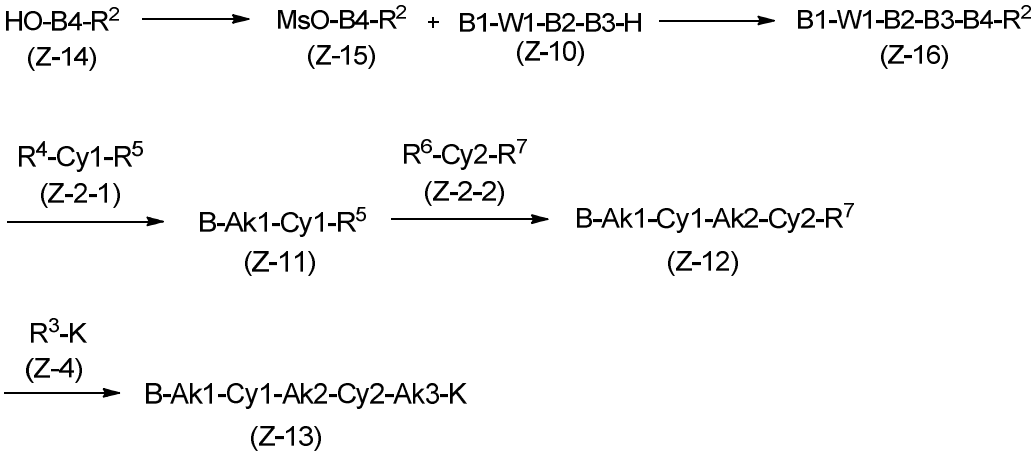


General formula (Z-14) is reacted with methanesulfonyl chloride to obtain general formula (Z-15), and general formula (Z-15) and general formula (Z-10) are subjected to nucleophilic substitution reaction to obtain general formula (Z-16), and if general formula (Z-16) has an amino protecting group at the reaction site, the amino protecting group is removed first, and then it is subjected to reductive amination with general formula (Z-2-1) to obtain the corresponding general formula (Z-11), and if general formula (Z-11) has an amino protecting group at the reaction site, the amino protecting group is removed first, and then it is subjected to reductive amination reaction with general formula (Z-2-2) to obtain general formula (Z-12), and if general formula (Z-12) has an amino protecting group at the reaction site, the amino protecting group is removed first, and then it is subjected to nucleophilic substitution reaction with general formula (Z-4) to obtain general formula (Z-13), namely, general formula (I).

See *J. Med. Chem.* **2015**, *58*, 9625-9638 for the synthetic method of general formula (Z-1); and

see WO 2017197056 for the synthetic method of general formula (Z-4);

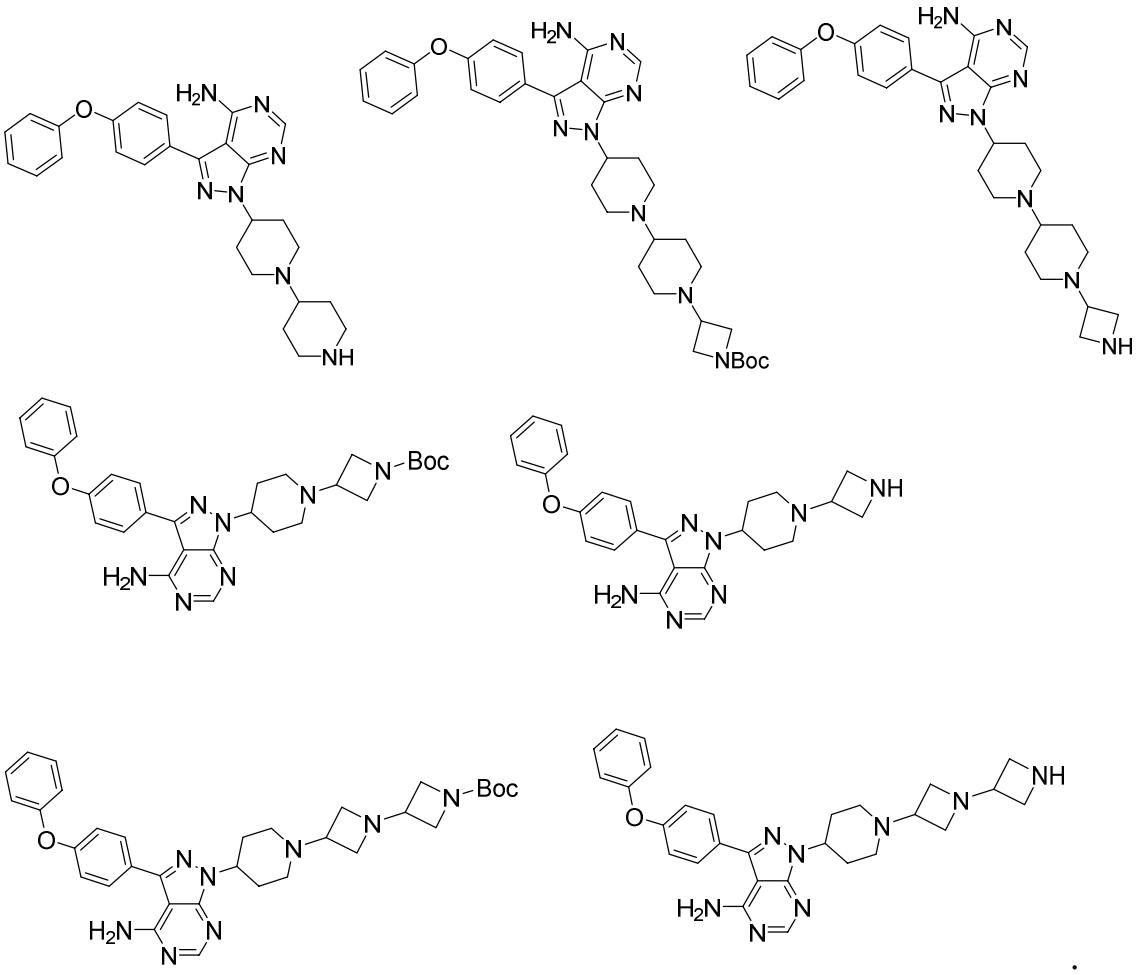
R^1 is selected from (=O), -CHO, F, Cl, Br, I, or OTf;

R^2 is selected from H, (=O), -CHO, F, Cl, Br, I or an amino protecting group, preferably Boc;

R^3 is selected from NH_2, F, Cl, Br, I, OTf, or OH;

R^4, R^5, R^6 and R^7 are each independently selected from H, (=O), -CHO, H, F, Cl, Br, I, OTf or an amino protecting group.

The present invention also provides the compounds shown below,



Unless stated to the contrary, the terms used in both the description and the

Claims

1. A compound represented by general formula (I) or a stereoisomer, a solvate, a prodrug, a metabolite, a pharmaceutically acceptable salt or a co-crystal thereof, characterized in that

B-L-K (I);

L is selected from -Ak1-Cy1-Ak2-Cy2-Ak3-Cy3-Ak4-Cy4-Ak5-;

Ak1, Ak2, Ak3, Ak4 and Ak5 are each independently selected from CH_2, O or a bond;

Cy1, Cy2, Cy3 and Cy4 are each independently selected from 3- to 12-membered heterocyclic ring, 3- to 12-membered cycloalkyl, 6- to 10-membered aryl or a bond, wherein the heterocyclic ring, cycloalkyl or aryl is optionally further substituted with 0 to 4 substituents selected from H, F, Cl, Br, I, OH, NH_2, oxo, C_{1-4} alkyl or C_{1-4} alkoxy, and the heterocyclic ring contains 1 to 4 heteroatoms selected from O, S or N;

Cy1, Cy2, Cy3 and Cy4 cannot all be a bond;

when Ak1, Ak2, Ak3, Ak4 or Ak5 is O, they cannot be directly connected to B;

when Ak1, Ak2, Ak3, Ak4 or Ak5 is not a bond, they cannot be directly connected to one another;

when 3 of Cy1, Cy2, Cy3 and Cy4 are a bond, at least one of Ak1, Ak2, Ak3, Ak4, and Ak5 is selected from CH_2 and is connected to B;

when 4 or more of Ak1, Cy1, Ak2, Cy2, Ak3, Cy3, Ak4, Cy4 and Ak5 are not a bond, at least one of Cy1, Cy2, Cy3 and Cy4 is not piperidyl, piperazinyl, pyrimidinyl or pyridyl;

B is selected from B1-W1-B2-B3-B4-;

B1 is selected from 6-membered heteroaryl ring or phenyl, wherein the heteroaryl ring or phenyl is optionally further substituted with 0 to 4 R^{b1}, and the heteroaryl ring contains 1 to 4 heteroatoms selected from O, S or N;

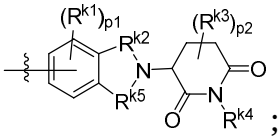
W1 is selected from -O-, -S-, -NH-, -NHCO- or -CONH-;

B2 is selected from 6-membered heteroaryl ring or phenyl, wherein the heteroaryl ring or phenyl is optionally further substituted with 0 to 4 R^{b2}, and the heteroaryl ring contains 1 to 4 heteroatoms selected from O, S or N;

B3 is selected from 8- to 10-membered fused heterocyclic ring, wherein the fused heterocyclic ring is optionally further substituted with 0 to 4 R^{b3}, and the fused heterocyclic ring contains 1 to 4 heteroatoms selected from O, S or N;

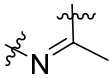
B4 is selected from 5- to 6-membered saturated heterocyclic ring, wherein the saturated heterocyclic ring is optionally further substituted with 0 to 4 R^{b4}, and the saturated heterocyclic ring contains 1 to 2 heteroatoms selected from O, S or N;

R^{b1}, R^{b2}, R^{b3} or R^{b4} is each independently selected from H, F, Cl, Br, I, OH, NH_2, CN, $CONH_2$, C_{1-4} alkyl or C_{1-4} alkoxy, wherein the alkyl and alkoxy are optionally further substituted with 0 to 4 substituents selected from H, F, Cl, Br, I, OH, NH_2, CN, $CONH_2$, C_{1-4} alkyl or C_{1-4} alkoxy;

K is selected from ;

R^{k2} is selected from CH_2, C=O, S=O, or SO_2;

R^{k1}, R^{k3} or R^{k4} is each independently selected from H, F, Cl, Br, I, OH, NH_2, CN, COOH, C_{1-4} alkyl or C_{1-4} alkoxy;

R^{k5} is selected from C=O or ; and p1 or p2 is each independently selected from 0, 1, 2, 3 or 4.

2. The compound according to claim 1, or a stereoisomer, a solvate, a prodrug, a metabolite, a pharmaceutically acceptable salt or a co-crystal thereof, characterized in that

Cy1, Cy2, Cy3 and Cy4 are each independently selected from a bond, 4- to 7-membered mono-heterocyclic ring, 5- to 10-membered fused heterocyclic ring, 6- to 12-membered spiro-heterocyclic ring, 7- to 10-membered bridged-heterocyclic ring, 4- to 7-membered monocycloalkyl, 5- to 10-membered fused cycloalkyl, 6- to 12-membered spiro cycloalkyl, 7- to 10-membered bridged cycloalkyl or 6- to 10-

membered aryl, wherein the aryl, cycloalkyl, mono-heterocyclic ring, fused heterocyclic ring, spiro-heterocyclic ring or bridged-heterocyclic ring is optionally further substituted with 0 to 4 substituents selected from H, F, Cl, Br, I, OH, NH_2, oxo, C_{1-4} alkyl or C_{1-4} alkoxy, and the mono-heterocyclic ring, fused heterocyclic ring, spiro-heterocyclic ring or bridged-heterocyclic ring contains 1 to 4 heteroatoms selected from O, S or N;

B1 is selected from phenyl or pyridyl, wherein the phenyl or pyridyl is optionally further substituted with 0 to 4 R^{b1}, and the heteroaryl ring contains 1 to 4 heteroatoms selected from O, S or N;

W1 is selected from -O-, -NHCO- or -CONH-;

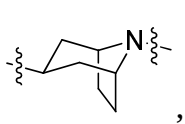
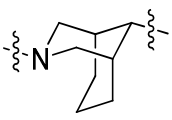
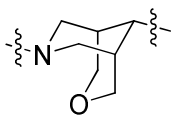
B2 is selected from phenyl or pyridyl, wherein the phenyl or pyridyl is optionally further substituted with 0 to 4 R^{b2}, and the heteroaryl ring contains 1 to 4 heteroatoms selected from O, S or N;

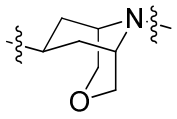
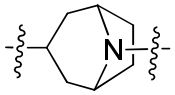
B3 is selected from substituted or unsubstituted imidazopyrimidine, pyrazolopyrimidine, imidazopyrazine, pyrazolopyrazine, imidazotetrahydropyrimidine, or pyrazolotetrahydropyrimidine which, when substituted, is optionally further substituted with 0 to 4 R^{b3}, and the fused heterocyclic ring contains 1 to 4 heteroatoms selected from O, S or N; and

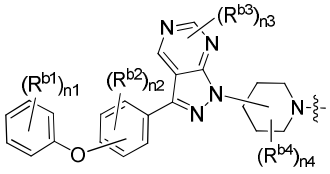
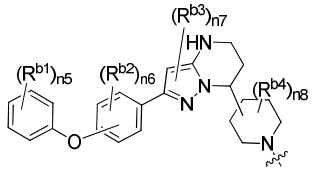
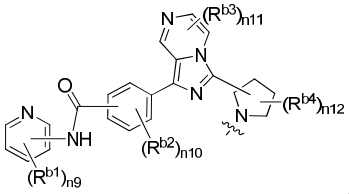
B4 is selected from substituted or unsubstituted azacyclopentyl, piperidine or piperazine, wherein the azacyclopentyl, piperidine or piperazine is optionally further substituted with 0 to 4 R^{b4}, and the saturated heterocyclic ring contains 1 to 2 heteroatoms selected from O, S or N.

3. The compound according to claim 2, or a stereoisomer, a solvate, a prodrug, a metabolite, a pharmaceutically acceptable salt or a co-crystal thereof, characterized in that

Cy1, Cy2, Cy3 and Cy4 are each independently selected from one of the following substituted or unsubstituted groups: a bond, phenyl, naphthyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclobutyl-fused-cyclobutyl, cyclobutyl-fused-cyclopentyl, cyclobutyl-fused-cyclohexyl, cyclopentyl-fused-cyclopentyl, cyclopentyl-fused-cyclohexyl, cyclohexyl-fused-cyclohexyl, cyclopropyl-fused-cyclobutyl,

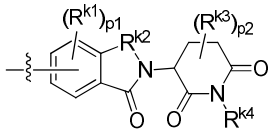
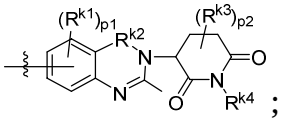
cyclopropyl-fused-cyclopentyl, cyclopropyl-fused-cyclohexyl, cyclobutyl-spiro-cyclobutyl, cyclobutyl-spiro-cyclopentyl, cyclobutyl-spiro-cyclohexyl, cyclopentyl-spiro-cyclopentyl, cyclopentyl-spiro-cyclohexyl, cyclohexyl-spiro-cyclohexyl, cyclopropyl-spiro-cyclobutyl, cyclopropyl-spiro-cyclopentyl, cyclopropyl-spiro-cyclohexyl, azetidinyl, azacyclopentyl, piperidyl, morpholinyl, piperazinyl, pyrrolyl, pyrazolyl, imidazolyl, thiazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazolyl, tetrazolyl, cyclopropyl-fused-azetidinyl, cyclopropyl-fused-azacyclopentyl, cyclopropyl-fused-azacyclohexyl, cyclopropyl-fused-piperidyl, cyclobutyl-fused-azetidinyl, cyclobutyl-fused-azacyclopentyl, cyclobutyl-fused-azacyclohexyl, cyclobutyl-fused-piperidyl, cyclopentyl-fused-azetidinyl, cyclopentyl-fused-azacyclopentyl, cyclopentyl-fused-azacyclohexyl, cyclopentyl-fused-piperidyl, cyclohexyl-fused-azetidinyl, cyclohexyl-fused-azacyclopentyl, cyclohexyl-fused-azacyclohexyl, cyclohexyl-fused-piperidyl, azetidinyl-fused-azetidinyl, azetidinyl-fused-azacyclopentyl, azetidinyl-fused-azacyclohexyl, azetidinyl-fused-piperidyl, azacyclopentyl-fused-azetidinyl, azacyclopentyl-fused-azacyclopentyl, azacyclopentyl-fused-azacyclohexyl, azacyclopentyl-fused-piperidyl, azacyclohexyl-fused-azetidinyl, azacyclohexyl-fused-azacyclopentyl, azacyclohexyl-fused-azacyclohexyl, azacyclohexyl-fused-piperidyl, cyclobutyl-spiro-azetidinyl, cyclobutyl-spiro-azacyclopentyl, cyclobutyl-spiro-azacyclohexyl, cyclopentyl-spiro-azetidinyl, cyclopentyl-spiro-azacyclopentyl, cyclopentyl-spiro-azacyclohexyl, cyclohexyl-spiro-azetidinyl, cyclohexyl-spiro-azacyclopentyl, cyclohexyl-spiro-azacyclohexyl, azetidinyl-spiro-azetidinyl, azetidinyl-spiro-azacyclopentyl, azetidinyl-spiro-azacyclohexyl, azacyclopentyl-spiro-azetidinyl, azacyclopentyl-spiro-azacyclopentyl, azacyclopentyl-spiro-azacyclohexyl, azacyclohexyl-spiro-azetidinyl, azacyclohexyl-spiro-azacyclopentyl, azacyclohexyl-spiro-azacyclohexyl, cyclobutyl-spiro-piperidyl, cyclopentyl-spiro-piperidyl, cyclohexyl-spiro-piperidyl, azetidinyl-spiro-piperidyl, azacyclopentyl-spiro-piperidyl, azacyclohexyl-spiro-piperidyl, , , ,


, , which, when substituted, are optionally further substituted with 0 to 4 substituents selected from H, F, Cl, Br, I, OH, NH_2, oxo, C_{1-4} alkyl or C_{1-4} alkoxy;

B is selected from ,  or ;

R^{b1}, R^{b2}, R^{b3} or R^{b4} is each independently selected from H, F, Cl, Br, I, OH, NH_2, CN, $CONH_2$, methyl or methoxy, wherein the methyl or methoxy is optionally further substituted with 0 to 4 substituents selected from H, F, Cl, Br or I;

n1, n2, n3, n4, n5, n6, n7, n8, n9, n10, n11, and n12 are each independently selected from 0, 1, 2, 3 or 4;

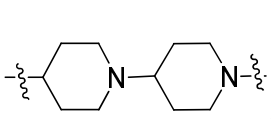
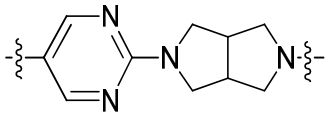
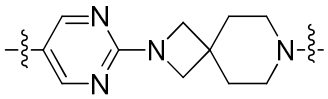
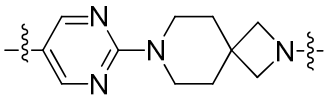
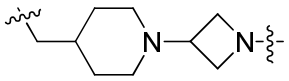
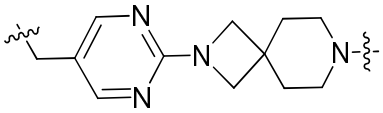
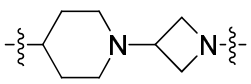
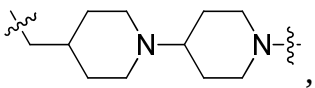
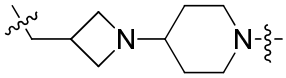
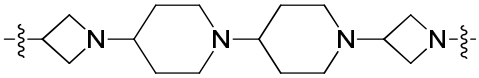
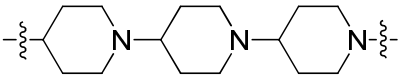
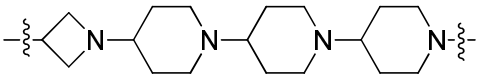
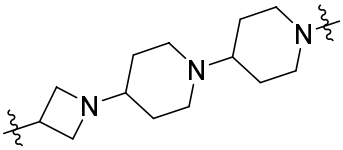
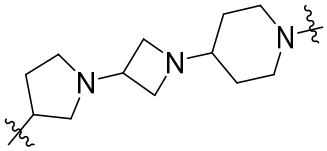
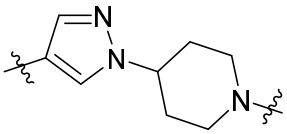
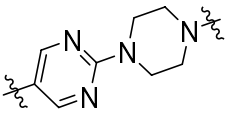
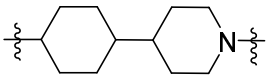
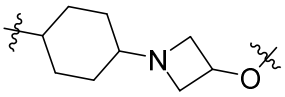
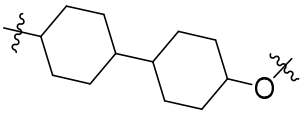
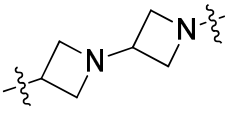
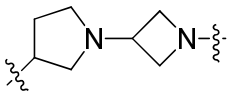
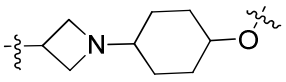
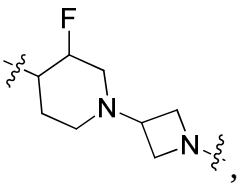
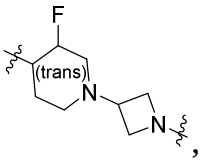
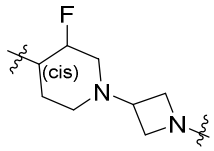
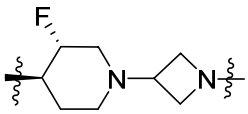
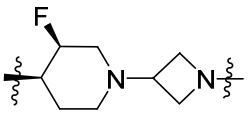
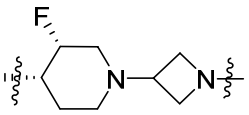
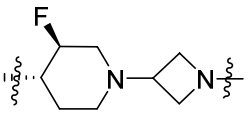
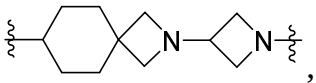
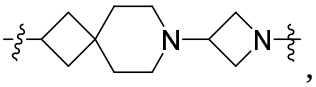
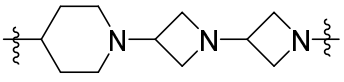
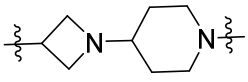
K is selected from  or ;

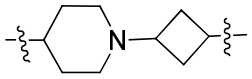
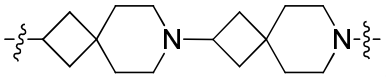
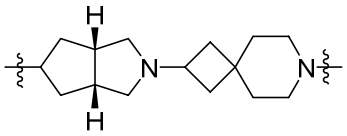
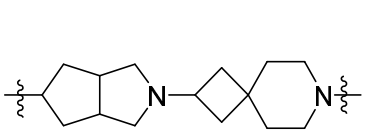
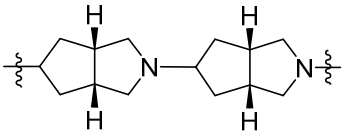
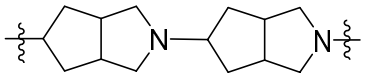
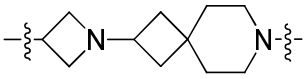
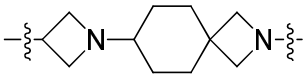
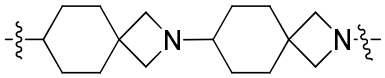
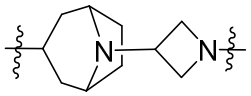
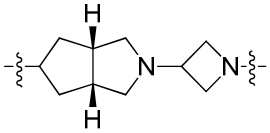
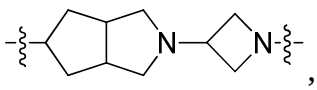
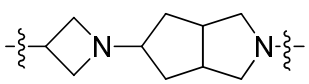
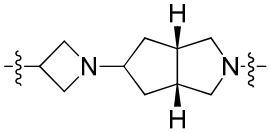
R^{k2} is selected from CH_2 or C=O;

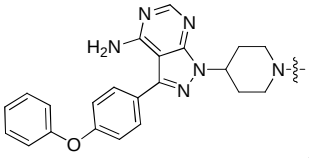
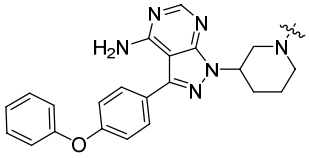
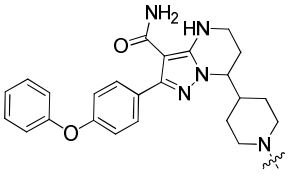
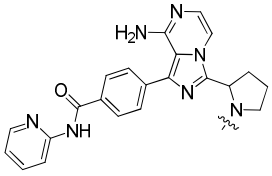
R^{k1}, R^{k3} or R^{k4} is each independently selected from H, F, Cl, Br, I, OH or NH_2; and

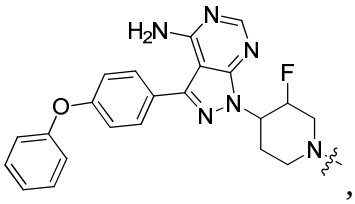
p1 or p2 is each independently selected from 0, 1 or 2.

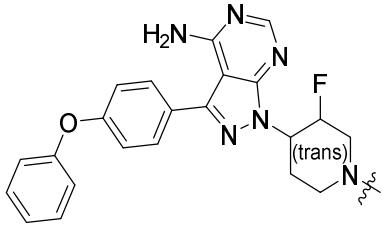
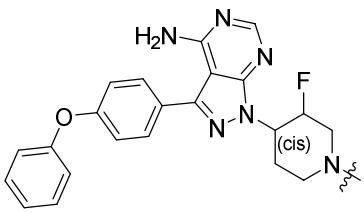
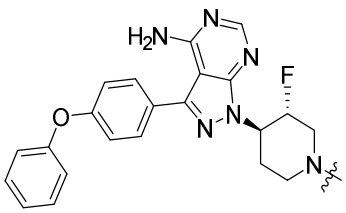
4. The compound according to claim 3, or a stereoisomer, a solvate, a prodrug, a metabolite, a pharmaceutically acceptable salt or a co-crystal thereof, characterized in that

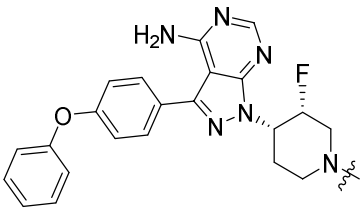
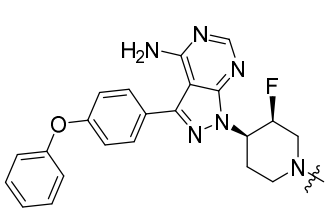
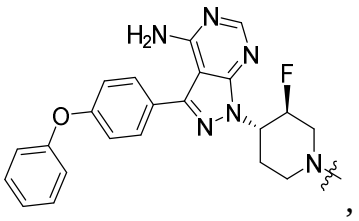
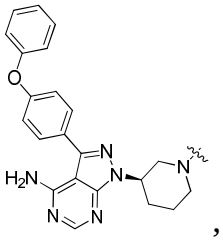
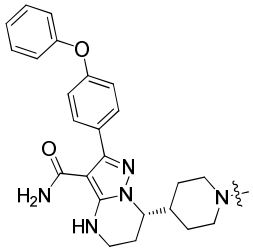
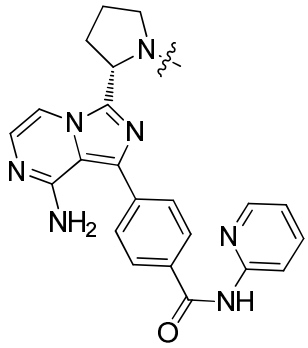
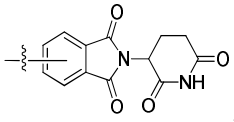
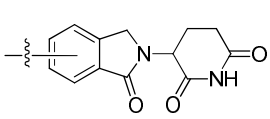
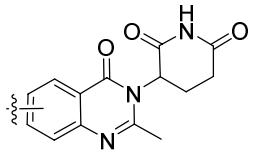
L is selected from , , , , , , , , , , , , , , , , , , , , or L can be selected from , , , , , , , , , , ,  or ;

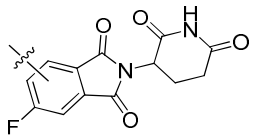
or L can be selected from , , , , , , , , , , , , , , , or L is connected to B on the left side, and is connected to K on the right side;

B is selected from , ,  or ,

or B can be selected from ,

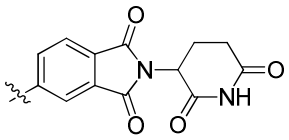
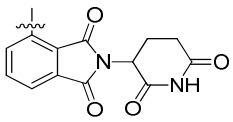
, , ,

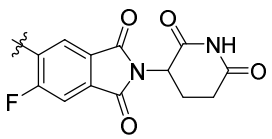
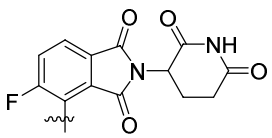
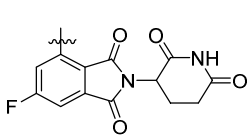
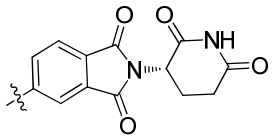
, , , ,  or ; K is selected from ,  or ;

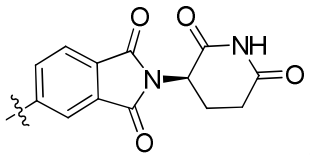
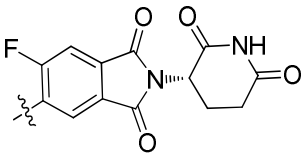
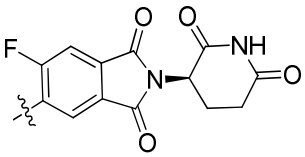
or K can be selected from .

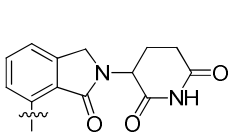
5

5. The compound according to claim 4, or a stereoisomer, a solvate, a prodrug, a metabolite, a pharmaceutically acceptable salt or a co-crystal thereof, characterized in that

K is selected from , ,

10 , , , ,

, , ,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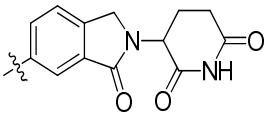
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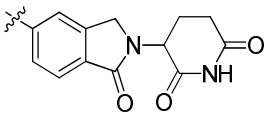
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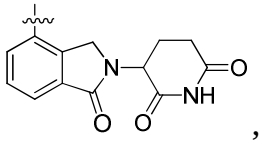
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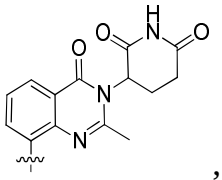
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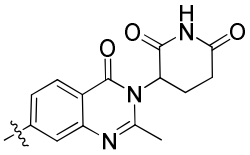
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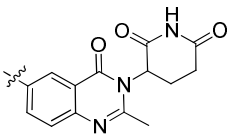
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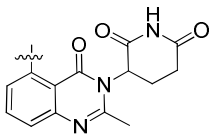
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6. The compound according to claim 4, or a stereoisomer, a solvate, a prodrug, a metabolite, a pharmaceutically acceptable salt or a co-crystal thereof, characterized in that

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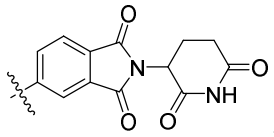
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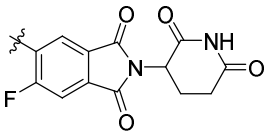
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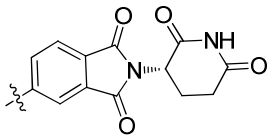
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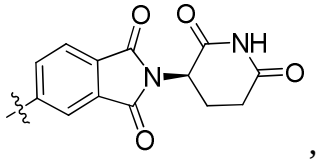
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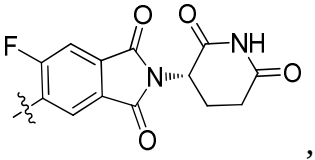
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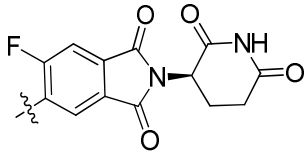
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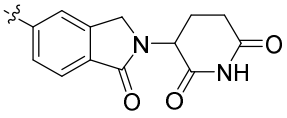
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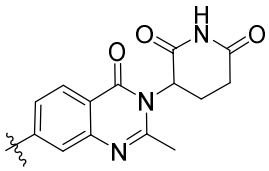
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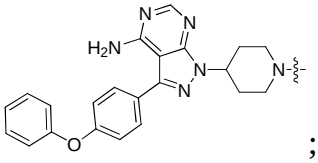
7. The compound according to claim 4, or a stereoisomer, a solvate, a prodrug, a metabolite, a pharmaceutically acceptable salt or a co-crystal thereof, characterized in that

B is selected from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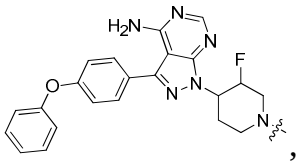
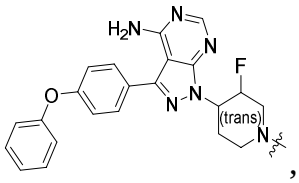
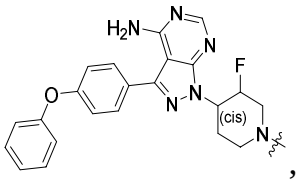
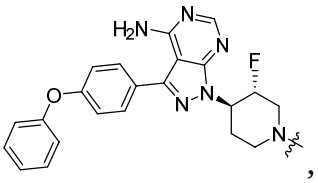
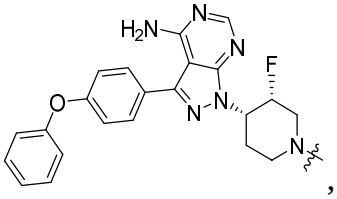
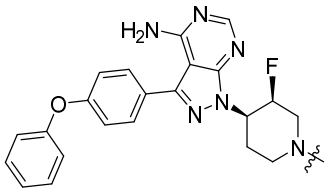
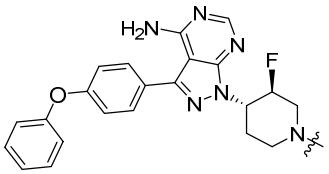
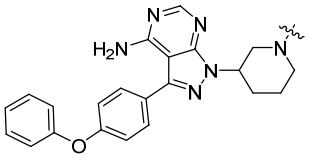
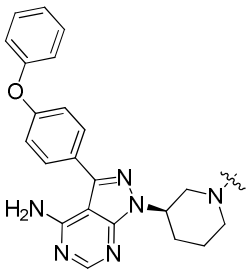
or B can be selected from , , , , ,  or .

8. The compound according to claim 4, or a stereoisomer, a solvate, a prodrug, a metabolite, a pharmaceutically acceptable salt or a co-crystal thereof, characterized in that

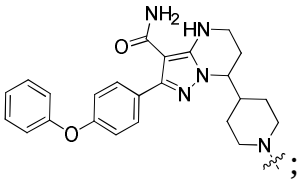
B is selected from

;

or B can be selected from .

9. The compound according to claim 4, or a stereoisomer, a solvate, a prodrug, a metabolite, a pharmaceutically acceptable salt or a co-crystal thereof, characterized in that

B is selected from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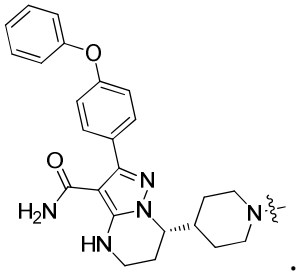
or B can be selected from 
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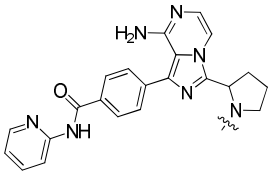
10. The compound according to claim 4, or a stereoisomer, a solvate, a prodrug, a metabolite, a pharmaceutically acceptable salt or a co-crystal thereof, characterized in that

B is selected from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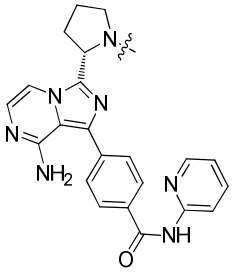
or B can be selected from 
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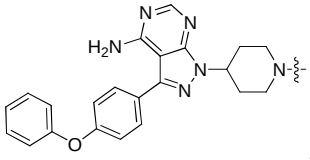
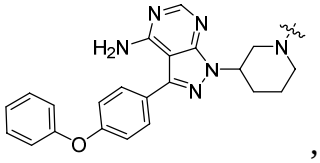
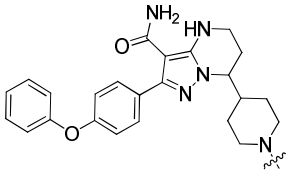
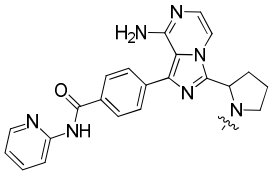
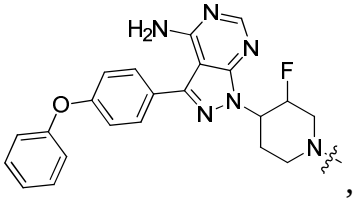
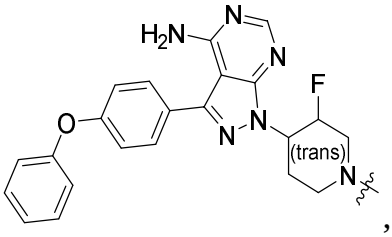
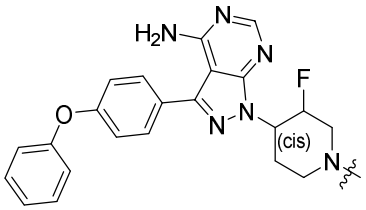
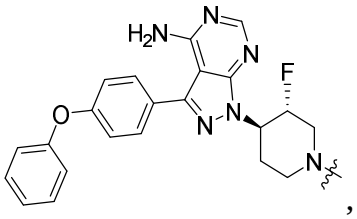
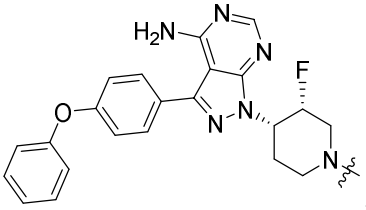
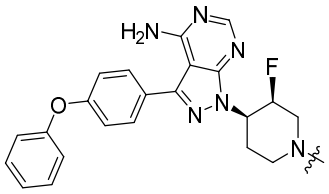
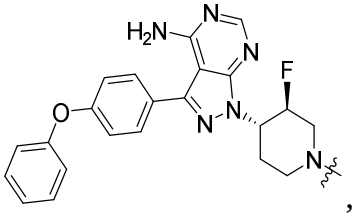
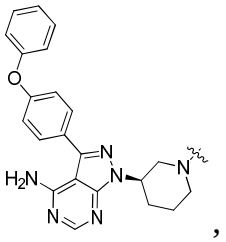
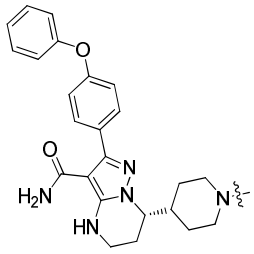
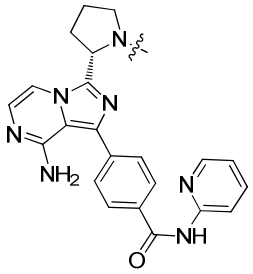
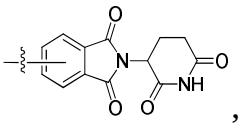
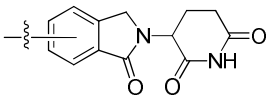
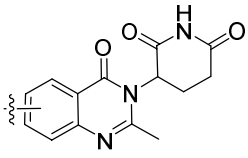
11. The compound according to claim 2, or a stereoisomer, a solvate, a prodrug, a metabolite, a pharmaceutically acceptable salt or a co-crystal thereof, characterized in that the compound is selected from a compound represented by general formula (Ia) or (Ib),

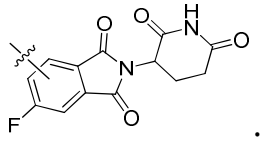
B-Cy1-Cy2-K (Ia)

B-Cy1-Cy2-Cy3-K (Ib)

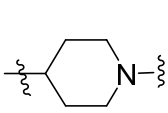
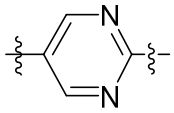
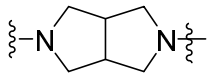
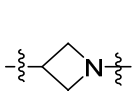
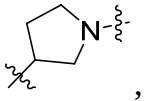
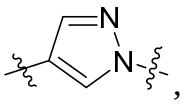
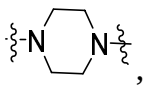
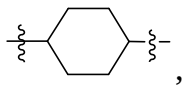
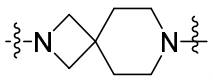
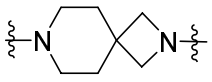
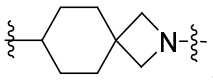
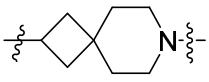
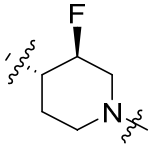
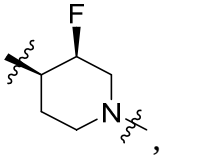
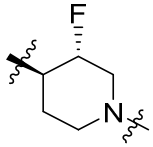
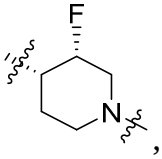
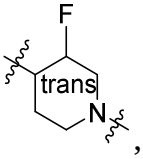
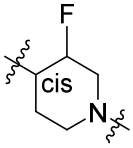
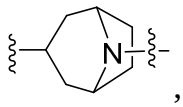
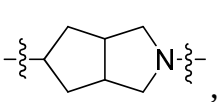
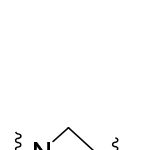
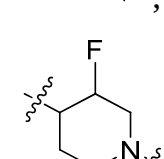
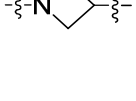
B is selected from , ,  or , , , , , , , , ,  or ;

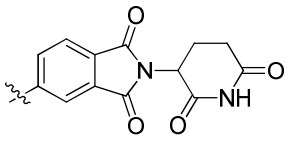
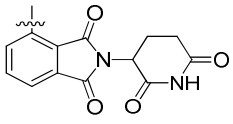
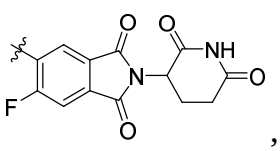
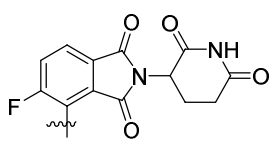
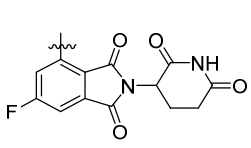
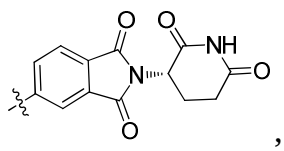
Cy1, Cy2, and Cy3 are each independently selected from one of the following substituted or unsubstituted groups: 4- to 6-membered nitrogen-containing mono-heterocyclic ring, 5- to 10-membered nitrogen-containing fused heterocyclic ring, 6- to 10-membered nitrogen-containing spiro-heterocyclic ring, 4- to 6-membered monocycloalkyl or phenyl, wherein the phenyl, cycloalkyl, mono-heterocyclic ring, fused heterocyclic ring or spiro-heterocyclic ring is optionally further substituted with 0 to 4 substituents selected from H, F, Cl, Br, I, OH, NH_2, oxo, C_{1-4} alkyl or C_{1-4} alkoxy, and the mono-heterocyclic ring, fused heterocyclic ring or spiro-heterocyclic ring contains 1 to 4 heteroatoms selected from O, S or N; and

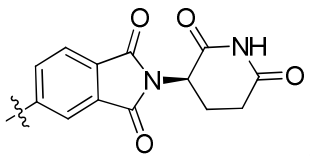
K is selected from , , 

or .

12. The compound according to claim 11, or a stereoisomer, a solvate, a prodrug, a metabolite, a pharmaceutically acceptable salt or a co-crystal thereof, characterized in that

Cy1, Cy2, and Cy3 are each independently selected from one of the following substituted or unsubstituted groups: , , , , , , , , , , , , , , , , , , , , , , , , , , , ; and

K is selected from , , , , , ,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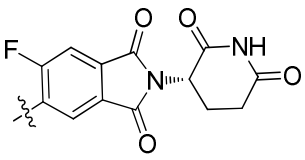
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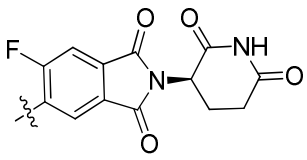
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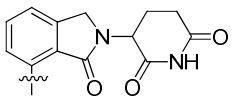
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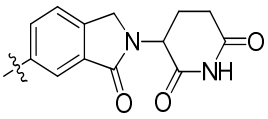
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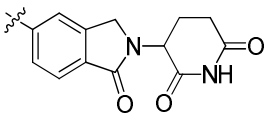
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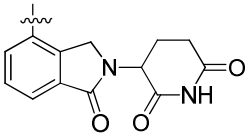
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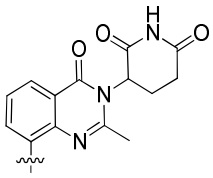
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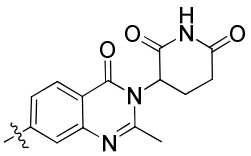
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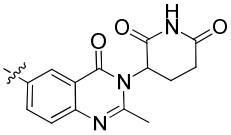
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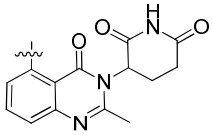
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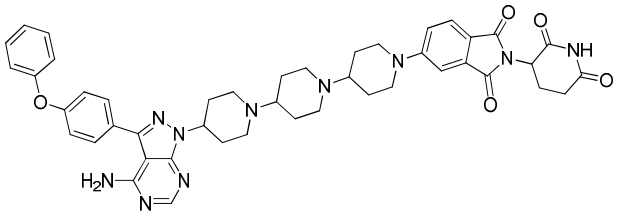
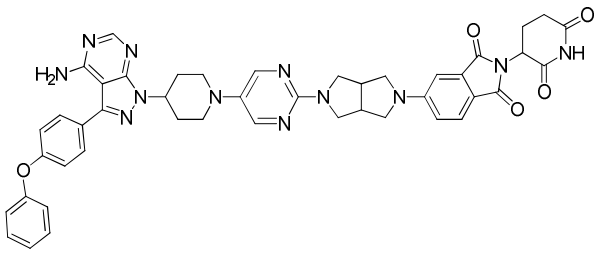
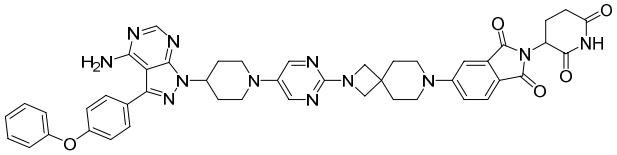
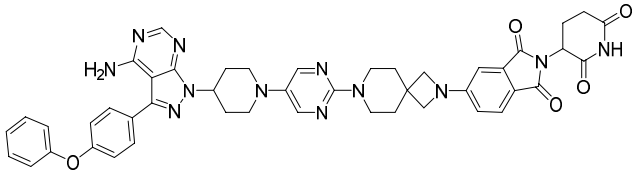
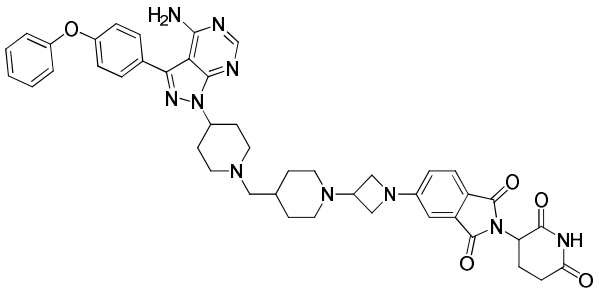
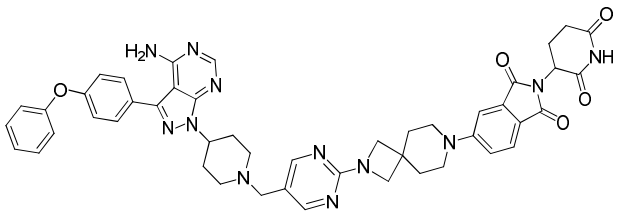
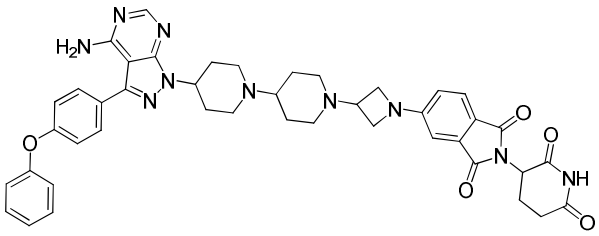
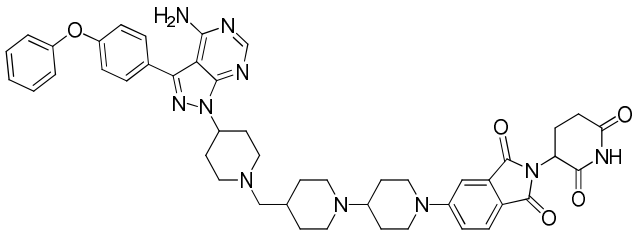

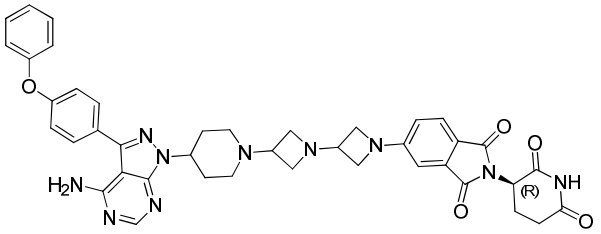

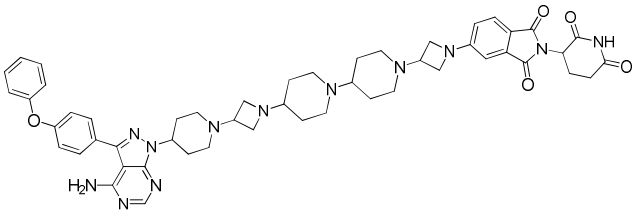

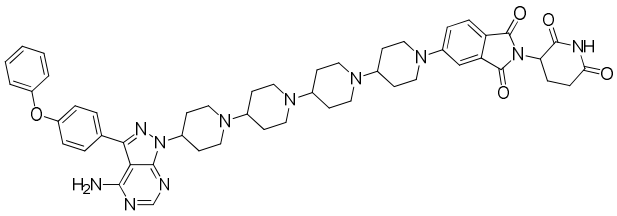

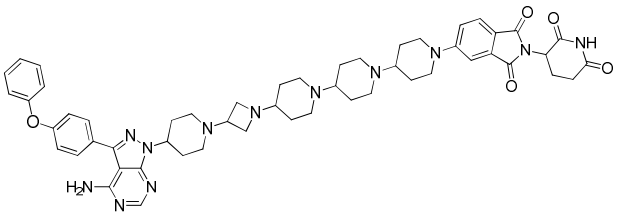

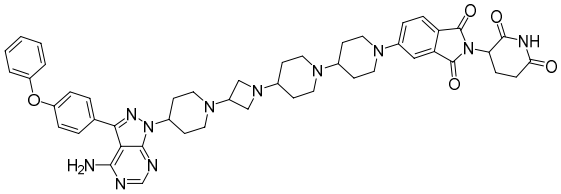

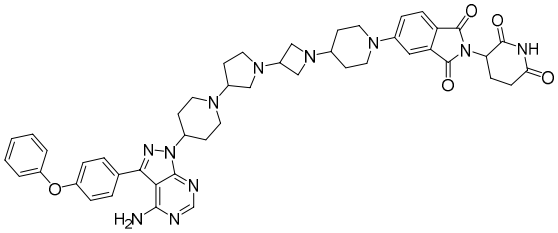

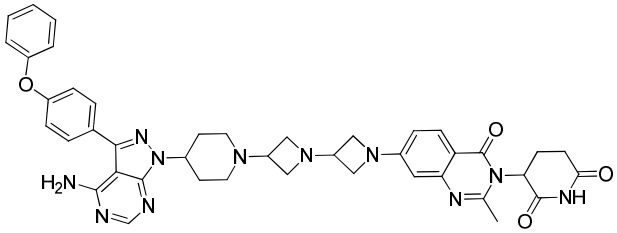

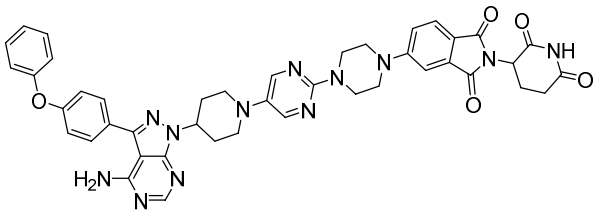

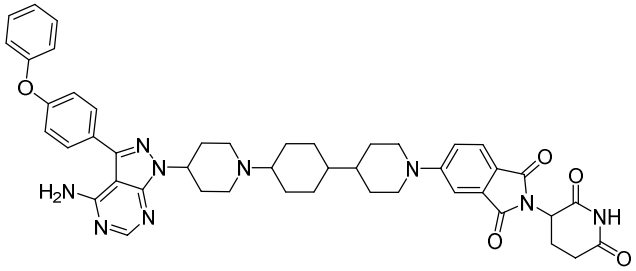

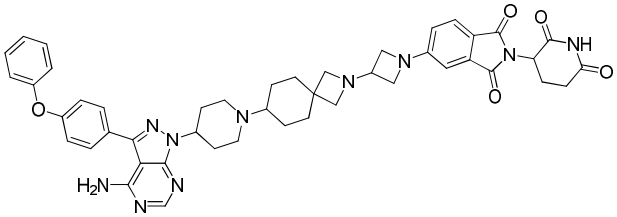

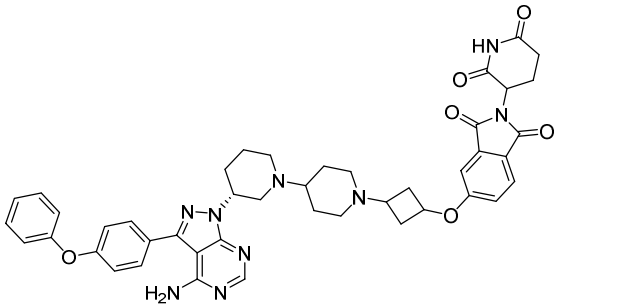

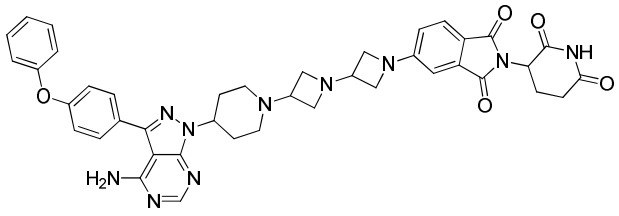

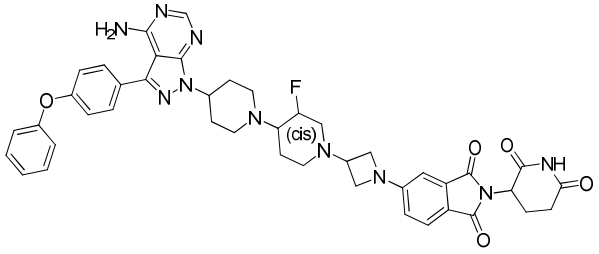

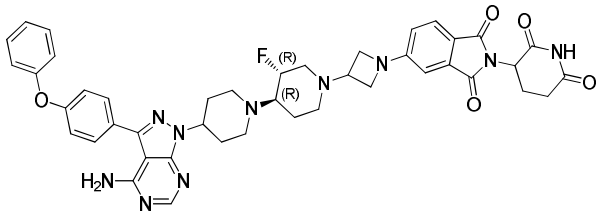

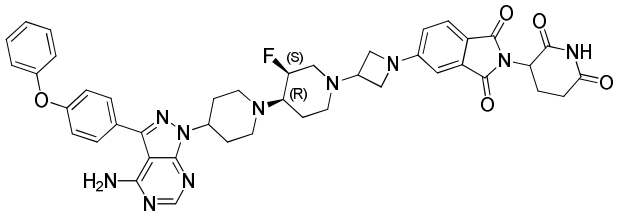

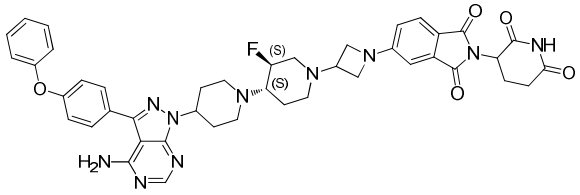

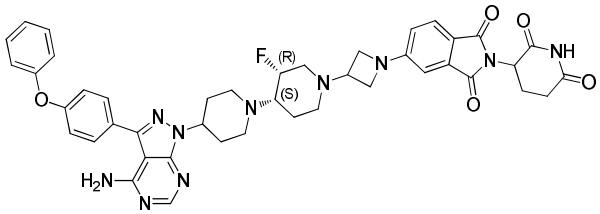

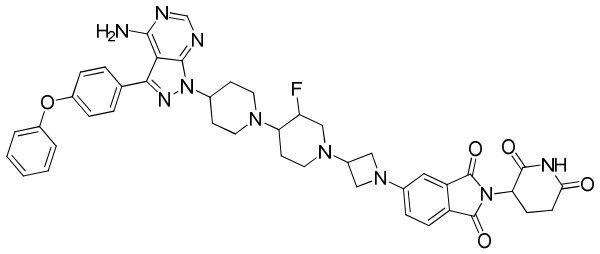

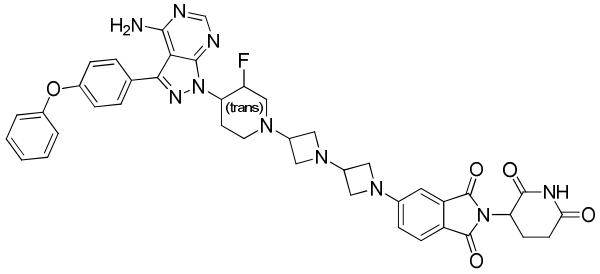

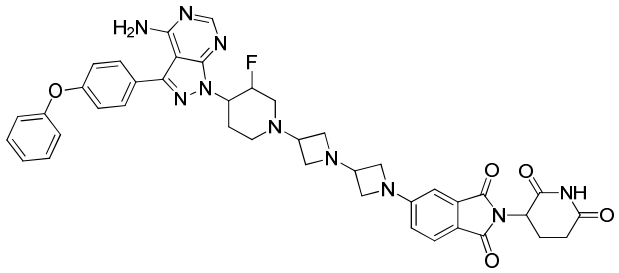

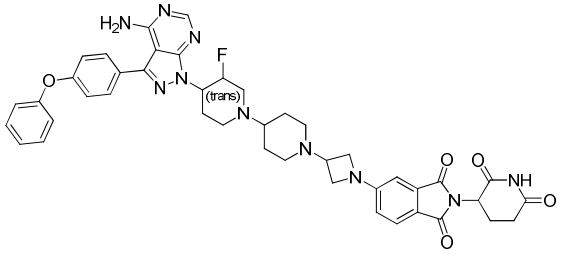

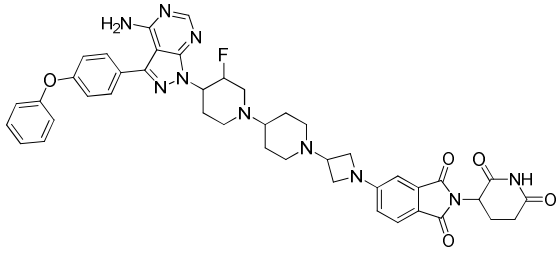

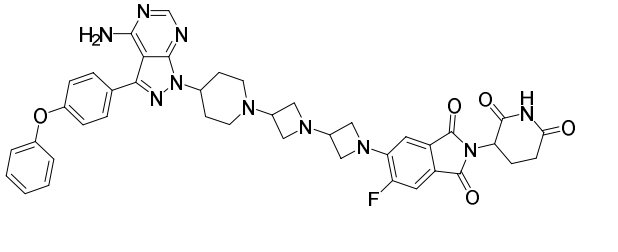

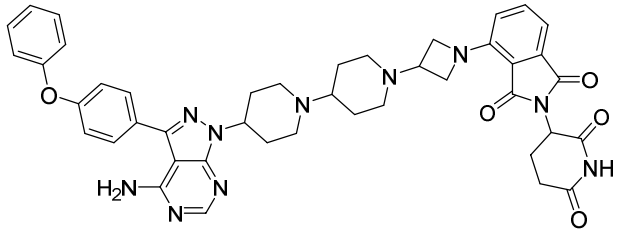

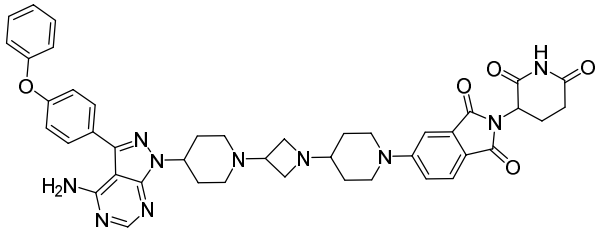

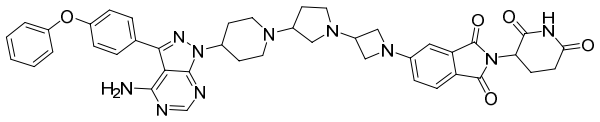

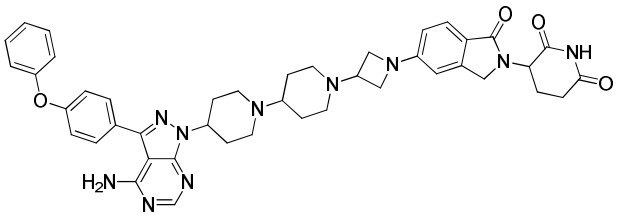

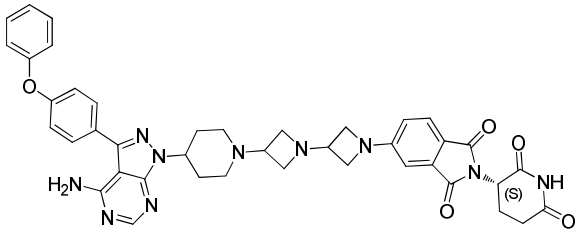

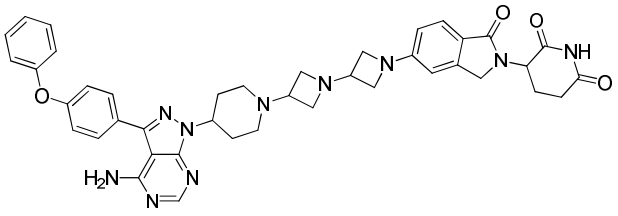

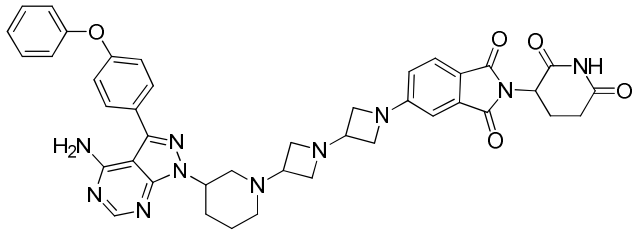

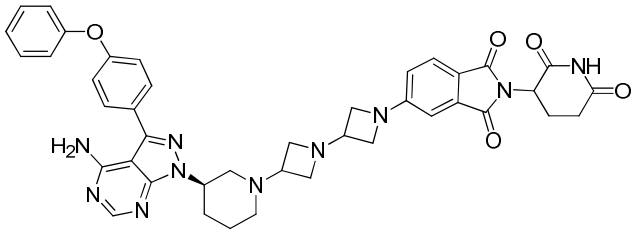

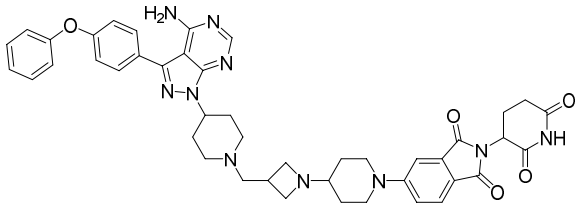

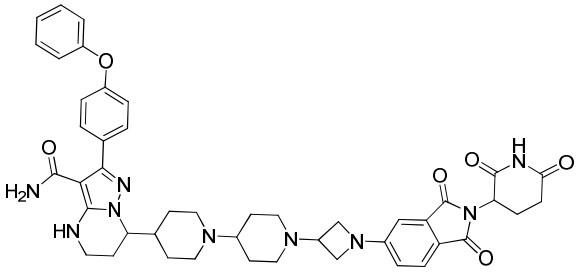

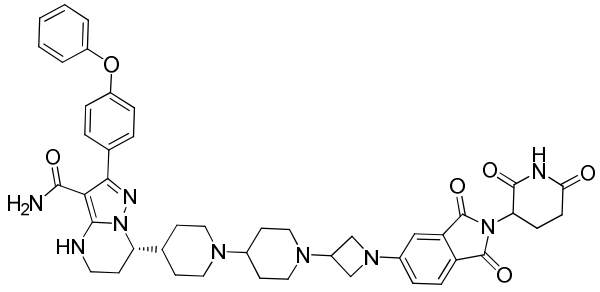

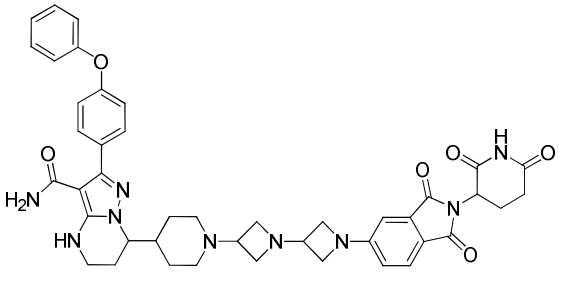

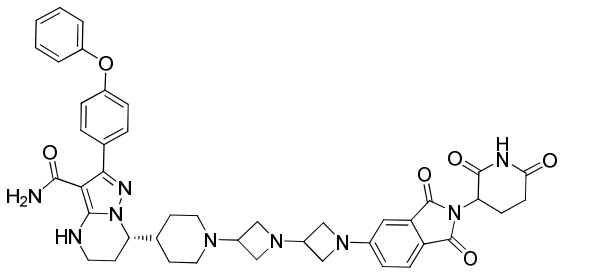

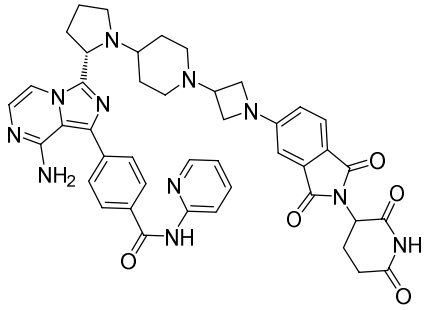

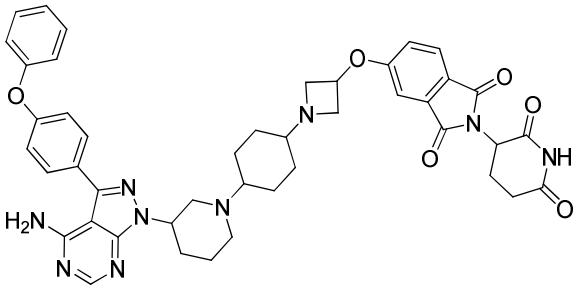

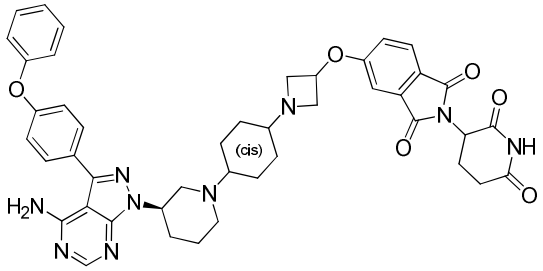
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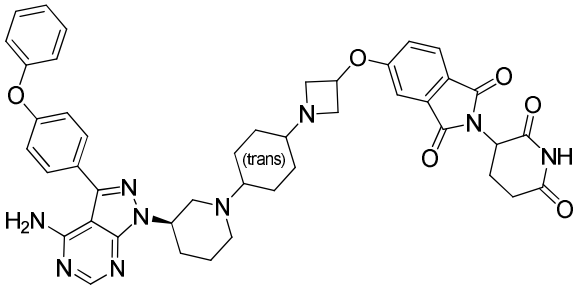
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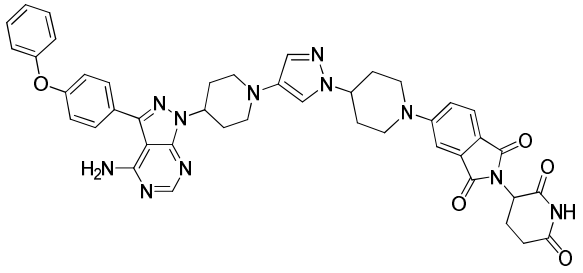

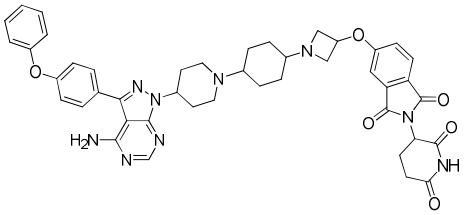

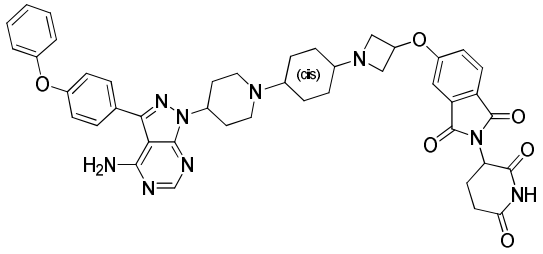
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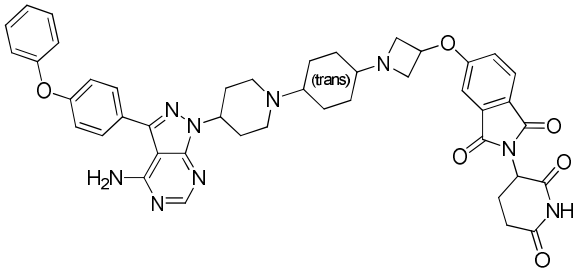
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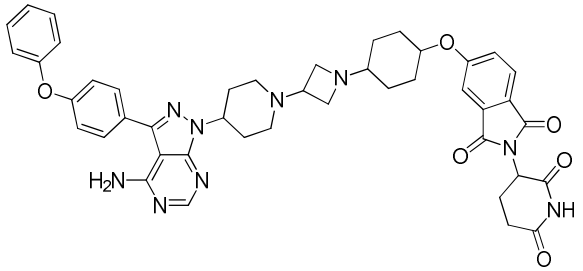

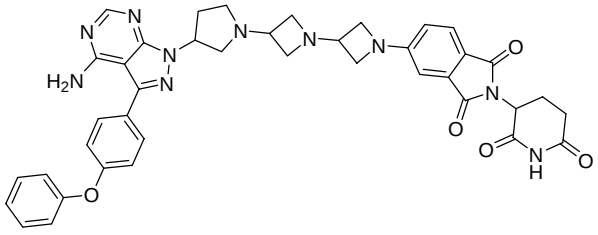

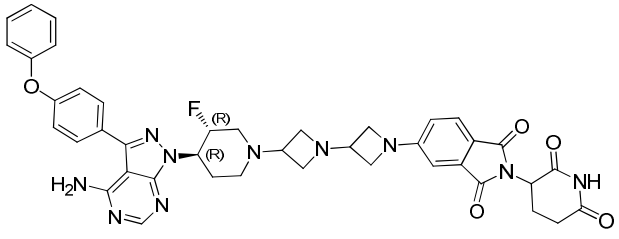
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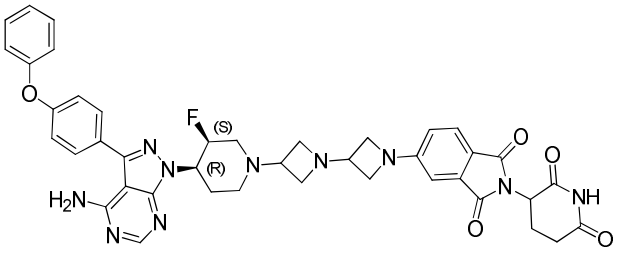
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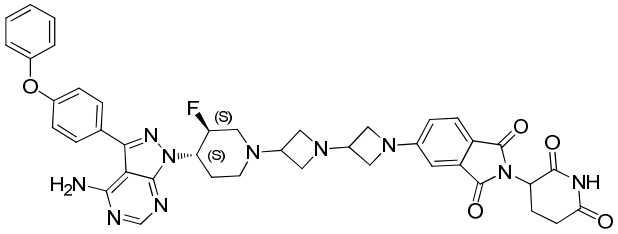

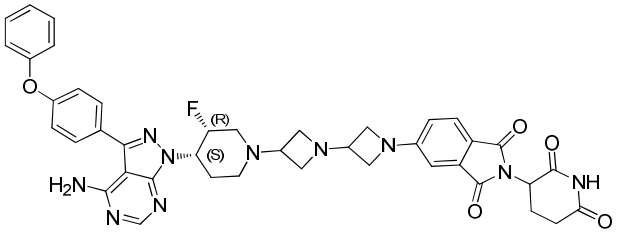

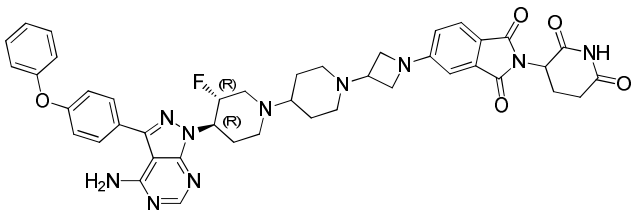

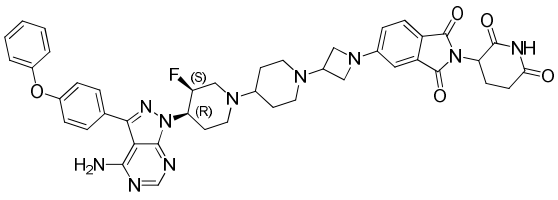

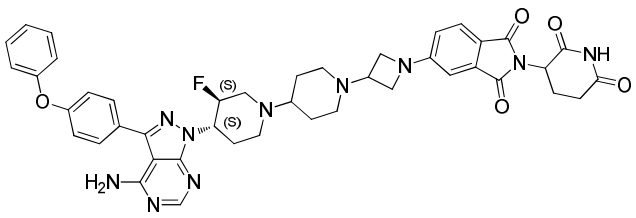

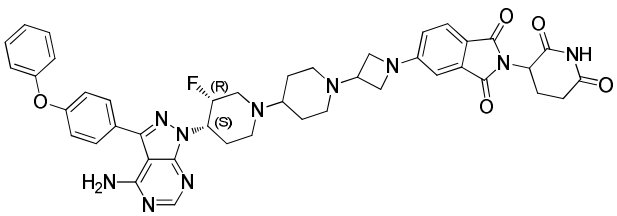

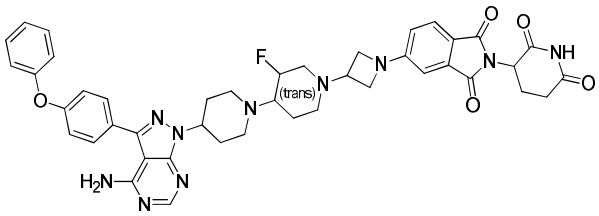

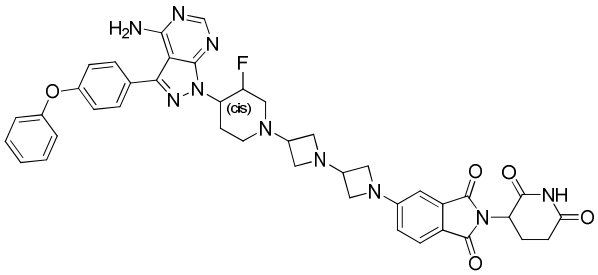

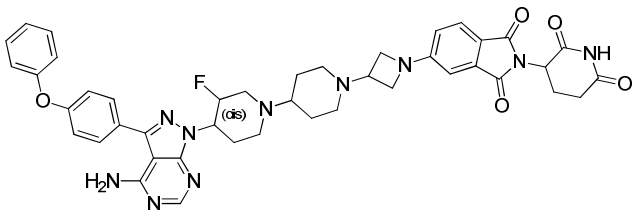

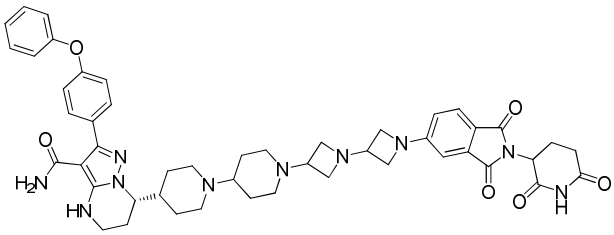

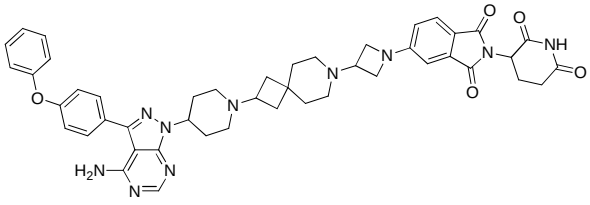

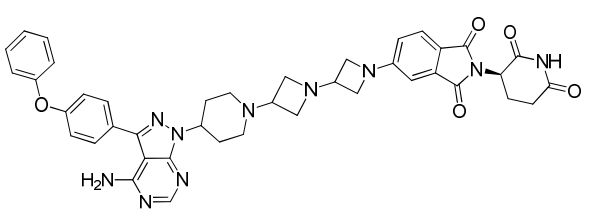

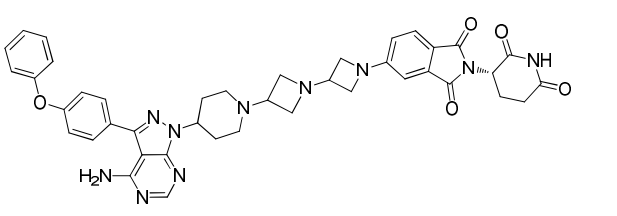



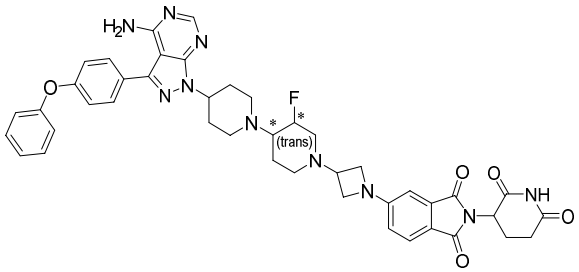
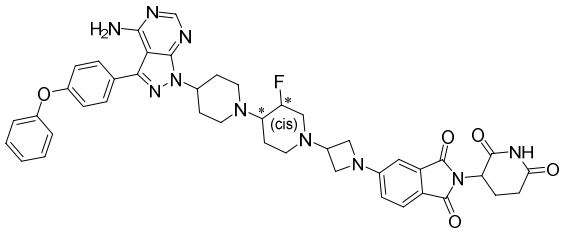
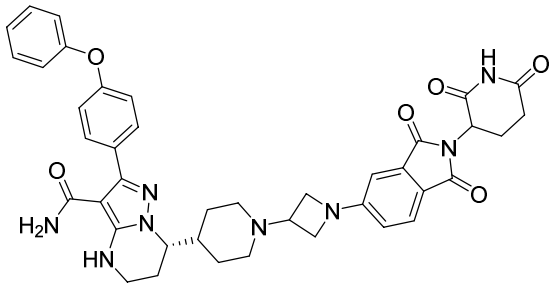
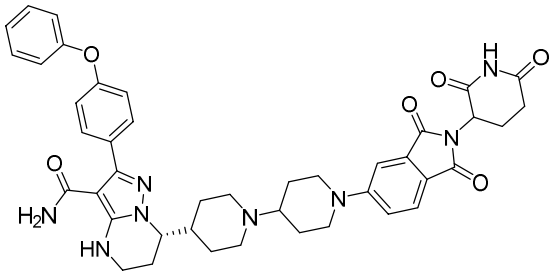
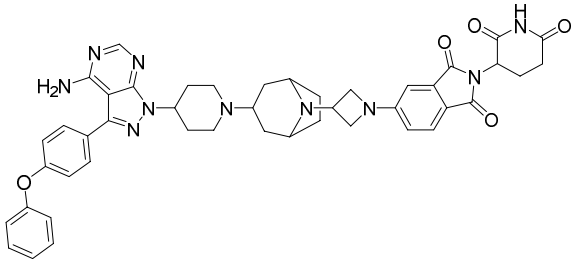
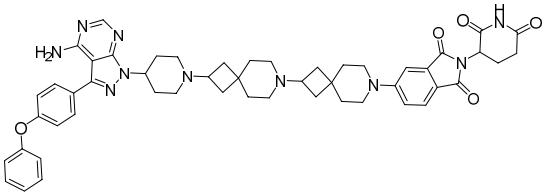
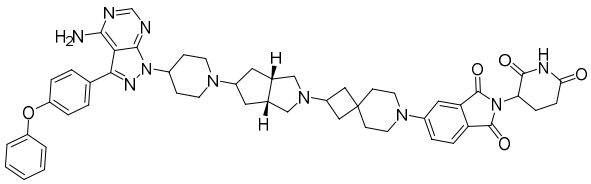
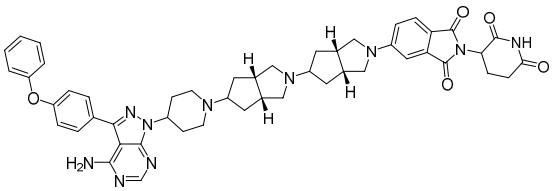
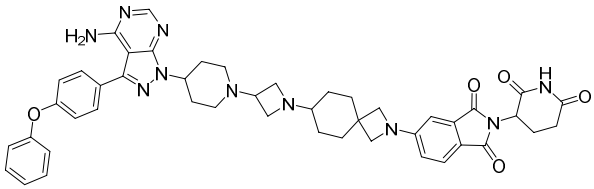
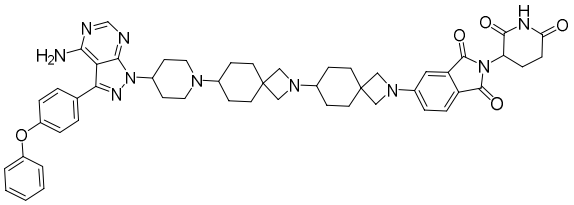
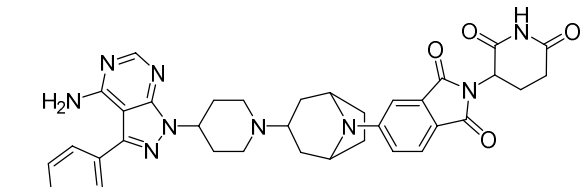
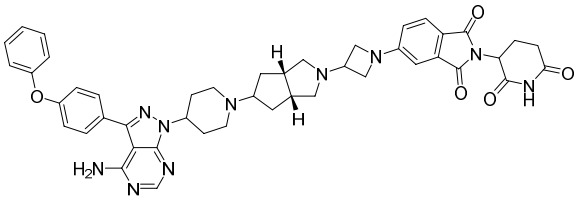

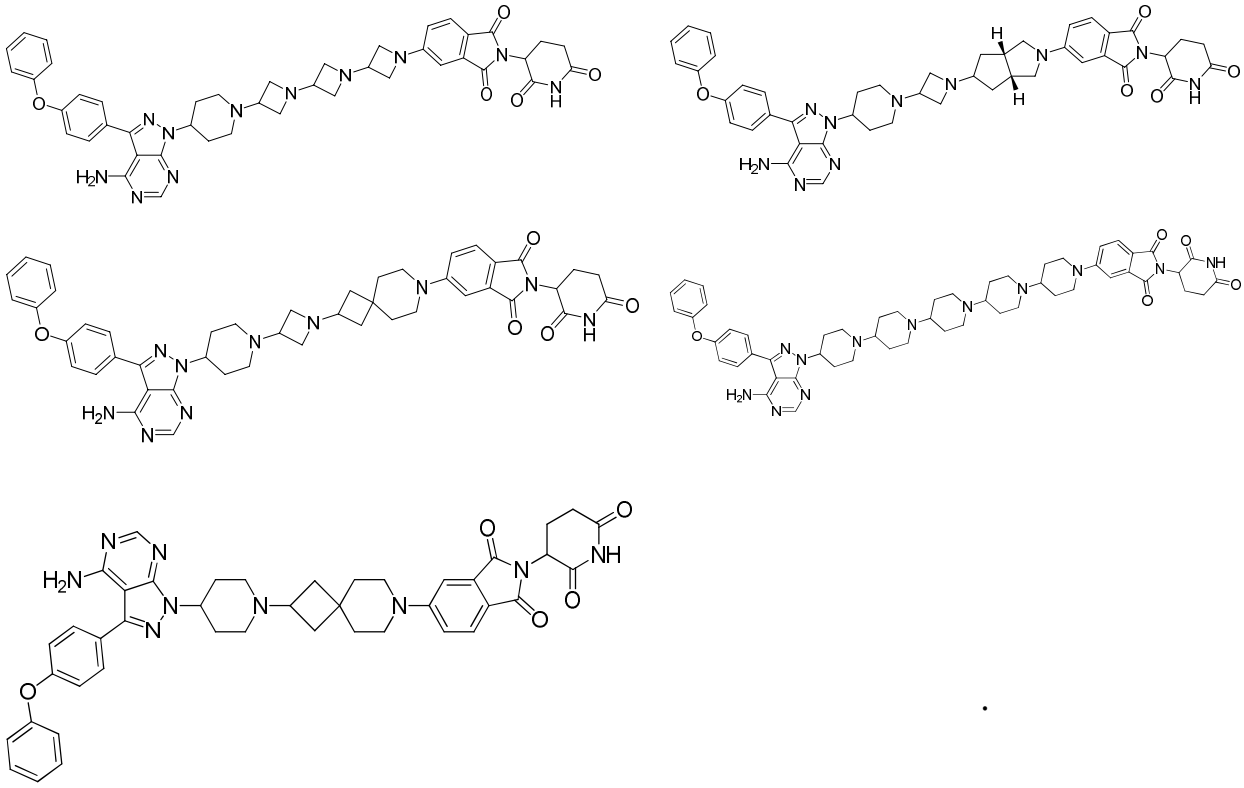

14. The compound according to any one of claims 1 to 13, or a stereoisomer, a solvate, a prodrug, a metabolite, a pharmaceutically acceptable salt or a co-crystal thereof, characterized in that the salt is selected from trifluoroacetate.

15. A pharmaceutical composition, comprising the compound according to any one of claims 1 to 14, or a stereoisomer, a solvate, a prodrug, a metabolite, a pharmaceutically acceptable salt or a co-crystal thereof, and a pharmaceutically acceptable carrier.

16. Use of the compound according to any one of claims 1 to 14, or a stereoisomer, a solvate, a prodrug, a metabolite, a pharmaceutically acceptable salt or a co-crystal thereof in the manufacture of a medicament for treating diseases related to BTK activity or expression level.

17. Use of the compound according to any one of claims 1 to 14, or a stereoisomer, a solvate, a prodrug, a metabolite, a pharmaceutically acceptable salt or

a co-crystal thereof in the manufacture of a medicament for treating diseases related to the inhibition or degradation of BTK.

18. Use according to any one of claims 16-17, characterized in that the disease is selected from tumors or autoimmune diseases.

19. Use according to claim 18, characterized in that the tumor is selected from non-Hodgkin's lymphoma, chronic lymphocytic leukaemia, mantle cell lymphoma, or B cell lymphoma; and the autoimmune disease is selected from rheumatoid arthritis or psoriasis.

20. A compound shown below,

