RAS INHIBITORS

Cross-Reference to Related Application

The present application claims the benefit of priority to U.S. Application No. 63/184,599, filed on May 5, 2021, which is hereby incorporated by reference in its entirety.

Background

The vast majority of small molecule drugs act by binding a functionally important pocket on a target protein, thereby modulating the activity of that protein. For example, cholesterol-lowering drugs known as statins bind the enzyme active site of HMG-CoA reductase, thus preventing the enzyme from engaging with its substrates. The fact that many such drug/target interacting pairs are known may have misled some into believing that a small molecule modulator could be discovered for most, if not all, proteins provided a reasonable amount of time, effort, and resources. This is far from the case. Current estimates are that only about 10% of all human proteins are targetable by small molecules. Bojadzic and Buchwald, Curr Top Med Chem 18: 674-699 (2019). The other 90% are currently considered refractory or intractable toward above-mentioned small molecule drug discovery. Such targets are commonly referred to as “undruggable.” These undruggable targets include a vast and largely untapped reservoir of medically important human proteins. Thus, there exists a great deal of interest in discovering new molecular modalities capable of modulating the function of such undruggable targets.

It has been well established in literature that Ras proteins (K-Ras, H-Ras and N-Ras) play an essential role in various human cancers and are therefore appropriate targets for anticancer therapy. Indeed, mutations in Ras proteins account for approximately 30% of all human cancers in the United States, many of which are fatal. Dysregulation of Ras proteins by activating mutations, overexpression or upstream activation is common in human tumors, and activating mutations in Ras are frequently found in human cancer. For example, activating mutations at codon 12 in Ras proteins function by inhibiting both GTPase-activating protein (GAP)-dependent and intrinsic hydrolysis rates of GTP, significantly skewing the population of Ras mutant proteins to the “on” (GTP-bound) state (Ras(ON)), leading to oncogenic MAPK signaling. Notably, Ras exhibits a picomolar affinity for GTP, enabling Ras to be activated even in the presence of low concentrations of this nucleotide. Mutations at codons 13 (e.g., G13D) and 61 (e.g., Q61K) of Ras are also responsible for oncogenic activity in some cancers.

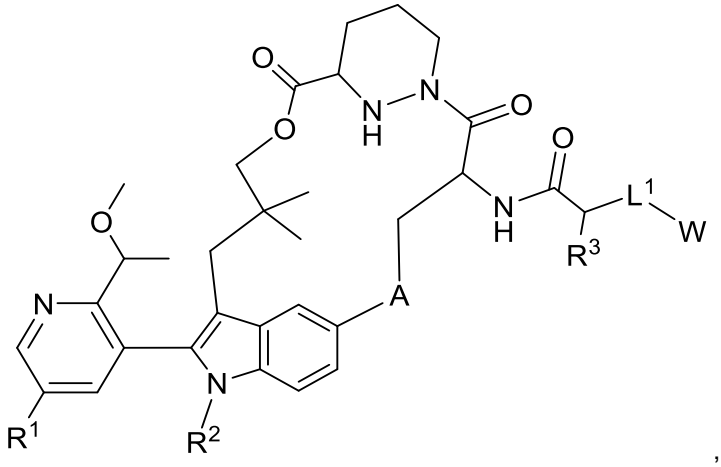
Despite extensive drug discovery efforts against Ras during the last several decades, a drug directly targeting Ras is still not approved. Additional efforts are needed to uncover additional medicines for cancers driven by the various Ras mutations.

Summary

Provided herein are Ras inhibitors. The approach described herein entails formation of a high affinity three-component complex, or conjugate, between a synthetic ligand and two intracellular proteins which do not interact under normal physiological conditions: the target protein of interest (e.g., Ras), and a widely expressed cytosolic chaperone (presenter protein) in the cell (e.g., cyclophilin A). More specifically, the inhibitors of Ras described herein induce a new binding pocket in Ras by driving formation of a high affinity tri-complex, or conjugate, between the Ras protein and the

widely expressed cytosolic chaperone, cyclophilin A (CYPA). Without being bound by theory, the inventors believe that one way the inhibitory effect on Ras is effected by compounds of the disclosure and the complexes, or conjugates, they form is by steric occlusion of the interaction site between Ras and downstream effector molecules, such as RAF and PI3K, which are required for propagating the oncogenic signal.

As such, the disclosure features a compound, or pharmaceutically acceptable salt thereof, of structural 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;

L^1 is absent or a linker;

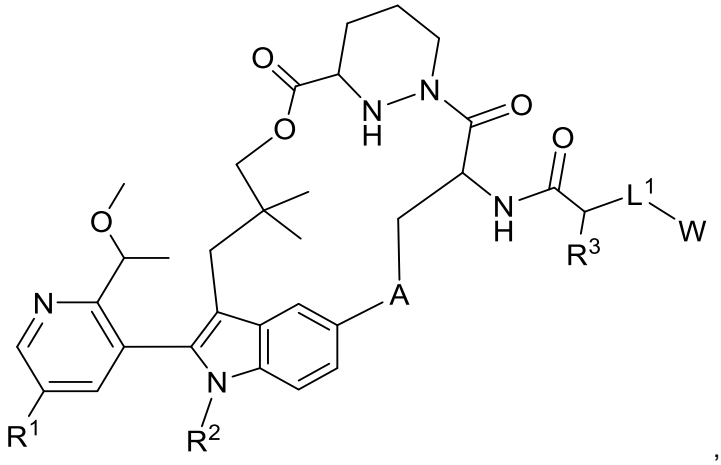
W is a cross-linking group comprising a vinyl ketone, vinyl sulfone, ynone, or an alkynyl sulfone;

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

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

R^3 is optionally substituted C_1-C_6 alkyl or optionally substituted C_1-C_3 heteroalkyl.

In one aspect, the present disclosure features a compound, or pharmaceutically acceptable salt thereof, having the structure of Formula I:

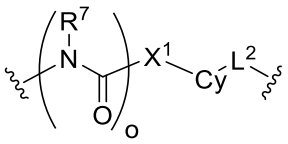


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Formula I

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;

L^1 is absent or a linker having the structure of formula IIIa:



Formula IIIa,

wherein o is 0 or 1;

R^7 is hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted 3 to 8-membered cycloalkylene, or optionally substituted 3 to 8-membered heterocycloalkylene;

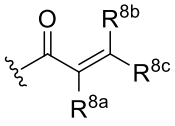
X^1 is absent, optionally substituted C_1-C_4 alkylene, O, NCH_3, or optionally substituted C_1-C_4 heteroalkylene;

Cy is optionally substituted 3 to 8-membered cycloalkylene, optionally substituted 3 to 12-membered heterocycloalkylene, optionally substituted 6-10 membered arylene, or optionally substituted 5 to 10-membered heteroarylene; and

L^2 is absent, -SO_2-, -NH-, optionally substituted C_1-C_4 alkylene, optionally substituted C_1-C_4 heteroalkylene, or optionally substituted 3 to 6-membered heterocycloalkylene;

W is a cross-linking group selected from: a vinyl ketone, vinyl sulfone, or ynone, where:

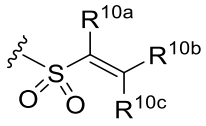
the vinyl ketone has the structure of Formula IVa:



Formula IVa,

wherein R^{8a}, R^{8b}, and R^{8c} are, independently, hydrogen, -CN, halogen, -C_1-C_3 alkyl, or -C_1-C_3 alkyl substituted with one or more substituents independently selected from -OH and -O-C_1-C_3 alkyl, -NH_2, -NH(C_1-C_3 alkyl), -N(C_1-C_3 alkyl)$_2$, or a 4 to 7-membered saturated heterocycloalkyl comprising one, two, three, or four heteroatoms independently selected from nitrogen, oxygen, and sulfur;

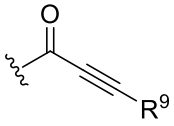
the vinyl sulfone has the structure of Formula IVc:



Formula IVc,

wherein R^{10a}, R^{10b}, and R^{10c} are, independently, hydrogen, -CN, -C_1-C_3 alkyl, or -C_1-C_3 alkyl substituted with one, two, three, or four substituents independently selected from -OH and -O-C_1-C_3 alkyl, -NH_2, -NH(C_1-C_3 alkyl), -N(C_1-C_3 alkyl)$_2$, or a 4 to 7-membered saturated heterocycloalkyl comprising one, two, three, or four heteroatoms independently selected from nitrogen, oxygen, and sulfur;

the ynone has the structure of Formula IVb:



Formula IVb,

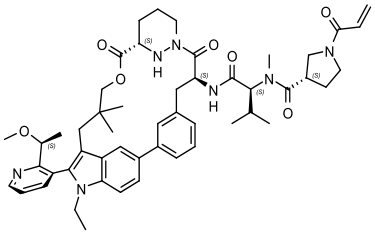
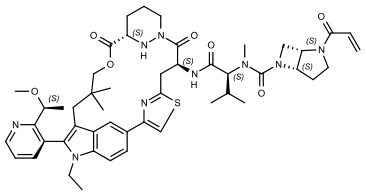
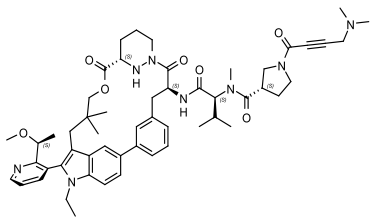
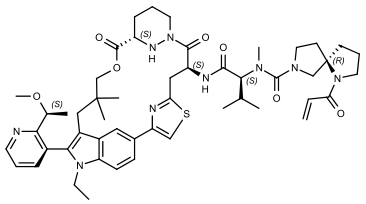
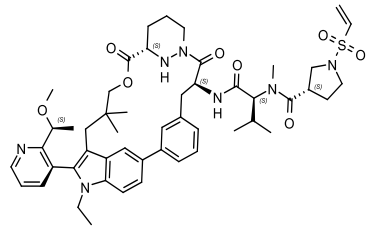
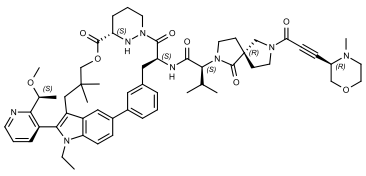
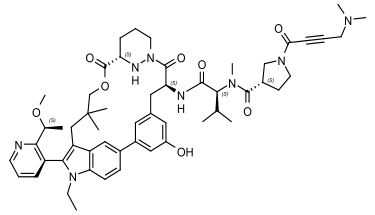
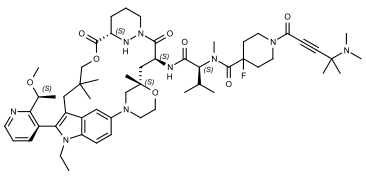
wherein R^9 is hydrogen, -C_1-C_3 alkyl, -C_1-C_3 alkyl substituted with one, two, three, or four substituents independently selected from -OH, -O-C_1-C_3 alkyl, -NH_2, -NH(C_1-C_3 alkyl), -N(C_1-C_3 alkyl)$_2$, a 4 to 7-membered saturated cycloalkyl, and a 4 to 7-membered saturated heterocycloalkyl comprising one, two, three, or four heteroatoms independently selected from nitrogen, oxygen, and sulfur;

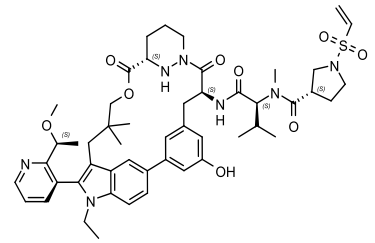
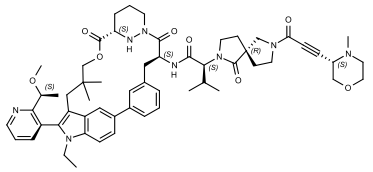
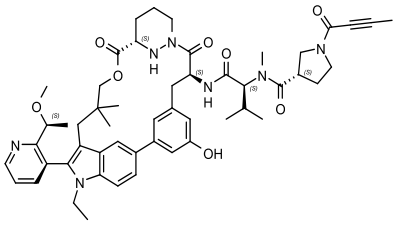
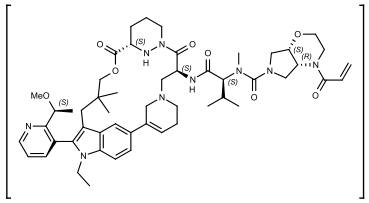
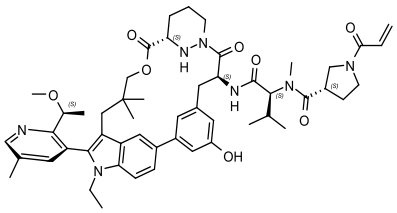
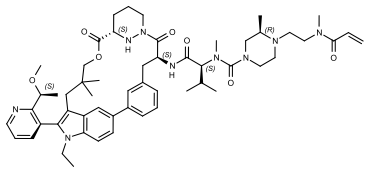
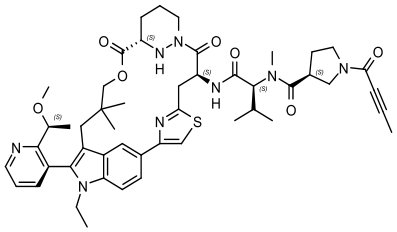
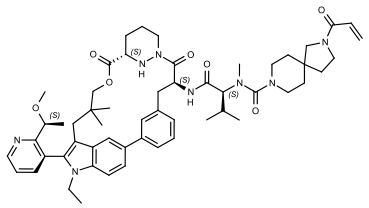
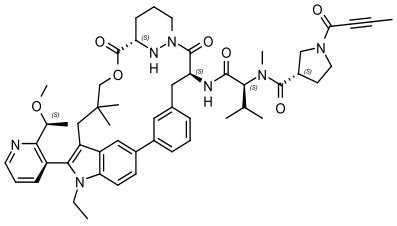
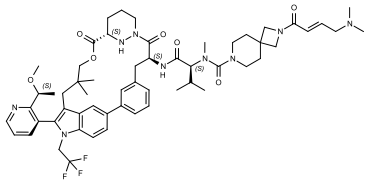
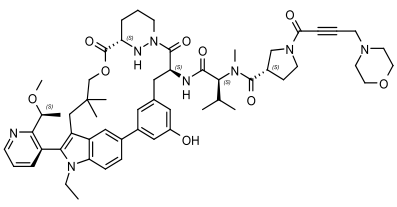
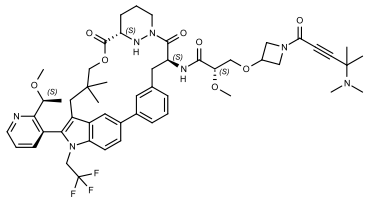
R^1 is hydrogen, optionally substituted 3 to 10-membered heterocycloalkyl, or optionally substituted C_1-C_6 heteroalkyl;

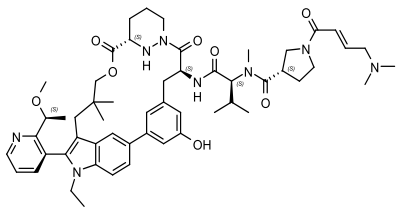
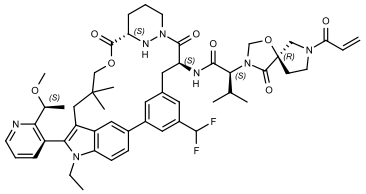
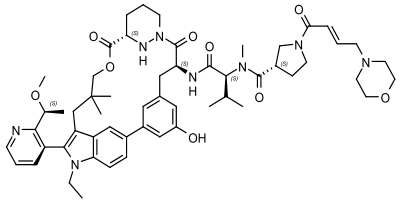
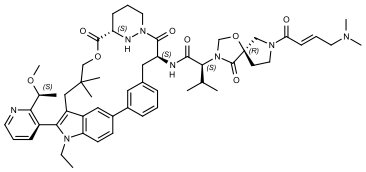
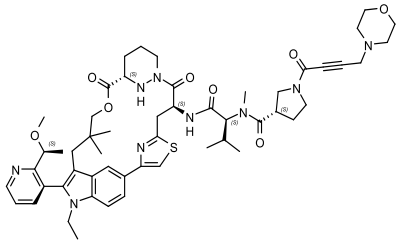
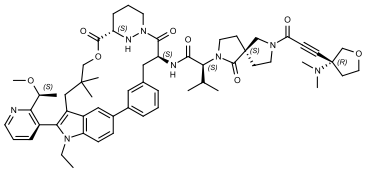
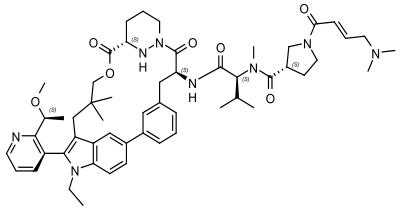
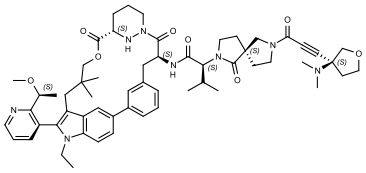
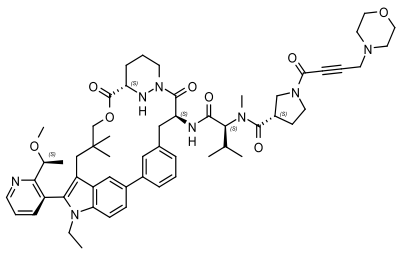
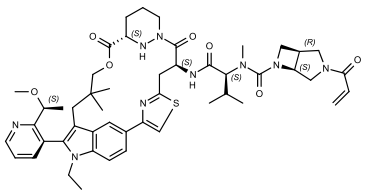
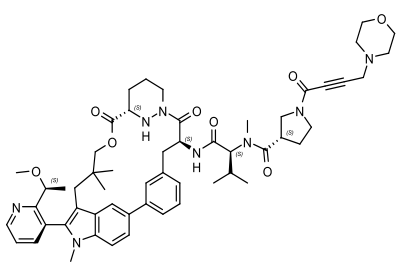
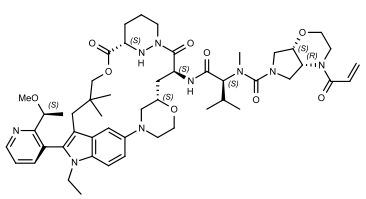
R^2 is optionally substituted C_1-C_6 alkyl; and

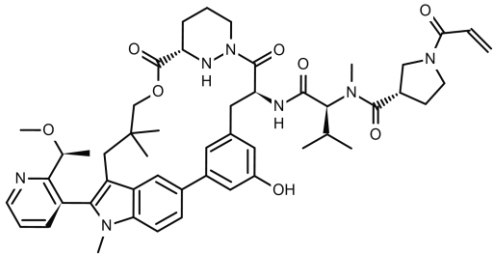
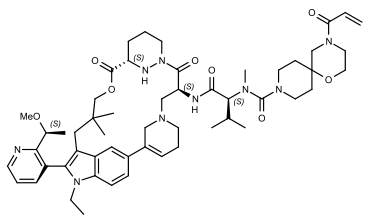
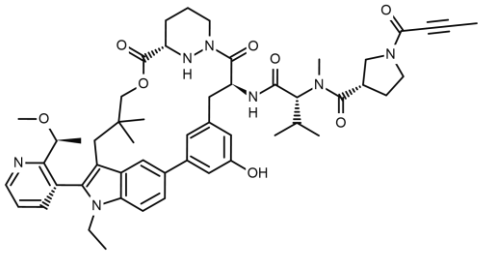
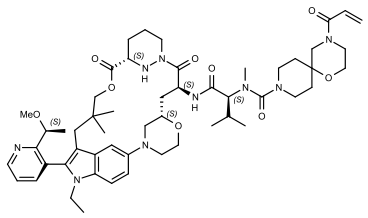
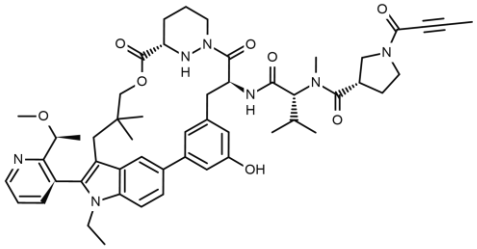
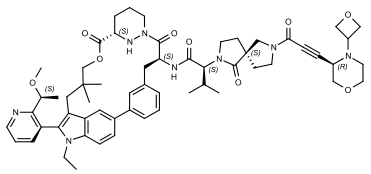
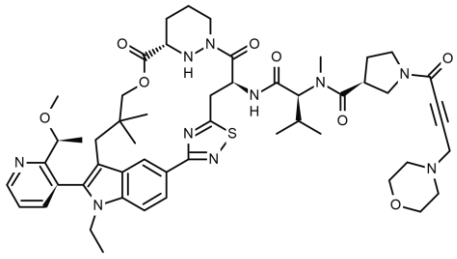
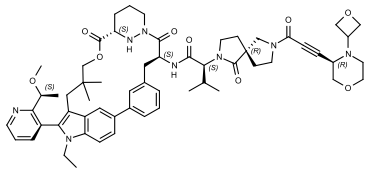
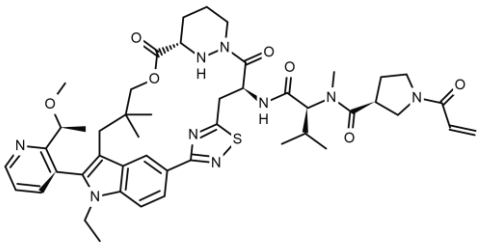
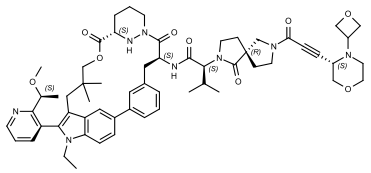
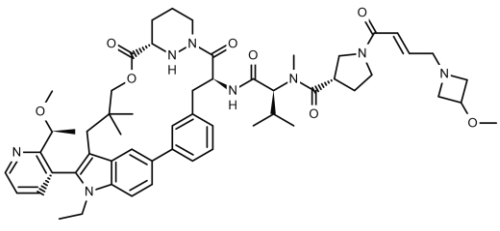
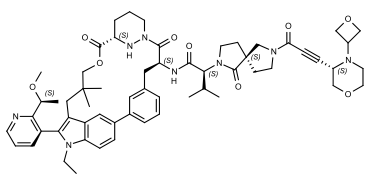
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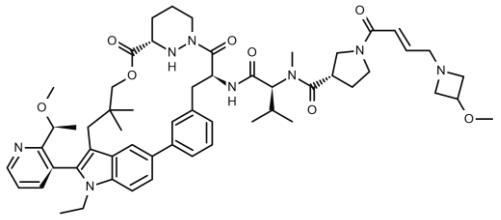
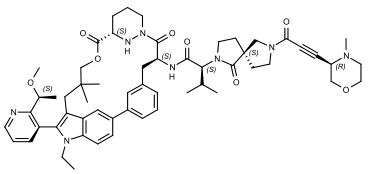
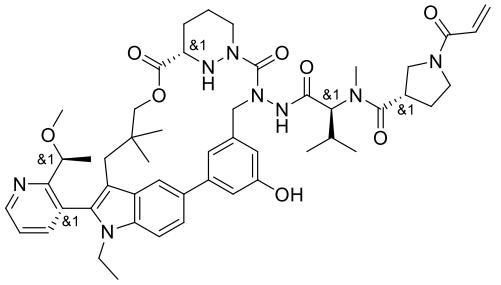
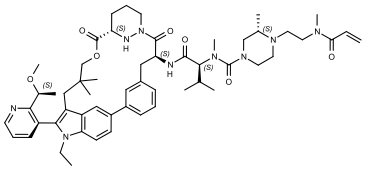
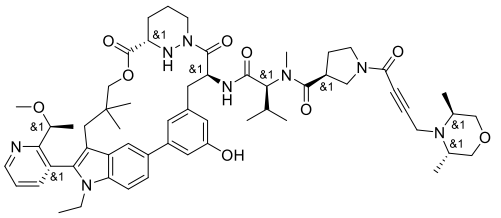
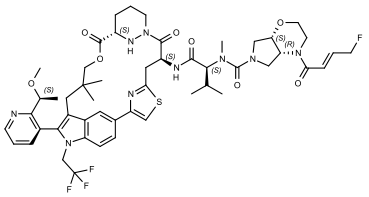
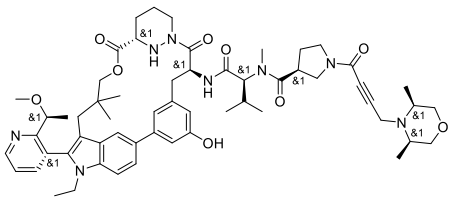
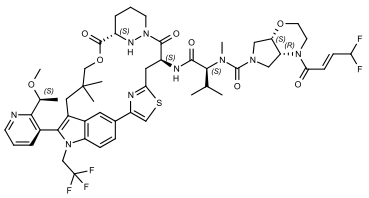
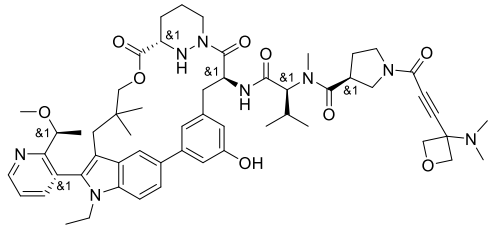
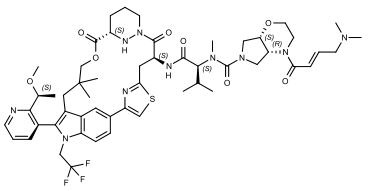
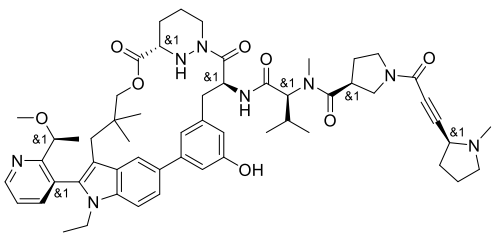
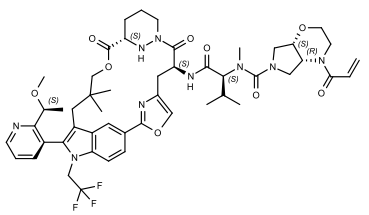
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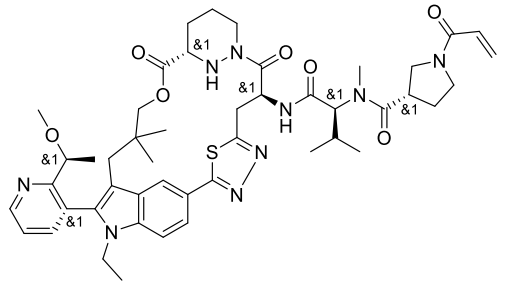
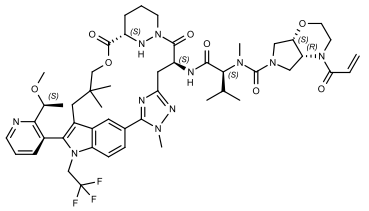
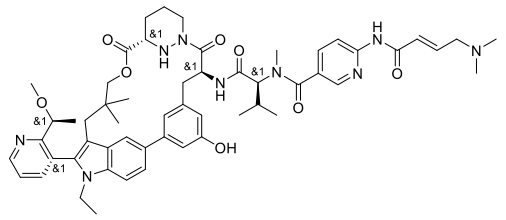
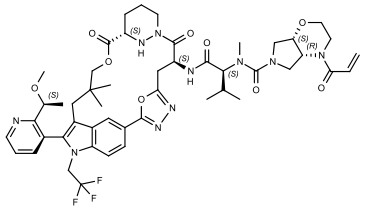
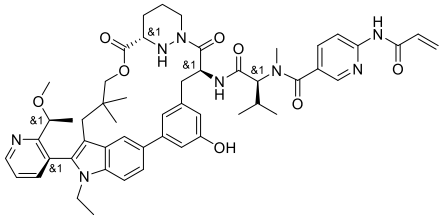
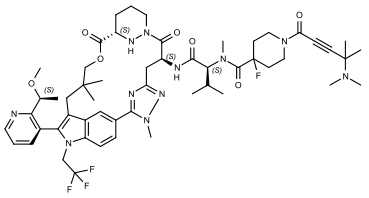
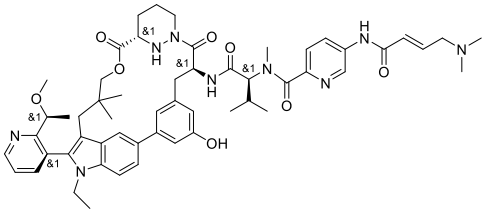
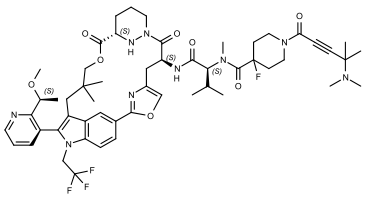
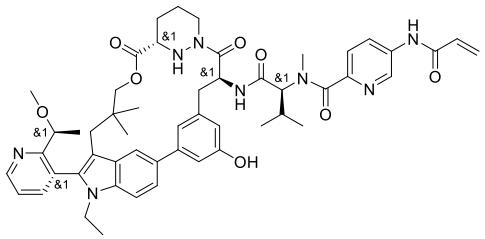
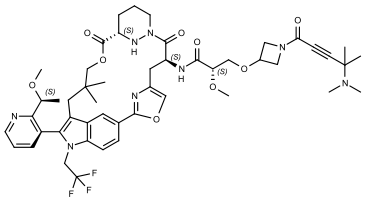
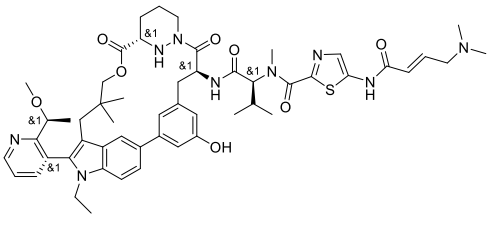
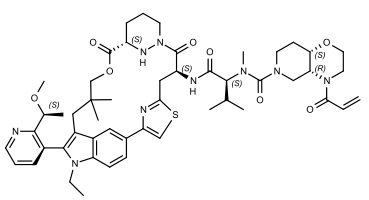
	
	
	
	

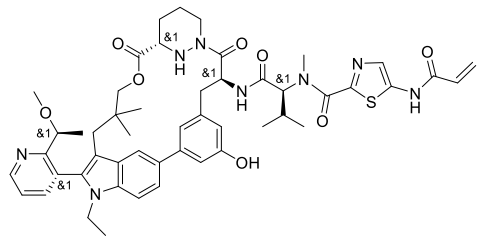
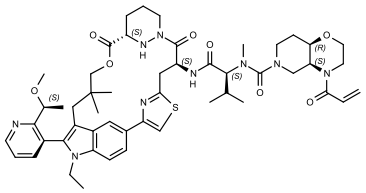
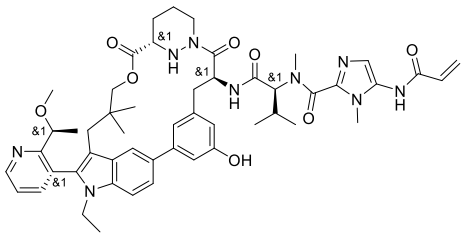
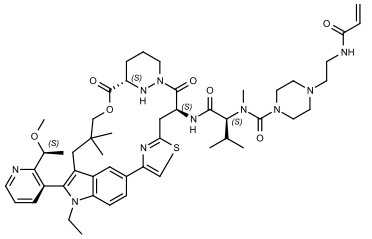
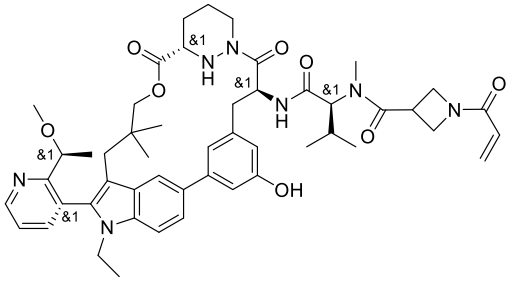
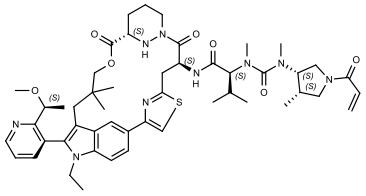
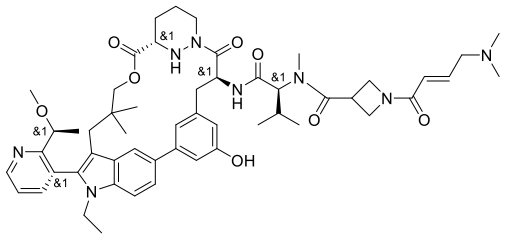
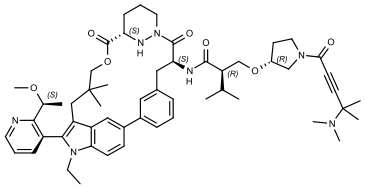
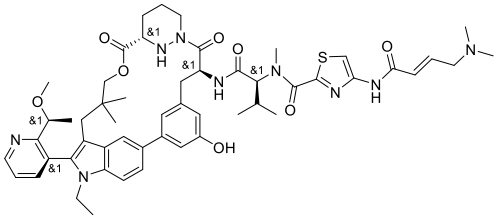
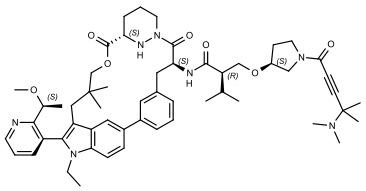
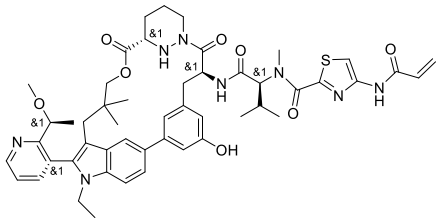
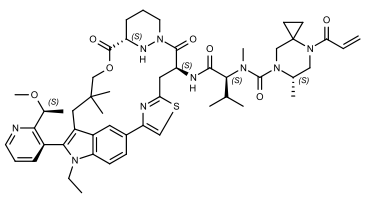
	
	
	
	
	
	

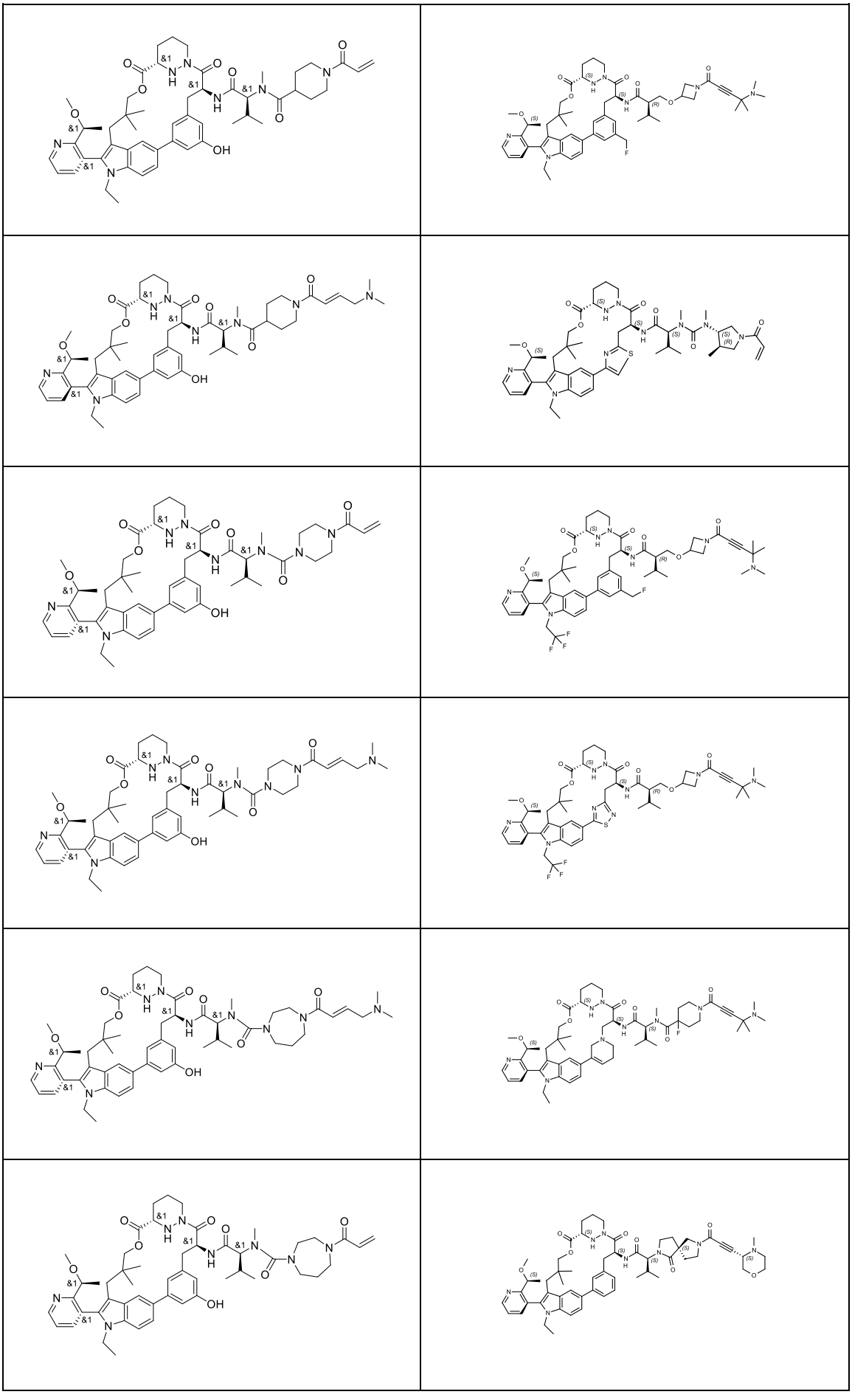
	
	
	
	
	
	

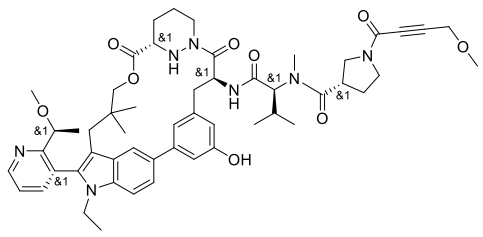
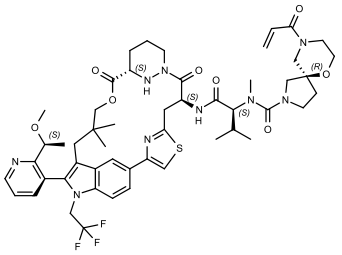
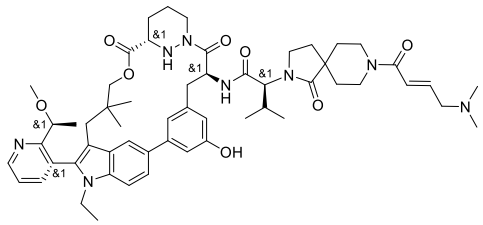
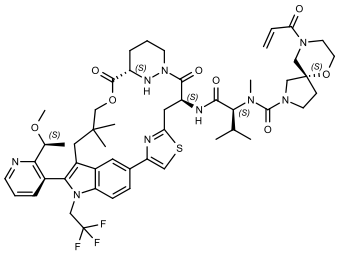
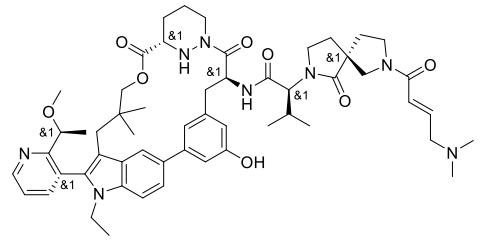
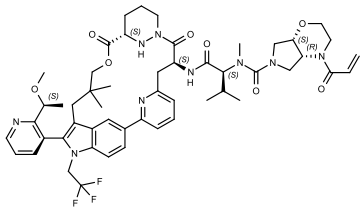
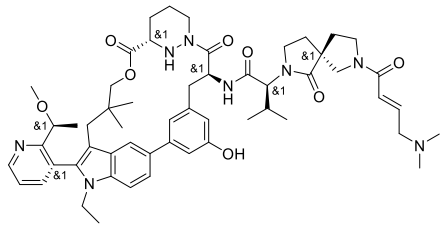
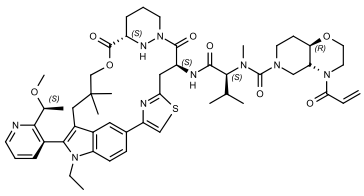
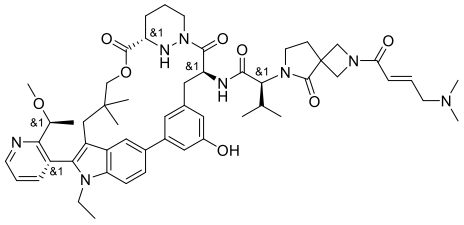
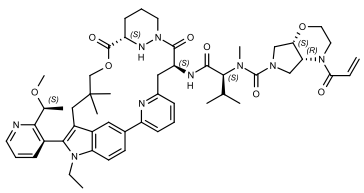
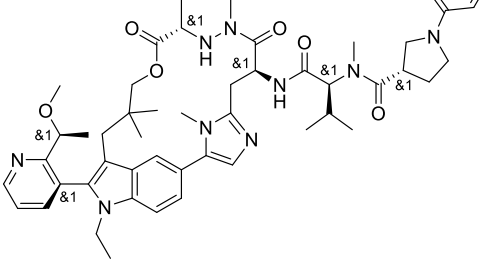
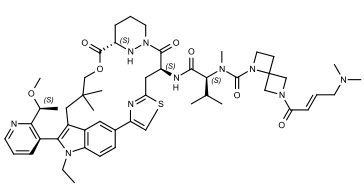
	
	
	
	
	
	

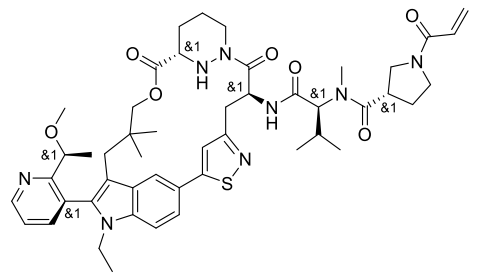
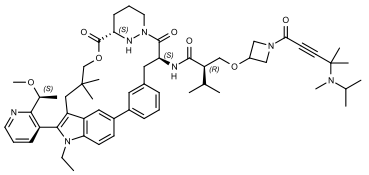
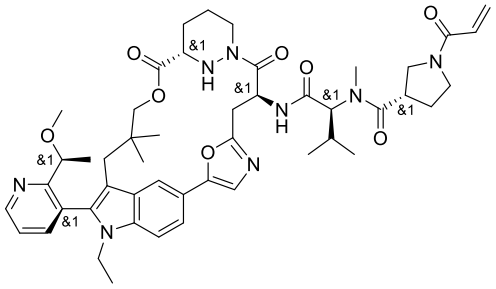
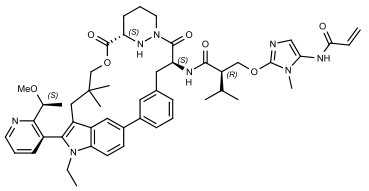
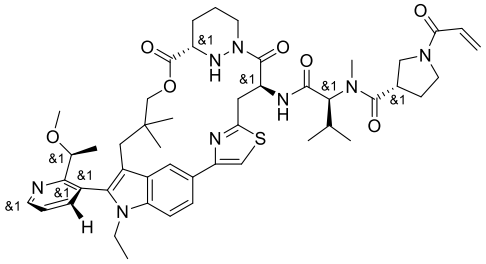
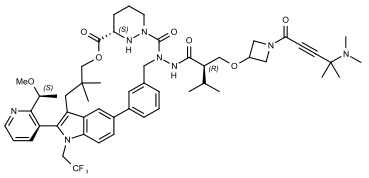
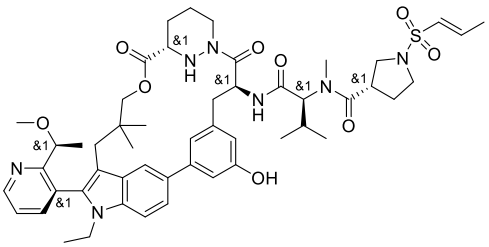
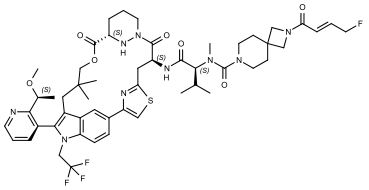
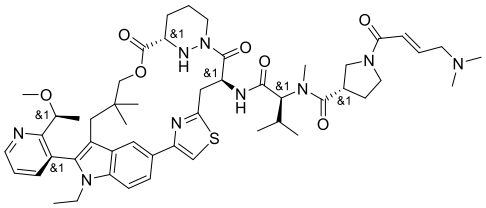
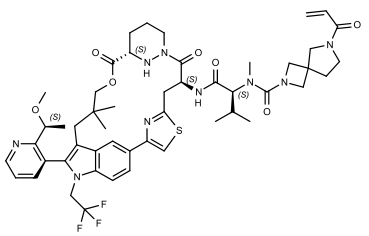
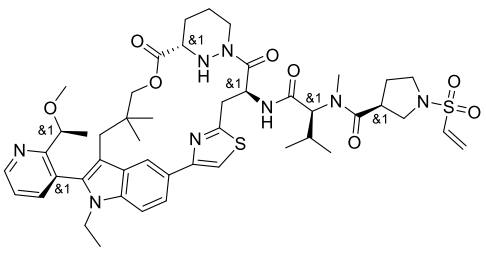
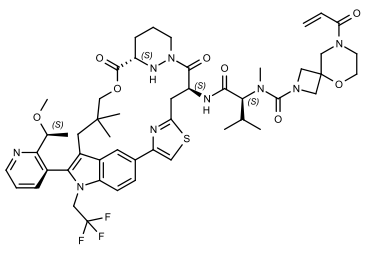
	
	
	
	
	
	

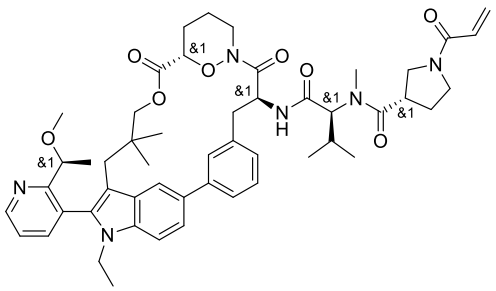
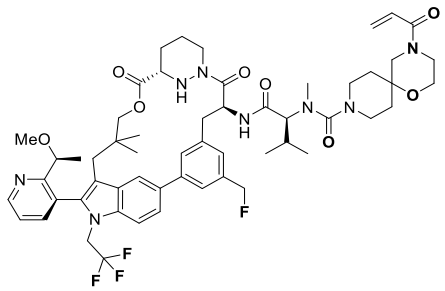
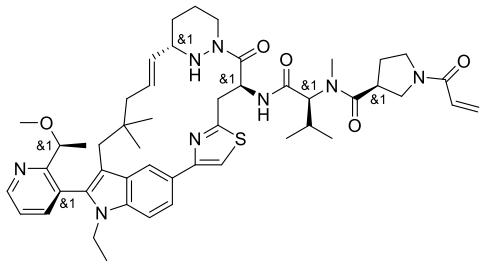
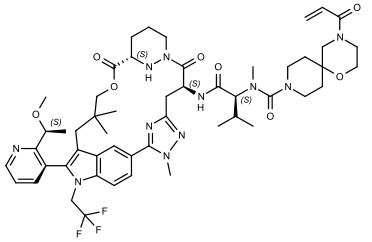
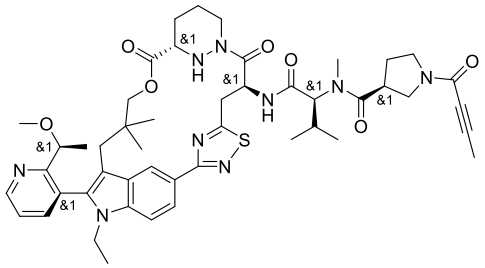
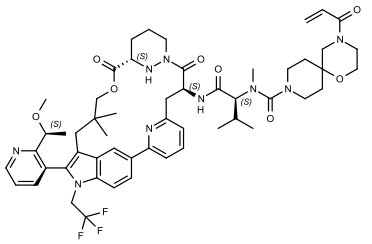
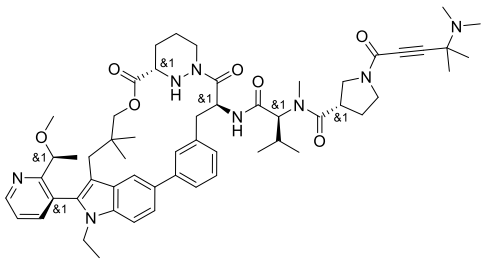
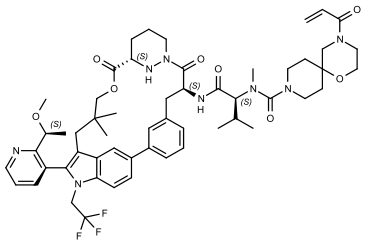
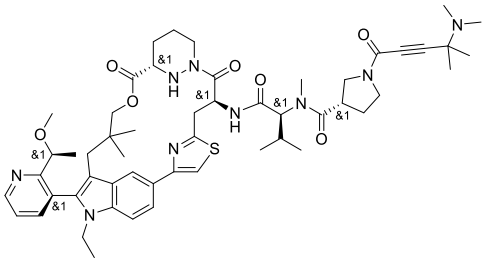
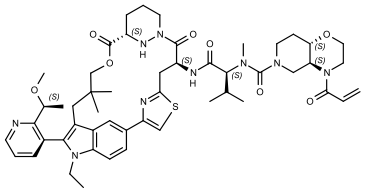
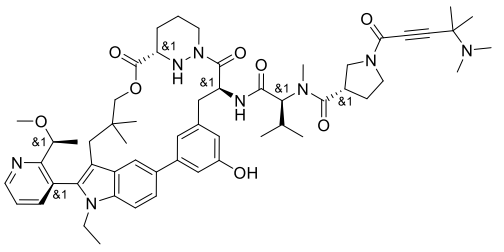
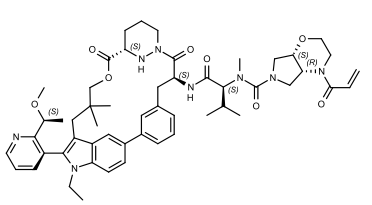
	
	
	
	
	
	

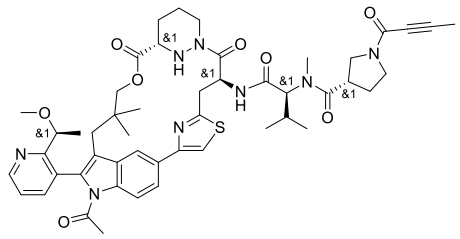
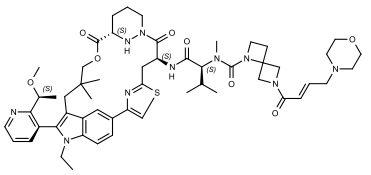
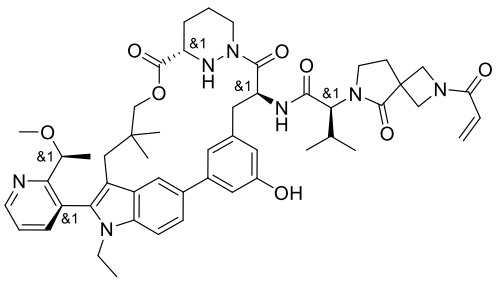
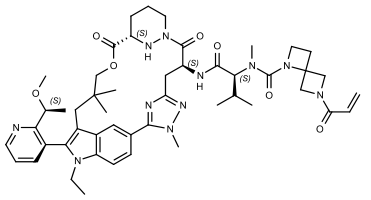
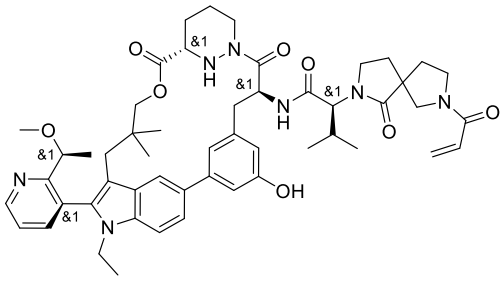
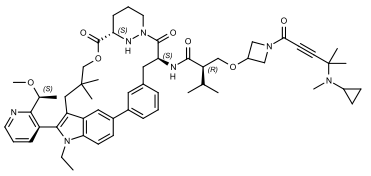
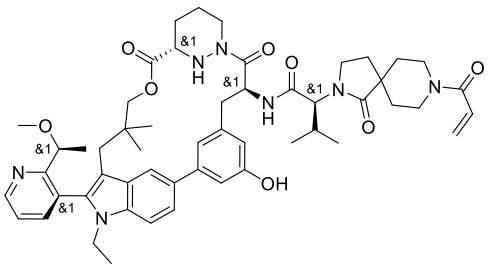
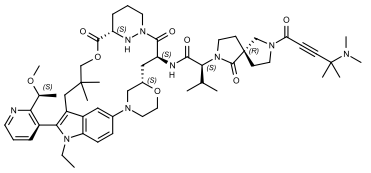
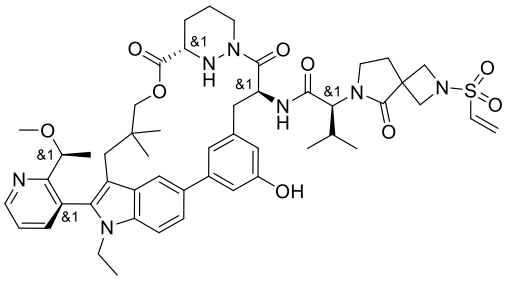
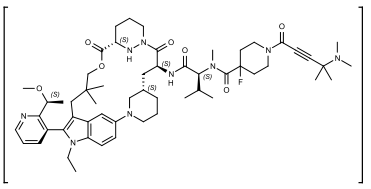
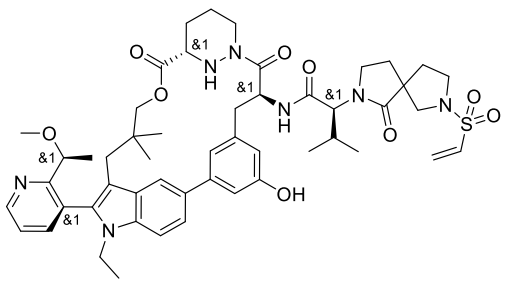
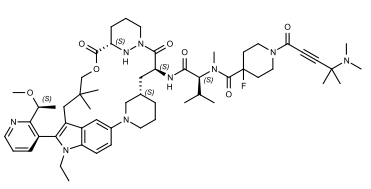
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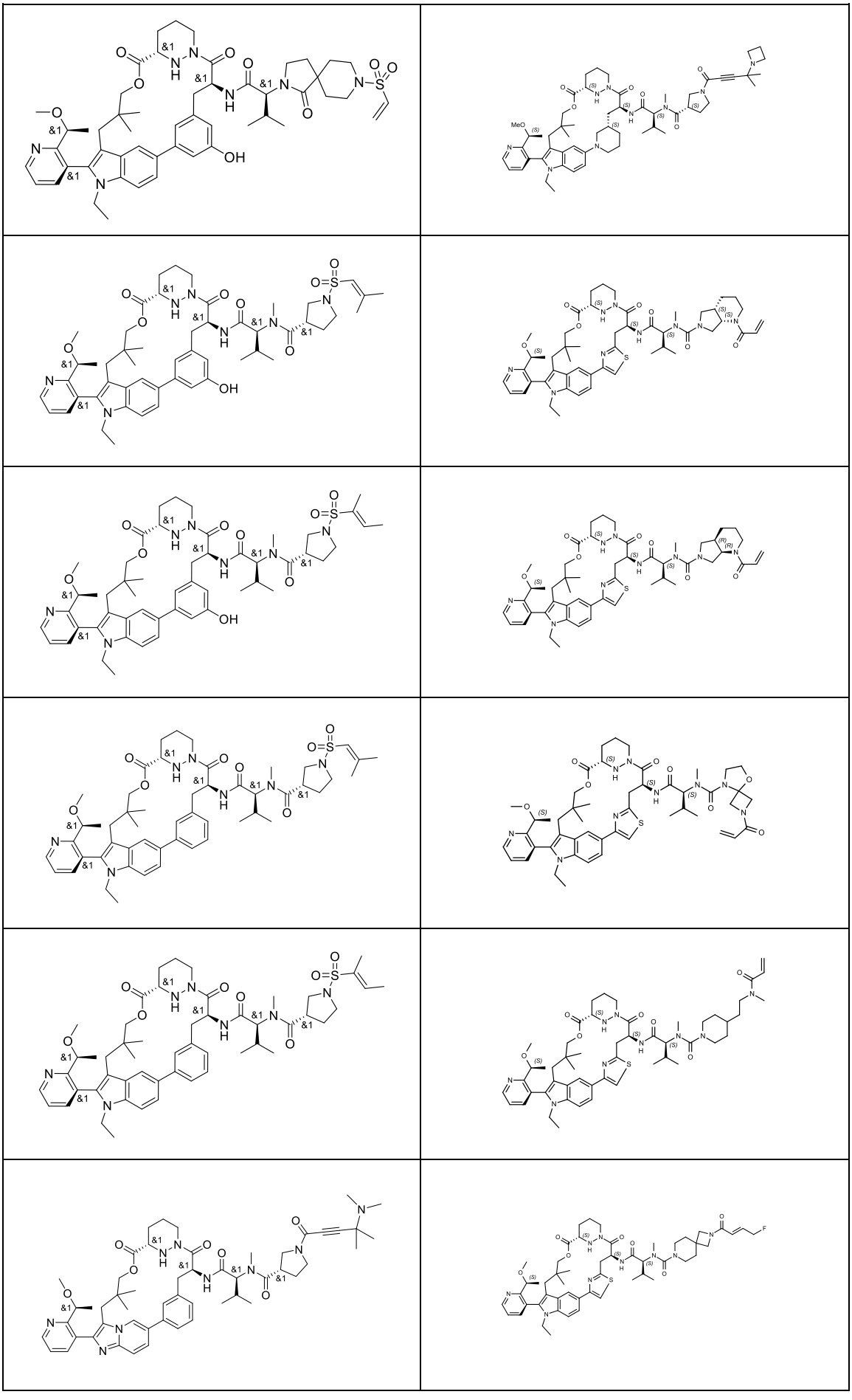


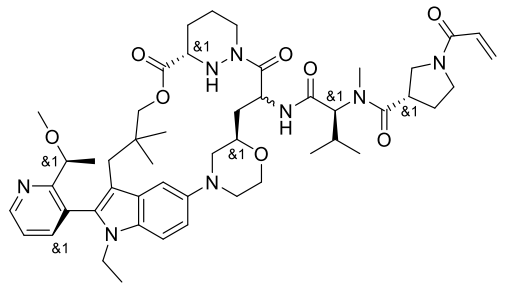
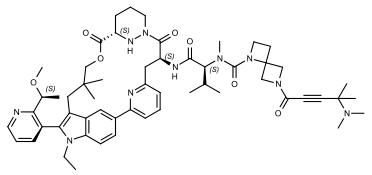
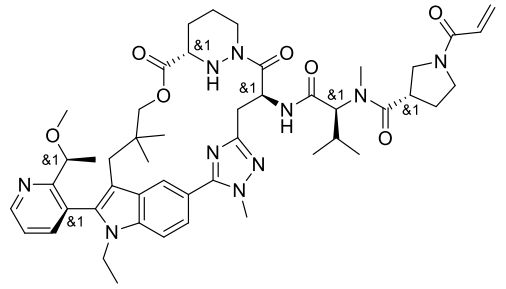
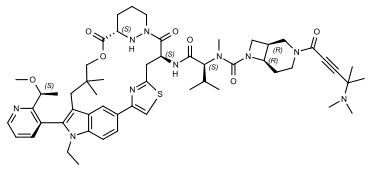
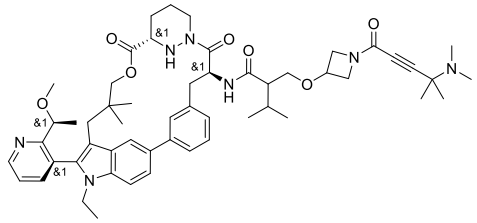
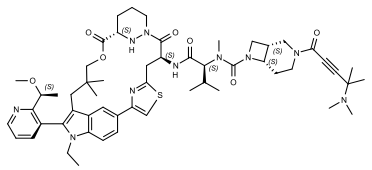
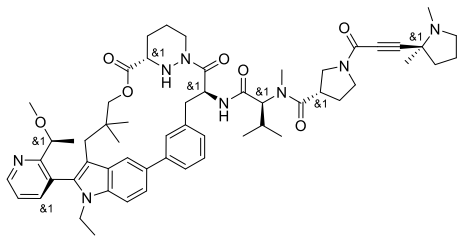
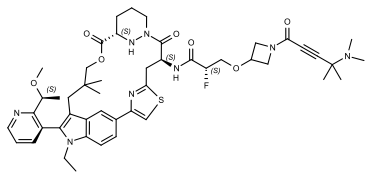
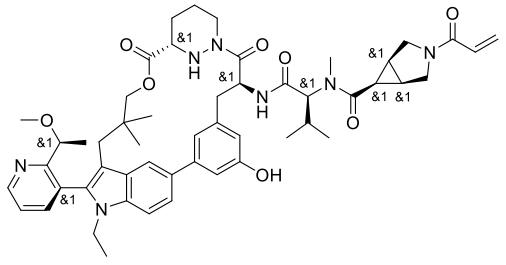
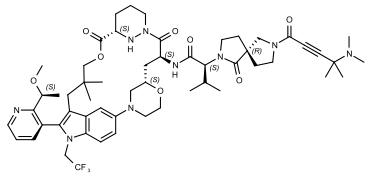
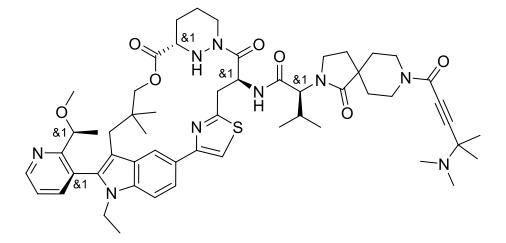
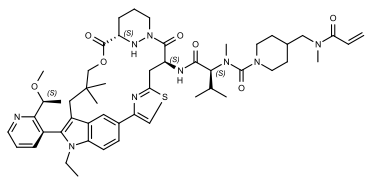
	
	
	
	
	
	

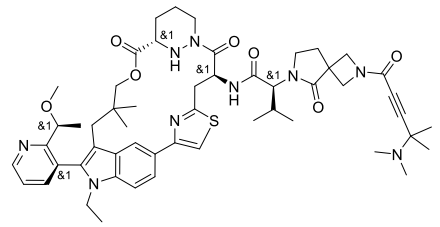
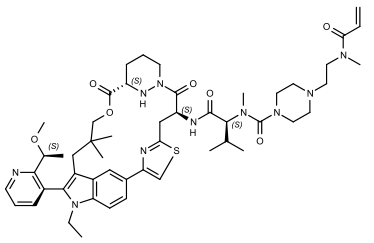
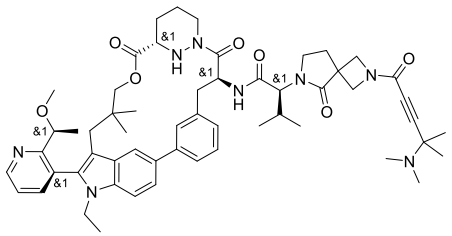
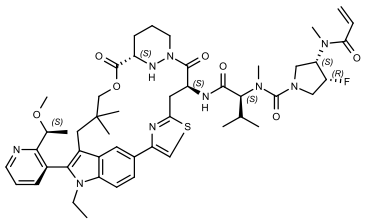
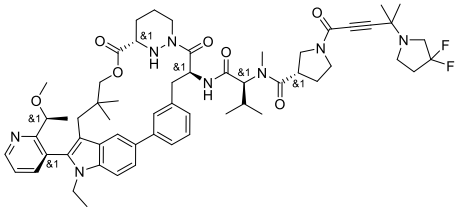
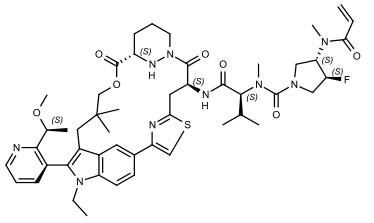
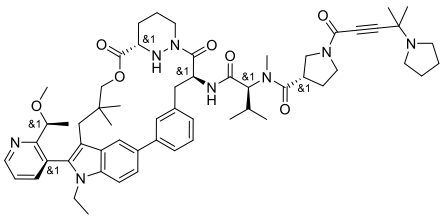
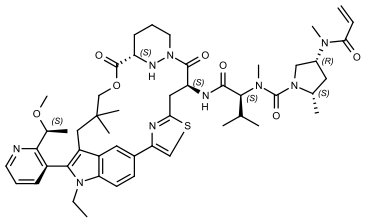
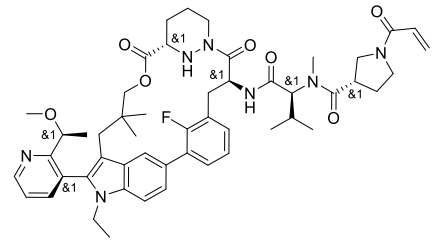
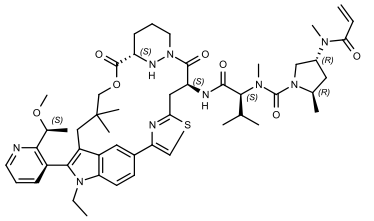
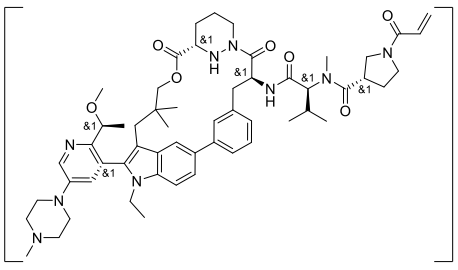
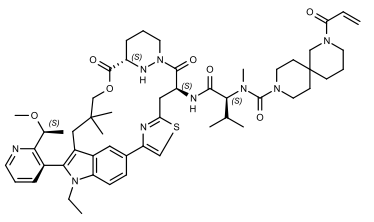
	
	
	
	
	
	

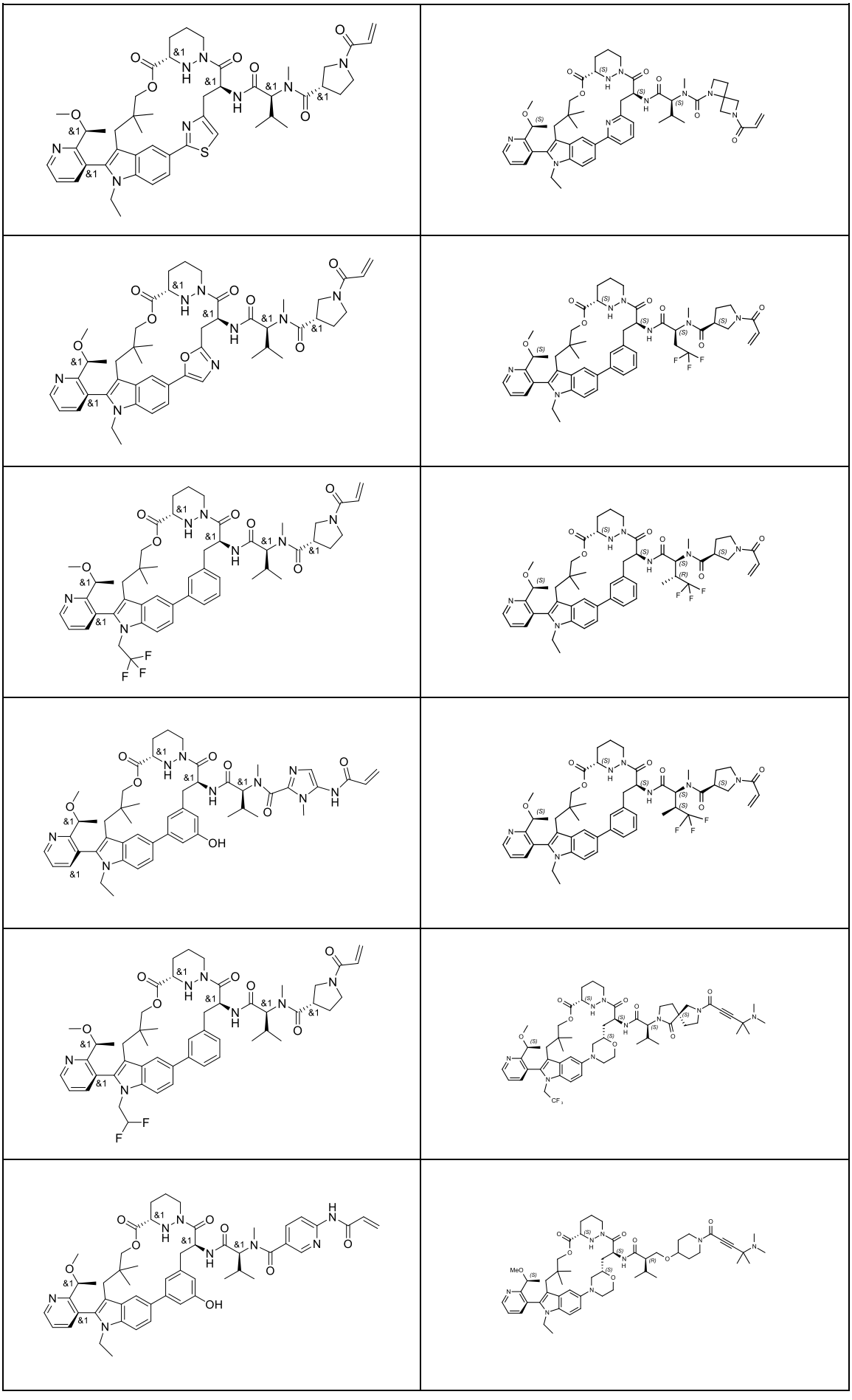
	
	
	
	
	
	

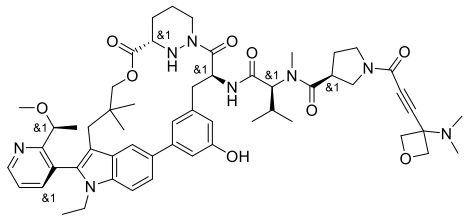
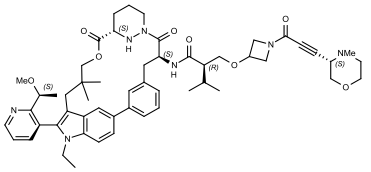
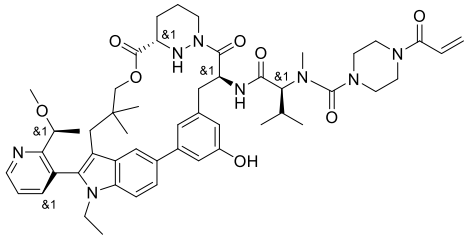
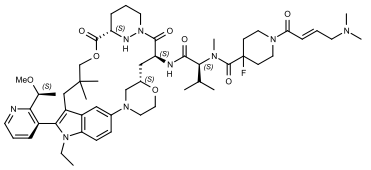
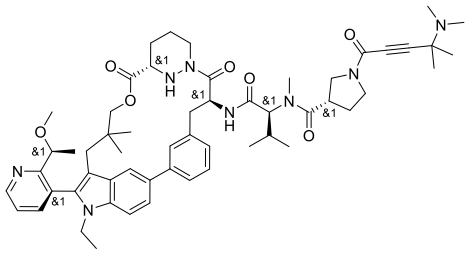
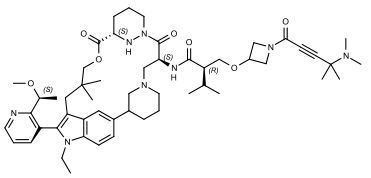
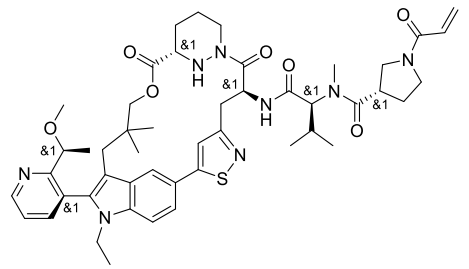
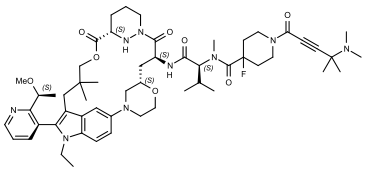
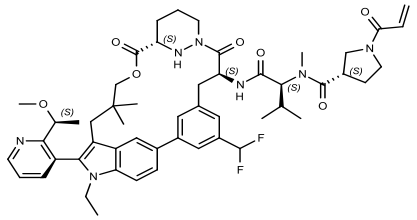
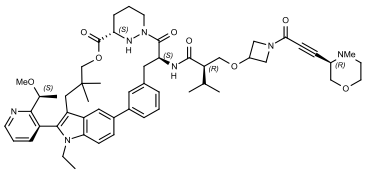
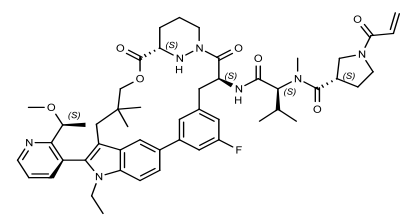
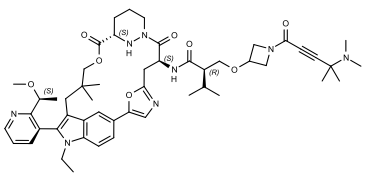
	
	
	
	
	
	

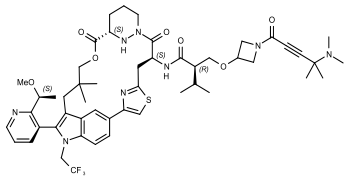
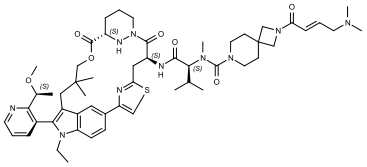
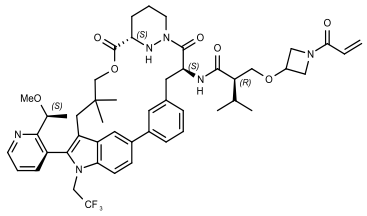
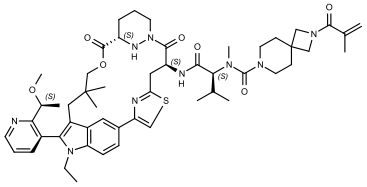
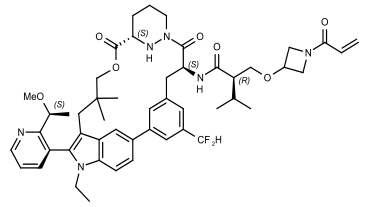
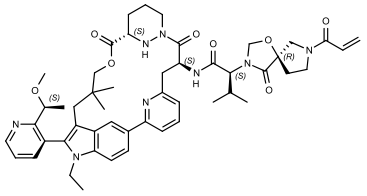
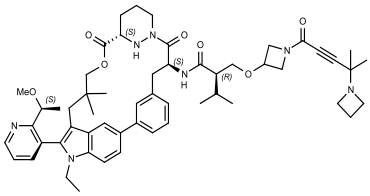
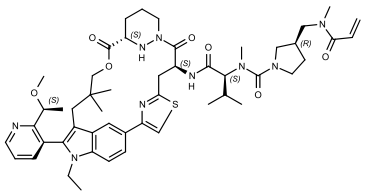
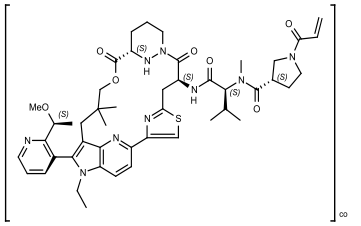
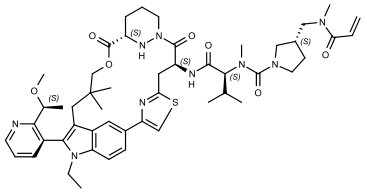
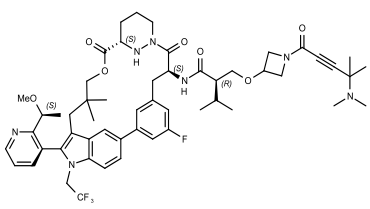
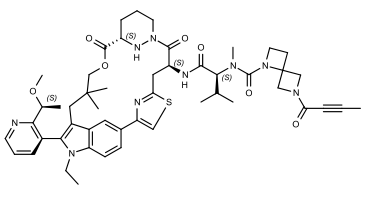


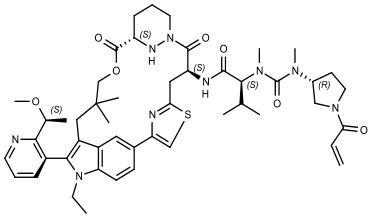
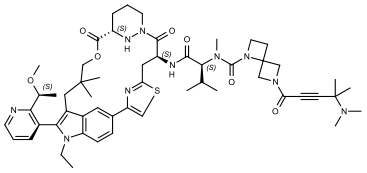
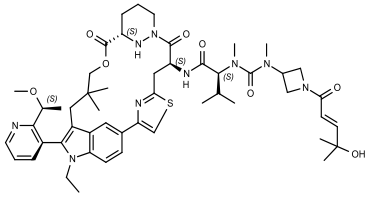
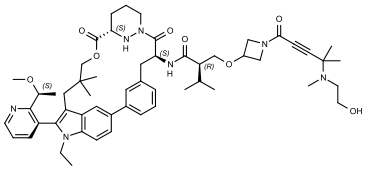
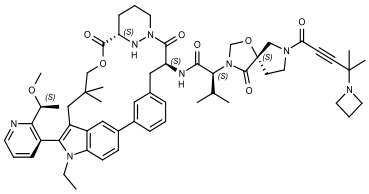
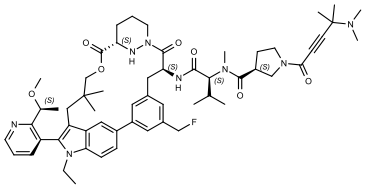
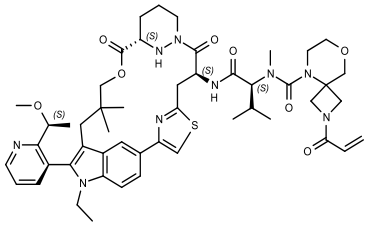
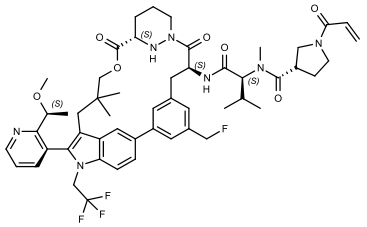
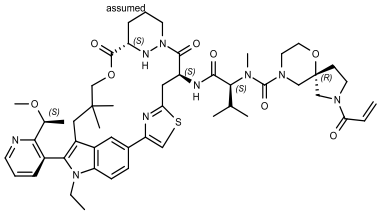
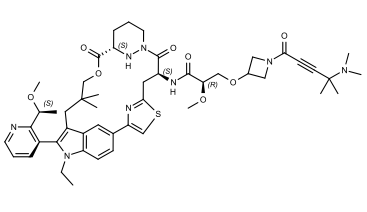
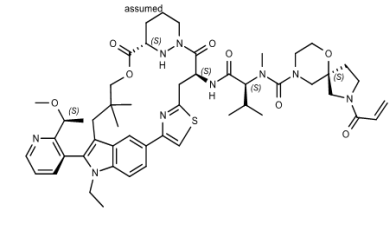
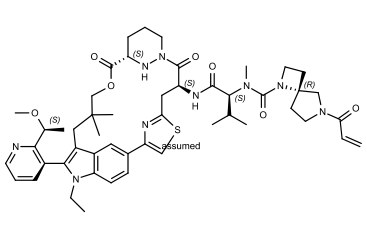
	
	
	
	
	
	

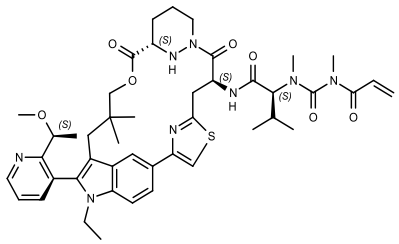
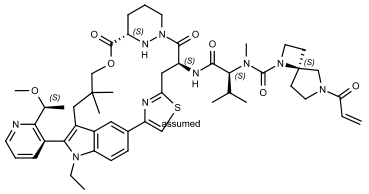
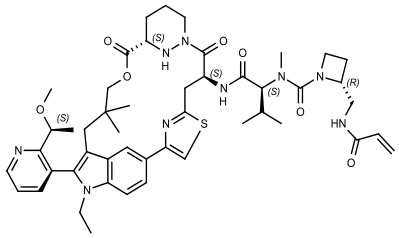
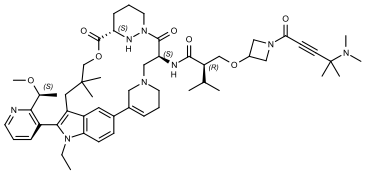
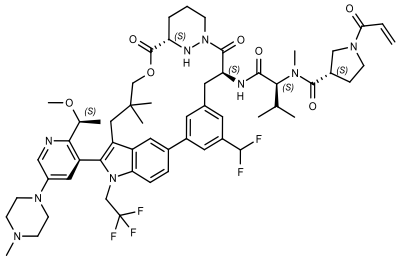
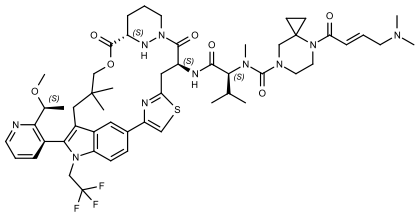
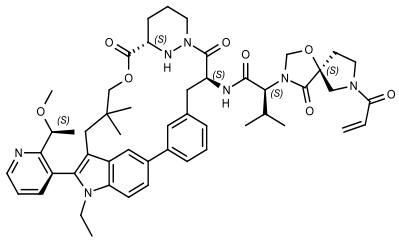
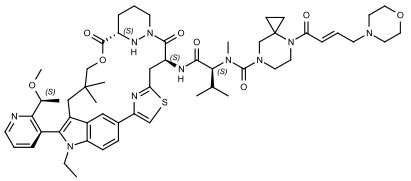
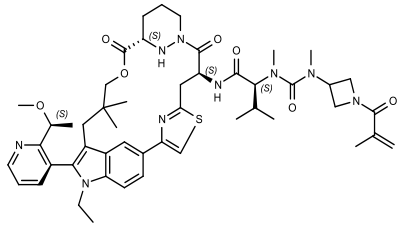
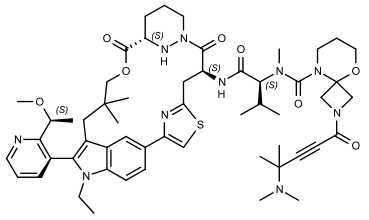
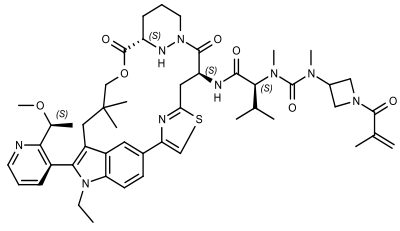
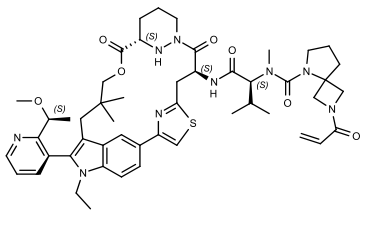


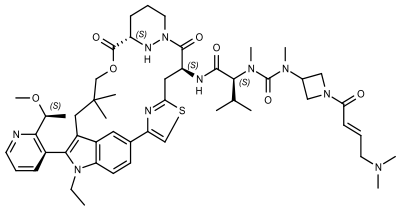
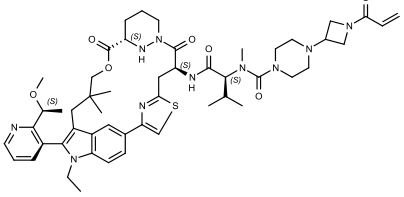
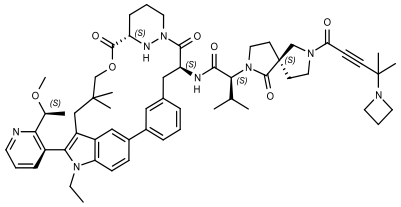
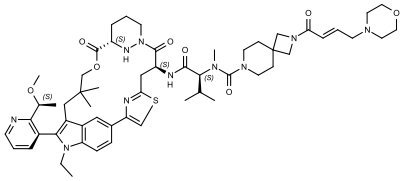
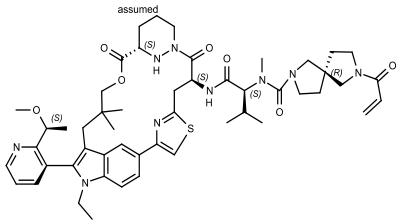
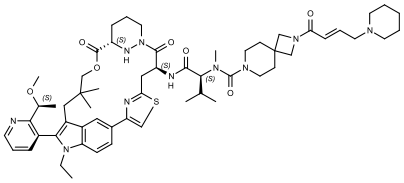
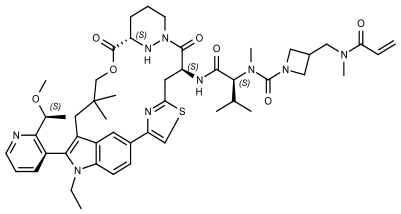
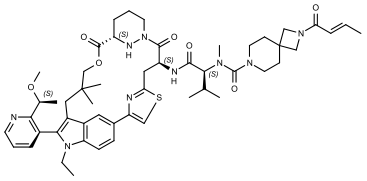
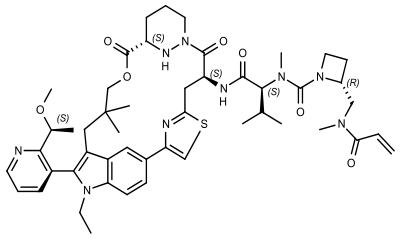
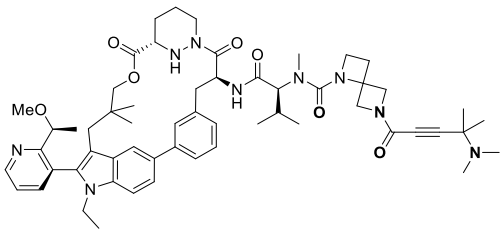
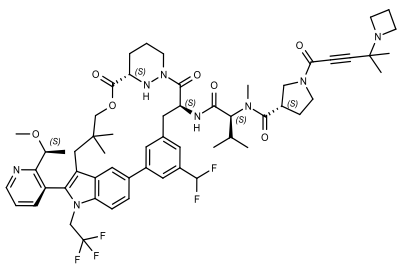
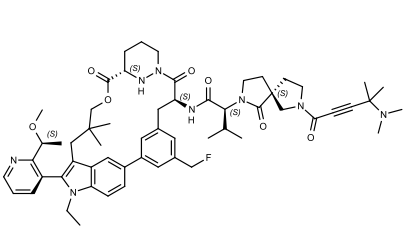
	
	
	
	
	
	

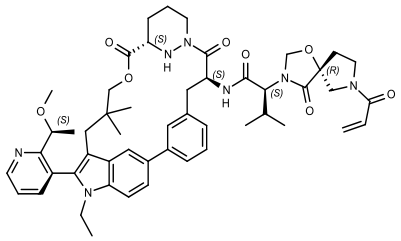
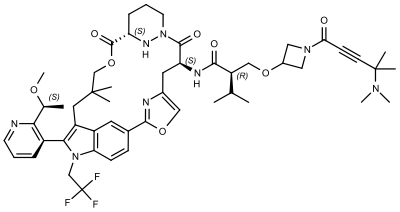
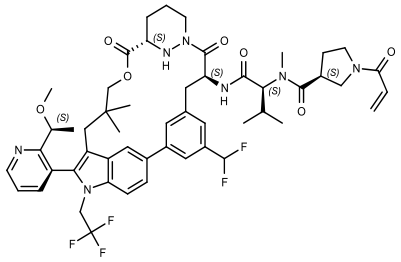
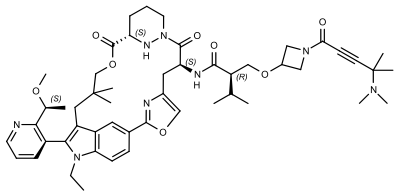
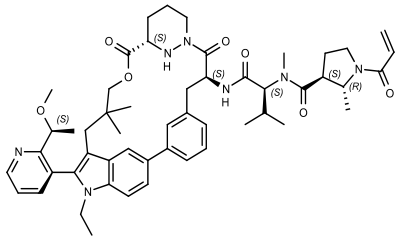
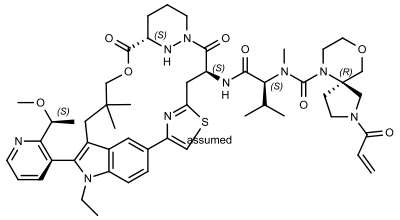
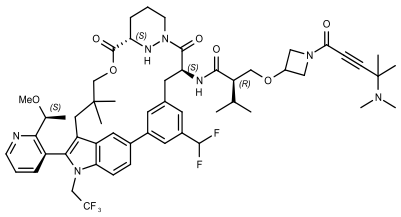
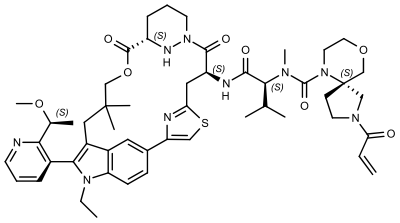
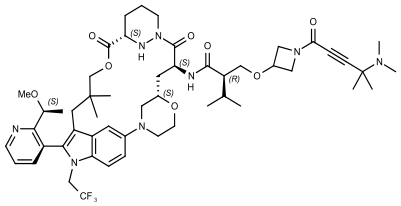
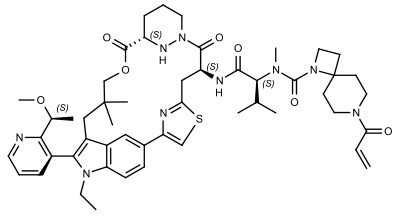
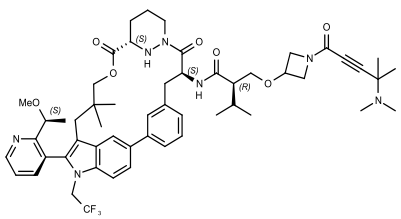
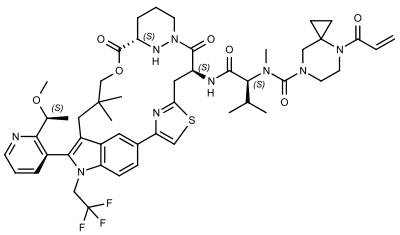
	
	
	
	
	
	

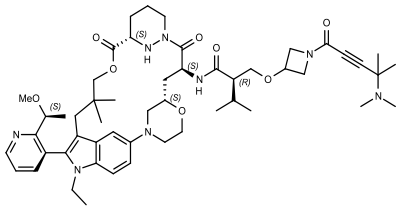
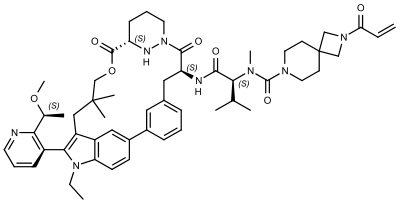
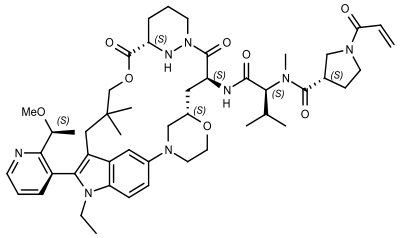
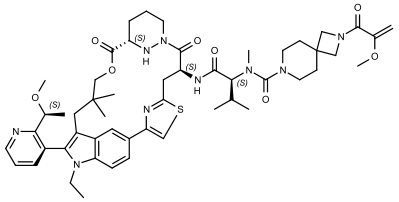
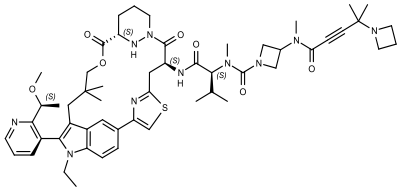
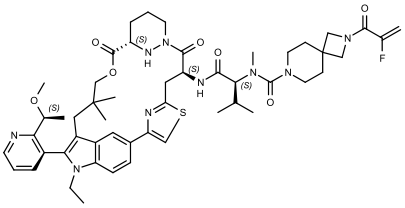
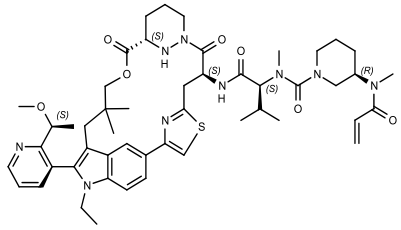
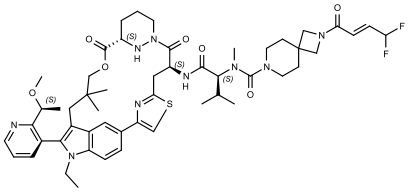
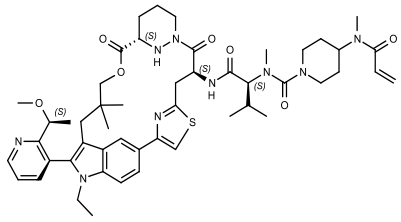
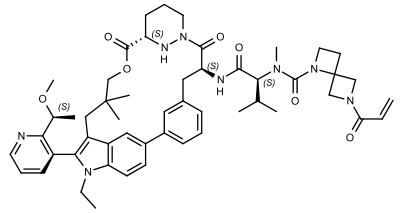
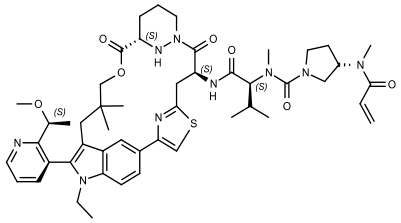
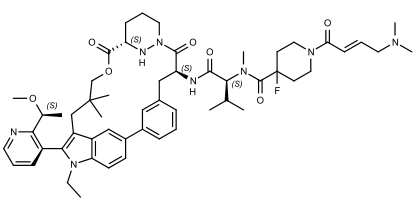
	
	
	
	
	
	

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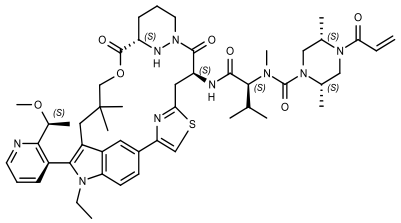
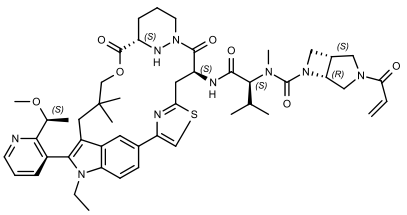
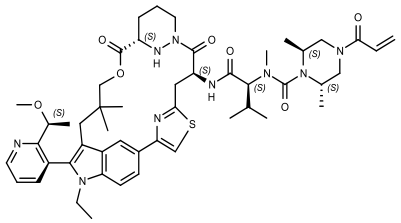
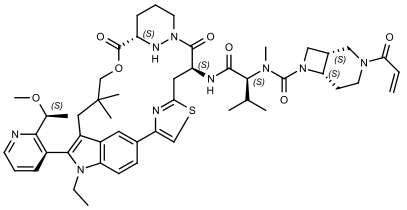
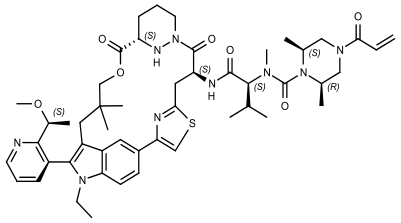
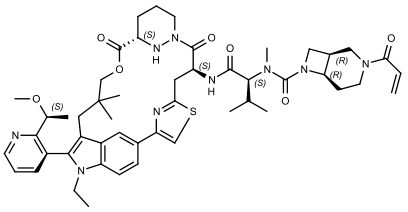
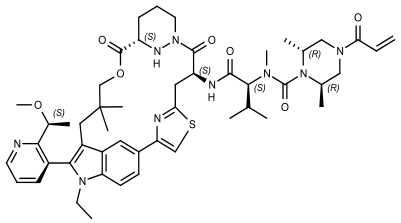
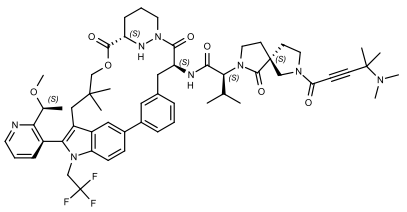
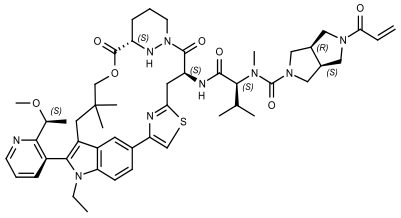
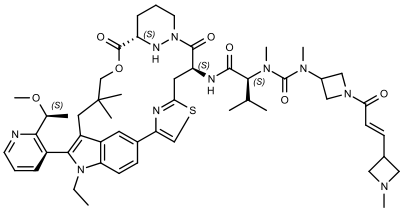
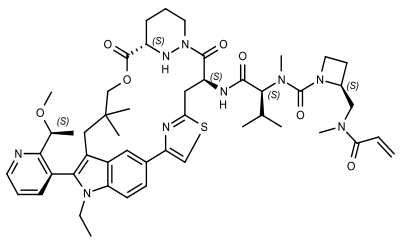
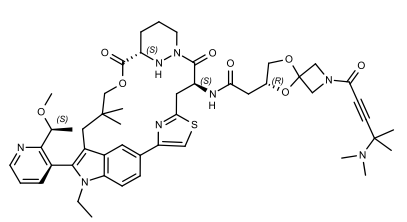
	
	
	
	
	
	

	
	
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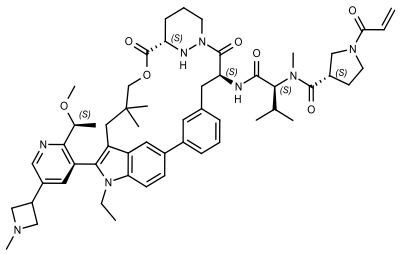
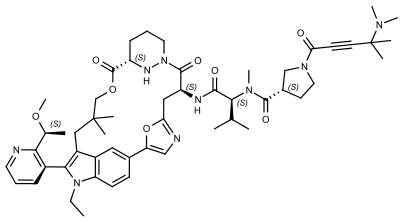
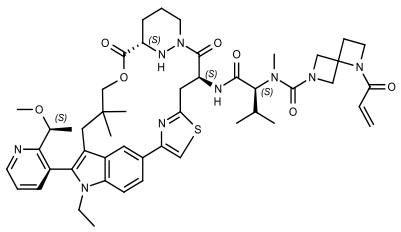
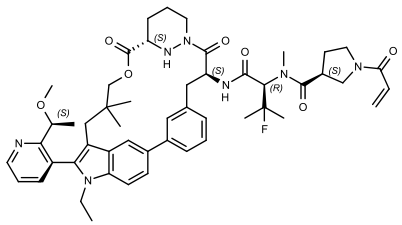
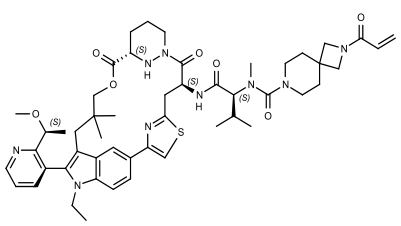
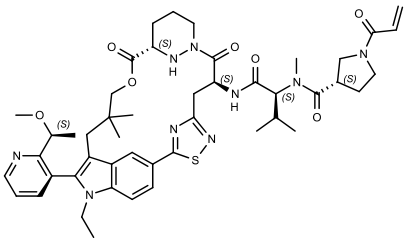
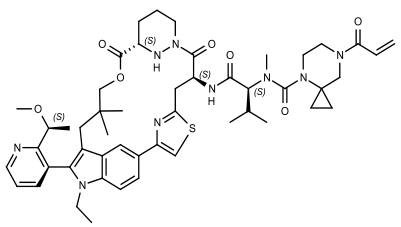
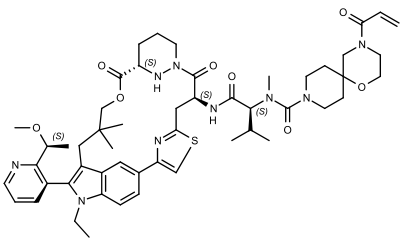
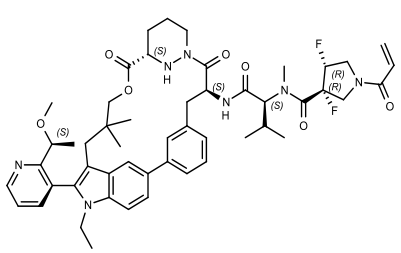
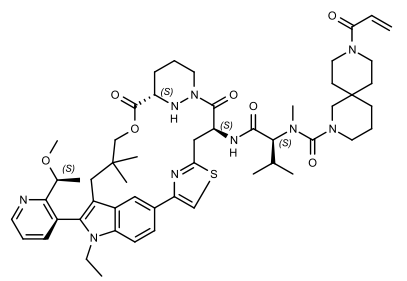
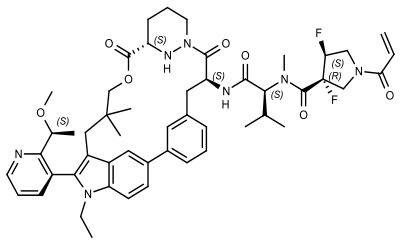
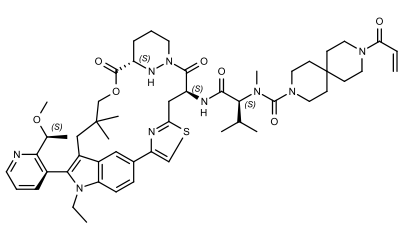
	
	
	
	
	
	

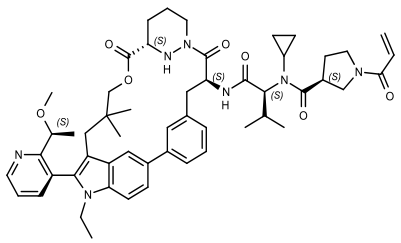
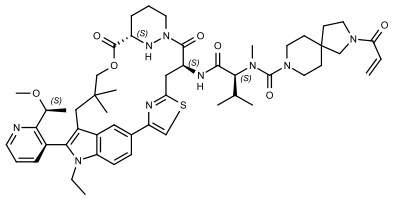
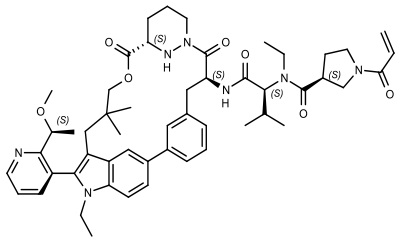
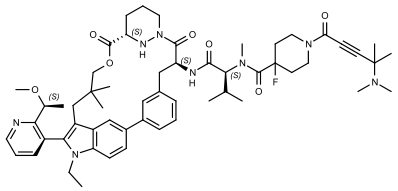
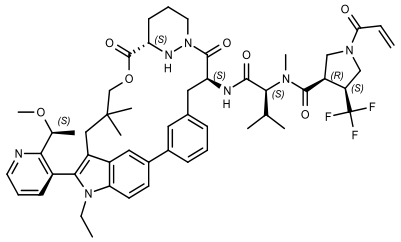
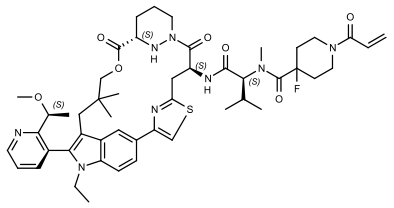
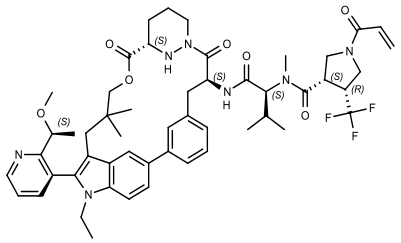
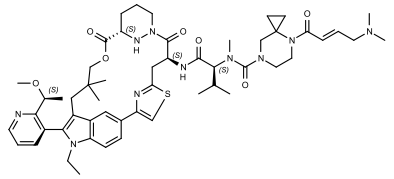
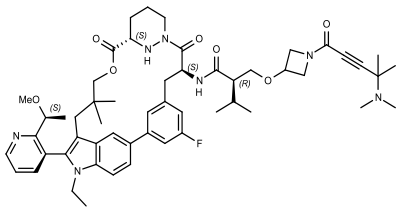
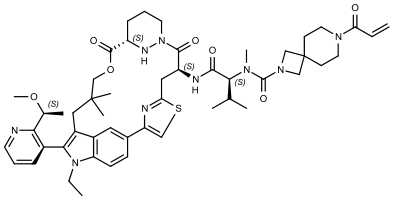
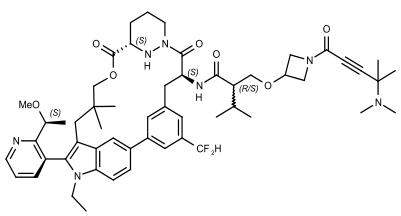
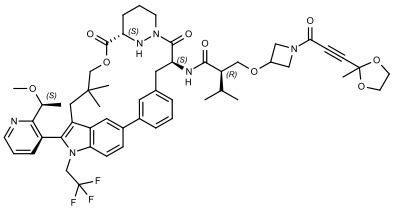
	
	
	
	
	
	

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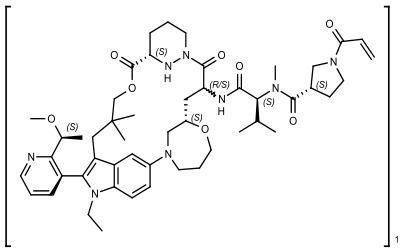
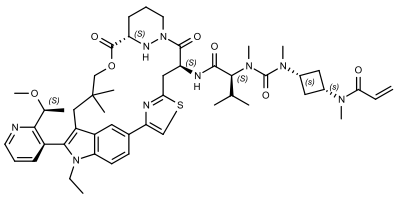
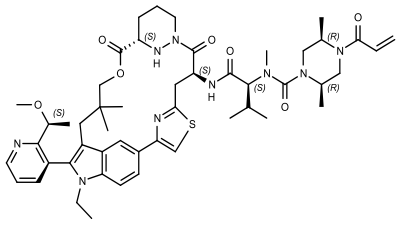
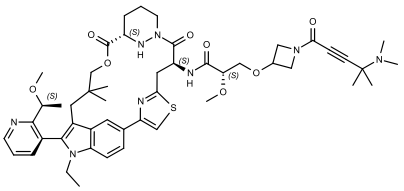
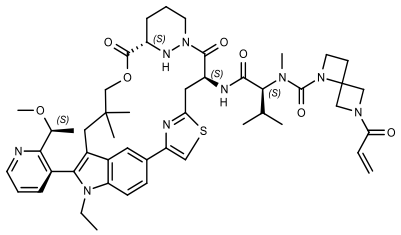
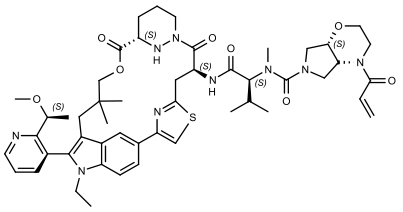
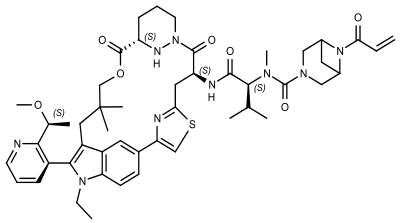
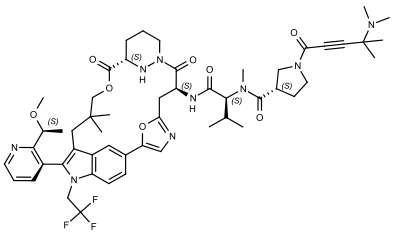
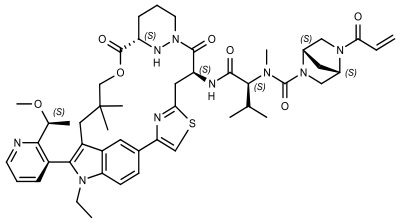
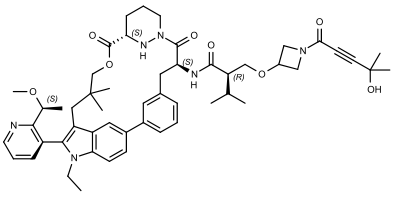
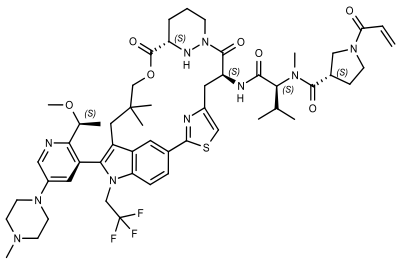
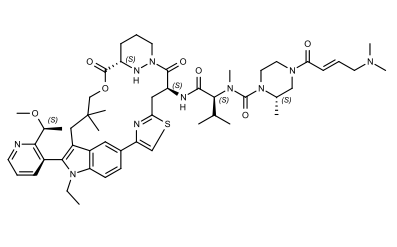
	
	
	
	
	
	

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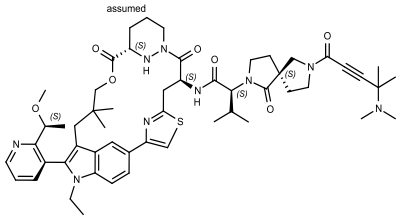
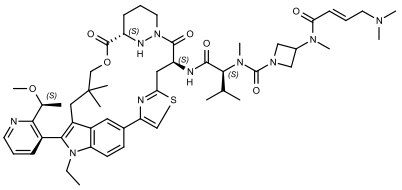
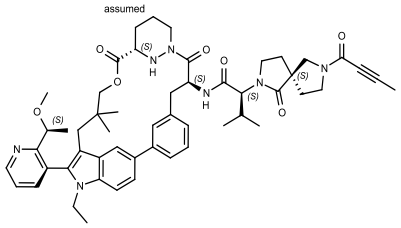
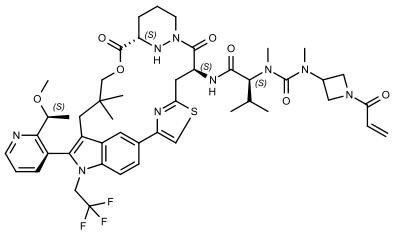
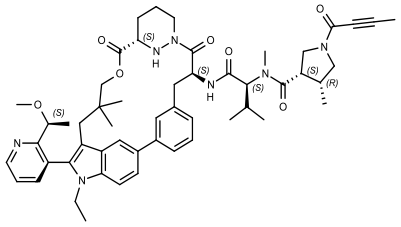
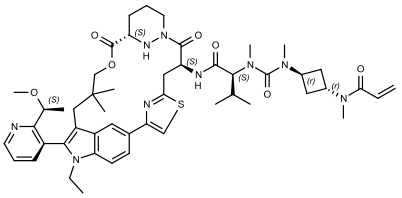
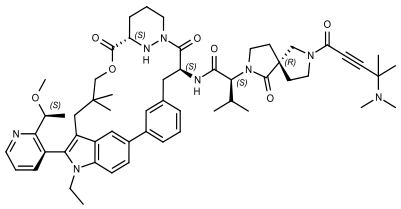
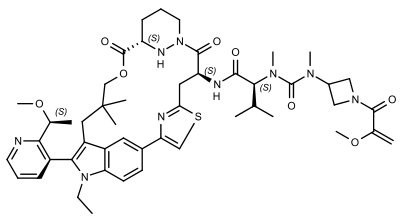
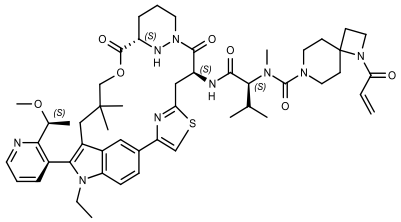
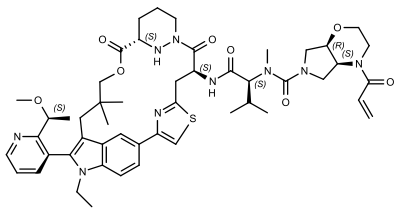
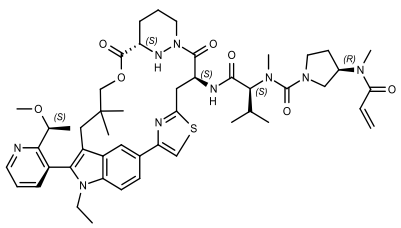
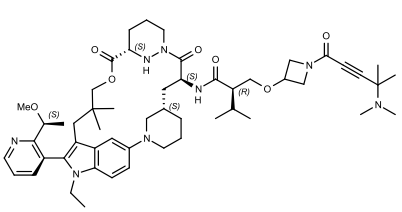
	
	
	
	
	
	

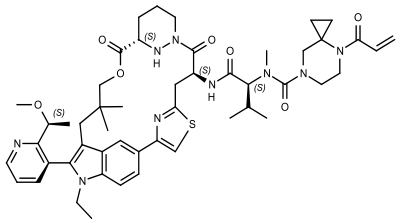
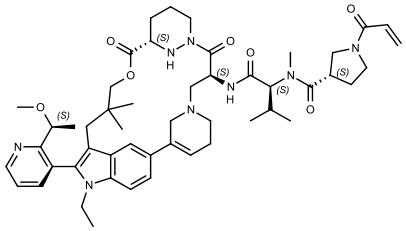
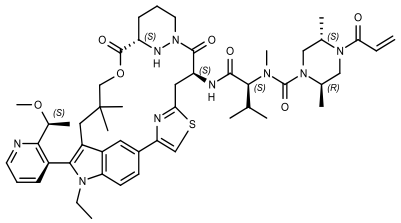
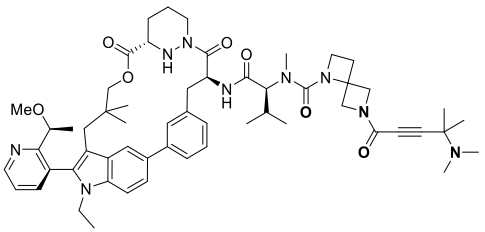
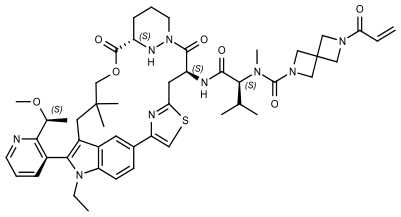
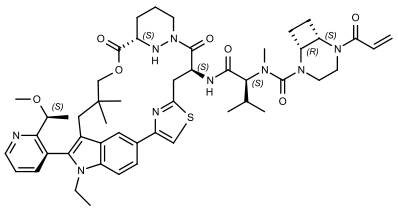
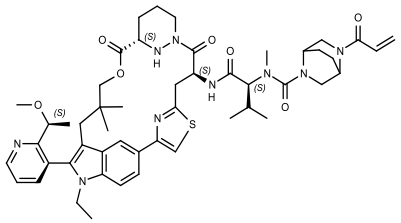
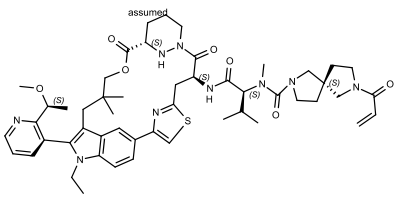
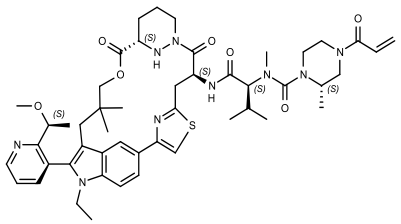
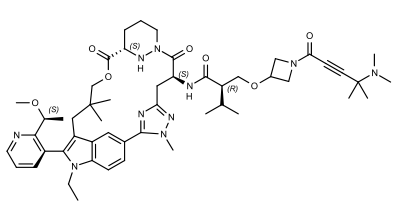
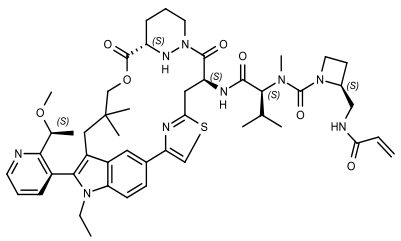
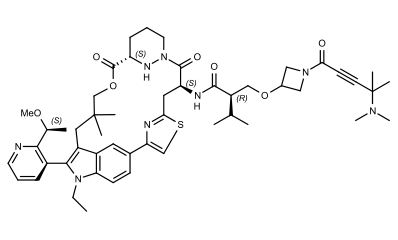
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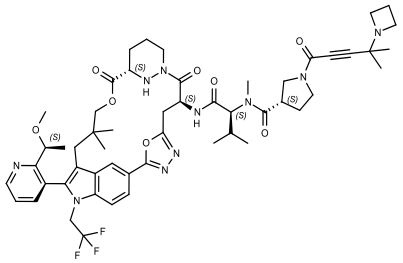
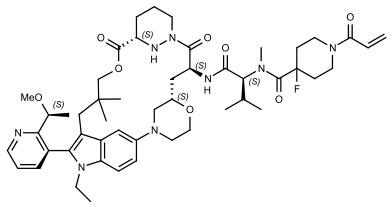
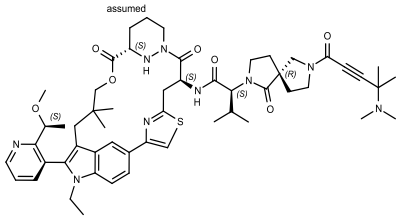
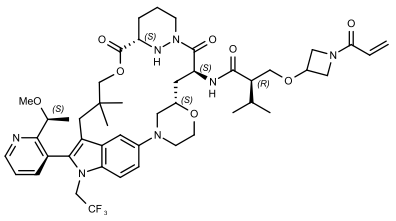
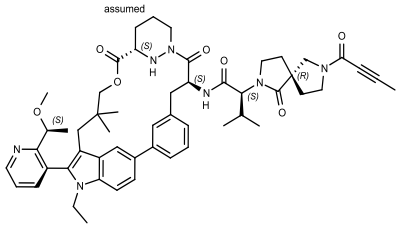
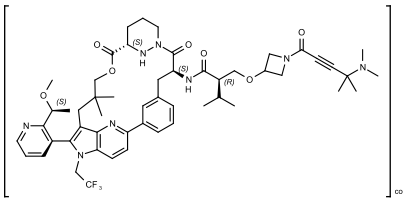
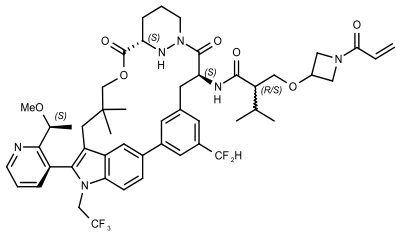
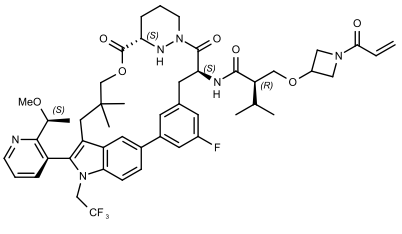
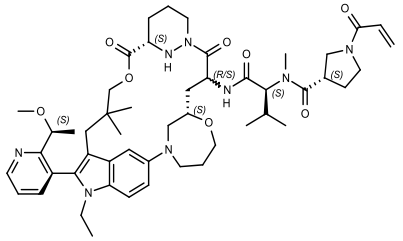
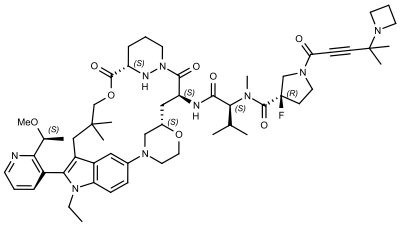
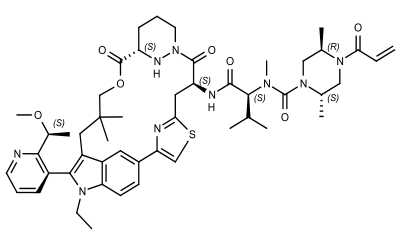
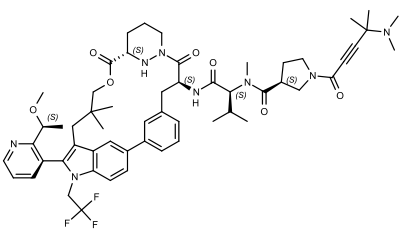
	
	
	
	
	
	

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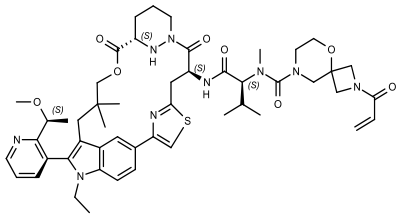
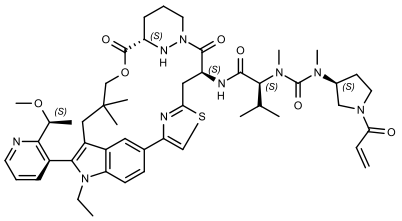
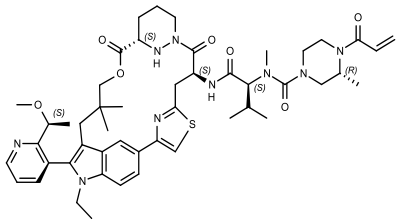
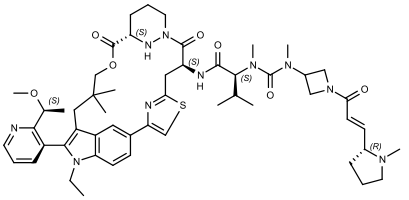
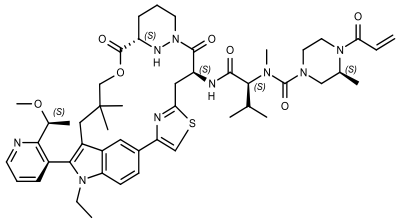
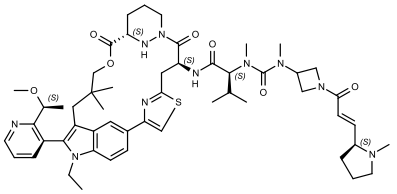
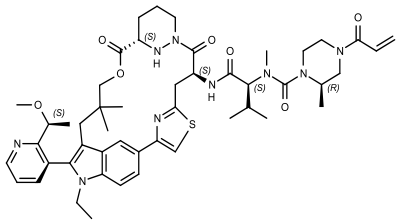
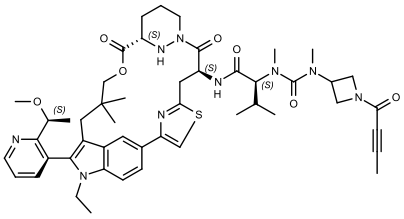
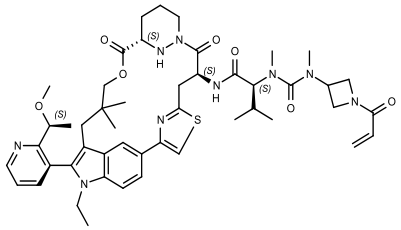
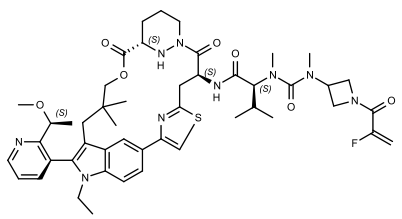
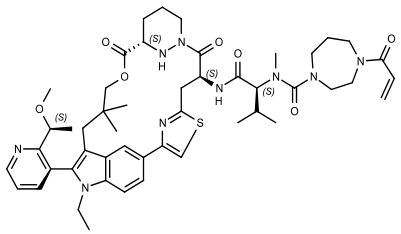
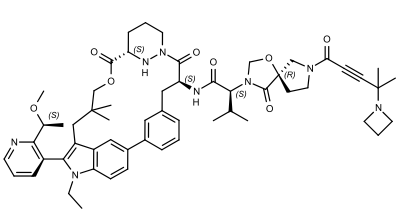
	
	
	
	
	
	

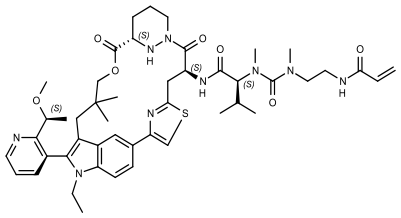
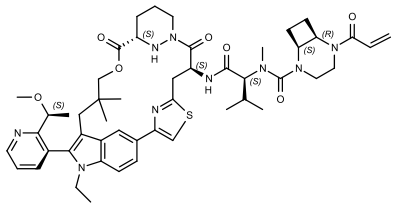
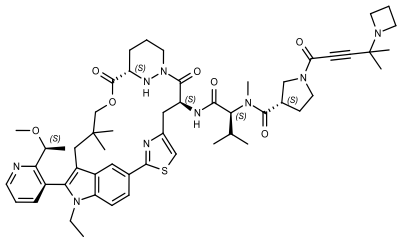
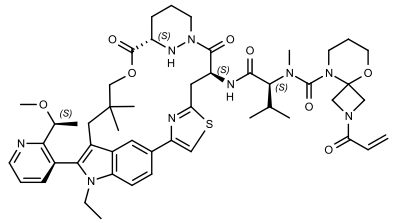
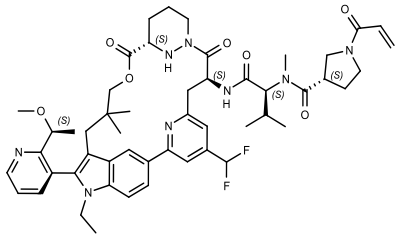
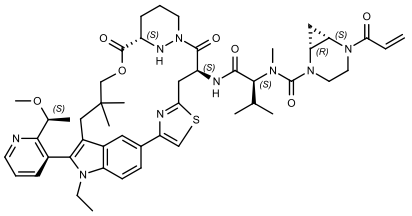
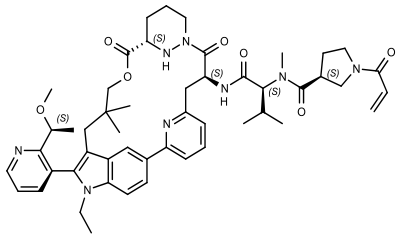
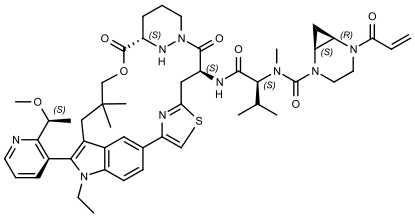
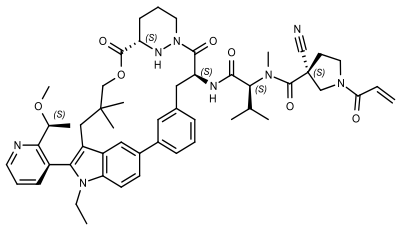
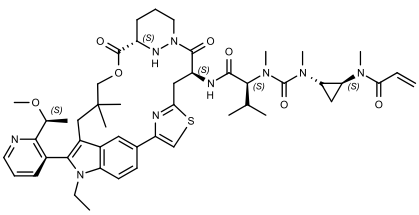
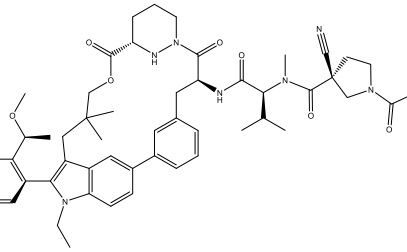
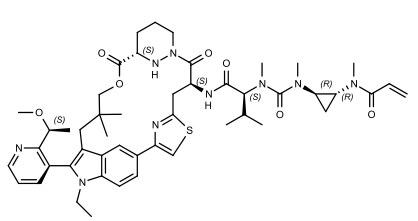
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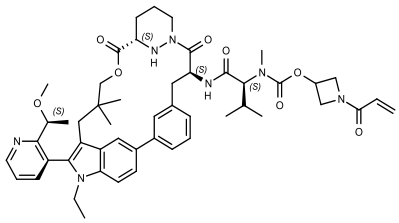
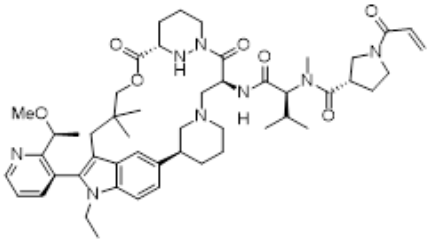
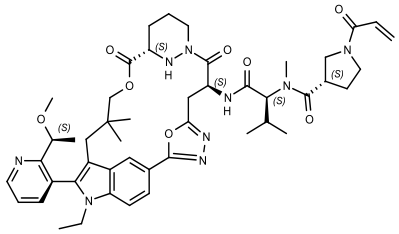
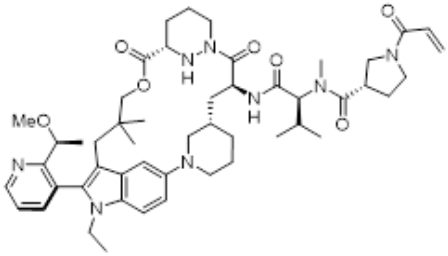
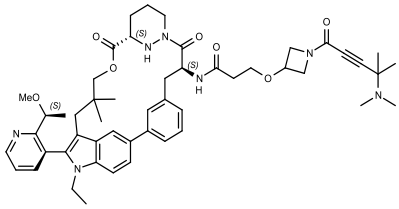
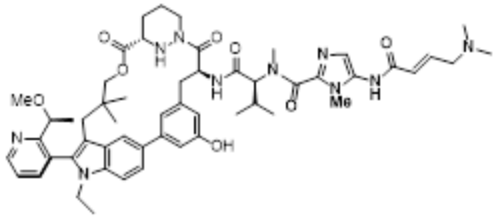
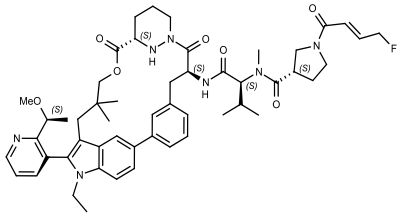
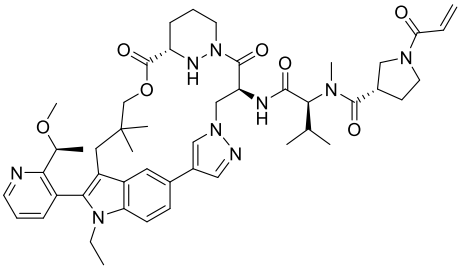
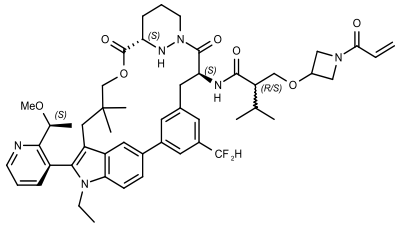
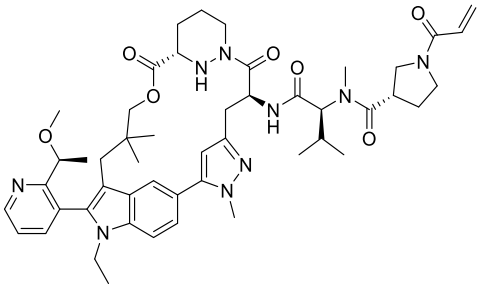
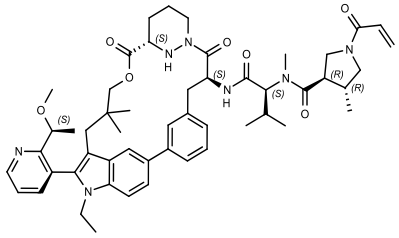
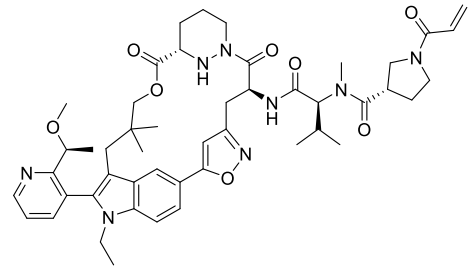
	
	
	
	
	
	

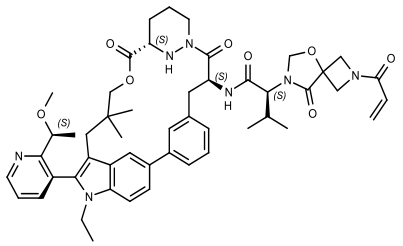
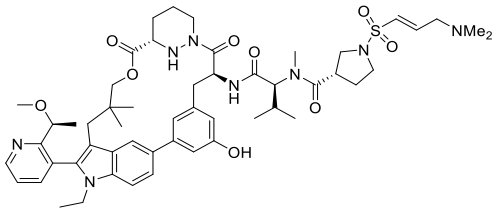
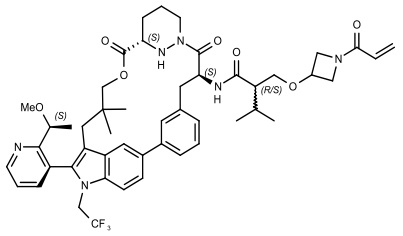
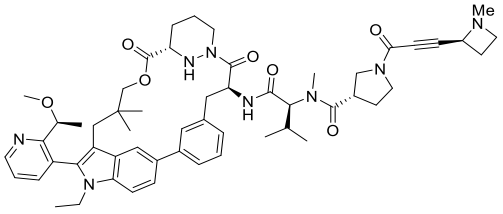
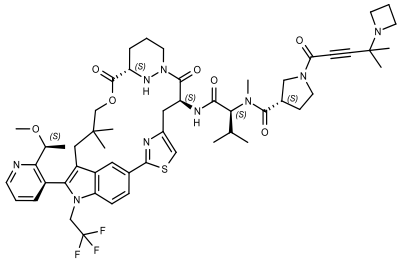
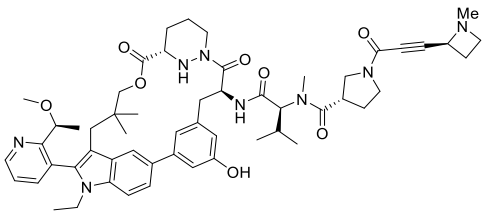
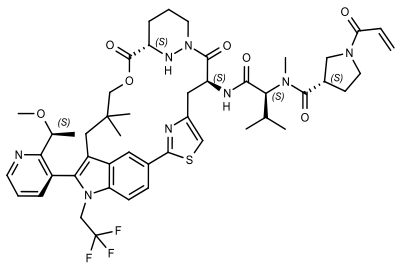
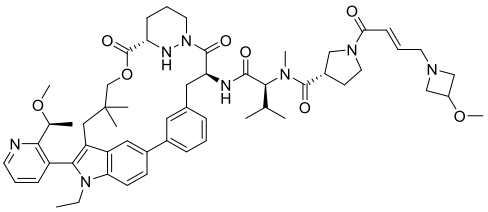
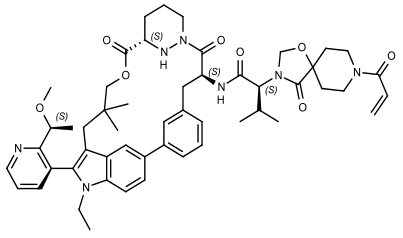
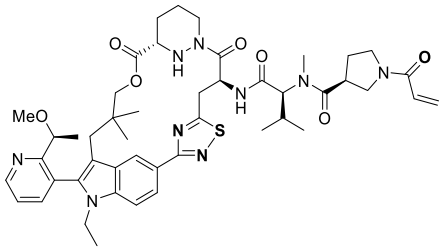
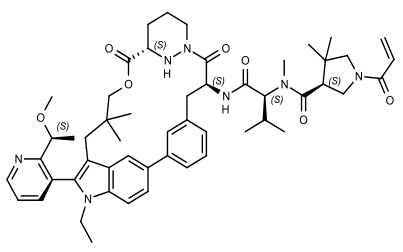
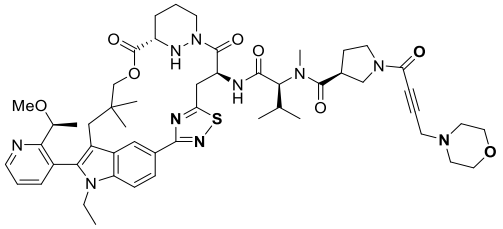
	
	
	
	
	
	

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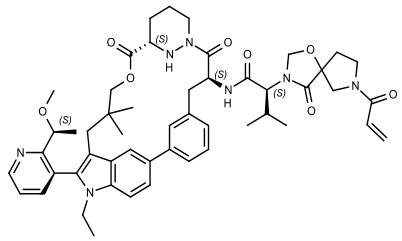
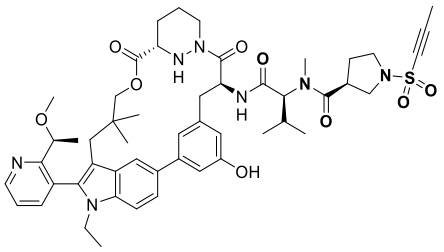
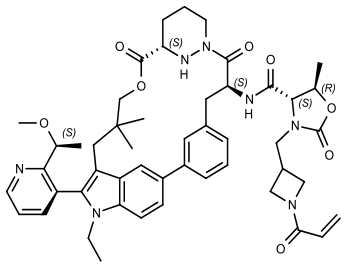
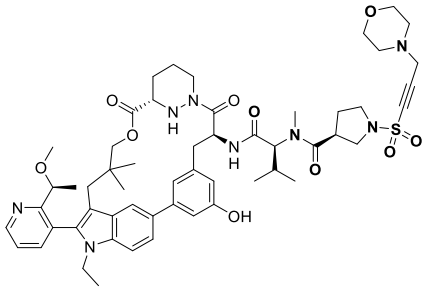
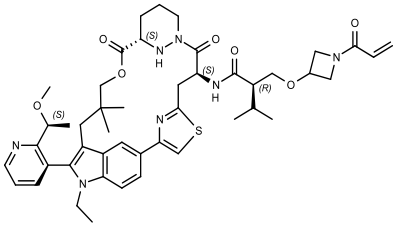
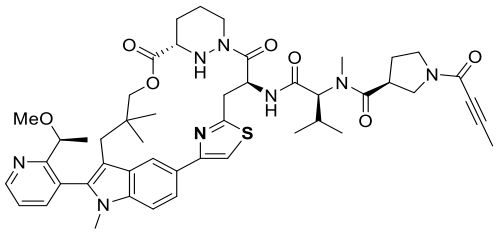
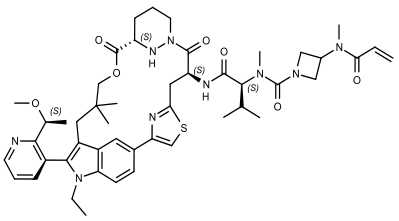
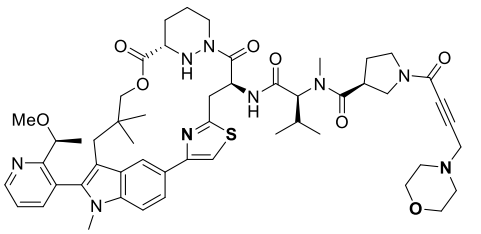
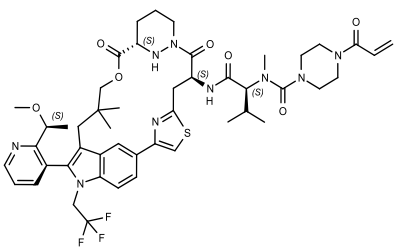
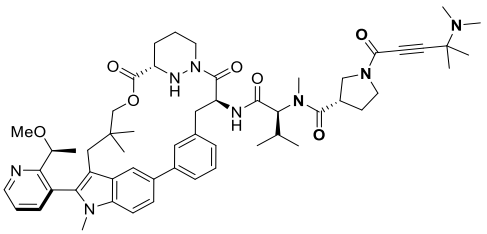
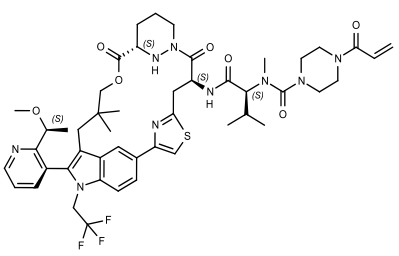
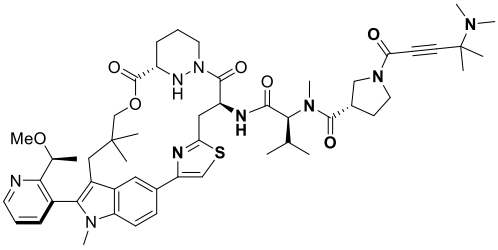
	
	
	
	
	
	

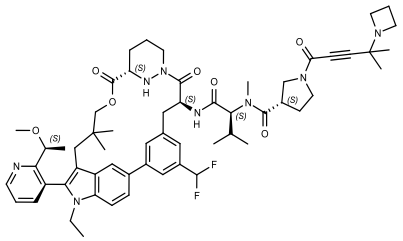
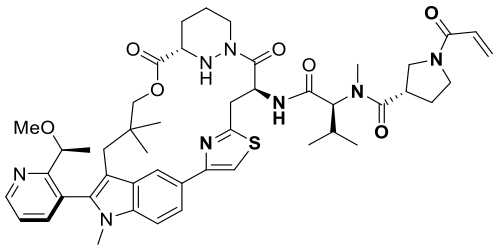
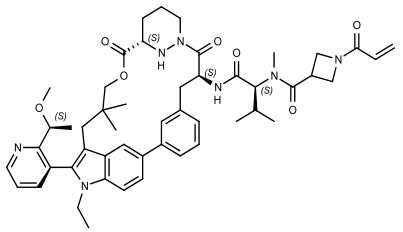
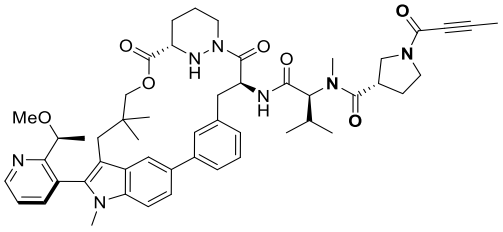
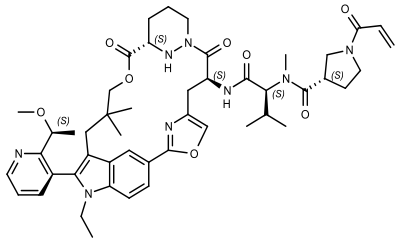
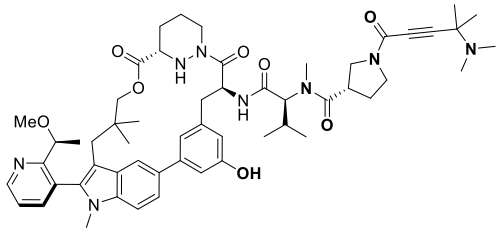
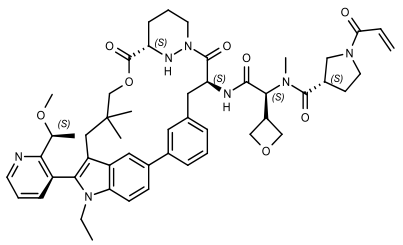
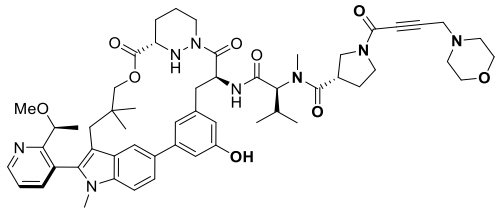
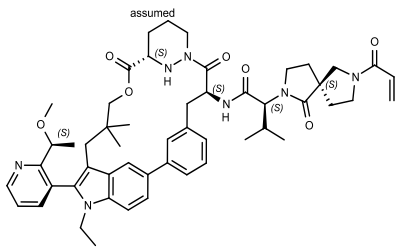
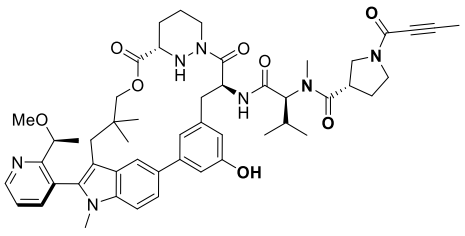
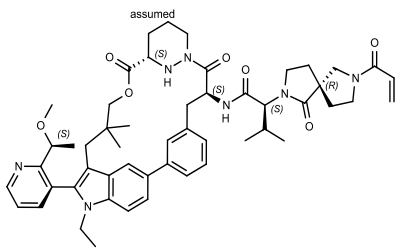
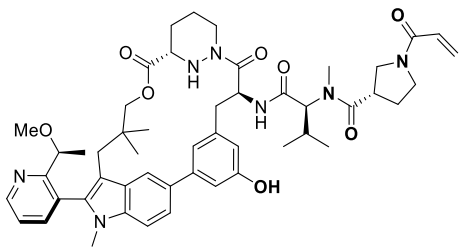
	
	
	
	
	
	

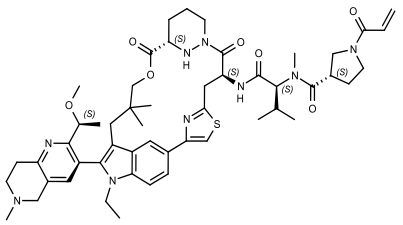
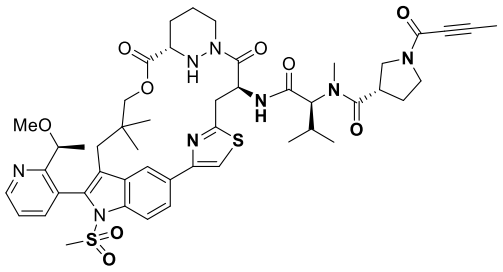
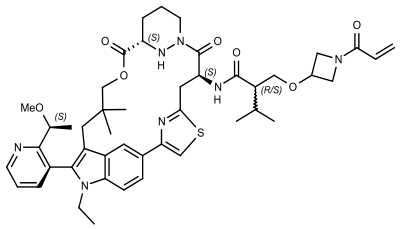
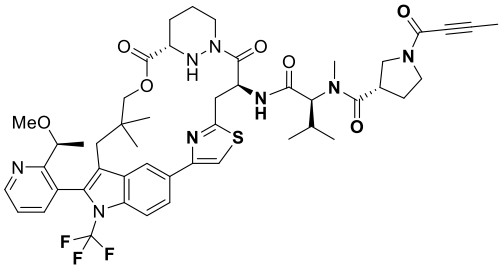
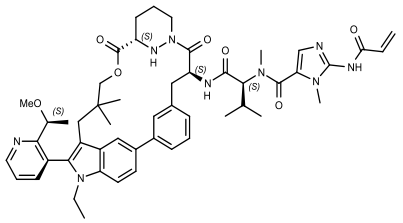
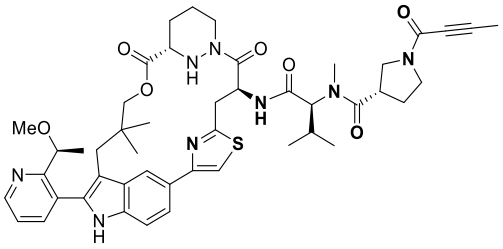
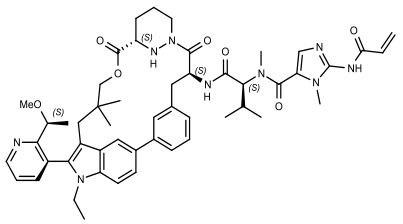
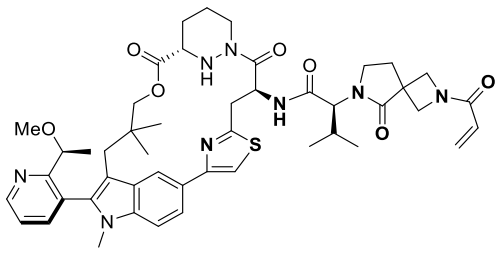
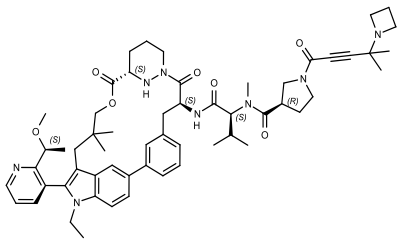
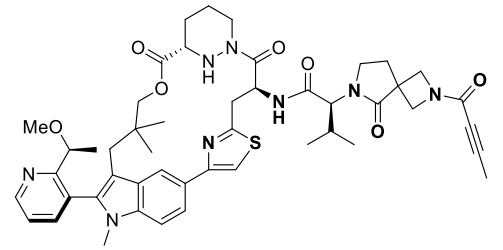
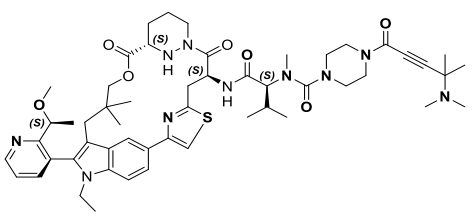
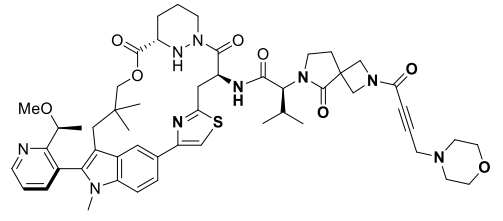
	
	
	
	
	
	

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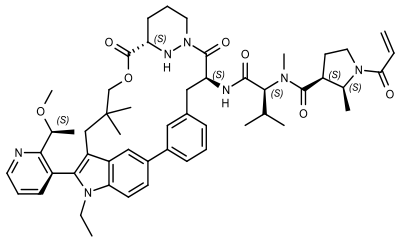
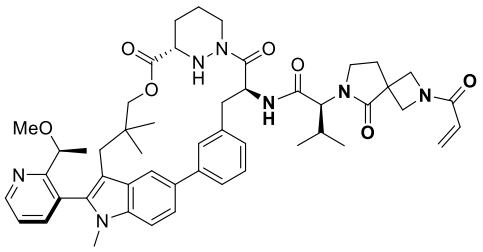
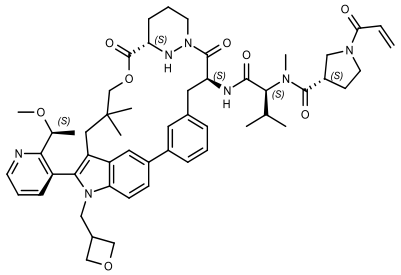
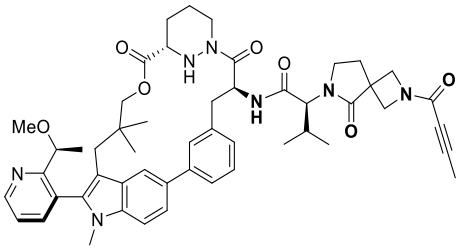
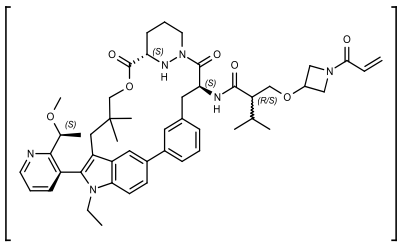
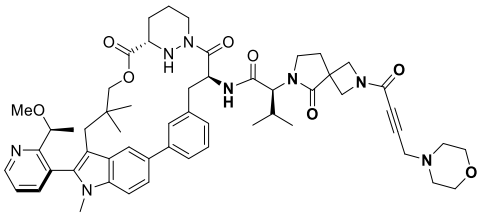
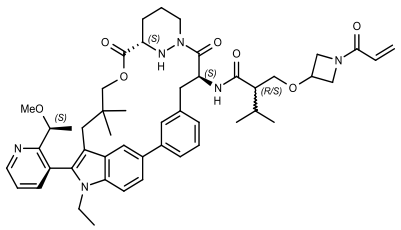
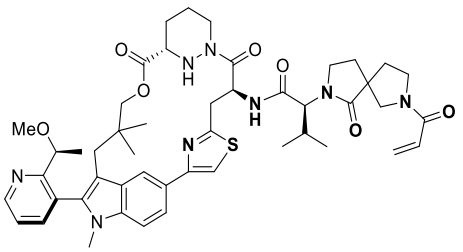
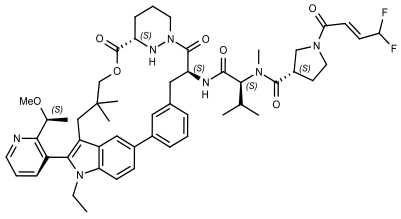
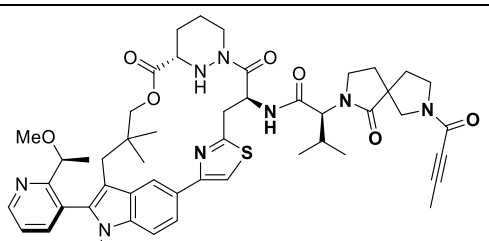
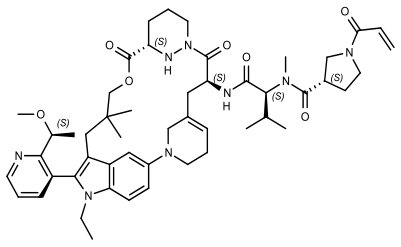
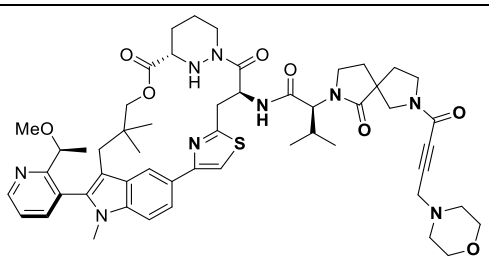
	
	
	
	
	
	

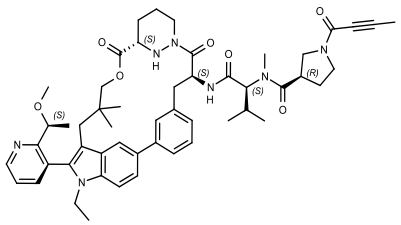
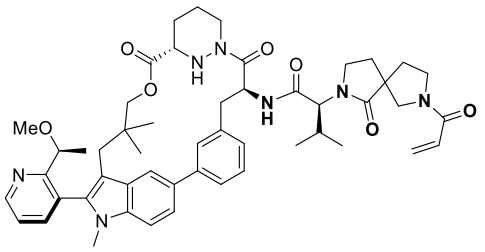
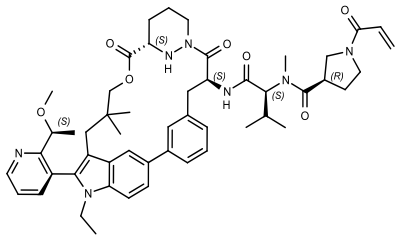
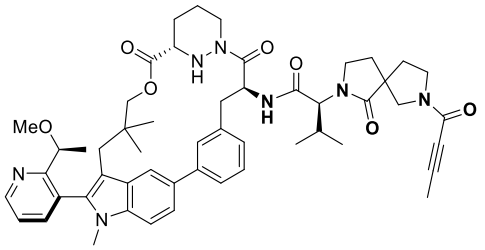
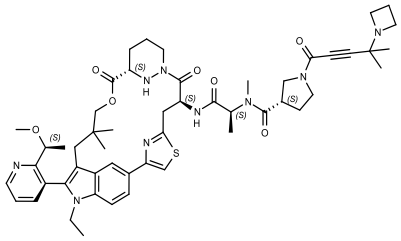
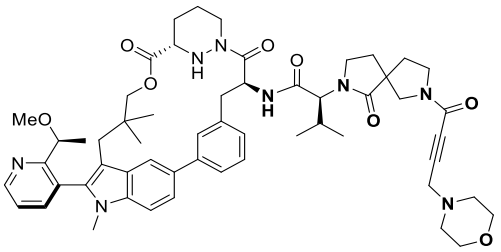
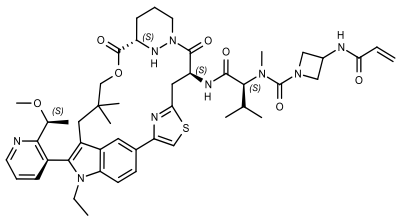
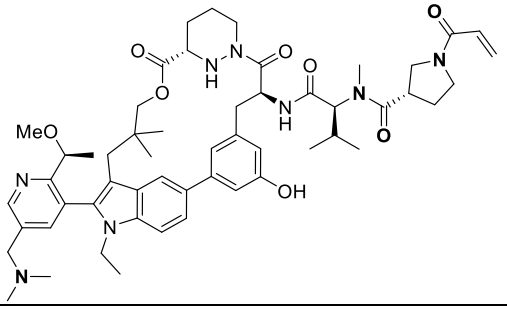
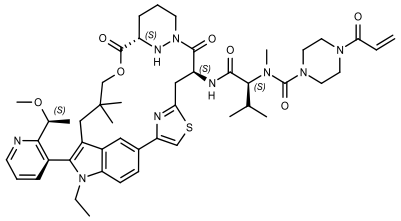
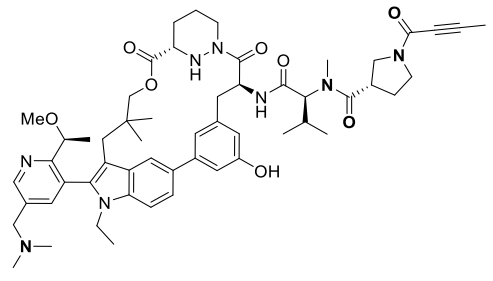
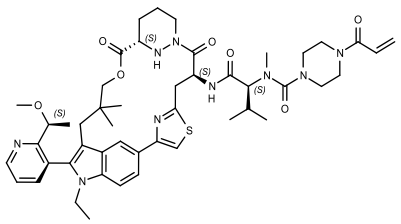
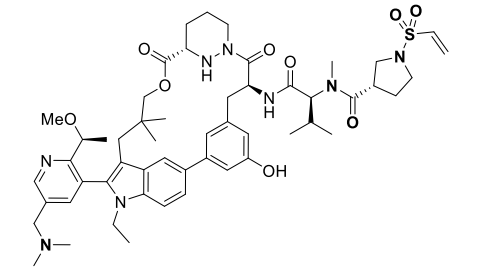
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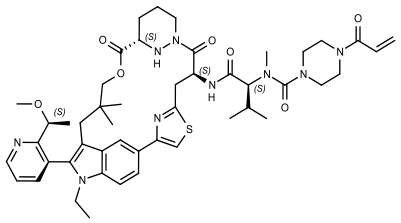
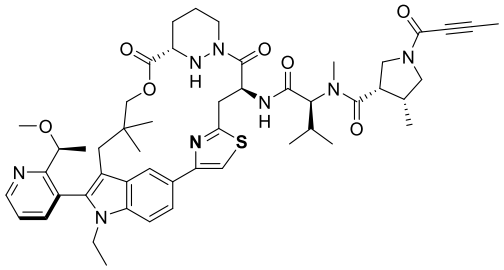
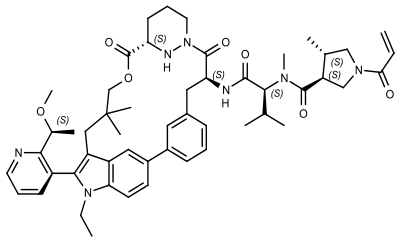
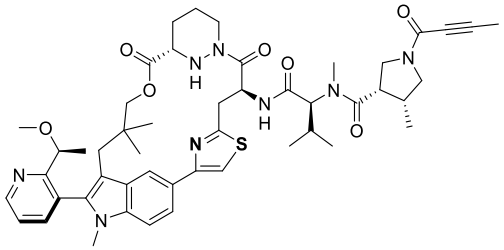
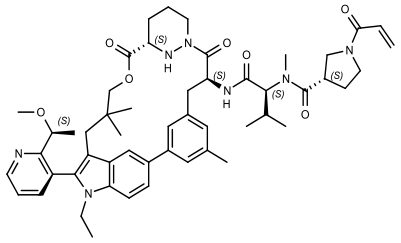
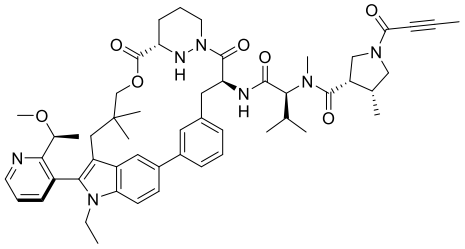
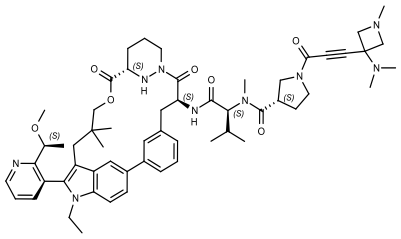
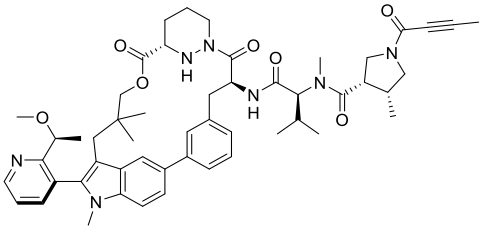
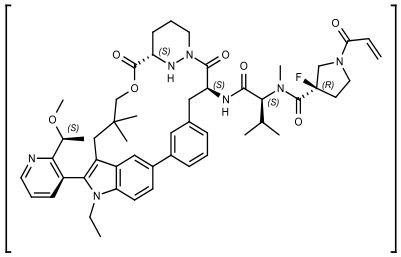
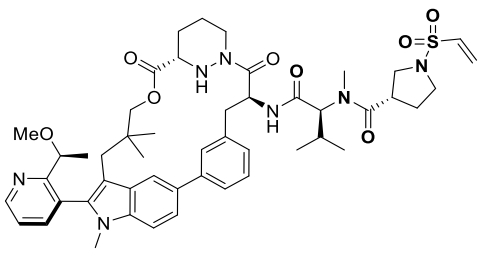
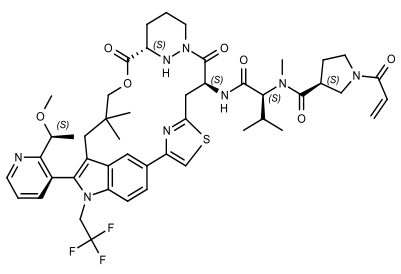
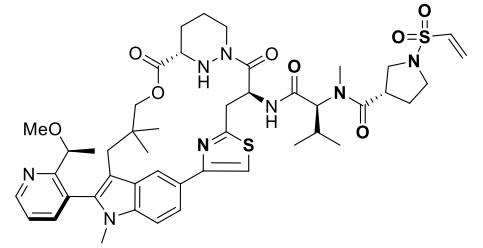
	
	
	
	
	
	

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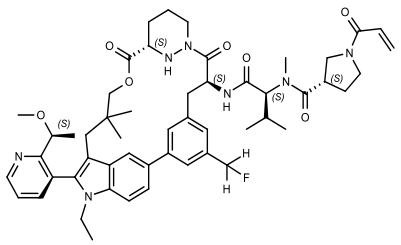
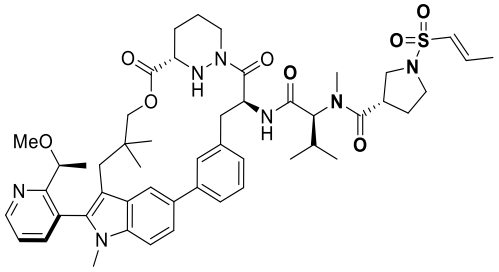
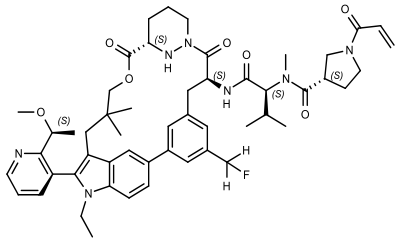
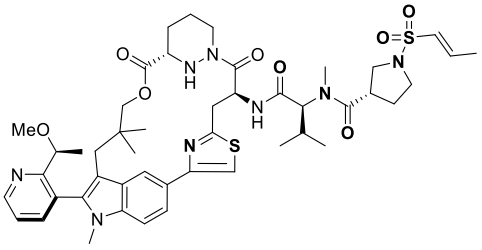
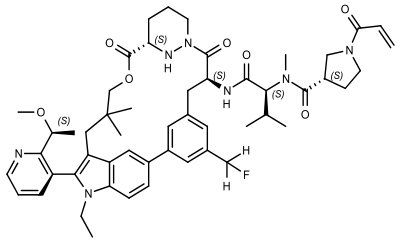
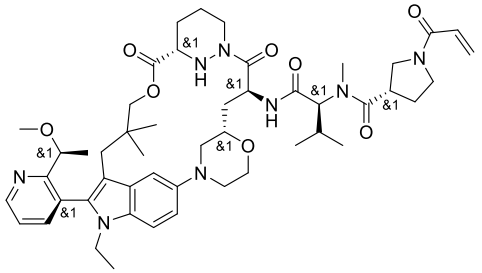
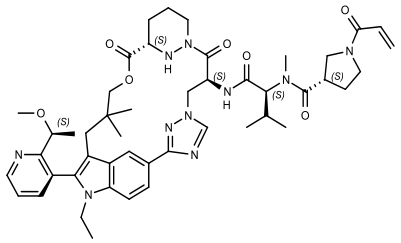
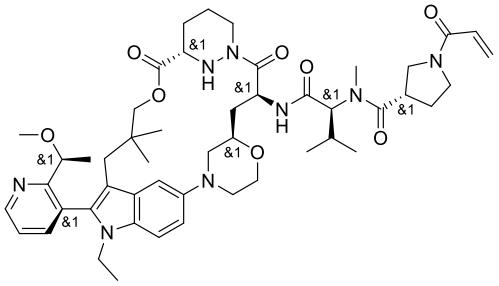
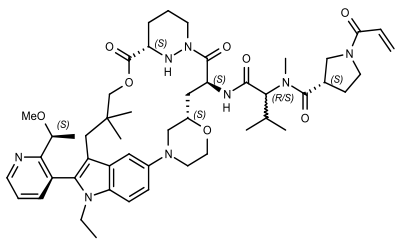
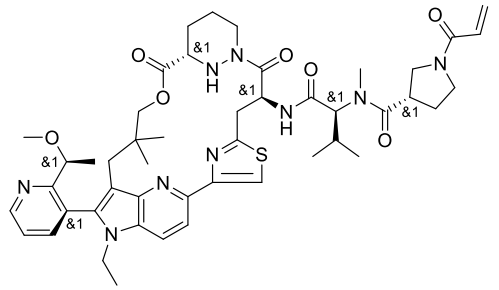
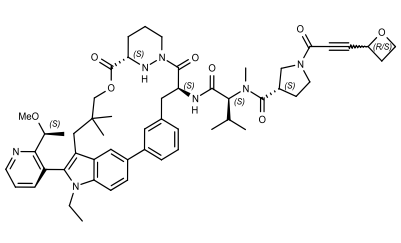
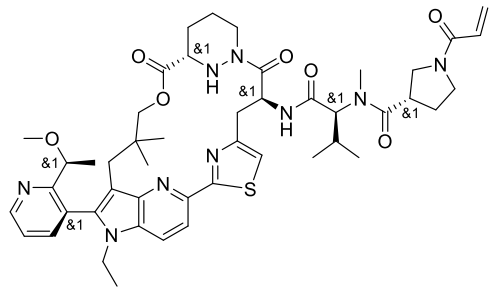
	
	
	
	
	
	

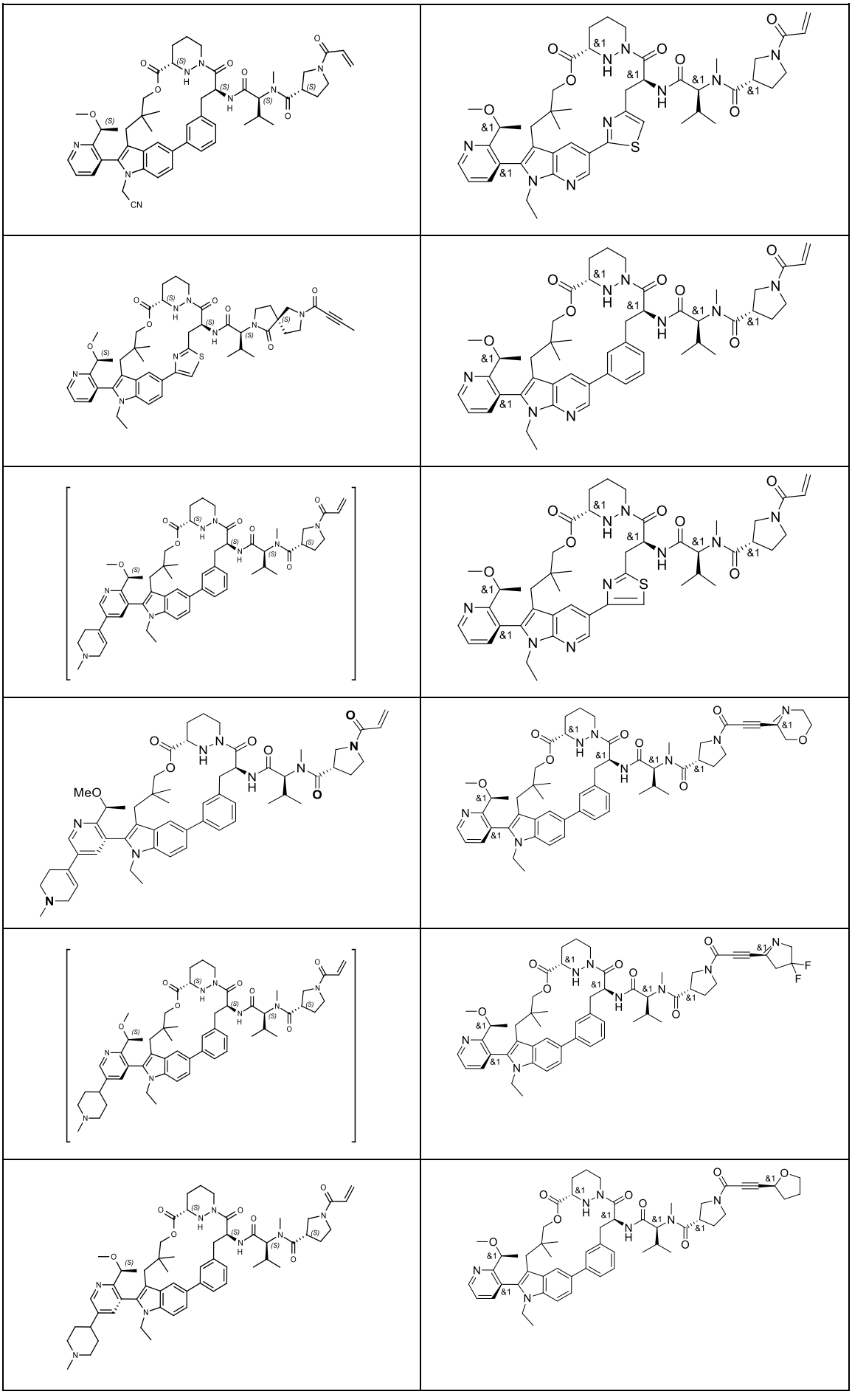
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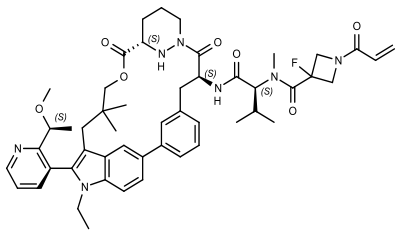
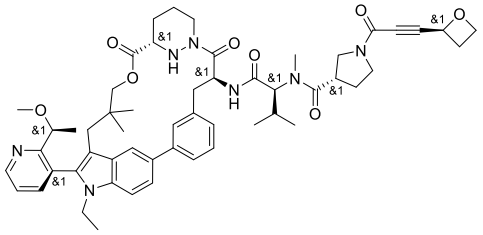
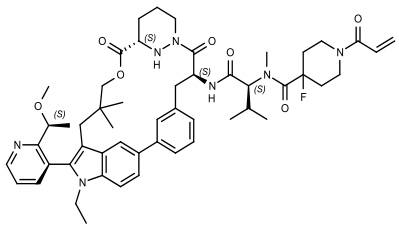
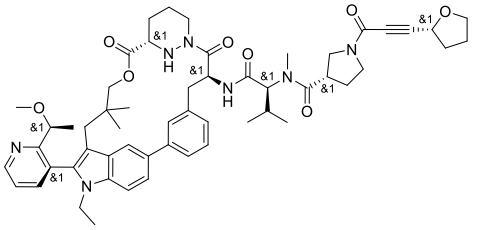
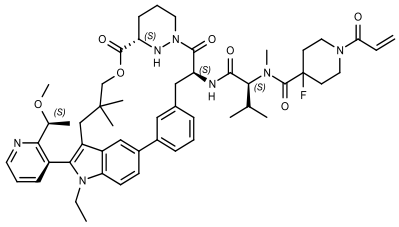
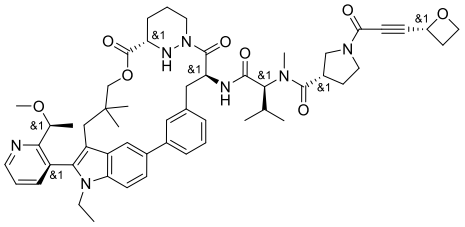
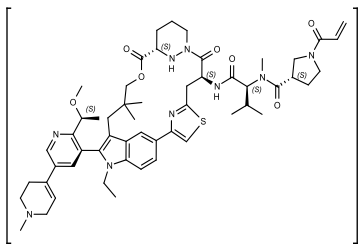
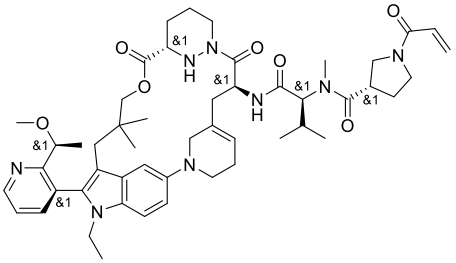
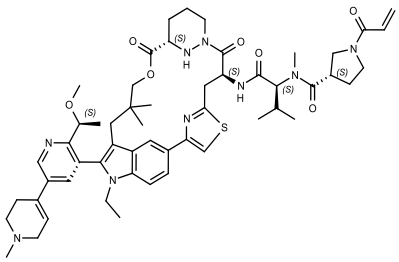
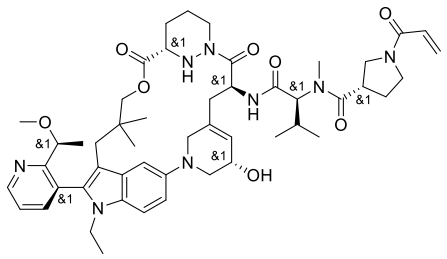
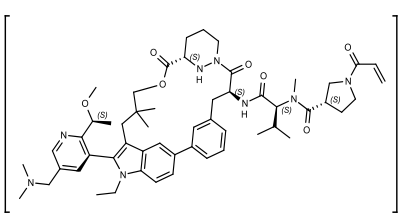
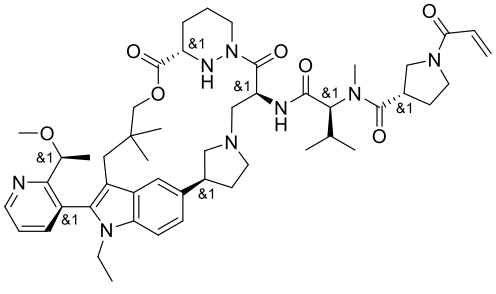
	
	
	
	
	
	

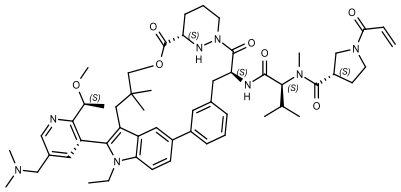
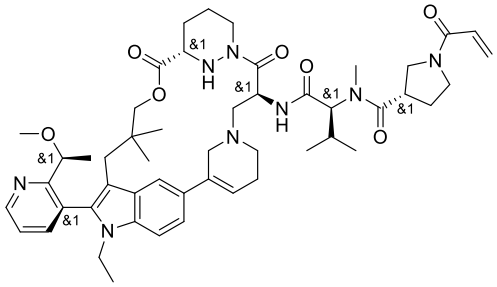
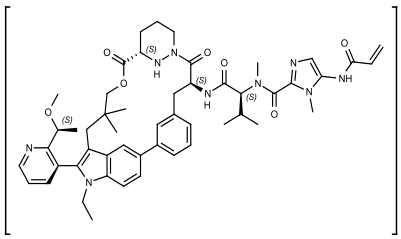
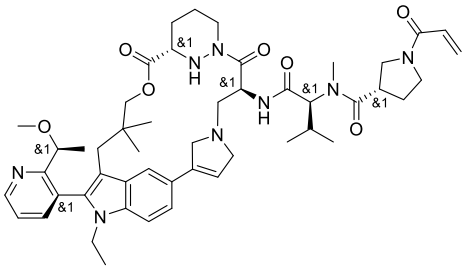
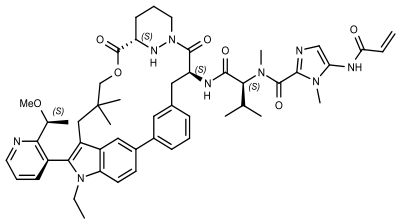
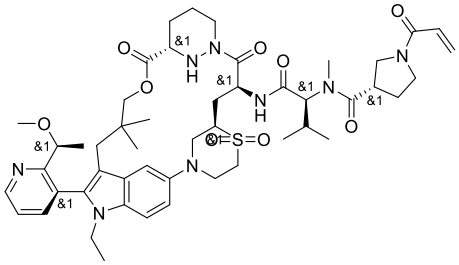
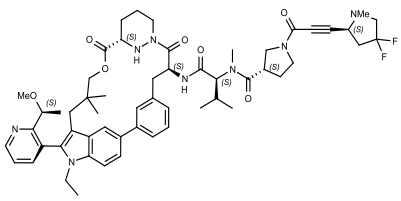
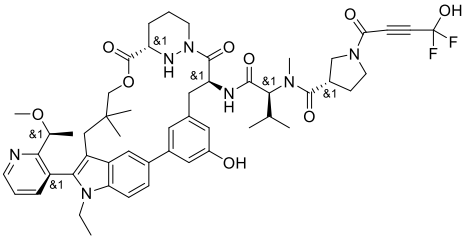
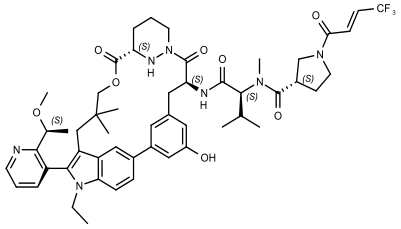
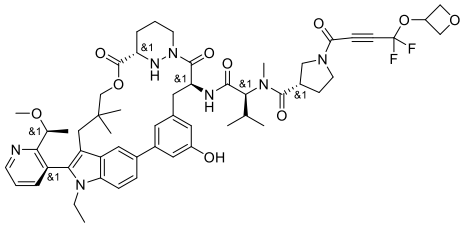
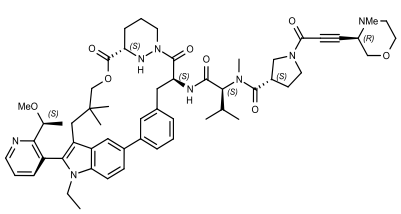
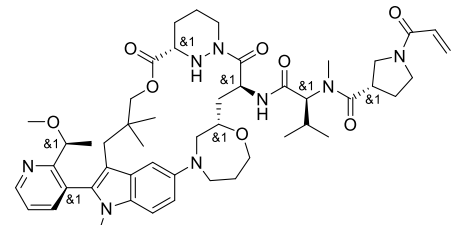
	
	
	
	
	
	

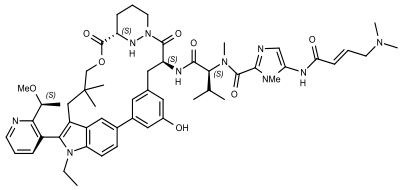
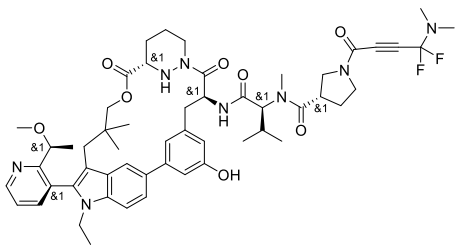
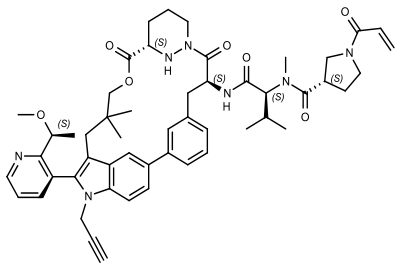
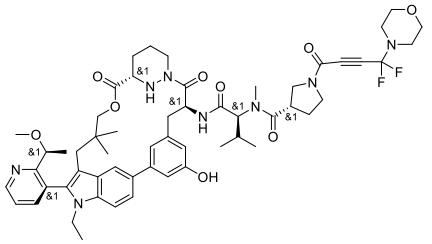
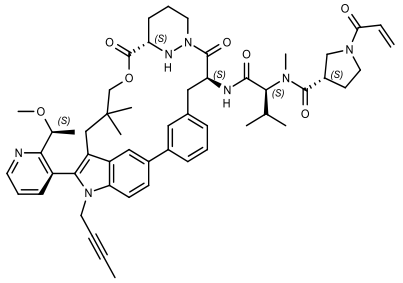
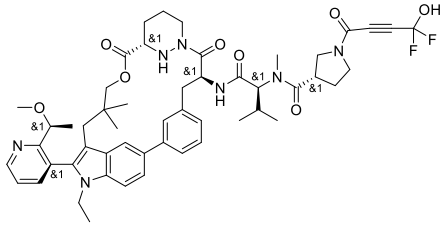
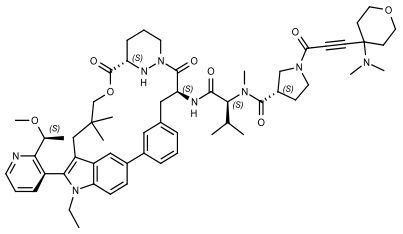
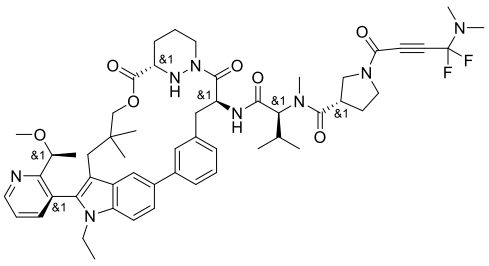
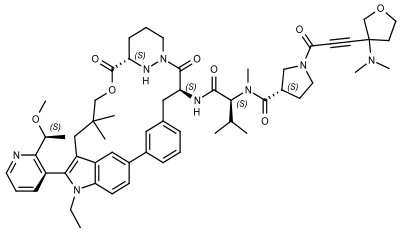
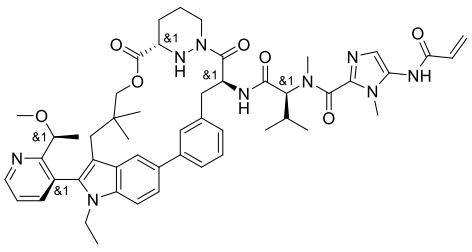
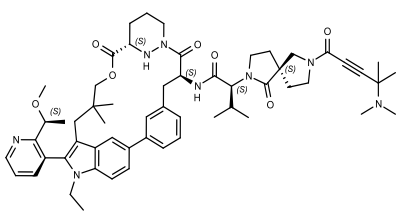
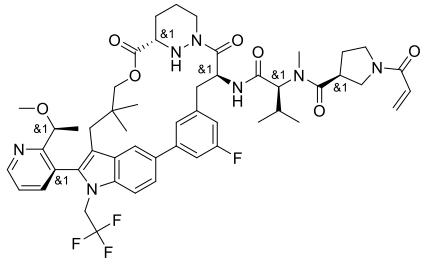
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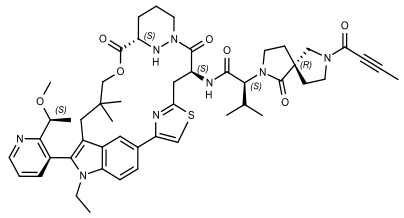
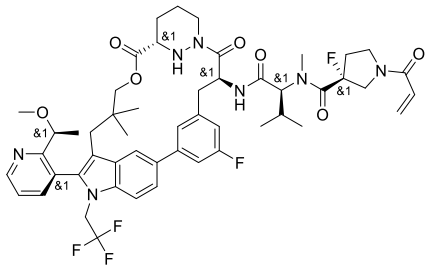
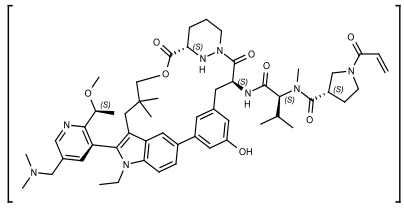
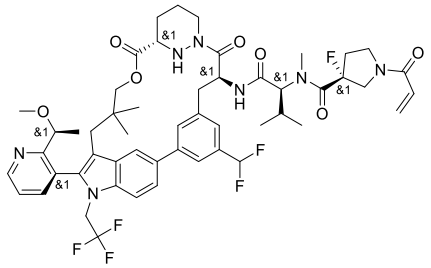
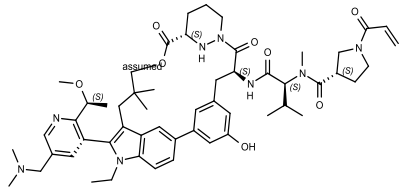
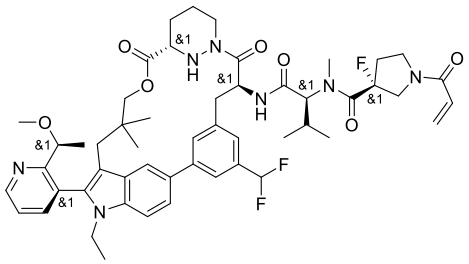
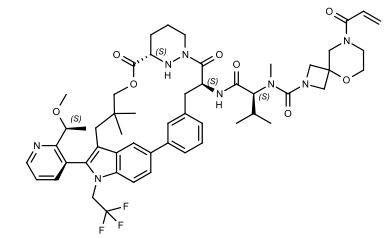
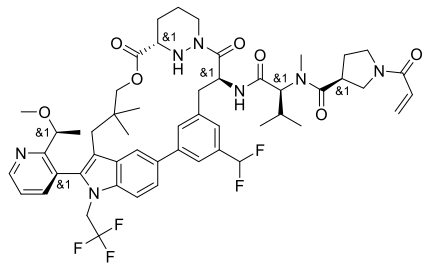
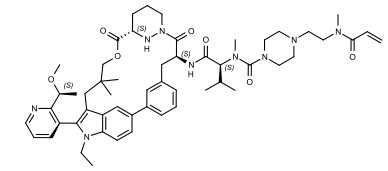
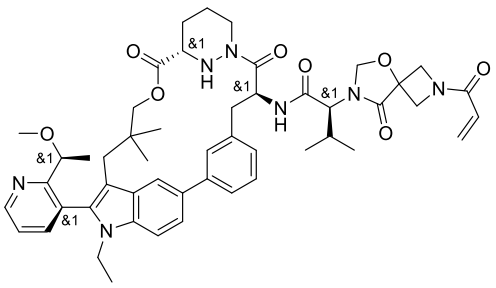
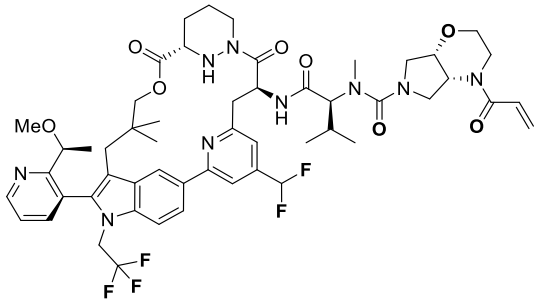
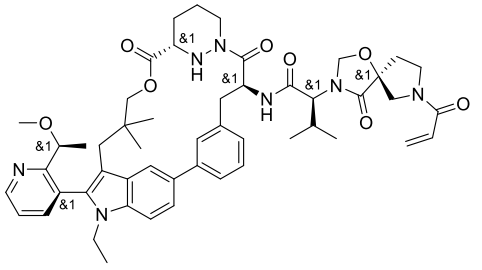
	
	
	
	
	
	

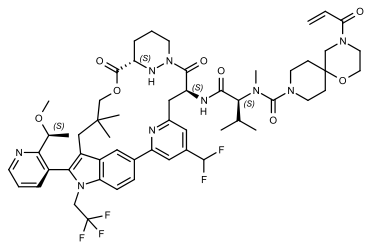
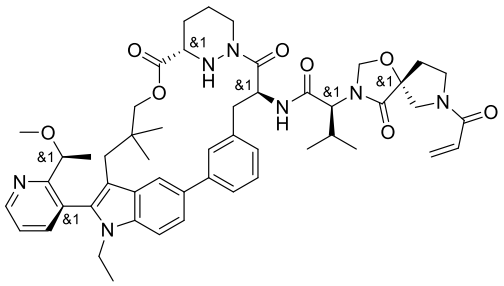
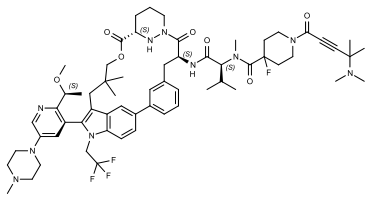
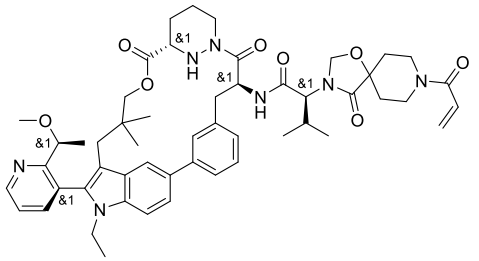
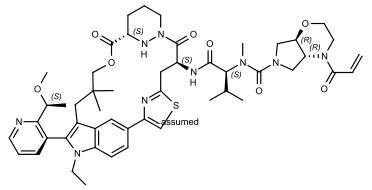
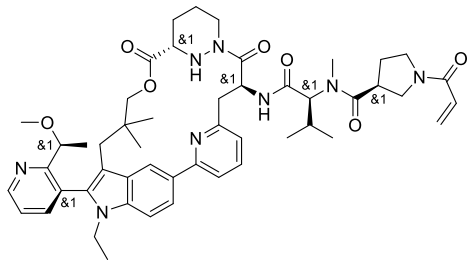
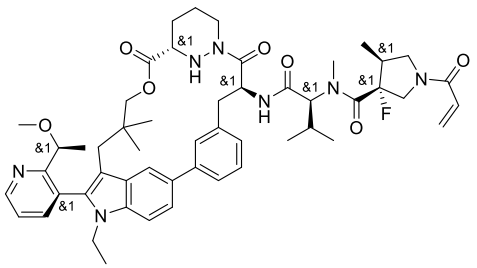
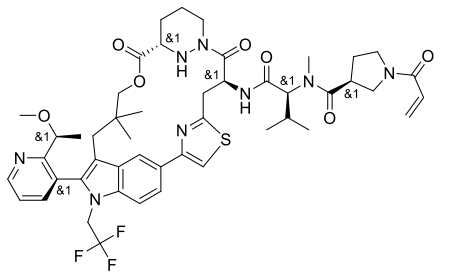
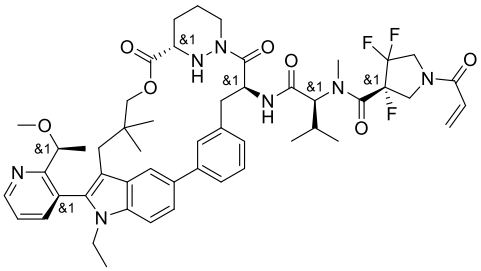
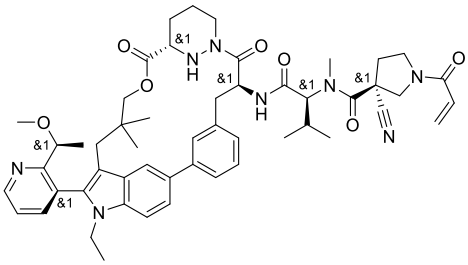
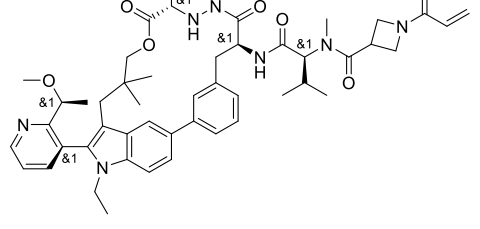
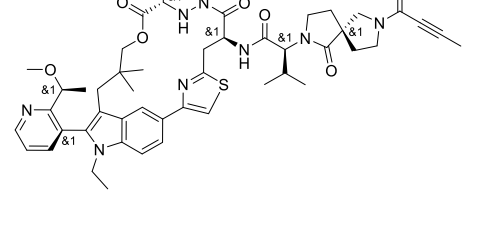


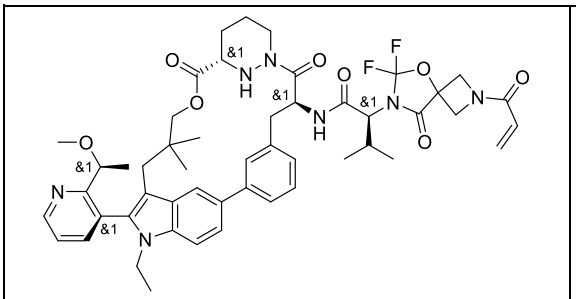
	
	
	
	
	
	

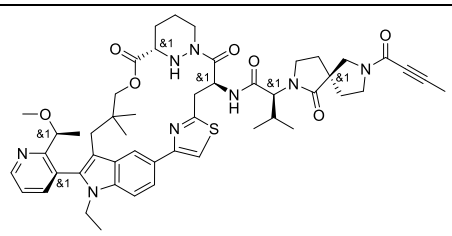
	
	
	
	
	
	

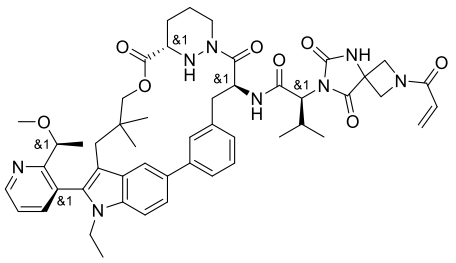
	
	
	
	
	
	

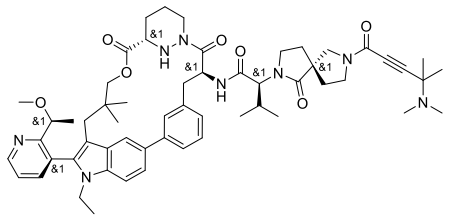
	
	
	
	
	
	

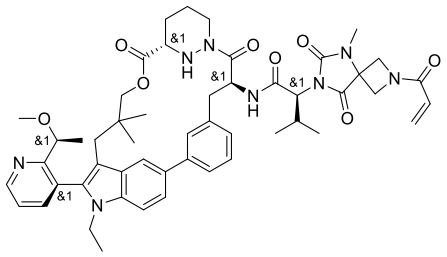
	
	
	
	
	
	

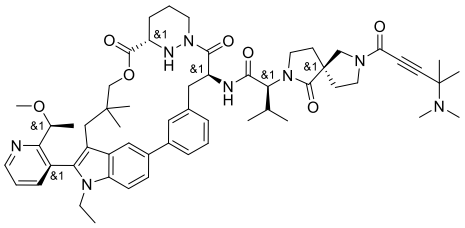


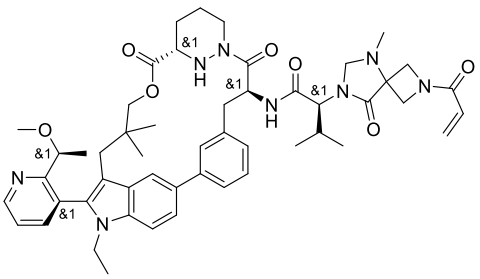


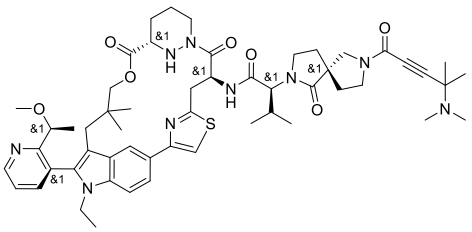


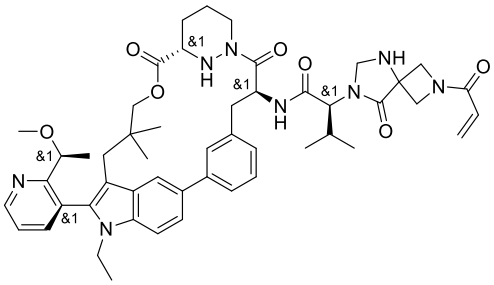


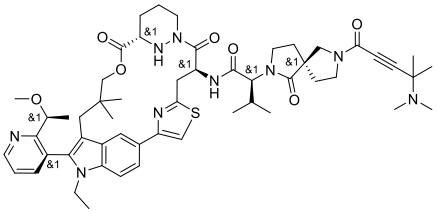


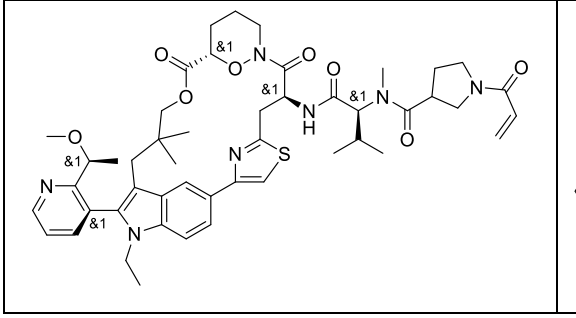


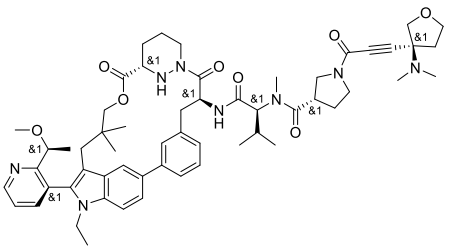




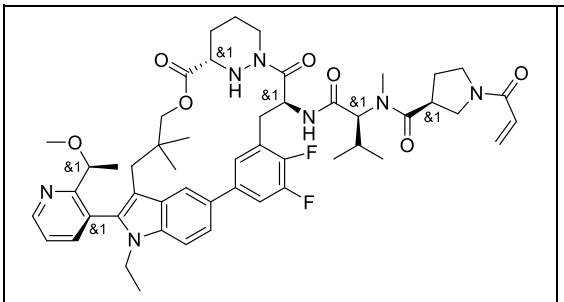


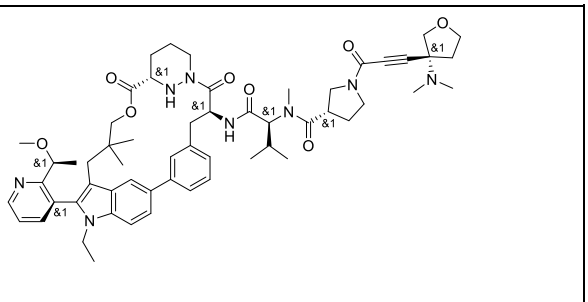


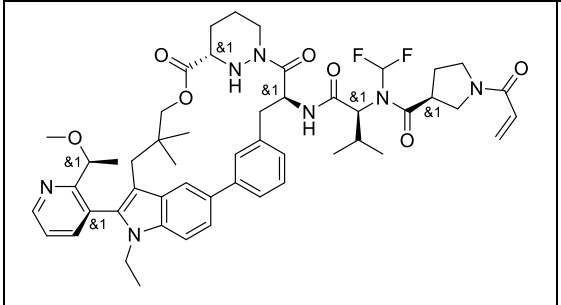


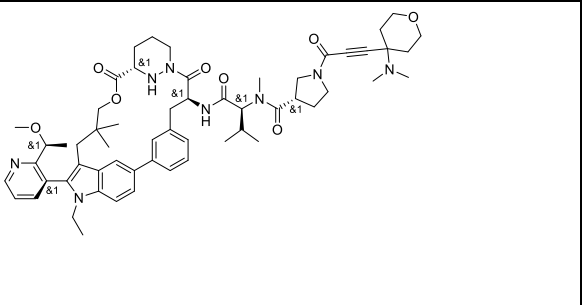


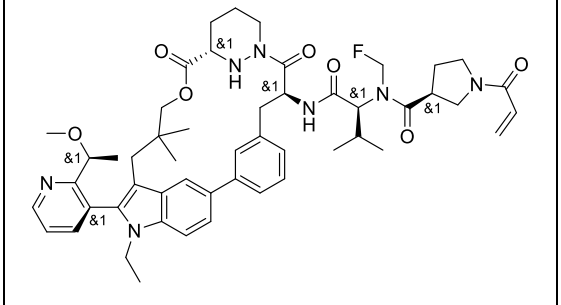
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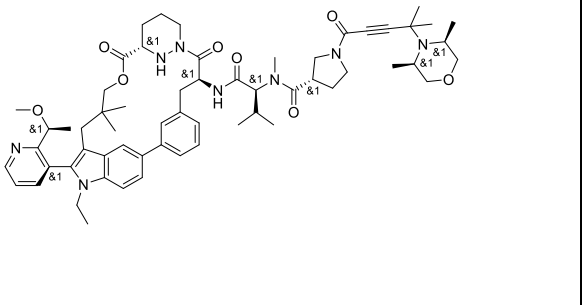


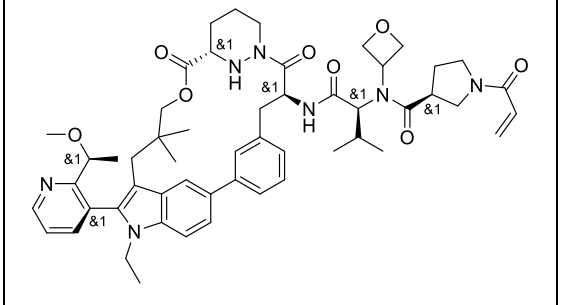


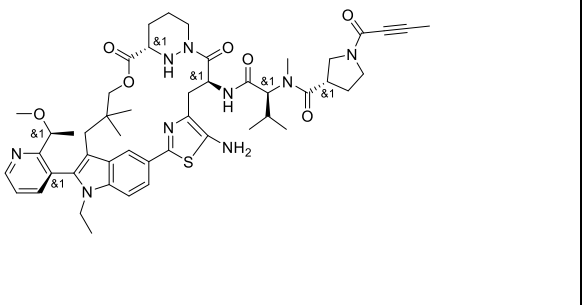


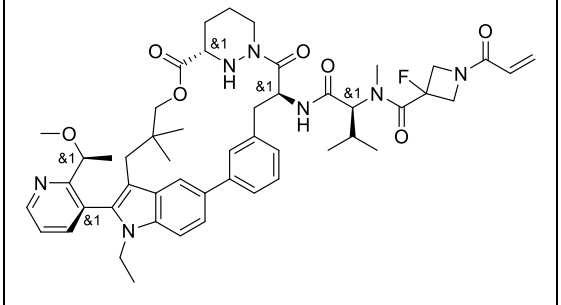


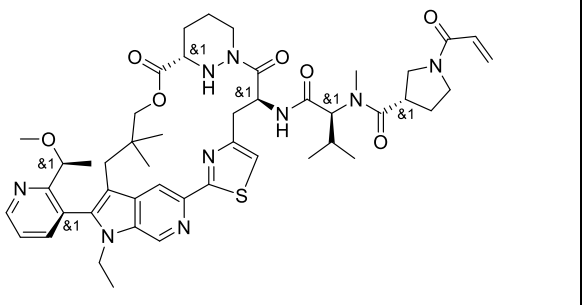


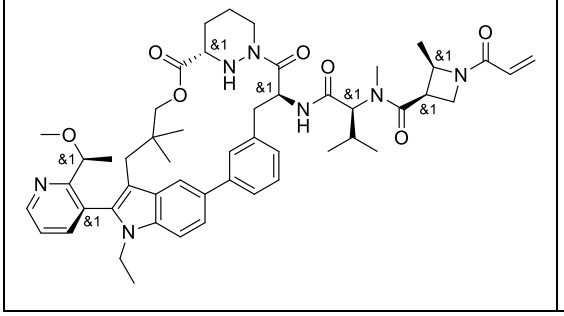


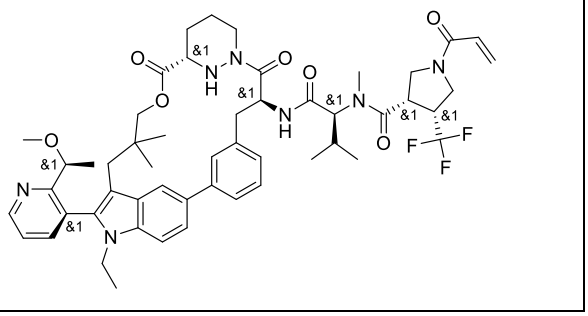


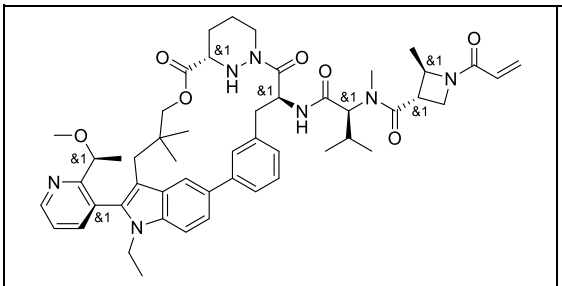


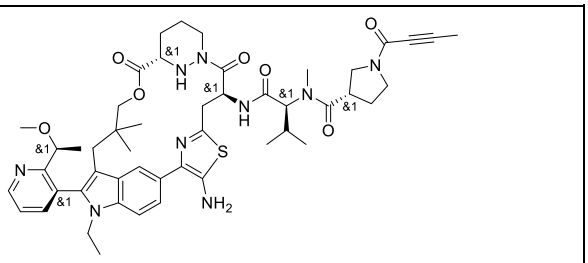


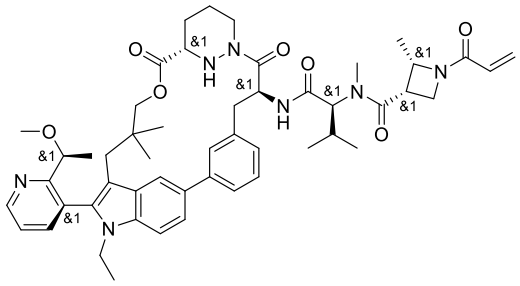


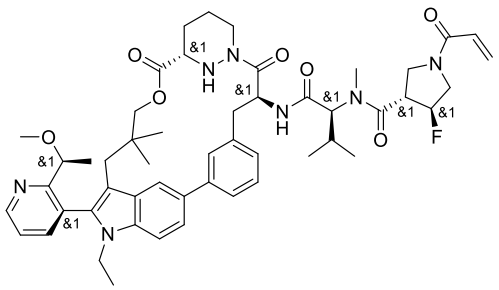


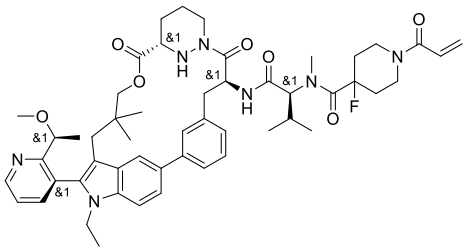


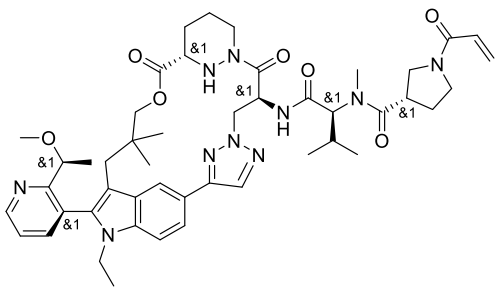


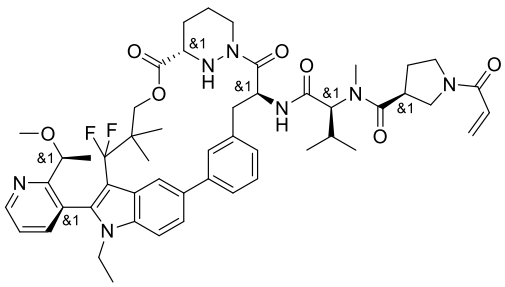


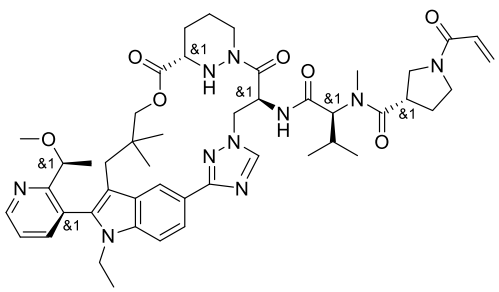


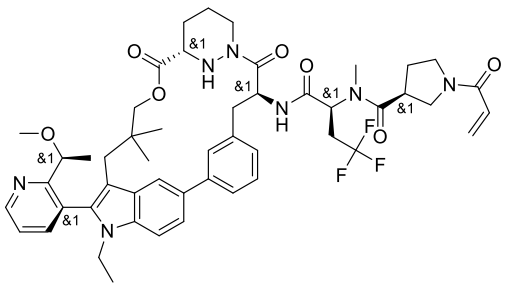


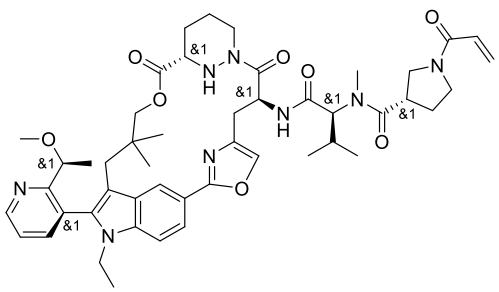


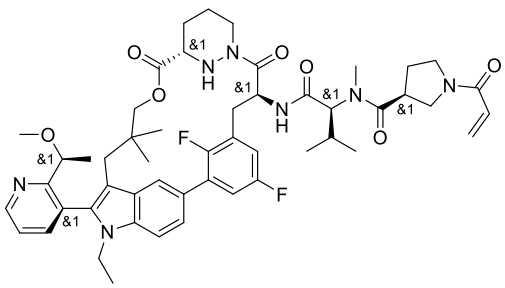


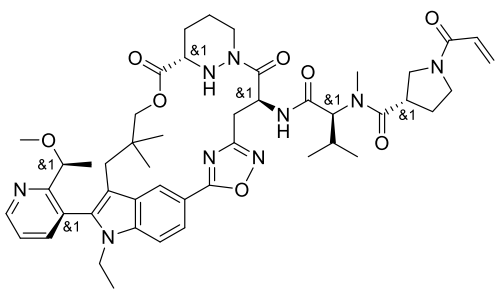




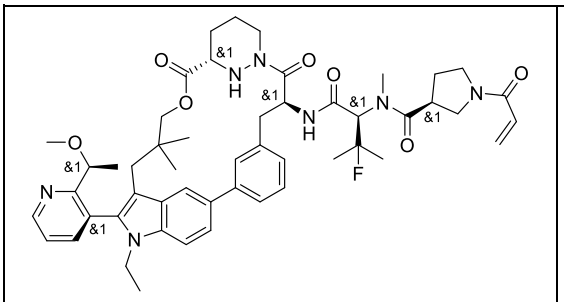


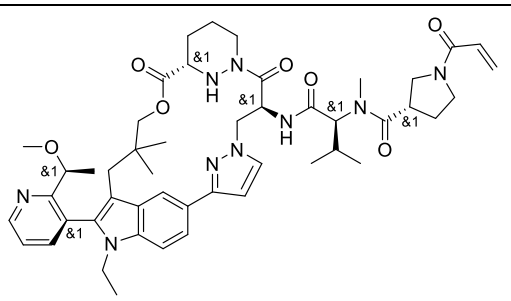


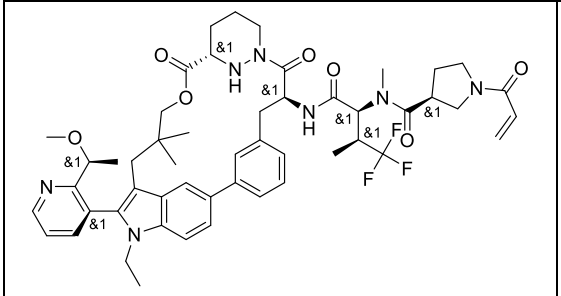


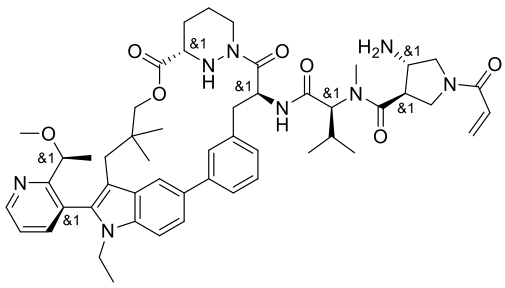


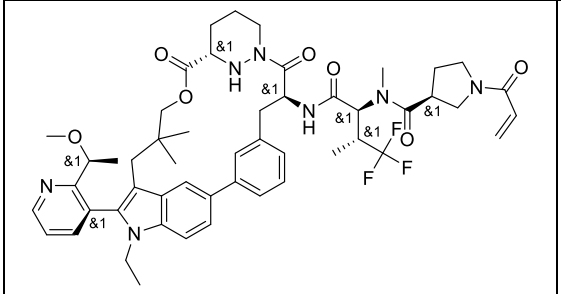
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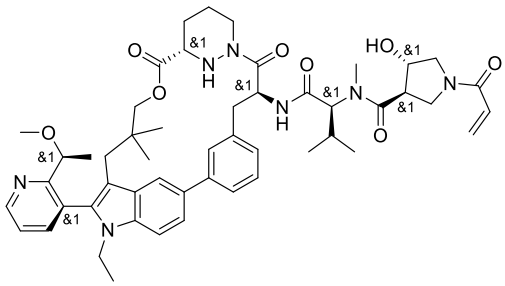


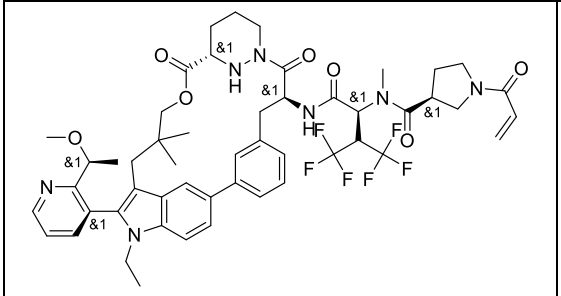


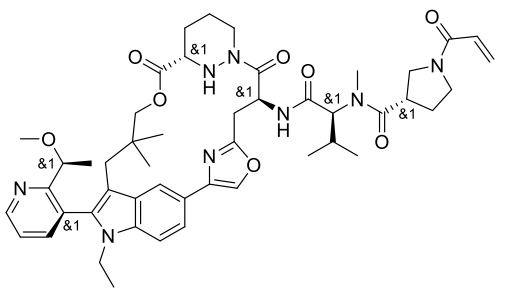


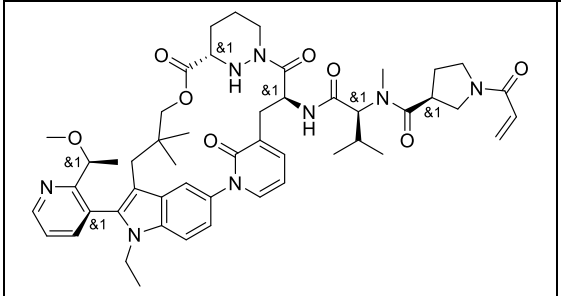


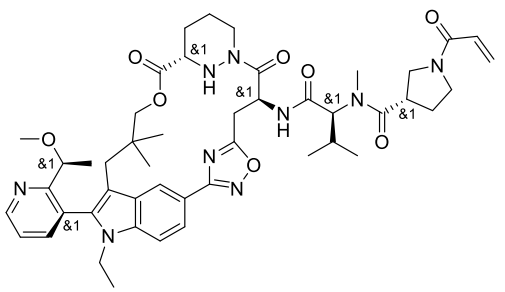


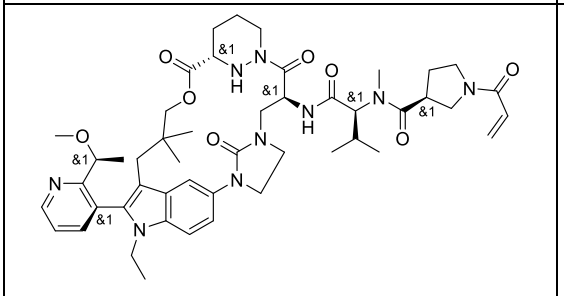


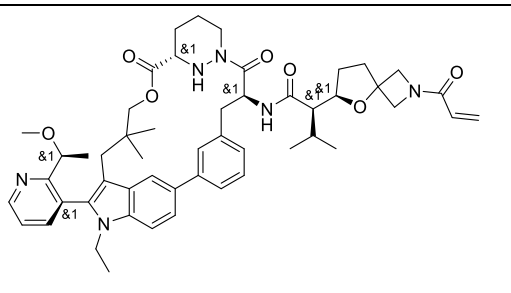




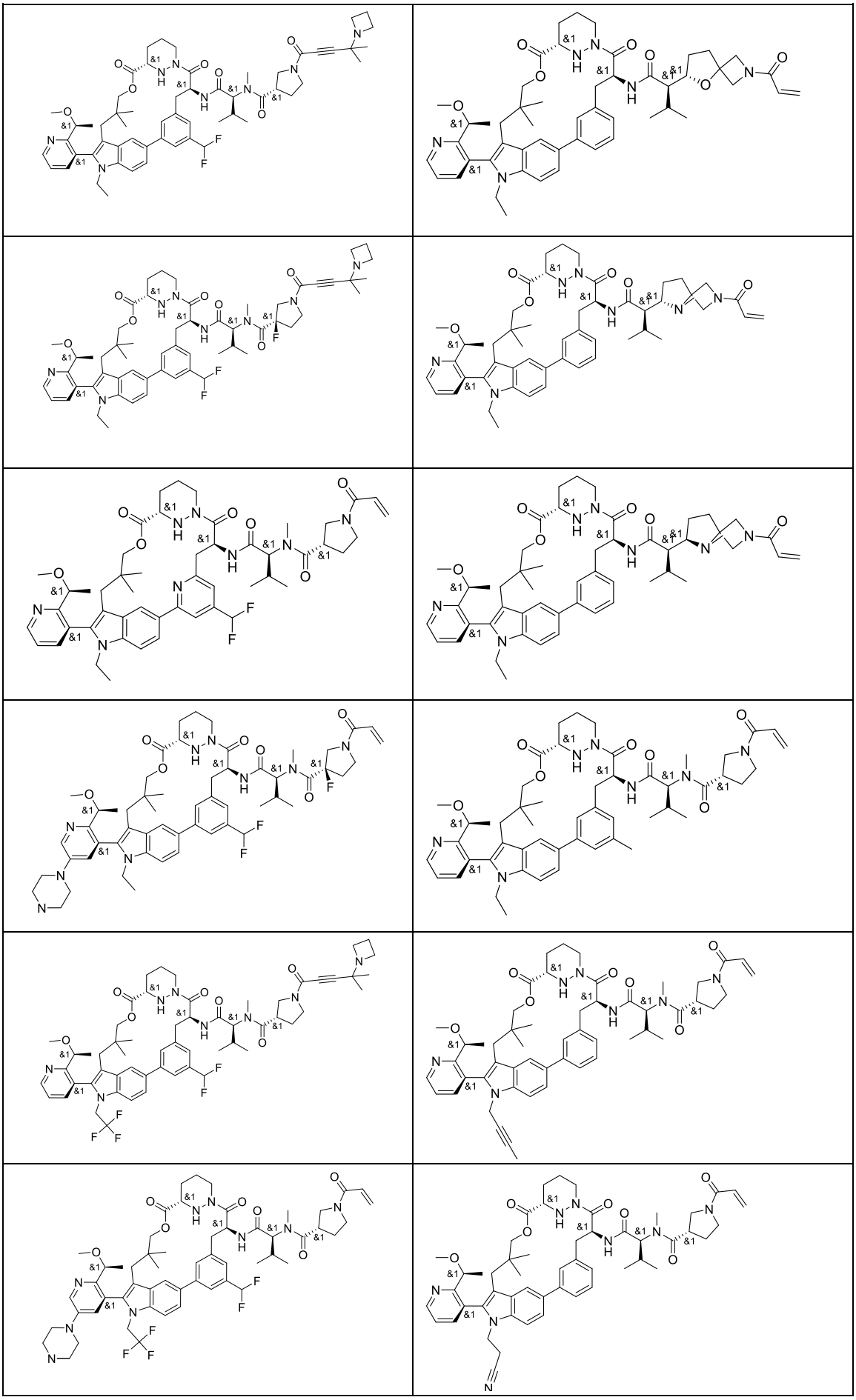




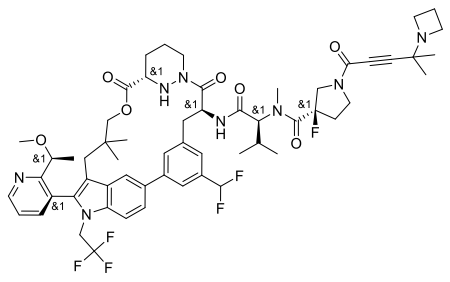
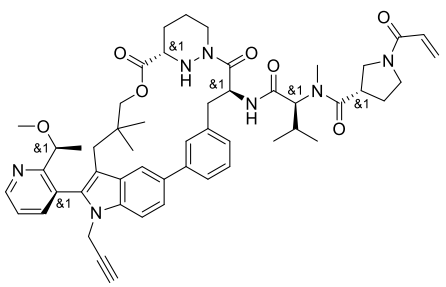
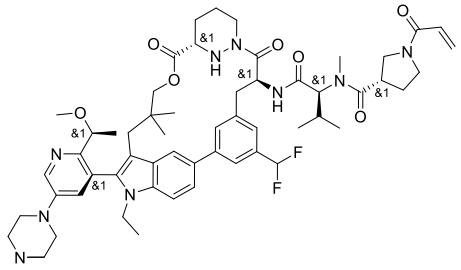
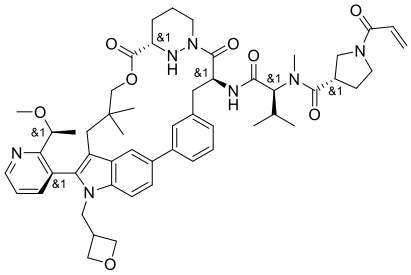
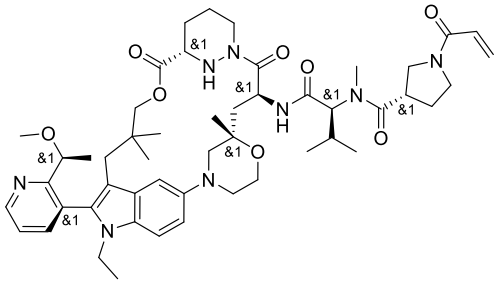
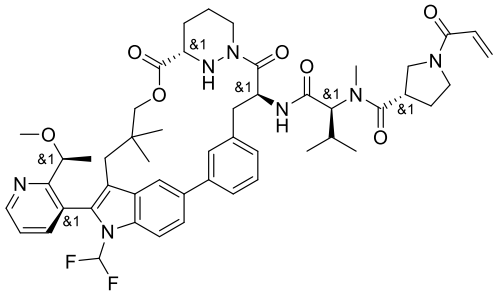
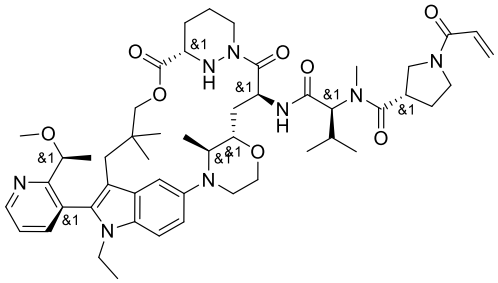
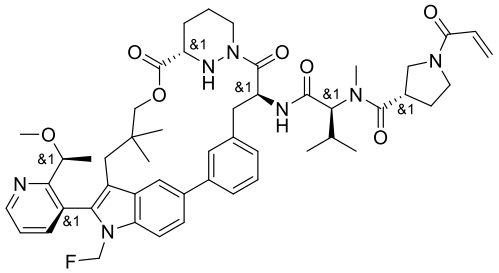
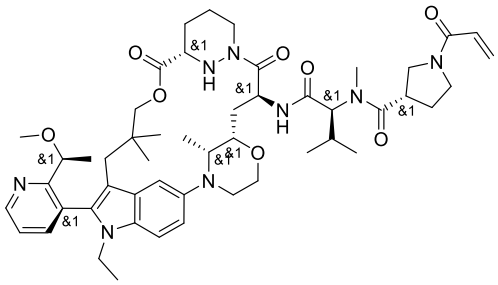
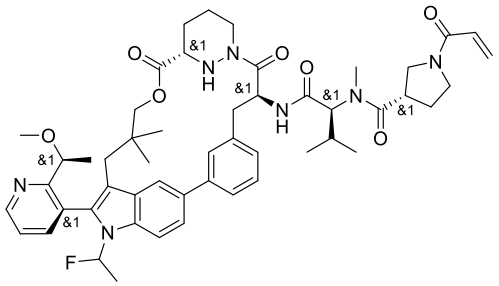
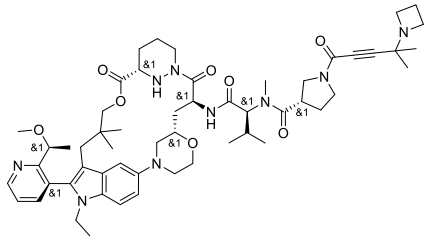
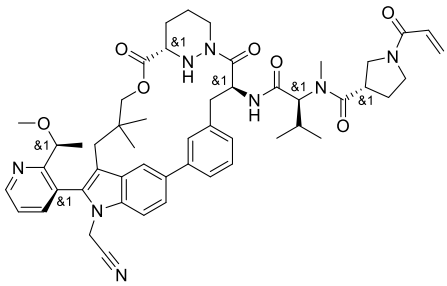


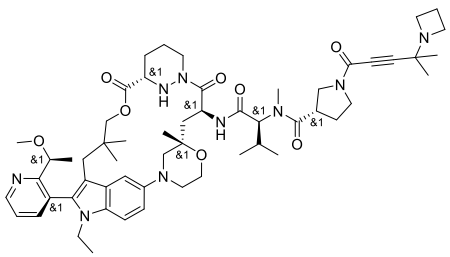
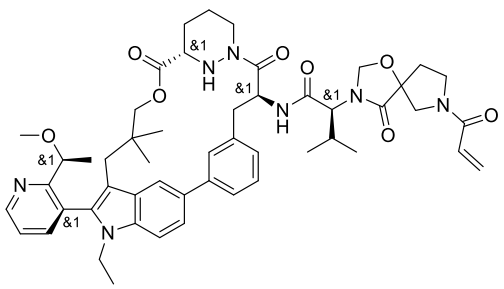
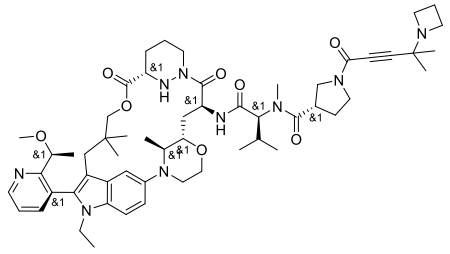
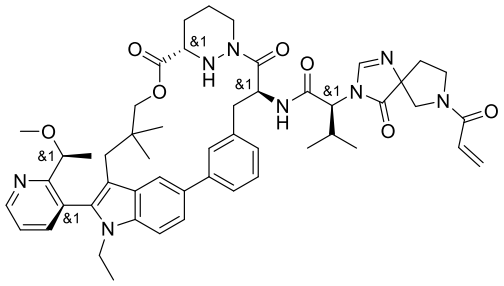
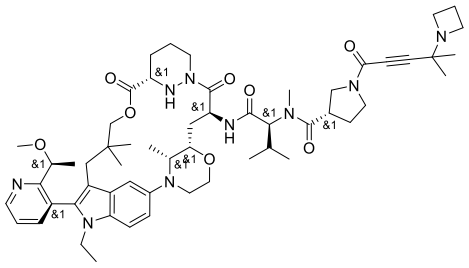
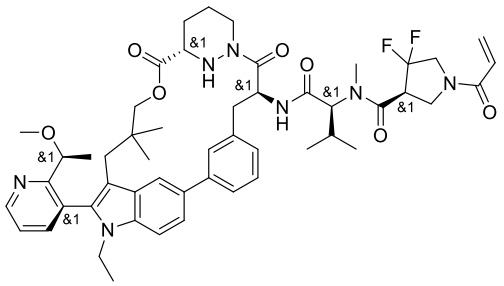
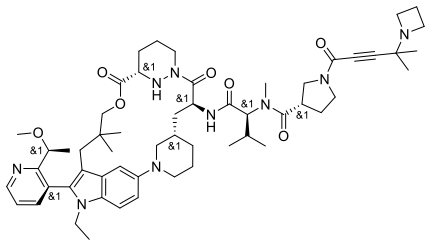
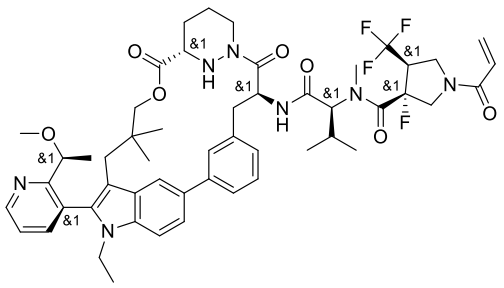
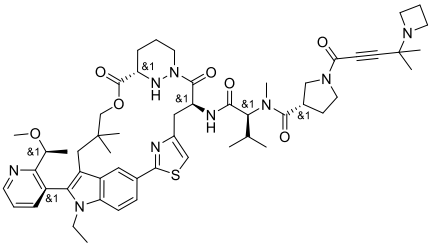
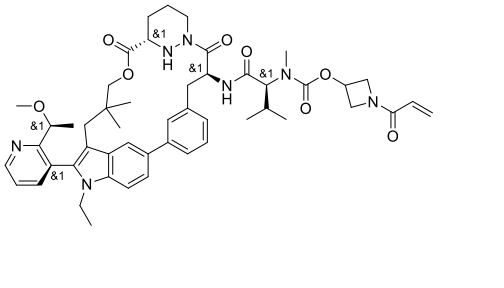
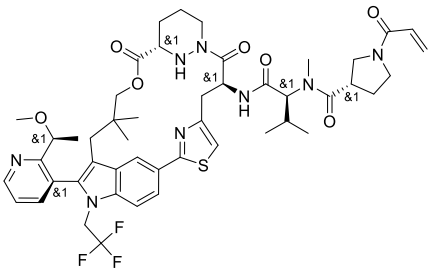
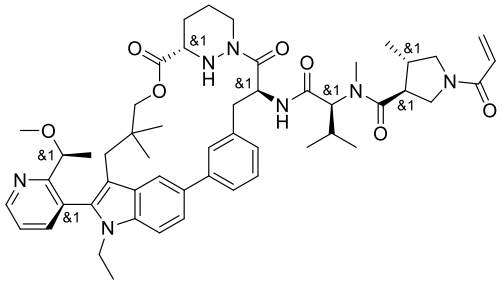


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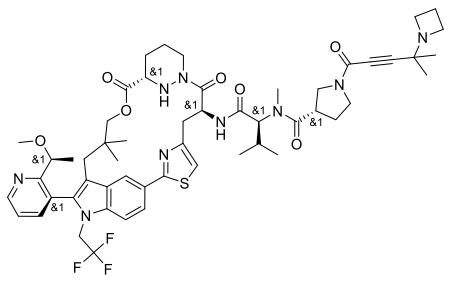
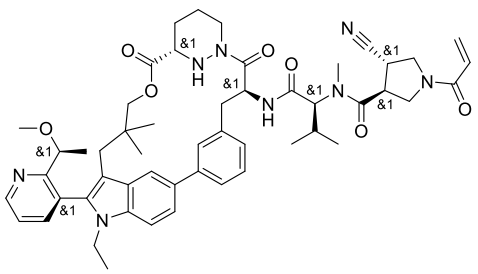
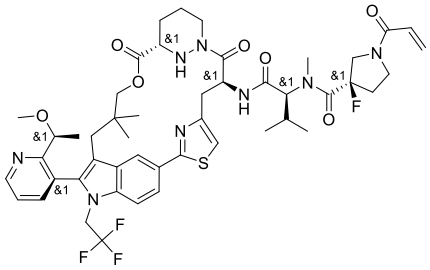
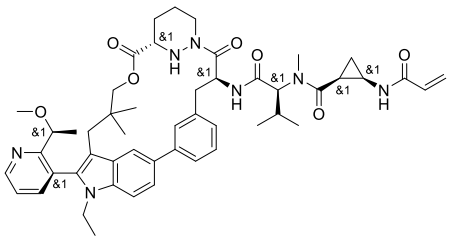
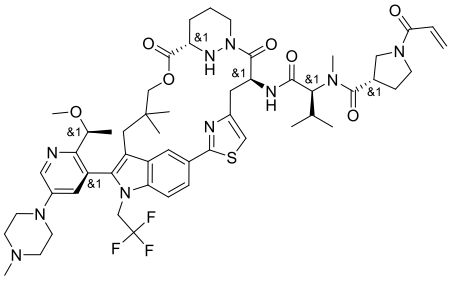
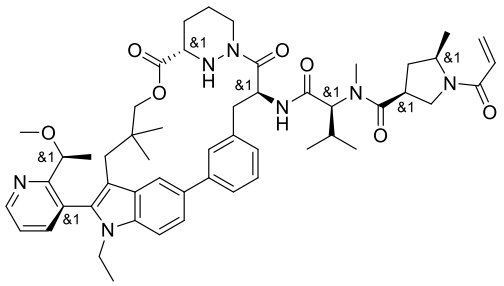
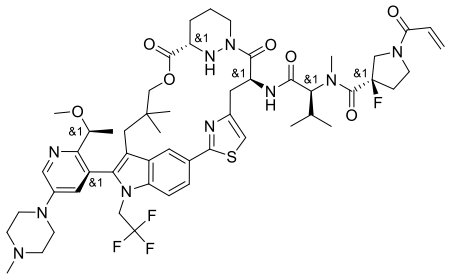
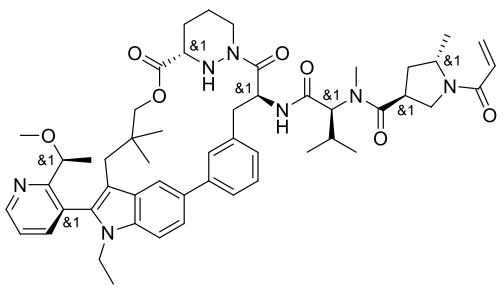
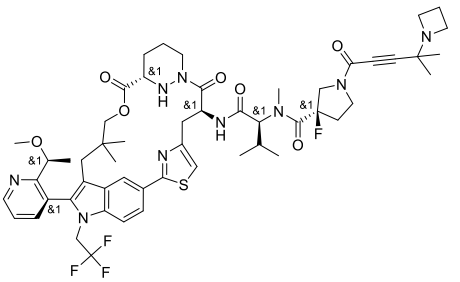
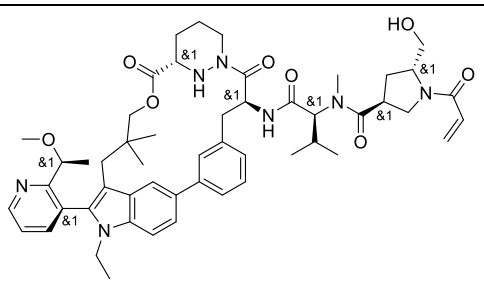
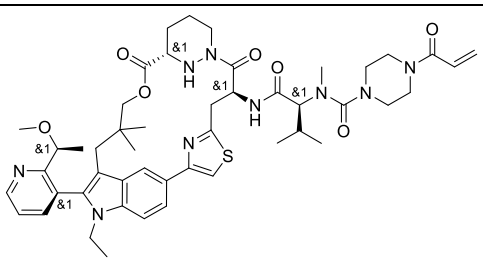
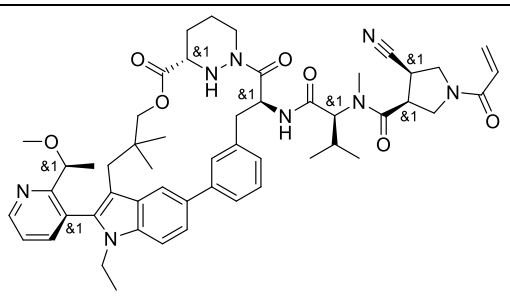


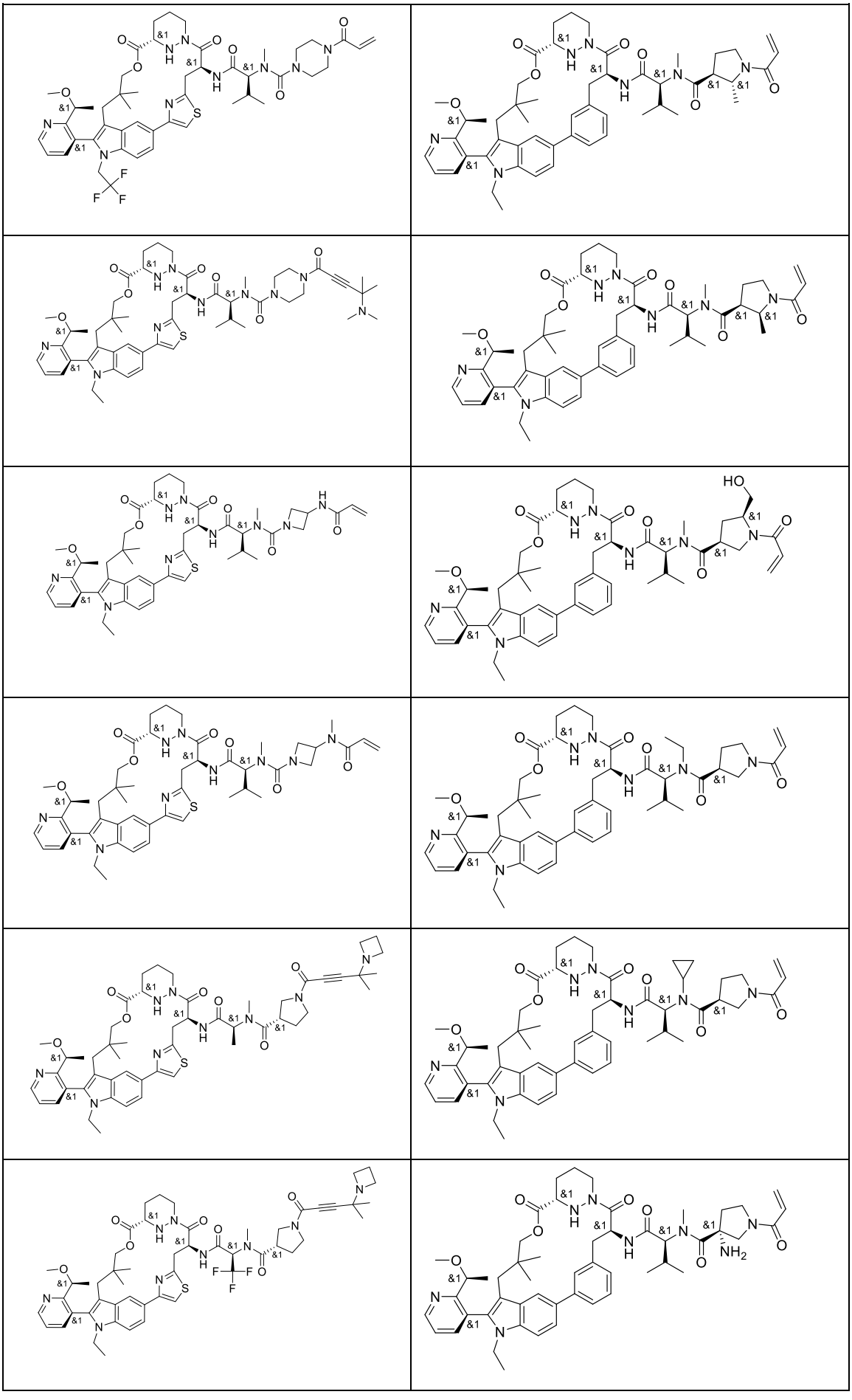
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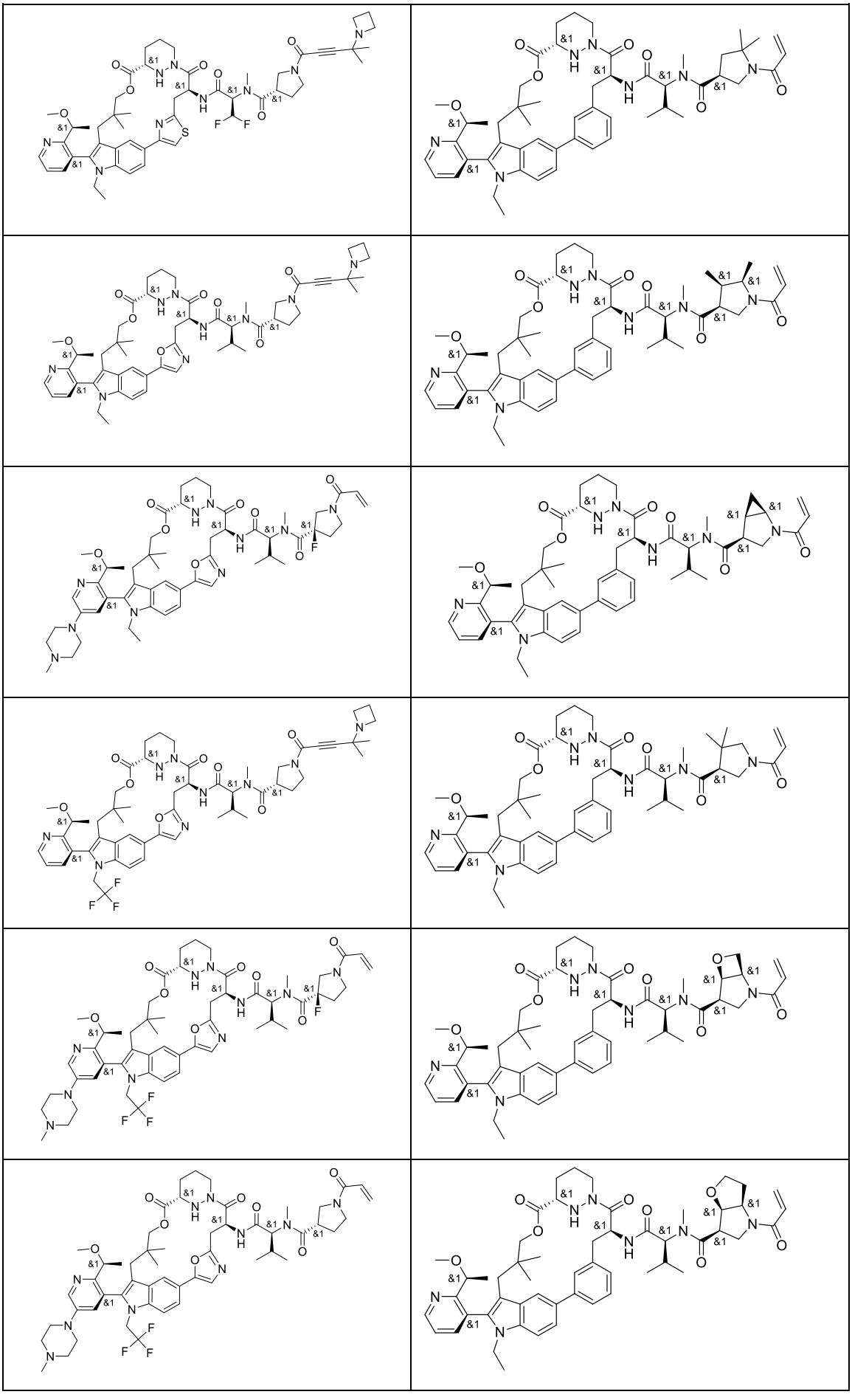
	
	
	
	
	
	

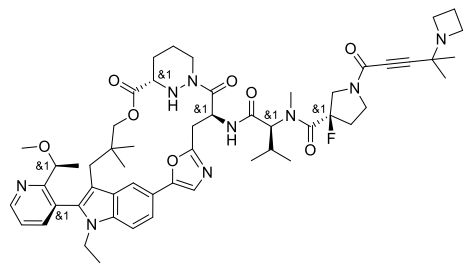
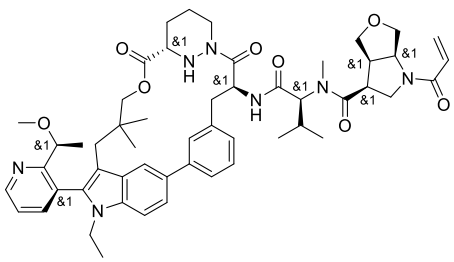
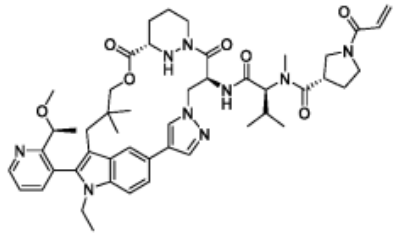
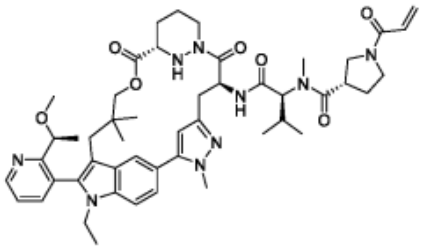
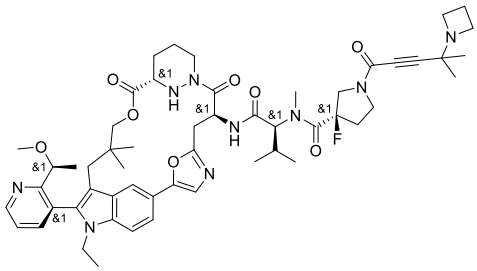
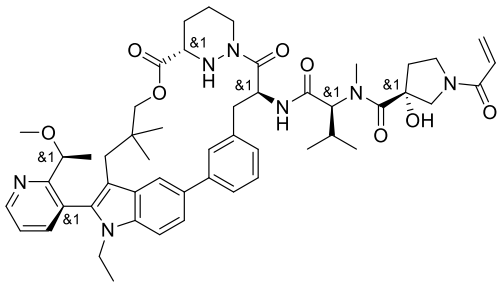
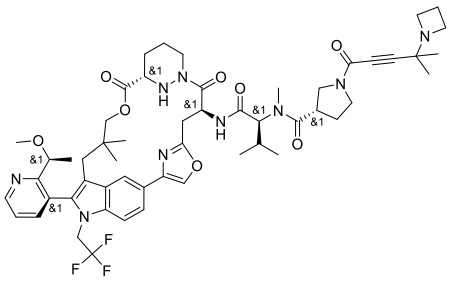
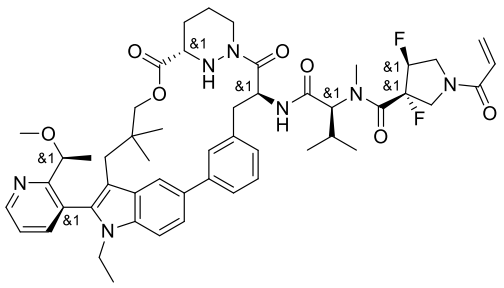
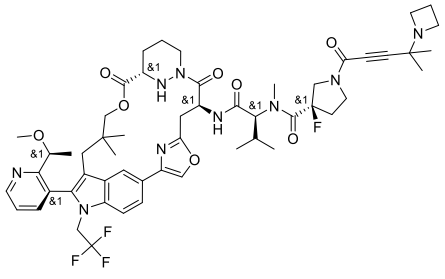
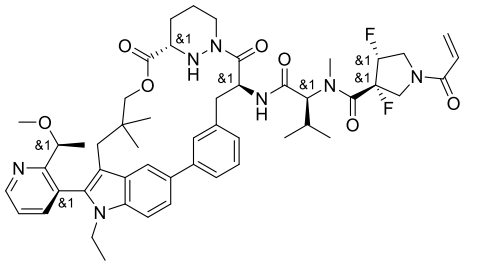
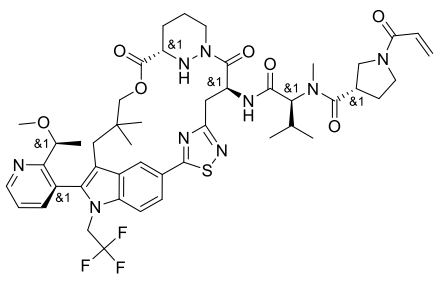
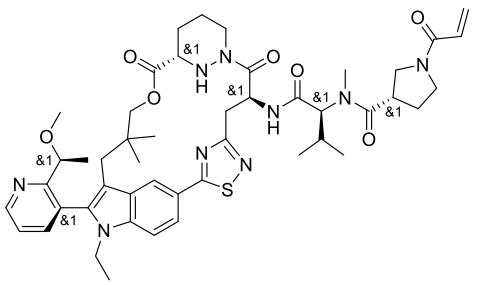
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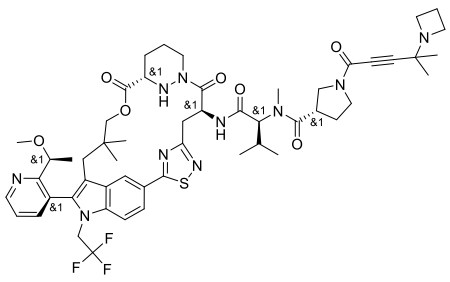
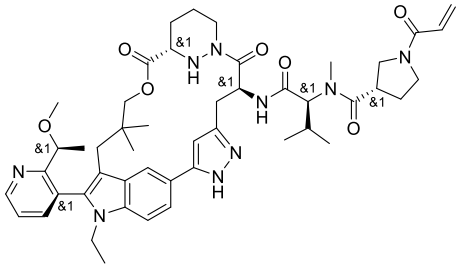
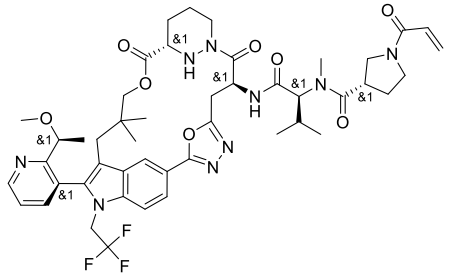
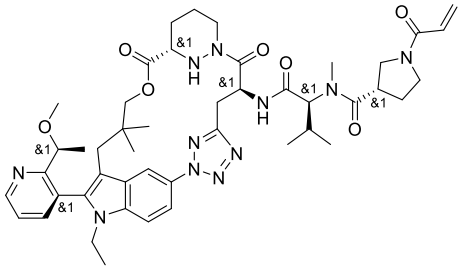
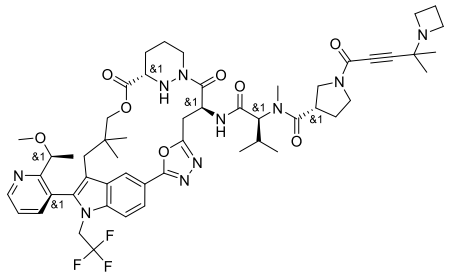
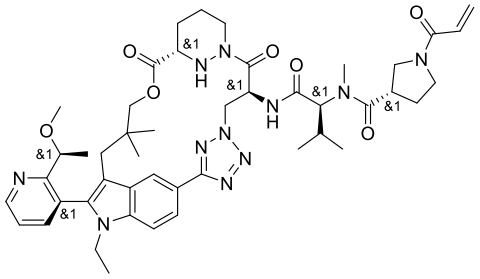
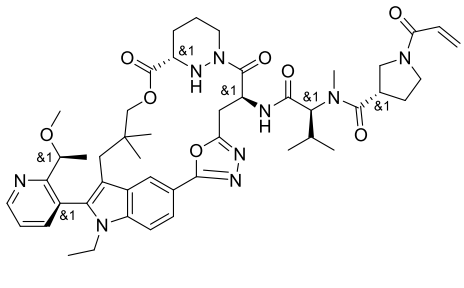
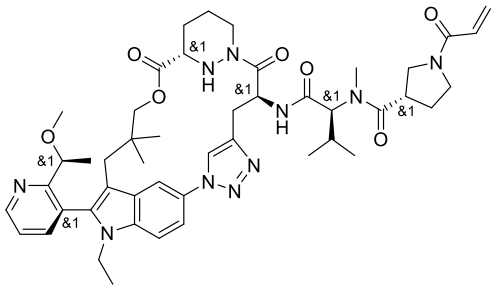
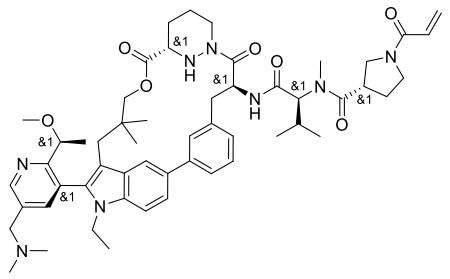
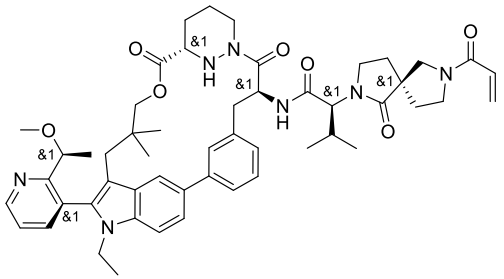
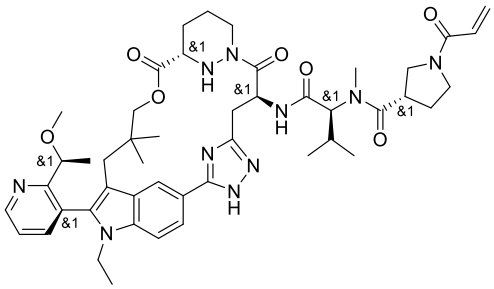
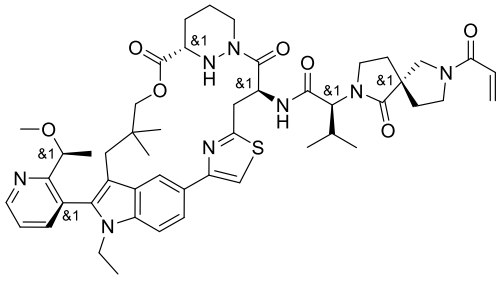
	
	
	
	
	
	

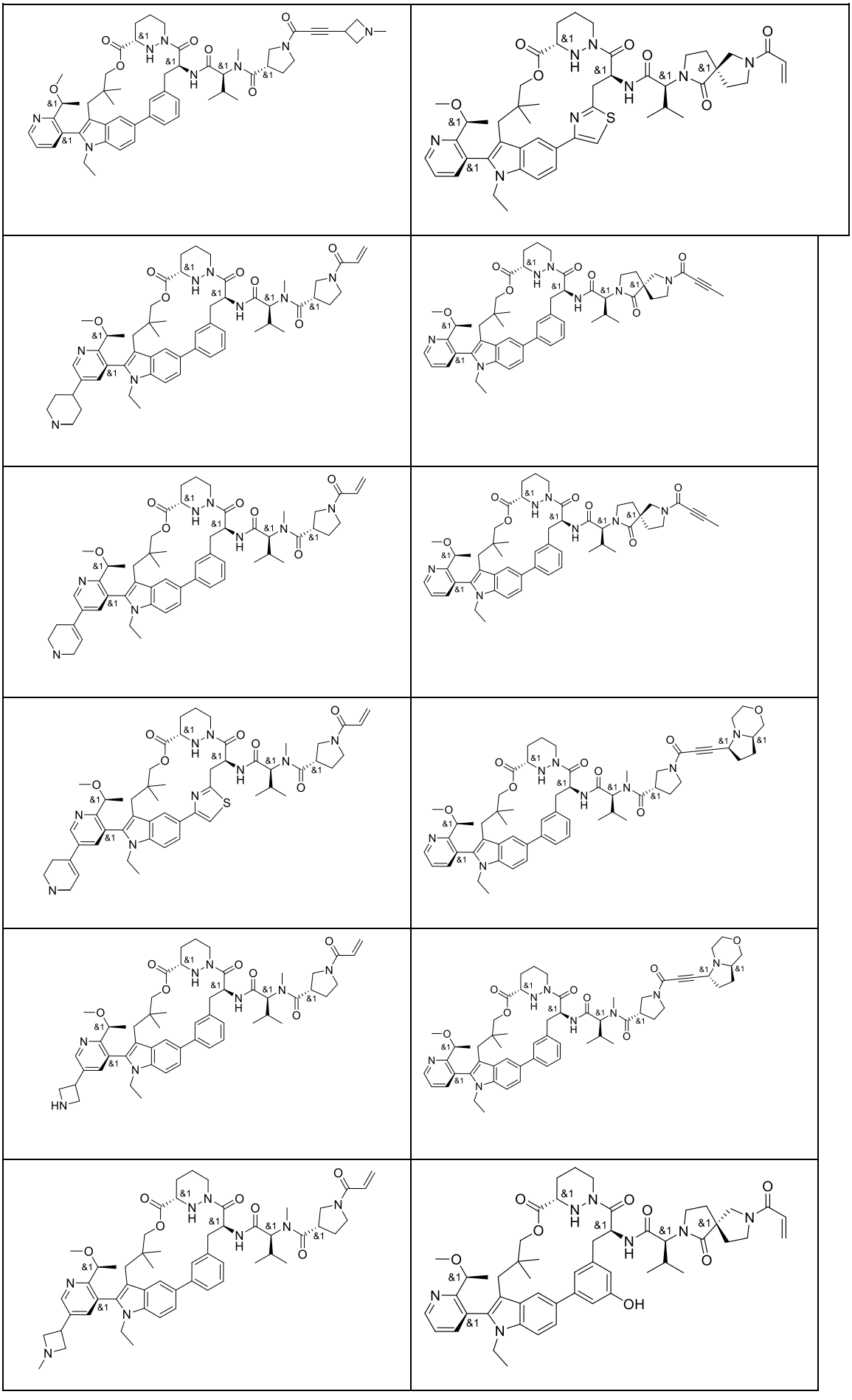


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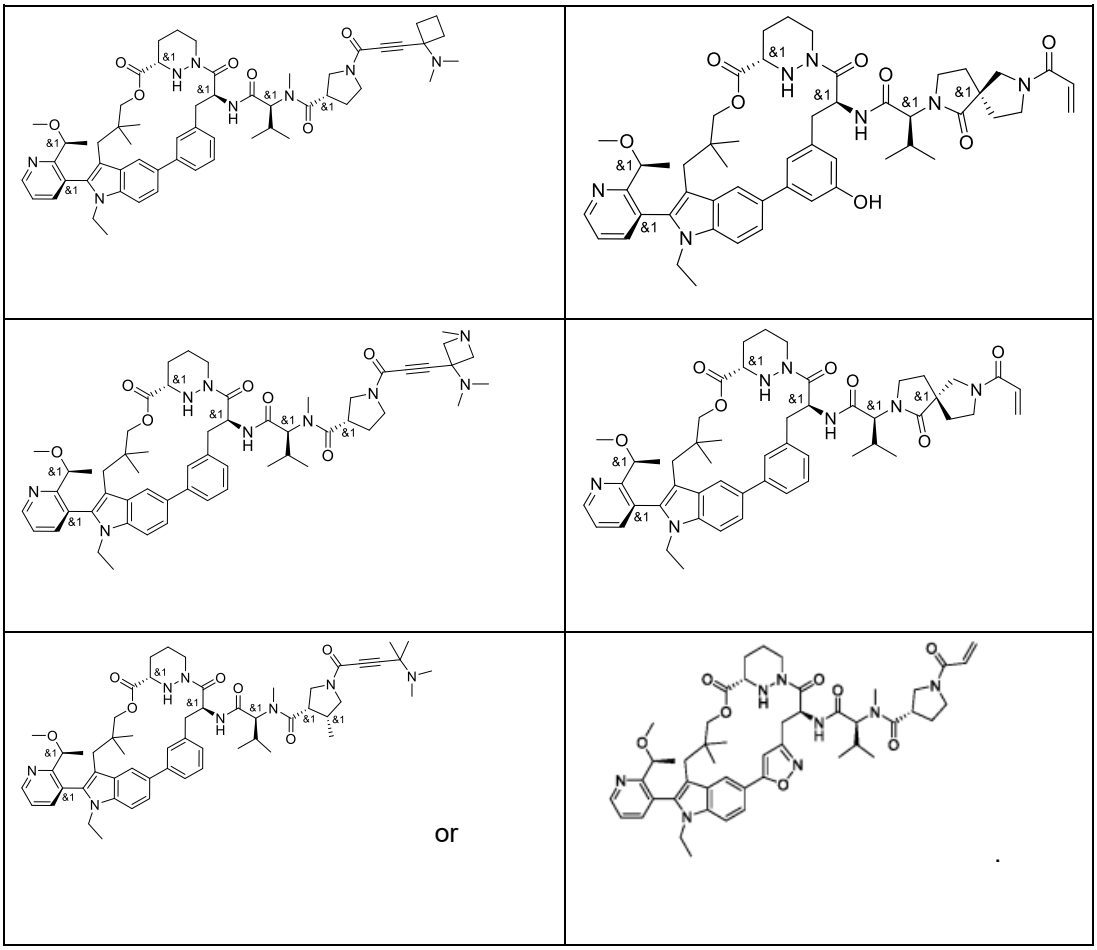


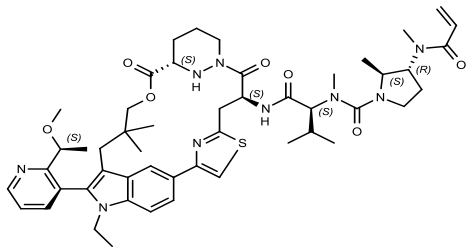
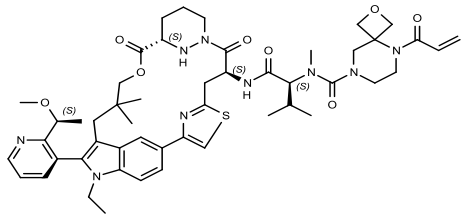
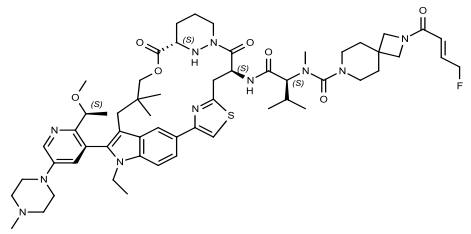
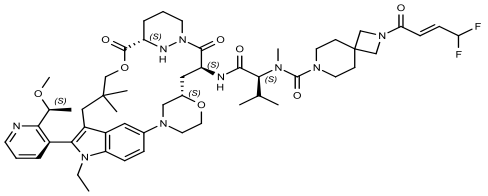
	
	
	
	
	
	

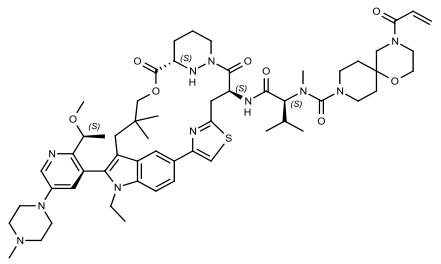
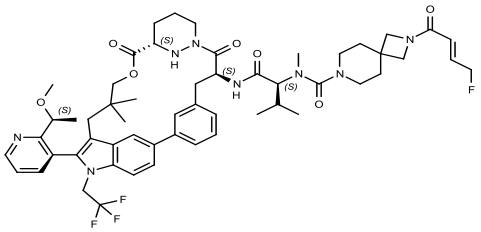
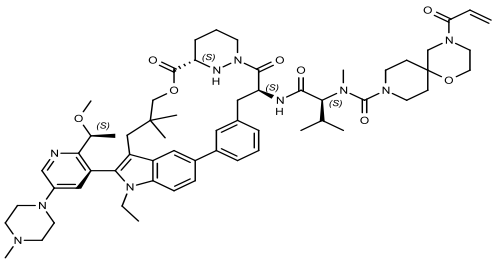
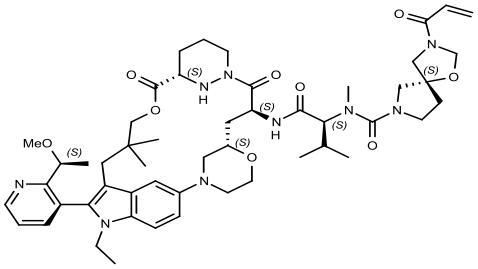
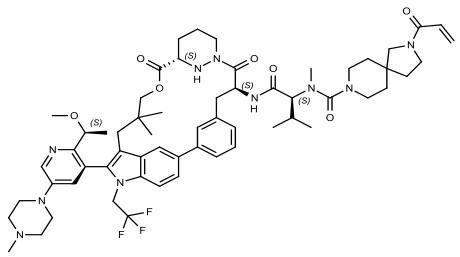
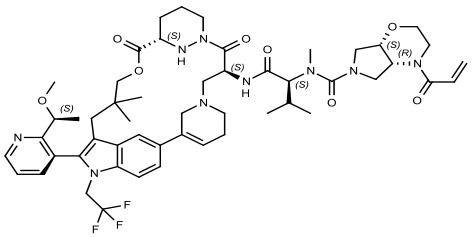
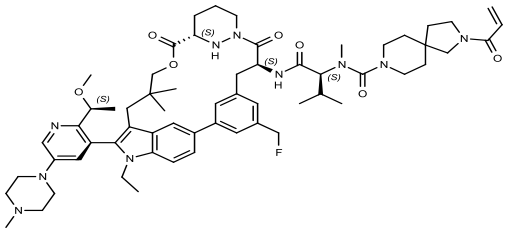
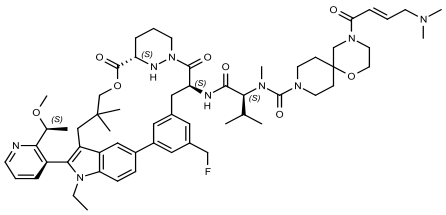
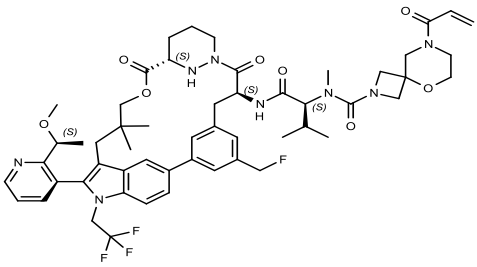
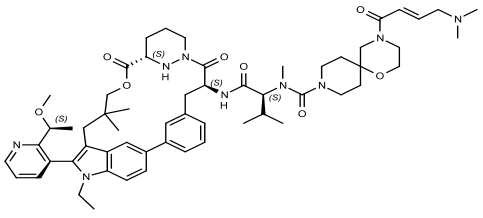


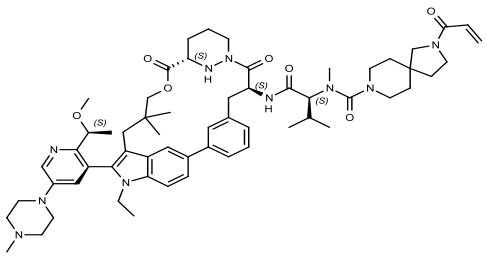
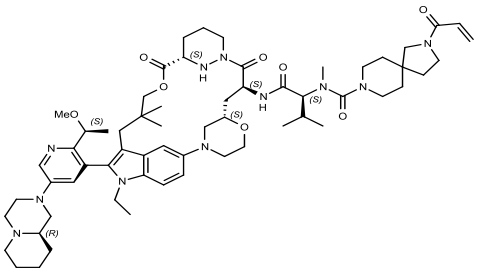
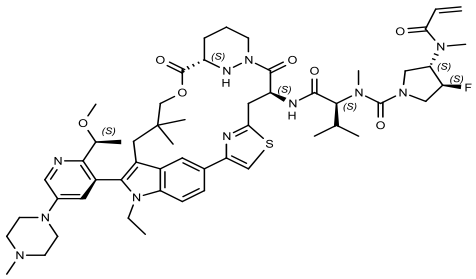
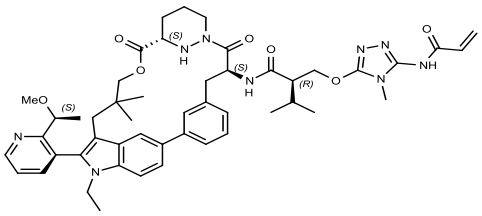
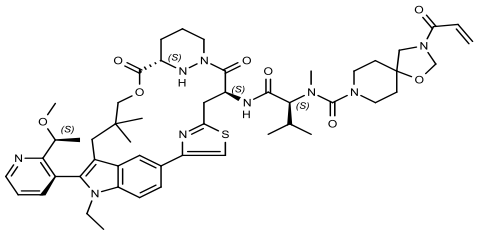
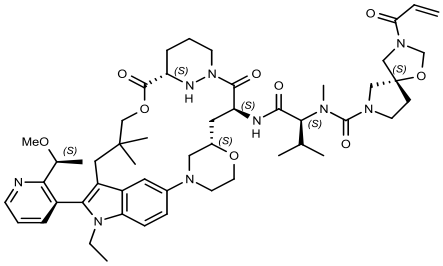
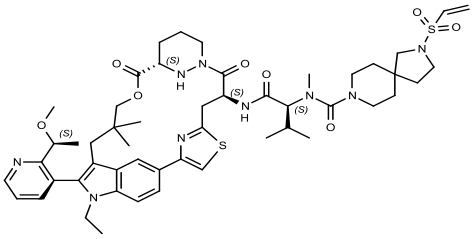
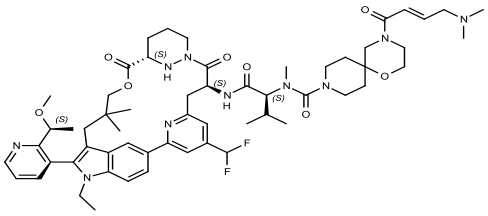
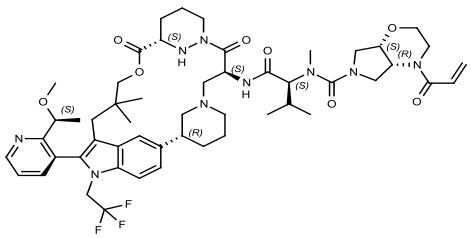
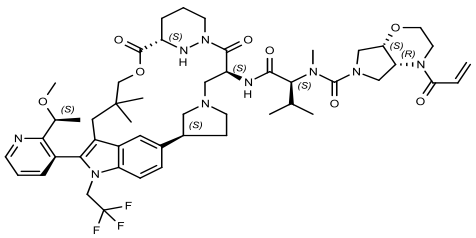
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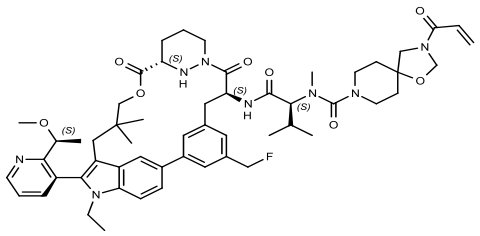
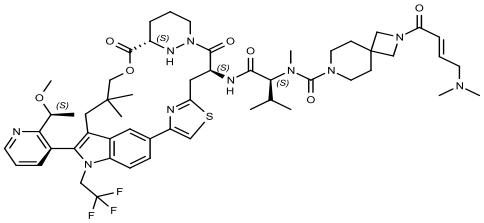
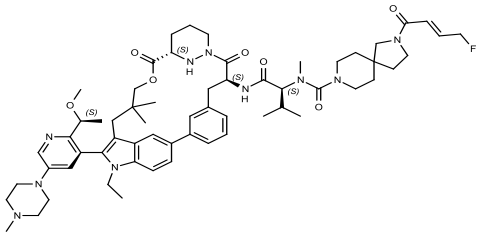
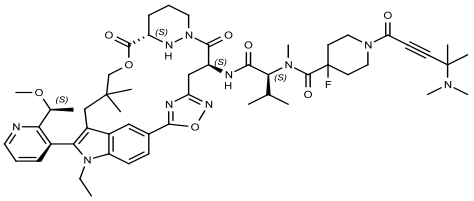
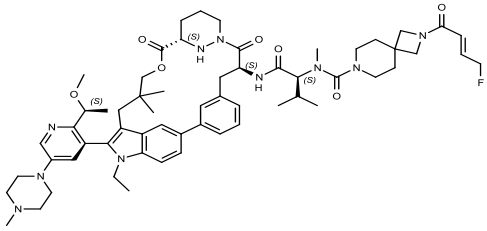
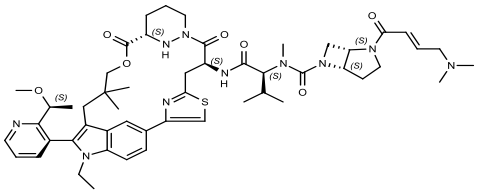
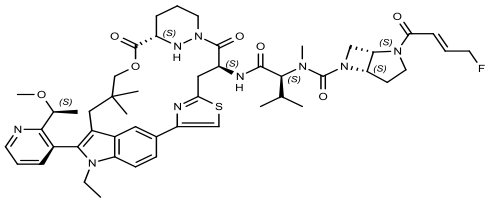
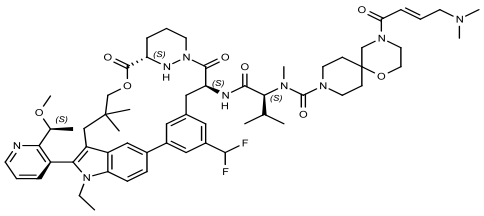
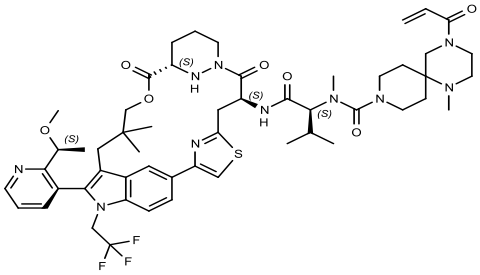
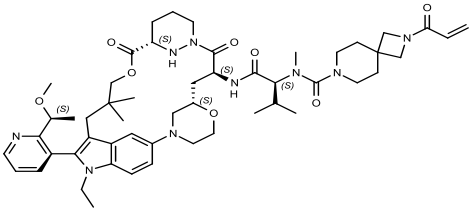


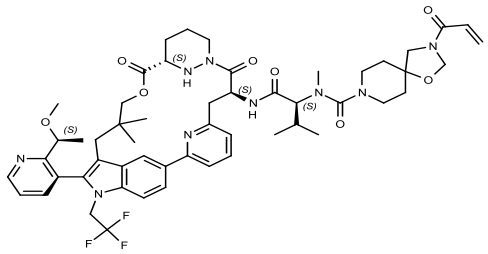
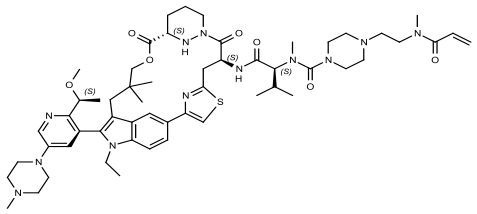
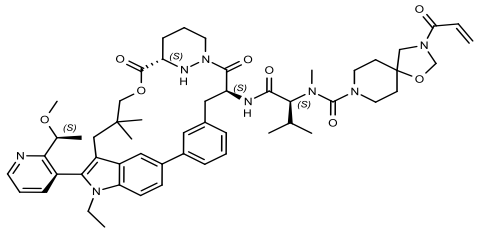
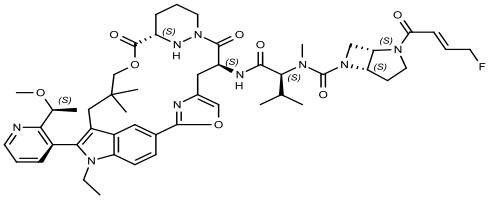
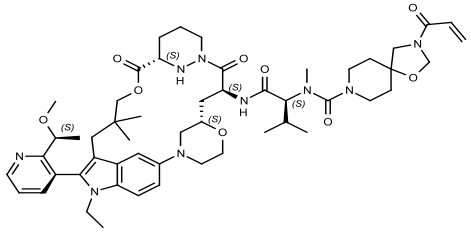
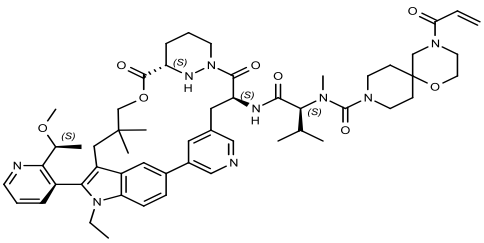
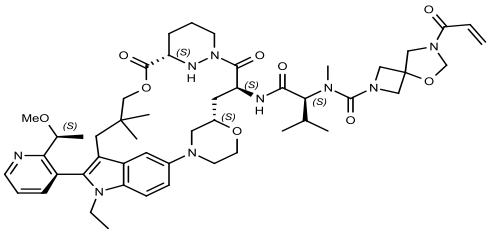
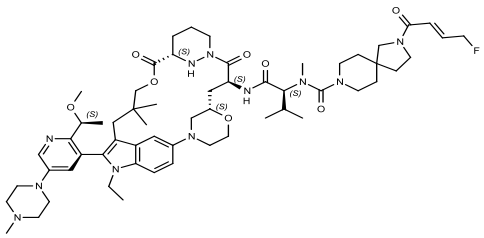
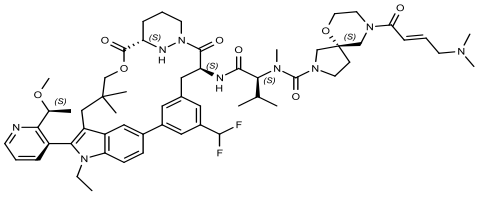
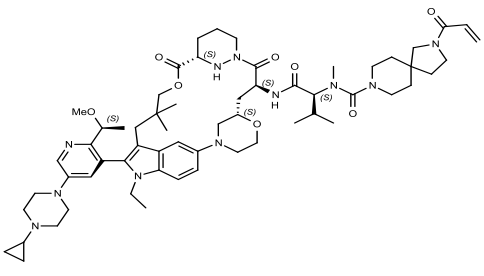
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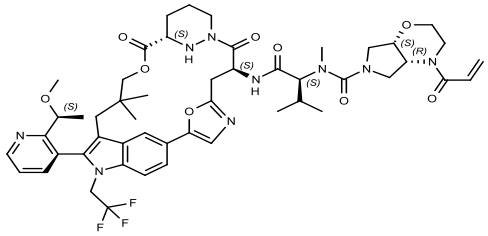
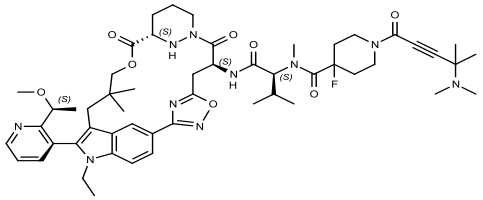
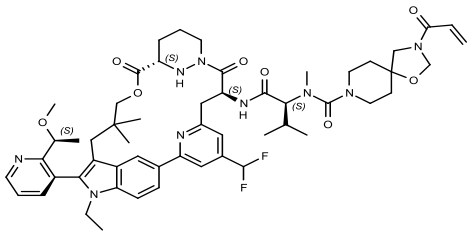
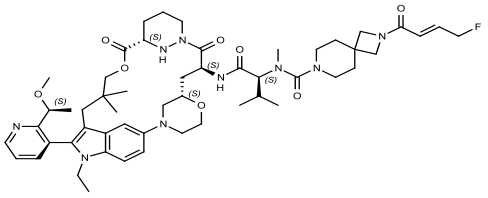
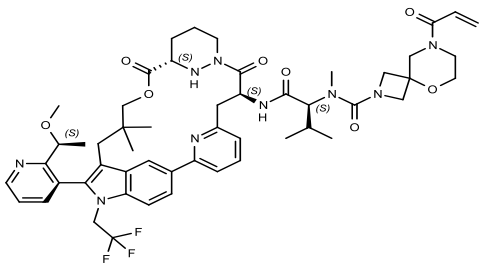
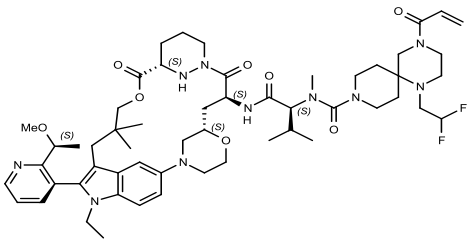
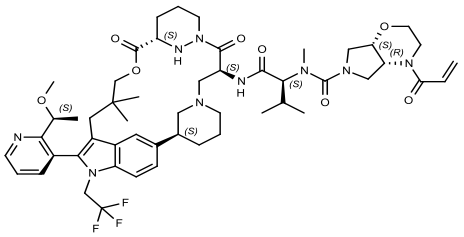
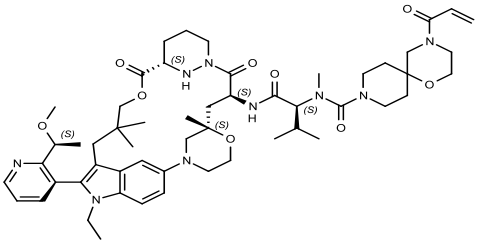
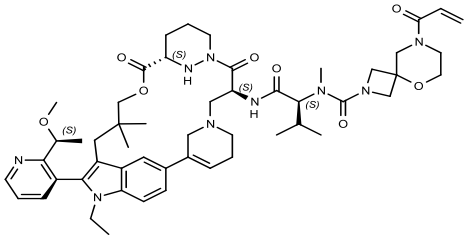
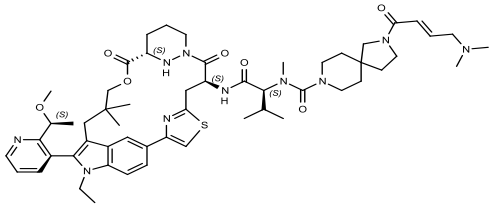
Ex#	Structure	Ex#	Structure
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A2		**A106**	

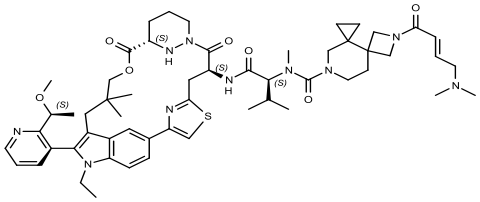
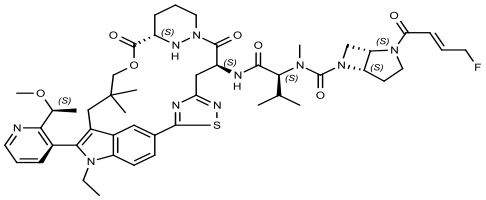
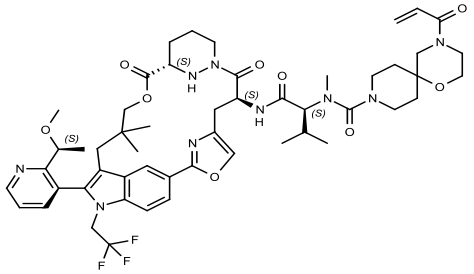
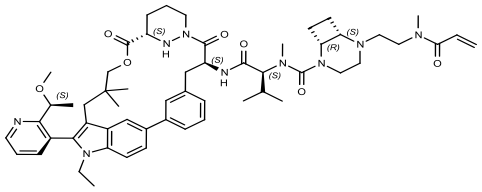
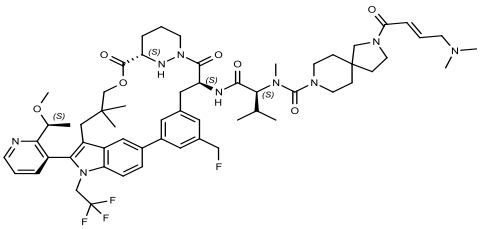
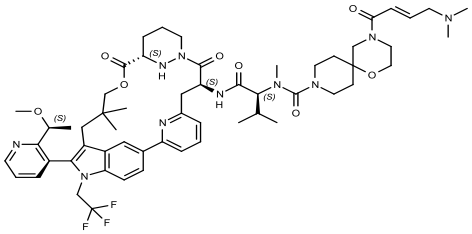
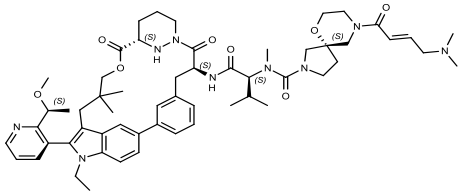
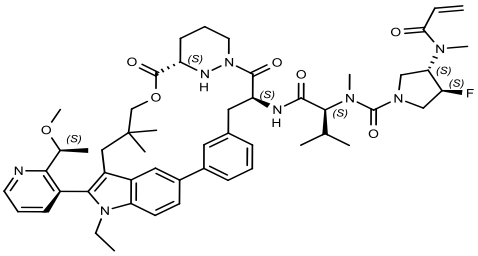
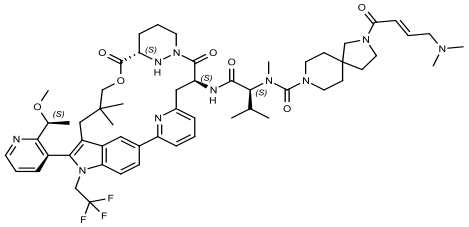
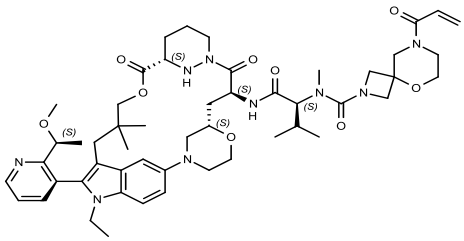
Ex#	Structure	Ex#	Structure
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A4		A108	
A5		A109	
A6		A110	
A7		A111	

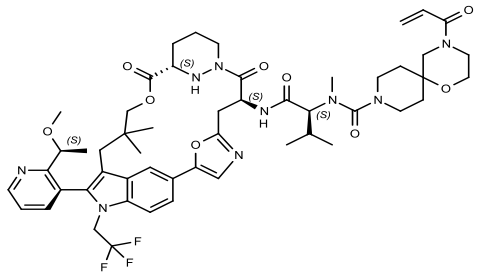
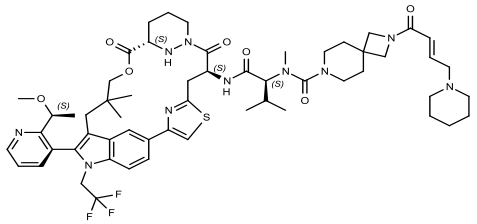
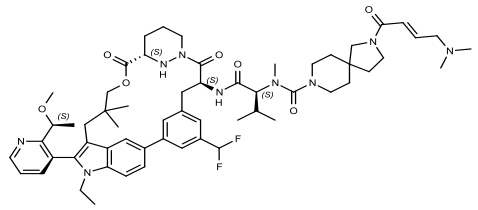
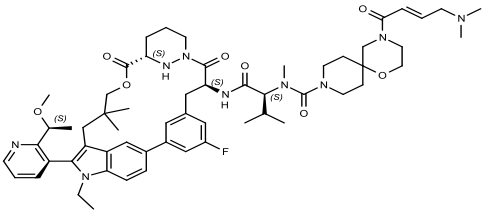
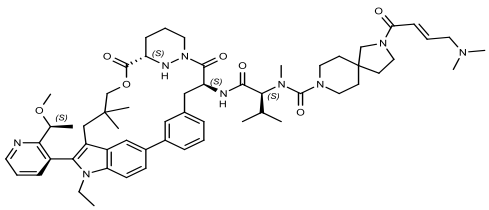
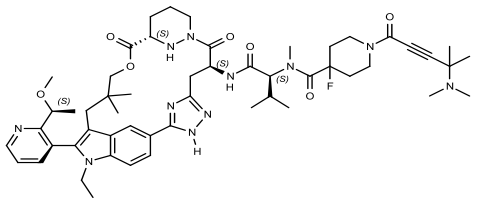
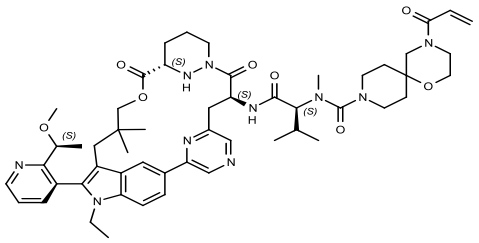
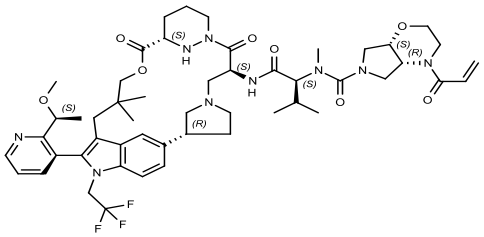
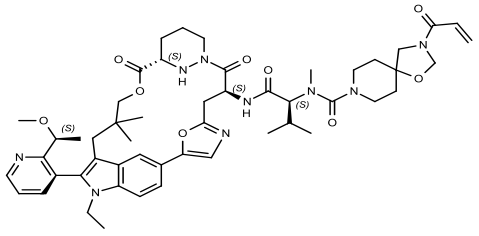
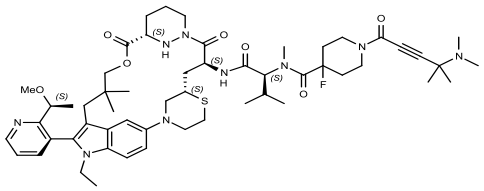
Ex#	Structure	Ex#	Structure
A8		A112	
A9		A113	
A10		A114	
A11		A115	
A12		A116	

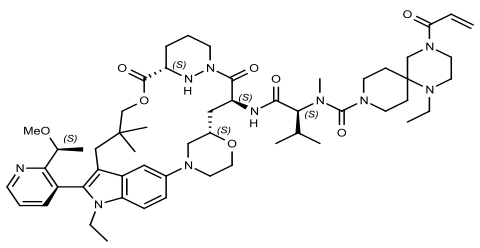
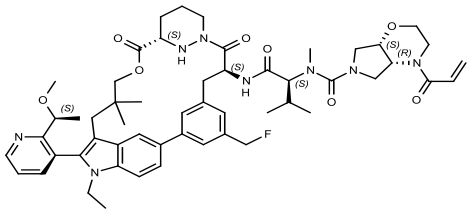
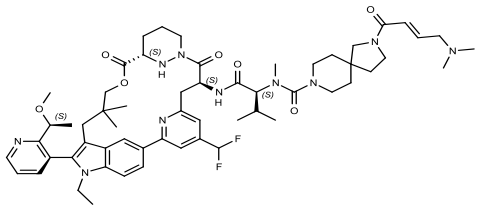
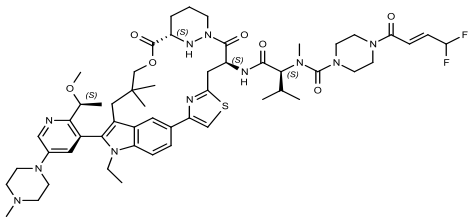
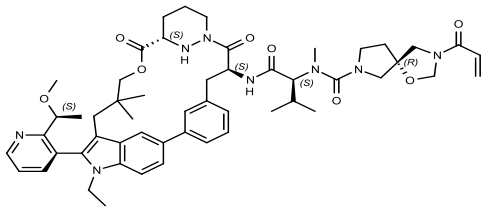
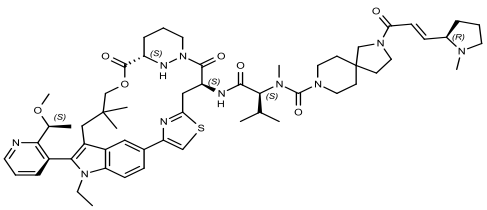
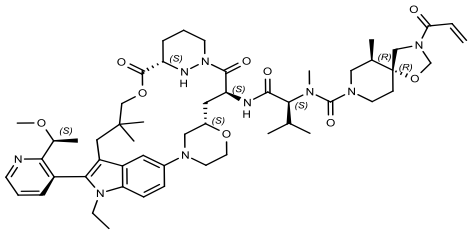
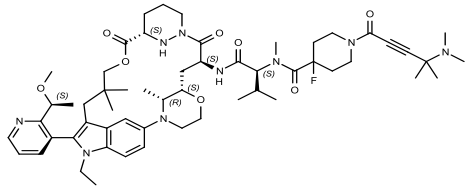
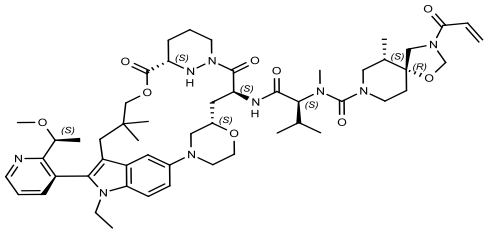
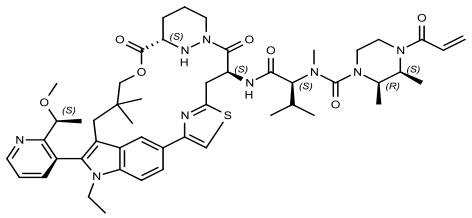
Ex#	Structure	Ex#	Structure
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A14		A118	
A15		A119	
A16		A120	
A17		A121	

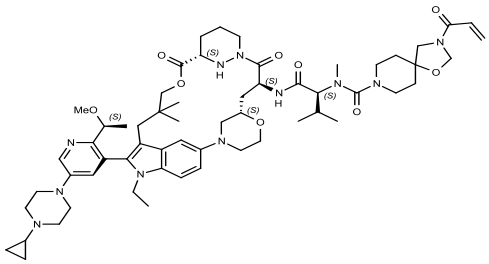
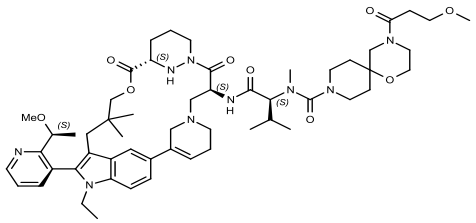
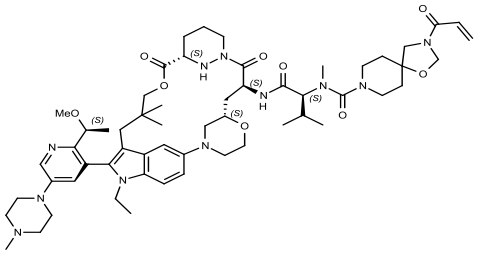
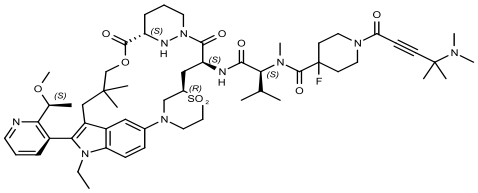
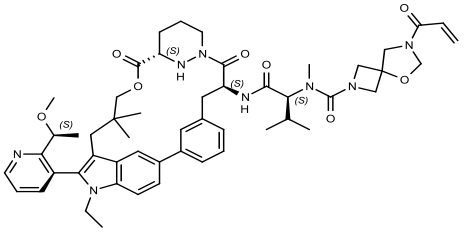
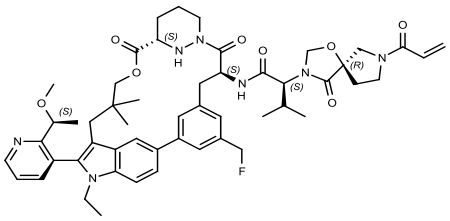
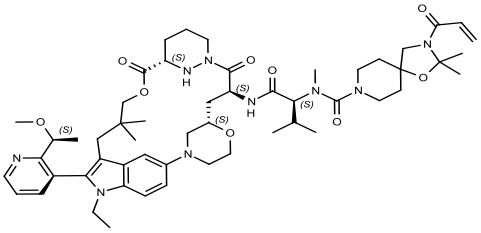
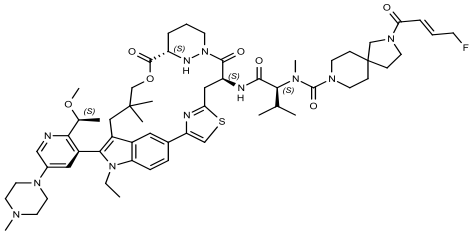
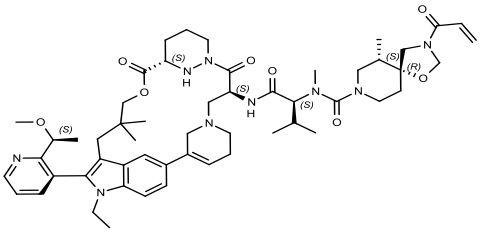
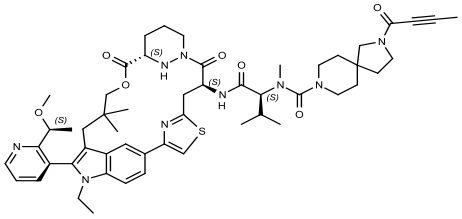
Ex#	Structure	Ex#	Structure
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A19		A123	
A20		A124	
A21		A125	
A22		A126	

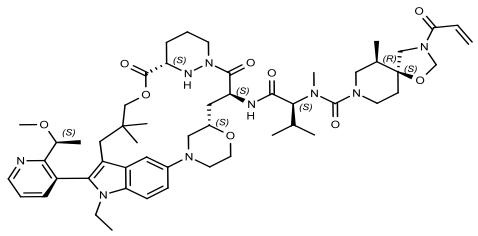
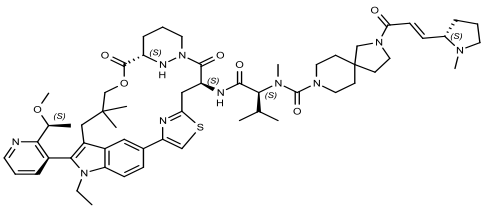
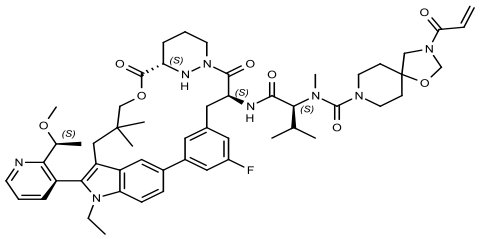
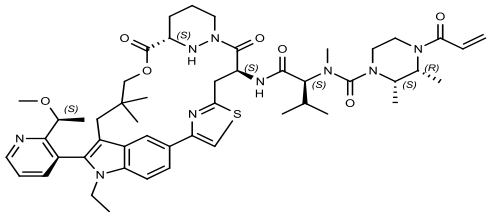
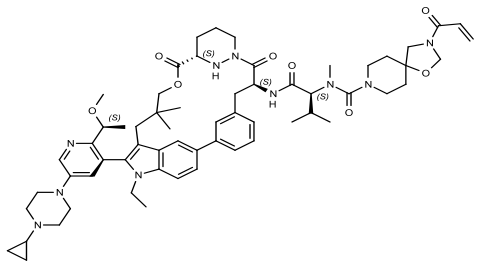
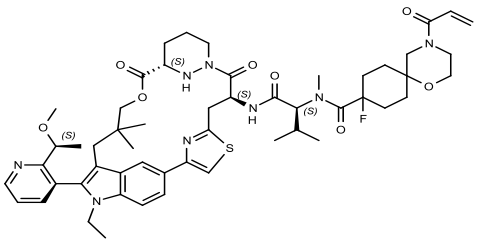
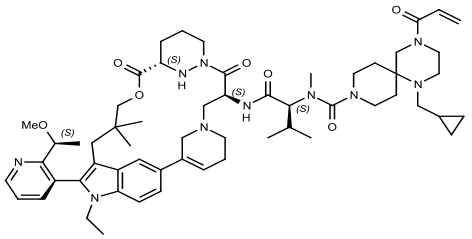
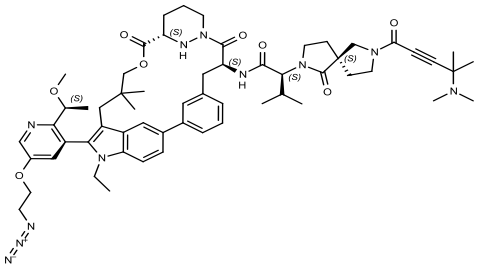
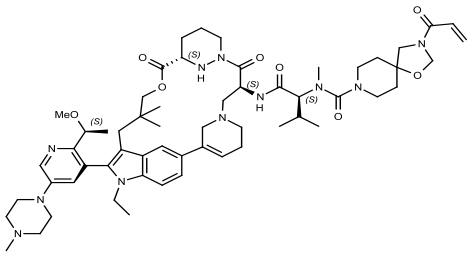
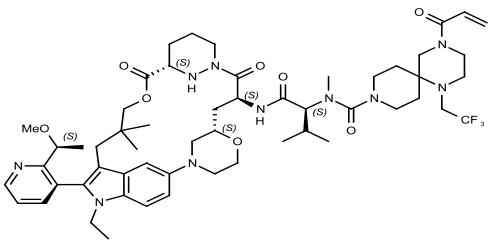
Ex#	Structure	Ex#	Structure
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A24		A128	
A25		A129	
A26		A130	
A27		A131	

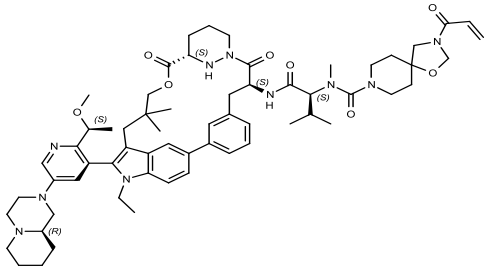
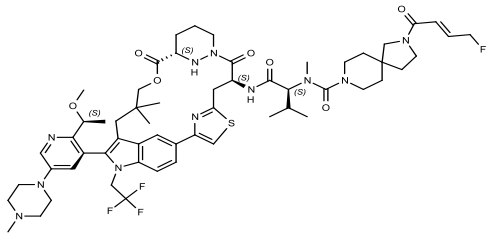
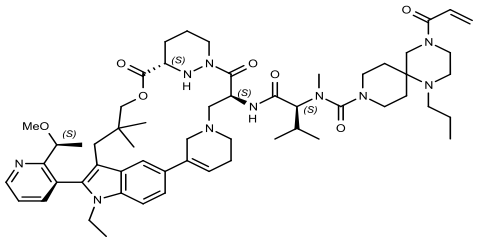
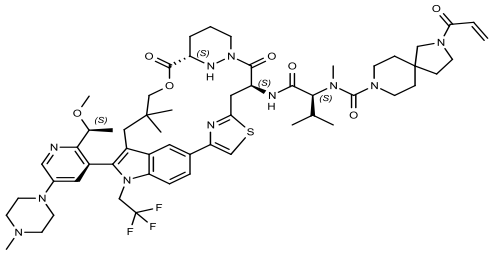
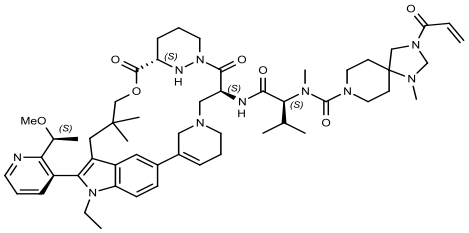
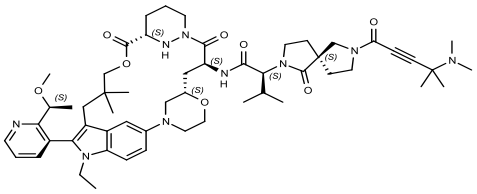
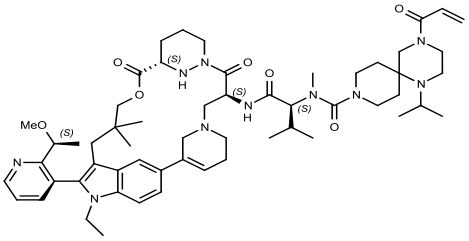
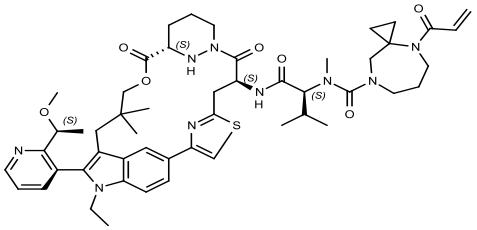
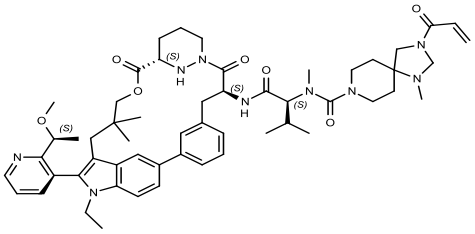
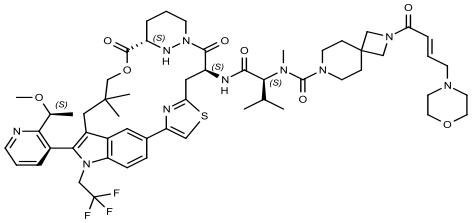
Ex#	Structure	Ex#	Structure
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A29		A133	
A30		A134	
A31		A135	
A32		A136	

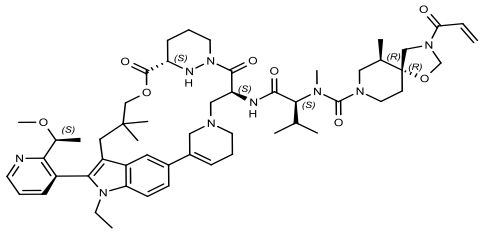
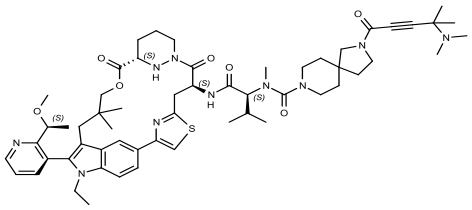
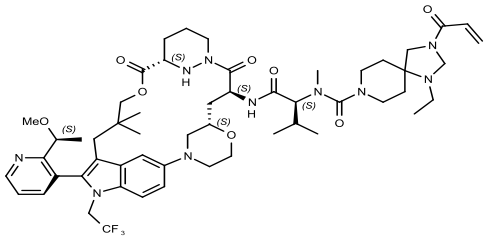
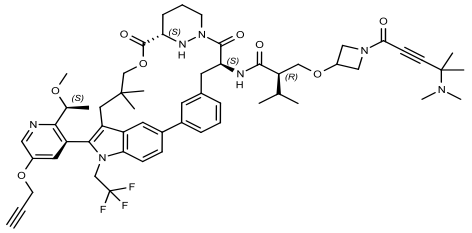
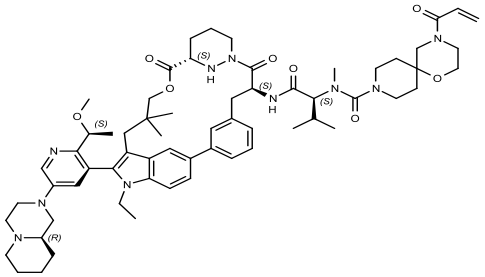
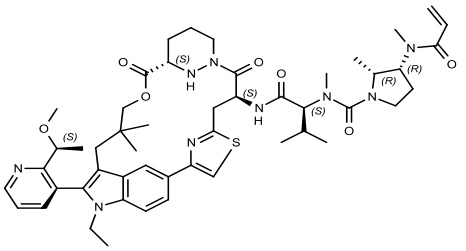
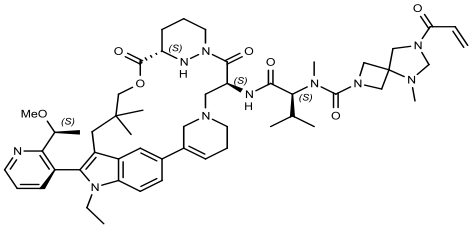
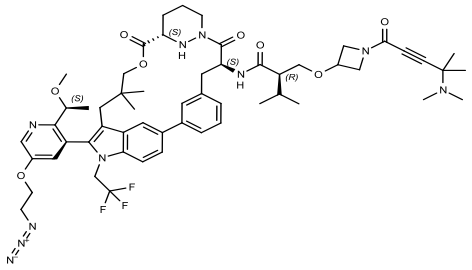
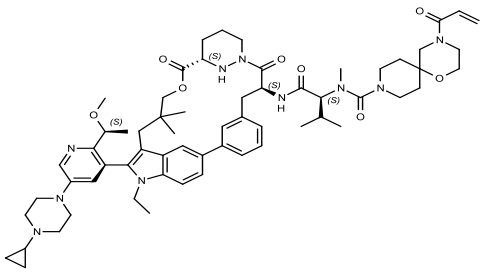
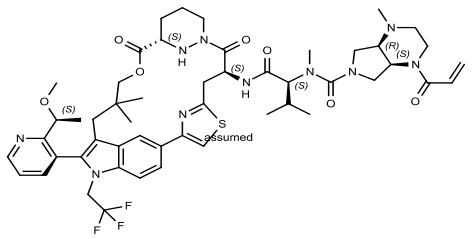
Ex#	Structure	Ex#	Structure
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A34		A138	
A35		A139	
A36		A140	
A37		A141	

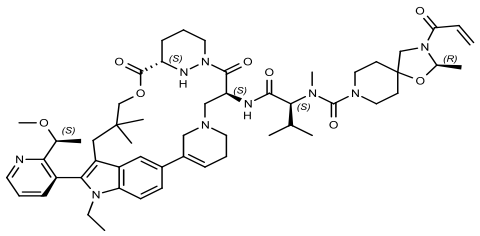
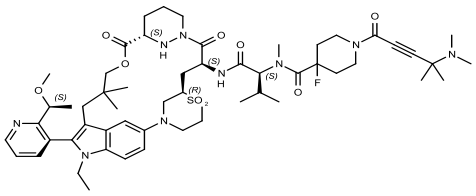
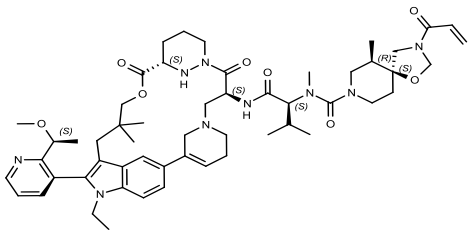
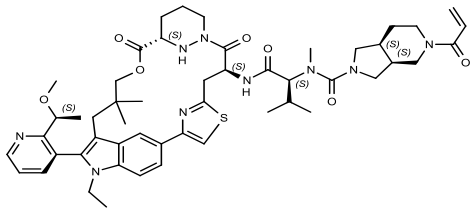
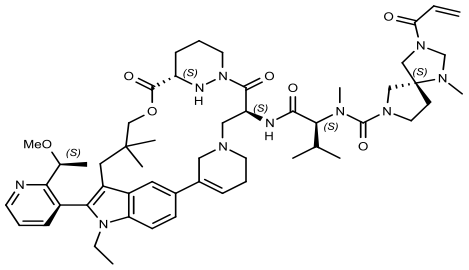
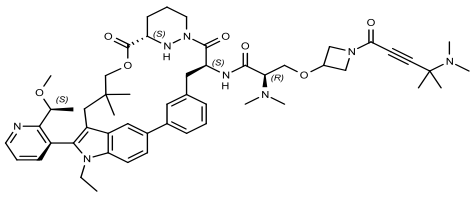
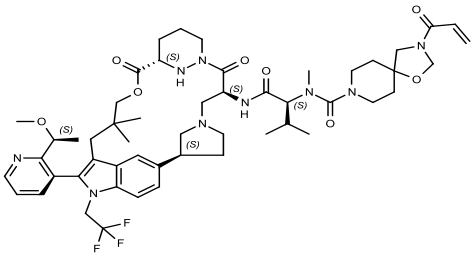
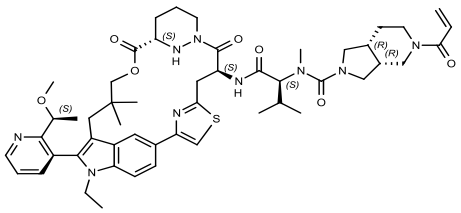
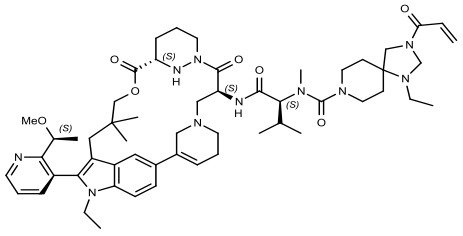
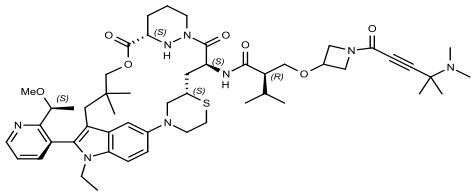
Ex#	Structure	Ex#	Structure
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A39		A143	
A40		A144	
A41		A145	
A42		A146	

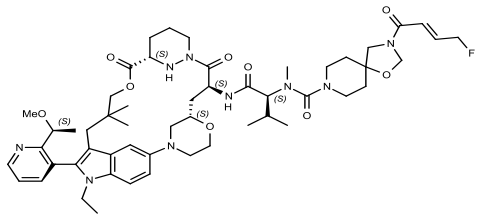
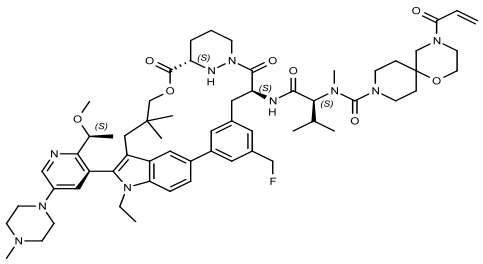
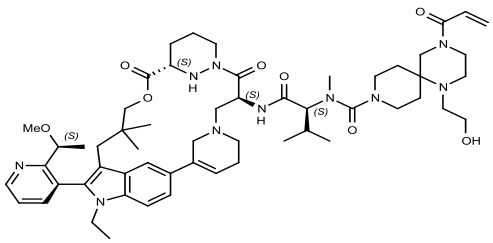
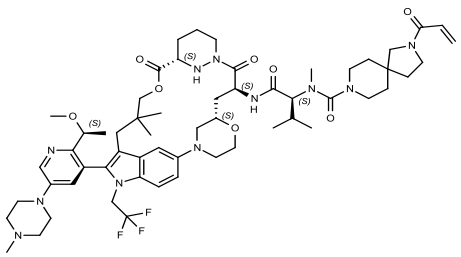
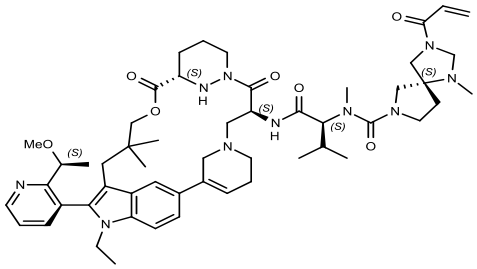
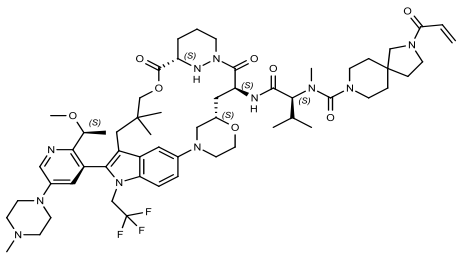
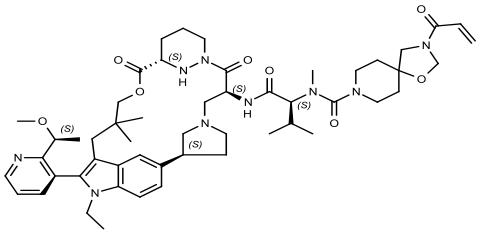
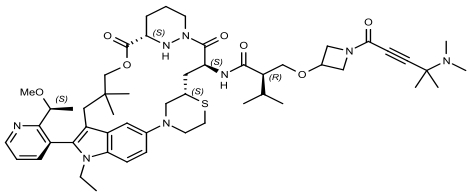
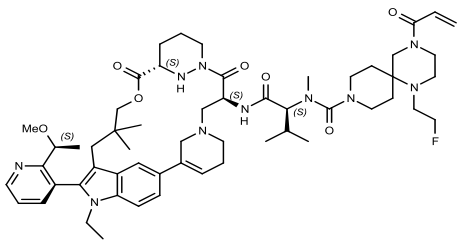
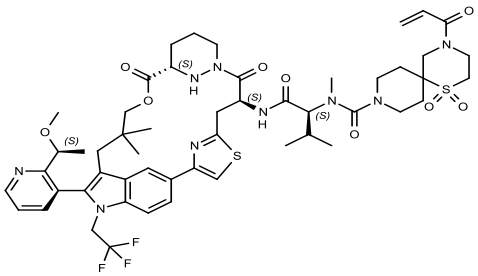
Ex#	Structure	Ex#	Structure
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A44		A148	
A45		A149	
A46		A150	
A47		A151	

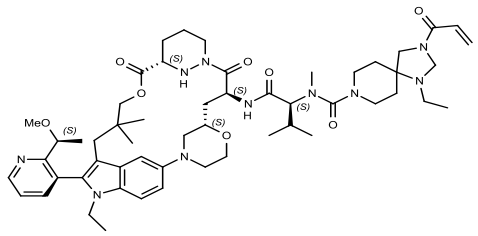
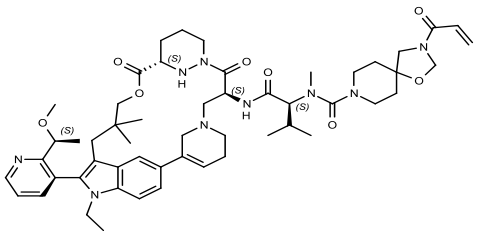
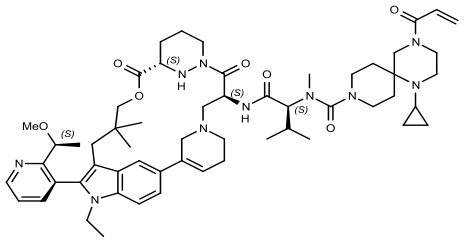
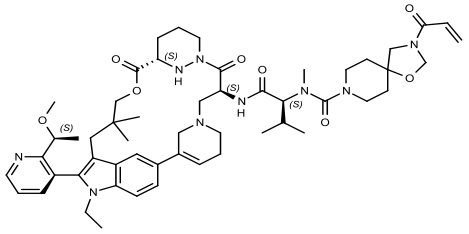
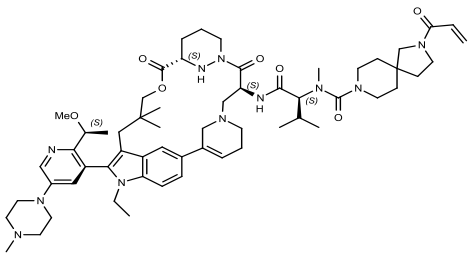
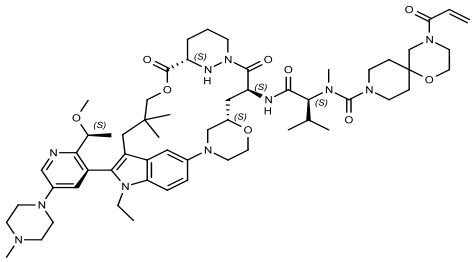
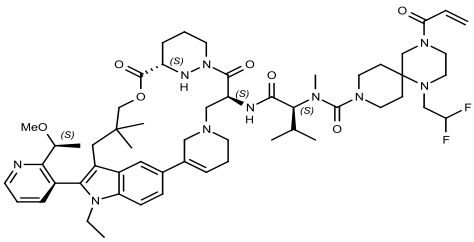
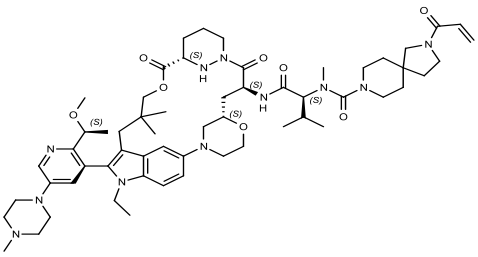
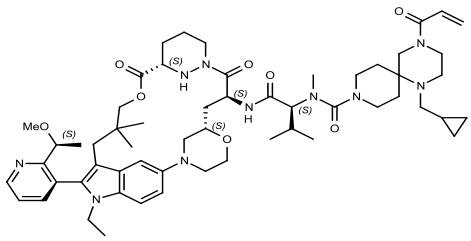
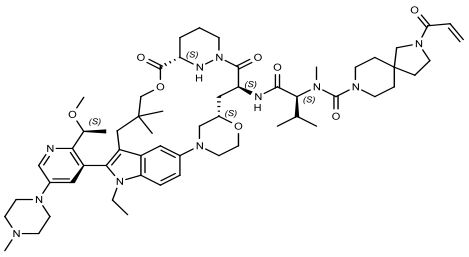
Ex#	Structure	Ex#	Structure
A48		A152	
A49		A153	
A50		A154	
A51		A155	
A52		A156	

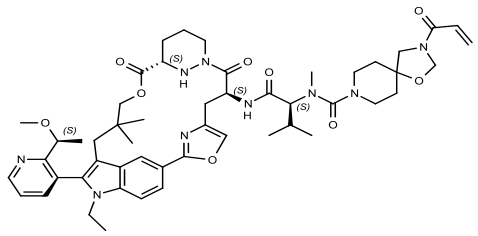
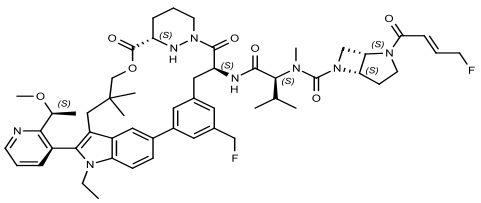
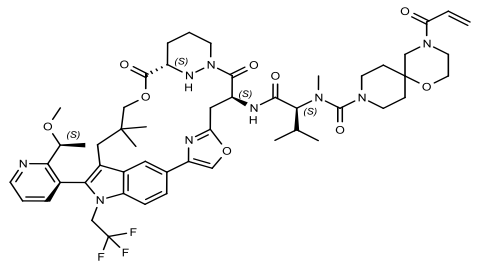
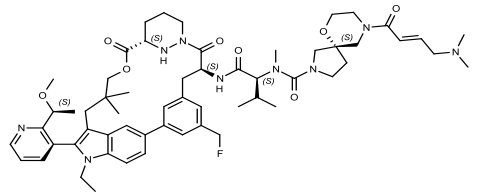
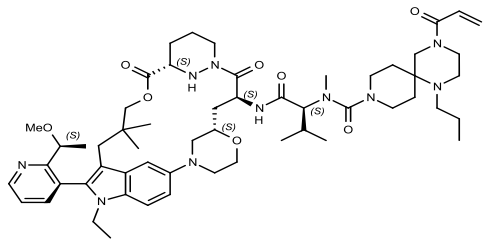
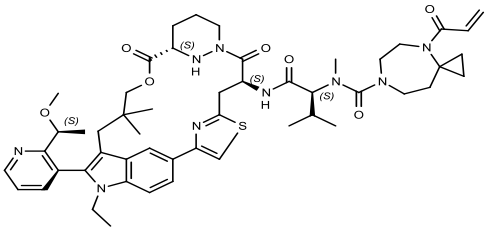
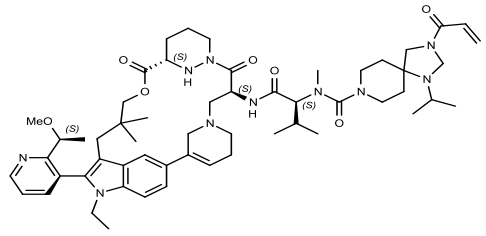
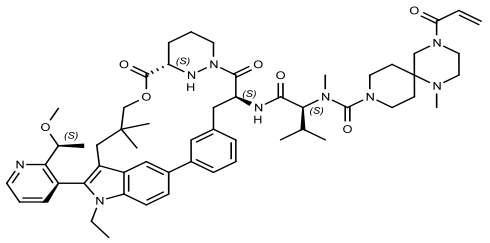
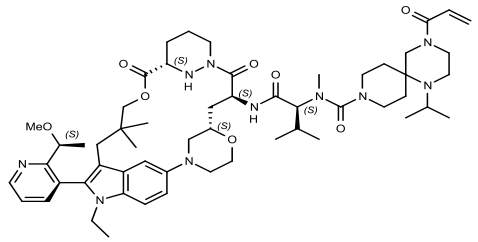
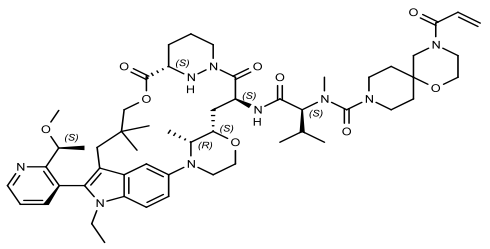
Ex#	Structure	Ex#	Structure
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A54		A158	
A55		A159	
A56		A160	
A57		A161	

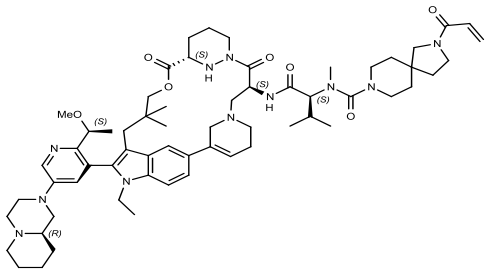
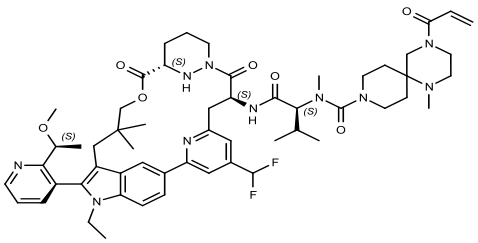
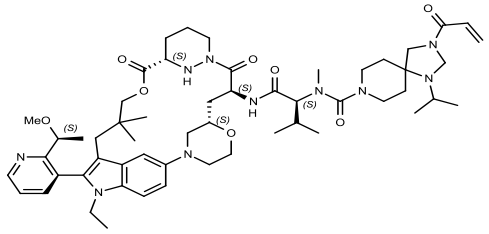
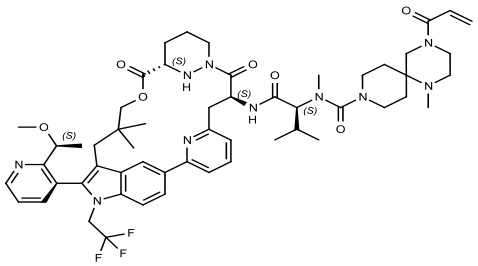
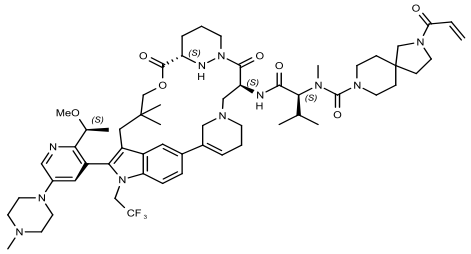
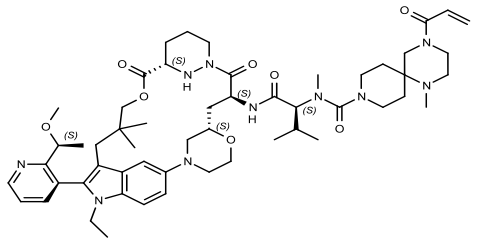
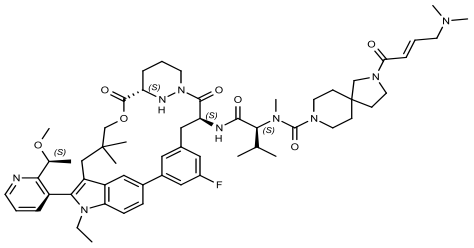
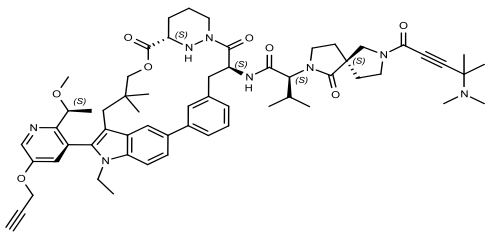
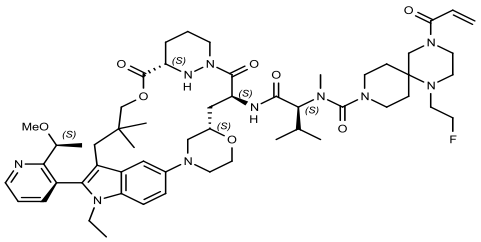
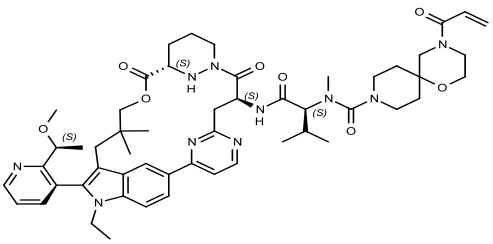
Ex#	Structure	Ex#	Structure
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A60		A164	
A61		A165	
A62		A166	

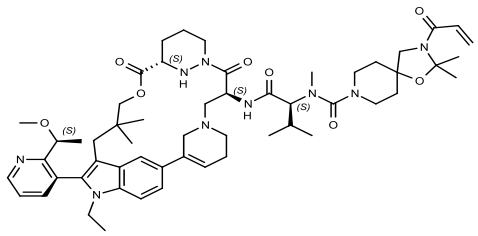
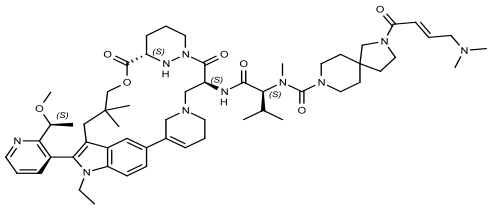
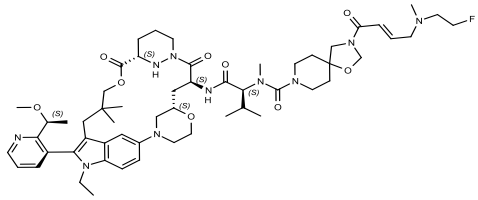
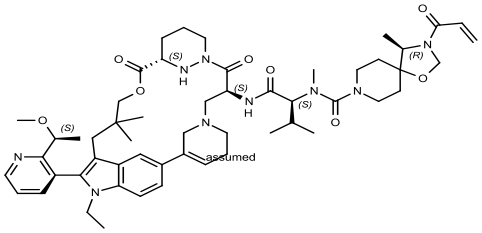
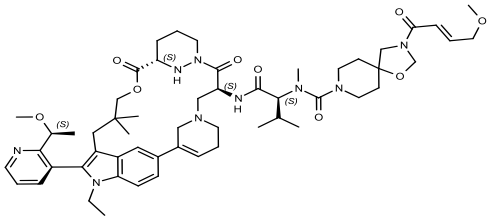
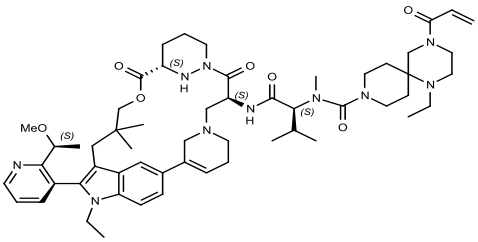
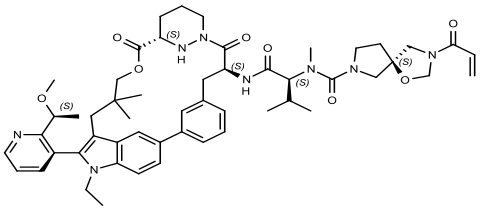
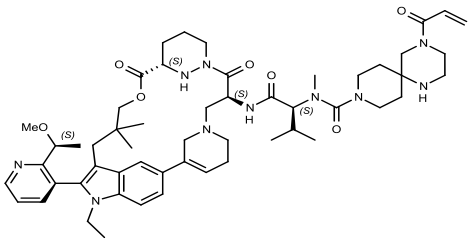
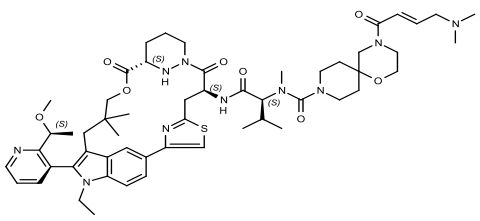
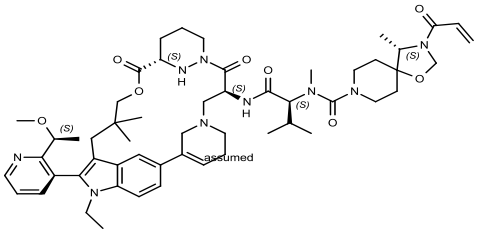
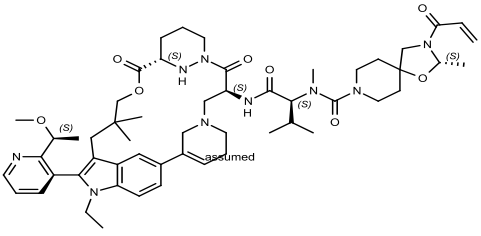
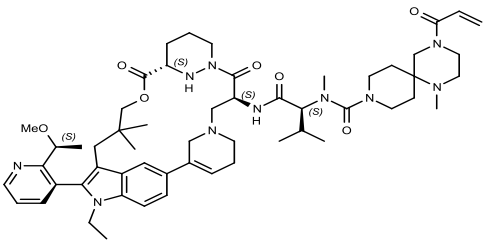
Ex#	Structure	Ex#	Structure
A63		A167	
A64		A168	
A65		A169	
A66		A170	
A67		A171	

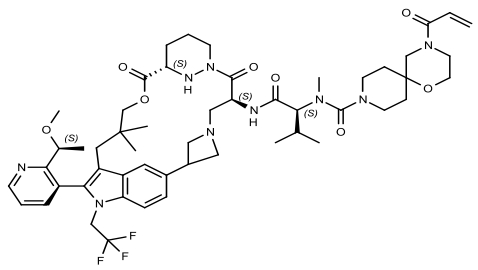
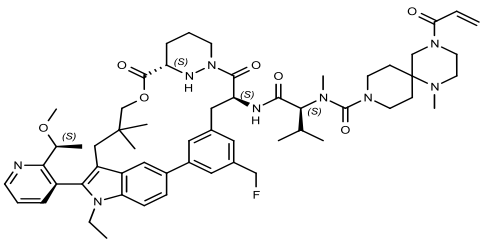
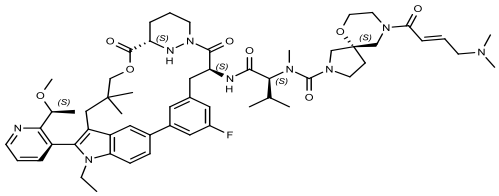
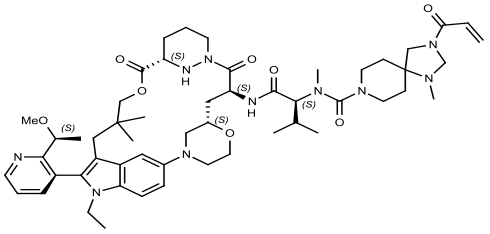
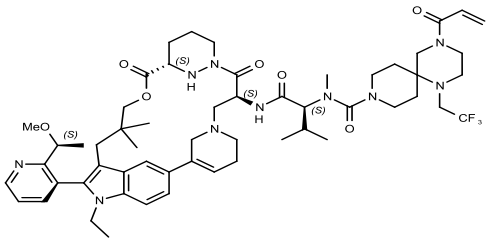
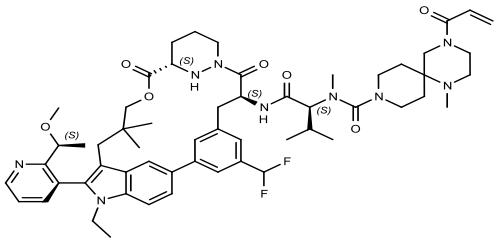
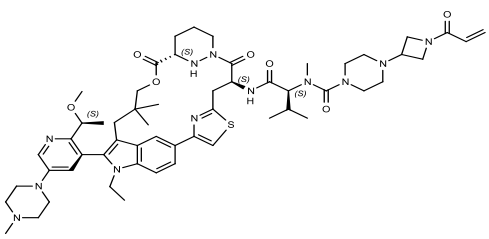
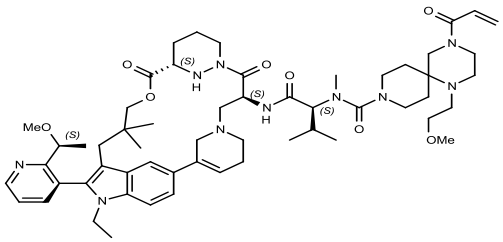
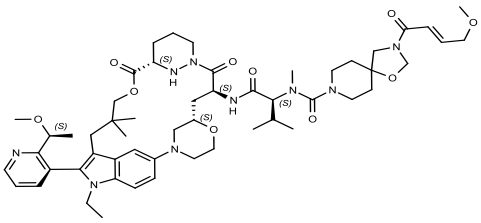
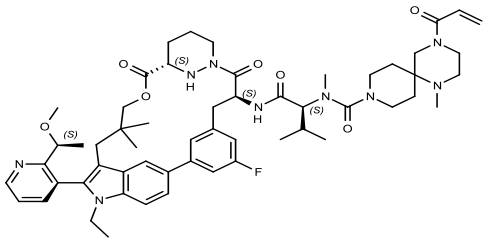
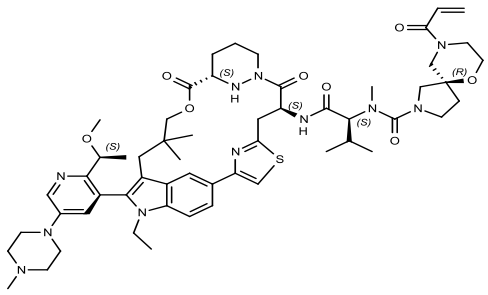
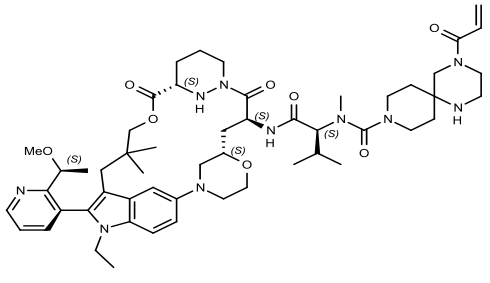
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A71		A175	
A72		A176	

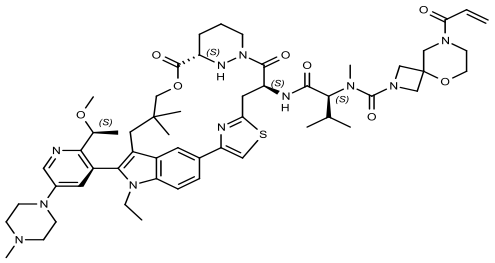
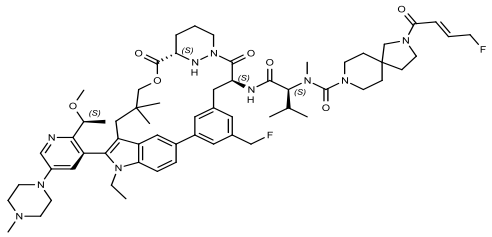
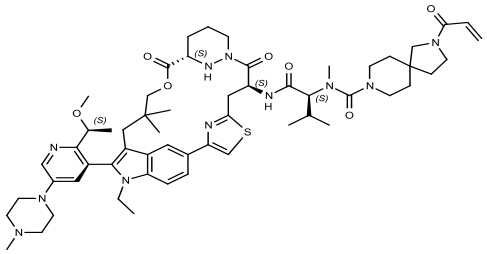
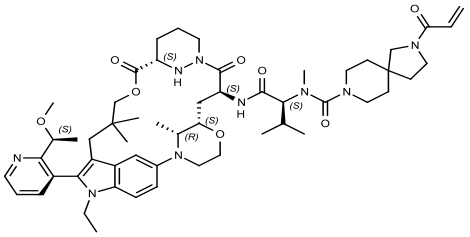
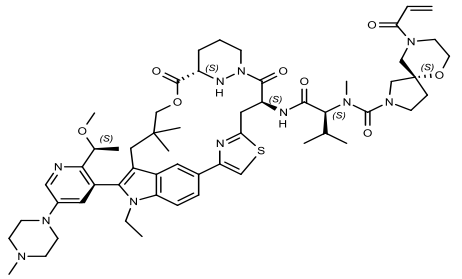
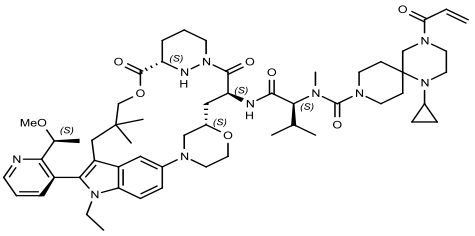
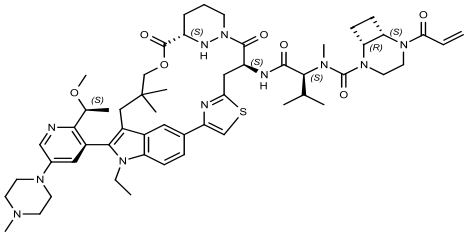
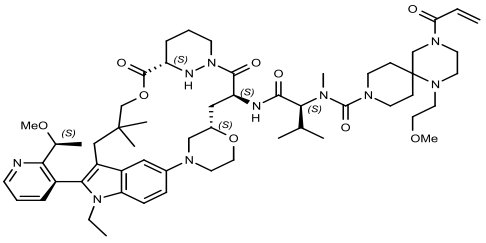
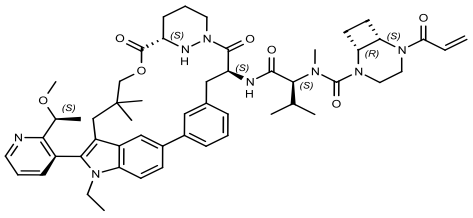
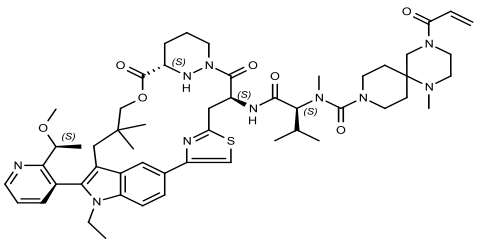
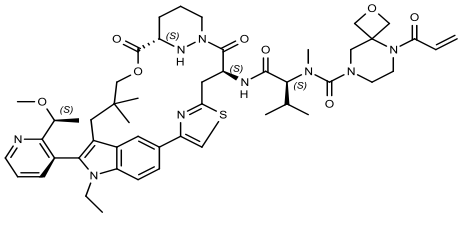
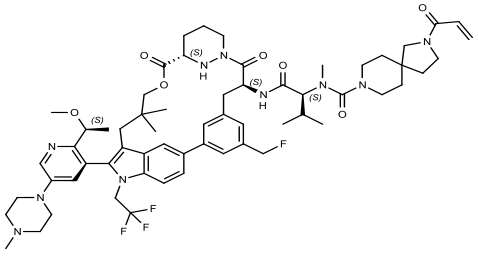
Ex#	Structure	Ex#	Structure
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A75		A179	
A76		A180	
A77		A181	

Ex#	Structure	Ex#	Structure
A78		A182	
A79		A183	
A80		A184	
A81		A185	
A82		A186	

A83		**A187**	
A84		**A188**	
A85		**A189**	
A86		**A190**	
A87		**A191**	

A88		**A192**	
A89		**A193**	
A90		**A194**	
A91		**A195**	
A92		**A196**	
A93		**A197**	

A94		**A198**	
A95		**A199**	
A96		**A200**	
A97		**A201**	
A98		**A202**	
A99		**A203**	

A100		**A204**	
A101		**A205**	
A102		**A206**	
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A104		**A208**	
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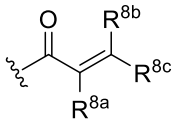
Also provided are pharmaceutical compositions comprising a compound of Formula I, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient. Also provided are pharmaceutical compositions comprising a compound of Table 1, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient. In yet another aspect, the present disclosure features a pharmaceutical composition comprising a compound of the present disclosure, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

In yet another aspect, the present disclosure features a conjugate, or salt thereof, comprising the structure of Formula V:

M-L-P

Formula V,

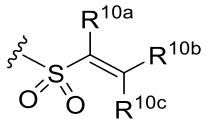
wherein L is a linker having the structure of:



Formula IVa,

wherein R^{8a}, R^{8b}, and R^{8c} are, independently, hydrogen, -CN, halogen, -C_1-C_3 alkyl, or -C_1-C_3 alkyl substituted with one or more substituents independently selected from -OH and -O-C_1-C_3 alkyl,

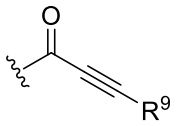
-NH_2, -NH(C_1-C_3 alkyl), -N(C_1-C_3 alkyl)$_2$, or a 4 to 7-membered saturated heterocycloalkyl comprising one, two, three, or four heteroatoms independently selected from nitrogen, oxygen, and sulfur;



Formula IVc,

wherein R^{10a}, R^{10b}, and R^{10c} are, independently, hydrogen, -CN, -C_1-C_3 alkyl, or -C_1-C_3 alkyl substituted with one, two, three, or four substituents independently selected from -OH and -O-C_1-C_3 alkyl,

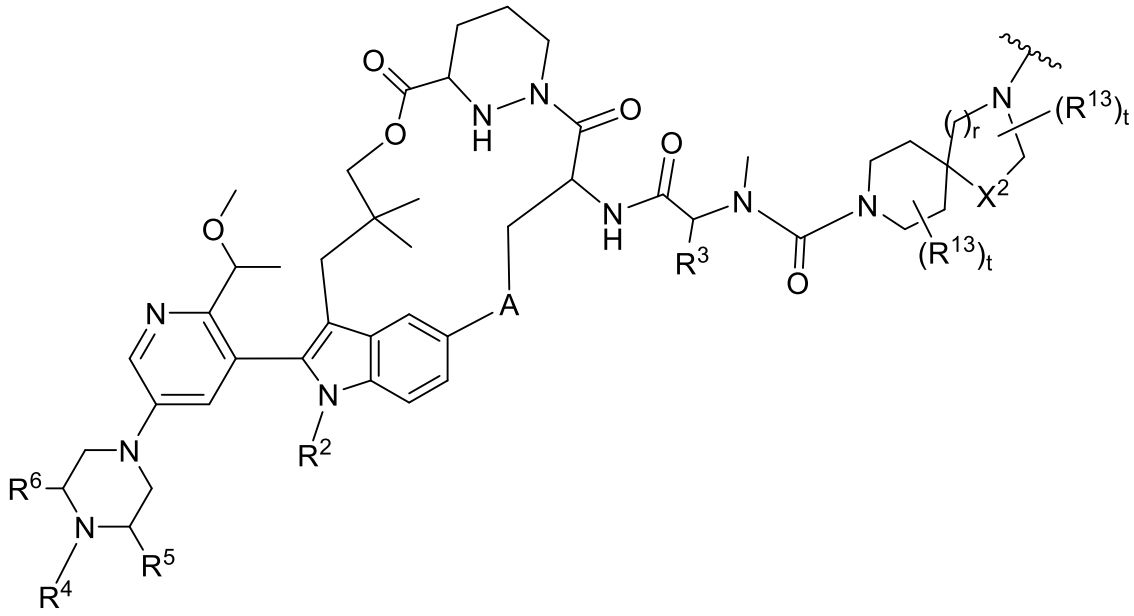
-NH_2, -NH(C_1-C_3 alkyl), -N(C_1-C_3 alkyl)$_2$, or a 4 to 7-membered saturated heterocycloalkyl comprising one, two, three, or four heteroatoms independently selected from nitrogen, oxygen, and sulfur;



Formula IVb,

wherein R^9 is hydrogen, -C_1-C_3 alkyl, -C_1-C_3 alkyl substituted with one, two, three, or four substituents independently selected from -OH, -O-C_1-C_3 alkyl, -NH_2, -NH(C_1-C_3 alkyl), -N(C_1-C_3 alkyl)$_2$, a 4 to 7-membered saturated cycloalkyl, and a 4 to 7-membered saturated heterocycloalkyl comprising one, two, three, or four heteroatoms independently selected from nitrogen, oxygen, and sulfur; P is a monovalent organic moiety wherein the monovalent organic moiety is a RAS protein selected from K-Ras G12C, K-Ras G13C, H-Ras G12C, H-Ras G13C, N-Ras G12C, or N-Ras G13C, and wherein the linker is bound to the monovalent organic moiety through a bond to a sulfhydryl group of an amino acid residue of the monovalent organic moiety; and

M has the structure of Formula VIa:



Formula VIa,

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;

R^2 is optionally substituted C_1-C_6 alkyl;

R^3 is optionally substituted C_1-C_6 alkyl or optionally substituted C_1-C_3 heteroalkyl;

X^2 is O, $C(R^{11})_2$, NR^{12}, S, or SO_2;

r is 1 or 2;

each t is, independently, 0, 1, or 2;

R^{11} and R^{12} are each, independently, hydrogen, optionally substituted C_1-C_4 alkyl, optionally substituted C_2-C_4 heteroalkyl, or optionally substituted 3 to 5-membered cycloalkyl;

each R^{13} is, independently, $-CH_3$; and

R^4, R^5, and R^6 are each independently selected from hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted 3 to 6-membered cycloalkyl, optionally substituted 3 to 6-membered heterocycloalkyl; or

R^4 and R^5 combine with the atoms to which they are attached to form an optionally substituted 3 to 8-membered cycloalkyl or an optionally substituted 3 to 8-membered heterocycloalkyl; or

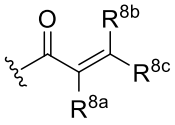
R^4 and R^6 combine with the atoms to which they are attached to form an optionally substituted 3 to 8-membered cycloalkyl or an optionally substituted 3 to 8-membered heterocycloalkyl.

In yet another aspect, the disclosure features A conjugate, or salt thereof, comprising the structure of Formula V:

M-L-P

Formula V,

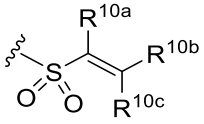
wherein L is a linker having the structure of:



Formula IVa,

wherein R^{8a}, R^{8b}, and R^{8c} are, independently, hydrogen, -CN, halogen, -C_1-C_3 alkyl, or -C_1-C_3 alkyl substituted with one or more substituents independently selected from -OH and -O-C_1-C_3 alkyl,

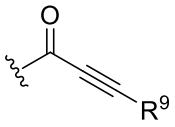
-NH_2, -NH(C_1-C_3 alkyl), -N(C_1-C_3 alkyl)$_2$, or a 4 to 7-membered saturated heterocycloalkyl comprising one, two, three, or four heteroatoms independently selected from nitrogen, oxygen, and sulfur;



Formula IVc,

wherein R^{10a}, R^{10b}, and R^{10c} are, independently, hydrogen, -CN, -C_1-C_3 alkyl, or -C_1-C_3 alkyl substituted with one, two, three, or four substituents independently selected from -OH and -O-C_1-C_3 alkyl,

-NH_2, -NH(C_1-C_3 alkyl), -N(C_1-C_3 alkyl)$_2$, or a 4 to 7-membered saturated heterocycloalkyl comprising one, two, three, or four heteroatoms independently selected from nitrogen, oxygen, and sulfur;

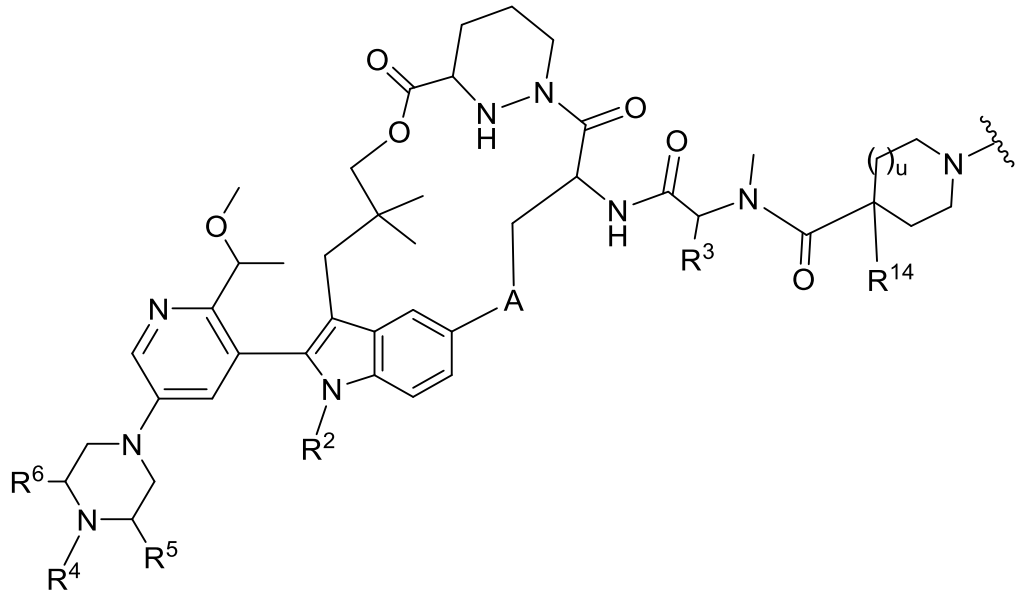


Formula IVb,

wherein R^9 is hydrogen, -C_1-C_3 alkyl, -C_1-C_3 alkyl substituted with one, two, three, or four substituents independently selected from -OH, -O-C_1-C_3 alkyl, -NH_2, -NH(C_1-C_3 alkyl), -N(C_1-C_3 alkyl)$_2$, a 4 to 7-membered saturated cycloalkyl, and a 4 to 7-membered saturated heterocycloalkyl comprising one, two, three, or four heteroatoms independently selected from nitrogen, oxygen, and sulfur;

P is a monovalent organic moiety wherein the monovalent organic moiety is a RAS protein selected from K-Ras G12C, K-Ras G13C, H-Ras G12C, H-Ras G13C, N-Ras G12C, or N-Ras G13C, and wherein the linker is bound to the monovalent organic moiety through a bond to a sulfhydryl group of an amino acid residue of the monovalent organic moiety; and

M has the structure of Formula VIb:



Formula VIb,

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;

R^2 is optionally substituted C_1-C_6 alkyl;

R^3 is optionally substituted C_1-C_6 alkyl or optionally substituted C_1-C_3 heteroalkyl;

R^{14} is fluoro, hydrogen, or C_1-C_3 alkyl;

u is 0 or 1; and

R^4, R^5, and R^6 are each independently selected from hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted 3 to 6-membered cycloalkyl, optionally substituted 3 to 6-membered heterocycloalkyl; or

R^4 and R^5 combine with the atoms to which they are attached to form an optionally substituted 3 to 8-membered cycloalkyl or an optionally substituted 3 to 8-membered heterocycloalkyl; or

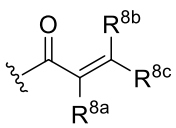
R^4 and R^6 combine with the atoms to which they are attached to form an optionally substituted 3 to 8-membered cycloalkyl or an optionally substituted 3 to 8-membered heterocycloalkyl.

In yet another aspect, the disclosure features a conjugate, or salt thereof, comprising the structure of Formula V:

M-L-P

Formula V,

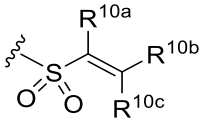
wherein L is a linker having the structure of:



Formula IVa,

wherein R^{8a}, R^{8b}, and R^{8c} are, independently, hydrogen, -CN, halogen, -C_1-C_3 alkyl, or -C_1-C_3 alkyl substituted with one or more substituents independently selected from -OH and -O-C_1-C_3 alkyl,

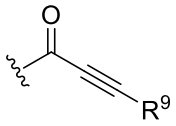
$-NH_2$, $-NH(C_1-C_3$ alkyl), $-N(C_1-C_3$ alkyl)$_2$, or a 4 to 7-membered saturated heterocycloalkyl comprising one, two, three, or four heteroatoms independently selected from nitrogen, oxygen, and sulfur;



Formula IVc,

wherein R^{10a}, R^{10b}, and R^{10c} are, independently, hydrogen, -CN, $-C_1-C_3$ alkyl, or $-C_1-C_3$ alkyl substituted with one, two, three, or four substituents independently selected from -OH and $-O-C_1-C_3$ alkyl,

$-NH_2$, $-NH(C_1-C_3$ alkyl), $-N(C_1-C_3$ alkyl)$_2$, or a 4 to 7-membered saturated heterocycloalkyl comprising one, two, three, or four heteroatoms independently selected from nitrogen, oxygen, and sulfur;

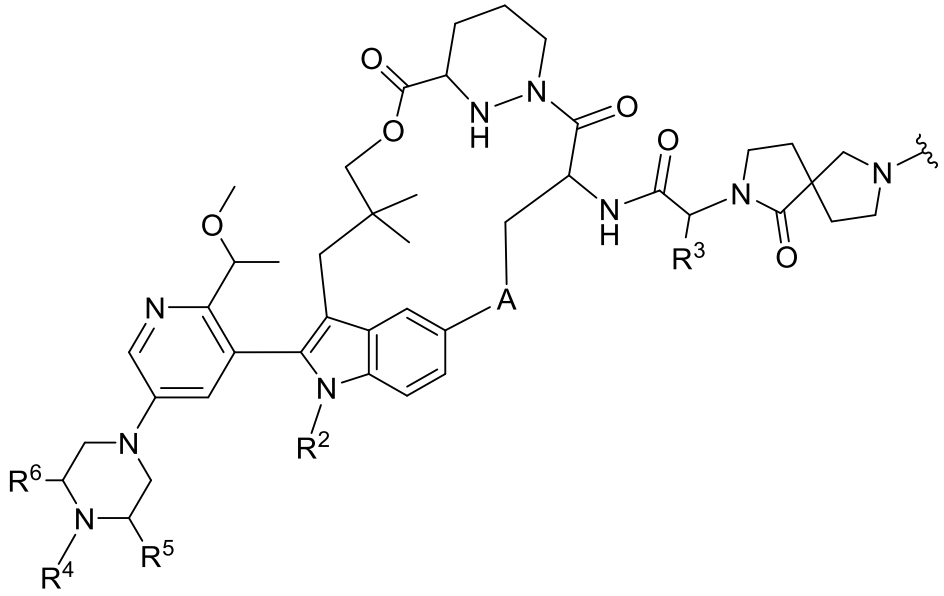


Formula IVb,

wherein R^9 is hydrogen, $-C_1-C_3$ alkyl, $-C_1-C_3$ alkyl substituted with one, two, three, or four substituents independently selected from -OH, $-O-C_1-C_3$ alkyl, $-NH_2$, $-NH(C_1-C_3$ alkyl), $-N(C_1-C_3$ alkyl)$_2$, a 4 to 7-membered saturated cycloalkyl, and a 4 to 7-membered saturated heterocycloalkyl comprising one, two, three, or four heteroatoms independently selected from nitrogen, oxygen, and sulfur;

P is a monovalent organic moiety wherein the monovalent organic moiety is a RAS protein selected from K-Ras G12C, K-Ras G13C, H-Ras G12C, H-Ras G13C, N-Ras G12C, or N-Ras G13C, and wherein the linker is bound to the monovalent organic moiety through a bond to a sulfhydryl group of an amino acid residue of the monovalent organic moiety; and

M has the structure of Formula VIc:



Formula VIc,

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;

R^2 is optionally substituted C_1-C_6 alkyl;

R^3 is optionally substituted C_1-C_6 alkyl or optionally substituted C_1-C_3 heteroalkyl; and

R^4, R^5, and R^6 are each independently selected from hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted 3 to 6-membered cycloalkyl, optionally substituted 3 to 6-membered heterocycloalkyl; or

R^4 and R^5 combine with the atoms to which they are attached to form an optionally substituted 3 to 8-membered cycloalkyl or an optionally substituted 3 to 8-membered heterocycloalkyl; or

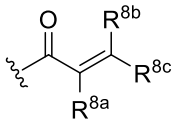
R^4 and R^6 combine with the atoms to which they are attached to form an optionally substituted 3 to 8-membered cycloalkyl or an optionally substituted 3 to 8-membered heterocycloalkyl.

In yet another aspect, the disclosure features a conjugate, or salt thereof, comprising the structure of Formula V:

M-L-P

Formula V,

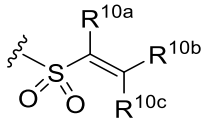
wherein L is a linker having the structure of:



Formula IVa,

wherein R^{8a}, R^{8b}, and R^{8c} are, independently, hydrogen, -CN, halogen, -C_1-C_3 alkyl, or -C_1-C_3 alkyl substituted with one or more substituents independently selected from -OH and -O-C_1-C_3 alkyl,

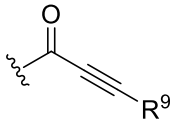
-NH_2, -NH(C_1-C_3 alkyl), -N(C_1-C_3 alkyl)$_2$, or a 4 to 7-membered saturated heterocycloalkyl comprising one, two, three, or four heteroatoms independently selected from nitrogen, oxygen, and sulfur;



Formula IVc,

wherein R^{10a}, R^{10b}, and R^{10c} are, independently, hydrogen, -CN, -C_1-C_3 alkyl, or -C_1-C_3 alkyl substituted with one, two, three, or four substituents independently selected from -OH and -O-C_1-C_3 alkyl,

-NH_2, -NH(C_1-C_3 alkyl), -N(C_1-C_3 alkyl)$_2$, or a 4 to 7-membered saturated heterocycloalkyl comprising one, two, three, or four heteroatoms independently selected from nitrogen, oxygen, and sulfur;



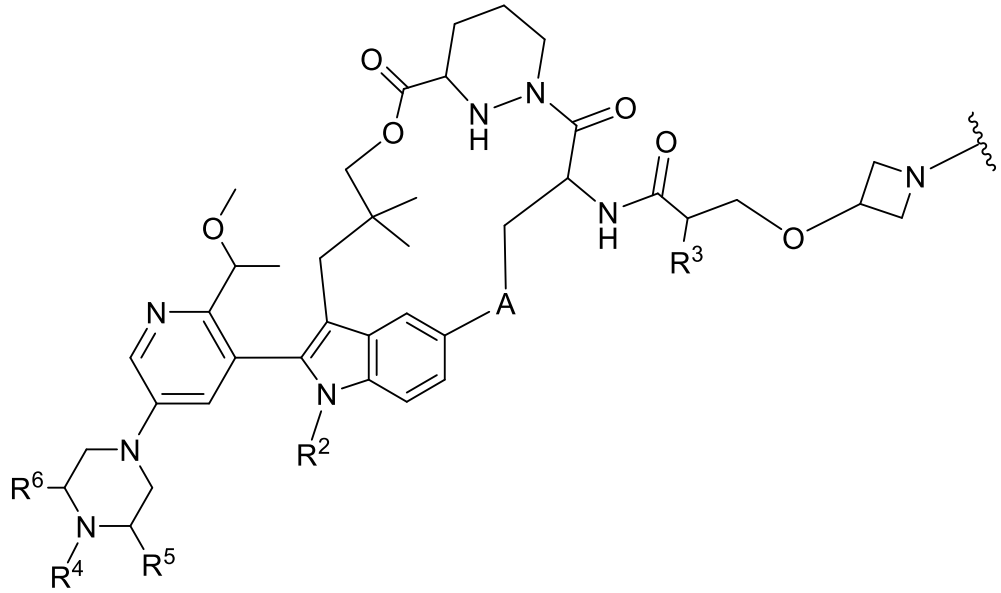
Formula IVb,

wherein R^9 is hydrogen, -C_1-C_3 alkyl, -C_1-C_3 alkyl substituted with one, two, three, or four substituents independently selected from -OH, -O-C_1-C_3 alkyl, -NH_2, -NH(C_1-C_3 alkyl), -N(C_1-C_3 alkyl)$_2$, a 4 to 7-membered saturated cycloalkyl, and a 4 to 7-membered saturated heterocycloalkyl comprising one, two, three, or four heteroatoms independently selected from nitrogen, oxygen, and sulfur;

P is a monovalent organic moiety wherein the monovalent organic moiety is a RAS protein selected from K-Ras G12C, K-Ras G13C, H-Ras G12C, H-Ras G13C, N-Ras G12C, or N-Ras G13C, and

wherein the linker is bound to the monovalent organic moiety through a bond to a sulfhydryl group of an amino acid residue of the monovalent organic moiety; and

M has the structure of Formula VId:



Formula VId,

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;

R^2 is optionally substituted C_1-C_6 alkyl;

R^3 is optionally substituted C_1-C_6 alkyl or optionally substituted C_1-C_3 heteroalkyl; and

R^4, R^5, and R^6 are each independently selected from hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted 3 to 6-membered cycloalkyl, optionally substituted 3 to 6-membered heterocycloalkyl; or

R^4 and R^5 combine with the atoms to which they are attached to form an optionally substituted 3 to 8-membered cycloalkyl or an optionally substituted 3 to 8-membered heterocycloalkyl; or

R^4 and R^6 combine with the atoms to which they are attached to form an optionally substituted 3 to 8-membered cycloalkyl or an optionally substituted 3 to 8-membered heterocycloalkyl.

Also provided is a method of treating cancer in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of a compound of the present disclosure, or a pharmaceutically acceptable salt thereof. In yet another aspect, the disclosure provides use of a compound of the present disclosure, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of the present disclosure, in the manufacture of a medicament for treating cancer.

Also provided is a method is provided of treating a Ras protein-related disorder in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of a compound of the present disclosure, or a pharmaceutically acceptable salt thereof. In yet another aspect, the disclosure provides use of a compound of the present disclosure, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of the present disclosure, in the manufacture of a

medicament for treating a Ras protein-related disorder, wherein the Ras protein related disorder is cancer, in a subject in need thereof.

Further provided is a method of inhibiting a Ras protein in a cell, the method comprising contacting the cell with an effective amount of a compound of the present disclosure, or a pharmaceutically acceptable salt thereof. In yet another aspect, the disclosure provides 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 of the present disclosure, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of the present disclosure.

In yet another aspect, the disclosure provides a compound of the present disclosure, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of the present disclosure, for use in therapy.

It is specifically contemplated that any limitation discussed with respect to one embodiment of the disclosure may apply to any other embodiment of the disclosure. Furthermore, any compound or composition of the disclosure may be used in any method of the disclosure, and any method of the disclosure may be used to produce or to utilize any compound or composition of the disclosure.

Definitions and Chemical Terms

In this application, unless otherwise clear from context, (i) the term “a” means “one or more”; (ii) the term "or" is used to mean "and/or" unless explicitly indicated to refer to alternatives only or the alternative are mutually exclusive, although the disclosure supports a definition that refers to only alternatives and "and/or”; (iii) the terms “comprising” and “including” are understood to encompass itemized components or steps whether presented by themselves or together with one or more additional components or steps; and (iv) where ranges are provided, endpoints are included.

As used herein, the term “about” is used to indicate that a value includes the standard deviation of error for the device or method being employed to determine the value. In certain embodiments, the term “about” refers to a range of values that fall within 25%, 20%, 19%, 18%, 17%, 16%, 15%, 14%, 13%, 12%, 11%, 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2%, 1%, or less in either direction (greater than or less than) of a stated value, unless otherwise stated or otherwise evident from the context (e.g., where such number would exceed 100% of a possible value).

As used herein, the term “adjacent” in the context of describing adjacent atoms refers to bivalent atoms that are directly connected by a covalent bond.

A “compound of the present invention” and similar terms as used herein, whether explicitly noted or not, refers to Ras inhibitors described herein, including compounds of Formula I and subformula thereof, for example, a compound of Table 1, as well as salts (e.g., pharmaceutically acceptable salts), solvates, hydrates, stereoisomers (including atropisomers), and tautomers thereof.

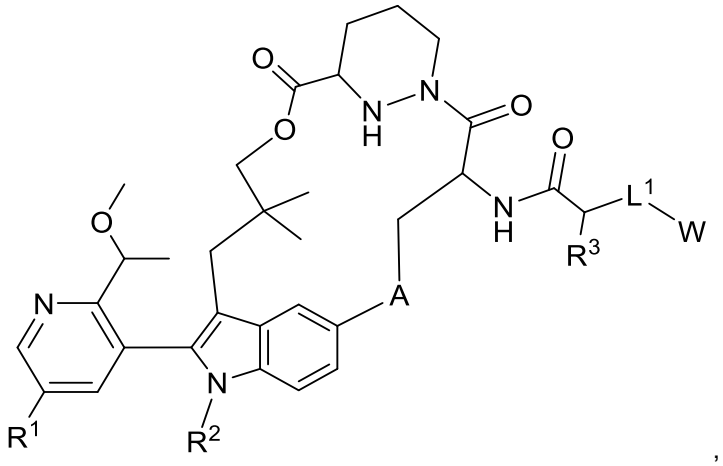
The term “wild-type” refers to an entity having a structure or activity as found in nature in a “normal” (as contrasted with mutant, diseased, altered, etc) state or context. Those of ordinary skill in the art will appreciate that wild-type genes and polypeptides often exist in multiple different forms (e.g., alleles).

Those skilled in the art will appreciate that certain compounds described herein can exist in one or more different isomeric (e.g., stereoisomers, geometric isomers, atropisomers, tautomers) or isotopic (e.g., in which one or more atoms has been substituted with a different isotope of the atom, such as hydrogen substituted for deuterium) forms. Unless otherwise indicated or clear from context, a depicted structure can be understood to represent any such isomeric or isotopic form, individually or in combination.

Compounds described herein can be asymmetric (e.g., having one or more stereocenters). All stereoisomers, such as enantiomers and diastereomers, are intended unless otherwise indicated. Compounds of the present disclosure that contain asymmetrically substituted carbon atoms can be isolated in optically active or racemic forms. Methods on how to prepare optically active forms from optically active starting materials are known in the art, such as by resolution of racemic mixtures or by stereoselective synthesis. Many geometric isomers of olefins, C=N double bonds, and the like can also be present in the compounds described herein, and all such stable isomers are contemplated in the

Claims

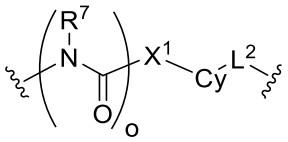
1. A compound, or pharmaceutically acceptable salt thereof, having the structure of Formula I:



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;

L^1 is absent or a linker having the structure of formula IIIa:



Formula IIIa,

wherein o is 0 or 1;

R^7 is hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted 3 to 8-membered cycloalkylene, or optionally substituted 3 to 8-membered heterocycloalkylene;

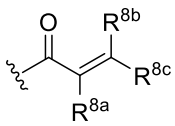
X^1 is absent, optionally substituted C_1-C_4 alkylene, O, NCH_3, or optionally substituted C_1-C_4 heteroalkylene;

Cy is optionally substituted 3 to 8-membered cycloalkylene, optionally substituted 3 to 12-membered heterocycloalkylene, optionally substituted 6-10 membered arylene, or optionally substituted 5 to 10-membered heteroarylene; and

L^2 is absent, -SO_2-, -NH-, optionally substituted C_1-C_4 alkylene, optionally substituted C_1-C_4 heteroalkylene, or optionally substituted 3 to 6-membered heterocycloalkylene;

W is a cross-linking group selected from: a vinyl ketone, vinyl sulfone, or ynone, where:

the vinyl ketone has the structure of Formula IVa:

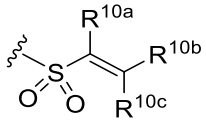


Formula IVa,

wherein R^{8a}, R^{8b}, and R^{8c} are, independently, hydrogen, -CN, halogen, -C_1-C_3 alkyl, or -C_1-C_3 alkyl substituted with one or more substituents independently selected from -OH and -O-C_1-C_3 alkyl,

-NH_2, -NH(C_1-C_3 alkyl), -N(C_1-C_3 alkyl)$_2$, or a 4 to 7-membered saturated heterocycloalkyl comprising one, two, three, or four heteroatoms independently selected from nitrogen, oxygen, and sulfur;

the vinyl sulfone has the structure of Formula IVc:

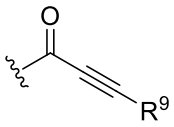


Formula IVc,

wherein R^{10a}, R^{10b}, and R^{10c} are, independently, hydrogen, -CN, -C_1-C_3 alkyl, or -C_1-C_3 alkyl substituted with one, two, three, or four substituents independently selected from -OH and -O-C_1-C_3 alkyl,

-NH_2, -NH(C_1-C_3 alkyl), -N(C_1-C_3 alkyl)$_2$, or a 4 to 7-membered saturated heterocycloalkyl comprising one, two, three, or four heteroatoms independently selected from nitrogen, oxygen, and sulfur;

the ynone has the structure of Formula IVb:



Formula IVb,

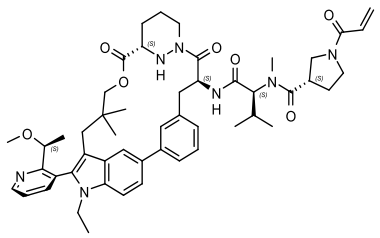
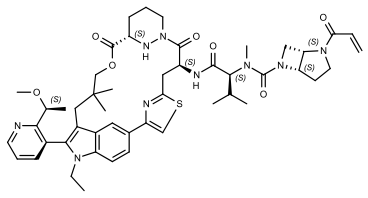
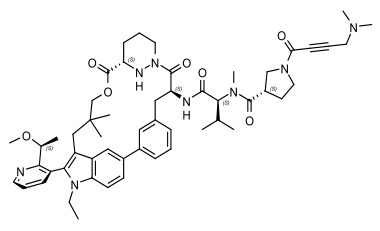
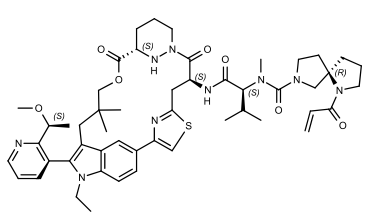
wherein R^9 is hydrogen, -C_1-C_3 alkyl, -C_1-C_3 alkyl substituted with one, two, three, or four substituents independently selected from -OH, -O-C_1-C_3 alkyl, -NH_2, -NH(C_1-C_3 alkyl), -N(C_1-C_3 alkyl)$_2$, a 4 to 7-membered saturated cycloalkyl, and a 4 to 7-membered saturated heterocycloalkyl comprising one, two, three, or four heteroatoms independently selected from nitrogen, oxygen, and sulfur;

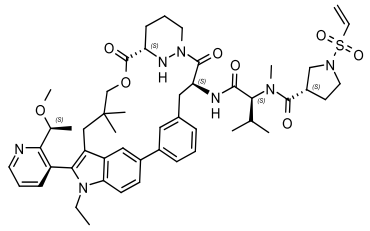
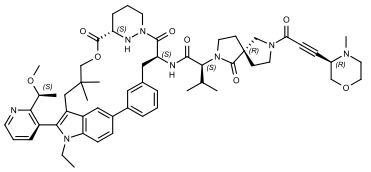
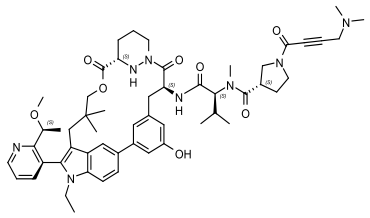
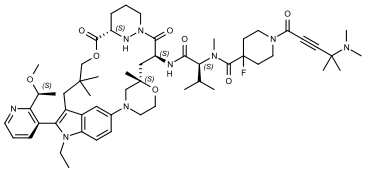
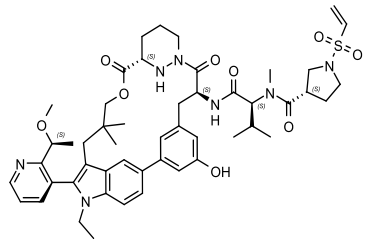
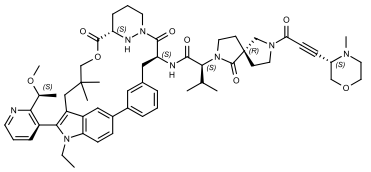
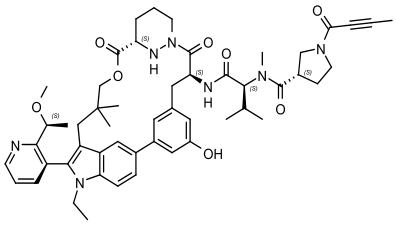
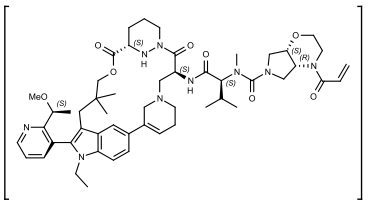
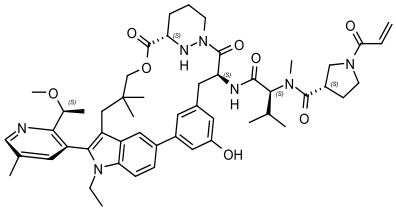
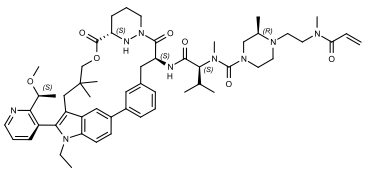
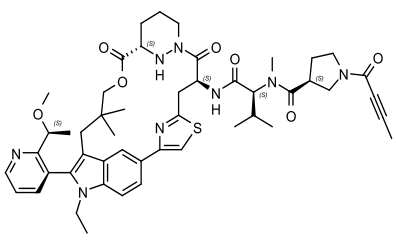
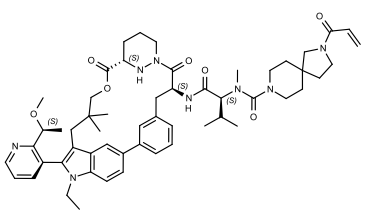
R^1 is hydrogen, optionally substituted 3 to 10-membered heterocycloalkyl, or optionally substituted C_1-C_6 heteroalkyl;

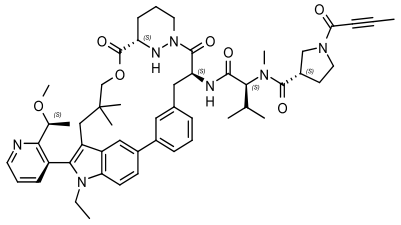
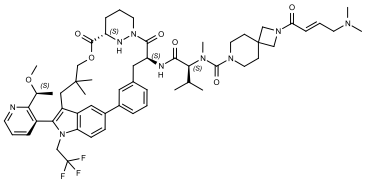
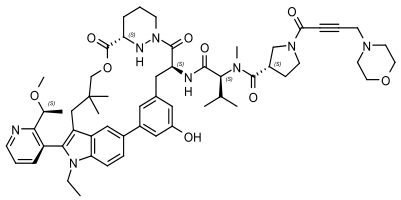
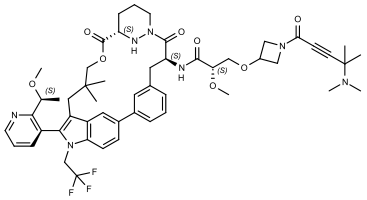
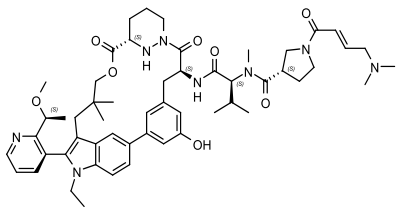
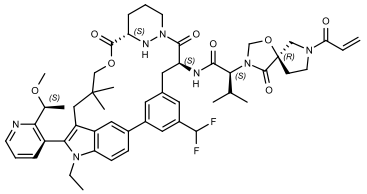
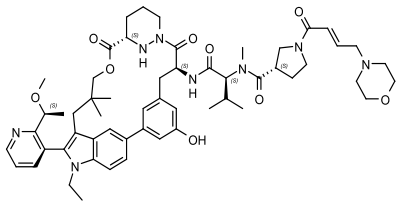
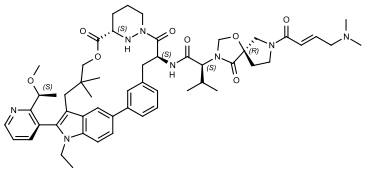
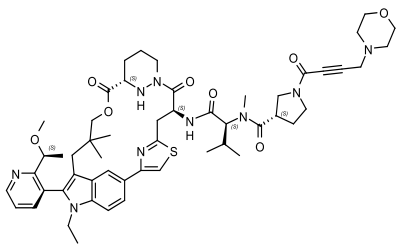
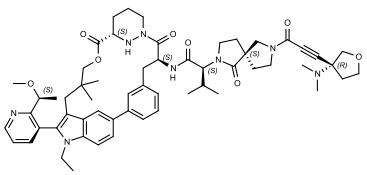
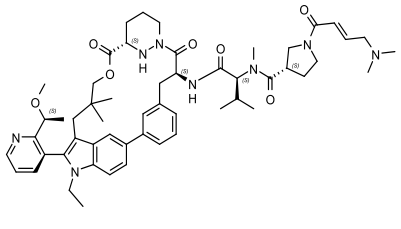
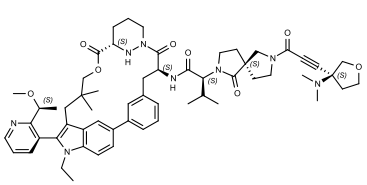
R^2 is optionally substituted C_1-C_6 alkyl; and

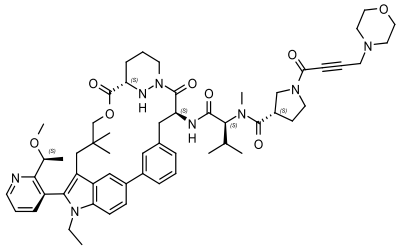
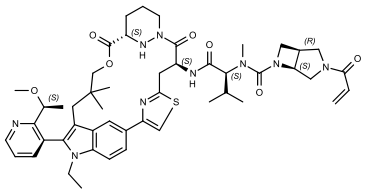
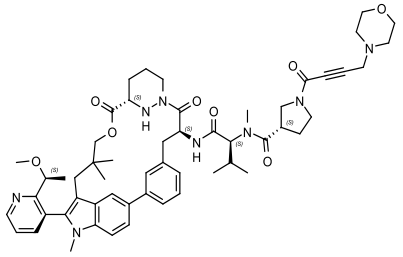
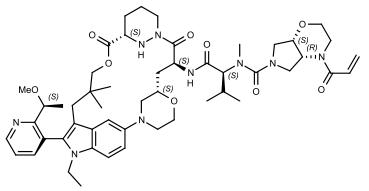
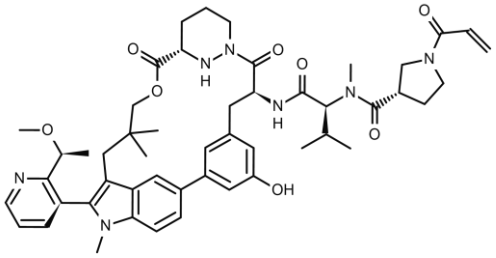
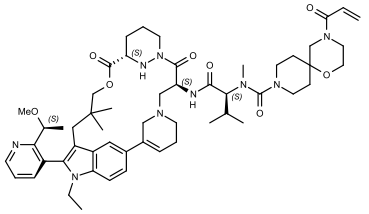
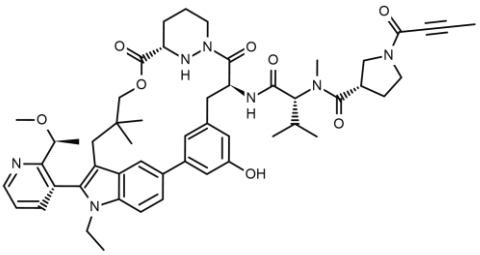
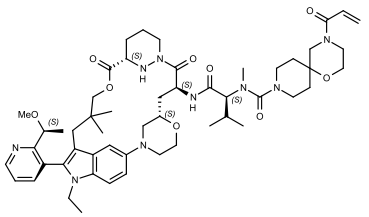
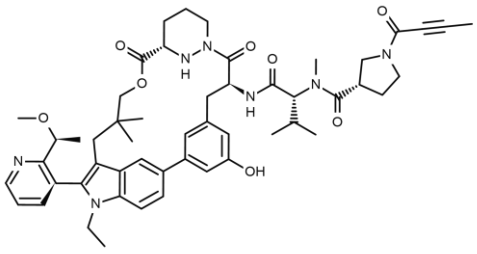
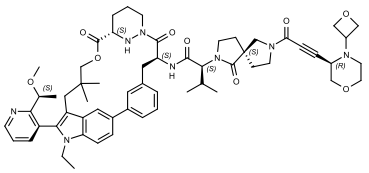
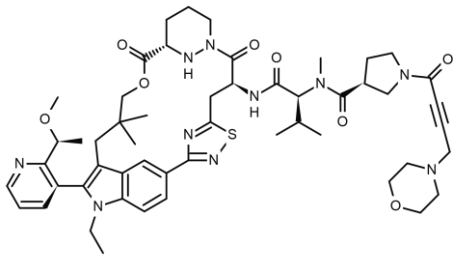
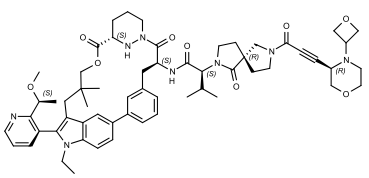
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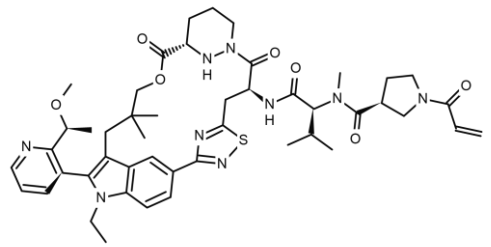
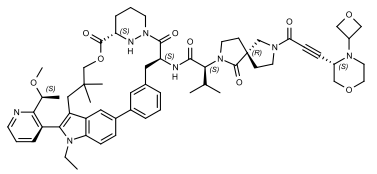
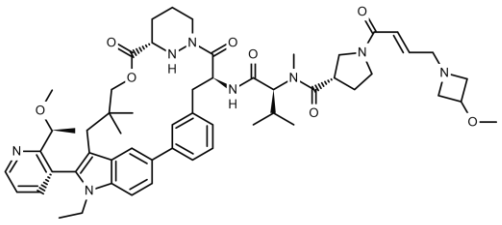
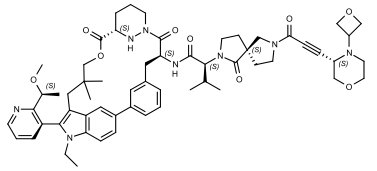
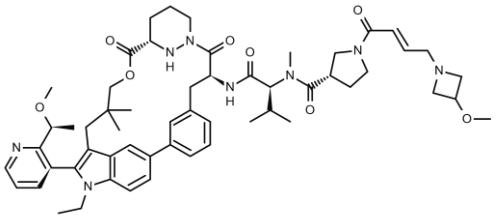
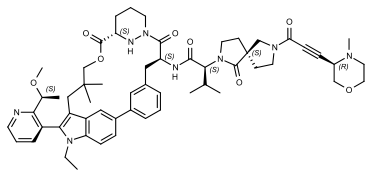
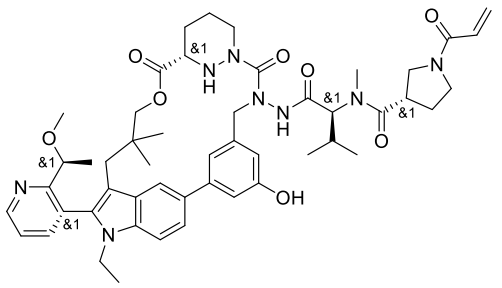
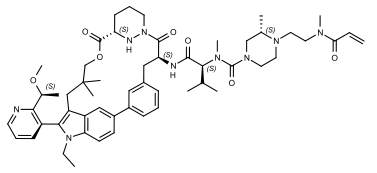
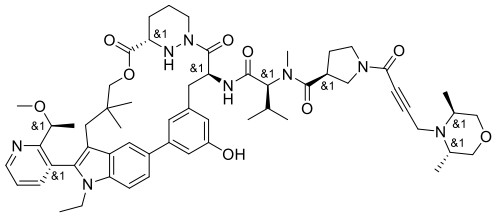
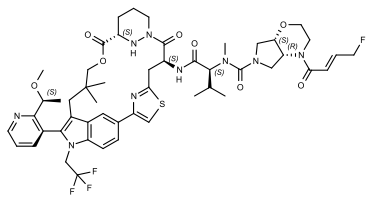
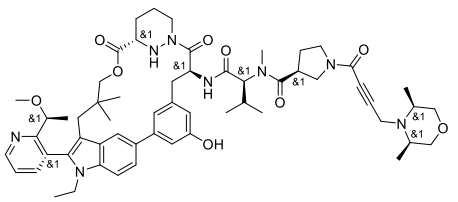
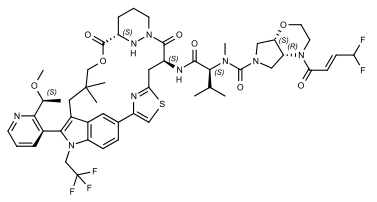
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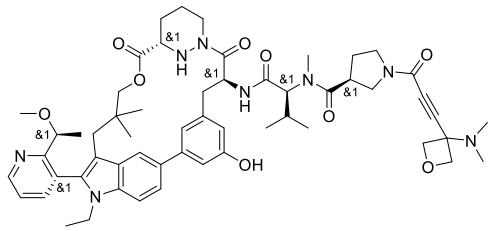
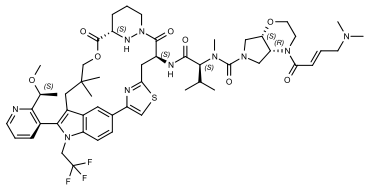
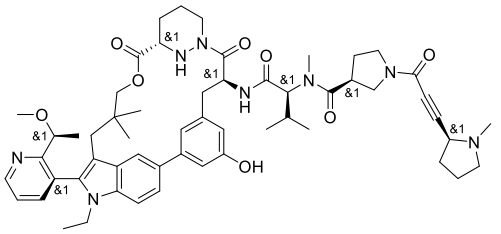
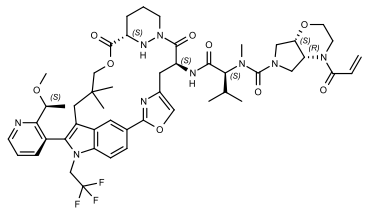
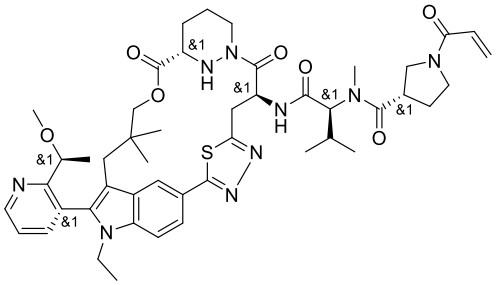
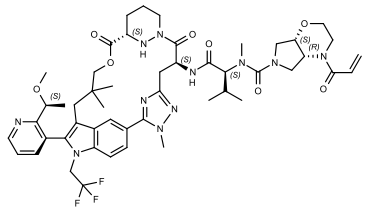
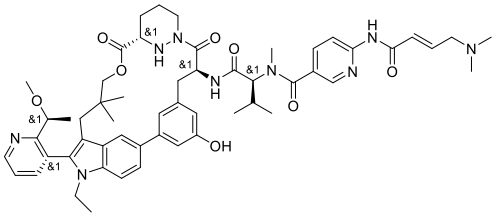
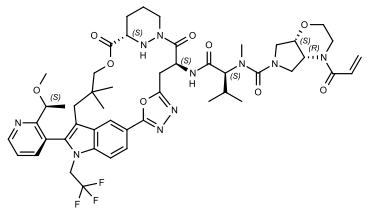
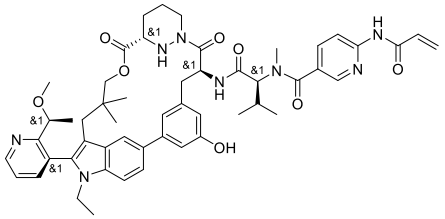
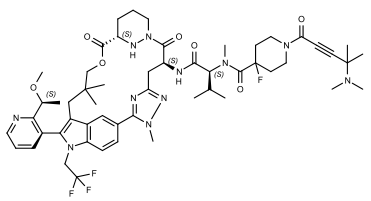
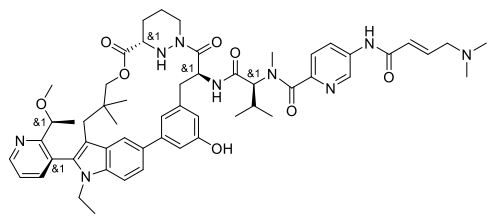
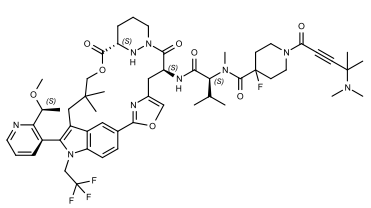
	
	

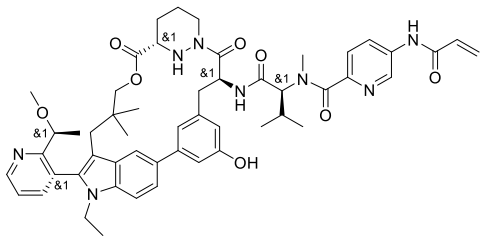
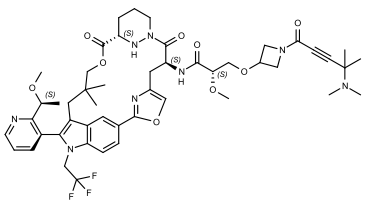
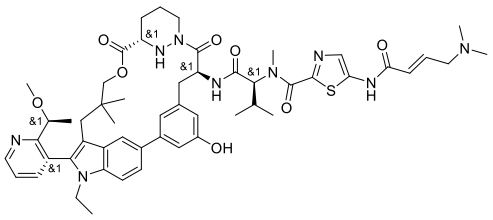
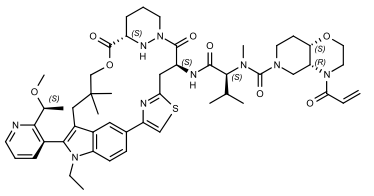
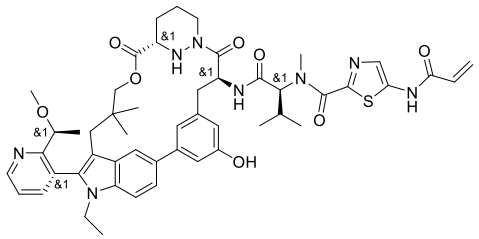
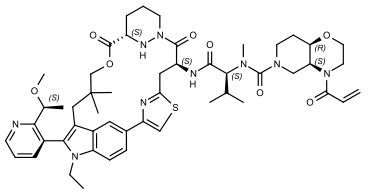
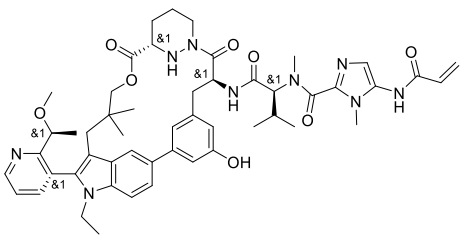
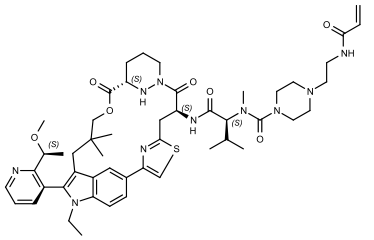
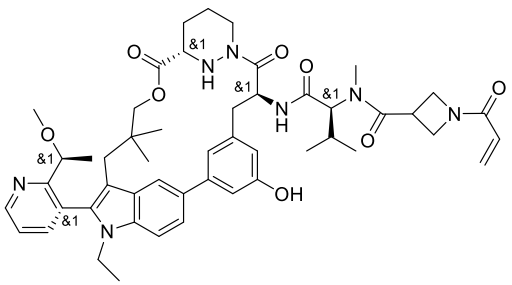
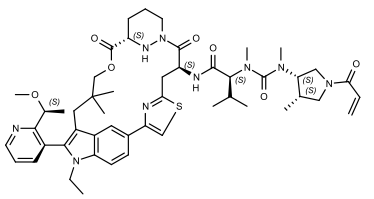
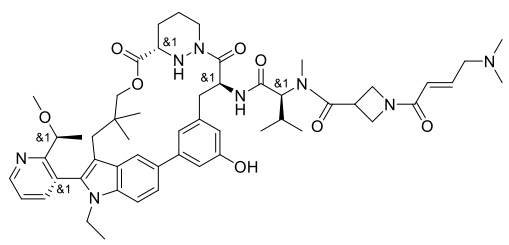
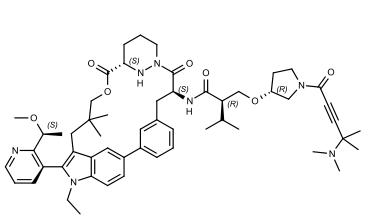
	
	
	
	
	
	

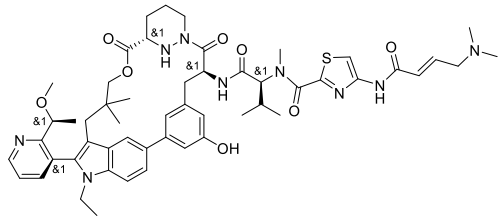
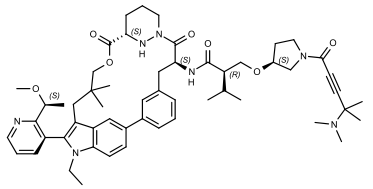
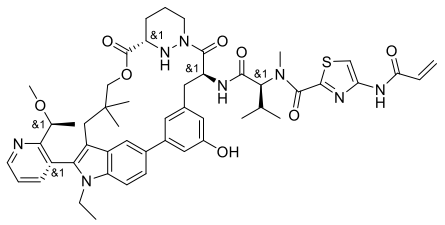
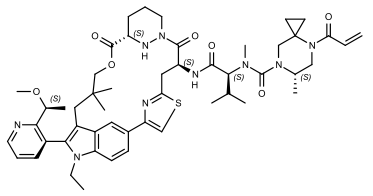
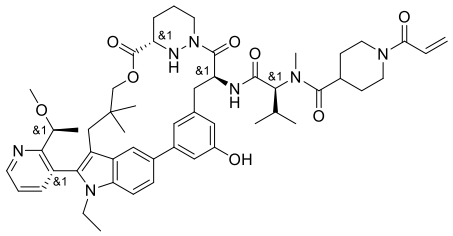
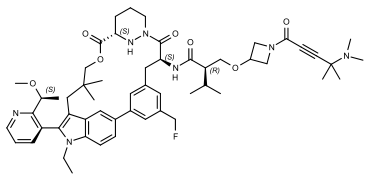
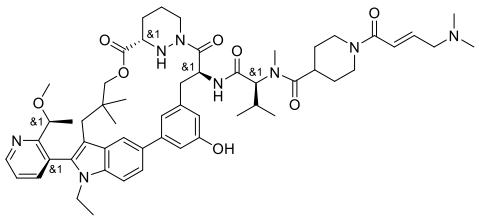
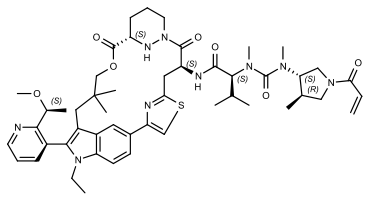
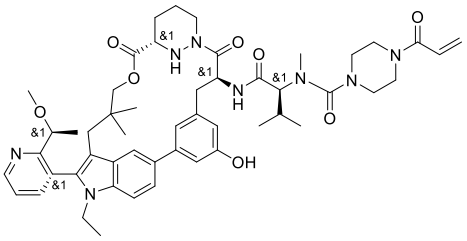
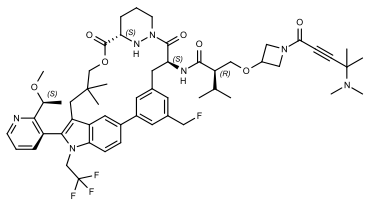
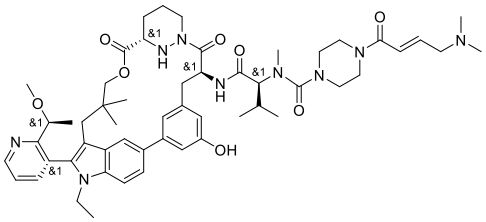
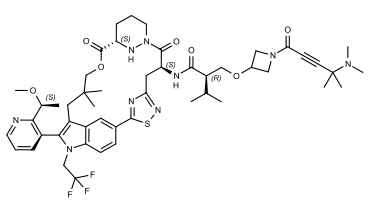
	
	
	
	
	
	

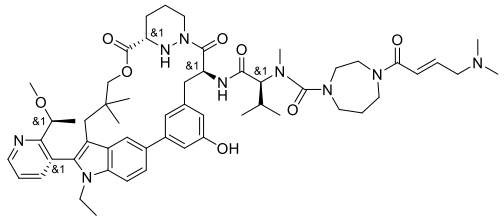
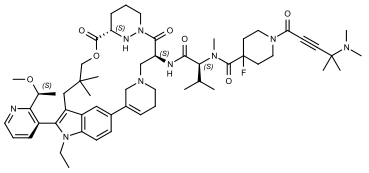
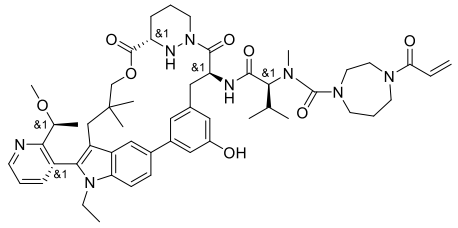
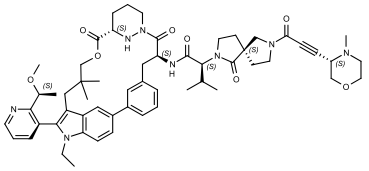
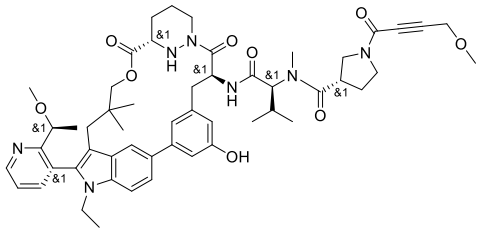
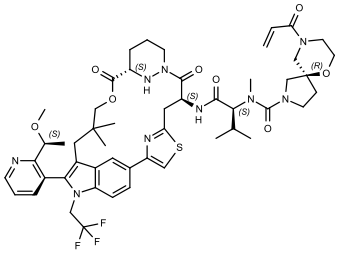
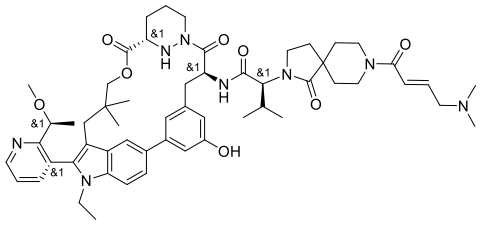
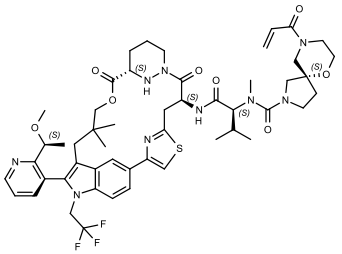
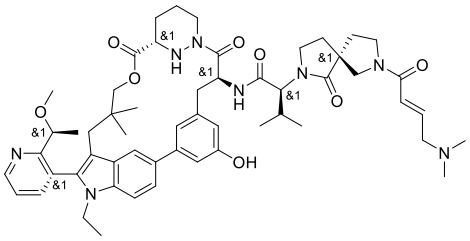
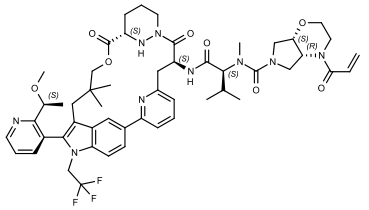
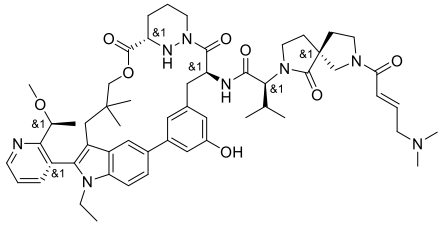
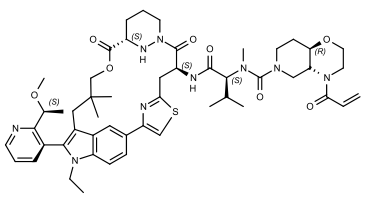
	
	
	
	
	
	

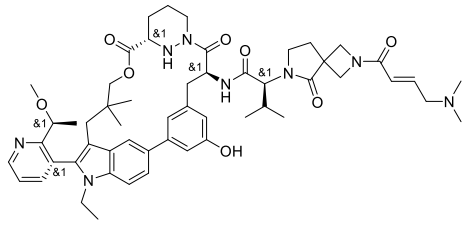
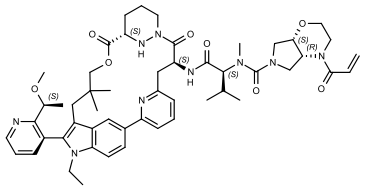
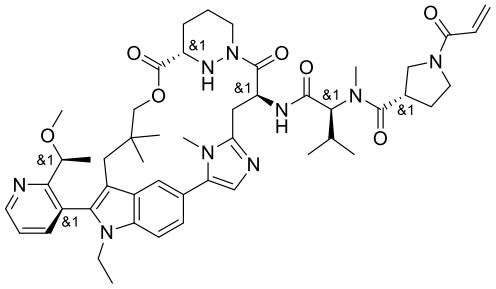
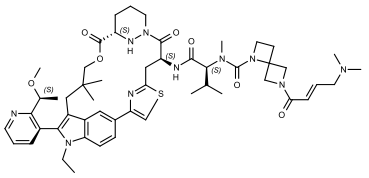
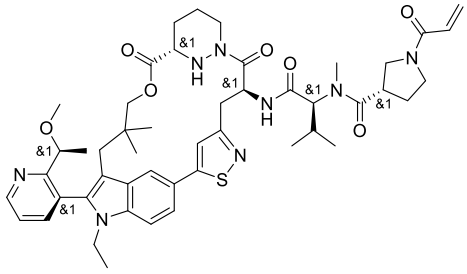
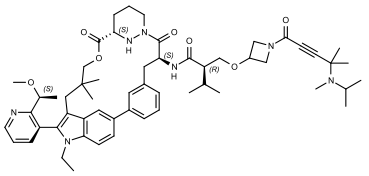
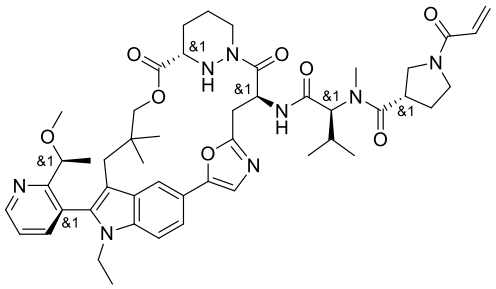
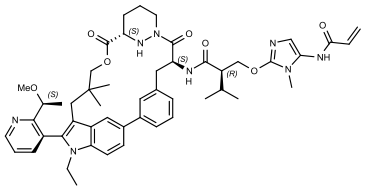
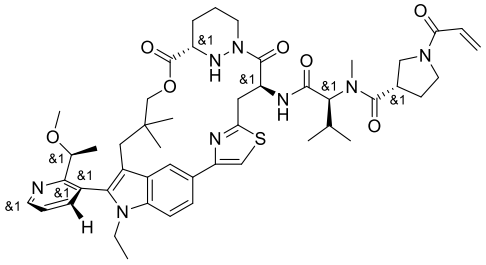
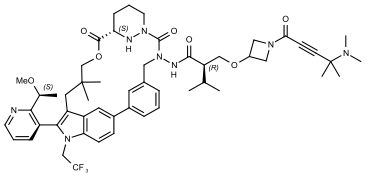
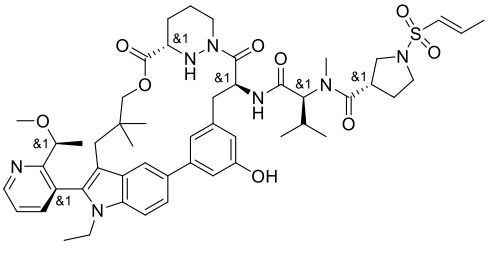
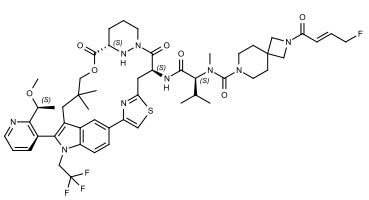
	
	
	
	
	
	

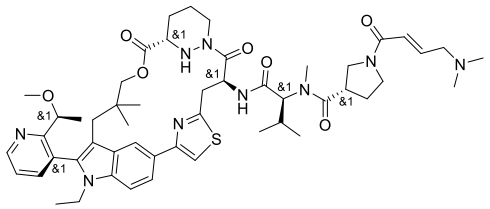
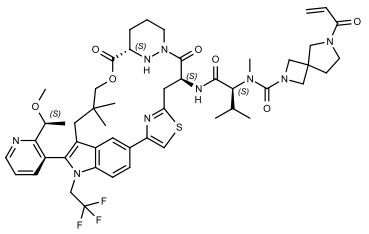
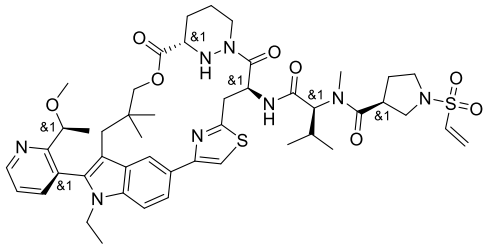
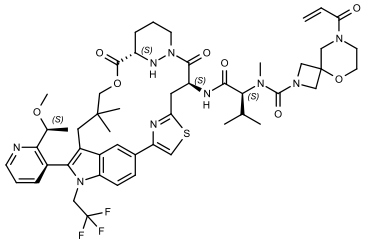
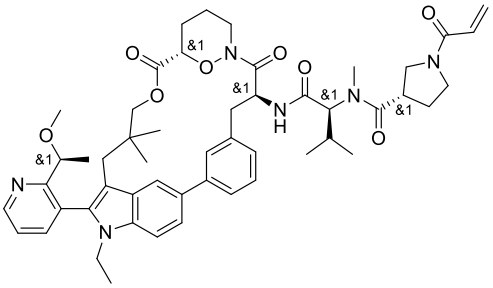
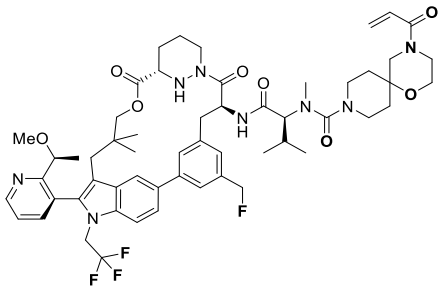
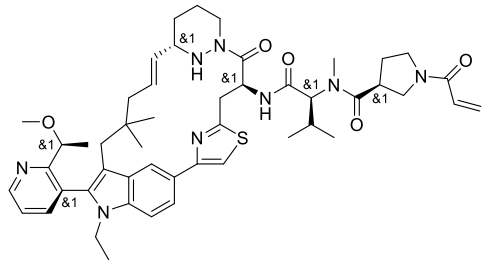
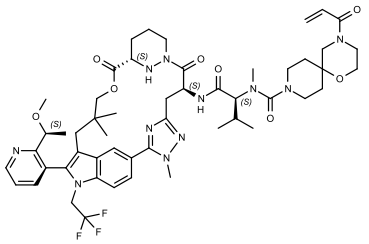
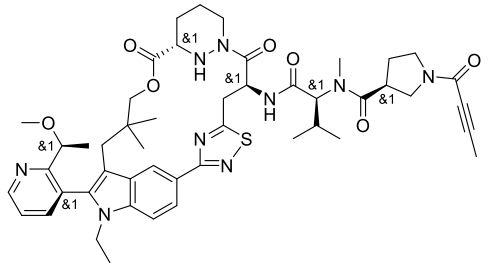
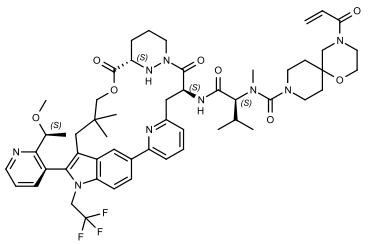
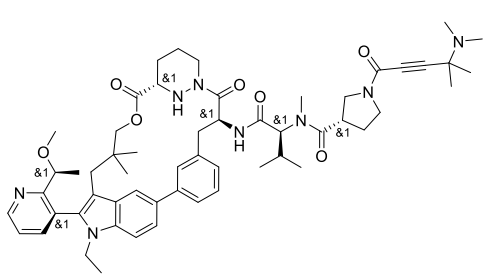
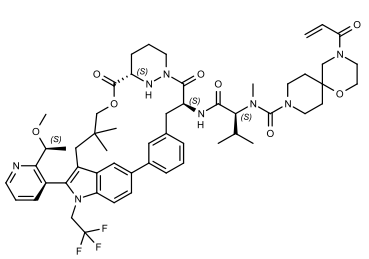
	
	
	
	
	
	

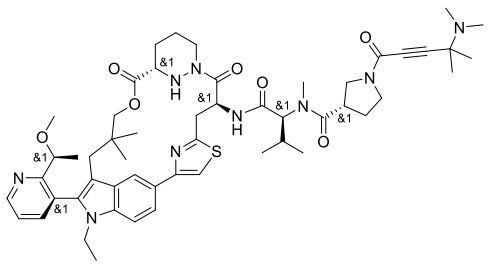
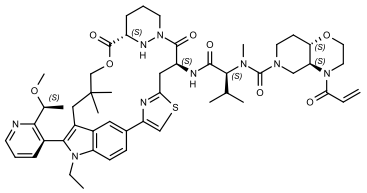
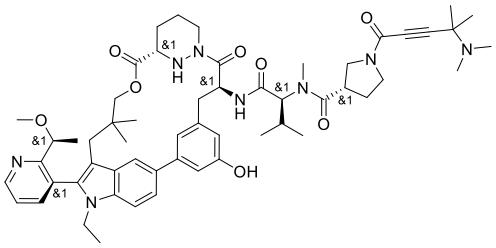
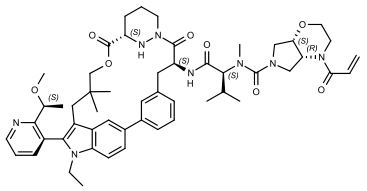
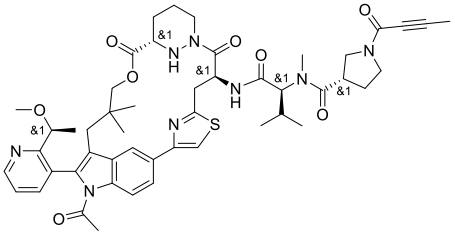
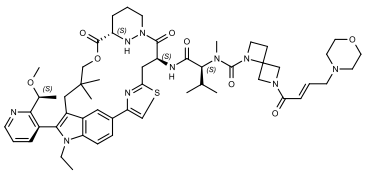
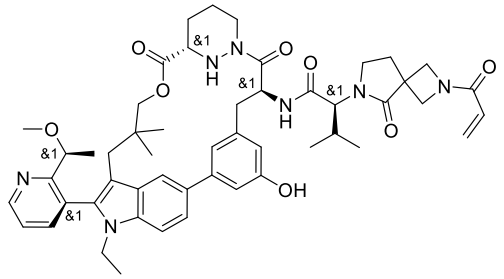
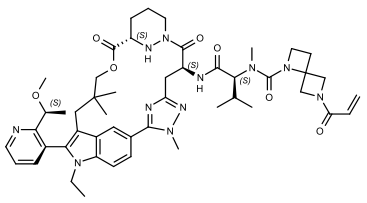
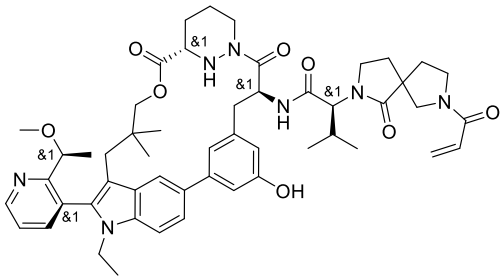
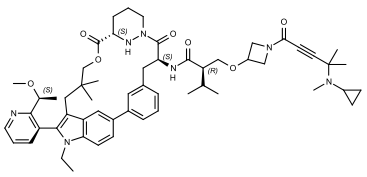
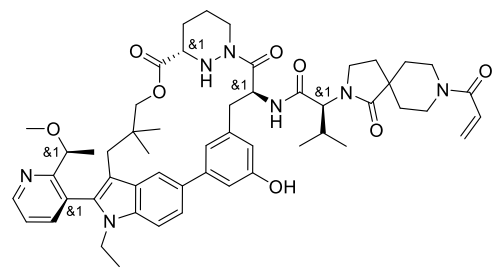
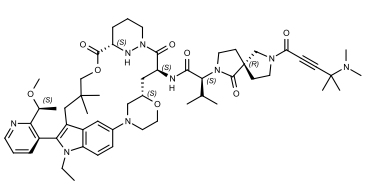
	
	
	
	
	
	

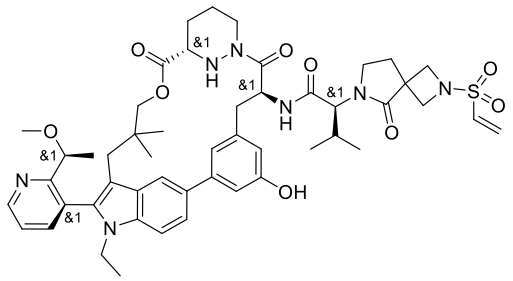
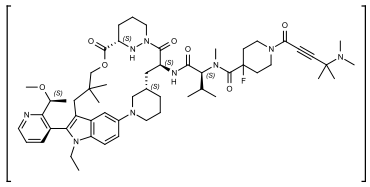
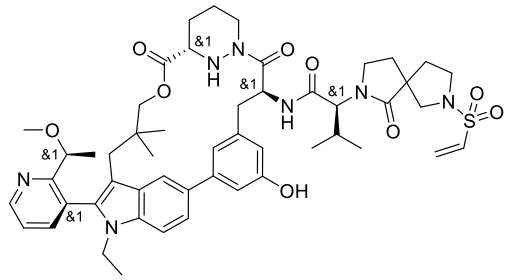
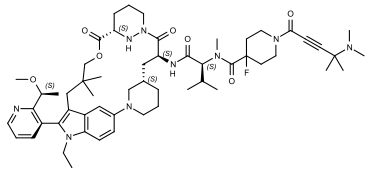
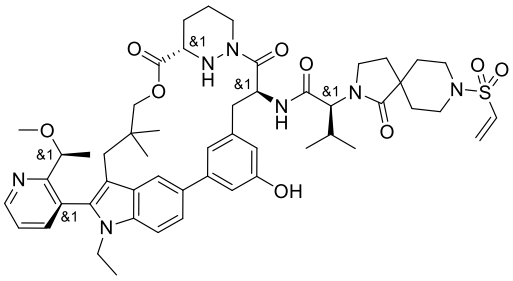
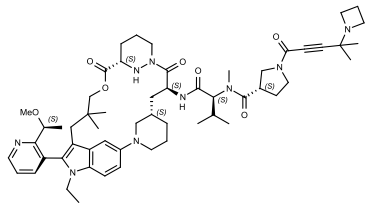
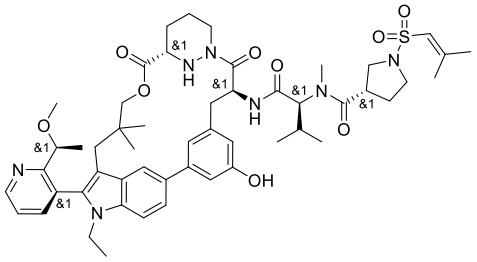
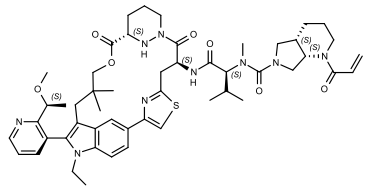
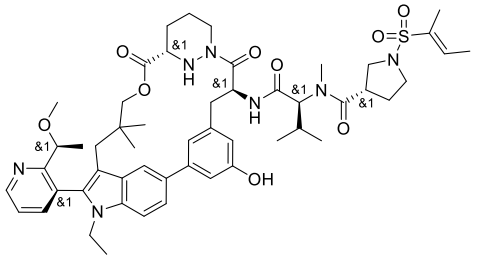
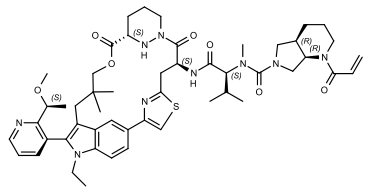
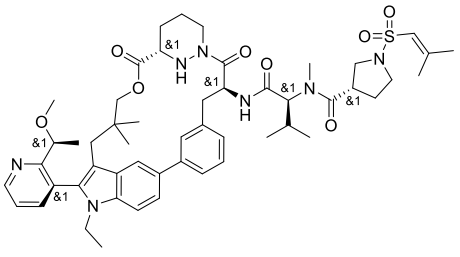
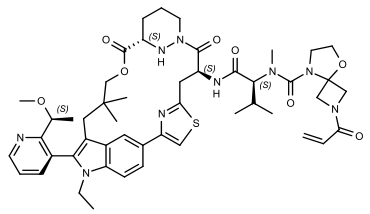
	
	
	
	
	
	

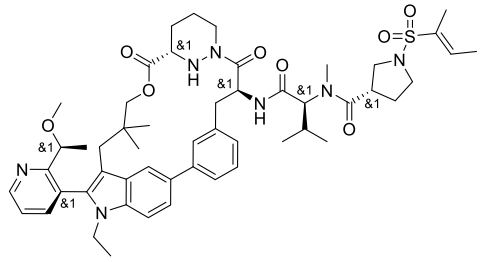
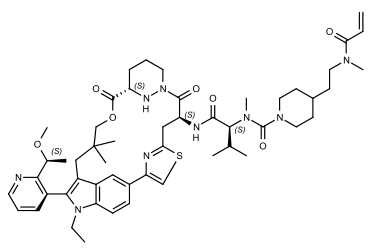
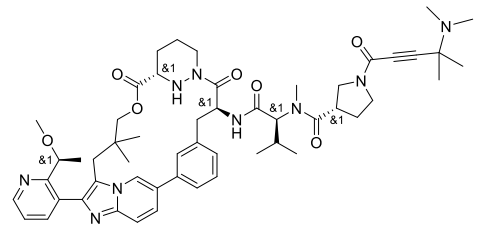
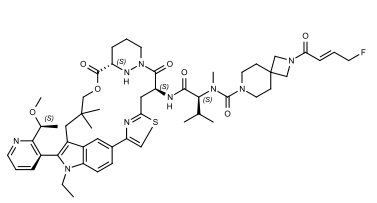
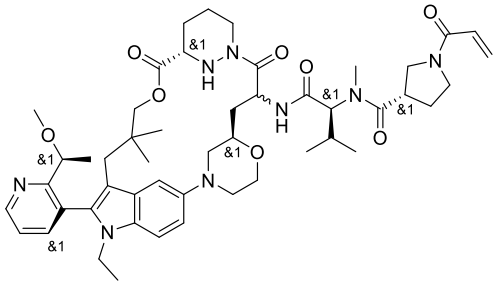
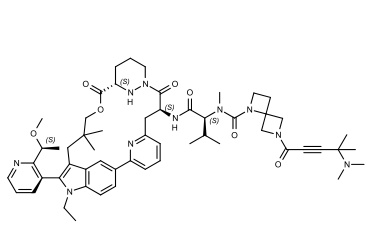
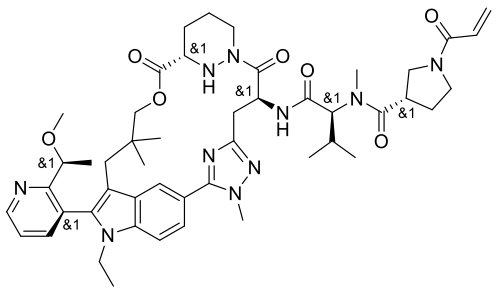
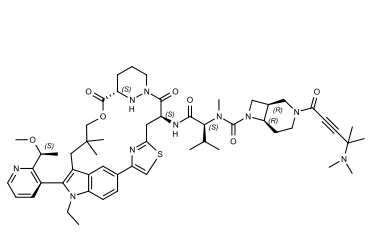
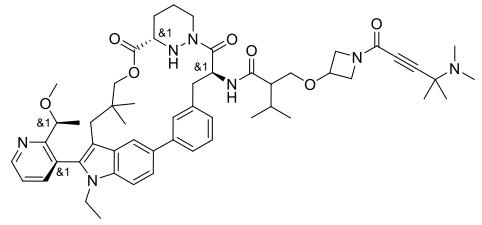
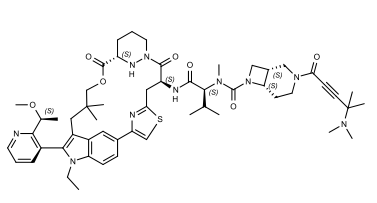
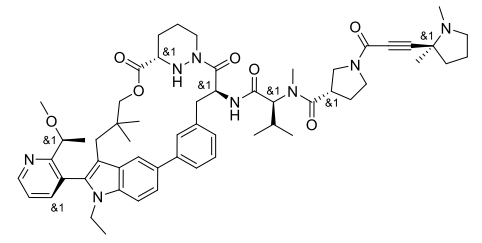
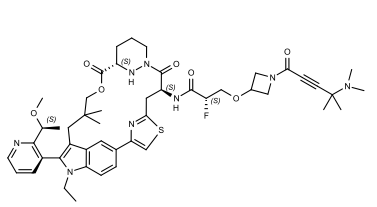
	
	
	
	
	
	

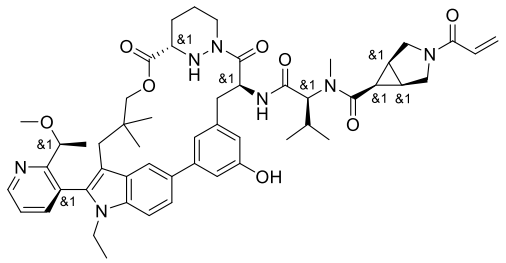
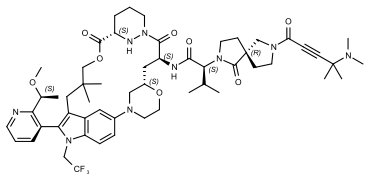
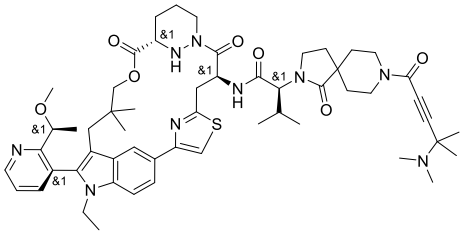
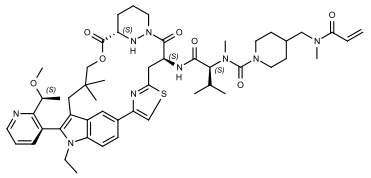
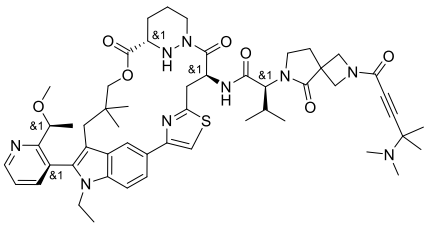
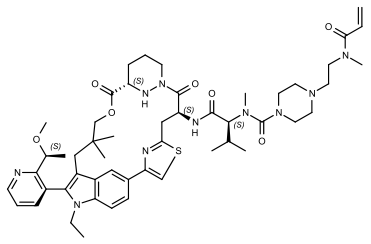
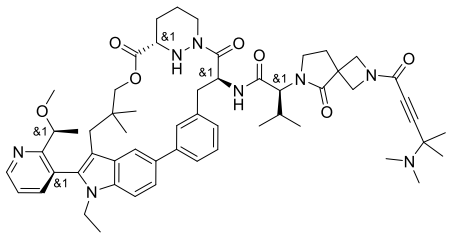
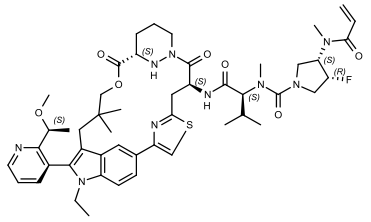
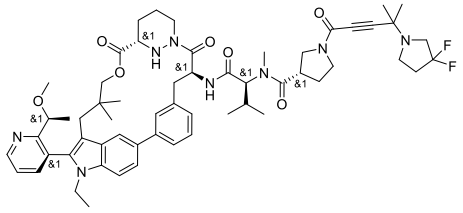
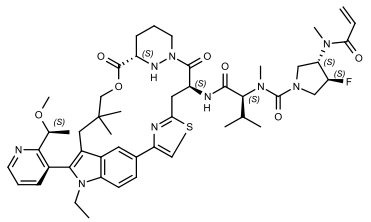
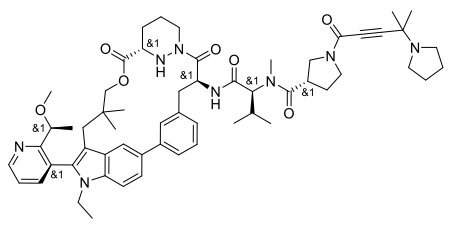
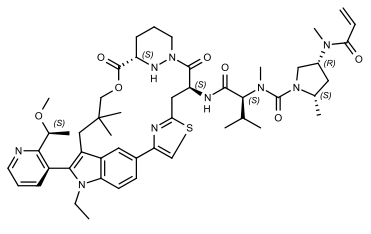
	
	
	
	
	
	

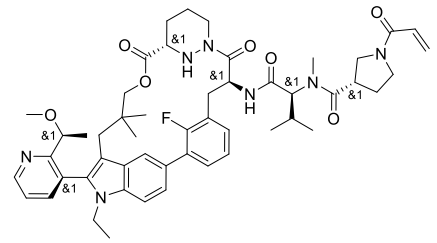
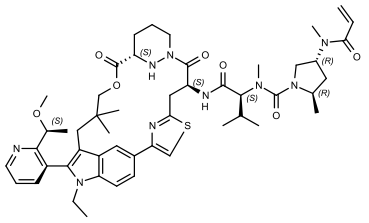
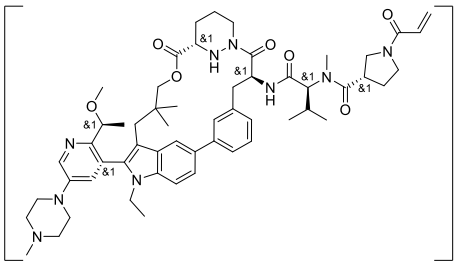
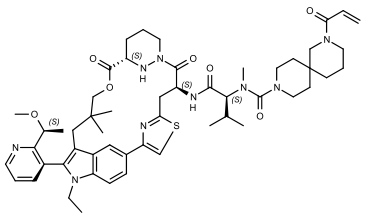
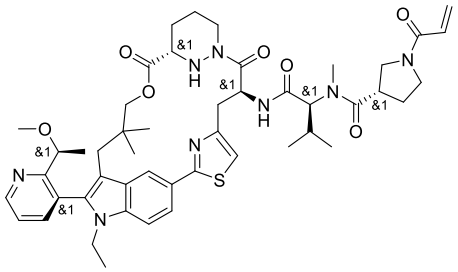
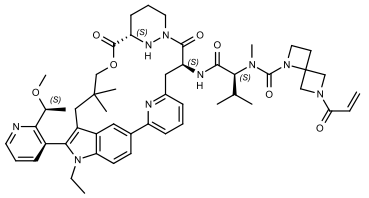
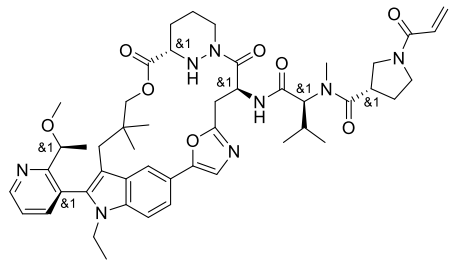
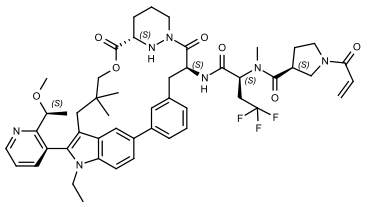
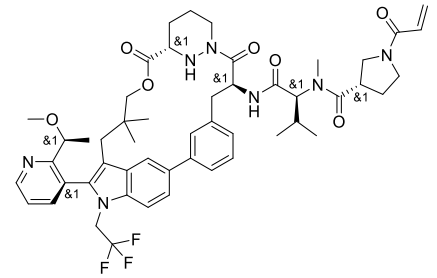
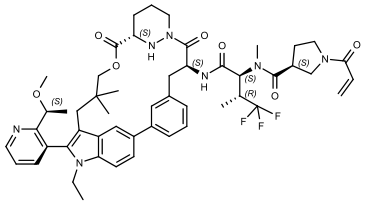
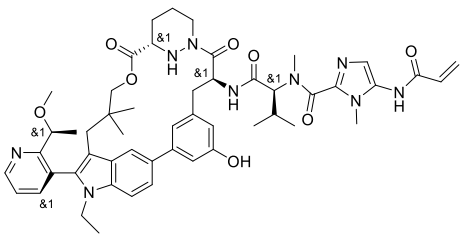
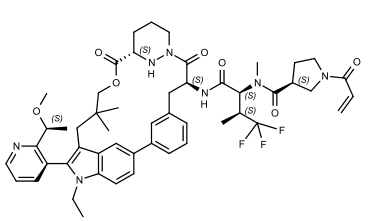
	
	
	
	
	
	

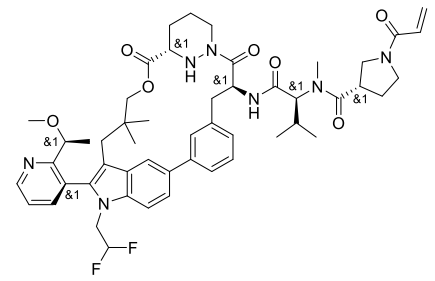
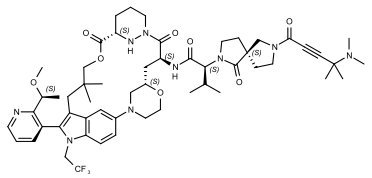
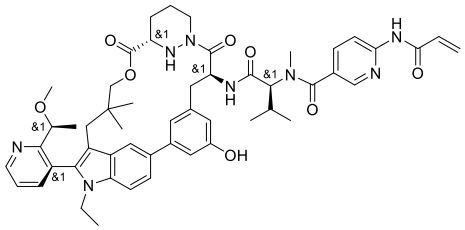
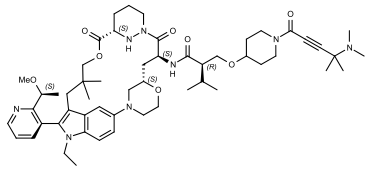
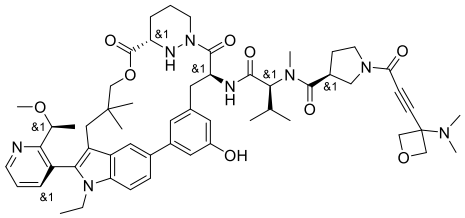
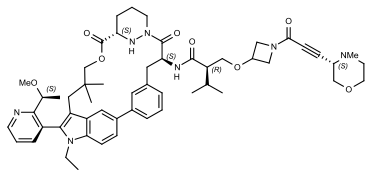
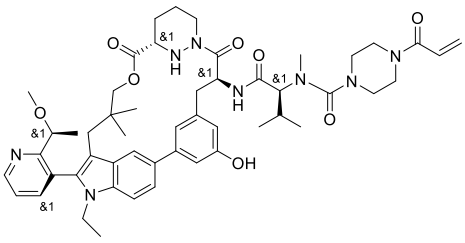
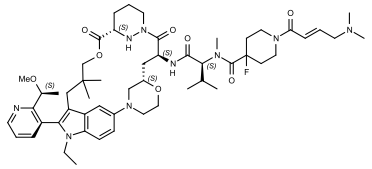
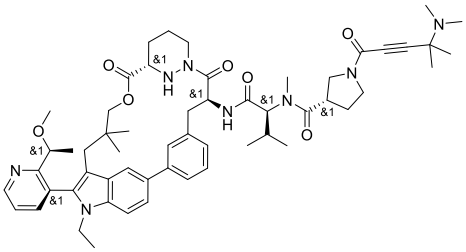
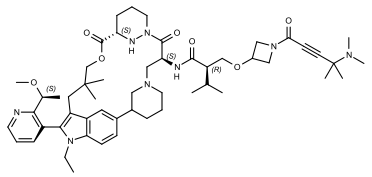
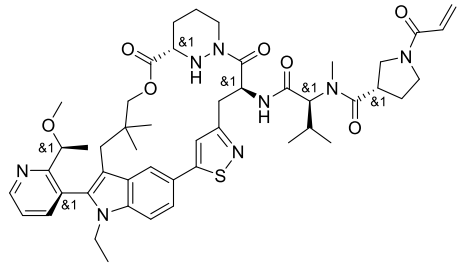
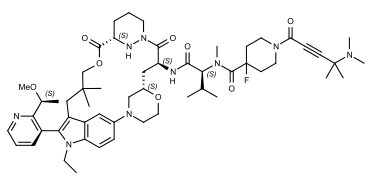
	
	
	
	
	
	

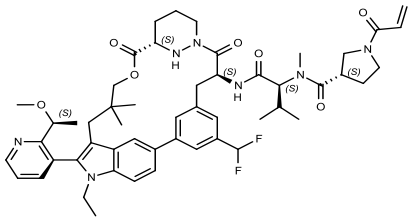
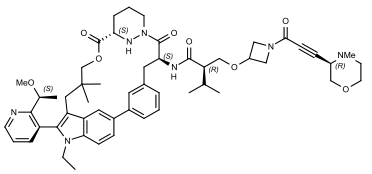
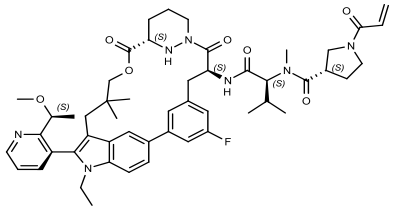
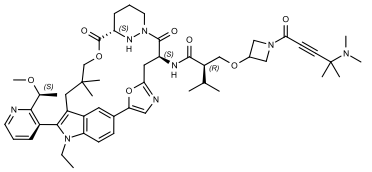
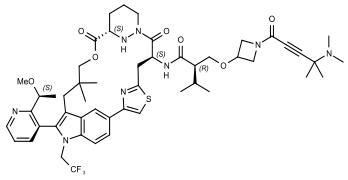
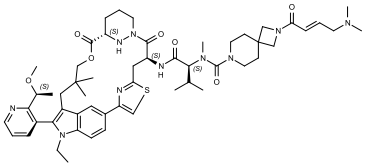
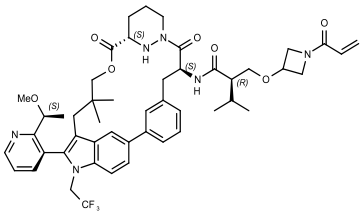
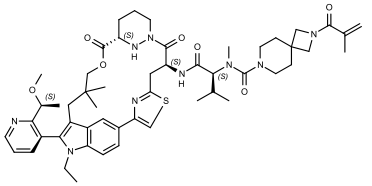
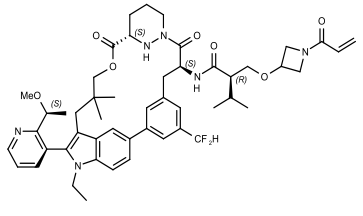
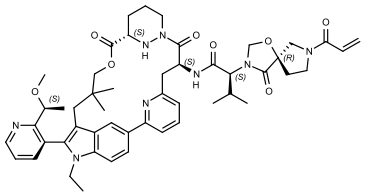
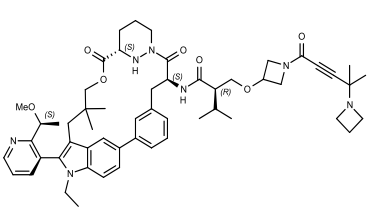
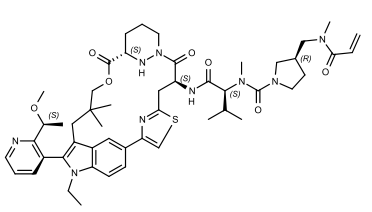
	
	
	
	
	
	

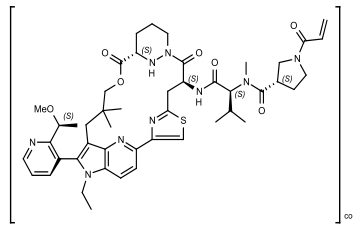
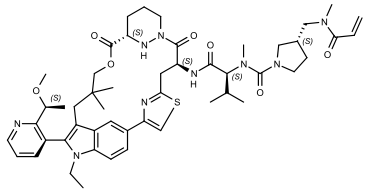
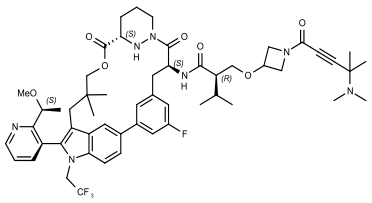
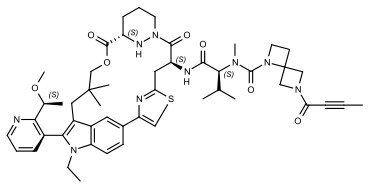
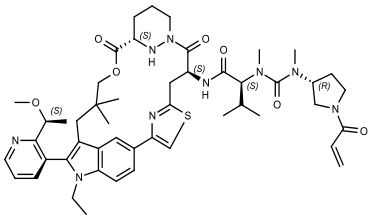
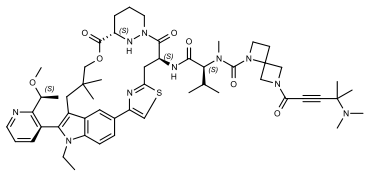
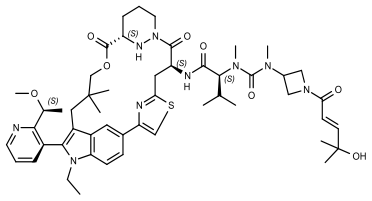
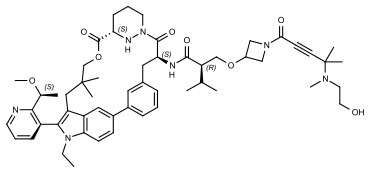
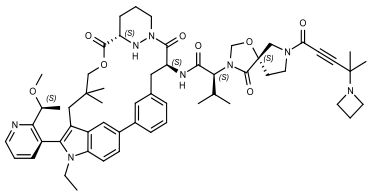
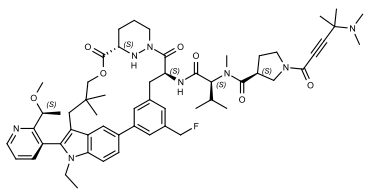
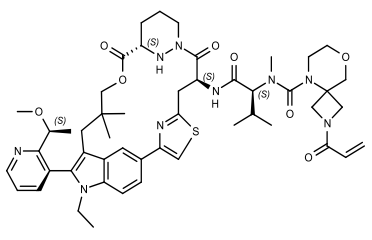
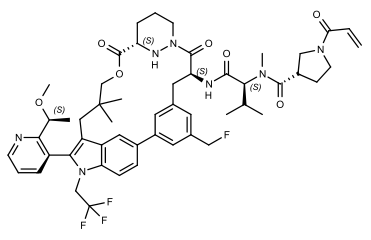
	
	
	
	
	
	

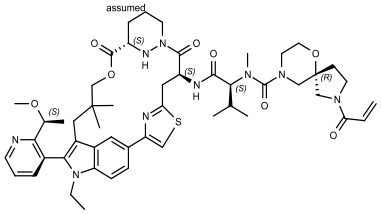
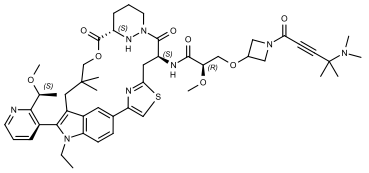
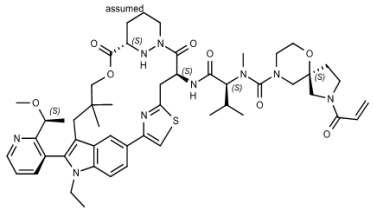
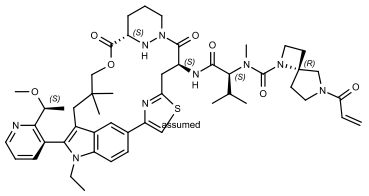
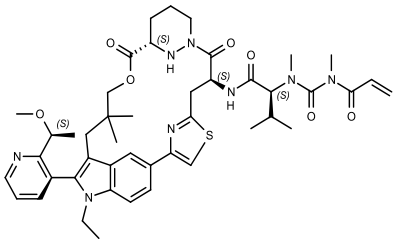
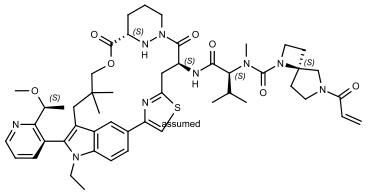
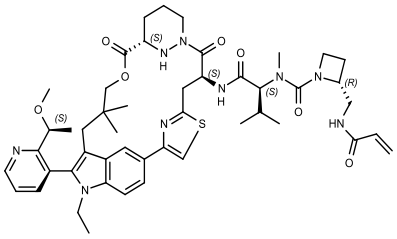
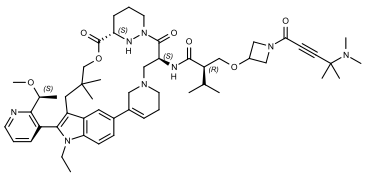
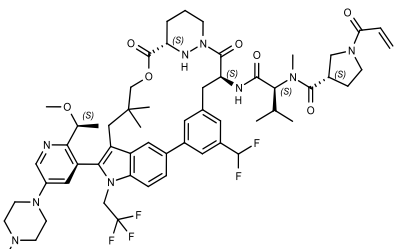
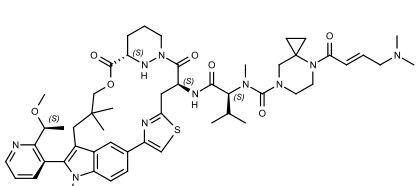
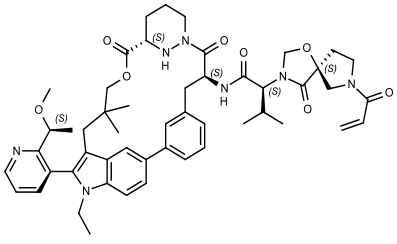
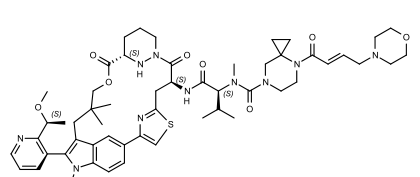
	
	
	
	
	
	

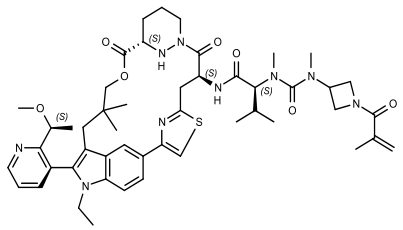
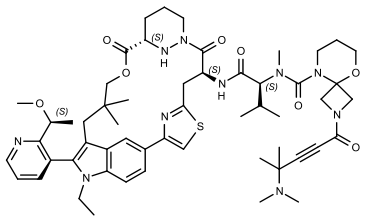
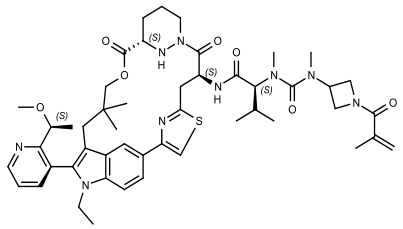
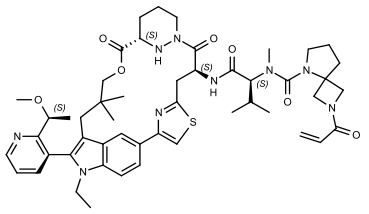
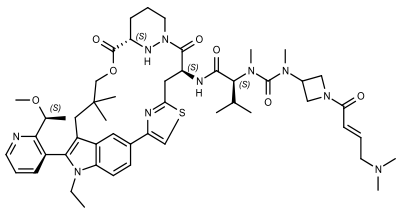
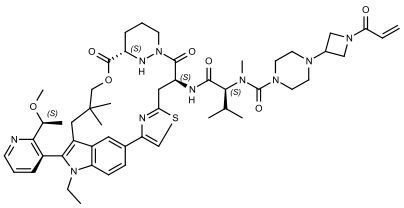
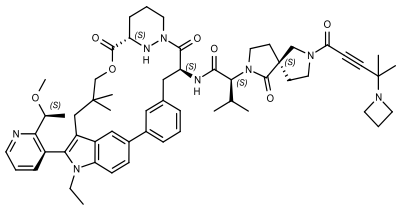
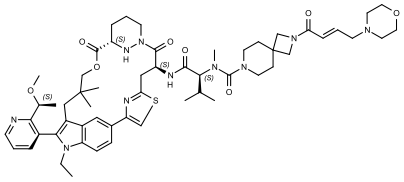
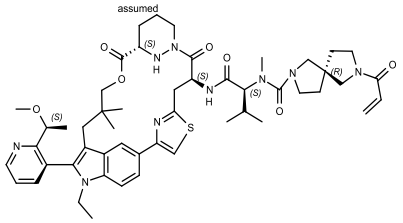
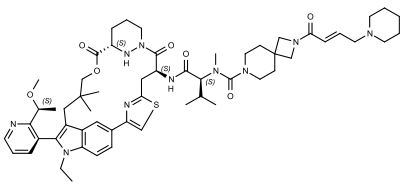
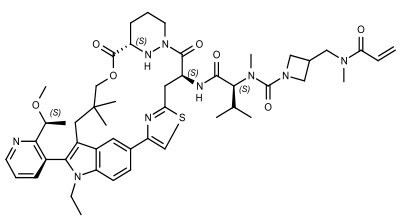
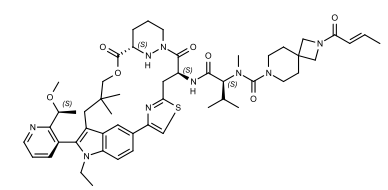
	
	
	
	
	
	

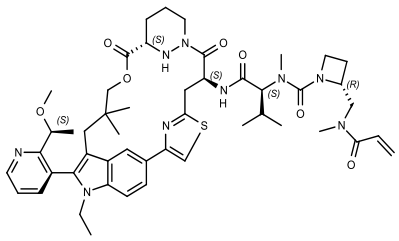
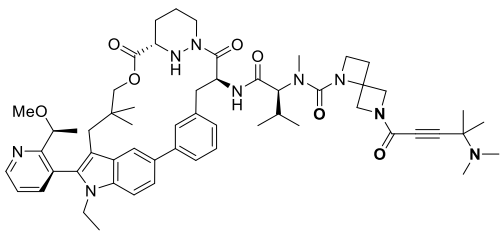
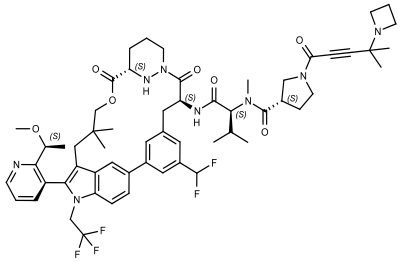
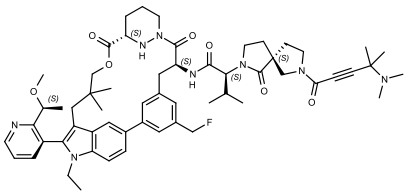
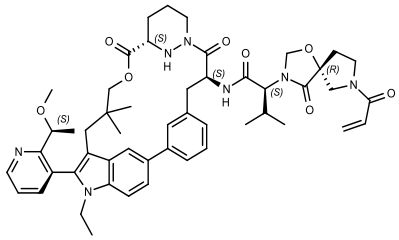
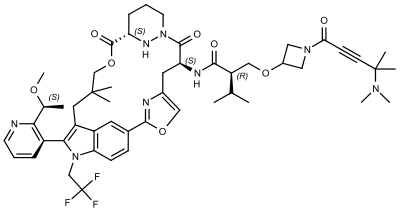
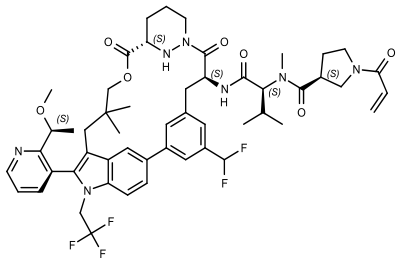
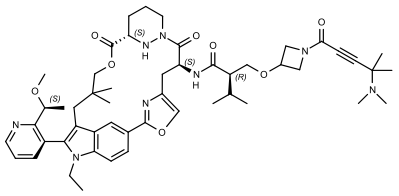
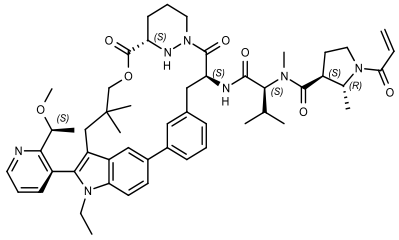
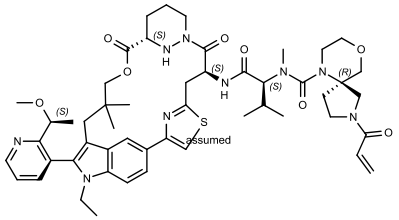
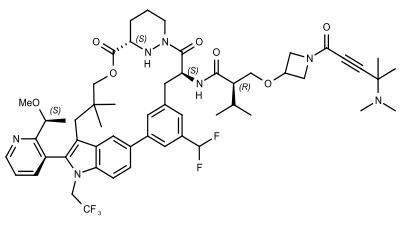
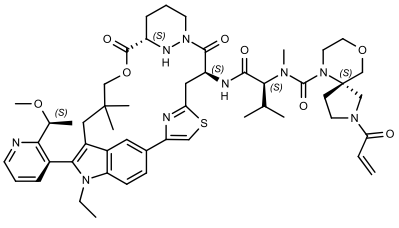
	
	
	
	
	
	

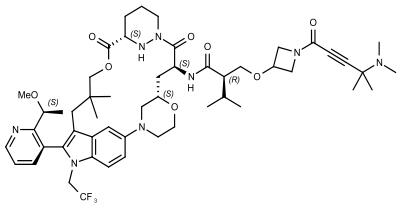
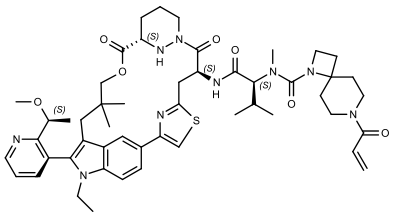
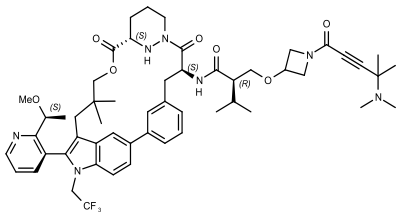
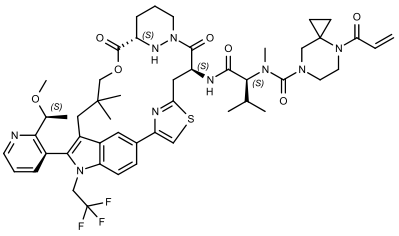
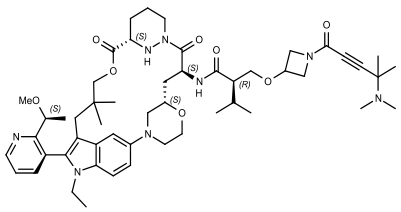
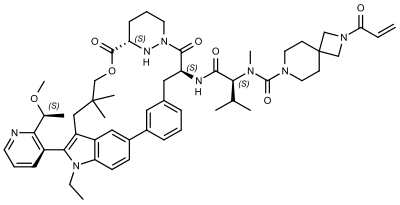
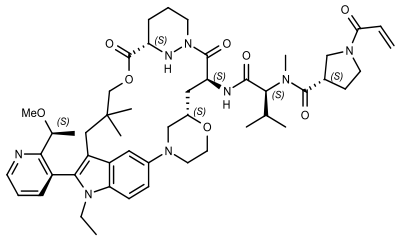
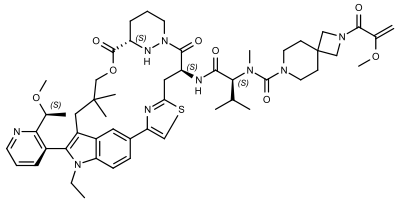
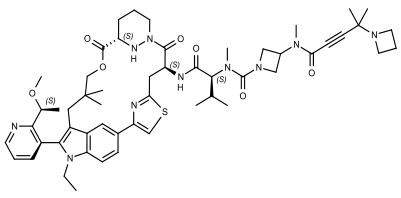
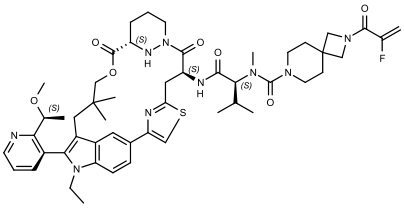
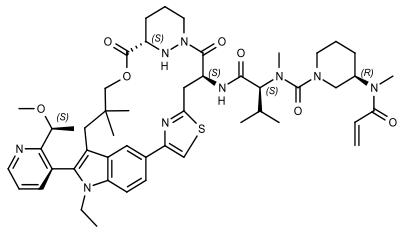
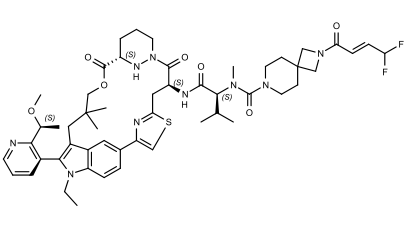
	
	
	
	
	
	

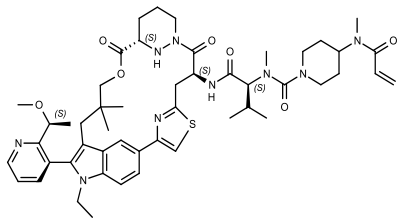
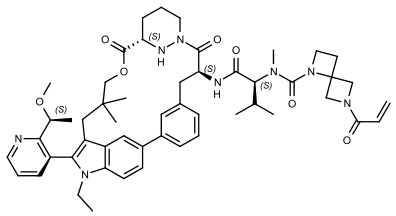
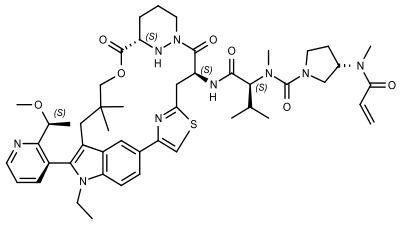
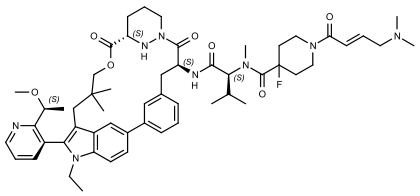
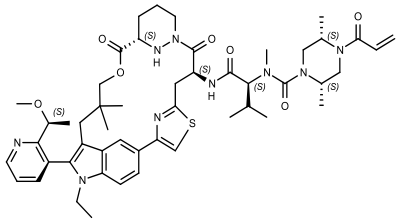
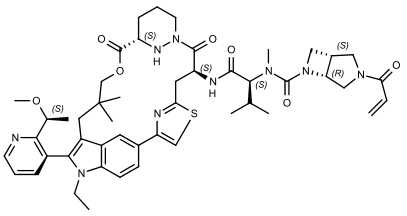
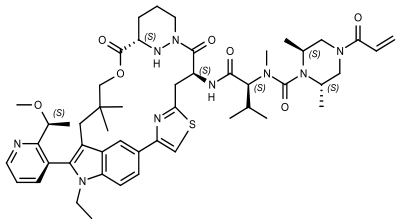
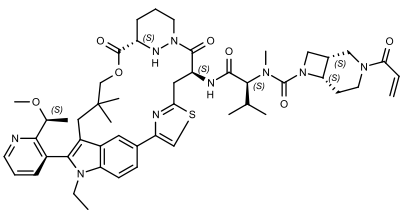
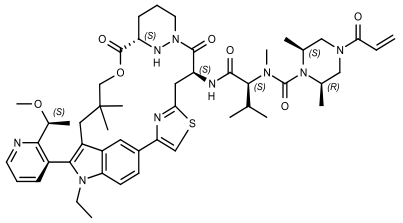
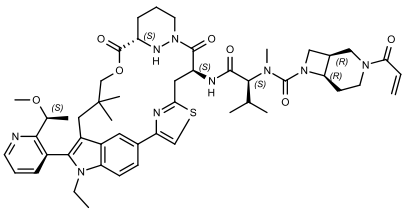
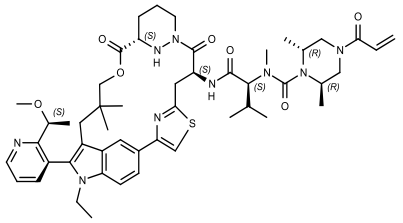
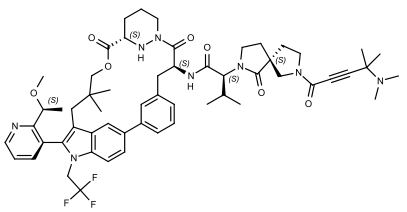
	
	
	
	
	
	

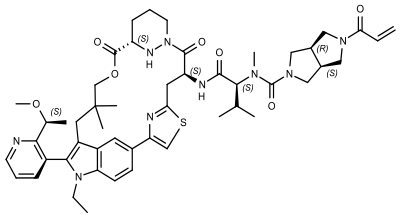
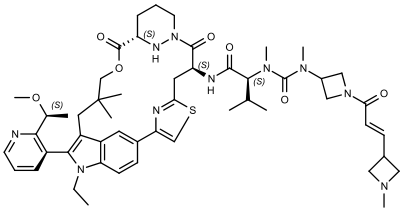
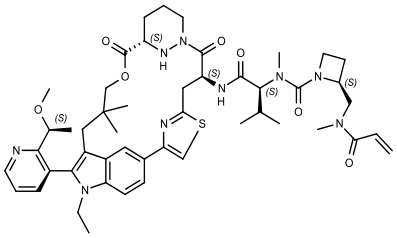
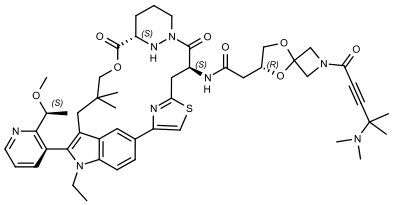
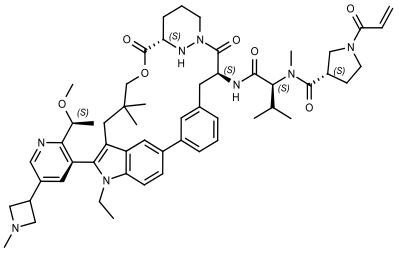
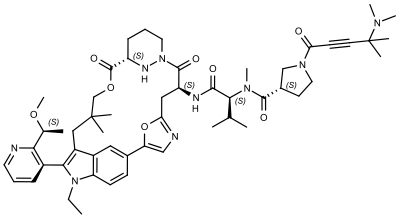
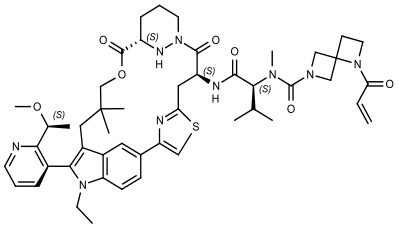
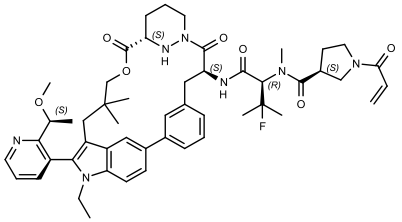
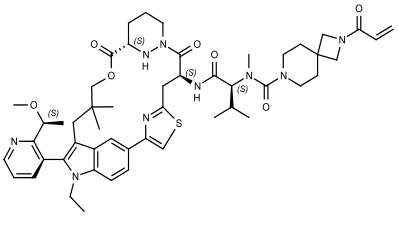
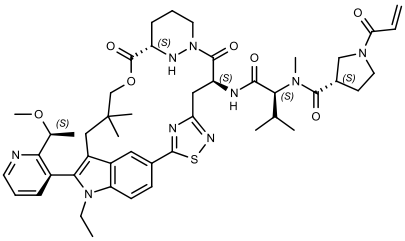
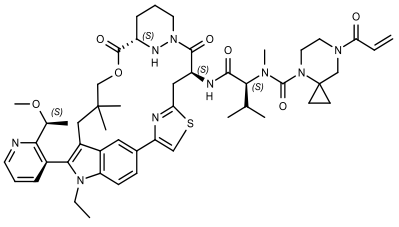
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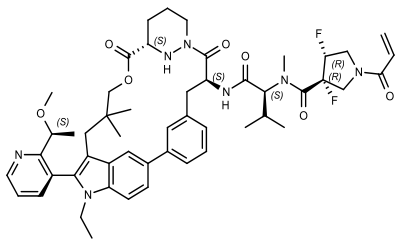
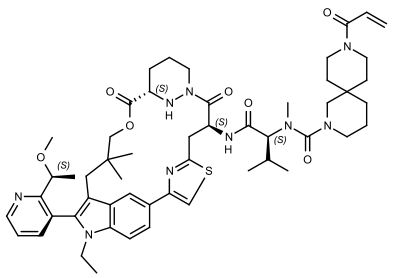
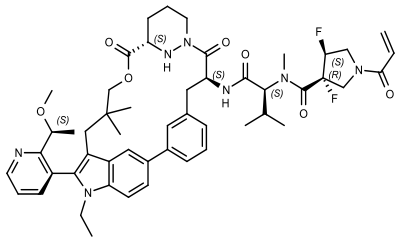
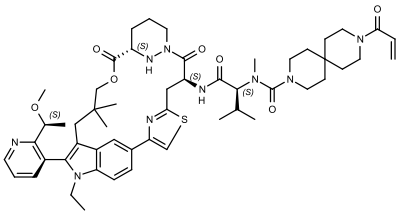
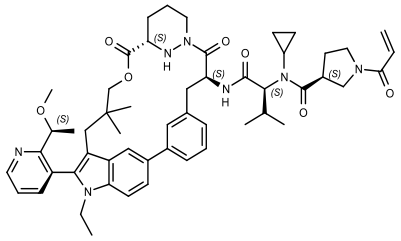
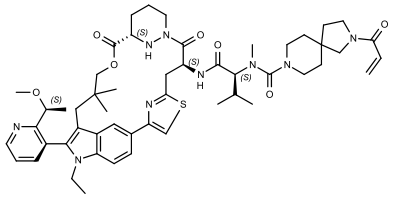
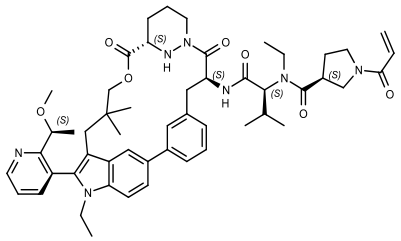
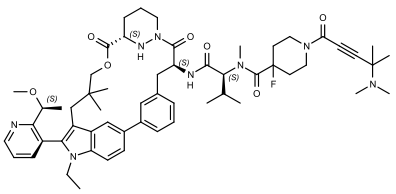
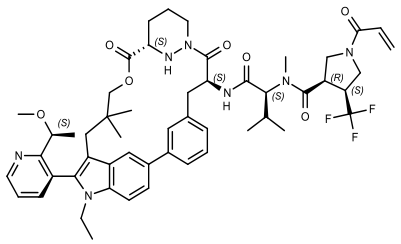
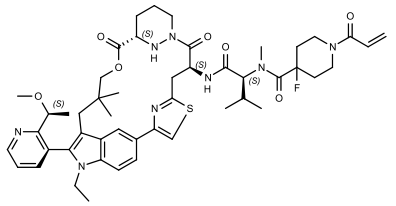
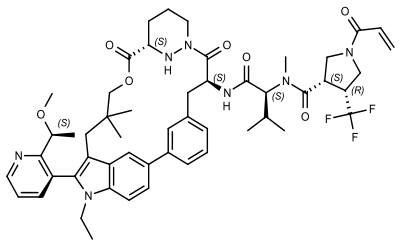
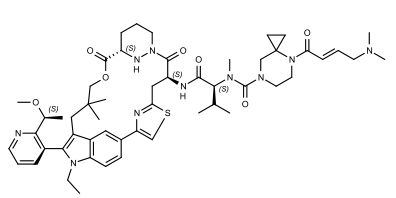
	
	
	
	
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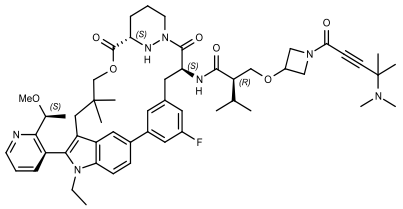
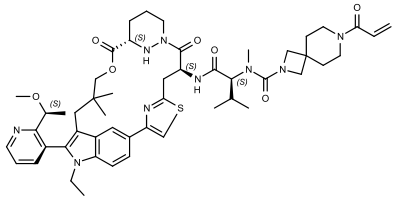
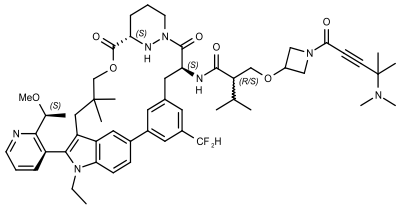
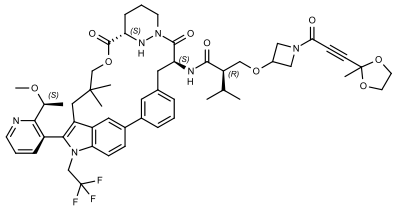
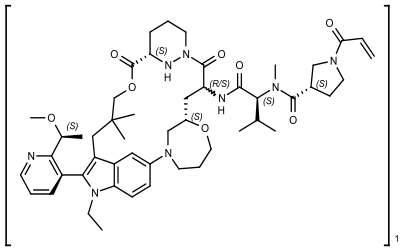
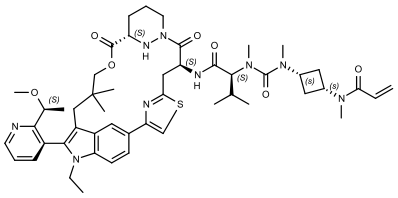
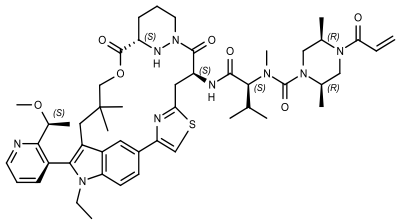
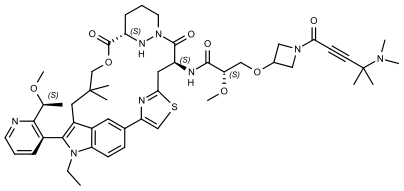
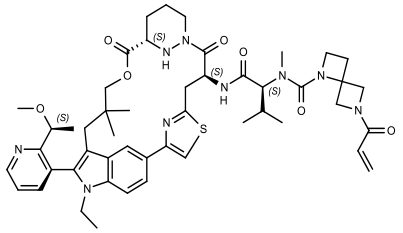
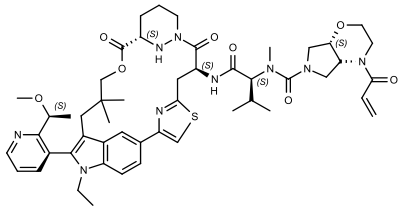
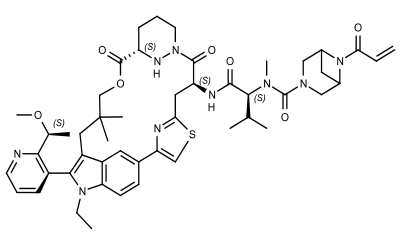
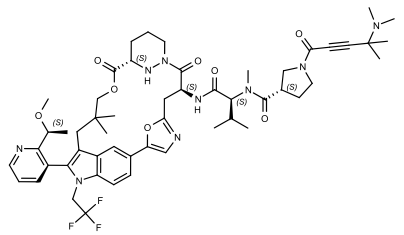
	
	
	
	
	
	

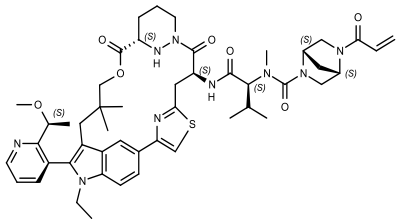
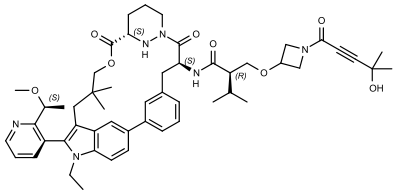
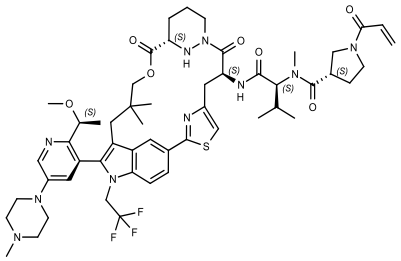
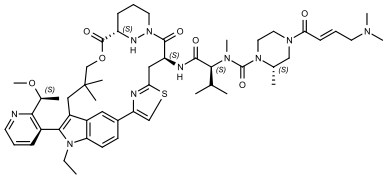
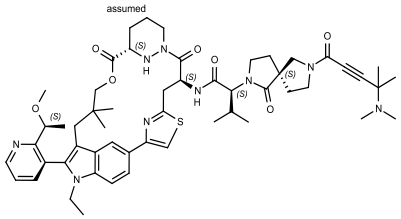
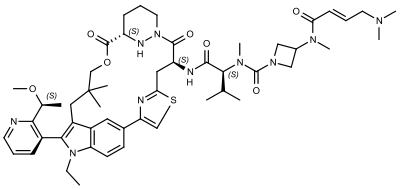
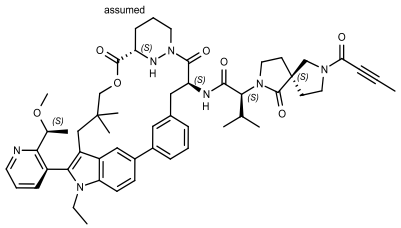
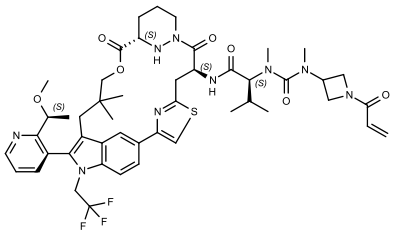
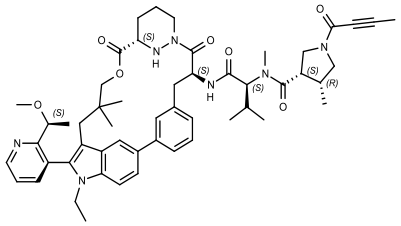
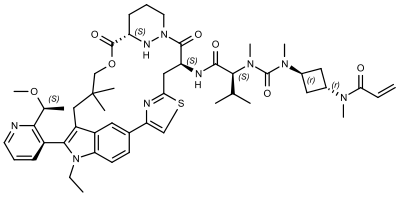
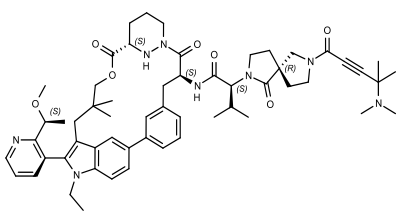
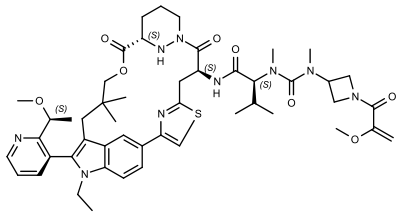
	
	
	
	
	
	

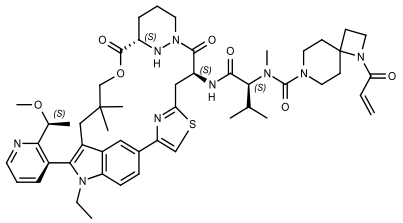
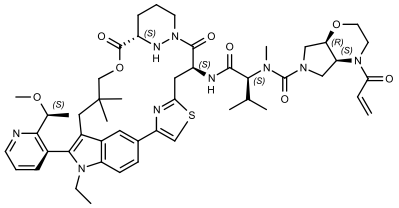
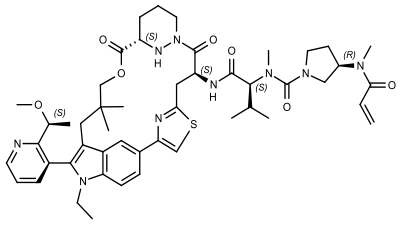
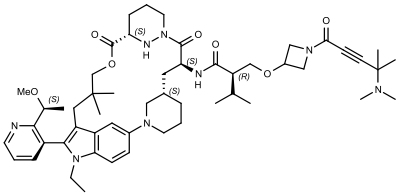
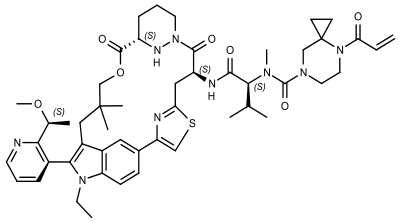
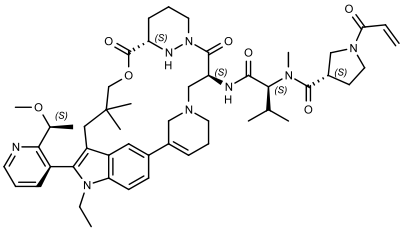
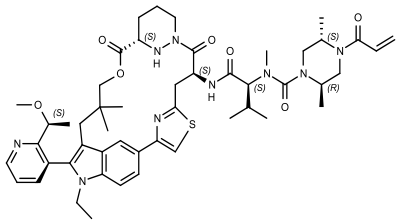
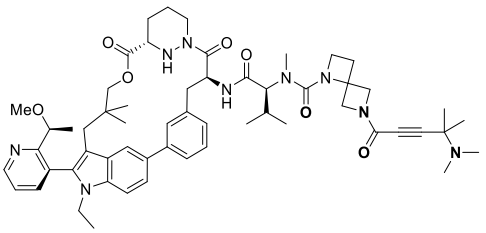
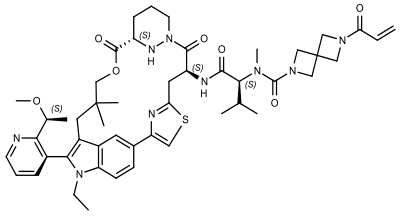
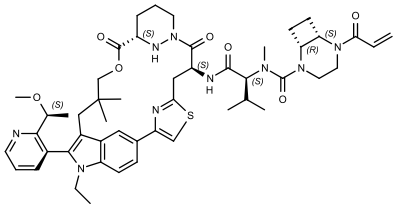
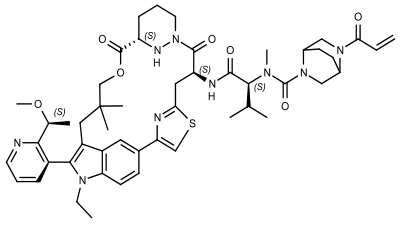
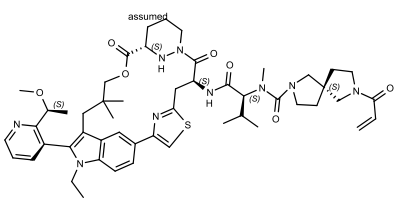
	
	
	
	
	
	

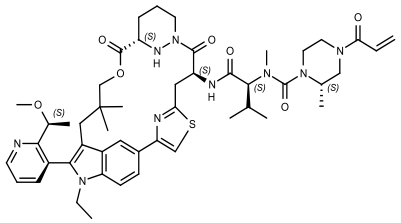
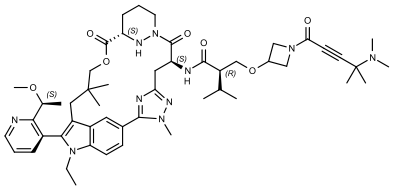
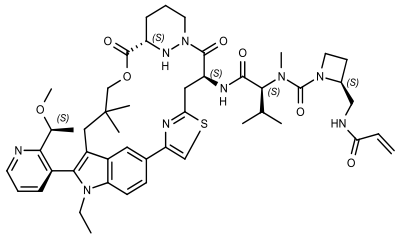
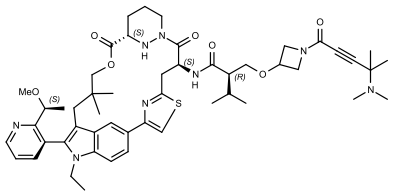
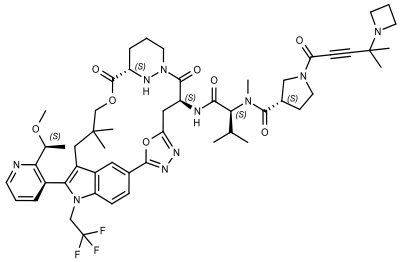
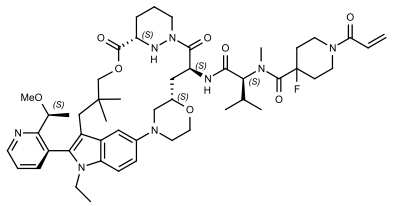
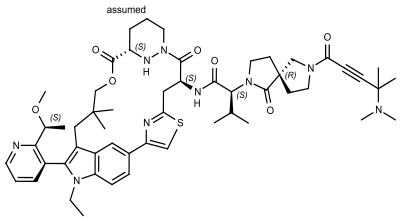
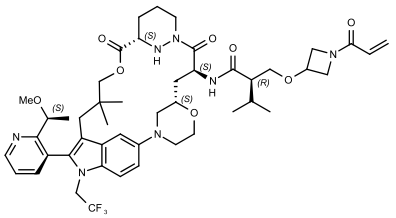
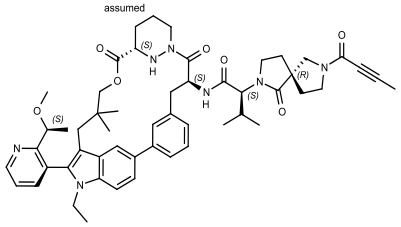
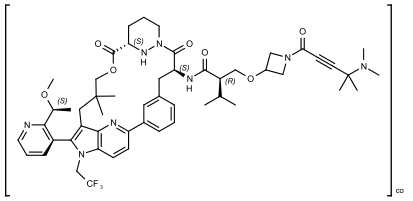
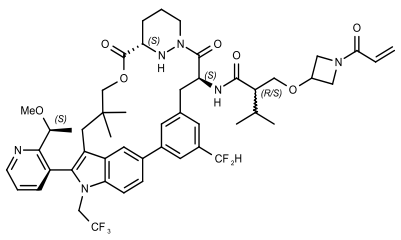
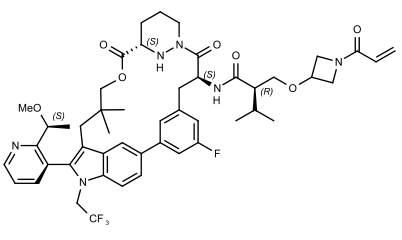
	
	
	
	
	
	

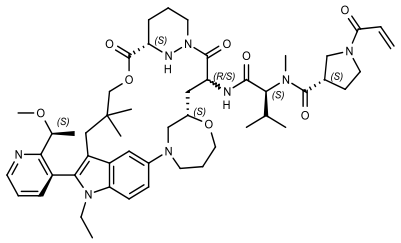
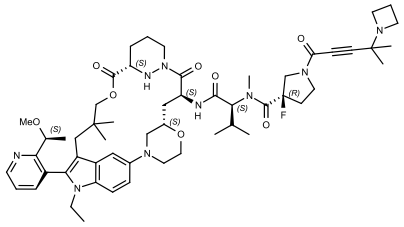
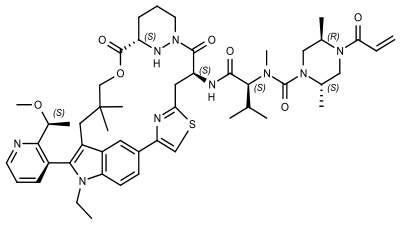
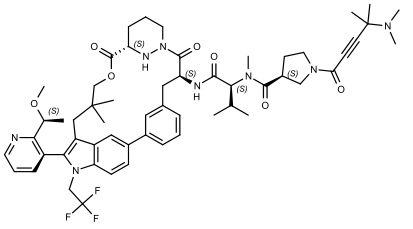
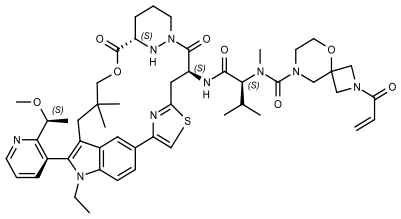
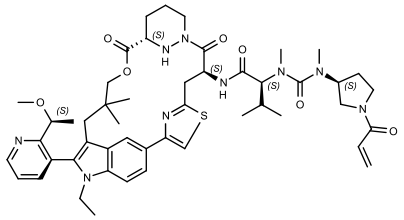
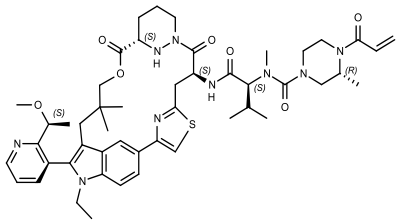
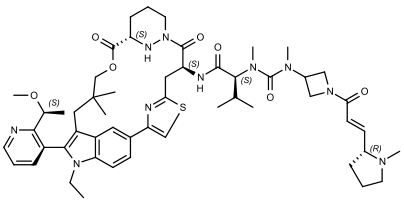
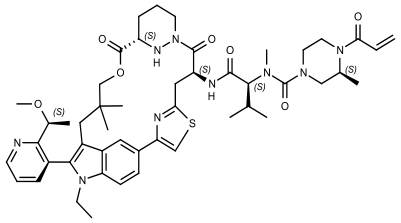
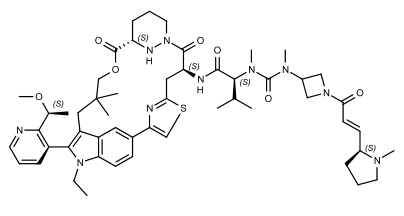
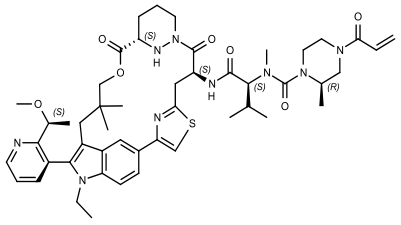
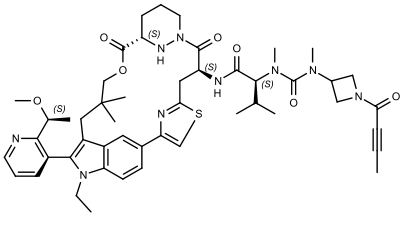
	
	
	
	
	
	

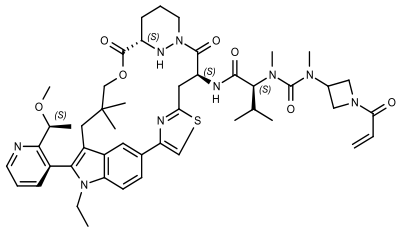
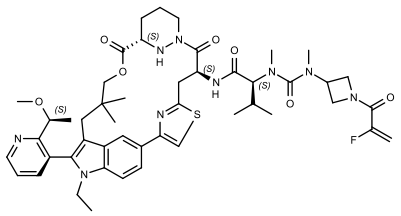
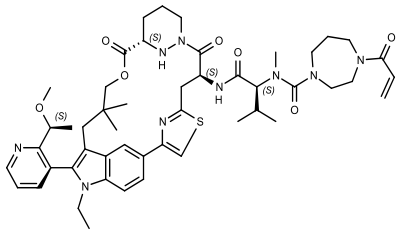
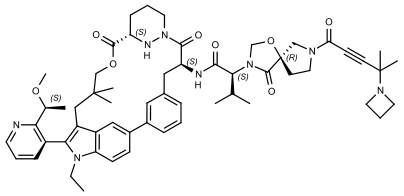
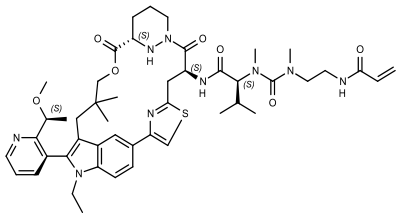
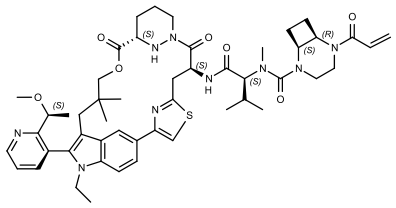
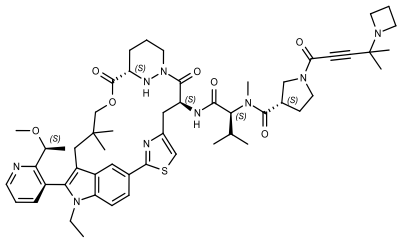
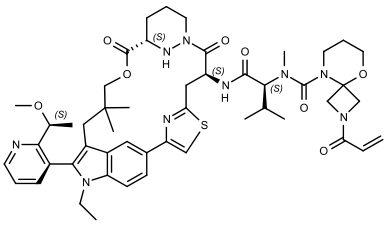
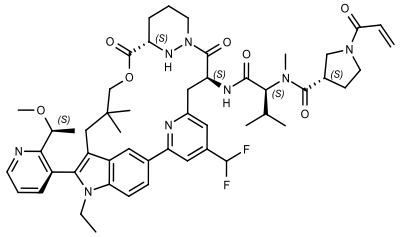
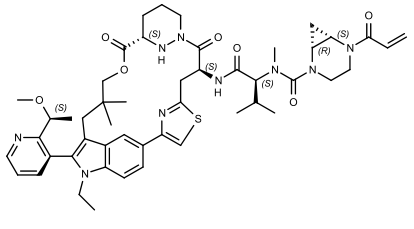
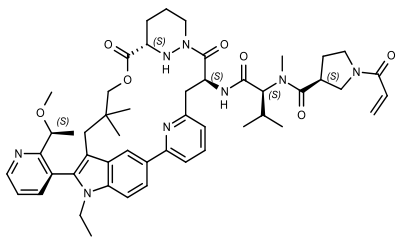
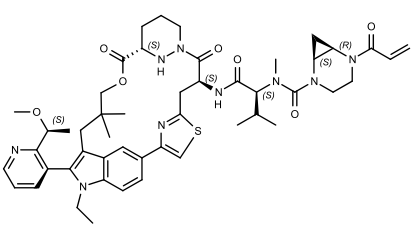
	
	
	
	
	
	

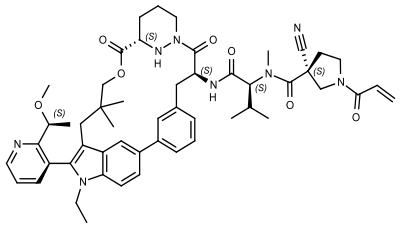
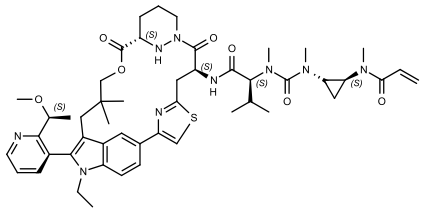
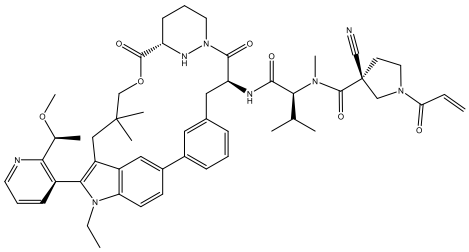
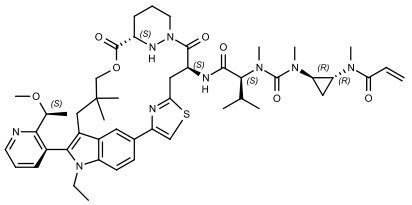
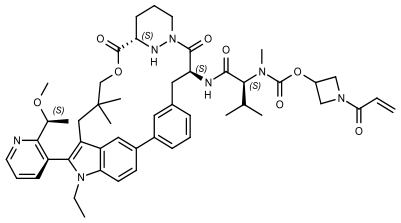
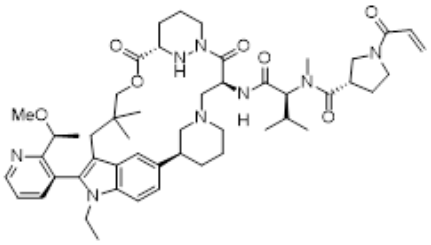
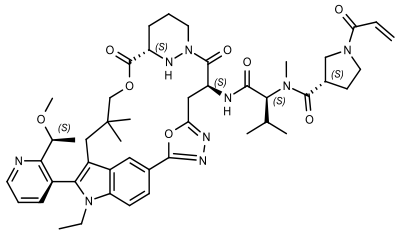
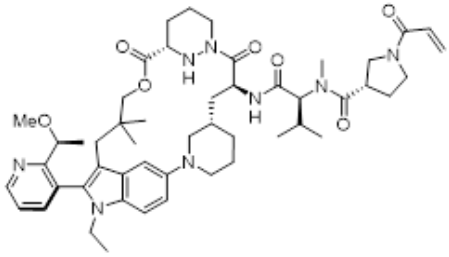
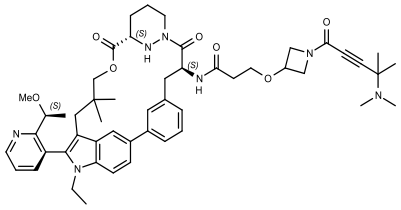
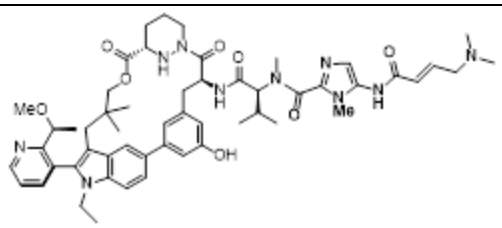
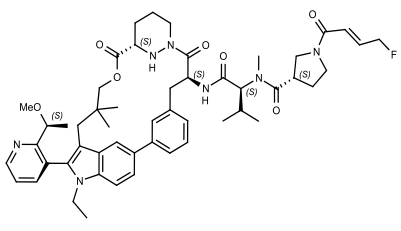
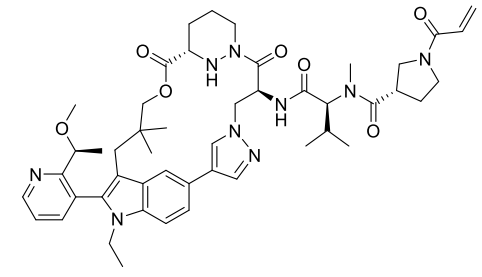
	
	
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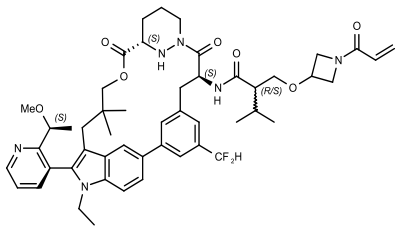
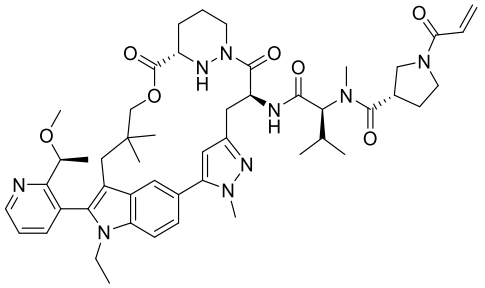
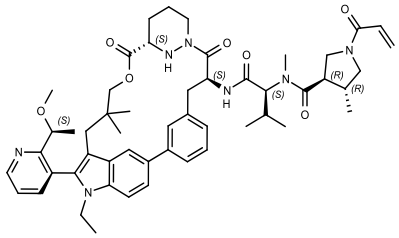
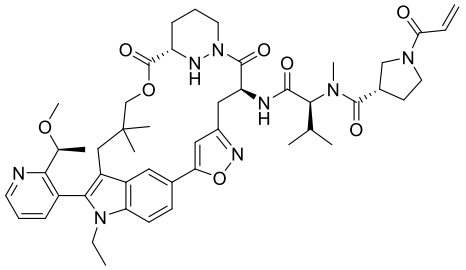
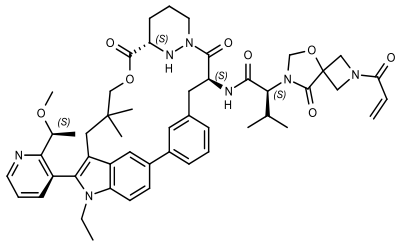
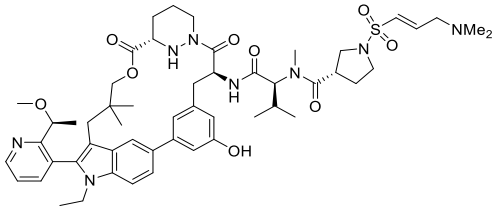
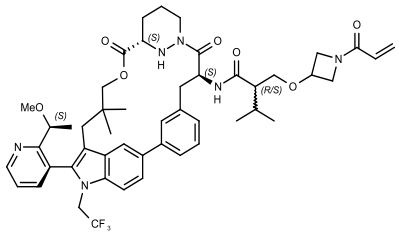
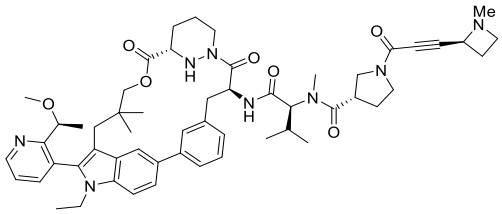
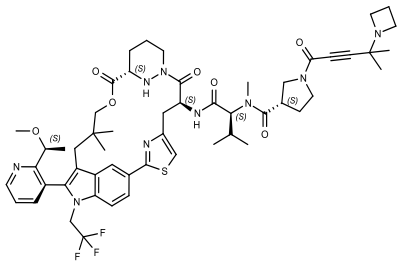
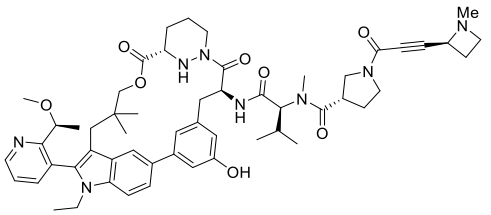
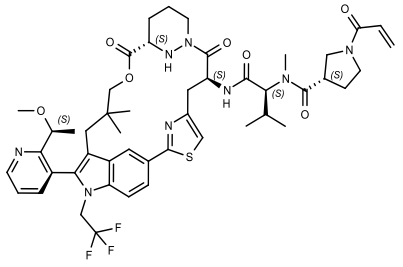
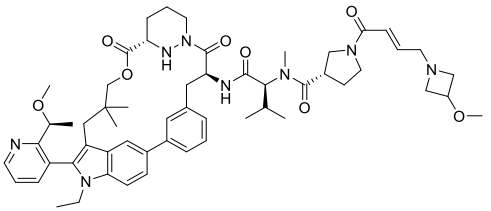
	
	
	
	
	
	

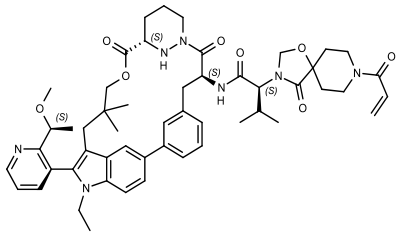
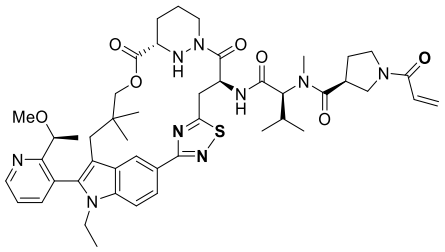
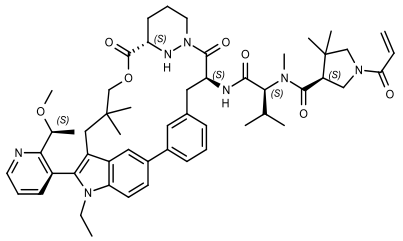
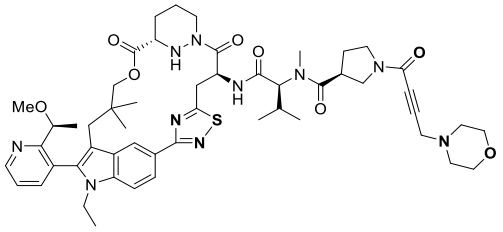
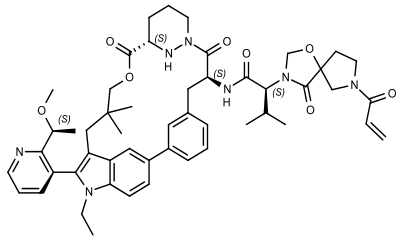
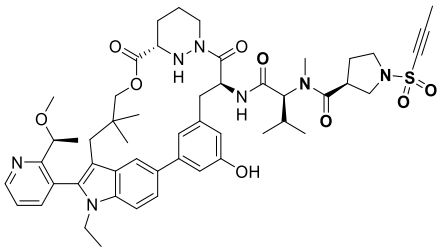
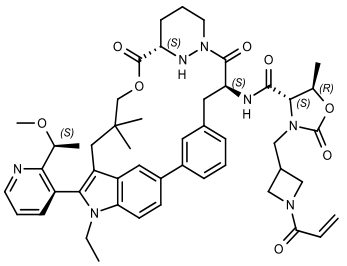
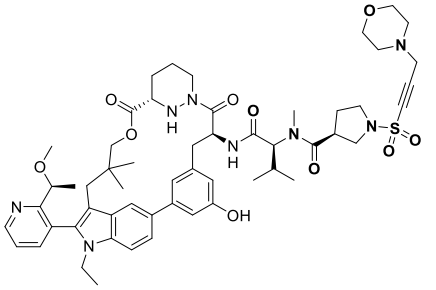
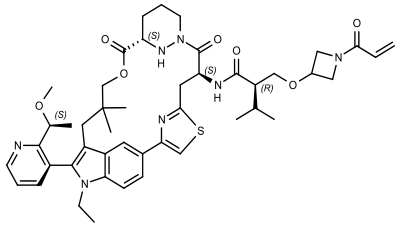
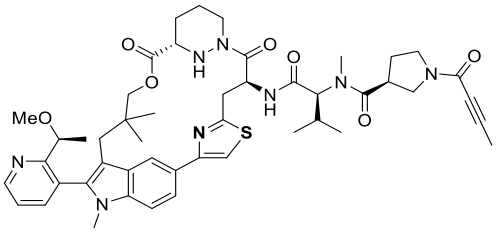
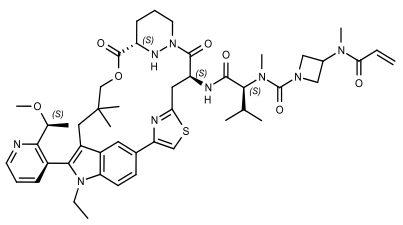
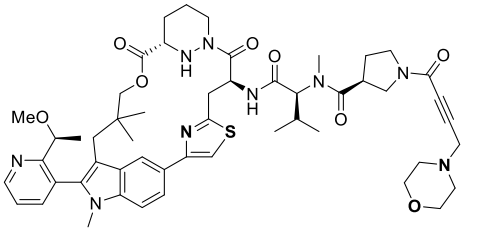
	
	
	
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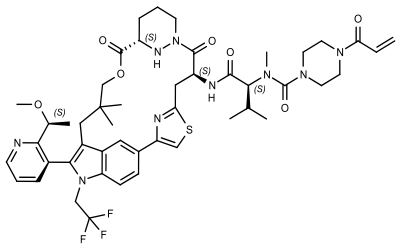
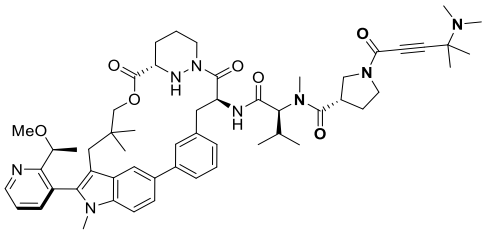
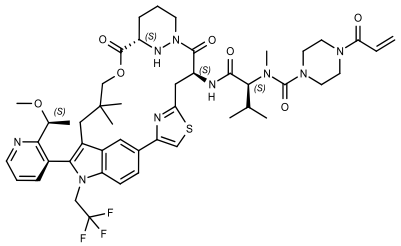
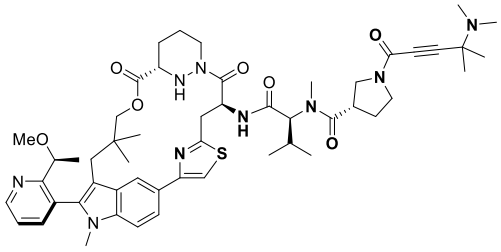
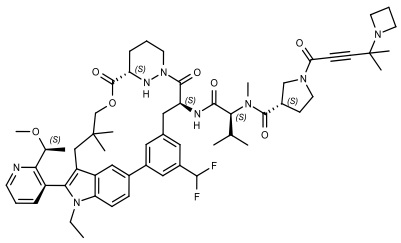
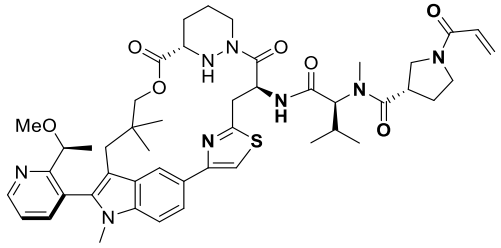
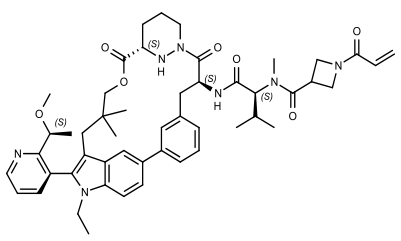
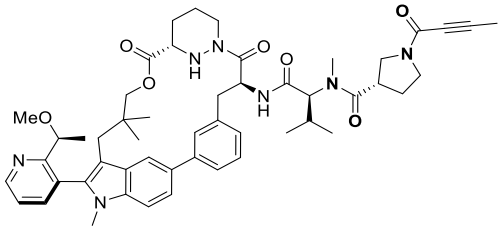
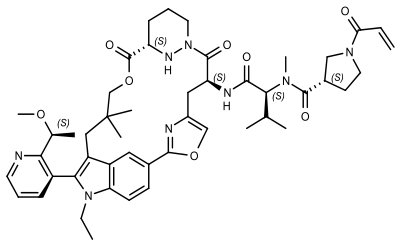
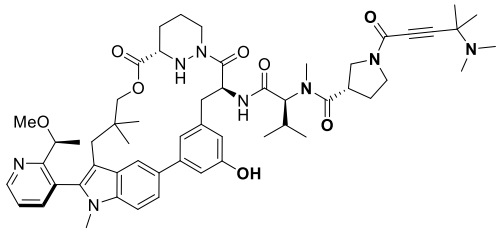
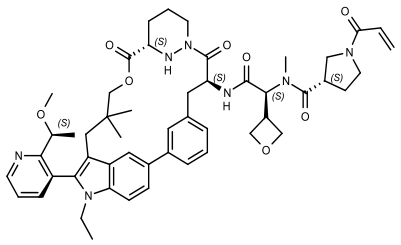
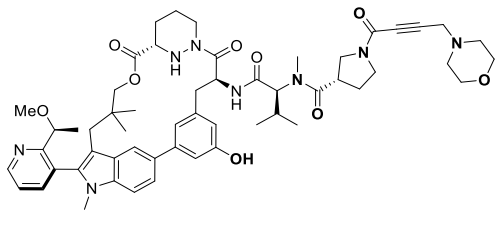
	
	
	
	
	
	

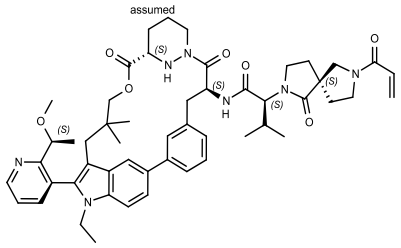
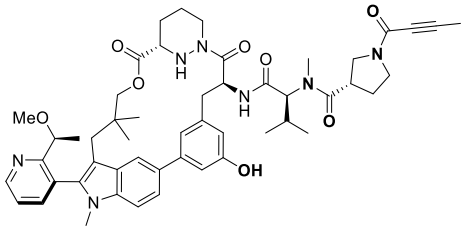
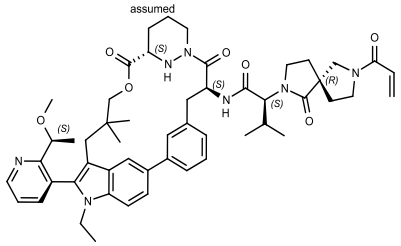
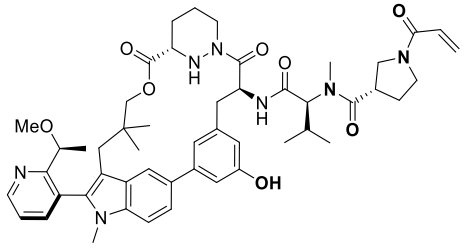
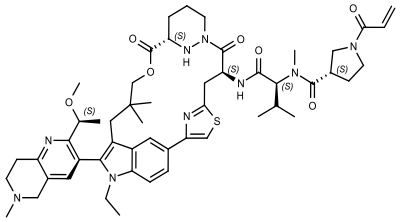
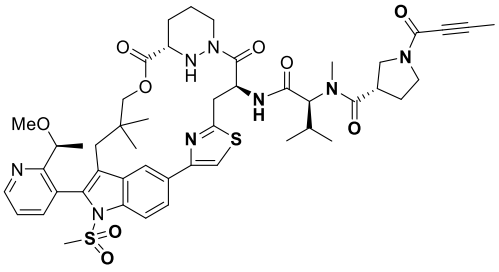
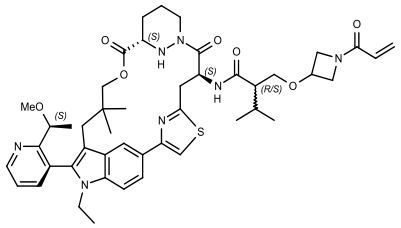
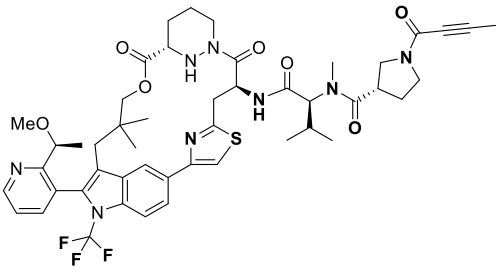
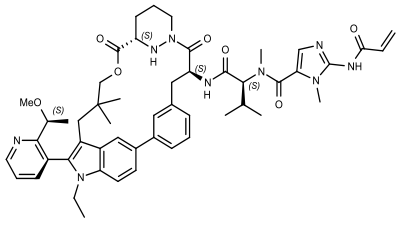
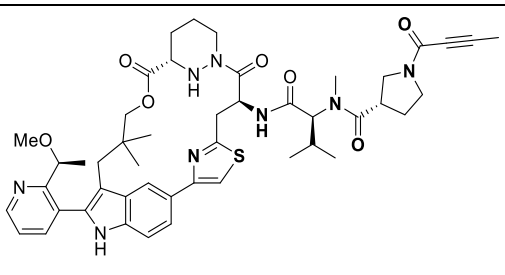
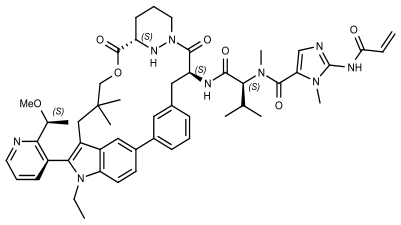
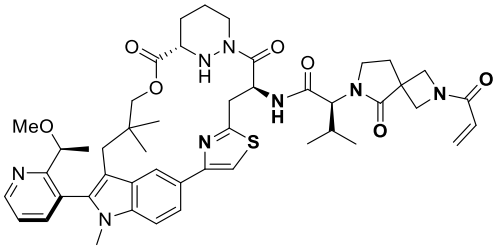
	
	
	
	
	
	

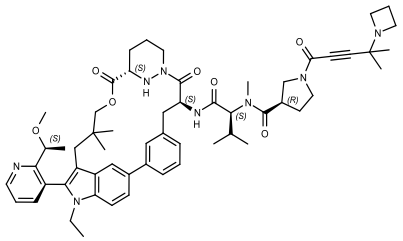
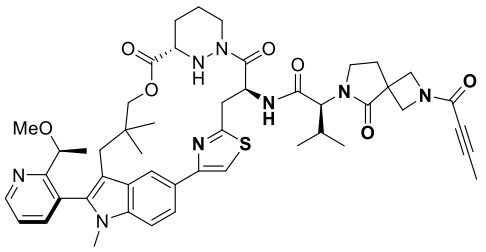
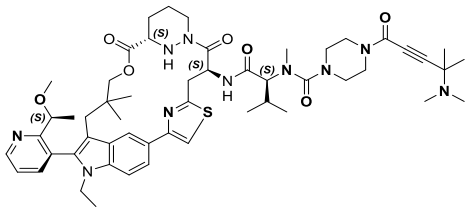
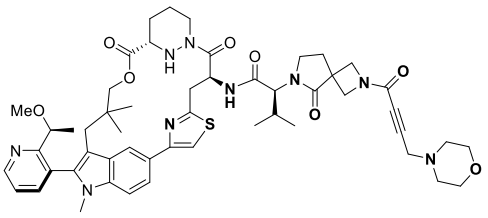
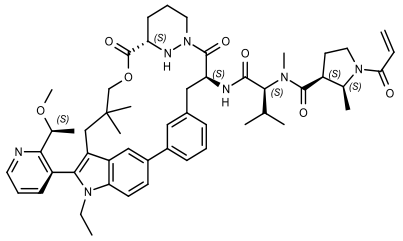
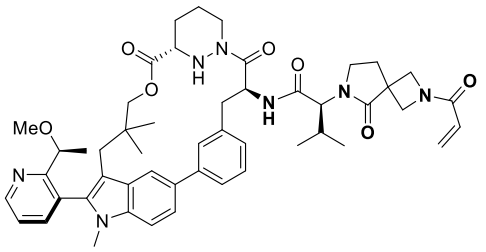
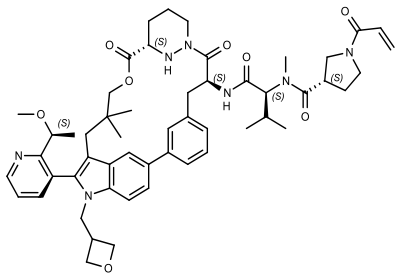
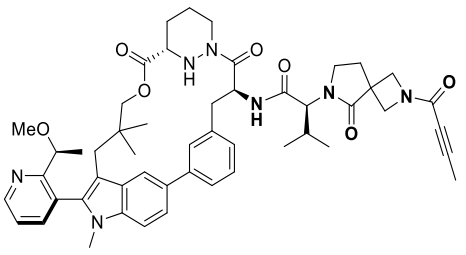
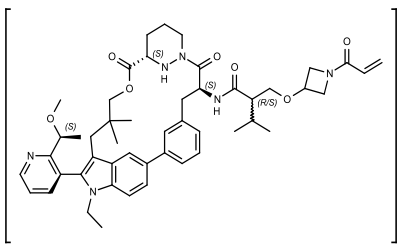
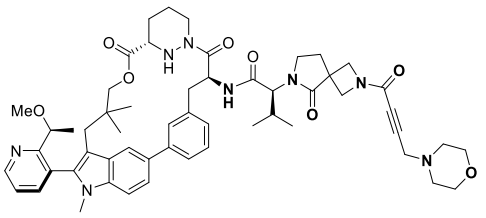
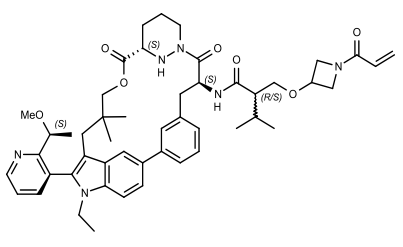
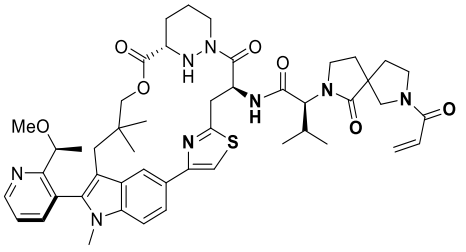
	
	
	
	
	
	

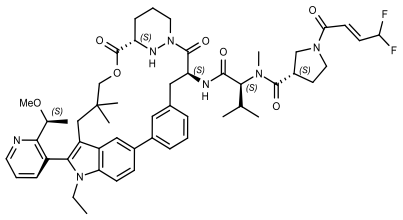
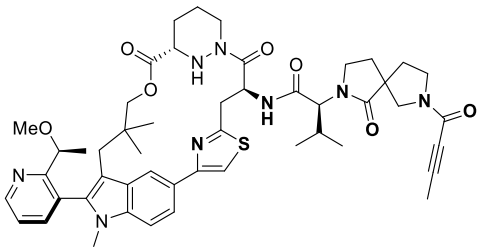
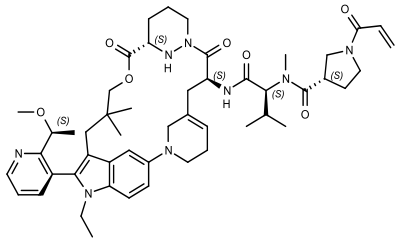
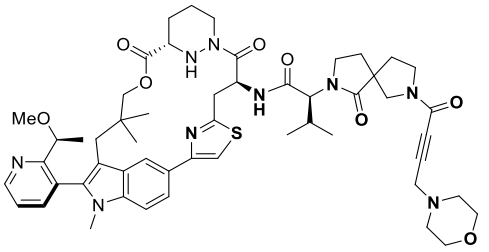
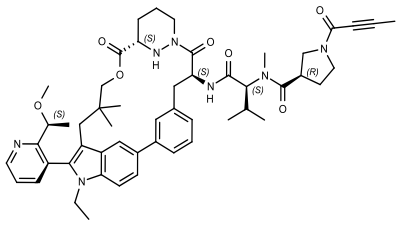
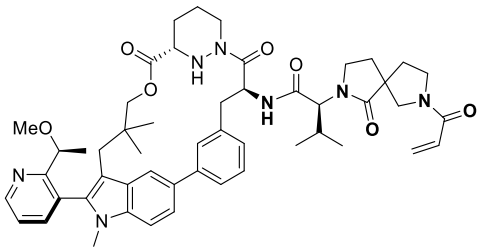
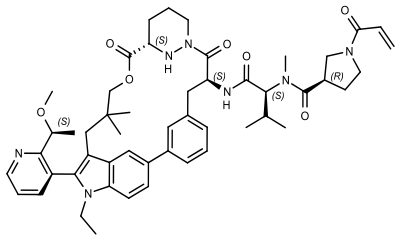
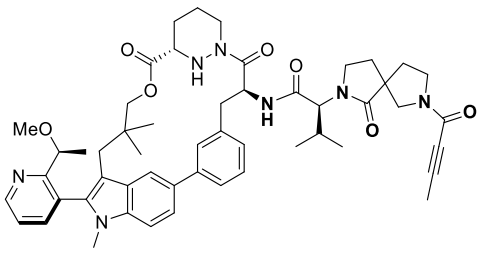
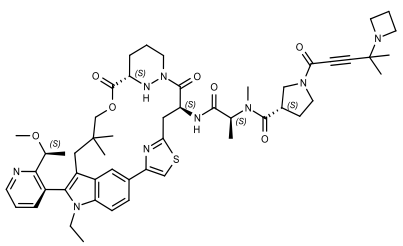
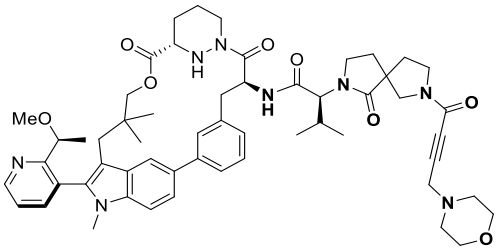
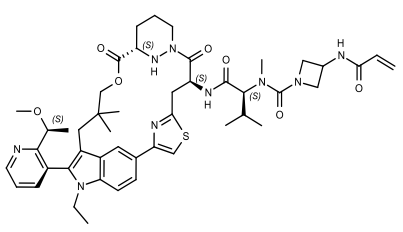
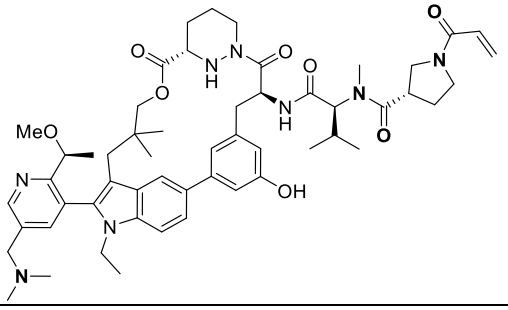
	
	
	
	
	
	

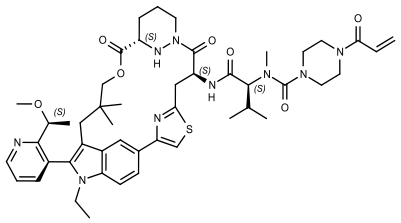
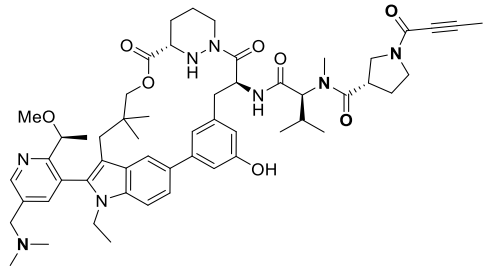
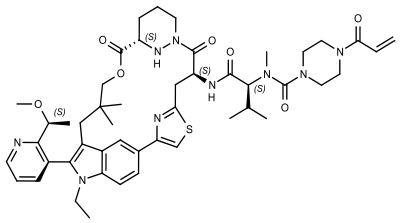
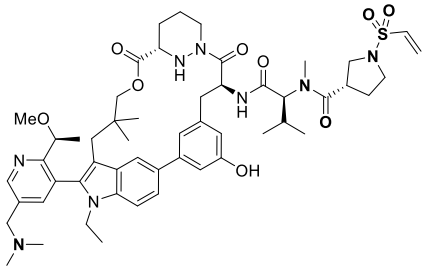
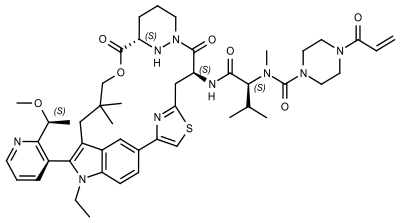
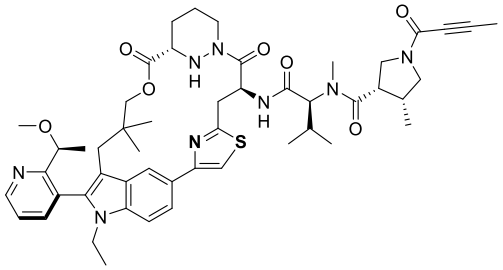
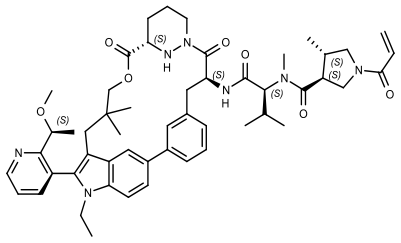
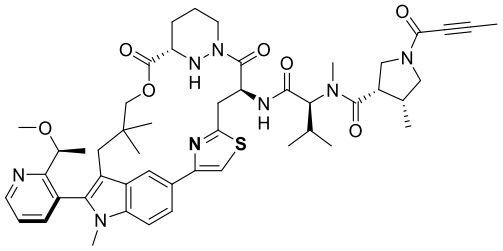
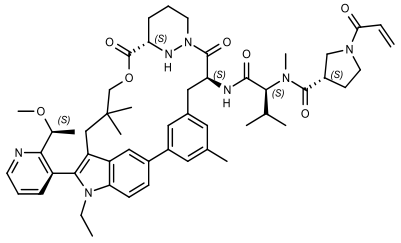
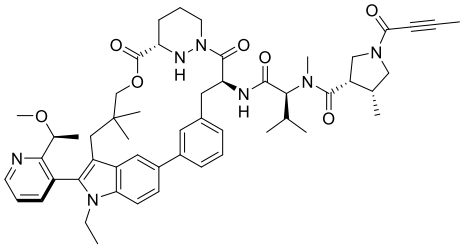
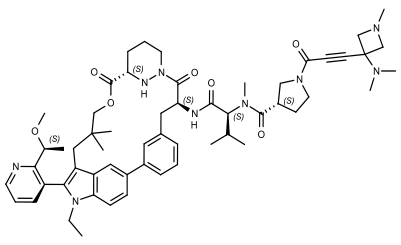
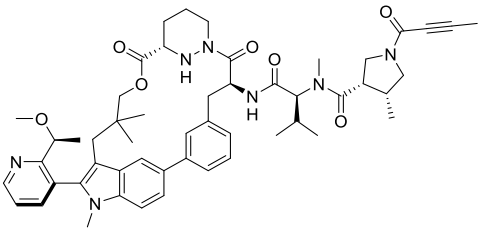
	
	
	
	
	
	

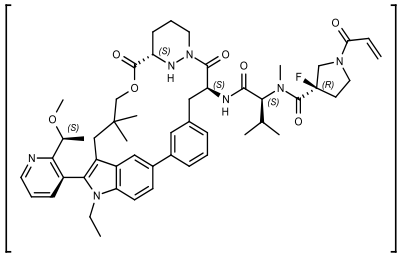
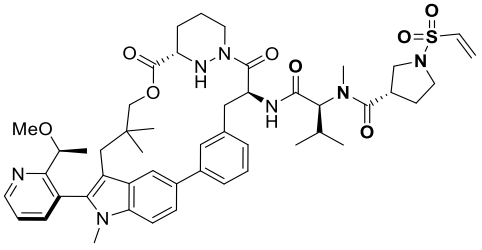
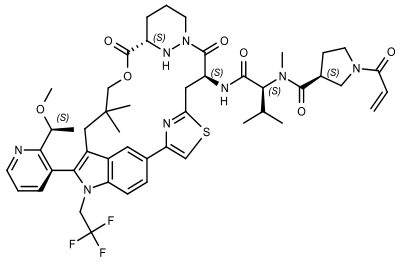
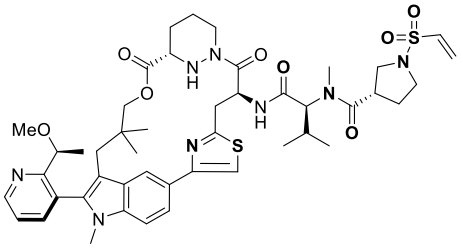
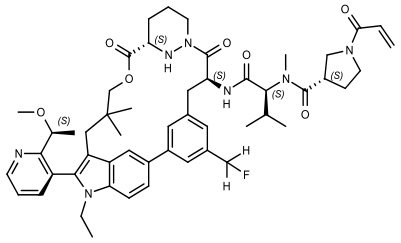
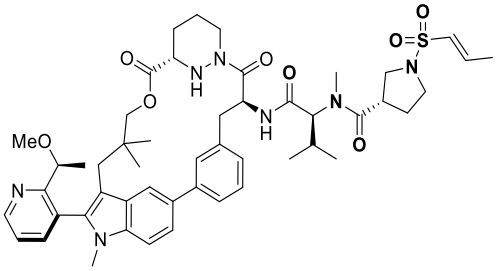
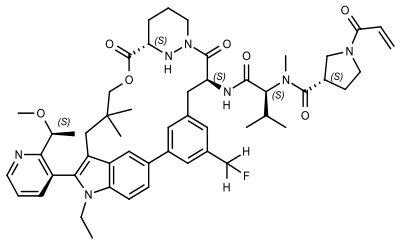
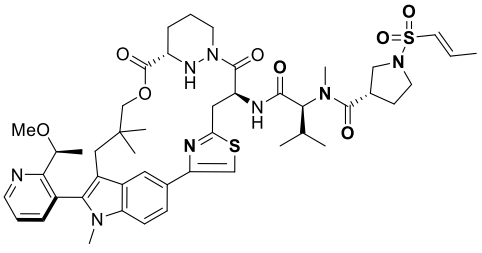
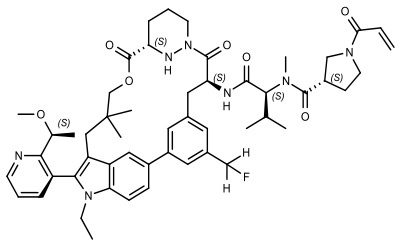
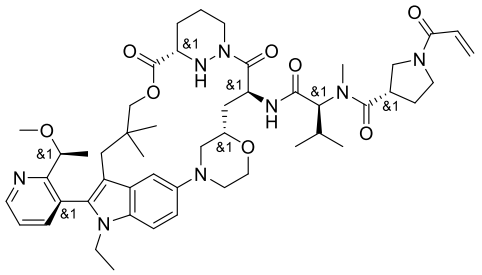
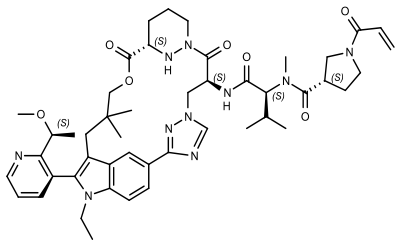
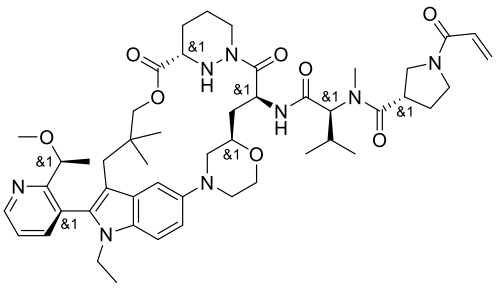
	
	
	
	
	
	

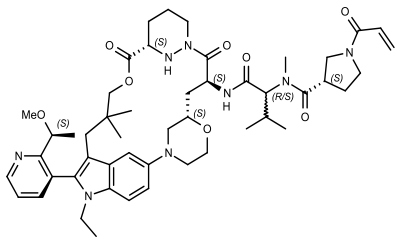
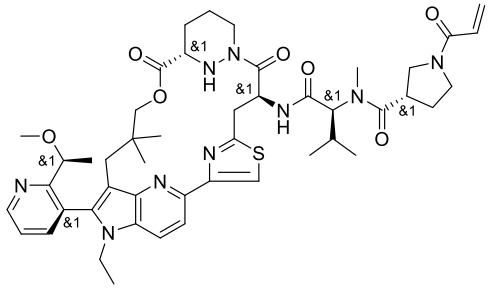
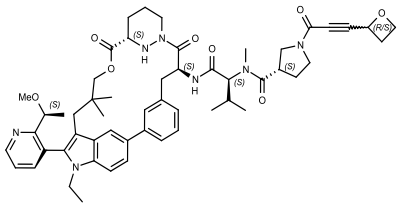
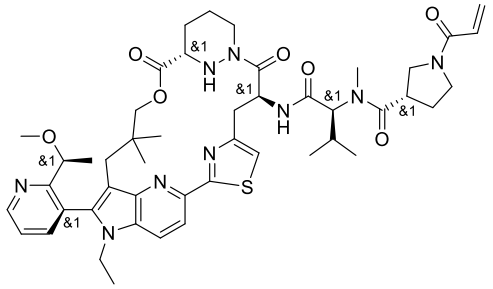
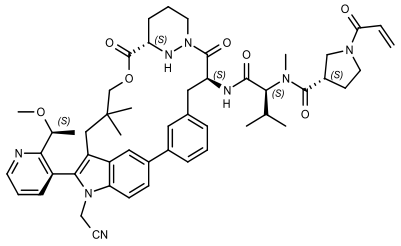
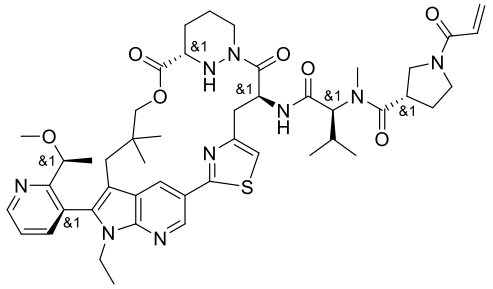
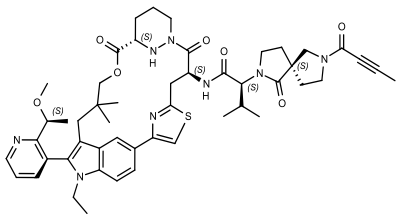
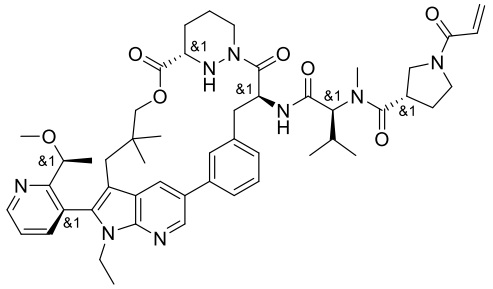
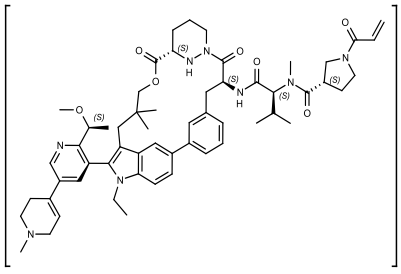
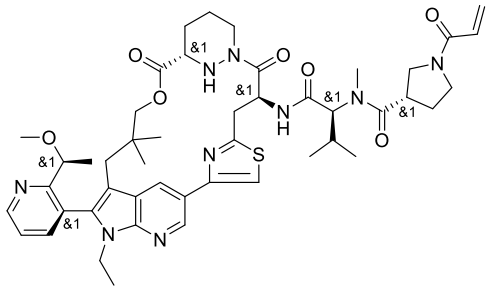
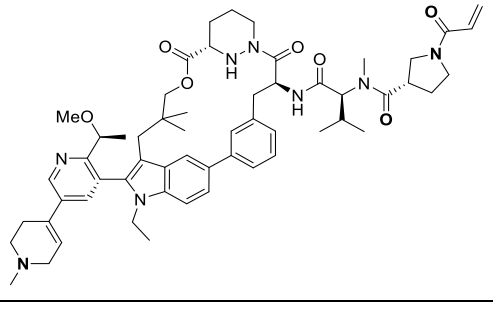
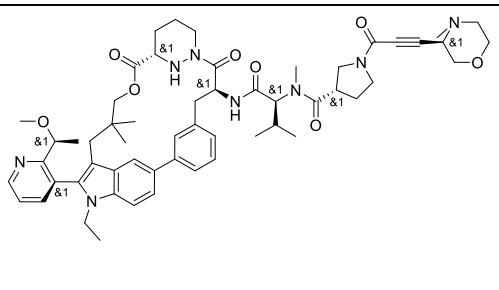
	
	
	
	
	
	

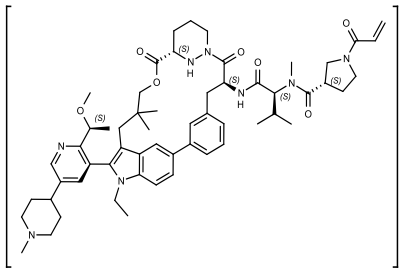
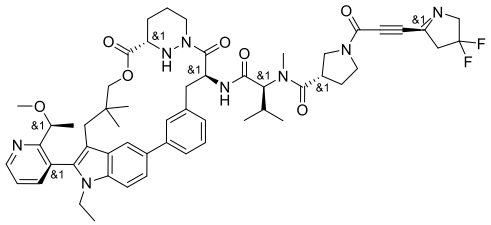
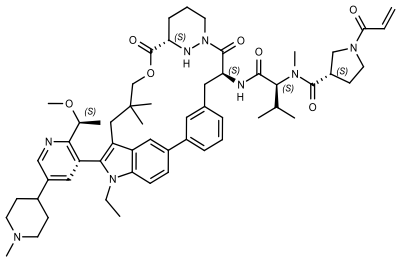
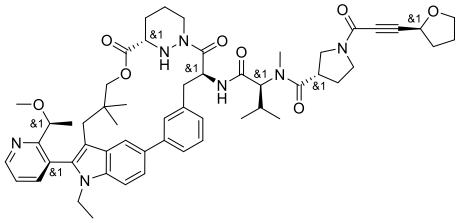
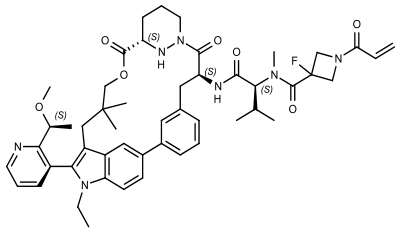
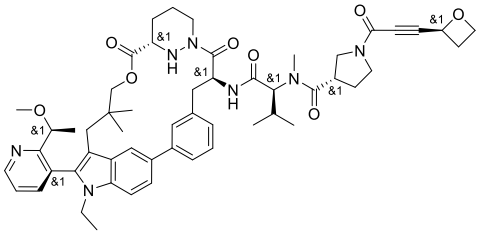
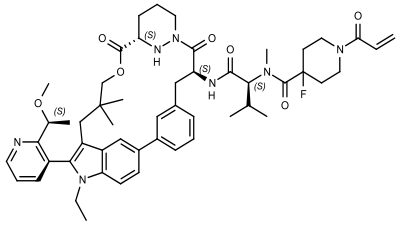
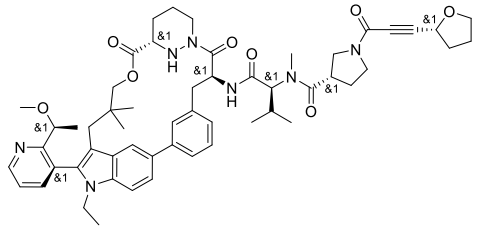
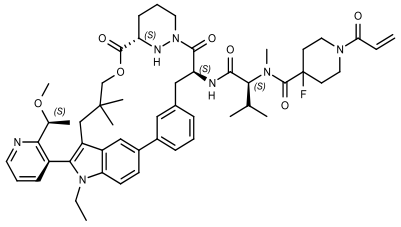
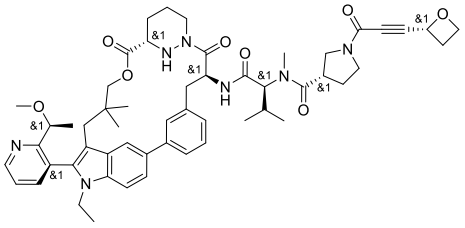
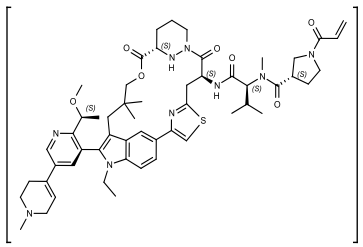
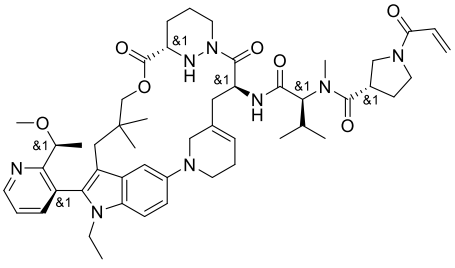
	
	
	
	
	
	

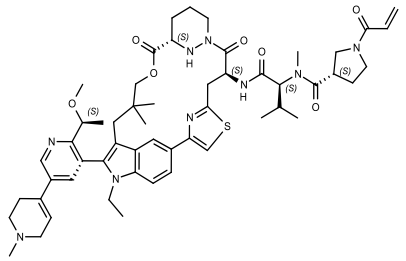
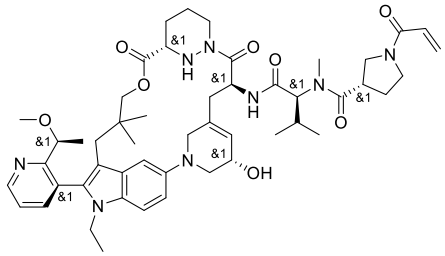
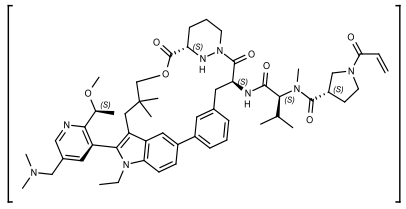
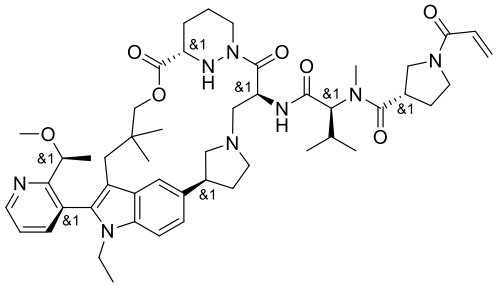
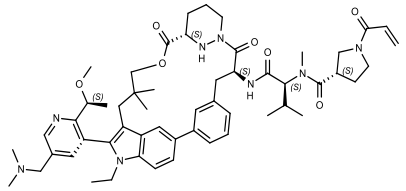
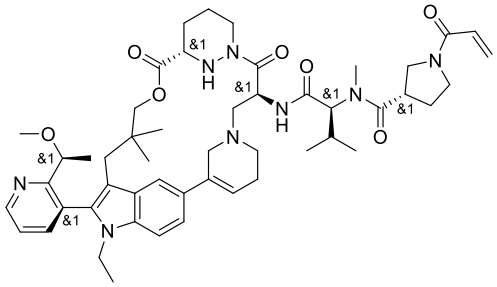
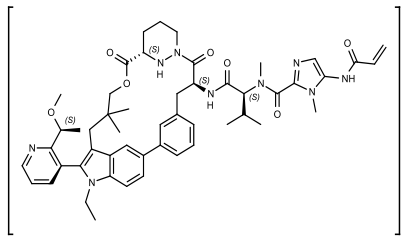
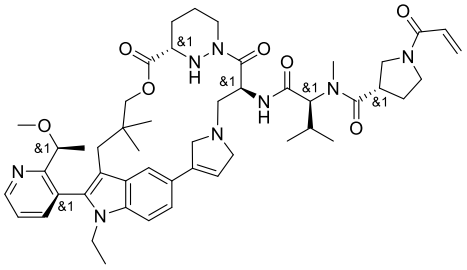
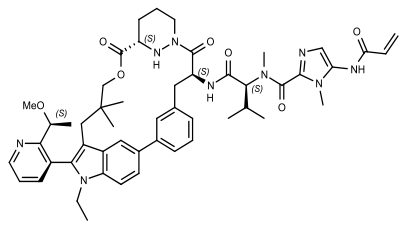
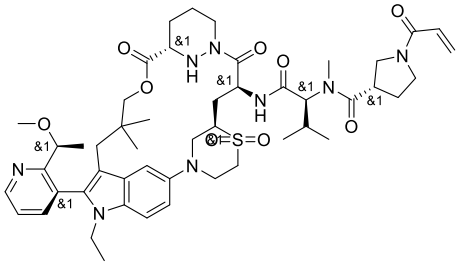
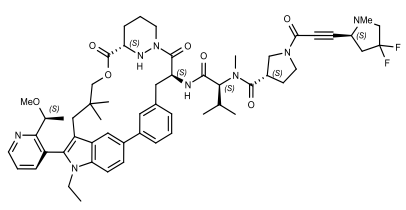
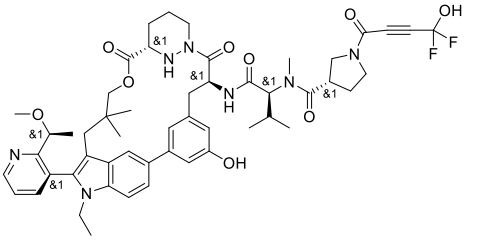
	
	
	
	
	
	

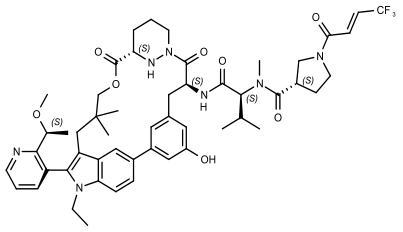
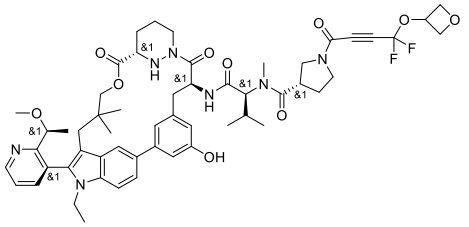
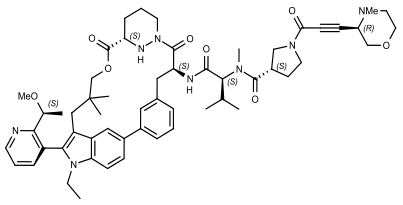
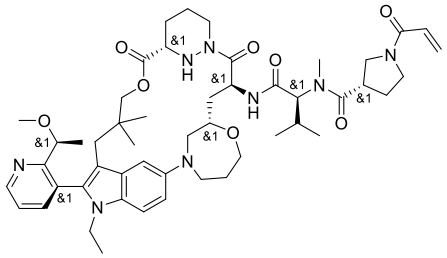
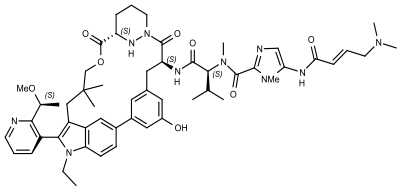
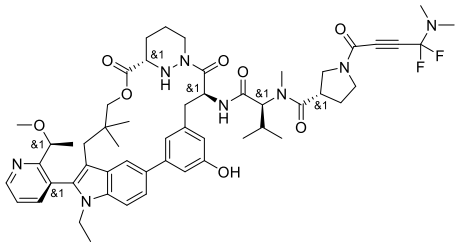
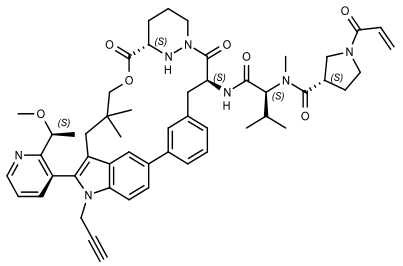
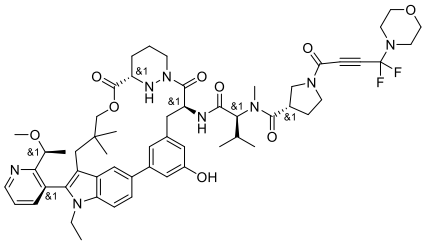
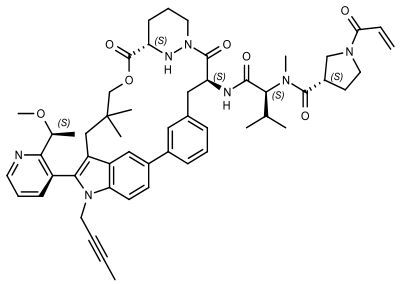
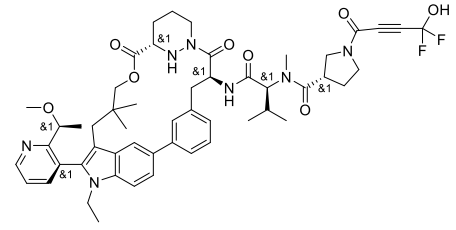
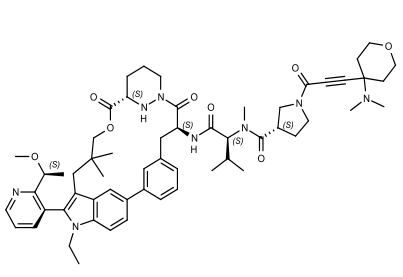
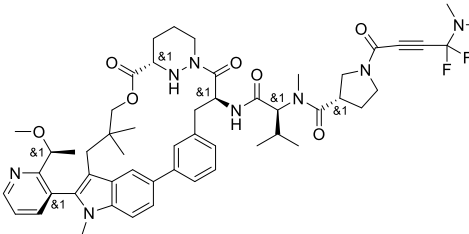
	
	
	
	
	
	

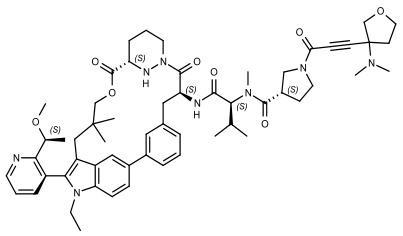
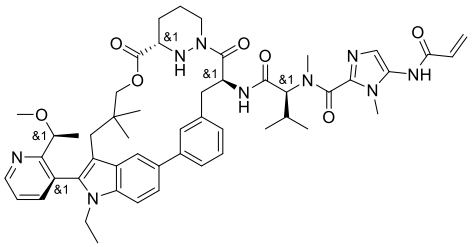
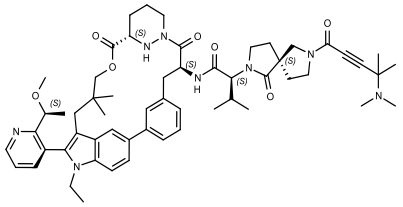
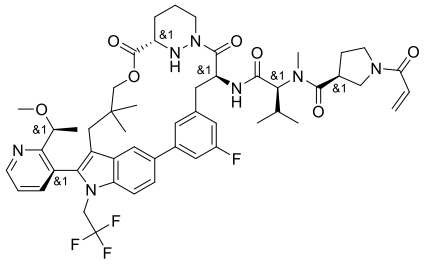
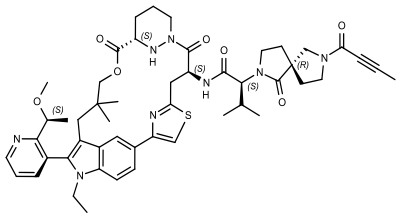
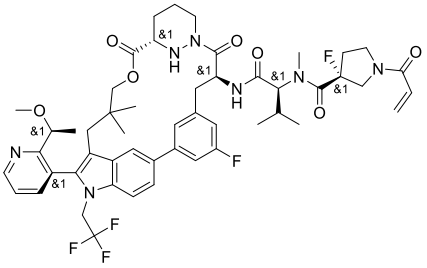
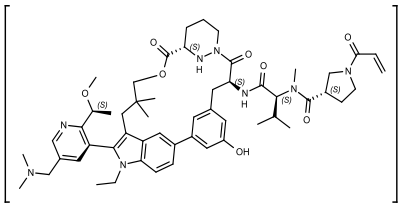
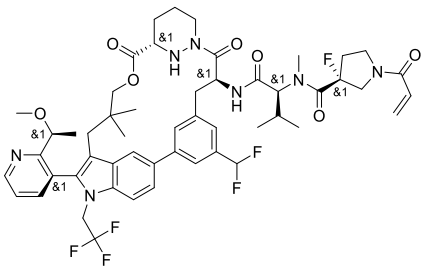
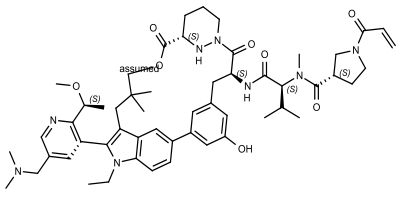
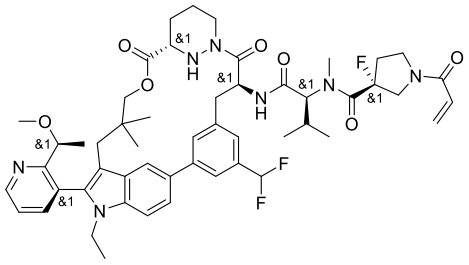
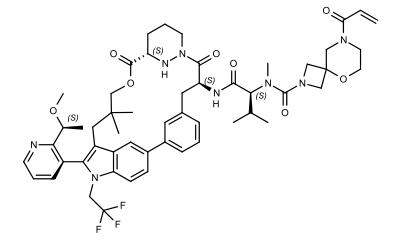
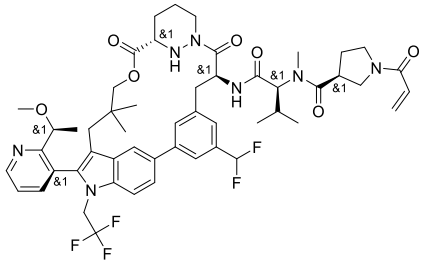
	
	
	
	
	
	

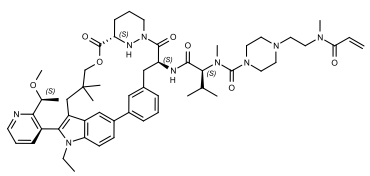
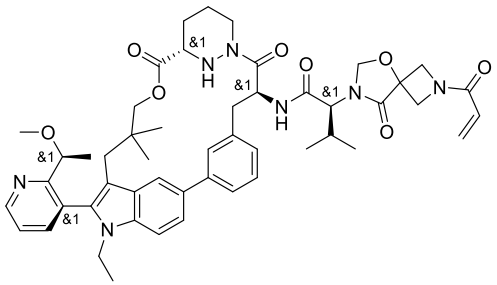
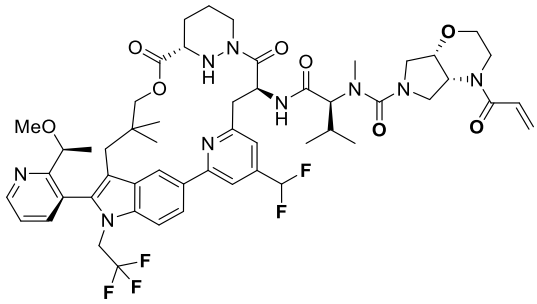
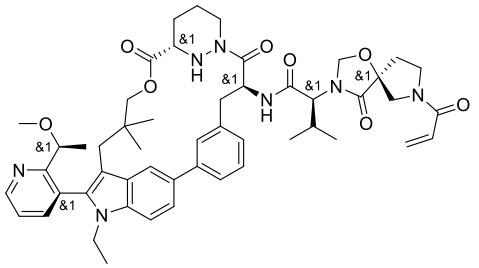
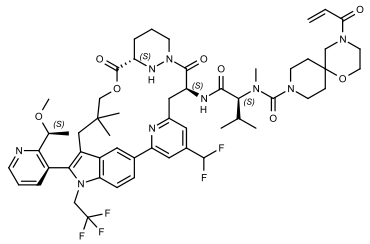
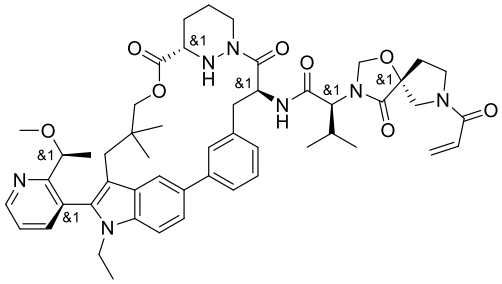
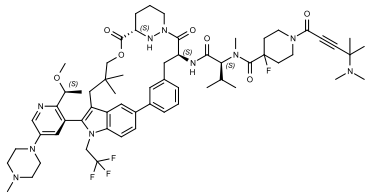
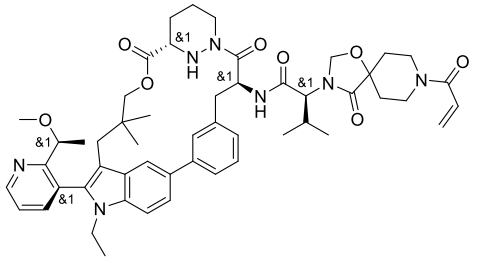
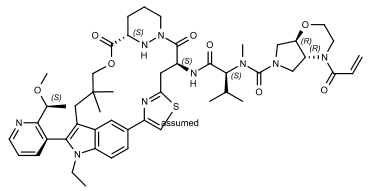
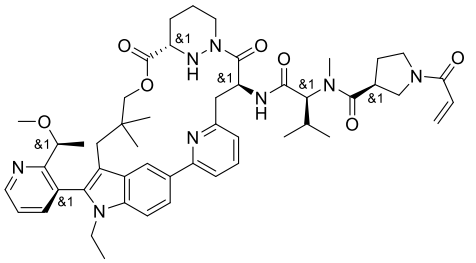
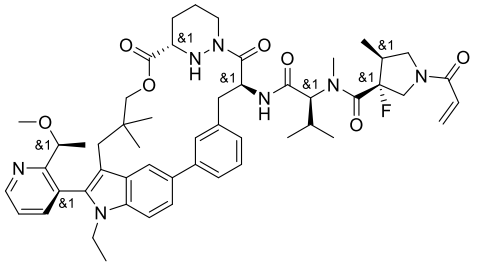
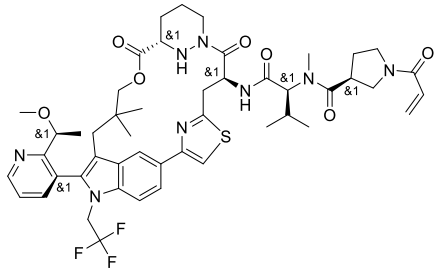
	
	
	
	
	
	

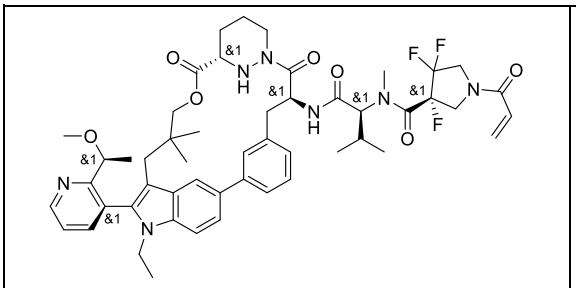
	
	
	
	
	
	

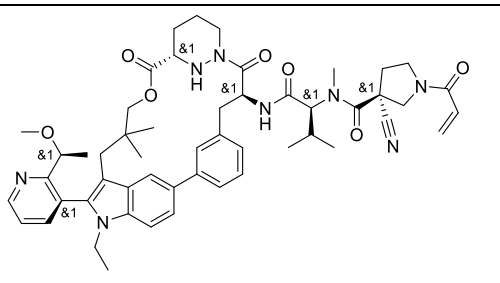
	
	
	
	
	
	

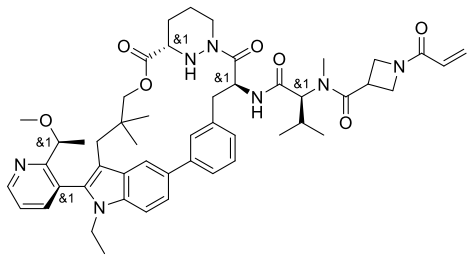
	
	
	
	
	
	

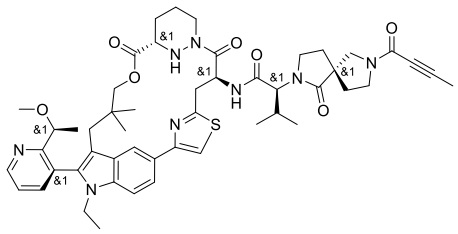
	
	
	
	
	
	

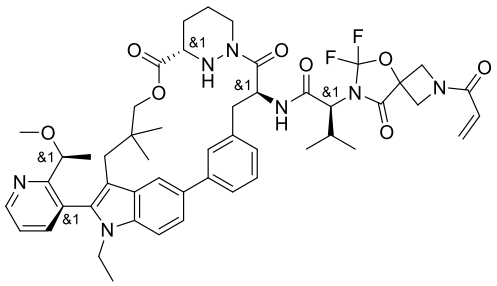
	
	
	
	
	
	

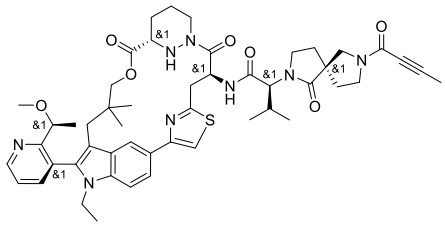


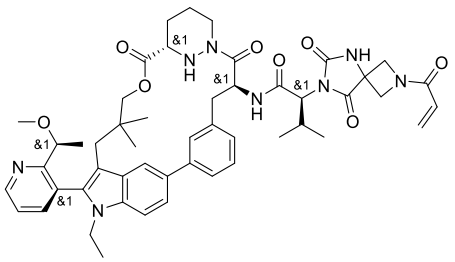


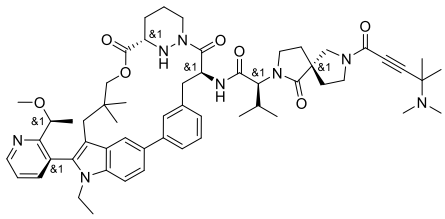


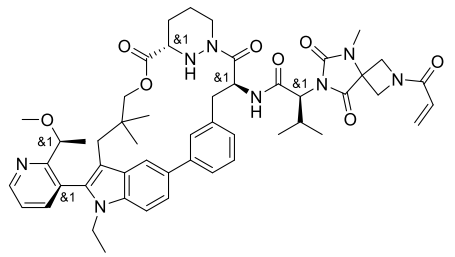


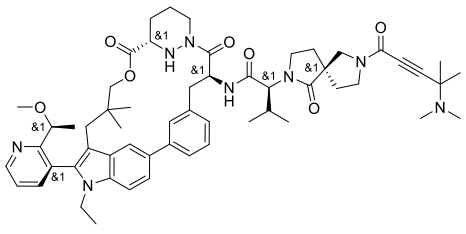


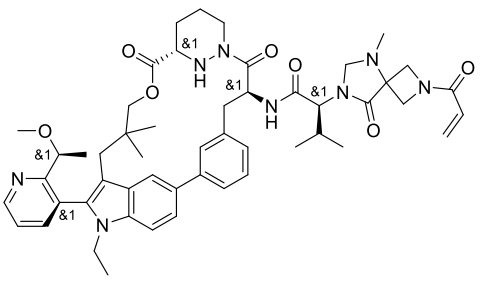


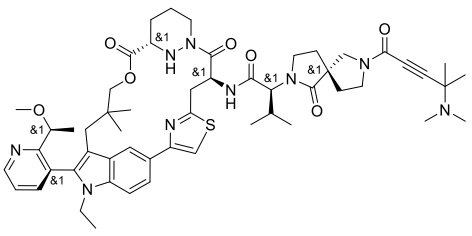


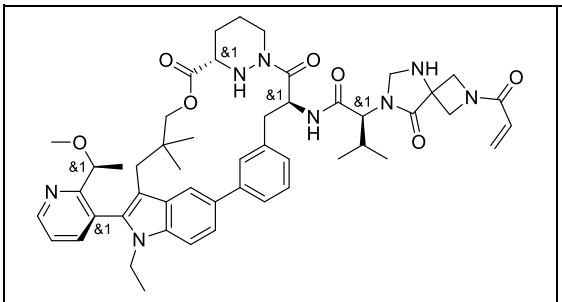


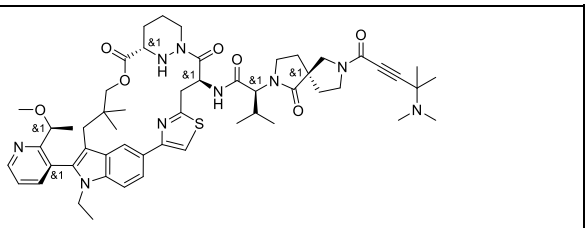


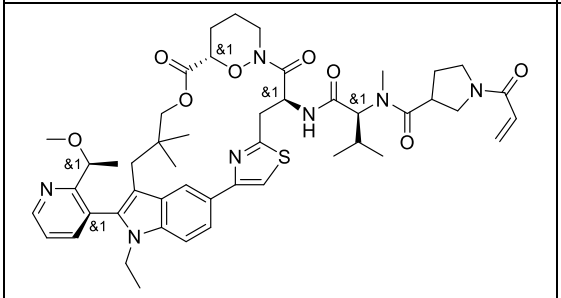


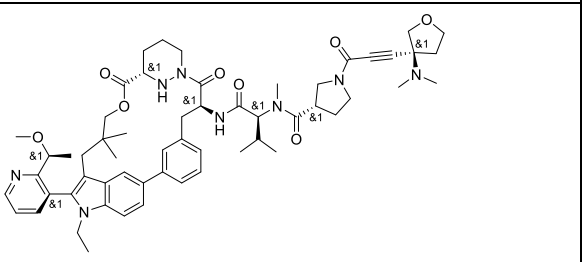


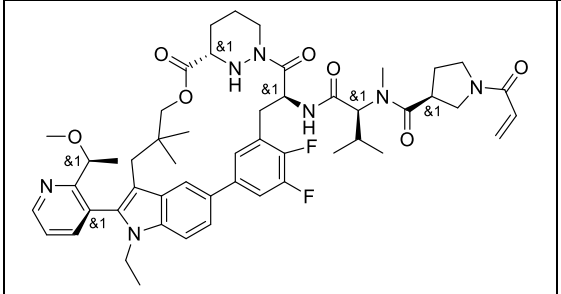


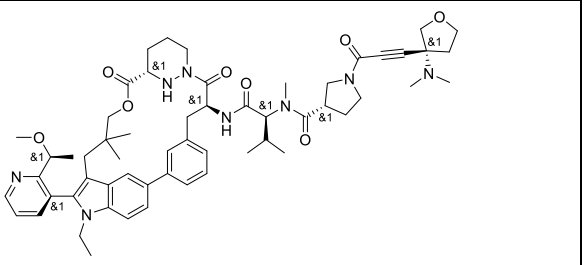


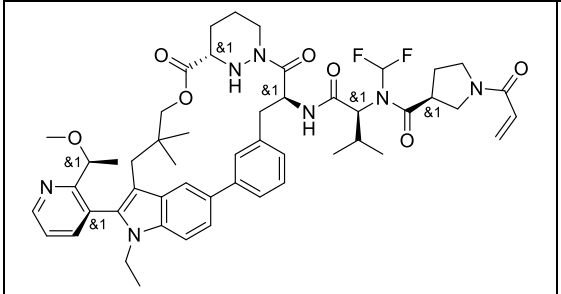


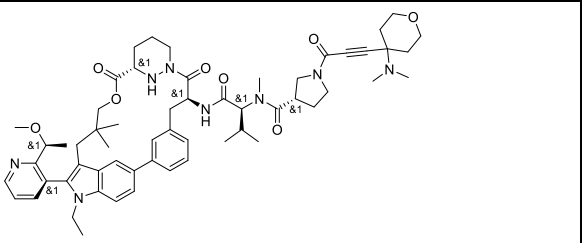


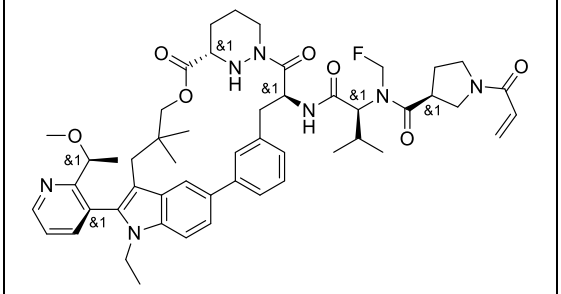


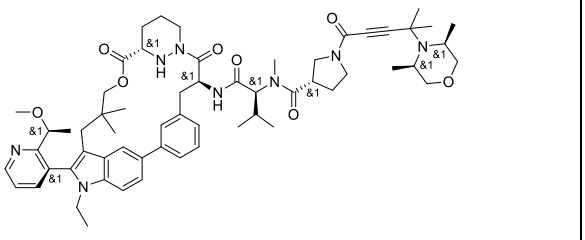


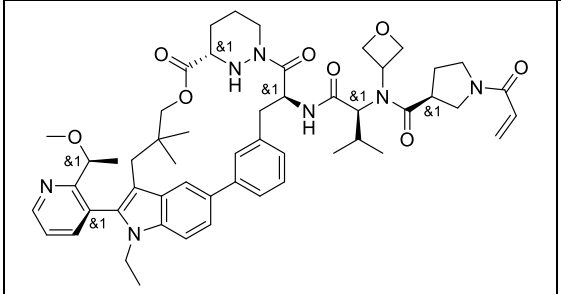


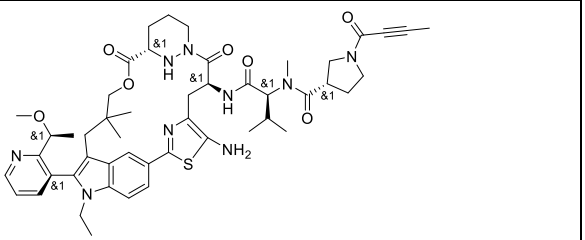


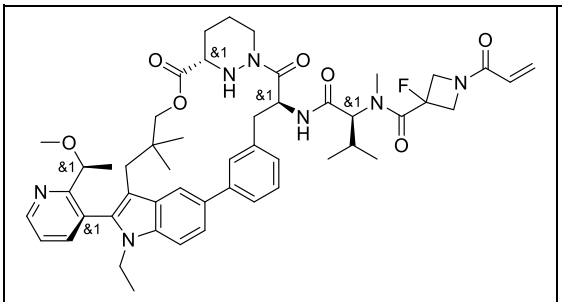


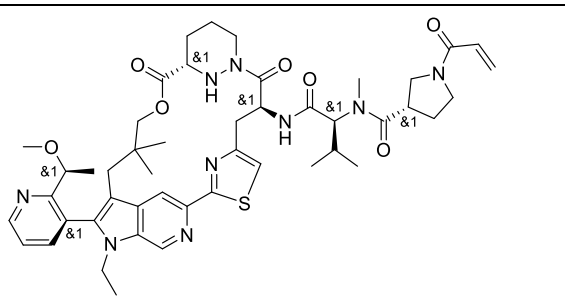


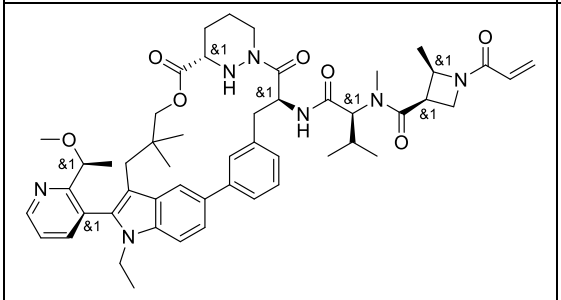


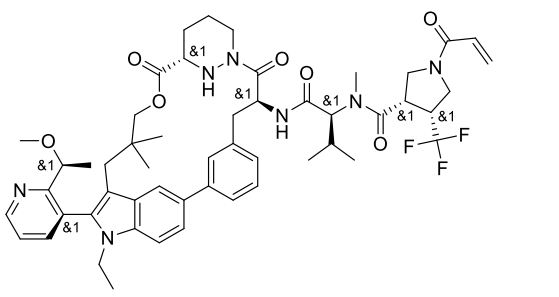


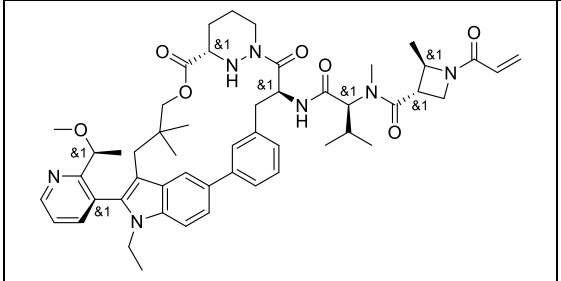


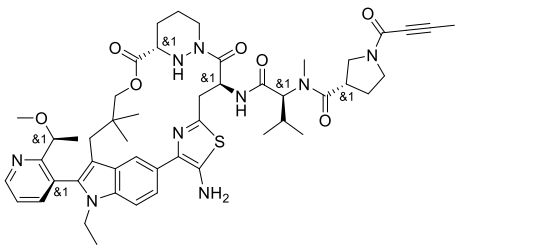


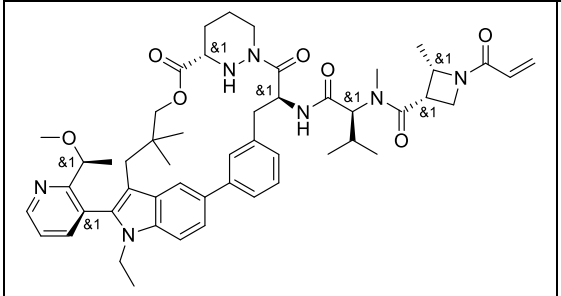


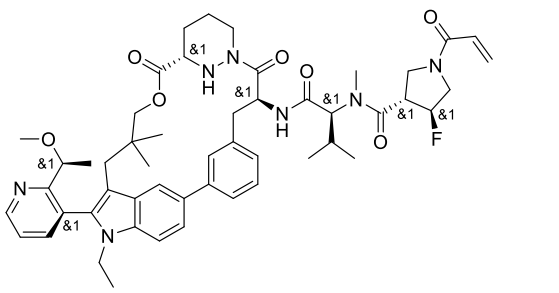


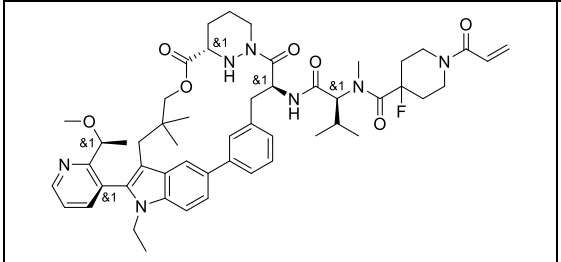


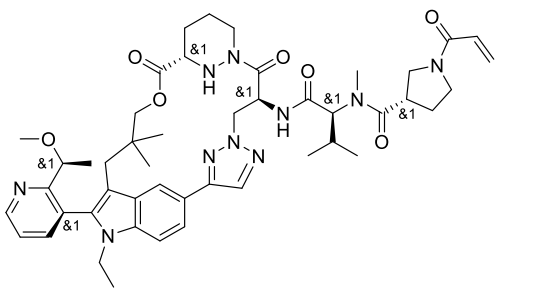


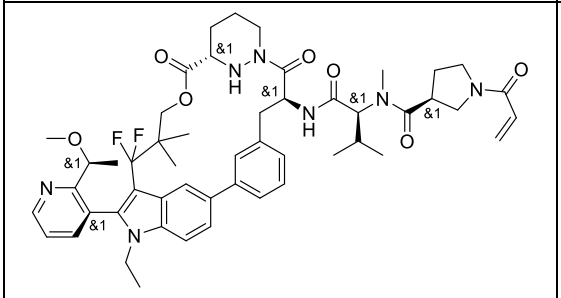


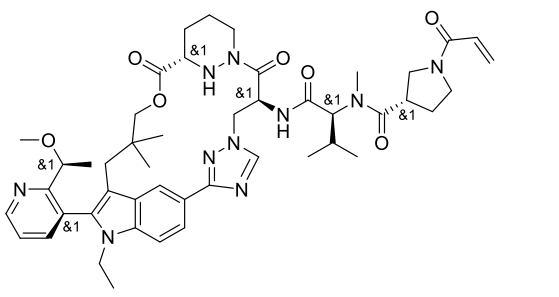


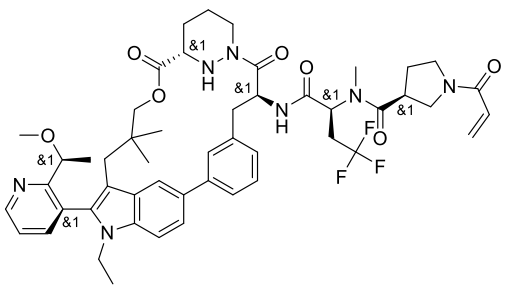
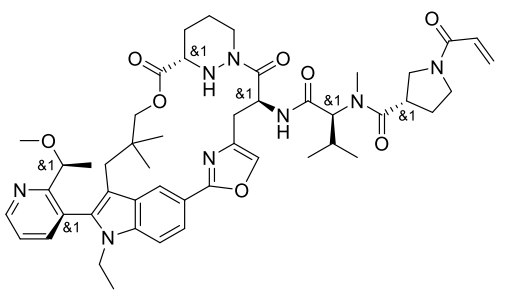
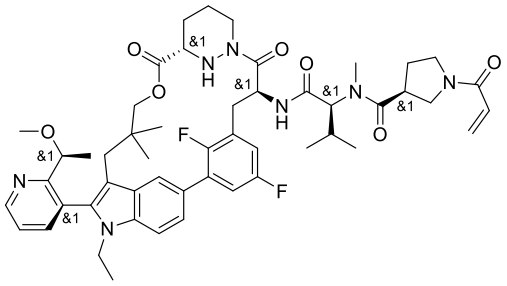
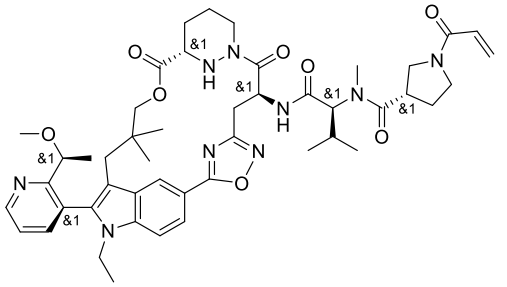
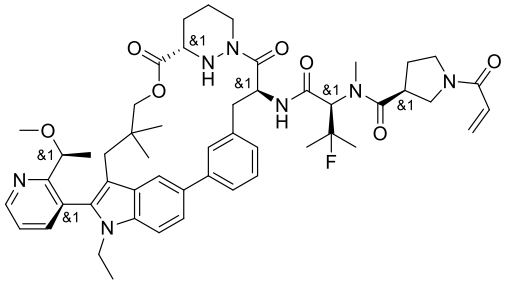
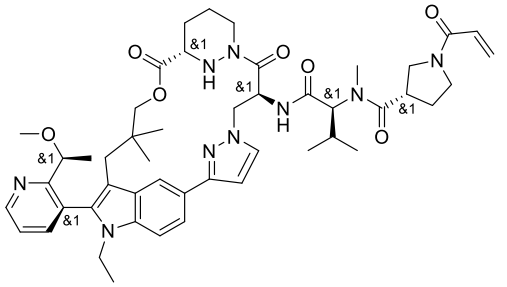
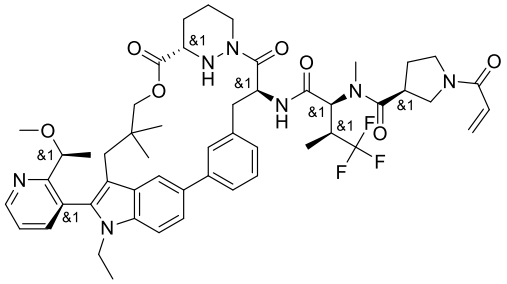
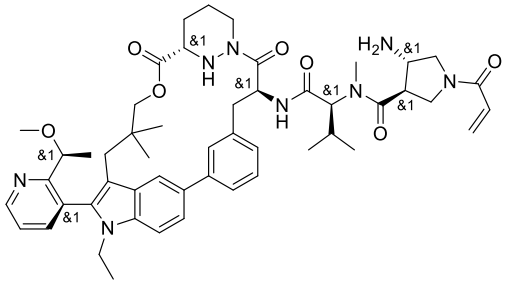
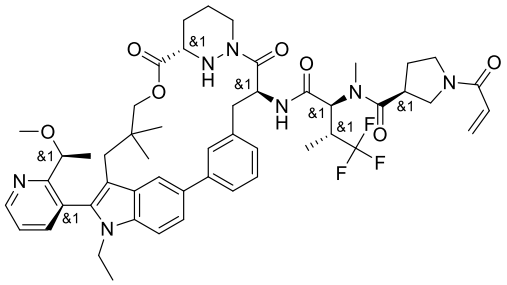
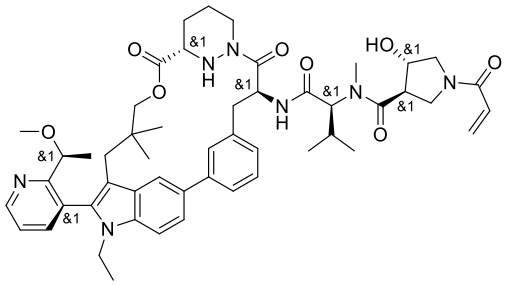
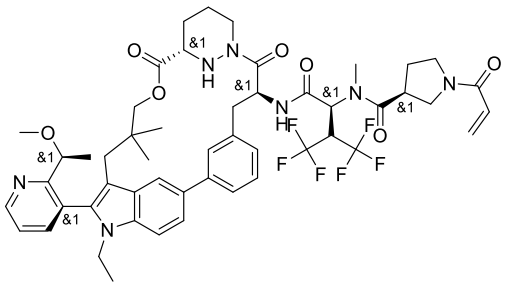
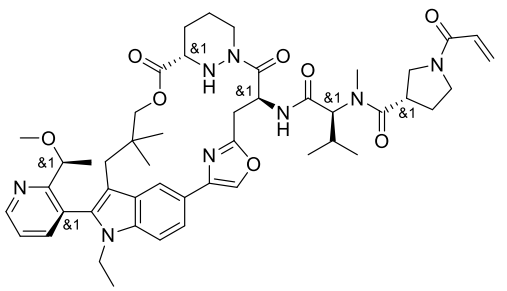


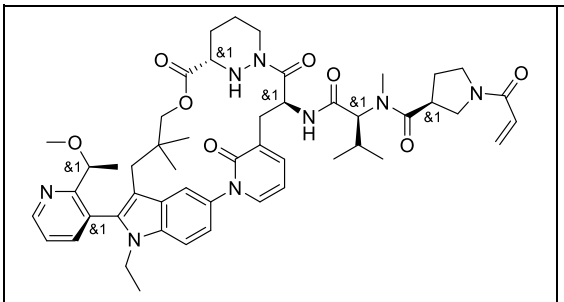


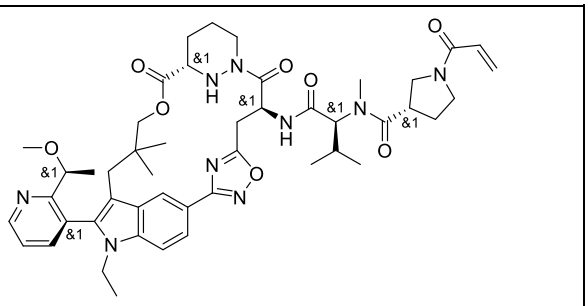


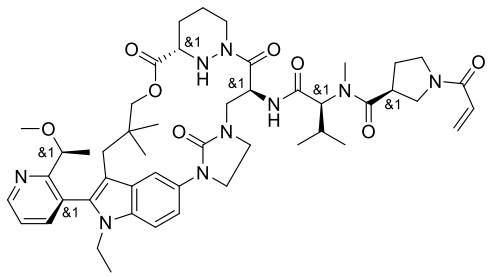


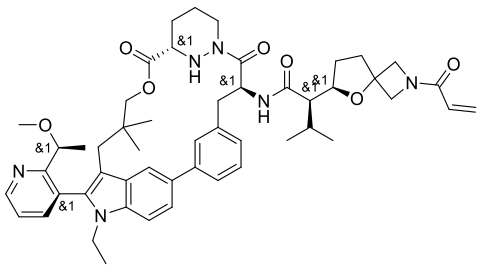


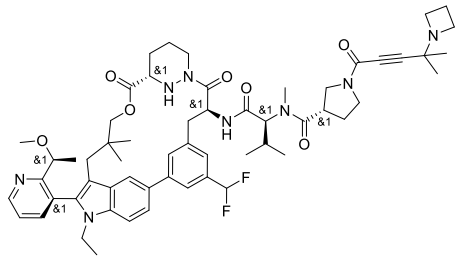
	
	
	
	
	
	

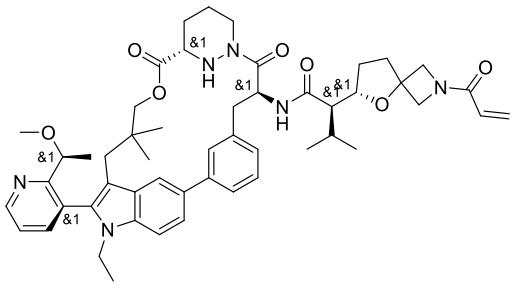


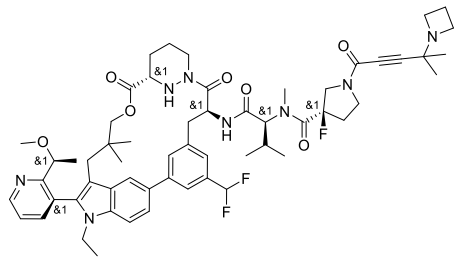


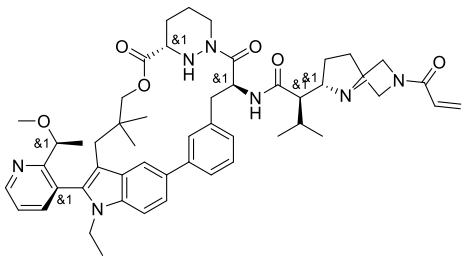


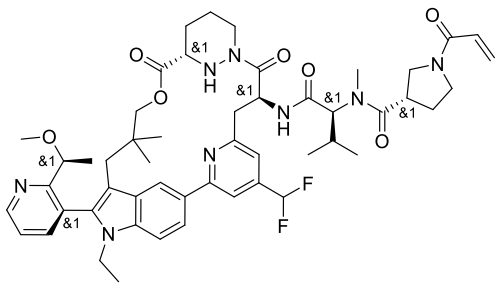


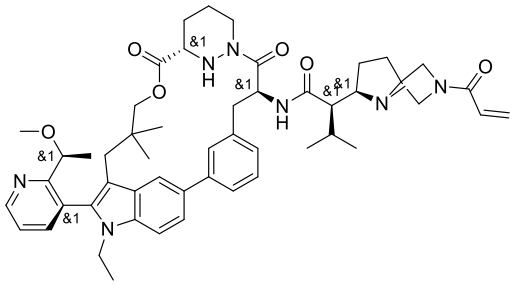


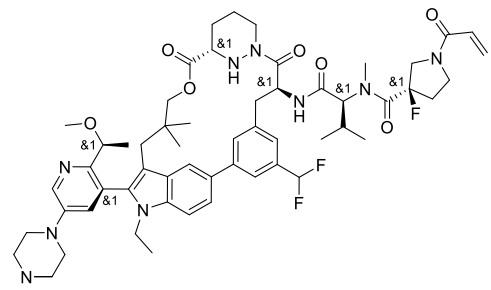


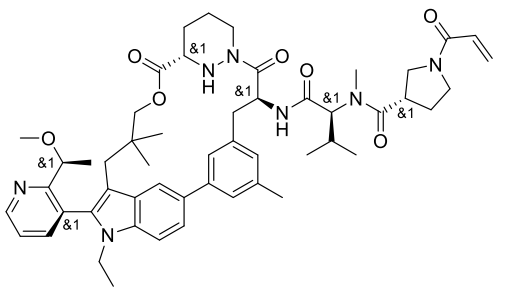


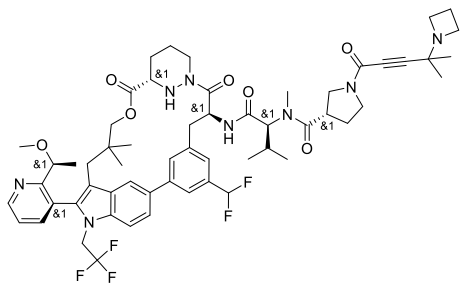
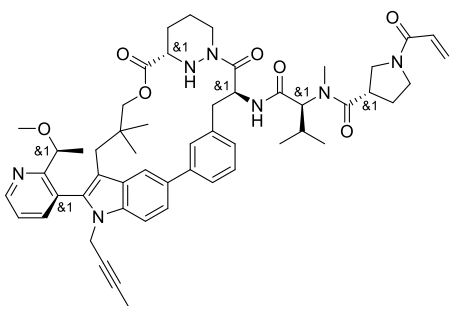
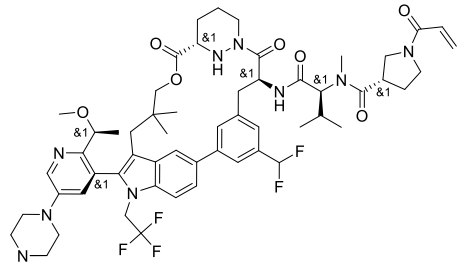
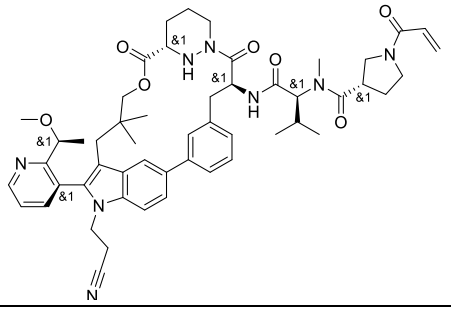
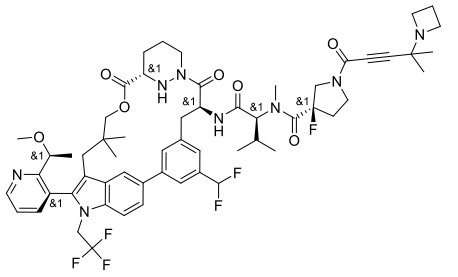
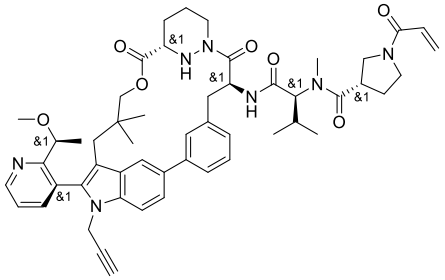
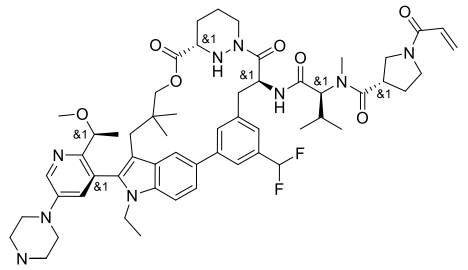
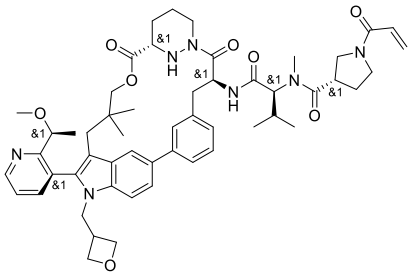
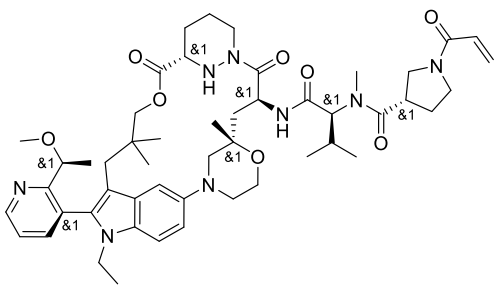
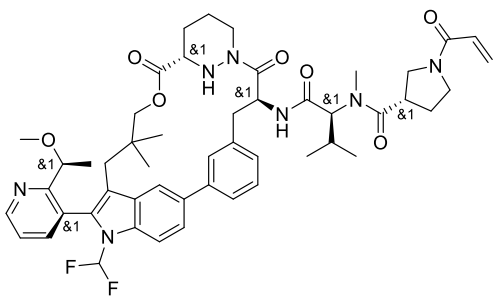
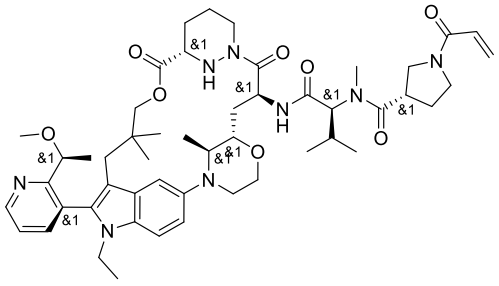
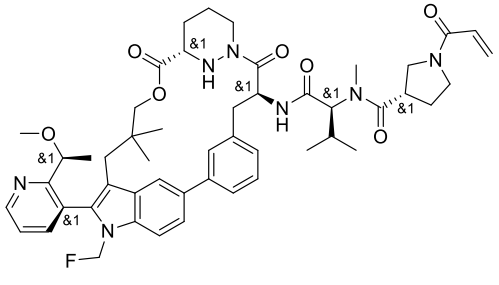


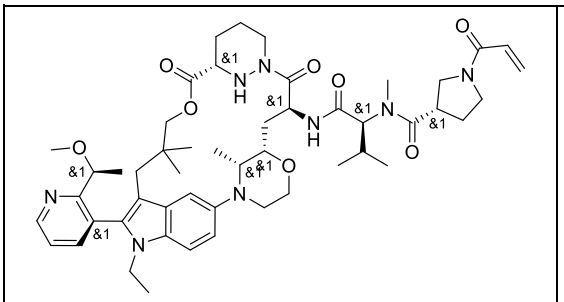
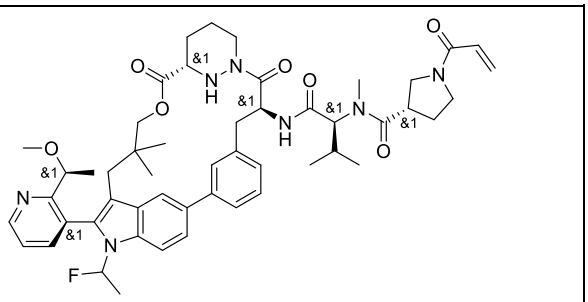
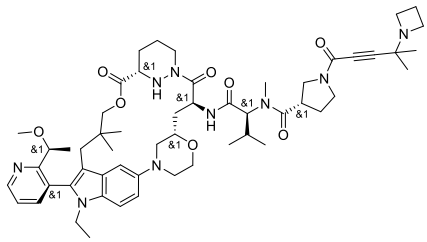
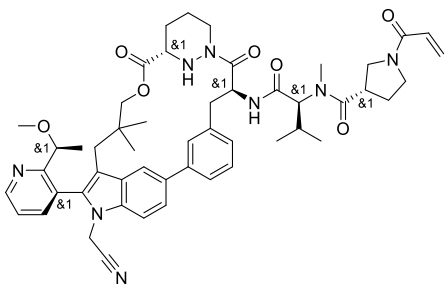
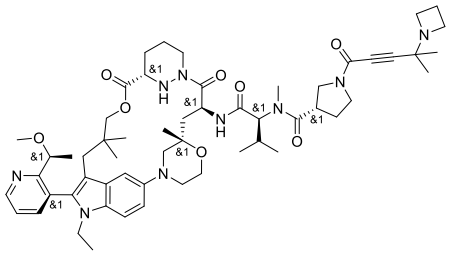
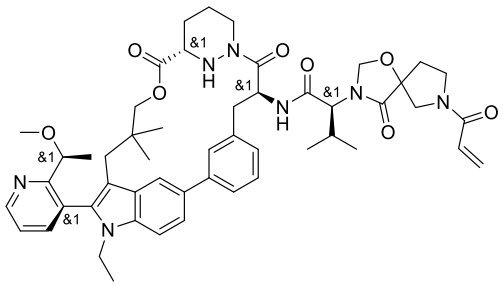
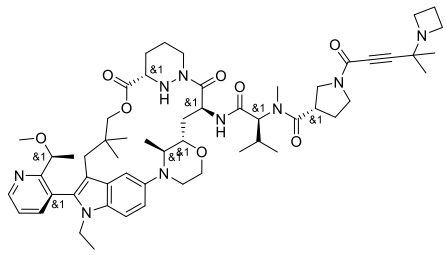
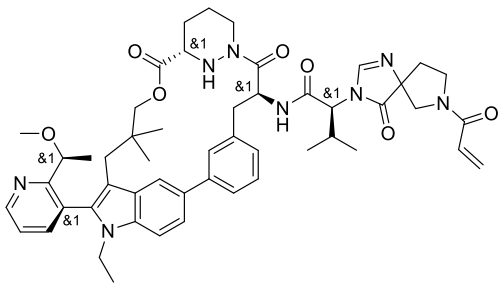
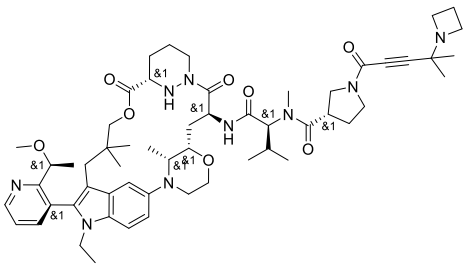
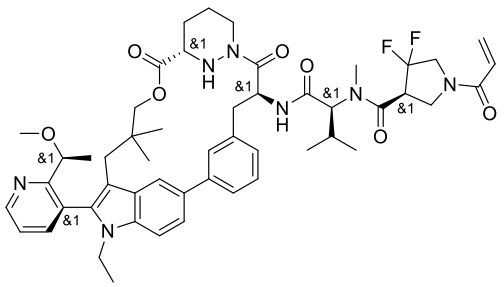
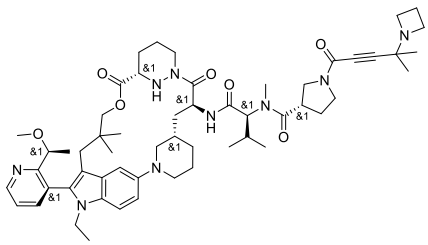
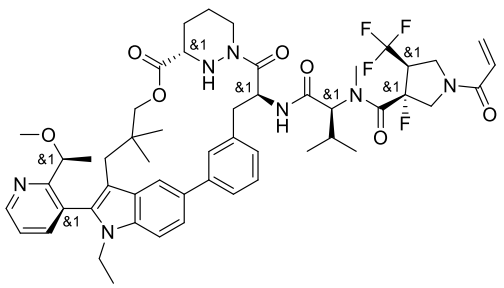


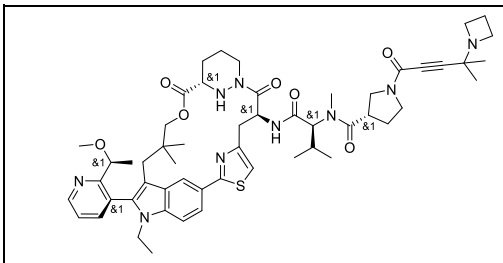


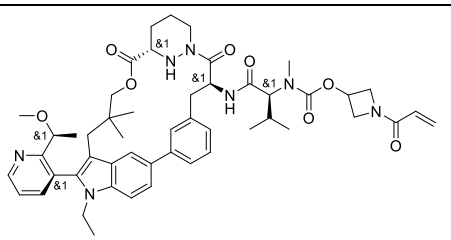


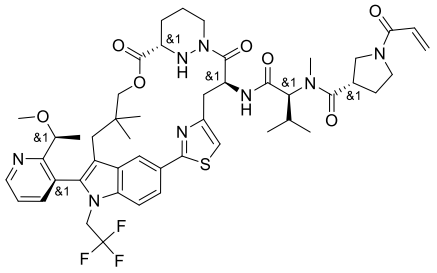


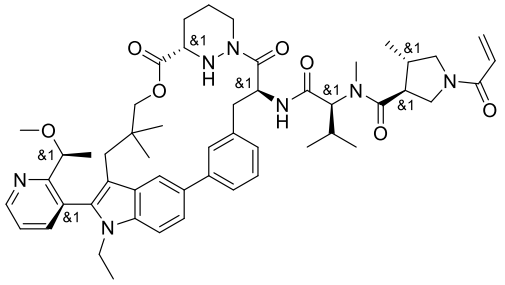
	
	
	
	
	
	

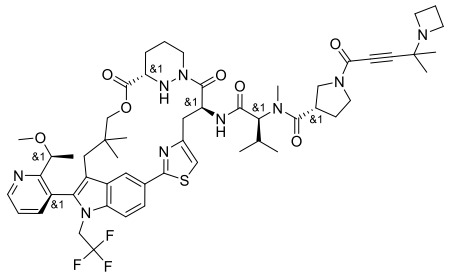













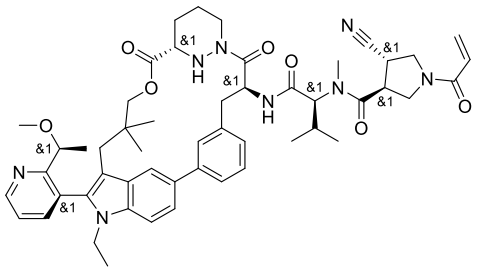


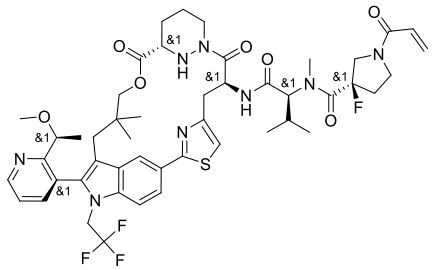


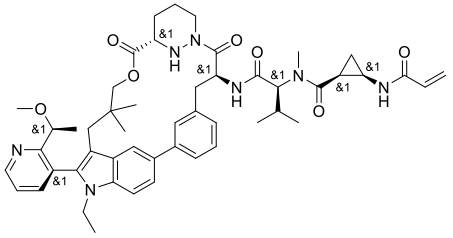


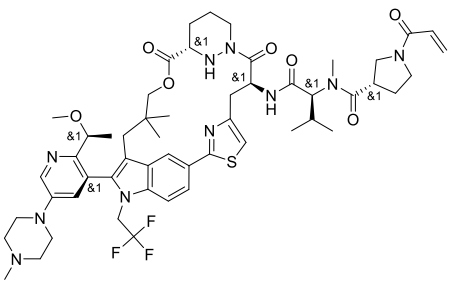


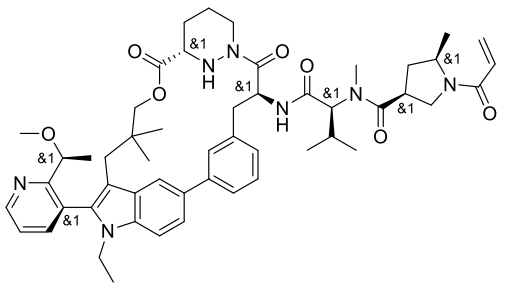


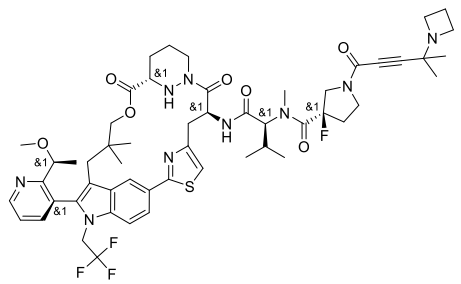
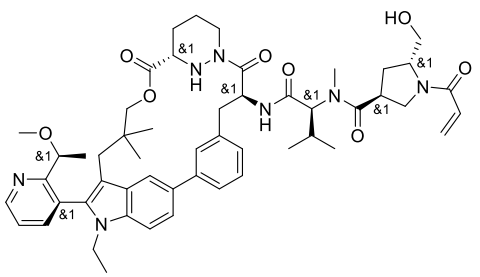
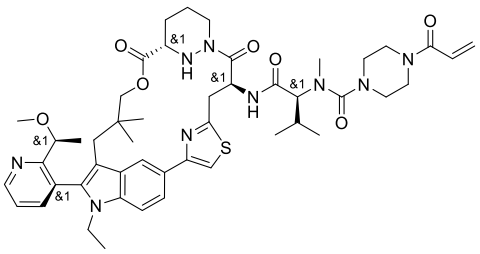
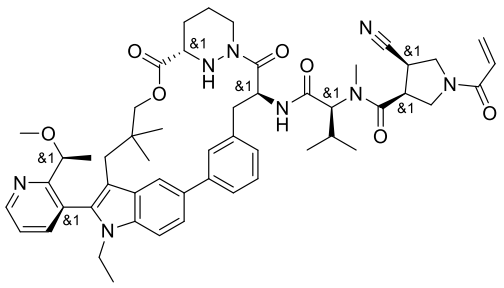
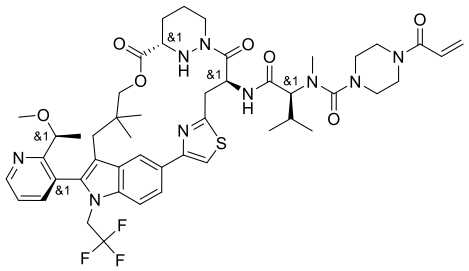
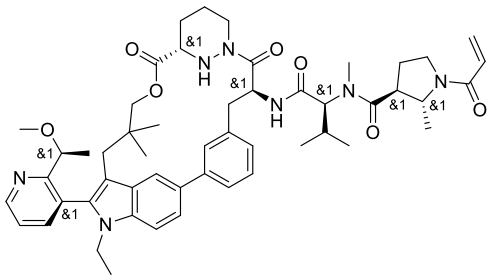
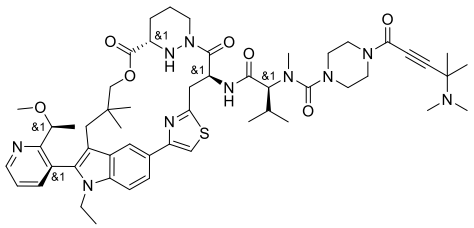
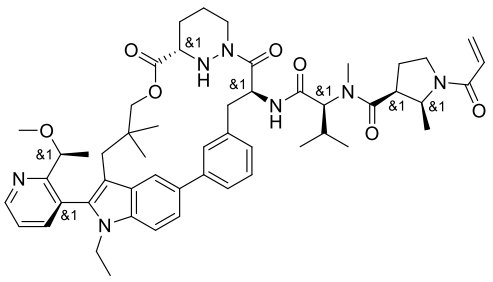
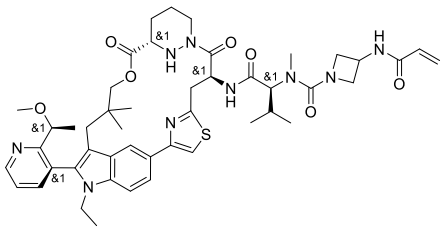
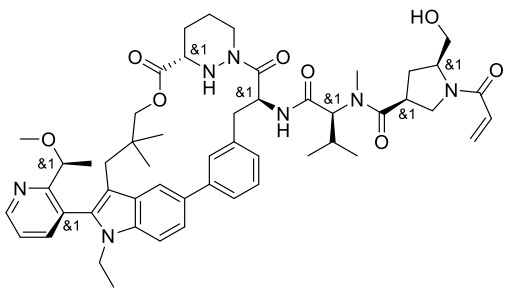
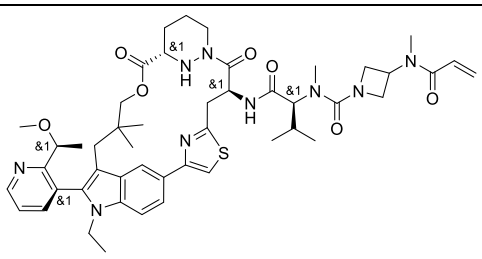
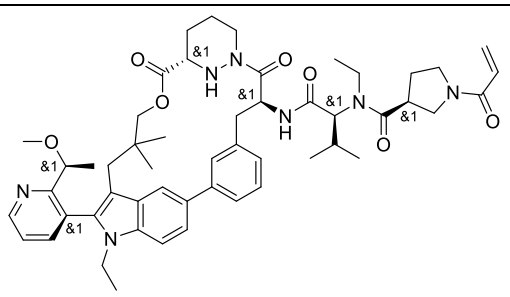


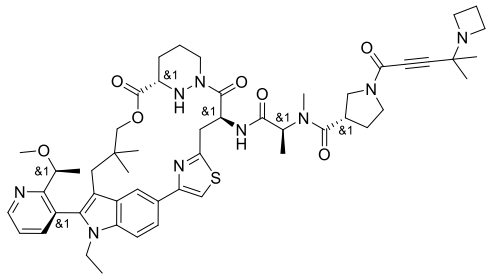
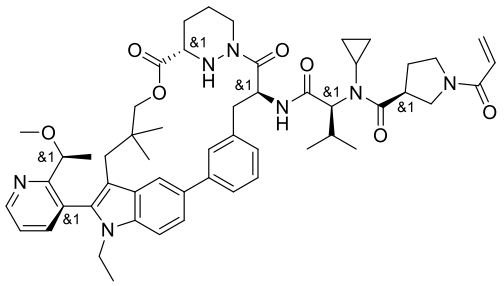
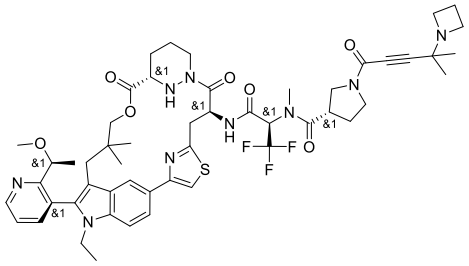
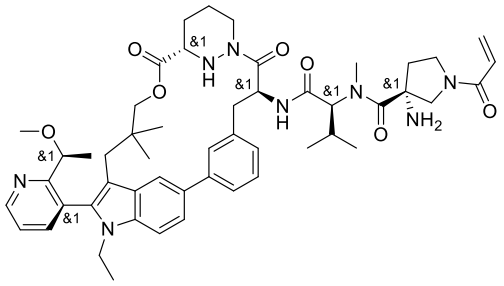
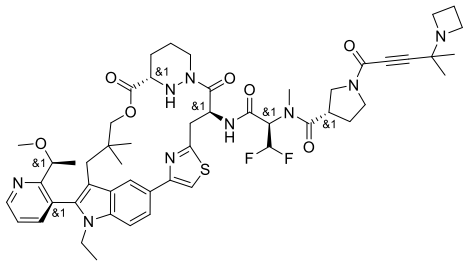
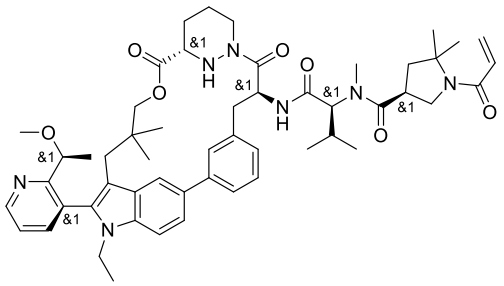
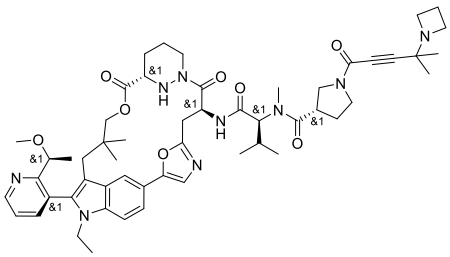
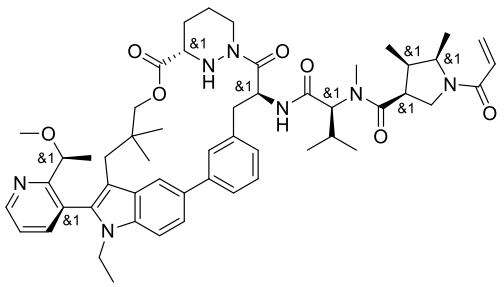
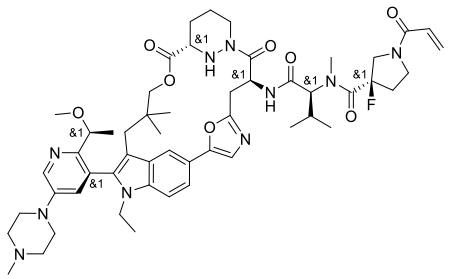
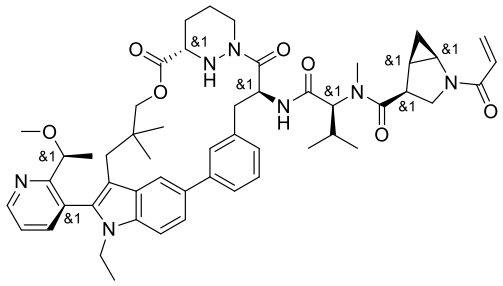
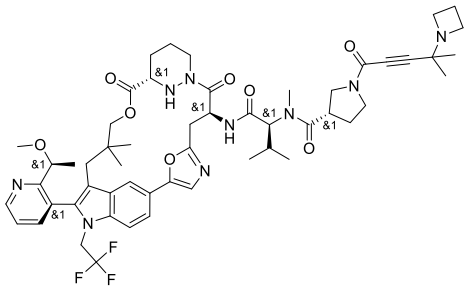
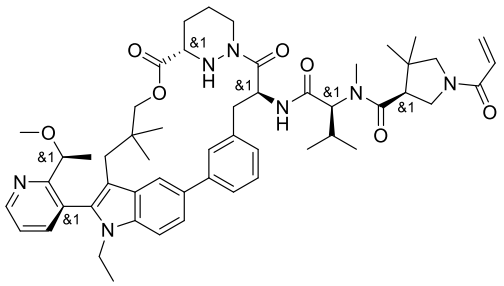


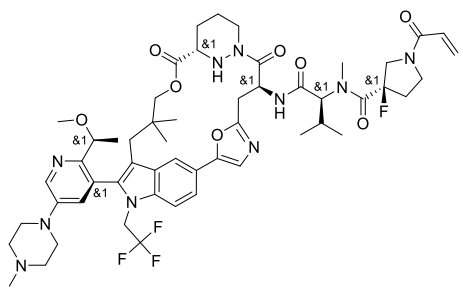
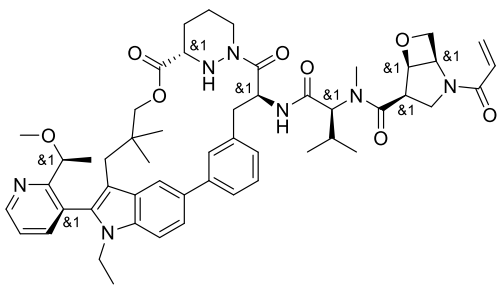
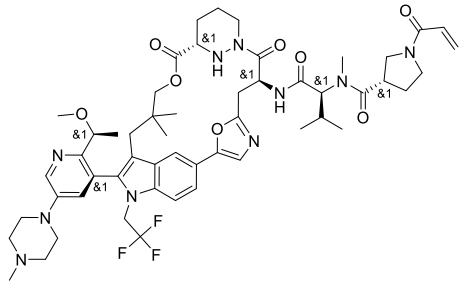
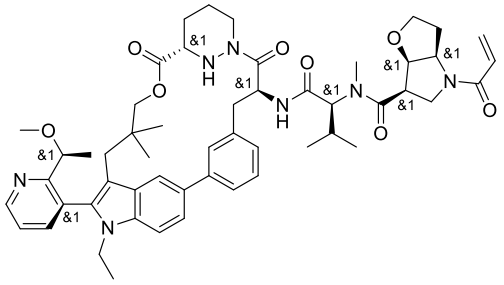
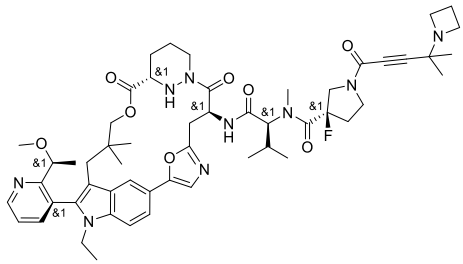
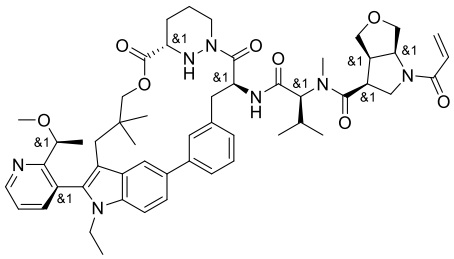
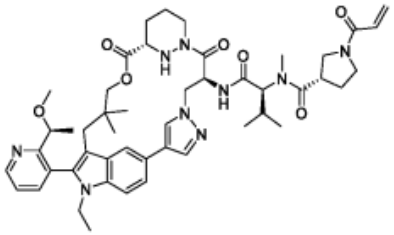
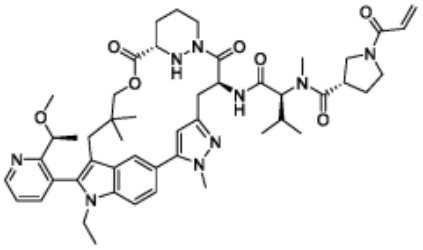
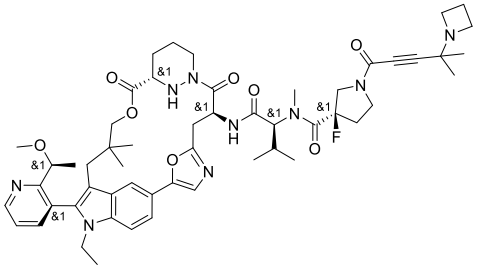
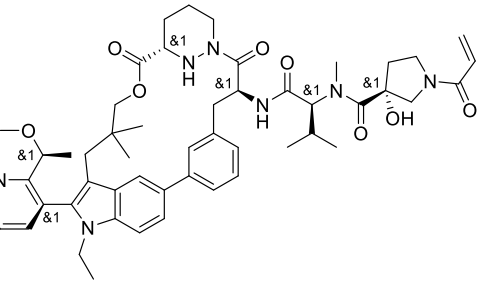
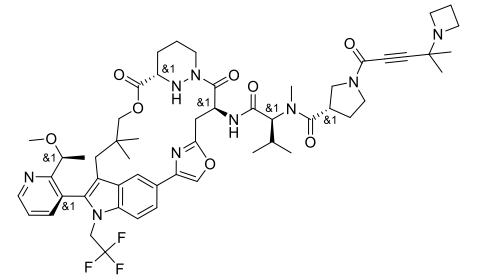
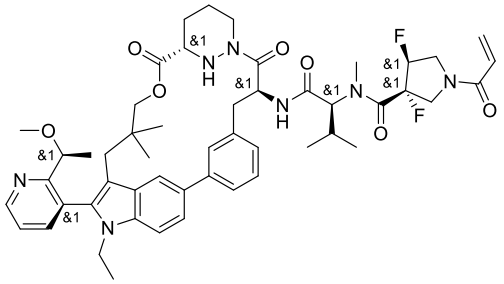


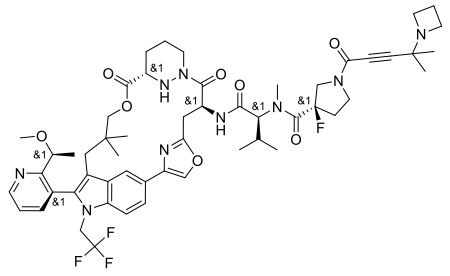
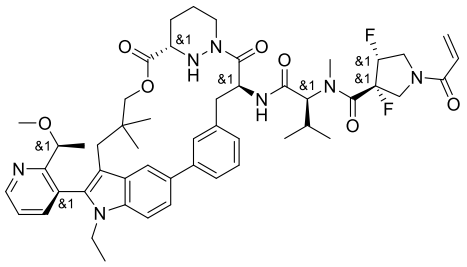
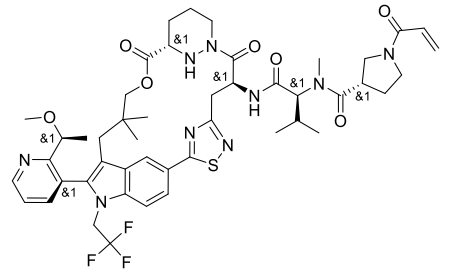
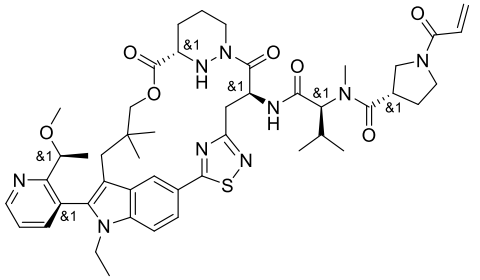
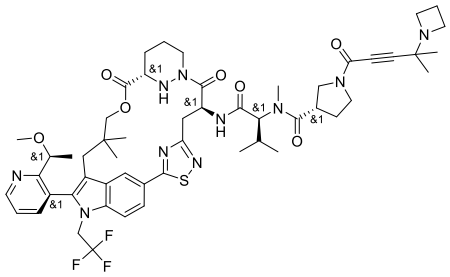
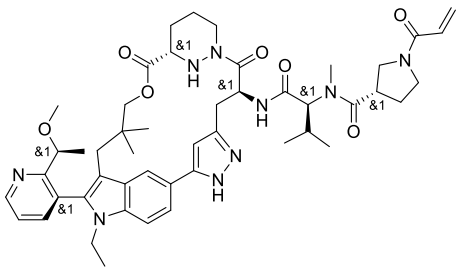
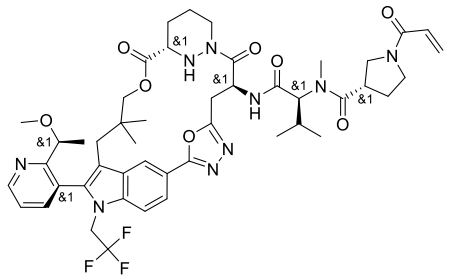
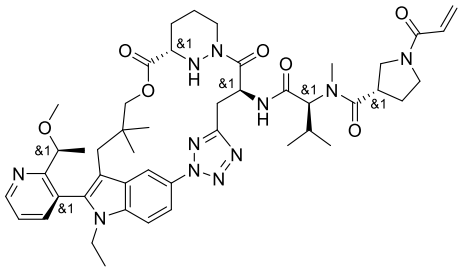
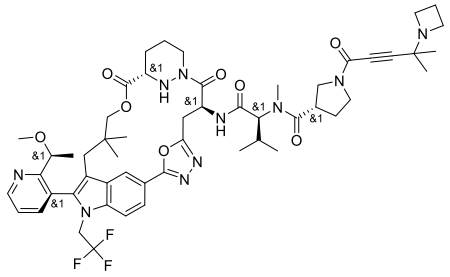
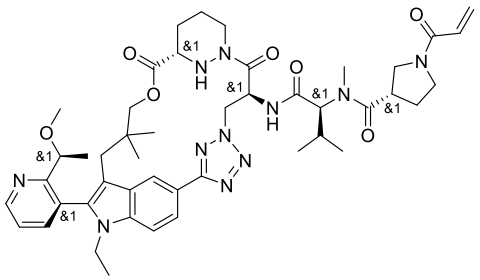
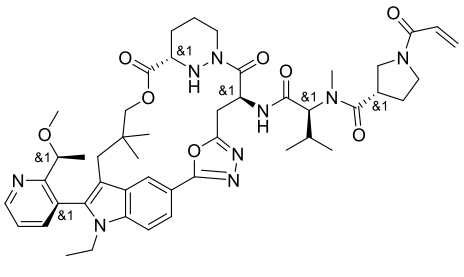
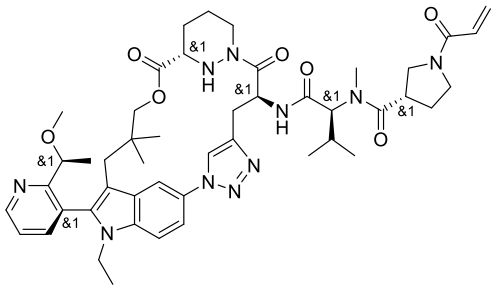


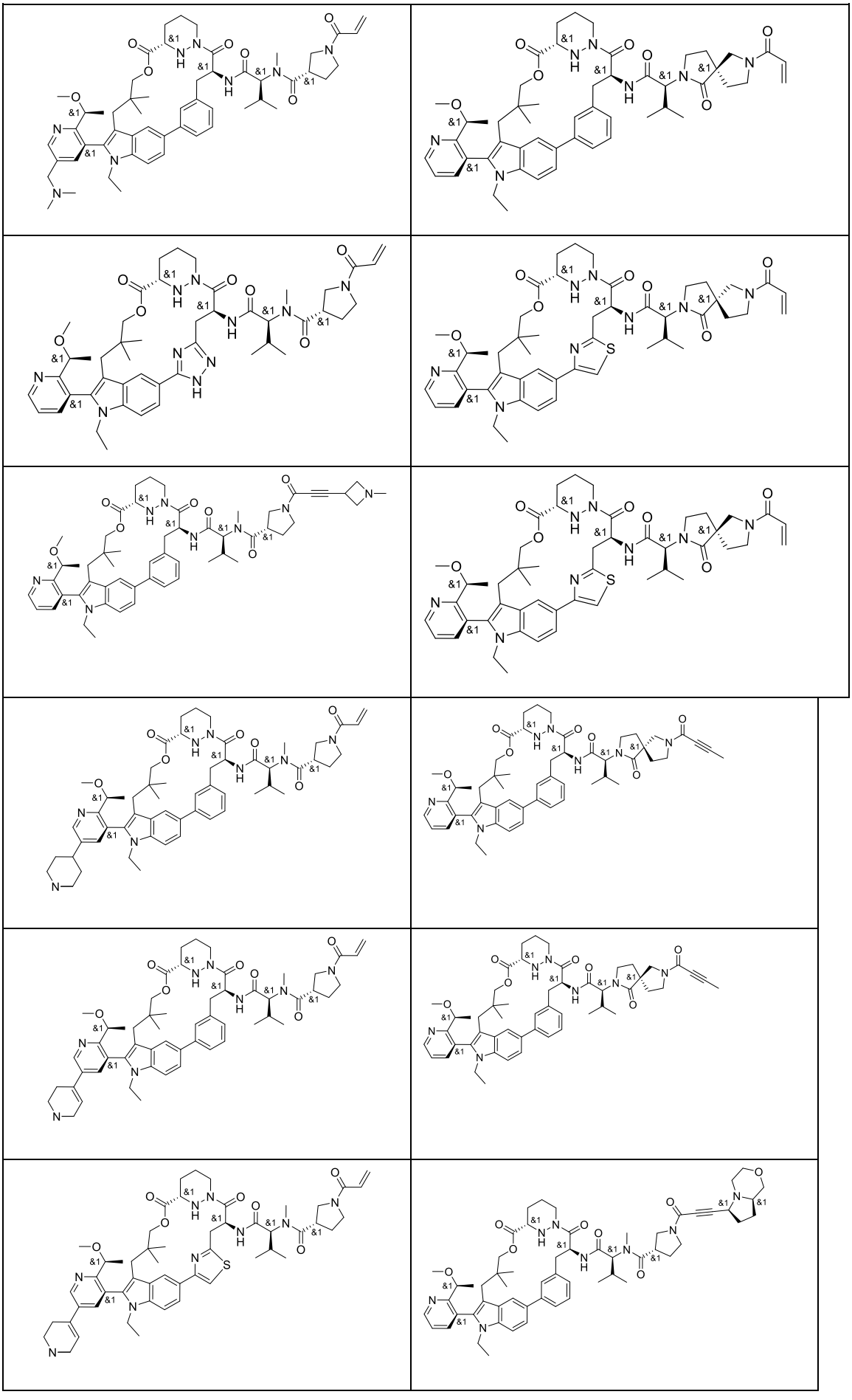


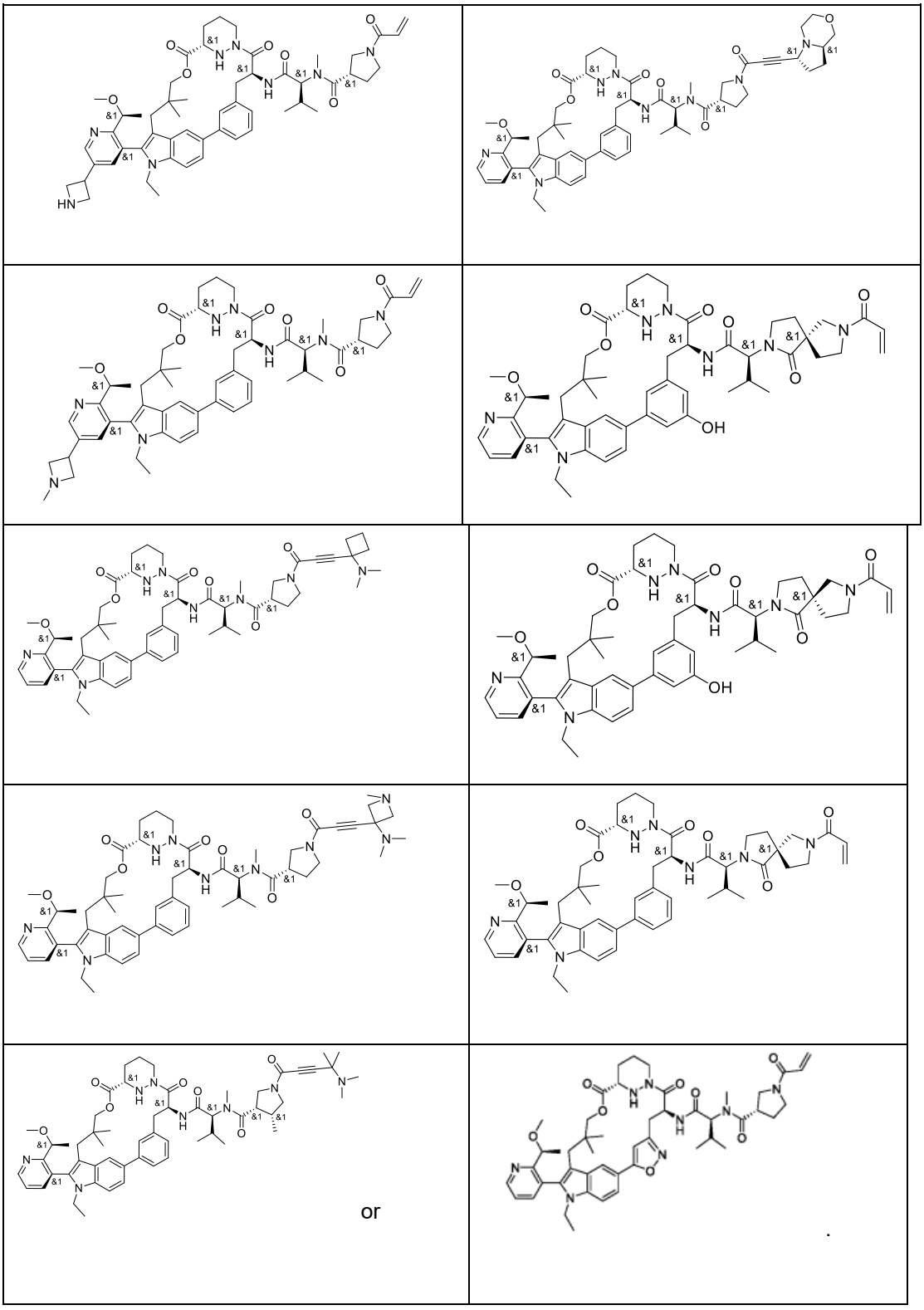
	
	
	
	
	
	



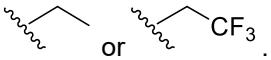


or

.

2. The compound of claim 1, or pharmaceutically acceptable salt thereof, wherein A is optionally substituted thiazole, optionally substituted oxazole, optionally substituted morpholino, optionally substituted pyrrolidinyl, optionally substituted pyridyl, optionally substituted azetidinyl, optionally substituted pyrazinyl, optionally substituted pyrimidine, optionally substituted piperidinyl, optionally substituted oxadiazole, optionally substituted thiadiazole, optionally substituted triazole, optionally substituted thiomorpholino, or optionally substituted phenyl.

3. The compound of claim 1 or 2, or pharmaceutically acceptable salt thereof, wherein R^2 is:



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

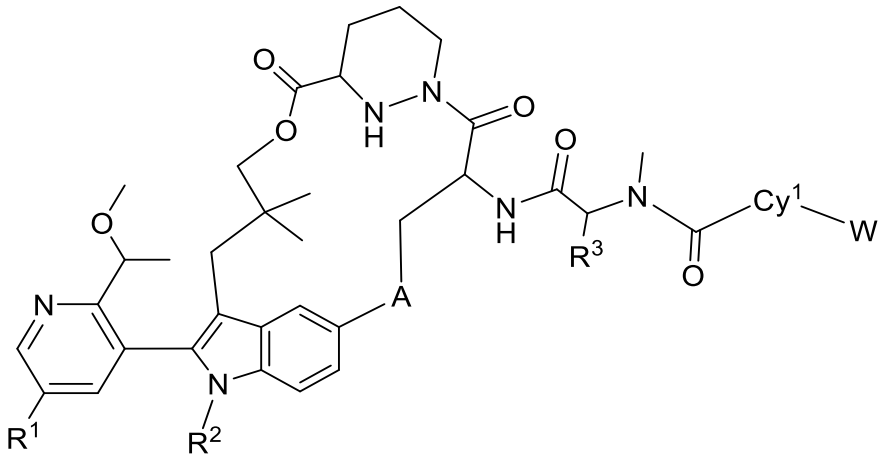
5. The compound of any one of claims 1 to 3, or pharmaceutically acceptable salt thereof, wherein R^3 is optionally substituted C_1-C_3 heteroalkyl.

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

7. The compound of any one of claims 1 to 5, or pharmaceutically acceptable salt thereof, wherein A is optionally substituted phenyl.

8. The compound of any one of claims 1 to 5, or pharmaceutically acceptable salt thereof, wherein A is optionally substituted 3 to 6-membered heterocycloalkylene.

9. The compound of any one of claims 1 to 8, or pharmaceutically acceptable salt thereof, having the structure of Formula II-5:



Formula II-5,

wherein Cy^1 is optionally substituted spirocyclic 8 to 11-membered heterocycloalkylene or optionally substituted bicyclic 7 to 9-membered heterocycloalkylene; and

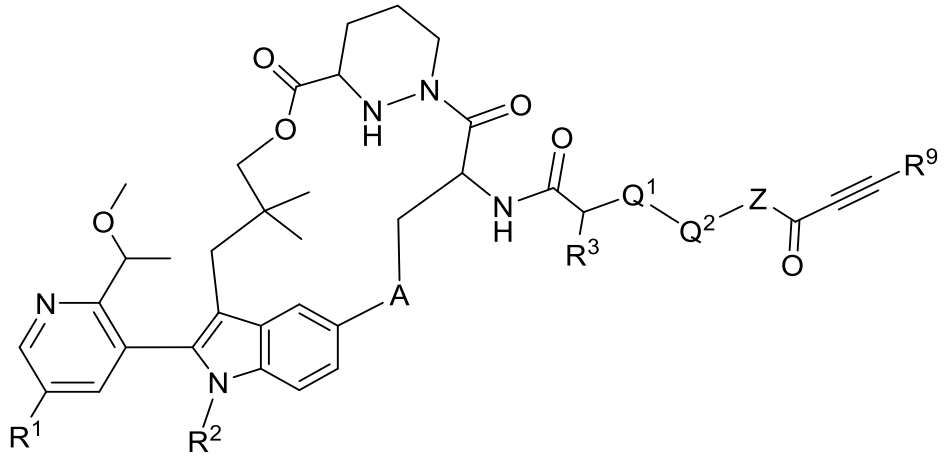
wherein W is the vinyl ketone of Formula IVa or the vinyl sulfone of Formula IVc.

10. The compound of any one of claims 1 to 9, or pharmaceutically acceptable salt thereof, wherein W is a cross-linking group comprising the vinyl ketone of Formula IVa.

11. The compound of any one of claims 1 to 9, or pharmaceutically acceptable salt thereof, wherein W is a cross-linking group comprising the vinyl sulfone of Formula IVc.

12. The compound of any one of claims 1 to 9, or pharmaceutically acceptable salt thereof, wherein W is a cross-linking group comprising the ynone of Formula IVb.

13. The compound of claim 12, or pharmaceutically acceptable salt thereof, having the structure of Formula II-6:



Formula II-6,

wherein

R^9 is hydrogen, -C_1-C_3 alkyl, -C_1-C_3 alkyl substituted with one, two, three, or four substituents independently selected from -OH, -O-C_1-C_3 alkyl, -NH_2, -NH(C_1-C_3 alkyl), -N(C_1-C_3 alkyl)$_2$, a 4 to 7-membered saturated cycloalkyl, and a 4 to 7-membered saturated heterocycloalkyl comprising one, two, three, or four heteroatoms independently selected from nitrogen, oxygen, and sulfur;

Q^1 is CH_2, NR^N, or O;

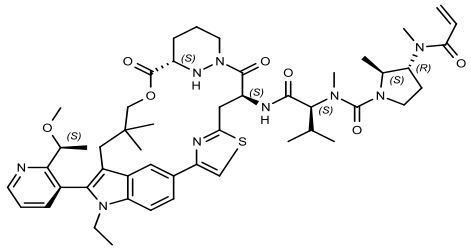
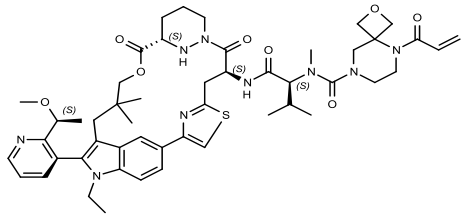
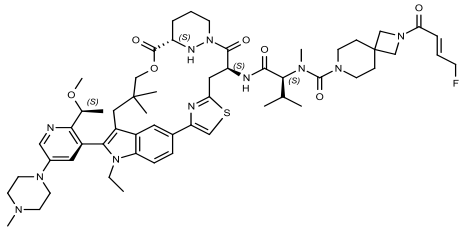
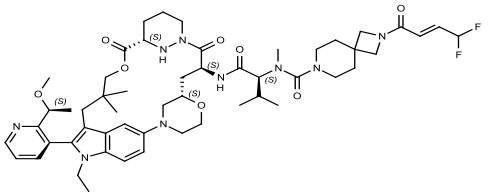
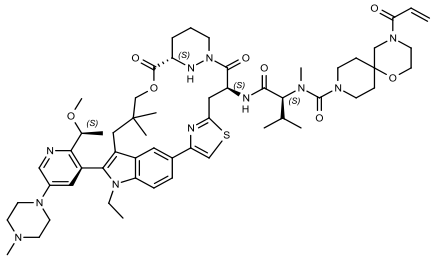
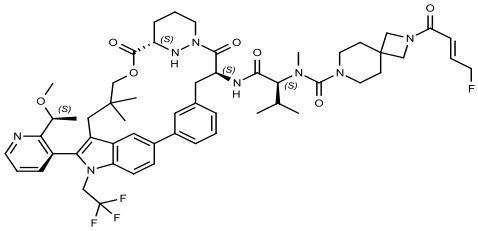
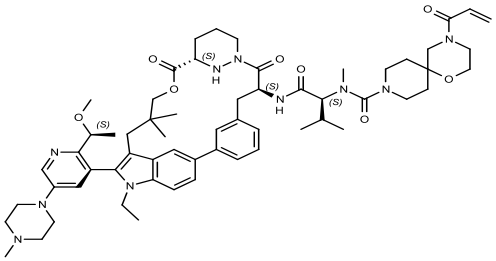
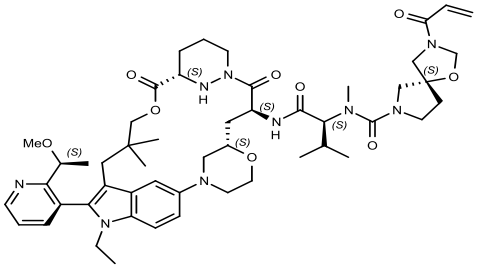
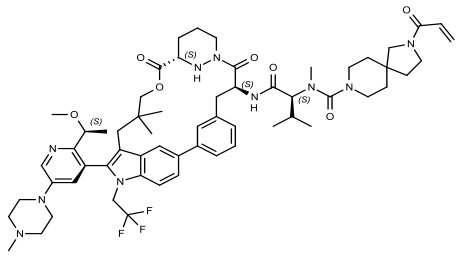
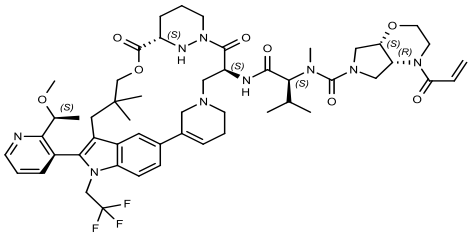
Q^2 is CO, NR^N, or O;

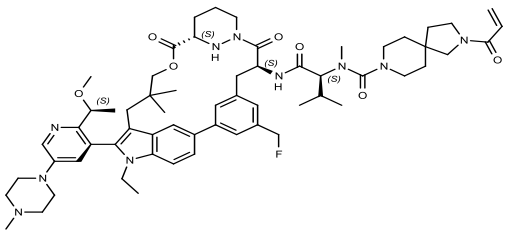
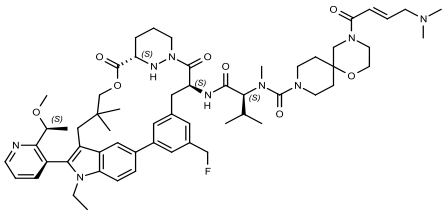
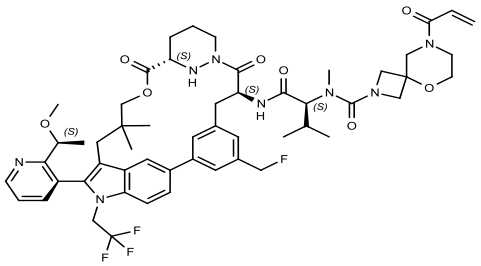
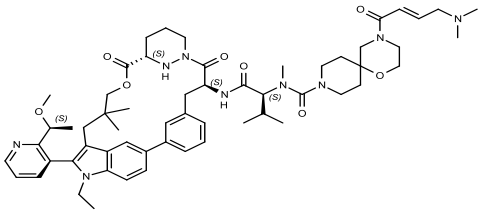
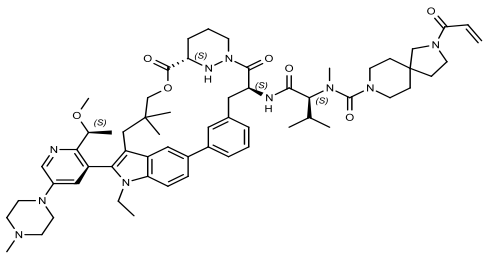
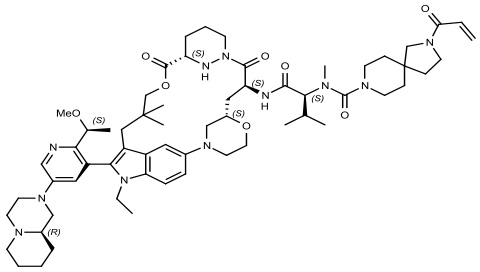
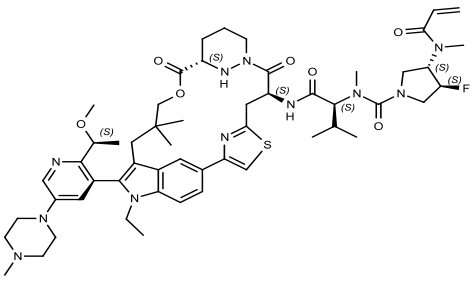
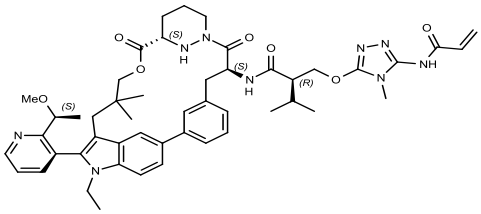
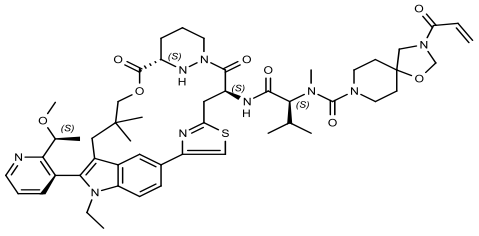
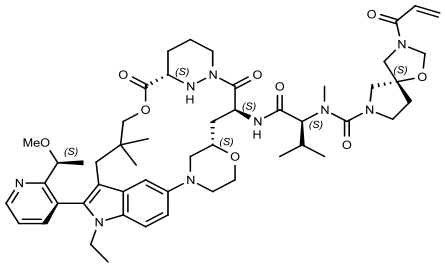
R^N is hydrogen, optionally substituted C_1–C_4 alkyl, optionally substituted C_2-C_4 alkenyl, optionally substituted C_2-C_4 alkynyl, optionally substituted 3 to 14-membered heterocycloalkyl, optionally substituted 6 to 10-membered aryl, or optionally substituted C_1-C_7 heteroalkyl; and

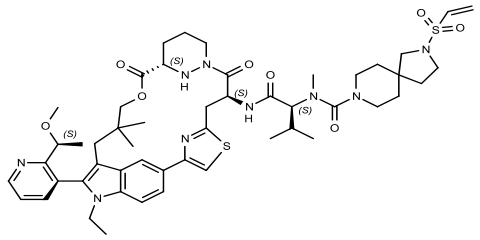
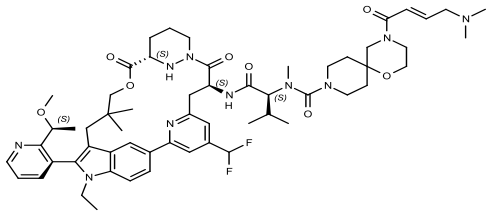
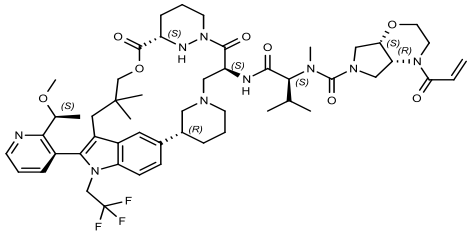
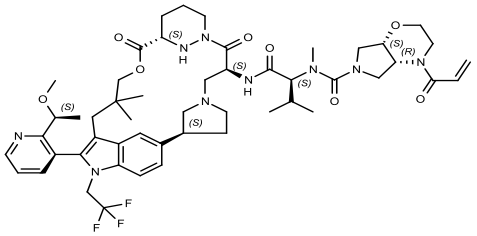
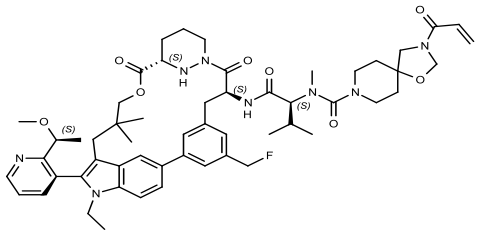
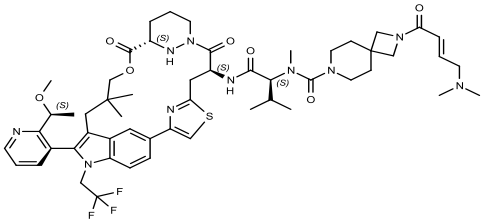
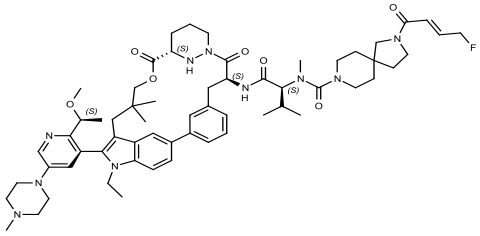
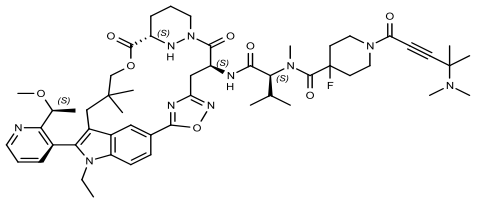
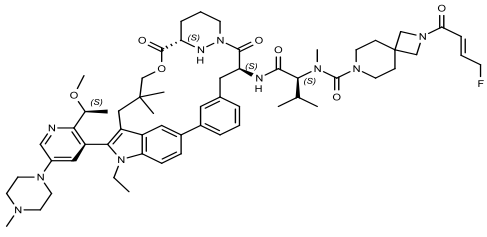
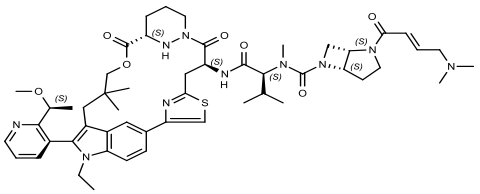
Z is optionally substituted 3 to 6-membered heterocycloalkylene or optionally substituted 5 to 10-membered heteroarylene; or

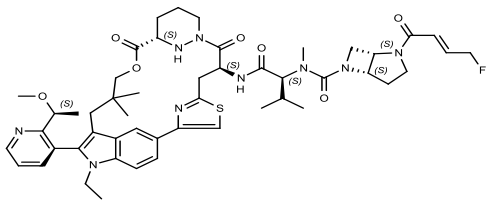
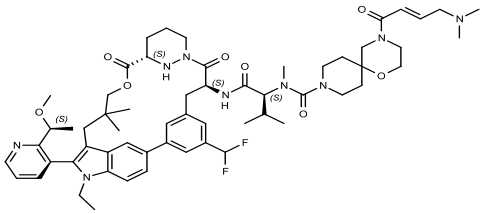
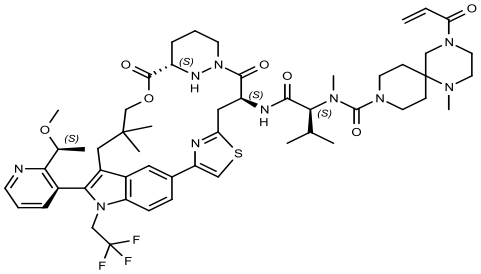
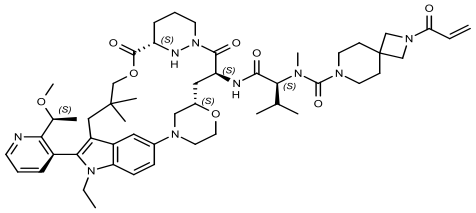
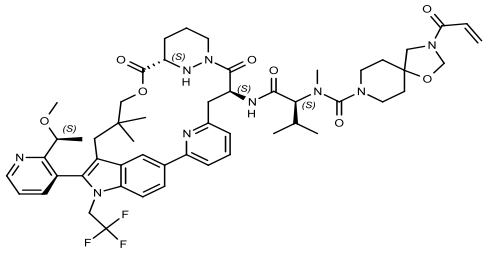
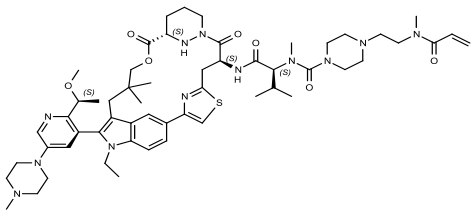
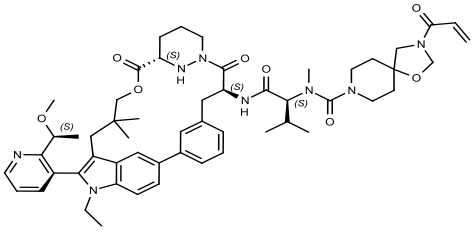
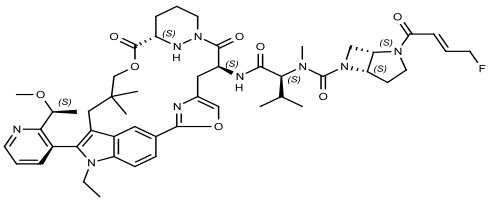
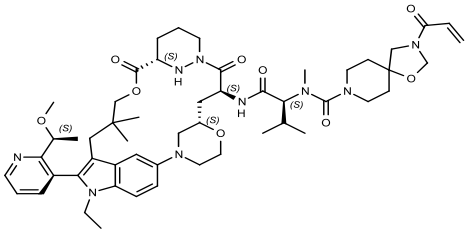
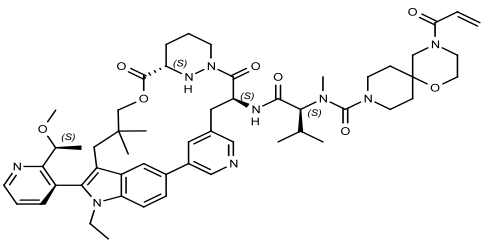
wherein Q^1-Q^2-Z is an optionally substituted 9 to 10-membered spirocyclic heterocycloalkylene.

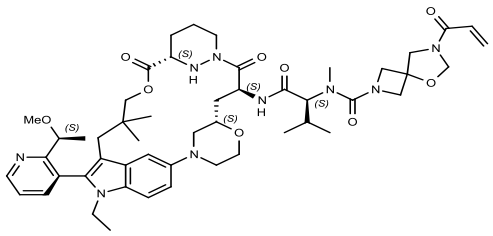
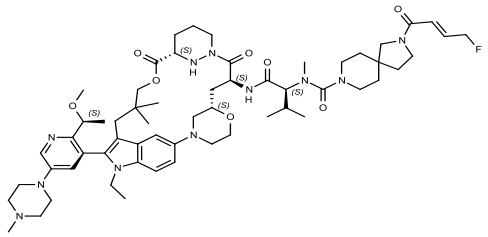
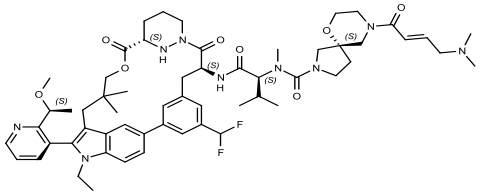
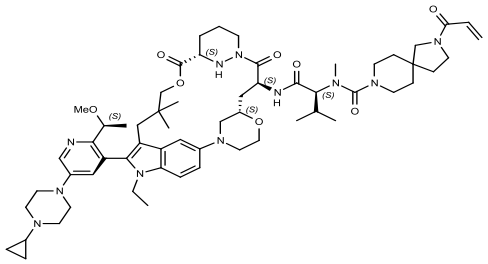
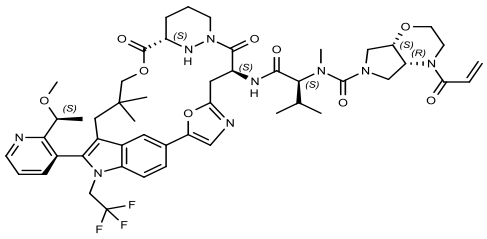
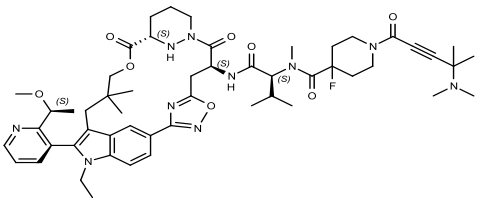
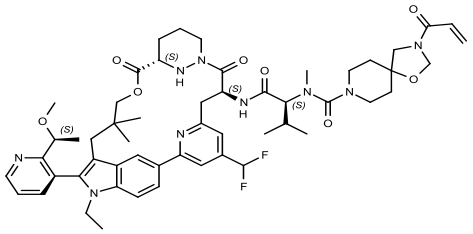
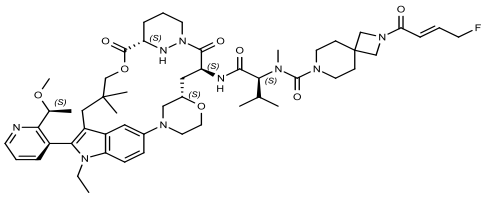
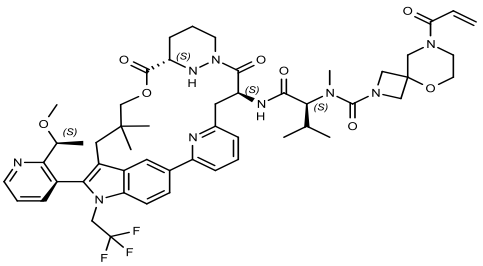
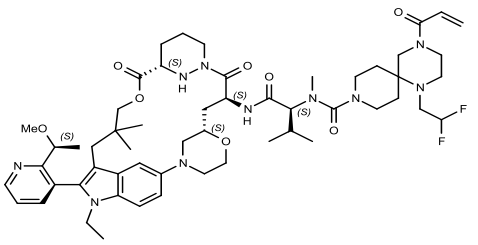
14. A compound, or a pharmaceutically acceptable salt thereof, selected from Table 1 as shown hereafter:

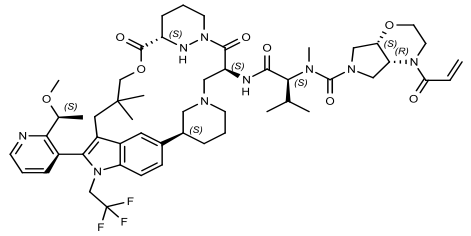
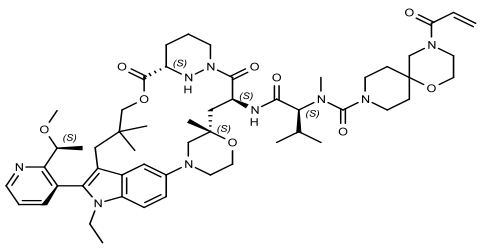
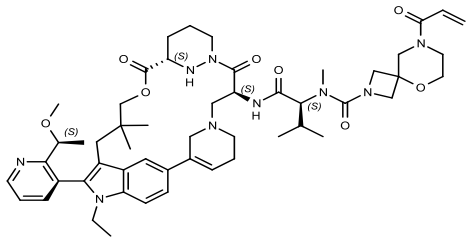
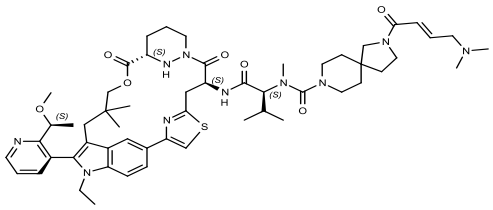
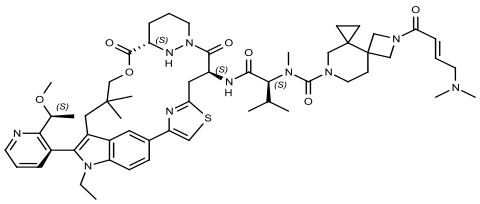
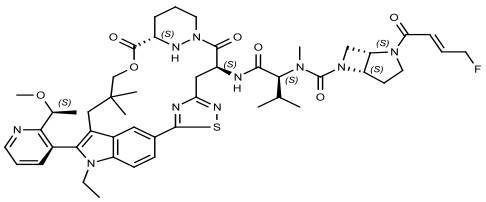
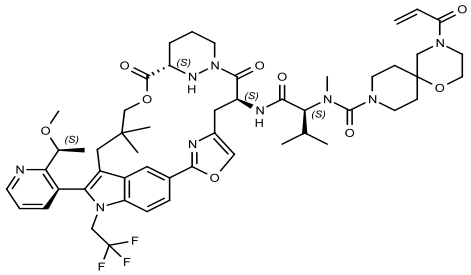
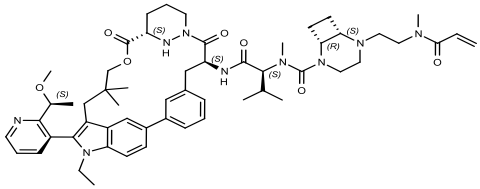
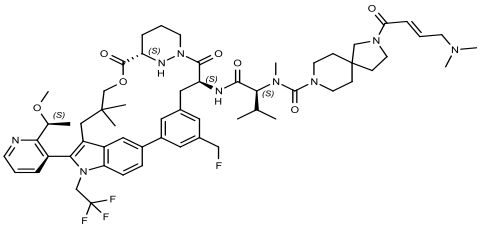
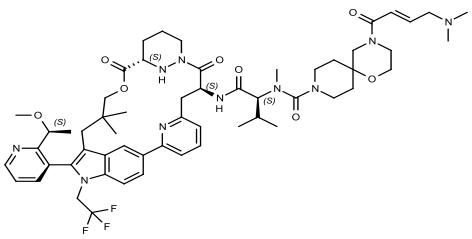
Ex#	Structure	Ex#	Structure
A1		A105	
A2		A106	
A3		A107	
A4		A108	
A5		A109	

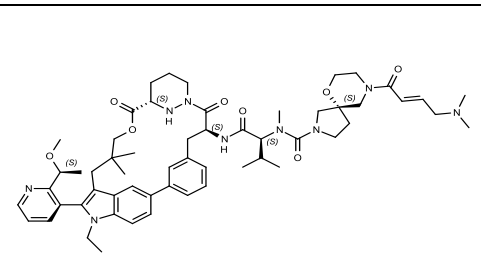
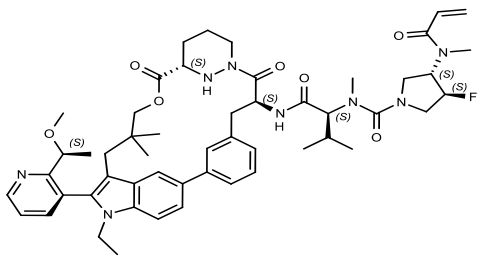
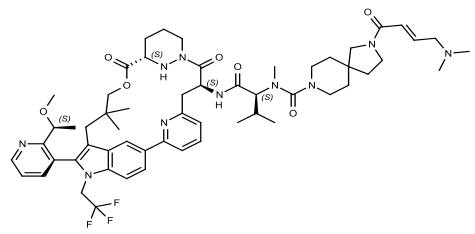
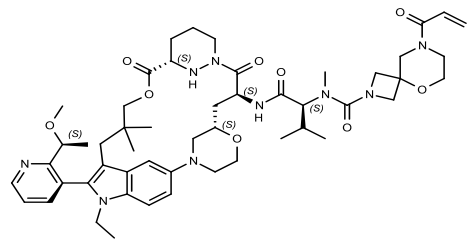
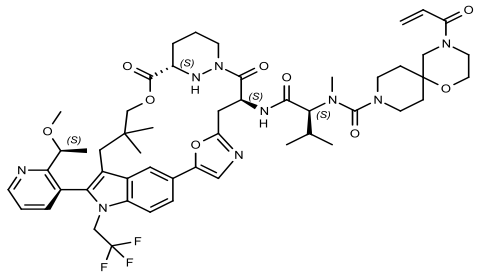
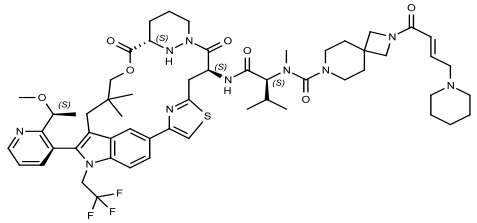
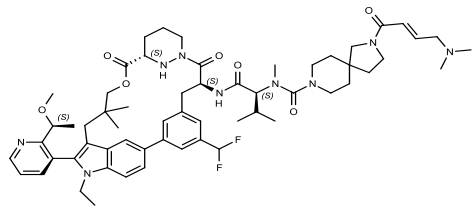
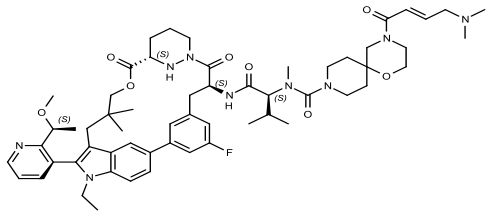
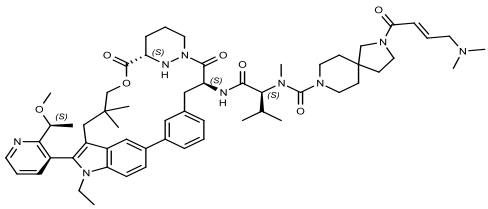
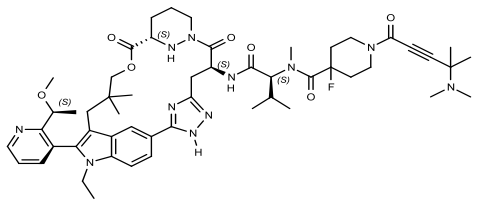
Ex#	Structure	Ex#	Structure
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A7		A111	
A8		A112	
A9		A113	
A10		A114	

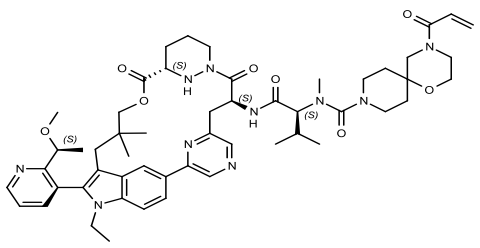
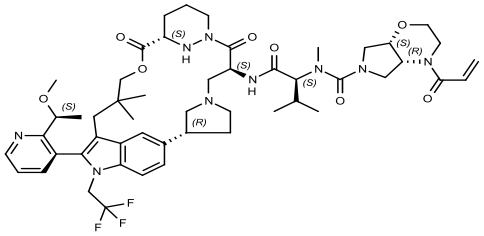
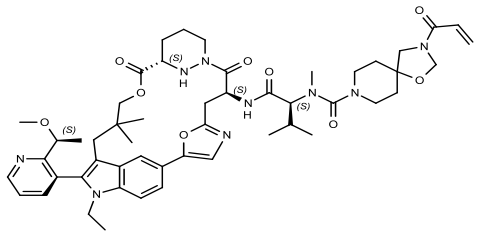
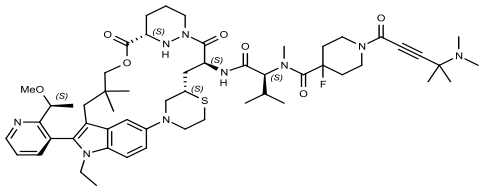
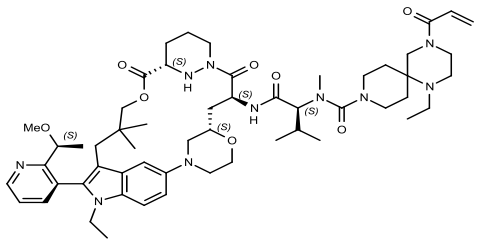
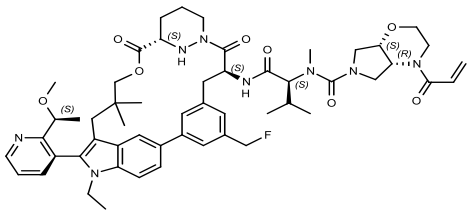
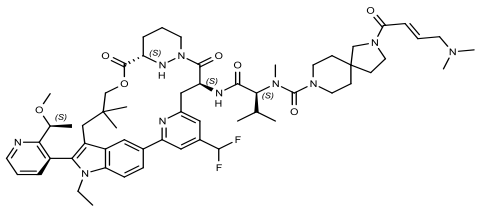
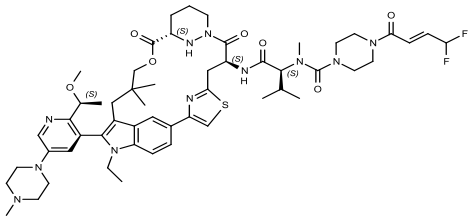
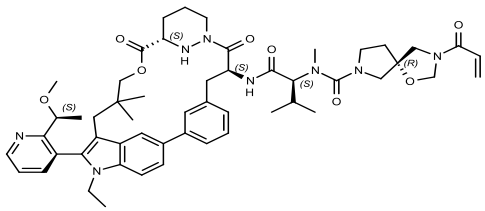
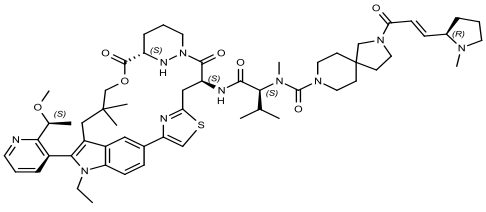
Ex#	Structure	Ex#	Structure
A11		A115	
A12		A116	
A13		A117	
A14		A118	
A15		A119	

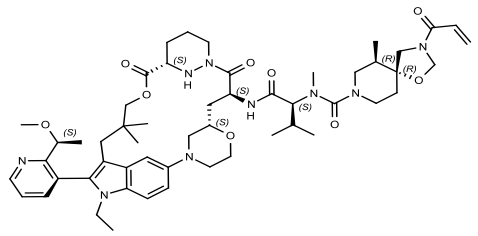
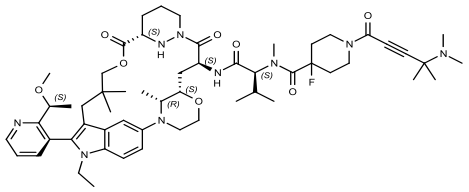
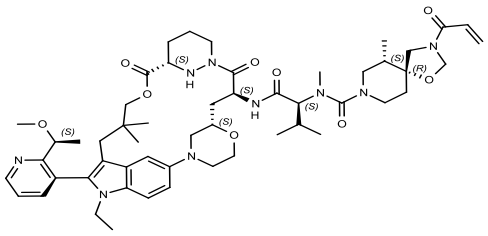
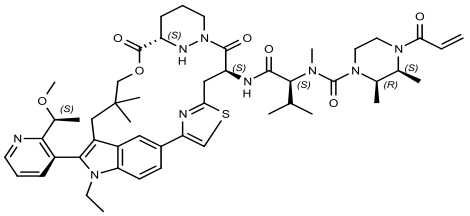
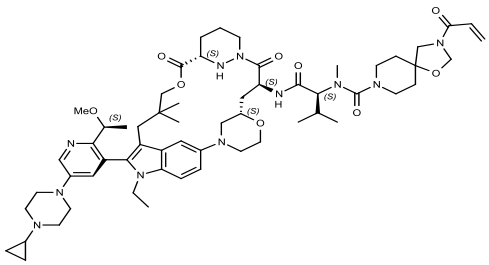
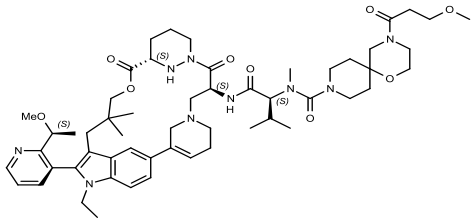
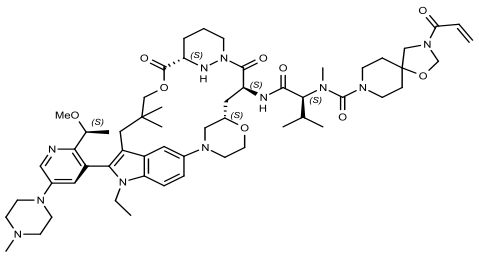
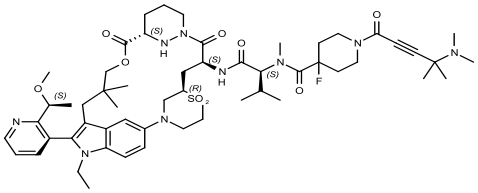
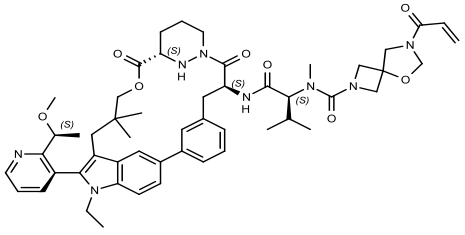
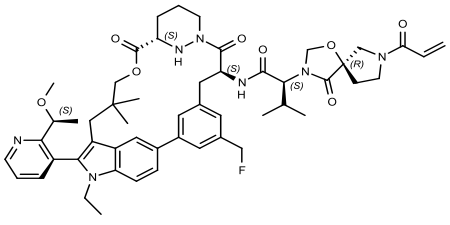
Ex#	Structure	Ex#	Structure
A16		A120	
A17		A121	
A18		A122	
A19		A123	
A20		A124	

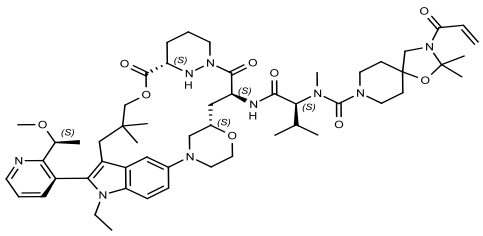
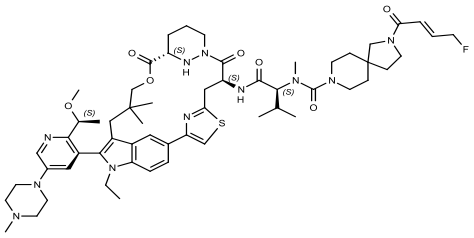
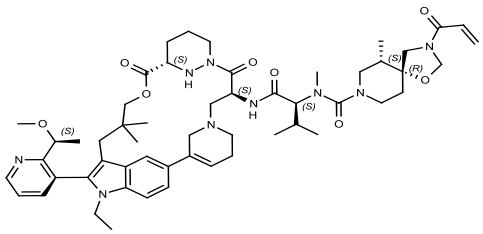
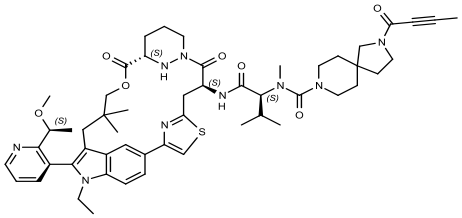
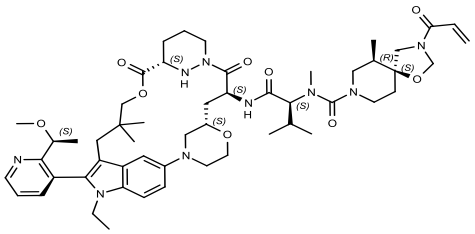
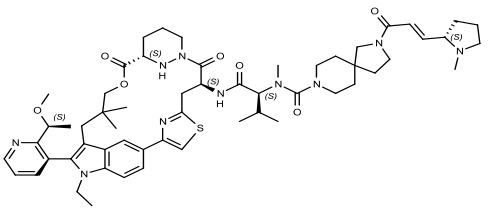
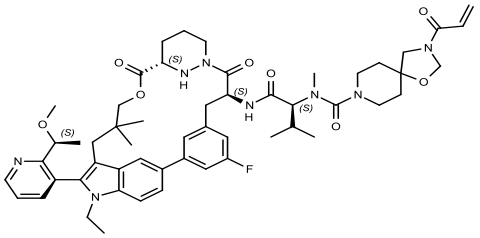
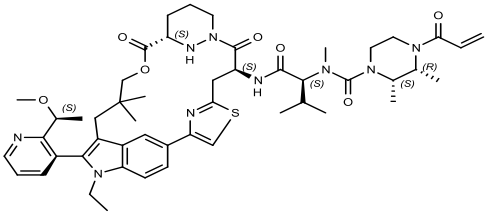
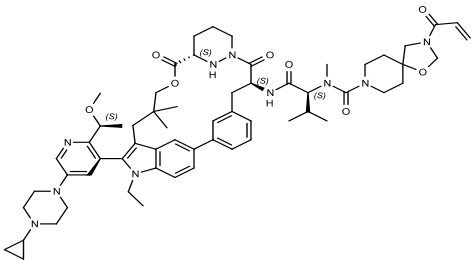
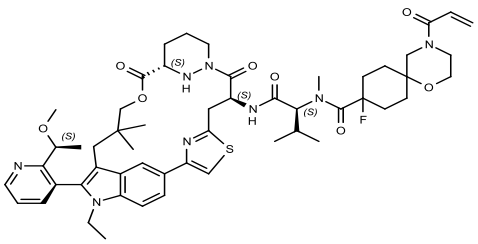
Ex#	Structure	Ex#	Structure
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A22		A126	
A23		A127	
A24		A128	
A25		A129	

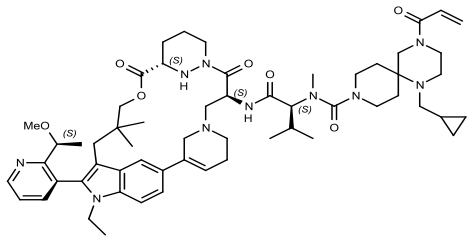
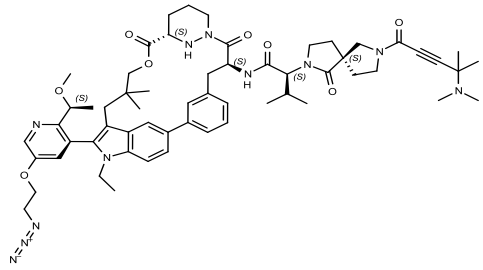
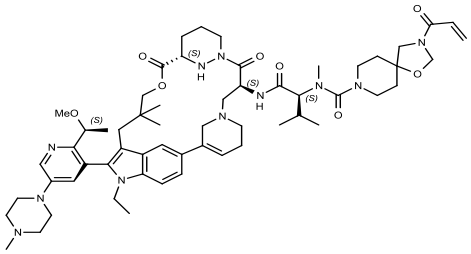
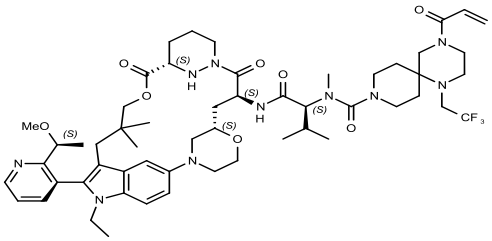
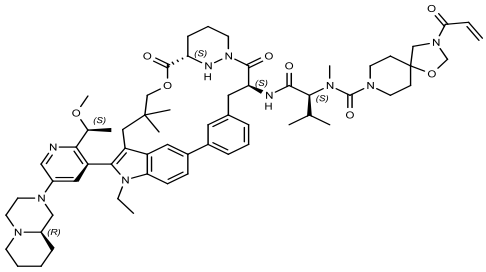
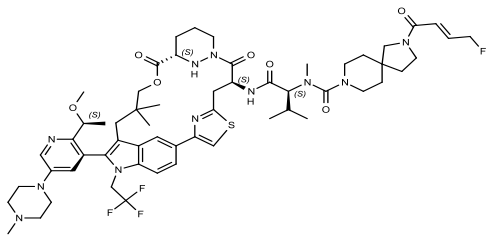
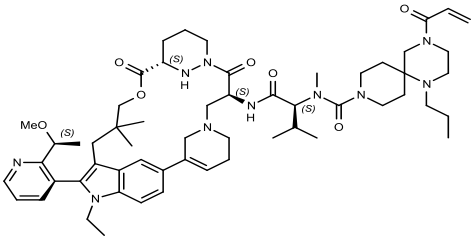
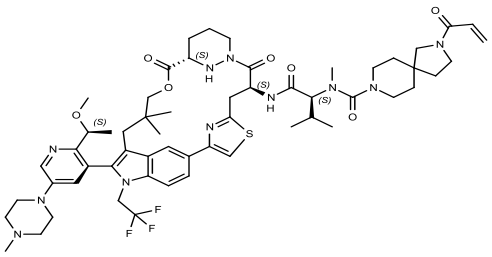
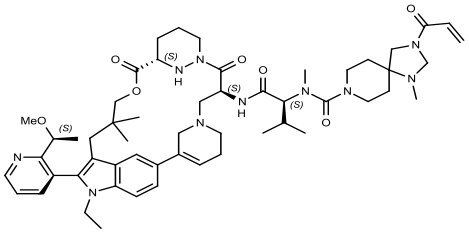
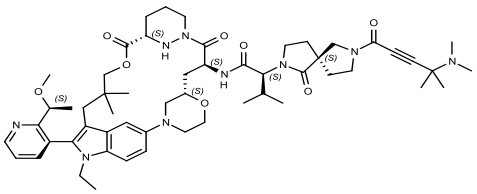
Ex#	Structure	Ex#	Structure
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A28		A132	
A29		A133	
A30		A134	

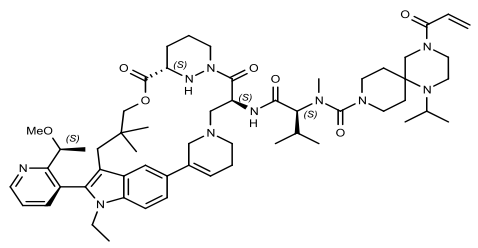
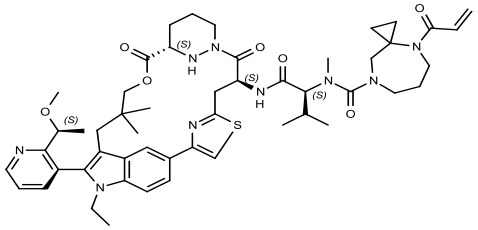
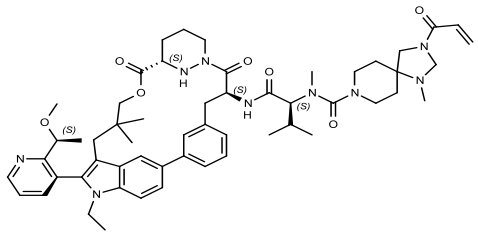
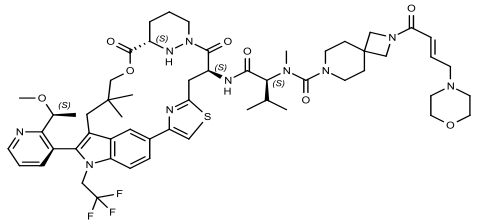
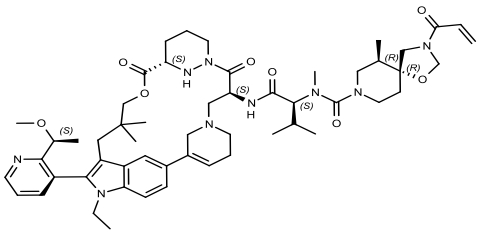
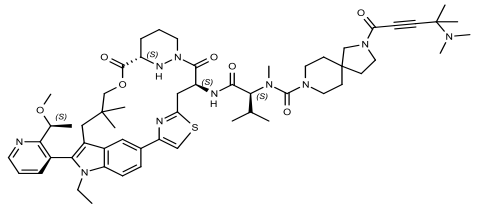
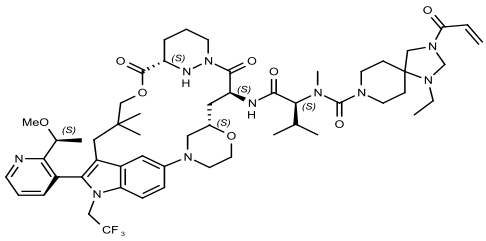
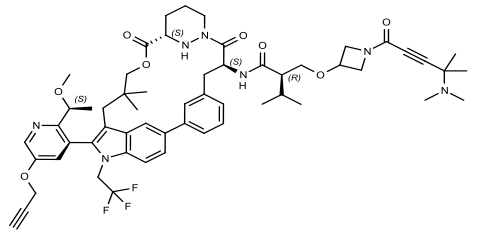
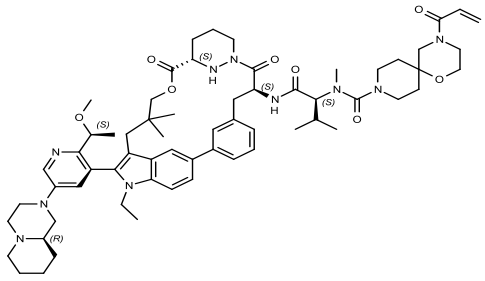
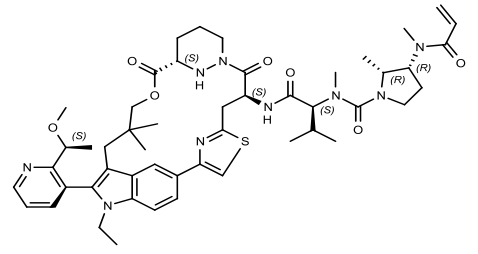
Ex#	Structure	Ex#	Structure
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A32		A136	
A33		A137	
A34		A138	
A35		A139	

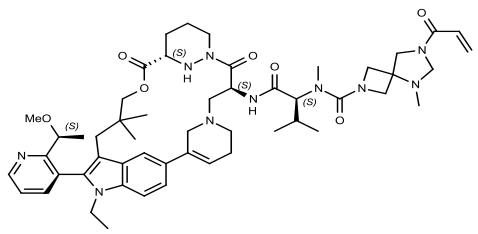
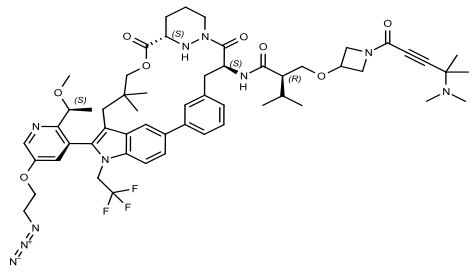
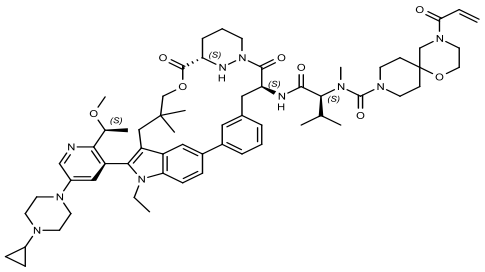
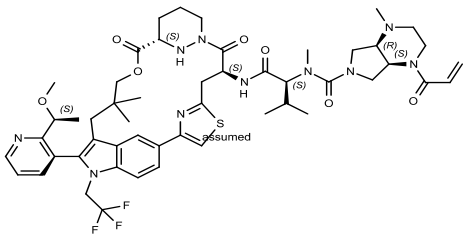
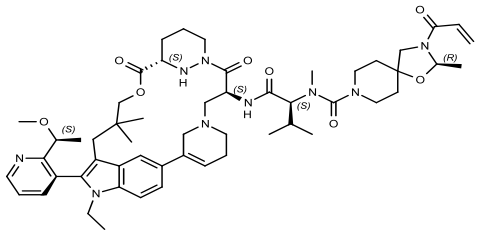
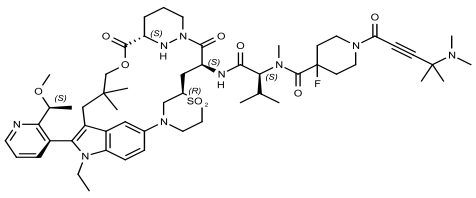
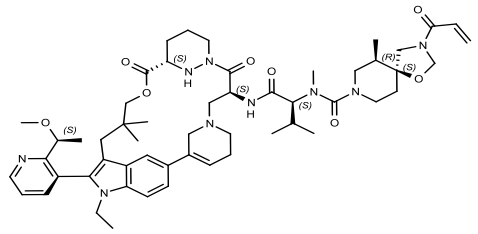
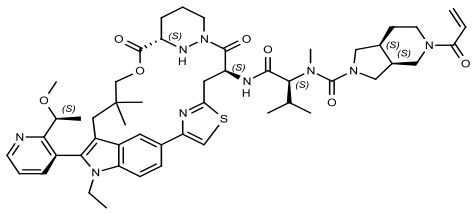
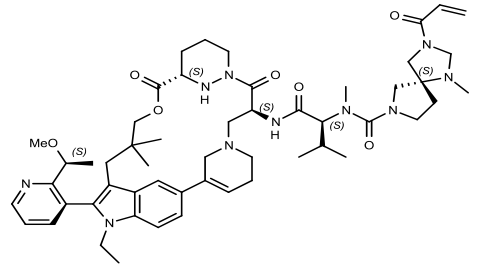
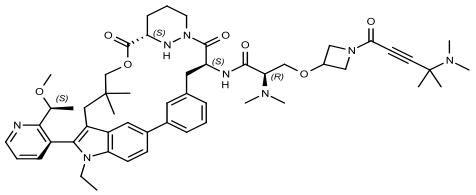
Ex#	Structure	Ex#	Structure
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A37		A141	
A38		A142	
A39		A143	
A40		A144	

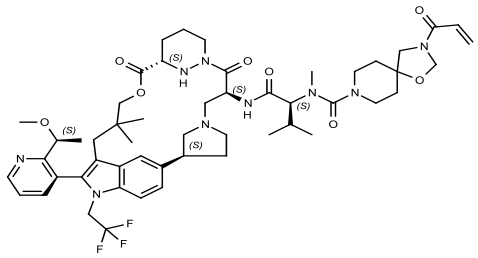
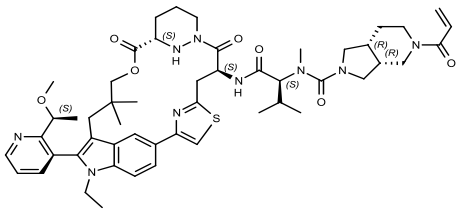
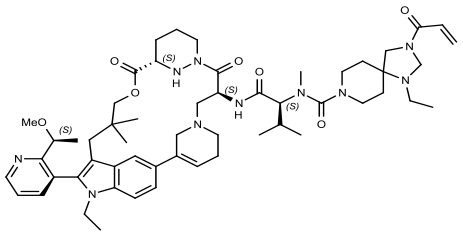
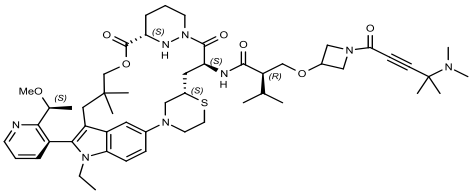
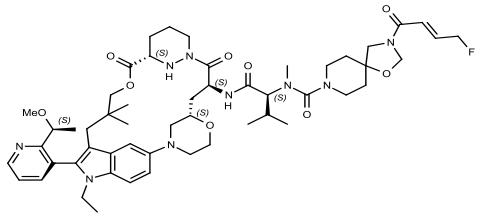
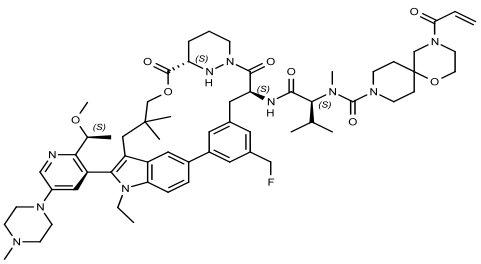
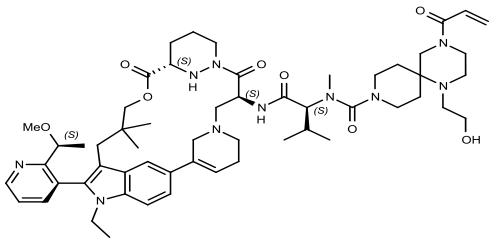
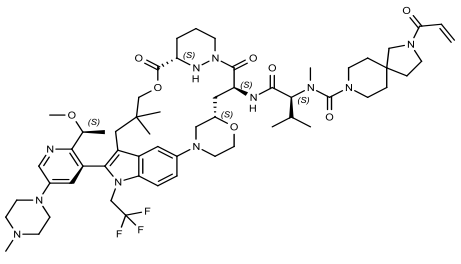
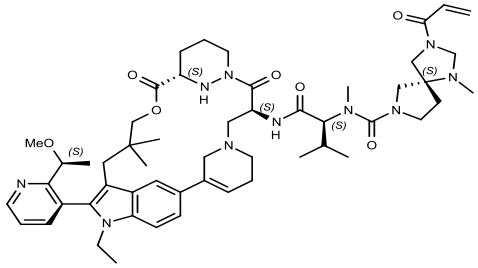
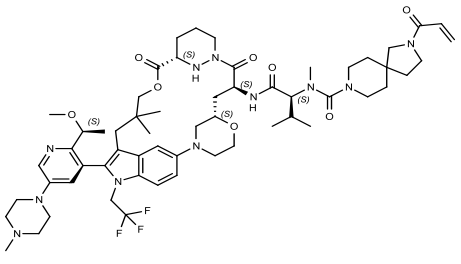
Ex#	Structure	Ex#	Structure
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A42		A146	
A43		A147	
A44		A148	
A45		A149	

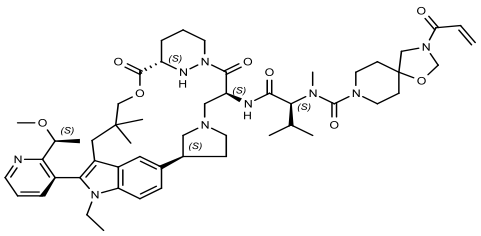
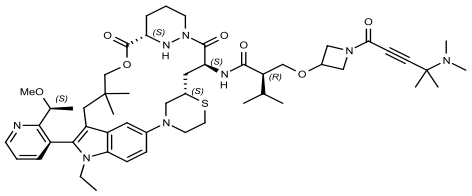
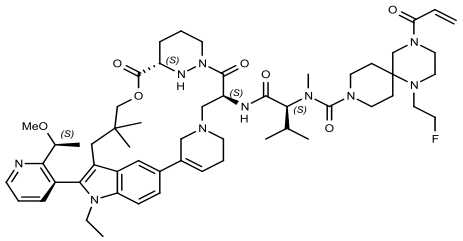
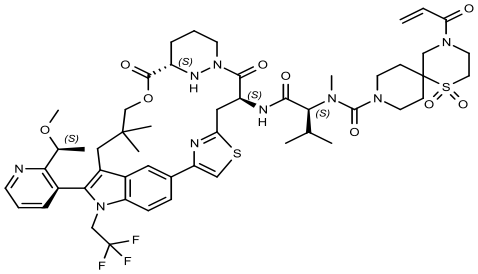
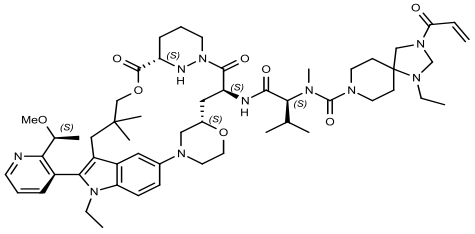
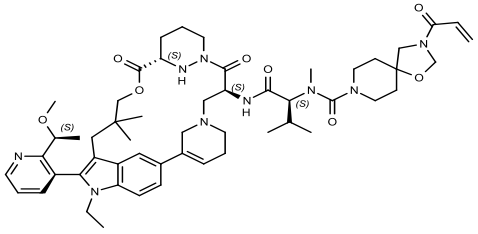
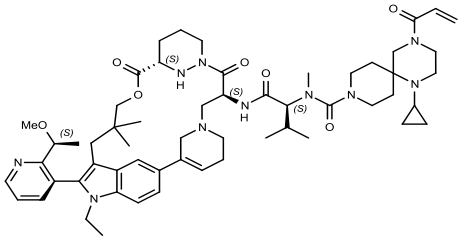
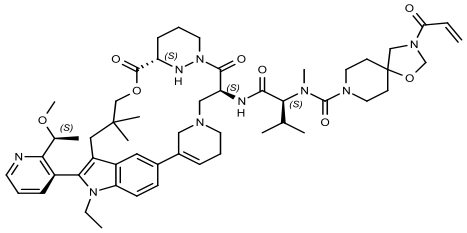
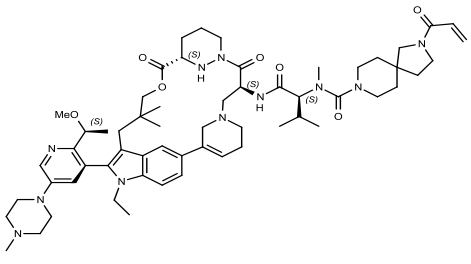
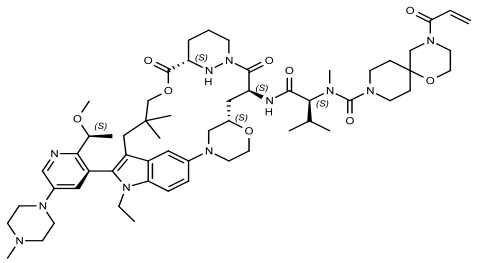
Ex#	Structure	Ex#	Structure
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A48		A152	
A49		A153	
A50		A154	

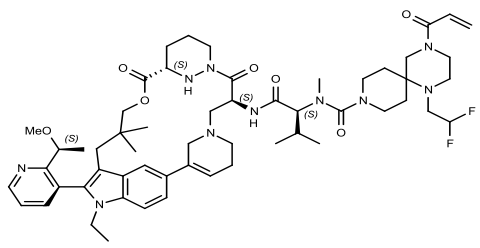
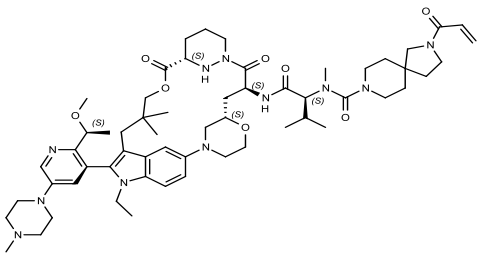
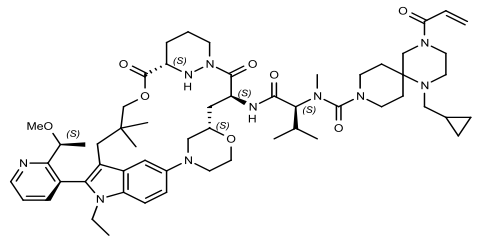
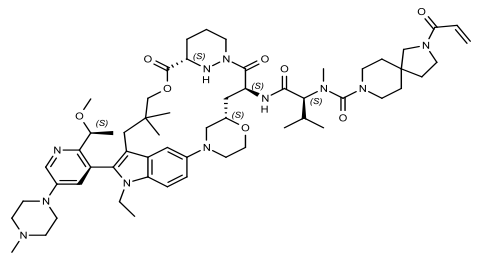
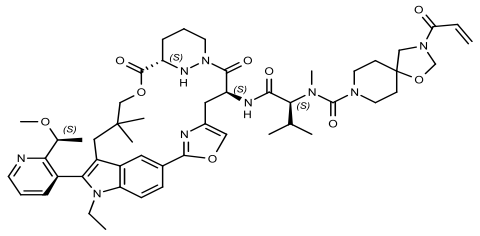
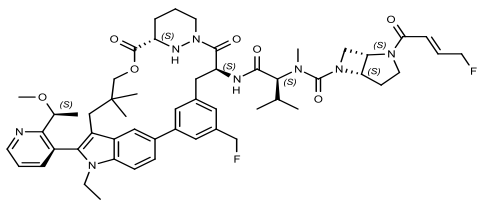
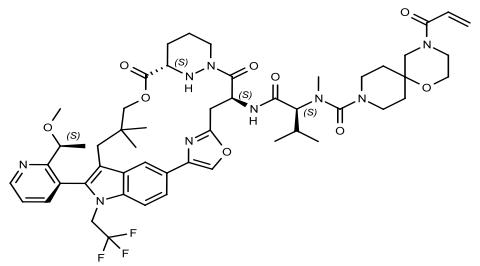
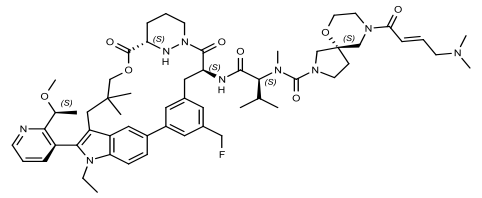
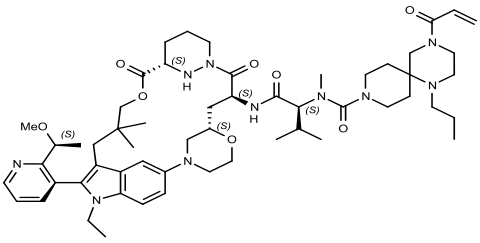
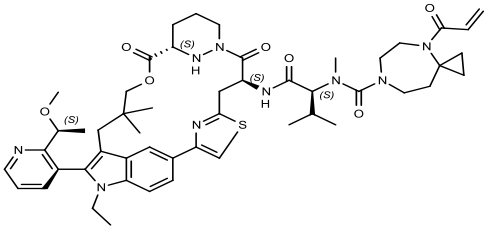
Ex#	Structure	Ex#	Structure
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A53		A157	
A54		A158	
A55		A159	

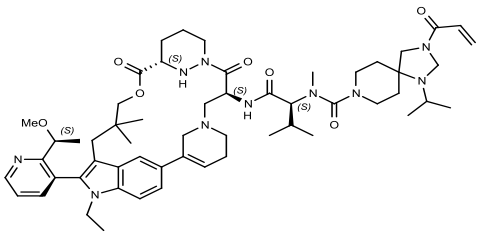
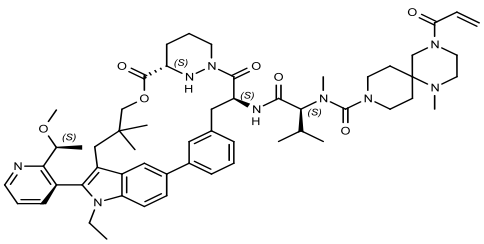
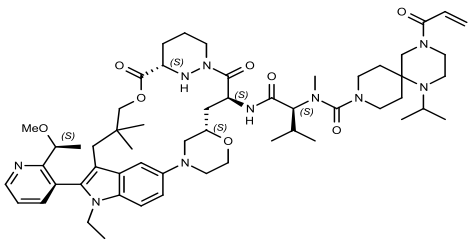
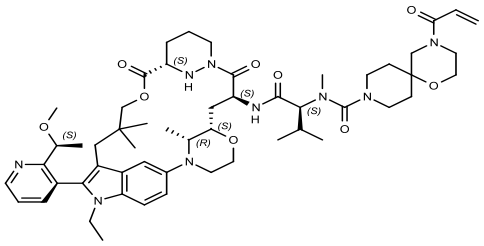
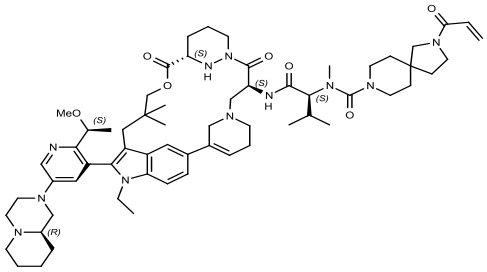
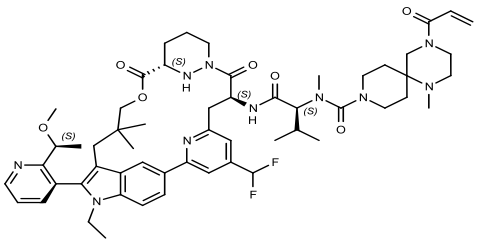
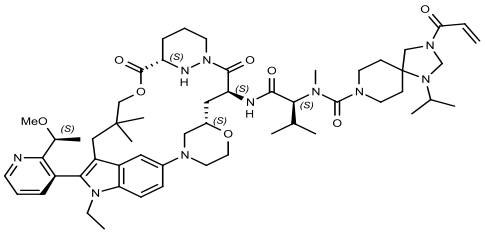
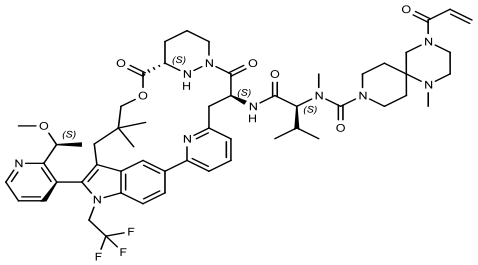
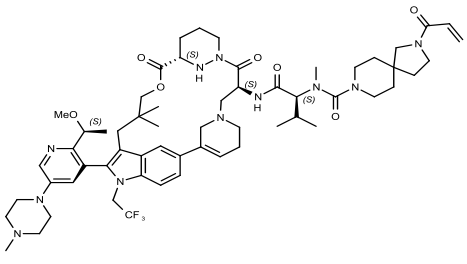
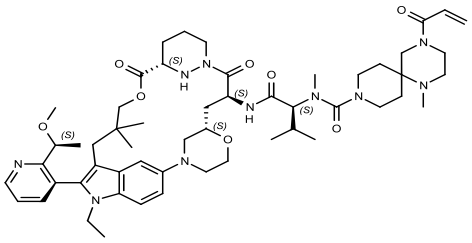
Ex#	Structure	Ex#	Structure
A56		A160	
A57		A161	
A58		A162	
A59		A163	
A60		A164	

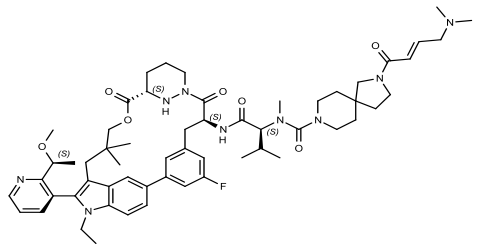
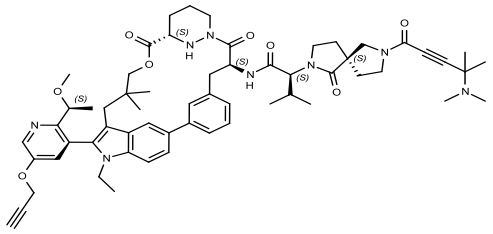
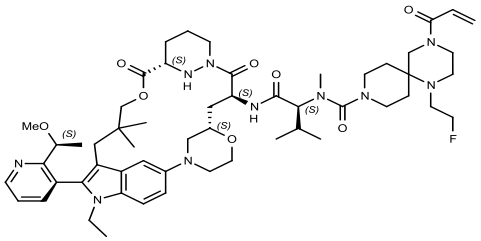
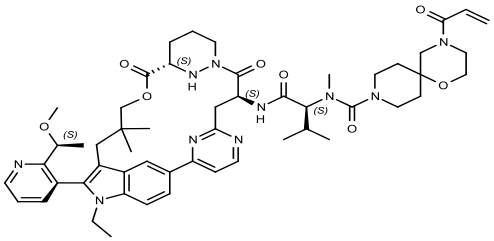
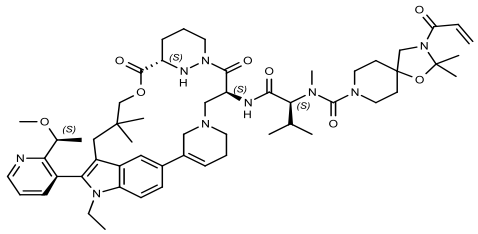
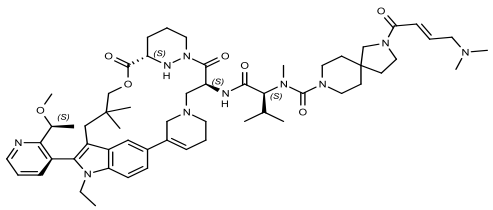
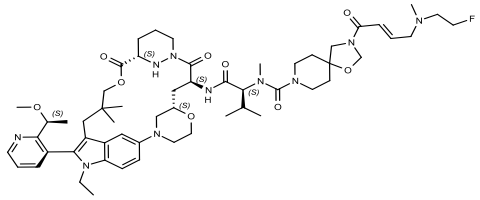
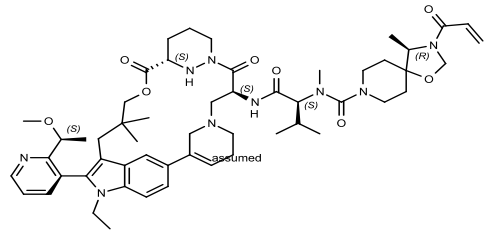
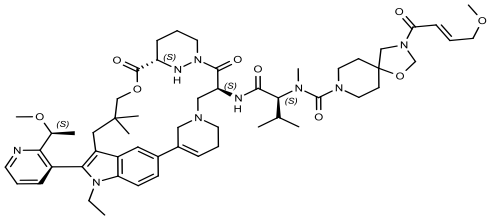
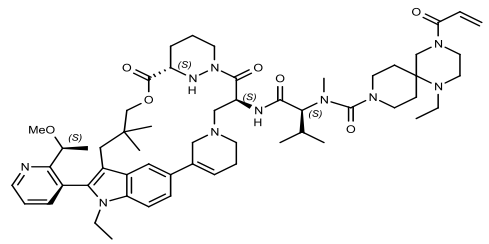
Ex#	Structure	Ex#	Structure
A61		A165	
A62		A166	
A63		A167	
A64		A168	
A65		A169	

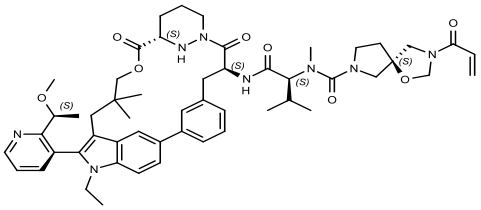
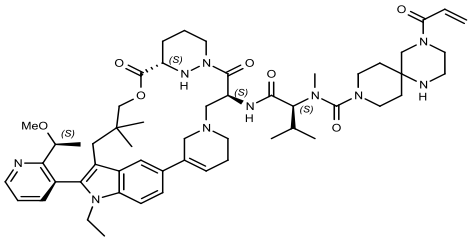
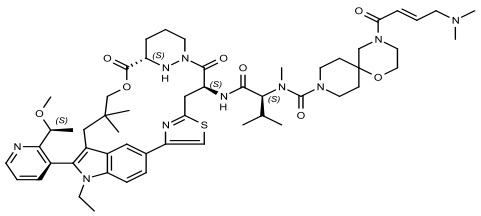
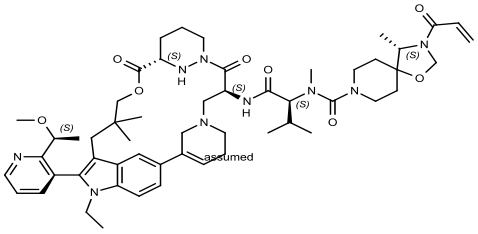
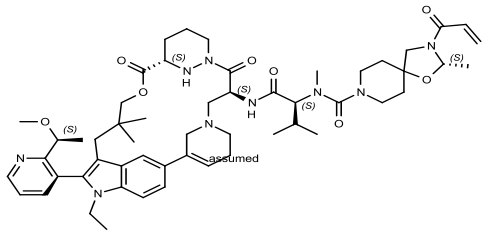
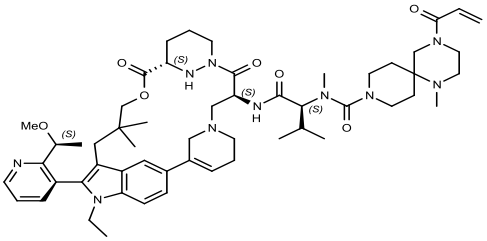
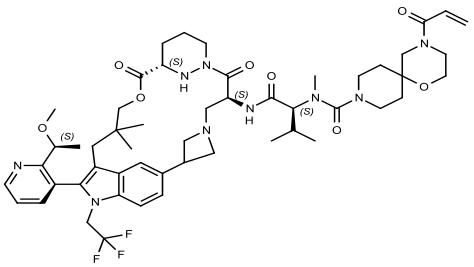
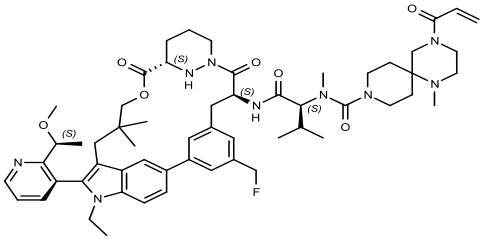
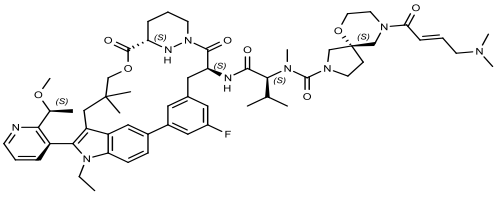
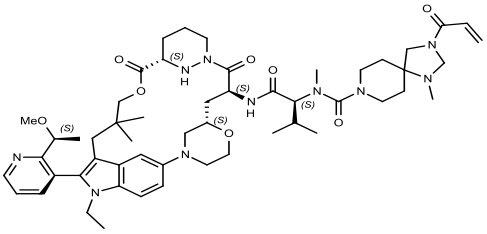
Ex#	Structure	Ex#	Structure
A66		A170	
A67		A171	
A68		A172	
A69		A173	
A70		A174	

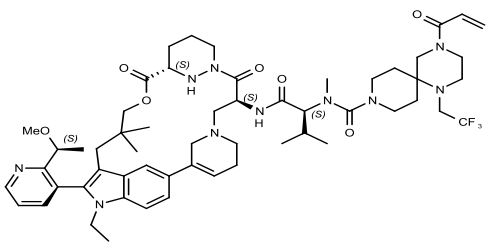
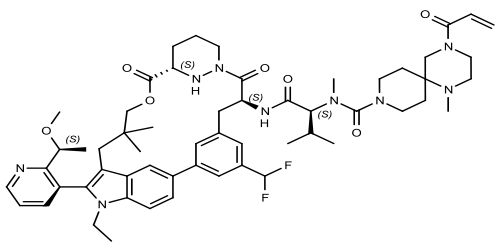
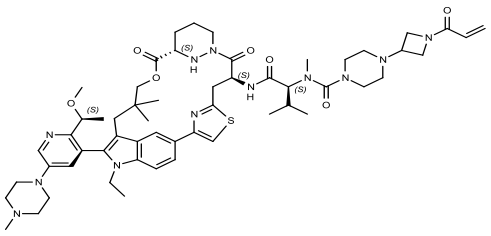
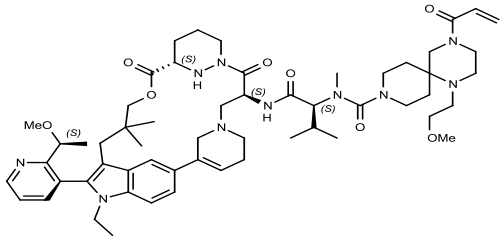
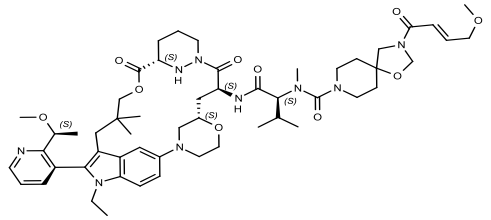
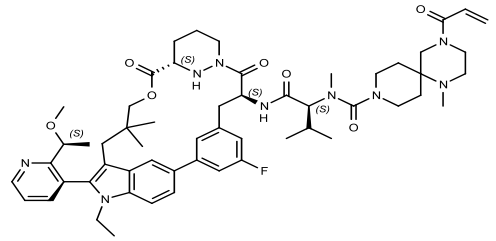
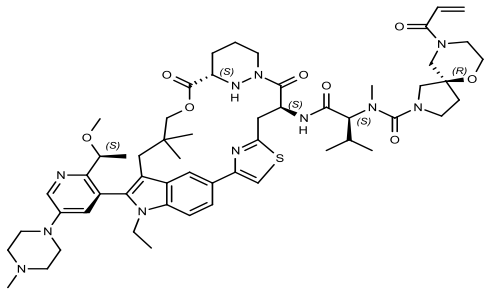
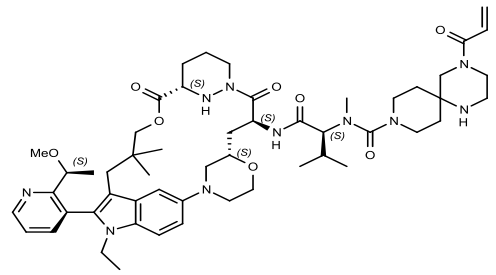
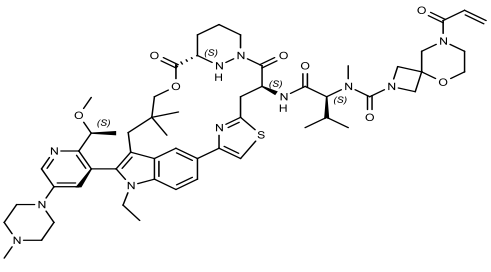
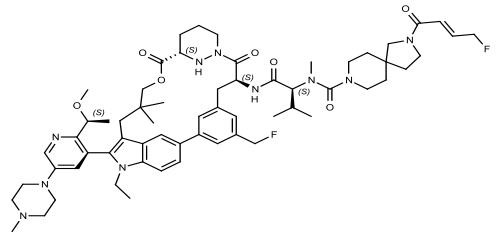
Ex#	Structure	Ex#	Structure
A71		A175	
A72		A176	
A73		A177	
A74		A178	
A75		A179	

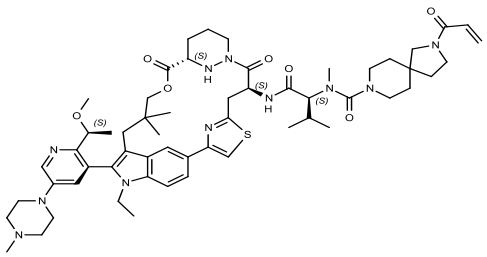
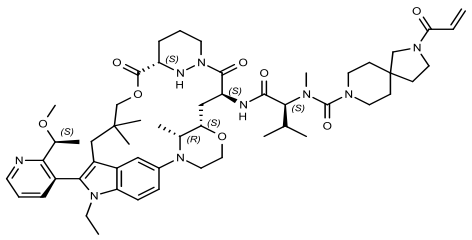
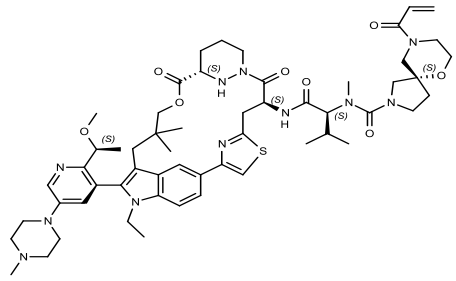
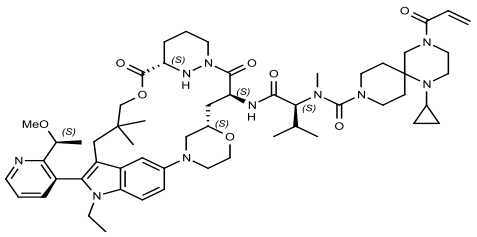
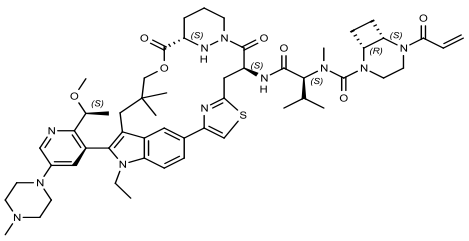
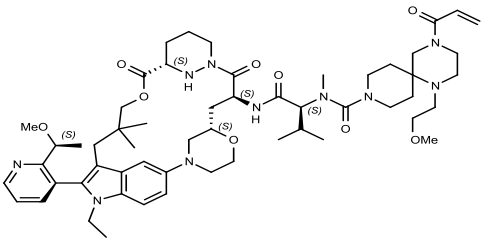
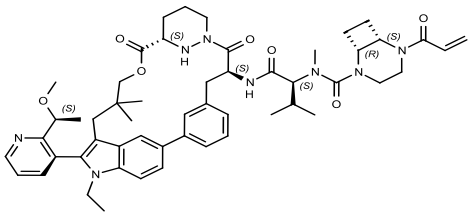
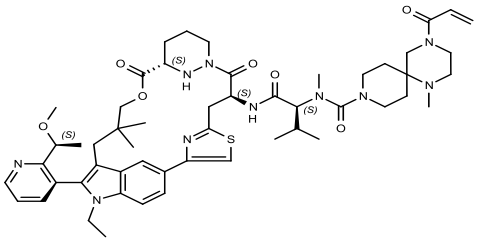
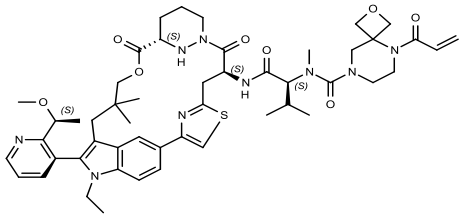
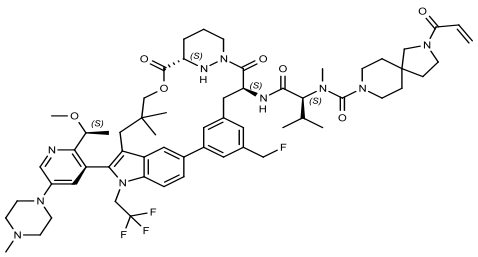
Ex#	Structure	Ex#	Structure
A76		A180	
A77		A181	
A78		A182	
A79		A183	
A80		A184	

Ex#	Structure	Ex#	Structure
A81		A185	
A82		A186	
A83		A187	
A84		A188	
A85		A189	

Ex#	Structure	Ex#	Structure
A86		A190	
A87		A191	
A88		A192	
A89		A193	
A90		A194	

Ex#	Structure	Ex#	Structure
A91		A195	
A92		A196	
A93		A197	
A94		A198	
A95		A199	

Ex#	Structure	Ex#	Structure
A96		A200	
A97		A201	
A98		A202	
A99		A203	
A100		A204	

Ex#	Structure	Ex#	Structure
A101		A205	
A102		A206	
A103		A207	
A104		A208	
A105		A209	

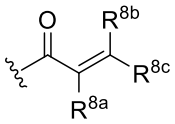
15. A pharmaceutical composition comprising a compound of any one of claims 1 to 14, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

16. A conjugate, or salt thereof, comprising the structure of Formula V:

M-L-P

Formula V,

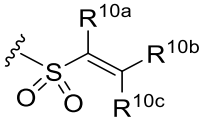
wherein L is a linker having the structure of:



Formula IVa,

wherein R^{8a}, R^{8b}, and R^{8c} are, independently, hydrogen, -CN, halogen, -C_1-C_3 alkyl, or -C_1-C_3 alkyl substituted with one or more substituents independently selected from -OH and -O-C_1-C_3 alkyl,

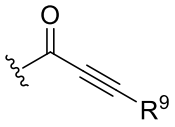
-NH_2, -NH(C_1-C_3 alkyl), -N(C_1-C_3 alkyl)$_2$, or a 4 to 7-membered saturated heterocycloalkyl comprising one, two, three, or four heteroatoms independently selected from nitrogen, oxygen, and sulfur;



Formula IVc,

wherein R^{10a}, R^{10b}, and R^{10c} are, independently, hydrogen, -CN, -C_1-C_3 alkyl, or -C_1-C_3 alkyl substituted with one, two, three, or four substituents independently selected from -OH and -O-C_1-C_3 alkyl,

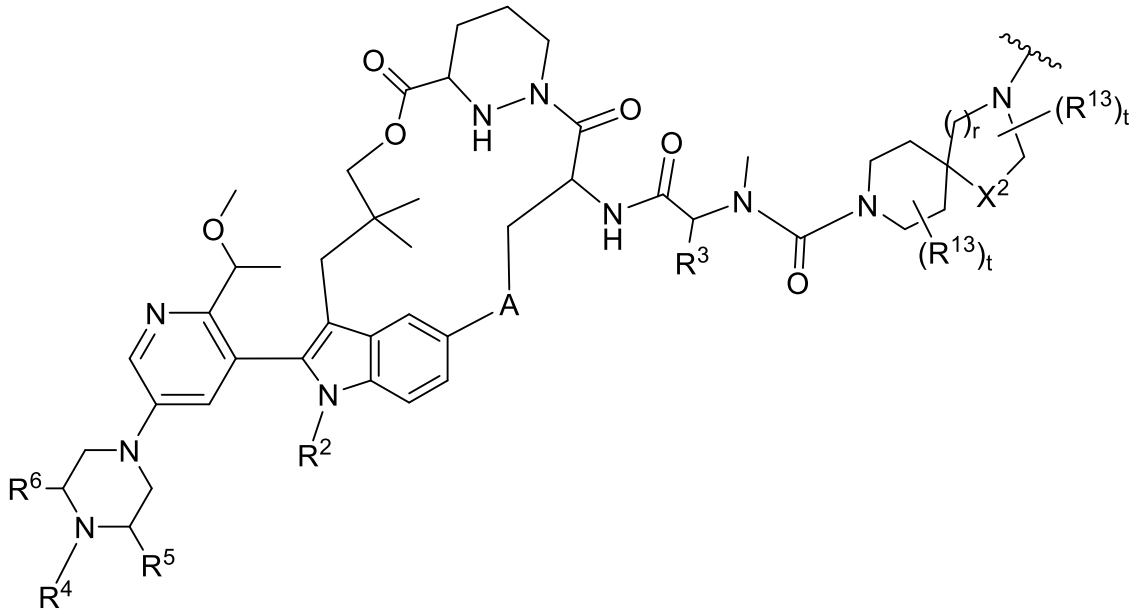
-NH_2, -NH(C_1-C_3 alkyl), -N(C_1-C_3 alkyl)$_2$, or a 4 to 7-membered saturated heterocycloalkyl comprising one, two, three, or four heteroatoms independently selected from nitrogen, oxygen, and sulfur;



Formula IVb,

wherein R^9 is hydrogen, -C_1-C_3 alkyl, -C_1-C_3 alkyl substituted with one, two, three, or four substituents independently selected from -OH, -O-C_1-C_3 alkyl, -NH_2, -NH(C_1-C_3 alkyl), -N(C_1-C_3 alkyl)$_2$, a 4 to 7-membered saturated cycloalkyl, and a 4 to 7-membered saturated heterocycloalkyl comprising one, two, three, or four heteroatoms independently selected from nitrogen, oxygen, and sulfur; P is a monovalent organic moiety wherein the monovalent organic moiety is a RAS protein selected from K-Ras G12C, K-Ras G13C, H-Ras G12C, H-Ras G13C, N-Ras G12C, or N-Ras G13C, and wherein the linker is bound to the monovalent organic moiety through a bond to a sulfhydryl group of an amino acid residue of the monovalent organic moiety; and

M has the structure of Formula VIa:



Formula VIa,

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;

R^2 is optionally substituted C_1-C_6 alkyl;

R^3 is optionally substituted C_1-C_6 alkyl or optionally substituted C_1-C_3 heteroalkyl;

X^2 is O, $C(R^{11})_2$, NR^{12}, S, or SO_2;

r is 1 or 2;

each t is, independently, 0, 1, or 2;

R^{11} and R^{12} are each, independently, hydrogen, optionally substituted C_1-C_4 alkyl, optionally substituted C_2-C_4 heteroalkyl, or optionally substituted 3 to 5-membered cycloalkyl;

each R^{13} is, independently, $-CH_3$; and

R^4, R^5, and R^6 are each independently selected from hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted 3 to 6-membered cycloalkyl, optionally substituted 3 to 6-membered heterocycloalkyl; or

R^4 and R^5 combine with the atoms to which they are attached to form an optionally substituted 3 to 8-membered cycloalkyl or an optionally substituted 3 to 8-membered heterocycloalkyl; or

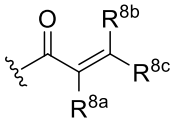
R^4 and R^6 combine with the atoms to which they are attached to form an optionally substituted 3 to 8-membered cycloalkyl or an optionally substituted 3 to 8-membered heterocycloalkyl.

17. A conjugate, or salt thereof, comprising the structure of Formula V:

M-L-P

Formula V,

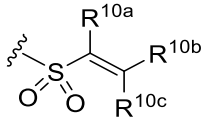
wherein L is a linker having the structure of:



Formula IVa,

wherein R^{8a}, R^{8b}, and R^{8c} are, independently, hydrogen, -CN, halogen, -C_1-C_3 alkyl, or -C_1-C_3 alkyl substituted with one or more substituents independently selected from -OH and -O-C_1-C_3 alkyl,

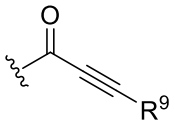
-NH_2, -NH(C_1-C_3 alkyl), -N(C_1-C_3 alkyl)$_2$, or a 4 to 7-membered saturated heterocycloalkyl comprising one, two, three, or four heteroatoms independently selected from nitrogen, oxygen, and sulfur;



Formula IVc,

wherein R^{10a}, R^{10b}, and R^{10c} are, independently, hydrogen, -CN, -C_1-C_3 alkyl, or -C_1-C_3 alkyl substituted with one, two, three, or four substituents independently selected from -OH and -O-C_1-C_3 alkyl,

-NH_2, -NH(C_1-C_3 alkyl), -N(C_1-C_3 alkyl)$_2$, or a 4 to 7-membered saturated heterocycloalkyl comprising one, two, three, or four heteroatoms independently selected from nitrogen, oxygen, and sulfur;

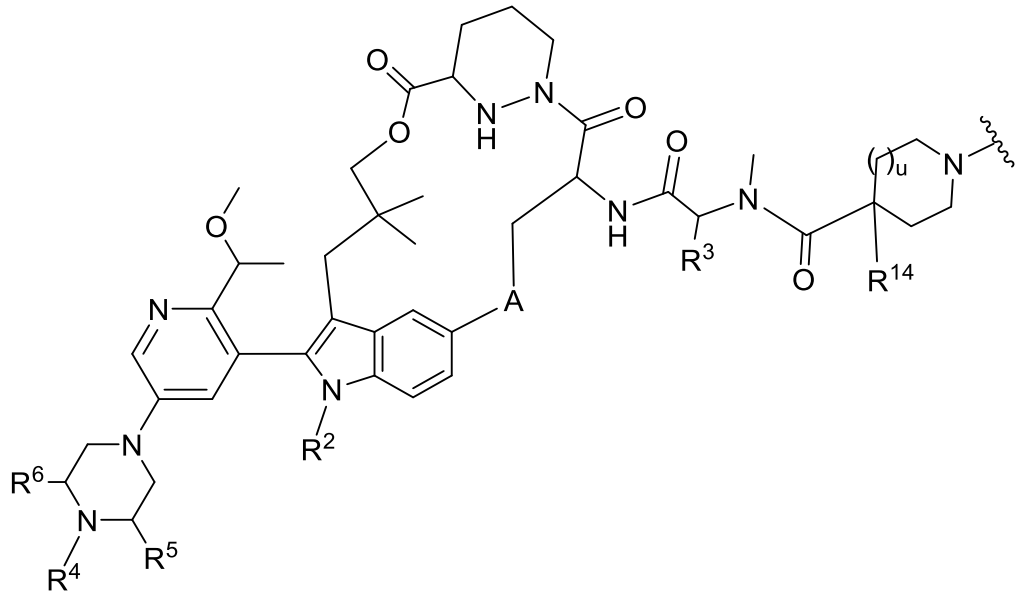


Formula IVb,

wherein R^9 is hydrogen, -C_1-C_3 alkyl, -C_1-C_3 alkyl substituted with one, two, three, or four substituents independently selected from -OH, -O-C_1-C_3 alkyl, -NH_2, -NH(C_1-C_3 alkyl), -N(C_1-C_3 alkyl)$_2$, a 4 to 7-membered saturated cycloalkyl, and a 4 to 7-membered saturated heterocycloalkyl comprising one, two, three, or four heteroatoms independently selected from nitrogen, oxygen, and sulfur;

P is a monovalent organic moiety wherein the monovalent organic moiety is a RAS protein selected from K-Ras G12C, K-Ras G13C, H-Ras G12C, H-Ras G13C, N-Ras G12C, or N-Ras G13C, and wherein the linker is bound to the monovalent organic moiety through a bond to a sulfhydryl group of an amino acid residue of the monovalent organic moiety; and

M has the structure of Formula VIb:



Formula VIb,

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;

R^2 is optionally substituted C_1-C_6 alkyl;

R^3 is optionally substituted C_1-C_6 alkyl or optionally substituted C_1-C_3 heteroalkyl;

R^{14} is fluoro, hydrogen, or C_1-C_3 alkyl;

u is 0 or 1; and

R^4, R^5, and R^6 are each independently selected from hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted 3 to 6-membered cycloalkyl, optionally substituted 3 to 6-membered heterocycloalkyl; or

R^4 and R^5 combine with the atoms to which they are attached to form an optionally substituted 3 to 8-membered cycloalkyl or an optionally substituted 3 to 8-membered heterocycloalkyl; or

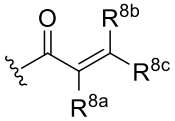
R^4 and R^6 combine with the atoms to which they are attached to form an optionally substituted 3 to 8-membered cycloalkyl or an optionally substituted 3 to 8-membered heterocycloalkyl.

18. A conjugate, or salt thereof, comprising the structure of Formula V:

M-L-P

Formula V,

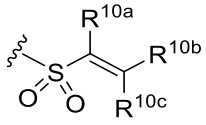
wherein L is a linker having the structure of:



Formula IVa,

wherein R^{8a}, R^{8b}, and R^{8c} are, independently, hydrogen, -CN, halogen, -C_1-C_3 alkyl, or -C_1-C_3 alkyl substituted with one or more substituents independently selected from -OH and -O-C_1-C_3 alkyl,

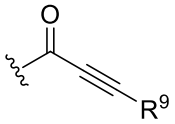
-NH_2, -$NH(C_1$-C_3 alkyl), -$N(C_1$-C_3 alkyl)$_2$, or a 4 to 7-membered saturated heterocycloalkyl comprising one, two, three, or four heteroatoms independently selected from nitrogen, oxygen, and sulfur;



Formula IVc,

wherein R^{10a}, R^{10b}, and R^{10c} are, independently, hydrogen, -CN, -C_1-C_3 alkyl, or -C_1-C_3 alkyl substituted with one, two, three, or four substituents independently selected from -OH and -O-C_1-C_3 alkyl,

-NH_2, -$NH(C_1$-C_3 alkyl), -$N(C_1$-C_3 alkyl)$_2$, or a 4 to 7-membered saturated heterocycloalkyl comprising one, two, three, or four heteroatoms independently selected from nitrogen, oxygen, and sulfur;

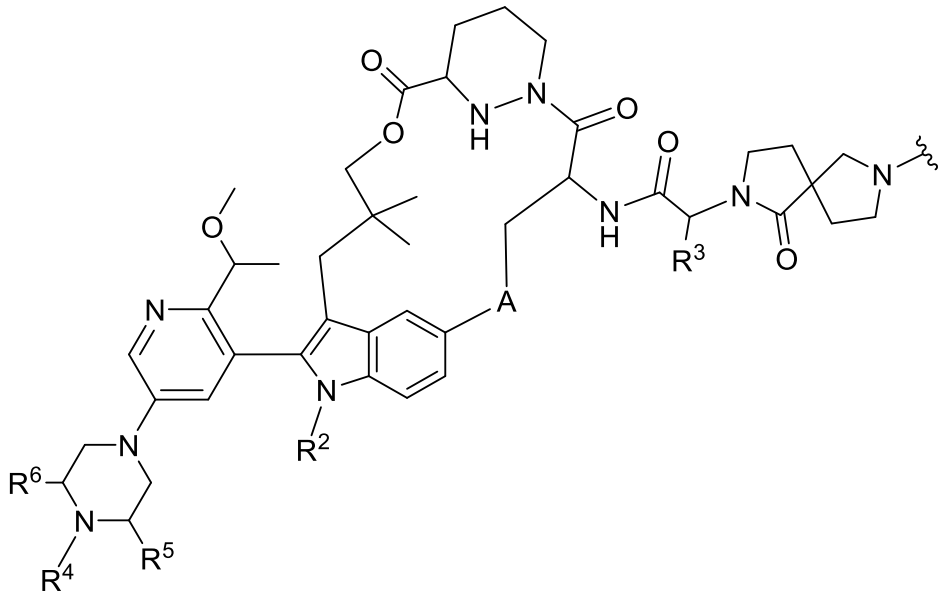


Formula IVb,

wherein R^9 is hydrogen, -C_1-C_3 alkyl, -C_1-C_3 alkyl substituted with one, two, three, or four substituents independently selected from -OH, -O-C_1-C_3 alkyl, -NH_2, -$NH(C_1$-C_3 alkyl), -$N(C_1$-C_3 alkyl)$_2$, a 4 to 7-membered saturated cycloalkyl, and a 4 to 7-membered saturated heterocycloalkyl comprising one, two, three, or four heteroatoms independently selected from nitrogen, oxygen, and sulfur;

P is a monovalent organic moiety wherein the monovalent organic moiety is a RAS protein selected from K-Ras G12C, K-Ras G13C, H-Ras G12C, H-Ras G13C, N-Ras G12C, or N-Ras G13C, and wherein the linker is bound to the monovalent organic moiety through a bond to a sulfhydryl group of an amino acid residue of the monovalent organic moiety; and

M has the structure of Formula VIc:



Formula VIc,

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;

R^2 is optionally substituted C_1-C_6 alkyl;

R^3 is optionally substituted C_1-C_6 alkyl or optionally substituted C_1-C_3 heteroalkyl; and

R^4, R^5, and R^6 are each independently selected from hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted 3 to 6-membered cycloalkyl, optionally substituted 3 to 6-membered heterocycloalkyl; or

R^4 and R^5 combine with the atoms to which they are attached to form an optionally substituted 3 to 8-membered cycloalkyl or an optionally substituted 3 to 8-membered heterocycloalkyl; or

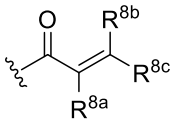
R^4 and R^6 combine with the atoms to which they are attached to form an optionally substituted 3 to 8-membered cycloalkyl or an optionally substituted 3 to 8-membered heterocycloalkyl.

19. A conjugate, or salt thereof, comprising the structure of Formula V:

M-L-P

Formula V,

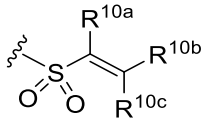
wherein L is a linker having the structure of:



Formula IVa,

wherein R^{8a}, R^{8b}, and R^{8c} are, independently, hydrogen, -CN, halogen, -C_1-C_3 alkyl, or -C_1-C_3 alkyl substituted with one or more substituents independently selected from -OH and -O-C_1-C_3 alkyl,

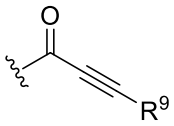
-NH_2, -NH(C_1-C_3 alkyl), -N(C_1-C_3 alkyl)$_2$, or a 4 to 7-membered saturated heterocycloalkyl comprising one, two, three, or four heteroatoms independently selected from nitrogen, oxygen, and sulfur;



Formula IVc,

wherein R^{10a}, R^{10b}, and R^{10c} are, independently, hydrogen, -CN, -C_1-C_3 alkyl, or -C_1-C_3 alkyl substituted with one, two, three, or four substituents independently selected from -OH and -O-C_1-C_3 alkyl,

-NH_2, -NH(C_1-C_3 alkyl), -N(C_1-C_3 alkyl)$_2$, or a 4 to 7-membered saturated heterocycloalkyl comprising one, two, three, or four heteroatoms independently selected from nitrogen, oxygen, and sulfur;



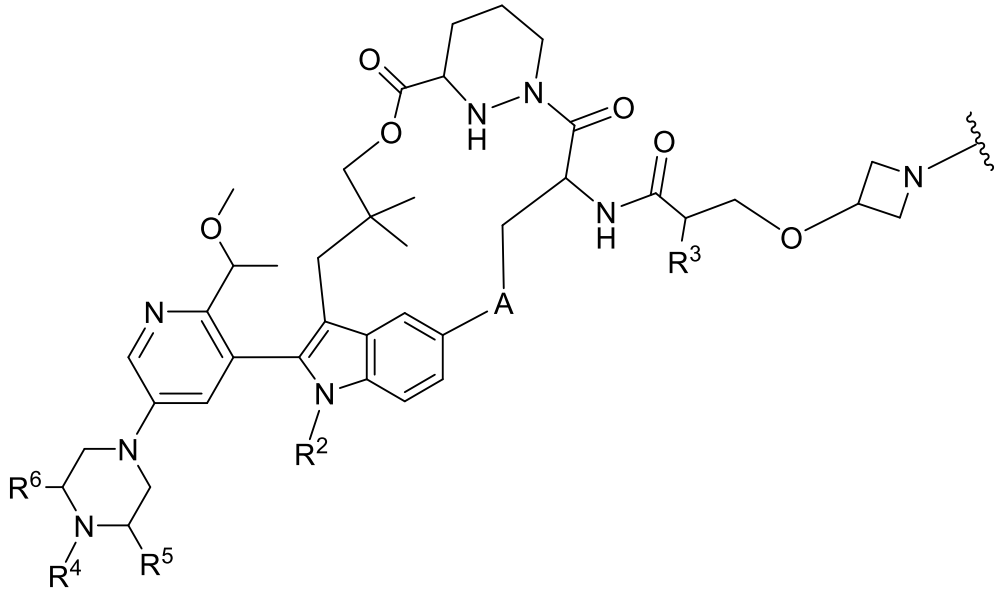
Formula IVb,

wherein R^9 is hydrogen, -C_1-C_3 alkyl, -C_1-C_3 alkyl substituted with one, two, three, or four substituents independently selected from -OH, -O-C_1-C_3 alkyl, -NH_2, -NH(C_1-C_3 alkyl), -N(C_1-C_3 alkyl)$_2$, a 4 to 7-membered saturated cycloalkyl, and a 4 to 7-membered saturated heterocycloalkyl comprising one, two, three, or four heteroatoms independently selected from nitrogen, oxygen, and sulfur;

P is a monovalent organic moiety wherein the monovalent organic moiety is a RAS protein selected from K-Ras G12C, K-Ras G13C, H-Ras G12C, H-Ras G13C, N-Ras G12C, or N-Ras G13C, and

wherein the linker is bound to the monovalent organic moiety through a bond to a sulfhydryl group of an amino acid residue of the monovalent organic moiety; and

M has the structure of Formula VId:



Formula VId,

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;

R^2 is optionally substituted C_1-C_6 alkyl;

R^3 is optionally substituted C_1-C_6 alkyl or optionally substituted C_1-C_3 heteroalkyl; and

R^4, R^5, and R^6 are each independently selected from hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted 3 to 6-membered cycloalkyl, optionally substituted 3 to 6-membered heterocycloalkyl; or

R^4 and R^5 combine with the atoms to which they are attached to form an optionally substituted 3 to 8-membered cycloalkyl or an optionally substituted 3 to 8-membered heterocycloalkyl; or

R^4 and R^6 combine with the atoms to which they are attached to form an optionally substituted 3 to 8-membered cycloalkyl or an optionally substituted 3 to 8-membered heterocycloalkyl.

20. Use of a compound of any one of claims 1 to 14, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 15, in the manufacture of a medicament for treating cancer.

21. Use of a compound of any one of claims 1 to 14, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 15, in the manufacture of a medicament for treating a Ras protein-related disorder, wherein the Ras protein related disorder is cancer, in a subject in need thereof.

22. 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 of any one of claims 1 to 14, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 15.

23. A compound of any one of claims 1 to 14, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 15, for use in therapy.