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

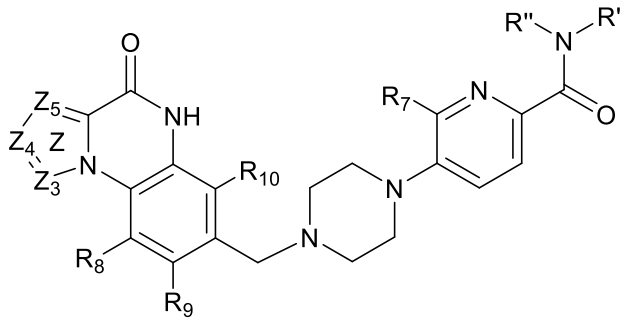
[0005] PARP2 is a protein of 559 amino acids with molecular mass of approximately 62 kDa and composed of DNA binding domain and catalytic domain (Ame et al., 1999 J Biol Chem 274: 17860-17868). The catalytic domain of PARP2 is very similar to that of PARP1. PARP2 is also found to have similar functions 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

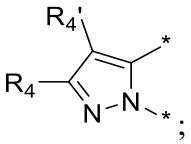
[0007b] In another aspect of the present disclosure, there is provided a compound of Formula IVb:



(IVb)

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

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



;

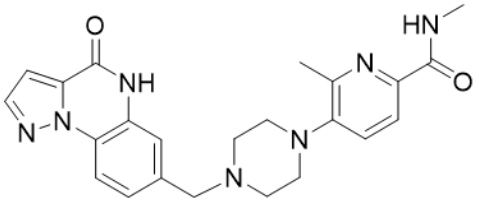
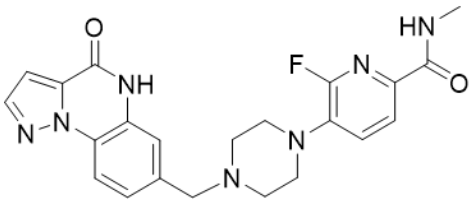
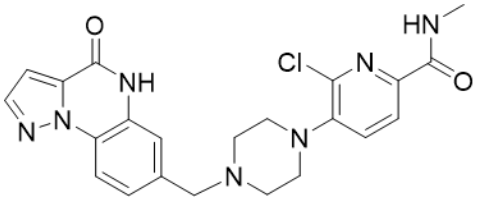
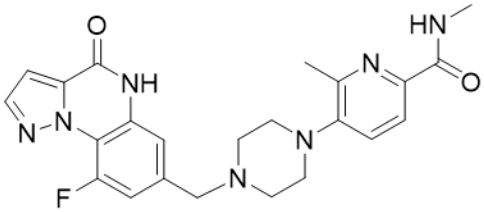
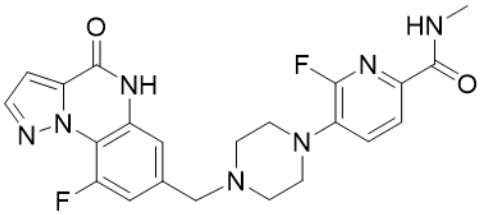
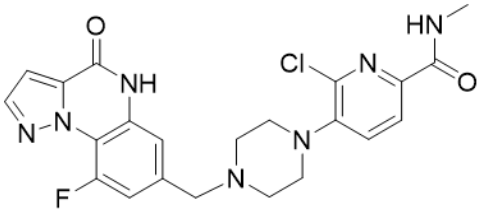
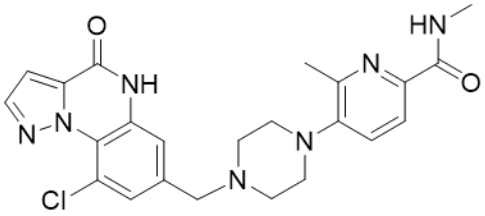
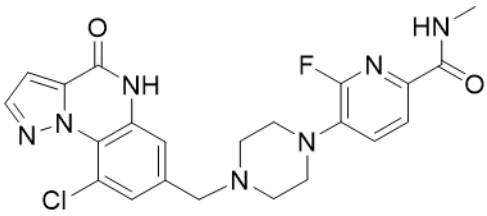
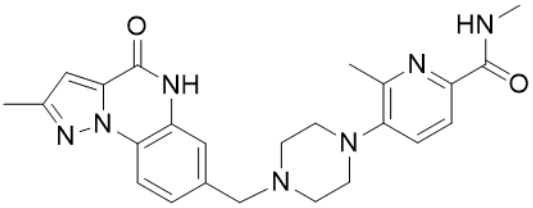
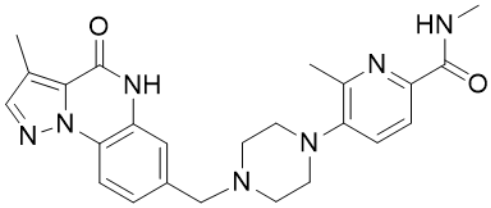
wherein R_4 and R_4' are independently selected from hydrogen, halogen and an optionally substituted alkyl;

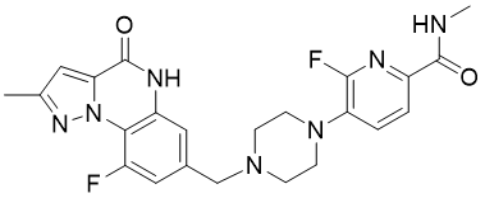
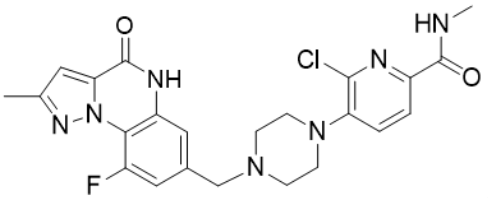
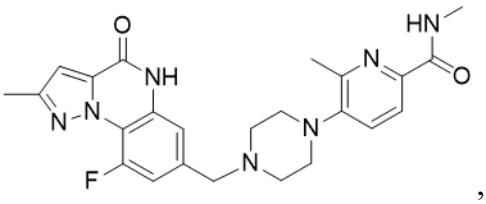
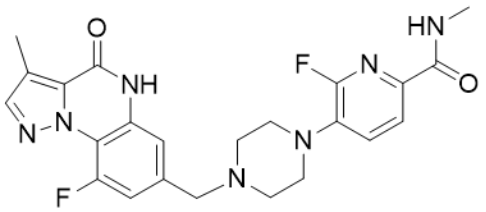
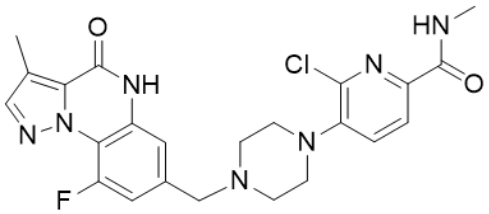
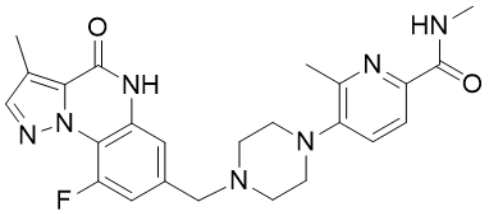
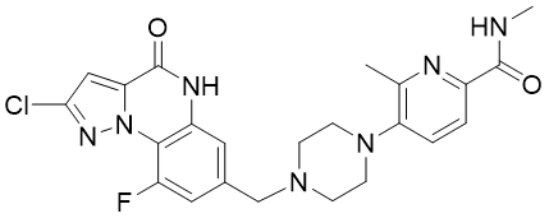
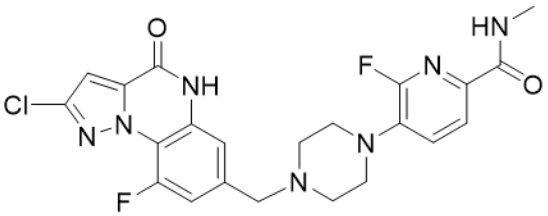
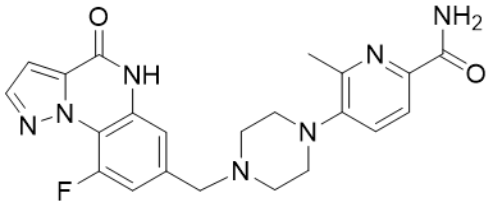
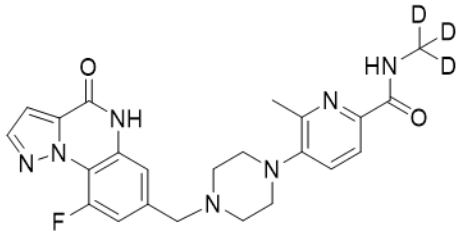
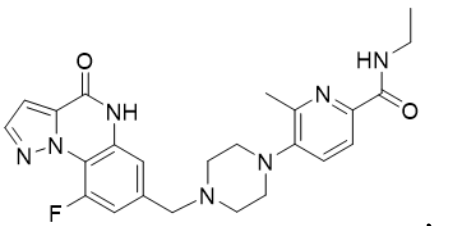
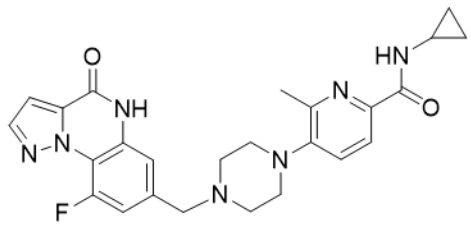
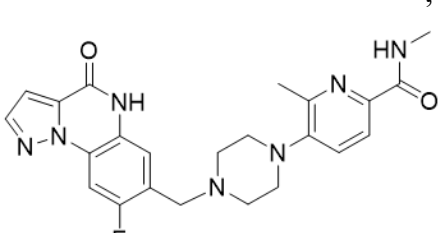
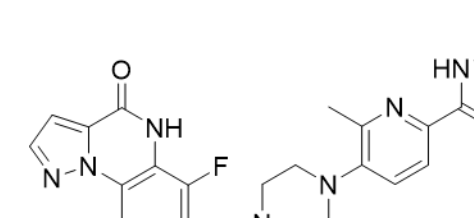
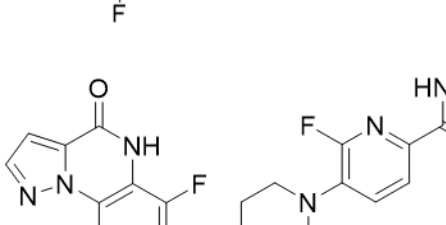
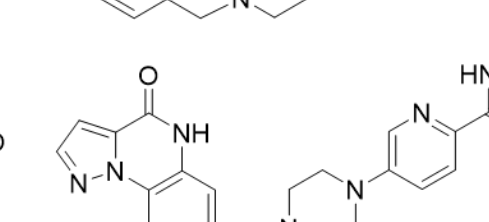
R_7 is selected from hydrogen, halogen, an optionally substituted alkyl, an optionally substituted alkoxy, an optionally substituted carbocyclic group, an optionally substituted alkenyl and an optionally substituted alkynyl;

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.

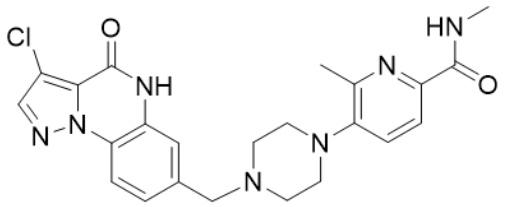
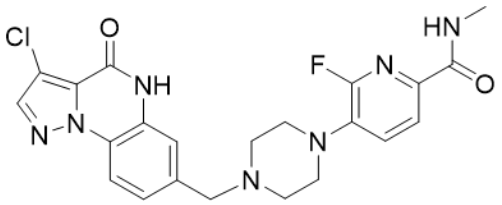
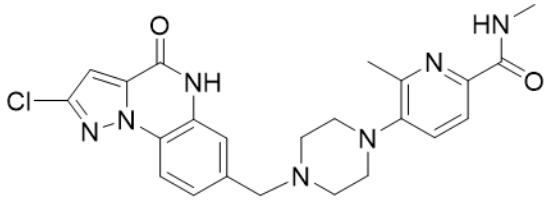
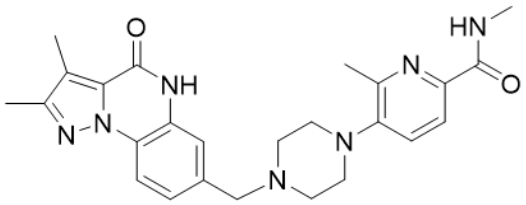
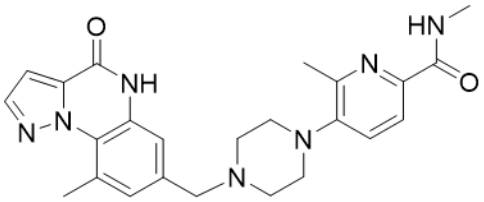
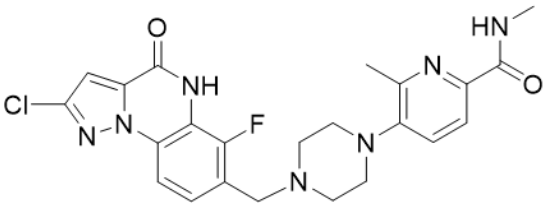
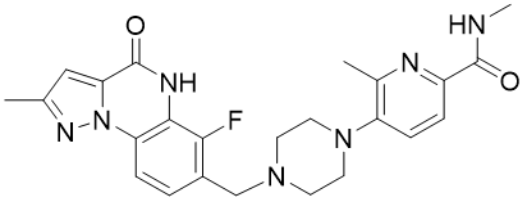
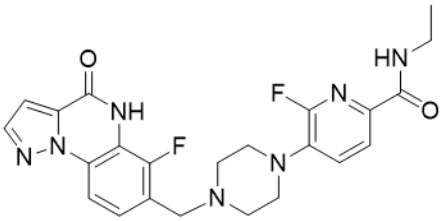
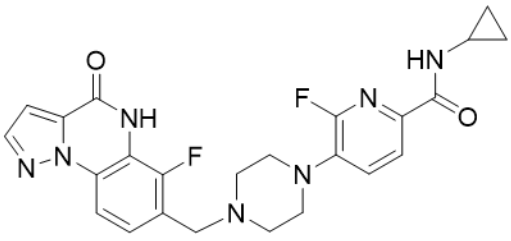
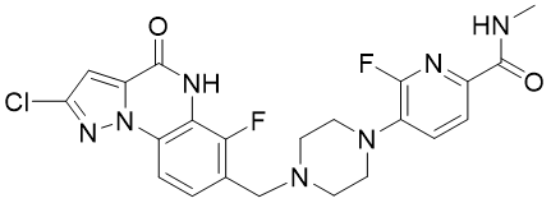
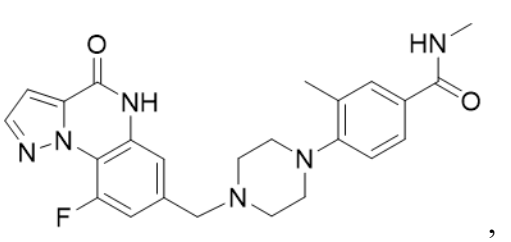
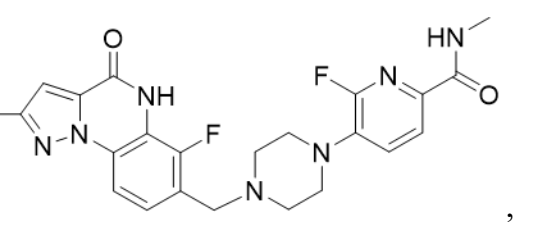
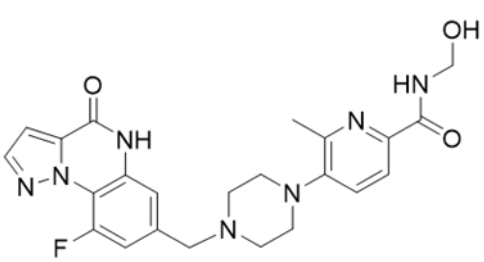
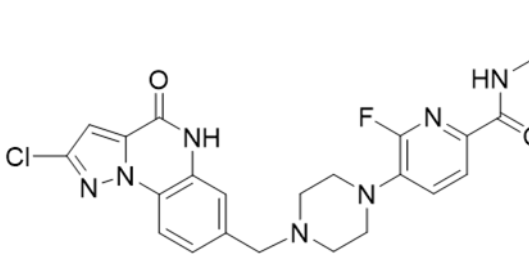
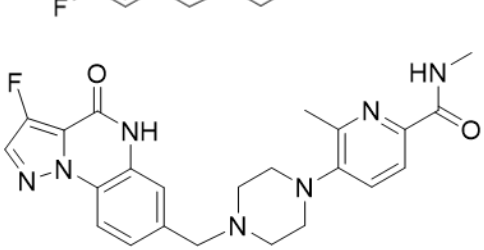
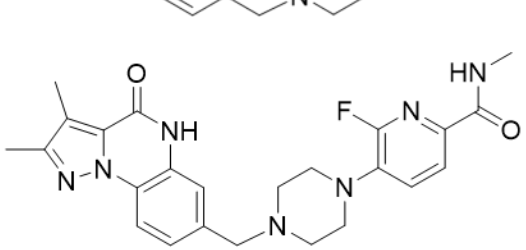
[0007c] In a further aspect of the present disclosure, there is provided a compound selected from:


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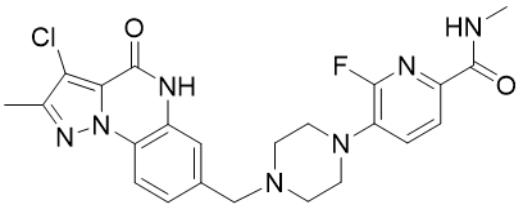
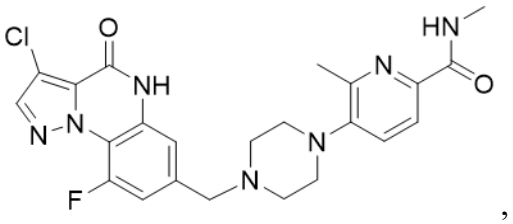
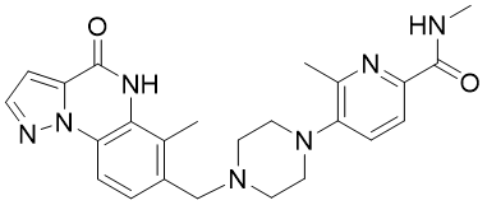
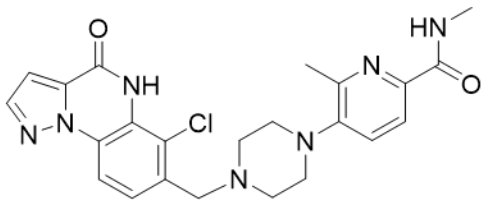
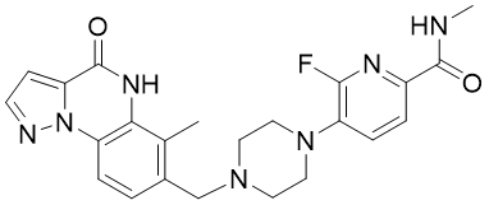
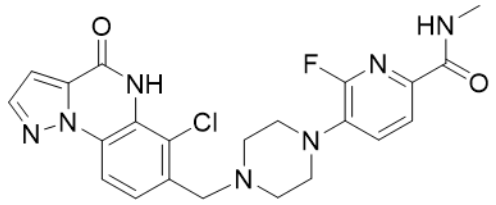
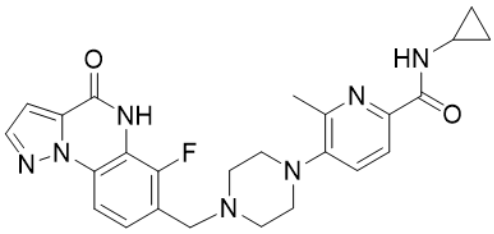
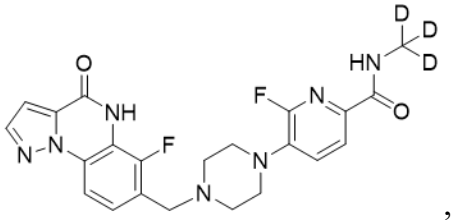
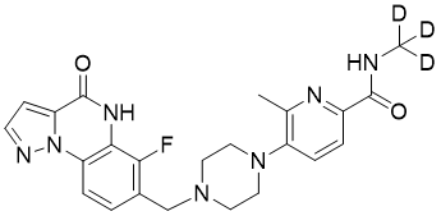
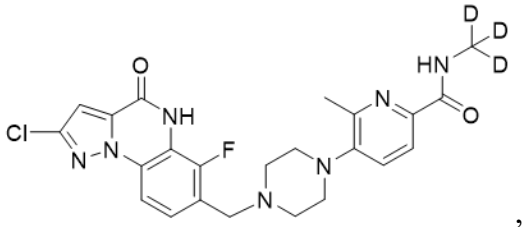
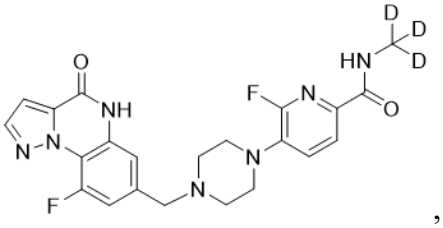
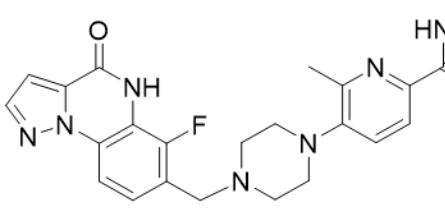
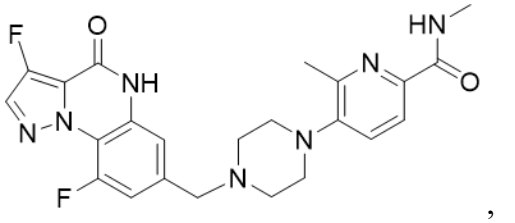
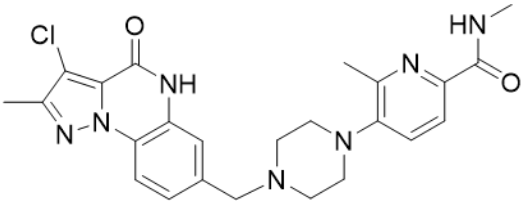
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or stereoisomers, tautomers, N-oxides, hydrates, solvates, isotope-substituted derivatives, or pharmaceutically acceptable salts thereof, or prodrugs thereof, or mixtures thereof.

[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 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 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, wherein the disease or condition responsive to the inhibition of PARP activity is cancer.

[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 mixtures thereof, or the pharmaceutical composition as disclosed herein, for use in therapy.

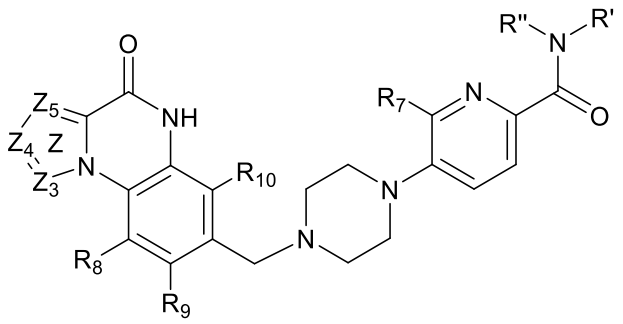
[0008] The disclosure provides compounds and analogues thereof as represented by Formula I (including Formulae II, III and IV). The compounds can be used as PARP inhibitors. In particular, the compounds of the disclosure are selective PARP1 inhibitors relative to PARP2.

[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.

WHAT IS CLAIMED IS:

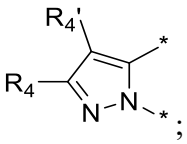
1. A compound of Formula IVb:



(IVb)

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

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



;

wherein R_4 and R_4' are 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.

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

3. The compound of claim 2, or stereoisomers, tautomers, N-oxides, hydrates, solvates, isotope-substituted derivatives, or pharmaceutically acceptable salts thereof, or mixtures thereof, wherein R_7 is hydrogen, C_{1-3} alkyl, C_{1-3} alkoxy, halogenated C_{1-3} alkyl or halogen.

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

5. The compound of claim 4, or stereoisomers, tautomers, N-oxides, hydrates, solvates, isotope-substituted derivatives, or pharmaceutically acceptable salts 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.

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

7. The compound of claim 6, or stereoisomers, tautomers, N-oxides, hydrates, solvates, isotope-substituted derivatives, or pharmaceutically acceptable salts thereof, or mixtures thereof, wherein R_8, R_9 and R_{10} are independently hydrogen, C_{1-3} alkyl or halogen.

8. The compound of claim 7, or stereoisomers, tautomers, N-oxides, hydrates, solvates, isotope-substituted derivatives, or pharmaceutically acceptable salts thereof, or mixtures thereof, wherein R_8 is C_{1-3} alkyl or halogen, and both of R_9 and R_{10} are hydrogen.

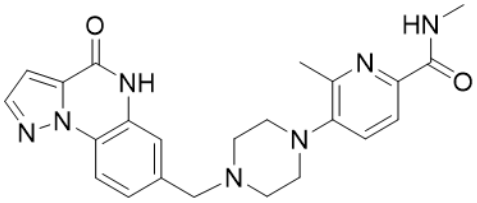
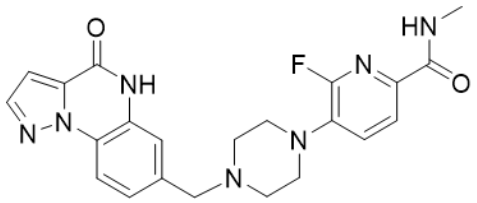
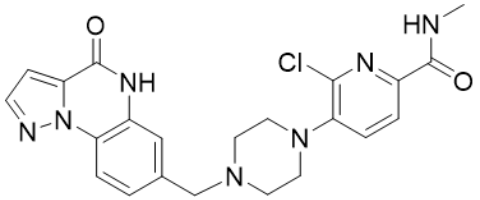
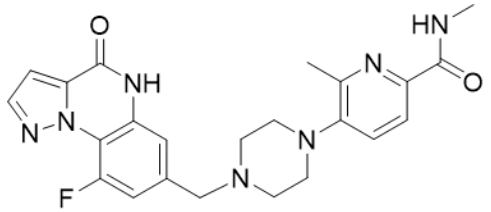
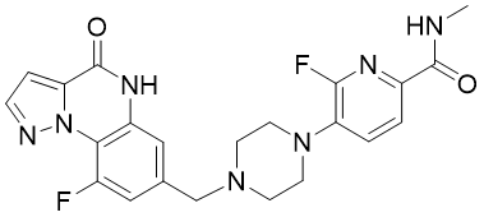
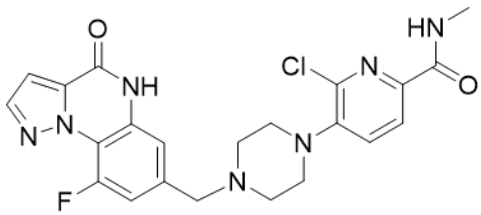
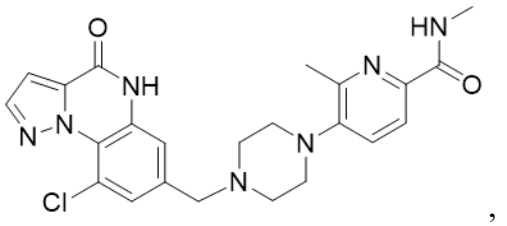
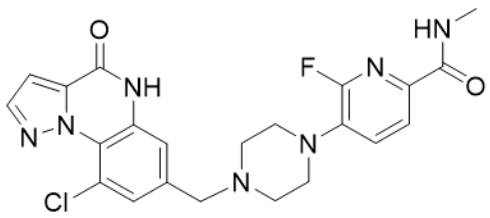
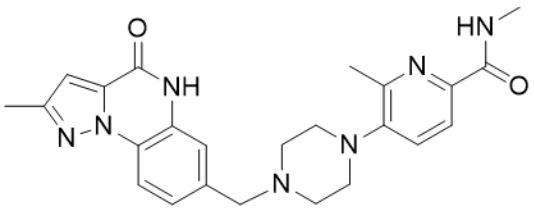
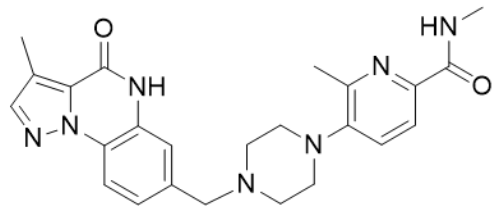
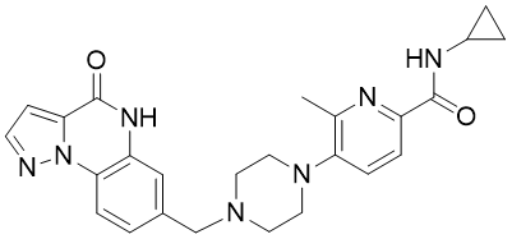
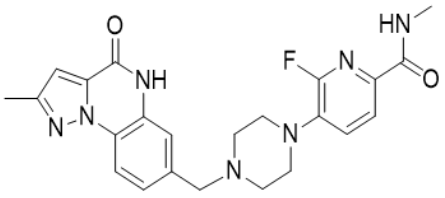
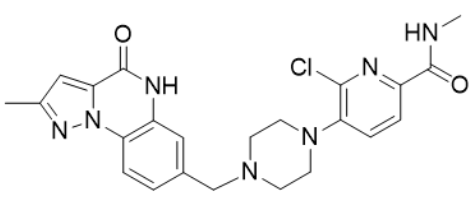
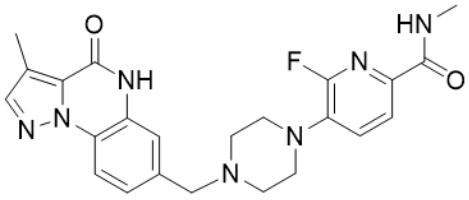
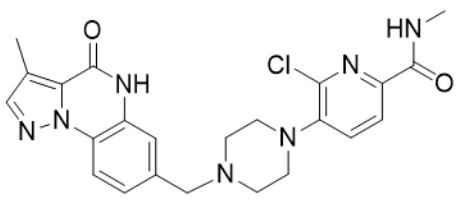
9. The compound of claim 7, or stereoisomers, tautomers, N-oxides, hydrates, solvates, isotope-substituted derivatives, or pharmaceutically acceptable salts thereof, or mixtures thereof, wherein both of R_8 and R_9 are hydrogen, and R_{10} is C_{1-3} alkyl or halogen.

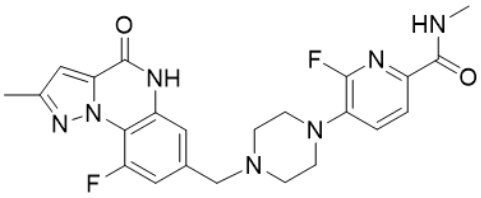
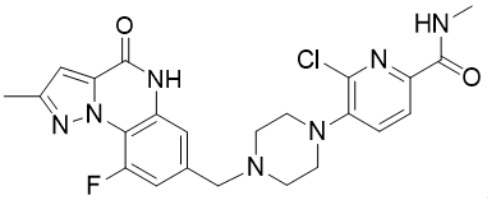
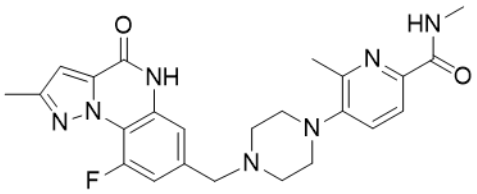
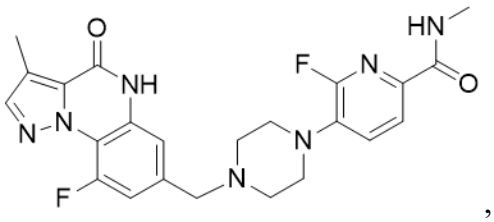
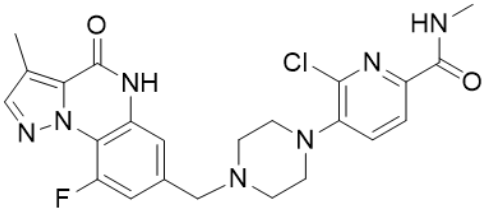
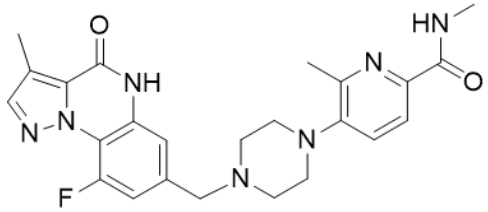
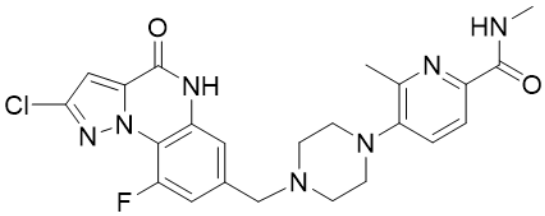
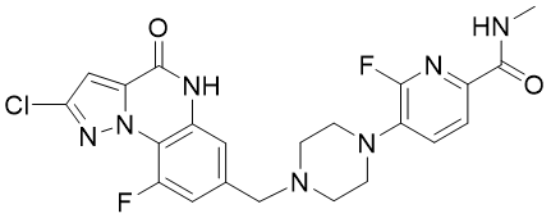
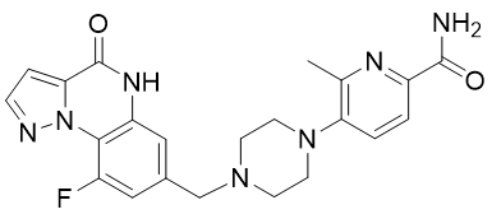
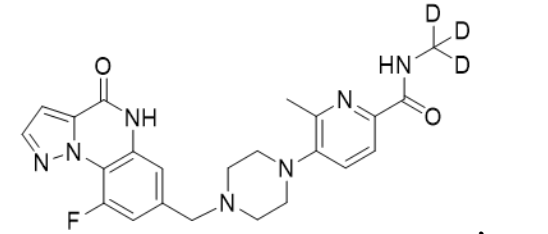
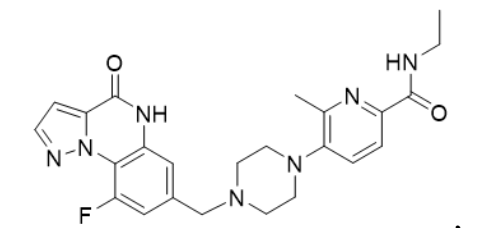
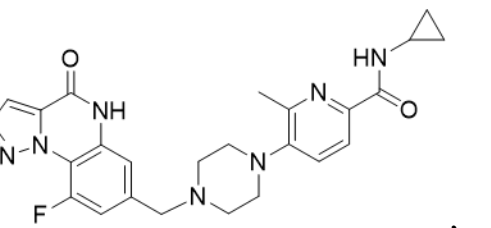
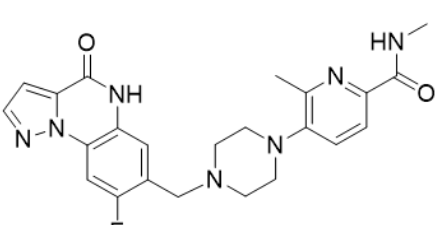
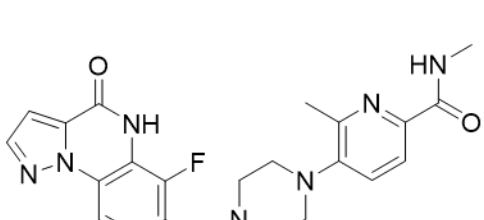
10. The compound of any one of claims 1 to 9, or stereoisomers, tautomers, N-oxides, hydrates, solvates, isotope-substituted derivatives, or pharmaceutically acceptable salts thereof, or mixtures thereof, wherein R' is hydrogen and R" is hydrogen or C_{1-3} alkyl.

11. The compound of any one of claims 1 to 10, or stereoisomers, tautomers, N-oxides, hydrates, solvates, isotope-substituted derivatives, or pharmaceutically acceptable salts thereof, or mixtures thereof, wherein R_7 is hydrogen, halogen, an optionally substituted C_{1-3} alkyl or an optionally substituted C_{1-3} alkoxy.

12. The compound of any one of claims 1 to 11, or stereoisomers, tautomers, N-oxides, hydrates, solvates, isotope-substituted derivatives, or pharmaceutically acceptable salts thereof, or mixtures thereof, wherein R_7 is hydrogen, C_{1-3} alkyl, halogenated C_{1-3} alkyl or halogen.

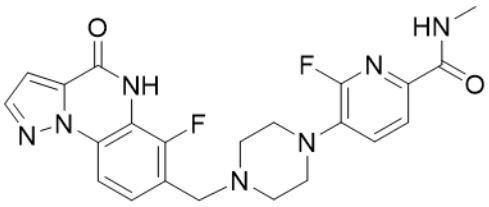
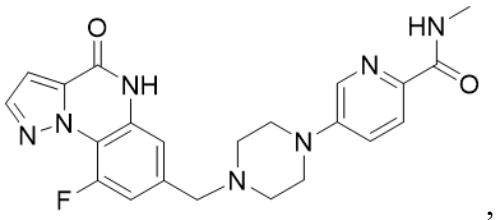
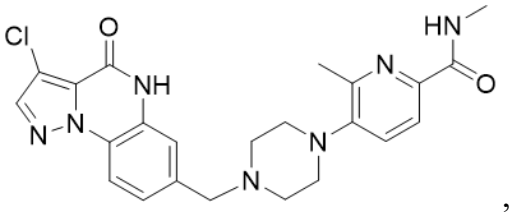
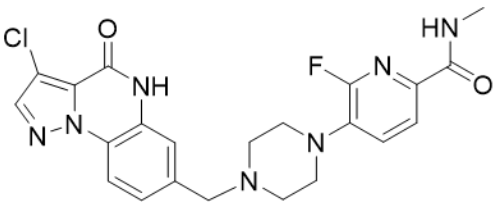
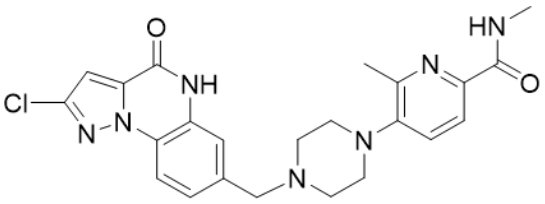
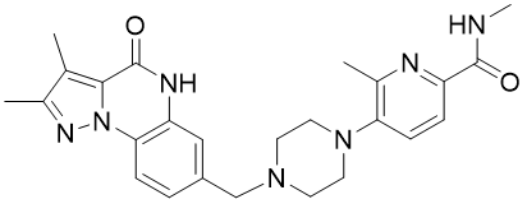
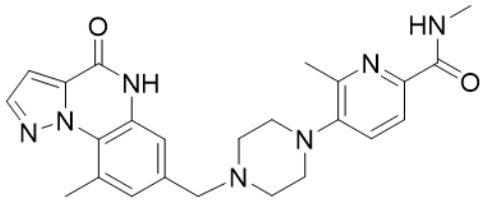
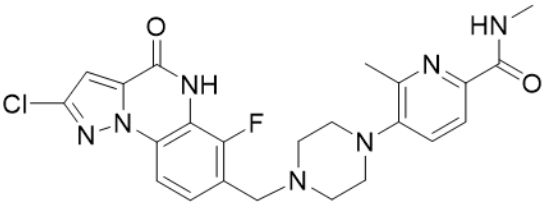
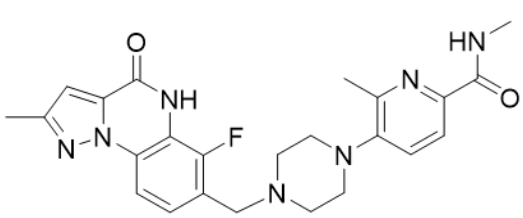
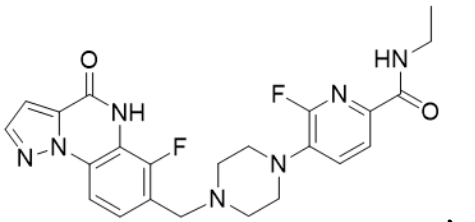
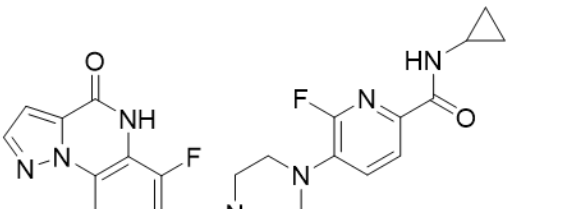
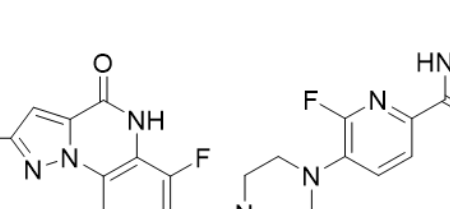
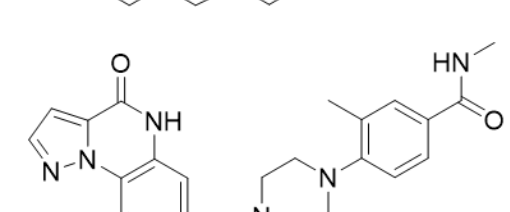
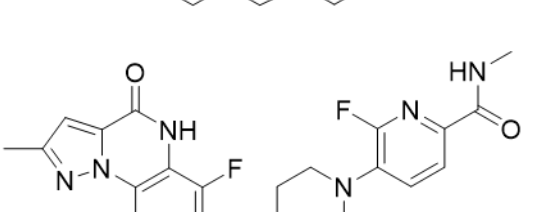
13. A compound selected from:


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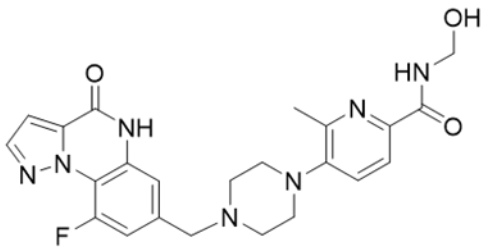
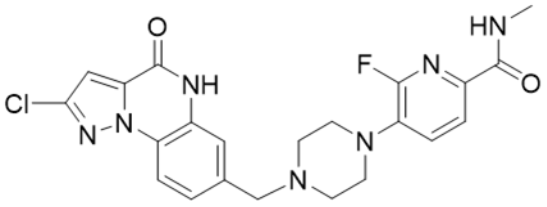
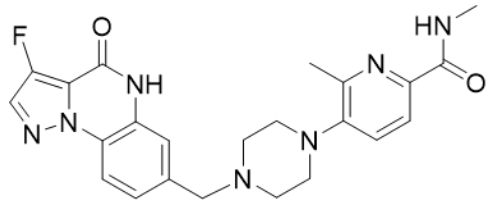
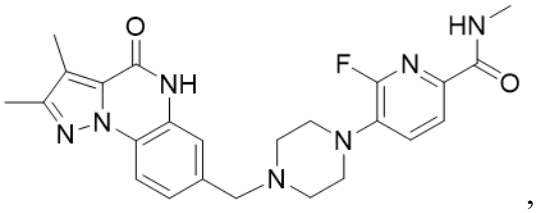
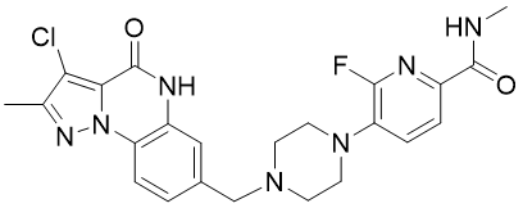
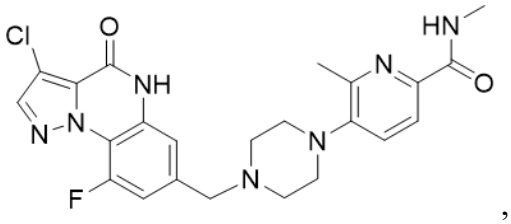
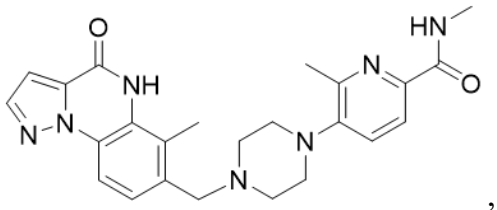
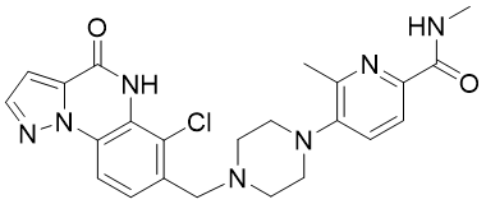
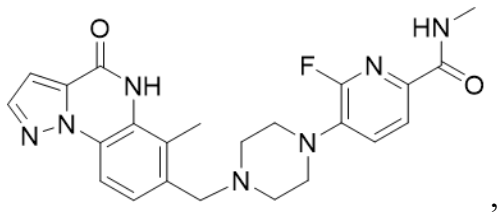
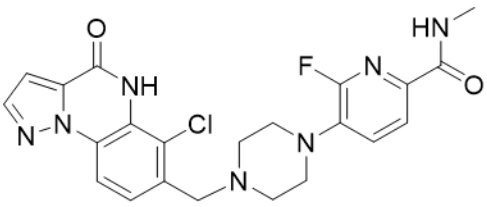
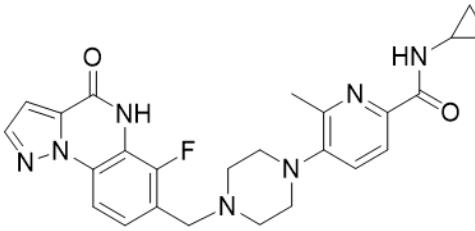
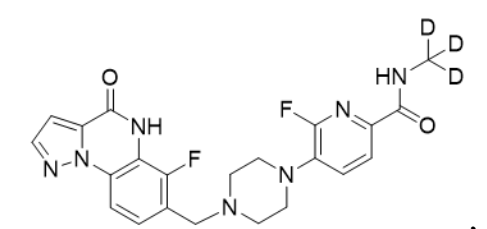
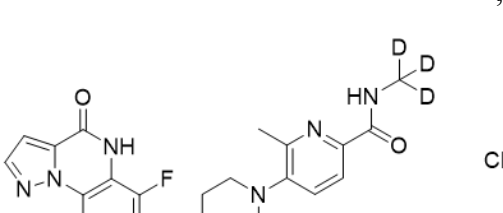
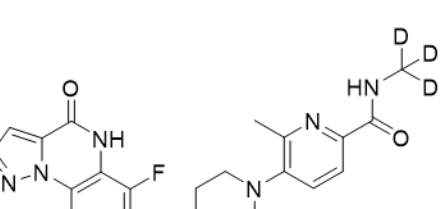
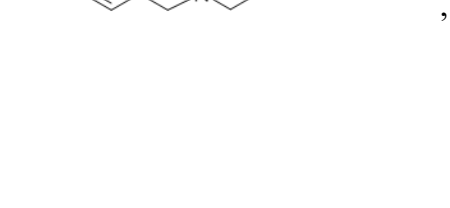
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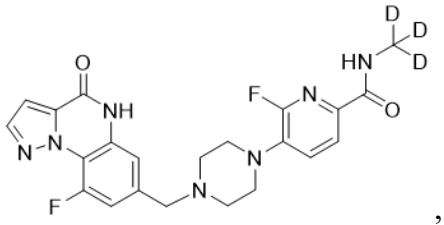
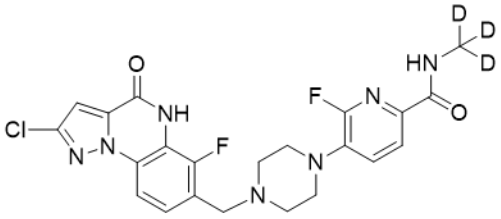
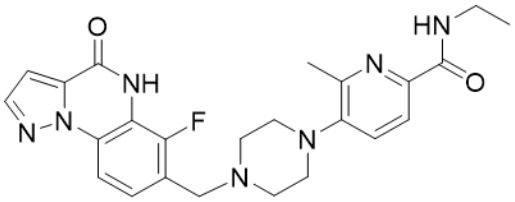
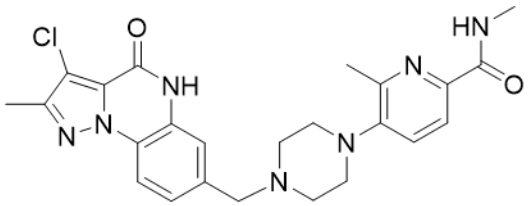
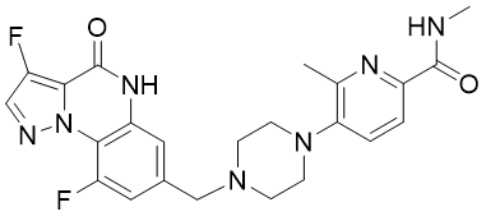

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or stereoisomers, tautomers, N-oxides, hydrates, solvates, isotope-substituted derivatives, or pharmaceutically acceptable salts thereof, or mixtures thereof.

14. A pharmaceutical composition comprising the compound of any one of claims 1-13, or stereoisomers, tautomers, N-oxides, hydrates, solvates, isotope-substituted derivatives, or pharmaceutically acceptable salts thereof, or mixtures thereof, and a pharmaceutically acceptable carrier.

15. The pharmaceutical composition of claim 14, wherein the composition further comprises at least one known anticancer drug or a pharmaceutically acceptable salt thereof.

16. The pharmaceutical composition of claim 15, 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, lapatinib, solutinib lafenib, regorafenib, vemurafenib, dabrafenib, aflibercept, sunitinib, nilotinib, dasatinib, bosutinib, ponatinib, ibrutinib, 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).

17. Use of the compound of any one of claims 1-13, or stereoisomers, tautomers, N-oxides, hydrates, isotope-substituted derivatives, solvates or pharmaceutically acceptable salts thereof, or mixtures thereof, or the pharmaceutical composition of any one of claims 14-16, 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, wherein the disease or condition responsive to the inhibition of PARP activity is cancer.

18. The use of claim 17, 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.

19. The use of any one of claims 17-18, 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.

20. The use of claim 19, 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, lapatinib, solutinib lafenib, regorafenib, vemurafenib, dabrafenib, aflibercept, sunitinib, nilotinib, dasatinib, bosutinib, ponatinib, ibrutinib, 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).

21. A compound of any one of claims 1-13, or stereoisomers, tautomers, N-oxides, hydrates, isotope-substituted derivatives, solvates or pharmaceutically acceptable salts thereof, or mixtures thereof, or the pharmaceutical composition of any one of claims 14-16, for use in therapy.