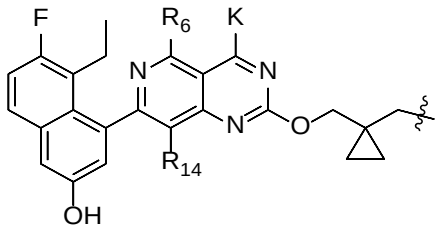
CLAIMS

1. A compound having an F-L-M structure, or a tautomer, racemate, enantiomer, diastereomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof, wherein:

F is a KRAS protein binding fragment represented by general formula (I);



(I)

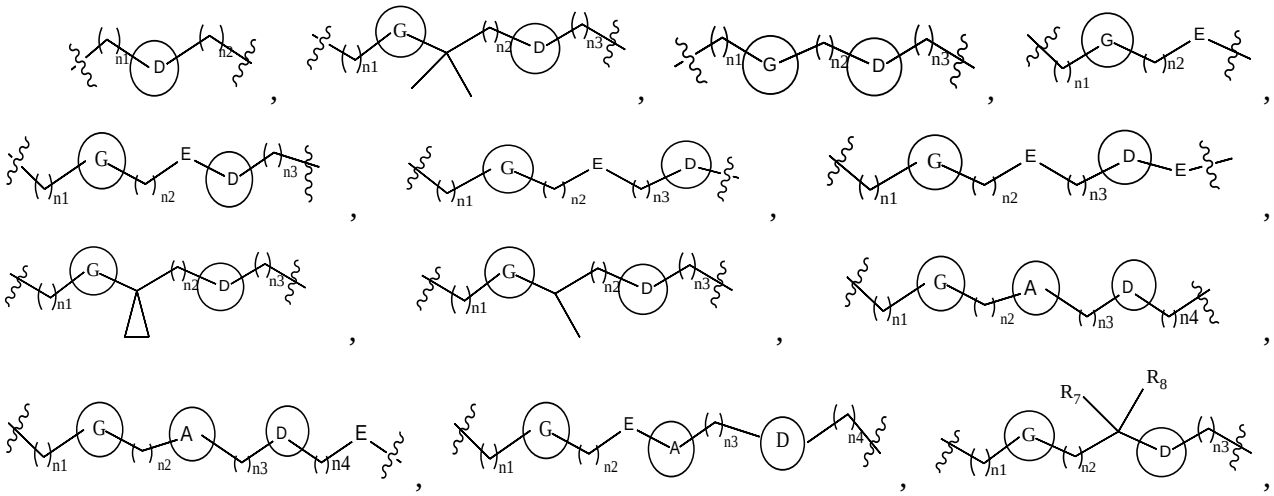
K is N-containing 6- to 12-membered heterocyclyl; K is optionally further substituted by one or more R_a;

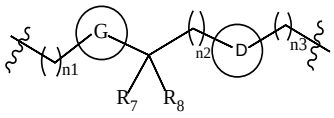
R_{14} is halogen;

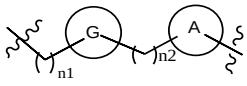
R_6 is selected from the group consisting of H, hydroxy, amino, cyano, halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy and C_{1-6} alkoxy; or R_6 is H; or

R_6 and K, together with the atoms to which they are bound, form 3- to 14-membered heterocyclyl; wherein the 3- to 14-membered heterocyclyl is optionally further substituted by one or more R_a;

L is a linking unit for linking F and M; L is selected from the group consisting of





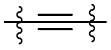
and 

;

wherein,

ring G and ring D are each independently selected from the group consisting of C_{6-14} aryl, 5- to 14-membered heteroaryl, C_{3-14} cycloalkyl and 3- to 14-membered heterocyclyl; wherein the C_{6-14} aryl, 5- to 14-membered heteroaryl, C_{3-14} cycloalkyl or 3- to 14-membered heterocyclyl is optionally further substituted by one or more R_a;

each ring A is independently 3- to 7-membered N-containing heterocyclyl; wherein the 3- to 7-membered N-containing heterocyclyl is optionally further substituted by one or more R_a; or each ring A is independently 3- to 6-membered N-containing heterocyclyl; the 3- to 6-membered N-containing heterocyclyl is optionally further substituted by one or more R_a;

each E is independently absent or selected from the group consisting of -O-, -NH-, , 

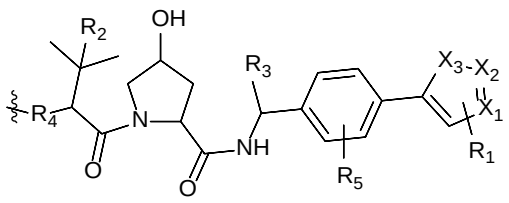
and -NCH_3-;

R_7 and R_8 are each independently selected from the group consisting of H, halogen, hydroxy, amino, oxo, cyano, halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy and C_{1-6} alkoxy; or

R_7 and R_8, together with the atoms to which they are bound, form C_{3-14} cycloalkyl or 3- to 14-membered heterocyclyl; wherein C_{3-14} cycloalkyl or 3- to 14-membered heterocyclyl is optionally further substituted by one or more R_a;

n1, n2, n3, and n4 are each independently selected from the group consisting of integers ranging from 0 to 10, or are each independently 0, 1, 2, 3, or 4;

M is a VHL binding fragment represented by general formula (II);



(II)

wherein, X_1 is selected from the group consisting of C, CH and N;

X_2 is selected from the group consisting of C, CH and N;

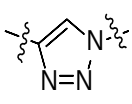
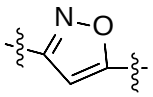
X_3 is selected from the group consisting of N, NH, O and S;

R_1 is selected from the group consisting of H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, halogen and cyano; or R_1 is methyl, ethyl, F or cyano;

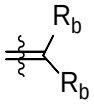
R_2 is selected from the group consisting of H, C_{1-6} alkyl and C_{1-6} haloalkyl; or R_2 is H or methyl;

R_3 is selected from the group consisting of H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, $-(CH_2)_nN(R_9)_2$, $-(CH_2)_n$-CO-OR_9 and $-(CH_2)_n$-CO-$N(R_9)_2$, wherein each R_9 is independently selected from the group consisting of H, C_{1-6} alkyl, C_{1-6} haloalkyl and C_{1-6} alkoxy; and/or the $-(CH_2)_n$-CO-$N(R_9)_2$ is $-(CH_2)_n$-CO-NH-$(CH_2)_n$-CH_3;

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

R_4 is selected from the group consisting of ,  and -NH-;

R_5 is selected from the group consisting of H, C_{1-6} alkyl and C_{1-6} haloalkyl;

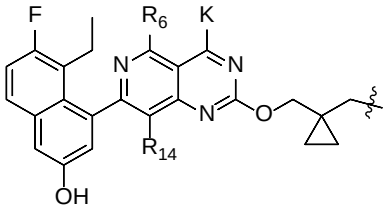
R_a is independently selected from the group consisting of H, hydroxy, amino, oxo, cyano, halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, $-C_{0-3}$ alkylene-OR_b, $-OC(=O)C_{1-6}$ alkyl, $-C_{0-3}$ alkylene-SR_b, $-C_{0-3}$ alkylene-$N(R_b)_2$, $-C_{0-3}$ alkylene-$S(=O)R_b$, $-C_{0-3}$ alkylene-$S(=O)_2R_b$, $-C_{0-3}$ alkylene-SR_b, $-C_{0-3}$ alkylene-$S(R_b)_5$, $-C_{0-3}$ alkylene-$C(=O)R_b$, $-C_{0-3}$ alkylene-$C(=O)OR_b$, $-C_{0-3}$ alkylene-$C(=O)N(R_b)_2$, C_{2-6} alkenyl, , C_{2-6} alkynyl, $-C_{0-3}$ alkylene-C_{3-14} cycloalkyl, $-C_{0-3}$ alkylene-(3- to 14-membered heterocyclyl), $-C_{0-3}$ alkylene-C_{6-18} aryl and $-C_{0-3}$ alkylene-(5- to 18-membered heteroaryl); wherein the hydroxy, amino, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{0-3} alkylene, C_{2-6} alkenyl, C_{2-6} alkynyl, $-C_{0-3}$ alkylene-C_{3-14} cycloalkyl, $-C_{0-3}$ alkylene-(3- to 14-membered heterocyclyl), $-C_{0-3}$ alkylene-C_{6-18} aryl or $-C_{0-3}$ alkylene-(5- to 18-membered heteroaryl) is optionally further substituted by one or more R_b;

each R_b is independently H, halogen, hydroxy, amino, cyano, C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{1-6} haloalkyl, C_{3-14} cycloalkyl, 3- to 14-membered heterocyclyl, C_{6-18} aryl or 5- to 18-membered heteroaryl; wherein hydroxy, amino, C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{1-6} haloalkyl, C_{3-14} cycloalkyl, 3- to 14-membered heterocyclyl, C_{6-18} aryl or 5- to 18-membered heteroaryl is optionally further substituted by one or more halogen, C_{1-6} alkyl or C_{1-6} haloalkyl; or two R_b bound to one atom, together with the atom to which they are bound, form C_{3-14} cycloalkyl, 3- to 14-membered

heterocyclyl, C_{6-18} aryl or 5- to 18-membered heteroaryl, and the C_{3-14} cycloalkyl, 3- to 14-membered heterocyclyl, C_{6-18} aryl or 5- to 18-membered heteroaryl is optionally further substituted by one or more halogen, amino, hydroxy, cyano, C_{1-6} alkyl, C_{3-6} cycloalkyl or C_{1-6} haloalkyl.

2. The compound according to claim 1, or the tautomer, racemate, enantiomer, diastereomer thereof, or the mixture thereof, or the pharmaceutically acceptable salt thereof, wherein:

F is a KRAS protein binding fragment represented by general formula (I);



(I)

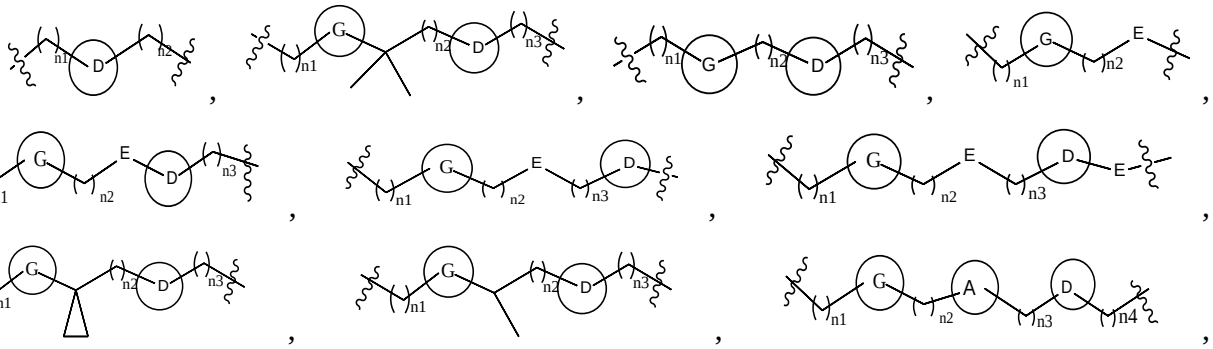
K is N-containing 6- to 12-membered heterocyclyl; K is optionally further substituted by one or more R_a;

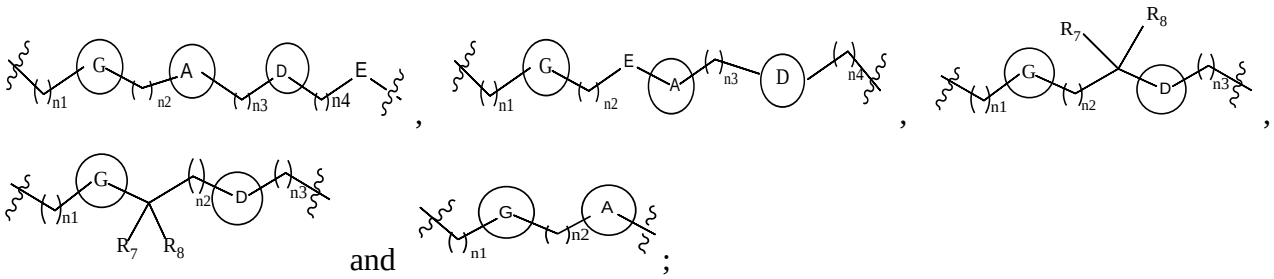
R_{14} is halogen;

R_6 is selected from the group consisting of H, hydroxy, amino, cyano, halogen, C_{1-6} alkyl, C_{1-6} haloalkyl and C_{1-6} alkoxy; or R_6 is H; or

R_6 and K, together with the atoms to which they are bound, form 3- to 14-membered heterocyclyl; wherein 3- to 14-membered heterocyclyl is optionally further substituted by one or more R_a;

L is a linking unit for linking F and M; L is selected from the group consisting of





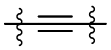
and

;

wherein,

ring G and ring D are each independently selected from the group consisting of C_{6-14} aryl, 5- to 14-membered heteroaryl, C_{3-14} cycloalkyl and 3- to 14-membered heterocyclyl; wherein the C_{6-14} aryl, 5- to 14-membered heteroaryl, C_{3-14} cycloalkyl or 3- to 14-membered heterocyclyl is optionally further substituted by one or more R_a;

each ring A is independently 3- to 7-membered N-containing heterocyclyl; wherein the 3- to 7-membered N-containing heterocyclyl is optionally further substituted by one or more R_a;or each ring A is independently 3- to 6-membered N-containing heterocyclyl; wherein the 3- to 6-membered N-containing heterocyclyl is optionally further substituted by one or more R_a;

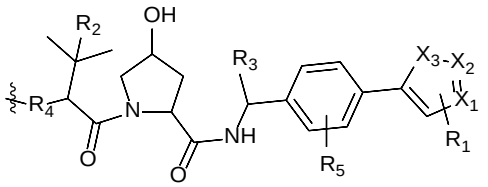
each E is independently absent or selected from the group consisting of -O-, -NH-, ,  and $-NCH_3-$;

R_7 and R_8 are each independently selected from the group consisting of H, halogen, hydroxy, amino, oxo, cyano, halogen, C_{1-6} alkyl, C_{1-6} haloalkyl and C_{1-6} alkoxy; or

R_7 and R_8, together with the atoms to which they are bound, form C_{3-14} cycloalkyl or 3- to 14-membered heterocyclyl; wherein the C_{3-14} cycloalkyl or 3- to 14-membered heterocyclyl is optionally further substituted by one or more R_a;

n1, n2, n3 and n4 are each independently selected from the group consisting of integers ranging from 0 to 10, or are each independently 0, 1, 2, 3 or 4;

M is a VHL binding fragment represented by general formula (II);



(II)

wherein, X_1 is selected from the group consisting of C, CH and N;

X_2 is selected from the group consisting of C, CH and N;

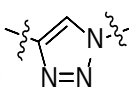
X_3 is selected from the group consisting of N, NH, O and S;

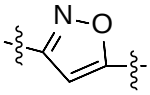
R_1 is selected from the group consisting of H, C_{1-6} alkyl, halogen and cyano, or R_1 is methyl, ethyl, F or cyano;

R_2 is selected from the group consisting of H and C_{1-6} alkyl, or R_2 is H or methyl;

R_3 is selected from the group consisting of H, C_{1-6} alkyl, C_{1-6} hydroxyalkyl, $-(CH_2)_nN(R_9)_2$, $-(CH_2)_n$-CO-OR_9 and $-(CH_2)_n$-CO-$N(R_9)_2$, wherein each R_9 is independently selected from the group consisting of H, C_{1-6} alkyl, C_{1-6} haloalkyl and C_{1-6} alkoxy; and/or the $-(CH_2)_n$-CO-$N(R_9)_2$ is $-(CH_2)_n$-CO-NH-$(CH_2)_n$-CH_3;

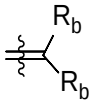
n is selected from the group consisting of 0, 1, 2 and 3;

R_4 is selected from the group consisting of 

, 

and -NH-;

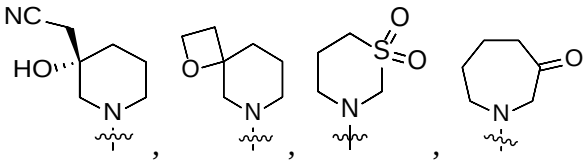
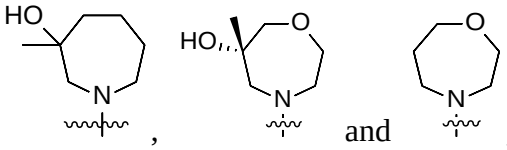
R_5 is selected from the group consisting of H, C_{1-6} alkyl and C_{1-6} haloalkyl;

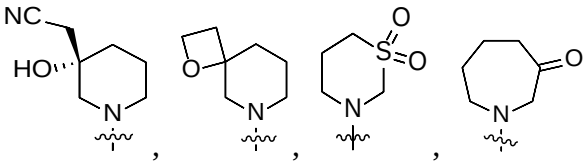
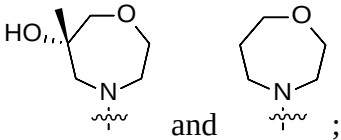
R_a is independently selected from the group consisting of H, hydroxy, amino, oxo, cyano, halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, $-C_{0-3}$ alkylene-OR_b, -OC(=O)C_{1-6} alkyl, $-C_{0-3}$ alkylene-SR_b, $-C_{0-3}$ alkylene-$N(R_b)_2$, $-C_{0-3}$ alkylene-$S(=O)R_b$, $-C_{0-3}$ alkylene-$S(=O)_2R_b$, $-C_{0-3}$ alkylene-SR_b, $-C_{0-3}$ alkylene-$S(R_b)_5$, $-C_{0-3}$ alkylene-$C(=O)R_b$, $-C_{0-3}$ alkylene-$C(=O)OR_b$, $-C_{0-3}$ alkylene-$C(=O)N(R_b)_2$, C_{2-6} alkenyl, 

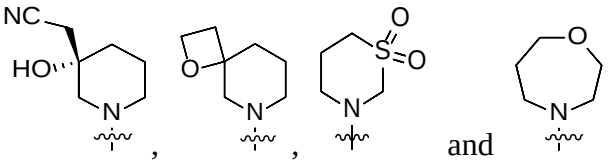
, C_{2-6} alkynyl, $-C_{0-3}$ alkylene-C_{3-14} cycloalkyl, $-C_{0-3}$ alkylene-(3- to 14-membered heterocyclyl), $-C_{0-3}$ alkylene-C_{6-18} aryl and $-C_{0-3}$ alkylene-(5- to 18-membered heteroaryl); wherein C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{2-6} alkenyl, C_{2-6} alkynyl, $-C_{0-3}$ alkylene-C_{3-14} cycloalkyl, $-C_{0-3}$ alkylene-(3- to 14-membered heterocyclyl), $-C_{0-3}$ alkylene-C_{6-18} aryl or $-C_{0-3}$ alkylene-(5- to 18-membered heteroaryl) is optionally further substituted by one or more R_b;

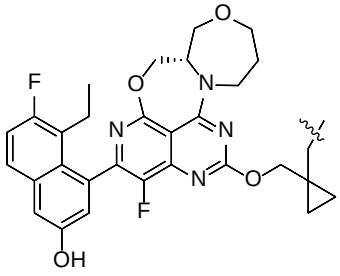
each R_b is independently H, halogen, hydroxy, cyano, C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{1-6} haloalkyl, C_{3-14} cycloalkyl, 3- to 14-membered heterocyclyl, C_{6-18} aryl or 5- to 18-membered heteroaryl; wherein the C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{1-6} haloalkyl, C_{3-14} cycloalkyl, 3- to 14-membered heterocyclyl, C_{6-18} aryl or 5- to 18-membered heteroaryl is optionally further

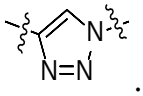
substituted by one or more halogen, C_{1-6} alkyl or C_{1-6} haloalkyl; or two R_b bound to one atom, together with the atom to which they are bound, form C_{3-14} cycloalkyl, 3- to 14-membered heterocyclyl, C_{6-18} aryl or 5- to 18-membered heteroaryl, wherein C_{3-14} cycloalkyl, 3- to 14-membered heterocyclyl, C_{6-18} aryl or 5- to 18-membered heteroaryl is optionally further substituted by one or more halogen, amino, hydroxy, cyano, C_{1-6} alkyl, C_{3-6} cycloalkyl or C_{1-6} haloalkyl.

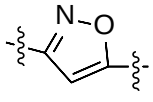
3. The compound according to claim 1 or 2, or the tautomer, racemate, enantiomer, diastereomer thereof, or the mixture thereof, or the pharmaceutically acceptable salt thereof, wherein K is selected from the group consisting of , ; or

K is selected from the group consisting of , ; or

K is selected from the group consisting of .

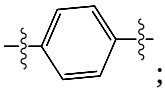
4. The compound according to any one of claims 1 to 3, or the tautomer, racemate, enantiomer, diastereomer thereof, or the mixture thereof, or the pharmaceutically acceptable salt thereof, wherein F is .

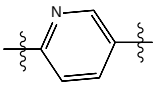
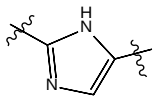
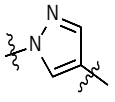
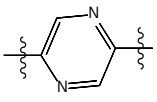
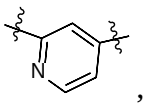
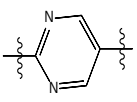
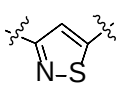
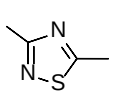
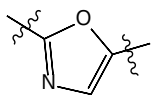
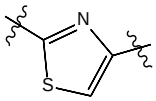
5. The compound according to any one of claims 1 to 4, or the tautomer, racemate, enantiomer, diastereomer thereof, or the mixture thereof, or the pharmaceutically acceptable salt thereof, wherein R_4 is .

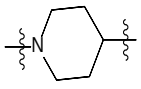
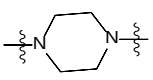
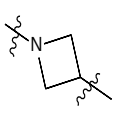
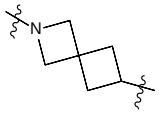
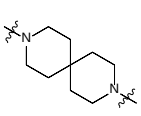
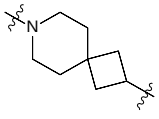
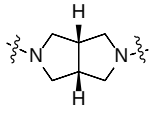
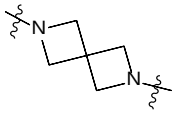
6. The compound according to any one of claims 1 to 4, or the tautomer, racemate, enantiomer, diastereomer thereof, or the mixture thereof, or the pharmaceutically acceptable salt thereof, wherein R_4 is .

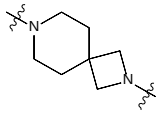
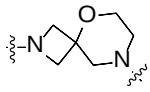
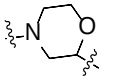
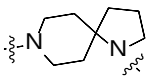
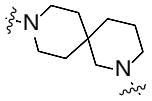
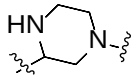
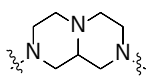
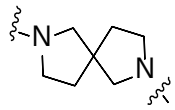
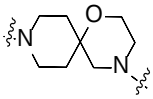
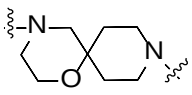
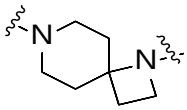
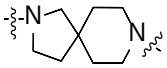
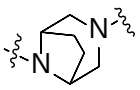
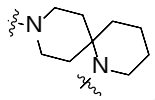
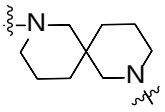
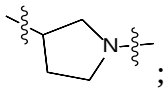
7. The compound according to any one of claims 1 to 4, or the tautomer, racemate, enantiomer, diastereomer thereof, or the mixture thereof, or the pharmaceutically acceptable salt thereof, wherein R_4 is -NH-.

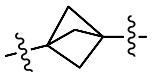
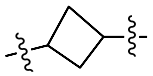
8. The compound according to any one of claims 1 to 7, or the tautomer, racemate, enantiomer, diastereomer thereof, or the mixture thereof, or the pharmaceutically acceptable salt thereof, wherein ring G or ring D in L is each independently selected from the group consisting of C_{6-14} aryl, 5- to 14-membered heteroaryl, C_{3-14} cycloalkyl and 3- to 14-membered heterocyclyl; wherein the C_{6-14} aryl, 5- to 14-membered heteroaryl, C_{3-14} cycloalkyl or 3- to 14-membered heterocyclyl is optionally further substituted by one or more halogen or C_{1-3} alkyl; and/or

C_{6-14} aryl is ; and/or

5- to 14-membered heteroaryl is selected from the group consisting of , , , , , , , , , and ; and/or

3- to 14-membered heterocyclyl is selected from the group consisting of , , , , , , , ,

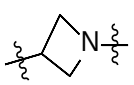
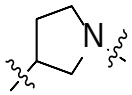
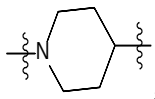
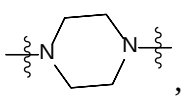
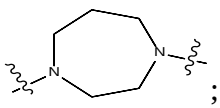
, , , , , , , , , , , , , ,  and ; and/or

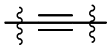
C_{3-14} cycloalkyl is selected from the group consisting of  and .

9. The compound according to any one of claims 1 to 8, or the tautomer, racemate, enantiomer, diastereomer thereof, or mixture thereof, or the pharmaceutically acceptable salt thereof, wherein

each ring D is independently 5- to 6-membered nitrogen-containing heteroaryl, and the 5- to 6-membered nitrogen-containing heteroaryl is optionally further substituted by one or more R_a;

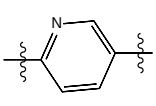
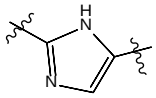
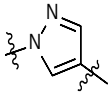
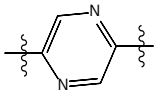
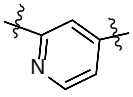
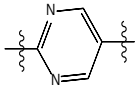
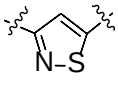
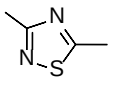
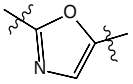
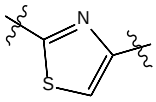
each ring G is independently selected from the group consisting of C_{6-14} aryl, 5- to 14-membered heteroaryl, C_{3-14} cycloalkyl and 3- to 14-membered heterocyclyl; wherein the C_{6-14} aryl, 5- to 14-membered heteroaryl, C_{3-14} cycloalkyl or 3- to 14-membered heterocyclyl is optionally further substituted by one or more R_a;

each ring A is independently 3- to 7-membered N-containing heterocyclyl, and the 3- to 7-membered N-containing heterocyclyl is optionally further substituted by one or more R_a; or each ring A is independently 3- to 7-membered N-containing heterocyclyl, and the 3- to 7-membered N-containing heterocyclyl is optionally further substituted by one or more halogen or C_{1-3} alkyl; or each ring A is independently 3- to 6-membered N-containing heterocyclyl, and the 3- to 6-membered N-containing heterocyclyl is optionally further substituted by one or more halogen or C_{1-3} alkyl; or the 3- to 7-membered N-containing heterocyclyl is , , , , or ;

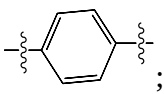
each E is independently absent or selected from the group consisting of -O-, -NH-,  and $-NCH_3-$; or E is selected from the group consisting of -O-, -NH-, and $-NCH_3-$;

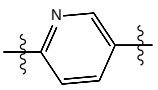
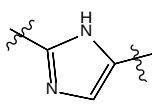
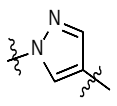
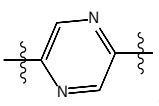
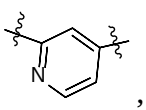
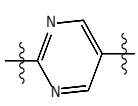
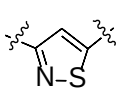
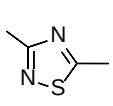
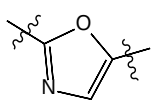
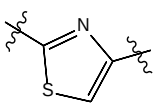
R_7 and R_8 are each independently selected from the group consisting of H, halogen, hydroxy, amino, oxo, cyano, halogen, C_{1-6} alkyl, C_{1-6} haloalkyl and C_{1-6} alkoxy; or R_7 and R_8, together with the atoms to which they are bound, form C_{3-14} cycloalkyl or 3- to 14-membered heterocyclyl, wherein the C_{3-14} cycloalkyl or 3- to 14-membered heterocyclyl is optionally further substituted by one or more R_a; and

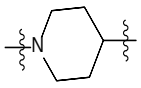
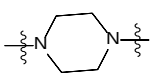
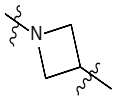
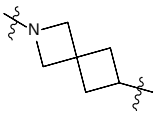
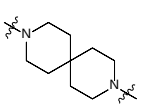
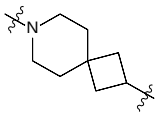
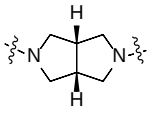
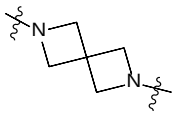
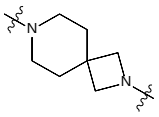
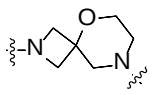
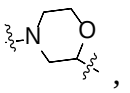
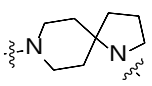
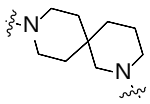
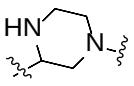
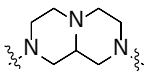
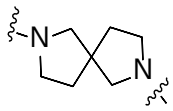
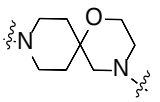
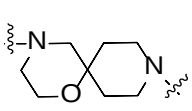
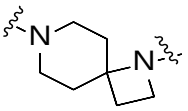
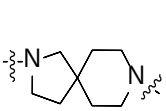
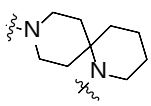
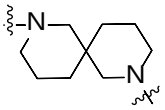
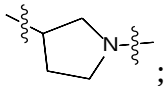
n1, n2, n3 and n4 are each independently selected from the group consisting of integers ranging from 0 to 10, or are each independently 0, 1, 2, 3 or 4.

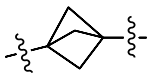
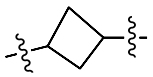
10. The compound according to any one of claims 1 to 9, or the tautomer, racemate, enantiomer, diastereomer thereof, or the mixture thereof, or the pharmaceutically acceptable salt thereof, wherein ring D is independently 5- to 6-membered nitrogen-containing heteroaryl, and the 5- to 6-membered nitrogen-containing heteroaryl is selected from the group consisting of , , , , , , , ,  and ; wherein, the 5- to 6-membered nitrogen-containing heteroaryl is optionally further substituted by one or more R_a; and R_a is selected from the group consisting of H, hydroxy, amino, oxo, cyano, halogen, C_{1-6} alkyl, C_{1-6} haloalkyl and C_{1-6} alkoxy.

11. The compound according to any one of claims 1 to 10, or the tautomer, racemate, enantiomer, diastereomer thereof, or the mixture thereof, or the pharmaceutically acceptable salt thereof, wherein ring G is independently selected from the group consisting of C_{6-14} aryl, 5- to 14-membered heteroaryl, C_{3-14} cycloalkyl and 3- to 14-membered heterocyclyl; wherein the C_{6-14} aryl, 5- to 14-membered heteroaryl, C_{3-14} cycloalkyl or 3- to 14-membered heterocyclyl is optionally further substituted by one or more R_a; and/or

C_{6-14} aryl is ; and/or

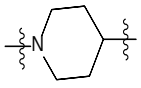
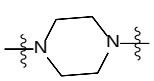
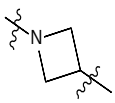
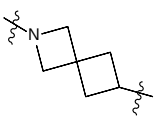
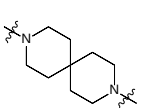
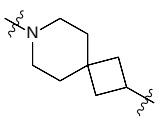
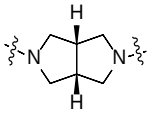
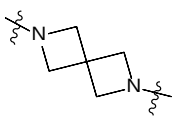
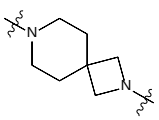
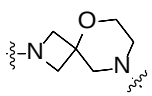
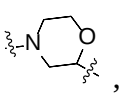
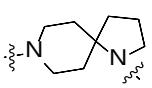
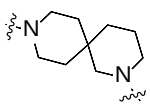
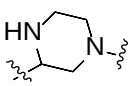
5- to 14-membered heteroaryl is selected from the group consisting of , , , , , , , ,  and ; and/or

3- to 14-membered heterocyclyl is selected from the group consisting of , , , , , , , , , , , , , , , , , , , , , , , and ; and/or

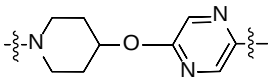
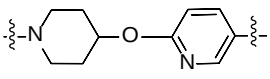
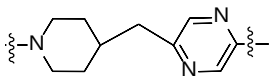
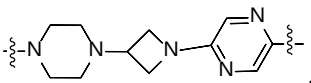
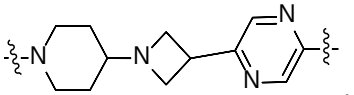
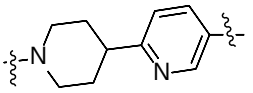
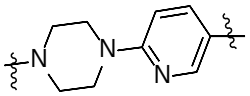
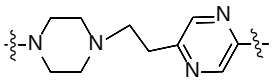
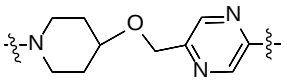
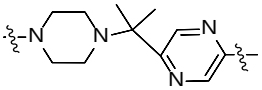
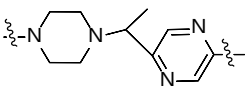
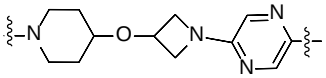
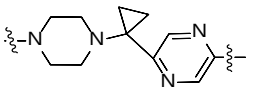
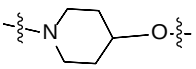
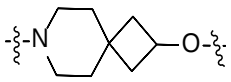
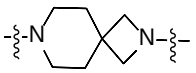
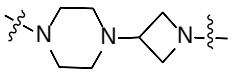
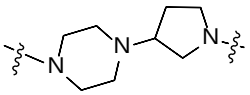
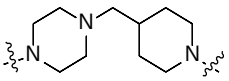
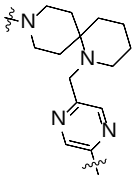
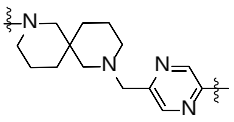
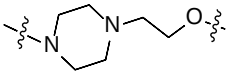
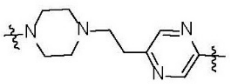
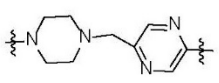
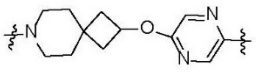
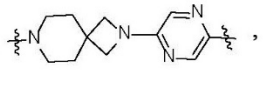
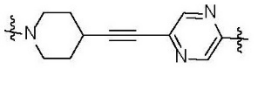
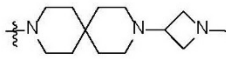
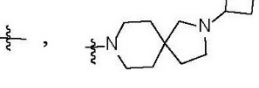
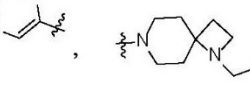
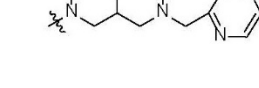
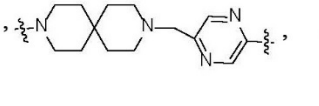
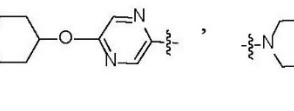
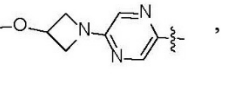
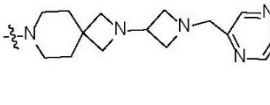
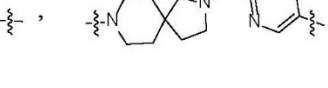
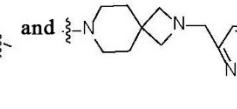
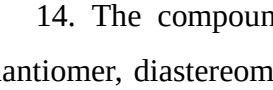
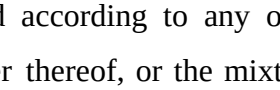
C_{3-14} cycloalkyl is selected from the group consisting of  and ;

R_a is selected from the group consisting of H, hydroxy, amino, oxo, cyano, halogen, C_{1-6} alkyl, C_{1-6} haloalkyl and C_{1-6} alkoxy;

12. The compound according to any one of claims 1 to 11, or the tautomer, racemate, enantiomer, diastereomer thereof, or the mixture thereof, or the pharmaceutically acceptable salt thereof, wherein ring G is independently 3- to 14-membered heterocyclyl, wherein 3- to 14-membered heterocyclyl is optionally further substituted by one or more R_a; and/or

3- to 14-membered heterocyclyl is selected from the group consisting of , , , , , , , , , , , , , , , , , , , , , , , and ; R_a is selected from the group consisting of H,

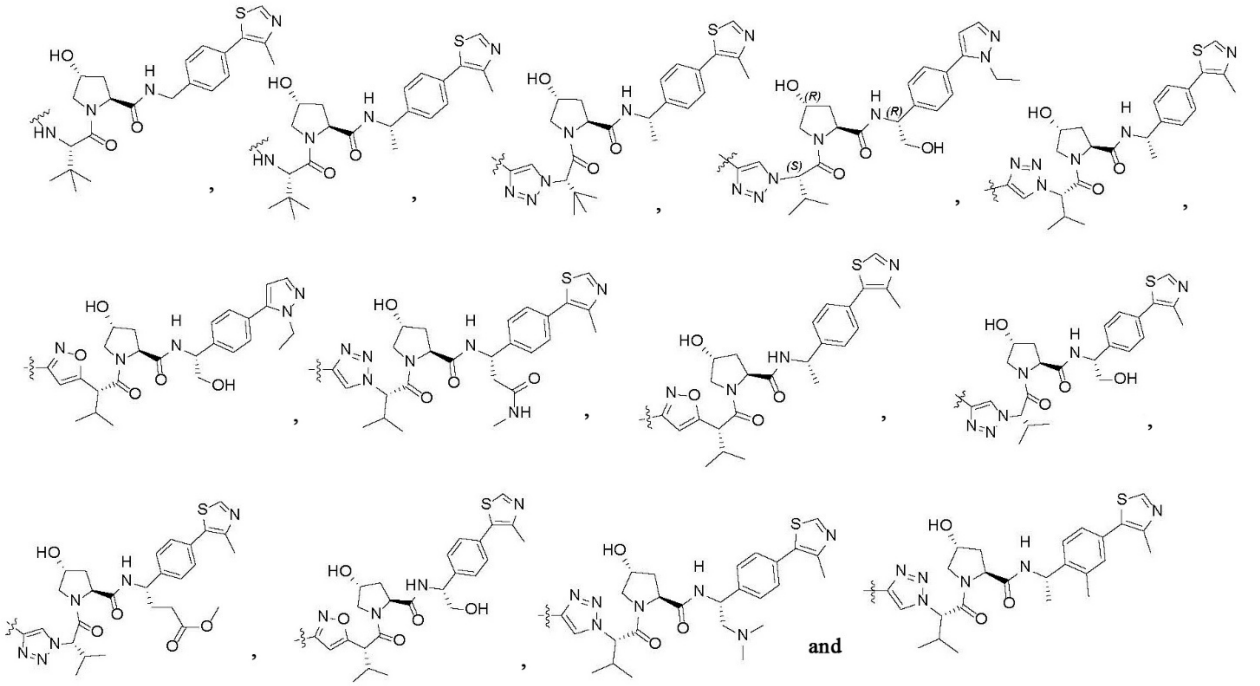
hydroxy, amino, oxo, cyano, halogen, C_{1-6} alkyl, C_{1-6} haloalkyl and C_{1-6} alkoxy.

13. The compound according to any one of claims 1 to 12, or the tautomer, racemate, enantiomer, diastereomer thereof, or the mixture thereof, or the pharmaceutically acceptable salt thereof, wherein L is selected from the group consisting of , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , and .

14. The compound according to any one of claims 1 to 12, or the tautomer, racemate, enantiomer, diastereomer thereof, or the mixture thereof, or the pharmaceutically acceptable salt thereof, wherein L is selected from the group consisting of , and .

15. The compound according to any one of claims 1 to 14, or the tautomer, racemate, enantiomer, diastereomer thereof, or the mixture thereof, or the pharmaceutically acceptable salt thereof, wherein R_3 is selected from the group consisting of H, methyl, hydroxymethyl, $-CH_2-CH_2-CO-O-CH_3$, $-CH_2-N(CH_3)_2$ and $-CH_2-CO-NH-CH_3$.

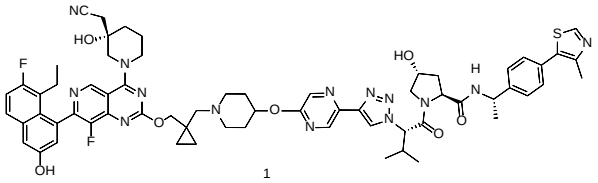
16. The compound according to any one of claims 1 to 15, or the tautomer, racemate, enantiomer, diastereomer thereof, or the mixture thereof, or the pharmaceutically acceptable salt thereof, wherein M is selected from the group consisting of



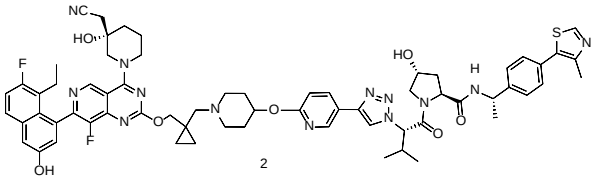
and

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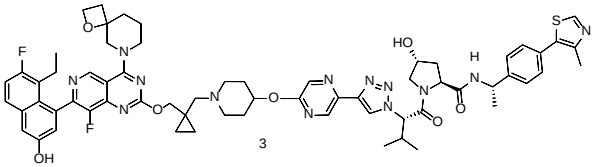
17. The compound according to claim 1, or the tautomer, racemate, enantiomer, diastereomer thereof, or the mixture thereof, or the pharmaceutically acceptable salt thereof, wherein the compound having the F-L-M structure is selected from the group consisting of the following compounds:



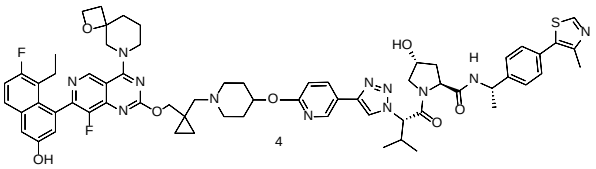
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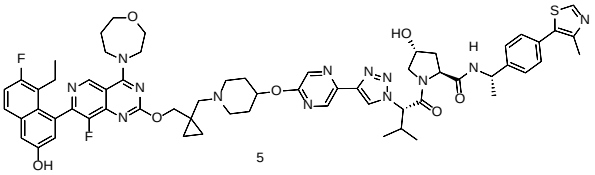
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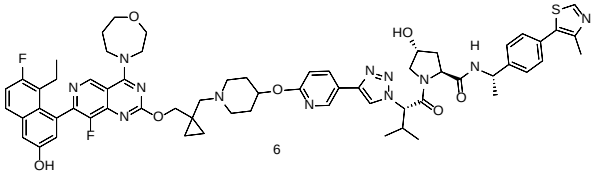
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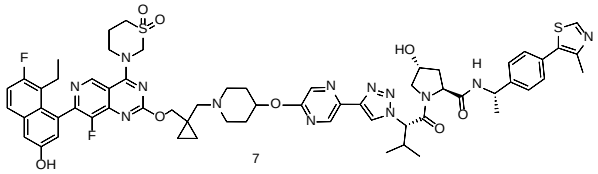
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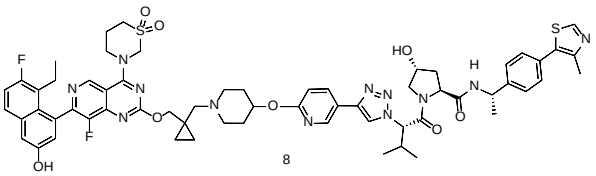
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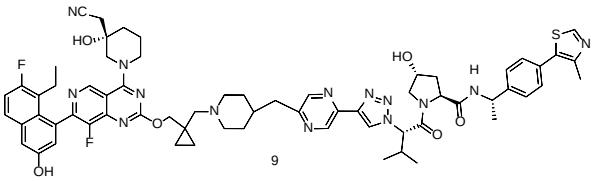
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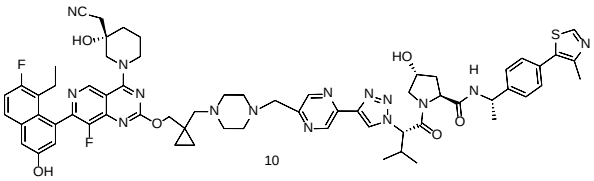
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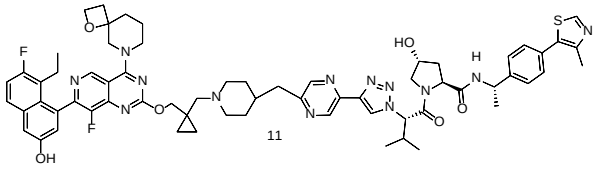
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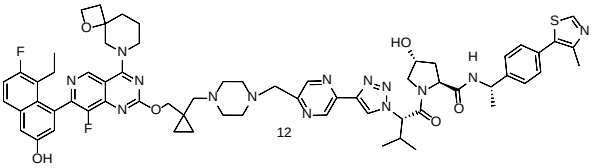
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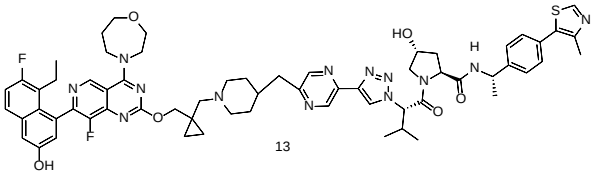
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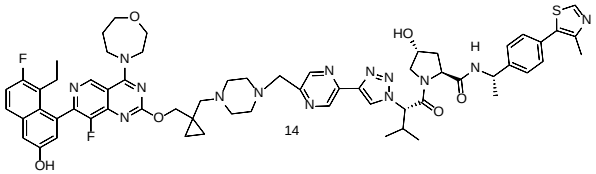
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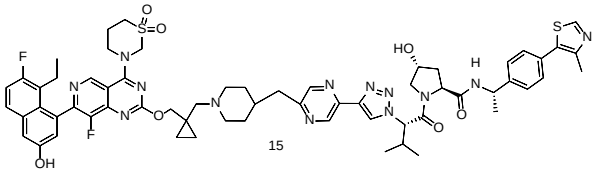
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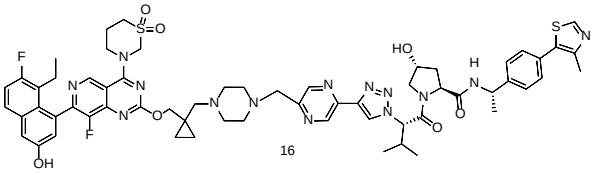
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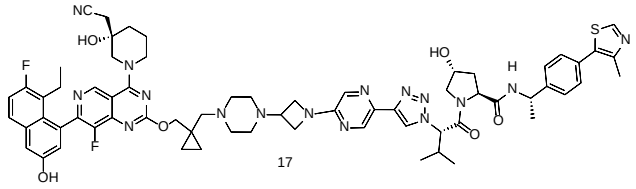
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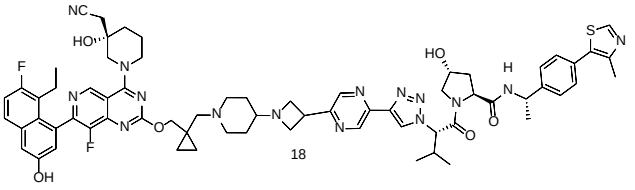
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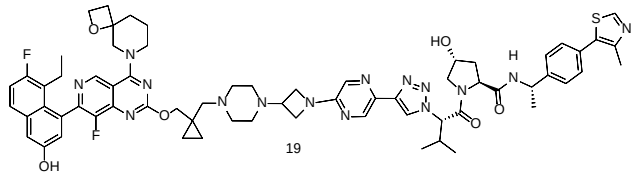
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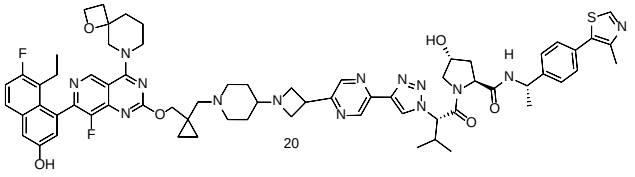
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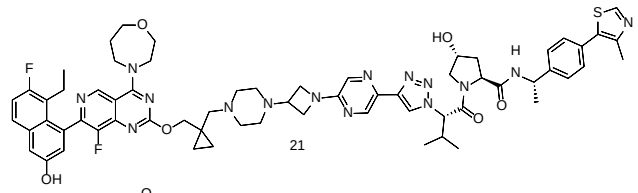
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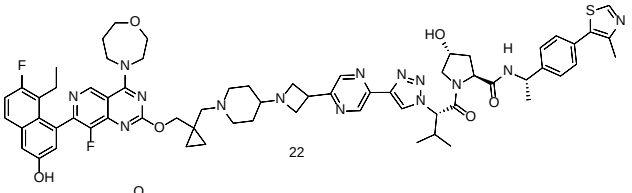
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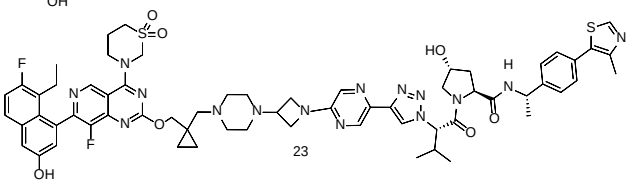
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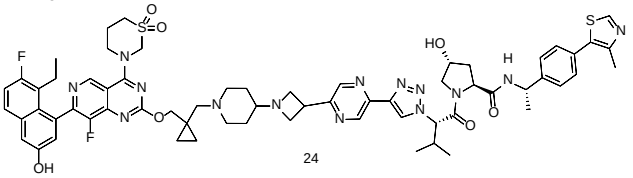
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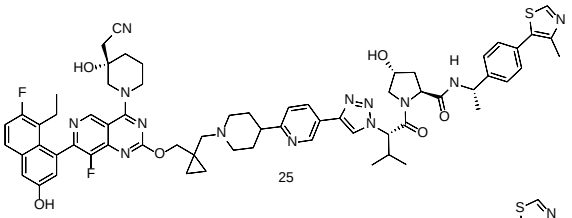
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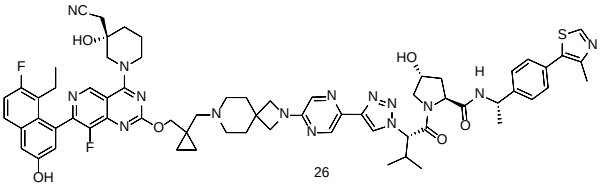
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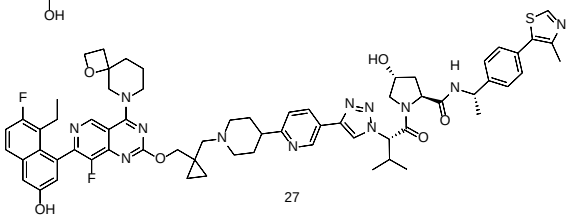
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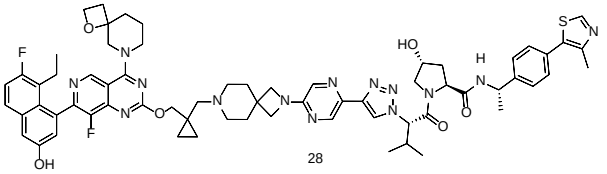
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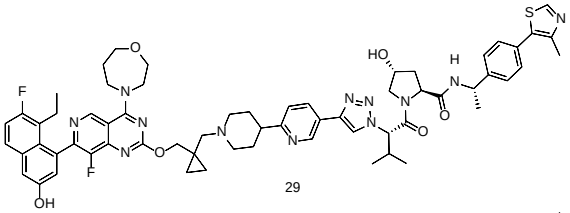
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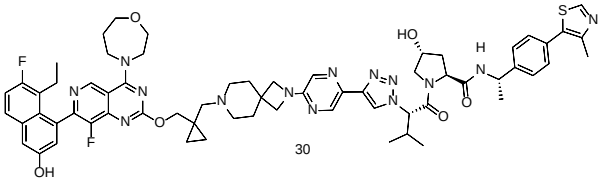
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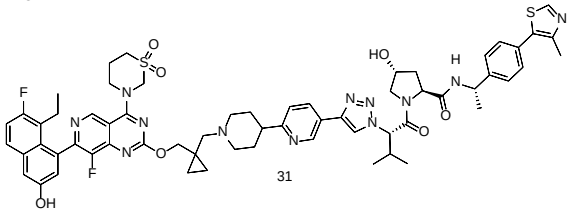
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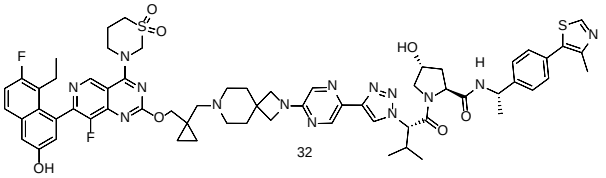
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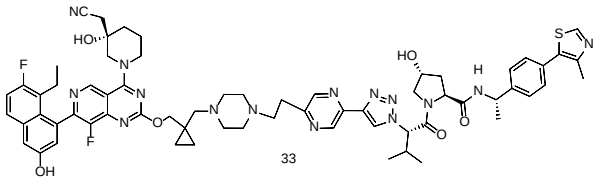
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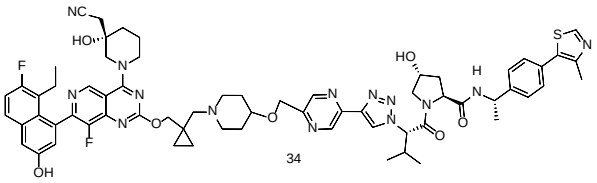
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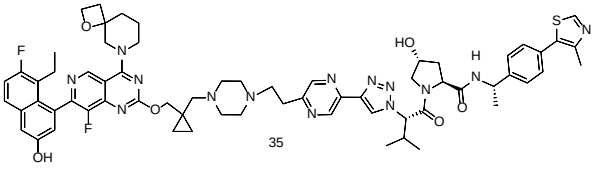
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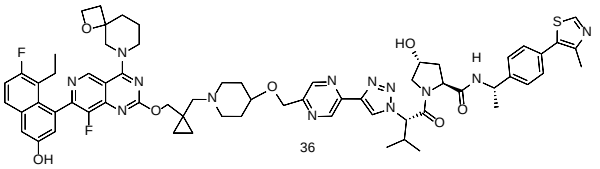
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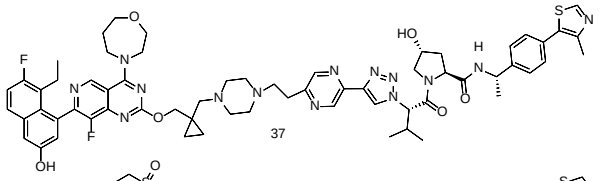
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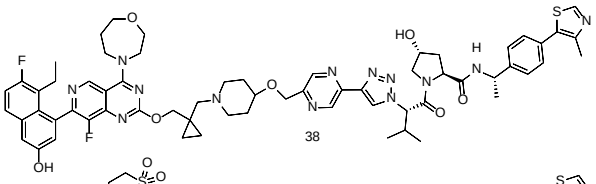
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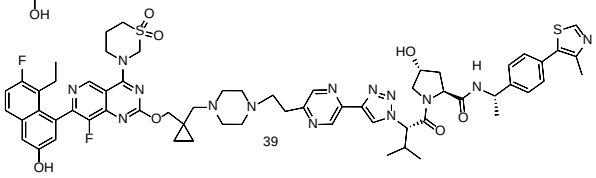
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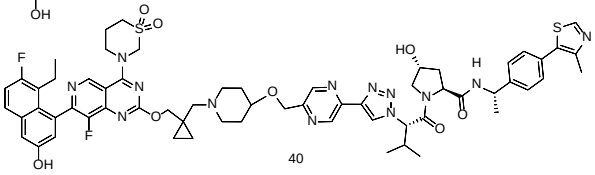
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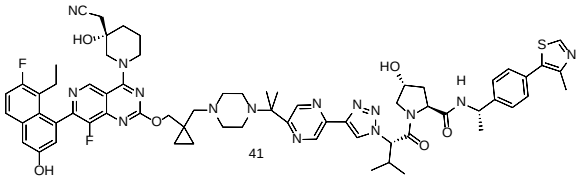
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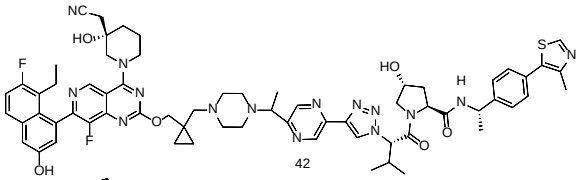
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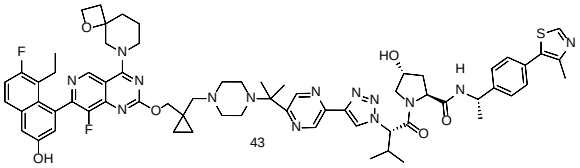
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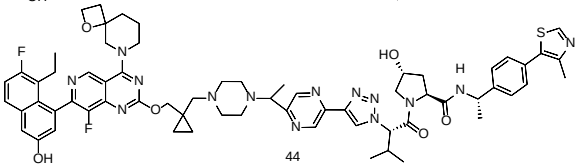
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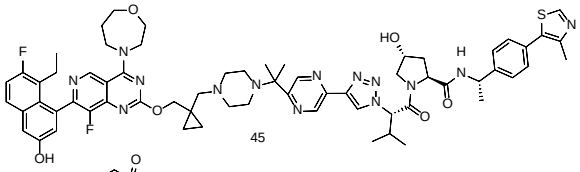
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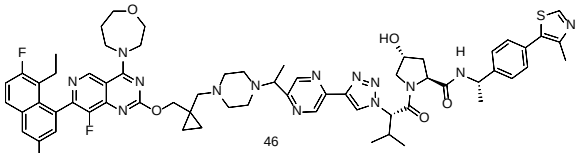
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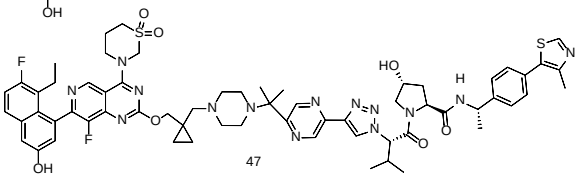
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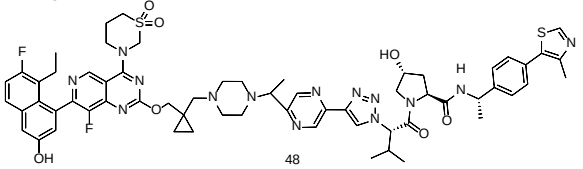
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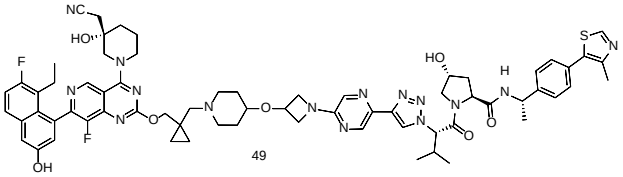
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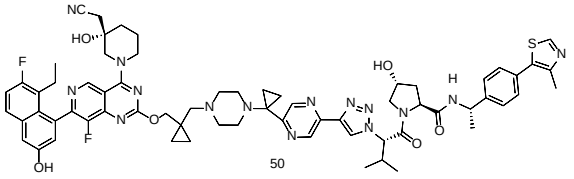
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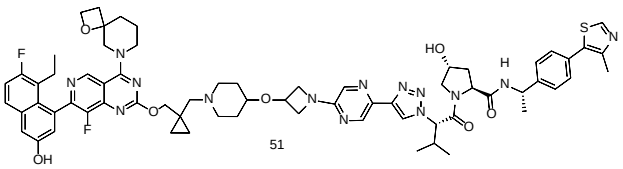
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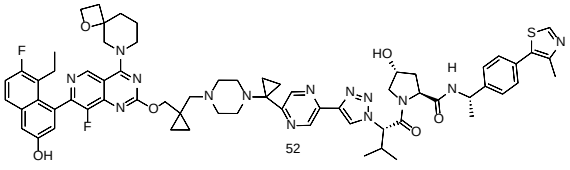
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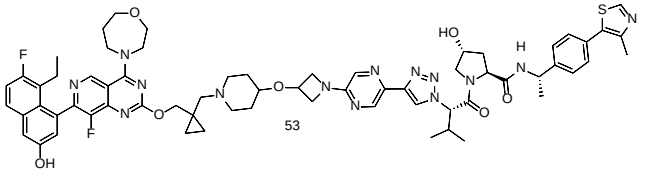
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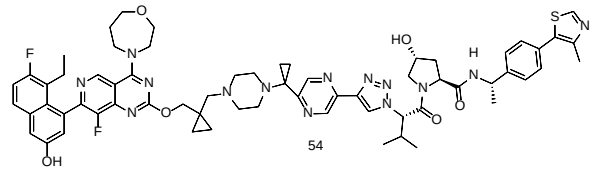
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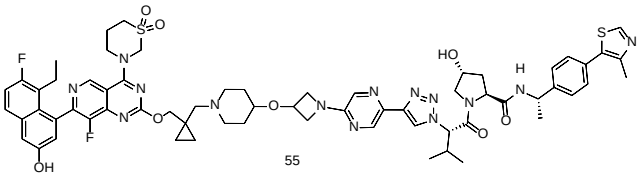
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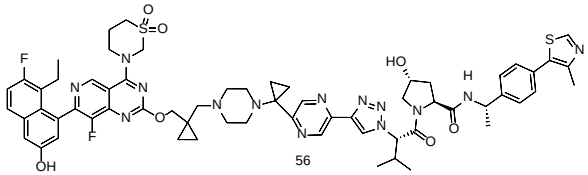
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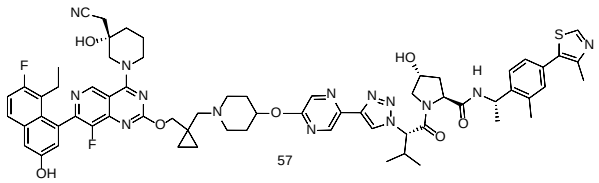
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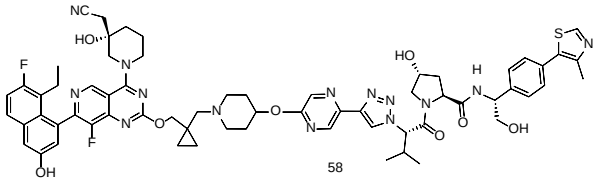
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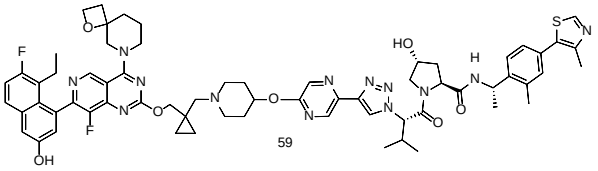
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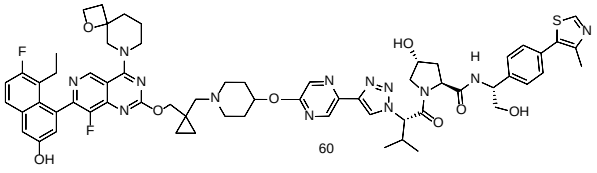
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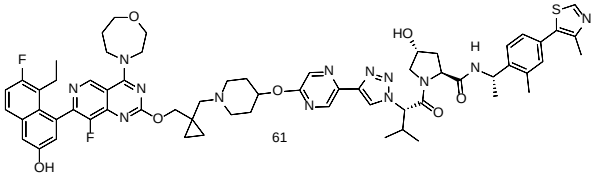
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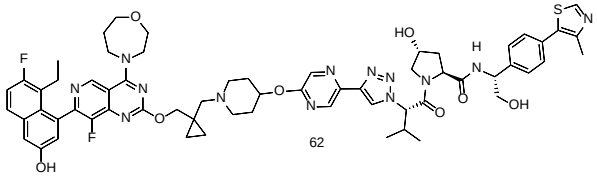
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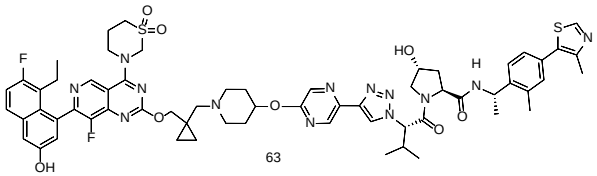
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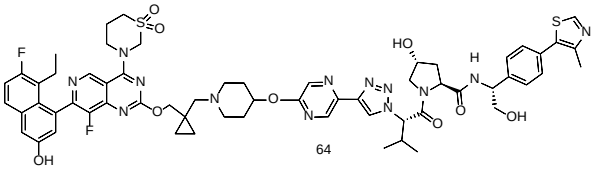
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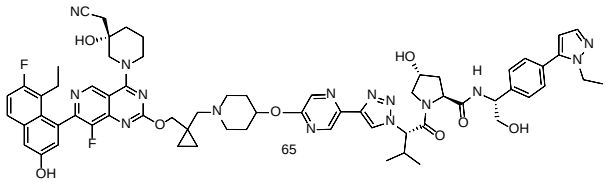
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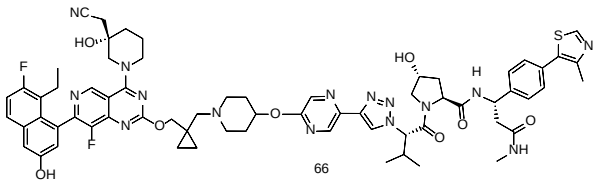
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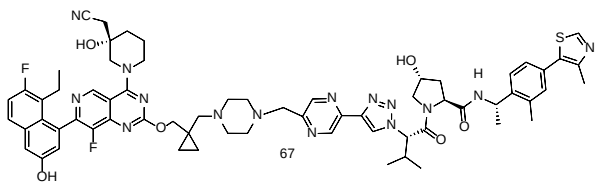
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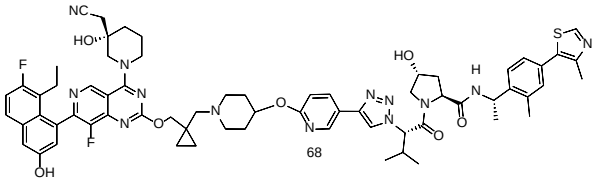
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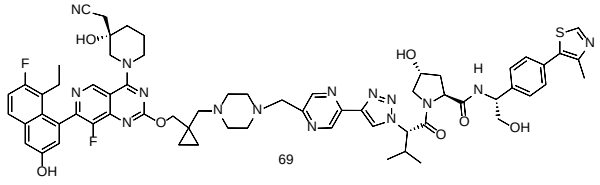
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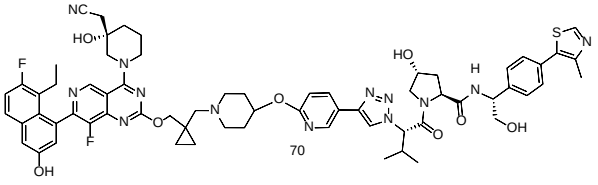
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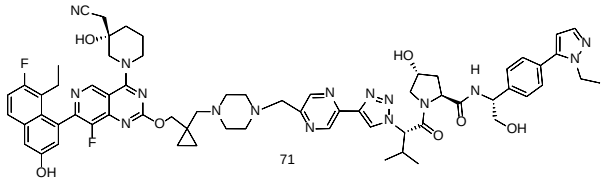
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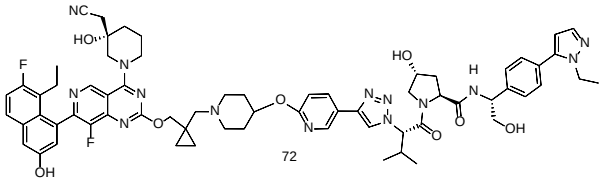
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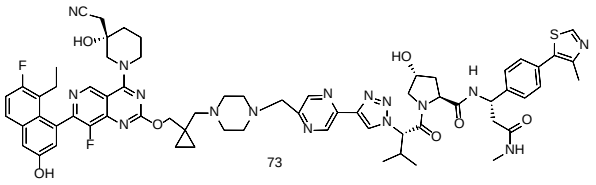
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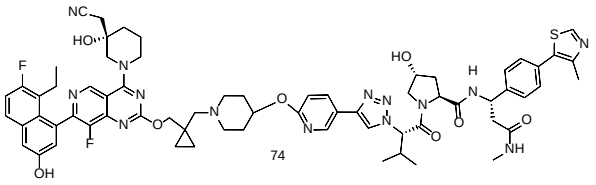
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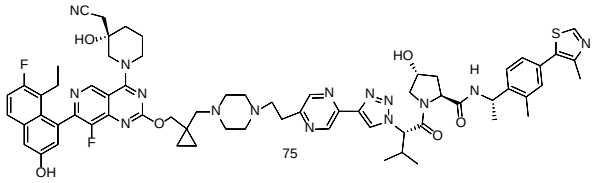
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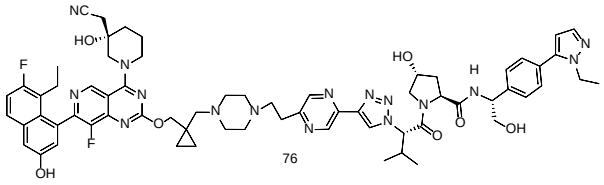
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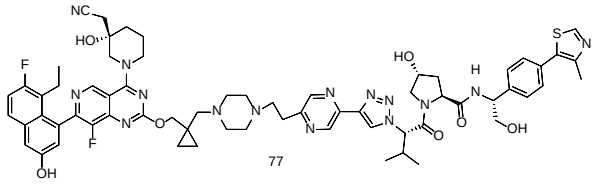
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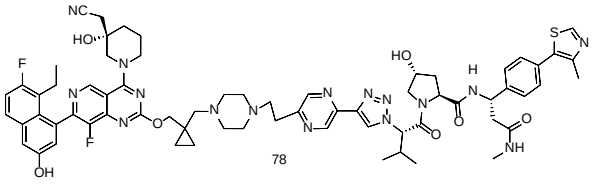
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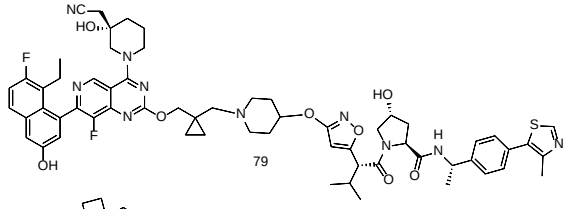
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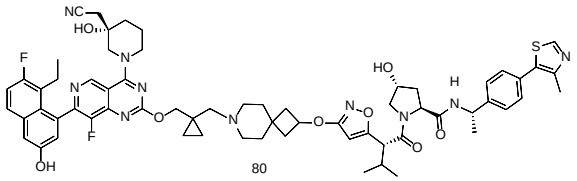
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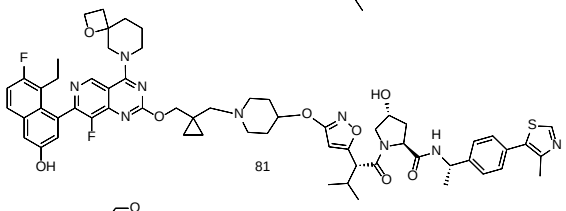
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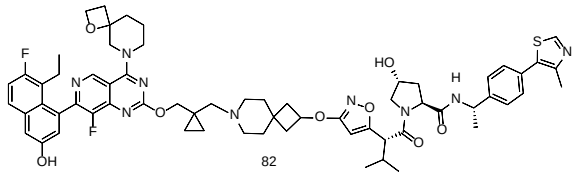
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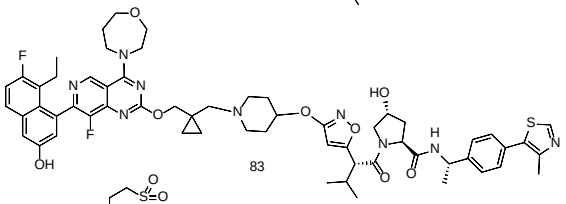
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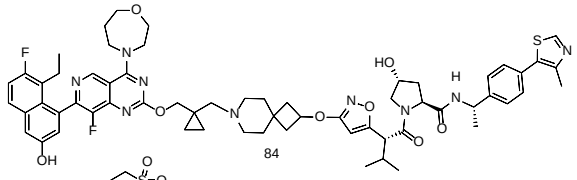
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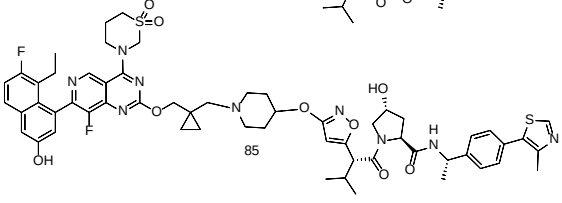
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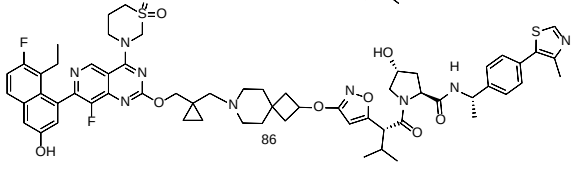
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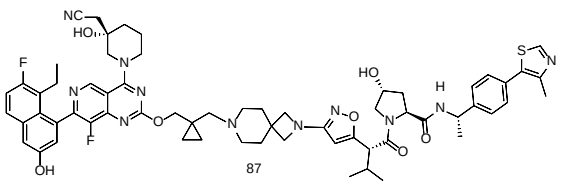
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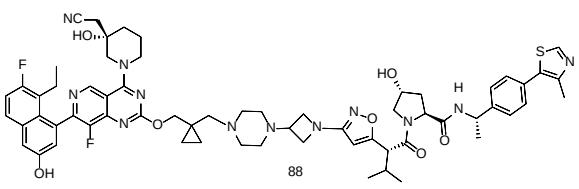
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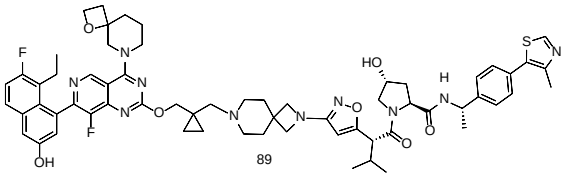
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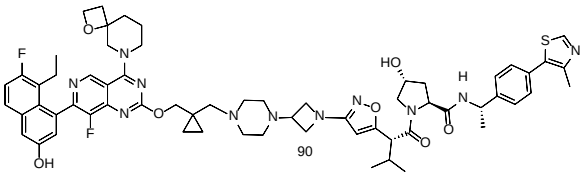
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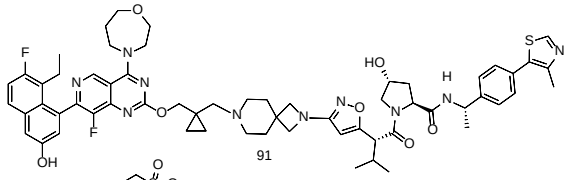
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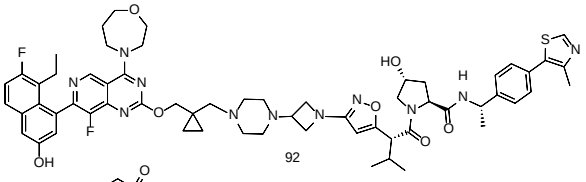
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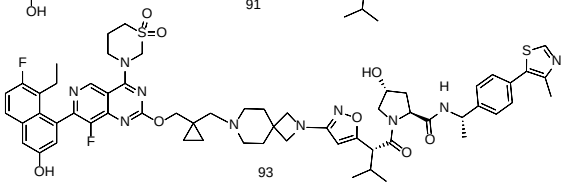
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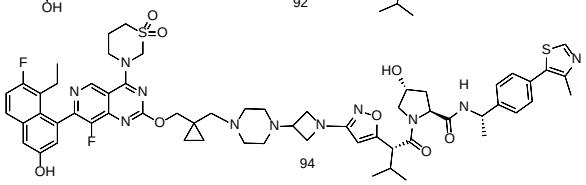
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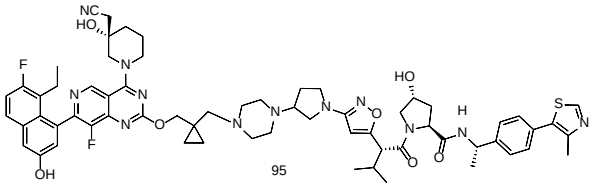
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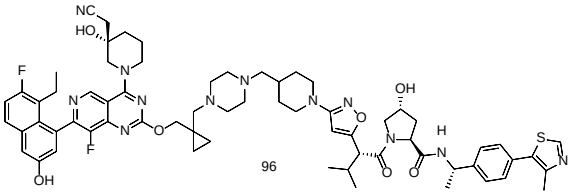
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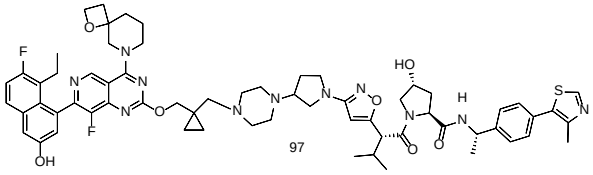
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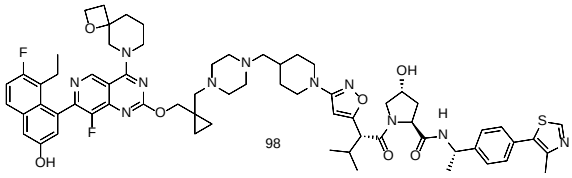
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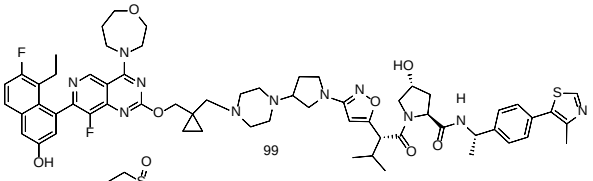
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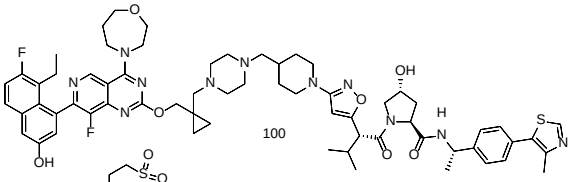
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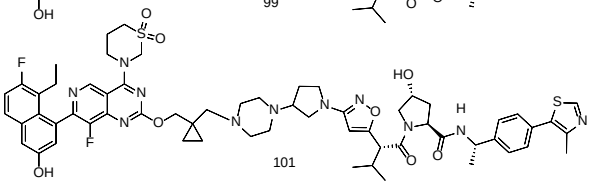
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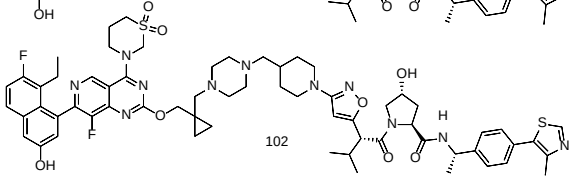
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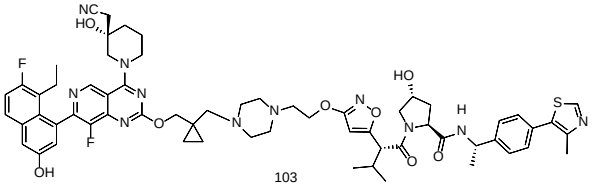
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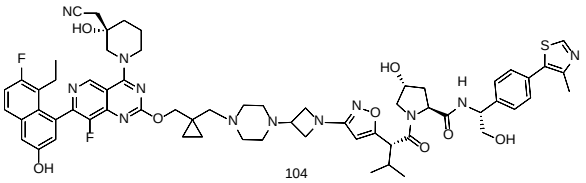
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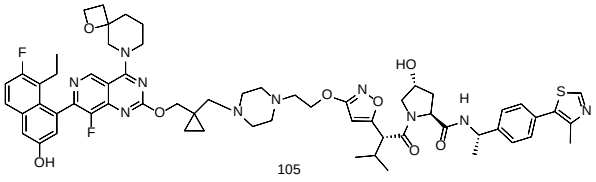
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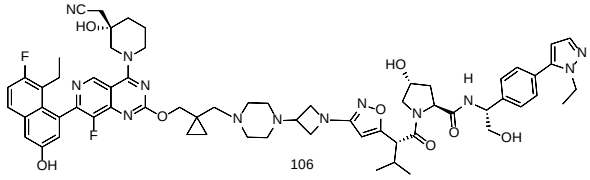
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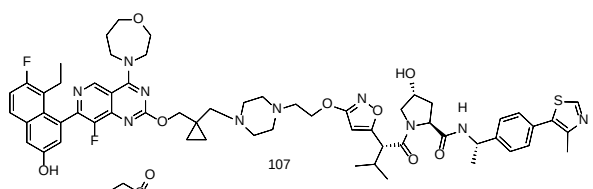
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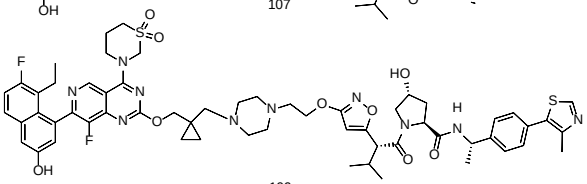
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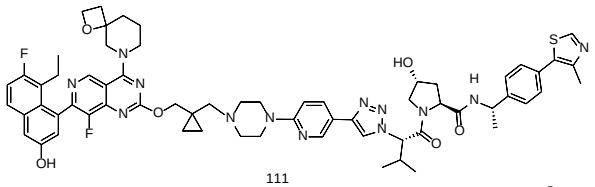
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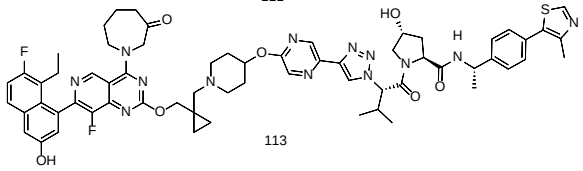
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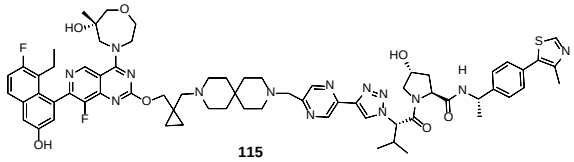
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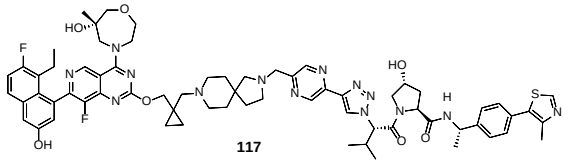
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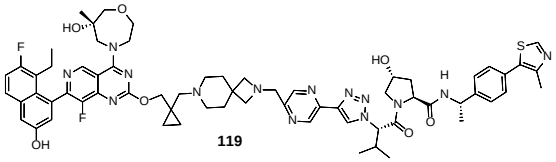
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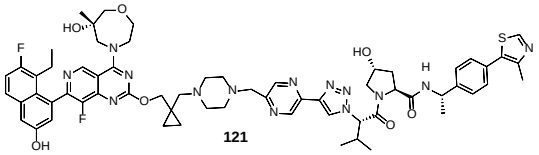
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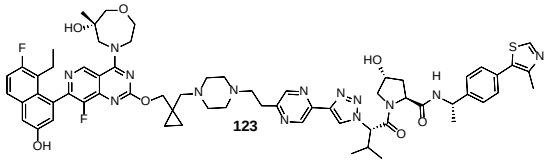
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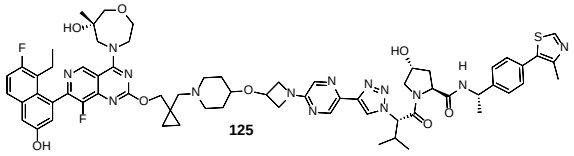
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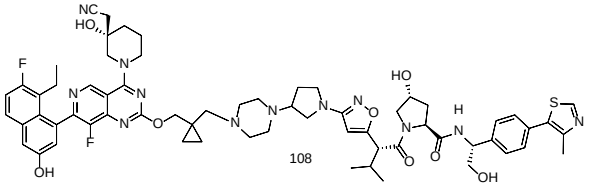
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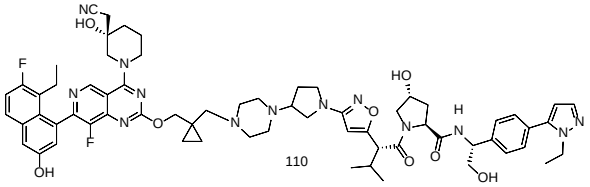
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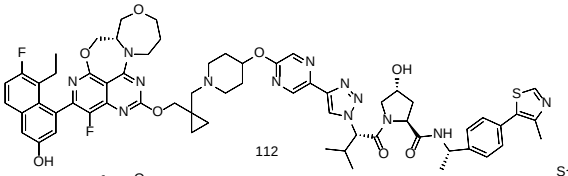
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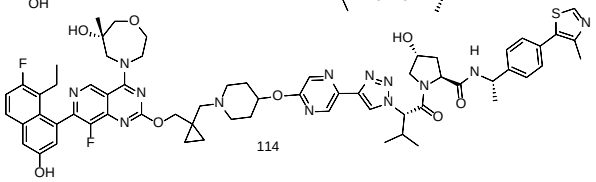
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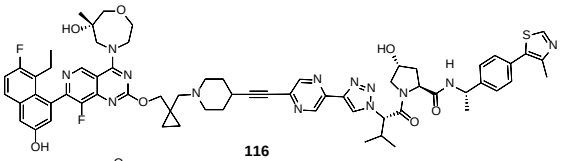
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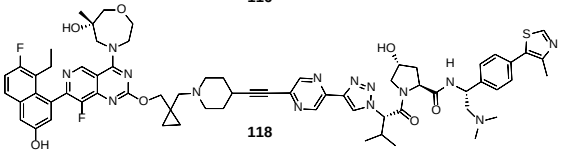
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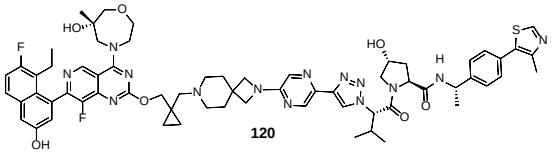
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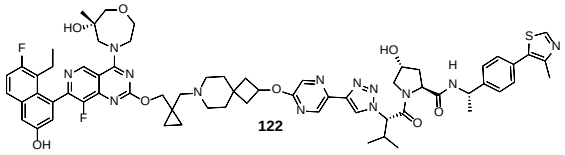
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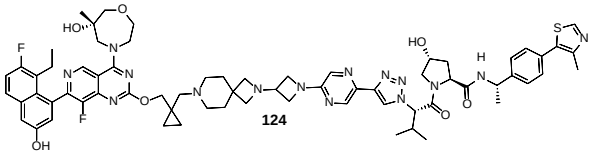
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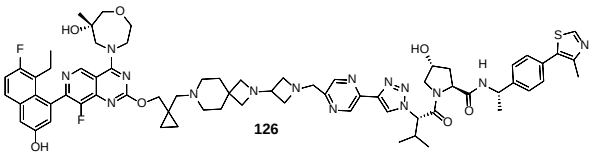
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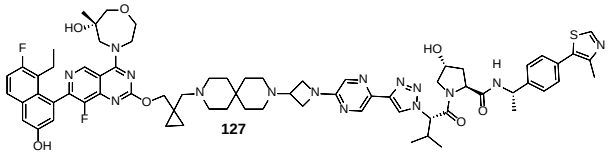
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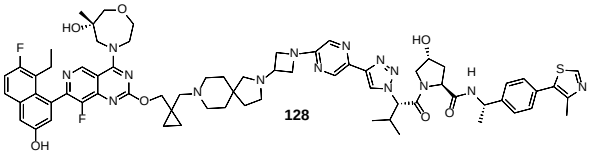
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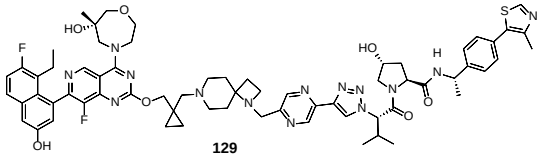
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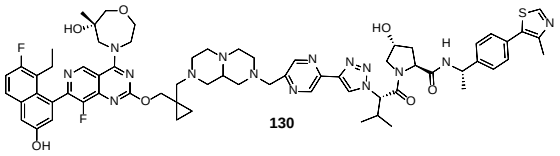
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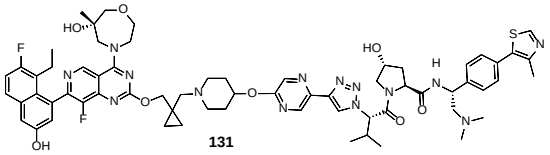
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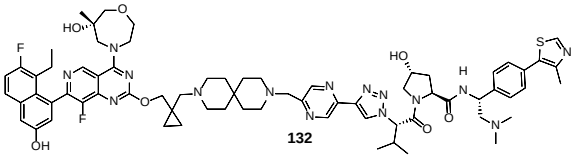
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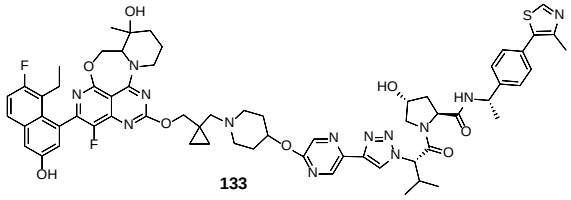
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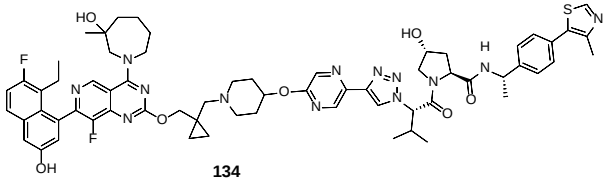
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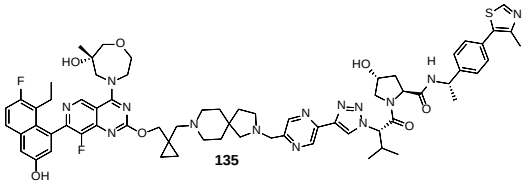
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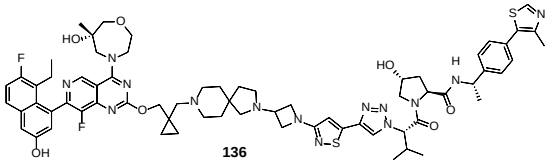
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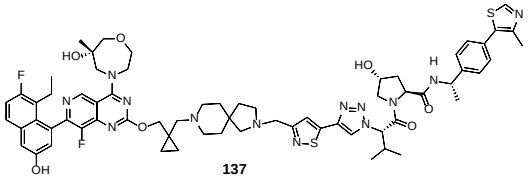
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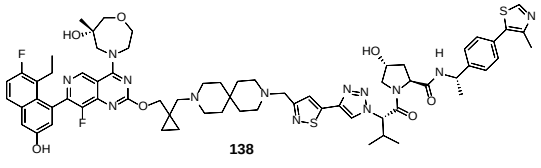
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18. A pharmaceutical composition, wherein the pharmaceutical composition comprises the compound according to any one of claims 1 to 17, or the tautomer, racemate, enantiomer, diastereomer thereof, or the mixture thereof, or the pharmaceutically acceptable salt thereof.

19. Use of the compound according to any one of claims 1 to 17, or the tautomer, racemate, enantiomer, diastereomer thereof, or the mixture thereof, or the pharmaceutically acceptable salt thereof, or the pharmaceutical composition according to claim 18 in the manufacture of a medicament for regulating ubiquitination and degradation of KRAS protein in a subject.

20. Use of the compound according to any one of claims 1 to 17, or the tautomer, racemate, enantiomer, diastereomer thereof, or the mixture thereof, or the pharmaceutically acceptable salt thereof, or the pharmaceutical composition according to claim 18 in the manufacture of a

medicament for treating and/or preventing a KRAS protein-mediated disease or a KRAS protein-dependent disease; optionally, the KRAS protein-mediated disease is a tumor; and/or the disease is selected from the group consisting of breast cancer, multiple myeloma, bladder cancer, endometrial cancer, gastric cancer, cervical cancer, rhabdomyosarcoma, non-small cell lung cancer, small cell lung cancer, pleomorphic lung cancer, ovarian cancer, esophageal cancer, melanoma, colorectal cancer, hepatocellular carcinoma, head and neck tumor, intrahepatic cholangiocarcinoma, myelodysplastic syndrome, malignant glioma, prostate cancer, thyroid cancer, Schwann cell tumor, pulmonary squamous cell carcinoma, lichenoid keratosis, synovial sarcoma, skin cancer, pancreatic cancer, testicular cancer and liposarcoma.