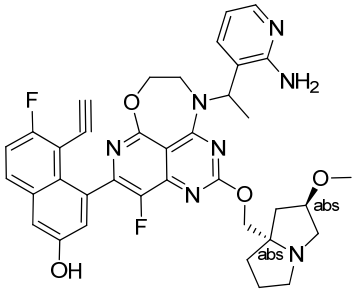

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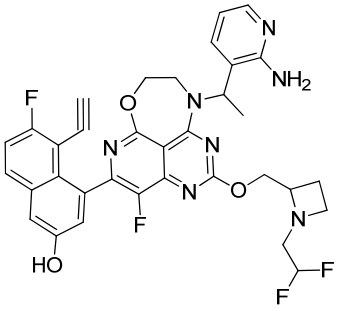
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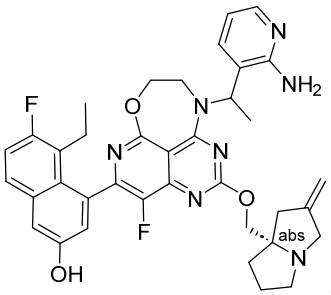
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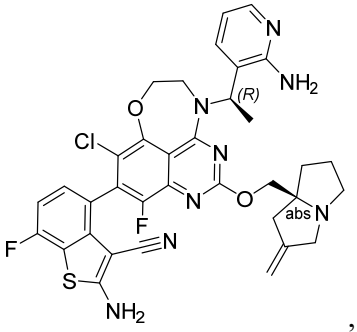
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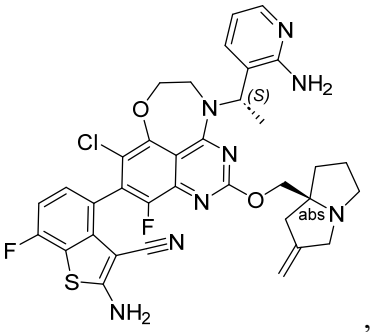
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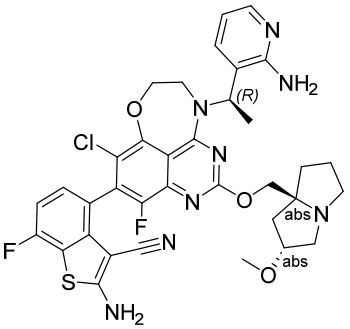
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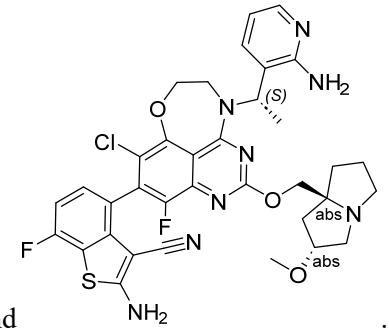


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and  .

【**Claim 8**】Use of the compound of any one of claims 1-7 and stereoisomers, diastereomers, enantiomers, atropisomers, isotopic variants, tautomers, solvates, and pharmaceutically acceptable salts thereof in the manufacture of a pharmaceutical composition for treating cancer.

【**Claim 9**】The use of claim 8, wherein the pharmaceutical composition exhibits KRAS protein inhibitory activity.