ovarian, pancreatic and prostate cancers with DNA damage repair deficient such as BRCA1/2 mutation.

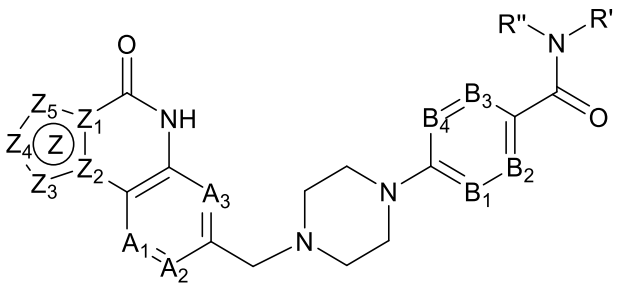
[0005] PARP2 is a protein of 559 amino acids with molecular mass of approximately 62 kDa and composed of DNA binding domain and catalytic domain (Ame et al., 1999 J Biol Chem 274: 17860-17868). The catalytic domain of PARP2 is very similar to that of PARP1. PARP2 is also found to have similar functions to PARP1 and is involved in the repair of DNA damage through BER mechanism (Schreiber et al., 2002 J Biol Chem 277: 23028-23036). Marketed PARP inhibitors, such as Olaparib, Niraparib, Talazoparib and Rucaparib, not only have inhibitory activities against PARP1, but also have similar inhibitory activities against PARP2. Based on the results of clinical trials, the therapeutic effects of these marketed PARP inhibitors are comparable whereas their toxicity profiles are quite different. For example, Talazoparib has toxicity similar to chemotherapy drugs such as hair loss. Talazoparib also shows more potent inhibitory activity against TNKS1/2 (Tankyrase 1 or Tankyrase 2) than other PARP inhibitors (PARPi) in biochemical assay (Ryan et al., 2021, J Biol Chem 296:100251/1-100251/13). TNKS1 and TNKS2 share 83% sequence identity overall, and their catalytic domain sequences are 89% identical. They play roles in DNA repair, telomere maintenance, and Wnt/β-catenin signaling. Targeting PARPs other than PARP1 may be the reason why PARP inhibitors cause off-targeted toxicity, such as hair loss and diarrhea. In addition, inhibition of PARP2 activity has been found to lead to hematotoxicity (Farrés et al., 2013 Blood 122: 44-54; Farrés et al., 2015 Cell Death and Differentiation 22: 1144-1157). The toxicity of these PARP inhibitors limits their clinical application as well as in combination with other targeted drugs.

[0006] Therefore, to improve, enhance and expand the clinical application of PARP inhibitors, it is important to explore highly selective PAPR1 inhibitor to reduce mechanism - related or mechanism - independent toxicity.

[0007] Various PARP1 inhibitors have been disclosed in, for example, WO2011006803, WO2013014038, WO2021013735 and WO2021260092.

Summary of the Disclosure

[0007a] In an aspect of the present disclosure, there is provided a compound of Formula IIIb:



(IIIb)

or stereoisomers, tautomers, N-oxides, hydrates, solvates, isotope-substituted derivatives, or pharmaceutically acceptable salts thereof, or prodrugs thereof, or mixtures thereof, wherein:

Z_1 and Z_2 are independently C or N, with the proviso that Z_1 and Z_2 are not N at the same time; Z_3, Z_4 and Z_5 are independently selected from CR_4, O, S, N, and NR_4; and when Z_1 is N, at least one of Z_3, Z_4 and Z_5 is N; or when Z_1 is N and all of Z_3, Z_4 and Z_5 are CR_4, A_1 is CR_1;

each R_4 is independently selected from hydrogen, halogen and an optionally substituted alkyl;

A_1, A_2 and A_3 are independently selected from N and CR_1;

R_1 is selected from hydrogen, halogen, an optionally substituted alkyl, an optionally substituted alkoxy and an optionally substituted carbocyclic group;

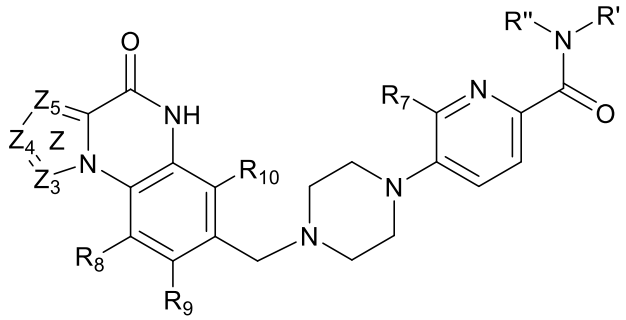
B_1, B_2, B_3 and B_4 are independently selected from N and CR_7;

each R_7 is independently selected from hydrogen, halogen, an optionally substituted alkyl, an optionally substituted alkoxy, an optionally substituted carbocyclic group, an optionally substituted alkenyl and an optionally substituted alkynyl; and

R' and R" are independently selected from hydrogen, an optionally substituted $C_{1\text{-}10}$ alkyl, an optionally substituted cycloalkyl, an optionally substituted aryl and an optionally substituted heteroaryl, optionally wherein R' and R" are independently deuterated $C_{1\text{-}3}$ alkyl; or

B_3 and R" together with the attached aminoacyl group form a 6-membered heterocyclic group.

[0007b] In another aspect of the present disclosure, there is provided a compound of Formula IVb:



(IVb)

or stereoisomers, tautomers, N-oxides, hydrates, solvates, isotope-substituted derivatives, or pharmaceutically acceptable salts thereof, or prodrugs thereof, or mixtures thereof, wherein:

Z_3, Z_4 and Z_5 are independently selected from CR_4, O, S, N, and NR_4;

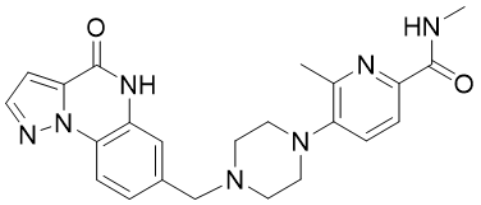
each R_4 is independently selected from hydrogen, halogen and an optionally substituted alkyl;

R_7 is selected from hydrogen, halogen, an optionally substituted alkyl, an optionally substituted alkoxy, an optionally substituted carbocyclic group, an optionally substituted alkenyl and an optionally substituted alkynyl;

R' and R" are independently selected from hydrogen, an optionally substituted C_{1-10} alkyl, an optionally substituted cycloalkyl, an optionally substituted aryl and an optionally substituted heteroaryl, optionally wherein R' and R" are independently deuterated C_{1-3} alkyl; and

R_8, R_9 and R_{10} are independently selected from hydrogen, halogen, an optionally substituted alkyl, and an optionally substituted alkoxy.

[0007c] In a further aspect of the present disclosure, there is provided a compound selected from: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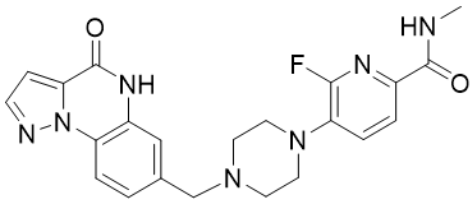
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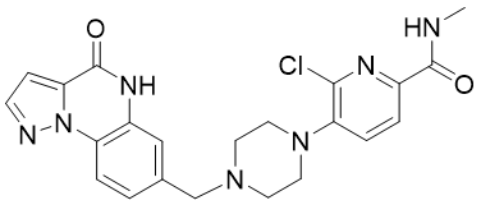
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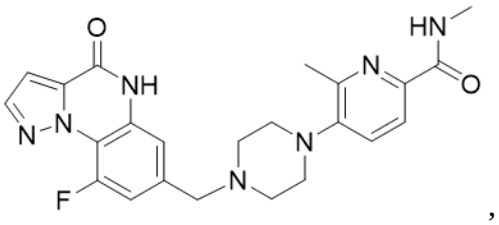
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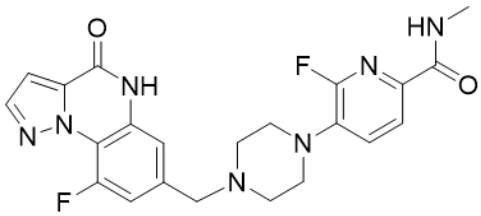
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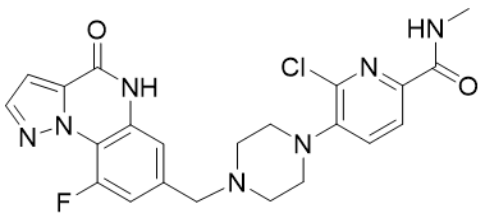
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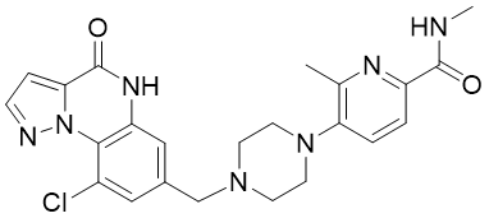
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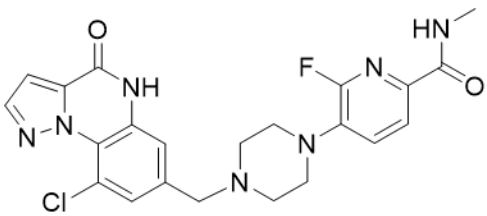
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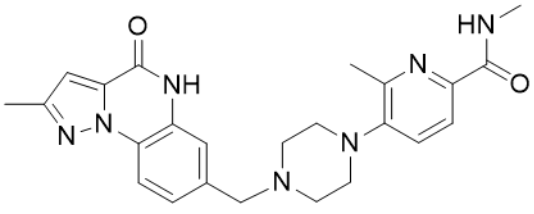
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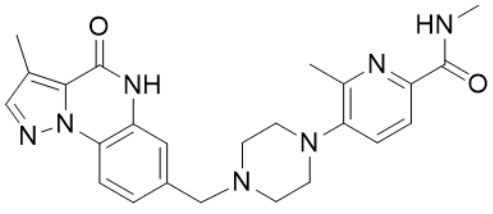
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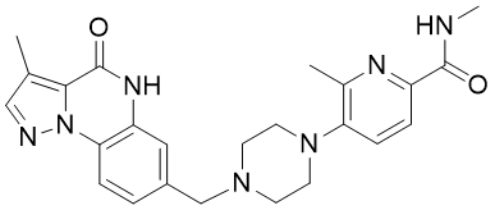
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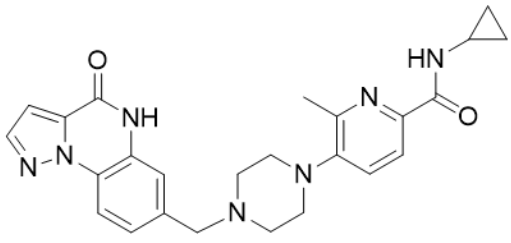
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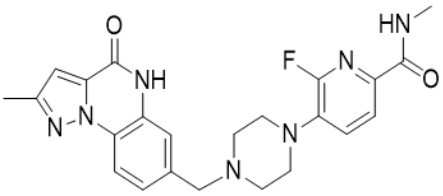
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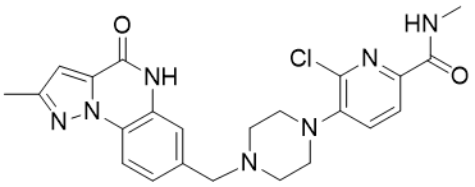
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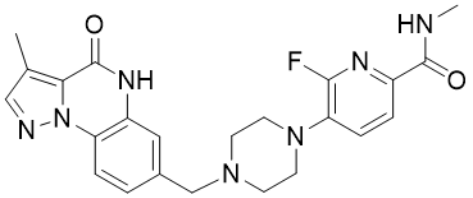
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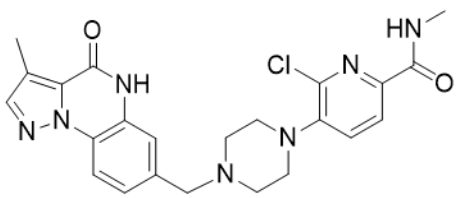
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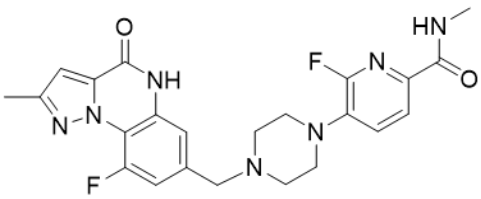
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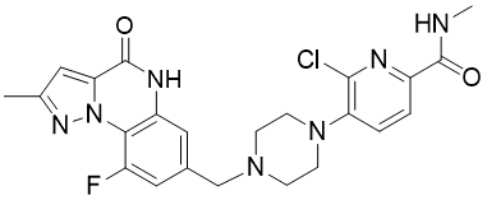
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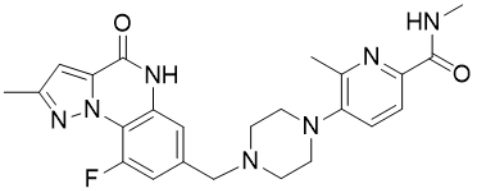
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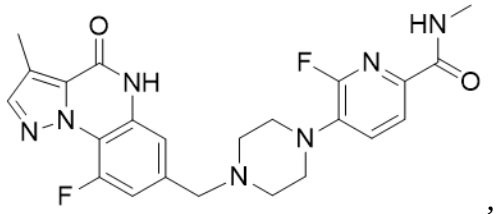
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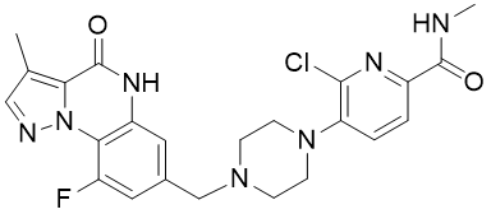
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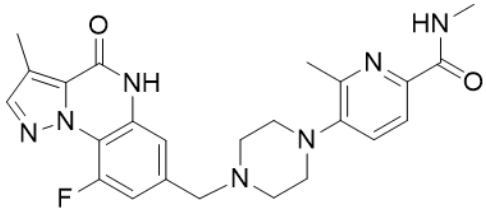
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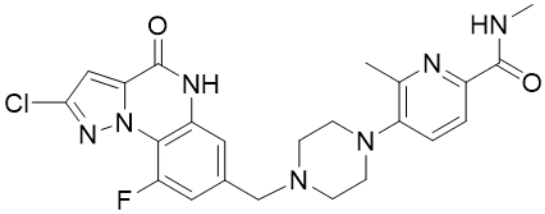
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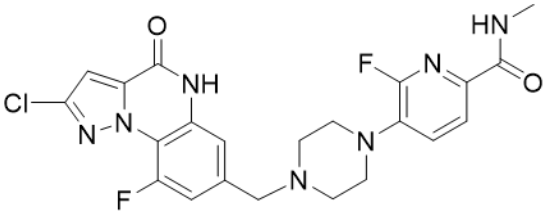
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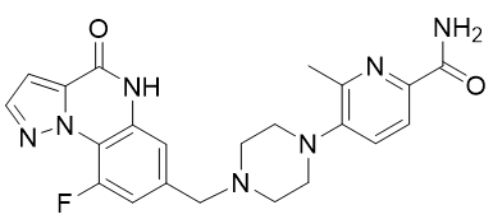
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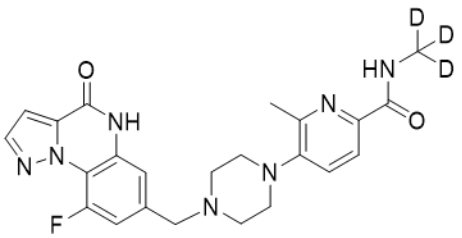
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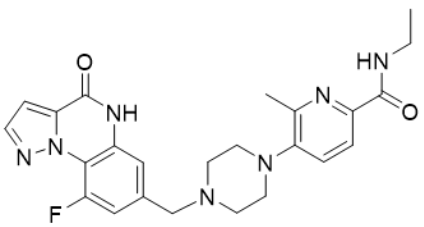
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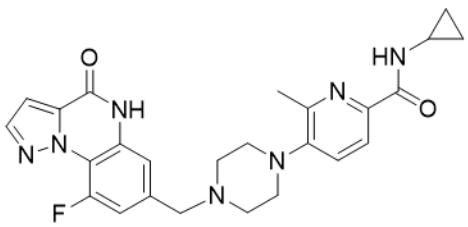
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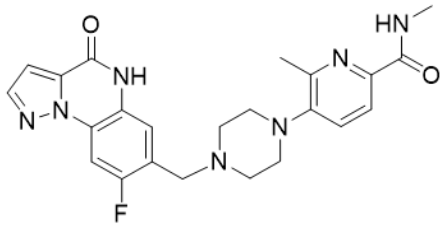
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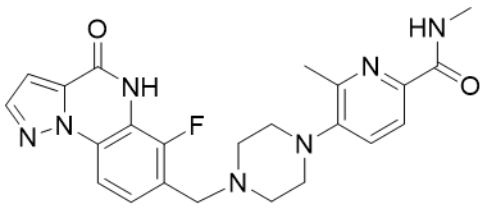
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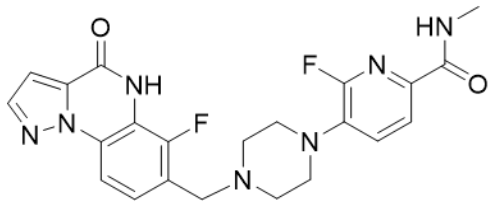
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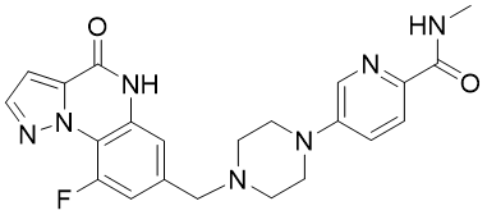
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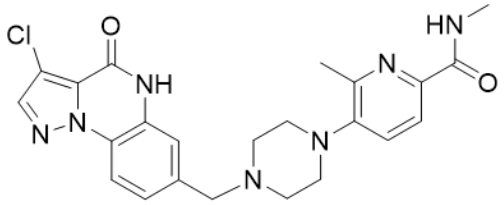
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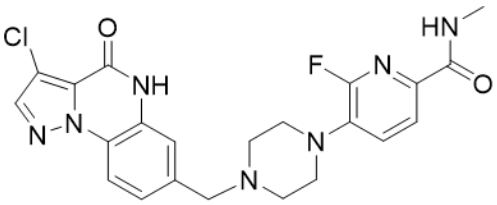
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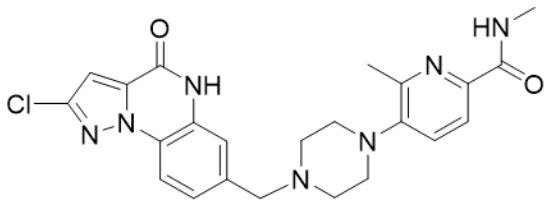
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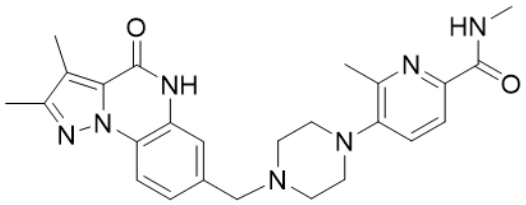
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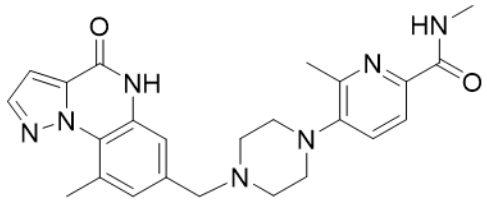
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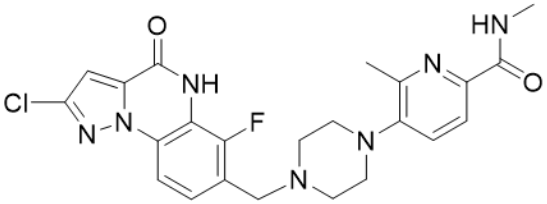
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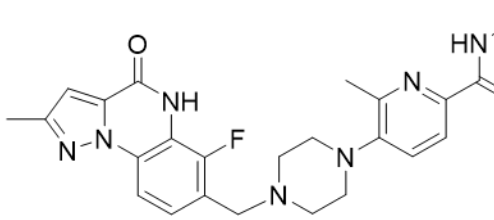
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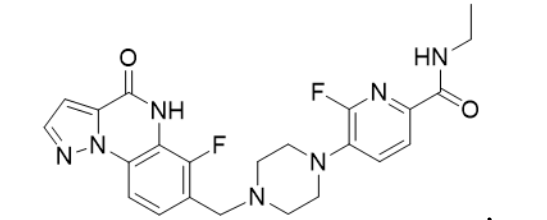
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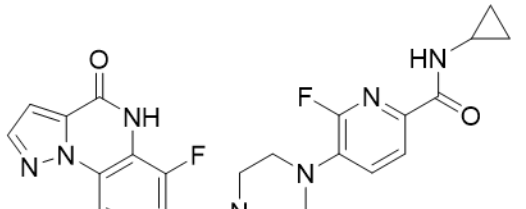
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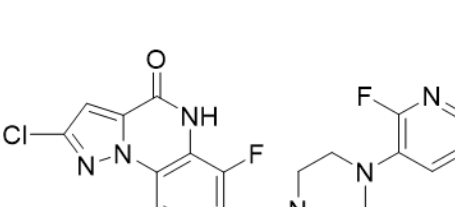
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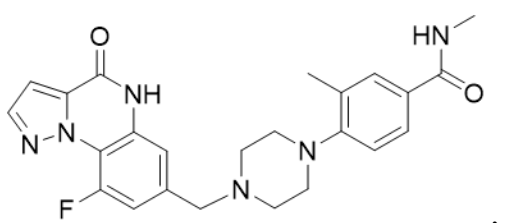
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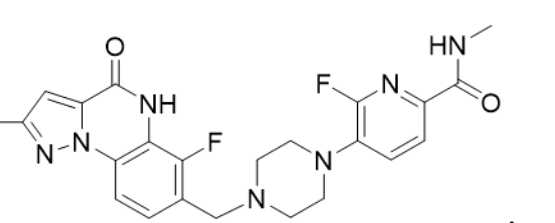
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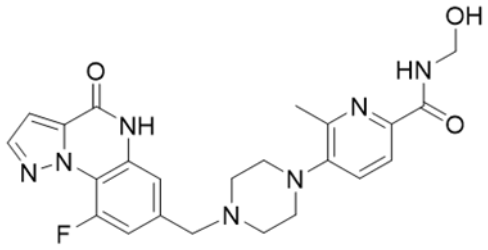
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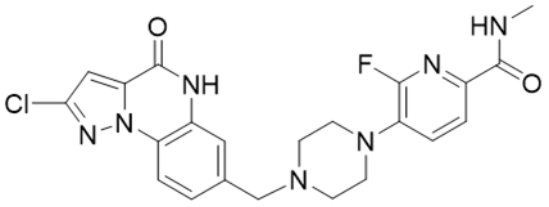
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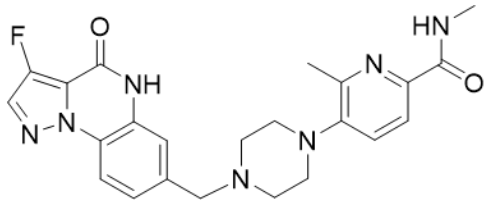
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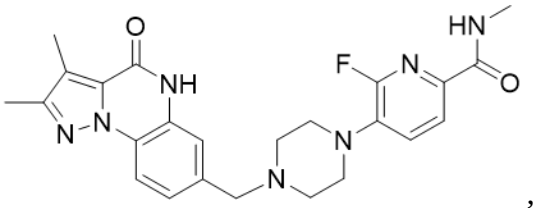
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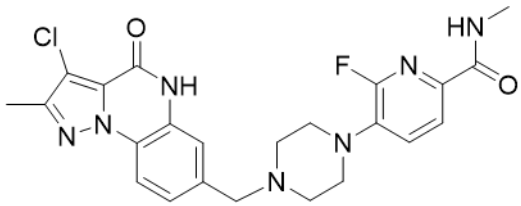
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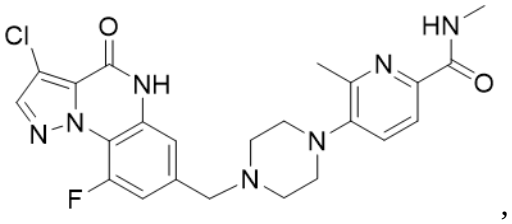
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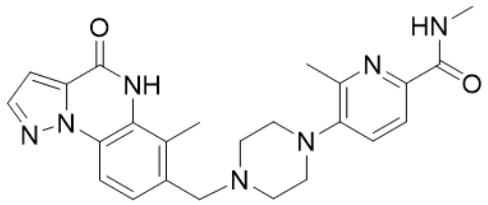
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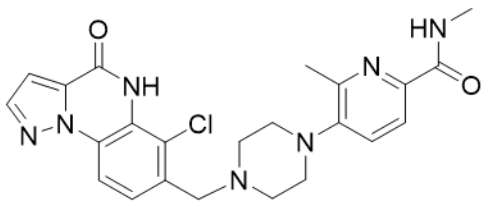
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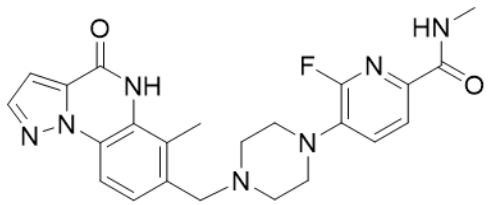
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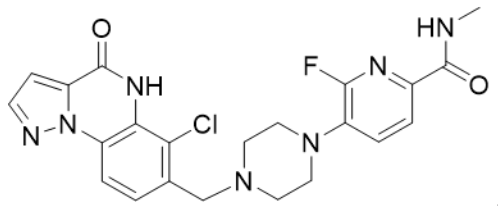
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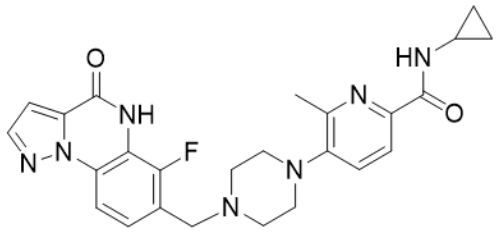
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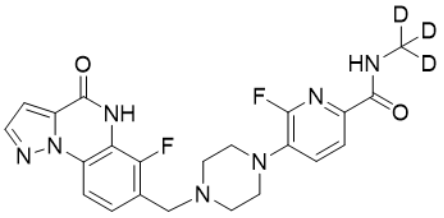
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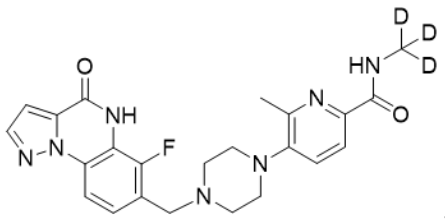
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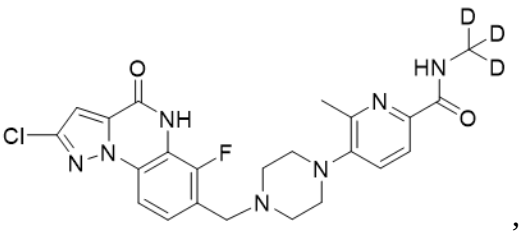
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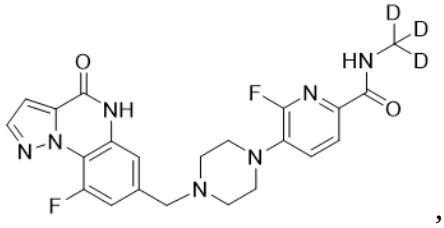
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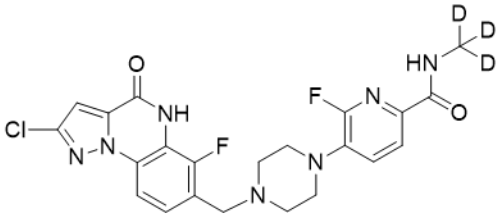
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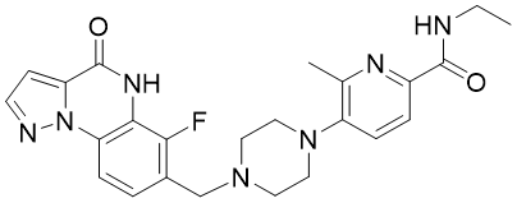

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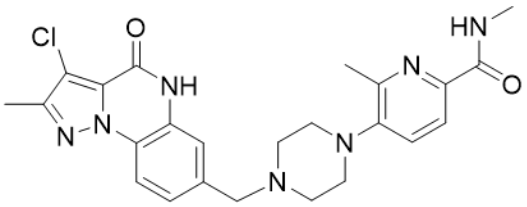

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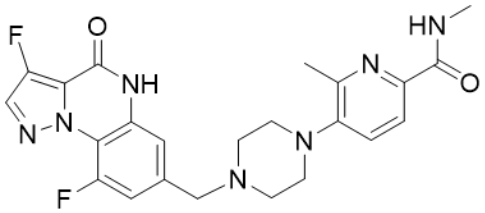

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or stereoisomers, tautomers, N-oxides, hydrates, solvates, isotope-substituted derivatives, or pharmaceutically acceptable salts thereof, or prodrugs thereof, or mixtures thereof.

[0007d] In another aspect of the present disclosure, there is provided a pharmaceutical composition comprising the compound as disclosed herein, or stereoisomers, tautomers, N-oxides, hydrates, solvates, isotope-substituted derivatives, or pharmaceutically acceptable salts thereof, or prodrugs thereof, or mixtures thereof, and a pharmaceutically acceptable carrier.

[0007e] In a further aspect of the present disclosure, there is provided a use of the compound as disclosed herein, or stereoisomers, tautomers, N-oxides, hydrates, isotope-substituted derivatives, solvates or pharmaceutically acceptable salts thereof, or prodrugs thereof, or mixtures thereof, or the pharmaceutical composition as disclosed herein, in the manufacture of a medicament for treating or preventing a disease or condition responsive to the inhibition of PARP activity in a subject in need thereof.

[0007f] In another aspect of the present disclosure, there is provided a compound as disclosed herein, or stereoisomers, tautomers, N-oxides, hydrates, isotope-substituted derivatives, solvates or pharmaceutically acceptable salts thereof, or prodrugs thereof, or mixtures thereof, or the pharmaceutical composition as disclosed herein, for use in therapy.

[0008] The disclosure provides compounds and analogues thereof as represented by Formula I (including Formulae II, III and IV). The compounds can be used as PARP inhibitors. In particular, the compounds of the disclosure are selective PARP1 inhibitors relative to PARP2.

[0009] The disclosure also provides pharmaceutical compositions comprising an effective amount of the compound of Formula I (including Formulae II, III and IV). The pharmaceutical compositions can be used for the treatment of cancer.

[0010] In a specific example, the pharmaceutical composition may further contain one or more pharmaceutically acceptable carriers, excipients or diluents.

[0011] In a specific example, the pharmaceutical composition may further contain at least one known anticancer drug or pharmaceutically acceptable salts thereof.

[0012] The disclosure is also directed to methods for the preparation of novel compounds of Formula I (including Formulae II, III and IV).

[0013] The disclosure also provides a method for treating or preventing a diseases or conditions responsive to the inhibition of PARP activity (especially PARP1 activity), comprising administering to a subject in need thereof an effective amount of the compound of Formula I (including Formulae II, III and IV) or a pharmaceutically acceptable salt thereof.

Detailed Description of the Disclosure

[0014] It should be understood that the characteristics of the embodiments described herein can be arbitrarily combined to form the technical solution of this disclosure. The definition of each group herein can apply to any of the embodiments described herein. For example, the definitions of the substituents of alkyl herein apply to any of the embodiments described herein unless the substituents of alkyl are clearly defined in the embodiment.

[0015] The term "hydrogen (H)" as empolyed herein includes its isotopes D and T.

[0016] The term "heteroatoms" as empolyed herein includes O, S and N.

[0017] The term "alkyl" as used herein refers to alkyl itself or a straight or branched chain radical of up to ten carbons. Useful alkyl groups include straight-chain or branched C_{1-10} alkyl groups, preferably C_{1-6} alkyl groups. In some embodiments, alkyl is C_{1-4} alkyl. In some embodiments, alkyl is C_{1-3} alkyl. In some embodiments, alkyl is deuterated C_{1-3} alkyl. Typical C_{1-10} alkyl groups include methyl, methyl-d3, ethyl, propyl, isopropyl, butyl, *sec*-butyl, *tert*-butyl, pentyl (such as 3-pentyl), hexyl and octyl groups, which may be optionally substituted.

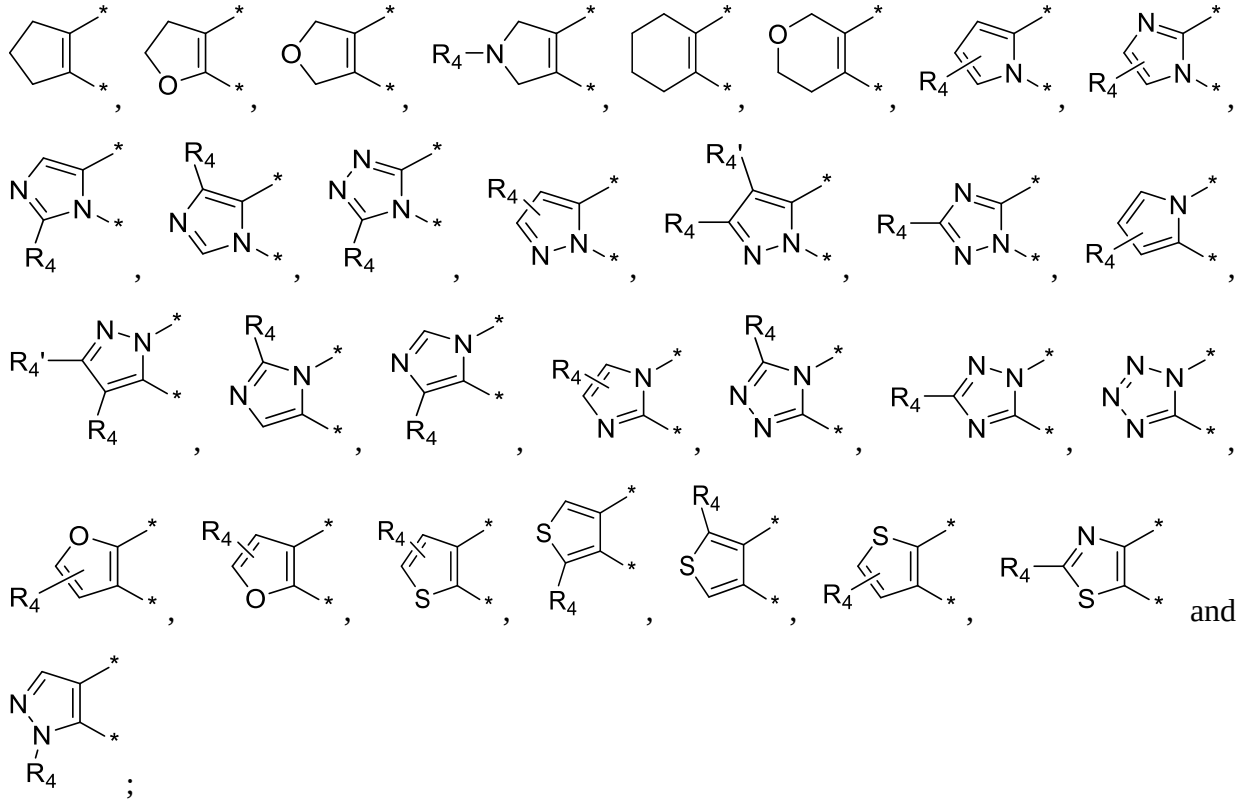
[0018] The term "alkenyl" as used herein refers to a straight or branched chain radical of 2-10 carbon atoms, unless the chain length is limited thereto, wherein there is at least one double bond between two of the carbon atoms in the chain; preferably, C_{2-6} alkenyl. Typical alkenyl groups include ethenyl, 1-propenyl, 2-propenyl, 2-methyl-1-propenyl, 1-butenyl and 2-butenyl.

[0019] The term "alkynyl" as used herein refers to a straight or branched chain radical of 2-10 carbon atoms, unless the chain length is limited thereto, wherein there is at least one triple bond between two of the carbon atoms in the chain; preferably, C_{2-6} alkynyl. Typical alkynyl groups include ethynyl, 1-propynyl, 1-methyl-2-propynyl, 2-propynyl, 1-butynyl and 2-butynyl.

[0020] Useful alkoxy groups include oxygen substituted by the above mentioned C_{1-10} alkyl groups, preferred C_{1-6} alkyl groups or C_{1-4} alkyl groups, e.g., methoxy, ethoxy, etc. The alkyl in the alkoxy groups may be optionally substituted. Substituents of alkoxy groups include, without limitation, halogen, morpholino, amino (including alkylamino and dialkylamino), and carboxy (including esters thereof).

heteroaryl and heterocyclic group can each be independently selected from 1-5 groups consisting of C_{1-4} alkyl, halogenated C_{1-4} alkyl, C_{1-4} alkoxy, halogen, hydroxyl, carboxyl, amino (-NR'R"), an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted heterocyclic group, halogen, amido, aminoacyl (-C(O)-NR'R") and carboxyl, etc.; wherein R' and R" each are independently hydrogen, an optionally substituted C_{1-10} alkyl, an optionally substituted C_{3-8} cycloalkyl, an optionally substituted aryl or an optionally substituted heteroaryl. Preferably, R' and R" each are independently hydrogen, an optionally substituted C_{1-4} alkyl, an optionally substituted C_{3-6} cycloalkyl. The number of substituents may be 1-5. The said optionally substituted aryl, optionally substituted heteroaryl and optionally substituted heterocyclic group may be optionally substituted by 1-5 groups selected from C_{1-4} alkyl, halogenated C_{1-4} alkyl, C_{1-4} alkoxy, halogen, hydroxyl, amino (-NR'R"), aminoacyl (-C(O)-NR'R") and carboxyl, wherein, the said R' and R" are preferably each independently H, optionally substituted C_{1-4} alkyl or optionally substituted C_{3-6} cycloalkyl. It should be understood, when the substituent is aryl, heteroaryl, heterocyclic group, cyano, nitro and carboxyl, the number thereof is usually 1. When the substituent is halogen, the number of substituents can be up to 5.

[0039] In one or more embodiments of the compound of Formula I, the Z ring is selected from the following groups:



preferably the Z ring is selected from the following groups:

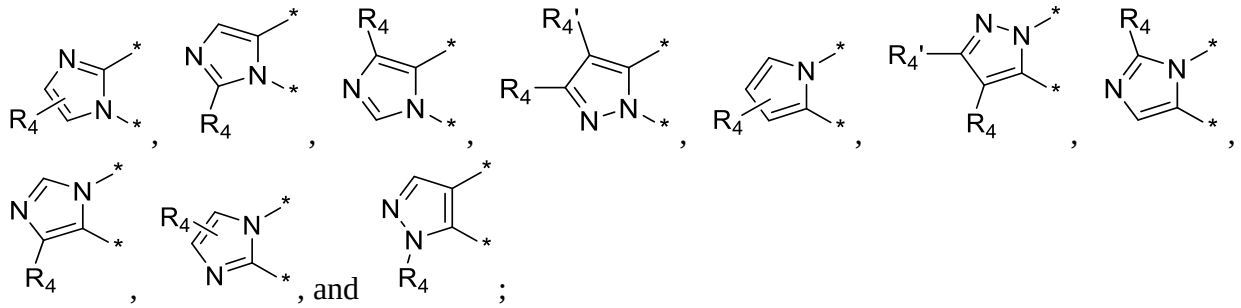
wherein each R_4 is independently selected from a group consisting of hydrogen, halogen and an optionally substituted alkyl, preferably hydrogen, halogen and an optionally substituted C_{1-3} alkyl; each R_4' is independently selected from a group consisting of hydrogen, halogen and an optionally substituted alkyl, preferably hydrogen, halogen and an optionally substituted C_{1-3} alkyl. In some embodiments, each R_4 is independently selected from a group consisting of hydrogen and an optionally substituted alkyl, preferably hydrogen and an optionally substituted C_{1-3} alkyl.

[0089] In one or more embodiments of the compound of Formula IV (including Formulae IVa, IVb and IVc), R_8, R_9 and R_{10} each are preferably hydrogen, halogen, an optionally substituted C_{1-3} alkyl or an optionally substituted C_{1-3} alkoxy, more preferably, R_8, R_9 and R_{10} each are hydrogen, C_{1-3} alkyl or halogen. In some embodiments, R_8 is C_{1-3} alkyl or halogen, and both of R_9 and R_{10} are H. In some embodiments, R_9 is C_{1-3} alkyl or halogen, and both of R_8 and R_{10} are H. In some embodiments, both of R_8 and R_9 are H, and R_{10} is C_{1-3} alkyl or halogen. In some embodiments, all of R_8, R_9 and R_{10} are H. Preferably, R_8 is C_{1-3} alkyl or halogen, both of R_9 and R_{10} are H; or both of R_8 and R_9 are H, R_{10} is C_{1-3} alkyl or halogen.

[0090] In one or more embodiments of the compound of Formula IV (including Formulae IVa, IVb and IVc), R_7 is selected from a group consisting of hydrogen, halogen, an optionally substituted C_{1-3} alkyl, and an optionally substituted C_{1-3} alkoxy, preferably, R_7 is H, C_{1-3} alkyl, C_{1-3} alkoxy, halogenated C_{1-3} alkyl or halogen. More preferably, R_7 is H, C_{1-3} alkyl or halogen.

[0091] In one or more embodiments of the compound of Formula IV, R' and R" each are independently hydrogen, an optionally substituted C_{1-4} alkyl or an optionally substituted C_{3-6} cycloalkyl; Preferably, R' is hydrogen, R" is hydrogen, C_{1-3} alkyl, halogenated C_{1-3} alkyl, hydroxy C_{1-3} alkyl or C_{3-6} cycloalkyl. More preferably, R' is hydrogen, R" is hydrogen, C_{1-3} alkyl, halogenated C_{1-3} alkyl, or hydroxy C_{1-3} alkyl.

[0092] In one or more embodiments of the compound of Formula IV, the 5-membered ring containing Z_3, Z_4 and Z_5 is selected from the following groups:


, and ;

wherein each R_4 is independently selected from a group consisting of hydrogen, halogen and C_{1-3} alkyl; each R_4' is independently selected from a group consisting of hydrogen, halogen and C_{1-3} alkyl; preferably, the 5-membered ring containing Z_3, Z_4 and Z_5 is selected from the following groups:

e) Preparation of 7-(bromomethyl)-1,5-dihydro-4H-pyrazolo[4,3-c]quinolin-4-one: A solution of tert-butyl 7-(hydroxymethyl)-4-oxo-4,5-dihydro-1H-pyrazolo[4,3-c]quinoline-1-carboxylate (450 mg, 1.3 mmol) in HBr (48% in water,10 mL) was stirred at 85°C for 3 hours. The reaction mixture was concentrated under reduced pressure. Acetonitrile (3 ml) was added to the crude product and the mixture was concentrated under reduced pressure to give the title compound (crude, off-white solid, 300 mg). MS(ESI, m/z): 275.85 $[M+H]^+$.

f) Preparation of tert-butyl 7-(bromomethyl)-4-oxo-4,5-dihydro-1H-pyrazolo[4,3-c]quinoline-1-carboxylate: To a solution of 7-(bromomethyl)-1,5-dihydro-4H-pyrazolo[4,3-c]quinolin-4-one (353 mg, 1.2 mmol) in DMF (4 mL) was added di-tert-butyl dicarbonate (287 mg, 1.3mmol) and DMAP (20 mg, 0.14 mmol) at room temperature. The mixture was stirred at room temperature 2 hours. The mixture was added water (20 ml) and extracted with EA (40 mL × 2). The combined organic phase was washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica gel (DCM/MeOH=10:1) to afford the title compound (131 mg, yellow solid, 33 %). MS(ESI, m/z): 378.00 $[M+H]^+$.

g) Preparation of tert-butyl 7-((4-(2-methyl-6-(methylcarbamoyl)pyridin-3-yl)piperazin-1-yl)methyl)-4-oxo-4,5-dihydro-1H-pyrazolo[4,3-c]quinoline-1-carboxylate: To a solution of tert-butyl 7-(bromomethyl)-4-oxo-4,5-dihydro-1H-pyrazolo[4,3-c]quinoline-1-carboxylate (13 mg, 0.34 mmol), KI (10.0 mg, 0.1 mmol) and N,6-dimethyl-5-(piperazin-1-yl)picolinamide (81 mg, 0.34 mmol) in acetonitrile (3 mL) was added DIEA (140.0 mg, 1.0 mmol) at room temperature under N_2. The resulting suspension was stirred at 80°C for 30 min. After completion, the solvent was removed under reduced pressure. The residue was washed with acetonitrile to give the title compound (95.0 mg, white solid, yield: 52 %). MS(ESI, m/z): 532.25 $[M+H]^+$.

h) Preparation of 7-((4-(2-methyl-6-(methylcarbamoyl)quinolin-3-yl)piperazin-1-yl)methyl)-1,5-dihydro-4H-pyrazolo[4,3-c]quinoline-4-one: To solution of tert-butyl 7-((4-(2-methyl-6-(methylcarbamoyl)pyridin-3-yl)piperazin-1-yl)methyl)-4-oxo-4,5-dihydro-1H-pyrazolo[4,3-c]quinoline-1-carboxylate (95 mg, 0.17 mmol) in dioxane (5 mL) was added HCl/dioxane (5 mL) under N_2. The resulting suspension was stirred at room temperature for 2 h. After completion, the solvent was removed under reduced pressure. The residue was purified by Prep-TLC (DCM/MeOH=10/1) to afford the target compound (5.0 mg, white solid, yield: 6 %).

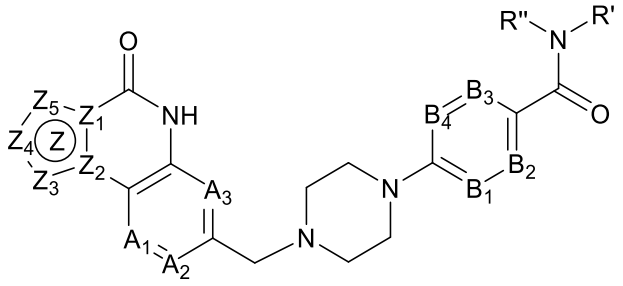
The following compounds of Examples 107-108, 121-122, 138-139, 143 and 149 were prepared using a synthesis method similar to that described in Example 83.

The following compounds of Examples 109-117, 123-130, 133-137, 140-142, 144, and 146-148 were prepared using a synthesis method similar to that described in Example 73.

The compound of Example 118 was prepared using a synthesis method similar to that described in Example 48.

WHAT IS CLAIMED IS:

1. A compound of Formula IIIb:



(IIIb)

or stereoisomers, tautomers, N-oxides, hydrates, solvates, isotope-substituted derivatives, or pharmaceutically acceptable salts thereof, or prodrugs thereof, or mixtures thereof, wherein:

Z_1 and Z_2 are independently C or N, with the proviso that Z_1 and Z_2 are not N at the same time; Z_3, Z_4 and Z_5 are independently selected from CR_4, O, S, N, and NR_4; and when Z_1 is N, at least one of Z_3, Z_4 and Z_5 is N; or when Z_1 is N and all of Z_3, Z_4 and Z_5 are CR_4, A_1 is CR_1;

each R_4 is independently selected from hydrogen, halogen and an optionally substituted alkyl;

A_1, A_2 and A_3 are independently selected from N and CR_1;

R_1 is selected from hydrogen, halogen, an optionally substituted alkyl, an optionally substituted alkoxy and an optionally substituted carbocyclic group;

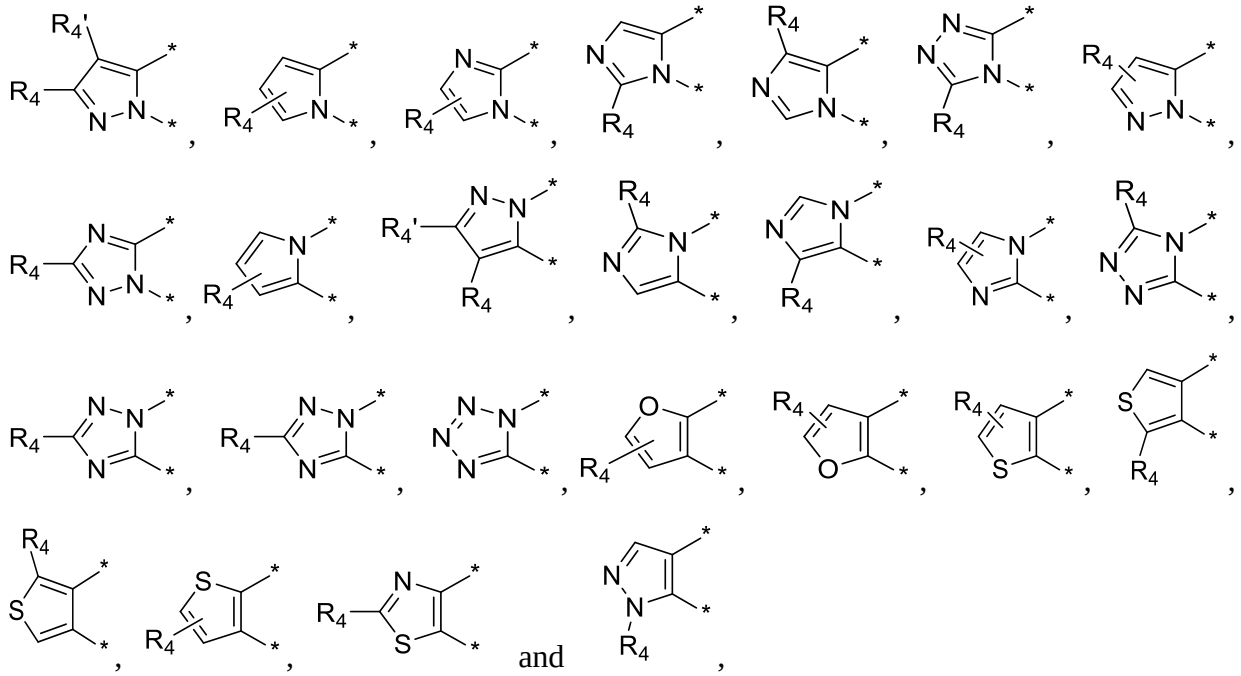
B_1, B_2, B_3 and B_4 are independently selected from N and CR_7;

each R_7 is independently selected from hydrogen, halogen, an optionally substituted alkyl, an optionally substituted alkoxy, an optionally substituted carbocyclic group, an optionally substituted alkenyl and an optionally substituted alkynyl; and

R' and R" are independently selected from hydrogen, an optionally substituted C_{1-10} alkyl, an optionally substituted cycloalkyl, an optionally substituted aryl and an optionally substituted heteroaryl, optionally wherein R' and R" are independently deuterated C_{1-3} alkyl; or

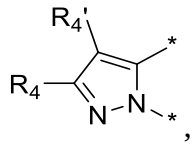
B_3 and R" together with the attached aminoacyl group form a 6-membered heterocyclic group.

2. The compound of claim 1, or stereoisomers, tautomers, N-oxides, hydrates, solvates, isotope-substituted derivatives, or pharmaceutically acceptable salts thereof, or prodrugs thereof, or mixtures thereof, wherein the Z ring is selected from:



wherein R_4 and R_4' are independently selected from hydrogen, halogen and an optionally substituted alkyl.

3. The compound of claim 2, or stereoisomers, tautomers, N-oxides, hydrates, solvates, isotope-substituted derivatives, or pharmaceutically acceptable salts thereof, or prodrugs thereof, or mixtures thereof, wherein the Z ring is:



wherein R_4 and R_4' are independently selected from hydrogen, halogen and an optionally substituted alkyl.

4. The compound of claim 3, or stereoisomers, tautomers, N-oxides, hydrates, solvates, isotope-substituted derivatives, or pharmaceutically acceptable salts thereof, or prodrugs thereof, or mixtures thereof, wherein

each R_1 is independently selected from hydrogen, halogen, and C_{1-3} alkyl.

5. The compound of claim 4, or stereoisomers, tautomers, N-oxides, hydrates, solvates, isotope-substituted derivatives, or pharmaceutically acceptable salts thereof, or prodrugs thereof, or mixtures thereof, wherein each R_7 is independently hydrogen, halogen, C_{1-3} alkyl, C_{1-3} alkoxy, or halogenated C_{1-3} alkyl.

6. The compound of claim 5, or stereoisomers, tautomers, N-oxides, hydrates, solvates, isotope-substituted derivatives, or pharmaceutically acceptable salts thereof, or prodrugs thereof,

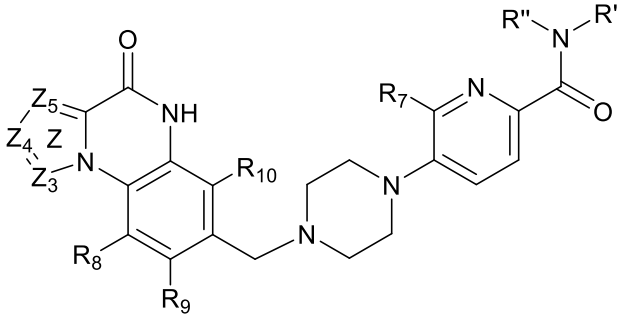
or mixtures thereof, wherein each R_7 is independently selected from hydrogen, C_{1-3} alkyl, halogenated C_{1-3} alkyl, and halogen.

7. The compound of claim 5, or stereoisomers, tautomers, N-oxides, hydrates, solvates, isotope-substituted derivatives, or pharmaceutically acceptable salts thereof, or prodrugs thereof, or mixtures thereof, wherein R' and R" are independently hydrogen, an optionally substituted C_{1-3} alkyl, or an optionally substituted C_{3-6} cycloalkyl, optionally wherein R' and R" are independently deuterated C_{1-3} alkyl.

8. The compound of claim 7, or stereoisomers, tautomers, N-oxides, hydrates, solvates, isotope-substituted derivatives, or pharmaceutically acceptable salts thereof, or prodrugs thereof, or mixtures thereof, wherein R' is hydrogen and R" is hydrogen, C_{1-3} alkyl, C_{3-6} cycloalkyl, or deuterated C_{1-3} alkyl.

9. The compound of claim 8, or stereoisomers, tautomers, N-oxides, hydrates, solvates, isotope-substituted derivatives, or pharmaceutically acceptable salts thereof, or prodrugs thereof, or mixtures thereof, wherein R_4 and R_4' are independently selected from hydrogen, halogen, and an optionally substituted C_{1-3} alkyl.

10. A compound of Formula IVb:



(IVb)

or stereoisomers, tautomers, N-oxides, hydrates, solvates, isotope-substituted derivatives, or pharmaceutically acceptable salts thereof, or prodrugs thereof, or mixtures thereof, wherein:

Z_3, Z_4 and Z_5 are independently selected from CR_4, O, S, N, and NR_4;

each R_4 is independently selected from hydrogen, halogen and an optionally substituted alkyl;

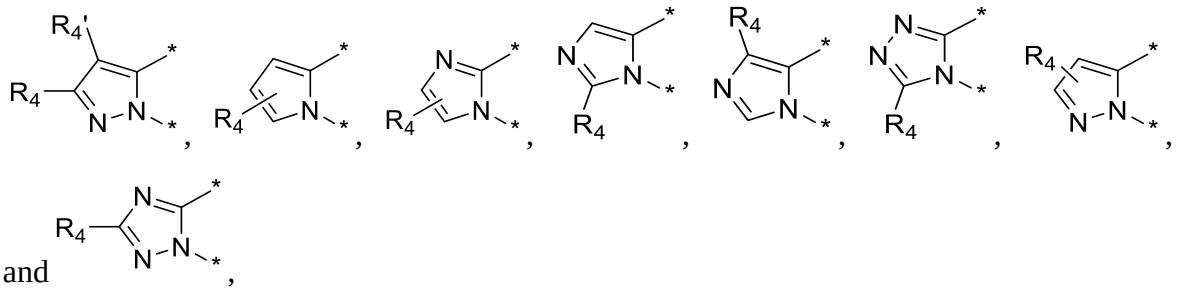
R_7 is selected from hydrogen, halogen, an optionally substituted alkyl, an optionally substituted alkoxy, an optionally substituted carbocyclic group, an optionally substituted alkenyl and an optionally substituted alkynyl;

R' and R" are independently selected from hydrogen, an optionally substituted C_{1-10} alkyl, an optionally substituted cycloalkyl, an optionally substituted aryl and an optionally substituted heteroaryl, optionally wherein R' and R" are independently deuterated C_{1-3} alkyl; and

R_8, R_9 and R_{10} are independently selected from hydrogen, halogen, an optionally substituted alkyl, and an optionally substituted alkoxy.

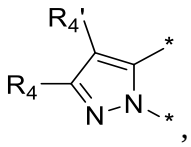
11. The compound of claim 10, or stereoisomers, tautomers, N-oxides, hydrates, solvates, isotope-substituted derivatives, or pharmaceutically acceptable salts thereof, or prodrugs thereof, or mixtures thereof, wherein

the 5-membered ring containing Z_3, Z_4 and Z_5 is selected from:



wherein R_4 and R_4' are independently selected from hydrogen, halogen and an optionally substituted alkyl.

12**.** The compound of claim 11, or stereoisomers, tautomers, N-oxides, hydrates, solvates, isotope-substituted derivatives, or pharmaceutically acceptable salts thereof, or prodrugs thereof, or mixtures thereof, wherein the Z ring is:



wherein R_4 and R_4' are independently selected from hydrogen, halogen and an optionally substituted alkyl.

13. The compound of claim 12, or stereoisomers, tautomers, N-oxides, hydrates, solvates, isotope-substituted derivatives, or pharmaceutically acceptable salts thereof, or prodrugs thereof, or mixtures thereof, wherein R_4 and R_4' are independently selected from hydrogen, halogen, and an optionally substituted C_{1-3} alkyl.

14. The compound of claim 13, or stereoisomers, tautomers, N-oxides, hydrates, solvates, isotope-substituted derivatives, or pharmaceutically acceptable salts thereof, or prodrugs thereof,

or mixtures thereof, wherein R_7 is hydrogen, C_{1-3} alkyl, C_{1-3} alkoxy, halogenated C_{1-3} alkyl or halogen.

15. The compound of claim 14, or stereoisomers, tautomers, N-oxides, hydrates, solvates, isotope-substituted derivatives, or pharmaceutically acceptable salts thereof, or prodrugs thereof, or mixtures thereof, wherein R_7 is hydrogen, C_{1-3} alkyl, or halogen.

16. The compound of claim 15, or stereoisomers, tautomers, N-oxides, hydrates, solvates, isotope-substituted derivatives, or pharmaceutically acceptable salts thereof, or prodrugs thereof, or mixtures thereof, wherein R' and R" are independently hydrogen, an optionally substituted C_{1-3} alkyl, or an optionally substituted C_{3-6} cycloalkyl, optionally wherein R' and R" are independently deuterated C_{1-3} alkyl.

17. The compound of claim 16, or stereoisomers, tautomers, N-oxides, hydrates, solvates, isotope-substituted derivatives, or pharmaceutically acceptable salts thereof, or prodrugs thereof, or mixtures thereof, wherein R' is hydrogen and R" is hydrogen, C_{1-3} alkyl, C_{3-6} cycloalkyl, or deuterated C_{1-3} alkyl.

18. The compound of claim 17, or stereoisomers, tautomers, N-oxides, hydrates, solvates, isotope-substituted derivatives, or pharmaceutically acceptable salts thereof, or prodrugs thereof, or mixtures thereof, wherein R_8, R_9 and R_{10} are independently hydrogen, C_{1-3} alkyl or halogen.

19. The compound of claim 18, or stereoisomers, tautomers, N-oxides, hydrates, solvates, isotope-substituted derivatives, or pharmaceutically acceptable salts thereof, or prodrugs thereof, or mixtures thereof, wherein R_8 is C_{1-3} alkyl or halogen, and both of R_9 and R_{10} are hydrogen.

20. The compound of claim 18, or stereoisomers, tautomers, N-oxides, hydrates, solvates, isotope-substituted derivatives, or pharmaceutically acceptable salts thereof, or prodrugs thereof, or mixtures thereof, wherein both of R_8 and R_9 are hydrogen, and R_{10} is C_{1-3} alkyl or halogen.

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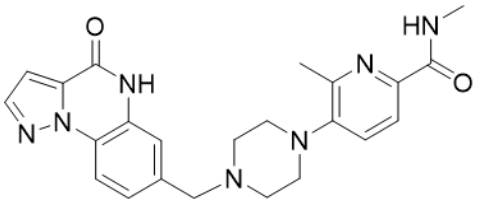

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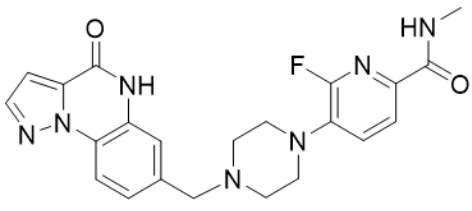

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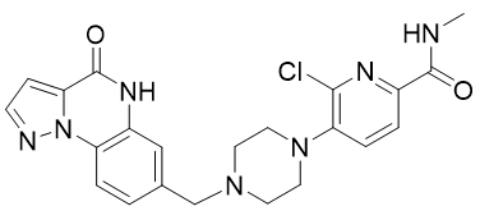

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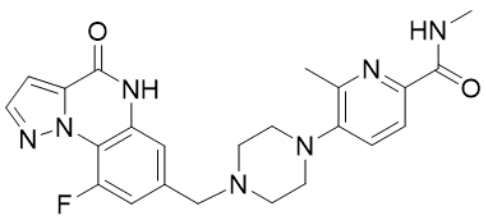

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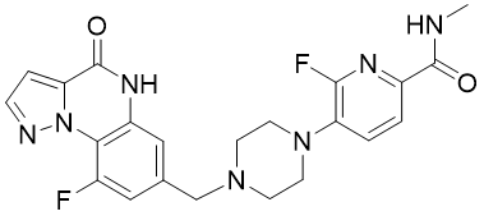
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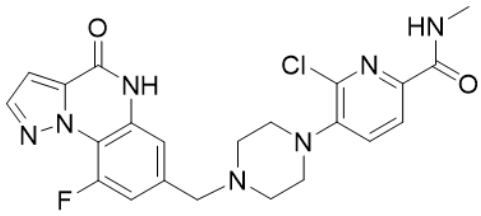
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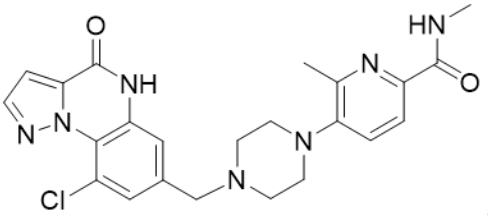
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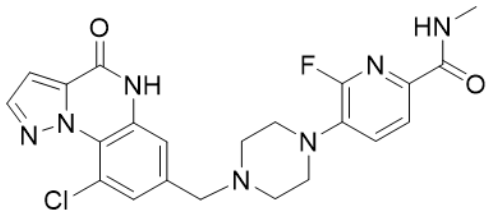
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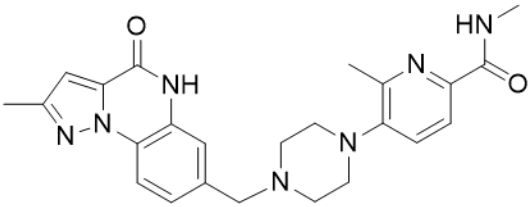
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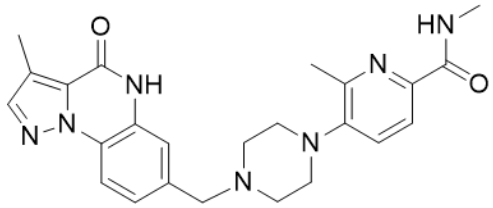
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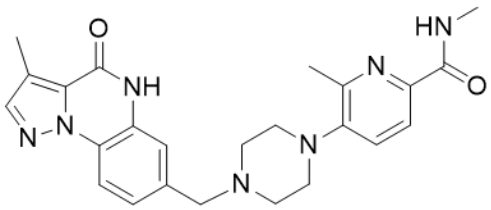
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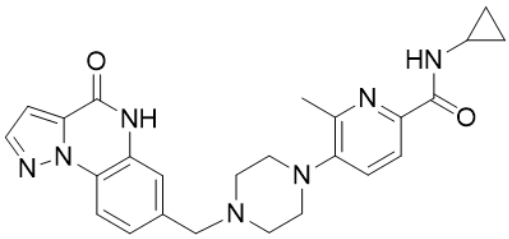
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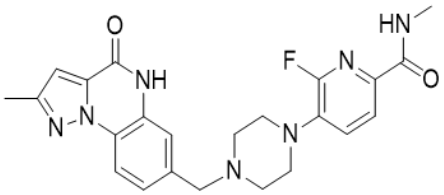
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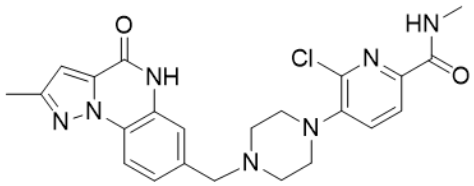
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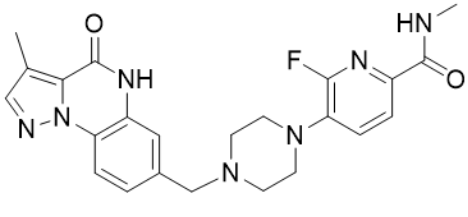
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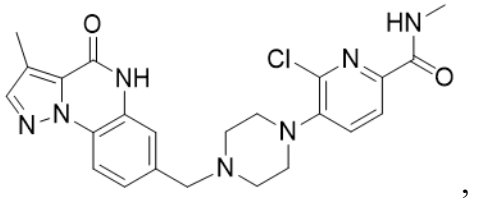
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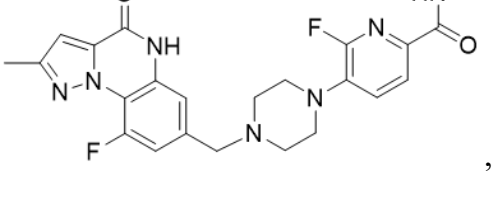
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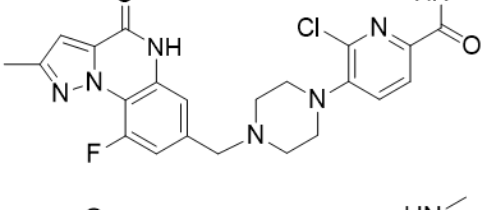
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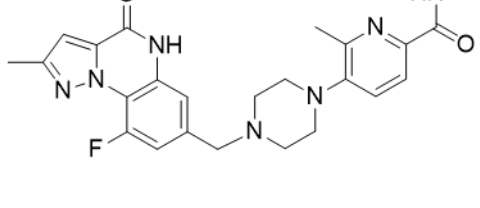
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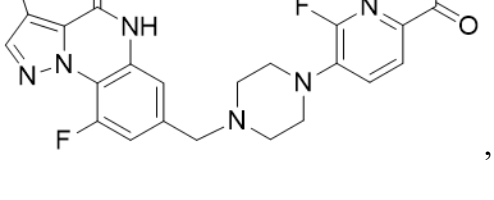
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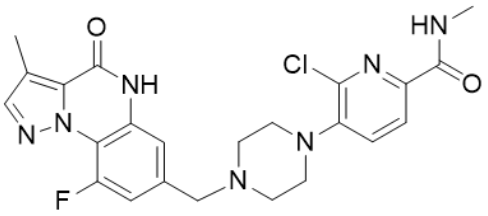
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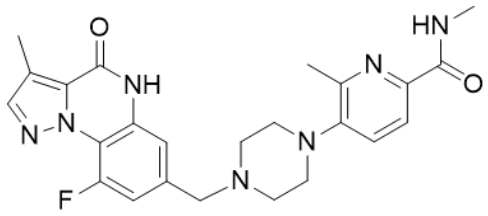
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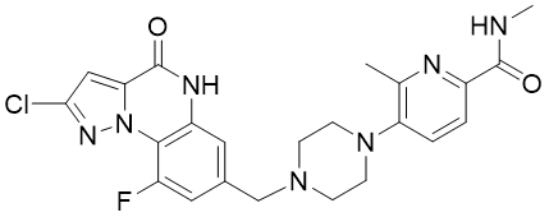
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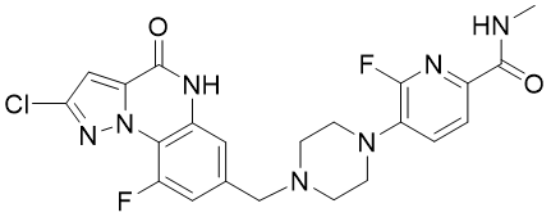
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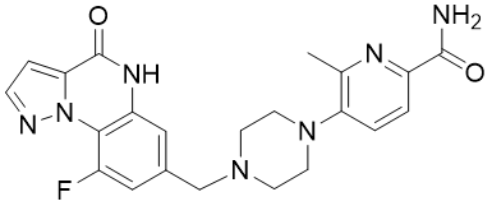
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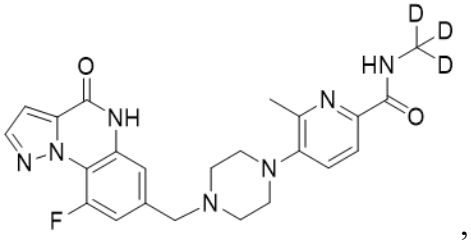
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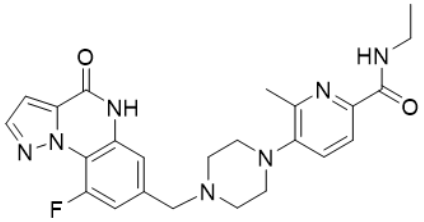
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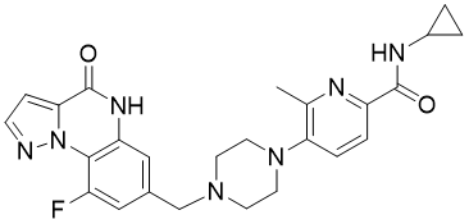
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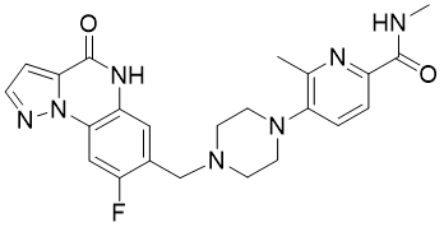
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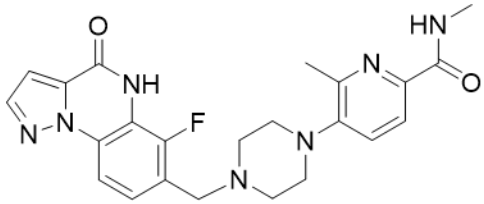
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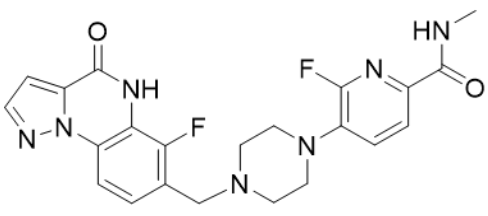
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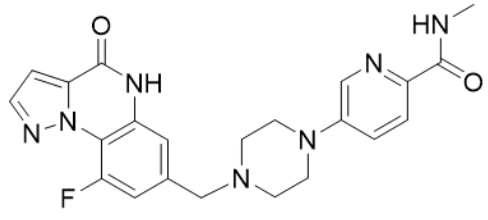
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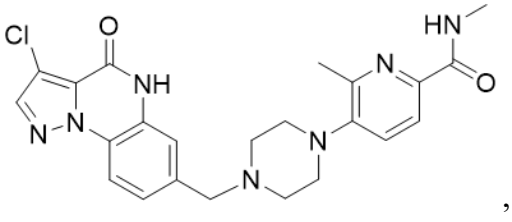
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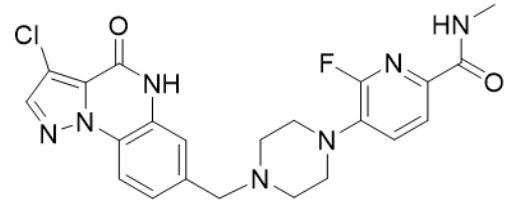
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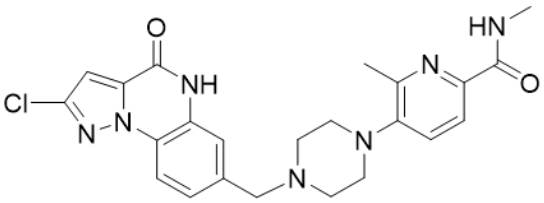
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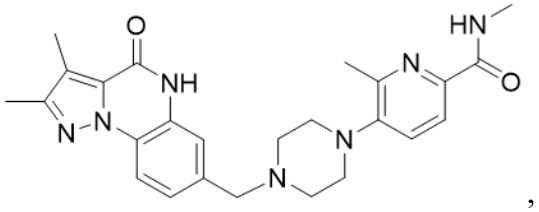
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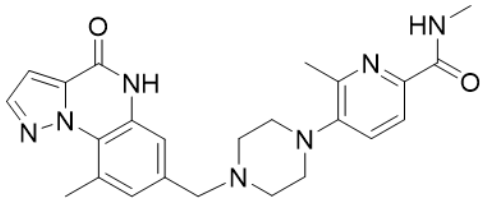
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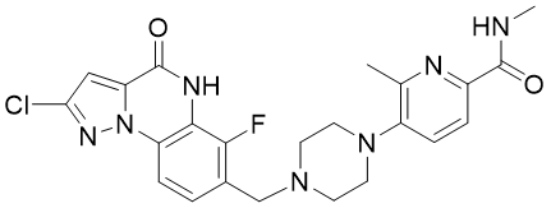
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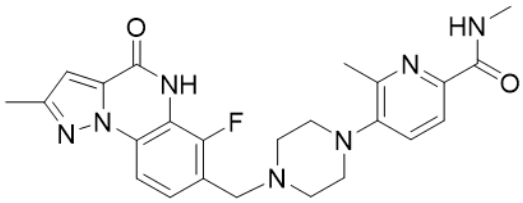
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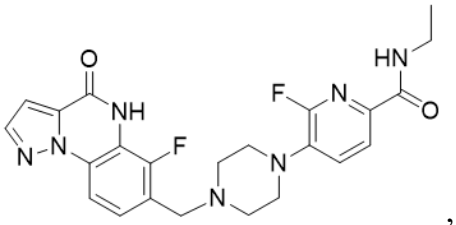
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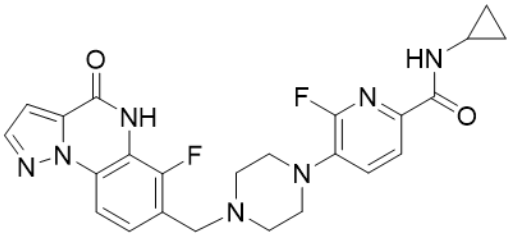
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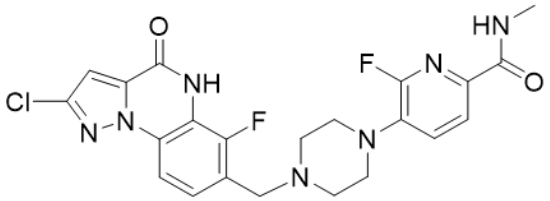
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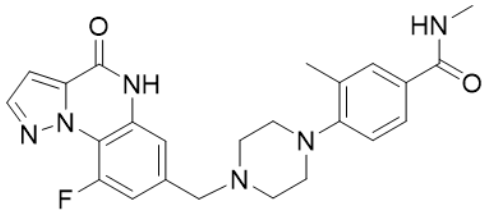
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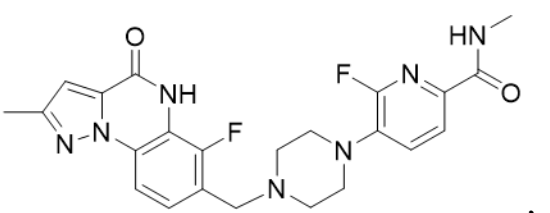
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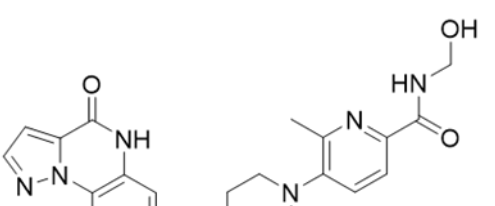
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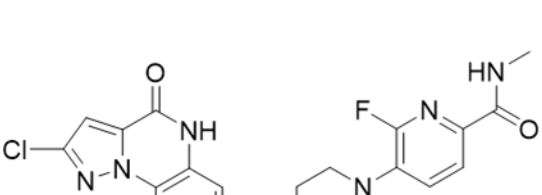
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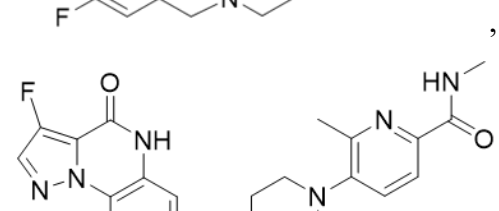
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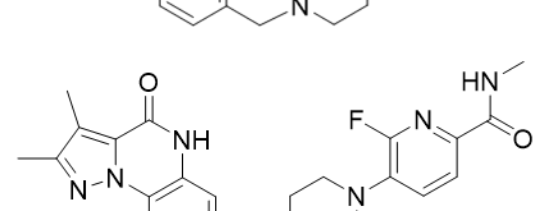
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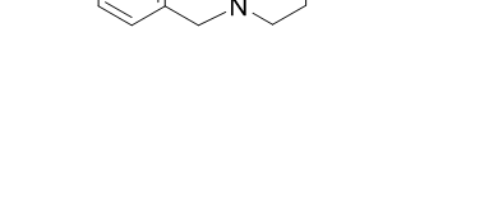
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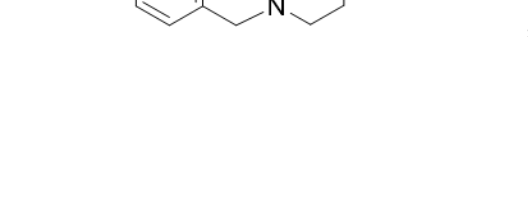
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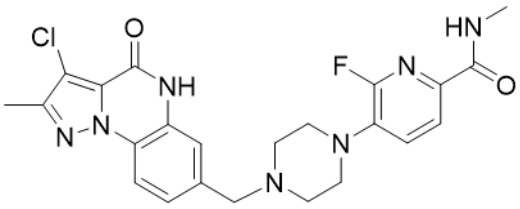
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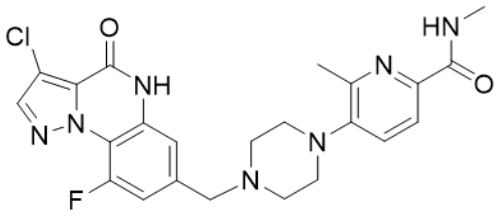
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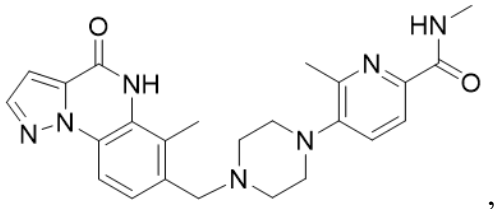
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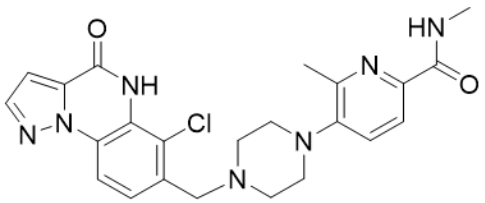
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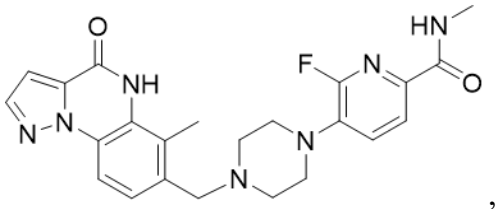
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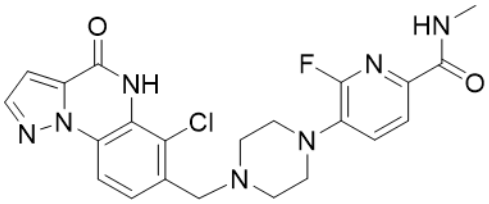
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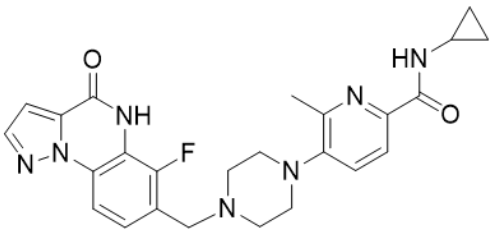
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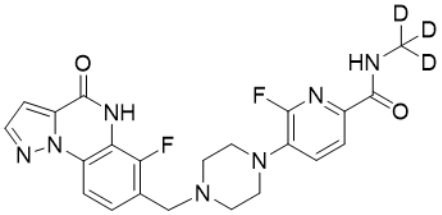
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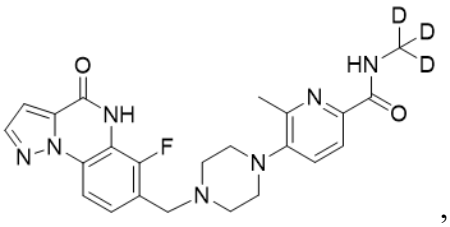
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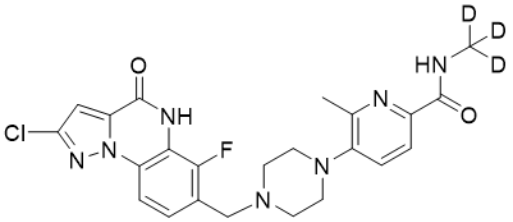
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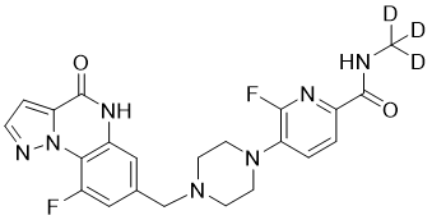
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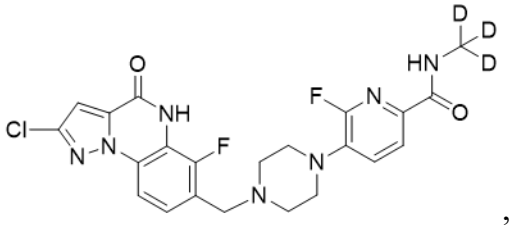
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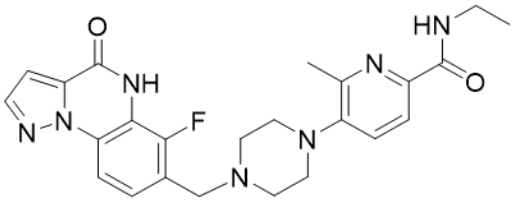
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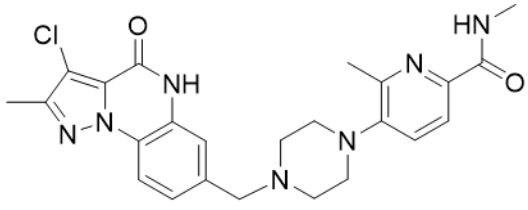
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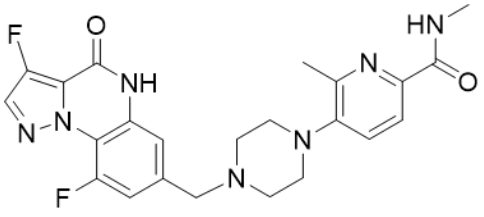
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or stereoisomers, tautomers, N-oxides, hydrates, solvates, isotope-substituted derivatives, or pharmaceutically acceptable salts thereof, or prodrugs thereof, or mixtures thereof.

22. A pharmaceutical composition comprising the compound of any one of claims 1-21, or stereoisomers, tautomers, N-oxides, hydrates, solvates, isotope-substituted derivatives, or pharmaceutically acceptable salts thereof, or prodrugs thereof, or mixtures thereof, and a pharmaceutically acceptable carrier.

23. The pharmaceutical composition of claim 22, wherein the composition further comprises at least one known anticancer drug or a pharmaceutically acceptable salt thereof.

24. The pharmaceutical composition of claim 23, wherein the at least one known anticancer drug is selected from busulfan, melphalan, chlorambucil, cyclophosphamide, ifosfamide, temozolomide, bendamustine, cis-platin, mitomycin C, bleomycin, carboplatin, camptothecin, irinotecan, topotecan, doxorubicin, epirubicin, aclarubicin, mitoxantrone, methylhydroxy ellipticine, etoposide, 5-azacytidine, gemcitabine, 5-fluorouracil, capecitabine, methotrexate, 5-fluoro-2'-deoxy-uridine, fludarabine, nelarabine, ara-C, pralatrexate, pemetrexed, hydroxyurea, thioguanine, colchicine, vinblastine, vincristine, vinorelbine, paclitaxel, ixabepilone, cabazitaxel, docetaxel, mAb, panitumumab, necitumumab, nivolumab, pembrolizumab, ramucirumab, bevacizumab, pertuzumab, trastuzumab, cetuximab, obinutuzumab, ofatumumab, rituximab, alemtuzumab, ibritumomab, tositumomab, brentuximab, daratumumab, elotuzumab, T-DM1, dinutuximab, blinatumomab, ipilimumab, avastin, herceptin, mabthera, trastuzumab deruxtecan, trastuzumab emtansine, datopotamab deruxtecan, gemtuzumab ozogamicin, brentuximab vedotin, inotuzumab ozogamicin, sacituzumab govitecan, enfortumab vedotin, belantamab mafodotin, imatinib, gefitinib, erlotinib, ostinib, afatinib, ceritinib, alectinib, crizotinib, erlotinib, lapatinib, solutinib lafenib, regorafenib, vemurafenib, dabrafenib, aflibercept, sunitinib, nilotinib, dasatinib, bosutinib, pratinib, brutinib, cabozantinib, lenvatinib, vandetanib, trametinib, cabitinib, axitinib, temsirolimus, idelalisib, pazopanib, everolimus, tamoxifen, letrozole, fulvestrant, mitoguanhydrazone, octreotide, retinoic acid, arsenic, zoledronic acid, bortezomib, carfilzomib, Ixazomib, vismodegib, sonidegib, denosumab, thalidomide, lenalidomide, Venetoclax, Aldesleukin (recombinant human interleukin-2), and sipuleucel-T (prostate cancer therapeutic vaccine).

25. Use of the compound of any one of claims 1-21, or stereoisomers, tautomers, N-oxides, hydrates, isotope-substituted derivatives, solvates or pharmaceutically acceptable salts thereof, or prodrugs thereof, or mixtures thereof, or the pharmaceutical composition of any one of claims

22-24, in the manufacture of a medicament for treating or preventing a disease or condition responsive to the inhibition of PARP activity in a subject in need thereof.

26. The use of claim 25, wherein the disease or condition responsive to the inhibition of PARP activity is cancer.

27. The use of claim 26, wherein the cancer is selected from liver cancer, melanoma, Hodgkin's disease, non-Hodgkin's lymphomas, acute lymphocytic leukemia, chronic lymphocytic leukemia, multiple myeloma, neuroblastoma, breast cancer, ovarian cancer, lung cancer (such as small cell lung cancer), Wilms' tumor, cervical cancer, testicular cancer, soft-tissue sarcoma, primary macroglobulinemia, bladder cancer, chronic myeloid leukemia, primary brain cancer, malignant melanoma, gastric cancer, colon cancer, malignant pancreatic islet tumor, malignant carcinoid cancer, choriocarcinoma, mycosis fungoide, head and neck cancer, osteogenic sarcoma, pancreatic cancer, acute myeloid leukemia, hairy cell leukemia, rhabdomyosarcoma, Kaposi's sarcoma, urogenital tumors, thyroid cancer, esophageal cancer, malignant hypercalcemia, cervical hyperplasia, renal cell carcinoma, endometrial cancer, polycythemia vera, idiopathic thrombocythemia, adrenocortical carcinoma, skin cancer, and prostatic cancer.

28. The use of any one of claims 25-27, wherein the medicament is to be administered to the subject, and wherein at least one known anticancer drug or pharmaceutically acceptable salts thereof is to be further administered to the subject.

29. The use of claim 28, wherein the at least one known anticancer drug is selected from busulfan, melphalan, chlorambucil, cyclophosphamide, ifosfamide, temozolomide, bendamustine, cis-platin, mitomycin C, bleomycin, carboplatin, camptothecin, irinotecan, topotecan, doxorubicin, epirubicin, aclarubicin, mitoxantrone, methylhydroxy ellipticine, etoposide, 5-azacytidine, gemcitabine, 5-fluorouracil, capecitabine, methotrexate, 5-fluoro-2'-deoxy-uridine, fludarabine, nelarabine, ara-C, pralatrexate, pemetrexed, hydroxyurea, thioguanine, colchicine, vinblastine, vincristine, vinorelbine, paclitaxel, ixabepilone, cabazitaxel, docetaxel, mAb, panitumumab, necitumumab, nivolumab, pembrolizumab, ramucirumab, bevacizumab, pertuzumab, trastuzumab, cetuximab, obinutuzumab, ofatumumab, rituximab, alemtuzumab, ibritumomab, tositumomab, brentuximab, daratumumab, elotuzumab, T-DM1, dinutuximab, blinatumomab, ipilimumab, avastin, herceptin, mabthera, trastuzumab deruxtecan, trastuzumab emtansine, datopotamab deruxtecan, gemtuzumab ozogamicin, brentuximab vedotin,

inotuzumab ozogamicin, sacituzumab govitecan, enfortumab vedotin, belantamab mafodotin, imatinib, gefitinib, erlotinib, ostinib, afatinib, ceritinib, alectinib, crizotinib, erlotinib, lapatinib, solutinib lafenib, regorafenib, vemurafenib, dabrafenib, aflibercept, sunitinib, nilotinib, dasatinib, bosutinib, pratinib, brutinib, cabozantinib, lenvatinib, vandetanib, trametinib, cabitinib, axitinib, temsirolimus, idelalisib, pazopanib, everolimus, tamoxifen, letrozole, fulvestrant, mitoguanhydrazone, octreotide, retinoic acid, arsenic, zoledronic acid, bortezomib, carfilzomib, Ixazomib, vismodegib, sonidegib, denosumab, thalidomide, lenalidomide, Venetoclax, Aldesleukin (recombinant human interleukin-2), and sipuleucel-T (prostate cancer therapeutic vaccine).

30. A compound of any one of claims 1-21, or stereoisomers, tautomers, N-oxides, hydrates, isotope-substituted derivatives, solvates or pharmaceutically acceptable salts thereof, or prodrugs thereof, or mixtures thereof, or the pharmaceutical composition of any one of claims 22-24, for use in therapy.