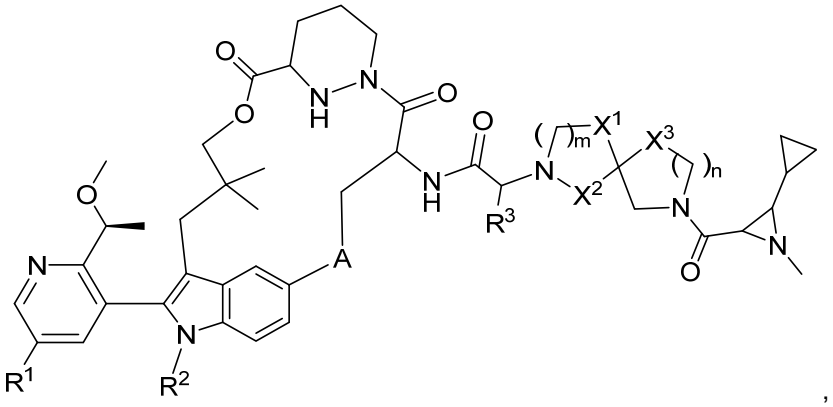
Claims

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



,

Formula I

wherein A is optionally substituted 3 to 6-membered heterocycloalkylene, optionally substituted 3 to 6-membered cycloalkylene, optionally substituted 6-membered arylene, or optionally substituted 5 to 10-membered heteroarylene;

X^1, X^2, and X^3 are each independently selected from CH_2, CHF, CF_2, C=O, or O;

m is 1 or 2;

n is 0 or 1;

R^1 is hydrogen, optionally substituted C_1-C_6 heteroalkyl, or optionally substituted 3 to 10-membered heterocycloalkyl;

R^2 is optionally substituted C_1-C_6 alkyl; and

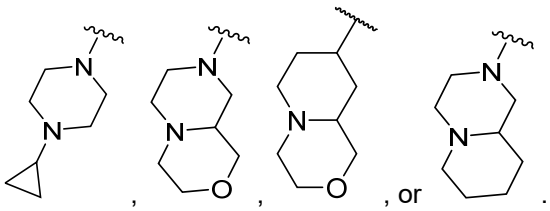
R^3 is optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted 3 to 6-membered cycloalkyl, or optionally substituted heterocycloalkyl,

and wherein each hydrogen is independently, optionally, isotopically enriched for deuterium.

2. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein R^1 is hydrogen or optionally substituted 3 to 10-membered heterocycloalkyl.

3. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein R^1 is optionally substituted 3 to 10-membered heterocycloalkyl.

4. The compound of claim 3, or a pharmaceutically acceptable salt thereof, wherein R^1 is:



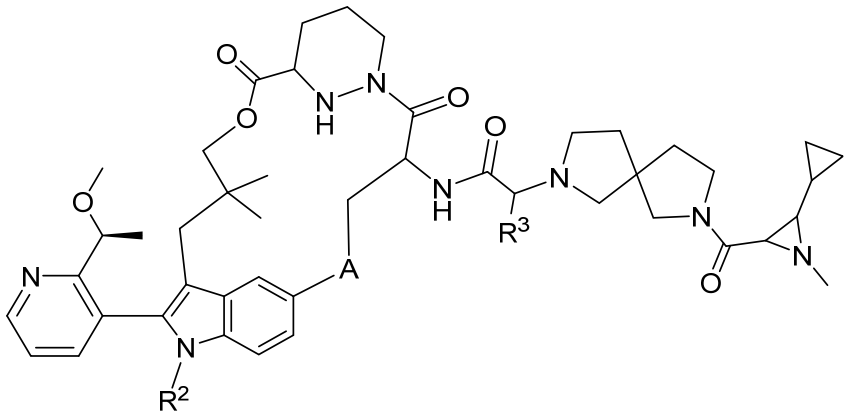
, , , , or .

5. The compound of any one of claims 1 to 4, or a pharmaceutically acceptable salt thereof, wherein m is 1.

6. The compound of any one of claims 1 to 5, or a pharmaceutically acceptable salt thereof, wherein n is 1.

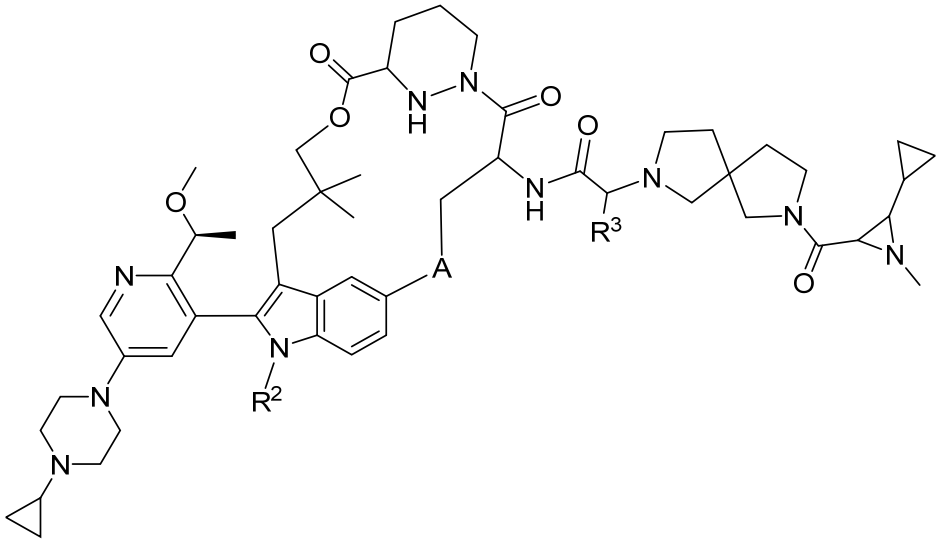
7. The compound of any one of claims 1 to 6, or a pharmaceutically acceptable salt thereof, wherein each of X^1, X^2, and X^3 is CH_2.

8. The compound of claim 1, or a pharmaceutically acceptable salt thereof, having the structure of Formula II:



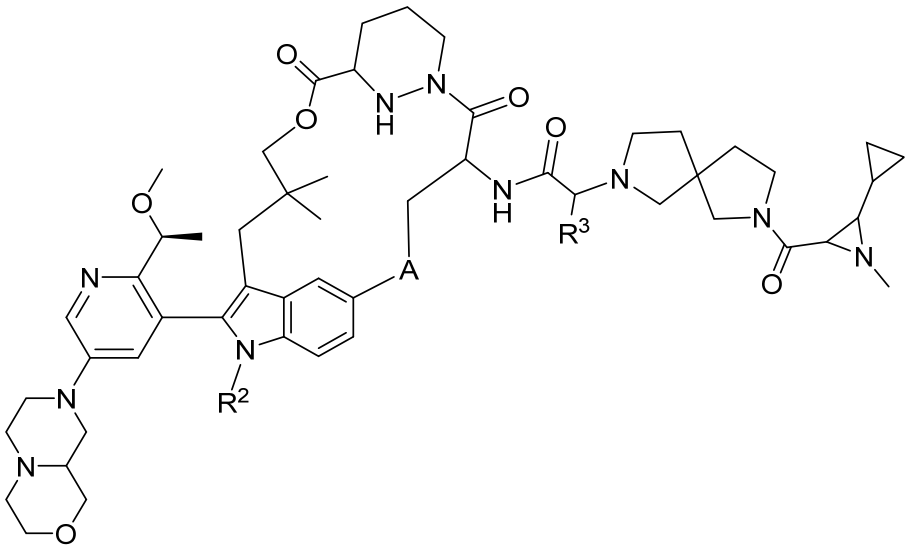
Formula II

9. The compound of claim 1, or a pharmaceutically acceptable salt thereof, having the structure of Formula V:



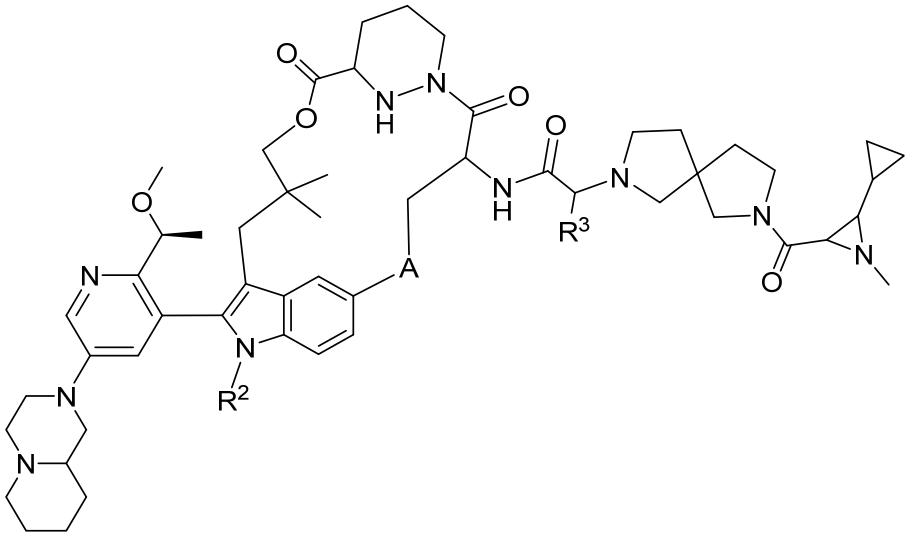
Formula V

10. The compound of claim 1, or a pharmaceutically acceptable salt thereof, having the structure of Formula VI:



Formula VI

11. The compound of claim 1, or a pharmaceutically acceptable salt thereof, having the structure of Formula VII:

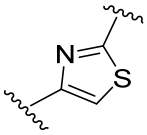


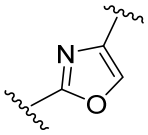
Formula VII

12. The compound of any one of claims 1 to 11, or a pharmaceutically acceptable salt thereof, wherein A is optionally substituted thiazole-diyl, optionally substituted oxazole-diyl, optionally substituted morpholine-diyl, optionally substituted pyrrolidine-diyl, optionally substituted piperidine-diyl, or optionally substituted phenylene.

13. The compound of any one of claims 1 to 11, or a pharmaceutically acceptable salt thereof, wherein A is optionally substituted 5 to 10-membered heteroarylene.

14. The compound of claim 13, or a pharmaceutically acceptable salt thereof, wherein A is:

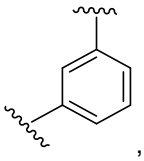
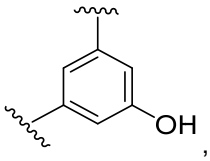


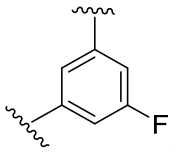
or 

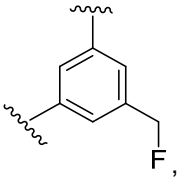
.

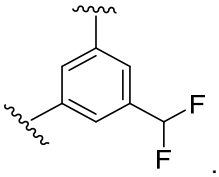
15. The compound of any one of claims 1 to 11, or a pharmaceutically acceptable salt thereof, wherein A is optionally substituted phenylene.

16. The compound of claim 15, or a pharmaceutically acceptable salt thereof, wherein A is:


, 

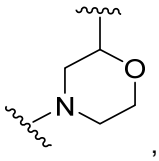
, 

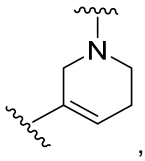
, 

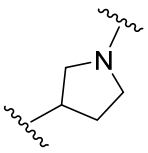
, or 

.

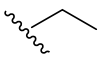
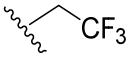
17. The compound of any one of claims 1 to 11, or a pharmaceutically acceptable salt thereof, wherein A is optionally substituted 3 to 6-membered heterocycloalkylene.

18. The compound of claim 17, or a pharmaceutically acceptable salt thereof, wherein A is selected from the following, or a stereoisomer thereof: 

, 

, or 

.

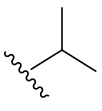
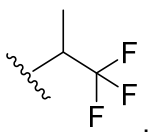
19. The compound of any one of claims 1 to 18, or a pharmaceutically acceptable salt thereof, wherein R^2 is:  or 

.

20. The compound of any one of claims 1 to 19, or a pharmaceutically acceptable salt thereof, wherein R^3 is optionally substituted C_1-C_6 alkyl or optionally substituted 3 to 6-membered cycloalkyl.

21. The compound of any one of claims 1 to 20, or a pharmaceutically acceptable salt thereof, wherein R^3 is optionally substituted C_1-C_6 alkyl.

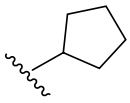
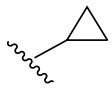
22. The compound of claim 21, or a pharmaceutically acceptable salt thereof, wherein R^3 is:


or 

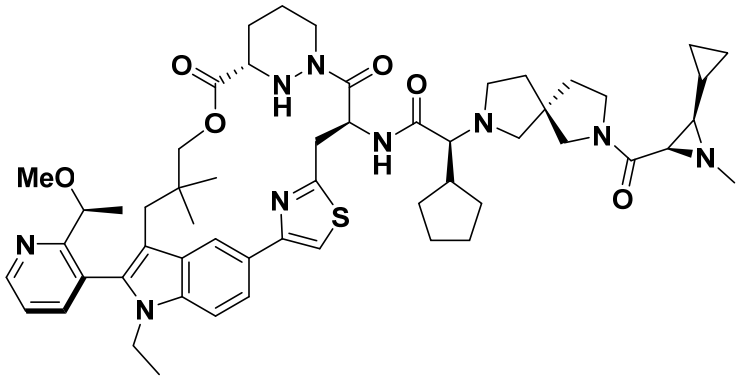
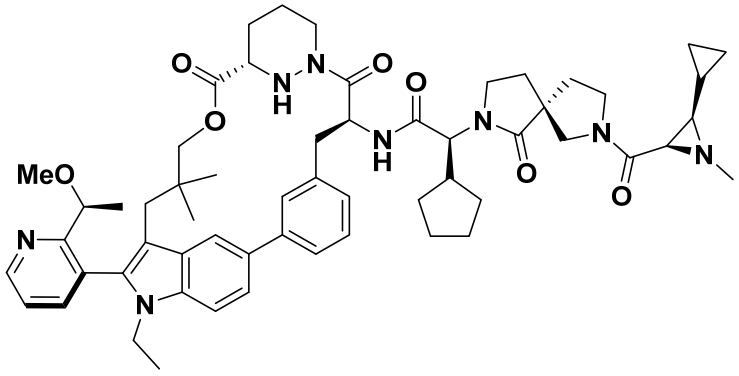
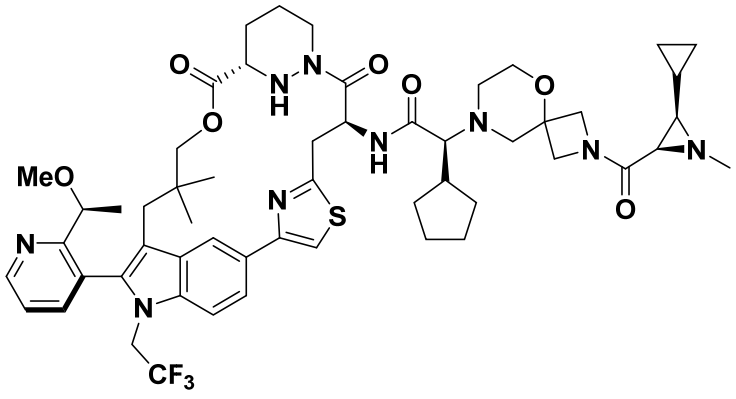
.

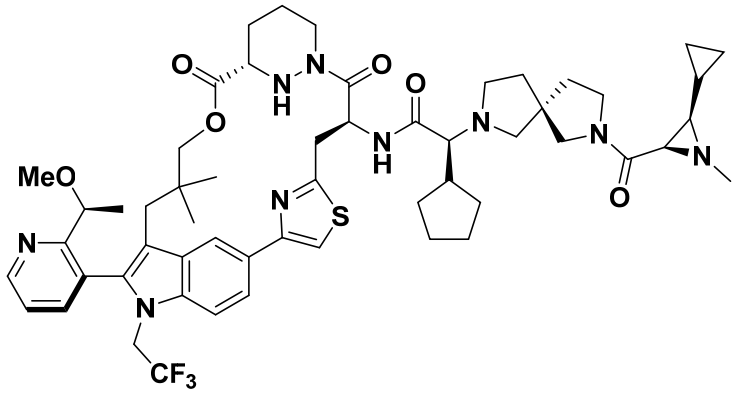
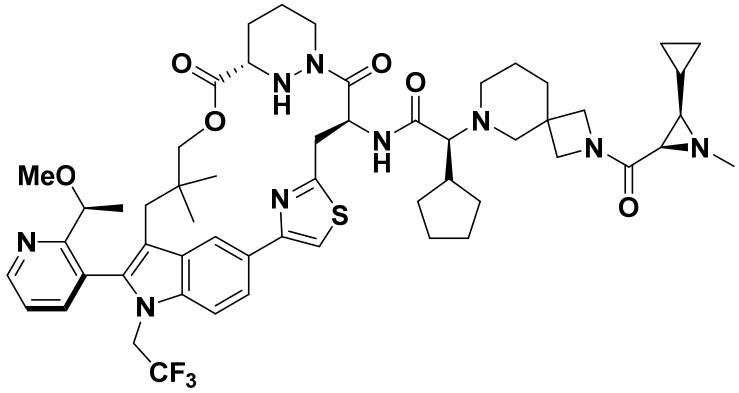
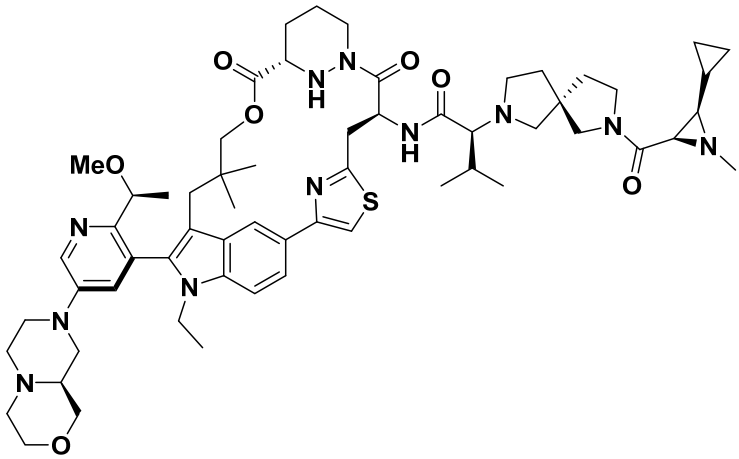
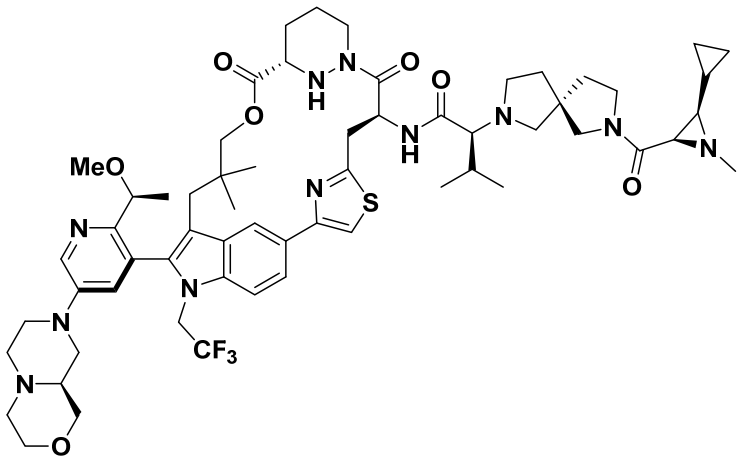
23. The compound of any one of claims 1 to 20, or a pharmaceutically acceptable salt thereof, wherein R^3 is or optionally substituted 3 to 6-membered cycloalkyl.

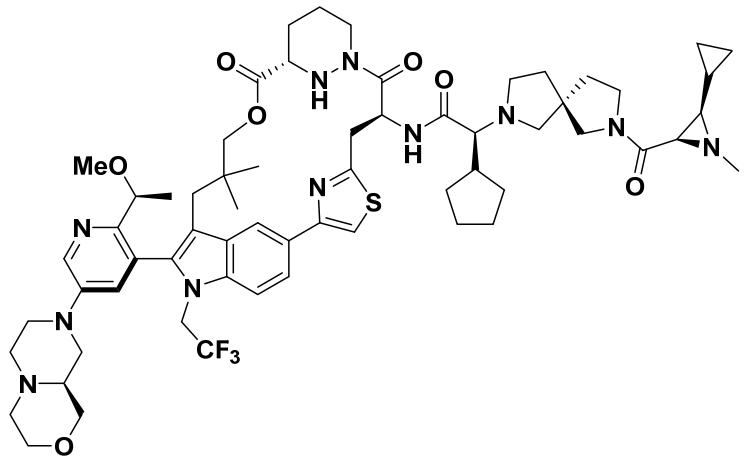
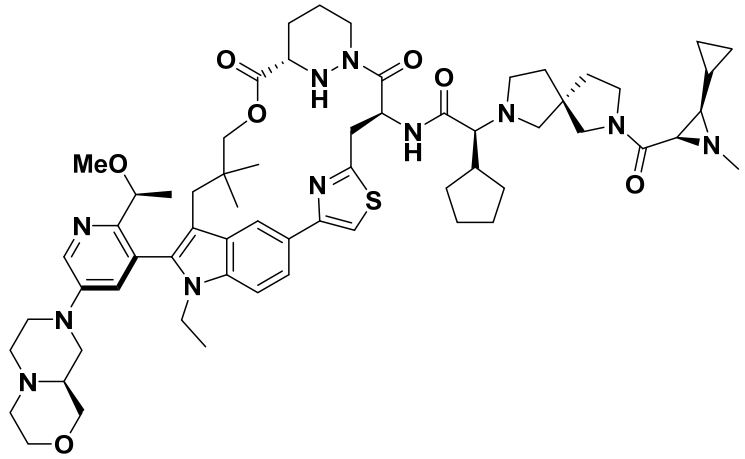
24. The compound of claim 23, or a pharmaceutically acceptable salt thereof, wherein R^3 is:

 or  .

25. The compound of any one of claims 1 to 24, or a pharmaceutically acceptable salt thereof, wherein the compound is not a compound selected from the group consisting of:

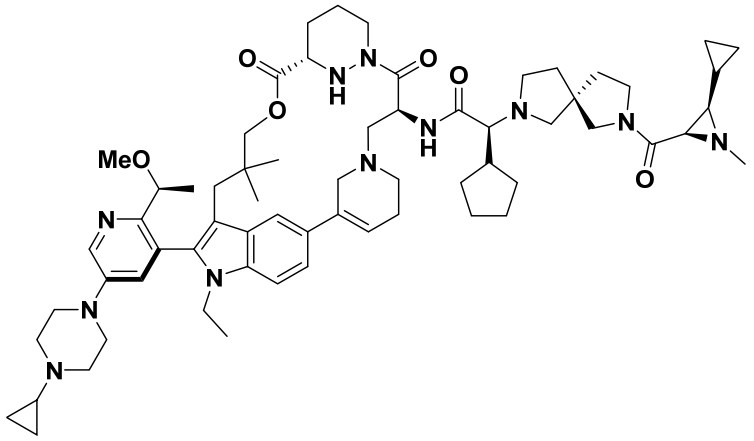
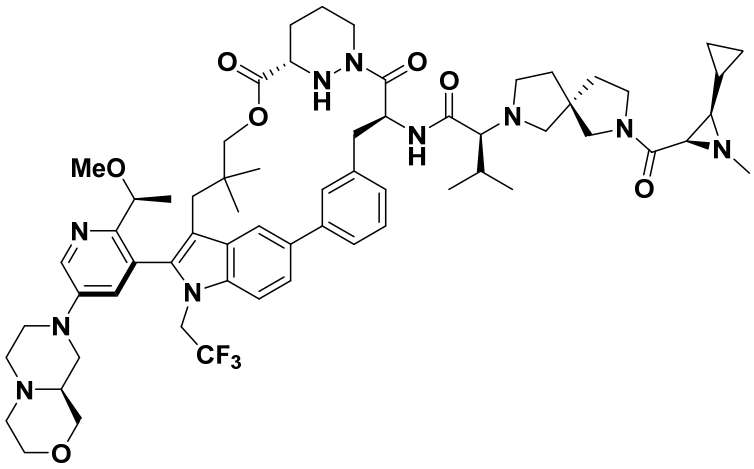
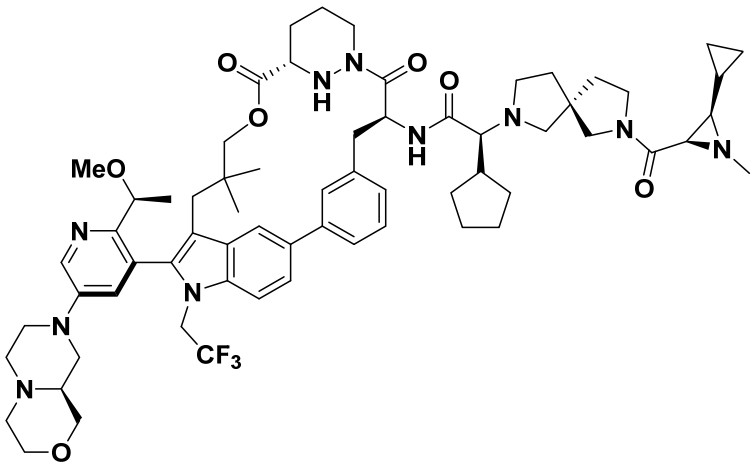
Ex#	Structure
C1	
C2	
C3	

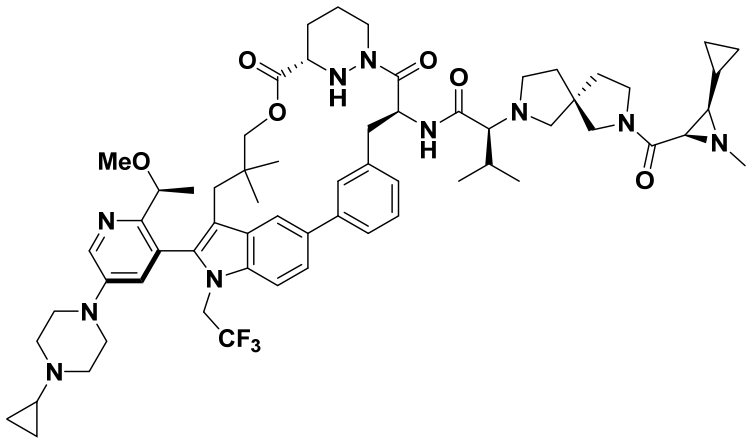
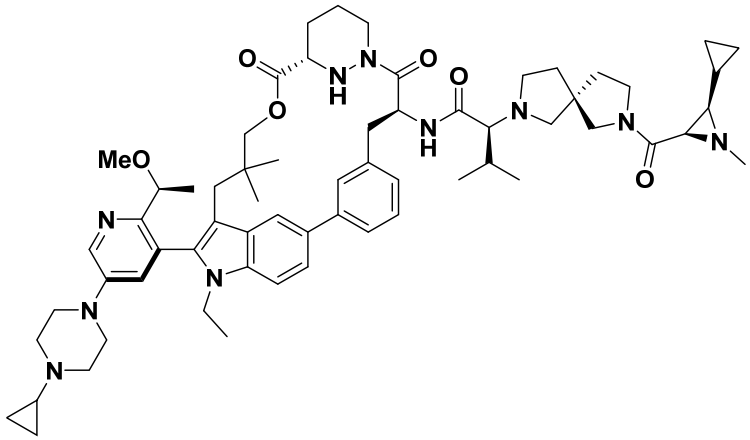
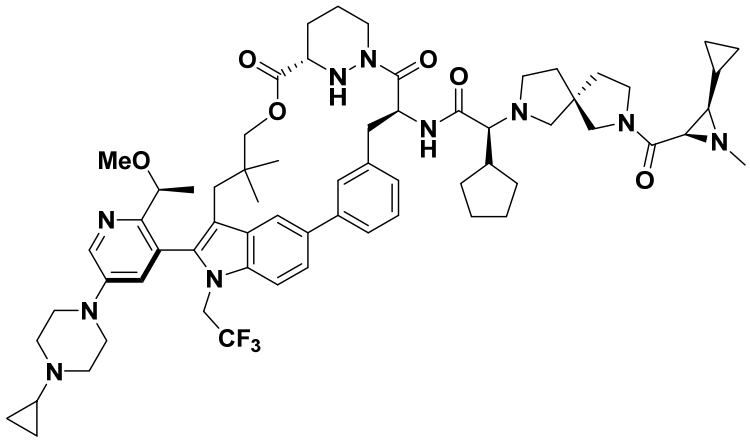
C4	
C5	
C6	
C7	

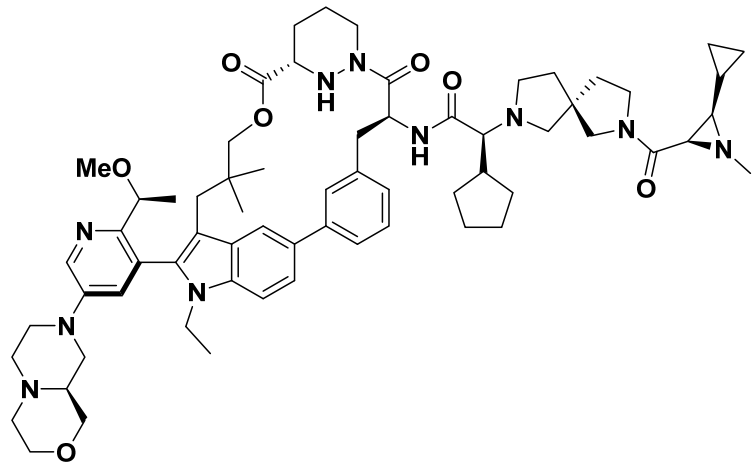
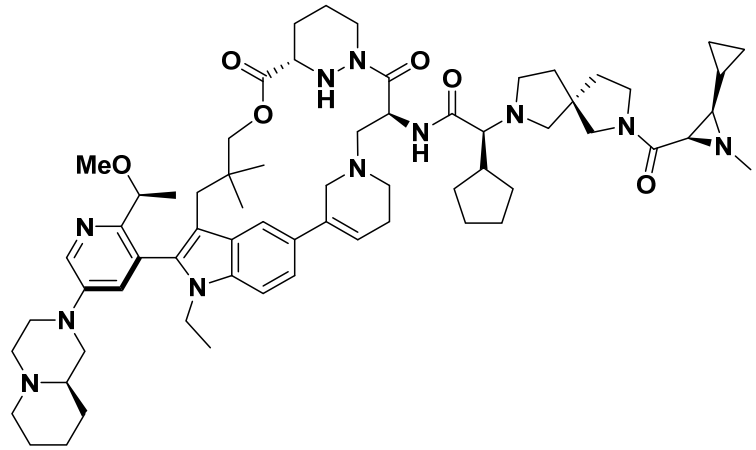
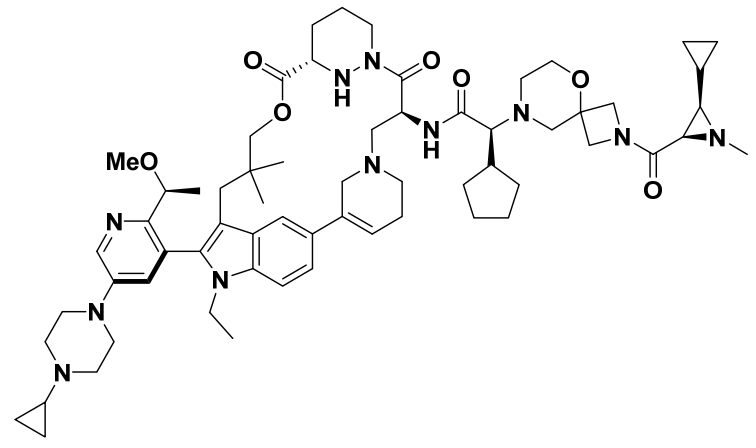
C8	 and
C9	

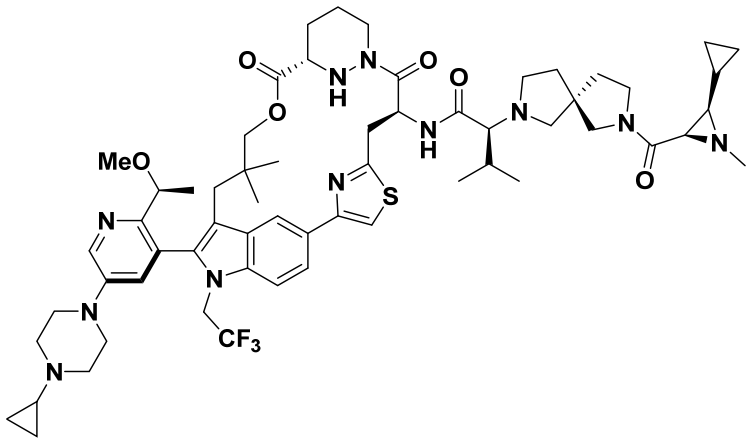
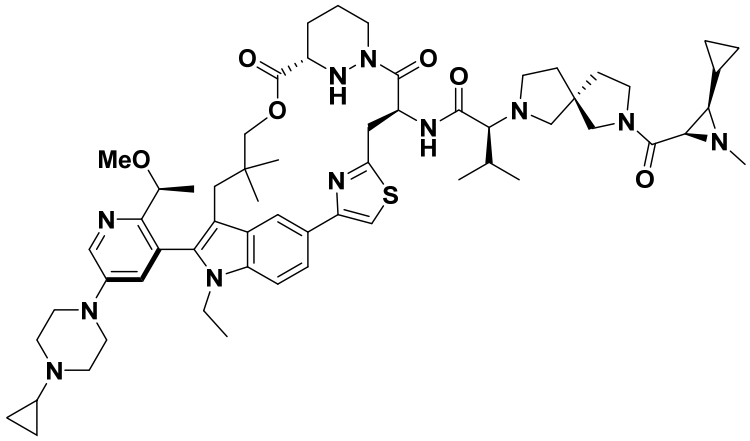
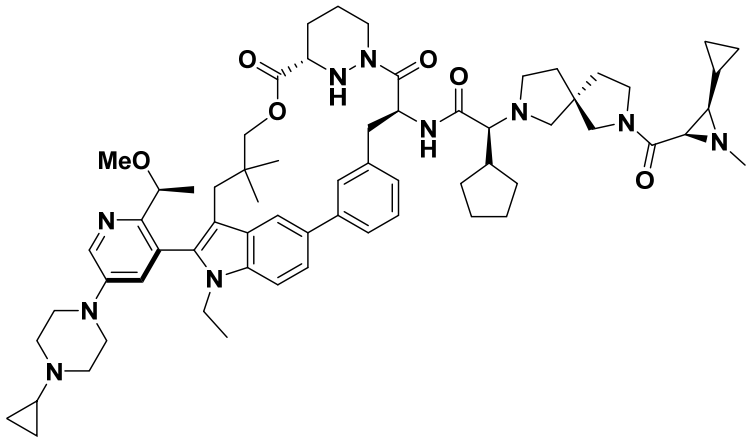
.

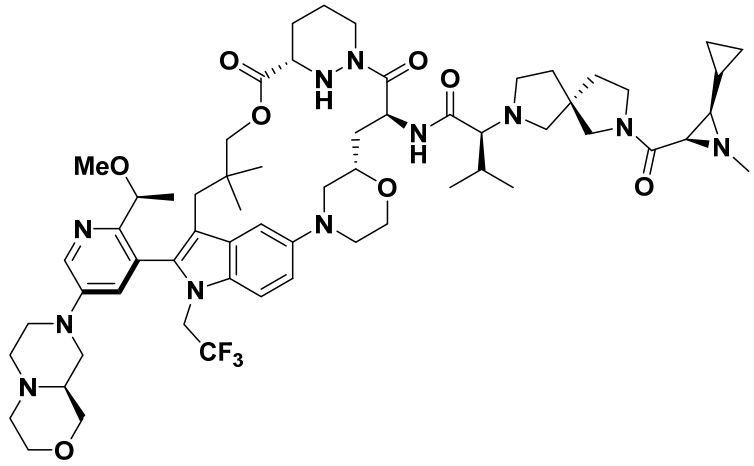
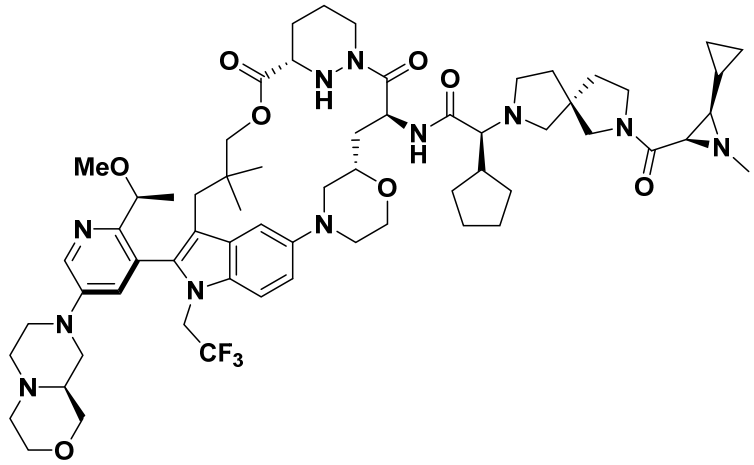
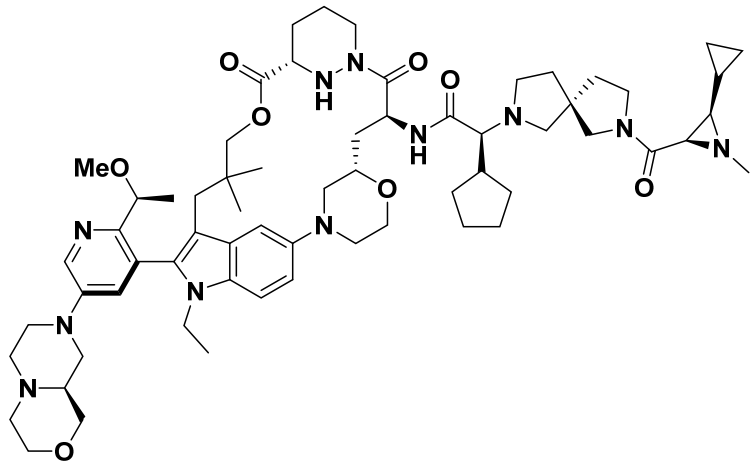
26. A compound, or a pharmaceutically acceptable salt thereof, having the structure of a compound selected from the group consisting of:

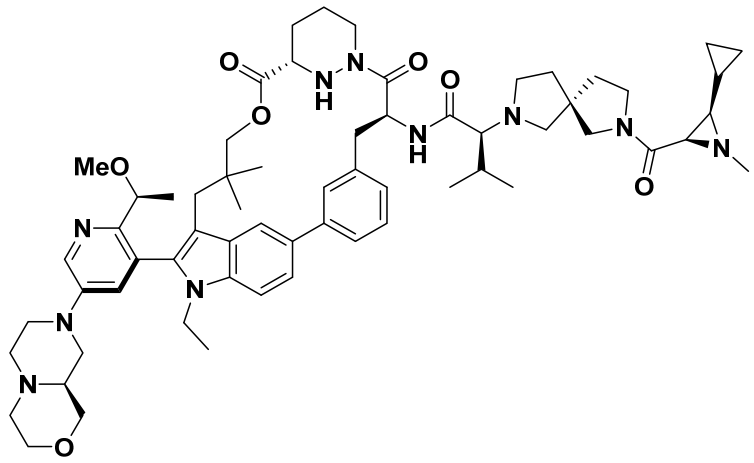
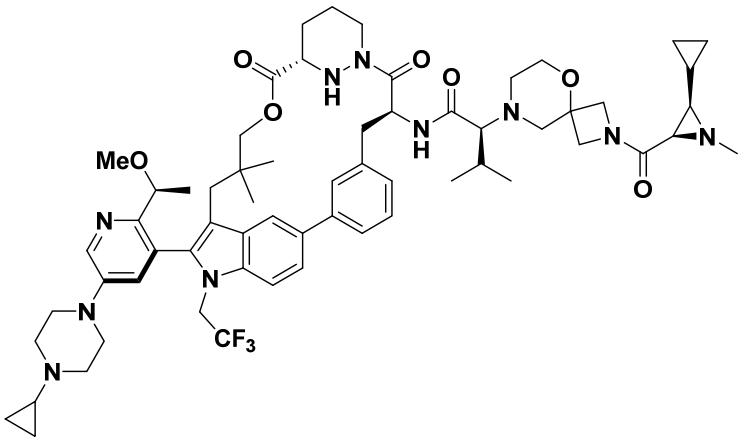
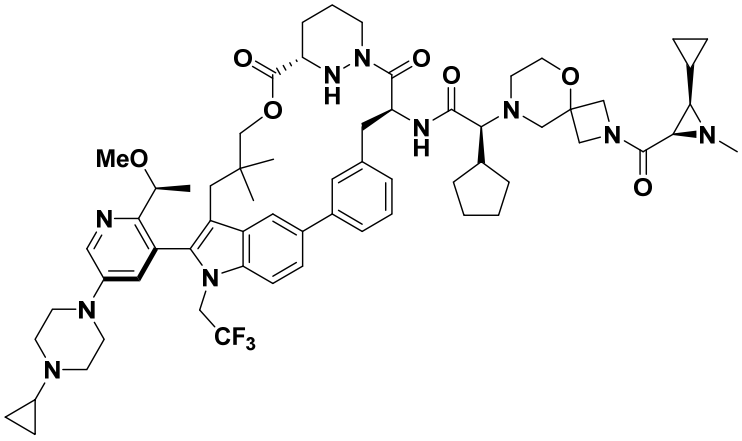
Ex#	Structure
A1	
A2	
A3	

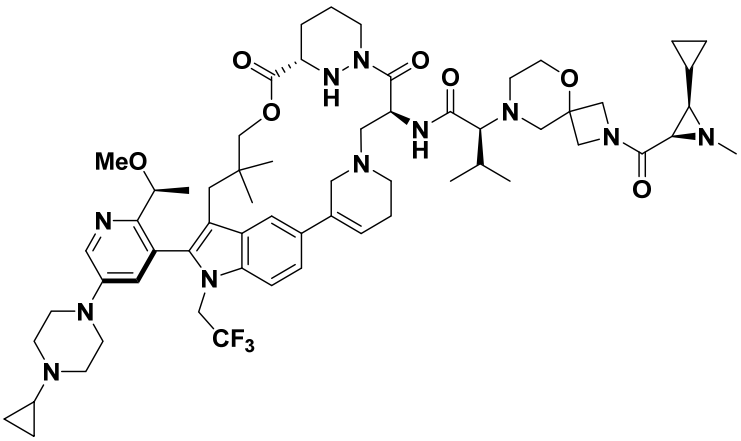
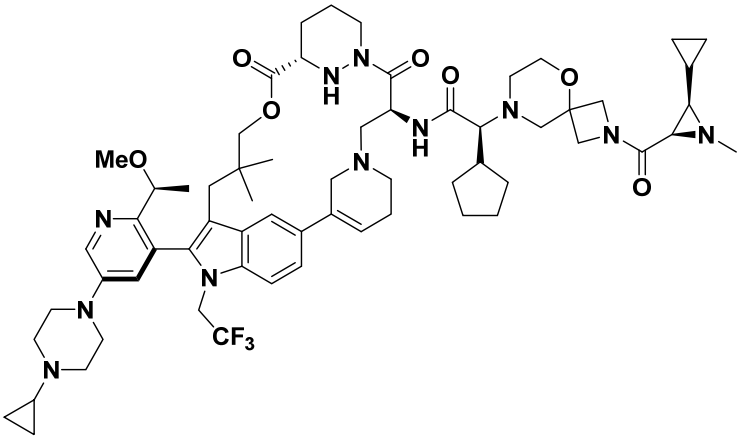
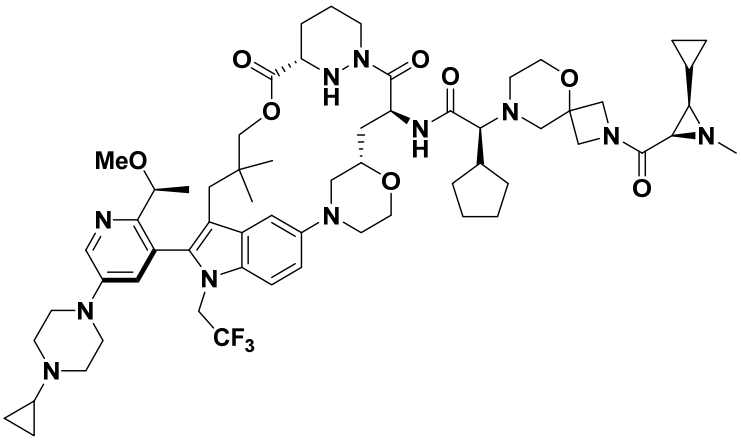
A4	
A5	
A6	

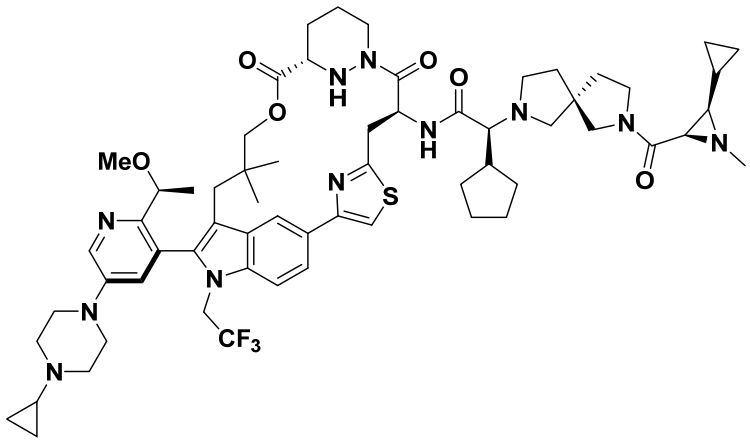
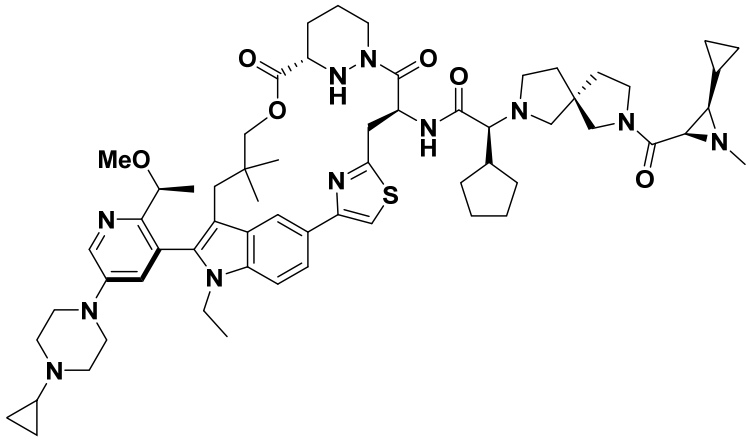
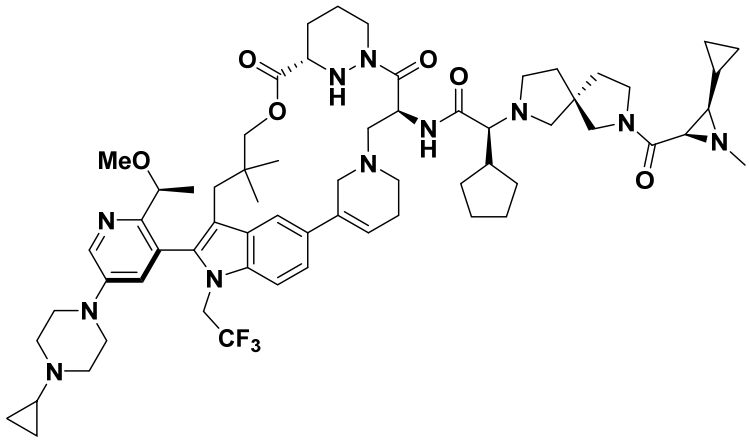
A7	
A8	
A9	

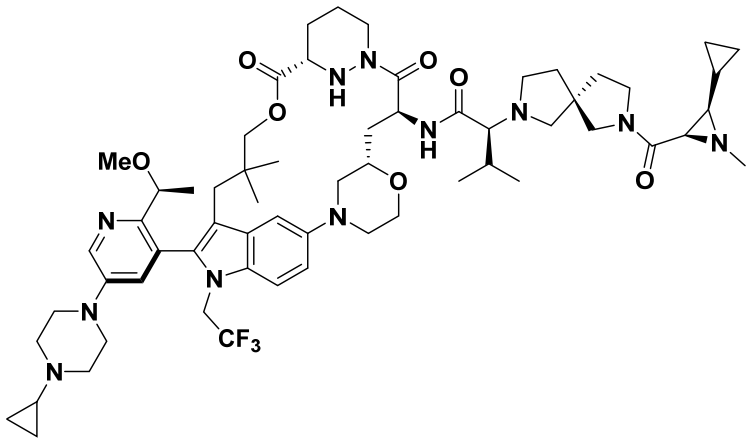
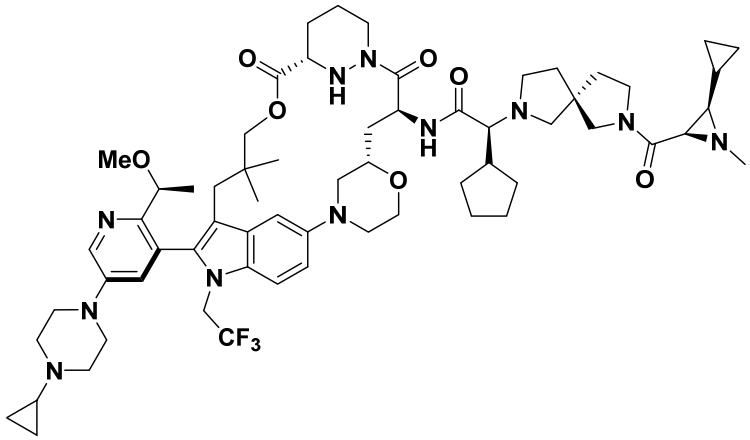
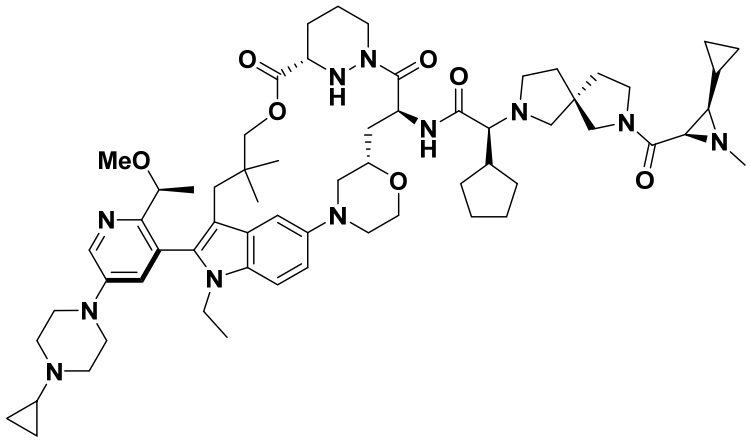
A10	
A11	
A12	

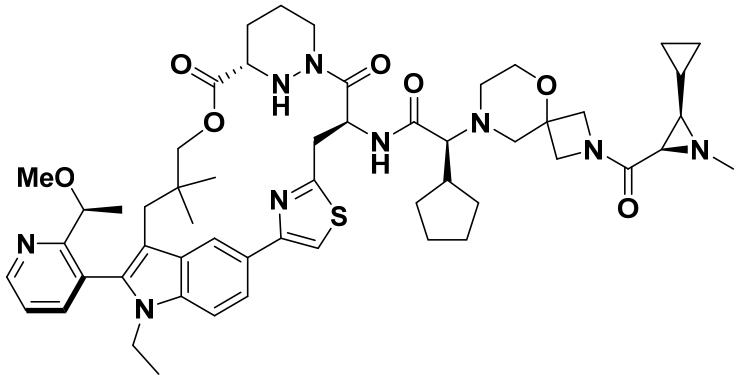
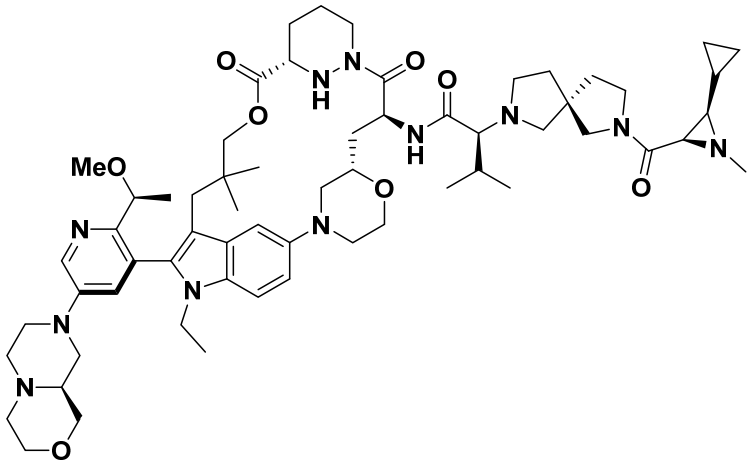
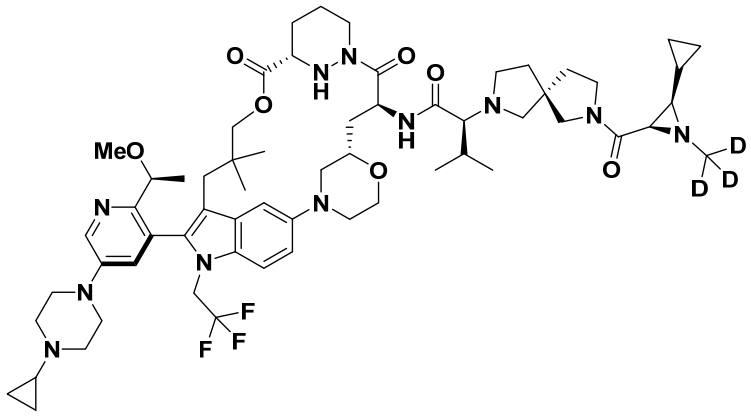
A13	
A14	
A15	

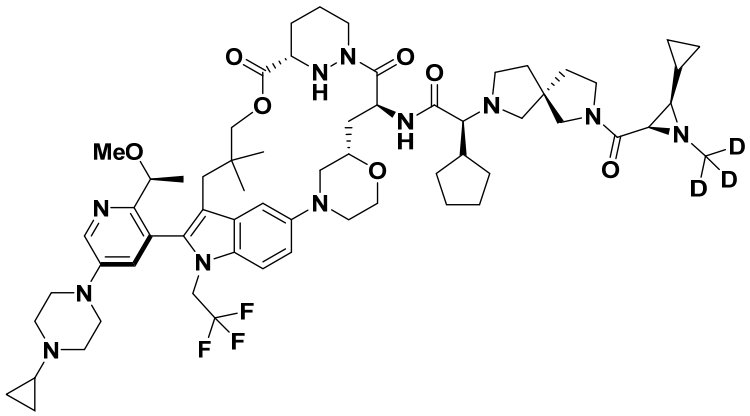
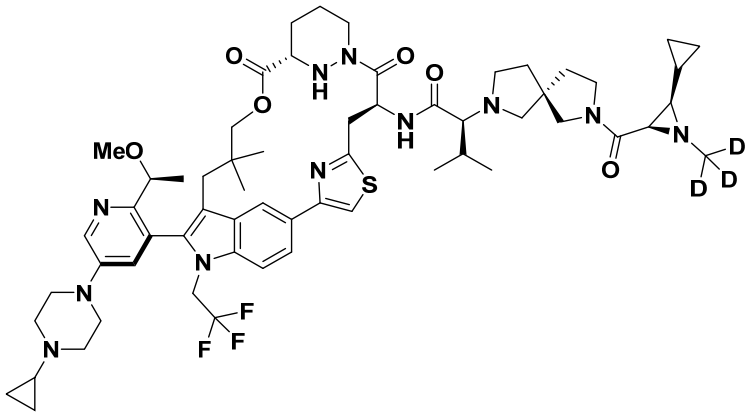
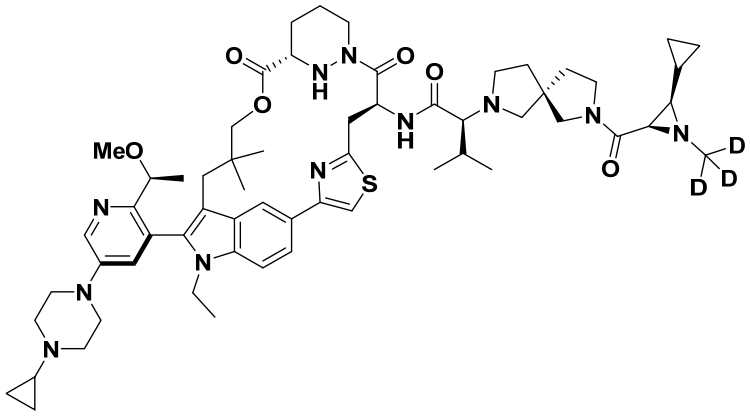
A16	
A17	
A18	

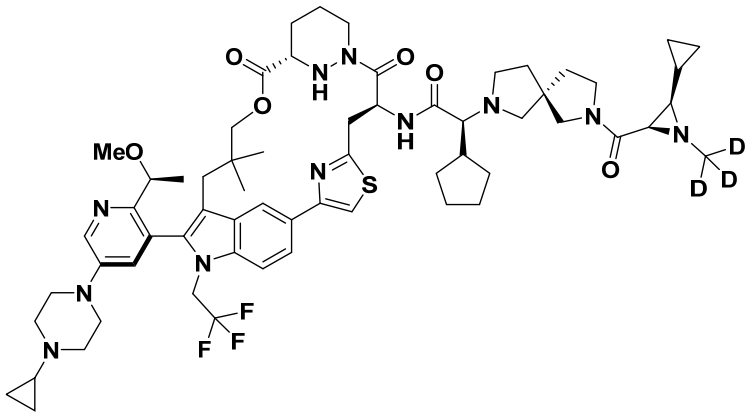
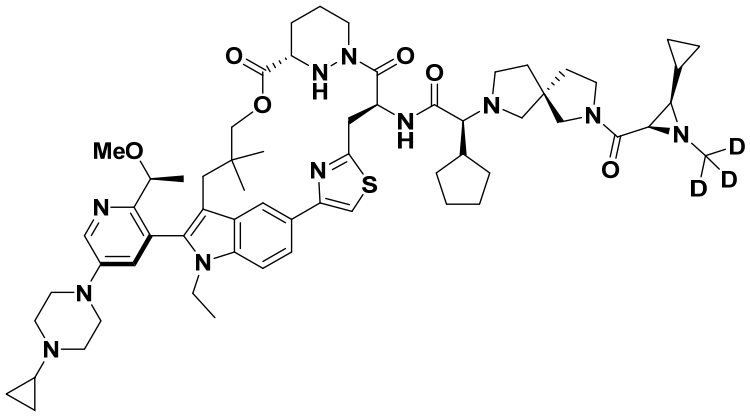
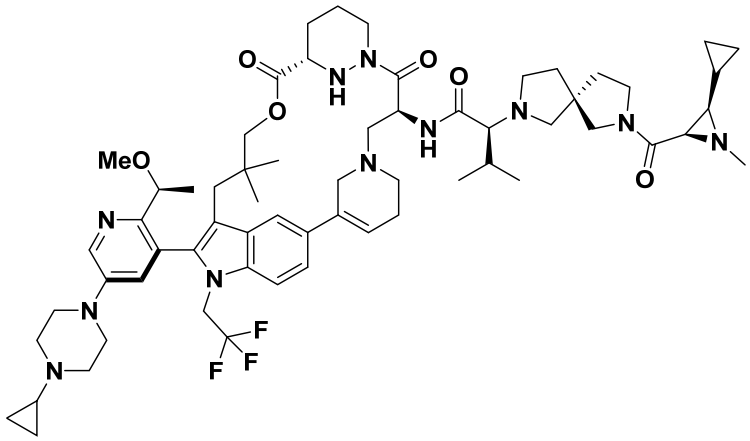
A19	
A20	
A21	

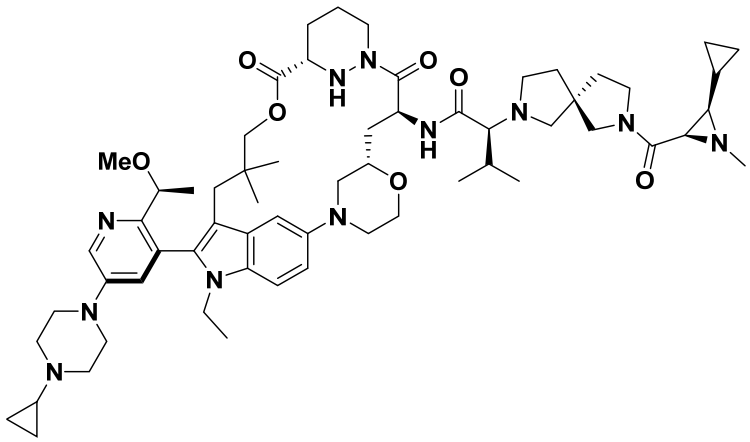
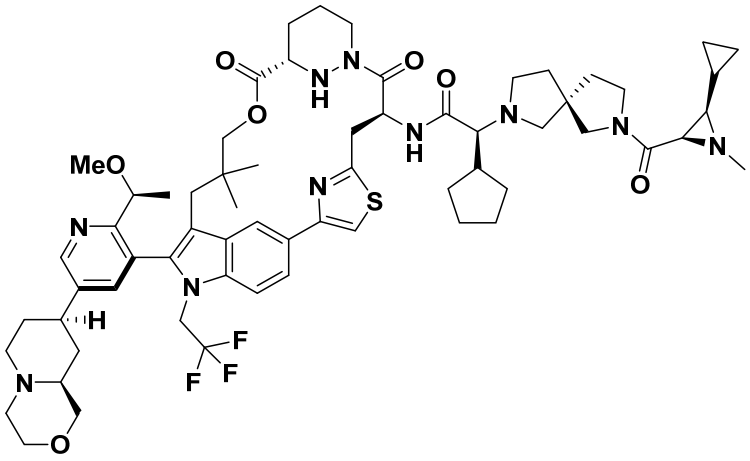
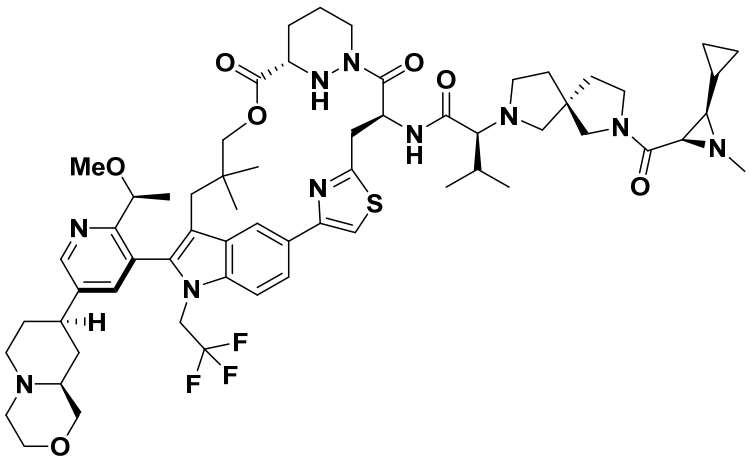
A22	
A23	
A24	

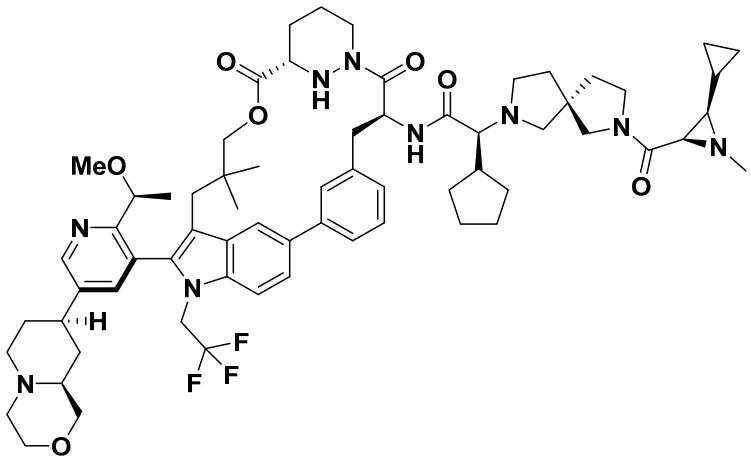
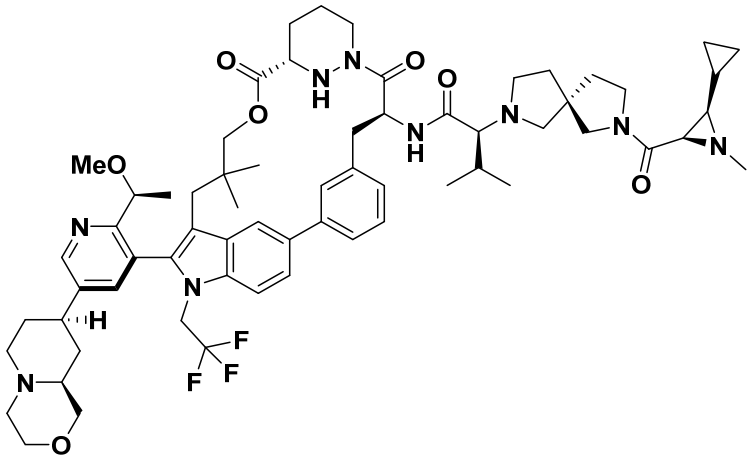
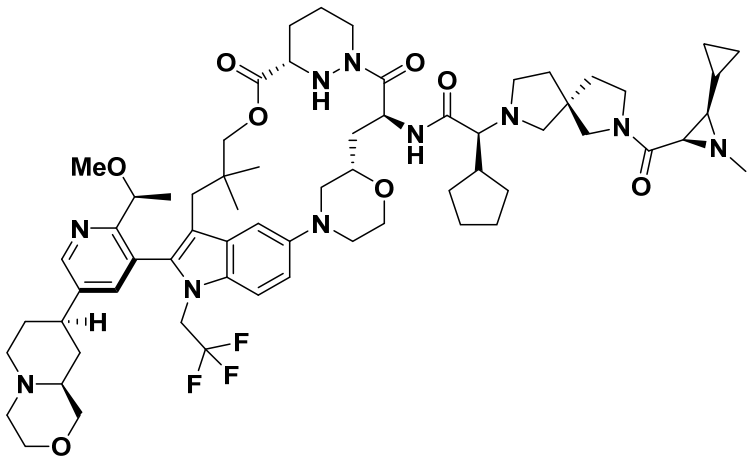
A25	
A26	
A27	

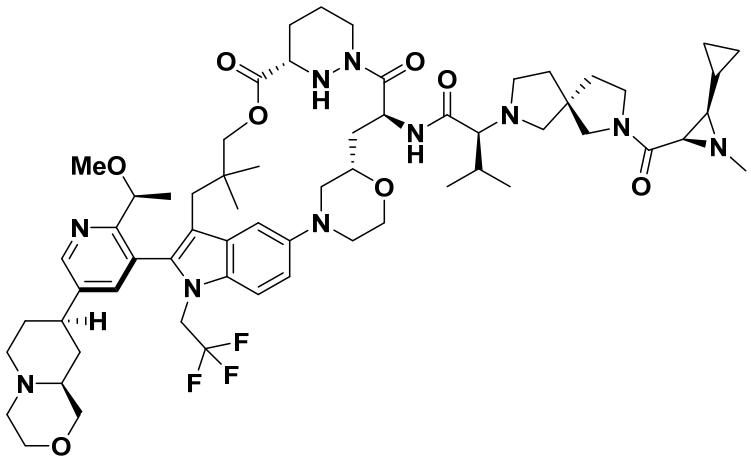
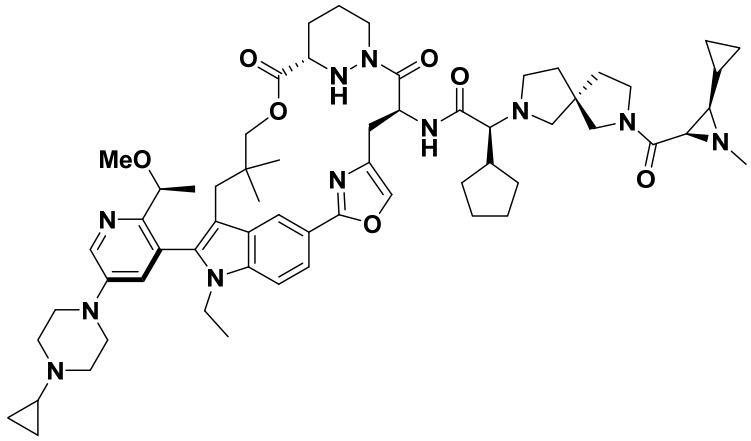
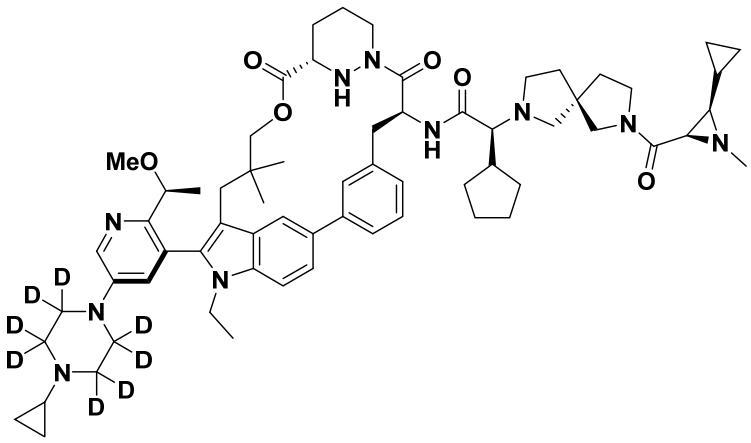
A28	
A29	
A30	

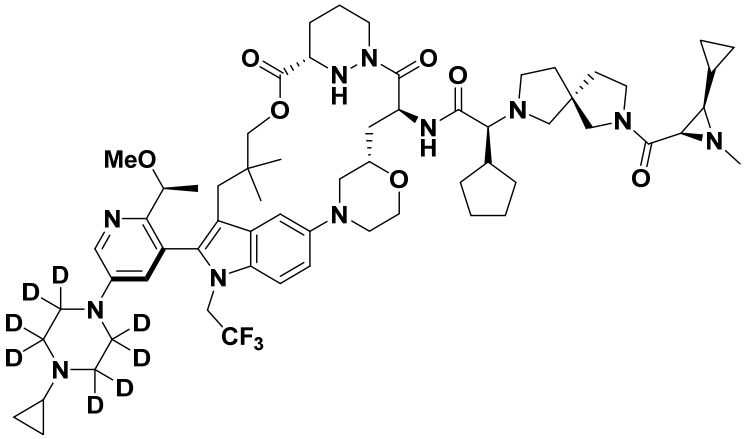
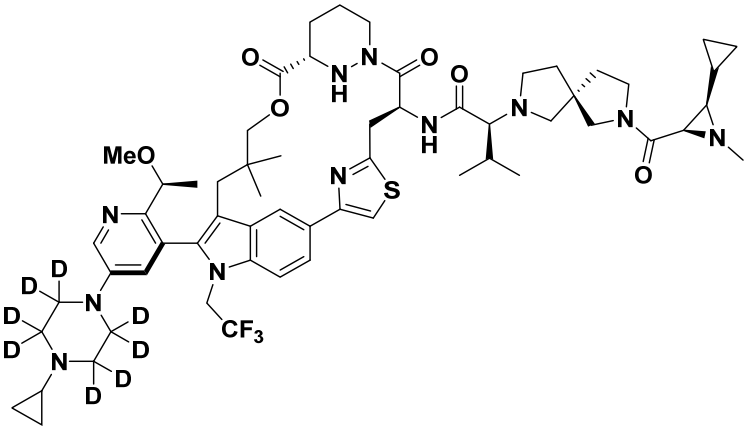
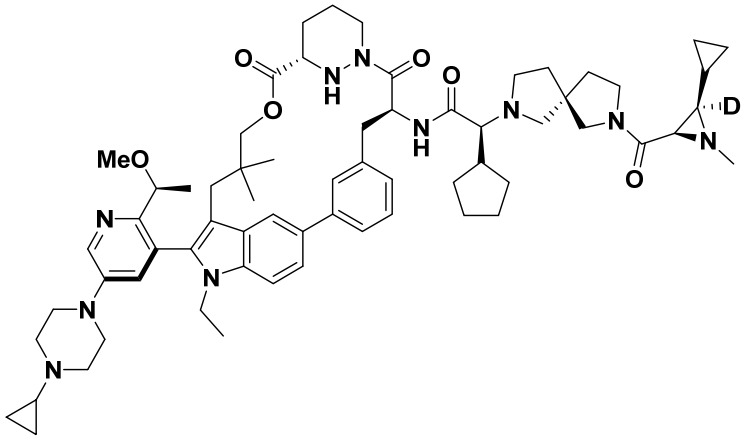
A31	
A32	
A33	

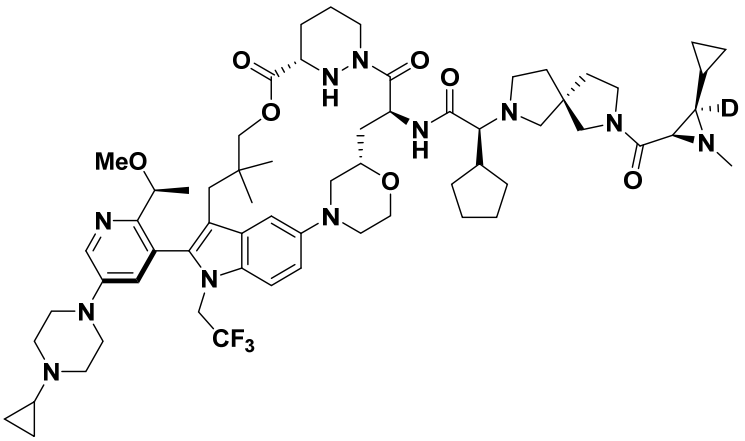
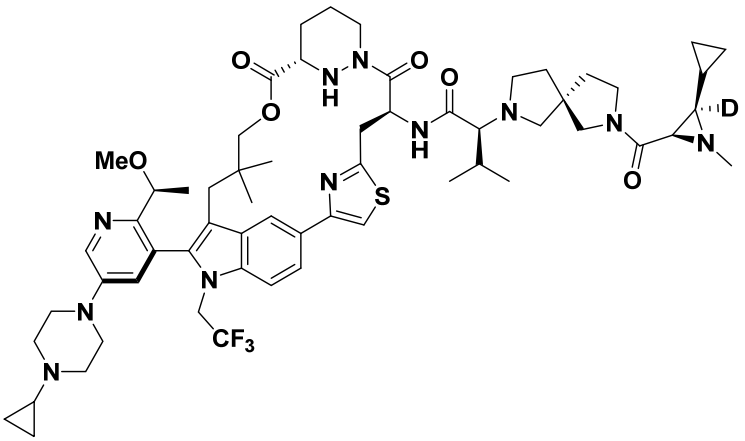
A34	
A35	
A36	

A37	
A38	
A39	

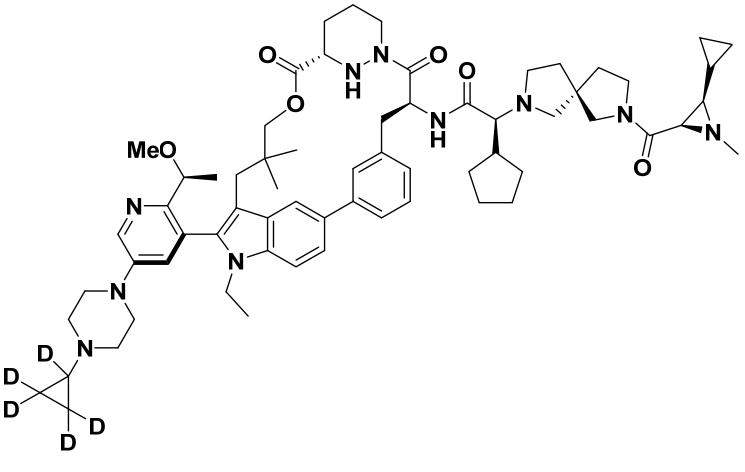
A40	
A41	
A42	

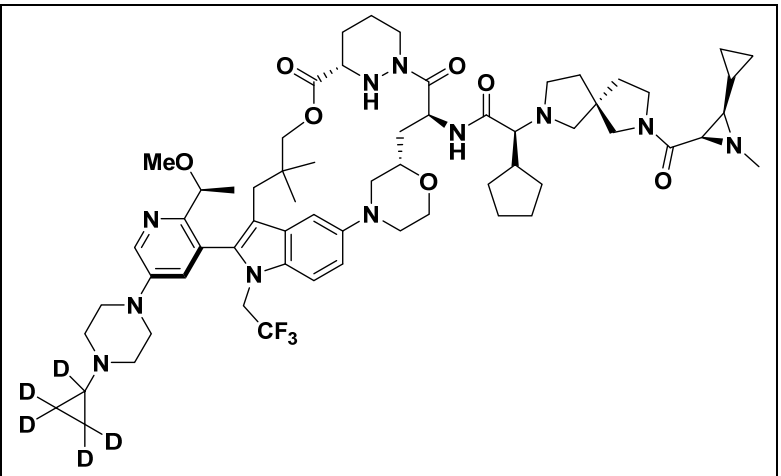
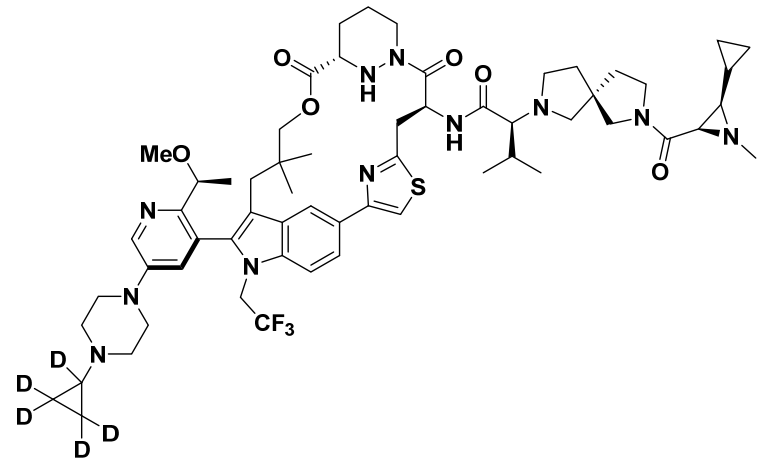
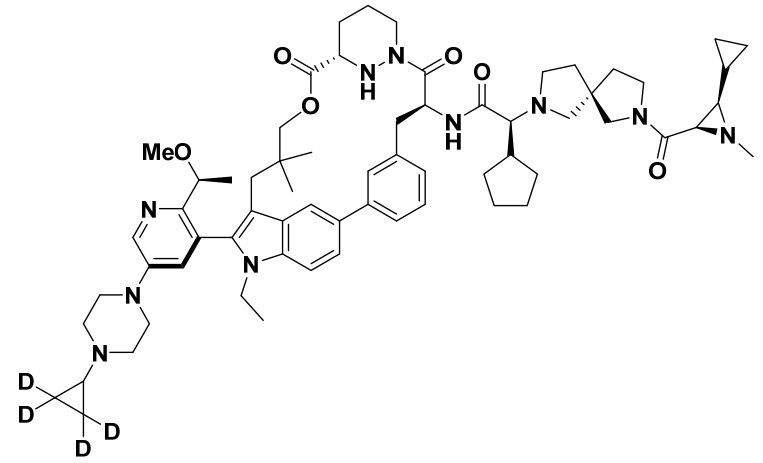
A43	
A44	
B7	

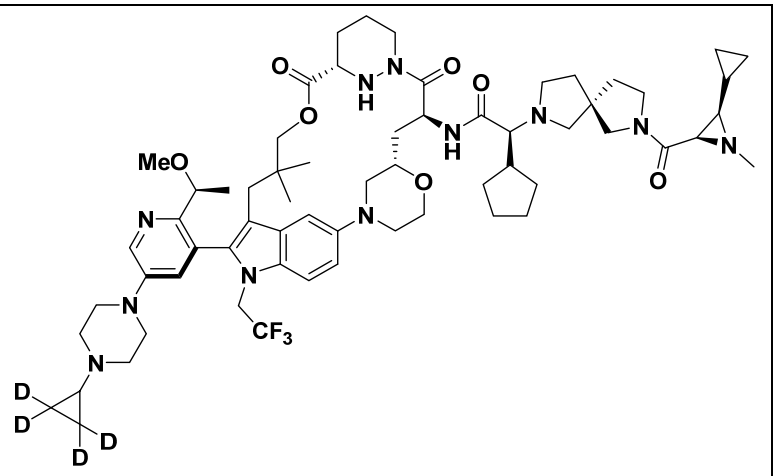
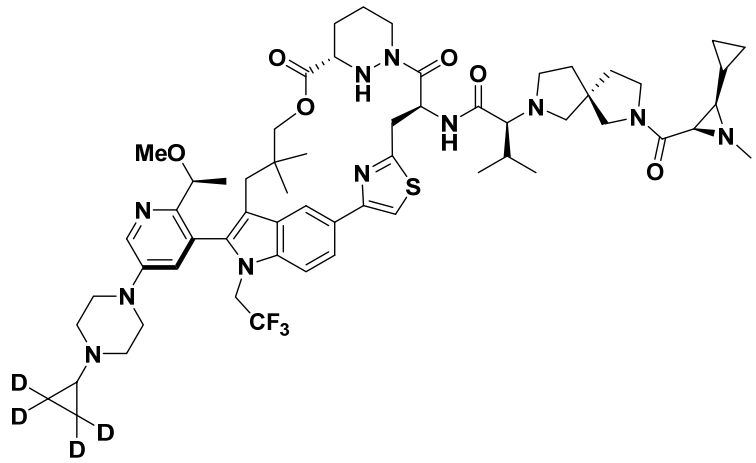
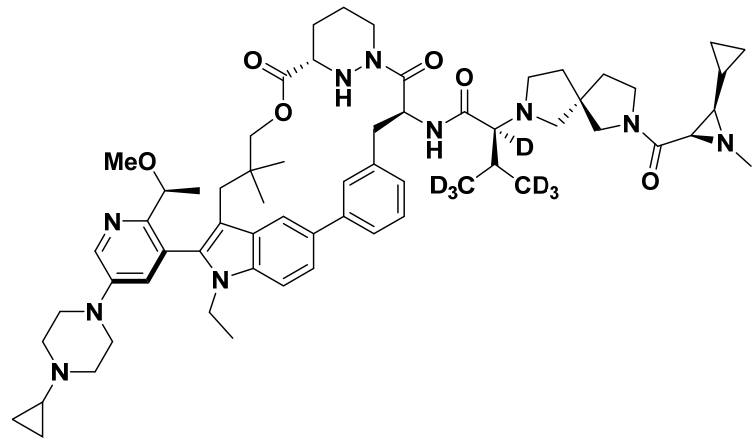
B8	
B9	
B28	

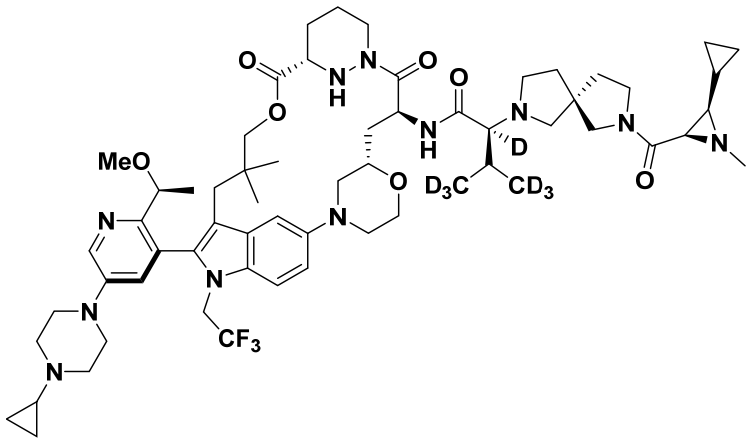
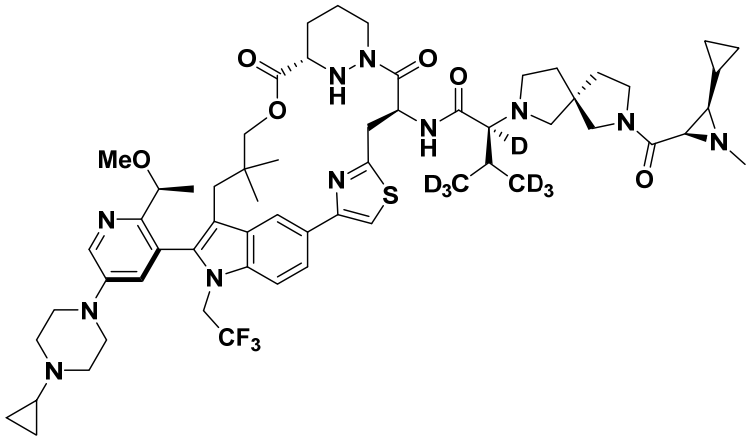
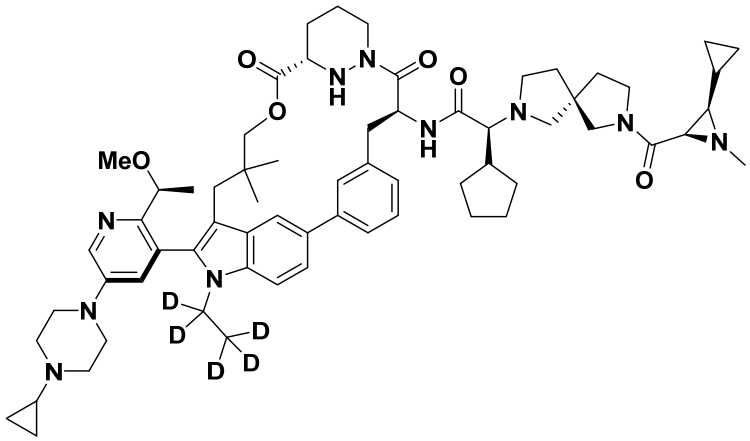
B29	 and
B30	

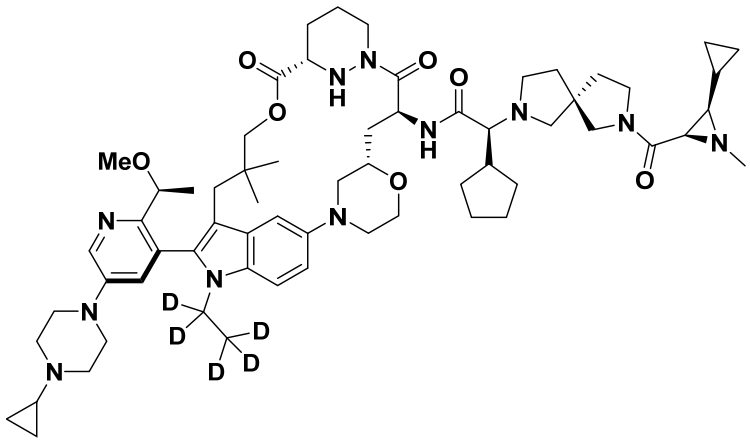
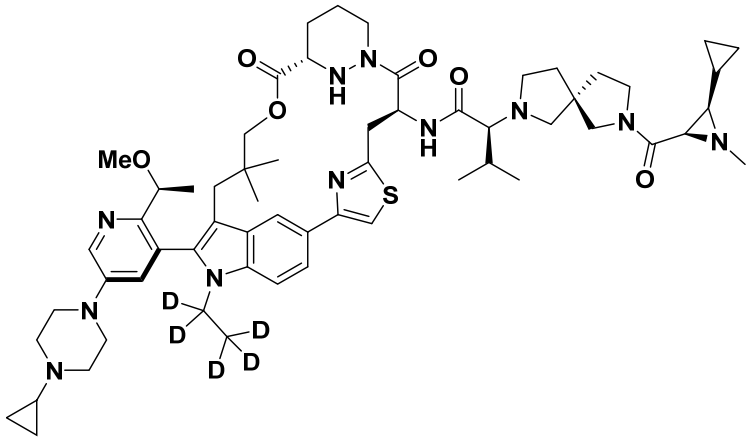
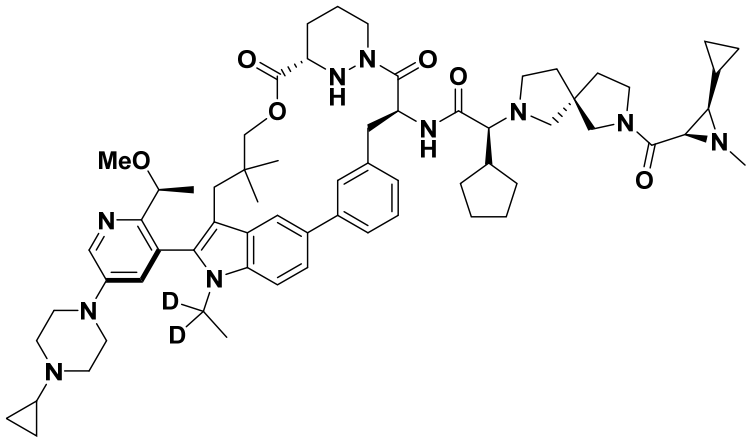
or the group consisting of:

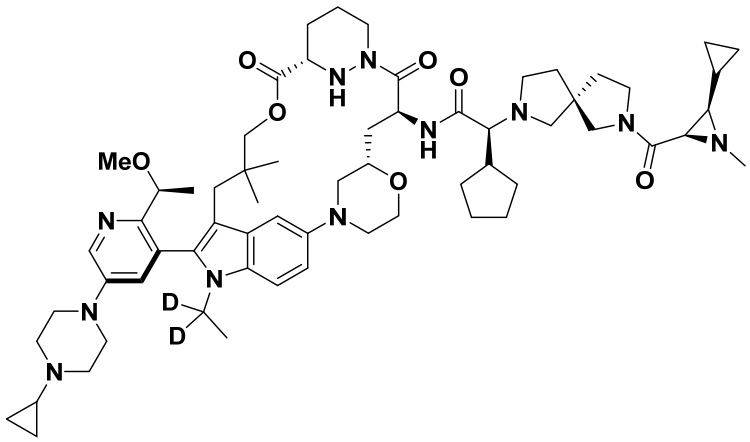
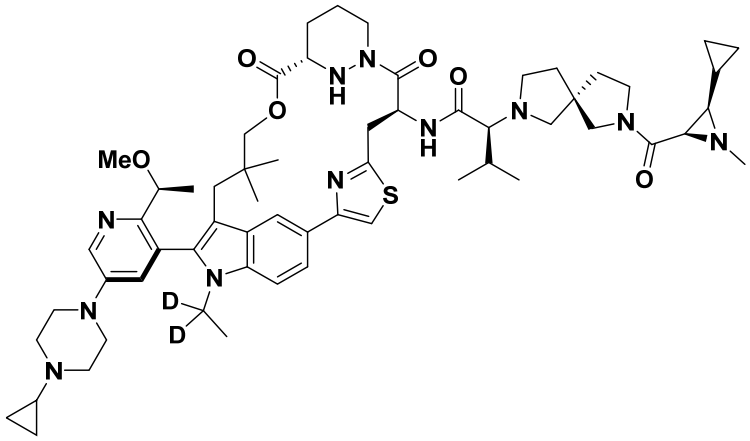
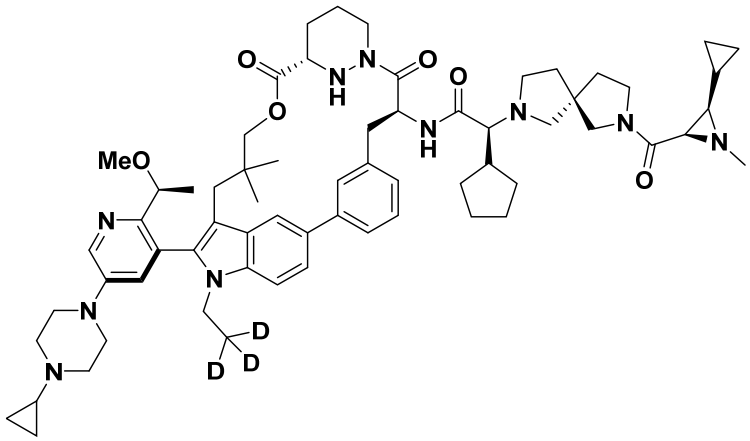
Ex#	Structure
B1	

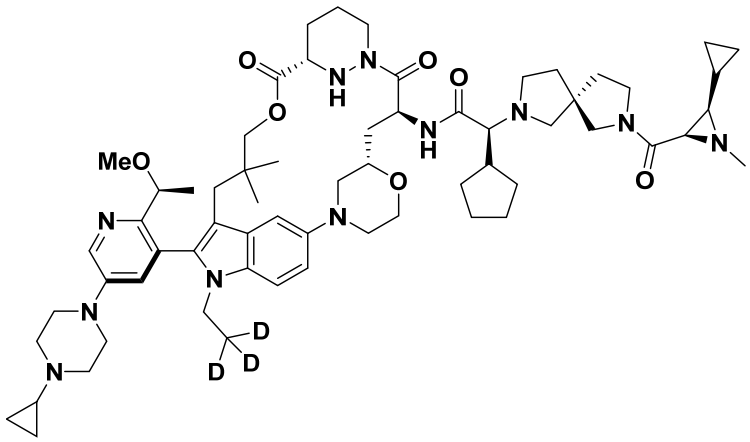
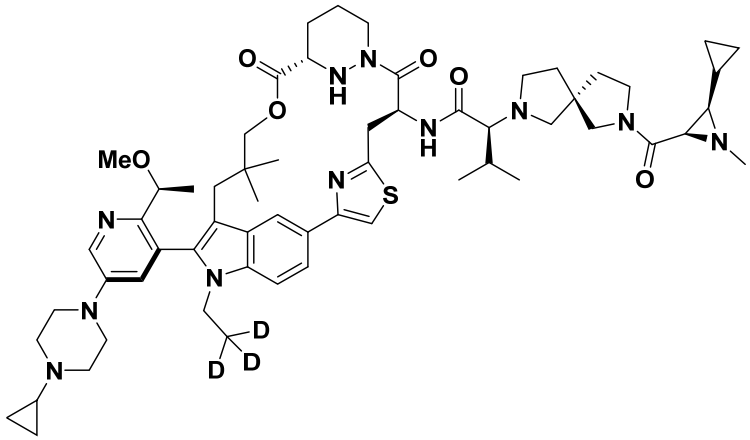
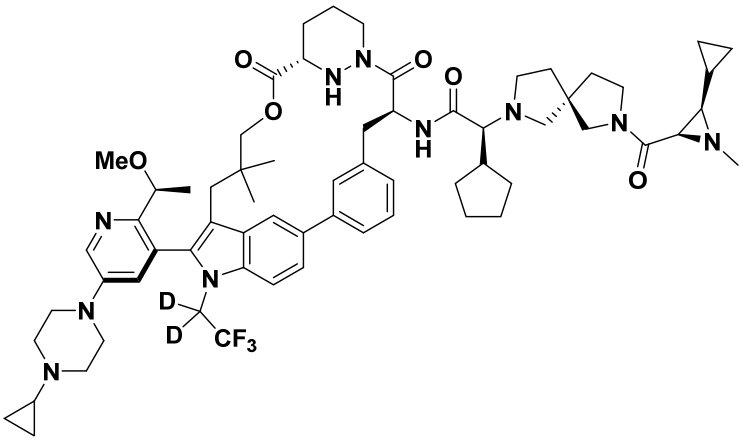
B2	
B3	
B4	

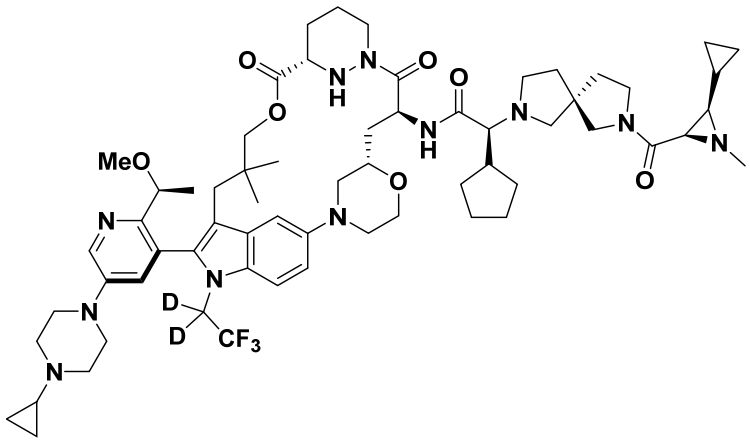
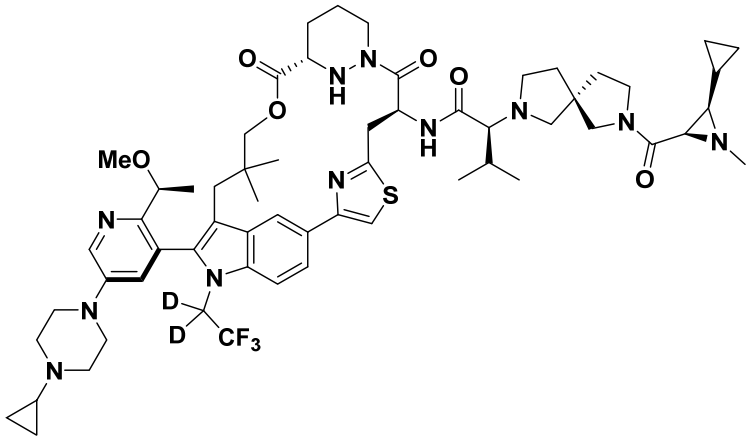
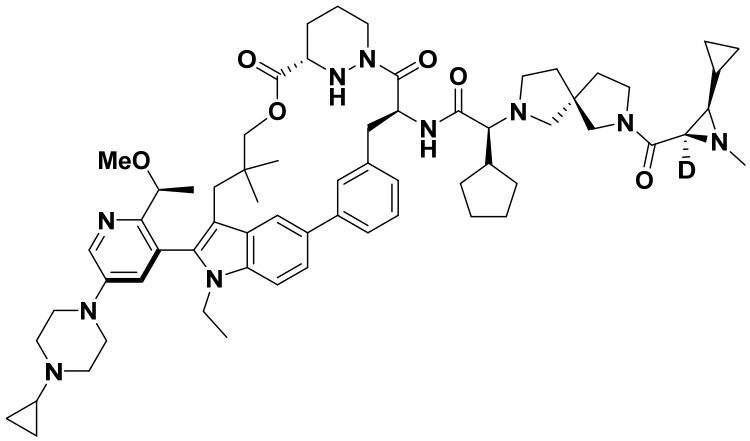
B5	
B6	
B10	

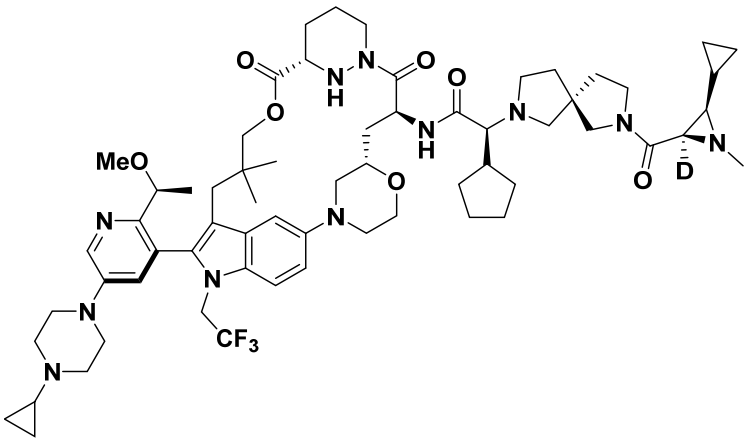
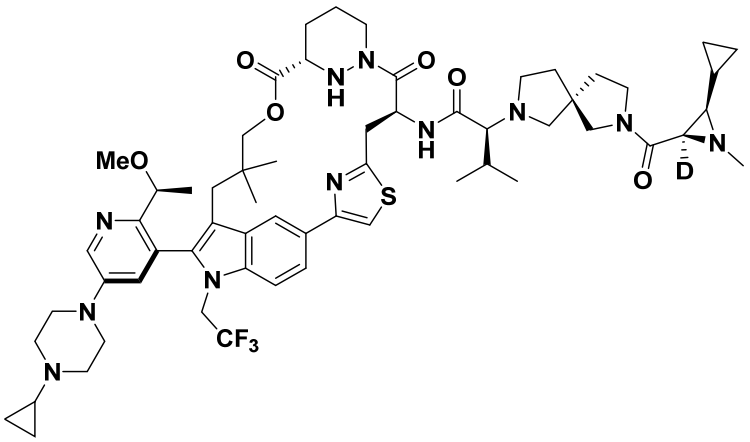
B11	
B12	
B13	

B14	
B15	
B16	

B17	
B18	
B19	

B20	
B21	
B22	

B23	
B24	
B25	

B26	 and
B27	

.

27. A pharmaceutical composition comprising a compound, or a pharmaceutically acceptable salt thereof, of any one of claims 1 to 26 and a pharmaceutically acceptable excipient.

28. Use of a compound, or a pharmaceutically acceptable salt thereof, of any one of claims 1 to 26 or a pharmaceutical composition of claim 27 in the manufacture of a medicament for treating cancer in a subject in need thereof, wherein a therapeutically effective amount of the medicament is to be administered to the subject.

29. The use of claim 28, wherein the cancer is pancreatic cancer, non-small cell lung cancer, colorectal cancer or endometrial cancer.

30. The use of claim 28 or 29, wherein the cancer comprises a Ras mutation.

31. The use of claim 30, wherein the Ras mutation is K-Ras G12D or K-Ras G13D.

32. Use of a compound, or a pharmaceutically acceptable salt thereof, of any one of claims 1 to 26 or a pharmaceutical composition of claim 27 in the manufacture of a medicament for treating a Ras protein-related disorder in a subject in need thereof, wherein a therapeutically effective amount of the medicament is to be administered to the subject.

33. An *in-vitro* or *ex-vivo* method of inhibiting a Ras protein in a cell, the method comprising contacting the cell with an effective amount of a compound, or a pharmaceutically acceptable salt thereof, of any one of claims 1 to 26 or a pharmaceutical composition of claim 27.

34. The method of claim 32 or 33, wherein the Ras protein is K-Ras G12D or K-Ras G13D.

35. The method of claim 33 or 34, wherein the cell is a cancer cell.

36. The method of claim 35, wherein the cancer cell is a pancreatic cancer cell, a non-small cell lung cancer cell, a colorectal cancer cell, or an endometrial cell.

37. The use of any one of claims 28 to 31 or the method of any one of claims 21 to 36, wherein an additional anticancer therapy is to be further administered.

38. The use or the method of claim 37, wherein the additional anticancer therapy is an EGFR inhibitor, a second Ras inhibitor, a SHP2 inhibitor, a SOS1 inhibitor, a Raf inhibitor, a MEK inhibitor, an ERK inhibitor, a PI3K inhibitor, a PTEN inhibitor, an AKT inhibitor, an mTORC1 inhibitor, a BRAF inhibitor, a PD-L1 inhibitor, a PD-1 inhibitor, a CDK4/6 inhibitor, a HER2 inhibitor, or a combination thereof.

39. A compound, or a pharmaceutically acceptable salt thereof, of any one of claims 1 to 26 or a pharmaceutical composition of claim 27 for use as a medicament.

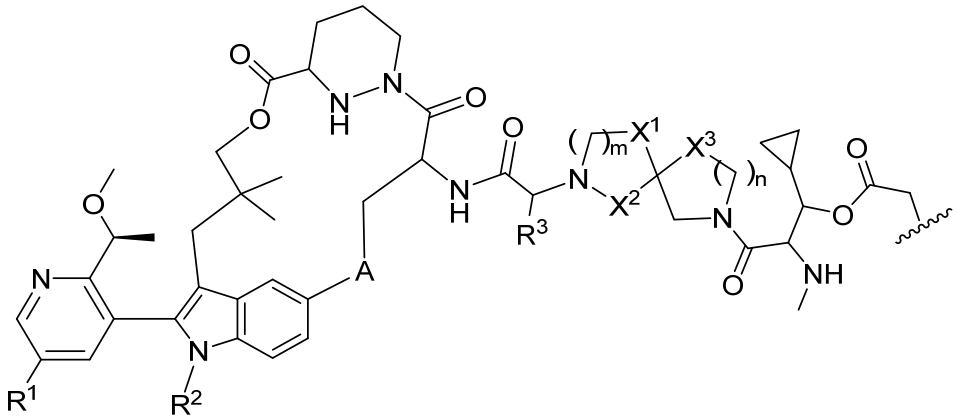
40. A conjugate, or a salt thereof, comprising the structure of Formula III:

$M\text{-}P^1$

Formula III

wherein P^1 is a monovalent organic moiety; and

M has the structure of Formula IV:



Formula IV,

wherein A is optionally substituted 3 to 6-membered heterocycloalkylene, optionally substituted 3 to 6-membered cycloalkylene, optionally substituted 6-membered arylene, or optionally substituted 5 to 10-membered heteroarylene;

X^1, X^2, and X^3 are each independently selected from CH_2, CHF, CF_2, C=O, or O;

m is 1 or 2;

n is 0 or 1;

R^1 is hydrogen, optionally substituted C_1-C_6 heteroalkyl, or optionally substituted 3 to 10-membered heterocycloalkyl;

R^2 is optionally substituted C_1-C_6 alkyl; and

R^3 is optionally substituted C_1-C_6 alkyl, optionally substituted 3 to 6-membered cycloalkyl, optionally substituted C_1-C_6 heteroalkyl, or optionally substituted heterocycloalkyl,

and wherein each hydrogen of Formula IV is independently, optionally, isotopically enriched for deuterium.