(12) **Translation of European patent specification**

(11) **NO/EP 3524603 B1**

(19) NO

NORWAY

(51) Int Cl.

C07D 471/04 (2006.01)
A61K 31/436 (2006.01)
A61K 31/4365 (2006.01)
A61K 31/437 (2006.01)
A61K 31/4375 (2006.01)
A61K 31/445 (2006.01)
A61K 31/497 (2006.01)
A61K 31/505 (2006.01)
A61K 31/506 (2006.01)
A61K 31/517 (2006.01)
A61K 31/519 (2006.01)
A61K 31/535 (2006.01)
A61K 31/5355 (2006.01)
A61K 31/537 (2006.01)
A61P 35/00 (2006.01)
C07D 491/044 (2006.01)
C07D 491/107 (2006.01)
C07D 495/04 (2006.01)
C07D 498/08 (2006.01)
C07D 513/04 (2006.01)

Norwegian Industrial Property Office

(45)	Translation Published	2022.08.15
(80)	Date of The European Patent Office Publication of the Granted Patent	2022.06.08
(86)	European Application Nr.	17883905.6
(86)	European Filing Date	2017.12.14
(87)	The European Application's Publication Date	2019.08.14
(30)	Priority	2016.12.19, CN, 201611177188 2017.06.15, CN, 201710453749
(84)	Designated Contracting States:	AL; AT; BE; BG; CH; CY; CZ; DE; DK; EE; ES; FI; FR; GB; GR; HR; HU; IE; IS; IT; LI; LT; LU; LV; MC; MK; MT; NL; NO; PL; PT; RO; RS; SE; SI; SK; SM; TR
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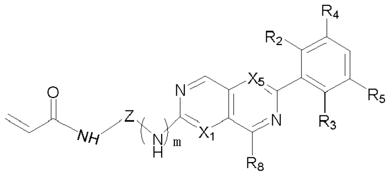
(54)	Title	**FGFR4 INHIBITOR, PREPARATION METHOD THEREFOR AND PHARMACEUTICAL USE THEREOF**
(56)	References Cited:	WO-A1-2015/061572, CN-A-104 540 809, WO-A1-2015/108992, WO-A2-2014/011900, WO-A1-2016/115412, CN-A-105 658 642, WO-A1-2014/144737, CN-A- 105 307 657 QIUMENG ZHANG ET AL: "Design, Synthesis and Anti-Proliferative Activities of 2,6-Substituted Thieno[3,2-d]pyrimidine Derivatives Containing Electrophilic Warheads", MOLECULES, vol. 22, no. 5, 12 May 2017 (2017-05-12), pages 1-16, XP055594292, DOI: 10.3390/molecules22050788

Enclosed is a translation of the patent claims in Norwegian. Please note that as per the Norwegian Patents Acts, section 66i the patent will receive protection in Norway only as far as there is agreement between the translation and the language of the application/patent granted at the EPO. In matters concerning the validity of the patent, language of the application/patent granted at the EPO will be used as the basis for the decision. The patent documents published by the EPO are available through Espacenet (http://worldwide.espacenet.com) or via the search engine on our website here: https://search.patentstyret.no/

Patentkrav

1. Forbindelse av formel (IVa-1), en stereoisomer eller farmasøytisk akseptabelt salt derav:

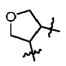
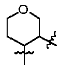


(IVa-1)

hvori X_5 er -CH- eller N;

m er 1 eller 0;

Z er

 eller ;

R_2, R_3, R_4 og R_5 er hver uavhengig valgt fra gruppen som består av H, deuterium, Cl, F, hydroksyl, metyl, isopropyl, syklopropyl, 3-oksasyklobutyl, trifluormetyl, trideuterometyl og -O-R_{11},

eller R_2 og R_4, R_3 og R_5 er tatt sammen med de direkte festede karbonatomene for å danne en 5–8-leddet heterosyklyl, heteroatomet er N eller O;

R_8 er valgt fra gruppen som består av H, deuterium, halogen, cyano, nitro, azido, C_{1-8}alkyl, C_{2-8}alkenyl, C_{2-8}alkynyl, C_{3-8}sykoalkyl, 3–10-leddet heterosyklyl, C_{5-10}aryl, 5–10-leddet heteroaryl, -C_{0-8}-S(O)$_r$$R_{10}$, -$C_{0-8}$-P(O)($R_{10}$)$_2$, -$C_{0-8}$-O-$R_{11}$, -$C_{0-8}$-C(O)O$R_{11}$, -$C_{0-8}$-C(O)$R_{12}$, -$C_{0-8}$-O-C(O)$R_{12}$, -$C_{0-8}$-N$R_{13}$$R_{14}$, -$C_{0-8}$-C(O)N$R_{13}$$R_{14}$, -$C_{0-8}$-N($R_{13}$)-C(O)$R_{12}$ og -C_{0-8}-N(R_{13})-C(O)OR_{11}, gruppene ovenfor er ytterligere eventuelt substituert med én eller flere substituenter valgt fra gruppen som består av deuterium, halogen, cyano, nitro, azido, C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, C_{1-4}halogenalkyl, C_{3-6}sykloalkyl, 3–8-leddet heterosyklyl, C_{5-8}aryl, 5–8-leddet heteroaryl, -C_{0-4}-S(O)$_r$$R_{10}$, -$C_{0-4}$-O-$R_{11}$, -$C_{0-4}$-C(O)O$R_{11}$, -$C_{0-4}$-C(O)$R_{12}$, -$C_{0-4}$-O-C(O)$R_{12}$, -$C_{0-4}$-N$R_{13}$$R_{14}$, -$C_{0-4}$-C(O)N$R_{13}$$R_{14}$, -$C_{0-4}$-N($R_{13}$)-C(O)$R_{12}$ og -C_{0-4}-N(R_{13})-C(O)OR_{11}, gruppene ovenfor er ytterligere mer eventuelt substituert med én eller flere substituenter valgt fra gruppen som består av deuterium, halogen, cyano, nitro, azido, C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, C_{1-4}halogenalkyl, C_{3-6}sykloalkyl, 3–8-leddet heterosyklyl, C_{5-8}aryl, 5–8-leddet heteroaryl, -C_{0-4}-S(O)$_r$$R_{10}$, -$C_{0-4}$-O-$R_{11}$, -$C_{0-4}$-

$C(O)OR_{11}$, $-C_{0\text{-}4}\text{-}C(O)R_{12}$, $-C_{0\text{-}4}\text{-}O\text{-}C(O)R_{12}$, $-C_{0\text{-}4}\text{-}NR_{13}R_{14}$, $-C_{0\text{-}4}\text{-}C(O)NR_{13}R_{14}$, $-C_{0\text{-}4}\text{-}N(R_{13})\text{-}C(0)R_{12}$ og $-C_{0\text{-}4}\text{-}N(R_{13})\text{-}C(O)OR_{11}$;

X_1 er -CH- eller N;

R_{10} er valgt fra gruppen som består av H, deuterium, $C_{1\text{-}8}$alkyl, $C_{2\text{-}8}$alkenyl, $C_{3\text{-}8}$sykloalkyl, 3–10-leddet heterosyklyl, $C_{1\text{-}8}$halogenalkyl, $C_{5\text{-}10}$aryl, 5–10-leddet heteroaryl, amino, mono-$C_{1\text{-}8}$alkylamino, di-$C_{1\text{-}8}$alkylamino og $C_{1\text{-}8}$alkanoylamino;

R_{11} er valgt fra gruppen som består av H, deuterium, $C_{1\text{-}8}$alkyl, $C_{2\text{-}8}$alkenyl, $C_{2\text{-}8}$alkynyl, $C_{3\text{-}8}$sykloalkyl, 3–10-leddet heterosyklyl, $C_{5\text{-}10}$aryl og 5–10-leddet heteroaryl, gruppene ovenfor er ytterligere eventuelt substituert med én eller flere substituenter valgt fra gruppen som består av deuterium, halogen, cyano, $C_{1\text{-}8}$alkyl, $C_{1\text{-}8}$alkoksy, $C_{1\text{-}8}$alkyltio, $C_{3\text{-}8}$sykloalkyl, 3–10-leddet heterosyklyl, $C_{5\text{-}10}$aryl, 5–10-leddet heteroaryl, $C_{1\text{-}8}$alkylsulfonyl, $C_{1\text{-}8}$alkylsulfonylamino, amino, mono-$C_{1\text{-}8}$alkylamino, di-$C_{1\text{-}8}$alkylamino, =O eller hydroksyl;

R_{12} er valgt fra gruppen som består av H, deuterium, $C_{1\text{-}8}$alkyl, $C_{2\text{-}8}$alkenyl, $C_{2\text{-}8}$alkynyl, $C_{1\text{-}8}$alkoksy, $C_{3\text{-}8}$sykloalkyl, $C_{3\text{-}8}$sykloalkyloksy, 3–10-leddet heterosyklyl, 3–10-leddet heterosyklyloksy, $C_{5\text{-}10}$aryl, 5–10-leddet heteroaryl, $C_{5\text{-}10}$aryloksy og 5–10-leddet heteroaryloksy, gruppene ovenfor er eventuelt ytterligere substituert med én eller flere substituenter valgt fra gruppen som består av deuterium, halogen, cyano, $C_{1\text{-}8}$alkyl, $C_{1\text{-}8}$alkoksy, $C_{1\text{-}8}$alkyltio, $C_{3\text{-}8}$sykloalkyl, 3–10-leddet heterosyklyl, $C_{5\text{-}10}$aryl, 5–10-leddet heteroaryl, $C_{1\text{-}8}$alkylsulfonyl, $C_{1\text{-}8}$alkylsulfonylamino, amino, mono-$C_{1\text{-}8}$alkylamino, di-$C_{1\text{-}8}$alkylamino, =O eller hydroksyl;

R_{13} og R_{14} er hver uavhengig valgt fra gruppen som består av H, deuterium, $C_{1\text{-}8}$alkyl, $C_{2\text{-}8}$alkenyl, $C_{2\text{-}8}$alkynyl, $C_{3\text{-}8}$sykloalkyl, 3–10-leddet heterosyklyl, $C_{5\text{-}10}$aryl, 5–10-leddet heteroaryl, $C_{1\text{-}8}$alkylsulfonyl og $C_{1\text{-}8}$alkanoyl eller R_{13} og R_{14} tas sammen med det direkte festede nitrogenatomet for å danne et 4–10-leddet heterosyklyl,

gruppene ovenfor er ytterligere eventuelt substituert med én eller flere substituenter valgt fra gruppen som består av deuterium, halogen, $C_{1\text{-}8}$alkyl, $C_{1\text{-}8}$alkoksy, $C_{1\text{-}8}$alkyltio, $C_{3\text{-}8}$sykloalkyl, 3–10-leddet heterosyklyl, $C_{5\text{-}10}$aryl, 5–10-leddet heteroaryl, $C_{1\text{-}8}$alkylsulfonyl, $C_{1\text{-}8}$alkylsulfonylamino, amino, mono-$C_{1\text{-}8}$alkylamino, di-$C_{1\text{-}8}$alkylamino, =O eller hydroksyl;

r er 0, 1 eller 2

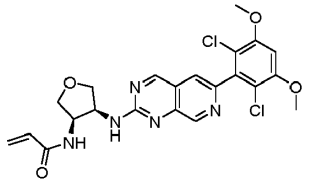
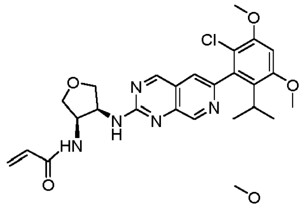
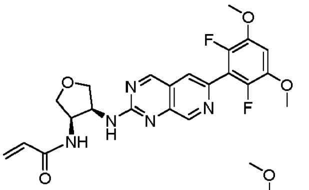
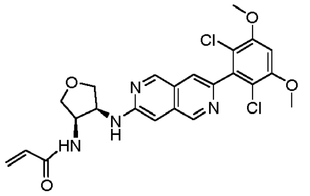
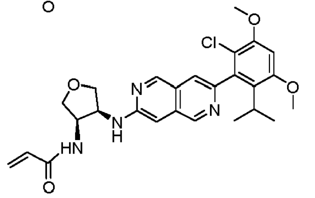
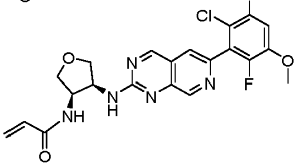
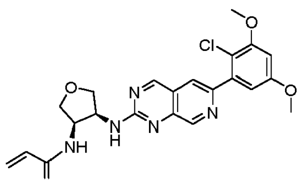
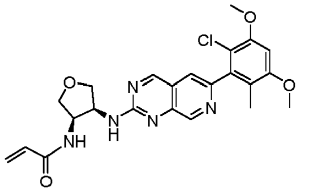
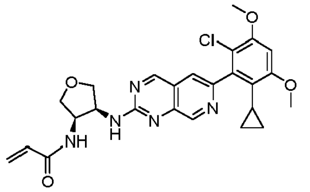
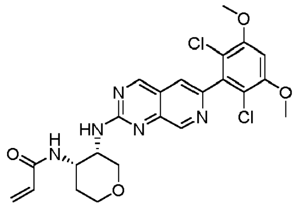
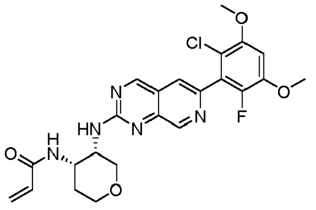
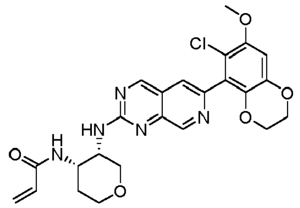
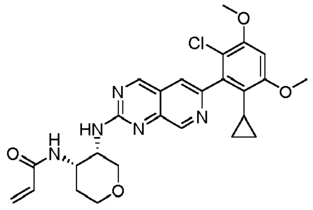
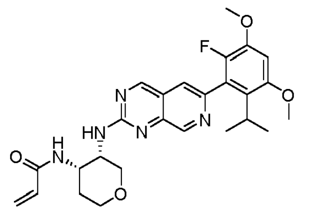
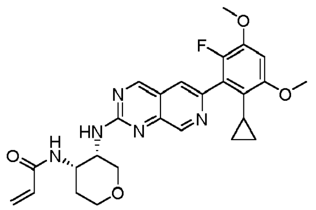
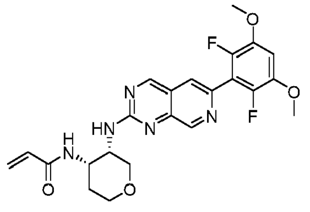
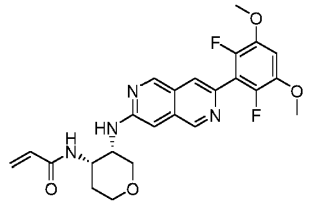
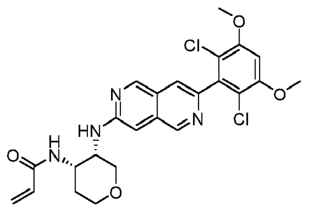
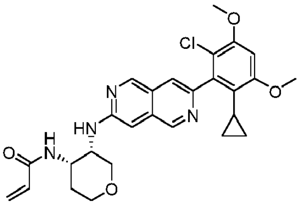
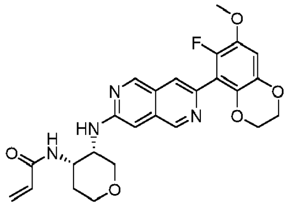
hvori sykloalkyl betyr en mettet eller delvis umettet monosyklisk eller polysyklisk hydrokarbonsubstituent.

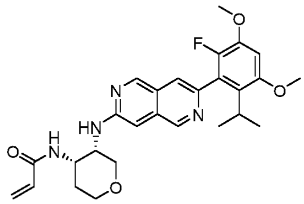
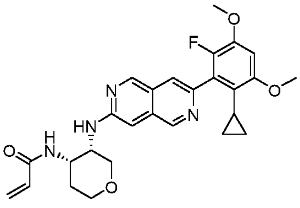
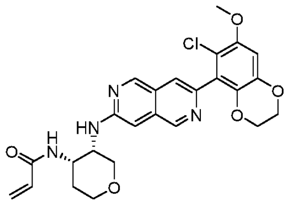
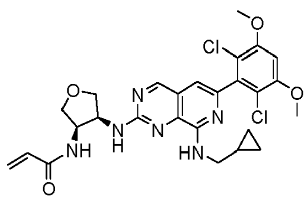
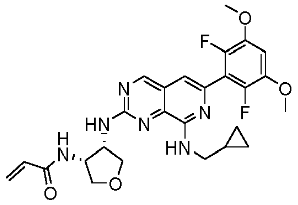
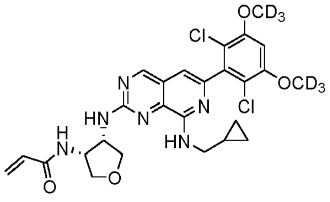
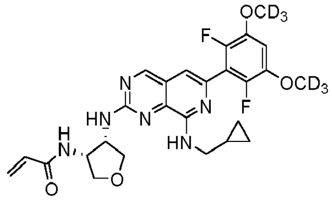
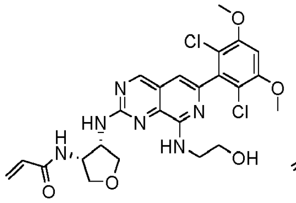
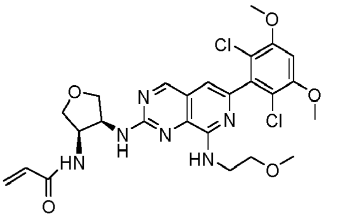
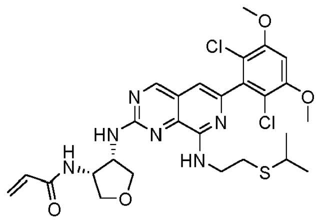
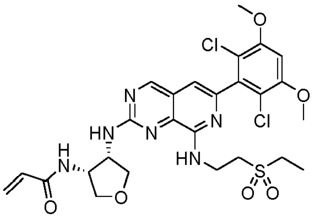
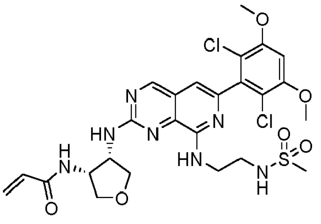
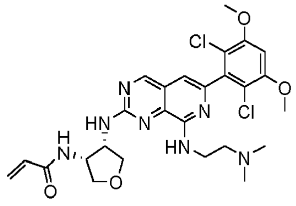
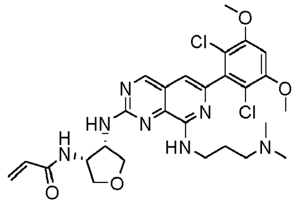
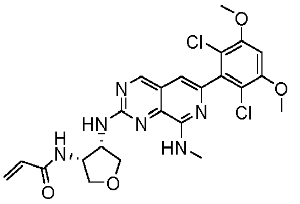
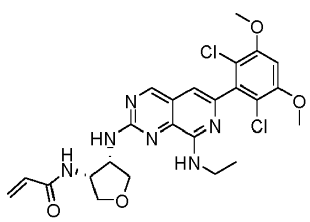
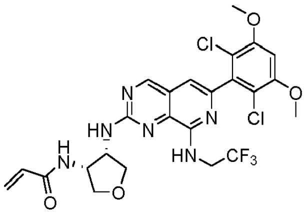
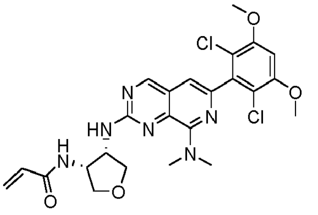
2. Forbindelsen av formel (IVa-1), stereoisomeren eller det farmasøytisk akseptable saltet derav ifølge krav 1, hvori,

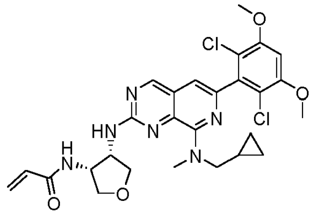
R_8 er valgt fra gruppen som består av H, deuterium, halogen, cyano, C_{1-8}alkyl, C_{2-8}alkenyl, C_{2-8}alkynyl, C_{3-8}sykloalkyl, 3–10-leddet heterosyklyl, C_{5-10}aryl, 5–10-leddet heteroaryl, $-C_{0-8}-O-R_{11}$, $-C_{0-8}-NR_{13}R_{14}$, $-C_{0-8}-N(R_{13})-C(O)R_{12}$ og $-C_{0-8}-N(R_{13})-C(O)\ OR_{11}$,

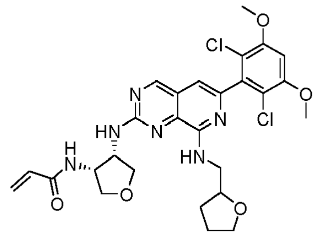
gruppene ovenfor er ytterligere eventuelt substituert med én eller flere substituenter valgt fra gruppen som består av deuterium, halogen, cyano, nitro, azido, C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, C_{1-4}halogenalkyl, C_{3-6}sykloalkyl, 3–8-leddet heterosyklyl, C_{5-8}aryl, 5–8-leddet heteroaryl, $-C_{0-4}-S(O)_rR_{10}$, $-C_{0-4}-O-R_{11}$, $-C_{0-4}-C(O)OR_{11}$, $-C_{0-4}-C(O)R_{12}$, $-C_{0-4}-O-C\ (O)R_{12}$, $-C_{0-4}-NR_{13}R_{14}$, $-C_{0-4}-C(O)NR_{13}R_{14}$, $-C_{0-4}-N(R_{13})-C(O)R_{12}$ og $-C_{0-4}-N(R_{13})-C(O)OR_{11}$, gruppene ovenfor er ytterligere mer eventuelt substituert med én eller flere substituenter valgt fra gruppen som består av deuterium, halogen, cyano, nitro, azido, C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, C_{1-4}halogenalkyl, C_{3-6}sykloalkyl, 3–8-leddet heterosyklyl, C_{5-8}aryl, 5–8-leddet heteroaryl, $-C_{0-4}-S(O)_rR_{10}$, $-C_{0-4}-O-R_{11}$, $-C_{0-4}-C(O)OR_{11}$, $-C_{0-4}-C(O)R_{12}$, $-C_{0-4}-O-C(O)R_{12}$, $-C_{0-4}-NR_{13}R_{14}$, $-C_{0-4}-C(O)NR_{13}R_{14}$, $-C_{0-4}-N(R_{13})-C(O)R_{12}$ og $-C_{0-4}-N(R_{13})-C(O)OR_{11}$.

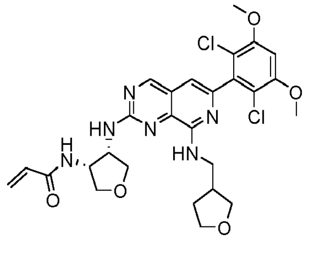
3. Forbindelsen av formel (IVa-1), stereoisomeren eller det farmasøytisk akseptable saltet derav ifølge krav 1 eller krav 2, hvori forbindelsen er valgt fra gruppen som består av:

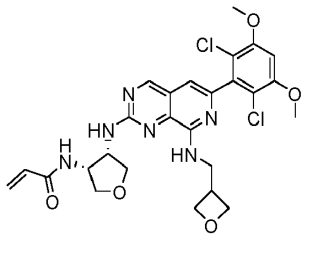





















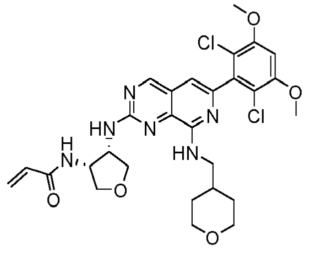



















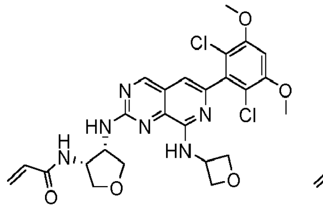


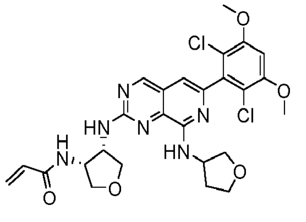


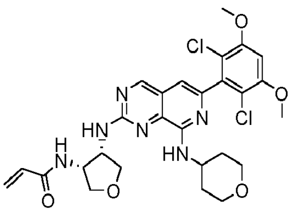


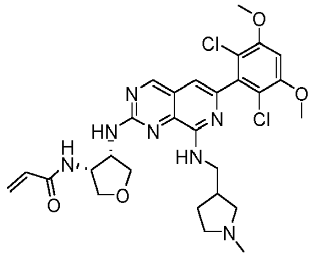


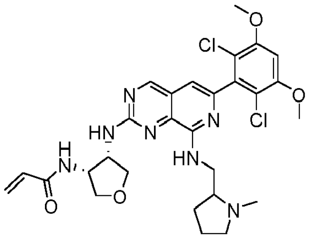


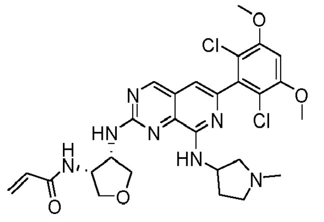


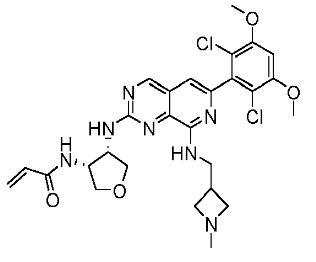


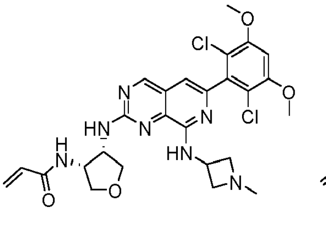


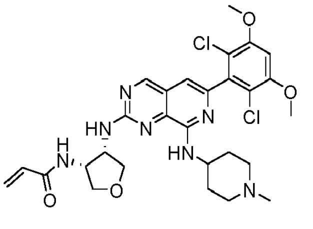


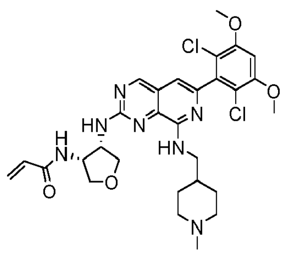


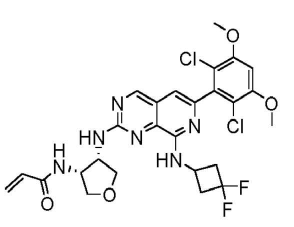


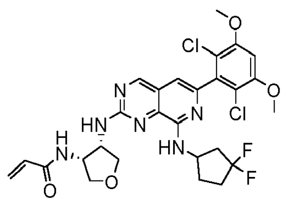


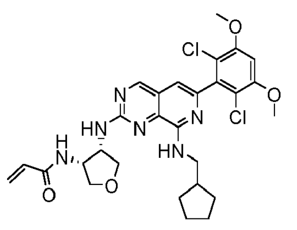


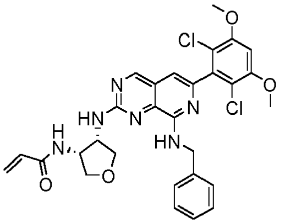


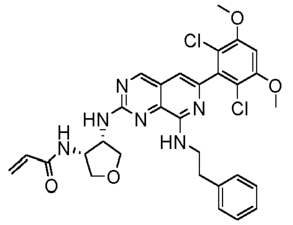


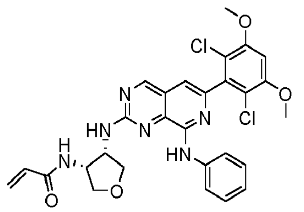


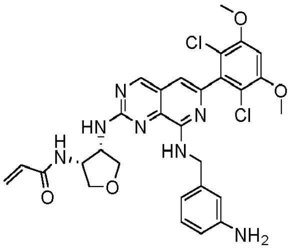


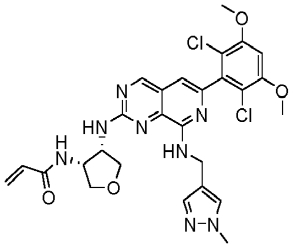


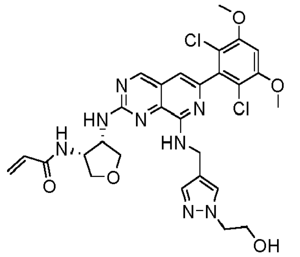


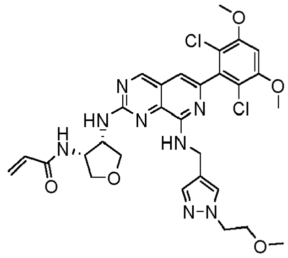


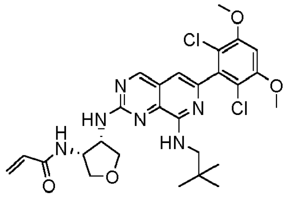


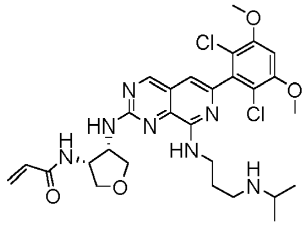


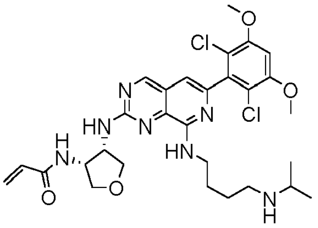


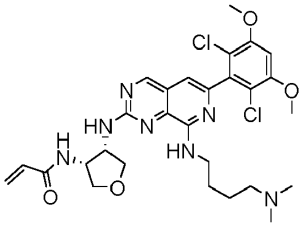


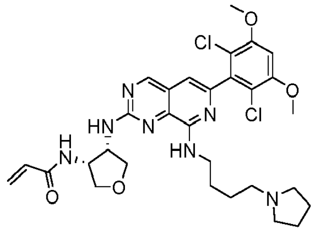


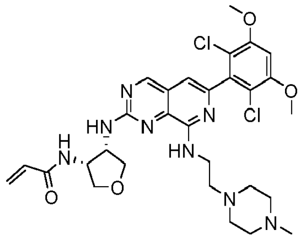


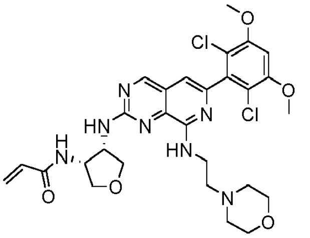


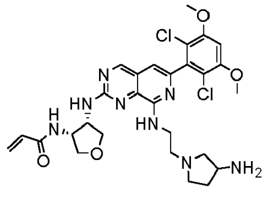


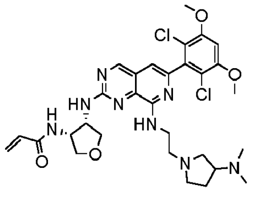


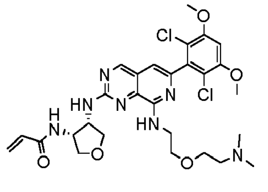


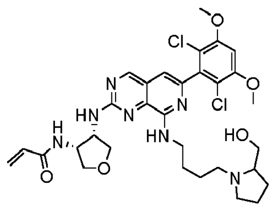


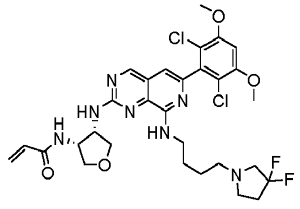


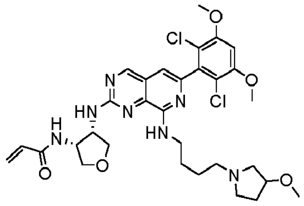


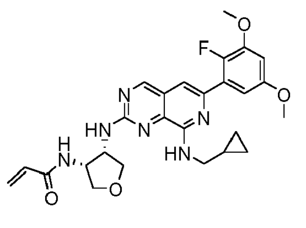


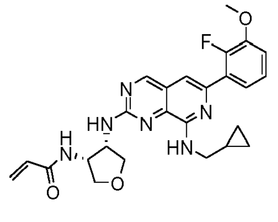


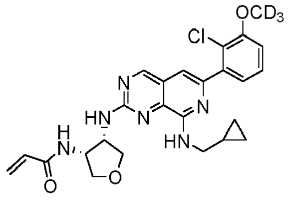


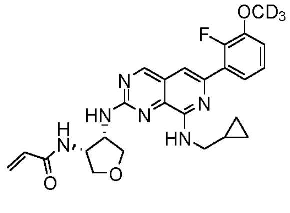


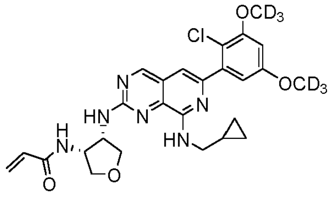


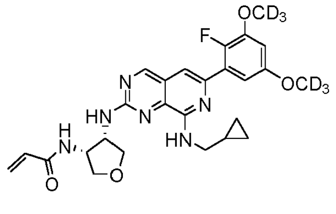


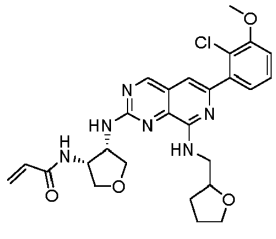


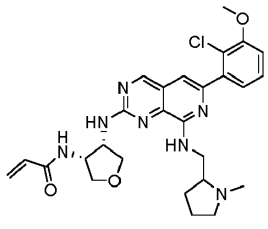


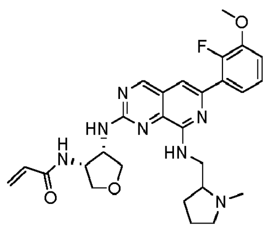


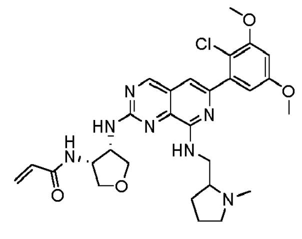


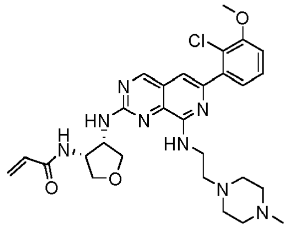


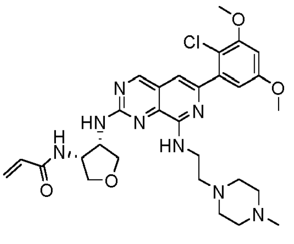


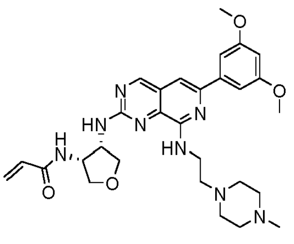


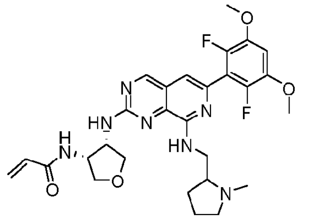
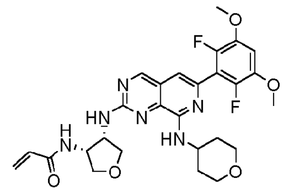
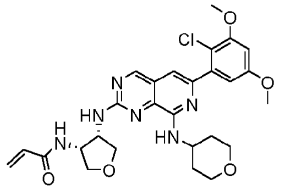
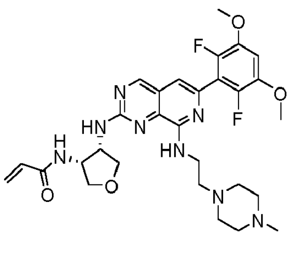
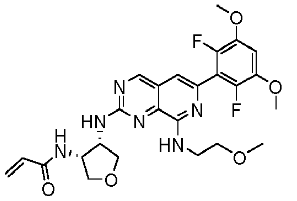
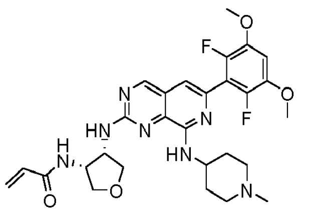
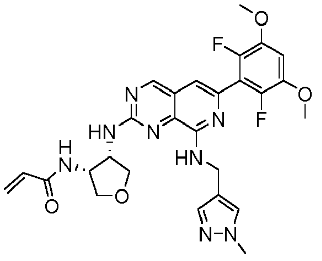
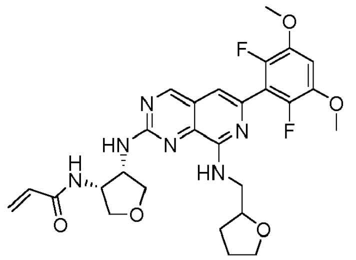
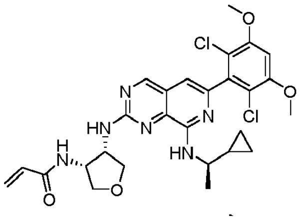
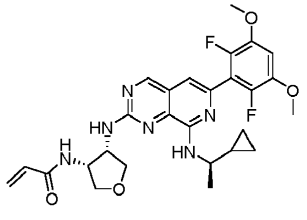
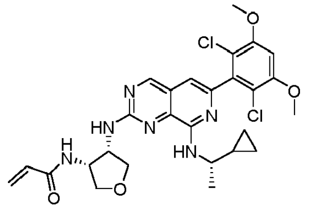
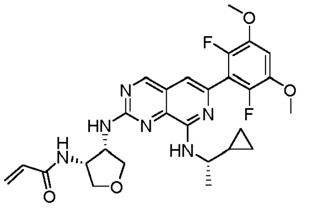
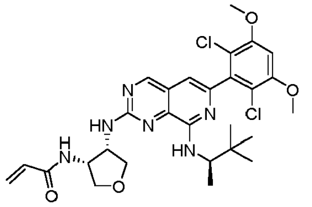
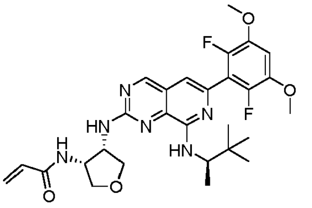
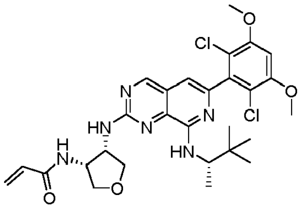
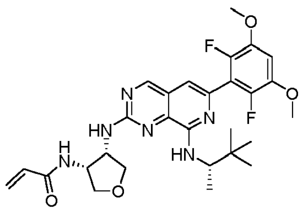


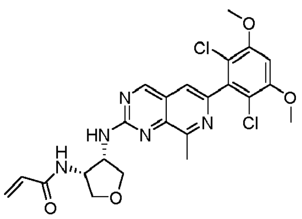
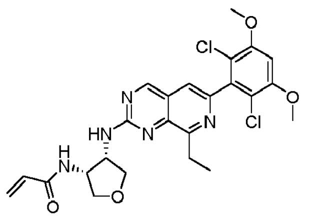
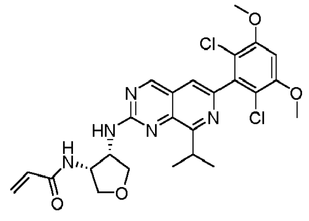


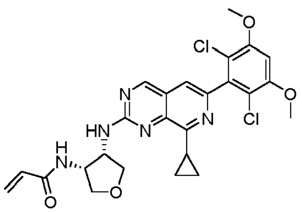
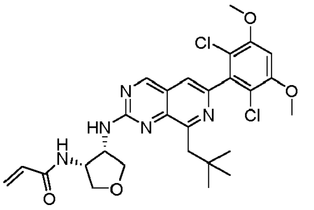
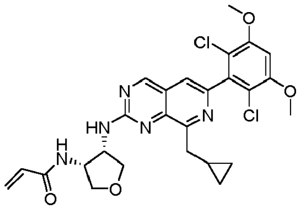


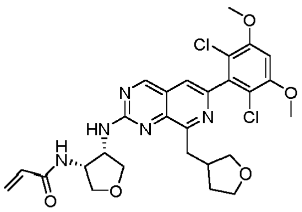
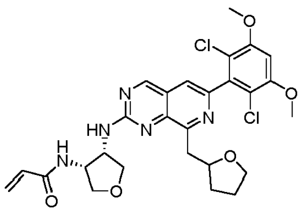
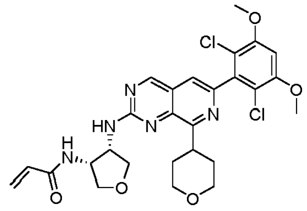


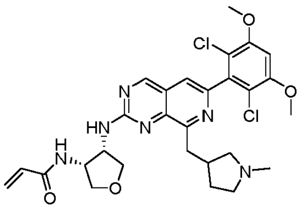
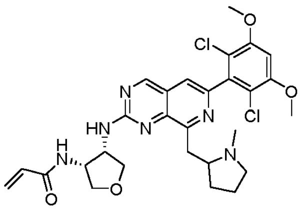
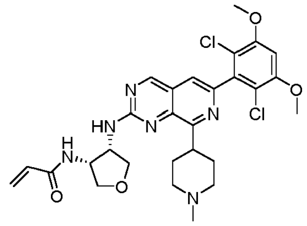


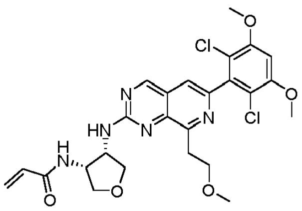
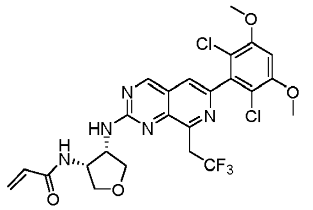
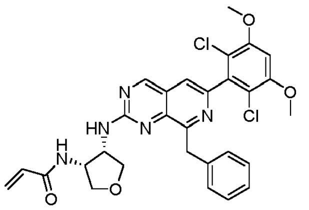

















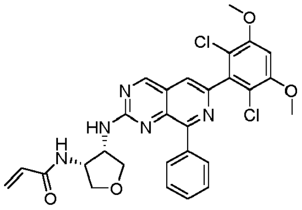
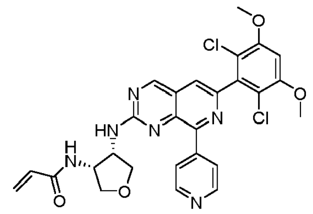
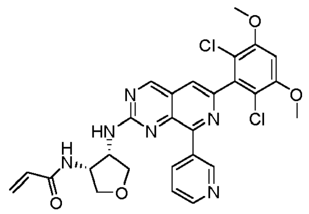




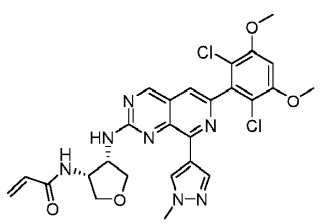
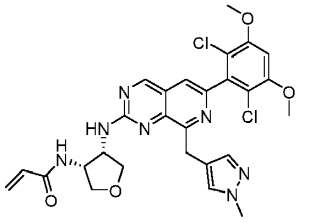
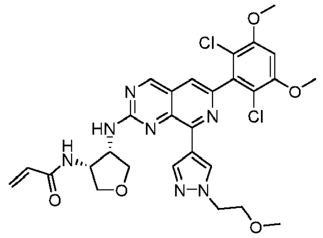
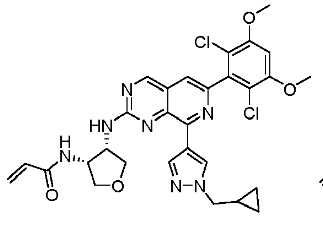
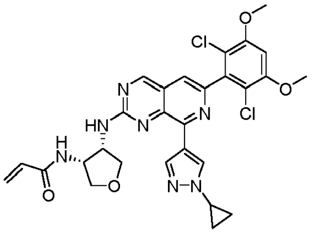
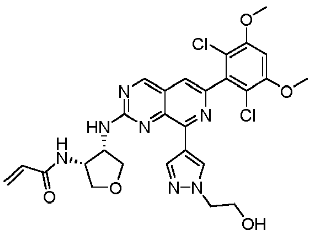
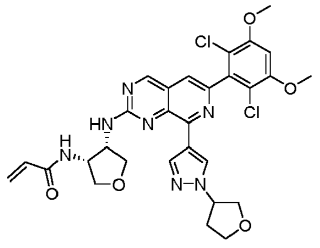
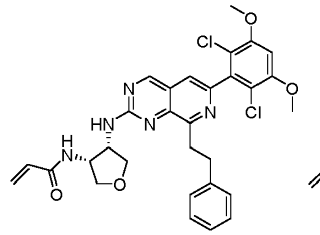
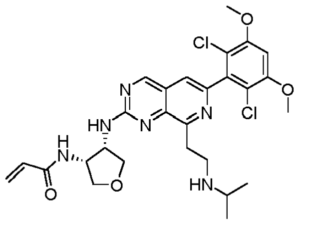
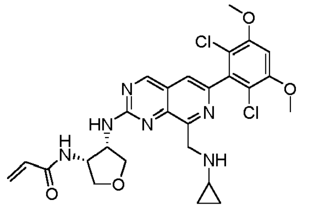
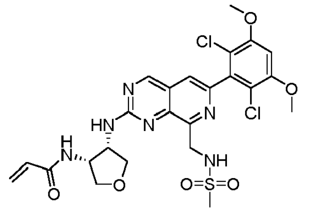
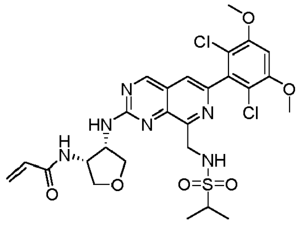
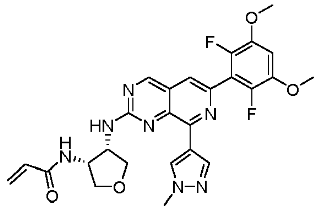
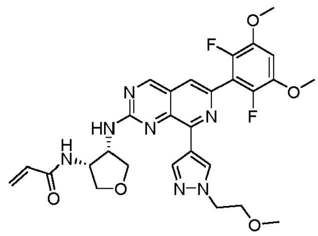
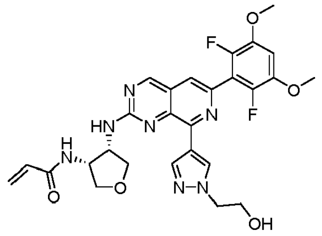
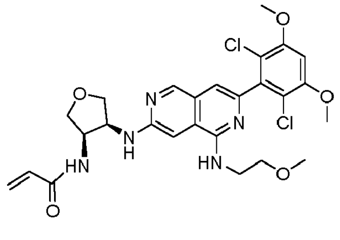
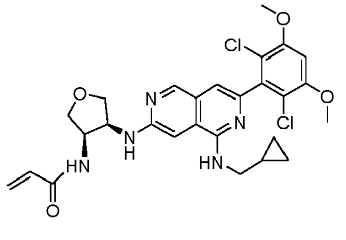




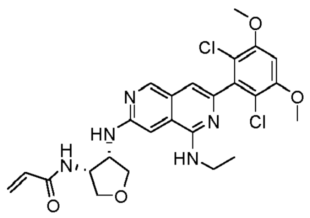
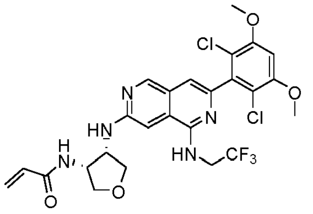
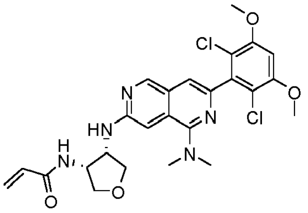




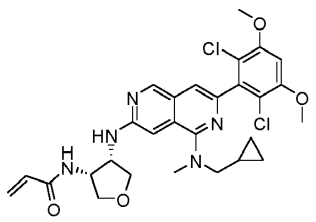
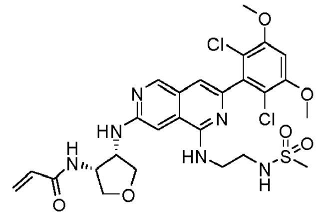
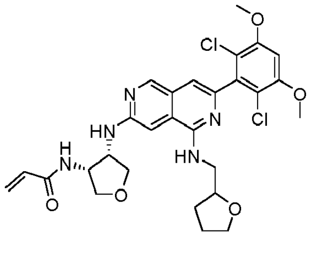




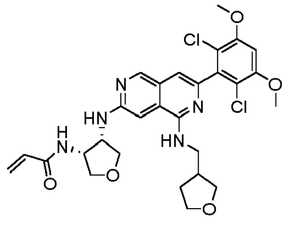
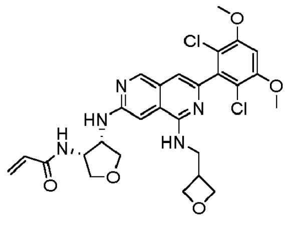
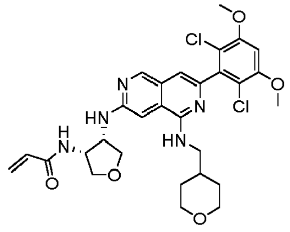




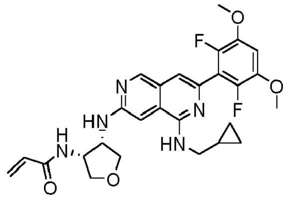
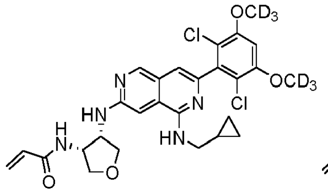
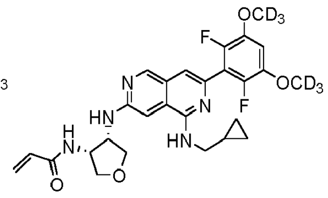




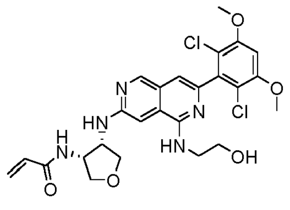
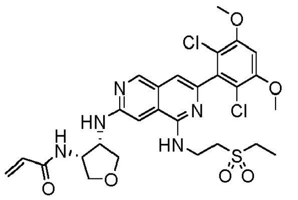
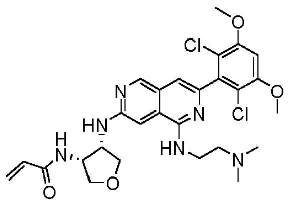


















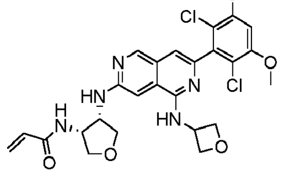
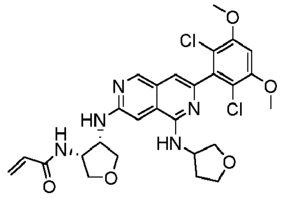
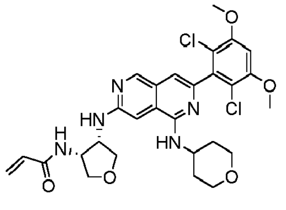




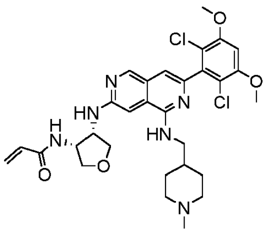




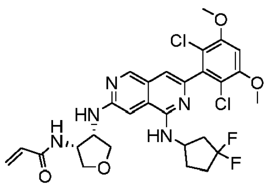




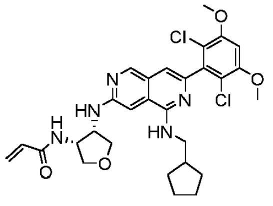




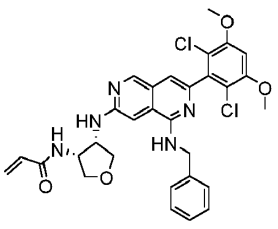




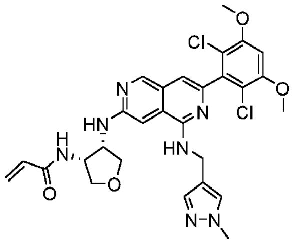




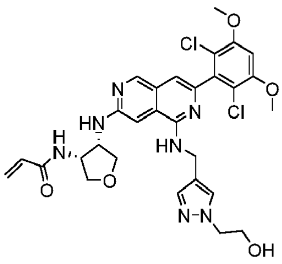


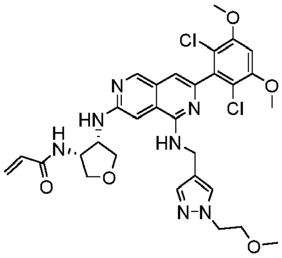


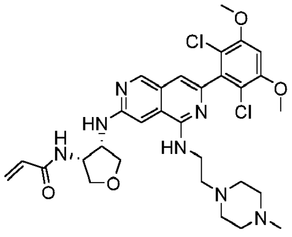


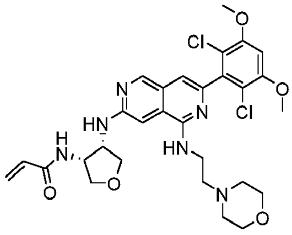


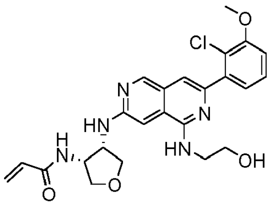


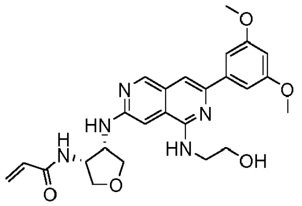


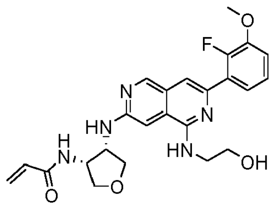


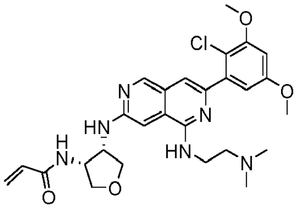


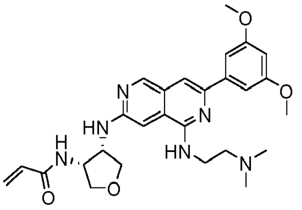


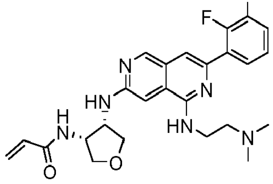


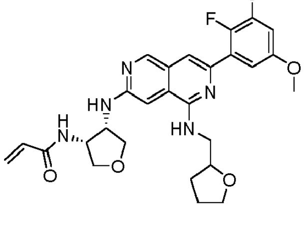


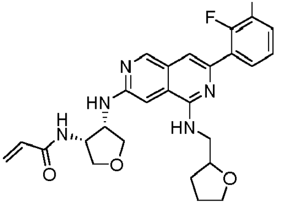


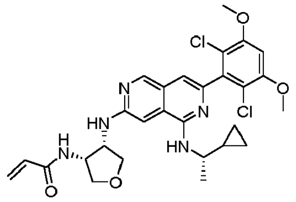








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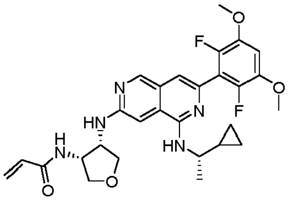
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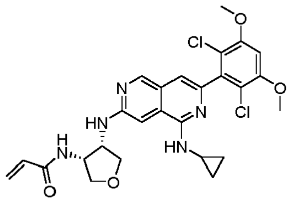
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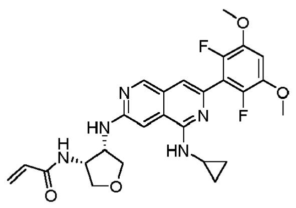
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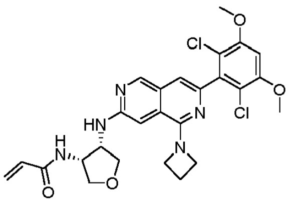
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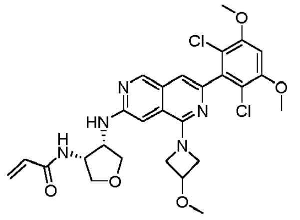
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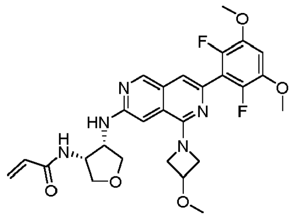
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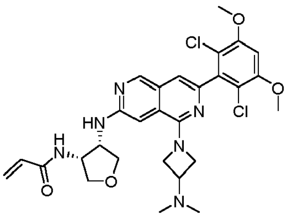
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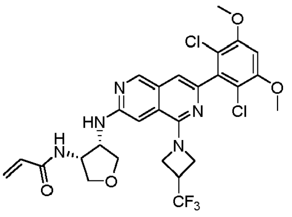
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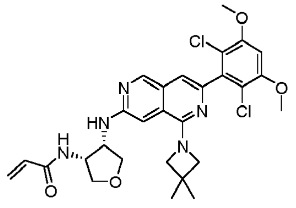
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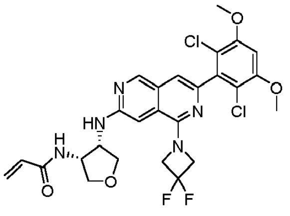
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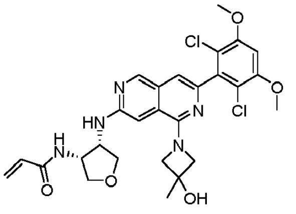
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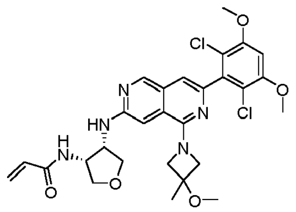
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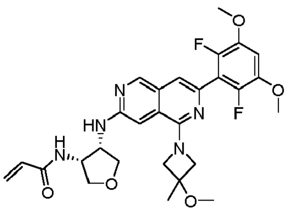
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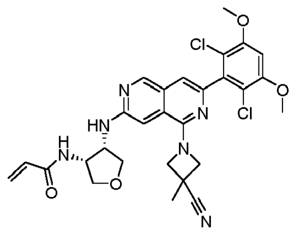
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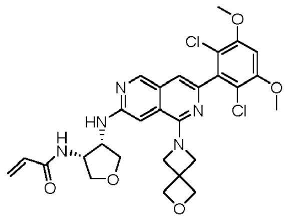
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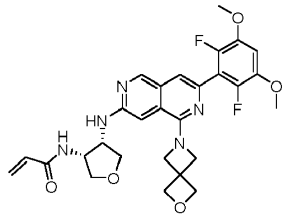
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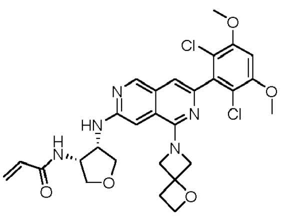
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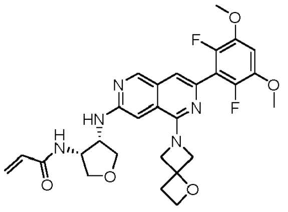

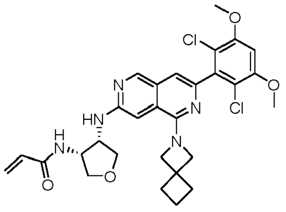

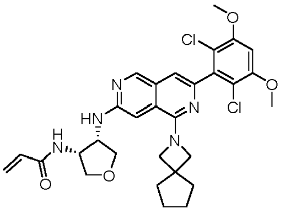

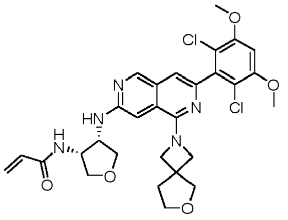

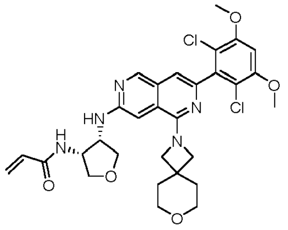

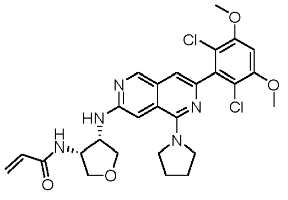

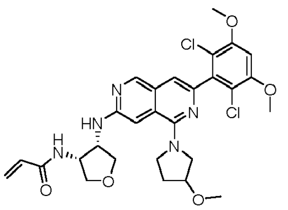

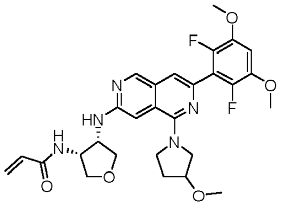

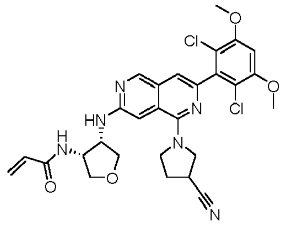

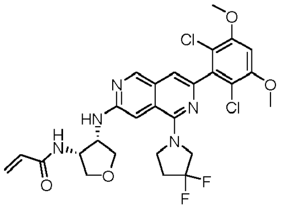

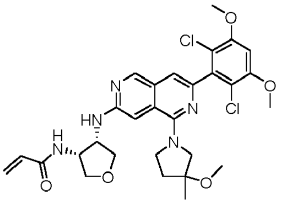

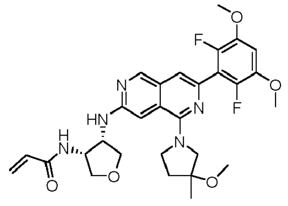

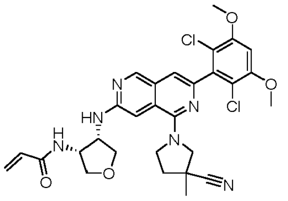

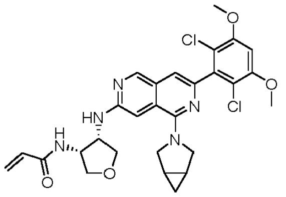

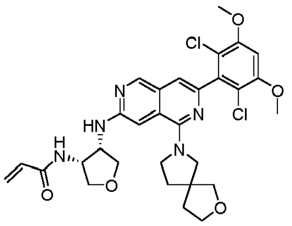

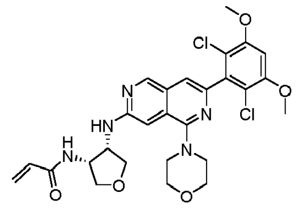

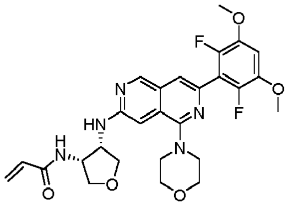

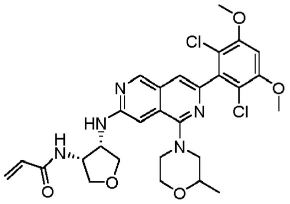
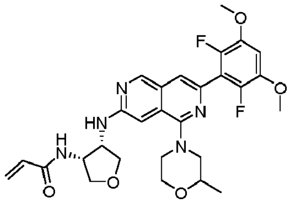
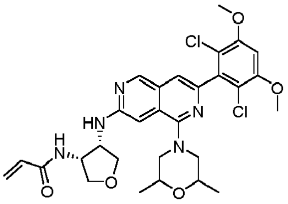
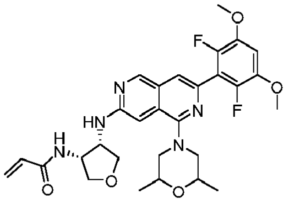
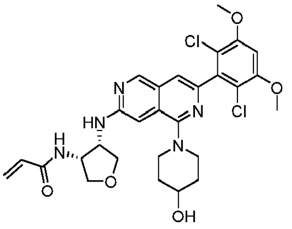
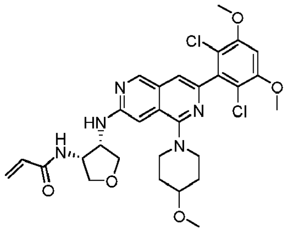
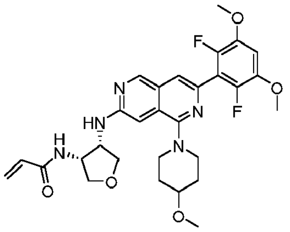
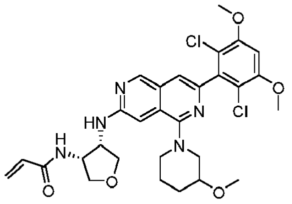
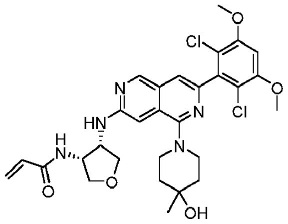
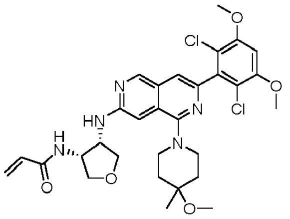
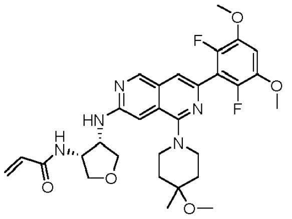
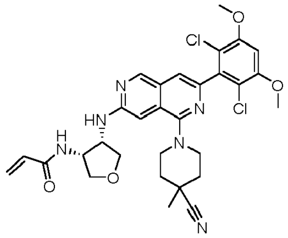
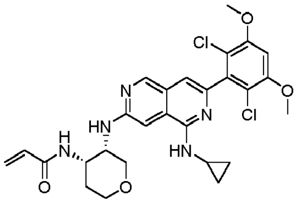
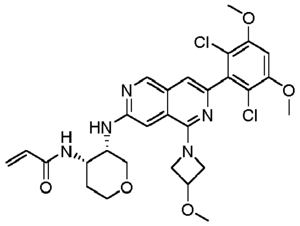
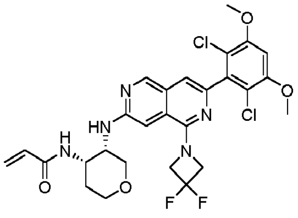
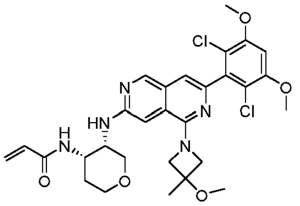
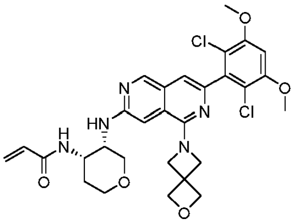
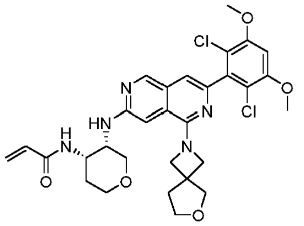

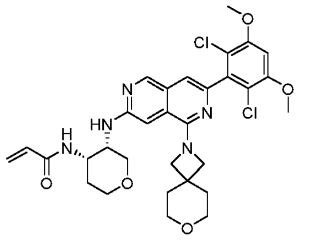
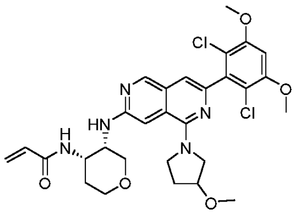
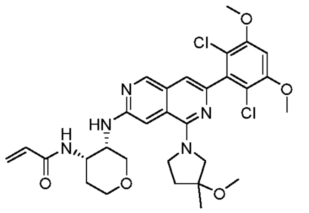
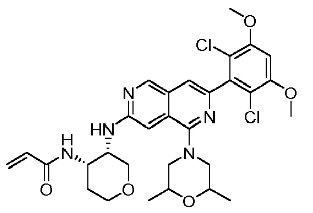
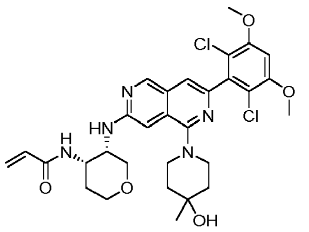
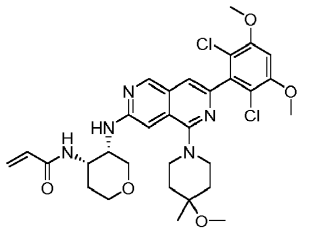
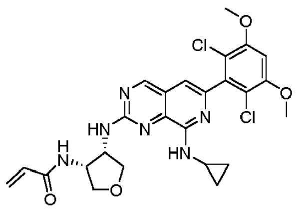
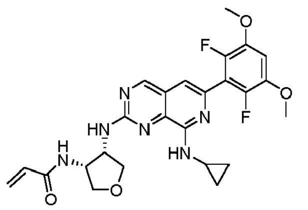
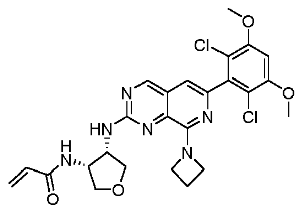
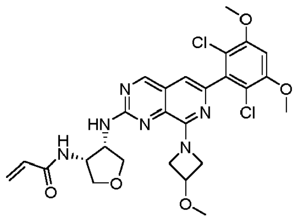
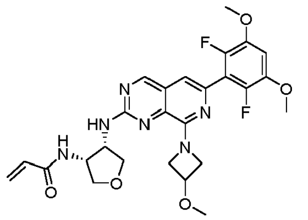
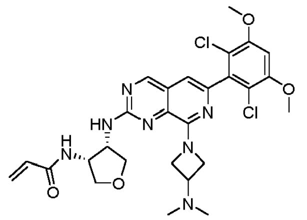
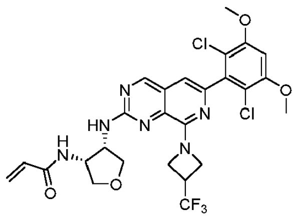
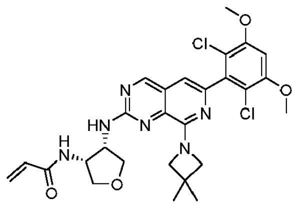
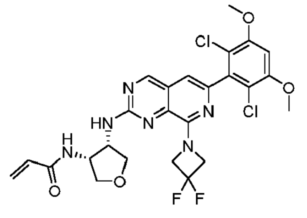
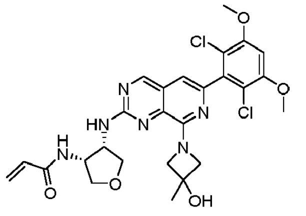
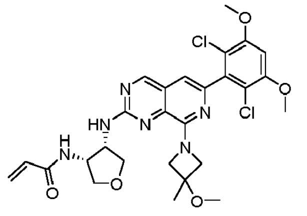
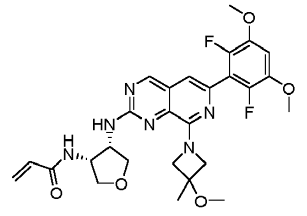

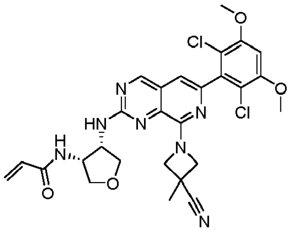

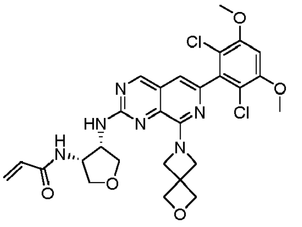

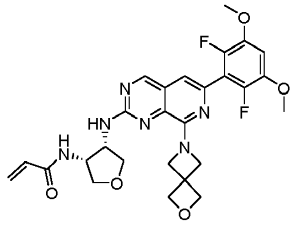

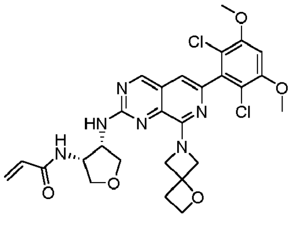

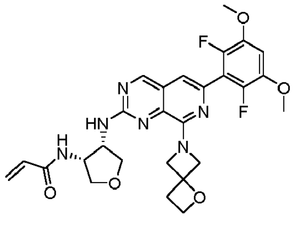

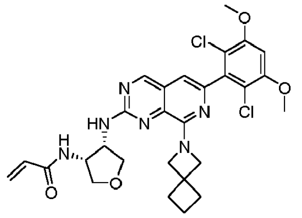

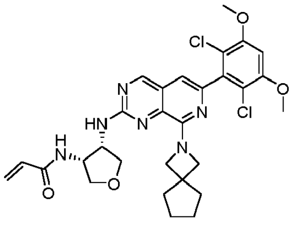

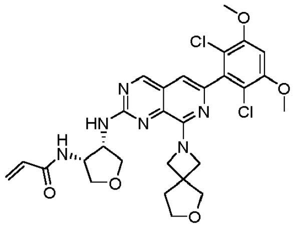

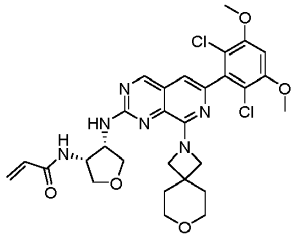

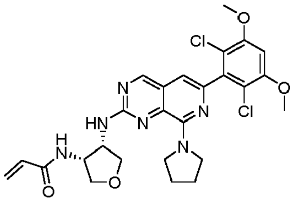

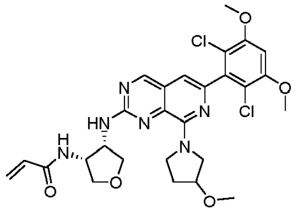

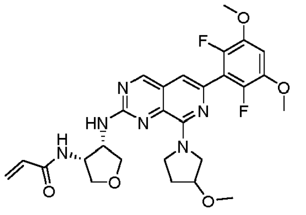

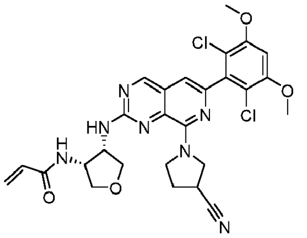

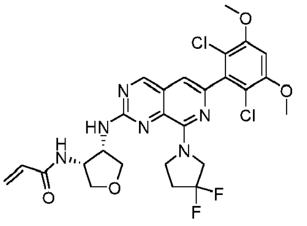

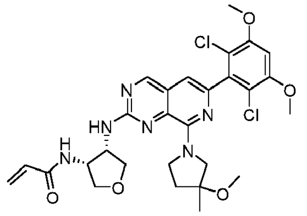

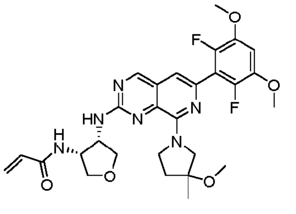

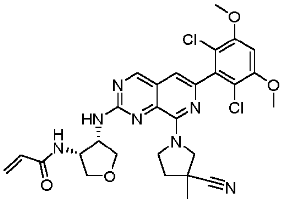

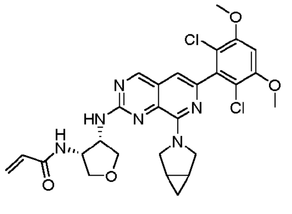

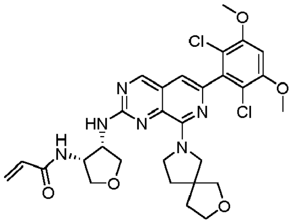

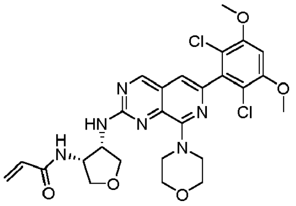

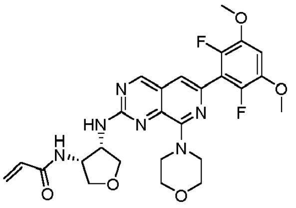

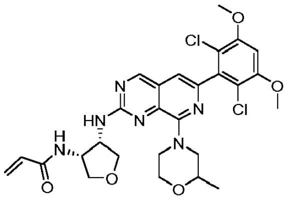

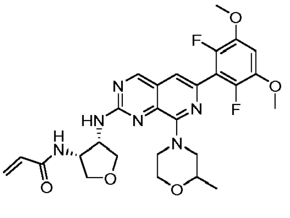

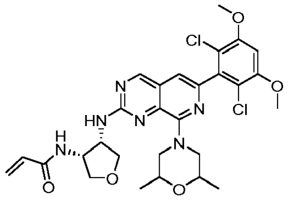

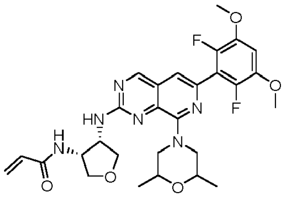

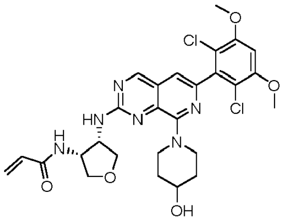

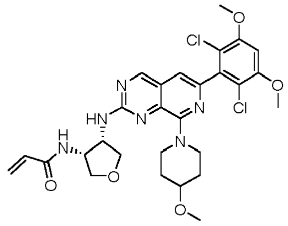

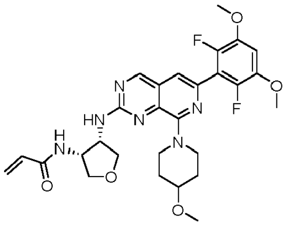

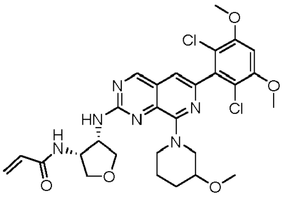

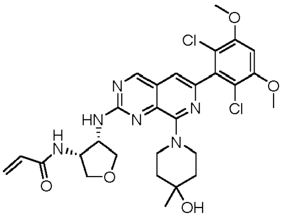

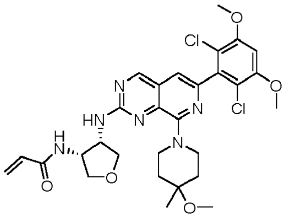

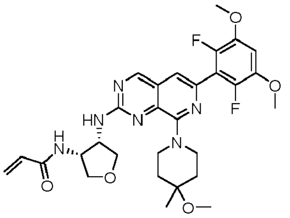

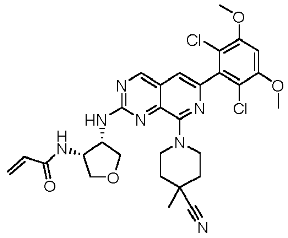

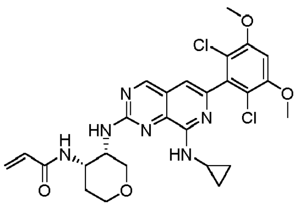

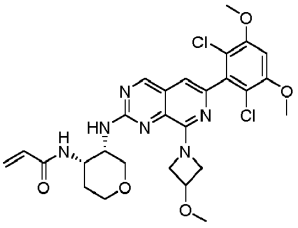

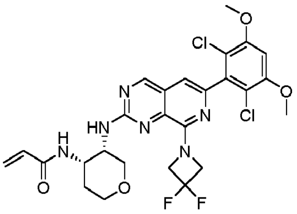

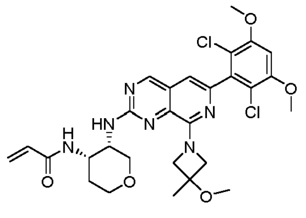

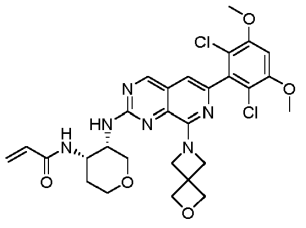

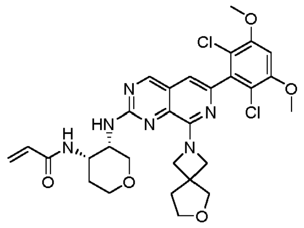

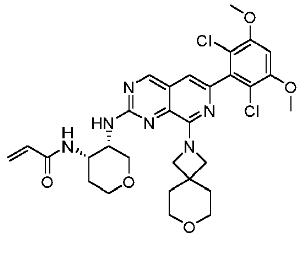

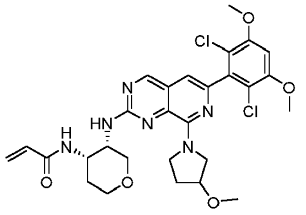

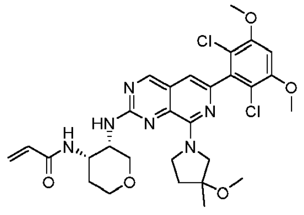

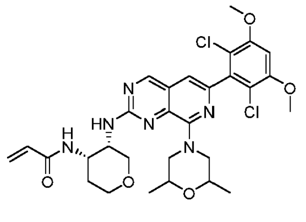

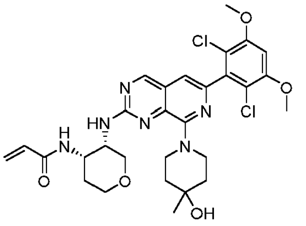

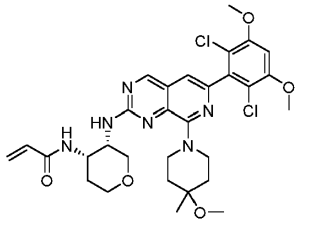

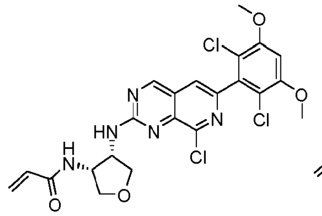

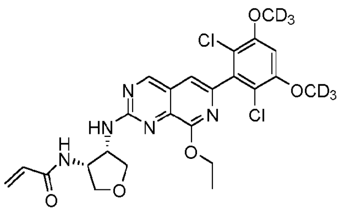

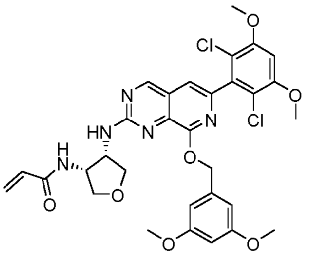

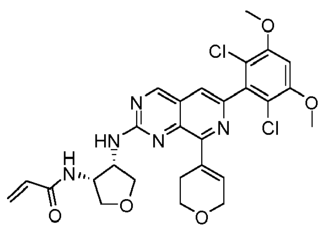

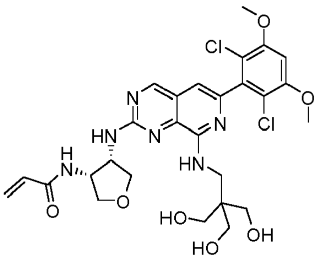

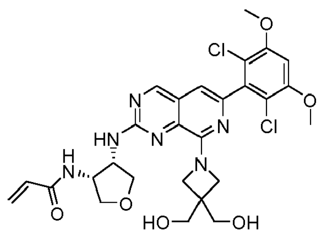

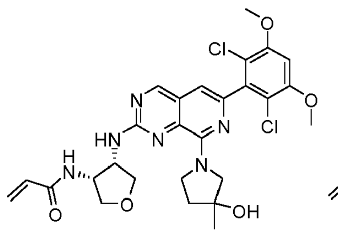

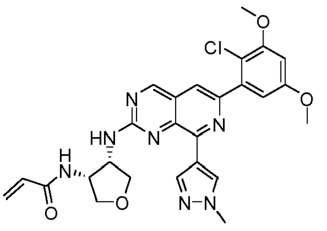

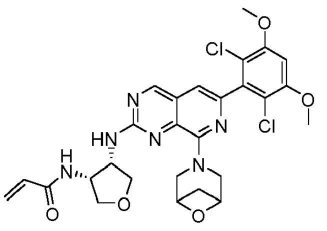

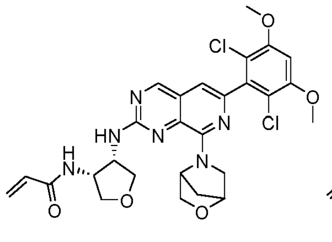
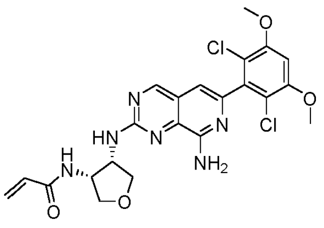
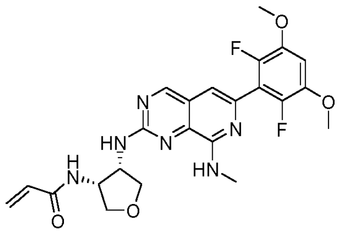
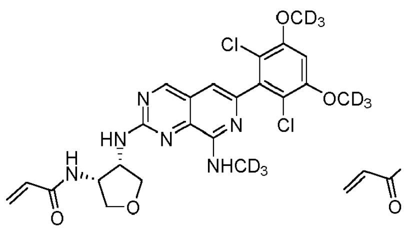
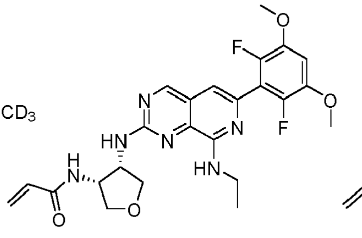
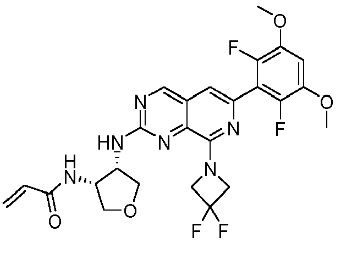
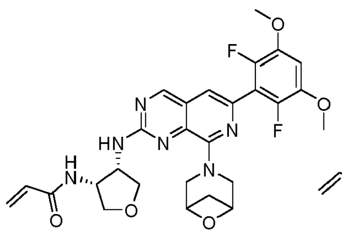
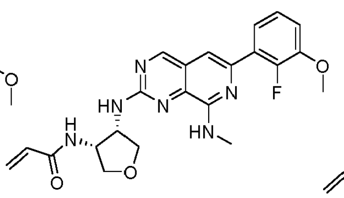
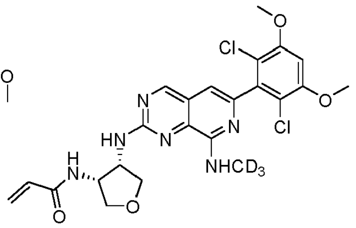
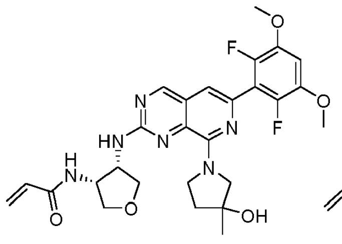
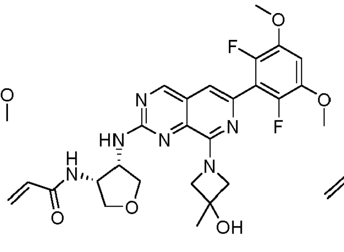
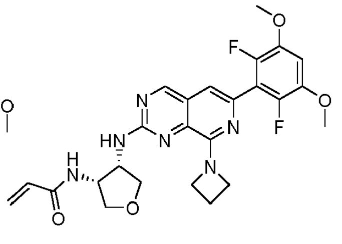
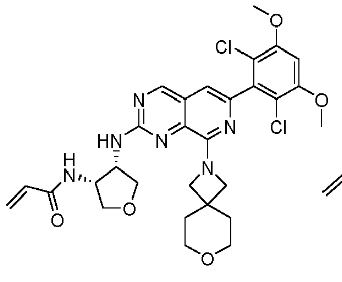
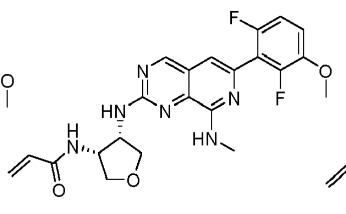
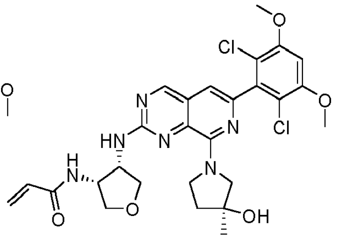
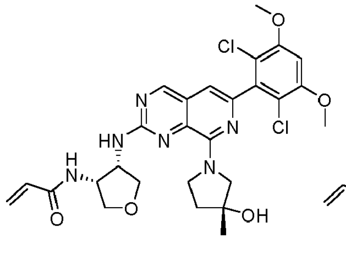
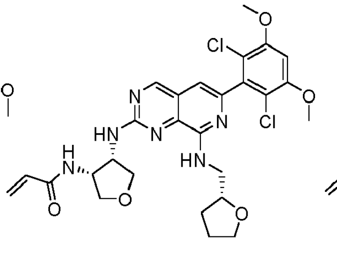
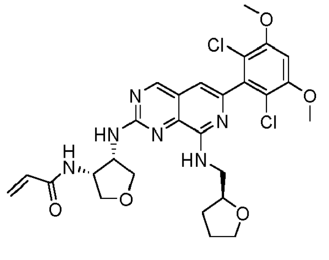

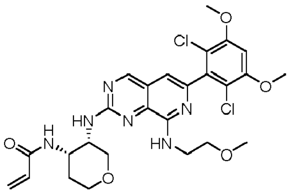

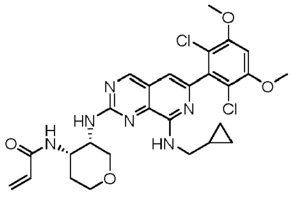

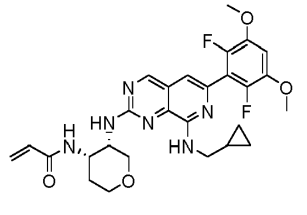

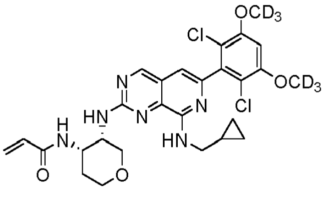

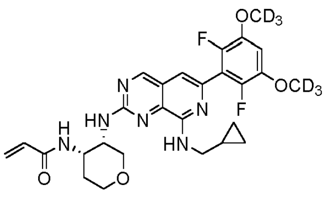

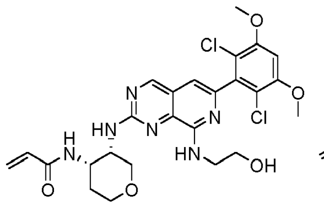

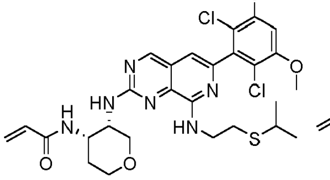

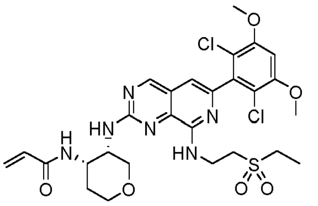

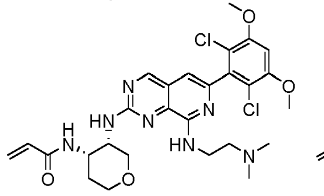

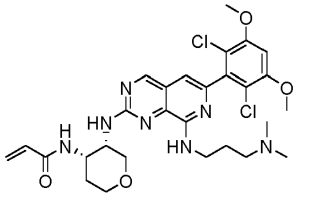

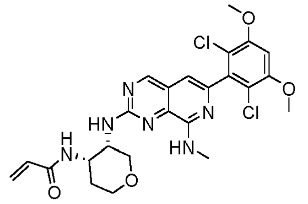

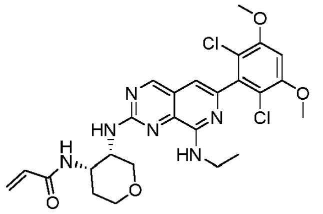

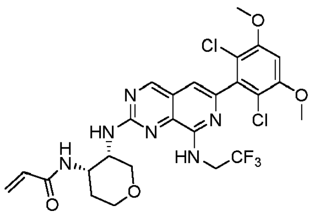

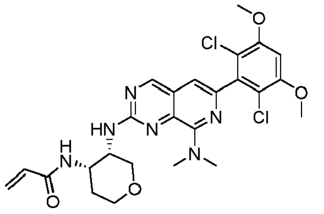

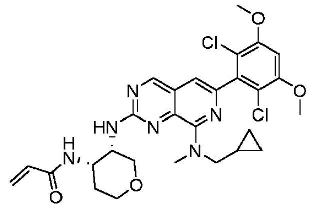

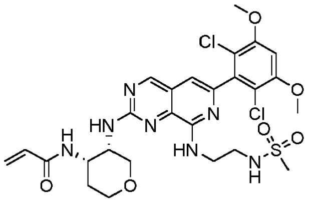

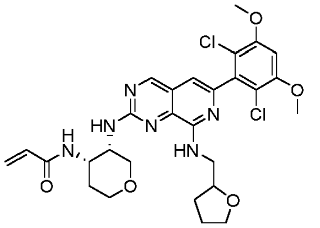

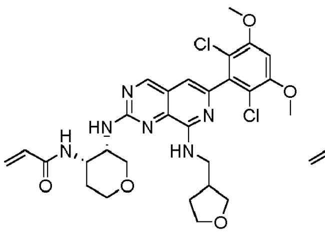

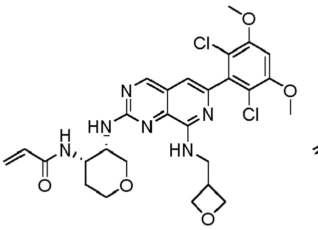

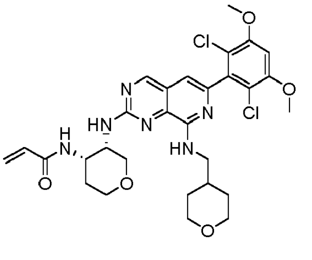

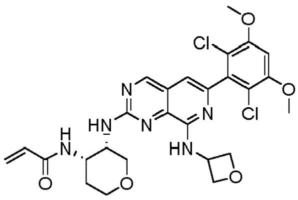
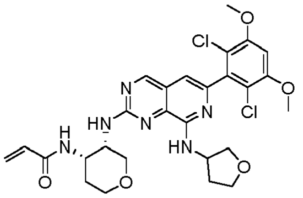
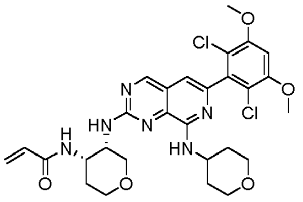

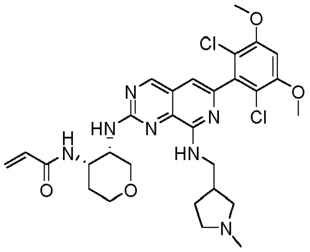
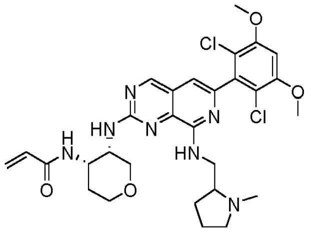
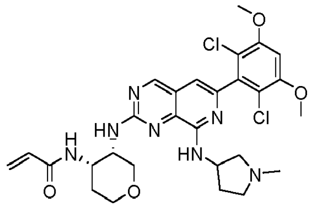

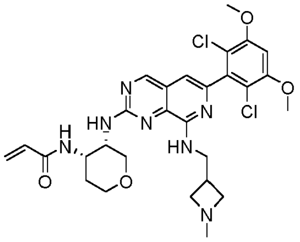
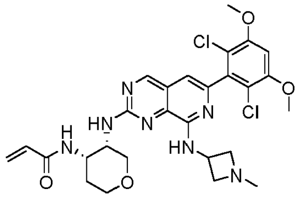
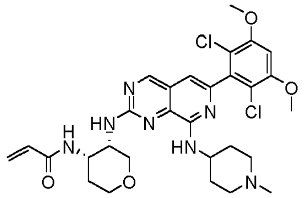

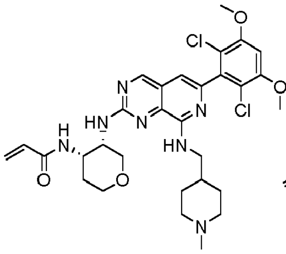
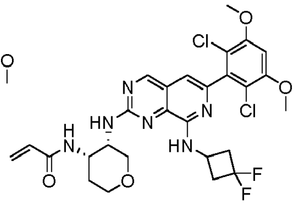
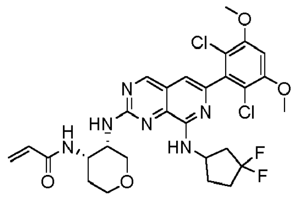

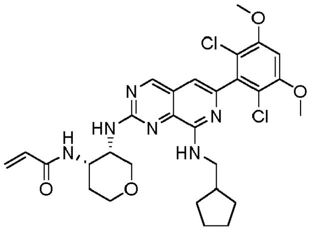
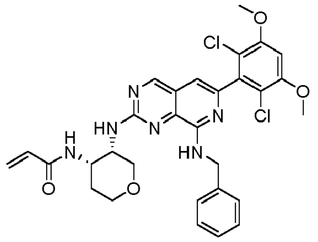
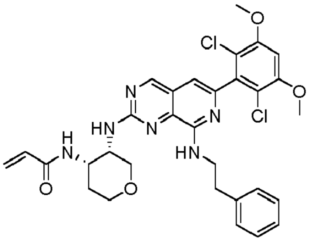

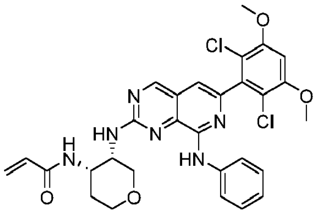
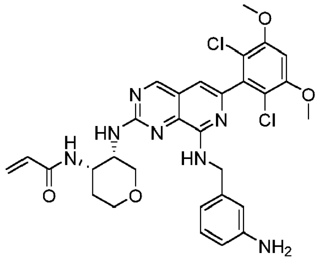
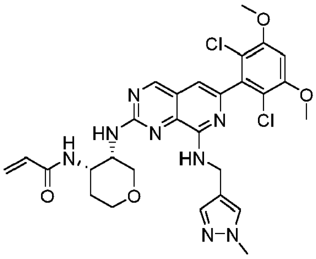

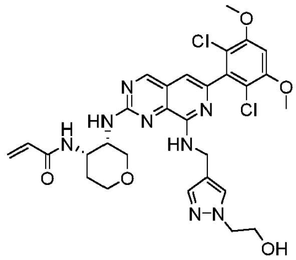

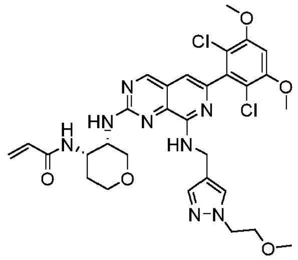

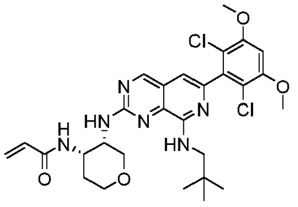

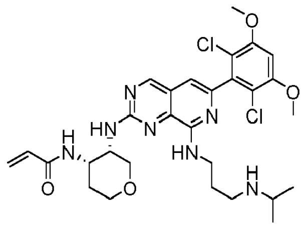

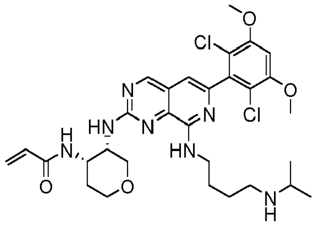

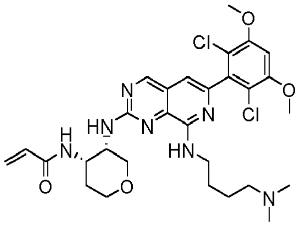

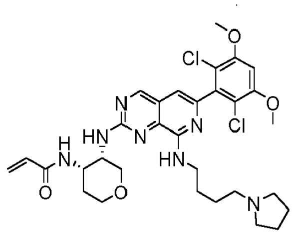

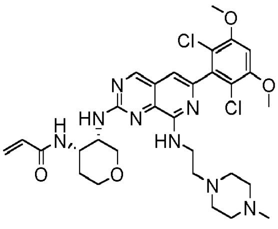

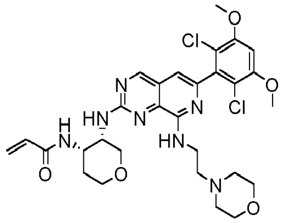

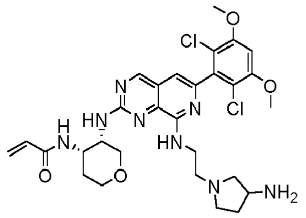

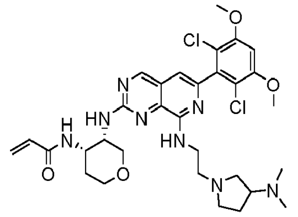

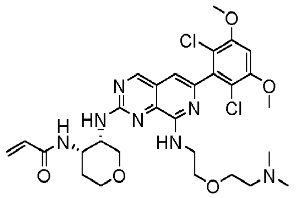

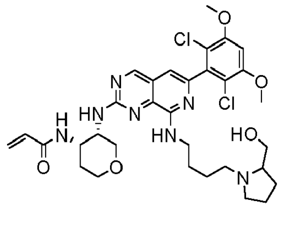

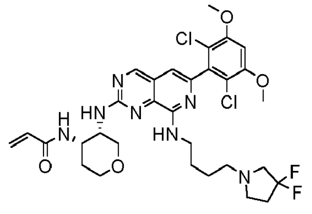

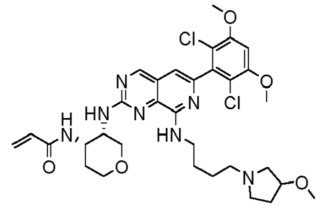

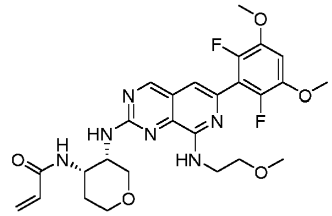

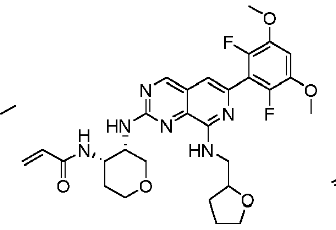

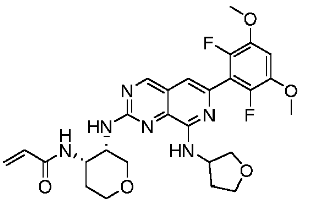

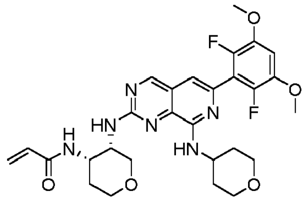

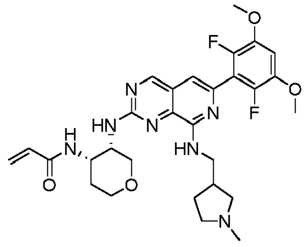

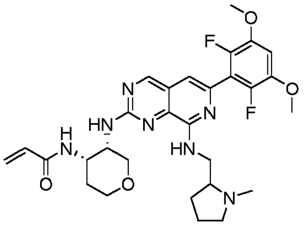

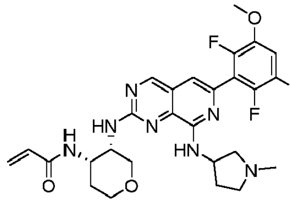

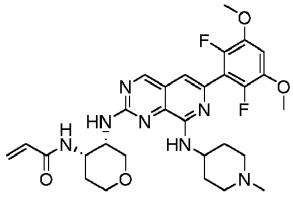

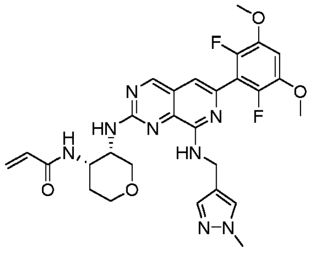

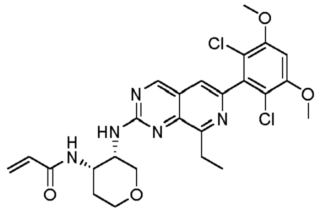

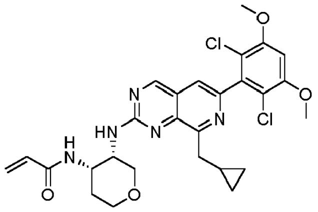

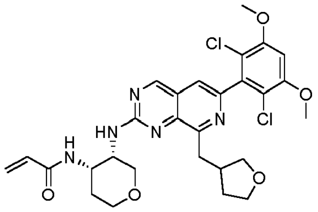

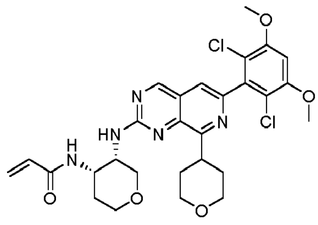

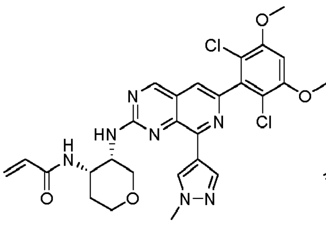

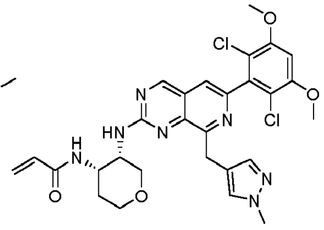

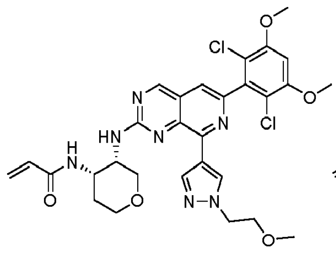

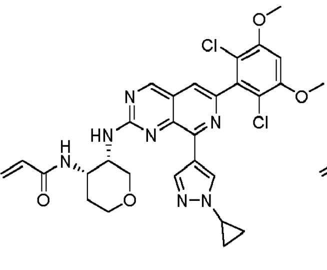

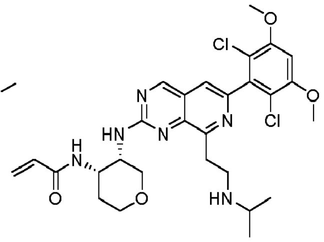

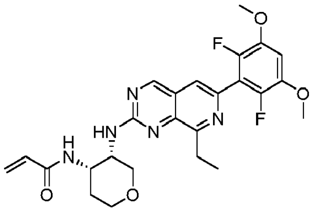
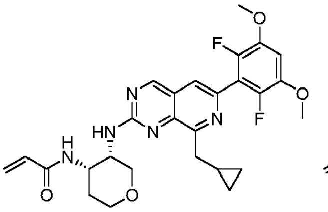
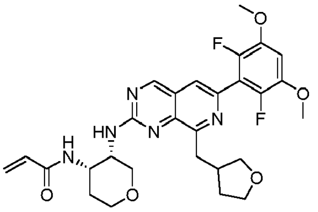
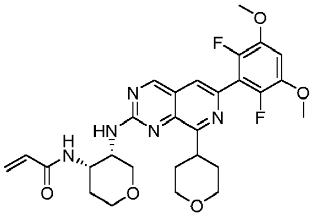
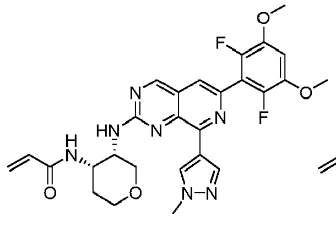
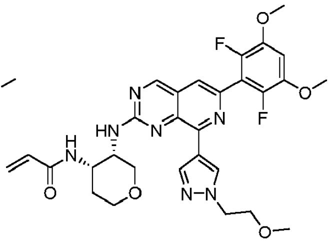
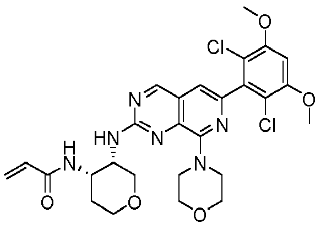
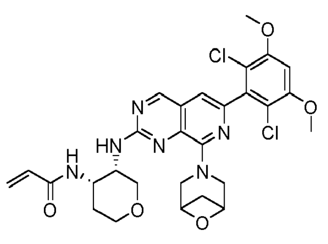
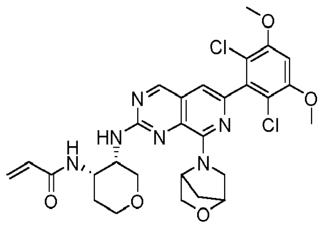
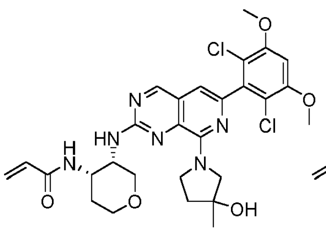
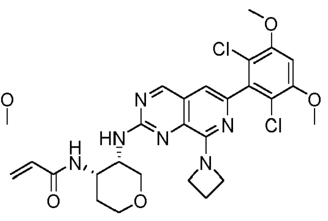
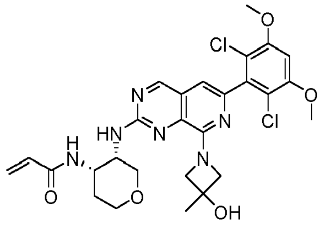
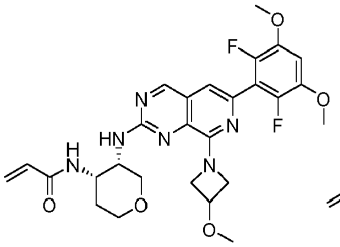
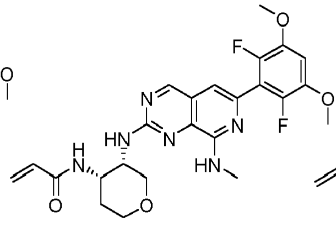
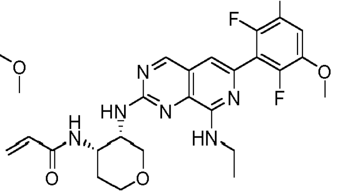
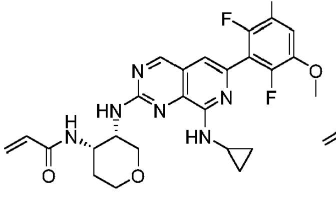
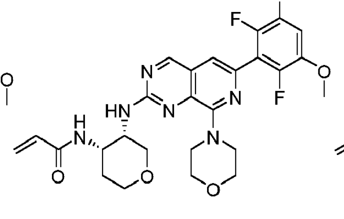
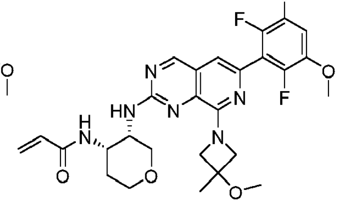

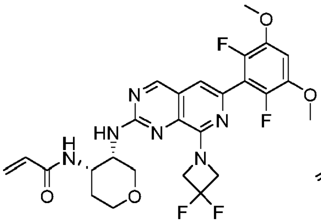

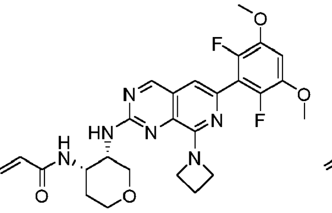

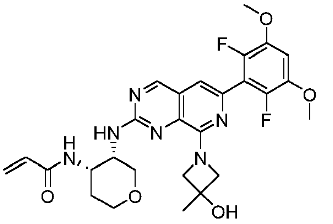

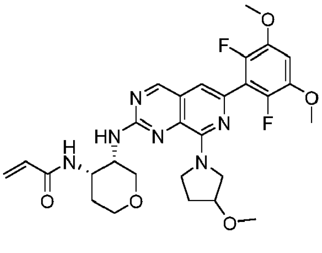

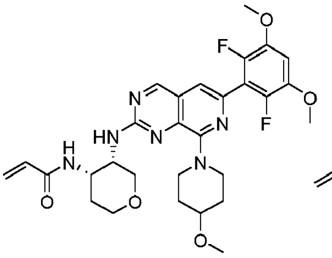

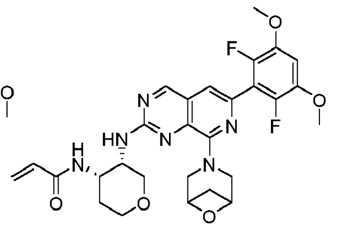

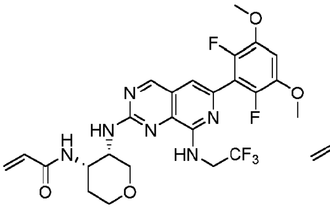

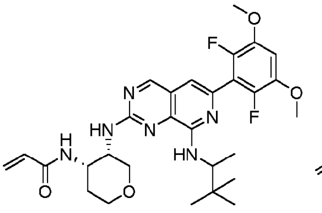

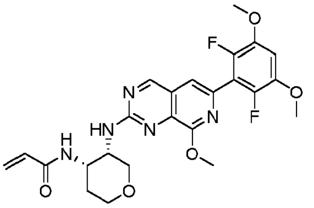

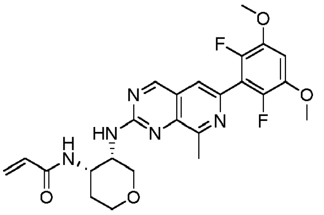

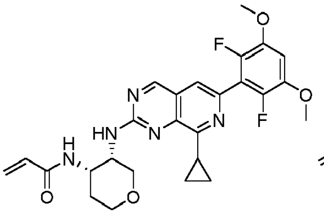

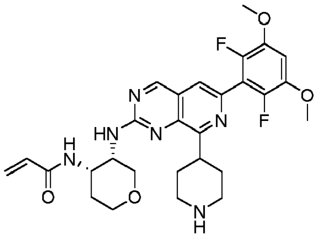

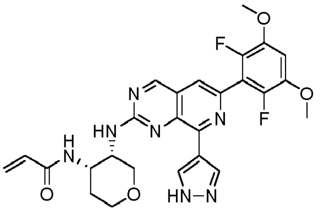

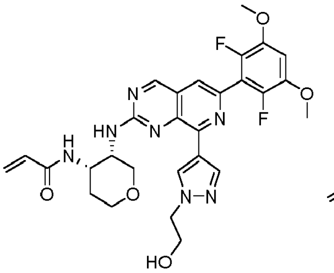

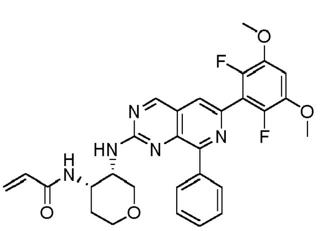

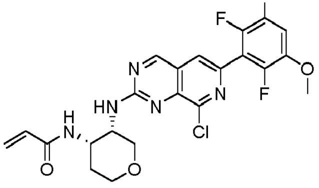

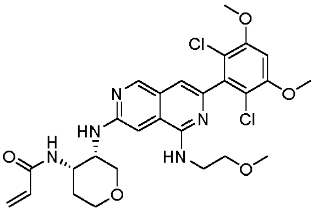

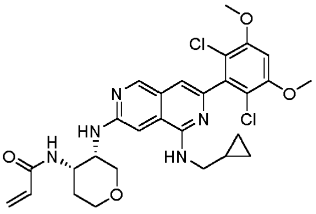

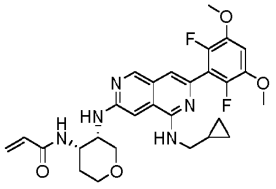

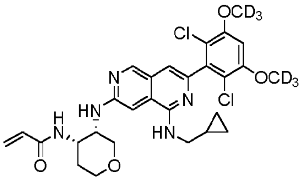

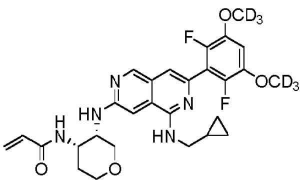

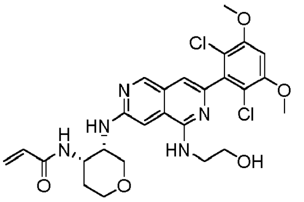

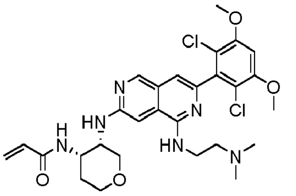

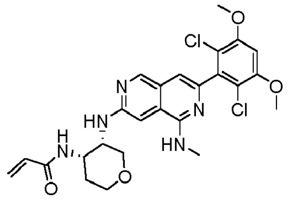

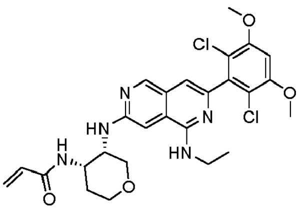

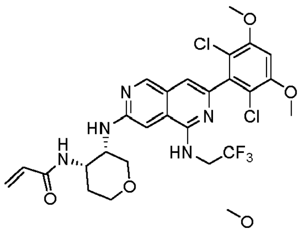

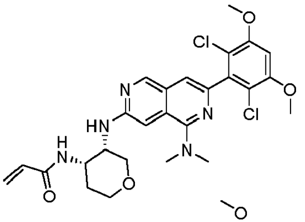

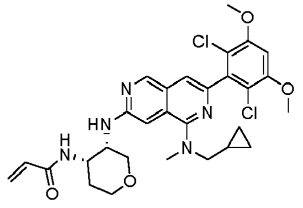

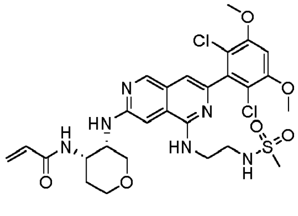

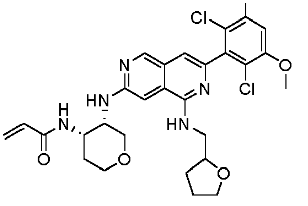

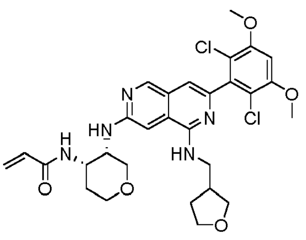

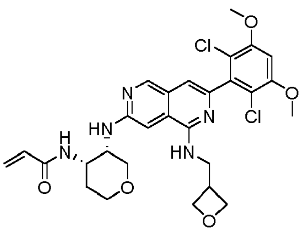

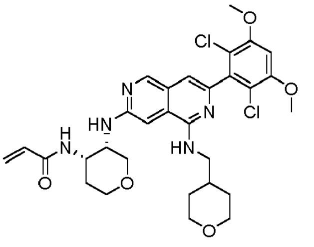

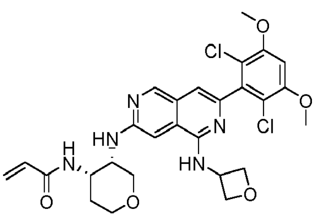

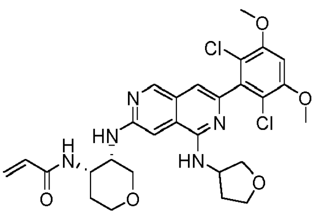

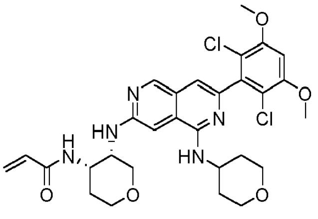

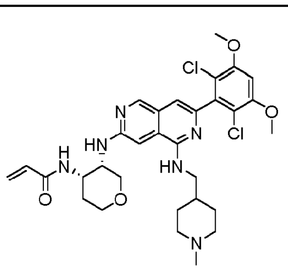
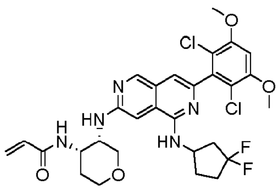
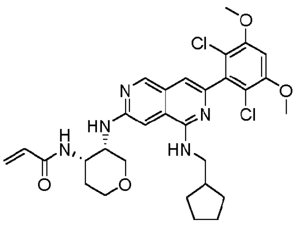
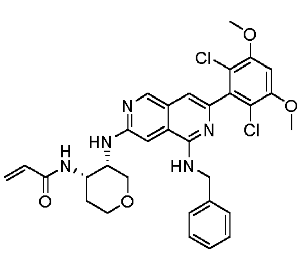
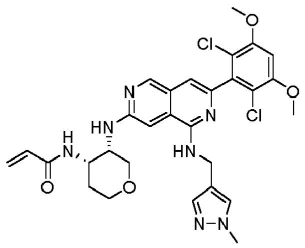
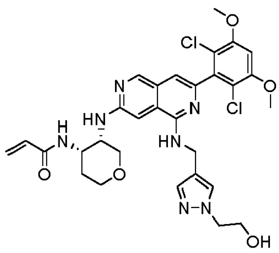
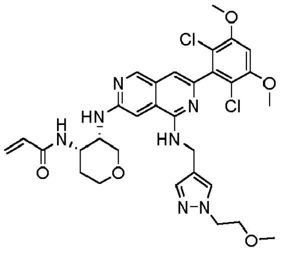
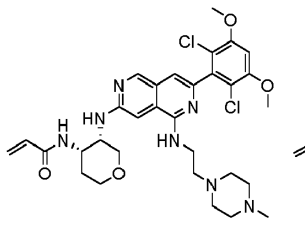
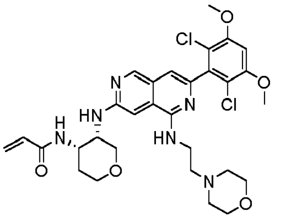
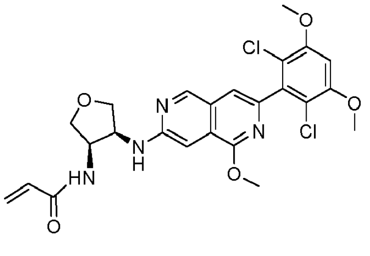
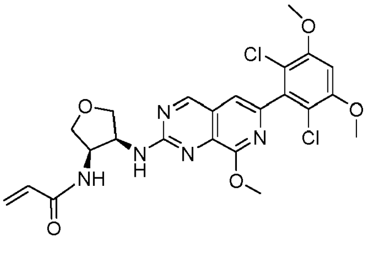
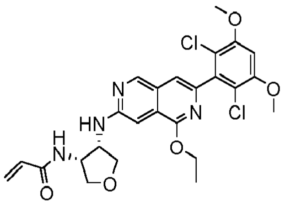
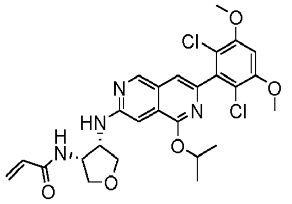
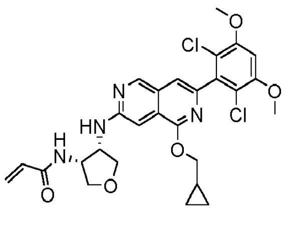
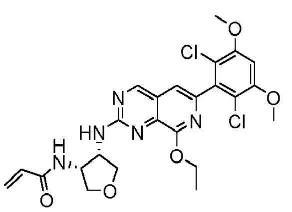
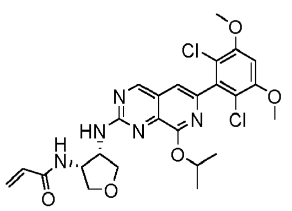
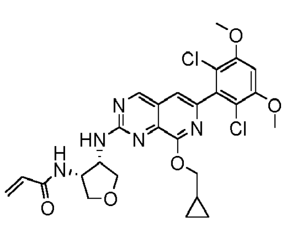

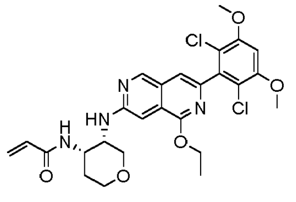

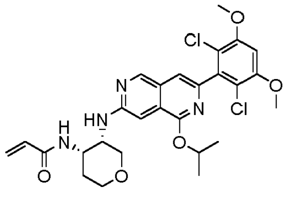

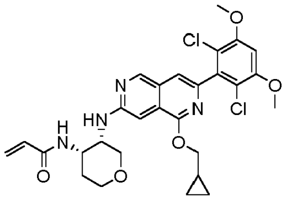

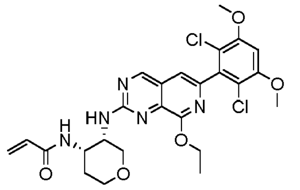

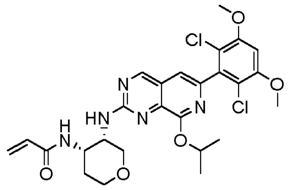

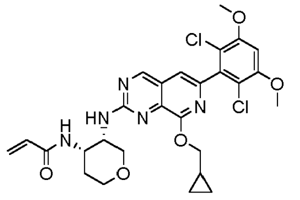

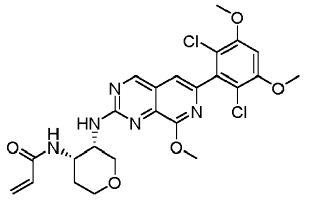

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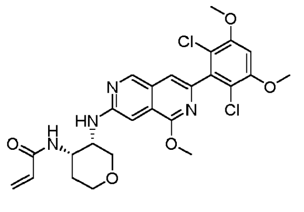
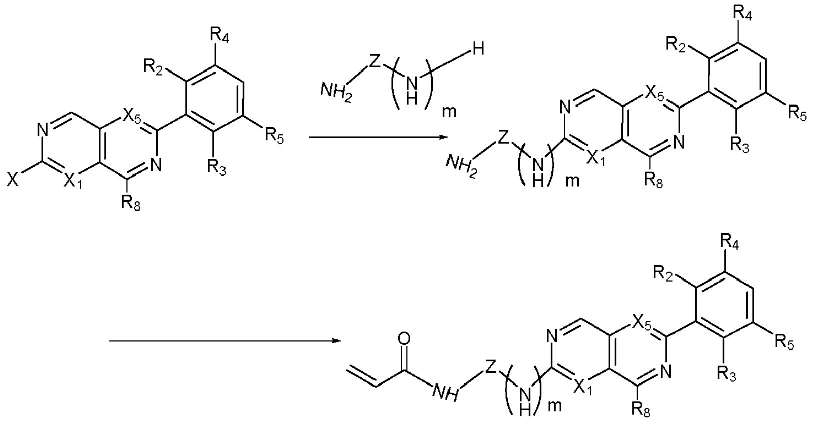


4. Fremgangsmåte for fremstilling av forbindelsen av formel (IVa-1), stereoisomeren eller det farmasøytisk akseptable saltet derav ifølge et hvilket som helst av kravene 1–3, hvori prosessen omfatter følgende trinn,



(IVa-1)

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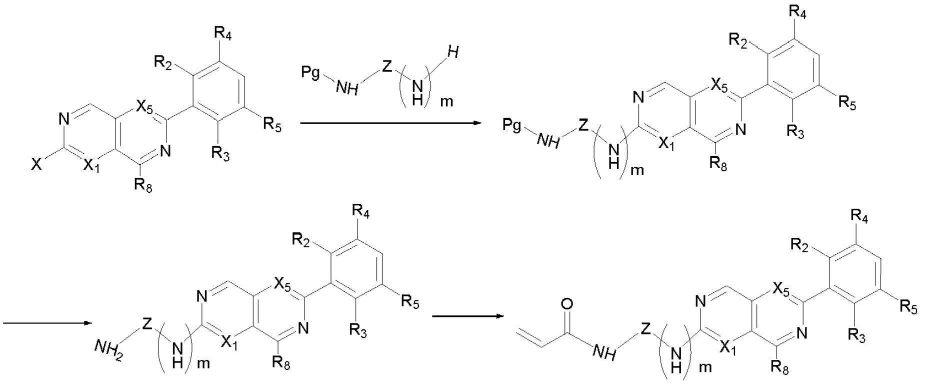
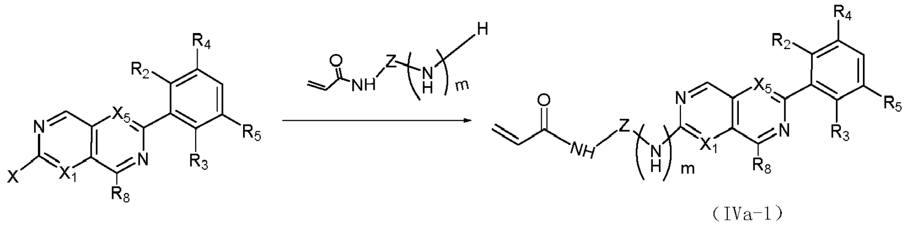
eller



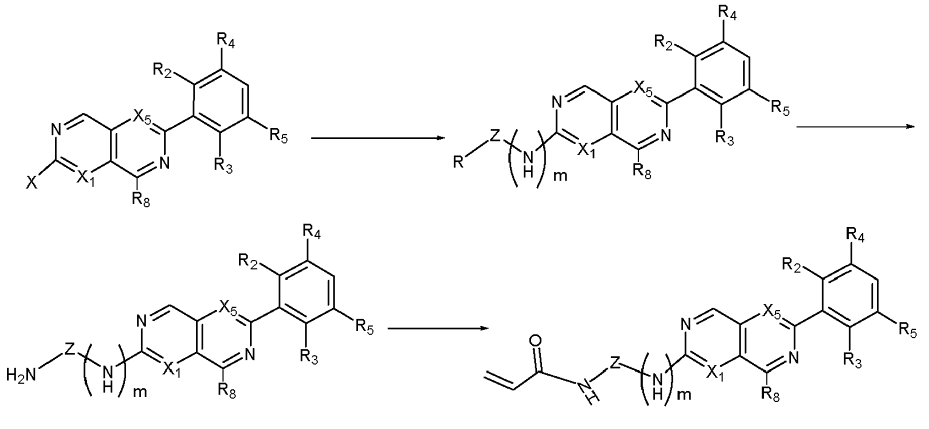
（IVa-1）

eller



（IVa-1）

eller



（IVa-1） ;

eventuelt utføres det en omdannelsesreaksjon videre mellom de forskjellige substituentene i henhold til den forskjellige substituenten;
hvori X er en utgående gruppe valgt fra gruppen som består av Cl, Br, metylsulfanyl, metylsulfonyl og metoksy; R er valgt fra gruppen som består av nitro, cyano og azido; Pg er en aminobeskyttende gruppe valgt fra gruppen som består av tert-butyloksykarbonyl, benzyloksykarbonyl, 2-bifenyl-2-propoksykarbonyl og p-toluensulfonyl; X_1, X_5, m, R_2, R_3, R_4, R_5, R_8 og Z er som beskrevet i krav 1.

5. Farmasøytisk sammensetning omfattende en terapeutisk effektiv mengde av forbindelsen av formel (IVa-1), stereoisomeren eller det farmasøytisk akseptable saltet derav ifølge et hvilket som helst av kravene 1–3, og en farmasøytisk akseptabel bærer.

6. Forbindelsen av formel (IVa-1), stereoisomeren eller det farmasøytisk akseptable saltet derav ifølge et hvilket som helst av kravene 1–3, eller den farmasøytiske sammensetningen ifølge krav 5 for anvendelse i behandlingen av kreft.

7. Forbindelsen for anvendelse ifølge krav 6, hvori kreften er prostatakreft, leverkreft, bukspyttkjertelkreft, spiserørskreft, magekreft, lungekreft, brystkreft, eggstokkreft, tykktarmskreft, hudkreft, glioblastom eller rabdomyosarkom.