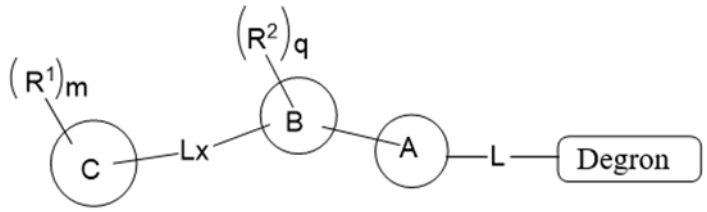
CLAIMS

1. A bifunctional compound represented by general formula (I), an isomer thereof, a deuterated compound thereof, or a pharmaceutically acceptable salt thereof,



Target structure

Formula (I)

wherein ring C is phenyl, 5- to 6-membered heteroaryl, or 9- to 10-membered fused heteroaryl;

R^1 is selected from the group consisting of -CN, $-NR^{1a}R^{1b}$, -OH, halogen, C_{1-6} alkyl, halo-C_{1-6} alkyl, hydroxy-C_{1-6} alkyl, C_{1-6} alkoxy, halo-C_{1-6} alkoxy, 3- to 6-membered cycloalkyl, 3- to 6-membered heterocyclyl, 7- to 9-membered bridged heterocyclyl, 6- to 10-membered fused heterocyclyl, 3- to 6-membered cycloalkyl-NH-, phenyl, 5- to 6-membered heteroaryl, and 9- to 10-membered fused heteroaryl, wherein the heterocyclyl, bridged heterocyclyl, fused heterocyclyl, cycloalkyl, heteroaryl, and fused heteroaryl are optionally substituted by one or more Rx, and the Rx is selected from the group consisting of $-NH_2$, $-NR^{1a}R^{1b}$, -CN, -OH, halogen, C_{1-6} alkyl, and halo-C_{1-6} alkyl;

R^{1a} and R^{1b} are each independently selected from the group consisting of H, C_{1-6} alkyl, halo-C_{1-6} alkyl, 3- to 6-membered cycloalkyl, 3- to 6-membered cycloalkyl-C_{1-6} alkyl-, 3- to 6-membered heterocyclyl, and 3- to 6-membered heterocyclyl-C_{1-6} alkyl-;

m is selected from the group consisting of 0, 1, 2, 3, and 4;

ring B is selected from the group consisting of 5- to 6-membered heteroaryl and 9- to 10-membered fused heteroaryl;

R^2 is selected from the group consisting of H, halogen, C_{1-6} alkyl, halo-C_{1-6} alkyl, hydroxy-C_{1-6} alkyl, C_{1-6} alkoxy, and halo-C_{1-6} alkoxy;

q is selected from the group consisting of 0, 1, 2, 3, and 4;

Lx is $-C(O)-NR^{La}-$;

R^{La} is selected from the group consisting of H, C_{1-6} alkyl, halo-C_{1-6} alkyl, and 3- to

6-membered cycloalkyl;

ring A is selected from the group consisting of divalent groups optionally substituted by one or more Rz: 7- to 11-membered spirocycloalkylene, 7- to 11-membered spiroheterocyclylene, 7- to 9-membered bridged cycloalkylene, and 7- to 9-membered bridged heterocyclylene, wherein the Rz is selected from the group consisting of halogen, -OH, -NH_2, C_{1-6} alkyl, halo-C_{1-6} alkyl, C_{1-6} alkoxy, halo-C_{1-6} alkoxy, 3- to 6-membered cycloalkyl, and 3- to 6-membered heterocyclyl;

L is -$(B^1)n_1$-$(B^2)n_2$-$(B^3)n_3$-;

B^1 is a C_{1-6} alkylene chain, any one methylene unit of which is optionally replaced by -O-, -C(O)-, -C(R^a)(R^b)-, -N(R^c)-, or -S-; n_1 is selected from the group consisting of 0 and 1;

B^2 is selected from the group consisting of the following divalent rings optionally substituted by one or more Ry: C_{3-6} cycloalkylene, C_{5-8} bridged cycloalkylene, 4- to 6-membered heterocyclylene, 6- to 8-membered bridged heterocyclylene, phenylene, and 6- to 8-membered heterocycloalkenylene, wherein the Ry is selected from the group consisting of oxo, halogen, C_{1-6} alkyl, and halo-C_{1-6} alkyl; n_2 is selected from the group consisting of 0 and 1;

B^3 is a saturated or unsaturated C_{1-6} hydrocarbylene chain, any one methylene unit of which is optionally replaced by -O-, -C(O)-, -C(R^a)(R^b)-, -N(R^c)-, or -S-; n_3 is selected from the group consisting of 0 and 1;

R^a and R^b are each independently selected from the group consisting of H, deuterium, halogen, C_{1-6} alkyl, and halo-C_{1-6} alkyl, and R^a and R^b are not simultaneously H;

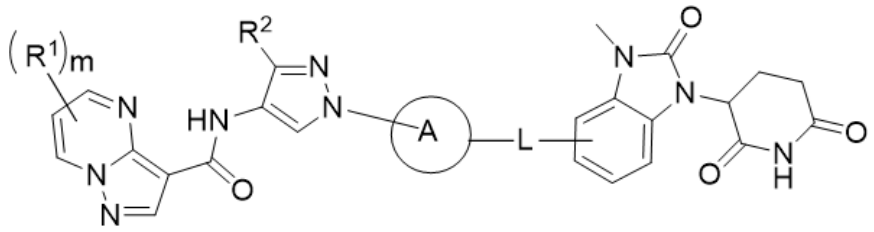
alternatively, R^a and R^b on the same carbon atom together with the carbon atom to which they are attached form a 3- to 6-membered cycloalkyl ring or a 3- to 6-membered heterocyclyl ring;

R^c is selected from the group consisting of H and C_{1-6} alkyl;

the degron is a ligand that binds to an E3 enzyme.

2. The bifunctional compound, the isomer thereof, the deuterated compound thereof, or the pharmaceutically acceptable salt thereof as claimed in claim 1, wherein the

bifunctional compound is represented by the following formula (IA),



Formula (IA)

wherein R^1 is selected from the group consisting of -CN, halogen, C_{1-4} alkyl, halo-C_{1-4} alkyl, C_{1-4} alkoxy, 5- to 6-membered heterocyclyl, 7- to 9-membered bridged heterocyclyl, 6- to 10-membered fused heterocyclyl, and 3- to 6-membered cycloalkyl-NH-, wherein the heterocyclyl, bridged heterocyclyl, fused heterocyclyl, and cycloalkyl are optionally substituted by one or more Rx, and the Rx is selected from the group consisting of -NH_2, -OH, halogen, C_{1-4} alkyl, and halo-C_{1-4} alkyl;

m is selected from the group consisting of 0, 1, 2, 3, and 4;

R^2 is selected from the group consisting of C_{1-4} alkyl and halo-C_{1-4} alkyl;

ring A is selected from the group consisting of the following divalent groups: 7- to 11-membered spirocycloalkylene, 7- to 11-membered spiroheterocyclylene, 7- to 9-membered bridged cycloalkylene, and 7- to 9-membered bridged heterocyclylene;

L is -$(B^1)n_1$-$(B^2)n_2$-$(B^3)n_3$-;

B^1 is a C_{1-3} alkylene chain, any one methylene unit of which is optionally replaced by -O-, -C(O)-, -C(R^a)(R^b)-, -N(R^c)-, or -S-; n_1 is selected from the group consisting of 0 and 1;

B^2 is selected from the group consisting of the following divalent rings optionally substituted by one or more Ry: C_{3-6} cycloalkylene, C_{5-8} bridged cycloalkylene, 4- to 6-membered heterocyclylene, 6- to 8-membered bridged heterocyclylene, phenylene, and 6- to 8-membered heterocycloalkenylene, wherein the Ry is selected from the group consisting of oxo, halogen, C_{1-4} alkyl, and halo-C_{1-4} alkyl; n_2 is selected from the group consisting of 0 and 1;

B^3 is a saturated or unsaturated C_{1-6} hydrocarbylene chain, any one methylene unit of

which is optionally replaced by -O-, -C(O)-, -C(R^a)(R^b)-, -N(R^c)-, or -S-; n_3 is selected from the group consisting of 0 and 1;

R^a and R^b are each independently selected from the group consisting of H, deuterium, halogen, C_{1-4} alkyl, and halo-C_{1-4} alkyl, and R^a and R^b are not simultaneously H;

alternatively, R^a and R^b on the same carbon atom together with the carbon atom to which they are attached form a 3- to 6-membered cycloalkyl ring;

R^c is selected from the group consisting of H and C_{1-4} alkyl.

3. The bifunctional compound, the isomer thereof, the deuterated compound thereof, or the pharmaceutically acceptable salt thereof as claimed in claim 1 or 2, wherein the bifunctional compound, the isomer thereof, the deuterated compound thereof, or the pharmaceutically acceptable salt thereof satisfies one or more of the following conditions:

(1) the heteroatom in the heterocyclyl, bridged heterocyclyl, fused heterocyclyl, heteroaryl, fused heteroaryl, or spiroheterocyclyl is independently selected from the group consisting of one, two, or three types of N, O, and S, and the number of heteroatoms is independently 1, 2, 3, or 4;

(2) R^1 is selected from the group consisting of -CN, halogen, C_{1-6} alkyl, halo-C_{1-6} alkyl, C_{1-6} alkoxy, 3- to 6-membered heterocyclyl, 7- to 9-membered bridged heterocyclyl, 6- to 10-membered fused heterocyclyl, and 3- to 6-membered cycloalkyl-NH-;

(3) Rx is selected from the group consisting of -NH_2 and C_{1-6} alkyl;

(4) m is selected from the group consisting of 1 and 2;

(5) ring B is 5- to 6-membered heteroaryl;

(6) R^2 is C_{1-6} alkyl or halo-C_{1-6} alkyl;

(7) q is 1;

(8) Lx is -C(O)-NR^{La}-*, wherein the * terminus is connected to ring B;

(9) in L, -(B^3)n_3- terminus is connected to the degron;

(10) ring A is selected from the group consisting of the following unsubstituted divalent groups: 7- to 11-membered spirocycloalkylene, 7- to 11-membered spiroheterocyclylene, 7- to 9-membered bridged cycloalkylene, and 7- to 9-membered bridged heterocyclylene.

4. The bifunctional compound, the isomer thereof, the deuterated compound thereof, or the pharmaceutically acceptable salt thereof as claimed in any one of claims 1 to 3, wherein the bifunctional compound, the isomer thereof, the deuterated compound thereof, or the pharmaceutically acceptable salt thereof satisfies one or more of the following conditions:

(1) R^1 is 7- to 9-membered bridged heterocyclyl;

(2) ring A is 7- to 9-membered nitrogen-containing spiroheterocyclylene;

(3) L is selected from the group consisting of $-B^1-B^2-B^3-$, $-B^1-B^3-$, and $-B^2-B^3$;

(4) L is $-B^3-$;

(5) the $-B^3-$ terminus is connected to the degron.

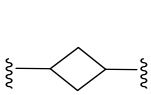
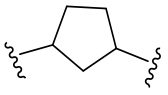
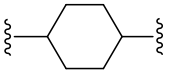
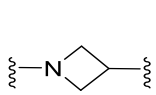
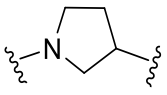
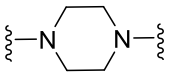
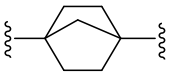
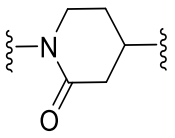
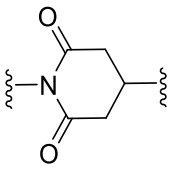
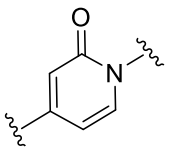
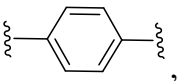
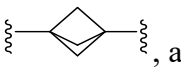
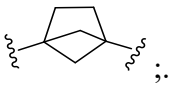
5. The bifunctional compound, the isomer thereof, the deuterated compound thereof, or the pharmaceutically acceptable salt thereof as claimed in any one of claims 1 to 4, wherein the bifunctional compound, the isomer thereof, the deuterated compound thereof, or the pharmaceutically acceptable salt thereof satisfies one or more of the following conditions:

(1) B^1 is a C_{1-3} alkylene chain, wherein 1 to 2 methylene units are optionally replaced by -O-, -C(O)-, $-C(R^a)(R^b)-$, or $-N(R^c)-$;

(2) B^3 is an unsaturated C_{2-6} hydrocarbylene chain, wherein 1 to 2 methylene units are optionally replaced by -O-, -C(O)-, or $-C(R^a)(R^b)-$; the hydrocarbylene chain is connected to the degron via the alkyne terminus;

(3) R^a and R^b are each independently selected from the group consisting of H, deuterium, and $-CH_3$; and R^a and R^b are not simultaneously H; alternatively, R^a and R^b on the same carbon atom together with the carbon atom to which they are attached form a cyclopropyl ring or a cyclobutyl ring;

(4) R^c is selected from the group consisting of H and $-CH_3$;

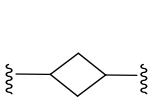
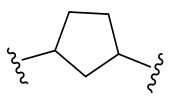
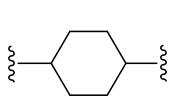
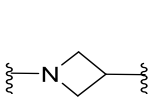
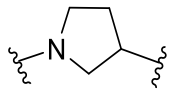
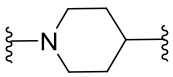
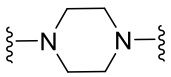
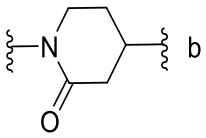
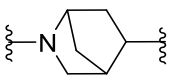
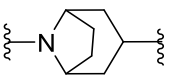
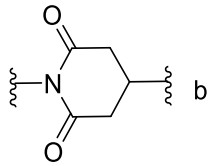
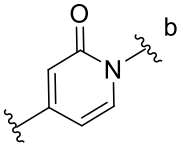
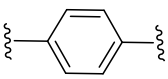
(5) B^2 is selected from the group consisting of the following groups: , , , , , , , , , , , , , , , , and ;.

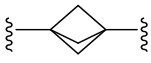
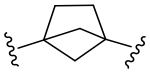
6. The bifunctional compound, the isomer thereof, the deuterated compound thereof, or the pharmaceutically acceptable salt thereof as claimed in any one of claims 1 to 5, wherein the bifunctional compound, the isomer thereof, the deuterated compound thereof, or the pharmaceutically acceptable salt thereof satisfies one or more of the following conditions:

(1) B^1 is a C_{1-3} alkylene chain, wherein 1 methylene unit is optionally replaced by -C(O);

(2) B^3 is an unsaturated C_{2-6} hydrocarbylene chain, wherein 1 methylene unit is optionally replaced by -O;

(3) R^c is H;

(4) B^2 is selected from the group consisting of the following groups: , , , , , , , , , , , , , , , ,

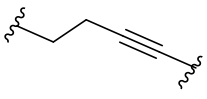
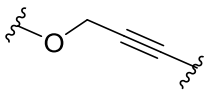
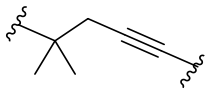
, and , wherein the b terminus is connected to -(B^3)n_3.

7. The bifunctional compound, the isomer thereof, the deuterated compound thereof, or the pharmaceutically acceptable salt thereof as claimed in any one of claims 1 to 6, wherein B^3 satisifies any one of the conditions:

(1) B^3 is a C_{2-6} alkynylene chain, wherein 1 to 2 methylene units are optionally replaced by -O- or -C(O)-; the alkynylene chain is connected to the degron via the alkyne terminus; (2) B^3 is a C_{2-6} alkynylene chain containing only one triple bond at the terminus; (3) B^3 is a C_{2-4} alkynylene chain containing only one triple bond at the terminus.

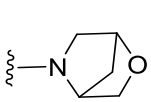
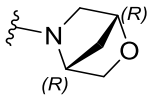
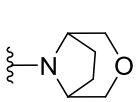
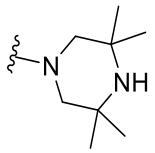
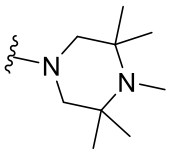
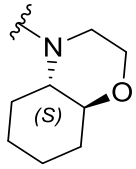
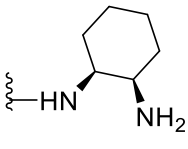
8. The bifunctional compound, the isomer thereof, the deuterated compound thereof, or the pharmaceutically acceptable salt thereof as claimed in any one of claims 1 to 7, wherein B^1 is selected from the group consisting of -CH_2-, -CD_2-, and -C(O)-;

B^2 is selected from the group consisting of the following divalent rings: C_{5-6} cycloalkylene, C_{6-8} bridged cycloalkylene, 6-membered heterocyclylene, and 6- to 8-membered bridged heterocyclylene;

B^3 is selected from the group consisting of , , and .

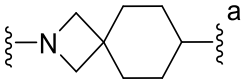
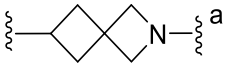
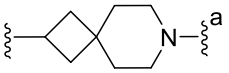
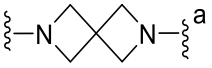
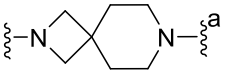
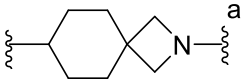
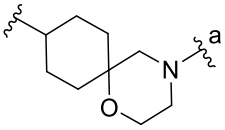
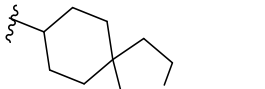
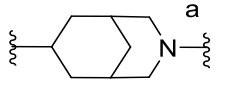
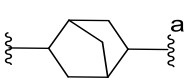
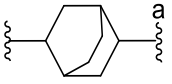
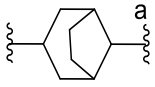
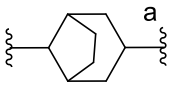
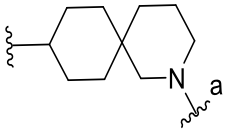
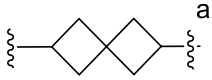
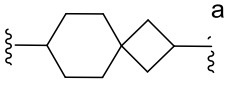
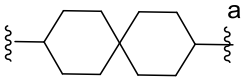
9. The bifunctional compound, the isomer thereof, the deuterated compound thereof, or the pharmaceutically acceptable salt thereof as claimed in any one of claims 1 to 8, wherein the bifunctional compound, the isomer thereof, the deuterated compound thereof, or the pharmaceutically acceptable salt thereof satisfies one or more of the following conditions:

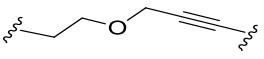
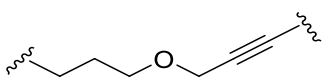
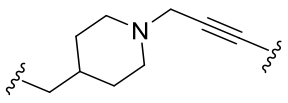
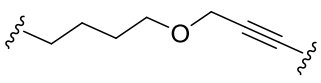
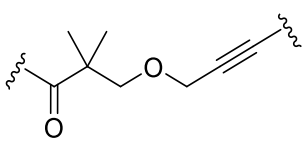
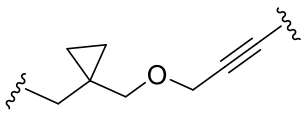
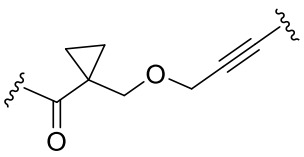
(1) R^1 is selected from the group consisting of -F, -CH_3, -CN, -CHF_2, -CF_3, -OCH_3,

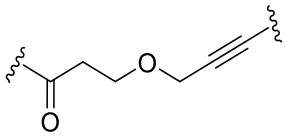
, , , , , , and ;

m is selected from the group consisting of 1 and 2;

(2) R^2 is selected from the group consisting of $-CH_3$, $-CH_2F$, $-CHF_2$, and $-CF_3$;

(3) ring A is selected from the group consisting of , , , , , , , , , , , , , , , , , , , , , , , and , wherein the "a" terminus denotes the end connected to L in general formula (IA);

(4) L is selected from the group consisting of , , , , , , ,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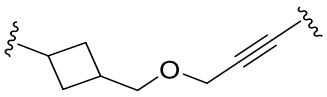
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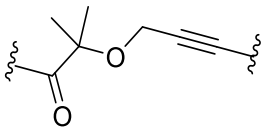
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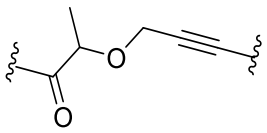
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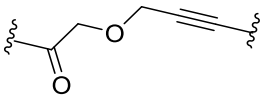
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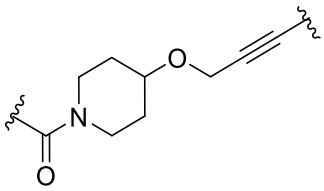
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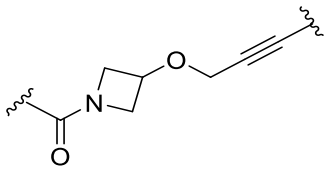
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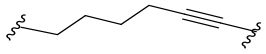
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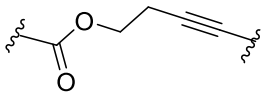
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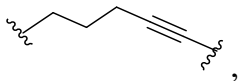
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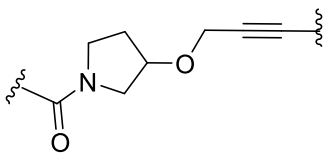
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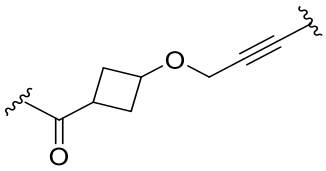
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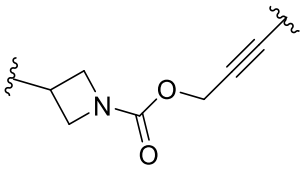
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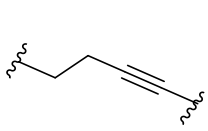
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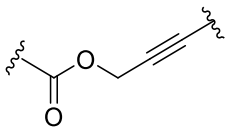
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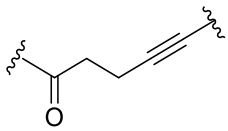
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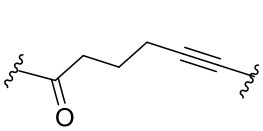
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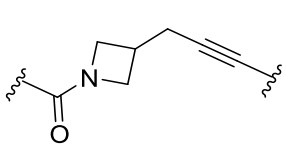
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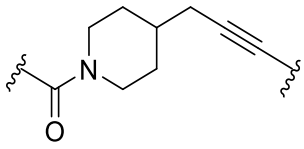
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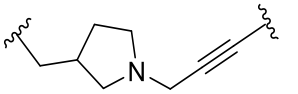
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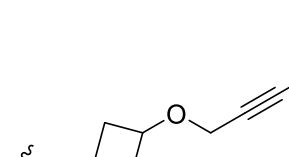
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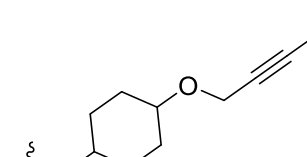
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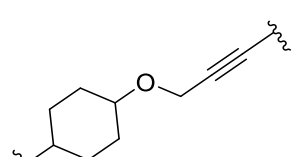
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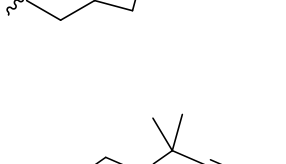
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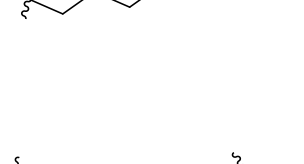
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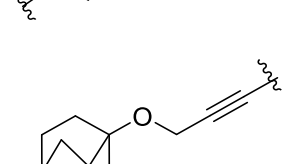
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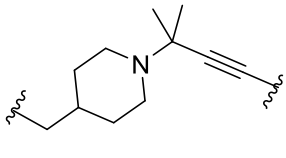
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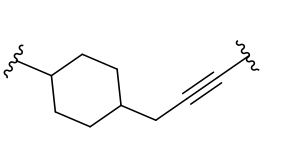
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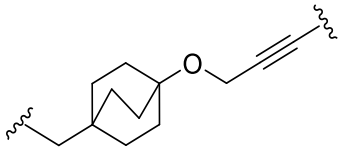
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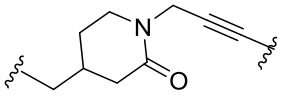
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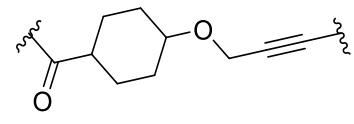
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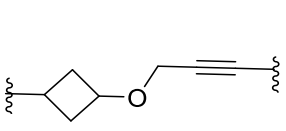
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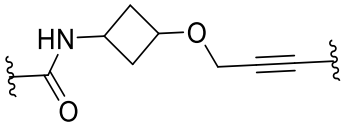
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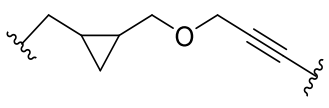
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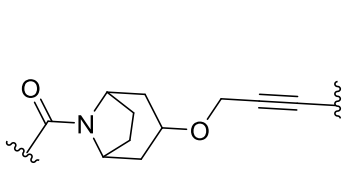
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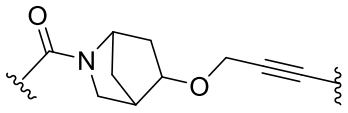
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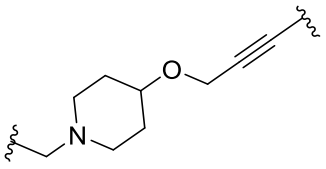
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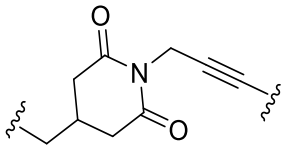
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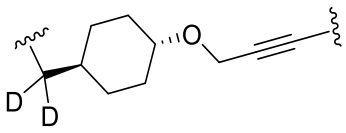
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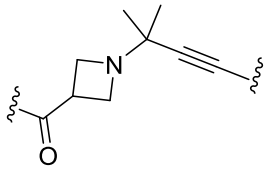
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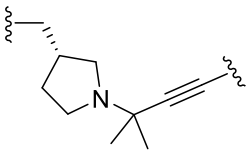
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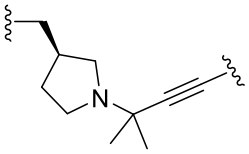
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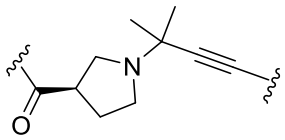
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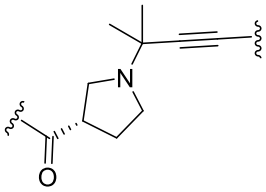
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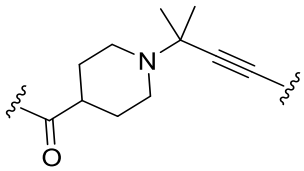
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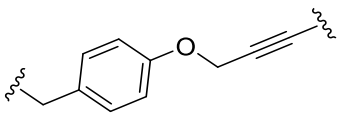
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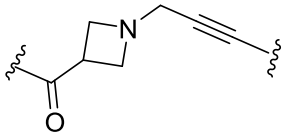
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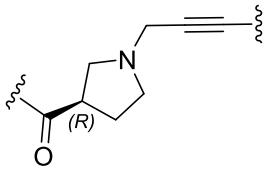
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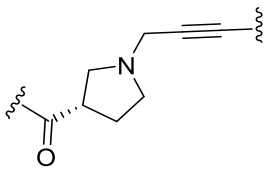
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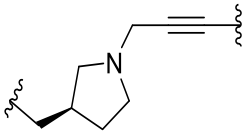
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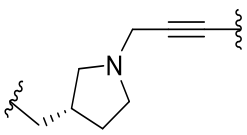
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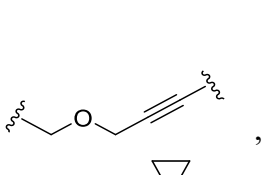
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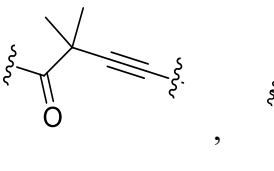
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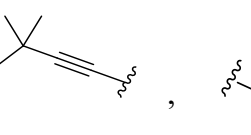
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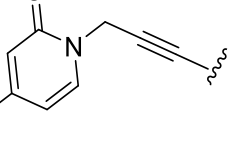
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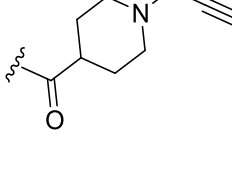
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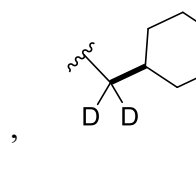
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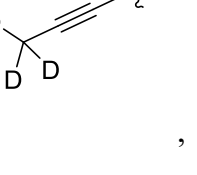
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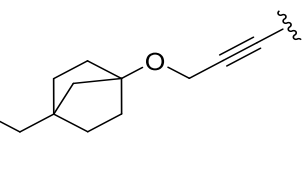
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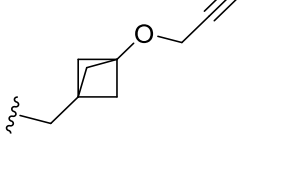
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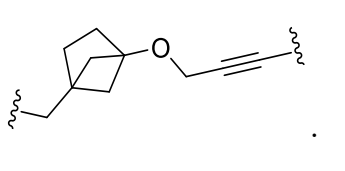
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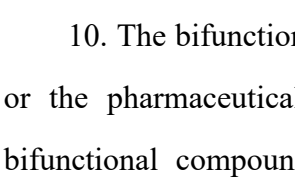
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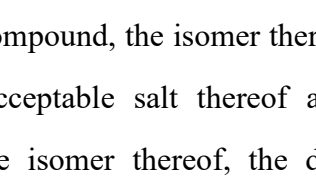
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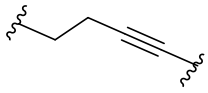
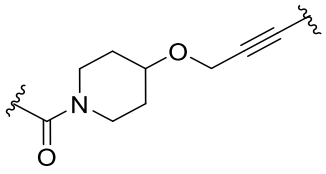
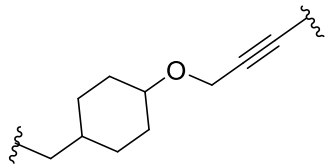
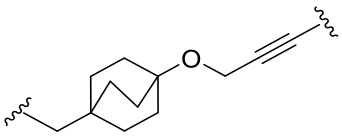
10. The bifunctional compound, the isomer thereof, the deuterated compound thereof, or the pharmaceutically acceptable salt thereof as claimed in claim 9, wherein the bifunctional compound, the isomer thereof, the deuterated compound thereof, or the

pharmaceutically acceptable salt thereof satisfies one or more of the following conditions:

(1) L is selected from the group consisting of , , , and ;

(2) the alkyne terminus of L is connected to the degron.

11. The bifunctional compound, the isomer thereof, the deuterated compound thereof, or the pharmaceutically acceptable salt thereof as claimed in any one of claims 1 to 10, wherein the bifunctional compound, the isomer thereof, the deuterated compound thereof, or the pharmaceutically acceptable salt thereof satisfies one or more of the following conditions:

(1) each 9- to 10-membered fused heteroaryl is pyrazolopyrimidinyl;

(2) each halogen is fluorine, chlorine, bromine, or iodine;

(3) each C_{1-6} alkyl is C_{1-4} alkyl;

(4) each C_{1-6} alkoxy is C_{1-4} alkoxy;

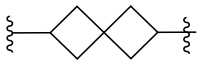
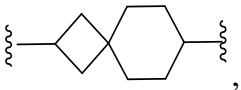
(5) the heteroatom in each 3- to 6-membered heterocyclyl is independently selected from the group consisting of one, two, or three types of N, O, and S, and the number of heteroatoms is independently 1 or 2;

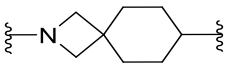
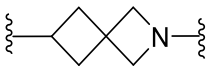
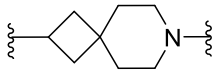
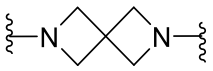
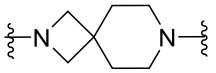
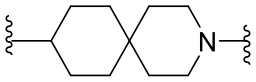
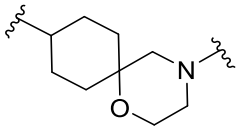
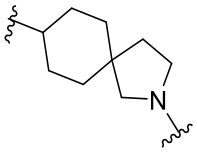
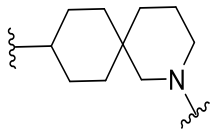
(6) the heteroatom in each 7- to 9-membered bridged heterocyclyl is independently selected from the group consisting of one, two, or three types of N, O, and S, and the number of heteroatoms is independently 1 or 2;

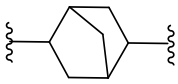
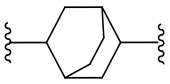
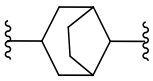
(7) the heteroatom in each 6- to 10-membered fused heterocyclyl is independently selected from the group consisting of one, two, or three types of N, O, and S, and the number of heteroatoms is independently 1 or 2;

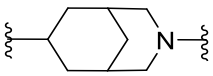
(8) each 3- to 6-membered cycloalkyl is cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl;

(9) each 5- to 6-membered heteroaryl is pyrazolyl;

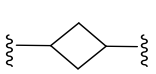
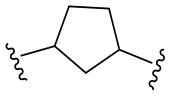
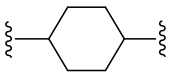
(10) each 7- to 11-membered spirocycloalkylene is , , or ;

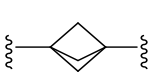
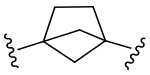
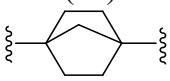
(11) each 7- to 11-membered spiroheterocyclylene is , , , , , , , , or ;

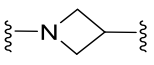
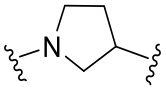
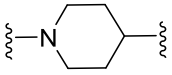
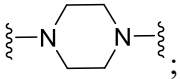
(12) each 7- to 9-membered bridged cycloalkylene is , , or ;

(13) each 7- to 9-membered bridged heterocyclylene is ;

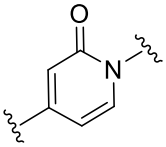
(14) each C_{1-6} alkylene chain is a C_{1-4} alkylene chain;

(15) each C_{3-6} cycloalkylene is , , , or ;

(16) each C_{5-8} bridged cycloalkylene is , , , or ;

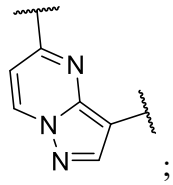
(17) each 4- to 6-membered heterocyclylene is , , , or ;

(18) each 6- to 8-membered bridged heterocyclylene is  or ;

(19) each 6- to 8-membered heterocycloalkenylene is ;

(20) each saturated or unsaturated C_{1-6} hydrocarbylene chain is an unsaturated C_{3-6} alkynylene chain.

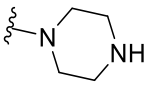
12. The bifunctional compound, the isomer thereof, the deuterated compound thereof, or the pharmaceutically acceptable salt thereof as claimed in claim 11, wherein the bifunctional compound, the isomer thereof, the deuterated compound thereof, or the pharmaceutically acceptable salt thereof satisfies one or more of the following conditions:

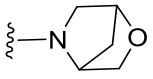
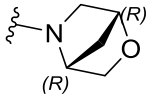
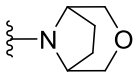
(1) each 9- to 10-membered fused heteroaryl is ;

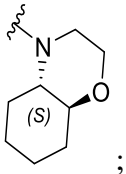
(2) each halogen is fluorine;

(3) each C_{1-6} alkyl is methyl;

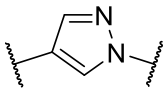
(4) each C_{1-6} alkoxy is methoxy;

(5) each 3- to 6-membered heterocyclyl is independently ;

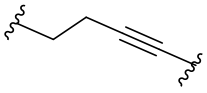
(6) each 7- to 9-membered bridged heterocyclyl is independently , , or ;

(7) each 6- to 10-membered fused heterocyclyl is independently ;

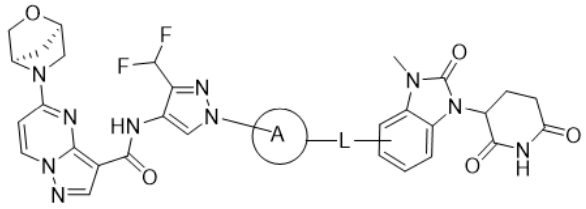
(8) each 3- to 6-membered cycloalkyl is cyclohexyl;

(9) each 5- to 6-membered heteroaryl is ;

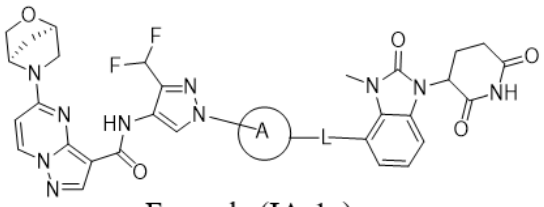
(10) each C_{1-6} alkylene chain is methylene or ethylene;

(11) each saturated or unsaturated C_{1-6} hydrocarbylene chain is .

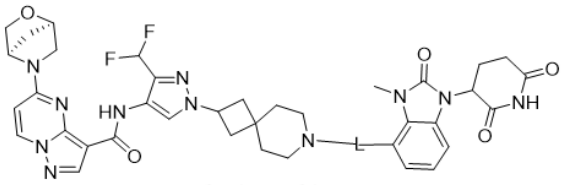
13. The bifunctional compound, the isomer thereof, the deuterated compound thereof, or the pharmaceutically acceptable salt thereof as claimed in any one of claims 1 to 12, wherein the bifunctional compound has a structure represented by the following general formula:



Formula (IA-1)



Formula (IA-1a)

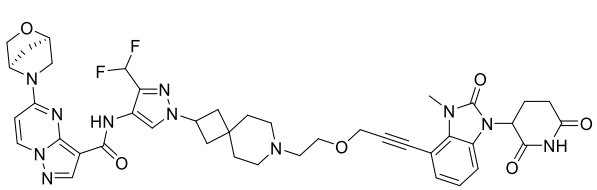


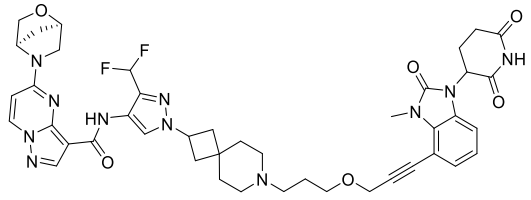
Formula (IA-1b)

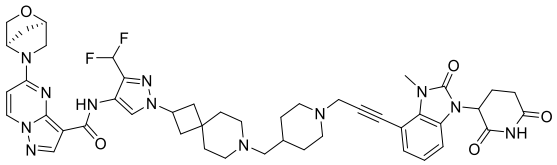
or

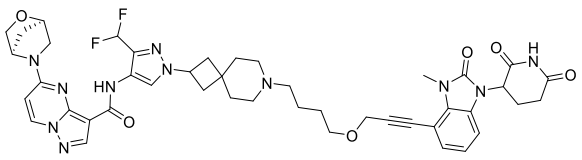
ring A and L are as defined in any one of claims 1 to 12.

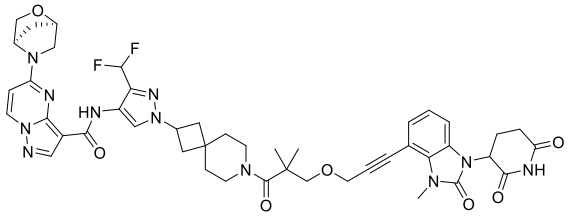
14. A bifunctional compound as shown below, an isomer thereof, a deuterated compound thereof, or a pharmaceutically acceptable salt thereof:

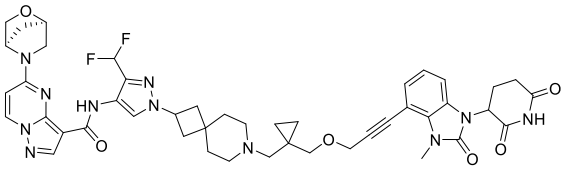


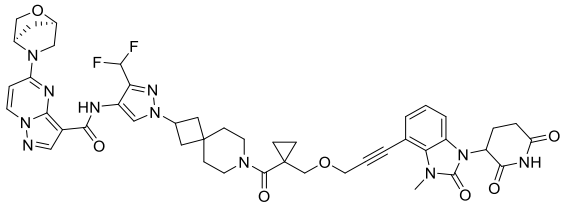
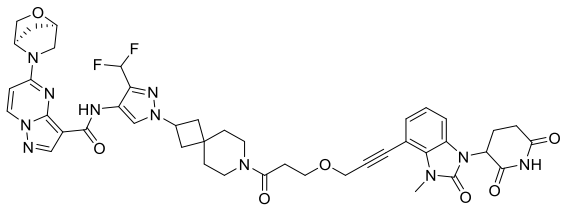
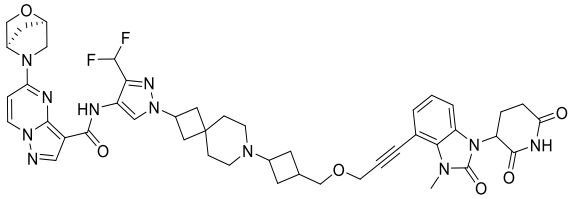


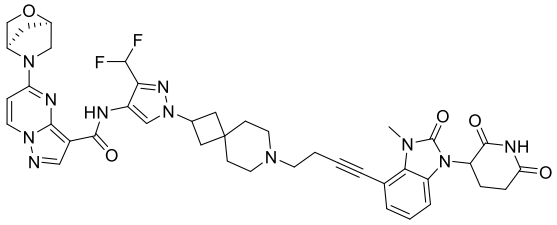
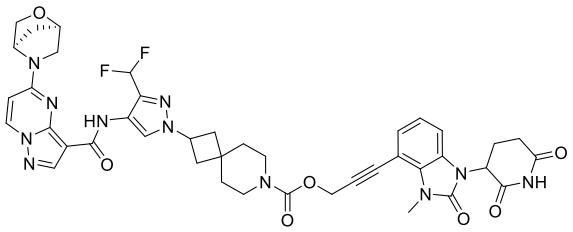
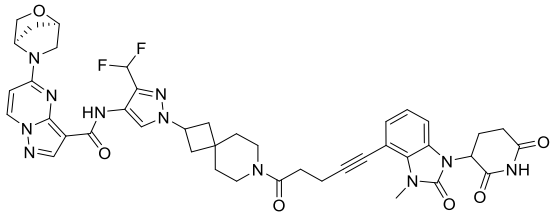


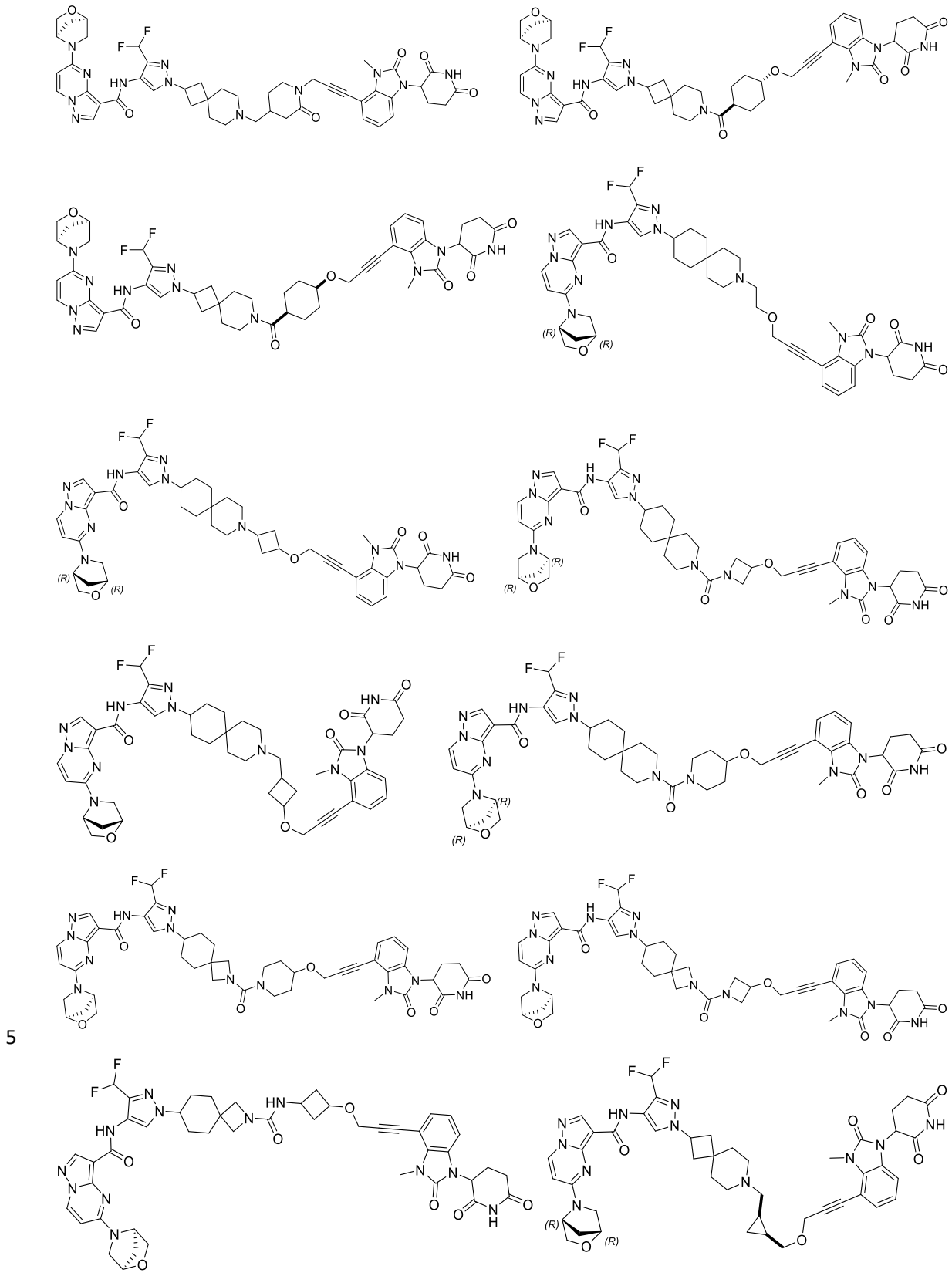


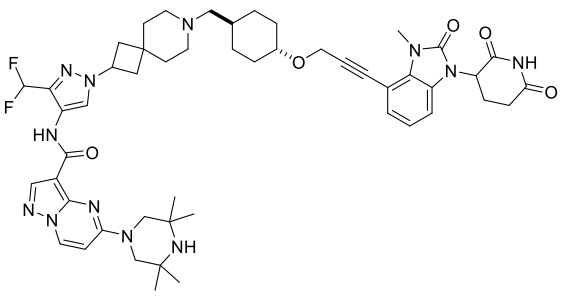


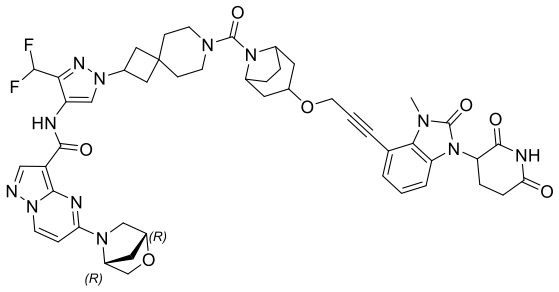


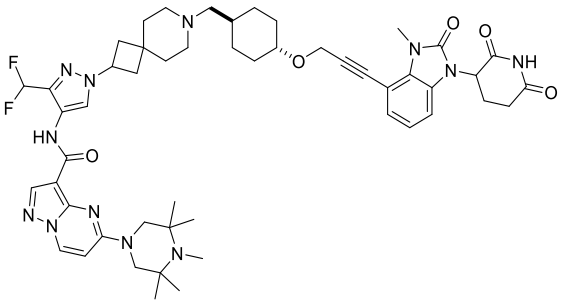




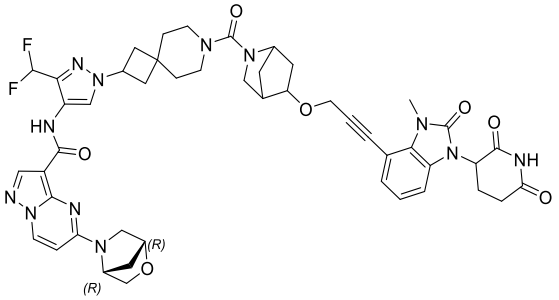




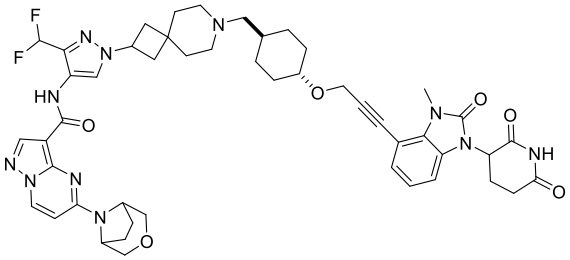


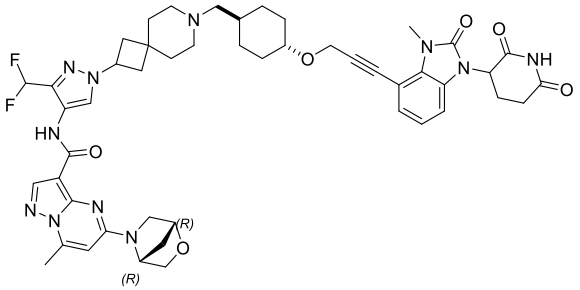


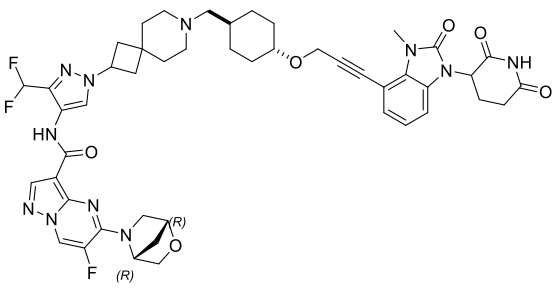


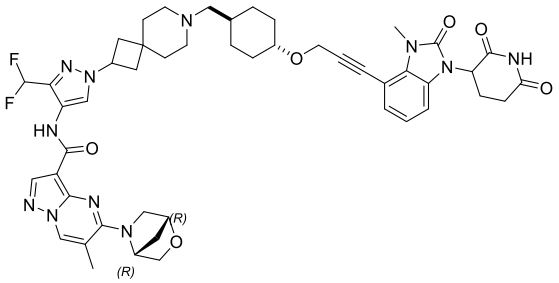


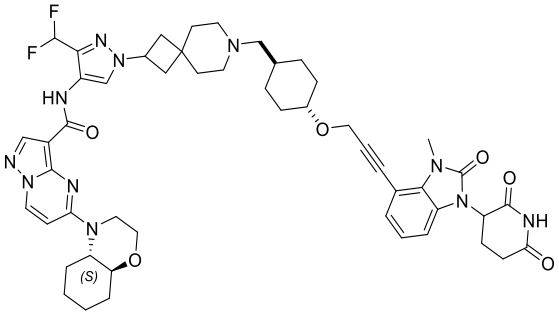


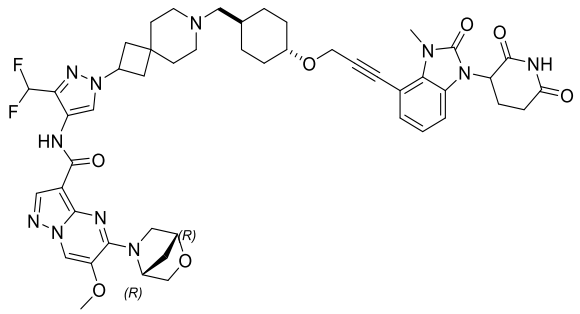












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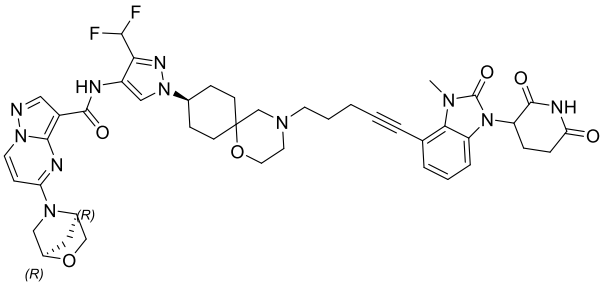

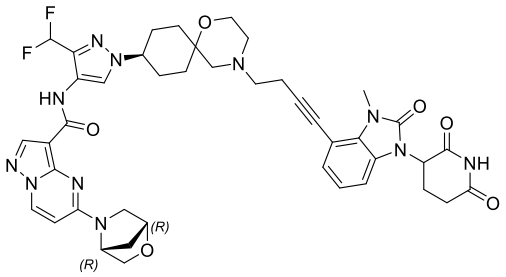

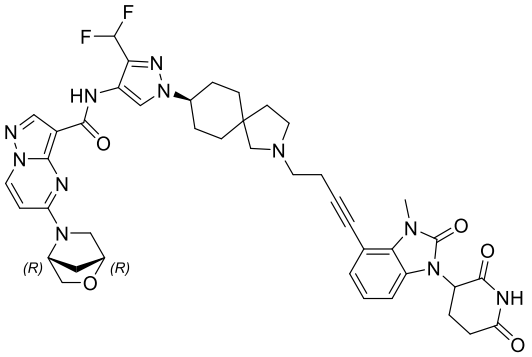

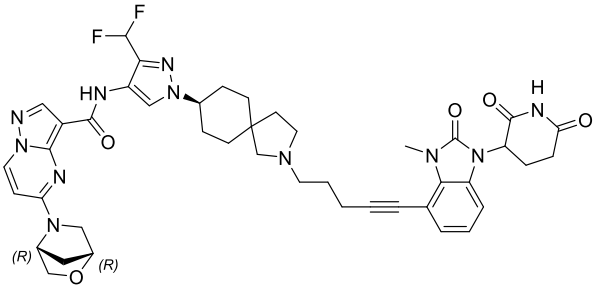

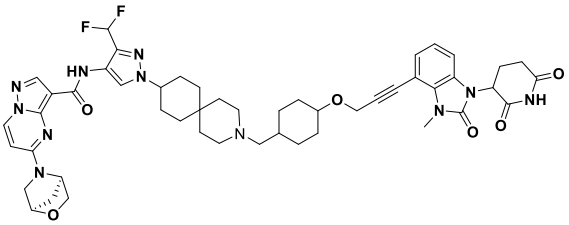

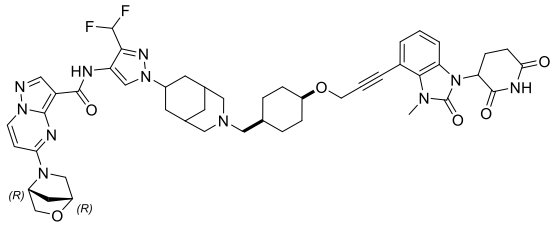

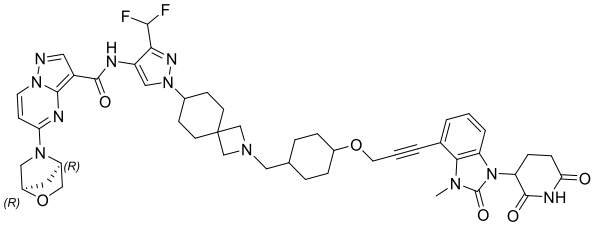

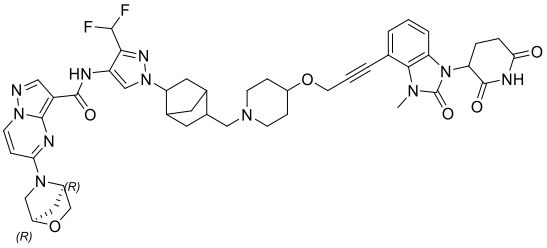

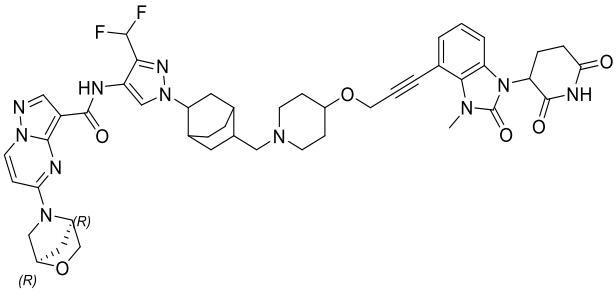

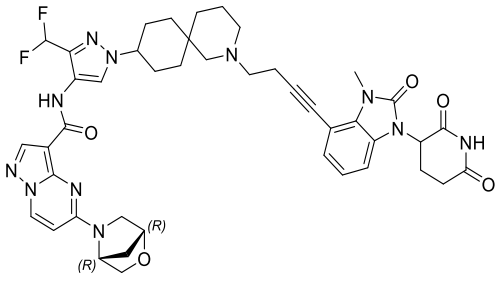

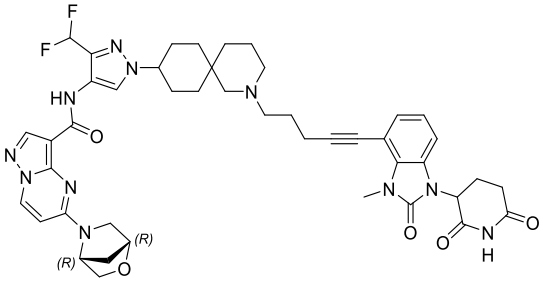

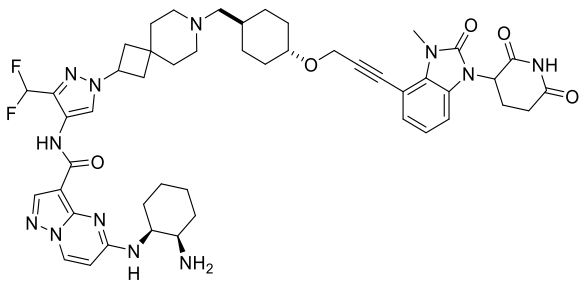

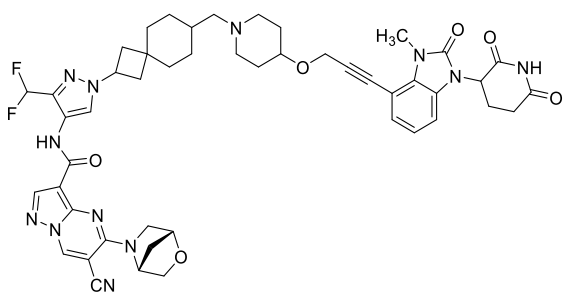

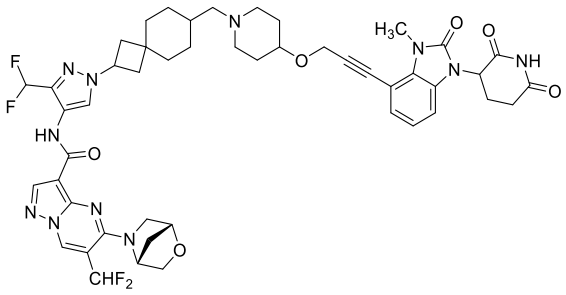

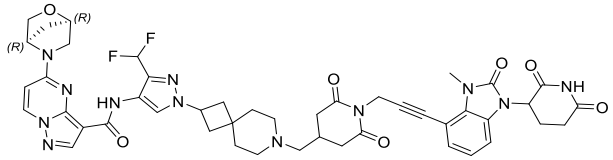

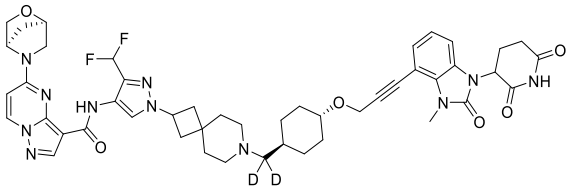

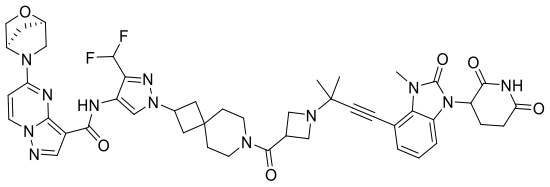

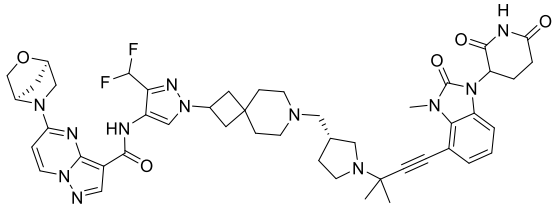

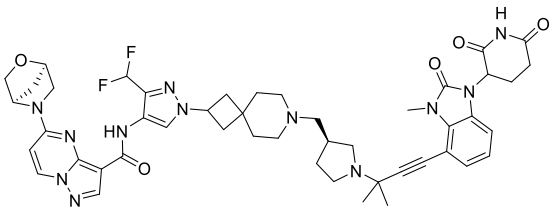

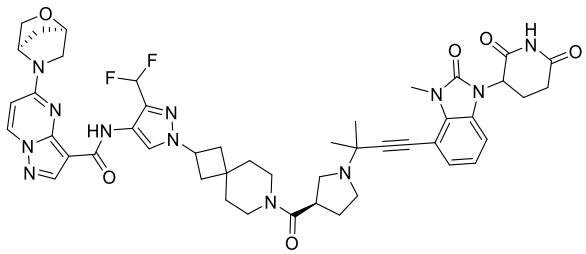

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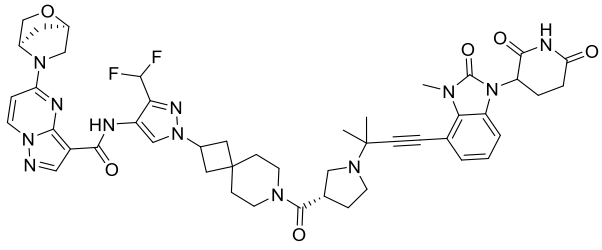
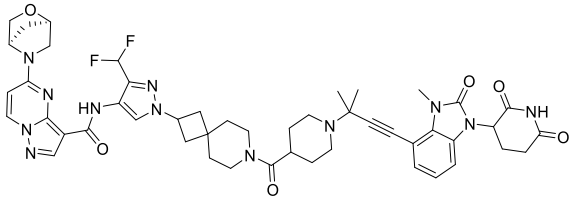
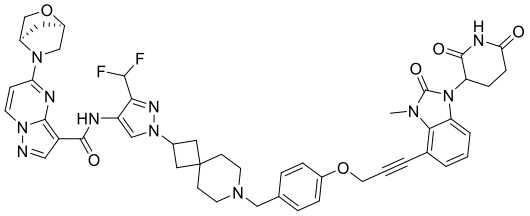
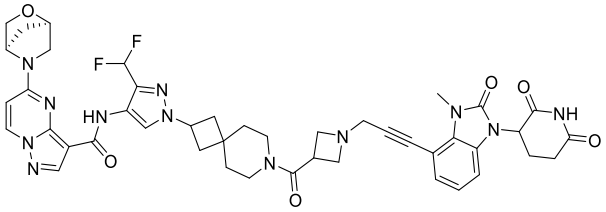
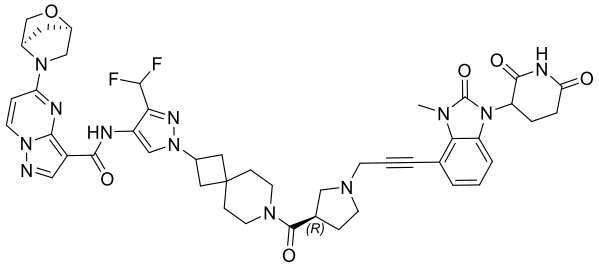
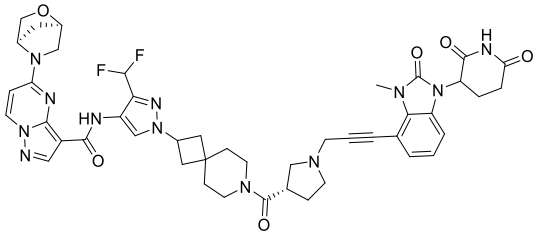


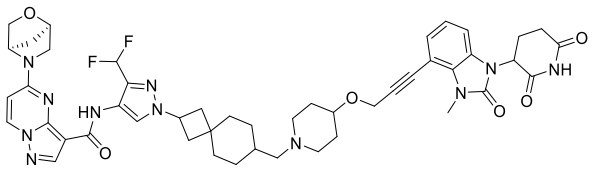


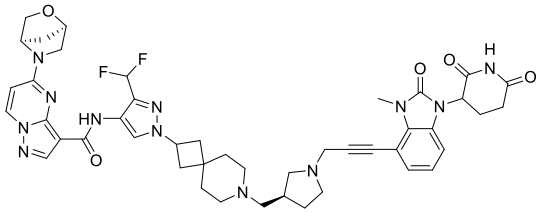


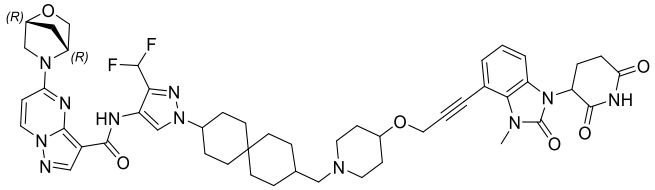


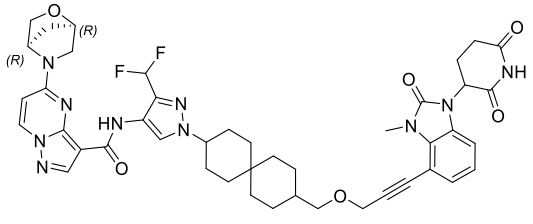


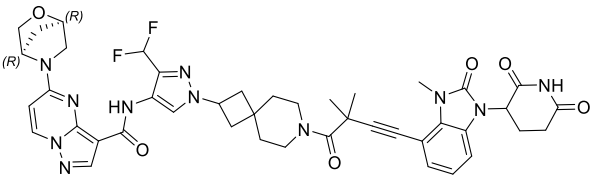


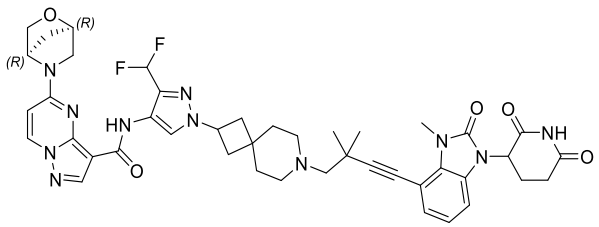


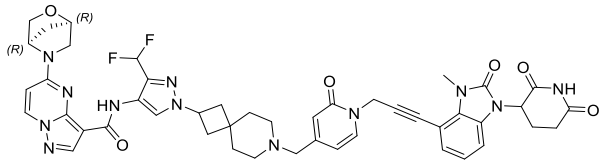


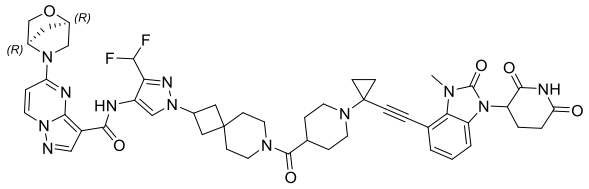


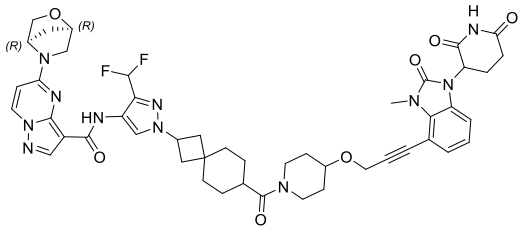


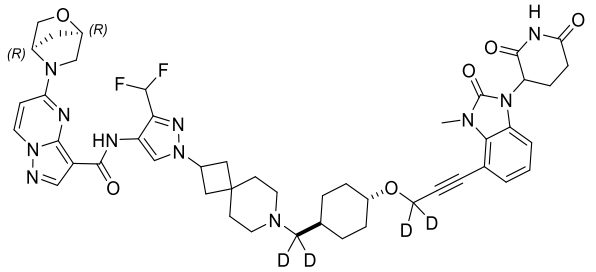


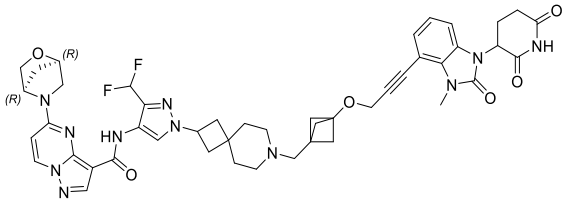


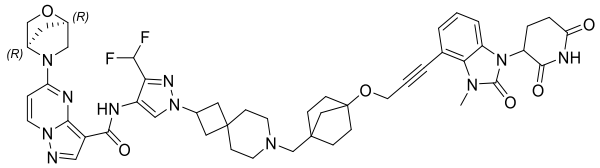


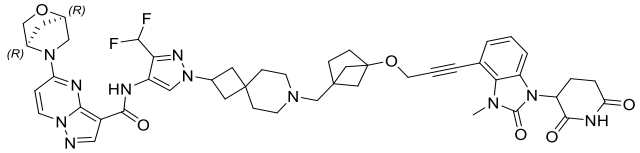


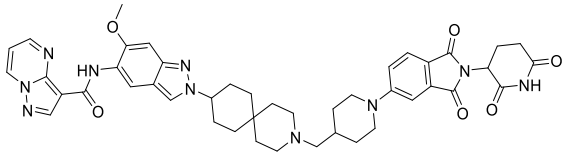


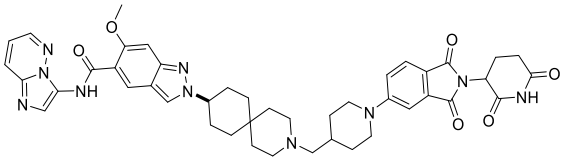


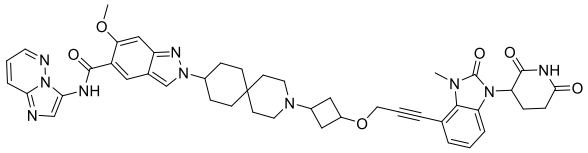


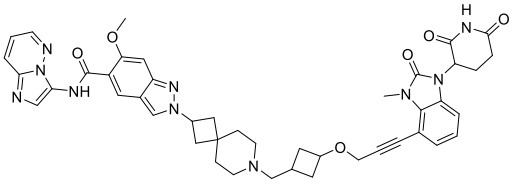


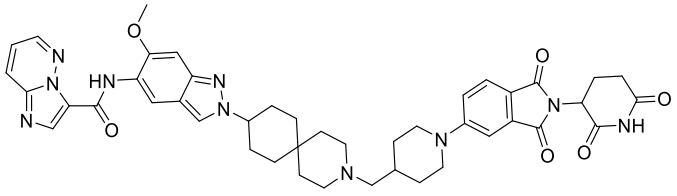












or .

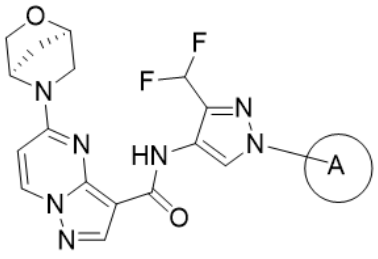
15. A pharmaceutical composition comprising the bifunctional compound, the isomer thereof, the deuterated compound thereof, or the pharmaceutically acceptable salt thereof

as defined in any one of claims 1 to 14, and one or more pharmaceutically acceptable excipients.

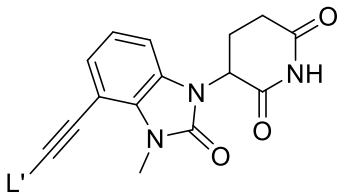
16. Use of the bifunctional compound, the isomer thereof, the deuterated compound thereof, or the pharmaceutically acceptable salt thereof as defined in any one of claims 1 to 14, or the composition as defined in claim 15 in the manufacture of a medicament for preventing and/or treating an IRAK4-mediated related disease.

17. The use of claim 16, wherein, the IRAK4-mediated related disease is selected from the group consisting of immune inflammatory diseases;or, the IRAK4-mediated related disease is selected from the group consisting of hidradenitis suppurativa, rheumatoid arthritis, atopic dermatitis, lupus erythematosus, gouty arthritis, psoriasis, asthma, chronic obstructive pulmonary disease, polypoid sinusitis, and inflammatory bowel disease.

18. A compound represented by formula (Z) or (X), an isomer thereof, a deuterated compound thereof, or a pharmaceutically acceptable salt thereof:



Formula (Z)



(X)

wherein

in formula (X),

L is B^{1-1}-B^{2}-B^{3-1}-;

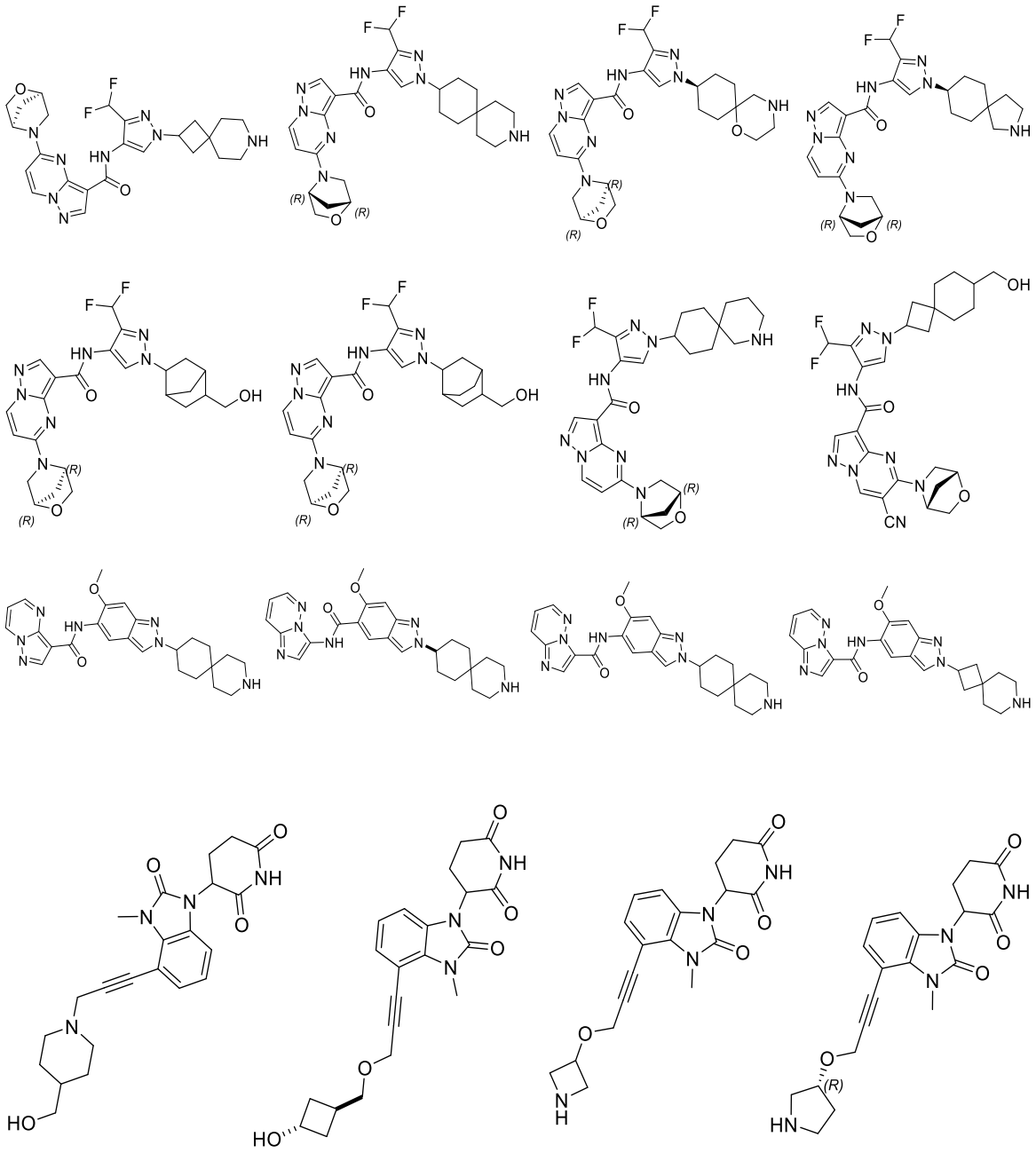
B^{1-1} is hydroxyl, amino, carboxyl, or hydroxy-substituted C_{1-3} alkyl;

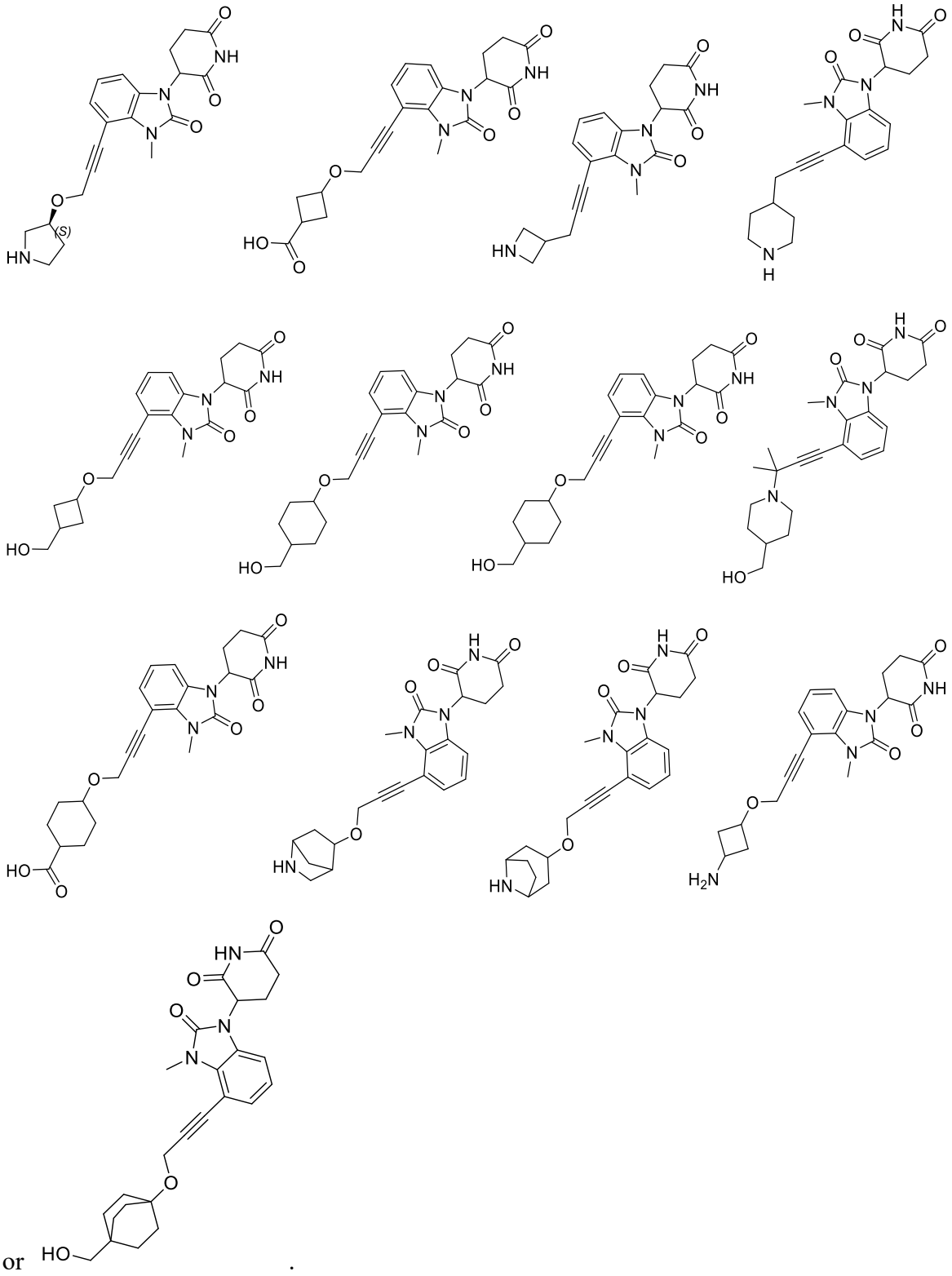
B^{3-1} is a C_{1-3} alkylene chain, any one methylene unit of which is optionally replaced by -O-, -C(O)-, -C(R^a)(R^b)-, -N(R^c)-, or -S-; R^a and R^b are each independently selected from the group consisting of H, deuterium, halogen, C_{1-6} alkyl, and halo-C_{1-6} alkyl, and R^a

and R^b are not simultaneously H;

ring A and B^2 are as defined in any one of claims 1 to 11.

19. A compound as shown below, an isomer thereof, a deuterated compound thereof, or a pharmaceutically acceptable salt thereof:





or .

20. An IRAK4 degrader, comprising the compound, the isomer thereof, the deuterated compound thereof, or the pharmaceutically acceptable salt thereof as defined in claim 18 or 19; preferably, the IRAK4 degrader is the bifunctional compound, the isomer thereof, the

deuterated compound thereof, or the pharmaceutically acceptable salt thereof as defined in claim 1.