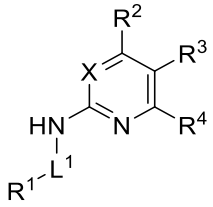
WHAT IS CLAIMED IS:

1. A compound of Formula I, or a pharmaceutically acceptable salt thereof:



Formula I

wherein:

L^1 is an optionally substituted phenylene, optionally substituted 5- or 6-membered heteroarylene, optionally substituted 4-8-membered heterocyclylene, or optionally substituted C_{3-8} carbocyclylene;

R^1 is hydrogen, OH, NH_2, $NHCH_3$, or $N(CH_3)_2$;

X is N or CR^{10};

R^2 is an optionally substituted 12-16 membered heteroaryl or heterocyclic ring structure having three or more rings, wherein the ring system includes at least one phenyl or heteroaryl ring, and wherein R^2 connects to the remainder of Formula I through a ring atom of a phenyl or heteroaryl portion of the ring system, and provided that said phenyl or heteroaryl portion is not fused to a 5-membered heteroaryl;

R^3 is hydrogen, deuterium, halogen, CN, OR^{11}, $NR^{12}R^{13}$, $C(O)NR^{12}R^{13}$, $COOR^A$, COR^B, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-4} alkenyl, optionally substituted C_{2-4} alkynyl, optionally substituted C_{1-4} heteroalkyl, optionally substituted C_{3-8} carbocyclyl, optionally substituted 4-10 membered heterocyclyl, or optionally substituted 5-10 membered heteroaryl;

R^4 is hydrogen, deuterium, halogen, optionally substituted C_{1-6} alkyl, or $NR^{12}R^{13}$;

wherein:

R^{10} is hydrogen, halogen, CN, -OH, an optionally substituted C_{1-4} alkyl, optionally substituted C_{1-4} heteroalkyl, optionally substituted C_{3-8} carbocyclyl, or optionally substituted 4-10 membered heterocyclyl;

R^{11} is hydrogen, an optionally substituted C_{1-6} alkyl, optionally substituted C_{3-8} carbocyclyl, optionally substituted phenyl, optionally substituted heteroaryl,

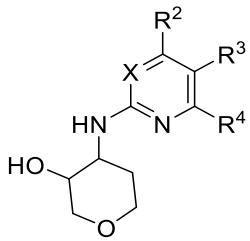
optionally substituted 4-10 membered heterocyclyl; or an oxygen protecting group;

each of R^{12} and R^{13}, at each occurrence, is independently hydrogen, an optionally substituted C_{1-6} alkyl, optionally substituted C_{3-8} carbocyclyl, optionally substituted phenyl, optionally substituted heteroaryl, optionally substituted 4-10 membered heterocyclyl; or a nitrogen protecting group; or R^{12} and R^{13} can be joined to form an optionally substituted 4-10 membered heterocyclyl or 5- or 6-membered heteroaryl;

R^A is hydrogen, an optionally substituted C_{1-6} alkyl, optionally substituted C_{3-8} carbocyclyl, optionally substituted phenyl, optionally substituted heteroaryl, optionally substituted 4-10 membered heterocyclyl; or an oxygen protecting group; and

R^B is hydrogen, an optionally substituted C_{1-6} alkyl, optionally substituted C_{3-8} carbocyclyl, optionally substituted phenyl, optionally substituted 4-10 membered heterocyclyl, or optionally substituted heteroaryl.

2. The compound of claim 1, or a pharmaceutically acceptable salt thereof, characterized as having Formula A-1:

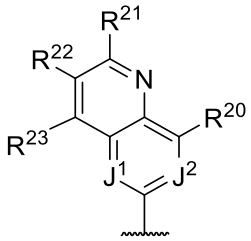


Formula A-1

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3. The compound of claim 1 or 2, or a pharmaceutically acceptable salt thereof, wherein X is N.

4. The compound of any one of claims 1-3, or a pharmaceutically acceptable salt thereof, wherein R^2 has a structure according to M-1:



M-1,

wherein:

J^1 and J^2 are independently N or CR^{30}, wherein R^{30} at each occurrence is independently hydrogen, halogen, C_{1-4} alkyl optionally substituted with F, or C_{1-4} heteroalkyl optionally substituted with F;

R^{20} is hydrogen, halogen, CN, C_{1-4} alkyl optionally substituted with F, C_{1-4} heteroalkyl optionally substituted with F, or an optionally substituted 3-6 membered ring structure; and

R^{21} is: (1) hydrogen or deuterium; (2) halogen, (3) CN, (4) C_{1-4} alkyl optionally substituted with 1-3 substituents each independently F, OH, NH_2, $NH(C_{1-4}$ alkyl), $N(C_{1-4}$ alkyl)(C_{1-4} alkyl), $NH(C_{3-6}$ cycloalkyl), $N(C_{1-4}$ alkyl)(C_{3-6} cycloalkyl), or $N(C_{3-6}$ cycloalkyl)(C_{3-6} cycloalkyl), (5) C_{1-4} heteroalkyl optionally substituted with F, or (6) a 3-6 membered ring structure optionally substituted 1-3 substituents each independently oxo, halo, OH, NH_2, C_{1-4} alkyl optionally substituted with F, or C_{1-4} heteroalkyl optionally substituted with F, and

R^{22} and R^{23}, together with the intervening atoms, are joined to form a 5-8 membered ring, which is optionally substituted with 1-3 substituents each independently selected from oxo, deuterium, halo, OH, NH_2, C_{1-4} alkyl optionally substituted with F, or C_{1-4} heteroalkyl optionally substituted with F;

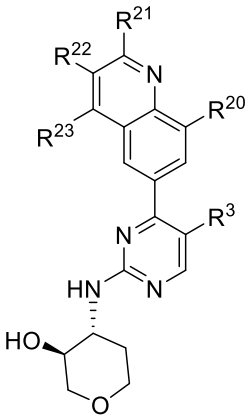
or

R^{23} is: (1) hydrogen or deuterium; (2) halogen, (3) CN, (4) C_{1-4} alkyl optionally substituted with 1-3 substituents each independently F, OH, NH_2, $NH(C_{1-4}$ alkyl), $N(C_{1-4}$ alkyl)(C_{1-4} alkyl), $NH(C_{3-6}$ cycloalkyl), $N(C_{1-4}$ alkyl)(C_{3-6} cycloalkyl), or $N(C_{3-6}$ cycloalkyl)(C_{3-6} cycloalkyl), (5) C_{1-4} heteroalkyl optionally substituted with F, or (6) a 3-6 membered ring structure optionally substituted 1-3

substituents each independently oxo, halo, OH, NH_2, C_{1-4} alkyl optionally substituted with F, or C_{1-4} heteroalkyl optionally substituted with F, and

R^{21} and R^{22}, together with the intervening atoms, are joined to form a 5-8 membered ring, which is optionally substituted with 1-3 substituents each independently selected from oxo, deuterium, halo, OH, NH_2, C_{1-4} alkyl optionally substituted with F, or C_{1-4} heteroalkyl optionally substituted with F.

5. The compound of claim 4, or a pharmaceutically acceptable salt thereof, wherein the compound is a compound of Formula I-1:



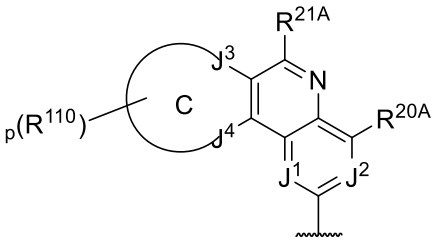
Formula I-1.

6. The compound of claim 4 or 5, or a pharmaceutically acceptable salt thereof, wherein R^{20} is hydrogen, F, Cl, methyl, or ethyl.

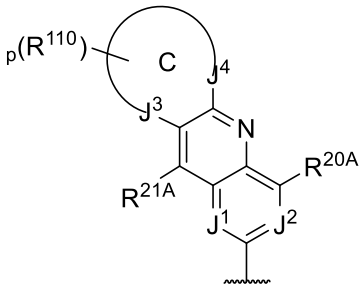
7. The compound of any one of claims 4-6, or a pharmaceutically acceptable salt thereof, wherein R^{21} and R^{22}, together with the intervening atoms, are joined together to form a 5 or 6 membered ring which is substituted with 1-3 substituents each independently F, OH, NH_2, C_{1-4} alkyl optionally substituted with F, C_{1-4} alkoxy optionally substituted with F, or NH(C_{1-4} alkyl).

8. The compound of any one of claims 4-6, or a pharmaceutically acceptable salt thereof, wherein R^{22} and R^{23}, together with the intervening atoms, are joined together to form a 5 or 6 membered ring which is substituted with 1-3 substituents each independently F, OH, NH_2, C_{1-4} alkyl optionally substituted with F, C_{1-4} alkoxy optionally substituted with F, or NH(C_{1-4} alkyl).

9. The compound of any one of claims 1-3, or a pharmaceutically acceptable salt thereof, wherein R^2 has a structure according to M-2 or M-5:



M-2, or



M-5,

wherein:

J^1 and J^2 are independently N or CR^{30}, wherein R^{30} at each occurrence is independently hydrogen, halogen, C_{1-4} alkyl optionally substituted with F, or C_{1-4} heteroalkyl optionally substituted with F;

Ring C is a heterocyclic ring or heteroaryl ring, which is optionally substituted with 1-5 instances of R^{110}, i.e., p is 0-5, as valency permits, wherein

R^{110} at each occurrence is independently (1) oxo, (2) halogen, (3) OH, NH_2, $NH(C_{1-4}$ alkyl), or $N(C_{1-4}$ alkyl)$(C_{1-4}$ alkyl), (4) C_{1-4} alkyl optionally substituted with 1-3 substituents each independently F, OH, NH_2, $NH(C_{1-4}$ alkyl), $N(C_{1-4}$ alkyl)$(C_{1-4}$ alkyl), $NH(C_{3-6}$ cycloalkyl), $N(C_{1-4}$ alkyl)$(C_{3-6}$ cycloalkyl), or $N(C_{3-6}$ cycloalkyl)$(C_{3-6}$ cycloalkyl), (5) C_{1-4} heteroalkyl optionally substituted with F, or (6) two instances of R^{110}, together with the intervening atom(s), are joined to form a 3-6 membered ring structure which is optionally substituted 1-3 substituents each independently oxo, halo, OH, NH_2, C_{1-4} alkyl optionally substituted with F, or C_{1-4} heteroalkyl optionally substituted with F,

J^3 and J^4 are independently N, NR^{31}, $CR^{32}R^{33}$, or CR^{34}, wherein

R^{31} at each occurrence is independently hydrogen, C_{1-4} alkyl optionally substituted with F, or an optionally substituted 3-6 membered ring structure,

each of R^{32} and R^{33} at each occurrence is independently (1) hydrogen or deuterium, (2) halogen, (3) OH, NH_2, $NH(C_{1-4}$ alkyl), or $N(C_{1-4}$ alkyl)$(C_{1-4}$ alkyl), (4) C_{1-4} alkyl optionally substituted with 1-3 substituents each independently F, OH, NH_2, $NH(C_{1-4}$ alkyl), $N(C_{1-4}$ alkyl)$(C_{1-4}$ alkyl), $NH(C_{3-6}$ cycloalkyl), $N(C_{1-4}$ alkyl)$(C_{3-6}$ cycloalkyl), or $N(C_{3-6}$ cycloalkyl)$(C_{3-6}$ cycloalkyl), (5) C_{1-4} heteroalkyl optionally substituted with F, or (6) an optionally substituted 3-6 membered ring structure; or (7) R^{32} and R^{33}, together with the carbon atom they are both bond to, are joined to

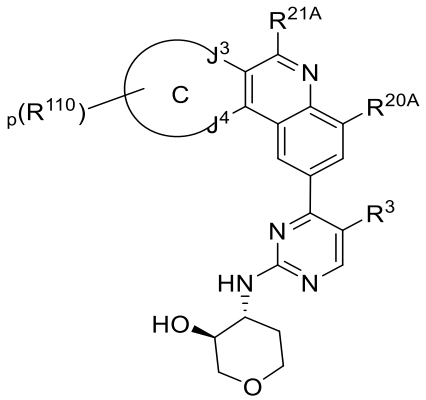
form a carbonyl (CO) or a 3-6 membered ring structure which is optionally substituted 1-3 substituents each independently oxo, halo, OH, NH_2, C_{1-4} alkyl optionally substituted with F, or C_{1-4} heteroalkyl optionally substituted with F; or

two instances of R^{32}, or one instance of R^{32} and one instance of R^{100}, together with the intervening atom(s), are joined to form a 3-6 membered ring structure which is optionally substituted 1-3 substituents each independently oxo, halo, OH, NH_2, C_{1-4} alkyl optionally substituted with F, or C_{1-4} heteroalkyl optionally substituted with F;

R^{34} at each occurrence is independently (1) hydrogen, (2) halogen, (3) OH, NH_2, $NH(C_{1-4}$ alkyl), or $N(C_{1-4}$ alkyl)(C_{1-4} alkyl), (4) C_{1-4} alkyl optionally substituted with 1-3 substituents each independently F, OH, NH_2, $NH(C_{1-4}$ alkyl), $N(C_{1-4}$ alkyl)(C_{1-4} alkyl), $NH(C_{3-6}$ cycloalkyl), $N(C_{1-4}$ alkyl)(C_{3-6} cycloalkyl), or $N(C_{3-6}$ cycloalkyl)(C_{3-6} cycloalkyl), (5) C_{1-4} heteroalkyl optionally substituted with F, or (6) an optionally substituted 3-6 membered ring structure; and

R^{20A} and R^{21A} are each independently hydrogen, deuterium, halogen, CN, C_{1-4} alkyl optionally substituted with F, C_{1-4} heteroalkyl optionally substituted with F, or an optionally substituted 3-6 membered ring structure .

10. The compound of claim 9, or a pharmaceutically acceptable salt thereof, wherein the compound is a compound of Formula I-2:

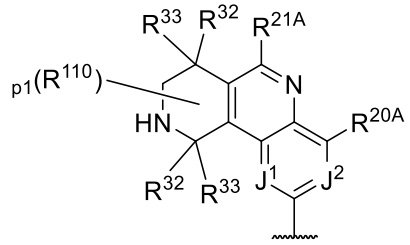
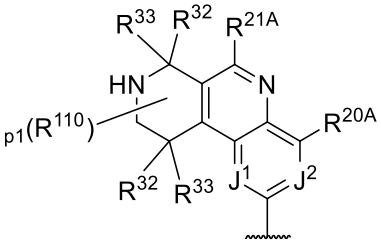
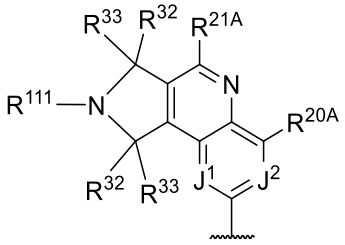
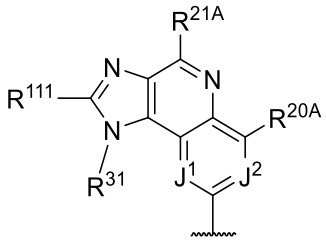
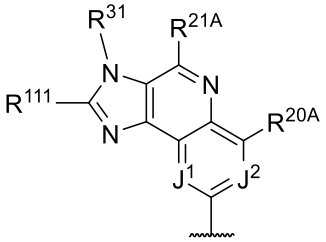
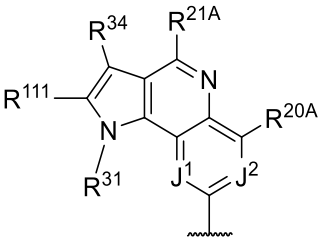
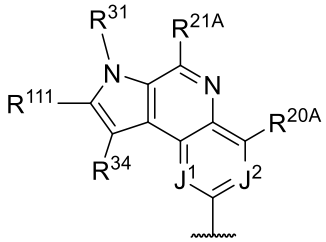
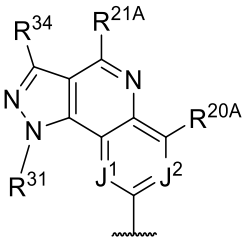
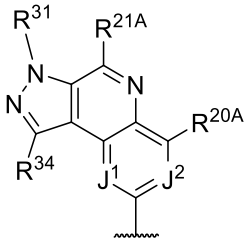
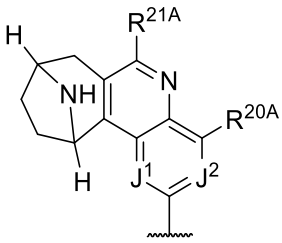
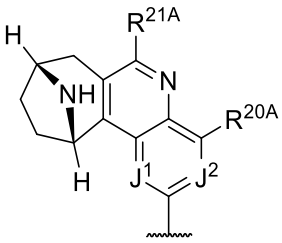
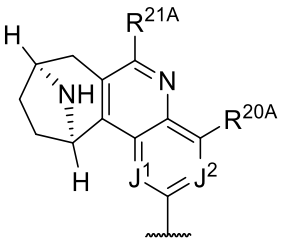


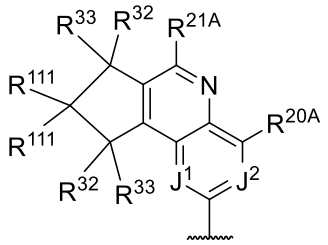
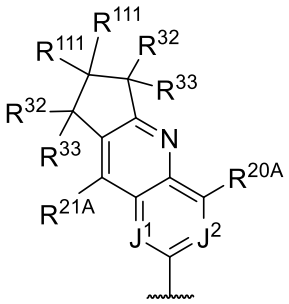
Formula I-2.

11. The compound of claim 9 or 10, or a pharmaceutically acceptable salt thereof, wherein R^{20A} is hydrogen, F, Cl, methyl, or ethyl.

12. The compound of any one of claims 9-11, or a pharmaceutically acceptable salt thereof, wherein p is 2, wherein R^{110} at each occurrence is independently C_{1-4} alkyl; or two R^{110} are joined together with the intervening atom(s) to form a 3-6 membered ring.

13. The compound of any one of claims 9-12, or a pharmaceutically acceptable salt thereof, wherein as applicable, R^2 is characterized as having a structure according to formula F-1, F-2, F-3, F-4, F-5, F-6, F-7, F-8, F-9, F-10, F-11, F-12, F-13, or F-14:

 F-1,	 F-2,	 F-3,
 F-4,	 F-5,	 F-6,
 F-7,	 F-8,	 F-9,
 F-10,	 F-11,	 F-12,

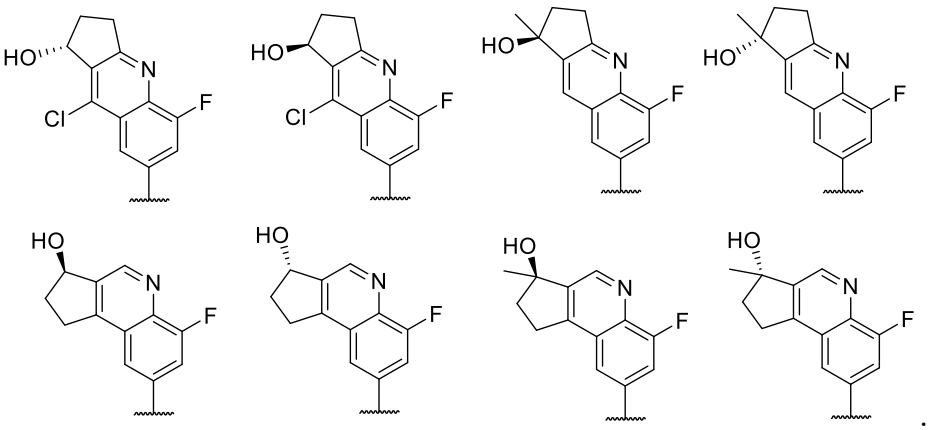
 F-13, or	 F-14,

wherein:

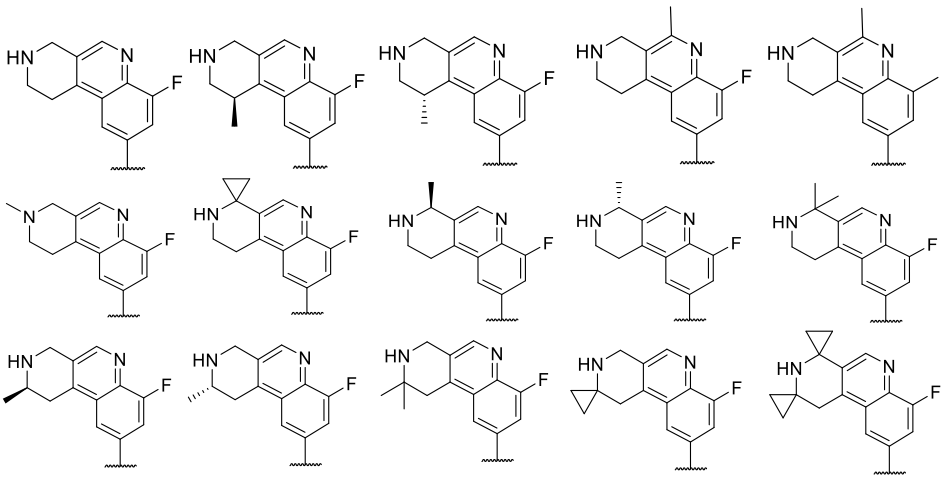
p1 is 0, 1, 2, or 3, as valency permits; and

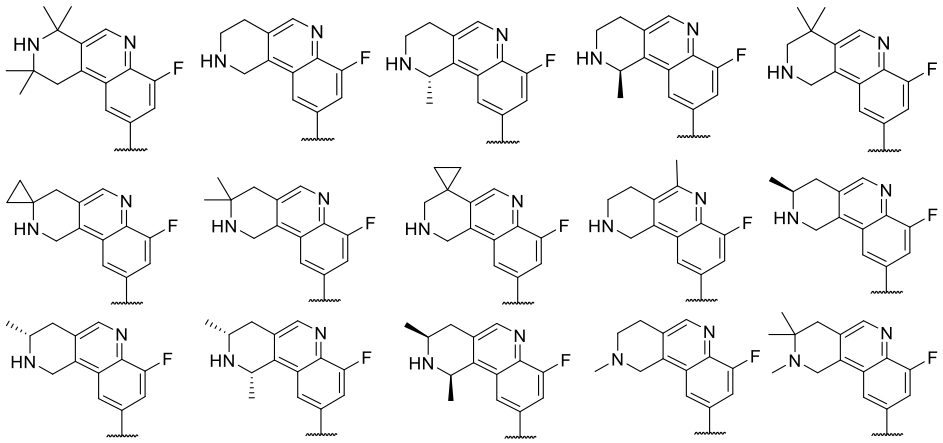
R^{111} is hydrogen or R^{110}.

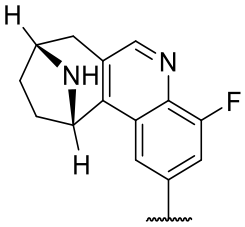
14. The compound of any one of claims 1-3, or a pharmaceutically acceptable salt thereof, wherein R^2 is selected from:

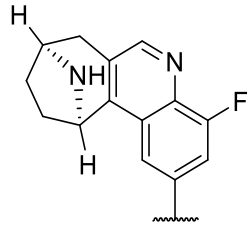


15. The compound of any one of claims 1-3, or a pharmaceutically acceptable salt thereof, wherein R^2 is selected from:

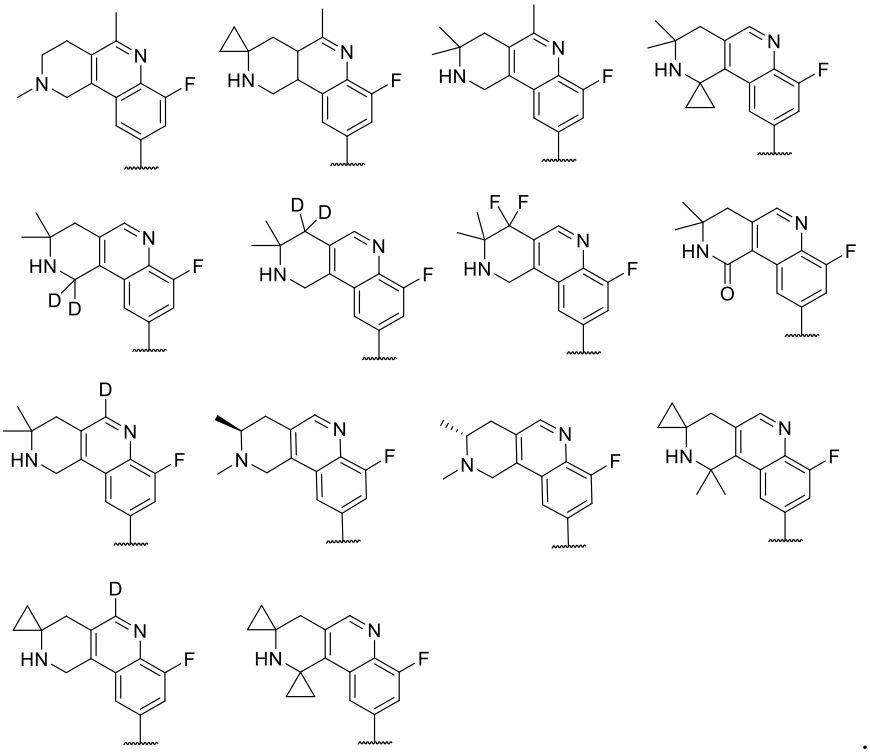






or R^2 is selected from  or ,

or R^2 is selected from:

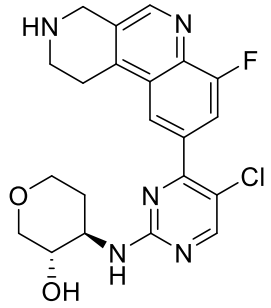
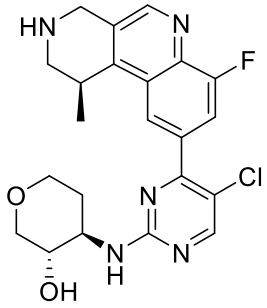
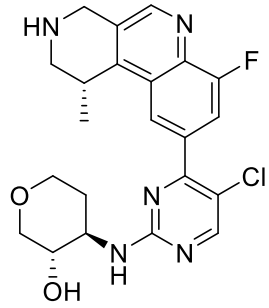
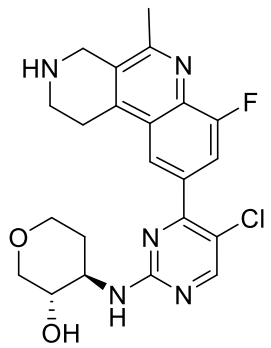
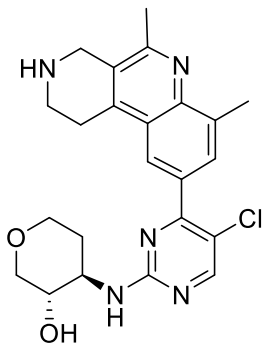
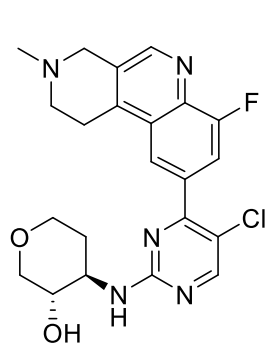
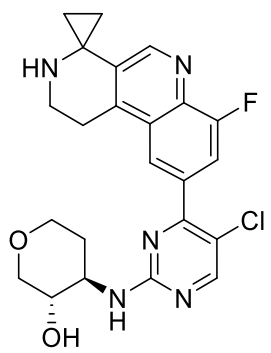
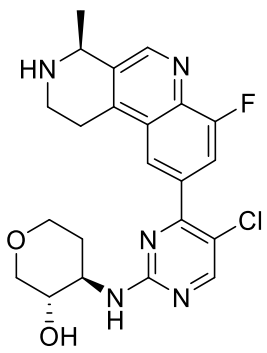
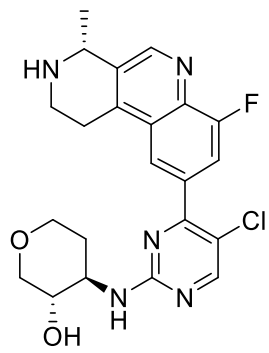
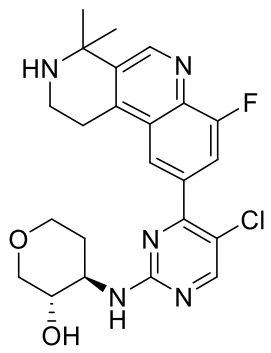
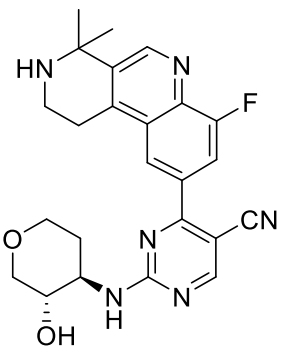
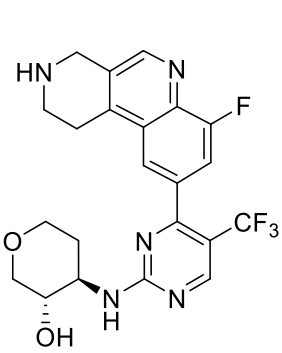


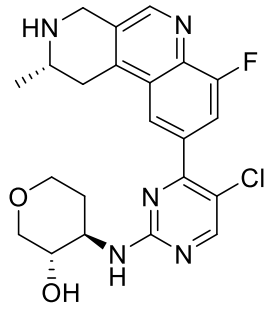
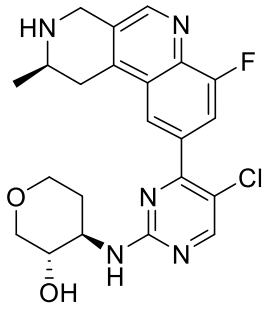
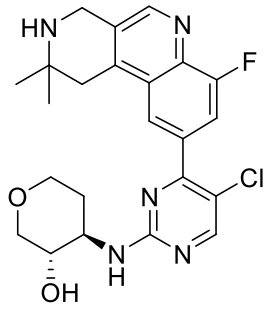
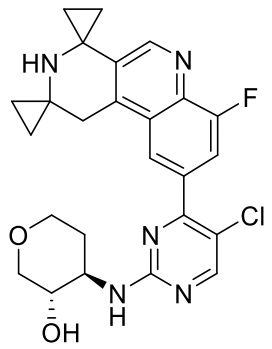
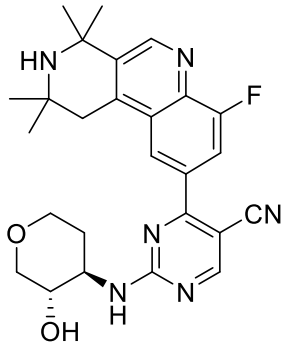
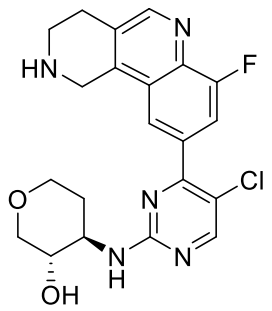
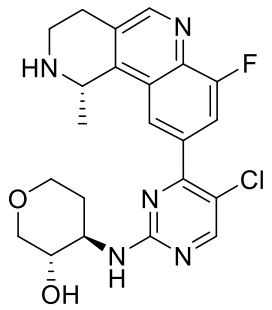
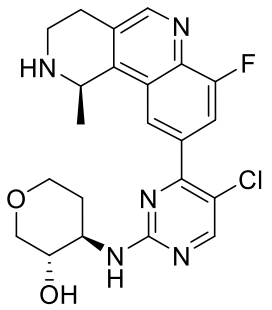
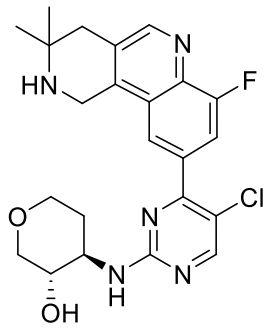
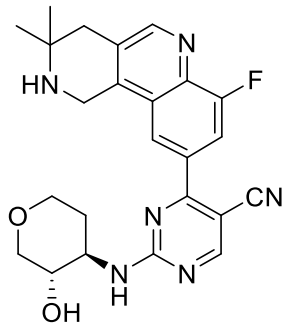
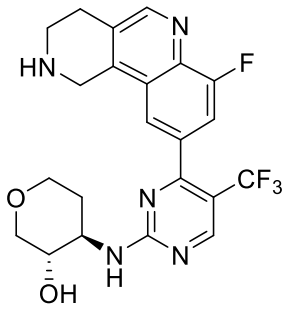
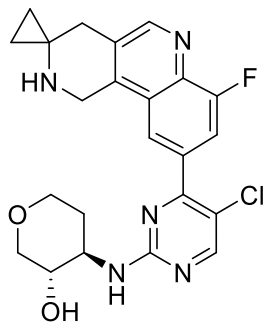
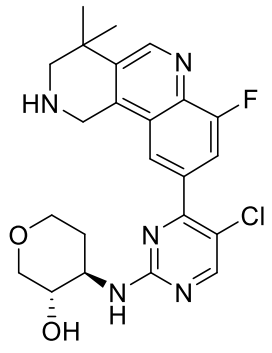
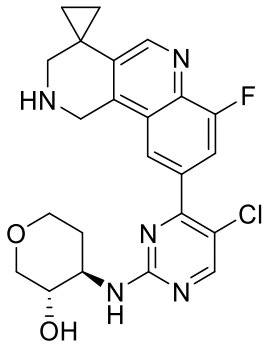
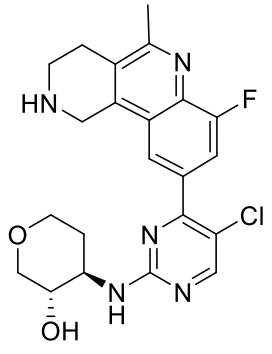
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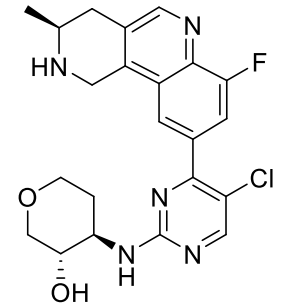
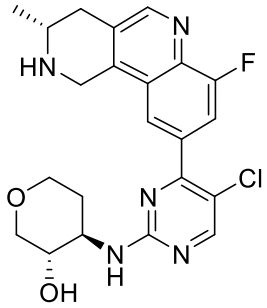
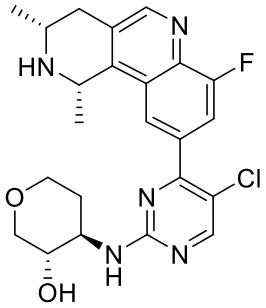
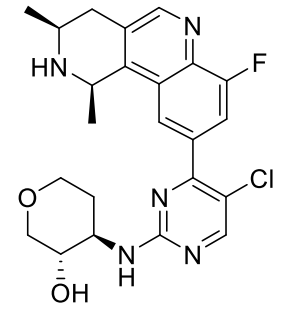
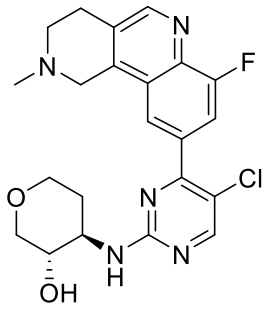
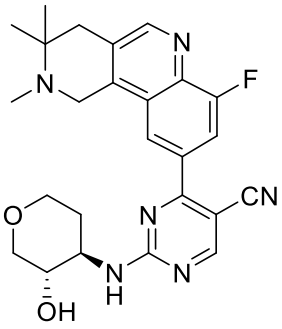
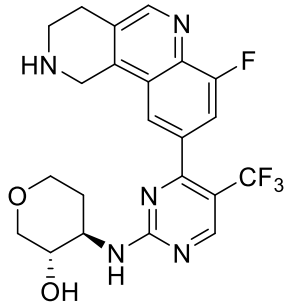
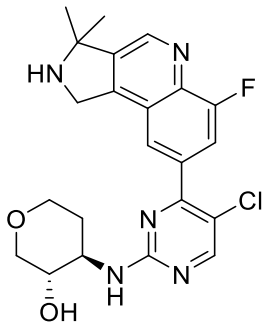
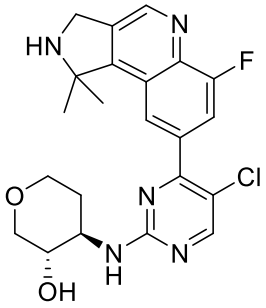
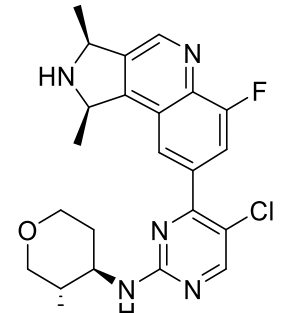
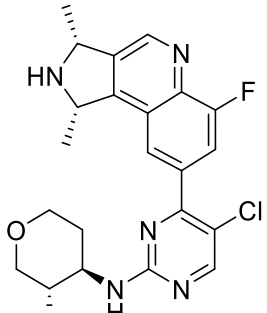
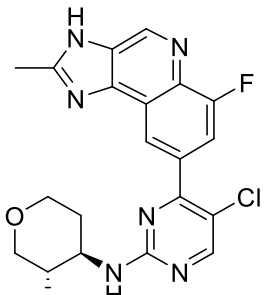
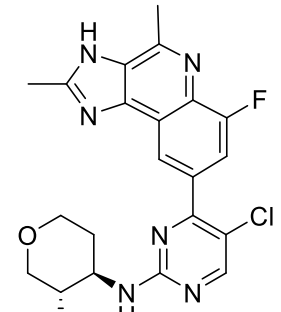
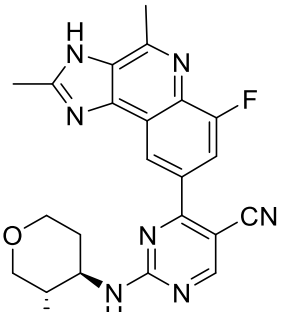
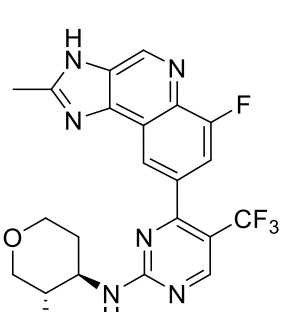
16. The compound of any one of claims 1-15, or a pharmaceutically acceptable salt thereof wherein R^3 is hydrogen, F, Cl, Br, C_{1-4} alkyl optionally substituted with F and/or deuterium, or CN.

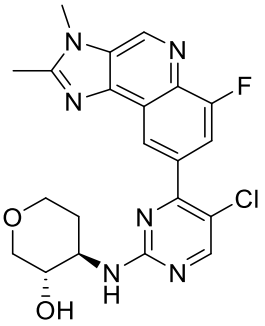
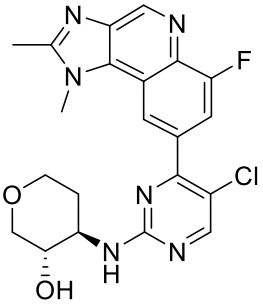
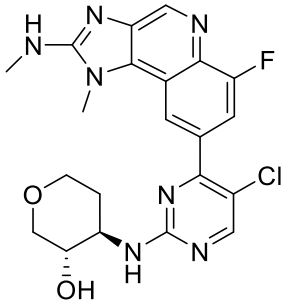
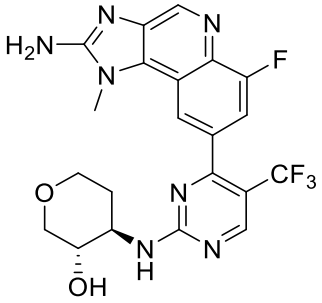
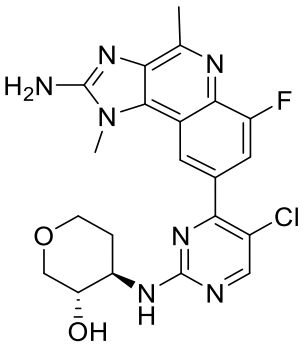
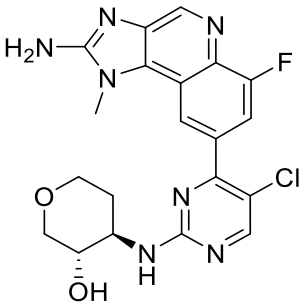
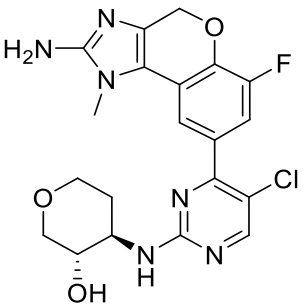
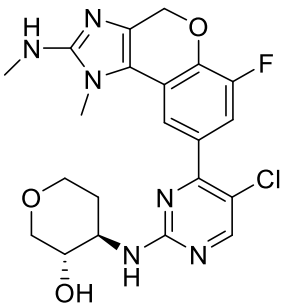
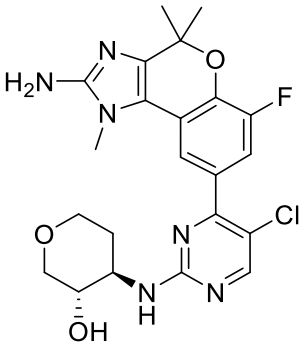
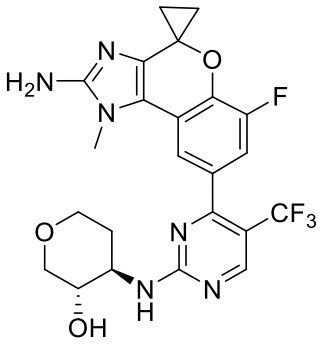
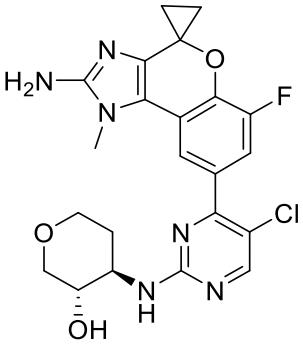
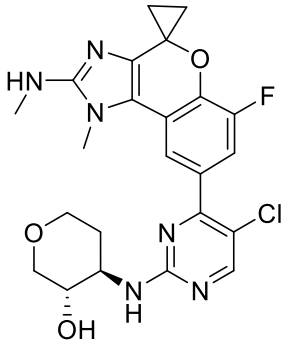
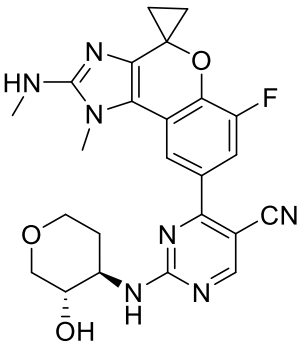
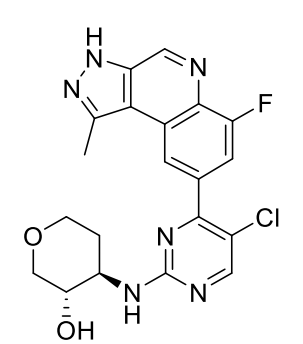
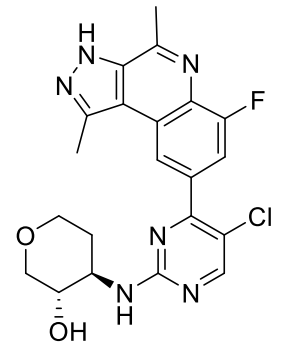
17. The compound of any one of claims 1-16, or a pharmaceutically acceptable salt thereof wherein R^4 is hydrogen or deuterium.

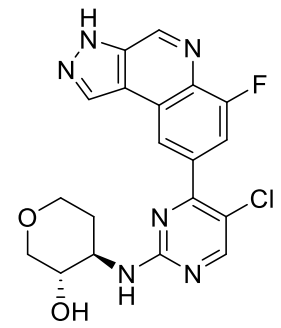
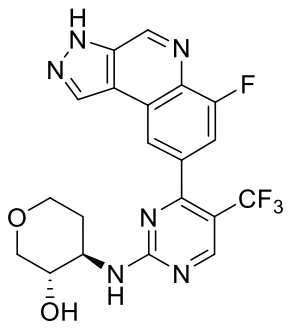
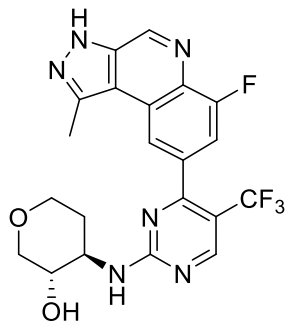
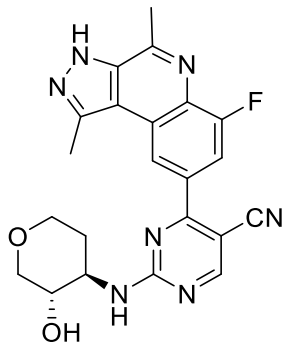
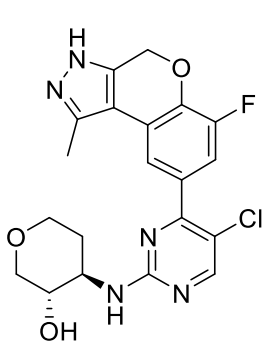
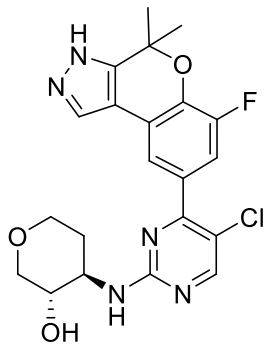
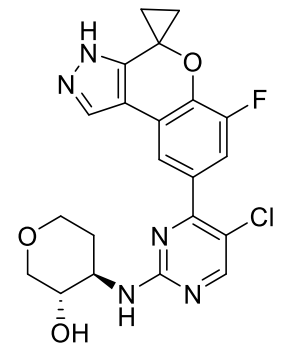
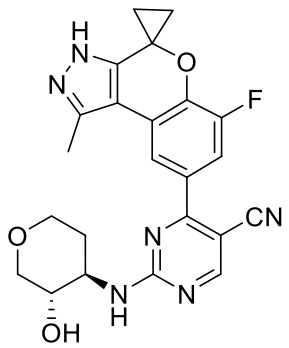
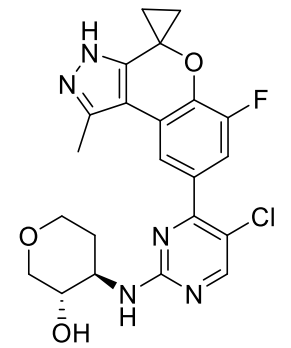
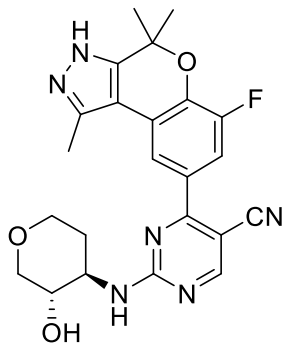
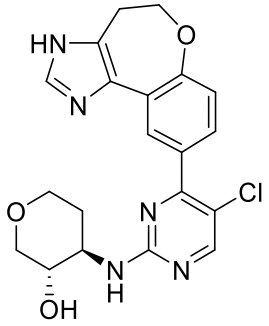
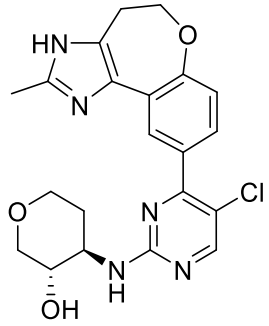
18. A compound, a stereoisomer thereof, a deuterated analog thereof, or a pharmaceutically acceptable salt thereof, wherein the compound is selected from:

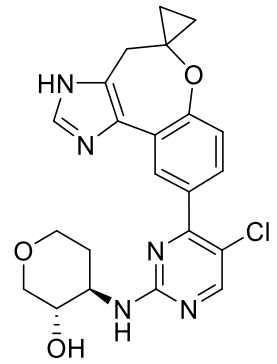
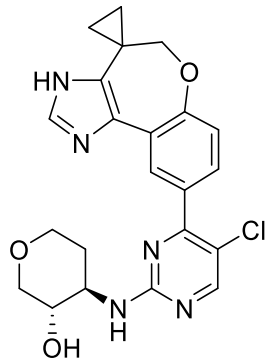
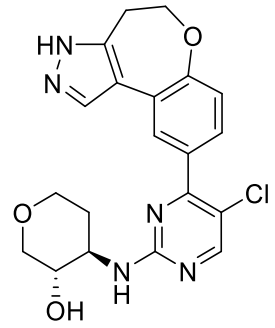
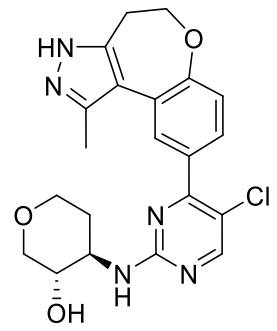
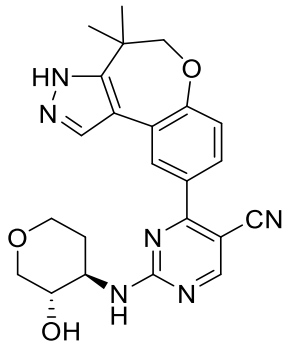
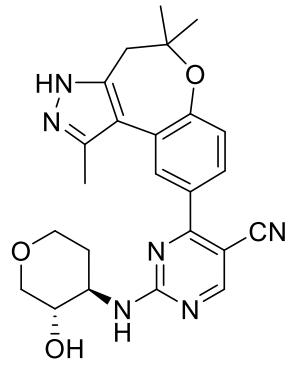
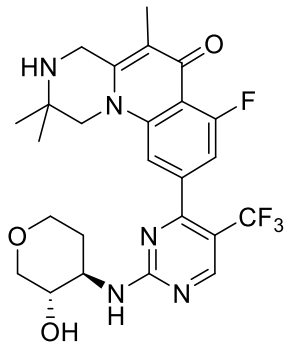
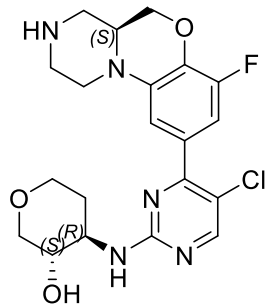
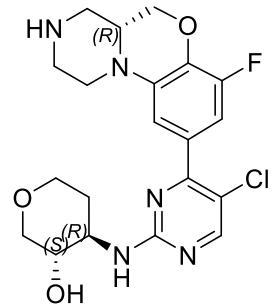
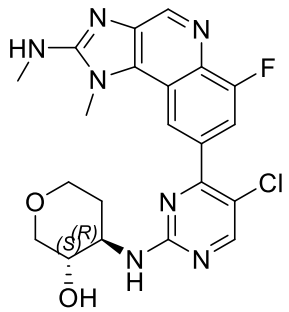
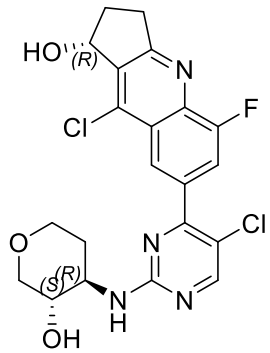
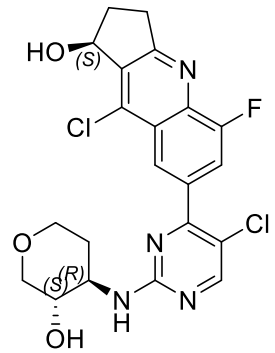
		
		
		
		

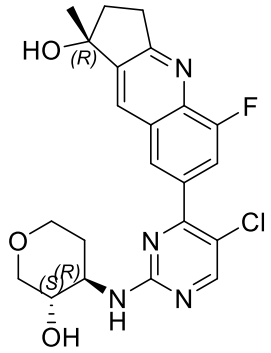
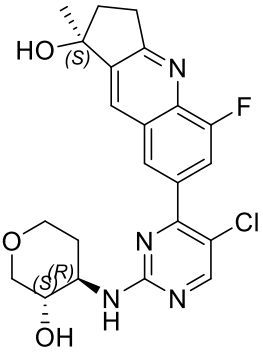
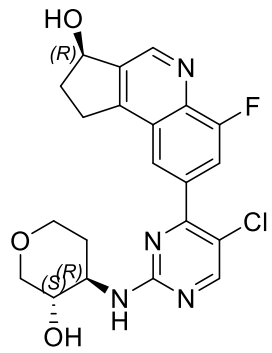
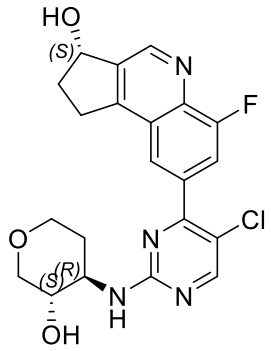
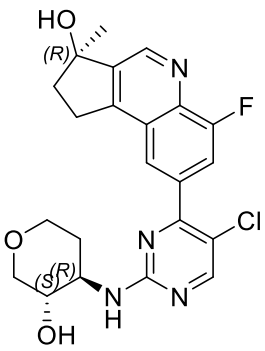
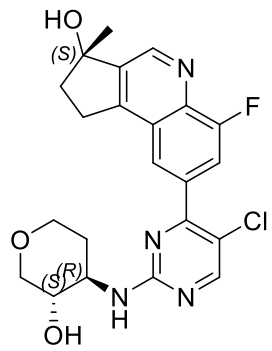
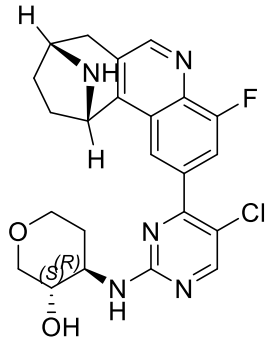
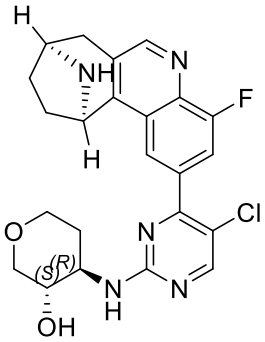
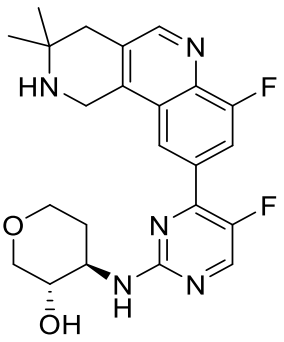
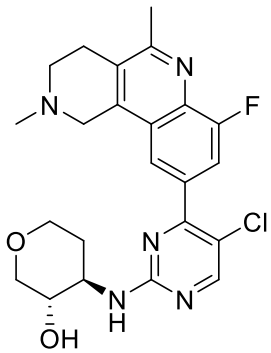
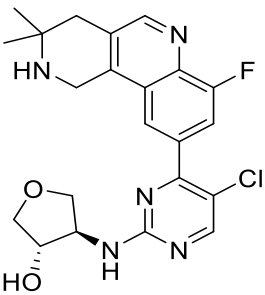
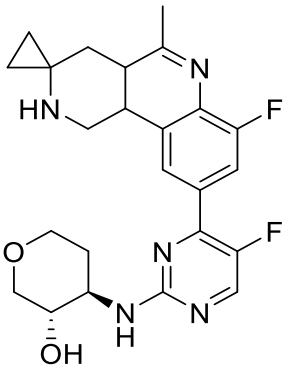
		
		
		
		
		

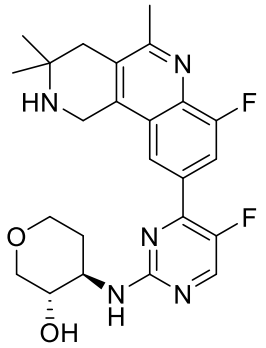
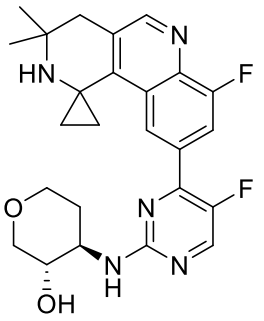
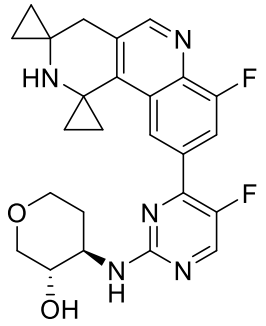
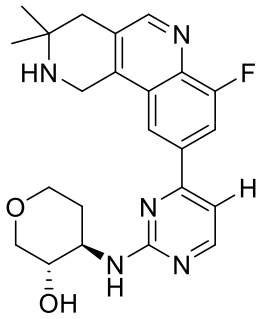
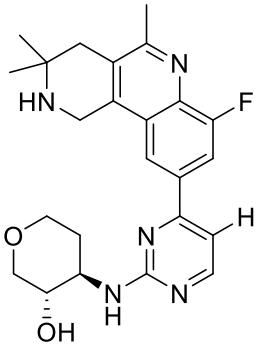
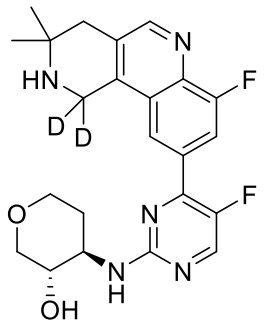
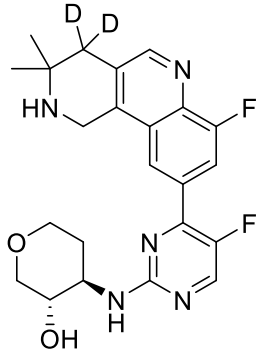
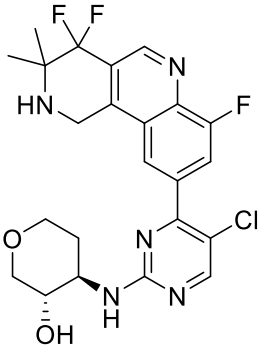
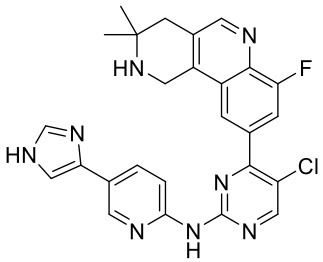
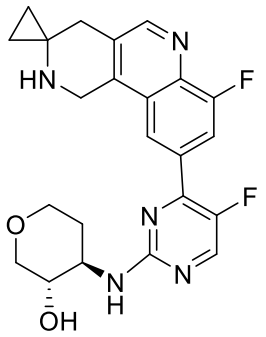
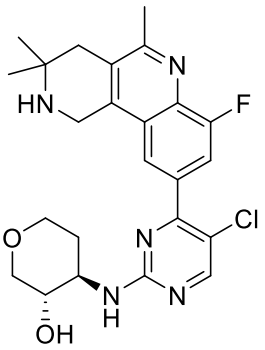
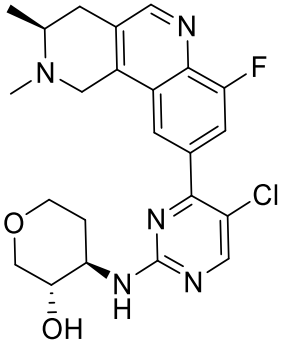
		
		
		
		
		

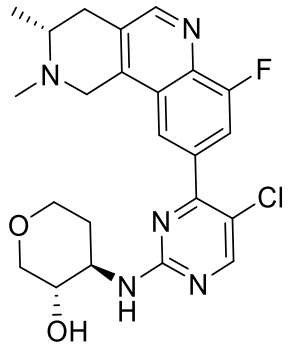
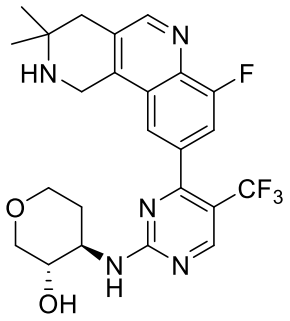
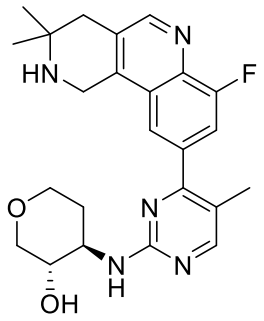
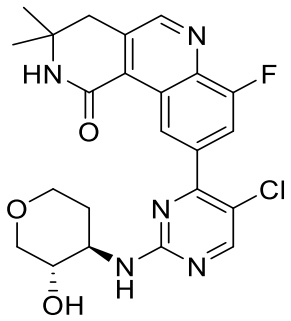
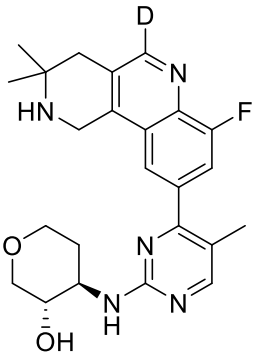
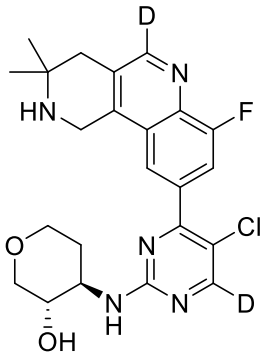
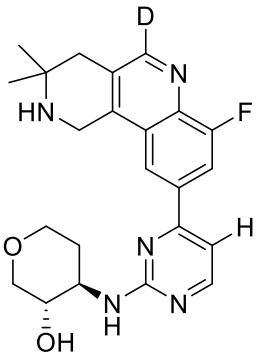
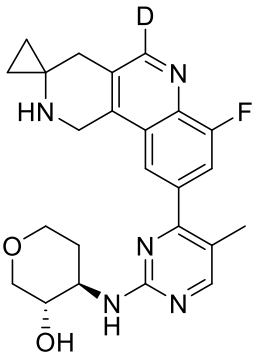
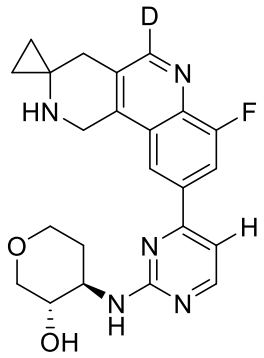
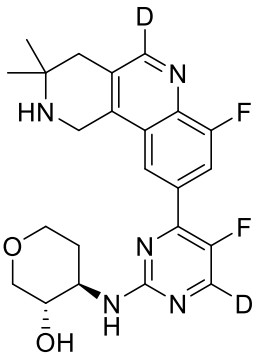
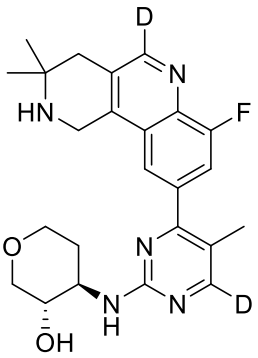
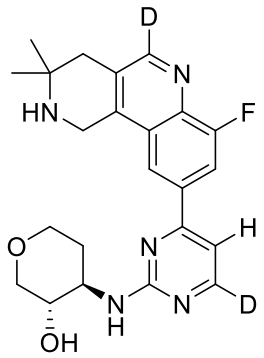
		
		
		
		
		

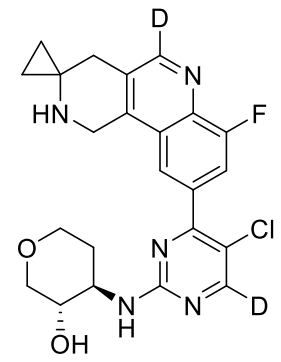
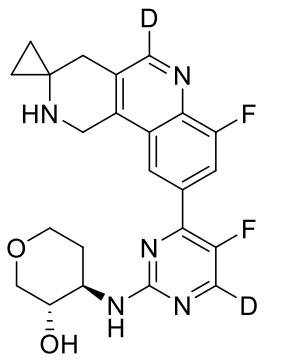
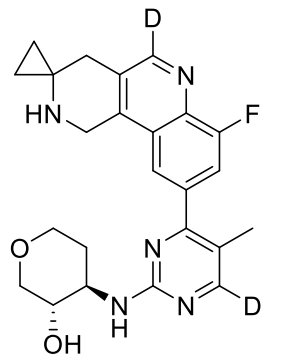
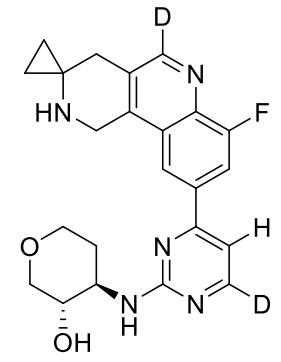
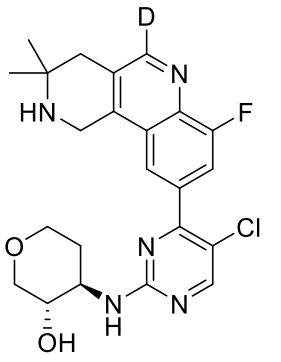
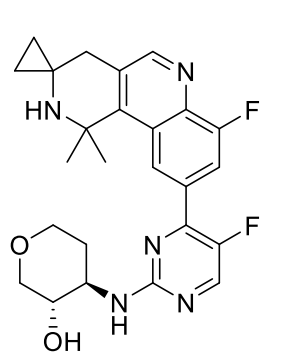
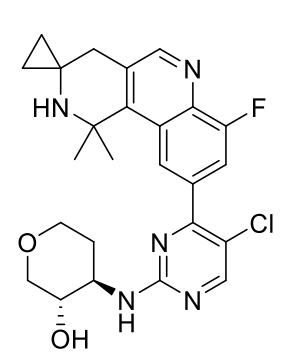
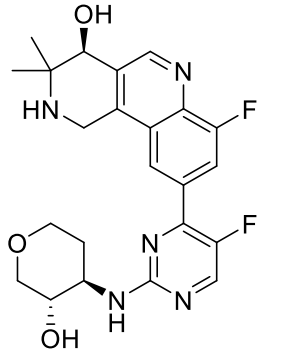
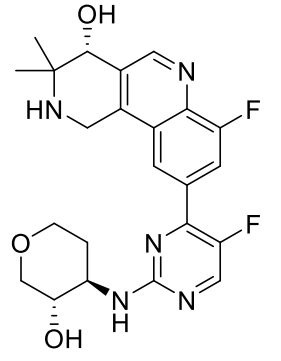
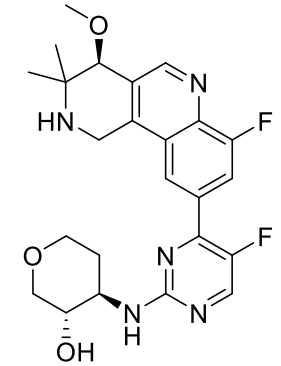
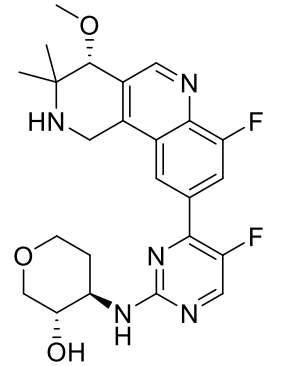
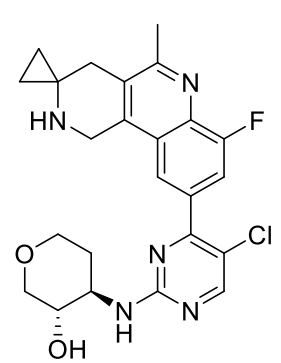
		
		
		
		

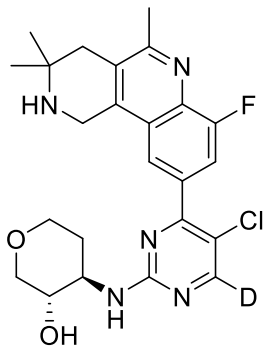
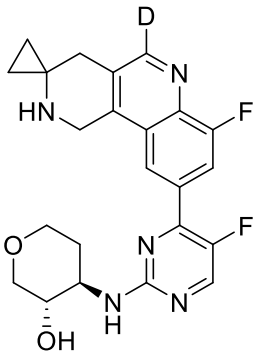
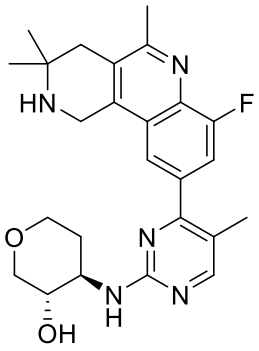
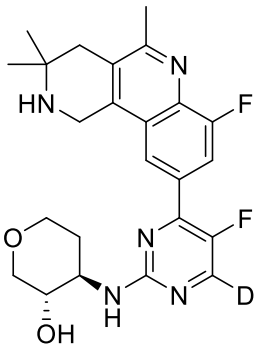
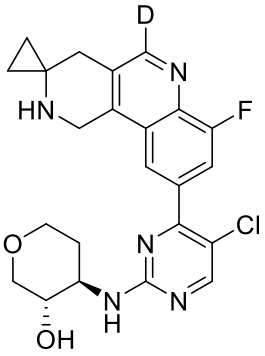
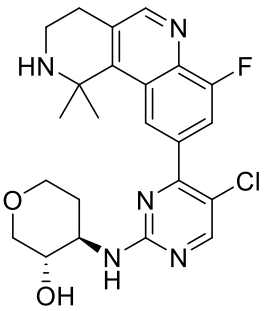
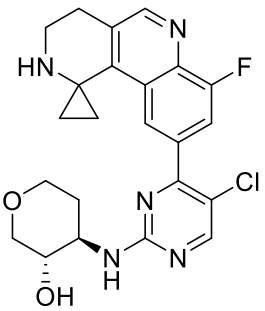
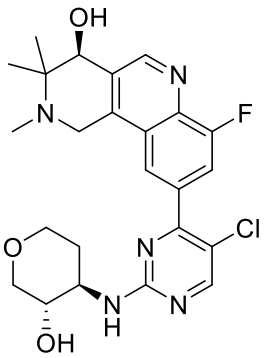
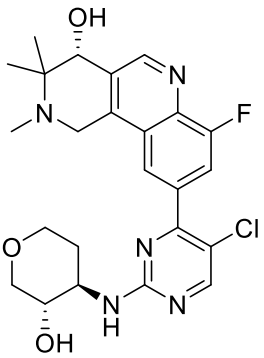
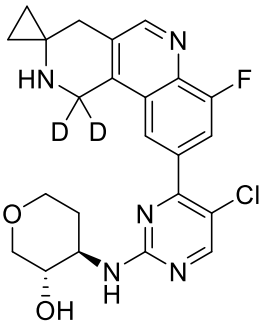
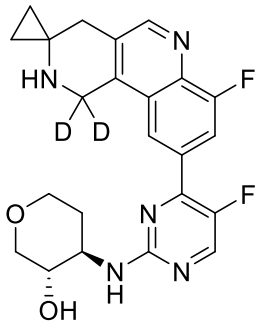
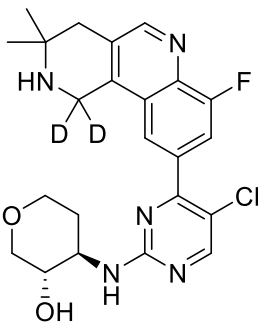
		
		
		
		

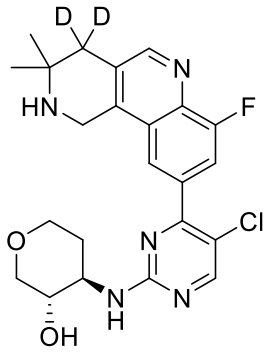
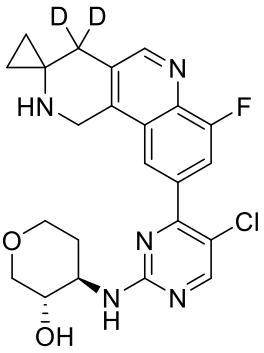
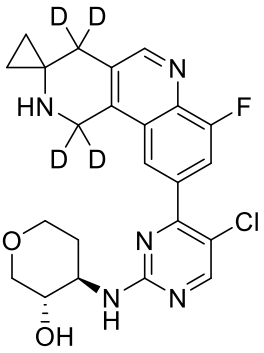
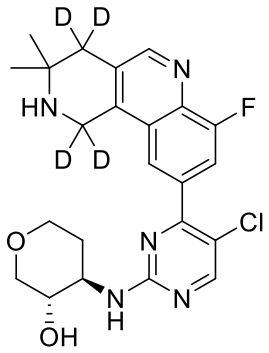
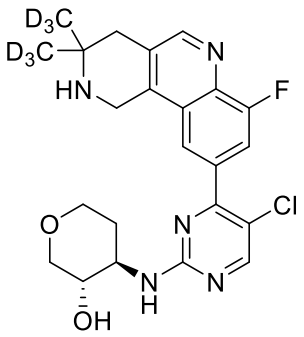
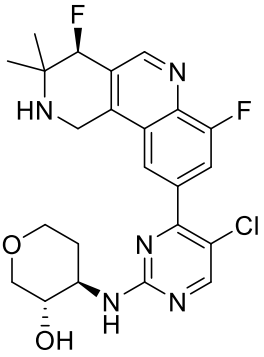
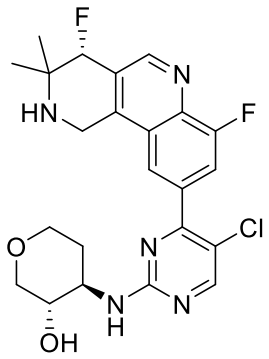
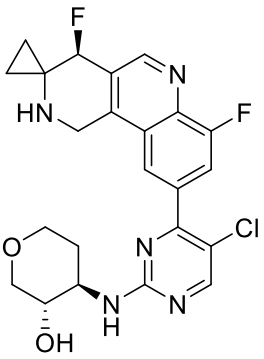
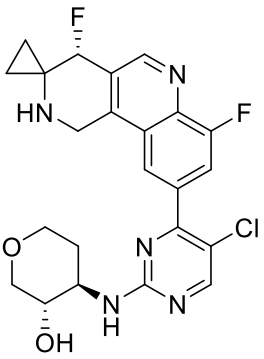
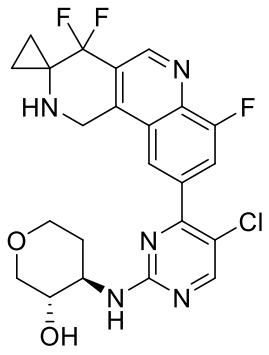
		
		
		
		

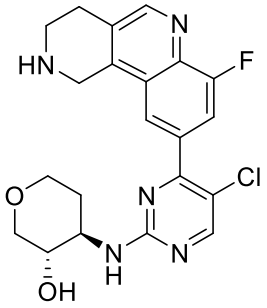
		
		
		
		

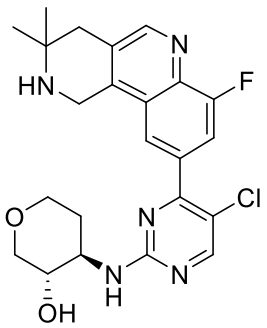
.

19. A compound, or a pharmaceutically acceptable salt thereof, wherein the compound is:



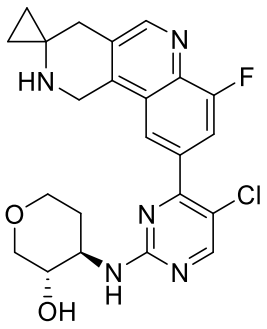
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20. A compound, or a pharmaceutically acceptable salt thereof, wherein the compound is:



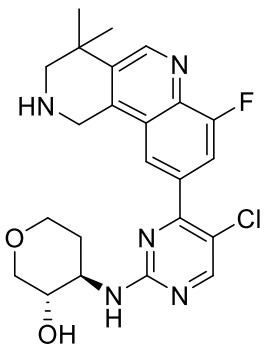
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21. A compound, or a pharmaceutically acceptable salt thereof, wherein the compound is:



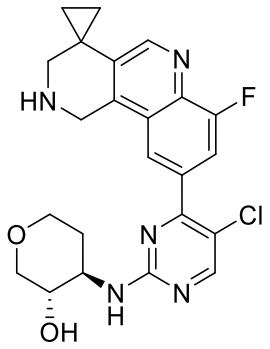
.

22. A compound, or a pharmaceutically acceptable salt thereof, wherein the compound is:



.

23. A compound, or a pharmaceutically acceptable salt thereof, wherein the compound is:



.

24. A composition comprising the compound of any one of claims 1-23, and a pharmaceutically acceptable excipient.

25. Use of a compound according to any one of claims 1-23, or a composition according to claim 24, in the manufacture of a medicament for the treatment of cancer; optionally breast cancer, ovarian cancer, bladder cancer, uterine cancer, prostate cancer, lung cancer, esophageal cancer, head and neck cancer, colorectal cancer, kidney cancer, liver cancer, pancreatic cancer, stomach cancer and/or thyroid cancer; optionally ovarian cancer.

26. Use of a compound or a composition according to claim 25, wherein the breast cancer is selected from ER-positive/HR-positive, HER2-negative breast cancer; ER-positive/HR-positive, HER2- positive breast cancer; triple negative breast cancer (TNBC); and inflammatory breast cancer; optionally endocrine resistant breast cancer, trastuzumab resistant breast cancer, or breast cancer demonstrating primary or acquired resistance to CDK4/CDK6 inhibition; optionally wherein the cancer is advanced or metastatic breast cancer; optionally wherein the cancer is mediated by CDK4.