	Apparent volume of distribution, Vd_{ss}/Vd_{ss},u(L/kg)	17.9/203	10.6/221
	$AUC_{0\text{-last}}$/AUC_u (nM.h)	544/53.3	653/31.3
Oral administration	Dose (mg/kg)	9.7	9.8
	Time-to-peak, T_{max} (h)	1.5	1.5
	Peak concentration, C_{max}/$C_{max,u}$ (nM)	218/21.3	220/10.6
	$AUC_{0\text{-last}}$/AUC_u (nM.h)	1211/119	995/47.8
	Bioavailability F (%)	44.5%	30.5%

[00516] Note: Vd_{ss},u is the apparent volume of distribution under unbound plasma protein (Vd_{ss},u=Vd_{ss}/PPB(Unbound%)); $C_{max,\ u}$, and $AUC_{0\text{-last},\ u}$ are the corresponding values under unbound plasma protein ($C_{max,u}$= C_{max} x PPB(Unbound%); $AUC_{0\text{-last},\ u}$ = $AUC_{0\text{-last}}$ x PPB(Unbound%))

[00517] Conclusion: PK assay showed that the compounds of the present disclosure have higher unbound plasma exposure and good oral bioavailability in rats.

[00518] 2) Assay on the pharmacokinetics of the assay compounds by oral administration and intravenous injection in CD mice

[00519] The assay compound was mixed with 5% dimethyl sulfoxide/95% (10% hydroxypropyl-β-cyclodextrin) solution. The mixture was vortexed and sonicated to prepare a 1 mg/mL clear solution, which was filtered through a microporous membrane for later use. Male CD mice aged 7 to 10 weeks were selected, and administered candidate compound solutions intravenously or orally. Whole blood was collected for a certain period of time, and prepared to obtain plasma. Drug concentration was analyzed by LC-MS/MS method, and pharmacokinetic parameters were calculated by Phoenix WinNonlin software (Pharsight, USA). The results of the assay are shown in Table 9:

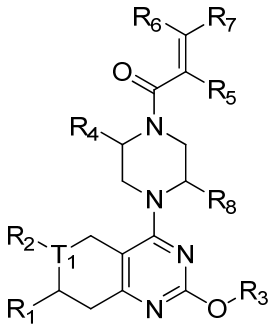
[00520] Table 9. Pharmacokinetic results of the assay compounds

Route of administration	Pharmacokinetic parameters	**Compound 178B**	**Compound 8B17**
	Plasma protein unbound rate PPB (Unbound %)	1.54	12.0
Intravenous injection administration	Dose (mg/kg)	2.39	2.0
	Half-life period, $T_{1/2}$ (h)	1.0	1.7

CLAIMS

~~What is claimed is:~~

1. A compound represented by formula (III) or a pharmaceutically acceptable salt thereof,



(III)

wherein

T_1 is selected from O and N;

R_1 is selected from C_{6-10} aryl and 5- to 10-membered heteroaryl, wherein the C_{6-10} aryl and 5- to 10-membered heteroaryl are optionally substituted with 1, 2, 3, 4 or 5 R_a;

when T_1 is O, R_2 is not present;

when T_1 is N, R_2 is selected from H, C_{1-3} alkyl, -C(=O)-C_{1-3} alkyl and -S(=O)$_2$-C_{1-3} alkyl, wherein the C_{1-3} alkyl, -C(=O)-C_{1-3} alkyl and -S(=O)$_2$-C_{1-3} alkyl are optionally substituted with 1, 2 or 3 R_b;

R_3 is C_{1-3} alkyl, wherein the C_{1-3} alkyl is optionally substituted with 1, 2 or 3 R_c;

R_4 is selected from H and C_{1-3} alkyl, wherein the C_{1-3} alkyl is optionally substituted with 1, 2 or 3 R_d;

R_5, R_6 and R_7 are each independently selected from H, F, Cl, Br, I, and C_{1-3} alkyl, wherein the C_{1-3} alkyl is optionally substituted with 1, 2 or 3 F;

R_8 is selected from H and CH_3;

R_a is each independently selected from F, Cl, Br, I, OH, NH_2, CN, C_{1-3} alkyl, C_{1-3} alkoxy, C_{2-3} alkynyl and C_{2-3} alkenyl, wherein the C_{1-3} alkyl, C_{1-3} alkoxy, C_{2-3} alkynyl and C_{2-3} alkenyl are optionally substituted with 1, 2 or 3 F;

R_b is each independently selected from F, Cl, Br, I, OH and NH_2;

R_c is each independently selected from 4- to 8-membered heterocycloalkyl, wherein the 4- to 8-membered heterocycloalkyl is optionally substituted with 1, 2 or 3 R;

R_d is each independently selected from F, Cl, Br, I, OH, NH_2 and CN;

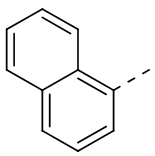
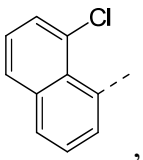
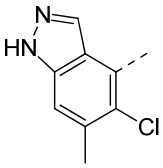
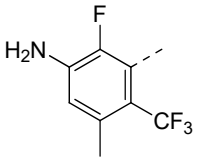
R is each independently selected from H, F, Cl, Br, OH, CN, C_{1-3} alkyl, C_{1-3} alkoxy and -C_{1-3} alkyl-O-C(=O)-C_{1-3} alkylamino;

provided that when R_1 is naphthyl, the naphthyl is optionally substituted with F, Cl, Br, OH, NH_2, CF_3, CH_2CH_3 and -C≡CH, and R_5, R_6 and R_7 are each independently H.

2. The compound according to claim 1, or a pharmaceutically acceptable salt thereof, wherein R_a is each independently selected from F, Cl, Br, I, OH, NH_2, CN, CH_3, CH_2CH_3, OCH_3, OCH_2CH_3, -CH=CH_2, -CH_2-CH=CH_2 and -C≡CH, wherein the CH_3, CH_2CH_3, OCH_3, OCH_2CH_3, -CH=CH_2, -CH_2-CH=CH_2 and -C≡CH are optionally substituted with 1, 2 or 3 F~~.~~; alternatively, wherein R_a is each independently selected from F, OH, NH_2, CH_3, CF_3, CH_2CH_3 and -C≡CH.

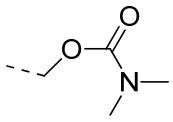
~~3. The compound according to claim 2, or a pharmaceutically acceptable salt thereof, wherein R_a is each independently selected from F, OH, NH_2, CH_3, CF_3, CH_2CH_3 and -C≡CH.~~

~~4~~3. The compound according to any one of claims 1-~~3~~2, or a pharmaceutically acceptable salt thereof, wherein R_1 is selected from phenyl, naphthyl, indolyl and indazolyl, wherein the phenyl, naphthyl, indolyl and indazolyl are optionally substituted with 1, 2 or 3 R_a.

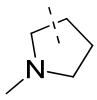
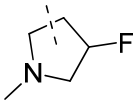
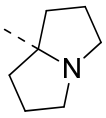
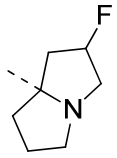
~~5~~4. The compound according to claim ~~4~~3, or a pharmaceutically acceptable salt thereof, wherein R_1 is selected from , ,  and .

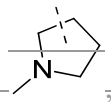
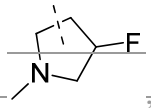
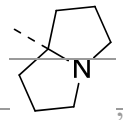
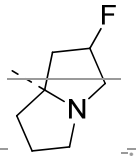
~~6~~5. The compound according to claim 1, or a pharmaceutically acceptable salt thereof, wherein R_2 is selected from H, CH_3, CH_2CH_3 and $CH(CH_3)_2$, wherein the CH_3, CH_2CH_3 and $CH(CH_3)_2$ are optionally substituted with 1, 2 or 3 R_b~~.~~; alternatively, wherein R_2 is selected from H and CH_3.

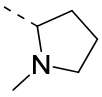
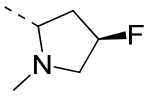
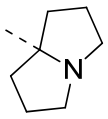
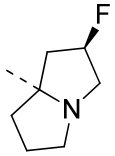
~~7. The compound according to claim 6, or a pharmaceutically acceptable salt thereof, wherein R_2 is selected from H and CH_3.~~

~~86~~. The compound according to claim 1, or a pharmaceutically acceptable salt thereof, wherein R is each independently selected from H, F, Cl, Br, OH, CN, CH_3, CH_2CH_3, CH_2CF_3, OCH_3, OCF_3 and .

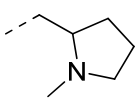
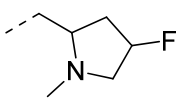
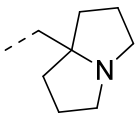
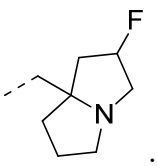
~~97~~. The compound according to claim 1, or a pharmaceutically acceptable salt thereof, wherein R_c is selected from tetrahydropyrrolyl and hexahydro-1H-pyrrolizinyl, wherein the tetrahydropyrrolyl and hexahydro-1H-pyrrolizinyl are optionally substituted with 1, 2 or 3 R_c~~,~~;

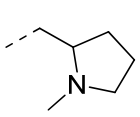
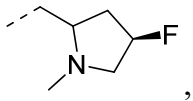
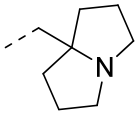
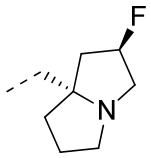
alternatively, wherein R_c is selected from , , , and .

~~10. The compound according to claim 9, or a pharmaceutically acceptable salt thereof, wherein R_c is selected from~~ ~~,~~ ~~,~~ ~~, and~~ ~~.~~

~~11~~8. The compound according to any one of claims 1, ~~9~~7, and ~~10~~8, or a pharmaceutically acceptable salt thereof, wherein R_c is selected from , , , and .

~~12~~9. The compound according to claim 1, or a pharmaceutically acceptable salt thereof, wherein R_3 is CH_3, wherein the CH_3 is optionally substituted with 1, 2 or 3 R_c.

~~13~~10. The compound according to claim ~~12~~9, or a pharmaceutically acceptable salt thereof, wherein R_3 is selected from , ,  and .

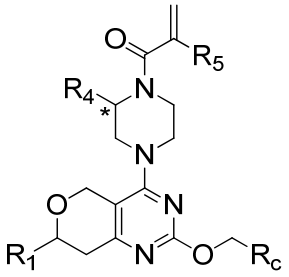
~~14~~11. The compound according to any one of claims 1, ~~12~~9, and ~~13~~10, or a pharmaceutically acceptable salt thereof, wherein R_3 is selected from , , ,  and .

~~15~~12. The compound according to claim 1, or a pharmaceutically acceptable salt thereof, wherein R_4 is selected from H and CH_3, wherein the CH_3 is optionally substituted with 1, 2 or 3 R_d~~.~~;

alternatively, wherein R_4 is selected from H, CH_3 and CH_2CN.

~~16. The compound according to claim 15, or a pharmaceutically acceptable salt thereof, wherein R_4 is selected from H, CH_3 and CH_2CN.~~

~~17~~13. The compound according to any one of claims 1-~~16~~12, or a pharmaceutically acceptable salt thereof, wherein the compound is selected from



(P-1)

wherein

R_1 is as defined in any one of claims 1-~~5~~4;

R_4 is C_{1-3} alkyl, wherein the C_{1-3} alkyl is optionally substituted with 1, 2 or 3 R_d;

R_d is each independently selected from F, Cl, Br, I, OH, NH_2 and CN;

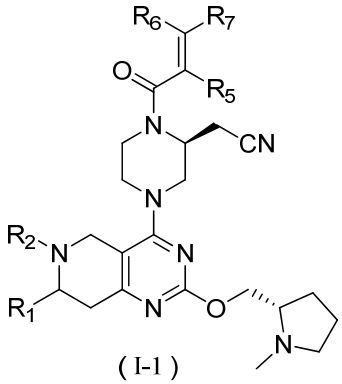
R_5 is as defined in claim 1;

R_c is as defined in any one of claims 1 and ~~8~~6-~~11~~8;

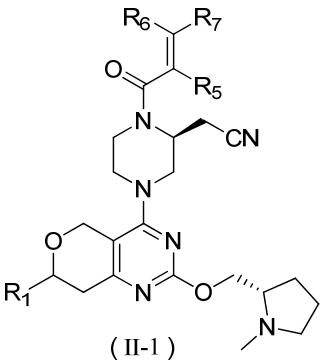
the carbon atom with "*" is a chiral carbon atom, which exists in the form of (R) or (S) single enantiomer or is enriched in one enantiomer.

~~18~~14. The compound according to any one of claims 1-~~16~~12, or a pharmaceutically acceptable

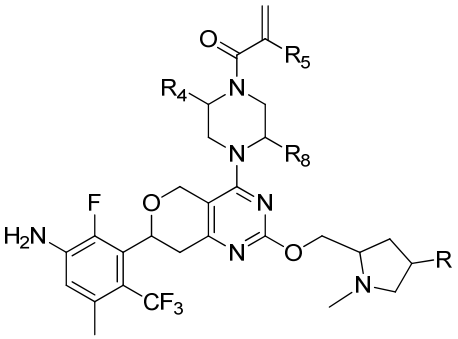
salt thereof, wherein the compound is selected from



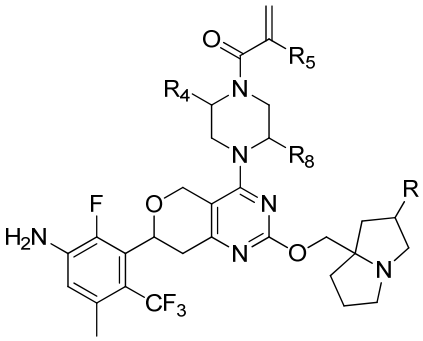
(I-1)



(II-1)



(IV-1)



(IV-2)

wherein

R_1 is as defined in any one of claims 1-~~5~~3;

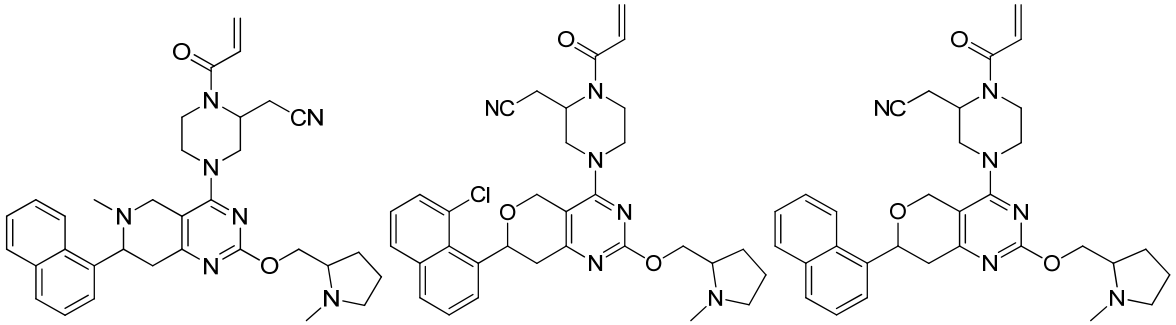
R_2 is as defined in any one of claims 1, ~~6~~ and ~~7~~5;

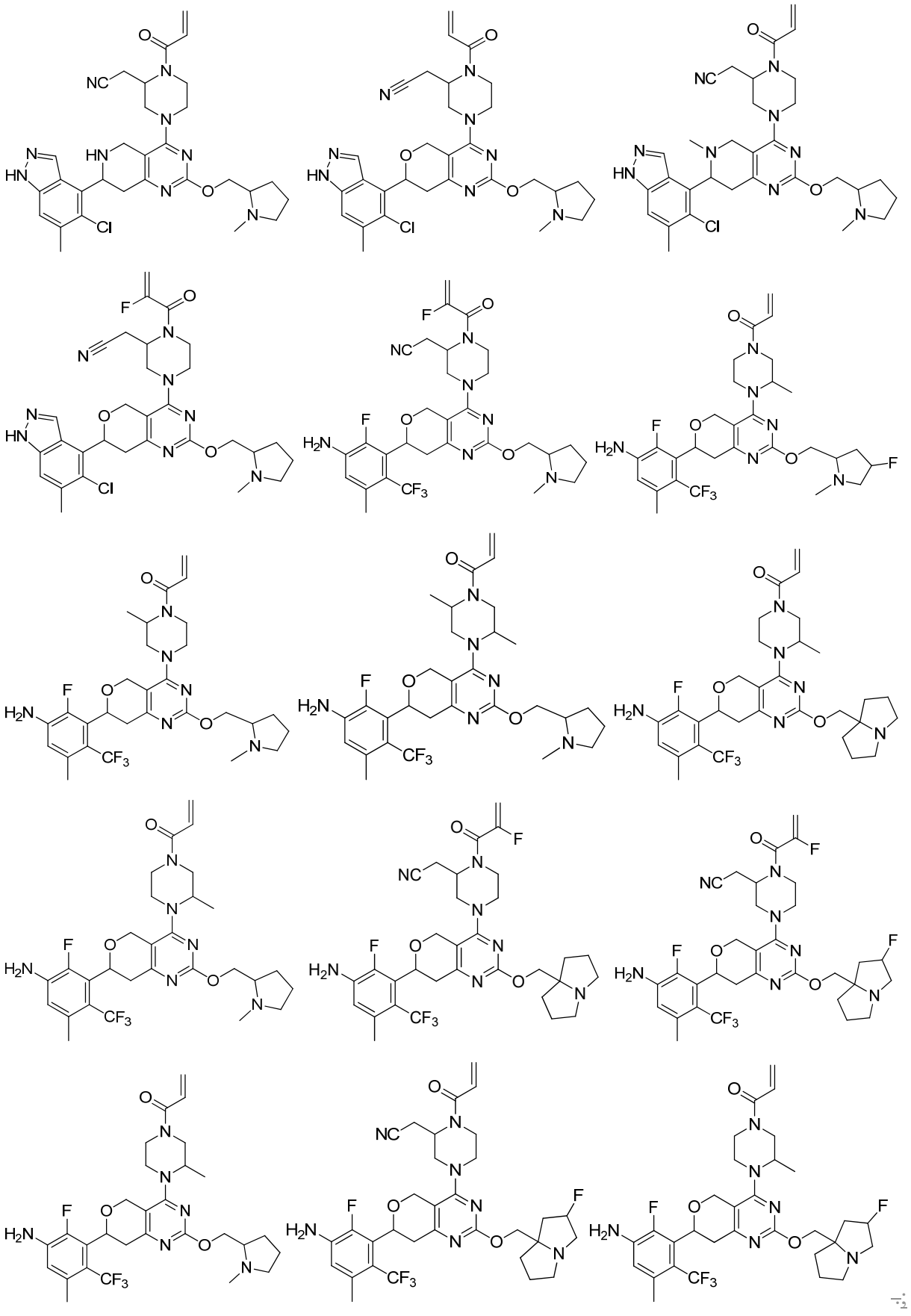
R_4 is as defined in any one of claims 1, ~~15~~ and ~~16~~12;

R_5, R_6, R_7 and R_8 are as defined in claim 1;

R is as defined in claim 1 or ~~8~~6.

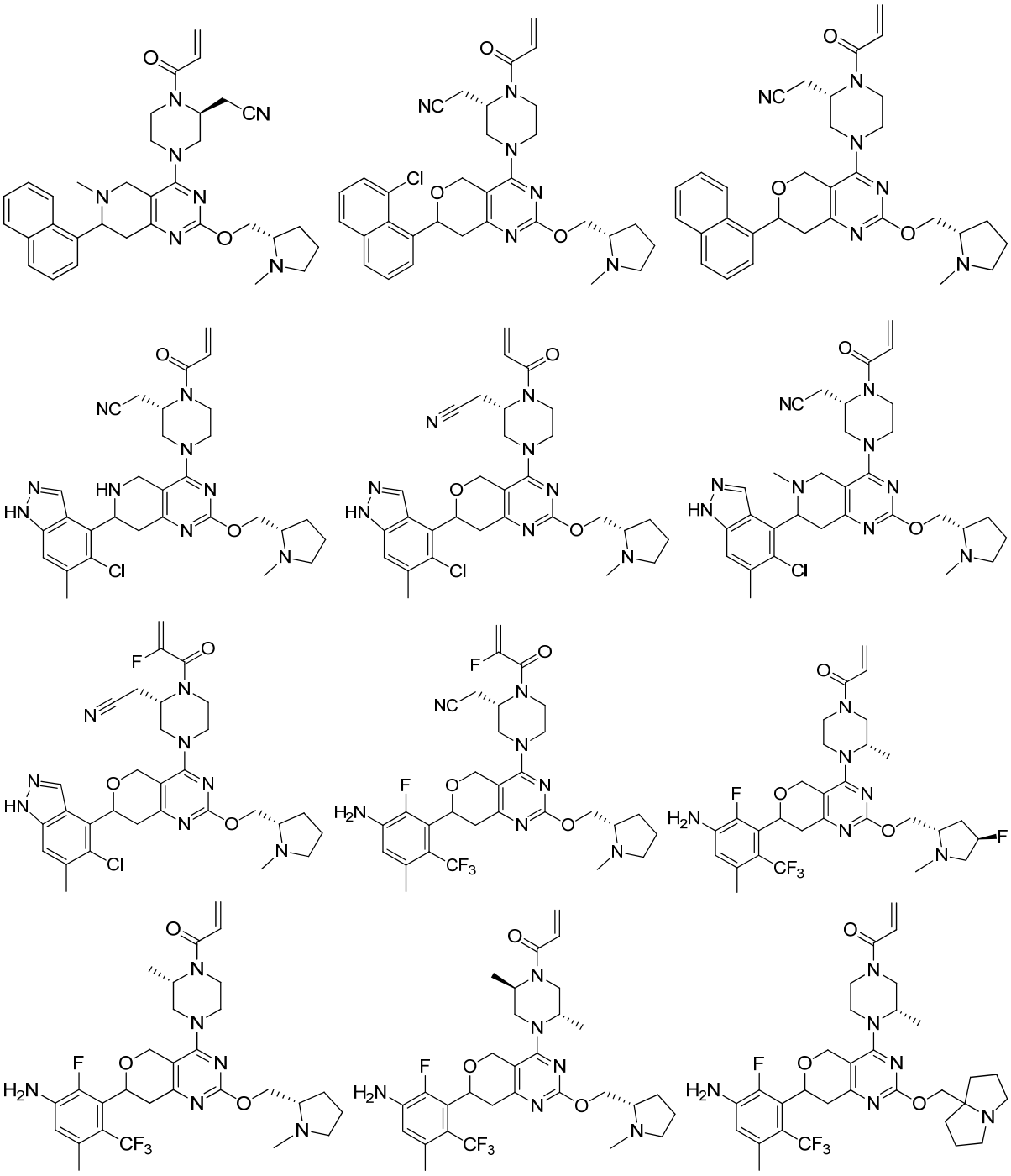
~~19~~15. A compound represented by the following formula, or a pharmaceutically acceptable salt thereof,

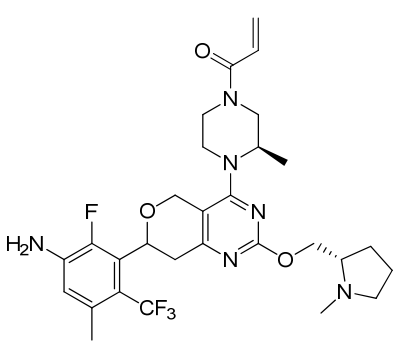
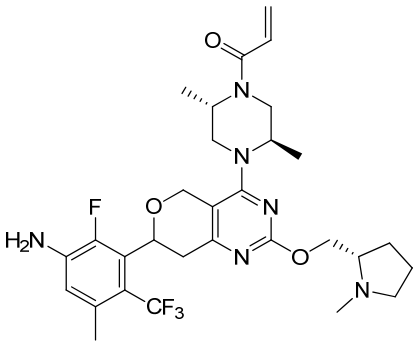
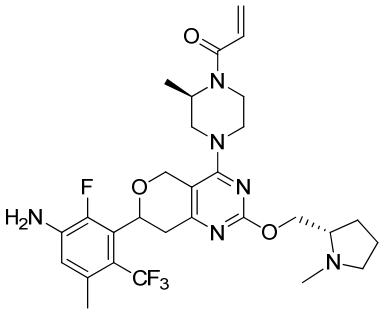
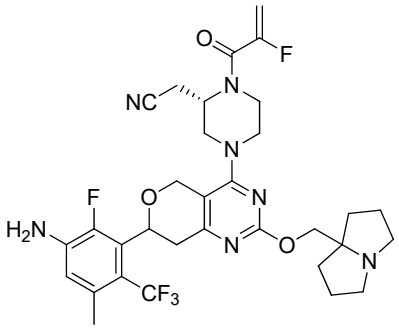
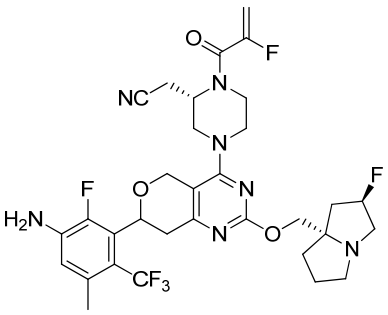
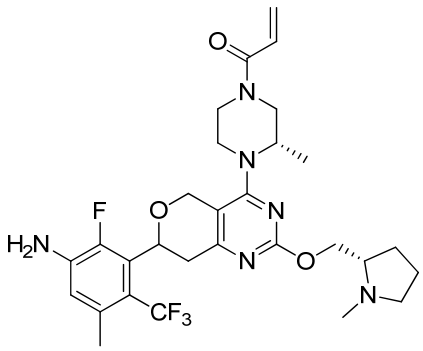
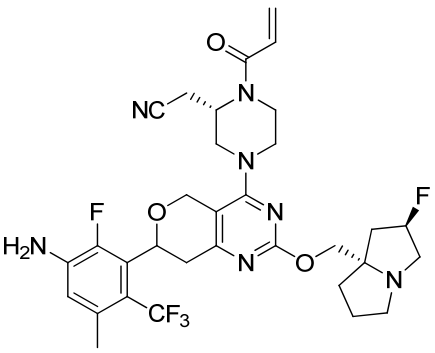
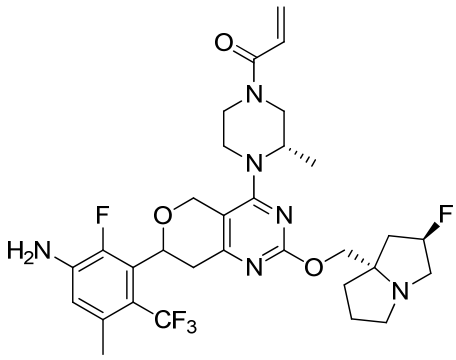




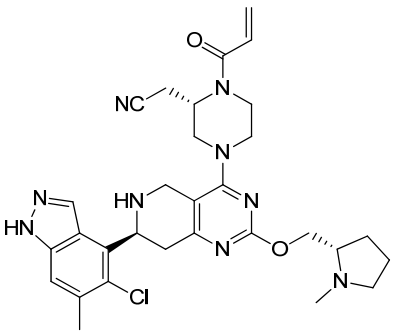
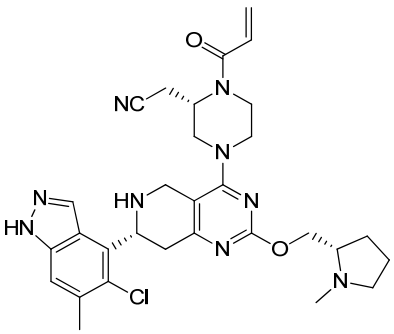
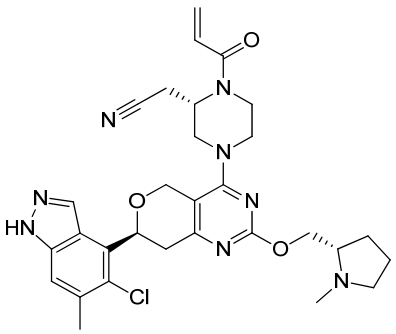
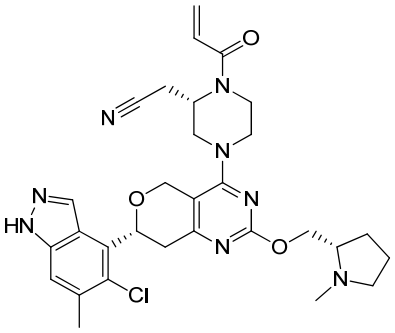
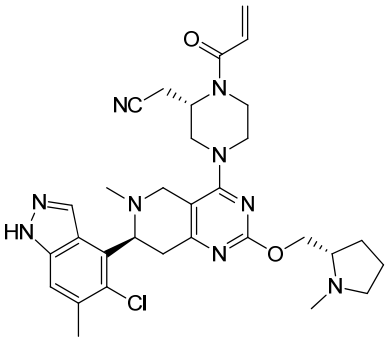
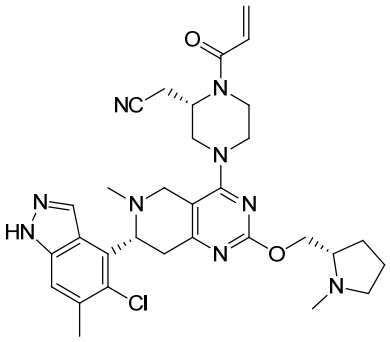
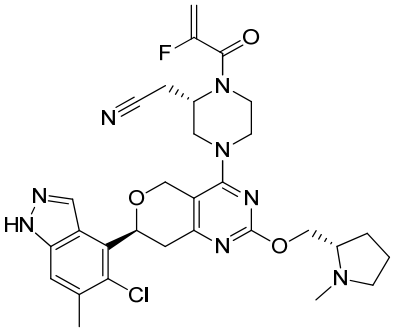
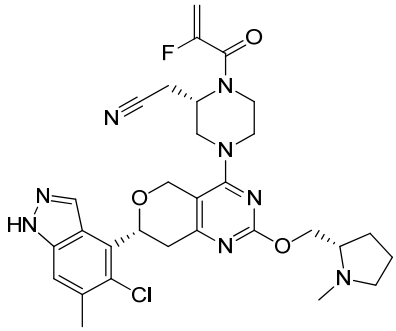
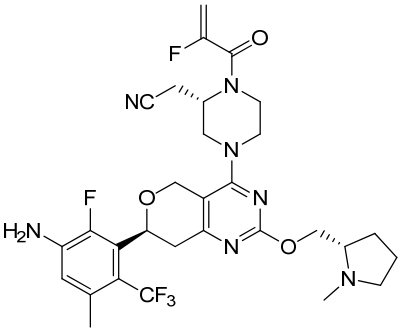
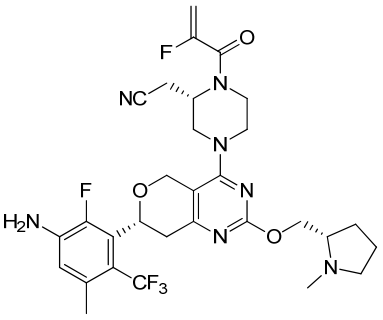
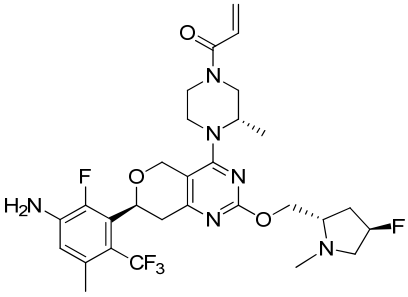
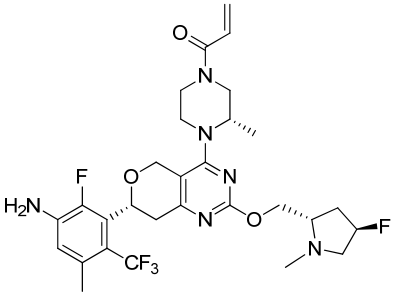
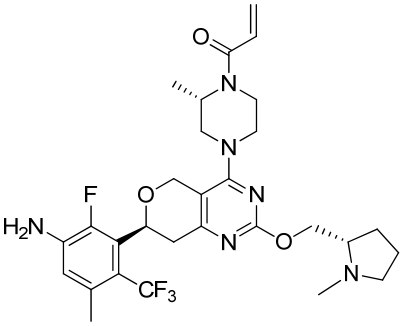
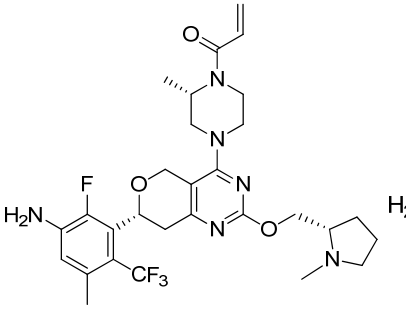
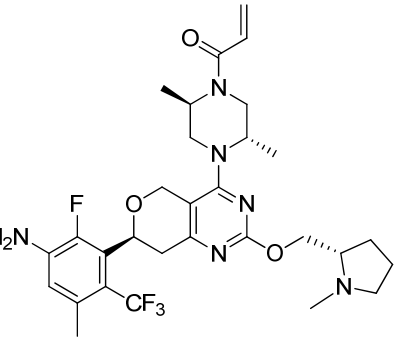
~~20. The compound of claim 19, or a pharmaceutically acceptable salt thereof~~alternatively,

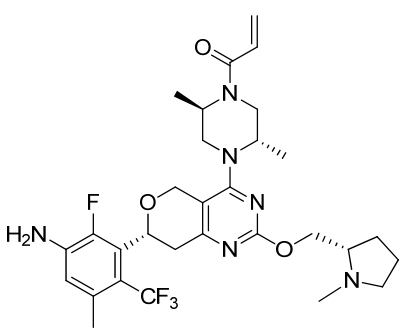
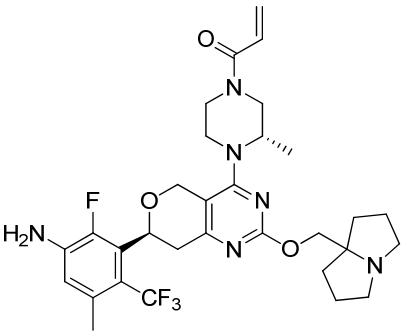
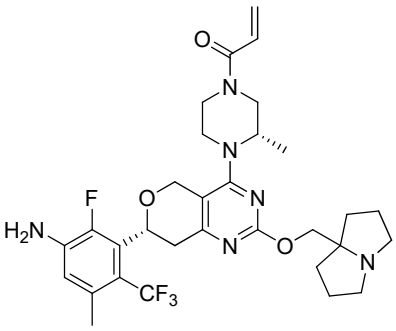
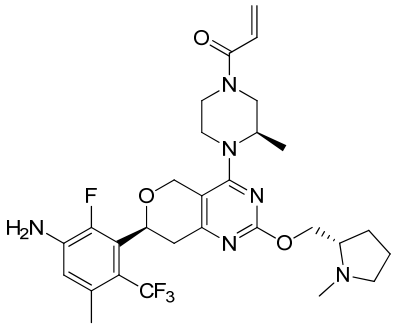
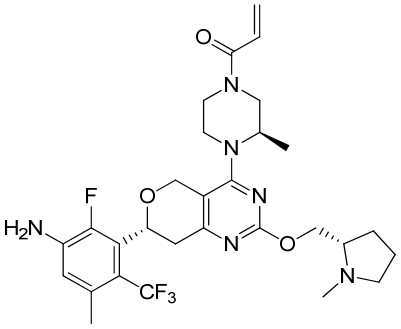
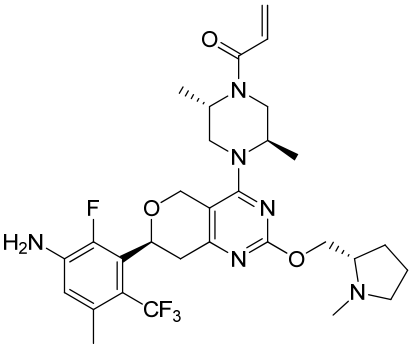
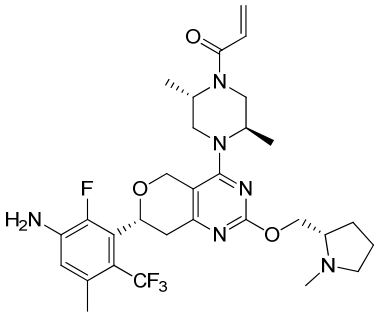
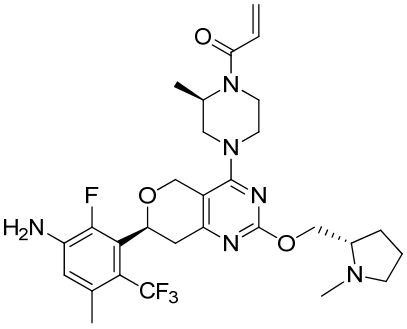
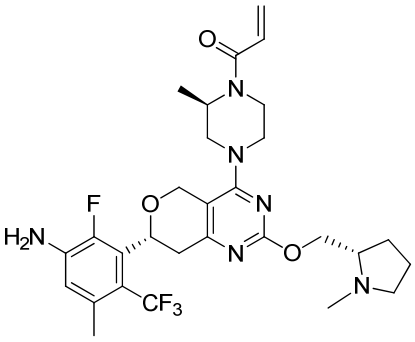
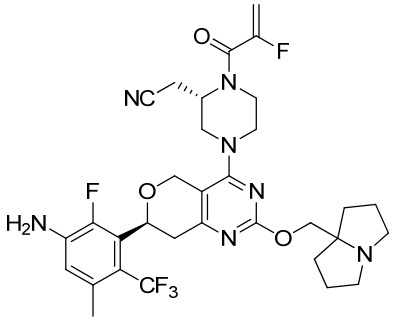
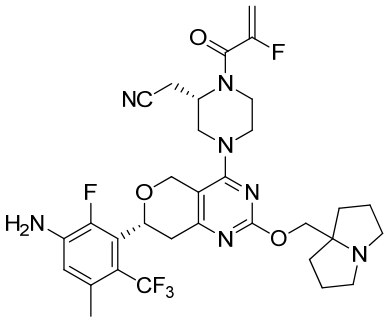
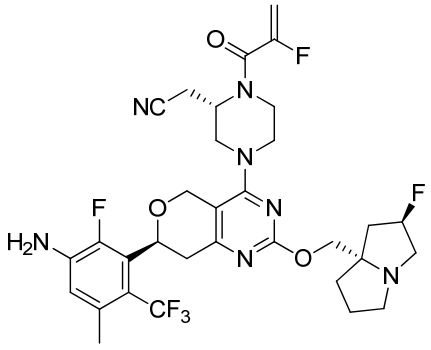
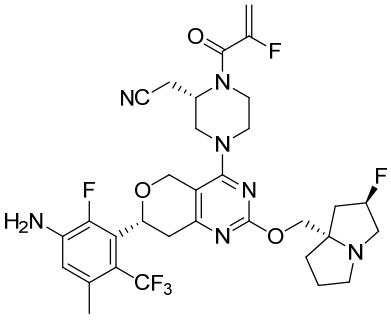
wherein the compound is selected from

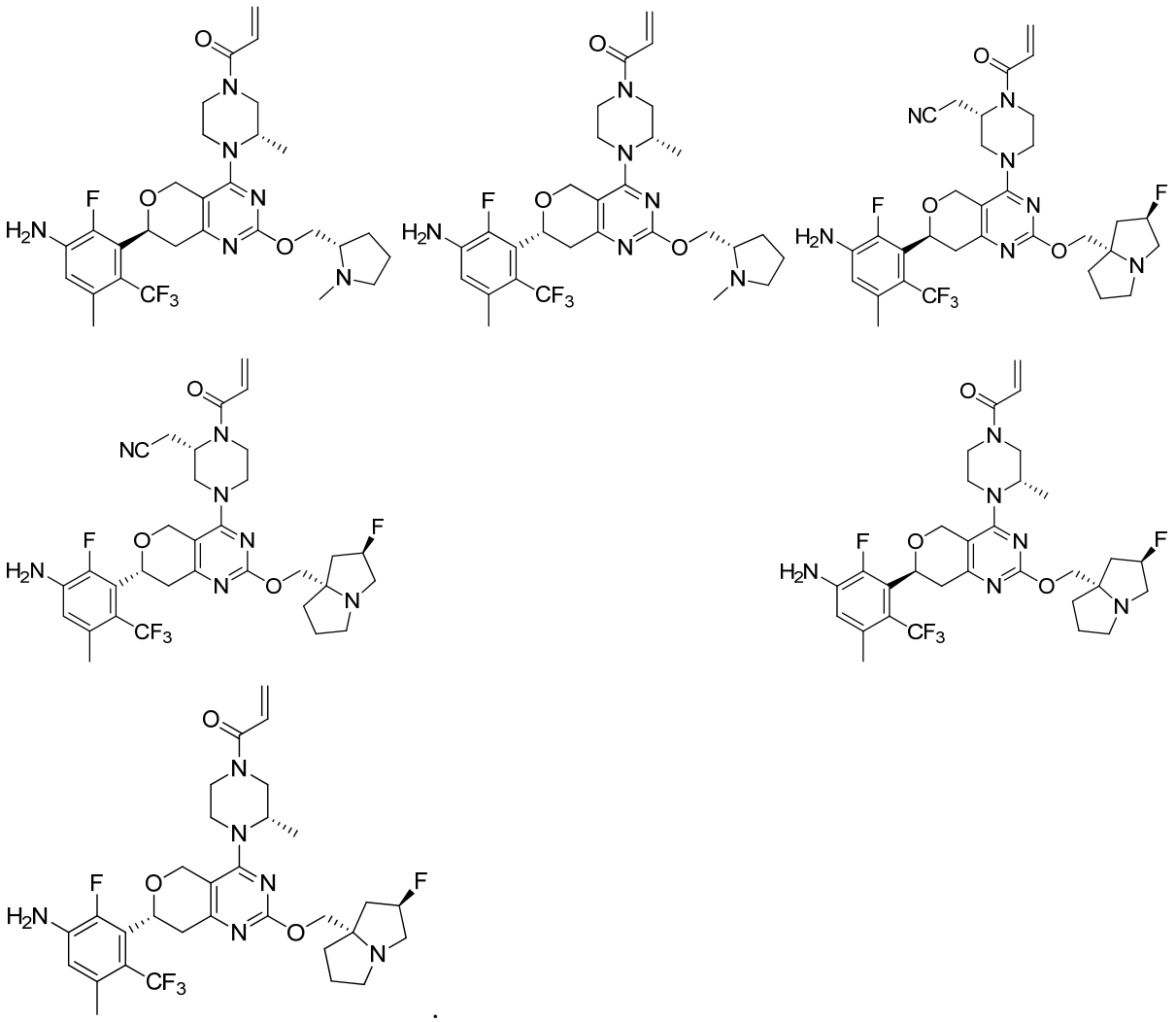


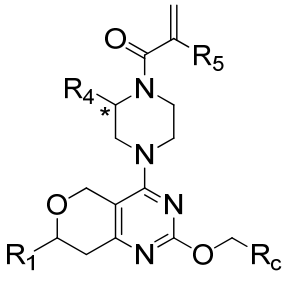
21. The compound of claim 20, or a pharmaceutically acceptable salt thereofalternatively, wherein the compound is selected from

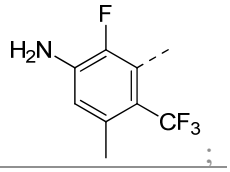


16. A compound, or a pharmaceutically acceptable salt thereof, wherein the compound is selected from



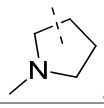
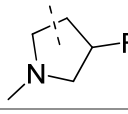
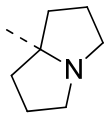
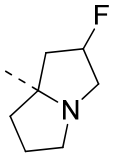
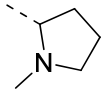
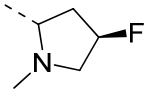
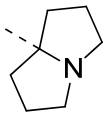
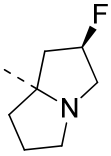
(P-1)

wherein

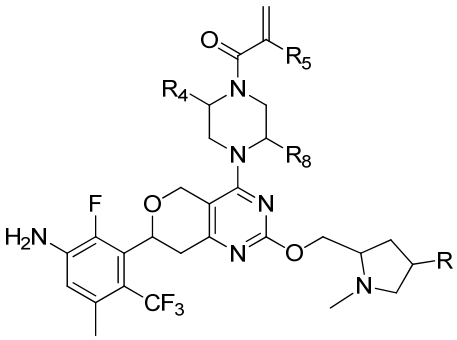
R_1 is ;

R_4 is CH_2CN, which exists in the form of (S) single enantiomer or is enriched in (S) enantiomer;

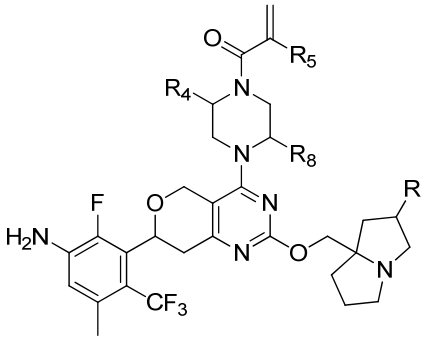
R_5 is selected from H, F, Cl, Br, I, and C_{1-3} alkyl, wherein the C_{1-3} alkyl is optionally substituted with 1, 2 or 3 F;

R_c is selected from , , , and , alternatively, is selected from , , , and .

17. A compound, or a pharmaceutically acceptable salt thereof, wherein the compound is selected from



(IV-1)



(IV-2)

wherein

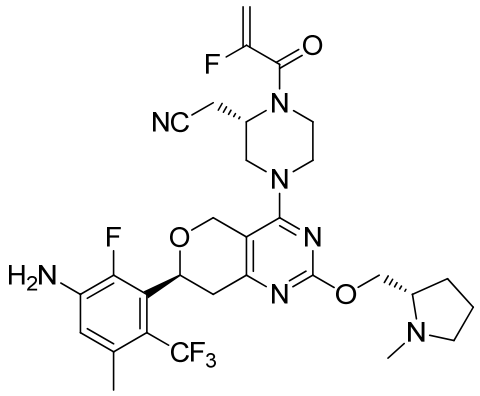
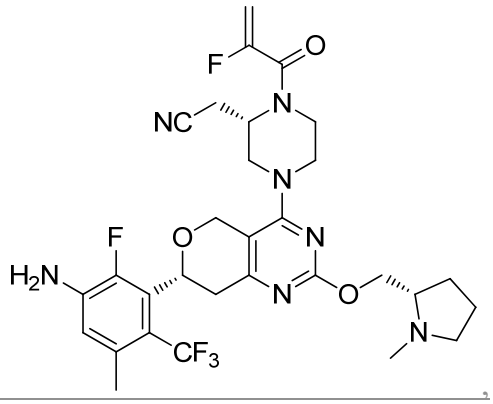
R_4 is selected from H, CH_3 and CH_2CN, which exists in the form of (R) single enantiomer or is enriched in (R) enantiomer;

R_8 is selected from H and CH_3, which exists in the form of (S) single enantiomer or is enriched in (S) enantiomer;

R_5 is selected from H, F, Cl, Br, I, and C_{1-3} alkyl, wherein the C_{1-3} alkyl is optionally substituted with 1, 2 or 3 F;

R is selected from H, F, Cl, Br, and C_{1-3} alkyl.

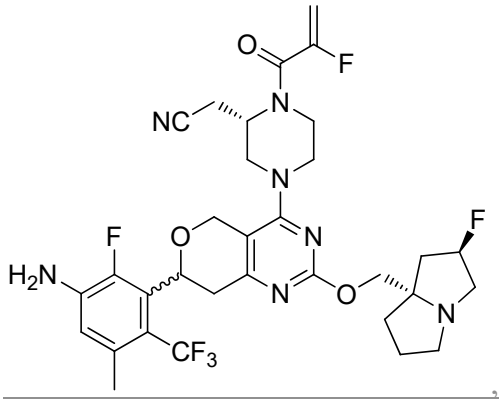
18. A compound, which is:

or ,

or a pharmaceutically acceptable salt thereof.

19. A compound, which is:



,

or a pharmaceutically acceptable salt thereof.

~~22~~20. A pharmaceutical composition, comprising~~Use of~~ the compound according to any one of claims 1 to ~~21~~ 19 or a pharmaceutically acceptable salt thereof ~~in the manufacture of a medicament for treating KRAS-related diseases~~.