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(54) **Titre : PROCEDES D'INHIBITION DE RAS**
(54) **Title: METHODS FOR INHIBITING RAS**

(57) **Abrégé/Abstract:**
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Abstract:

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METHODS FOR INHIBITING RAS

Cross-Reference to Related Application

The present application claims the benefit of priority to U.S. Application No. 63/192,837, filed on May 25, 2021, which is hereby incorporated by reference in its entirety.

Background

Cancer remains one of the most-deadly threats to human health. In the U.S., cancer affects nearly 1.3 million new patients each year, and is the second leading cause of death after heart disease, accounting for approximately 1 in 4 deaths.

It has been well established in literature that RAS proteins (KRAS, HRAS, and NRAS) 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. RAS converts between a GDP-bound "off" and a GTP-bound "on" state. The conversion between states is facilitated by interplay between a guanine nucleotide exchange factor (GEF) protein (e.g., SOS1), which loads RAS with GTP, and a GTPase-activating protein (GAP) protein (e.g., NF1), which hydrolyzes GTP, thereby inactivating RAS. Additionally, the SH2 domain-containing protein tyrosine phosphatase-2 (SHP2) associates with the receptor signaling apparatus and becomes active upon RTK activation, and then promotes RAS activation. Mutations in RAS proteins can lock the protein in the "on" state resulting in a constitutively active signaling pathway that leads to uncontrolled cell growth. For example, activating mutations at codon 12 in RAS proteins function by inhibiting both 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.

First-in-class covalent inhibitors of the "off" form of RAS (RAS(OFF)) have demonstrated promising anti-tumor activity in cancer patients with oncogenic mutations in RAS. Further, therapeutic inhibition of the RAS pathway, although often initially efficacious, can ultimately prove ineffective as it may, for example, lead to over-activation of RAS pathway signaling via a number of mechanisms including, e.g., reactivation of the pathway via relief of the negative feedback machineries that naturally operate in these pathways, or may lead to resistance to RAS(OFF) inhibitors. Mutations contributing to resistance to such inhibitors have been reported (Tanaka et al., Clinical acquired resistance to KRASG12C inhibition through a novel KRAS switch-II pocket mutation and polyclonal alterations converging on RAS-MAPK reactivation, Cancer Discovery, April 6, 2021. DOI: 10.1158/2159-8290.CD-21-0365; Awad et al., Mechanisms of acquired resistance to $KRAS^{G12C}$ inhibition in cancer, AACR Annual Meeting 2021, April 10, 2021). As a result, cells that were initially sensitive to such inhibitors may become resistant. Thus, a need exists for methods of effectively inhibiting RAS pathway signaling in cancer patients for whom RAS(OFF) inhibitors are not or may not be successful, including patients naïve to RAS(OFF) therapy.

Summary

The present disclosure provides methods for inhibiting RAS and for the treatment of cancer. The inventors observed that cancer cells treated with a RAS(OFF) inhibitor may develop resistance, e.g., through the acquisition of one or more mutations that render the RAS(OFF) inhibitor less effective or ineffective. The disclosure is based, at least in part, on the observation that some cancers resistant to treatment with a RAS(OFF) inhibitor remain responsive to treatment with a RAS(ON) inhibitor. Thus, administering a RAS(ON) inhibitor to a subject having cancer can slow or halt oncogenic signaling or disease progression where the cancer is resistant to treatment with a RAS(OFF) inhibitor. Additionally, administration of a RAS(ON) inhibitor, e.g., administered in combination with a RAS(OFF) inhibitor, may prevent the acquisition of one or more mutations in RAS that confer resistance to the RAS(OFF) inhibitor. In addition, compounds disclosed herein may provide a clinical benefit for patients naïve to RAS(OFF) therapy.

In any embodiment herein, a RAS(ON) inhibitor may be a tri-complex RAS(ON) inhibitor, as that term is defined herein.

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.

Numbered Embodiments

1. A method of treating cancer in a subject in need thereof, wherein the cancer comprises:
   (a) a first RAS mutation that is G12C and a second RAS mutation at a position selected from the group consisting of Y96, H95, R68, G13 and Q61; or
   (b) a first RAS mutation at position G12,

wherein the cancer is resistant to treatment with a RAS(OFF) inhibitor, the method comprising administering to the subject a RAS(ON) inhibitor.

2. The method of embodiment 1, wherein the cancer does not comprise a KRAS Y96D mutation.

3. The method of embodiment 1, wherein the cancer does not comprise any of the following mutations: KRAS G12D, KRAS G12V, KRAS G12C, KRAS G12R, KRAS G12A, KRAS G12S, KRAS G12F, KRAS G12L, HRAS G12S, HRAS G12D, HRAS G12C, HRAS G12V, HRAS G12A, HRAS G12N, HRAS G12R, NRAS G12D, NRAS G12S, NRAS G12C, NRAS G12V, NRAS G12A, or NRAS G12R, or any combination thereof.

4. The method of any one of embodiments 1-3, wherein the cancer does not comprise a KRAS mutation selected from the group consisting of $G12C^{amp}$, G12D, G12R, G12V, G12W, G13D, Q61H, R68S, H95D, H95Q, H95R and Y96C, or any combination thereof.

5. The method of any one of embodiments 1-4, further comprising administering to the subject a RAS(OFF) inhibitor.

6. The method of embodiment 5, wherein the RAS(ON) inhibitor and the RAS(OFF) inhibitor are administered simultaneously or sequentially.

7. The method of embodiment 5 or 6 wherein the RAS(ON) inhibitor and the RAS(OFF) inhibitor are administered as a single formulation or in separate formulations.

8. The method of embodiment 6, wherein:

the RAS(OFF) inhibitor is administered for a first period of time; and

the RAS(ON) inhibitor is administered for a second period of time,

wherein the first period of time and the second period of time do not overlap and the first period of time precedes the second period of time.

9. The method of embodiment 6, wherein:

the RAS(OFF) inhibitor is administered for a first period of time; and

the RAS(OFF) inhibitor and RAS(ON) inhibitor are administered for a second period of time,

wherein the first period of time and the second period of time do not overlap and the first period of time precedes the second period of time.

10. The method of any one of embodiments 5-9, wherein the subject's cancer progresses on the RAS(OFF) inhibitor.

11. The method of embodiment 1, wherein the cancer comprises a first RAS mutation that is G12C and a second RAS mutation at position Y96.

12. The method of embodiment 1 or embodiment 11, wherein the second RAS mutation is selected from the group consisting of Y96C, Y96D, Y96F, Y96H, Y96N and Y96S.

13. The method of embodiment 1 or embodiment 11, wherein the second RAS mutation is selected from the group consisting of Y96D, Y96F, Y96H, Y96N and Y96S.

14. The method of embodiment 1 or embodiment 11, wherein the second RAS mutation is selected from the group consisting of Y96C, Y96F, Y96H, Y96N and Y96S.

15. The method of embodiment 1 or embodiment 11, wherein the second RAS mutation is selected from the group consisting of Y96F, Y96H, Y96N and Y96S.

16. The method of embodiment 1, wherein the cancer comprises a first RAS mutation that is G12C and a second RAS mutation at position H95 or R68.

17. The method of embodiment 1 or embodiment 16, wherein the first RAS mutation is G12C and the second RAS mutation is at position H95.

18. The method of any one of embodiments 1, 16 or 17, wherein the second RAS mutation is selected from the group consisting of H95D, H95L, H95N, H95P, H95Q, H95R and H95Y.

19. The method of any one of embodiments 1, 16 or 17, wherein the second RAS mutation is selected from the group consisting of H95L, H95N, H95P and H95Y.

20. The method of embodiment 1 or embodiment 16, wherein the first RAS mutation is G12C and the second RAS mutation is at position R68.

21. The method of any one of embodiments 1, 16 or 20, wherein the second mutation is selected from the group consisting of R68G, R68K, R68M, R68S, R68T and R68W.

22. The method of any one of embodiments 1, 16 or 20, wherein the second mutation is selected from the group consisting of R68G, R68K, R68M, R68T and R68W.

23. The method of any one of embodiments 1-4 and 11-22, wherein the subject has been treated with a RAS(OFF) inhibitor.

24. A method of treating cancer in a subject in need thereof, wherein the cancer comprises an amino acid substitution at RAS Y96, H95, or R68, the method comprising administering to the subject a RAS(ON) inhibitor.

25. The method of embodiment 24, wherein the cancer comprises a first RAS mutation that is G12C and a second RAS mutation at position Y96.

26. The method of embodiment 24 or embodiment 25, wherein the cancer does not comprise a Y96D RAS mutation.

27. The method of embodiment 25 or embodiment 26, wherein the second RAS mutation is selected from the group consisting of Y96C, Y96D, Y96F, Y96H, Y96N and Y96S.

28. The method of embodiment 25 or embodiment 26, wherein the second RAS mutation is selected from the group consisting of Y96D, Y96F, Y96H, Y96N and Y96S.

29. The method of embodiment 25 or embodiment 26, wherein the second RAS mutation is selected from the group consisting of Y96C, Y96F, Y96H, Y96N and Y96S.

30. The method of embodiment 25 or embodiment 26, wherein the second RAS mutation is selected from the group consisting of Y96F, Y96H, Y96N and Y96S.

31. The method of embodiment 25, wherein the cancer comprises a first RAS mutation that is G12C and a second RAS mutation at position H95 or R68.

32. The method of embodiment 25 or embodiment 31, wherein the first RAS mutation is G12C and the second RAS mutation is at position H95.

33. The method of any one of embodiments 25, 31 or 32, wherein the second RAS mutation is selected from the group consisting of H95D, H95L, H95N, H95P, H95Q, H95R and H95Y.

34. The method of any one of embodiments 25, 31 or 32, wherein the second RAS mutation is selected from the group consisting of H95L, H95N, H95P and H95Y.

35. The method of embodiment 25 or embodiment 31, wherein the first RAS mutation is G12C and the second RAS mutation is at position R68.

36. The method of any one of embodiments 25, 31 or 35, wherein the second mutation is selected from the group consisting of R68G, R68K, R68M, R68S, R68T and R68W.

37. The method of any one of embodiments 25, 31 or 35, wherein the second mutation is selected from the group consisting of R68G, R68K, R68M, R68T and R68W.

38. The method of embodiment 1, wherein the second mutation is Q61H.

39. The method of embodiment 1, wherein the second mutation is G13D.

40. The method of any one of embodiments 27-39, wherein the subject has been treated with a RAS(OFF) inhibitor.

41. The method of any one of embodiments 27-40, wherein the cancer is resistant to treatment with a RAS(OFF) inhibitor.

42. The method of embodiment 40 or embodiment 41, wherein the subject's cancer progresses on the RAS(OFF) inhibitor.

43. The method of any one of embodiments 1-42, wherein any RAS mutation is a KRAS mutation.

44. The method of any one of embodiments 1-42, wherein any RAS mutation is a NRAS mutation.

45. The method of any one of embodiments 1-42, wherein any RAS mutation is an HRAS mutation.

46. A method of treating cancer in a subject in need thereof, wherein the cancer comprises a RAS mutation selected from the group consisting of G12H, G12I, G12K, G12M, G12N, G12P, G12Q, G12T, G12W and G12Y, or a combination thereof, the method comprising administering to the subject a RAS(ON) inhibitor.

47. The method of embodiment 46, wherein the cancer further comprises a G12C RAS mutation.

48. The method of embodiment 46 or 47, wherein the subject has been treated with a RAS(OFF) inhibitor.

49. The method of any one of embodiments 46-48, wherein the cancer is resistant to treatment with a RAS(OFF) inhibitor.

50. The method of embodiment 48 or embodiment 49, wherein the subject's cancer progresses on the RAS(OFF) inhibitor.

51. A method of inhibiting RAS in a cell, wherein the RAS comprises an amino acid substitution at Y96, H95 or R68, the method comprising contacting the cell with a RAS(ON) inhibitor.

52. A method of inhibiting RAS in a cell, wherein the RAS comprises an amino acid substitution at H95 or R68, the method comprising contacting the cell with a RAS(ON) inhibitor.

53. The method of embodiment 51 or embodiment 52, wherein the cell is in vitro.

54. The method of embodiment 51 or clam 52, wherein the cell is in vivo.

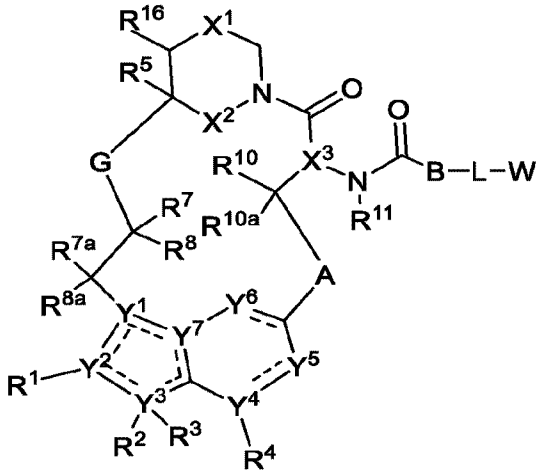
55. The method of any one of embodiments 1-54, wherein the RAS(ON) inhibitor is an inhibitor selective for RAS G12C, G13D, or G12D.

56. The method of any one of embodiments 1-54, wherein the RAS(ON) inhibitor is a RAS(ON)^{MULTI} inhibitor.

57. The method of any one of embodiments 1-56, wherein the RAS(ON) inhibitor is a tri-complex RAS(ON) inhibitor.

58. The method of any one of embodiments 1-57, wherein the RAS(ON) inhibitor is selected from a compound disclosed in WO 2020132597.

59. The method of any one of embodiments 1-57, wherein the RAS(ON) inhibitor is a compound of Formula AI:



Formula AI

or a pharmaceutically acceptable salt thereof,

wherein the dotted lines represent zero, one, two, three, or four non-adjacent double bonds;

A is -N(H or CH_3)C(O)-(CH_2)- where the amino nitrogen is bound to the carbon atom of -CH(R^{10})-, optionally substituted 3 to 6-membered cycloalkylene, optionally substituted 3 to 6-membered

heterocycloalkylene, optionally substituted 6-membered arylene, or optionally substituted 5 to 10-membered heteroarylene;

B is absent, -CH(R^9)-, or >C=C$R^9R^{9'}$ where the carbon is bound to the carbonyl carbon of -N(R^{11})C(O)-, optionally substituted 3 to 6-membered cycloalkylene, optionally substituted 3 to 6-membered heterocycloalkylene, optionally substituted 6-membered arylene, or 5 to 6-membered heteroarylene;

G is optionally substituted C_1-C_4 alkylene, optionally substituted C_1-C_4 alkenylene, optionally substituted C_1-C_4 heteroalkylene, -C(O)O-**C**H(R^6)- where **C** is bound to -C(R^7R^8)-, -C(O)NH-**C**H(R^6)- where **C** is bound to -C(R^7R^8)-, optionally substituted C_1-C_4 heteroalkylene, or 3 to 8-membered heteroarylene;

L is absent or a linker;

W is hydrogen, cyano, $S(O)_2R'$, optionally substituted amino, optionally substituted amido, optionally substituted C_1-C_4 alkoxy, optionally substituted C_1-C_4 hydroxyalkyl, optionally substituted C_1-C_4 aminoalkyl, optionally substituted C_1-C_4 haloalkyl, optionally substituted C_1-C_4 alkyl, optionally substituted C_1-C_4 guanidinoalkyl, C_0-C_4 alkyl optionally substituted 3 to 11-membered heterocycloalkyl, optionally substituted 3 to 8-membered cycloalkyl, or optionally substituted 3 to 8-membered heteroaryl;

X^1 is optionally substituted C_1-C_2 alkylene, NR, O, or $S(O)_n$;

X^2 is O or NH;

X^3 is N or CH;

n is 0, 1, or 2;

R is hydrogen, cyano, optionally substituted C_1-C_4 alkyl, optionally substituted C_2-C_4 alkenyl, optionally substituted C_2-C_4 alkynyl, C(O)R', C(O)OR', $C(O)N(R')_2$, S(O)R', $S(O)_2R'$, or $S(O)_2N(R')_2$;

each R' is, independently, H or optionally substituted C_1-C_4 alkyl;

Y^1 is C, CH, or N;

Y^2, Y^3, Y^4, and Y^7 are, independently, C or N;

Y^5 is CH, CH_2, or N;

Y^6 is C(O), CH, CH_2, or N;

R^1 is cyano, 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 cycloalkenyl, optionally substituted 3 to 6-membered heterocycloalkyl, optionally substituted 6 to 10-membered aryl, or optionally substituted 5 to 10-membered heteroaryl, or

R^1 and R^2 combine with the atoms to which they are attached to form an optionally substituted 3 to 14-membered heterocycloalkyl;

R^2 is absent, hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 alkynyl, optionally substituted 3 to 6-membered cycloalkyl, optionally substituted 3 to 7-membered heterocycloalkyl, optionally substituted 6-membered aryl, optionally substituted 5 or 6-membered heteroaryl;

R^3 is absent, or

R^2 and R^3 combine with the atom to which they are attached to form an optionally substituted 3 to 8-membered cycloalkyl or optionally substituted 3 to 14-membered heterocycloalkyl;

R^4 is absent, hydrogen, halogen, cyano, or methyl optionally substituted with 1 to 3 halogens;

R^5 is hydrogen, C_1-C_4 alkyl optionally substituted with halogen, cyano, hydroxy, or C_1-C_4 alkoxy, cyclopropyl, or cyclobutyl;

R^6 is hydrogen or methyl; R^7 is hydrogen, halogen, or optionally substituted C_1-C_3 alkyl, or

R^6 and R^7 combine with the carbon atoms to which they are attached to form an optionally substituted 3 to 6-membered cycloalkyl or optionally substituted 3 to 7-membered heterocycloalkyl;

R^8 is hydrogen, halogen, hydroxy, cyano, optionally substituted C_1-C_3 alkoxy, optionally substituted C_1-C_3 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 alkynyl, optionally substituted 3 to 8-membered cycloalkyl, optionally substituted 3 to 14-membered heterocycloalkyl, optionally substituted 5 to 10-membered heteroaryl, or optionally substituted 6 to 10-membered aryl, or

R^7 and R^8 combine with the carbon atom to which they are attached to form $C=CR^{7'}R^{8'}$; C=N(OH), C=N(O-C_1-C_3 alkyl), C=O, C=S, C=NH, optionally substituted 3 to 6-membered cycloalkyl, or optionally substituted 3 to 7-membered heterocycloalkyl;

R^{7a} and R^{8a} are, independently, hydrogen, halo, optionally substituted C_1-C_3 alkyl, or combine with the carbon to which they are attached to form a carbonyl;

$R^{7'}$ is hydrogen, halogen, or optionally substituted C_1-C_3 alkyl; $R^{8'}$ is hydrogen, halogen, hydroxy, cyano, optionally substituted C_1-C_3 alkoxy, optionally substituted C_1-C_3 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 alkynyl, optionally substituted 3 to 8-membered cycloalkyl, optionally substituted 3 to 14-membered heterocycloalkyl, optionally substituted 5 to 10-membered heteroaryl, or optionally substituted 6 to 10-membered aryl, or

$R^{7'}$ and $R^{8'}$ combine with the carbon atom to which they are attached to form optionally substituted 3 to 6-membered cycloalkyl or optionally substituted 3 to 7-membered heterocycloalkyl;

R^9 is hydrogen, F, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted 3 to 6-membered cycloalkyl, or optionally substituted 3 to 7-membered heterocycloalkyl, or

R^9 and L combine with the atoms to which they are attached to form an optionally substituted 3 to 14-membered heterocycloalkyl;

$R^{9'}$ is hydrogen or optionally substituted C_1-C_6 alkyl;

R^{10} is hydrogen, halo, hydroxy, C_1-C_3 alkoxy, or C_1-C_3 alkyl;

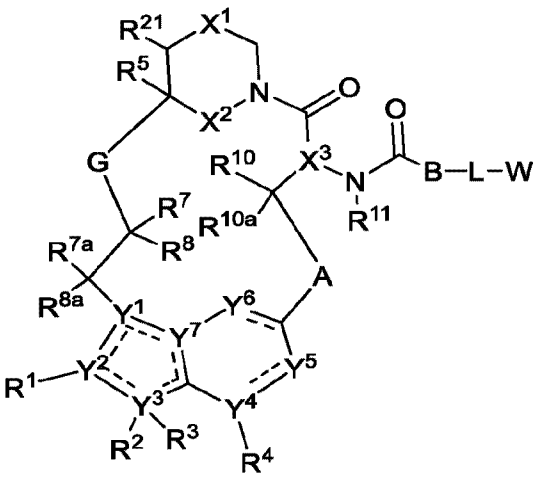
R^{10a} is hydrogen or halo;

R^{11} is hydrogen or C_1-C_3 alkyl;

R^{16} is hydrogen or C_1-C_3 alkyl.

60. The method of any one of embodiments 1-57, wherein the RAS(ON) inhibitor is selected from a compound of Table A1 or Table A2, or a pharmaceutically acceptable salt thereof.

61. The method of any one of embodiments 1-57, wherein the RAS(ON) inhibitor is a compound of Formula BI:



Formula BI

or a pharmaceutically acceptable salt thereof,

wherein the dotted lines represent zero, one, two, three, or four non-adjacent double bonds;

A is -N(H or CH_3)C(O)-(CH_2)- where the amino nitrogen is bound to the carbon atom of -CH(R^{10})-, optionally substituted 3 to 6-membered cycloalkylene, optionally substituted 3 to 6-membered heterocycloalkylene, optionally substituted 6-membered arylene, or optionally substituted 5 to 10-membered heteroarylene;

B is absent, -CH(R^9)-, >C=CR^9R$^{9'}$, or >CR^9R$^{9'}$ where the carbon is bound to the carbonyl carbon of -N(R^{11})C(O)-, optionally substituted 3 to 6-membered cycloalkylene, optionally substituted 3 to 6-membered heterocycloalkylene, optionally substituted 6-membered arylene, or 5 to 6-membered heteroarylene;

G is optionally substituted C_1-C_4 alkylene, optionally substituted C_1-C_4 alkenylene, optionally substituted C_1-C_4 heteroalkylene, -C(O)O-**C**H(R^6)- where **C** is bound to -C(R^7R^8)-, -C(O)NH-**C**H(R^6)- where **C** is bound to -C(R^7R^8)-, optionally substituted C_1-C_4 heteroalkylene, or 3 to 8-membered heteroarylene;

L is absent or a linker;

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

X^1 is optionally substituted C_1-C_2 alkylene, NR, O, or S(O)$_n$;

X^2 is O or NH;

X^3 is N or CH;

n is 0, 1, or 2;

R is hydrogen, cyano, optionally substituted C_1-C_4 alkyl, optionally substituted C_2-C_4 alkenyl, optionally substituted C_2-C_4 alkynyl, C(O)R', C(O)OR', C(O)N(R')$_2$, S(O)R', S(O)$_2$R', or S(O)$_2$N(R')$_2$;

each R' is, independently, H or optionally substituted C_1-C_4 alkyl;

Y^1 is C, CH, or N;

Y^2, Y^3, Y^4, and Y^7 are, independently, C or N;

Y^5 is CH, CH_2, or N;

Y^6 is C(O), CH, CH_2, or N;

R^1 is cyano, 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 cycloalkenyl, optionally substituted 3 to 6-membered heterocycloalkyl, optionally substituted 6 to 10-membered aryl, or optionally substituted 5 to 10-membered heteroaryl, or

R^1 and R^2 combine with the atoms to which they are attached to form an optionally substituted 3 to 14-membered heterocycloalkyl;

R^2 is absent, hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 alkynyl, optionally substituted 3 to 6-membered cycloalkyl, optionally substituted 3 to 7-membered heterocycloalkyl, optionally substituted 6-membered aryl, optionally substituted 5 or 6-membered heteroaryl; R^3 is absent, or

R^2 and R^3 combine with the atom to which they are attached to form an optionally substituted 3 to 8-membered cycloalkyl or optionally substituted 3 to 14-membered heterocycloalkyl;

R^4 is absent, hydrogen, halogen, cyano, or methyl optionally substituted with 1 to 3 halogens;

R^5 is hydrogen, C_1-C_4 alkyl optionally substituted with halogen, cyano, hydroxy, or C_1-C_4 alkoxy, cyclopropyl, or cyclobutyl;

R^6 is hydrogen or methyl; R^7 is hydrogen, halogen, or optionally substituted C_1-C_3 alkyl, or

R^6 and R^7 combine with the carbon atoms to which they are attached to form an optionally substituted 3 to 6-membered cycloalkyl or optionally substituted 3 to 7-membered heterocycloalkyl;

R^8 is hydrogen, halogen, hydroxy, cyano, optionally substituted C_1-C_3 alkoxy, optionally substituted C_1-C_3 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 alkynyl, optionally substituted 3 to 8-membered cycloalkyl, optionally substituted 3 to 14-membered heterocycloalkyl, optionally substituted 5 to 10-membered heteroaryl, or optionally substituted 6 to 10-membered aryl, or

R^7 and R^8 combine with the carbon atom to which they are attached to form $C=CR^{7'}R^{8'}$; C=N(OH), C=N(O-C_1-C_3 alkyl), C=O, C=S, C=NH, optionally substituted 3 to 6-membered cycloalkyl, or optionally substituted 3 to 7-membered heterocycloalkyl;

R^{7a} and R^{8a} are, independently, hydrogen, halo, optionally substituted C_1-C_3 alkyl, or combine with the carbon to which they are attached to form a carbonyl;

$R^{7'}$ is hydrogen, halogen, or optionally substituted C_1-C_3 alkyl; $R^{8'}$ is hydrogen, halogen, hydroxy, cyano, optionally substituted C_1-C_3 alkoxy, optionally substituted C_1-C_3 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 alkynyl, optionally substituted 3 to 8-membered cycloalkyl, optionally substituted 3 to 14-membered heterocycloalkyl, optionally substituted 5 to 10-membered heteroaryl, or optionally substituted 6 to 10-membered aryl, or

$R^{7'}$ and $R^{8'}$ combine with the carbon atom to which they are attached to form optionally substituted 3 to 6-membered cycloalkyl or optionally substituted 3 to 7-membered heterocycloalkyl;

R^9 is H, F, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted 3 to 6-membered cycloalkyl, or optionally substituted 3 to 7-membered heterocycloalkyl, or

R^9 and L combine with the atoms to which they are attached to form an optionally substituted 3 to 14-membered heterocycloalkyl;

$R^{9'}$ is hydrogen or optionally substituted C_1-C_6 alkyl; or

R^9 and $R^{9'}$, combined with the atoms to which they are attached, form a 3 to 6-membered cycloalkyl or a 3 to 6-membered heterocycloalkyl;

R^{10} is hydrogen, halo, hydroxy, C_1-C_3 alkoxy, or C_1-C_3 alkyl;

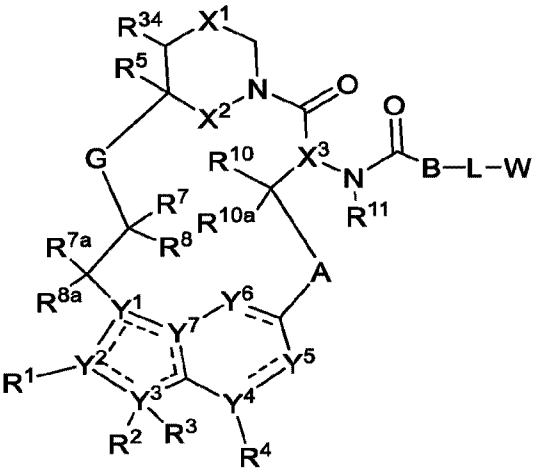
R^{10a} is hydrogen or halo;

R^{11} is hydrogen or C_1-C_3 alkyl; and

R^{21} is hydrogen or C_1-C_3 alkyl.

62. The method of any one of embodiments 1-57, wherein the RAS(ON) inhibitor is selected from a compound of Table B1 or Table B2, or a pharmaceutically acceptable salt thereof.

63. The method of any one of embodiments 1-57, wherein the RAS(ON) inhibitor is a compound of Formula CI, or a pharmaceutically acceptable salt thereof.



Formula CI

wherein the dotted lines represent zero, one, two, three, or four non-adjacent double bonds;

A is -N(H or CH_3)C(O)-(CH_2)- where the amino nitrogen is bound to the carbon atom of -CH(R^{10})-, optionally substituted 3 to 6-membered cycloalkylene, optionally substituted 3 to 6-membered heterocycloalkylene, optionally substituted 6-membered arylene, or optionally substituted 5 to 10-membered heteroarylene;

B is -CH(R^9)- or >C=C$R^9R^{9'}$ where the carbon is bound to the carbonyl carbon of -N(R^{11})C(O)-, optionally substituted 3 to 6-membered cycloalkylene, optionally substituted 3 to 6-membered heterocycloalkylene, optionally substituted 6-membered arylene, or 5 to 6-membered heteroarylene;

G is optionally substituted C_1-C_4 alkylene, optionally substituted C_1-C_4 alkenylene, optionally substituted C_1-C_4 heteroalkylene, -C(O)O-**C**H(R^6)- where **C** is bound to -C(R^7R^8)-, -C(O)NH-**C**H(R^6)- where **C** is bound to -C(R^7R^8)-, optionally substituted C_1-C_4 heteroalkylene, or 3 to 8-membered heteroarylene;

L is absent or a linker;

W is a cross-linking group comprising a carbodiimide, an oxazoline, a thiazoline, a chloroethyl urea, a chloroethyl thiourea, a chloroethyl carbamate, a chloroethyl thiocarbamate, an aziridine, a trifluoromethyl ketone, a boronic acid, a boronic ester, an *N*-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline (EEDQ), an iso-EEDQ or other EEDQ derivative, an epoxide, an oxazolium, or a glycal;

X^1 is optionally substituted C_1-C_2 alkylene, NR, O, or S(O)$_n$;

X^2 is O or NH;

X^3 is N or CH;

n is 0, 1, or 2;

R is hydrogen, cyano, optionally substituted C_1-C_4 alkyl, optionally substituted C_2-C_4 alkenyl, optionally substituted C_2-C_4 alkynyl, C(O)R', C(O)OR', $C(O)N(R')_2$, S(O)R', $S(O)_2R'$, or $S(O)_2N(R')_2$;

each R' is, independently, H or optionally substituted C_1-C_4 alkyl;

Y^1 is C, CH, or N;

Y^2, Y^3, Y^4, and Y^7 are, independently, C or N;

Y^5 is CH, CH_2, or N;

Y^6 is C(O), CH, CH_2, or N;

R^1 is cyano, 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 cycloalkenyl, optionally substituted 3 to 6-membered heterocycloalkyl, optionally substituted 6 to 10-membered aryl, or optionally substituted 5 to 10-membered heteroaryl, or

R^1 and R^2 combine with the atoms to which they are attached to form an optionally substituted 3 to 14-membered heterocycloalkyl;

R^2 is absent, hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 alkynyl, optionally substituted 3 to 6-membered cycloalkyl, optionally substituted 3 to 7-membered heterocycloalkyl, optionally substituted 6-membered aryl, optionally substituted 5 or 6-membered heteroaryl; R^3 is absent, or

R^2 and R^3 combine with the atom to which they are attached to form an optionally substituted 3 to 8-membered cycloalkyl or optionally substituted 3 to 14-membered heterocycloalkyl;

R^4 is absent, hydrogen, halogen, cyano, or methyl optionally substituted with 1 to 3 halogens;

R^5 is hydrogen, C_1-C_4 alkyl optionally substituted with halogen, cyano, hydroxy, or C_1-C_4 alkoxy, cyclopropyl, or cyclobutyl;

R^6 is hydrogen or methyl; R^7 is hydrogen, halogen, or optionally substituted C_1-C_3 alkyl, or

R^6 and R^7 combine with the carbon atoms to which they are attached to form an optionally substituted 3 to 6-membered cycloalkyl or optionally substituted 3 to 7-membered heterocycloalkyl;

R^8 is hydrogen, halogen, hydroxy, cyano, optionally substituted C_1-C_3 alkoxyl, optionally substituted C_1-C_3 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 alkynyl, optionally substituted 3 to 8-membered cycloalkyl, optionally substituted 3 to 14-membered heterocycloalkyl, optionally substituted 5 to 10-membered heteroaryl, or optionally substituted 6 to 10-membered aryl, or

R^7 and R^8 combine with the carbon atom to which they are attached to form $C=CR^{7'}R^{8'}$; C=N(OH), C=N(O-C_1-C_3 alkyl), C=O, C=S, C=NH, optionally substituted 3 to 6-membered cycloalkyl, or optionally substituted 3 to 7-membered heterocycloalkyl;

R^{7a} and R^{8a} are, independently, hydrogen, halo, optionally substituted C_1-C_3 alkyl, or combine with the carbon to which they are attached to form a carbonyl;

$R^{7'}$ is hydrogen, halogen, or optionally substituted C_1-C_3 alkyl; $R^{8'}$ is hydrogen, halogen, hydroxy, cyano, optionally substituted C_1-C_3 alkoxyl, optionally substituted C_1-C_3 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 alkynyl, optionally substituted 3 to 8-membered cycloalkyl, optionally substituted 3 to 14-membered heterocycloalkyl, optionally substituted 5 to 10-membered heteroaryl, or optionally substituted 6 to 10-membered aryl, or

$R^{7'}$ and $R^{8'}$ combine with the carbon atom to which they are attached to form optionally substituted 3 to 6-membered cycloalkyl or optionally substituted 3 to 7-membered heterocycloalkyl;

R^9 is hydrogen, F, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted 3 to 6-membered cycloalkyl, or optionally substituted 3 to 7-membered heterocycloalkyl, or

R^9 and L combine with the atoms to which they are attached to form an optionally substituted 3 to 14-membered heterocycloalkyl;

$R^{9'}$ is hydrogen or optionally substituted C_1-C_6 alkyl;

R^{10} is hydrogen, halo, hydroxy, C_1-C_3 alkoxy, or C_1-C_3 alkyl;

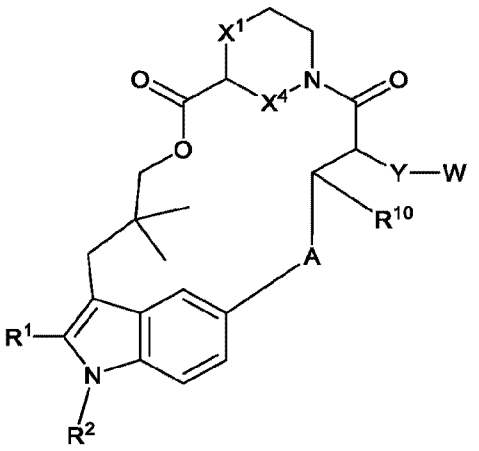
R^{10a} is hydrogen or halo; and

R^{11} is hydrogen or C_1-C_3 alkyl; and

R^{34} is hydrogen or C_1-C_3 alkyl.

64. The method of any one of embodiments 1-57, wherein the RAS(ON) inhibitor is selected from a compound of Table C1 or Table C2, or a pharmaceutically acceptable salt thereof.

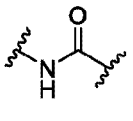
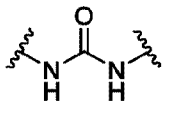
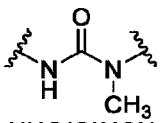
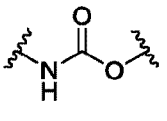
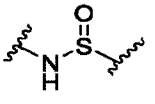
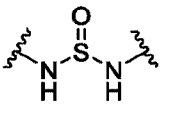
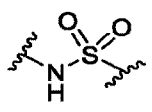
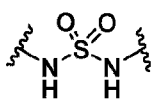
65. The method of any one of embodiments 1-57, wherein the RAS(ON) inhibitor is a compound of Formula DIa:



Formula DIa

or a pharmaceutically acceptable salt thereof,

wherein A is optionally substituted 3 to 6-membered cycloalkylene, optionally substituted 3 to 6-membered heterocycloalkylene, optionally substituted 6-membered arylene, optionally substituted 5 to 6-membered heteroarylene, optionally substituted C_2-C_4 alkylene, or optionally substituted C_2-C_4 alkenylene;

Y is  -NHC(O)-,  -NHC(O)NH-,  -NHC(O)NCH$_3$-,  -NHC(O)O-,  -NHC(S)-,  -NHC(S)NH-,  -NHS(O)$_2$-, or  -NHS(O)$_2$NH-;

W is hydrogen, C_1-C_4 alkyl, optionally substituted C_1-C_3 heteroalkyl, optionally substituted 3 to 10-membered heterocycloalkyl, optionally substituted 3 to 10-membered cycloalkyl, optionally substituted 6 to 10-membered aryl, or optionally substituted 5 to 10-membered heteroaryl;

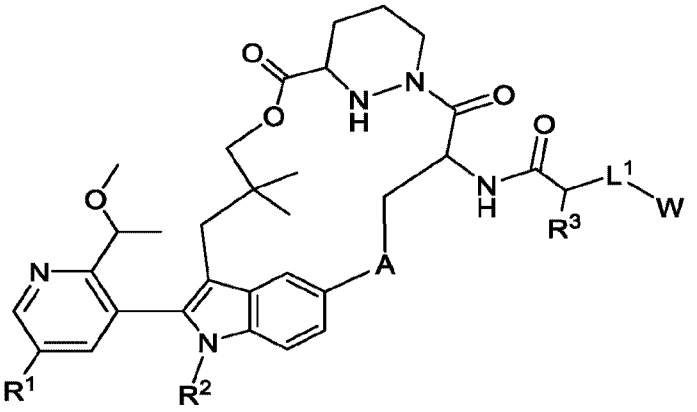
X^1 and X^4 are each, independently, CH_2 or NH;

R^1 is 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 cycloalkenyl, optionally substituted 3 to 15-membered heterocycloalkyl, optionally substituted 6 to 10-membered aryl, or optionally substituted 5 to 10-membered heteroaryl; and

R^2 is hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 alkynyl, optionally substituted 3 to 6-membered cycloalkyl, optionally substituted 3 to 7-membered heterocycloalkyl, optionally substituted 6-membered aryl, optionally substituted 5 or 6-membered heteroaryl; and R^{10} is hydrogen, hydroxy, optionally substituted C_1-C_3 alkyl, or optionally substituted C_1-C_6 heteroalkyl.

66. The method of any one of embodiments 1-57, wherein the RAS(ON) inhibitor is selected from a compound of Table D1a or D1b, or a pharmaceutically acceptable salt thereof.

67. The method of any one of embodiments 1-57, wherein the RAS(ON) inhibitor is a compound of Formula EI:



Formula EI,

or a pharmaceutically acceptable salt thereof,

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;

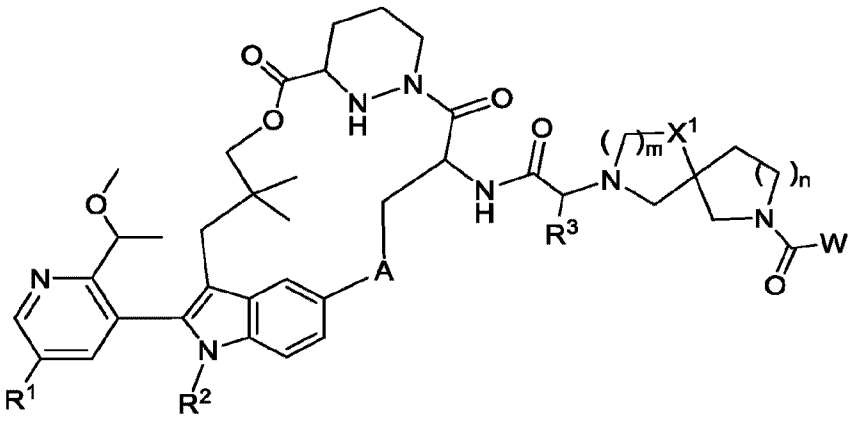
R^1 is hydrogen, optionally substituted 3 to 10-membered heterocycloalkyl, or optionally substituted C_1-C_6 heteroalkyl;

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.

68. The method of any one of embodiments 1-57, wherein the RAS(ON) inhibitor is selected from a compound of Table E1, or a pharmaceutically acceptable salt thereof.

69. The method of any one of embodiments 1-57, wherein the RAS(ON) inhibitor is a compound of Formula FI:



Formula FI

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;

W is a cross-linking group comprising an aziridine, an epoxide, a carbodiimide, an oxazoline, a thiazoline, a chloroethyl urea, a chloroethyl thiourea, a chloroethyl carbamate, a chloroethyl thiocarbamate, a trifluoromethyl ketone, a boronic acid, a boronic ester, an N-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline (EEDQ), an iso-EEDQ or other EEDQ derivative, an oxazolium, or a glycal;

X^1 is CH_2 or O;

m is 1 or 2;

n is 0 or 1;

R^1 is hydrogen or optionally substituted 3 to 10-membered heterocycloalkyl;

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

R^3 is optionally substituted C_1-C_6 alkyl or optionally substituted 3 to 6-membered cycloalkyl.

70. The method of any one of embodiments 1-57, wherein the RAS(ON) inhibitor is selected from a compound of Table F1, Table F2, Table F3, Table F4, Table F5, or Table F6.

71. The method of any one of embodiments 1-23, 40-45, or 48-50, wherein the RAS(OFF) inhibitor selectively targets RAS G12C.

72. The method of any one of embodiments 1-23, 40-45, or 48-50, wherein the RAS(OFF) inhibitor is selected from sotorasib (AMG 510), adagrasib (MRTX849), MRTX1257, JNJ-74699157 (ARS-3248), LY3537982, LY3499446, ARS-853, ARS-1620, GDC-6036, JDQ443, BPI-421286, JAB-21000, RSC-1255, ERAS-3490, D-1553, JAB-21822, GH-35, ICP-915, IBI351, and BI1823911.

73. The method of any one of embodiments 1-72, wherein the cancer is selected from colorectal cancer, non-small cell lung cancer, small-cell lung cancer, pancreatic cancer, appendiceal cancer, acute myeloid leukemia, small bowel cancer, ampullary cancer, germ cell cancer, cervical cancer, cancer of unknown primary origin, endometrial cancer, esophagogastric cancer, GI neuroendocrine cancer, ovarian cancer, sex cord stromal tumor cancer, hepatobiliary cancer, bladder cancer and melanoma.

74. The method of embodiment 76, wherein the cancer is non-small cell lung cancer.

75. The method of any one of embodiments 1-74, wherein the method further comprises administering to the subject or the cell an additional anti-cancer therapy.

Brief Description of the Figures

FIG. 1A and FIG. 1B. Compound AA, a tri-complex KRAS^{G12C}(ON) inhibitor disclosed herein as a compound of Formula B1 herein, and also a compound of Table B1 herein, and also found in WO 2021/091982, is active against second site mutations conferring resistance to KRAS^{G12C}(OFF) inhibitors MRTX849 and AMG 510. FIG. 1A is a heatmap representing cellular RAS/RAF disruption assay results regarding various KRAS mutations in the presence of different RAS inhibitors. Certain mutations have been observed in patients treated with AMG 510 (e.g., Y96C, Y96D, H95D, H95Q, H95R, R68S) (Tanaka et al., Clinical acquired resistance to KRASG12C inhibition through a novel KRAS switch-II pocket mutation and polyclonal alterations converging on RAS-MAPK reactivation, Cancer Discovery, April 6, 2021. DOI: 10.1158/2159-8290.CD-21-0365; Awad et al., Mechanisms of acquired resistance to KRAS^{G12C} inhibition in cancer, AACR Annual Meeting 2021, April 10, 2021). FIG. 1B shows the IC50 value associated with each colored bar of the heatmap. See Example 1.

FIG. 2A and FIG. 2B. Compound A, a tri-complex KRAS^{MULTI}(ON) inhibitor disclosed herein as a compound of Formula D1 herein, and also a compound of Table D1 herein, and also found in WO 2022/060836, is active against RAS oncogene switching mutations observed in KRAS^{G12C}(OFF) resistance. FIG. 2A is a heatmap representing cellular RAS/RAF disruption assay results regarding various KRAS mutations in the presence of different RAS inhibitors. Certain mutations have been observed in patients treated with AMG 510 (e.g., G12C, G12F, G12R, G12V, G12W) (Tanaka et al.; Awad et al.). FIG. 2B shows the IC50 value associated with each colored bar of the heatmap. See Example 2.

FIG. 3 demonstrates in vitro efficacy of Compound A, a tri-complex KRAS^{MULTI}(ON) inhibitor disclosed herein, in multiple RAS-driven cancer cell lines. Each graph shows cell proliferation (% relative to control) vs. log M [Compound A]. Potency of in vitro cell proliferation inhibition of Capan-1 (KRAS^{G12V}), AsPC-1 (KRAS^{G12D}), HCT116 (KRAS^{G13D}), SK-MEL-30 (NRAS^{Q61K}), NCI-H1975 (EGFR$^{T790M/L858R}$), and A375 (BRAF^{V600E}) cells exposed to Compound A for 120 hours. Data represent the mean of multiple experiments. See Example 3.

Detailed Description

The present disclosure relates generally to methods for inhibiting RAS and for the treatment of cancer. In some embodiments, the disclosure provides methods for delaying, preventing, or treating acquired resistance to a RAS(OFF) inhibitor by administering a RAS(ON) inhibitor. In some embodiments, administration of a RAS(ON) inhibitor, e.g., administered in combination with a RAS(OFF) inhibitor, may prevent the acquisition of one or more mutations in RAS that confers resistance to the RAS(OFF) inhibitor. In addition, compounds disclosed herein may provide a clinical benefit for patients naïve to RAS(OFF) therapy.

The heatmaps shown in FIG. 1A and FIG. 2A represent relative potencies observed in cellular assays measuring the abundance of protein complexes between the active form of RAS, RAS(ON), and its signaling partner, RAF kinase. Each tri-complex KRAS(ON) inhibitor maximally disrupted KRAS^{G12C}(ON)/CRAF complexes (data not shown), indicative of blockade of KRAS^{G12C} activation of RAF and the MAPK cascade.

Recently, two groups published the first descriptions of genetic mutations observed in ctDNA samples from patients who had exhibited resistance to adagrasib therapy (MRTX849, a KRAS^{G12C}(OFF)

inhibitor in clinical development). Tanaka et al., Clinical acquired resistance to $KRAS^{G12C}$ inhibition through a novel KRAS switch-II pocket mutation and polyclonal alterations converging on RAS-MAPK reactivation, Cancer Discovery, April 6, 2021. DOI: 10.1158/2159-8290.CD-21-0365; Awad et al., Mechanisms of acquired resistance to $KRAS^{G12C}$ inhibition in cancer, AACR Annual Meeting 2021, April 10, 2021. Some of these mutations were studied herein, as described below.

One set of mutations (FIG. 1A, FIG. 1B) convey second site mutations in $KRAS^{G12C}$, occurring on the same allele as the G12C mutation (in cis). These mutations confer resistance to $KRAS^{G12C}$(OFF) inhibitors via alteration of the binding site of that inhibitor class. This resistance is clearly represented in the heatmap (FIG. 1A) which reflects fold change in inhibitor IC50 for the indicated double mutant relative to the single G12C mutant – with yellow representing the largest fold change. For the $KRAS^{G12C}$(OFF) inhibitors MRTX849 and AMG 510, there is a decrease in potency (i.e., increase in fold change) for the majority of the double mutants relative to the single G12C mutant (all second site mutations are measured in cis with G12C). Compound AA, a tri-complex $KRAS^{G12C}$(ON) inhibitor disclosed herein, is active against all of the second site mutations tested with minimal fold change in potency relative to the single G12C mutant, indicating these mutations are not sufficient to confer resistance to Compound AA, or more broadly, as the inventors surmise, tri-complex G12C(ON) inhibitors generally (see, e.g., Tanaka et al.) and also that Compound AA and other tri-complex RAS(ON) inhibitors disclosed herein may offer clinical benefit in treating patients who are not only resistant to (e.g., have progressed on) $KRAS^{G12C}$(OFF) inhibitors, but patients naïve to such treatment whose tumors bear one or more of these second site KRAS mutations, as well as comparable positions in HRAS and NRAS.

The second set of mutations (FIG. 2A, FIG. 2B) are alternative oncogenic RAS mutations. The inventors have previously disclosed cellular data demonstrating the ability of a tri-complex $KRAS^{MULTI}$(ON) inhibitor to inhibit the proliferation of cancer cells bearing a range of oncogenic RAS mutants (FIG. 3). The heatmap (FIG. 2A) demonstrates comprehensively that Compound A, a tri-complex $KRAS^{MULTI}$(ON) inhibitor disclosed herein, can inhibit $KRAS^{G12X}$/RAF complex formation and therefore signaling driven by all possible G12 mutants of KRAS. These data indicate that Compound A, or more broadly, as the inventors surmise, tri-complex RAS(ON) inhibitors generally (see, e.g., Tanaka et al.), may offer clinical benefit in treating not only patients who are resistant to (e.g., have progressed on) $KRAS^{G12C}$(OFF) inhibitors, but patients naïve to such treatment whose tumors bear one or more of these alternative KRAS mutations, as well as comparable 12 position in HRAS and NRAS.

General Methods

The practice of the present disclosure will employ, unless otherwise indicated, conventional techniques of cell culturing, molecular biology (including recombinant techniques), microbiology, cell biology, biochemistry, and immunology, which are within the skill of the art. Such techniques are explained fully in the literature, such as, Molecular Cloning: A Laboratory Manual, third edition (Sambrook et al., 2001) Cold Spring Harbor Press; Oligonucleotide Synthesis (P. Herdewijn, ed., 2004); Animal Cell Culture (R. I. Freshney), ed., 1987); Methods in Enzymology (Academic Press, Inc.); Handbook of Experimental Immunology (D. M. Weir & C. C. Blackwell, eds.); Gene Transfer Vectors for Mammalian Cells (J. M. Miller & M. P. Calos, eds., 1987); Current Protocols in Molecular Biology (F. M. Ausubel et al., eds., 1987); PCR: The Polymerase Chain Reaction, (Mullis et al., eds., 1994); Current Protocols in Immunology (J. E. Coligan et al., eds., 1991); Short Protocols in Molecular Biology (Wiley and Sons,

1999); Manual of Clinical Laboratory Immunology (B. Detrick, N. R. Rose, and J. D. Folds eds., 2006); Immunochemical Protocols (J. Pound, ed., 2003); Lab Manual in Biochemistry: Immunology and Biotechnology (A. Nigam and A. Ayyagari, eds. 2007); Immunology Methods Manual: The Comprehensive Sourcebook of Techniques (Ivan Lefkovits, ed., 1996); Using Antibodies: A Laboratory Manual (E. Harlow and D. Lane, eds.,1988); and others.

Definitions

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.

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 present disclosure. Cis and trans geometric isomers of the compounds of the present disclosure are described and may be isolated as a mixture of isomers or as separated isomeric forms.

In some embodiments, one or more compounds depicted herein may exist in different tautomeric forms. As will be clear from context, unless explicitly excluded, references to such compounds encompass all such tautomeric forms. In some embodiments, tautomeric forms result from the swapping of a single bond with an adjacent double bond and the concomitant migration of a proton. In certain embodiments, a tautomeric form may be a prototropic tautomer, which is an isomeric protonation states having the same empirical formula and total charge as a reference form. Examples of moieties with

prototropic tautomeric forms are ketone - enol pairs, amide - imidic acid pairs, lactam - lactim pairs, amide - imidic acid pairs, enamine - imine pairs, and annular forms where a proton can occupy two or more positions of a heterocyclic system, such as, 1H- and 3H-imidazole, 1H-, 2H- and 4H-1,2,4-triazole, 1H- and 2H- isoindole, and 1H- and 2H-pyrazole. In some embodiments, tautomeric forms can be in equilibrium or sterically locked into one form by appropriate substitution. In certain embodiments, tautomeric forms result from acetal interconversion.

Unless otherwise stated, structures depicted herein are also meant to include compounds that differ only in the presence of one or more isotopically enriched atoms. Exemplary isotopes that can be incorporated into compounds of the present disclosure include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorus, sulfur, fluorine, chlorine, and iodine, such as ^{2}H, ^{3}H, ^{11}C, ^{13}C, ^{14}C, ^{13}N, ^{15}N, ^{15}O, ^{17}O, ^{18}O, ^{32}P, ^{33}P, ^{35}S, ^{18}F, ^{36}Cl, ^{123}I and ^{125}I. Isotopically-labeled compounds (e.g., those labeled with ^{3}H and ^{14}C) can be useful in compound or substrate tissue distribution assays. Tritiated (i.e., ^{3}H) and carbon-14 (i.e., ^{14}C) isotopes can be useful for their ease of preparation and detectability. Further, substitution with heavier isotopes such as deuterium (i.e., ^{2}H) may afford certain therapeutic advantages resulting from greater metabolic stability (e.g., increased in vivo half-life or reduced dosage requirements). In some embodiments, one or more hydrogen atoms are replaced by ^{2}H or ^{3}H, or one or more carbon atoms are replaced by ^{13}C- or ^{14}C-enriched carbon. Positron emitting isotopes such as ^{15}O, ^{13}N, ^{11}C, and ^{18}F are useful for positron emission tomography (PET) studies to examine substrate receptor occupancy. Preparations of isotopically labelled compounds are known to those of skill in the art. For example, isotopically labeled compounds can generally be prepared by following procedures analogous to those disclosed for compounds of the present disclosure described herein, by substituting an isotopically labeled reagent for a non-isotopically labeled reagent.

As is known in the art, many chemical entities can adopt a variety of different solid forms such as, for example, amorphous forms or crystalline forms (e.g., polymorphs, hydrates, solvate). In some embodiments, compounds of the present disclosure may be utilized in any such form, including in any solid form. In some embodiments, compounds described or depicted herein may be provided or utilized in hydrate or solvate form.

Those of ordinary skill in the art, reading the present disclosure, will appreciate that certain compounds described herein may be provided or utilized in any of a variety of forms such as, for example, salt forms, protected forms, pro-drug forms, ester forms, isomeric forms (e.g., optical or structural isomers), isotopic forms, etc. In some embodiments, reference to a particular compound may relate to a specific form of that compound. In some embodiments, reference to a particular compound may relate to that compound in any form. In some embodiments, for example, a preparation of a single stereoisomer of a compound may be considered to be a different form of the compound than a racemic mixture of the compound; a particular salt of a compound may be considered to be a different form from another salt form of the compound; a preparation containing one conformational isomer ((Z) or (E)) of a double bond may be considered to be a different form from one containing the other conformational isomer ((E) or (Z)) of the double bond; a preparation in which one or more atoms is a different isotope than is present in a reference preparation may be considered to be a different form.

At various places in the present specification, substituents of compounds of the present disclosure are disclosed in groups or in ranges. It is specifically intended that the present disclosure include each and every individual subcombination of the members of such groups and ranges. For

example, the term "C_1-C_6 alkyl" is specifically intended to individually disclose methyl, ethyl, C_3 alkyl, C_4 alkyl, C_5 alkyl, and C_6 alkyl. Furthermore, where a compound includes a plurality of positions at which substituents are disclosed in groups or in ranges, unless otherwise indicated, the present disclosure is intended to cover individual compounds and groups of compounds (e.g., genera and subgenera) containing each and every individual subcombination of members at each position.

The term "optionally substituted X" (e.g., "optionally substituted alkyl") is intended to be equivalent to "X, wherein X is optionally substituted" (e.g., "alkyl, wherein said alkyl is optionally substituted"). It is not intended to mean that the feature "X" (e.g., alkyl) *per se* is optional. As described herein, certain compounds of interest may contain one or more "optionally substituted" moieties. In general, the term "substituted", whether preceded by the term "optionally" or not, means that one or more hydrogens of the designated moiety are replaced with a suitable substituent, e.g., any of the substituents or groups described herein. Unless otherwise indicated, an "optionally substituted" group may have a suitable substituent at each substitutable position of the group, and when more than one position in any given structure may be substituted with more than one substituent selected from a specified group, the substituent may be either the same or different at every position. For example, in the term "optionally substituted C_1-C_6 alkyl-C_2-C_9 heteroaryl," the alkyl portion, the heteroaryl portion, or both, may be optionally substituted. Combinations of substituents envisioned by the present disclosure are preferably those that result in the formation of stable or chemically feasible compounds. The term "stable", as used herein, refers to compounds that are not substantially altered when subjected to conditions to allow for their production, detection, and, in certain embodiments, their recovery, purification, and use for one or more of the purposes disclosed herein.

Suitable monovalent substituents on a substitutable carbon atom of an "optionally substituted" group may be, independently, deuterium; halogen; $-(CH_2)_{0-4}R^\circ$; $-(CH_2)_{0-4}OR^\circ$; $-O(CH_2)_{0-4}R^\circ$; $-O-(CH_2)_{0-4}C(O)OR^\circ$; $-(CH_2)_{0-4}CH(OR^\circ)_2$; $-(CH_2)_{0-4}SR^\circ$; $-(CH_2)_{0-4}Ph$, which may be substituted with R°; $-(CH_2)_{0-4}O(CH_2)_{0-1}Ph$ which may be substituted with R°; $-CH=CHPh$, which may be substituted with R°; $-(CH_2)_{0-4}O(CH_2)_{0-1}$-pyridyl which may be substituted with R°; 4-8 membered saturated or unsaturated heterocycloalkyl (e.g., pyridyl); 3-8 membered saturated or unsaturated cycloalkyl (e.g., cyclopropyl, cyclobutyl, or cyclopentyl); $-NO_2$; $-CN$; $-N_3$; $-(CH_2)_{0-4}N(R^\circ)_2$; $-(CH_2)_{0-4}N(R^\circ)C(O)R^\circ$; $-N(R^\circ)C(S)R^\circ$; $-(CH_2)_{0-4}N(R^\circ)C(O)NR^\circ_2$; $-N(R^\circ)C(S)NR^\circ_2$; $-(CH_2)_{0-4}N(R^\circ)C(O)OR^\circ$; $-N(R^\circ)N(R^\circ)C(O)R^\circ$; $-N(R^\circ)N(R^\circ)C(O)NR^\circ_2$; $-N(R^\circ)N(R^\circ)C(O)OR^\circ$; $-(CH_2)_{0-4}C(O)R^\circ$; $-C(S)R^\circ$; $-(CH_2)_{0-4}C(O)OR^\circ$; $-(CH_2)_{0-4}$-$C(O)$-$N(R^\circ)_2$; $-(CH_2)_{0-4}$-$C(O)$-$N(R^\circ)$-$S(O)_2$-R°; $-C(NCN)NR^\circ_2$; $-(CH_2)_{0-4}C(O)SR^\circ$; $-(CH_2)_{0-4}C(O)OSiR^\circ_3$; $-(CH_2)_{0-4}OC(O)R^\circ$; $-OC(O)(CH_2)_{0-4}SR^\circ$; $-SC(S)SR^\circ$; $-(CH_2)_{0-4}SC(O)R^\circ$; $-(CH_2)_{0-4}C(O)NR^\circ_2$; $-C(S)NR^\circ_2$; $-C(S)SR^\circ$; $-(CH_2)_{0-4}OC(O)NR^\circ_2$; $-C(O)N(OR^\circ)R^\circ$; $-C(O)C(O)R^\circ$; $-C(O)CH_2C(O)R^\circ$; $-C(NOR^\circ)R^\circ$; $-(CH_2)_{0-4}SSR^\circ$; $-(CH_2)_{0-4}S(O)_2R^\circ$; $-(CH_2)_{0-4}S(O)_2OR^\circ$; $-(CH_2)_{0-4}OS(O)_2R^\circ$; $-S(O)_2NR^\circ_2$; $-(CH_2)_{0-4}S(O)R^\circ$; $-N(R^\circ)S(O)_2NR^\circ_2$; $-N(R^\circ)S(O)_2R^\circ$; $-N(OR^\circ)R^\circ$; $-C(NOR^\circ)NR^\circ_2$; $-C(NH)NR^\circ_2$; $-P(O)_2R^\circ$; $-P(O)R^\circ_2$; $-P(O)(OR^\circ)_2$; $-OP(O)R^\circ_2$; $-OP(O)(OR^\circ)_2$; $-OP(O)(OR^\circ)R^\circ$, $-SiR^\circ_3$; $-(C_{1-4}$ straight or branched alkylene$)O-N(R^\circ)_2$; or $-(C_{1-4}$ straight or branched alkylene$)C(O)O-N(R^\circ)_2$, wherein each R° may be substituted as defined below and is independently hydrogen, $-C_{1-6}$ aliphatic, $-CH_2Ph$, $-O(CH_2)_{0-1}Ph$, $-CH_2$-(5-6 membered heteroaryl ring), or a 3-6-membered saturated, partially unsaturated, or aryl ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or, notwithstanding the definition above, two independent occurrences of R°, taken together with their intervening atom(s), form a

3-12-membered saturated, partially unsaturated, or aryl mono- or bicyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, which may be substituted as defined below.

Suitable monovalent substituents on R° (or the ring formed by taking two independent occurrences of R° together with their intervening atoms), may be, independently, halogen, $-(CH_2)_{0-2}R^•$, $-(haloR^•)$, $-(CH_2)_{0-2}OH$, $-(CH_2)_{0-2}OR^•$, $-(CH_2)_{0-2}CH(OR^•)_2$; $-O(haloR^•)$, $-CN$, $-N_3$, $-(CH_2)_{0-2}C(O)R^•$, $-(CH_2)_{0-2}C(O)OH$, $-(CH_2)_{0-2}C(O)OR^•$, $-(CH_2)_{0-2}SR^•$, $-(CH_2)_{0-2}SH$, $-(CH_2)_{0-2}NH_2$, $-(CH_2)_{0-2}NHR^•$, $-(CH_2)_{0-2}NR^•_2$, $-NO_2$, $-SiR^•_3$, $-OSiR^•_3$, $-C(O)SR^•$, $-(C_{1-4}$ straight or branched alkylene$)C(O)OR^•$, or $-SSR^•$ wherein each $R^•$ is unsubstituted or where preceded by "halo" is substituted only with one or more halogens, and is independently selected from C_{1-4} aliphatic, $-CH_2Ph$, $-O(CH_2)_{0-1}Ph$, or a 5-6-membered saturated, partially unsaturated, or aryl ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur. Suitable divalent substituents on a saturated carbon atom of R° include =O and =S.

Suitable divalent substituents on a saturated carbon atom of an "optionally substituted" group include the following: =O, =S, $=NNR^*_2$, $=NNHC(O)R^*$, $=NNHC(O)OR^*$, $=NNHS(O)_2R^*$, $=NR^*$, $=NOR^*$, $-O(C(R^*_2))_{2-3}O-$, or $-S(C(R^*_2))_{2-3}S-$, wherein each independent occurrence of R^* is selected from hydrogen, C_{1-6} aliphatic which may be substituted as defined below, or an unsubstituted 5-6-membered saturated, partially unsaturated, or aryl ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur. Suitable divalent substituents that are bound to vicinal substitutable carbons of an "optionally substituted" group include: $-O(CR^*_2)_{2-3}O-$, wherein each independent occurrence of R^* is selected from hydrogen, C_{1-6} aliphatic which may be substituted as defined below, or an unsubstituted 5-6-membered saturated, partially unsaturated, or aryl ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

Suitable substituents on the aliphatic group of R^* include halogen, $-R^•$, $-(haloR^•)$, $-OH$, $-OR^•$, $-O(haloR^•)$, $-CN$, $-C(O)OH$, $-C(O)OR^•$, $-NH_2$, $-NHR^•$, $-NR^•_2$, or $-NO_2$, wherein each $R^•$ is unsubstituted or where preceded by "halo" is substituted only with one or more halogens, and is independently C_{1-4} aliphatic, $-CH_2Ph$, $-O(CH_2)_{0-1}Ph$, or a 5-6-membered saturated, partially unsaturated, or aryl ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

Suitable substituents on a substitutable nitrogen of an "optionally substituted" group include $-R^†$, $-NR^†_2$, $-C(O)R^†$, $-C(O)OR^†$, $-C(O)C(O)R^†$, $-C(O)CH_2C(O)R^†$, $-S(O)_2R^†$, $-S(O)_2NR^†_2$, $-C(S)NR^†_2$, $-C(NH)NR^†_2$, or $-N(R^†)S(O)_2R^†$; wherein each $R^†$ is independently hydrogen, C_{1-6} aliphatic which may be substituted as defined below, unsubstituted $-OPh$, or an unsubstituted 3-6-membered saturated, partially unsaturated, or aryl ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or, notwithstanding the definition above, two independent occurrences of $R^†$, taken together with their intervening atom(s) form an unsubstituted 3-12-membered saturated, partially unsaturated, or aryl mono- or bicyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

Suitable substituents on an aliphatic group of $R^†$ are independently halogen, $-R^•$, $-(haloR^•)$, $-OH$, $-OR^•$, $-O(haloR^•)$, $-CN$, $-C(O)OH$, $-C(O)OR^•$, $-NH_2$, $-NHR^•$, $-NR^•_2$, or $-NO_2$, wherein each $R^•$ is unsubstituted or where preceded by "halo" is substituted only with one or more halogens, and is independently C_{1-4} aliphatic, $-CH_2Ph$, $-O(CH_2)_{0-1}Ph$, or a 5-6-membered saturated, partially unsaturated, or aryl ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur. Suitable divalent substituents on a saturated carbon atom of $R^†$ include =O and =S.

The term "acetyl," as used herein, refers to the group $-C(O)CH_3$.

As used herein, the term "administration" refers to the administration of a composition (e.g., a compound, or a preparation that includes a compound as described herein) to a subject or system. Administration also includes administering a prodrug derivative or analog of the compound or pharmaceutically acceptable salt of the compound or composition to the subject, which can form an equivalent amount of active compound within the subject's body. Administration to an animal subject (e.g., to a human) may be by any appropriate route. For example, in some embodiments, administration may be bronchial (including by bronchial instillation), buccal, enteral, interdermal, intra-arterial, intradermal, intragastric, intramedullary, intramuscular, intranasal, intraperitoneal, intrathecal, intravenous, intraventricular, mucosal, nasal, oral, rectal, subcutaneous, sublingual, topical, tracheal (including by intratracheal instillation), transdermal, vaginal or vitreal.

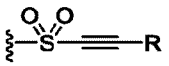
The term "alkoxy," as used herein, refers to a -O-C_1-C_{20} alkyl group, wherein the alkoxy group is attached to the remainder of the compound through an oxygen atom.

The term "alkyl," as used herein, refers to a saturated, straight or branched monovalent hydrocarbon group containing from 1 to 20 (e.g., from 1 to 10 or from 1 to 6) carbons. In some embodiments, an alkyl group is unbranched (i.e., is linear); in some embodiments, an alkyl group is branched. Alkyl groups are exemplified by, but not limited to, methyl, ethyl, *n*- and *iso*-propyl, *n*-, *sec*-, *iso*- and *tert*-butyl, and neopentyl.

The term "alkylene," as used herein, represents a saturated divalent hydrocarbon group derived from a straight or branched chain saturated hydrocarbon by the removal of two hydrogen atoms, and is exemplified by methylene, ethylene, isopropylene, and the like. The term "C_x-C_y alkylene" represents alkylene groups having between x and y carbons. Exemplary values for x are 1, 2, 3, 4, 5, and 6, and exemplary values for y are 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 14, 16, 18, or 20 (e.g., C_1-C_6, C_1-C_{10}, C_2-C_{20}, C_2-C_6, C_2-C_{10}, or C_2-C_{20} alkylene). In some embodiments, the alkylene can be further substituted with 1, 2, 3, or 4 substituent groups as defined herein.

The term "alkenyl," as used herein, represents monovalent straight or branched chain groups of, unless otherwise specified, from 2 to 20 carbons (e.g., from 2 to 6 or from 2 to 10 carbons) containing one or more carbon-carbon double bonds and is exemplified by ethenyl, 1-propenyl, 2-propenyl, 2-methyl-1-propenyl, 1-butenyl, and 2-butenyl. Alkenyls include both cis and trans isomers. The term "alkenylene," as used herein, represents a divalent straight or branched chain groups of, unless otherwise specified, from 2 to 20 carbons (e.g., from 2 to 6 or from 2 to 10 carbons) containing one or more carbon-carbon double bonds.

The term "alkynyl," as used herein, represents monovalent straight or branched chain groups from 2 to 20 carbon atoms (e.g., from 2 to 4, from 2 to 6, or from 2 to 10 carbons) containing a carbon-carbon triple bond and is exemplified by ethynyl, and 1-propynyl.

The term "alkynyl sulfone," as used herein, represents a group comprising the structure  , wherein R is any chemically feasible substituent described herein.

The term "amino," as used herein, represents -N(R^1)$_2$, e.g., -NH_2 and -N(CH_3)$_2$.

The term "aminoalkyl," as used herein, represents an alkyl moiety substituted on one or more carbon atoms with one or more amino moieties.

The term "amino acid," as described herein, refers to a molecule having a side chain, an amino group, and an acid group (e.g., -CO_2H or -SO_3H), wherein the amino acid is attached to the parent

molecular group by the side chain, amino group, or acid group (e.g., the side chain). As used herein, the term "amino acid" in its broadest sense, refers to any compound or substance that can be incorporated into a polypeptide chain, e.g., through formation of one or more peptide bonds. In some embodiments, an amino acid has the general structure H_2N-C(H)(R)-COOH. In some embodiments, an amino acid is a naturally-occurring amino acid. In some embodiments, an amino acid is a synthetic amino acid; in some embodiments, an amino acid is a D-amino acid; in some embodiments, an amino acid is an L-amino acid. "Standard amino acid" refers to any of the twenty standard L-amino acids commonly found in naturally occurring peptides. Exemplary amino acids include alanine, arginine, asparagine, aspartic acid, cysteine, glutamic acid, glutamine, glycine, histidine, optionally substituted hydroxylnorvaline, isoleucine, leucine, lysine, methionine, norvaline, ornithine, phenylalanine, proline, pyrrolysine, selenocysteine, serine, taurine, threonine, tryptophan, tyrosine, and valine.

An "amino acid substitution," as used herein, refers to the substitution of a wild-type amino acid of a protein with a non-wild-type amino acid. Amino acid substitutions can result from genetic mutations and may alter one or more properties of the protein (e.g., may confer altered binding affinity or specificity, altered enzymatic activity, altered structure, or altered function). For example, where a RAS protein includes an amino acid substitution at position Y96, this notation indicates that the wild-type amino acid at position 96 of the RAS protein is a Tyrosine (Y), and that the RAS protein including the amino acid substitution at position Y96 includes any amino acid other than Tyrosine (Y) at position 96. The notation Y96D indicates that the wild-type Tyrosine (Y) residue at position 96 has been substituted with an Aspartic Acid (D) residue.

The term "aryl," as used herein, represents a monovalent monocyclic, bicyclic, or multicyclic ring system formed by carbon atoms, wherein the ring attached to the pendant group is aromatic. Examples of aryl groups are phenyl, naphthyl, phenanthrenyl, and anthracenyl. An aryl ring can be attached to its pendant group at any heteroatom or carbon ring atom that results in a stable structure and any of the ring atoms can be optionally substituted unless otherwise specified.

The term "C_0," as used herein, represents a bond. For example, part of the term -N(C(O)-(C_0-C_5 alkylene-H)- includes -N(C(O)-(C_0 alkylene-H)-, which is also represented by -N(C(O)-H)-.

The terms "carbocyclic" and "carbocyclyl," as used herein, refer to a monovalent, optionally substituted C_3-C_{12} monocyclic, bicyclic, or tricyclic ring structure, which may be bridged, fused or spirocyclic, in which all the rings are formed by carbon atoms and at least one ring is non-aromatic. Carbocyclic structures include cycloalkyl, cycloalkenyl, and cycloalkynyl groups. Examples of carbocyclyl groups are cyclohexyl, cyclohexenyl, cyclooctynyl, 1,2-dihydronaphthyl, 1,2,3,4-tetrahydronaphthyl, fluorenyl, indenyl, indanyl, decalinyl, and the like. A carbocyclic ring can be attached to its pendant group at any ring atom that results in a stable structure and any of the ring atoms can be optionally substituted unless otherwise specified.

The term "carbonyl," as used herein, represents a C(O) group, which can also be represented as C=O.

The term "carboxyl," as used herein, means -CO_2H, (C=O)(OH), COOH, or C(O)OH or the unprotonated counterparts.

The term "combination therapy" refers to a method of treatment including administering to a subject at least two therapeutic agents, optionally as one or more pharmaceutical compositions, as part of a therapeutic regimen. For example, a combination therapy may include administration of a single

pharmaceutical composition including at least two therapeutic agents and one or more pharmaceutically acceptable carrier, excipient, diluent, or surfactant. A combination therapy may include administration of two or more pharmaceutical compositions, each composition including one or more therapeutic agent and one or more pharmaceutically acceptable carrier, excipient, diluent, or surfactant. In various embodiments, at least one of the therapeutic agents is a RAS(ON) inhibitor (e.g., any one or more KRAS(ON) inhibitors disclosed herein or known in the art). In various embodiments, at least one of the therapeutic agents is a RAS(OFF) inhibitor (e.g., any one or more KRAS(OFF) inhibitors disclosed herein or known in the art). The two or more agents may optionally be administered simultaneously (as a single or as separate compositions) or sequentially (as separate compositions). The therapeutic agents may be administered in an effective amount. The therapeutic agent may be administered in a therapeutically effective amount. In some embodiments, the effective amount of one or more of the therapeutic agents may be lower when used in a combination therapy than the therapeutic amount of the same therapeutic agent when it is used as a monotherapy, e.g., due to an additive or synergistic effect of combining the two or more therapeutics.

The term "cyano," as used herein, represents a -CN group.

The term "cycloalkyl," as used herein, represents a monovalent saturated cyclic hydrocarbon group, which may be bridged, fused or spirocyclic having from three to eight ring carbons, unless otherwise specified, and is exemplified by cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cycloheptyl.

The term "cycloalkenyl," as used herein, represents a monovalent, non-aromatic, saturated cyclic hydrocarbon group, which may be bridged, fused or spirocyclic having from three to eight ring carbons, unless otherwise specified, and containing one or more carbon-carbon double bonds.

The term "diastereomer," as used herein, means stereoisomers that are not mirror images of one another and are non-superimposable on one another.

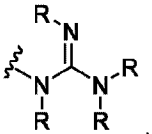
As used herein, the term "dosage form" refers to a physically discrete unit of a compound (e.g., a compound of the present disclosure) for administration to a subject. Each unit contains a predetermined quantity of compound. In some embodiments, such quantity is a unit dosage amount (or a whole fraction thereof) appropriate for administration in accordance with a dosing regimen that has been determined to correlate with a desired or beneficial outcome when administered to a relevant population (i.e., with a therapeutic dosing regimen). Those of ordinary skill in the art appreciate that the total amount of a therapeutic composition or compound administered to a particular subject is determined by one or more attending physicians and may involve administration of multiple dosage forms.

As used herein, the term "dosing regimen" refers to a set of unit doses (typically more than one) that are administered individually to a subject, typically separated by periods of time. In some embodiments, a given therapeutic compound (e.g., a compound of the present disclosure) has a recommended dosing regimen, which may involve one or more doses. In some embodiments, a dosing regimen includes a plurality of doses each of which are separated from one another by a time period of the same length; in some embodiments, a dosing regimen includes a plurality of doses and at least two different time periods separating individual doses. In some embodiments, all doses within a dosing regimen are of the same unit dose amount. In some embodiments, different doses within a dosing regimen are of different amounts. In some embodiments, a dosing regimen includes a first dose in a first dose amount, followed by one or more additional doses in a second dose amount different from the first

dose amount. In some embodiments, a dosing regimen includes a first dose in a first dose amount, followed by one or more additional doses in a second dose amount same as the first dose amount. In some embodiments, a dosing regimen is correlated with a desired or beneficial outcome when administered across a relevant population (i.e., is a therapeutic dosing regimen).

The term "disorder" is used in this disclosure to mean, and is used interchangeably with, the terms disease, condition, or illness, unless otherwise indicated.

The term "enantiomer," as used herein, means each individual optically active form of a compound of the invention, having an optical purity or enantiomeric excess (as determined by methods standard in the art) of at least 80% (i.e., at least 90% of one enantiomer and at most 10% of the other enantiomer), preferably at least 90% and more preferably at least 98%.

The term "guanidinyl," refers to a group having the structure:  , wherein each R is, independently, any any chemically feasible substituent described herein.

The term "guanidinoalkyl alkyl," as used herein, represents an alkyl moiety substituted on one or more carbon atoms with one or more guanidinyl moieties.

The term "haloacetyl," as used herein, refers to an acetyl group wherein at least one of the hydrogens has been replaced by a halogen.

The term "haloalkyl," as used herein, represents an alkyl moiety substituted on one or more carbon atoms with one or more of the same of different halogen moieties.

The term "halogen," as used herein, represents a halogen selected from bromine, chlorine, iodine, or fluorine.

The term "heteroalkyl," as used herein, refers to an "alkyl" group, as defined herein, in which at least one carbon atom has been replaced with a heteroatom (e.g., an O, N, or S atom). The heteroatom may appear in the middle or at the end of the radical.

The term "heteroaryl," as used herein, represents a monovalent, monocyclic or polycyclic ring structure that contains at least one fully aromatic ring: i.e., they contain $4n$+2 pi electrons within the monocyclic or polycyclic ring system and contains at least one ring heteroatom selected from N, O, or S in that aromatic ring. Exemplary unsubstituted heteroaryl groups are of 1 to 12 (e.g., 1 to 11, 1 to 10, 1 to 9, 2 to 12, 2 to 11, 2 to 10, or 2 to 9) carbons. The term "heteroaryl" includes bicyclic, tricyclic, and tetracyclic groups in which any of the above heteroaromatic rings is fused to one or more, aryl or carbocyclic rings, e.g., a phenyl ring, or a cyclohexane ring. Examples of heteroaryl groups include, but are not limited to, pyridyl, pyrazolyl, benzooxazolyl, benzoimidazolyl, benzothiazolyl, imidazolyl, thiazolyl, quinolinyl, tetrahydroquinolinyl, and 4-azaindolyl. A heteroaryl ring can be attached to its pendant group at any ring atom that results in a stable structure and any of the ring atoms can be optionally substituted unless otherwise specified. In some embodiment, the heteroaryl is substituted with 1, 2, 3, or 4 substituents groups.

The term "heterocycloalkyl," as used herein, represents a monovalent monocyclic, bicyclic or polycyclic ring system, which may be bridged, fused or spirocyclic, wherein at least one ring is non-aromatic and wherein the non-aromatic ring contains one, two, three, or four heteroatoms independently selected from the group consisting of nitrogen, oxygen, and sulfur. The 5-membered ring has zero to two

double bonds, and the 6- and 7-membered rings have zero to three double bonds. Exemplary unsubstituted heterocycloalkyl groups are of 1 to 12 (e.g., 1 to 11, 1 to 10, 1 to 9, 2 to 12, 2 to 11, 2 to 10, or 2 to 9) carbons. The term "heterocycloalkyl" also represents a heterocyclic compound having a bridged multicyclic structure in which one or more carbons or heteroatoms bridges two non-adjacent members of a monocyclic ring, e.g., a quinuclidinyl group. The term "heterocycloalkyl" includes bicyclic, tricyclic, and tetracyclic groups in which any of the above heterocyclic rings is fused to one or more aromatic, carbocyclic, heteroaromatic, or heterocyclic rings, e.g., an aryl ring, a cyclohexane ring, a cyclohexene ring, a cyclopentane ring, a cyclopentene ring, a pyridine ring, or a pyrrolidine ring. Examples of heterocycloalkyl groups are pyrrolidinyl, piperidinyl, 1,2,3,4-tetrahydroquinolinyl, decahydroquinolinyl, dihydropyrrolopyridine, and decahydronapthyridinyl. A heterocycloalkyl ring can be attached to its pendant group at any ring atom that results in a stable structure and any of the ring atoms can be optionally substituted unless otherwise specified.

The term "hydroxy," as used herein, represents a -OH group.

The term "hydroxyalkyl," as used herein, represents an alkyl moiety substituted on one or more carbon atoms with one or more -OH moieties.

As used herein, the term "inhibitor" refers to a compound that prevents a biomolecule, (e.g., a protein, nucleic acid) from completing or initiating a reaction. An inhibitor can inhibit a reaction by competitive, uncompetitive, or non-competitive means, for example. With respect to its binding mechanism, an inhibitor may be an irreversible inhibitor or a reversible inhibitor. Exemplary inhibitors include, but are not limited to, nucleic acids, DNA, RNA, shRNA, siRNA, proteins, protein mimetics, peptides, peptidomimetics, antibodies, small molecules, chemicals, analogs that mimic the binding site of an enzyme, receptor, or other protein. In some embodiments, the inhibitor is a small molecule, e.g., a low molecular weight organic compound, e.g., an organic compound having a molecular weight (MW) of less than 1200 Daltons (Da). In some embodiments, the MW is less than 1100 Da. In some embodiments, the MW is less than 1000 Da. In some embodiments, the MW is less than 900 Da. In some embodiments, the range of the MW of the small molecule is between 800 Da and 1200 Da. Small molecule inhibitors include cyclic and acyclic compounds. Small molecules inhibitors include natural products, derivatives, and analogs thereof. Small molecule inhibitors can include a covalent cross-linking group capable of forming a covalent cross-link, e.g., with an amino acid side-chain of a target protein.

The term "isomer," as used herein, means any tautomer, stereoisomer, atropiosmer, enantiomer, or diastereomer of any compound of the invention. It is recognized that the compounds of the invention can have one or more chiral centers or double bonds and, therefore, exist as stereoisomers, such as double-bond isomers (i.e., geometric E/Z isomers) or diastereomers (e.g., enantiomers (i.e., (+) or (-)) or cis/trans isomers). According to the invention, the chemical structures depicted herein, and therefore the compounds of the invention, encompass all the corresponding stereoisomers, that is, both the stereomerically pure form (e.g., geometrically pure, enantiomerically pure, or diastereomerically pure) and enantiomeric and stereoisomeric mixtures, e.g., racemates. Enantiomeric and stereoisomeric mixtures of compounds of the invention can typically be resolved into their component enantiomers or stereoisomers by well-known methods, such as chiral-phase gas chromatography, chiral-phase high performance liquid chromatography, crystallizing the compound as a chiral salt complex, or crystallizing the compound in a chiral solvent. Enantiomers and stereoisomers can also be obtained from stereomerically or

enantiomerically pure intermediates, reagents, and catalysts by well-known asymmetric synthetic methods.

As used herein, the term "linker" refers to a divalent organic moiety connecting a first moiety (e.g., a macrocyclic moiety or B) to a second moiety (e.g., W) in a compound of any one of Formula AI, Formula BI, Formula CI, Formula DIA, Formula EI, Formula FI, Formula FIII, or a subformula thereof, such that the resulting compound is capable of achieving an IC50 of 2 uM or less in the Ras-RAF disruption assay protocol provided here:

The purpose of this biochemical assay is to measure the ability of test compounds to facilitate ternary complex formation between a nucleotide-loaded Ras isoform and cyclophilin A; the resulting ternary complex disrupts binding to a $BRAF^{RBD}$ construct, inhibiting Ras signaling through a RAF effector.

In assay buffer containing 25 mM HEPES pH 7.3, 0.002% Tween20, 0.1% BSA, 100 mM NaCl and 5 mM $MgCl_2$, tagless Cyclophilin A, His6-K-Ras-GMPPNP (or other Ras variant), and GST-$BRAF^{RBD}$ are combined in a 384-well assay plate at final concentrations of 25 µM, 12.5 nM and 50 nM, respectively. Compound is present in plate wells as a 10-point 3-fold dilution series starting at a final concentration of 30 µM. After incubation at 25°C for 3 hours, a mixture of Anti-His Eu-W1024 and anti-GST allophycocyanin is then added to assay sample wells at final concentrations of 10 nM and 50 nM, respectively, and the reaction incubated for an additional 1.5 hours. TR-FRET signal is read on a microplate reader (Ex 320 nm, Em 665/615 nm). Compounds that facilitate disruption of a Ras:RAF complex are identified as those eliciting a decrease in the TR-FRET ratio relative to DMSO control wells.

In some embodiments, the linker comprises 20 or fewer linear atoms. In some embodiments, the linker comprises 15 or fewer linear atoms. In some embodiments, the linker comprises 10 or fewer linear atoms. In some embodiments, the linker has a molecular weight of under 500 g/mol. In some embodiments, the linker has a molecular weight of under 400 g/mol. In some embodiments, the linker has a molecular weight of under 300 g/mol. In some embodiments, the linker has a molecular weight of under 200 g/mol. In some embodiments, the linker has a molecular weight of under 100 g/mol. In some embodiments, the linker has a molecular weight of under 50 g/mol.

As used herein, a "monovalent organic moiety" is less than 500 kDa. In some embodiments, a "monovalent organic moiety" is less than 400 kDa. In some embodiments, a "monovalent organic moiety" is less than 300 kDa. In some embodiments, a "monovalent organic moiety" is less than 200 kDa. In some embodiments, a "monovalent organic moiety" is less than 100 kDa. In some embodiments, a "monovalent organic moiety" is less than 50 kDa. In some embodiments, a "monovalent organic moiety" is less than 25 kDa. In some embodiments, a "monovalent organic moiety" is less than 20 kDa. In some embodiments, a "monovalent organic moiety" is less than 15 kDa. In some embodiments, a "monovalent organic moiety" is less than 10 kDa. In some embodiments, a "monovalent organic moiety" is less than 1 kDa. In some embodiments, a "monovalent organic moiety" is less than 500 g/mol. In some embodiments, a "monovalent organic moiety" ranges between 500 g/mol and 500 kDa.

The term "mutation" as used herein indicates any modification of a nucleic acid or polypeptide which results in an altered nucleic acid or polypeptide. The term "mutation" may include, for example, point mutations, deletions or insertions of single or multiple residues in a polynucleotide, which includes alterations arising within a protein-encoding region of a gene as well as alterations in regions outside of a

protein-encoding sequence, such as, but not limited to, regulatory or promoter sequences, as well as amplifications or chromosomal breaks or translocations. In particular embodiments, the mutation results in an amino acid substitution in the encoded-protein.

A "patient" or "subject" is a mammal, e.g., a human, mouse, rat, guinea pig, dog, cat, horse, cow, pig, or non-human primate, such as a monkey, chimpanzee, baboon or rhesus.

The term "prevent" or "preventing" with regard to a subject refers to keeping a disease or disorder from afflicting the subject. Preventing includes prophylactic treatment. For instance, preventing can include administering to the subject a compound disclosed herein before a subject is afflicted with a disease and the administration will keep the subject from being afflicted with the disease.

The term "preventing acquired resistance," as used herein, means avoiding the occurrence of acquired or adaptive resistance. For example, the use of a RAS(ON) inhibitor described herein in preventing acquired/adaptive resistance to a RAS(OFF) inhibitor means that the RAS(ON) inhibitor is administered prior to any detectable existence of resistance to the RAS(OFF) inhibitor and the result of such administration of the RAS(ON) inhibitor is that no resistance to the RAS(OFF) inhibitor occurs.

As used herein, the term "pharmaceutical composition" refers to a compound, such as a compound of the present disclosure, or a pharmaceutically acceptable salt thereof, formulated together with a pharmaceutically acceptable excipient.

A "pharmaceutically acceptable excipient," as used herein, refers any inactive ingredient (for example, a vehicle capable of suspending or dissolving the active compound) having the properties of being nontoxic and non-inflammatory in a subject. Typical excipients include, for example: antiadherents, antioxidants, binders, coatings, compression aids, disintegrants, dyes (colors), emollients, emulsifiers, fillers (diluents), film formers or coatings, flavors, fragrances, glidants (flow enhancers), lubricants, preservatives, printing inks, sorbents, suspensing or dispersing agents, sweeteners, or waters of hydration. Excipients include, but are not limited to: butylated optionally substituted hydroxyltoluene (BHT), calcium carbonate, calcium phosphate (dibasic), calcium stearate, croscarmellose, crosslinked polyvinyl pyrrolidone, citric acid, crospovidone, cysteine, ethylcellulose, gelatin, optionally substituted hydroxylpropyl cellulose, optionally substituted hydroxylpropyl methylcellulose, lactose, magnesium stearate, maltitol, mannitol, methionine, methylcellulose, methyl paraben, microcrystalline cellulose, polyethylene glycol, polyvinyl pyrrolidone, povidone, pregelatinized starch, propyl paraben, retinyl palmitate, shellac, silicon dioxide, sodium carboxymethyl cellulose, sodium citrate, sodium starch glycolate, sorbitol, starch (corn), stearic acid, stearic acid, sucrose, talc, titanium dioxide, vitamin A, vitamin E, vitamin C, and xylitol. Those of ordinary skill in the art are familiar with a variety of agents and materials useful as excipients. See, e.g., Ansel, et al., Ansel's Pharmaceutical Dosage Forms and Drug Delivery Systems. Philadelphia: Lippincott, Williams & Wilkins, 2004; Gennaro, et al., Remington: The Science and Practice of Pharmacy. Philadelphia: Lippincott, Williams & Wilkins, 2000; and Rowe, Handbook of Pharmaceutical Excipients. Chicago, Pharmaceutical Press, 2005. In some embodiments, a composition includes at least two different pharmaceutically acceptable excipients.

The term "pharmaceutically acceptable salt," as use herein, refers to those salts of the compounds described herein that are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and other animals without undue toxicity, irritation, allergic response and the like, and are commensurate with a reasonable benefit/risk ratio. Pharmaceutically acceptable salts are well known in the art. For example, pharmaceutically acceptable salts are described in: Berge

et al., *J. Pharmaceutical Sciences* 66:1-19, 1977 and in *Pharmaceutical Salts: Properties, Selection, and Use*, (Eds. P.H. Stahl and C.G. Wermuth), Wiley-VCH, 2008. The salts can be prepared in situ during the final isolation and purification of the compounds described herein or separately by reacting the free base group with a suitable organic acid.

The terms "RAS inhibitor" and "inhibitor of [a] RAS" are used interchangeably to refer to any inhibitor that targets, that is, selectively binds to or inhibits a RAS protein. In various embodiments, these terms include RAS(OFF) and RAS(ON) inhibitors.

As used herein, the term "RAS(ON) inhibitor" refers to an inhibitor that targets, that is, selectively binds to or inhibits, the GTP-bound, active state of RAS (e.g., selective over the GDP-bound, inactive state of RAS). Inhibition of the GTP-bound, active state of RAS includes, for example, the inhibition of oncogenic signaling from the GTP-bound, active state of RAS. In some embodiments, the RAS(ON) inhibitor is an inhibitor that selectively binds to and inhibits the GTP-bound, active state of RAS. In certain embodiments, RAS(ON) inhibitors may also bind to or inhibit the GDP-bound, inactive state of RAS (e.g., with a lower affinity or inhibition constant than for the GTP-bound, active state of RAS). RAS(ON) inhibitors described herein include compounds of Formula AI, Formula BI, Formula CI, Formula DIa, Formula EI, Formula FI, Formula FIII, and subformulas thereof, and compounds of Table A1, Table A2, Table B1, Table B2, Table C1, Table C2, Table D1a, Table D1b, Table D2, Table D3, Table E1, Table F1, Table F2, Table F3, Table F4, Table F5, Table F6, as well as salts (e.g., pharmaceutically acceptable salts), solvates, hydrates, stereoisomers (including atropisomers), and tautomers thereof. In some embodiments, a RAS(ON) inhibitor is a tri-complex RAS(ON) inhibitor, as that term is defined herein.

As used herein, the term "RAS(OFF) inhibitor" refers to an inhibitor that targets, that is, selectively binds to or inhibits the GDP-bound, inactive state of RAS (e.g., selective over the GTP-bound, active state of RAS). Inhibition of the GDP-bound, inactive state of RAS includes, for example, sequestering the inactive state by inhibiting the exchange of GDP for GTP, thereby inhibiting RAS from adopting the active conformation. In certain embodiments, RAS(OFF) inhibitors may also bind to or inhibit the GTP-bound, active state of RAS (e.g., with a lower affinity or inhibition constant than for the GDP-bound, inactive state of RAS).

As used herein, the term "RAS^{MULTI}(ON) inhibitor" refers to a RAS(ON) inhibitor of at least 3 RAS variants with missense mutations at one of the following positions: 12, 13, 59, 61, or 146. In some embodiments, a RAS^{MULTI}(ON) inhibitor refers to a RAS^{MULTI}(ON) inhibitor of at least 3 RAS variants with missense mutations at one of the following positions: 12, 13, and 61. In some embodiments, a RAS^{MULTI}(ON) inhibitor is a tri-complex RAS^{MULTI}(ON) inhibitor.

The terms "RAS pathway" and "RAS/MAPK pathway" are used interchangeably herein to refer to a signal transduction cascade downstream of various cell surface growth factor receptors in which activation of RAS (and its various isoforms and alleotypes) is a central event that drives a variety of cellular effector events that determine the proliferation, activation, differentiation, mobilization, and other functional properties of the cell. SHP2 conveys positive signals from growth factor receptors to the RAS activation/deactivation cycle, which is modulated by guanine nucleotide exchange factors (GEFs, such as SOS1) that load GTP onto RAS to produce functionally active GTP-bound RAS as well as GTP-accelerating proteins (GAPs, such as NF1) that facilitate termination of the signals by conversion of GTP to GDP. GTP-bound RAS produced by this cycle conveys essential positive signals to a series of

serine/threonine kinases including RAF and MAP kinases, from which emanate additional signals to various cellular effector functions.

As used herein, the term "resistant to treatment" refers to a treatment of a disorder with a therapeutic agent, where the therapeutic agent is ineffective or where the therapeutic agent was previously effective and has become less effective over time. Resistance to treatment includes acquired resistance to treatment, which refers to a decrease in the efficacy of a treatment over a period of time where the subject is being administered the therapeutic agent. Acquired resistance to treatment may result from the acquisition of a mutation in a target protein that renders the treatment ineffective or less effective. Accordingly, resistance to treatment may persist even after cessation of administration of the therapeutic agent. In particular, a cancer may become resistant to treatment with a RAS(OFF) inhibitor by the acquisition of a mutation (e.g., in the RAS protein) that decreases the efficacy of the RAS(OFF) inhibitor. Measurement of a decrease in the efficacy of the treatment will depend on the disorder being treated, and such methods are known to those of skill in the art. For example, efficacy of a cancer treatment may be measured by the progression of the disease. An effective treatment may slow or halt the progression of the disease. A cancer that is resistant to treatment with a therapeutic agent, e.g., a RAS(OFF) inhibitor, may fail to slow or halt the progression of the disease.

The term "stereoisomer," as used herein, refers to all possible different isomeric as well as conformational forms which a compound may possess (e.g., a compound of any formula described herein), in particular all possible stereochemically and conformationally isomeric forms, all diastereomers, enantiomers or conformers of the basic molecular structure, including atropisomers. Some compounds of the present invention may exist in different tautomeric forms, all of the latter being included within the scope of the present invention.

The term "sulfonyl," as used herein, represents an $-S(O)_2-$ group.

A "therapeutic agent" is any substance, e.g., a compound or composition, capable of treating a disease or disorder. In some embodiments, therapeutic agents that are useful in connection with the present disclosure include RAS inhibitors and cancer chemotherapeutics. Many such therapeutic agents are known in the art and are disclosed herein.

The term "therapeutically effective amount" means an amount that is sufficient, when administered to a population suffering from or susceptible to a disease, disorder, or condition in accordance with a therapeutic dosing regimen, to treat the disease, disorder, or condition. In some embodiments, a therapeutically effective amount is one that reduces the incidence or severity of, or delays onset of, one or more symptoms of the disease, disorder, or condition. Those of ordinary skill in the art will appreciate that the term "therapeutically effective amount" does not in fact require successful treatment be achieved in a particular individual. Rather, a therapeutically effective amount may be that amount that provides a particular desired pharmacological response in a significant number of subjects when administered to patients in need of such treatment. It is specifically understood that particular subjects may, in fact, be "refractory" to a "therapeutically effective amount." In some embodiments, reference to a therapeutically effective amount may be a reference to an amount as measured in one or more specific tissues (e.g., a tissue affected by the disease, disorder or condition) or fluids (e.g., blood, saliva, serum, sweat, tears, urine). Those of ordinary skill in the art will appreciate that, in some embodiments, a therapeutically effective amount may be formulated or administered in a single dose. In

some embodiments, a therapeutically effective amount may be formulated or administered in a plurality of doses, for example, as part of a dosing regimen.

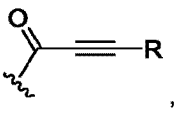
A "therapeutic regimen" refers to a dosing regimen whose administration across a relevant population is correlated with a desired or beneficial therapeutic outcome.

The term "thiocarbonyl," as used herein, refers to a -C(S)- group. The term "treatment" (also "treat" or "treating"), in its broadest sense, refers to any administration of a substance (e.g., a compound of the present disclosure) that partially or completely alleviates, ameliorates, relieves, inhibits, delays onset of, reduces severity of, or reduces incidence of one or more symptoms, features, or causes of a particular disease, disorder, or condition. In some embodiments, such treatment may be administered to a subject who does not exhibit signs of the relevant disease, disorder or condition or of a subject who exhibits only early signs of the disease, disorder, or condition. Alternatively, or additionally, in some embodiments, treatment may be administered to a subject who exhibits one or more established signs of the relevant disease, disorder or condition. In some embodiments, treatment may be of a subject who has been diagnosed as suffering from the relevant disease, disorder, or condition. In some embodiments, treatment may be of a subject known to have one or more susceptibility factors that are statistically correlated with increased risk of development of the relevant disease, disorder, or condition.

The term "treatment" (also "treat" or "treating"), in its broadest sense, refers to any administration of a substance (e.g., a compound of the present disclosure) that partially or completely alleviates, ameliorates, relieves, inhibits, delays onset of, reduces severity of, or reduces incidence of one or more symptoms, features, or causes of a particular disease, disorder, or condition. In some embodiments, such treatment may be administered to a subject who does not exhibit signs of the relevant disease, disorder or condition or of a subject who exhibits only early signs of the disease, disorder, or condition. Alternatively, or additionally, in some embodiments, treatment may be administered to a subject who exhibits one or more established signs of the relevant disease, disorder or condition. In some embodiments, treatment may be of a subject who has been diagnosed as suffering from the relevant disease, disorder, or condition. In some embodiments, treatment may be of a subject known to have one or more susceptibility factors that are statistically correlated with increased risk of development of the relevant disease, disorder, or condition.

The term "vinyl ketone," as used herein, refers to a group comprising a carbonyl group directly connected to a carbon-carbon double bond.

The term "vinyl sulfone," as used herein, refers to a group comprising a sulfonyl group directed connected to a carbon-carbon double bond.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).

The term "ynone," as used herein, refers to a group comprising the structure 

, wherein R is any any chemically feasible substituent described herein.

RAS Inhibitors

Provided herein are compounds that inhibit RAS and uses thereof. Also provided are pharmaceutical compositions including one or more RAS inhibitor compounds, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient. RAS inhibitor compounds may be used in methods of inhibiting RAS (e.g., in a subject or in a cell) and methods of treating cancer, as described herein. In some embodiments, a compound of the present disclosure is or acts as a prodrug, such as with respect to administration to a cell or to a subject in need thereof.

RAS(ON) inhibitors

Provided herein are RAS(ON) inhibitors. A RAS(ON) inhibitor targets, that is, selectively binds to or inhibits the GTP-bound, active state of RAS (e.g., selective over the GDP-bound, inactive state of RAS). Inhibition of the GTP-bound, active state of RAS includes, for example, the inhibition of oncogenic signaling from the GTP-bound, active state of RAS. In some embodiments, the RAS(ON) inhibitor is an inhibitor that selectively binds to and inhibits the GTP-bound, active state of RAS. In certain embodiments, RAS(ON) inhibitors may also bind to or inhibit the GDP-bound, inactive state of RAS (e.g., with a lower affinity or inhibition constant than for the GTP-bound, active state of RAS).

In some embodiments, the RAS(ON) inhibitor is selected from a tri-complex inhibitor disclosed in WO 202132597, WO 2021091956, WO 2021091982, or WO 2021091967, or a compound disclosed in Table A1, Table A2, Table B1, Table B2, Table C1, Table C2, Table D1a, Table D1b, Table D2, Table D3, Table E1, Table F1, Table F2, Table F3, Table F4, Table F5, Table F6, or a compound of Formula AI, Formula BI, Formula CI, Formula DIa, Formula EI, Formula FI, Formula FIII, and subformulas thereof, o. In some embodiments, the RAS(ON) inhibitor is a compound described by a Formula in WO 2020132597, such as a compound of Figure 1 therein, or a pharmaceutically acceptable salt thereof.

In some embodiments, the RAS(ON) inhibitor is selective for RAS that includes an amino acid substitution at G12, G13, Q61, or a combination thereof. In some embodiments, the RAS(ON) inhibitor is selective for RAS that includes an amino acid substitution selected from G12C, G12D, G12V, G13C, G13D, Q61L, or a combination thereof. In some embodiments, the RAS(ON) inhibitor is selective for RAS that includes a G12C amino acid substitution.

In some embodiments, the RAS(ON) inhibitor is a KRAS(ON) inhibitor, where a KRAS(ON) inhibitor refers to an inhibitor that targets, that is, selectively binds to or inhibits the GTP-bound, active state of KRAS (e.g., selective over the GDP-bound, inactive state of KRAS). In some embodiments, the KRAS(ON) inhibitor is selective for KRAS that includes an amino acid substitution at G12, G13, Q61, A146, K117, L19, Q22, V14, A59, or a combination thereof. In some embodiments, the KRAS(ON) inhibitor is selective for KRAS that includes an amino acid substitution selected from G12D, G12V, G12C, G13D, G12R, G12A, Q61H, G12S, A146T, G13C, Q61L, Q61R, K117N, A146V, G12F, Q61K, L19F, Q22K, V14I, A59T, A146P, G13R, G12L, G13V, or a combination thereof.

In some embodiments, the RAS(ON) inhibitor is an NRAS(ON) inhibitor, where an NRAS(ON) inhibitor refers to an inhibitor that targets, that is, selectively binds to or inhibits the GTP-bound, active state of NRAS (e.g., selective over the GDP-bound, inactive state of NRAS). In some embodiments, the NRAS(ON) inhibitor is selective for NRAS that includes an amino acid substitution at G12, G13, Q61, P185, A146, G60, A59, E132, E49, T50, or a combination thereof. In some embodiments, the NRAS(ON)

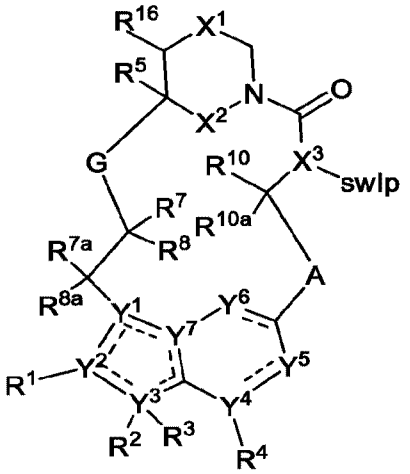
inhibitor is selective for NRAS that includes an amino acid substitution selected from Q61R, Q61K, G12D, Q61L, Q61H, G13R, G13D, G12S, G12C, G12V, G12A, G13V, G12R, P185S, G13C, A146T, G60E, Q61P, A59D, E132K, E49K, T50I, A146V, A59T, or a combination thereof.

In some embodiments, the RAS(ON) inhibitor is an HRAS(ON) inhibitor, where an HRAS(ON) inhibitor refers to an inhibitor that targets, that is selectively binds to or inhibits the GTP-bound, active state of HRAS (e.g., selective over the GDP-bound, inactive state of HRAS). In some embodiments, the HRAS(ON) inhibitor is selective for HRAS that includes an amino acid substitution at G12, G13, Q61, K117, A59, A18, D119, A66, A146, or a combination thereof. In some embodiments, the HRAS(ON) inhibitor is selective for NRAS that includes an amino acid substitution selected from Q61R, G13R, Q61K, G12S, Q61L, G12D, G13V, G13D, G12C, K117N, A59T, G12V, G13C, Q61H, G13S, A18V, D119N, G13N, A146T, A66T, G12A, A146V, G12N, G12R, or a combination thereof.

In some embodiments, the RAS(ON) inhibitor is a RAS(ON)^{MULTI} inhibitor.

In some embodiments, a RAS(ON) inhibitor described herein entails formation of a high affinity three-component complex ("tri complex") 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, in some embodiments, the RAS(ON) inhibitors described herein induce a new binding pocket in RAS by driving formation of a high affinity tri-complex between the RAS protein and the widely expressed cytosolic chaperone, cyclophilin A (CYPA). Without being bound by theory, one way the inhibitory effect on Ras is affected by compounds of the invention and the complexes 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. In some embodiments, a RAS(ON) inhibitor is a tri-complex RAS^{G12C}(ON) inhibitor. In some embodiments, a RAS(ON) inhibitor is a tri-complex RAS^{G12D}(ON) inhibitor. In some embodiments, a RAS(ON) inhibitor is a tri-complex RAS^{MULTI}(ON) inhibitor. Such tri-complex RAS(ON) inhibitors may inhibit KRAS, HRAS or NRAS, or a combination thereof.

In some embodiments, the RAS(ON) inhibitor is a compound, or pharmaceutically acceptable salt thereof, having the structure of Formula A00:



Formula A00

wherein the dotted lines represent zero, one, two, three, or four non-adjacent double bonds;

A is -N(H or CH_3)C(O)-(CH_2)- where the amino nitrogen is bound to the carbon atom of -CH(R^{10})-, optionally substituted 3 to 6-membered cycloalkylene, optionally substituted 3 to 6-membered heterocycloalkylene, optionally substituted 6-membered arylene, or optionally substituted 5 to 10-membered heteroarylene;

G is optionally substituted C_1-C_4 alkylene, optionally substituted C_1-C_4 alkenylene, optionally substituted C_1-C_4 heteroalkylene, -C(O)O-**C**H(R^6)- where **C** is bound to -C(R^7R^8)-, -C(O)NH-**C**H(R^6)- where **C** is bound to -C(R^7R^8)-, optionally substituted C_1-C_4 heteroalkylene, or 3 to 8-membered heteroarylene;

swIp (Switch I/P-loop) refers to an organic moiety that non-covalently binds to both the Switch I binding pocket and residues 12 or 13 of the P-loop of a Ras protein (see, e.g., Johnson et al., 292:12981-12993 (2017), incorporated herein by reference);

X^1 is optionally substituted C_1-C_2 alkylene, NR, O, or $S(O)_n$;

X^2 is O or NH;

X^3 is N or CH;

n is 0, 1, or 2;

R is hydrogen, cyano, optionally substituted C_1-C_4 alkyl, optionally substituted C_2-C_4 alkenyl, optionally substituted C_2-C_4 alkynyl, C(O)R', C(O)OR', C(O)N(R')$_2$, S(O)R', $S(O)_2$R', or $S(O)_2$N(R')$_2$;

each R' is, independently, H or optionally substituted C_1-C_4 alkyl;

Y^1 is C, CH, or N;

Y^2, Y^3, Y^4, and Y^7 are, independently, C or N;

Y^5 is CH, CH_2, or N;

Y^6 is C(O), CH, CH_2, or N;

R^1 is cyano, 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 cycloalkenyl, optionally substituted 3 to 6-membered heterocycloalkyl, optionally substituted 6 to 10-membered aryl, or optionally substituted 5 to 10-membered heteroaryl, or

R^1 and R^2 combine with the atoms to which they are attached to form an optionally substituted 3 to 14-membered heterocycloalkyl;

R^2 is absent, hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 alkynyl, optionally substituted 3 to 6-membered cycloalkyl, optionally substituted 3 to 7-membered heterocycloalkyl, optionally substituted 6-membered aryl, optionally substituted 5 or 6-membered heteroaryl;

R^3 is absent, or

R^2 and R^3 combine with the atom to which they are attached to form an optionally substituted 3 to 8-membered cycloalkyl or optionally substituted 3 to 14-membered heterocycloalkyl;

R^4 is absent, hydrogen, halogen, cyano, or methyl optionally substituted with 1 to 3 halogens;

R^5 is hydrogen, C_1-C_4 alkyl optionally substituted with halogen, cyano, hydroxy, or C_1-C_4 alkoxy, cyclopropyl, or cyclobutyl;

R^6 is hydrogen or methyl; R^7 is hydrogen, halogen, or optionally substituted C_1-C_3 alkyl, or

R^6 and R^7 combine with the carbon atoms to which they are attached to form an optionally substituted 3 to 6-membered cycloalkyl or optionally substituted 3 to 7-membered heterocycloalkyl;

R^8 is hydrogen, halogen, hydroxy, cyano, optionally substituted C_1-C_3 alkoxy, optionally substituted C_1-C_3 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 alkynyl, optionally substituted 3 to 8-membered cycloalkyl, optionally substituted 3 to 14-membered heterocycloalkyl, optionally substituted 5 to 10-membered heteroaryl, or optionally substituted 6 to 10-membered aryl, or

R^7 and R^8 combine with the carbon atom to which they are attached to form $C=CR^{7'}R^{8'}$; C=N(OH), C=N(O-C_1-C_3 alkyl), C=O, C=S, C=NH, optionally substituted 3 to 6-membered cycloalkyl, or optionally substituted 3 to 7-membered heterocycloalkyl;

R^{7a} and R^{8a} are, independently, hydrogen, halo, optionally substituted C_1-C_3 alkyl, or combine with the carbon to which they are attached to form a carbonyl;

$R^{7'}$ is hydrogen, halogen, or optionally substituted C_1-C_3 alkyl; $R^{8'}$ is hydrogen, halogen, hydroxy, cyano, optionally substituted C_1-C_3 alkoxy, optionally substituted C_1-C_3 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 alkynyl, optionally substituted 3 to 8-membered cycloalkyl, optionally substituted 3 to 14-membered heterocycloalkyl, optionally substituted 5 to 10-membered heteroaryl, or optionally substituted 6 to 10-membered aryl, or

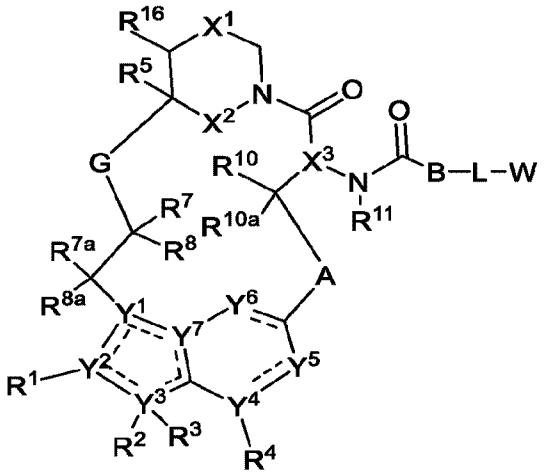
$R^{7'}$ and $R^{8'}$ combine with the carbon atom to which they are attached to form optionally substituted 3 to 6-membered cycloalkyl or optionally substituted 3 to 7-membered heterocycloalkyl;

R^{10} is hydrogen, halo, hydroxy, C_1-C_3 alkoxy, or C_1-C_3 alkyl;

R^{10a} is hydrogen or halo; and

R^{16} is hydrogen or C_1-C_3 alkyl (e.g., methyl). In some embodiments, the resulting compound is capable of achieving an IC50 of 2 uM or less (e.g., 1.5 uM, 1 uM, 500 nM, or 100 nM or less) in the Ras-RAF disruption assay protocol described herein.

In some embodiments, the disclosure features a compound, or pharmaceutically acceptable salt thereof, of structural Formula AI:



Formula AI

wherein the dotted lines represent zero, one, two, three, or four non-adjacent double bonds;

A is -N(H or CH_3)C(O)-(CH_2)- where the amino nitrogen is bound to the carbon atom of -CH(R^{10})-, optionally substituted 3 to 6-membered cycloalkylene, optionally substituted 3 to 6-membered heterocycloalkylene, optionally substituted 6-membered arylene, or optionally substituted 5 to 10-membered heteroarylene;

B is absent, -CH(R^9)-, or >C=C$R^9R^{9'}$ where the carbon is bound to the carbonyl carbon of -N(R^{11})C(O)-, optionally substituted 3 to 6-membered cycloalkylene, optionally substituted 3 to 6-membered heterocycloalkylene, optionally substituted 6-membered arylene, or 5 to 6-membered heteroarylene;

G is optionally substituted C_1-C_4 alkylene, optionally substituted C_1-C_4 alkenylene, optionally substituted C_1-C_4 heteroalkylene, -C(O)O-**C**H(R^6)- where **C** is bound to -C(R^7R^8)-, -C(O)NH-**C**H(R^6)- where **C** is bound to -C(R^7R^8)-, optionally substituted C_1-C_4 heteroalkylene, or 3 to 8-membered heteroarylene;

L is absent or a linker;

W is hydrogen, cyano, $S(O)_2R'$, optionally substituted amino, optionally substituted amido, optionally substituted C_1-C_4 alkoxy, optionally substituted C_1-C_4 hydroxyalkyl, optionally substituted C_1-C_4 aminoalkyl, optionally substituted C_1-C_4 haloalkyl, optionally substituted C_1-C_4 alkyl, optionally substituted C_1-C_4 guanidinoalkyl, C_0-C_4 alkyl optionally substituted 3 to 11-membered heterocycloalkyl, optionally substituted 3 to 8-membered cycloalkyl, or optionally substituted 3 to 8-membered heteroaryl;

X^1 is optionally substituted C_1-C_2 alkylene, NR, O, or $S(O)_n$;

X^2 is O or NH;

X^3 is N or CH;

n is 0, 1, or 2;

R is hydrogen, cyano, optionally substituted C_1-C_4 alkyl, optionally substituted C_2-C_4 alkenyl, optionally substituted C_2-C_4 alkynyl, C(O)R', C(O)OR', $C(O)N(R')_2$, S(O)R', $S(O)_2R'$, or $S(O)_2N(R')_2$;

each R' is, independently, H or optionally substituted C_1-C_4 alkyl;

Y^1 is C, CH, or N;

Y^2, Y^3, Y^4, and Y^7 are, independently, C or N;

Y^5 is CH, CH_2, or N;

Y^6 is C(O), CH, CH_2, or N;

R^1 is cyano, 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 cycloalkenyl, optionally substituted 3 to 6-membered heterocycloalkyl, optionally substituted 6 to 10-membered aryl, or optionally substituted 5 to 10-membered heteroaryl, or

R^1 and R^2 combine with the atoms to which they are attached to form an optionally substituted 3 to 14-membered heterocycloalkyl;

R^2 is absent, hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 alkynyl, optionally substituted 3 to 6-membered cycloalkyl, optionally substituted 3 to 7-membered heterocycloalkyl, optionally substituted 6-membered aryl, optionally substituted 5 or 6-membered heteroaryl;

R^3 is absent, or

R^2 and R^3 combine with the atom to which they are attached to form an optionally substituted 3 to 8-membered cycloalkyl or optionally substituted 3 to 14-membered heterocycloalkyl;

R^4 is absent, hydrogen, halogen, cyano, or methyl optionally substituted with 1 to 3 halogens;

R^5 is hydrogen, C_1-C_4 alkyl optionally substituted with halogen, cyano, hydroxy, or C_1-C_4 alkoxy, cyclopropyl, or cyclobutyl;

R^6 is hydrogen or methyl; R^7 is hydrogen, halogen, or optionally substituted C_1-C_3 alkyl, or

R^6 and R^7 combine with the carbon atoms to which they are attached to form an optionally substituted 3 to 6-membered cycloalkyl or optionally substituted 3 to 7-membered heterocycloalkyl;

R^8 is hydrogen, halogen, hydroxy, cyano, optionally substituted C_1-C_3 alkoxy, optionally substituted C_1-C_3 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 alkynyl, optionally substituted 3 to 8-membered cycloalkyl, optionally substituted 3 to 14-membered heterocycloalkyl, optionally substituted 5 to 10-membered heteroaryl, or optionally substituted 6 to 10-membered aryl, or

R^7 and R^8 combine with the carbon atom to which they are attached to form $C=CR^{7'}R^{8'}$; C=N(OH), C=N(O-C_1-C_3 alkyl), C=O, C=S, C=NH, optionally substituted 3 to 6-membered cycloalkyl, or optionally substituted 3 to 7-membered heterocycloalkyl;

R^{7a} and R^{8a} are, independently, hydrogen, halo, optionally substituted C_1-C_3 alkyl, or combine with the carbon to which they are attached to form a carbonyl;

$R^{7'}$ is hydrogen, halogen, or optionally substituted C_1-C_3 alkyl; $R^{8'}$ is hydrogen, halogen, hydroxy, cyano, optionally substituted C_1-C_3 alkoxy, optionally substituted C_1-C_3 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 alkynyl, optionally substituted 3 to 8-membered cycloalkyl, optionally substituted 3 to 14-membered heterocycloalkyl, optionally substituted 5 to 10-membered heteroaryl, or optionally substituted 6 to 10-membered aryl, or

$R^{7'}$ and $R^{8'}$ combine with the carbon atom to which they are attached to form optionally substituted 3 to 6-membered cycloalkyl or optionally substituted 3 to 7-membered heterocycloalkyl;

R^9 is hydrogen, F, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted 3 to 6-membered cycloalkyl, or optionally substituted 3 to 7-membered heterocycloalkyl, or

R^9 and L combine with the atoms to which they are attached to form an optionally substituted 3 to 14-membered heterocycloalkyl;

$R^{9'}$ is hydrogen or optionally substituted C_1-C_6 alkyl;

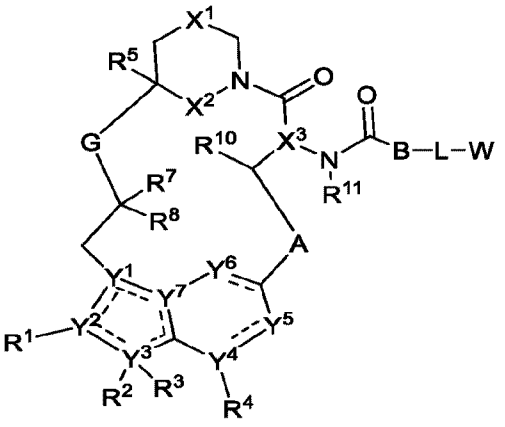
R^{10} is hydrogen, halo, hydroxy, C_1-C_3 alkoxy, or C_1-C_3 alkyl;

R^{10a} is hydrogen or halo;

R^{11} is hydrogen or C_1-C_3 alkyl;

R^{16} is hydrogen or C_1-C_3 alkyl (e.g., methyl).

In some embodiments, the disclosure features a compound, or pharmaceutically acceptable salt thereof, of structural Formula AIa:



Formula AIa

wherein the dotted lines represent zero, one, two, three, or four non-adjacent double bonds;

A is -N(H or CH_3)C(O)-(CH_2)- where the amino nitrogen is bound to the carbon atom of -CH(R^{10})-, optionally substituted 3 to 6-membered cycloalkylene, optionally substituted 3 to 6-membered heterocycloalkylene, optionally substituted 6-membered arylene, or optionally substituted 5 to 10-membered heteroarylene;

B is -CH(R^9)- or >C=C$R^9R^{9'}$ where the carbon is bound to the carbonyl carbon of -N(R^{11})C(O)-, optionally substituted 3 to 6-membered cycloalkylene, optionally substituted 3 to 6-membered heterocycloalkylene, optionally substituted 6-membered arylene, or 5 to 6-membered heteroarylene;

G is optionally substituted C_1-C_4 alkylene, optionally substituted C_1-C_4 alkenylene, optionally substituted C_1-C_4 heteroalkylene, -C(O)O-**C**H(R^6)- where **C** is bound to -C(R^7R^8)-, -C(O)NH-**C**H(R^6)- where **C** is bound to -C(R^7R^8)-, optionally substituted C_1-C_4 heteroalkylene, or 3 to 8-membered heteroarylene;

L is absent or a linker;

W is hydrogen, optionally substituted amino, optionally substituted C_1-C_4 alkoxy, optionally substituted C_1-C_4 hydroxyalkyl, optionally substituted C_1-C_4 aminoalkyl, optionally substituted C_1-C_4 haloalkyl, optionally substituted C_1-C_4 alkyl, optionally substituted C_1-C_4 guanidinoalkyl, C_0-C_4 alkyl optionally substituted 3 to 11-membered heterocycloalkyl, optionally substituted 3 to 8-membered cycloalkyl, or optionally substituted 3 to 8-membered heteroaryl;

X^1 is optionally substituted C_1-C_2 alkylene, NR, O, or $S(O)_n$;

X^2 is O or NH;

X^3 is N or CH;

n is 0, 1, or 2;

R is hydrogen, cyano, optionally substituted C_1-C_4 alkyl, optionally substituted C_2-C_4 alkenyl, optionally substituted C_2-C_4 alkynyl, C(O)R', C(O)OR', C(O)N(R')$_2$, S(O)R', $S(O)_2$R', or $S(O)_2$N(R')$_2$;

each R' is, independently, H or optionally substituted C_1-C_4 alkyl;

Y^1 is C, CH, or N;

Y^2, Y^3, Y^4, and Y^7 are, independently, C or N;

Y^5 is CH, CH_2, or N;

Y^6 is C(O), CH, CH_2, or N;

R^1 is cyano, 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 cycloalkenyl, optionally substituted 3 to 6-membered heterocycloalkyl, optionally substituted 6 to 10-membered aryl, or optionally substituted 5 to 10-membered heteroaryl, or

R^1 and R^2 combine with the atoms to which they are attached to form an optionally substituted 3 to 14-membered heterocycloalkyl;

R^2 is absent, hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 alkynyl, optionally substituted 3 to 6-membered cycloalkyl, optionally substituted 3 to 7-membered heterocycloalkyl, optionally substituted 6-membered aryl, optionally substituted 5 or 6-membered heteroaryl;

R^3 is absent, or

R^2 and R^3 combine with the atom to which they are attached to form an optionally substituted 3 to 8-membered cycloalkyl or optionally substituted 3 to 14-membered heterocycloalkyl;

R^4 is absent, hydrogen, halogen, cyano, or methyl optionally substituted with 1 to 3 halogens;

R^5 is hydrogen, C_1-C_4 alkyl optionally substituted with halogen, cyano, hydroxy, or C_1-C_4 alkoxy, cyclopropyl, or cyclobutyl;

R^6 is hydrogen or methyl; R^7 is hydrogen, halogen, or optionally substituted C_1-C_3 alkyl, or

R^6 and R^7 combine with the carbon atoms to which they are attached to form an optionally substituted 3 to 6-membered cycloalkyl or optionally substituted 3 to 7-membered heterocycloalkyl;

R^8 is hydrogen, halogen, hydroxy, cyano, optionally substituted C_1-C_3 alkoxy, optionally substituted C_1-C_3 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 alkynyl, optionally substituted 3 to 8-membered cycloalkyl, optionally substituted 3 to 14-membered heterocycloalkyl, optionally substituted 5 to 10-membered heteroaryl, or optionally substituted 6 to 10-membered aryl, or

R^7 and R^8 combine with the carbon atom to which they are attached to form $C=CR^{7'}R^{8'}$; C=N(OH), C=N(O-C_1-C_3 alkyl), C=O, C=S, C=NH, optionally substituted 3 to 6-membered cycloalkyl, or optionally substituted 3 to 7-membered heterocycloalkyl;

R^{7a} and R^{8a} are, independently, hydrogen, halo, optionally substituted C_1-C_3 alkyl, or combine with the carbon to which they are attached to form a carbonyl;

$R^{7'}$ is hydrogen, halogen, or optionally substituted C_1-C_3 alkyl; $R^{8'}$ is hydrogen, halogen, hydroxy, cyano, optionally substituted C_1-C_3 alkoxy, optionally substituted C_1-C_3 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 alkynyl, optionally substituted 3 to 8-membered cycloalkyl, optionally substituted 3 to 14-membered heterocycloalkyl, optionally substituted 5 to 10-membered heteroaryl, or optionally substituted 6 to 10-membered aryl, or

$R^{7'}$ and $R^{8'}$ combine with the carbon atom to which they are attached to form optionally substituted 3 to 6-membered cycloalkyl or optionally substituted 3 to 7-membered heterocycloalkyl;

R^9 is optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted 3 to 6-membered cycloalkyl, or optionally substituted 3 to 7-membered heterocycloalkyl, or

R^9 and L combine with the atoms to which they are attached to form an optionally substituted 3 to 14-membered heterocycloalkyl;

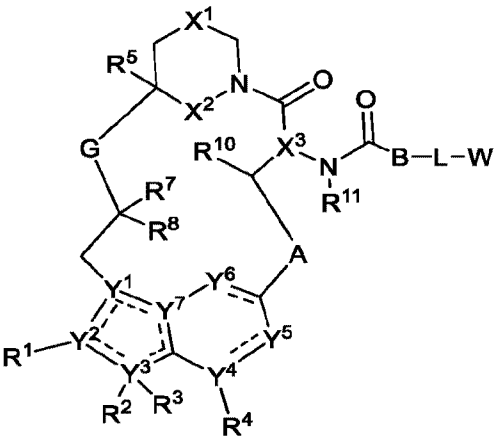
$R^{9'}$ is hydrogen or optionally substituted C_1-C_6 alkyl;

R^{10} is hydrogen, halo, hydroxy, C_1-C_3 alkoxy, or C_1-C_3 alkyl;

R^{10a} is hydrogen or halo; and

R^{11} is hydrogen or C_1-C_3 alkyl.

In some embodiments, the disclosure features a compound, or pharmaceutically acceptable salt thereof, of structural Formula AIb:



Formula AIb

wherein the dotted lines represent zero, one, two, three, or four non-adjacent double bonds;

A is -N(H or CH_3)C(O)-(CH_2)- where the amino nitrogen is bound to the carbon atom of -CH(R^{10})-, optionally substituted 3 to 6-membered cycloalkylene, optionally substituted 3 to 6-membered heterocycloalkylene, optionally substituted 6-membered arylene, or optionally substituted 5 to 6-membered heteroarylene;

B is -CH(R^9)- where the carbon is bound to the carbonyl carbon of -N(R^{11})C(O)-, optionally substituted 3 to 6-membered cycloalkylene, optionally substituted 3 to 6-membered heterocycloalkylene, optionally substituted 6-membered arylene, or 5 to 6-membered heteroarylene;

G is optionally substituted C_1-C_4 alkylene, optionally substituted C_1-C_4 alkenylene, optionally substituted C_1-C_4 heteroalkylene, -C(O)O-**C**H(R^6)- where **C** is bound to -C(R^7R^8)-, -C(O)NH-**C**H(R^6)- where **C** is bound to -C(R^7R^8)-, optionally substituted C_1-C_4 heteroalkylene, or 3 to 8-membered heteroarylene;

L is absent or a linker;

W is hydrogen, optionally substituted amino, optionally substituted C_1-C_4 alkoxy, optionally substituted C_1-C_4 hydroxyalkyl, optionally substituted C_1-C_4 aminoalkyl, optionally substituted C_1-C_4 haloalkyl, optionally substituted C_1-C_4 alkyl, optionally substituted C_1-C_4 guanidinoalkyl, C_0-C_4 alkyl optionally substituted 3 to 11-membered heterocycloalkyl, optionally substituted 3 to 8-membered cycloalkyl, or optionally substituted 3 to 8-membered heteroaryl;

X^1 is optionally substituted C_1-C_2 alkylene, NR, O, or $S(O)_n$;

X^2 is O or NH;

X^3 is N or CH;

n is 0, 1, or 2;

R is hydrogen, cyano, optionally substituted C_1-C_4 alkyl, optionally substituted C_2-C_4 alkenyl, optionally substituted C_2-C_4 alkynyl, C(O)R', C(O)OR', C(O)N(R')$_2$, S(O)R', $S(O)_2$R', or $S(O)_2$N(R')$_2$;

each R' is, independently, H or optionally substituted C_1-C_4 alkyl;

Y^1 is C, CH, or N;

Y^2, Y^3, Y^4, and Y^7 are, independently, C or N;

Y^5 and Y^6 are, independently, CH or N;

R^1 is cyano, 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 cycloalkenyl, optionally substituted 3 to 6-membered heterocycloalkyl, optionally substituted 6 to 10-membered aryl, or optionally substituted 5 to 10-membered heteroaryl;

R^2 is hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted 3 to 6-membered cycloalkyl, optionally substituted 3 to 7-membered heterocycloalkyl, optionally substituted 6-membered aryl, optionally substituted 5 or 6-membered heteroaryl; R^3 is absent, or

R^2 and R^3 combine with the atom to which they are attached to form an optionally substituted 3 to 8-membered cycloalkyl or optionally substituted 3 to 14-membered heterocycloalkyl;

R^4 is absent, hydrogen, halogen, cyano, or methyl optionally substituted with 1 to 3 halogens;

R^5 is hydrogen, C_1-C_4 alkyl optionally substituted with halogen, cyano, hydroxy, or C_1-C_4 alkoxy, cyclopropyl, or cyclobutyl;

R^6 is hydrogen or methyl; R^7 is hydrogen, halogen, or optionally substituted C_1-C_3 alkyl, or

R^6 and R^7 combine with the carbon atoms to which they are attached to form an optionally substituted 3 to 6-membered cycloalkyl or optionally substituted 3 to 7-membered heterocycloalkyl;

R^8 is hydrogen, halogen, hydroxy, cyano, optionally substituted C_1-C_3 alkoxy, optionally substituted C_1-C_3 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 alkynyl, optionally substituted 3 to 8-membered cycloalkyl, optionally substituted 3 to 14-membered heterocycloalkyl, optionally substituted 5 to 10-membered heteroaryl, or optionally substituted 6 to 10-membered aryl, or

R^7 and R^8 combine with the carbon atom to which they are attached to form $C=CR^{7'}R^{8'}$; C=N(OH), C=N(O-C_1-C_3 alkyl), C=O, C=S, C=NH, optionally substituted 3 to 6-membered cycloalkyl, or optionally substituted 3 to 7-membered heterocycloalkyl;

$R^{7'}$ is hydrogen, halogen, or optionally substituted C_1-C_3 alkyl; $R^{8'}$ is hydrogen, halogen, hydroxy, cyano, optionally substituted C_1-C_3 alkoxy, optionally substituted C_1-C_3 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 alkynyl, optionally substituted 3 to 8-membered cycloalkyl, optionally substituted 3 to 14-membered heterocycloalkyl, optionally substituted 5 to 10-membered heteroaryl, or optionally substituted 6 to 10-membered aryl, or

$R^{7'}$ and $R^{8'}$ combine with the carbon atom to which they are attached to form optionally substituted 3 to 6-membered cycloalkyl or optionally substituted 3 to 7-membered heterocycloalkyl;

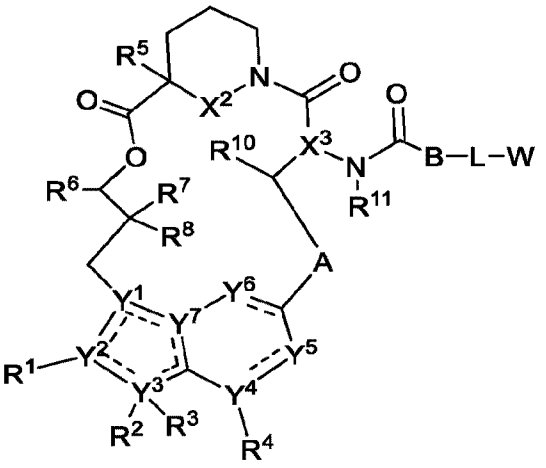
R^9 is optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted 3 to 6-membered cycloalkyl, or optionally substituted 3 to 7-membered heterocycloalkyl;

R^{10} is hydrogen, hydroxy, C_1-C_3 alkoxy, or C_1-C_3 alkyl; and

R^{11} is hydrogen or C_1-C_3 alkyl.

In some embodiments of Formula AI and subformula thereof, G is optionally substituted C_1-C_4 heteroalkylene.

In some embodiments, the RAS(ON) inhibitor has the structure of Formula AIc, or a pharmaceutically acceptable salt thereof:



Formula AIc

wherein the dotted lines represent zero, one, two, three, or four non-adjacent double bonds;

A is -N(H or CH_3)C(O)-(CH_2)- where the amino nitrogen is bound to the carbon atom of -CH(R^{10})-, optionally substituted 3 to 6-membered cycloalkylene, optionally substituted 3 to 6-membered heterocycloalkylene, optionally substituted 6-membered arylene, or optionally substituted 5 to 6-membered heteroarylene;

B is -CH(R^9)- where the carbon is bound to the carbonyl carbon of -N(R^{11})C(O)-, optionally substituted 3 to 6-membered cycloalkylene, optionally substituted 3 to 6-membered heterocycloalkylene, optionally substituted 6-membered arylene, or 5 to 6-membered heteroarylene;

L is absent or a linker;

W is hydrogen, optionally substituted amino, optionally substituted C_1-C_4 alkoxy, optionally substituted C_1-C_4 hydroxyalkyl, optionally substituted C_1-C_4 aminoalkyl, optionally substituted C_1-C_4 haloalkyl, optionally substituted C_1-C_4 alkyl, optionally substituted C_1-C_4 guanidinoalkyl, C_0-C_4 alkyl optionally substituted 3 to 11-membered heterocycloalkyl, optionally substituted 3 to 8-membered cycloalkyl, or optionally substituted 3 to 8-membered heteroaryl;

X^2 is O or NH;

X^3 is N or CH;

n is 0, 1, or 2;

R is hydrogen, cyano, optionally substituted C_1-C_4 alkyl, optionally substituted C_2-C_4 alkenyl, optionally substituted C_2-C_4 alkynyl, C(O)R', C(O)OR', C(O)N(R')$_2$, S(O)R', S(O)$_2$R', or S(O)$_2$N(R')$_2$;

each R' is, independently, H or optionally substituted C_1-C_4 alkyl;

Y^1 is C, CH, or N;

Y^2, Y^3, Y^4, and Y^7 are, independently, C or N;

Y^5 and Y^6 are, independently, CH or N;

R^1 is cyano, 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 cycloalkenyl, optionally substituted 3 to 6-membered heterocycloalkyl, optionally substituted 6 to 10-membered aryl, or optionally substituted 5 to 10-membered heteroaryl;

R^2 is hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted 3 to 6-membered cycloalkyl, optionally substituted 3 to 7-membered heterocycloalkyl, optionally substituted 6-membered aryl, optionally substituted 5 or 6-membered heteroaryl;

R^3 is absent, or

R^2 and R^3 combine with the atom to which they are attached to form an optionally substituted 3 to 8-membered cycloalkyl or optionally substituted 3 to 14-membered heterocycloalkyl;

R^4 is absent, hydrogen, halogen, cyano, or methyl optionally substituted with 1 to 3 halogens;

R^5 is hydrogen, C_1-C_4 alkyl optionally substituted with halogen, cyano, hydroxy, or C_1-C_4 alkoxy, cyclopropyl, or cyclobutyl;

R^6 is hydrogen or methyl; R^7 is hydrogen, halogen, or optionally substituted C_1-C_3 alkyl, or

R^6 and R^7 combine with the carbon atoms to which they are attached to form an optionally substituted 3 to 6-membered cycloalkyl or optionally substituted 3 to 7-membered heterocycloalkyl;

R^8 is hydrogen, halogen, hydroxy, cyano, optionally substituted C_1-C_3 alkoxy, optionally substituted C_1-C_3 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 alkynyl, optionally substituted 3 to 8-membered cycloalkyl, optionally substituted 3 to 14-membered heterocycloalkyl, optionally substituted 5 to 10-membered heteroaryl, or optionally substituted 6 to 10-membered aryl, or

R^7 and R^8 combine with the carbon atom to which they are attached to form $C=CR^{7'}R^{8'}$; C=N(OH), C=N(O-C_1-C_3 alkyl), C=O, C=S, C=NH, optionally substituted 3 to 6-membered cycloalkyl, or optionally substituted 3 to 7-membered heterocycloalkyl;

$R^{7'}$ is hydrogen, halogen, or optionally substituted C_1-C_3 alkyl; $R^{8'}$ is hydrogen, halogen, hydroxy, cyano, optionally substituted C_1-C_3 alkoxy, optionally substituted C_1-C_3 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 alkynyl, optionally substituted 3 to 8-membered cycloalkyl, optionally substituted 3 to 14-membered heterocycloalkyl, optionally substituted 5 to 10-membered heteroaryl, or optionally substituted 6 to 10-membered aryl, or

$R^{7'}$ and $R^{8'}$ combine with the carbon atom to which they are attached to form optionally substituted 3 to 6-membered cycloalkyl or optionally substituted 3 to 7-membered heterocycloalkyl;

R^9 is optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted 3 to 6-membered cycloalkyl, or optionally substituted 3 to 7-membered heterocycloalkyl;

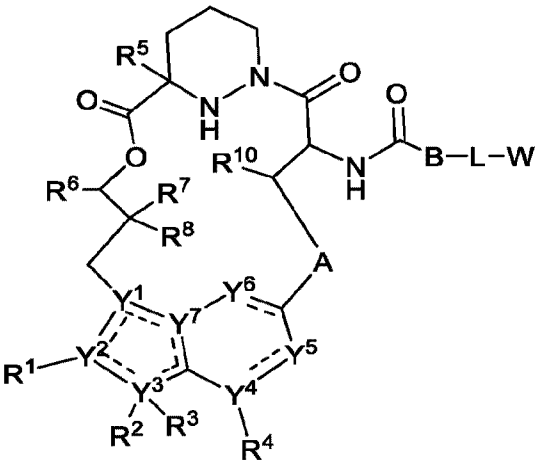
R^{10} is hydrogen, hydroxy, C_1-C_3 alkoxy, or C_1-C_3 alkyl; and

R^{11} is hydrogen or C_1-C_3 alkyl.

In some embodiments of Formula AI and subformula thereof, X^2 is NH. In some embodiments of Formula AI and subformula thereof, X^3 is CH.

In some embodiments of Formula AI and subformula thereof, R^{11} is hydrogen. In some embodiments of Formula AI and subformula thereof, R^{11} is C_1-C_3 alkyl. In some embodiments of Formula AI and subformula thereof, R^{11} is methyl.

In some embodiments, the RAS(ON) inhibitor has the structure of Formula AId, or a pharmaceutically acceptable salt thereof:



Formula AId

wherein the dotted lines represent zero, one, two, three, or four non-adjacent double bonds;

A is -N(H or CH_3)C(O)-(CH_2)- where the amino nitrogen is bound to the carbon atom of -CH(R^{10})-, optionally substituted 3 to 6-membered cycloalkylene, optionally substituted 3 to 6-membered heterocycloalkylene, optionally substituted 6-membered arylene, or optionally substituted 5 to 6-membered heteroarylene;

B is -CH(R^9)- where the carbon is bound to the carbonyl carbon of -NHC(O)-, optionally substituted 3 to 6-membered cycloalkylene, optionally substituted 3 to 6-membered heterocycloalkylene, optionally substituted 6-membered arylene, or 5 to 6-membered heteroarylene;

L is absent or a linker;

W is hydrogen, optionally substituted amino, optionally substituted C_1-C_4 alkoxy, optionally substituted C_1-C_4 hydroxyalkyl, optionally substituted C_1-C_4 aminoalkyl, optionally substituted C_1-C_4 haloalkyl, optionally substituted C_1-C_4 alkyl, optionally substituted C_1-C_4 guanidinoalkyl, C_0-C_4 alkyl optionally substituted 3 to 11-membered heterocycloalkyl, optionally substituted 3 to 8-membered cycloalkyl, or optionally substituted 3 to 8-membered heteroaryl;

n is 0, 1, or 2;

R is hydrogen, cyano, optionally substituted C_1-C_4 alkyl, optionally substituted C_2-C_4 alkenyl, optionally substituted C_2-C_4 alkynyl, C(O)R', C(O)OR', C(O)N(R')$_2$, S(O)R', S(O)$_2$R', or S(O)$_2$N(R')$_2$;

each R' is, independently, H or optionally substituted C_1-C_4 alkyl;

Y^1 is C, CH, or N;

Y^2, Y^3, Y^4, and Y^7 are, independently, C or N;

Y^5 and Y^6 are, independently, CH or N;

R^1 is cyano, 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 cycloalkenyl, optionally substituted 3 to 6-membered heterocycloalkyl, optionally substituted 6 to 10-membered aryl, or optionally substituted 5 to 10-membered heteroaryl;

R^2 is hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted 3 to 6-membered cycloalkyl, optionally substituted 3 to 7-membered heterocycloalkyl,

optionally substituted 6-membered aryl, optionally substituted 5 or 6-membered heteroaryl; R^3 is absent, or

R^2 and R^3 combine with the atom to which they are attached to form an optionally substituted 3 to 8-membered cycloalkyl or optionally substituted 3 to 14-membered heterocycloalkyl;

R^4 is absent, hydrogen, halogen, cyano, or methyl optionally substituted with 1 to 3 halogens;

R^5 is hydrogen, C_1-C_4 alkyl optionally substituted with halogen, cyano, hydroxy, or C_1-C_4 alkoxy, cyclopropyl, or cyclobutyl;

R^6 is hydrogen or methyl; R^7 is hydrogen, halogen, or optionally substituted C_1-C_3 alkyl, or

R^6 and R^7 combine with the carbon atoms to which they are attached to form an optionally substituted 3 to 6-membered cycloalkyl or optionally substituted 3 to 7-membered heterocycloalkyl;

R^8 is hydrogen, halogen, hydroxy, cyano, optionally substituted C_1-C_3 alkoxy, optionally substituted C_1-C_3 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 alkynyl, optionally substituted 3 to 8-membered cycloalkyl, optionally substituted 3 to 14-membered heterocycloalkyl, optionally substituted 5 to 10-membered heteroaryl, or optionally substituted 6 to 10-membered aryl, or

R^7 and R^8 combine with the carbon atom to which they are attached to form $C=CR^{7'}R^{8'}$; C=N(OH), C=N(O-C_1-C_3 alkyl), C=O, C=S, C=NH, optionally substituted 3 to 6-membered cycloalkyl, or optionally substituted 3 to 7-membered heterocycloalkyl;

$R^{7'}$ is hydrogen, halogen, or optionally substituted C_1-C_3 alkyl; $R^{8'}$ is hydrogen, halogen, hydroxy, cyano, optionally substituted C_1-C_3 alkoxy, optionally substituted C_1-C_3 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 alkynyl, optionally substituted 3 to 8-membered cycloalkyl, optionally substituted 3 to 14-membered heterocycloalkyl, optionally substituted 5 to 10-membered heteroaryl, or optionally substituted 6 to 10-membered aryl, or

$R^{7'}$ and $R^{8'}$ combine with the carbon atom to which they are attached to form optionally substituted 3 to 6-membered cycloalkyl or optionally substituted 3 to 7-membered heterocycloalkyl;

R^9 is optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted 3 to 6-membered cycloalkyl, or optionally substituted 3 to 7-membered heterocycloalkyl; and

R^{10} is hydrogen, hydroxy, C_1-C_3 alkoxy, or C_1-C_3 alkyl.

In some embodiments of compounds of the present invention, X^1 is optionally substituted C_1-C_2 alkylene. In some embodiments, X^1 is methylene. In some embodiments, X^1 is methylene substituted with a C_1-C_6 alkyl group or a halogen. In some embodiments, X^1 is -CH(Br)-. In some embodiments, X^1 is -CH(CH_3)-.

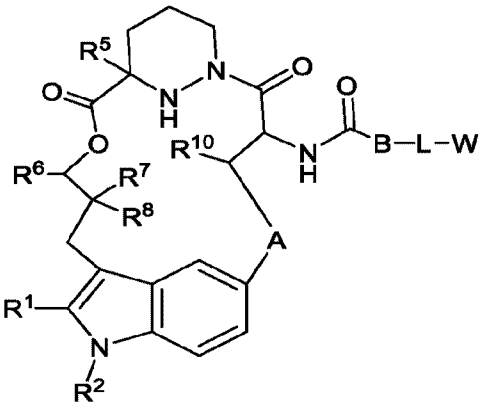
In some embodiments of Formula AI and subformula thereof, R^3 is absent.

In some embodiments of Formula AI and subformula thereof, R^4 is hydrogen.

In some embodiments of Formula AI and subformula thereof, R^5 is hydrogen. In some embodiments of Formula AI and subformula thereof, R^5 is C_1-C_4 alkyl optionally substituted with halogen. In some embodiments of Formula AI and subformula thereof, R^5 is methyl.

In some embodiments of of Formula AI and subformula thereof, Y^4 is C. In some embodiments of Formula AI and subformula thereof, Y^5 is CH. In some embodiments of Formula AI and subformula thereof, Y^6 is CH. In some embodiments of Formula AI and subformula thereof, Y^1 is C. In some embodiments of Formula AI and subformula thereof, Y^2 is C. In some embodiments of Formula AI and subformula thereof, Y^3 is N. In some embodiments of Formula AI and subformula thereof, Y^7 is C.

In some embodiments, the RAS(ON) inhibitor has the structure of Formula AIe, or a pharmaceutically acceptable salt thereof:



Formula AIe

wherein A is -N(H or CH_3)C(O)-(CH_2)- where the amino nitrogen is bound to the carbon atom of -CH(R^{10})-, optionally substituted 3 to 6-membered cycloalkylene, optionally substituted 3 to 6-membered heterocycloalkylene, optionally substituted 6-membered arylene, or optionally substituted 5 to 6-membered heteroarylene;

B is -CH(R^9)- where the carbon is bound to the carbonyl carbon of -NHC(O)-, optionally substituted 3 to 6-membered cycloalkylene, optionally substituted 3 to 6-membered heterocycloalkylene, optionally substituted 6-membered arylene, or 5 to 6-membered heteroarylene;

L is absent or a linker;

W is hydrogen, optionally substituted amino, optionally substituted C_1-C_4 alkoxy, optionally substituted C_1-C_4 hydroxyalkyl, optionally substituted C_1-C_4 aminoalkyl, optionally substituted C_1-C_4 haloalkyl, optionally substituted C_1-C_4 alkyl, optionally substituted C_1-C_4 guanidinoalkyl, C_0-C_4 alkyl optionally substituted 3 to 11-membered heterocycloalkyl, optionally substituted 3 to 8-membered cycloalkyl, or optionally substituted 3 to 8-membered heteroaryl;

R^1 is cyano, 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 cycloalkenyl, optionally substituted 3 to 6-membered heterocycloalkyl, optionally substituted 6 to 10-membered aryl, or optionally substituted 5 to 10-membered heteroaryl;

R^2 is hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted 3 to 6-membered cycloalkyl, optionally substituted 3 to 7-membered heterocycloalkyl, optionally substituted 6-membered aryl, optionally substituted 5 or 6-membered heteroaryl; R^3 is absent, or

R^2 and R^3 combine with the atom to which they are attached to form an optionally substituted 3 to 8-membered cycloalkyl or optionally substituted 3 to 14-membered heterocycloalkyl;

R^5 is hydrogen, C_1-C_4 alkyl optionally substituted with halogen, cyano, hydroxy, or C_1-C_4 alkoxy, cyclopropyl, or cyclobutyl;

R^6 is hydrogen or methyl; R^7 is hydrogen, halogen, or optionally substituted C_1-C_3 alkyl, or

R^6 and R^7 combine with the carbon atoms to which they are attached to form an optionally substituted 3 to 6-membered cycloalkyl or optionally substituted 3 to 7-membered heterocycloalkyl;

R^8 is hydrogen, halogen, hydroxy, cyano, optionally substituted C_1-C_3 alkoxy, optionally substituted C_1-C_3 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 alkynyl, optionally substituted 3 to 8-membered cycloalkyl, optionally substituted 3 to 14-membered heterocycloalkyl, optionally substituted 5 to 10-membered heteroaryl, or optionally substituted 6 to 10-membered aryl, or

R^7 and R^8 combine with the carbon atom to which they are attached to form $C=CR^{7'}R^{8'}$; C=N(OH), C=N(O-C_1-C_3 alkyl), C=O, C=S, C=NH, optionally substituted 3 to 6-membered cycloalkyl, or optionally substituted 3 to 7-membered heterocycloalkyl;

$R^{7'}$ is hydrogen, halogen, or optionally substituted C_1-C_3 alkyl; $R^{8'}$ is hydrogen, halogen, hydroxy, cyano, optionally substituted C_1-C_3 alkoxy, optionally substituted C_1-C_3 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 alkynyl, optionally substituted 3 to 8-membered cycloalkyl, optionally substituted 3 to 14-membered heterocycloalkyl, optionally substituted 5 to 10-membered heteroaryl, or optionally substituted 6 to 10-membered aryl, or

$R^{7'}$ and $R^{8'}$ combine with the carbon atom to which they are attached to form optionally substituted 3 to 6-membered cycloalkyl or optionally substituted 3 to 7-membered heterocycloalkyl;

R^9 is optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted 3 to 6-membered cycloalkyl, or optionally substituted 3 to 7-membered heterocycloalkyl; and

R^{10} is hydrogen, hydroxy, C_1-C_3 alkoxy, or C_1-C_3 alkyl.

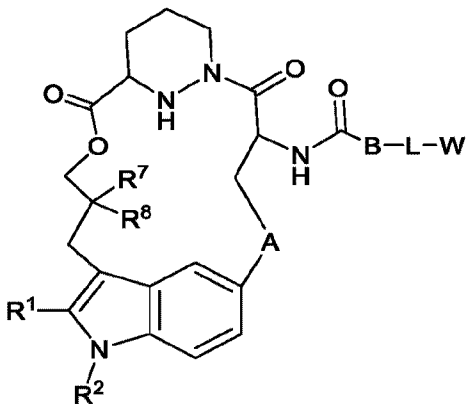
In some embodiments of Formula AI and subformula thereof, R^6 is hydrogen.

In some embodiments of Formula AI and subformula thereof, R^2 is hydrogen, cyano, optionally substituted C_1-C_6 alkyl, optionally substituted 3 to 6-membered cycloalkyl, or optionally substituted 3 to 6-membered heterocycloalkyl. In some embodiments of Formula AI and subformula thereof, R^2 is optionally substituted C_1-C_6 alkyl, such as ethyl. In some embodiments of Formula AI and subformula thereof, R^2 is fluoro C_1-C_6 alkyl, such as $-CH_2CH_2F$, $-CH_2CHF_2$, or $-CH_2CF_3$.

In some embodiments of Formula AI and subformula thereof, R^7 is optionally substituted C_1-C_3 alkyl. In some embodiments of Formula AI and subformula thereof, R^7 is C_1-C_3 alkyl.

In some embodiments of Formula AI and subformula thereof, R^8 is optionally substituted C_1-C_3 alkyl. In some embodiments of Formula AI and subformula thereof, R^8 is C_1-C_3 alkyl, such as methyl.

In some embodiments, the RAS(ON) inhibitor has the structure of Formula AIf, or a pharmaceutically acceptable salt thereof:



Formula AIf

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

B is -CH(R^9)- where the carbon is bound to the carbonyl carbon of -NHC(O)-, optionally substituted 3 to 6-membered cycloalkylene, optionally substituted 3 to 6-membered heterocycloalkylene, optionally substituted 6-membered arylene, or 5 to 6-membered heteroarylene;

L is absent or a linker;

W is hydrogen, optionally substituted amino, optionally substituted C_1-C_4 alkoxy, optionally substituted C_1-C_4 hydroxyalkyl, optionally substituted C_1-C_4 aminoalkyl, optionally substituted C_1-C_4 haloalkyl, optionally substituted C_1-C_4 alkyl, optionally substituted C_1-C_4 guanidinoalkyl, C_0-C_4 alkyl optionally substituted 3 to 11-membered heterocycloalkyl, optionally substituted 3 to 8-membered cycloalkyl, or optionally substituted 3 to 8-membered heteroaryl;

R^1 is cyano, 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 cycloalkenyl, optionally substituted 3 to 6-membered heterocycloalkyl, optionally substituted 6 to 10-membered aryl, or optionally substituted 5 to 10-membered heteroaryl;

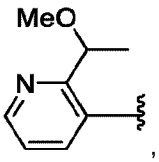
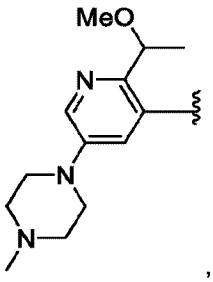
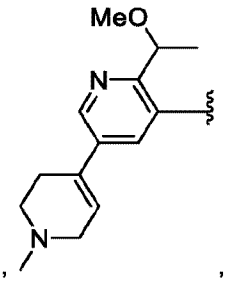
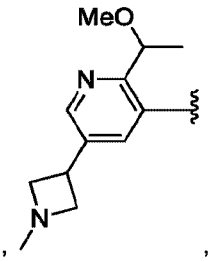
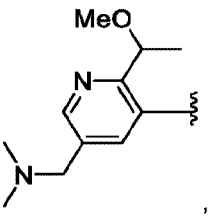
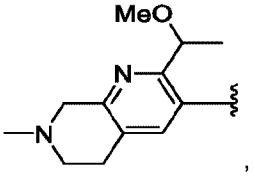
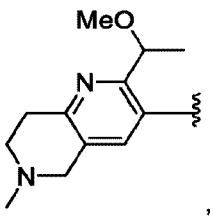
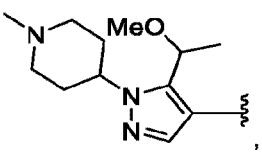
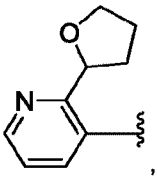
R^2 is C_1-C_6 alkyl or 3 to 6-membered cycloalkyl;

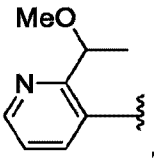
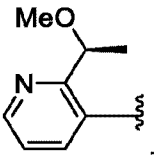
R^7 is C_1-C_3 alkyl;

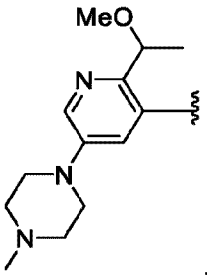
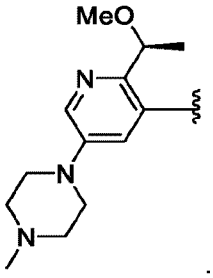
R^8 is C_1-C_3 alkyl; and

R^9 is optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted 3 to 6-membered cycloalkyl, or optionally substituted 3 to 7-membered heterocycloalkyl.

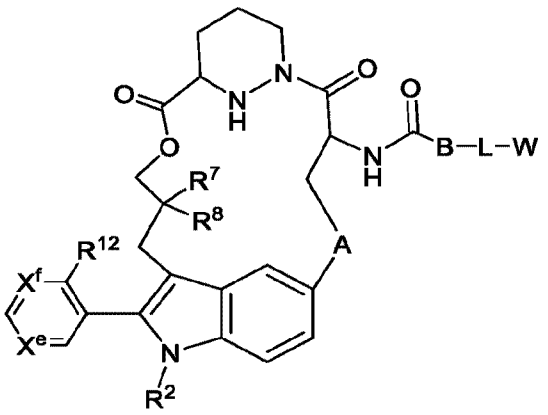
In some embodiments of Formula AI and subformula thereof, R^1 is 5 to 10-membered heteroaryl. In some embodiments, R^1 is optionally substituted 6-membered aryl or optionally substituted 6-membered heteroaryl.

In some embodiments of of Formula AI and subformula thereof, R_1 is  ,  ,  ,  ,  ,  ,  ,  , or  , or a stereoisomer thereof. In some

embodiments, R_1 is  , or a stereoisomer thereof. In some embodiments, R_1 is  .

In some embodiments, R_1 is  , or a stereoisomer thereof. In some embodiments, R_1 is  .

In some embodiments, the RAS(ON) inhibitor has the structure of Formula AIg, or a pharmaceutically acceptable salt thereof:



Formula AIg

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

B is -CH(R^9)- where the carbon is bound to the carbonyl carbon of -NHC(O)-, optionally substituted 3 to 6-membered cycloalkylene, optionally substituted 3 to 6-membered heterocycloalkylene, optionally substituted 6-membered arylene, or 5 to 6-membered heteroarylene;

L is absent or a linker;

W is hydrogen, optionally substituted amino, optionally substituted C_1-C_4 alkoxy, optionally substituted C_1-C_4 hydroxyalkyl, optionally substituted C_1-C_4 aminoalkyl, optionally substituted C_1-C_4 haloalkyl, optionally substituted C_1-C_4 alkyl, optionally substituted C_1-C_4 guanidinoalkyl, C_0-C_4 alkyl

optionally substituted 3 to 11-membered heterocycloalkyl, optionally substituted 3 to 8-membered cycloalkyl, or optionally substituted 3 to 8-membered heteroaryl;

R^2 is C_1-C_6 alkyl or 3 to 6-membered cycloalkyl;

R^7 is C_1-C_3 alkyl;

R^8 is C_1-C_3 alkyl;

R^9 is optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted 3 to 6-membered cycloalkyl, or optionally substituted 3 to 7-membered heterocycloalkyl;

X^e is N, CH, or CR^{17};

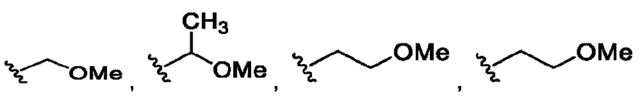
X^f is N or CH;

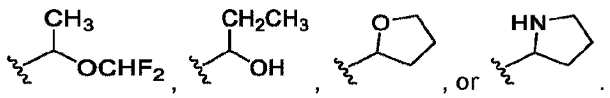
R^{12} is optionally substituted C_1-C_6 alkyl or optionally substituted C_1-C_6 heteroalkyl; and

R^{17} is 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 cycloalkenyl, optionally substituted 3 to 6-membered heterocycloalkyl, optionally substituted 6 to 10-membered aryl, or optionally substituted 5 to 10-membered heteroaryl.

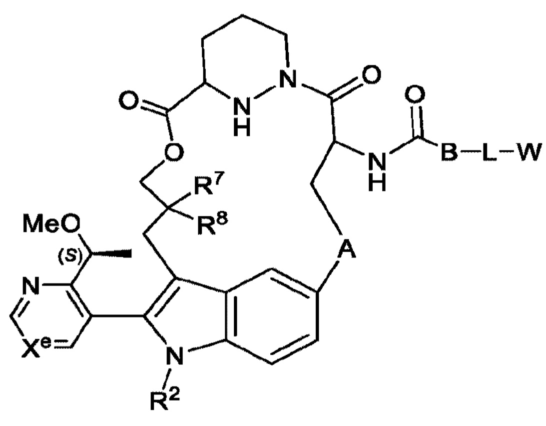
In some embodiments of Formula AI and subformula thereof, X^e is N and X^f is CH. In some embodiments, X^e is CH and X^f is N. In some embodiments, X^e is CR^{17} and X^f is N.

In some embodiments of Formula AI and subformula thereof, R^{12} is optionally substituted C_1-C_6 heteroalkyl. In some embodiments, R^{12} is





In some embodiments, the RAS(ON) inhibitor has the structure of Formula AIh, or a pharmaceutically acceptable salt thereof:



Formula AIh

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

B is -CH(R^9)- where the carbon is bound to the carbonyl carbon of -NHC(O)-, optionally substituted 3 to 6-membered cycloalkylene, optionally substituted 3 to 6-membered heterocycloalkylene, optionally substituted 6-membered arylene, or 5 to 6-membered heteroarylene;

L is absent or a linker;

W is hydrogen, optionally substituted amino, optionally substituted C_1-C_4 alkoxy, optionally substituted C_1-C_4 hydroxyalkyl, optionally substituted C_1-C_4 aminoalkyl, optionally substituted C_1-C_4 haloalkyl, optionally substituted C_1-C_4 alkyl, optionally substituted C_1-C_4 guanidinoalkyl, C_0-C_4 alkyl optionally substituted 3 to 11-membered heterocycloalkyl, optionally substituted 3 to 8-membered cycloalkyl, or optionally substituted 3 to 8-membered heteroaryl;

R^2 is C_1-C_6 alkyl or 3 to 6-membered cycloalkyl;

R^7 is C_1-C_3 alkyl;

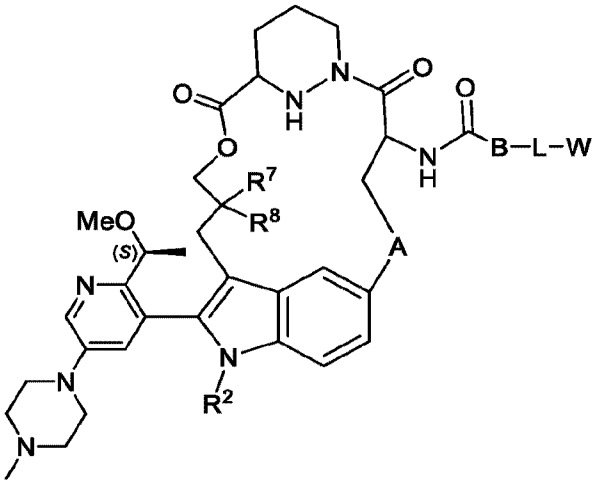
R^8 is C_1-C_3 alkyl;

R^9 is optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted 3 to 6-membered cycloalkyl, or optionally substituted 3 to 7-membered heterocycloalkyl;

X^e is CH, or CR^{17}; and

R^{17} is 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 cycloalkenyl, optionally substituted 3 to 6-membered heterocycloalkyl, optionally substituted 6 to 10-membered aryl, or optionally substituted 5 to 10-membered heteroaryl.

In some embodiments, the RAS(ON) inhibitor has the structure of Formula AIi, or a pharmaceutically acceptable salt thereof:



Formula AIi

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

B is -CH(R^9)- where the carbon is bound to the carbonyl carbon of -NHC(O)-, optionally substituted 3 to 6-membered cycloalkylene, optionally substituted 3 to 6-membered heterocycloalkylene, optionally substituted 6-membered arylene, or 5 to 6-membered heteroarylene;

L is absent or a linker;

W is hydrogen, optionally substituted amino, optionally substituted C_1-C_4 alkoxy, optionally substituted C_1-C_4 hydroxyalkyl, optionally substituted C_1-C_4 aminoalkyl, optionally substituted C_1-C_4 haloalkyl, optionally substituted C_1-C_4 alkyl, optionally substituted C_1-C_4 guanidinoalkyl, C_0-C_4 alkyl optionally substituted 3 to 11-membered heterocycloalkyl, optionally substituted 3 to 8-membered cycloalkyl, or optionally substituted 3 to 8-membered heteroaryl;

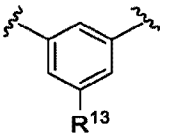
R^2 is C_1-C_6 alkyl or 3 to 6-membered cycloalkyl;

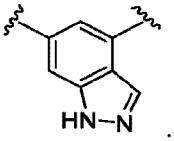
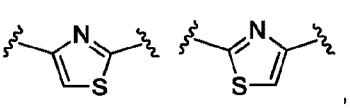
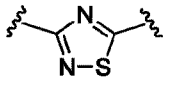
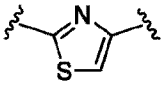
R^7 is C_1-C_3 alkyl;

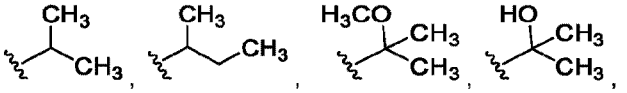
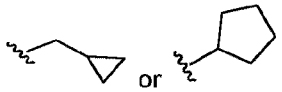
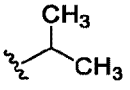
R^8 is C_1-C_3 alkyl; and

R^9 is optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted 3 to 6-membered cycloalkyl, or optionally substituted 3 to 7-membered heterocycloalkyl.

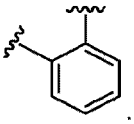
In some embodiments of Formula AI and subformula thereof, A is optionally substituted 6-membered arylene. In some embodiments, A has the structure:



wherein R^{13} is hydrogen, hydroxy, amino, cyano, optionally substituted C_1-C_6 alkyl, or optionally substituted C_1-C_6 heteroalkyl. In some embodiments, R^{13} is hydrogen. In some embodiments, R^{13} is hydroxy. In some embodiments, A is an optionally substituted 5 to 10-membered heteroarylene. In some embodiments, A is:  . In some embodiments, A is optionally substituted 5 to 6-membered heteroarylene. In some embodiments, A is:  , or  . In some embodiments, A is  .

In some embodiments of Formula AI and subformula thereof, B is -CHR^9-. In some embodiments, R^9 is optionally substituted C_1-C_6 alkyl or optionally substituted 3 to 6-membered cycloalkyl. In some embodiments, R^9 is:  ,  or . In some embodiments, R^9 is:  . In some embodiments, R^9 is optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted 3 to 6-membered cycloalkyl, or optionally substituted 3 to 7-membered heterocycloalkyl.

In some embodiments of Formula AI and subformula thereof, B is optionally substituted 6-membered arylene.

In some embodiments, B is 6-membered arylene. In some embodiments, B is:  . In some embodiments B is absent.

In some embodiments of Formula AI and subformula thereof, R^7 is methyl.

In some embodiments of Formula AI and subformula thereof, R^8 is methyl.

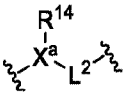
In some embodiments of Formula AI and subformula thereof, R^{16} is hydrogen.

In some embodiments of Formula AI and subformula thereof, the linker is the structure of Formula AII:

$$A^1\text{-}(B^1)_f\text{-}(C^1)_g\text{-}(B^2)_h\text{-}(D^1)\text{-}(B^3)_i\text{-}(C^2)_j\text{-}(B^4)_k\text{–}A^2$$

Formula AII

where A^1 is a bond between the linker and B; A^2 is a bond between W and the linker; B^1, B^2, B^3, and B^4 each, independently, is selected from optionally substituted C_1-C_2 alkylene, optionally substituted C_1-C_3 heteroalkylene, O, S, and NR^N; R^N is hydrogen, optionally substituted C_1-C_4 alkyl, optionally substituted C_1-C_3 cycloalkyl, optionally substituted $C_{2\text{-}C4}$ alkenyl, optionally substituted $C_{2\text{-}C4}$ alkynyl, optionally substituted 3 to 14-membered heterocycloalkyl, optionally substituted 6 to 10-membered aryl, or optionally substituted C_1-C_7 heteroalkyl; C^1 and C^2 are each, independently, selected from carbonyl, thiocarbonyl, sulphonyl, or phosphoryl; f, g, h, i, j, and k are each, independently, 0 or 1; and D^1 is optionally substituted C_1-C_{10} alkylene, optionally substituted C_2-C_{10} alkenylene, optionally substituted C_2-C_{10} alkynylene, optionally substituted 3 to 14-membered heterocycloalkylene, optionally substituted 5 to 10-membered heteroarylene, optionally substituted 3 to 8-membered cycloalkylene, optionally substituted 6 to 10-membered arylene, optionally substituted C_2-C_{10} polyethylene glycolene, or optionally substituted C_1-C_{10} heteroalkylene, or a chemical bond linking $A^1\text{-}(B^1)_f\text{-}(C^1)_g\text{-}(B^2)_h$- to -$(B^3)_i\text{-}(C^2)_j\text{-}(B^4)_k\text{–}A^2$. In some embodiments, the linker is acyclic. In some embodiments, the linker has the structure of Formula AIIa:

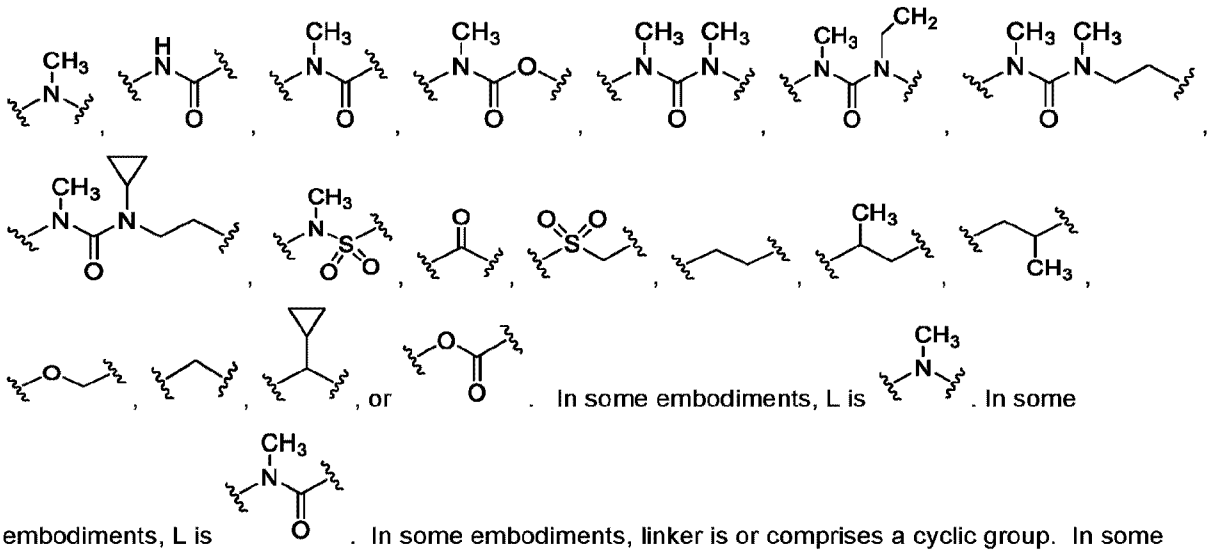


Formula AIIa

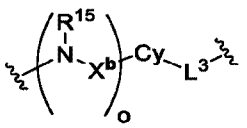
wherein X^a is absent or N;

R^{14} is absent, hydrogen or optionally substituted C_1-C_6 alkyl or optionally substituted C_1-C_3 cycloalkyl; and

L^2 is absent, -C(O)-, -SO_2-, optionally substituted C_1-C_4 alkylene or optionally substituted C_1-C_4 heteroalkylene, wherein at least one of X^a, R^{14}, or L^2 is present. In some embodiments, the linker has the structure:



. In some embodiments, L is . In some embodiments, L is . In some embodiments, linker is or comprises a cyclic group. In some embodiments of Formula AI and subformula thereof, the linker has the structure of Formula AIIb:



Formula AIIb

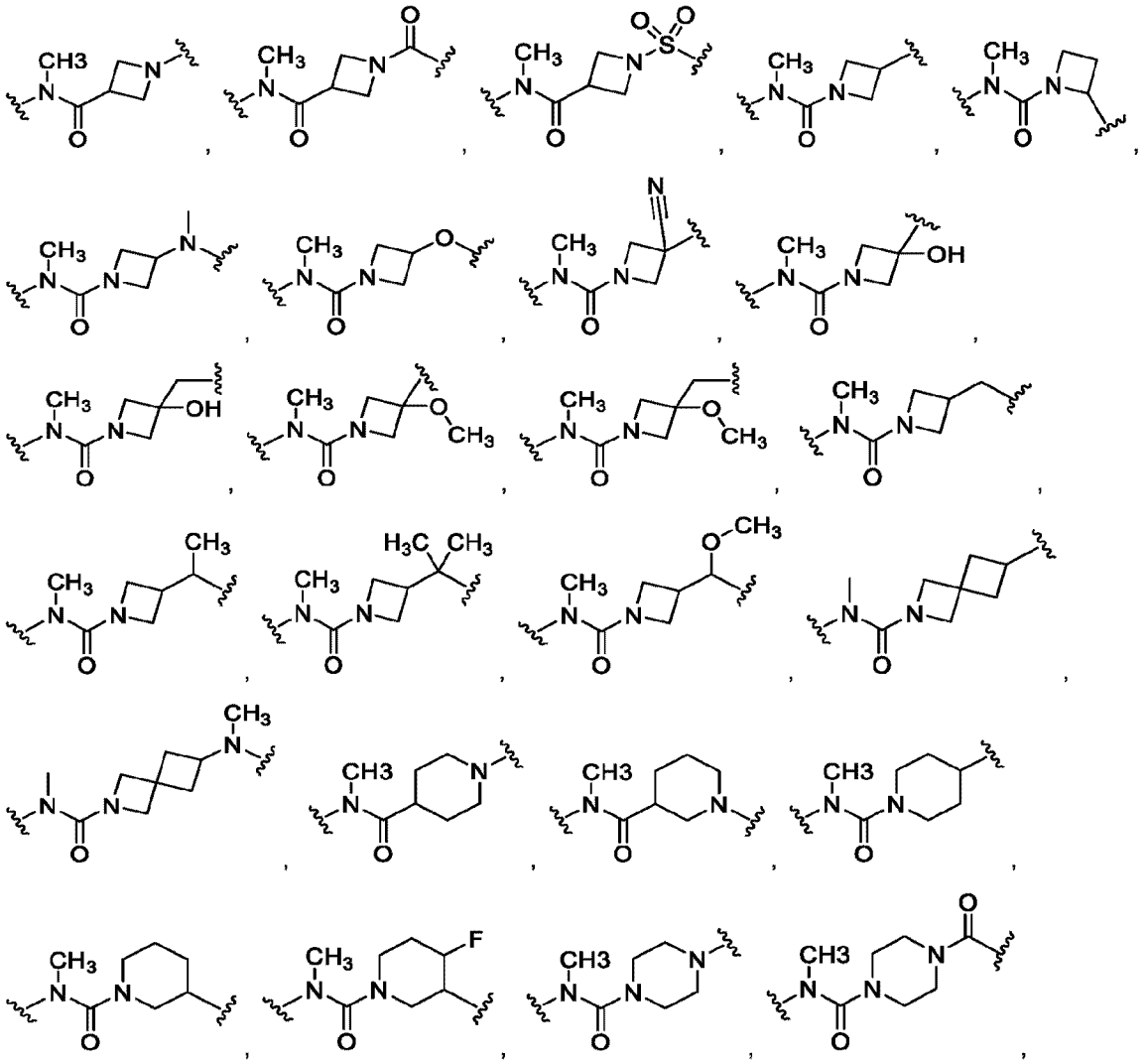
wherein o is 0 or 1;

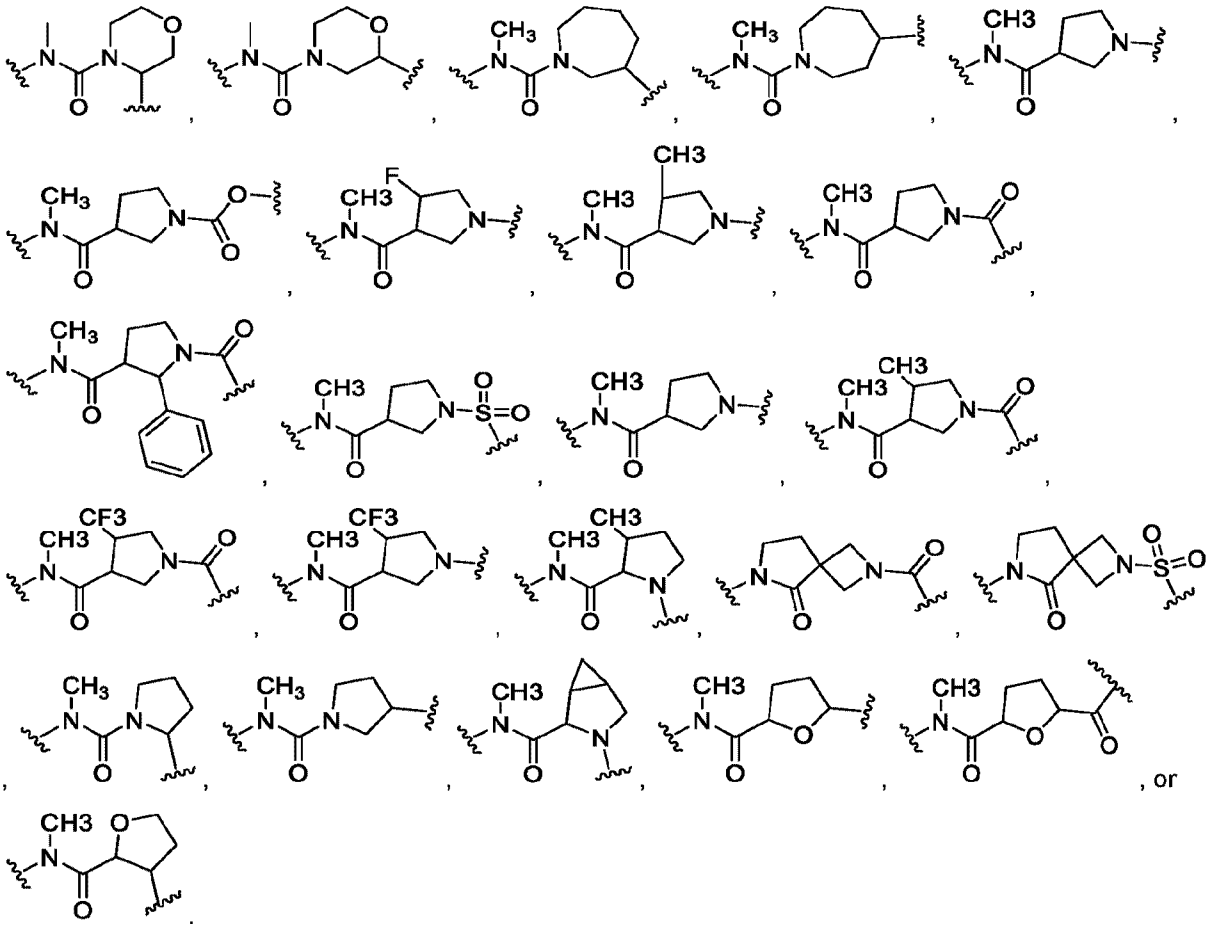
X^b is C(O) or SO_2;

R^{15} is hydrogen or optionally substituted C_1-C_6 alkyl;

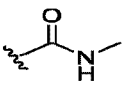
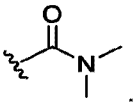
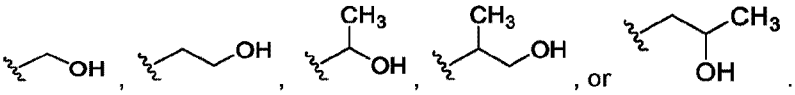
Cy is optionally substituted 3 to 8-membered cycloalkylene, optionally substituted 3 to 8-membered heterocycloalkylene, optionally substituted 6-10 membered arylene, or optionally substituted 5 to 10-membered heteroarylene; and

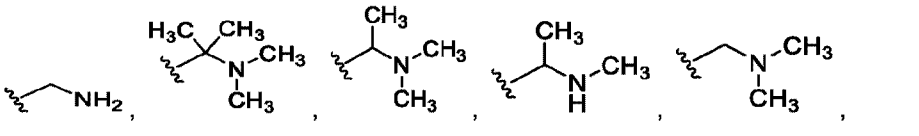
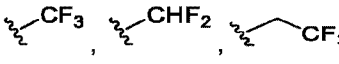
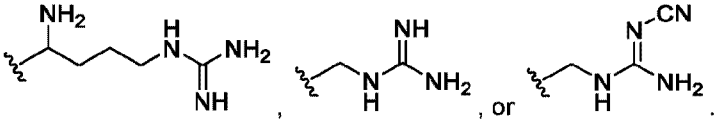
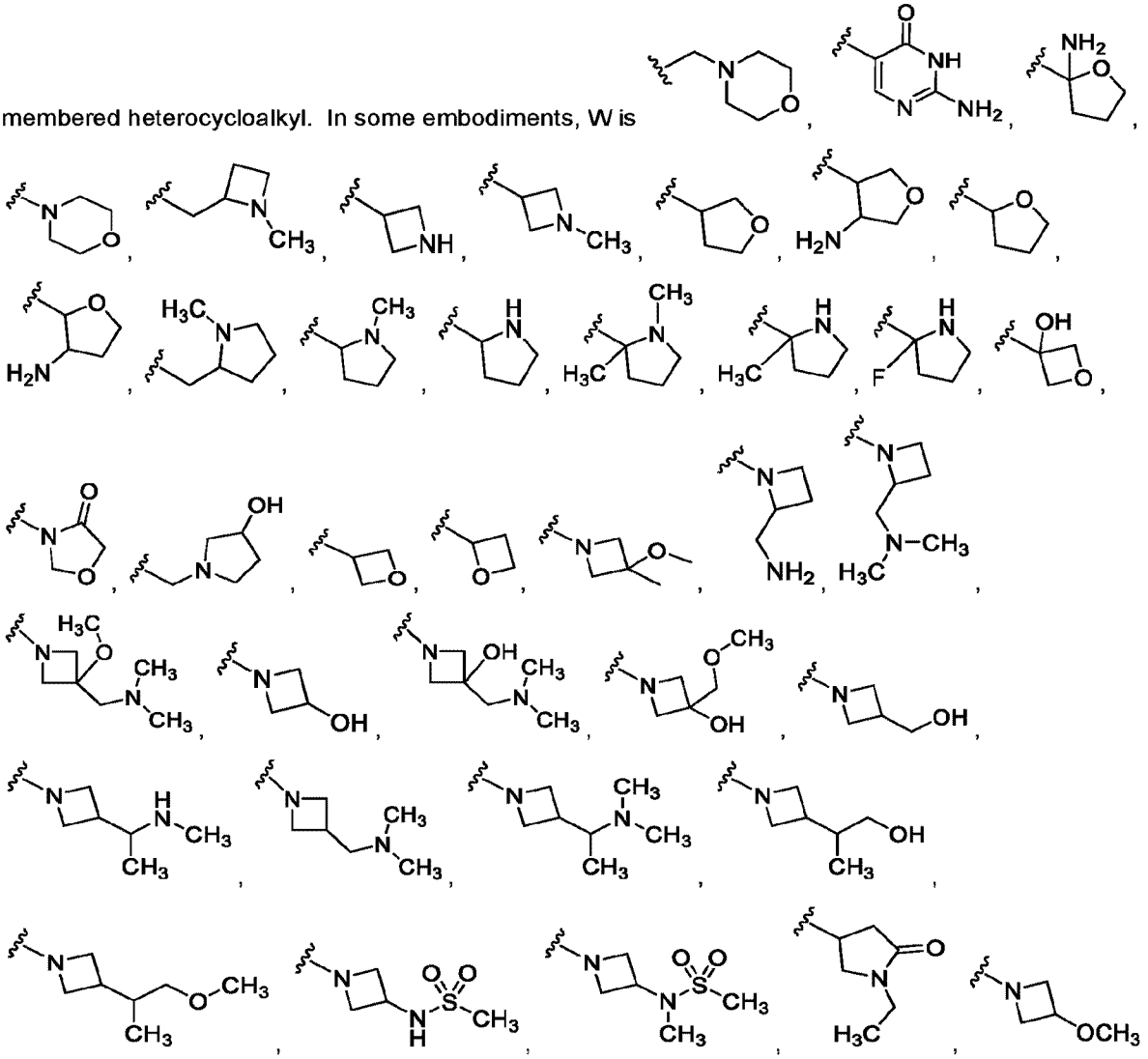
L^3 is absent, -C(O)-, -SO_2-, optionally substituted C_1-C_4 alkylene or optionally substituted C_1-C_4 heteroalkylene. In some embodiments, the linker has the structure:

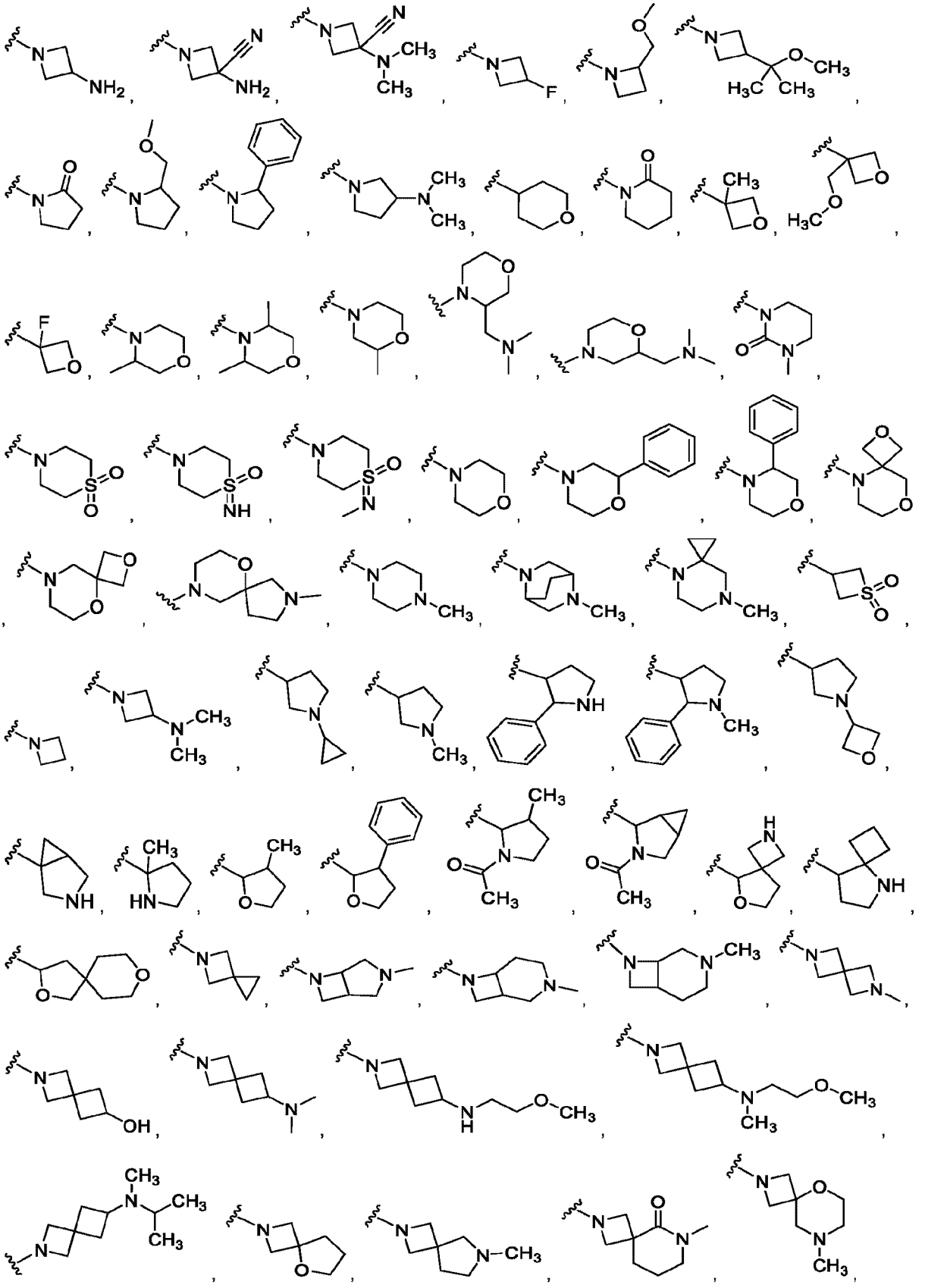


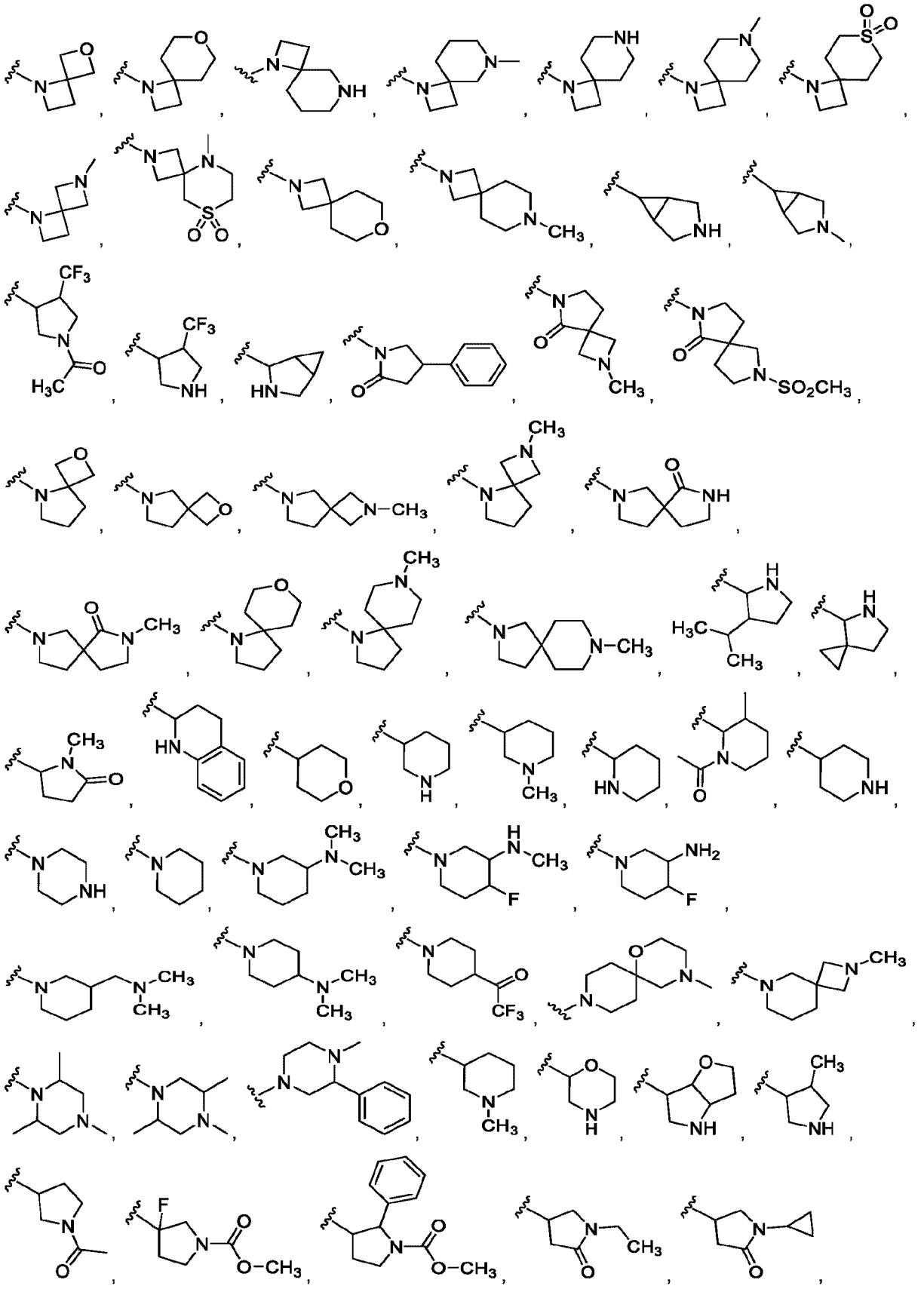


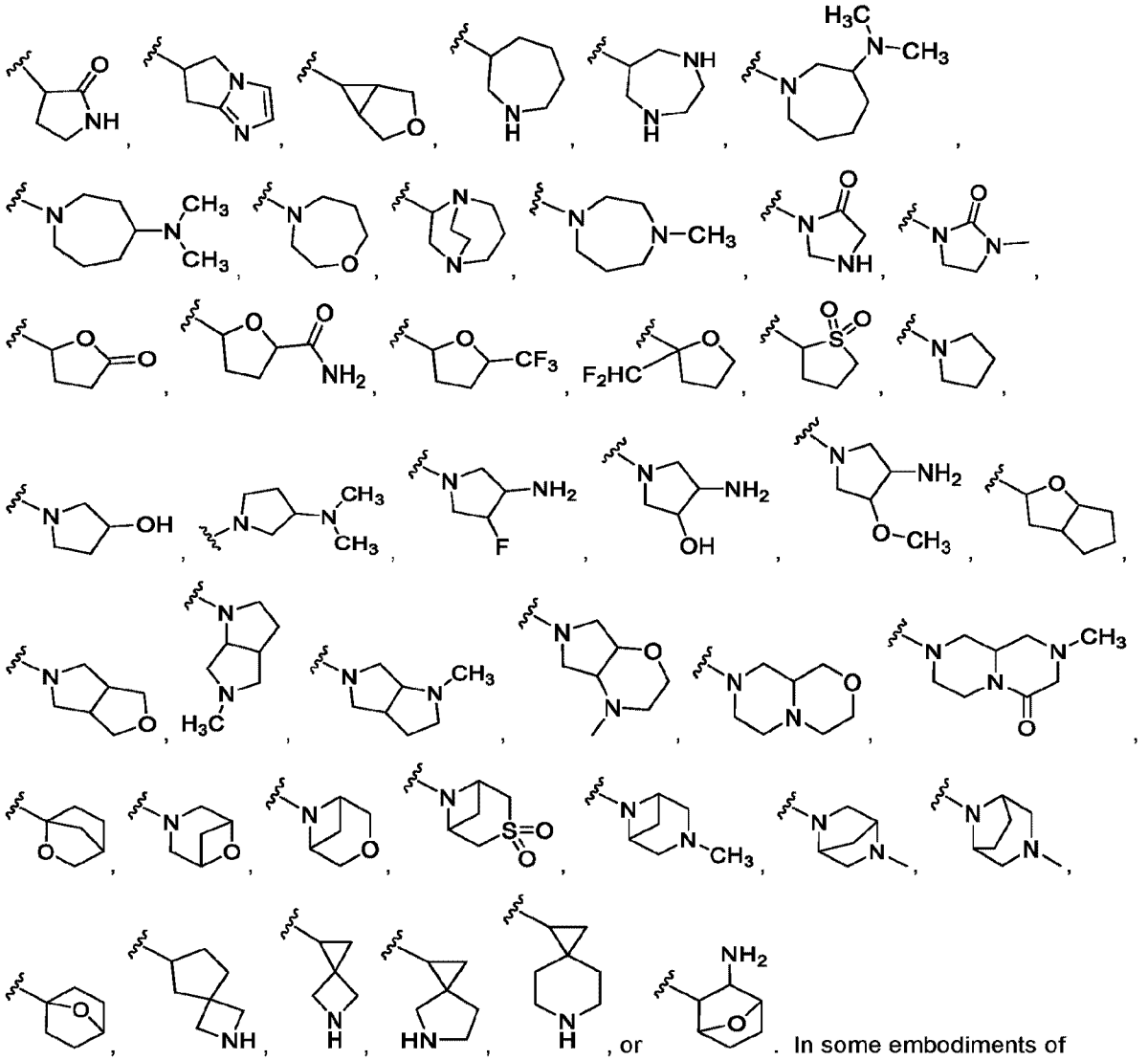
In some embodiments of Formula AI and subformula thereof, W is hydrogen, optionally substituted amino, optionally substituted C_1-C_4 alkoxy, optionally substituted C_1-C_4 hydroxyalkyl, optionally substituted C_1-C_4 aminoalkyl, optionally substituted C_1-C_4 haloalkyl, optionally substituted C_1-C_4 alkyl, optionally substituted C_1-C_4 guanidinoalkyl, C_0-C_4 alkyl optionally substituted 3 to 8-membered heterocycloalkyl, optionally substituted 3 to 8-membered cycloalkyl, or 3 to 8-membered heteroaryl.

In some embodiments of Formula AI and subformula thereof, W is hydrogen. In some embodiments of Formula AI and subformula thereof, W is optionally substituted amino. In some embodiments of Formula AI and subformula thereof, W is $-NHCH_3$ or $-N(CH_3)_2$. In some embodiments of Formula AI and subformula thereof, W is optionally substituted C_1-C_4 alkoxy. In some embodiments, W is methoxy or iso-propoxy. In some embodiments of Formula AI and subformula thereof, W is optionally substituted C_1-C_4 alkyl. In some embodiments, W is methyl, ethyl, iso-propyl, tert-butyl, or benzyl. In some embodiments of Formula AI and subformula thereof, W is optionally substituted amido. In some embodiments, W is  . In some embodiments, W is  . In some embodiments of Formula AI and subformula thereof, W is optionally substituted C_1-C_4 hydroxyalkyl. In some embodiments, W is  .

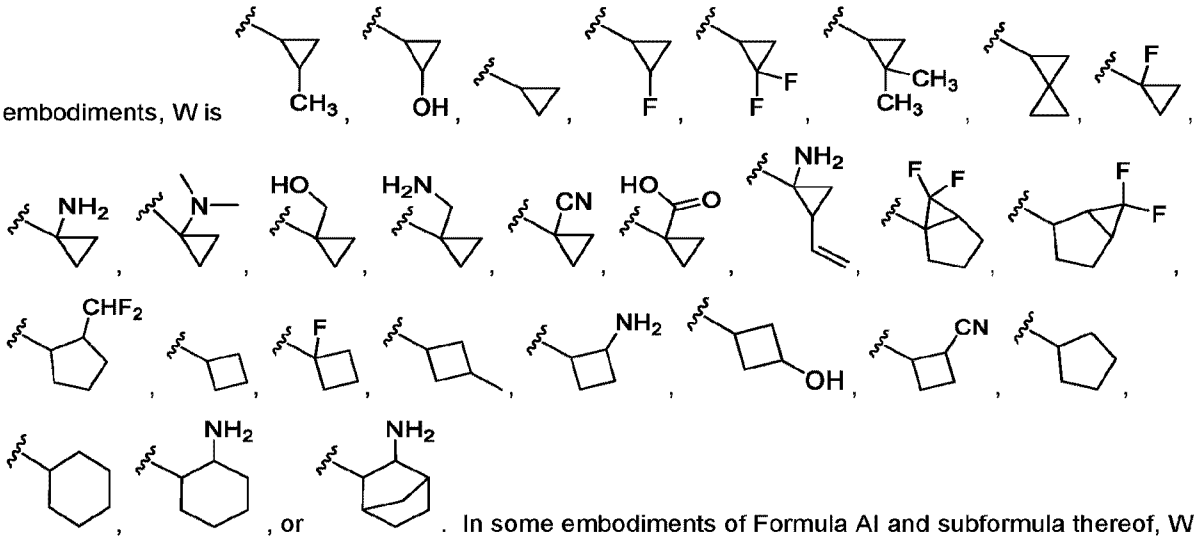
embodiments of Formula AI and subformula thereof, W is optionally substituted C_1-C_4 aminoalkyl. In some embodiments, W is  . In some embodiments of Formula AI and subformula thereof, W is optionally substituted C_1-C_4 haloalkyl. In some embodiments, W is  . In some embodiments of Formula AI and subformula thereof, W is optionally substituted C_1-C_4 guanidinoalkyl. In some embodiments, W is  . In some embodiments of Formula AI and subformula thereof, W is C_0-C_4 alkyl optionally substituted 3 to 11-membered heterocycloalkyl. In some embodiments, W is 



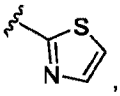
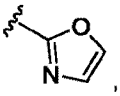
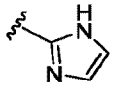
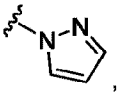
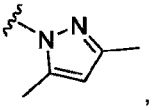
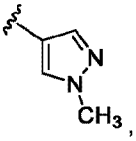
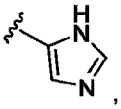
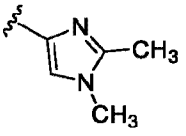
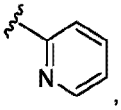
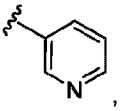
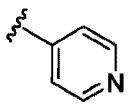
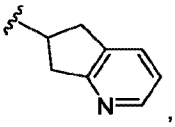
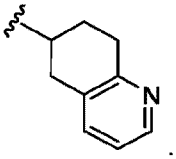




. In some embodiments of Formula AI and subformula thereof, W is optionally substituted 3 to 8-membered cycloalkyl. In some embodiments, W is

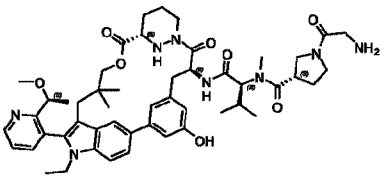
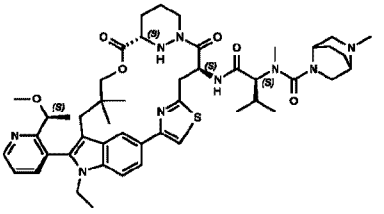
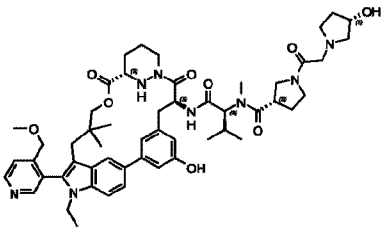
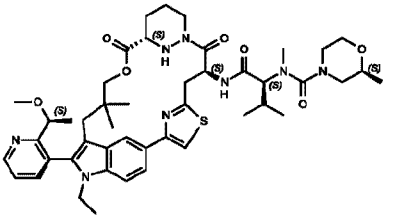
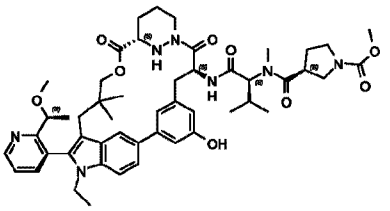
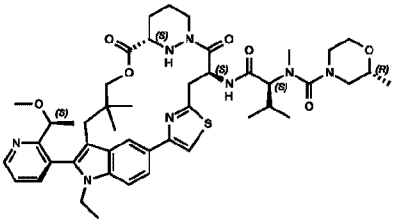


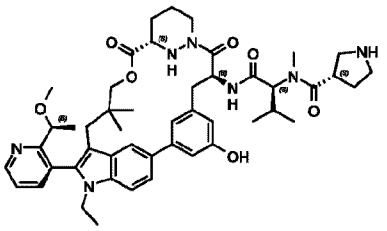
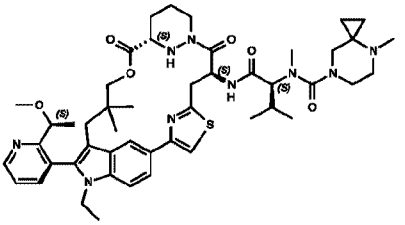
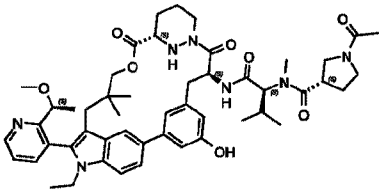
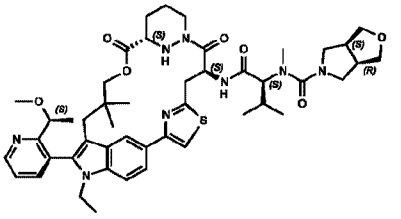
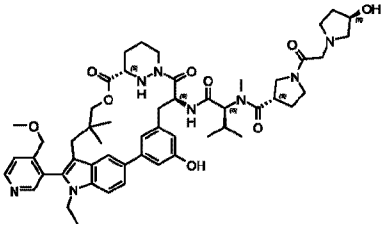
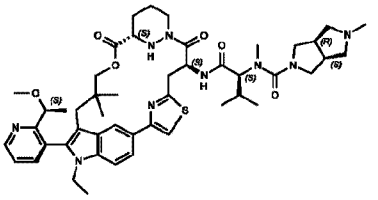
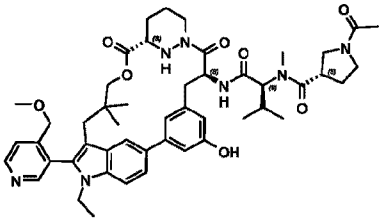
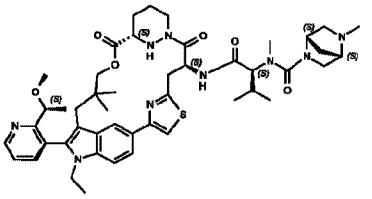
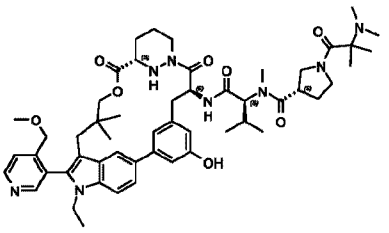
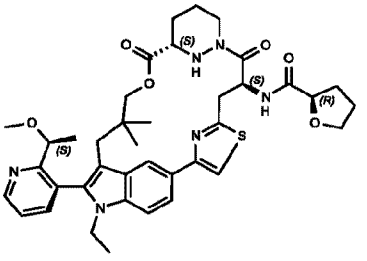
. In some embodiments of Formula AI and subformula thereof, W

is optionally substituted 3 to 8-membered heteroaryl. In some embodiments, W is  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , or  . In some embodiments of Formula AI and subformula thereof, W is optionally substituted 6- to 10-membered aryl (e.g., phenyl, 4-hydroxy-phenyl, or 2,4-methoxy-phenyl).

In some embodiments, the RAS(ON) inhibitor is selected from Table A1, or a pharmaceutically acceptable salt or stereoisomer thereof. In some embodiments, the RAS(ON) inhibitor is selected from Table A1, or a pharmaceutically acceptable salt or atropisomer thereof.

Table A1: Certain Compounds of the Present Invention

Ex#	Structure	Ex#	Structure
AA 1		AA 308	
AA 2		AA 309	
AA 3		AA 310	

Ex#	Structure	Ex#	Structure
AA 4		AA 311	
AA 5		AA 312	
AA 6		AA 313	
AA 7		AA 314	
AA 8		AA 315	

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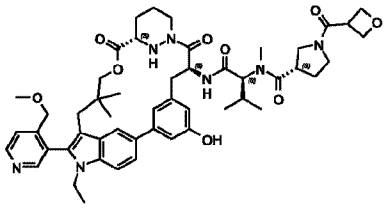
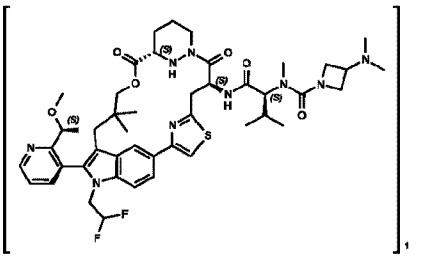
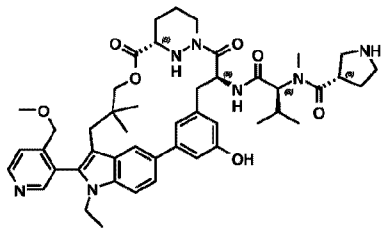
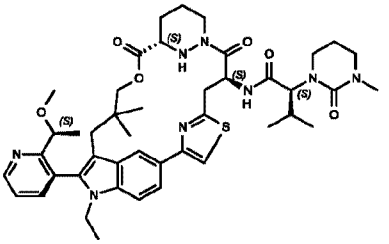
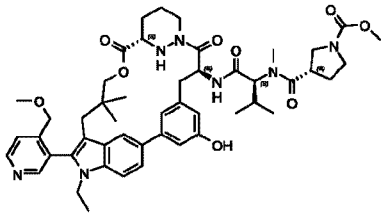
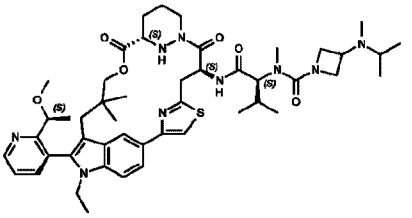
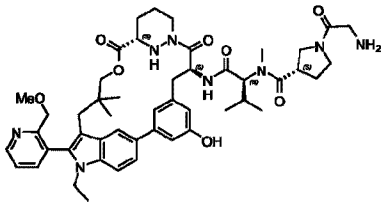
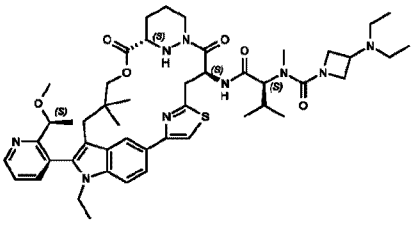
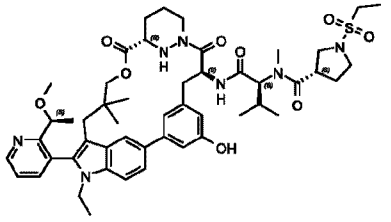
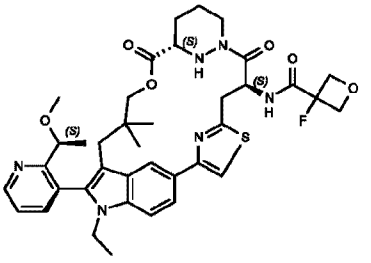
AA 9		AA 316	
AA 10		AA 317	
AA 11		AA 318	
AA 12		AA 319	
AA 13		AA 320	

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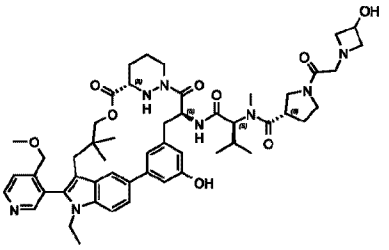
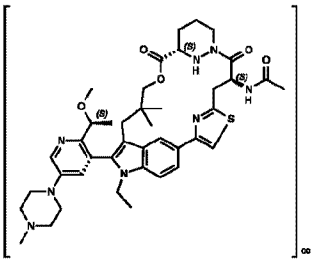
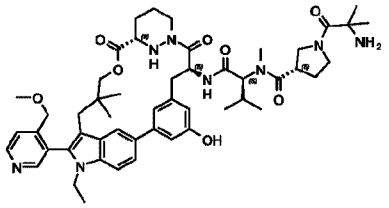
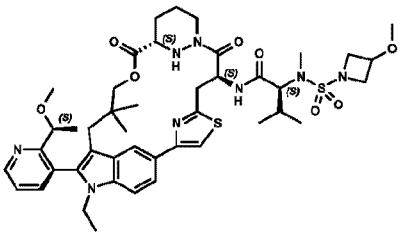
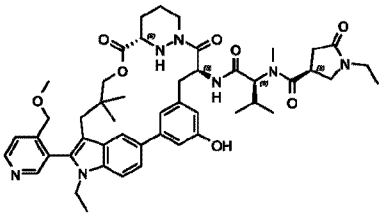
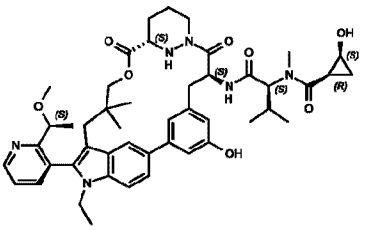
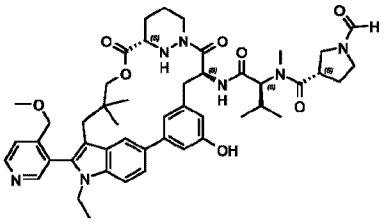
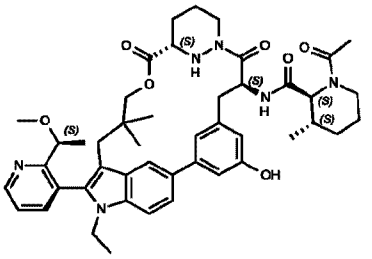
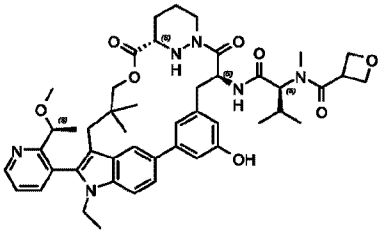
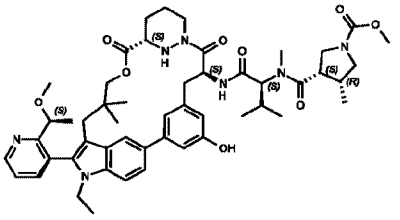
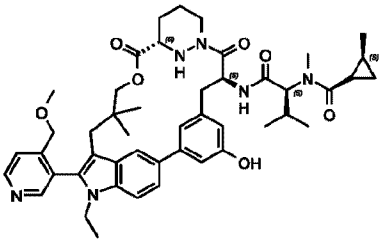
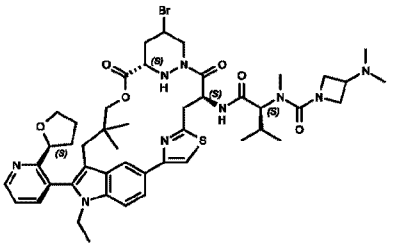
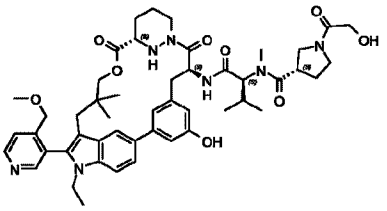
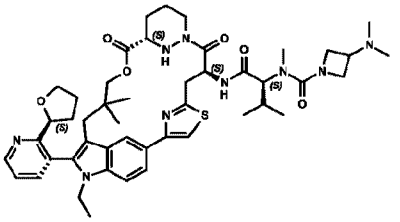
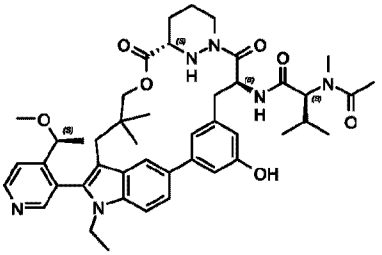
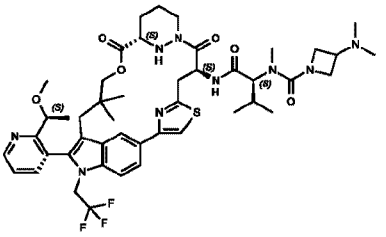
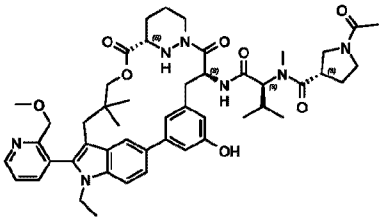
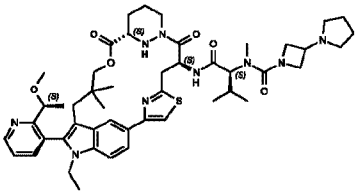
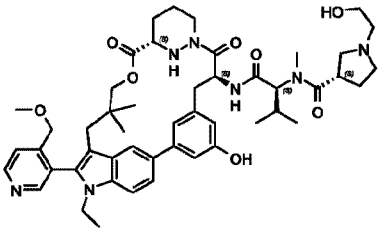
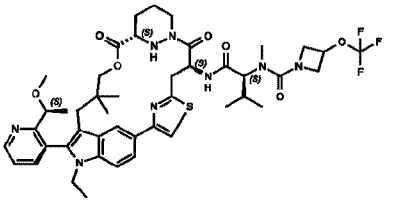
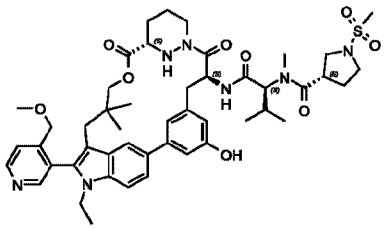
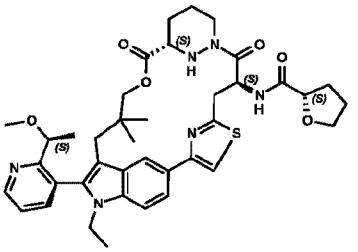
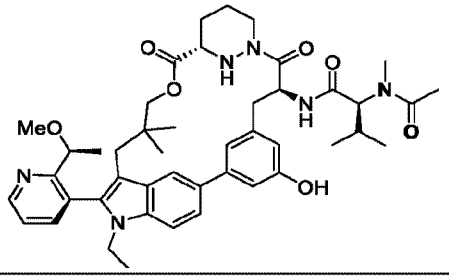
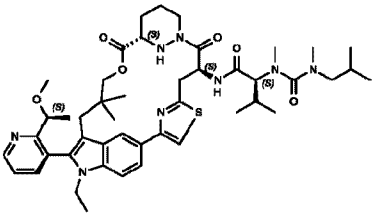
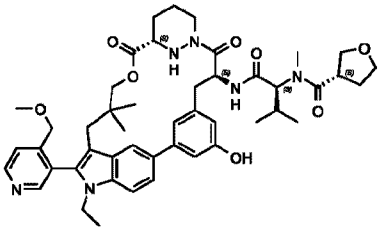
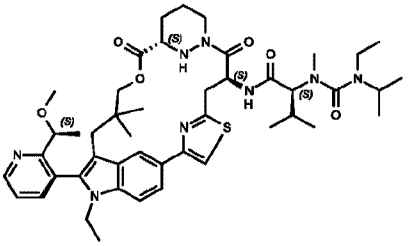
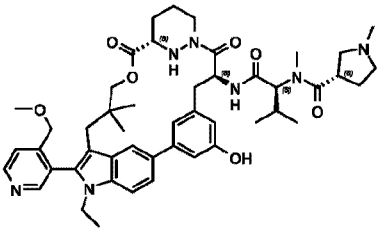
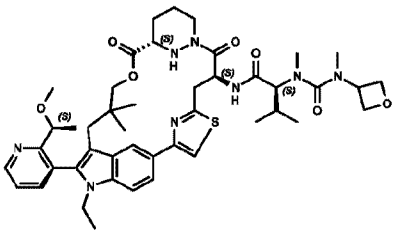
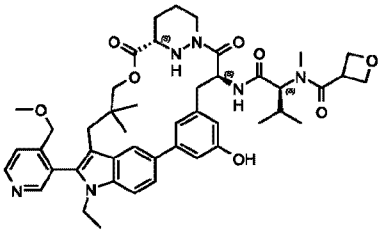
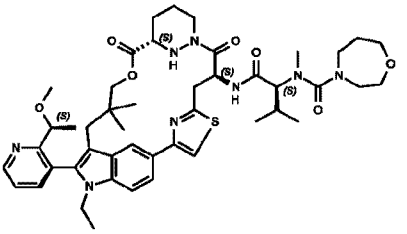
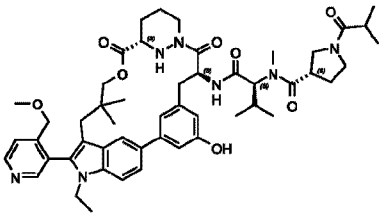
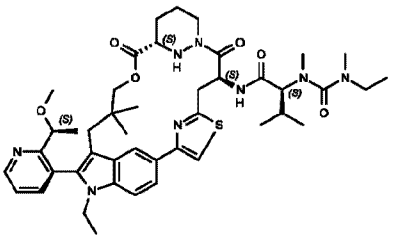
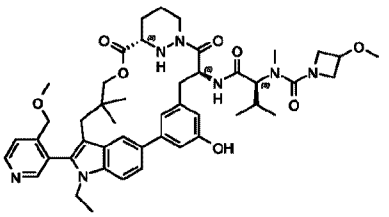
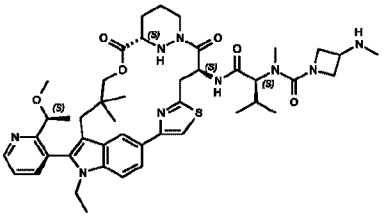
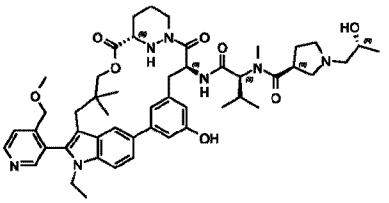
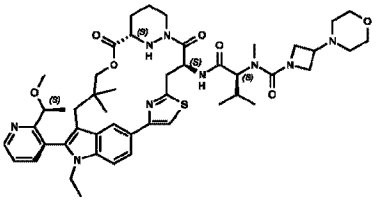
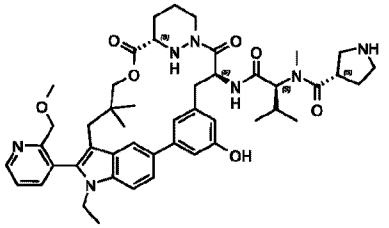
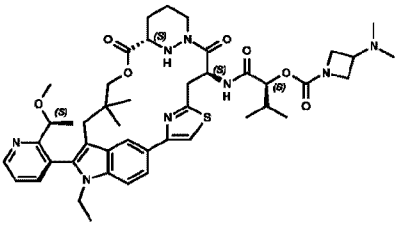
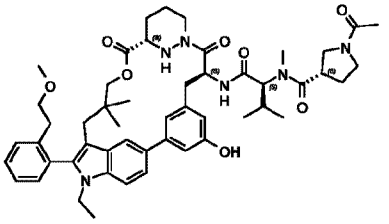
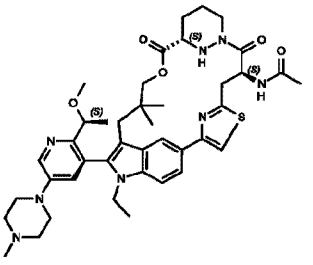
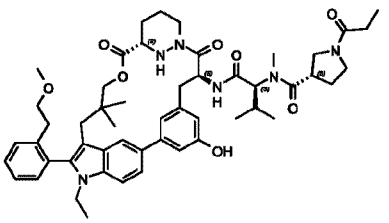
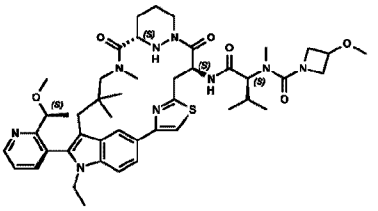
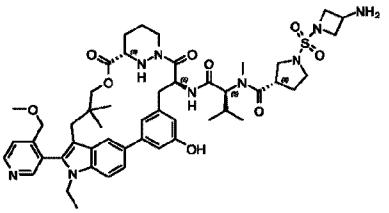
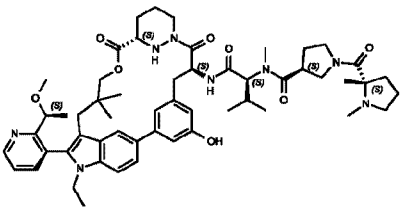
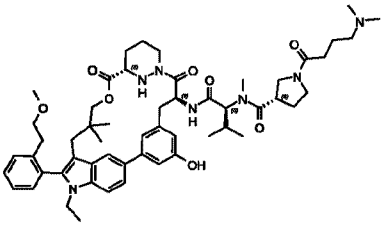
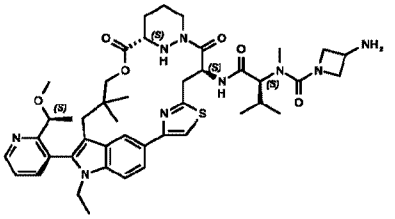
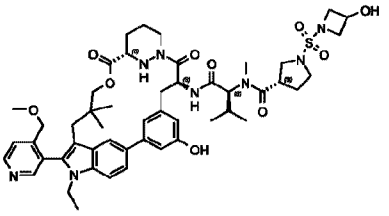
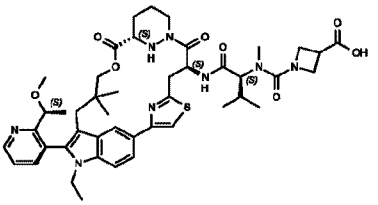
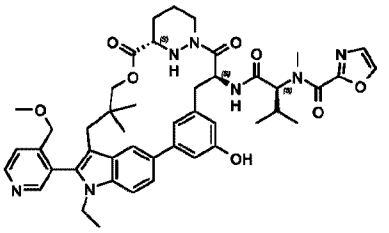
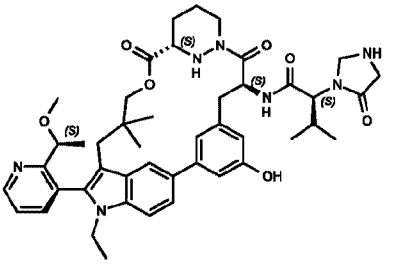
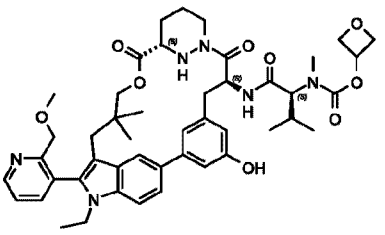
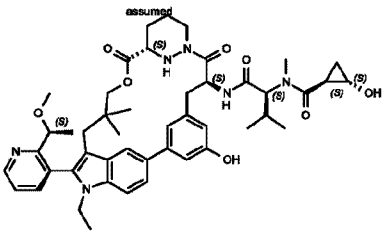
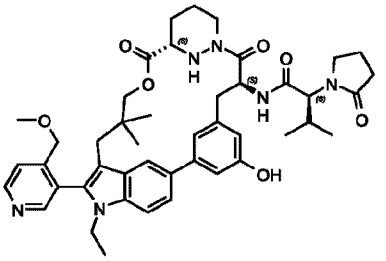
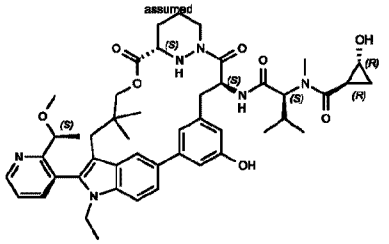
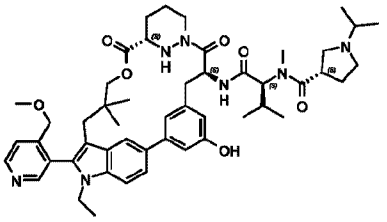
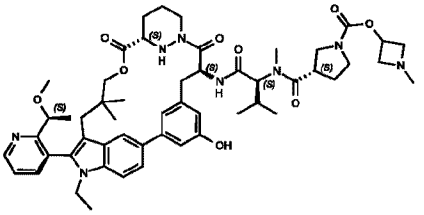
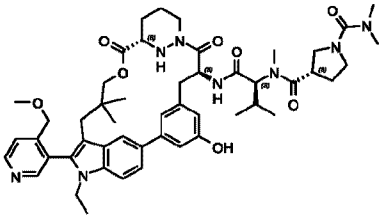
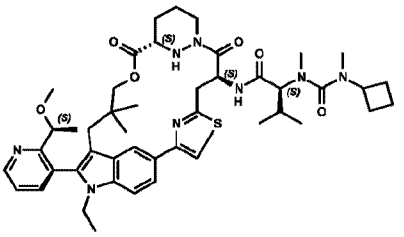
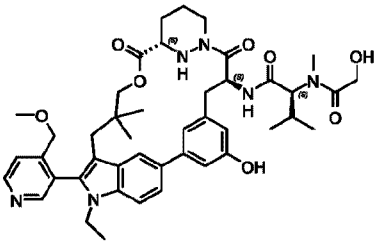
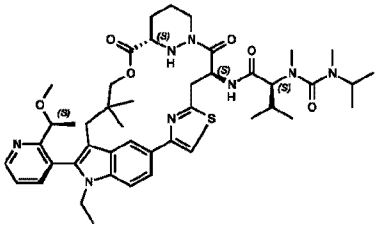
AA 14		AA 321	
AA 15		AA 322	
AA 16		AA 323	
AA 17		AA 324	
AA 18		AA 325	

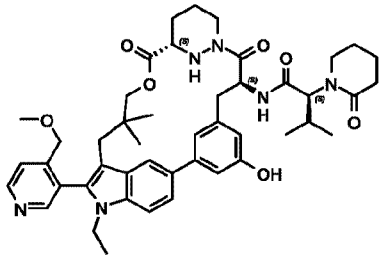
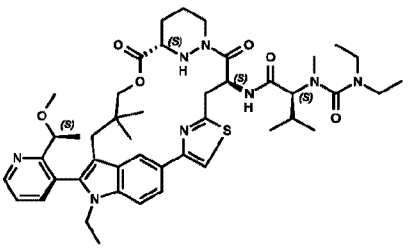
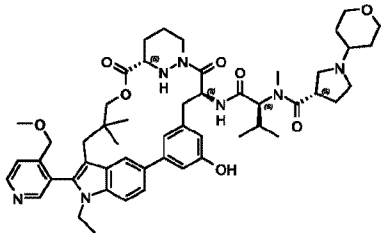
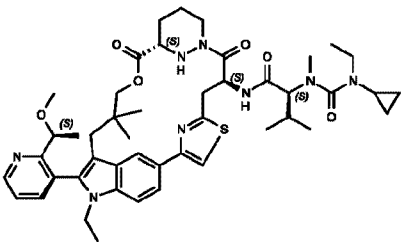
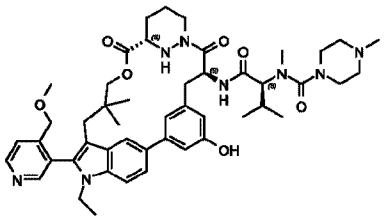
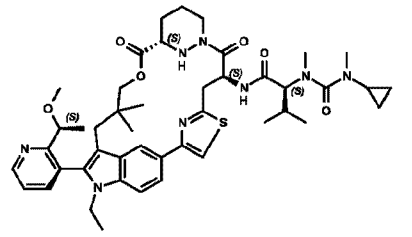
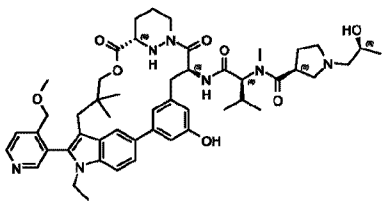
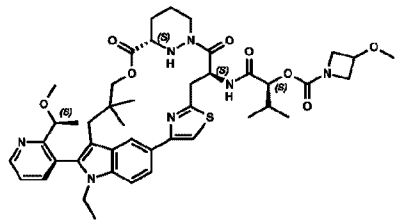
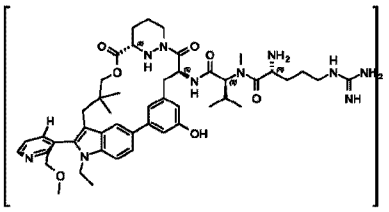
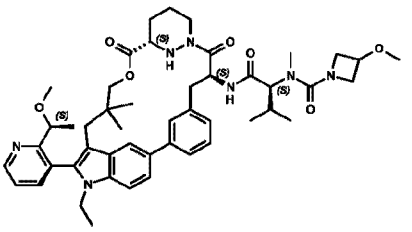
Ex#	Structure	Ex#	Structure
AA 19		AA 326	
AA 20		AA 327	
AA 21		AA 328	
AA 22		AA 329	
AA 23		AA 330	

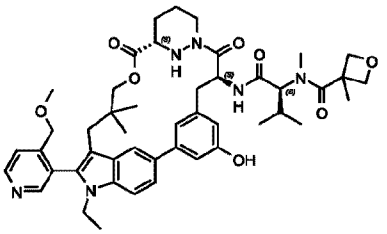
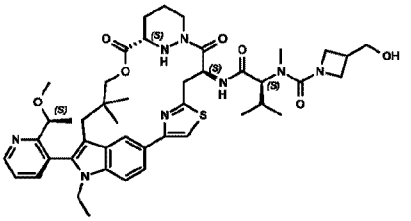
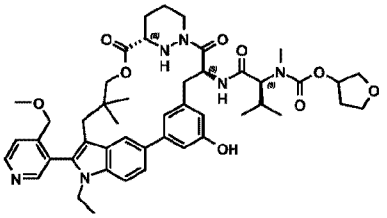
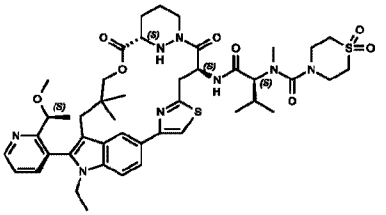
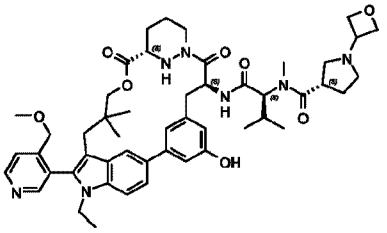
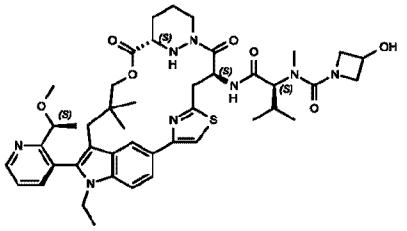
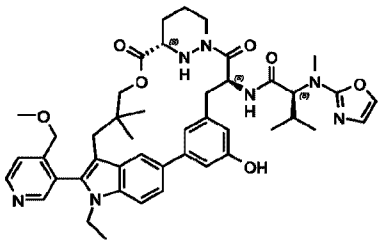
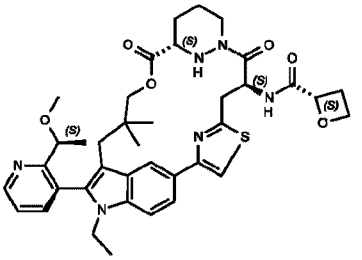
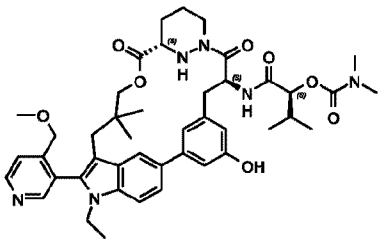
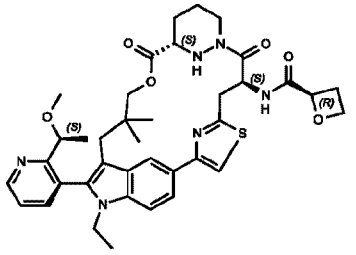
Ex#	Structure	Ex#	Structure
AA 24		AA 331	
AA 25		AA 332	
AA 26		AA 333	
AA 27		AA 334	
AA 28		AA 335	

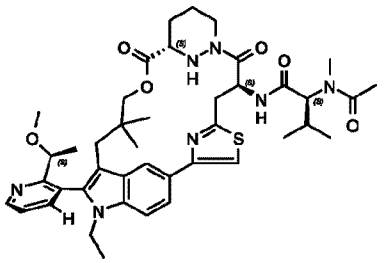
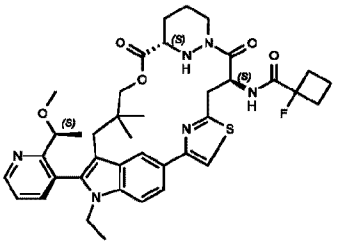
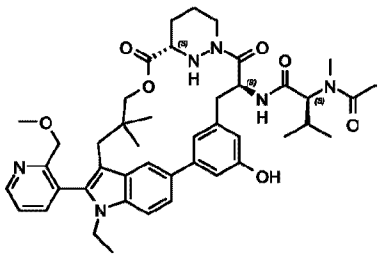
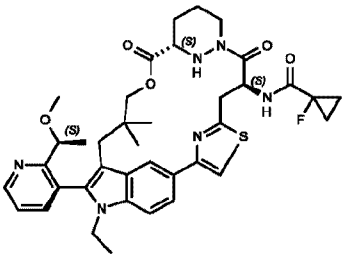
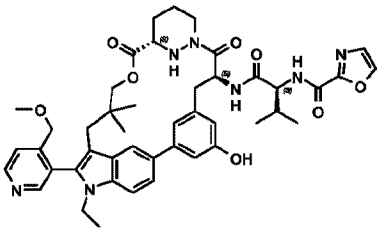
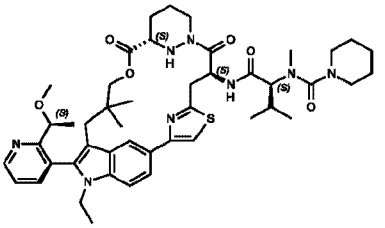
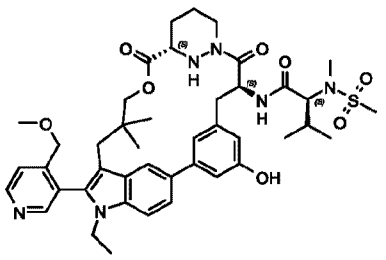
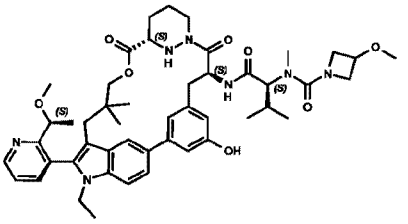
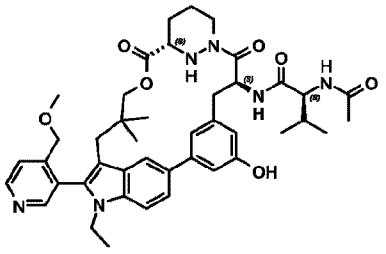
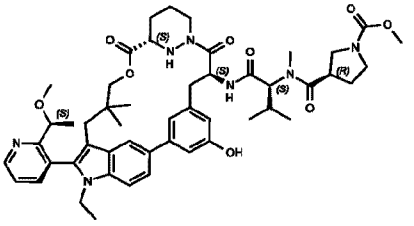
Ex#	Structure	Ex#	Structure
AA 29		AA 336	
AA 30		AA 337	
AA 31		AA 338	
AA 32		AA 339	
AA 33		AA 340	

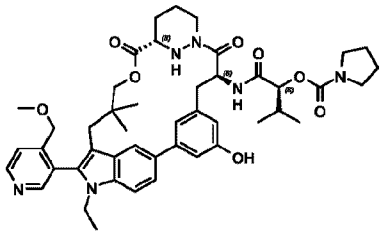
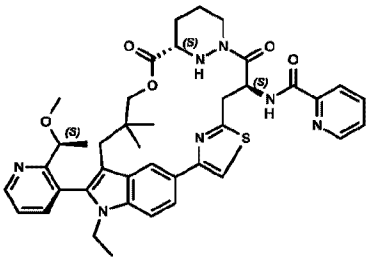
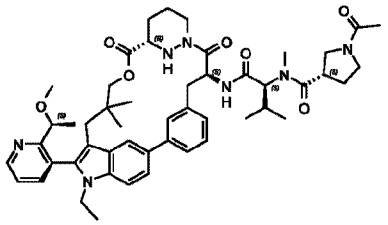
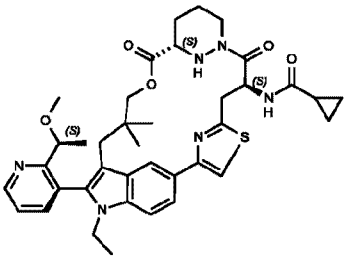
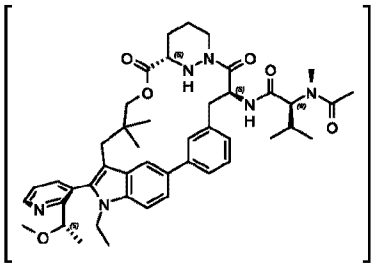
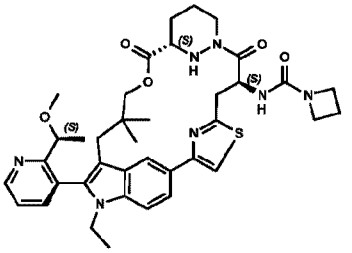
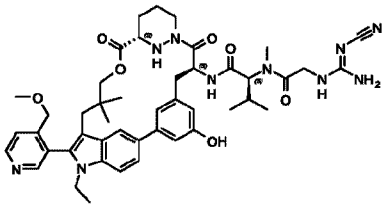
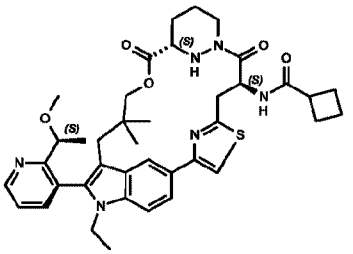
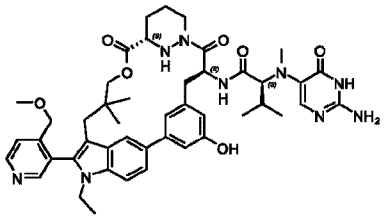
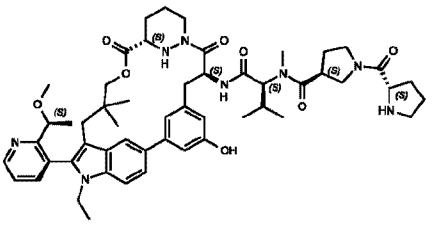
Ex#	Structure	Ex#	Structure
AA 34		AA 341	
AA 35		AA 342	
AA 36		AA 343	
AA 37		AA 344	
AA 38		AA 345	

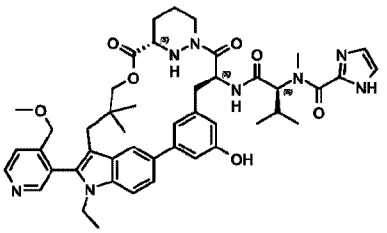
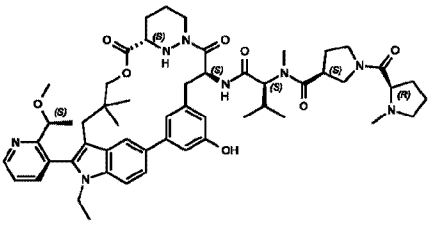
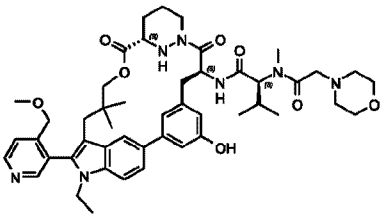
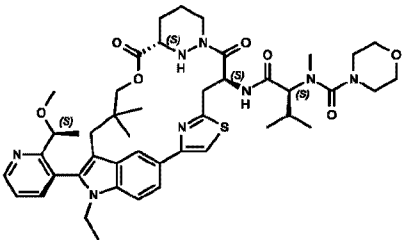
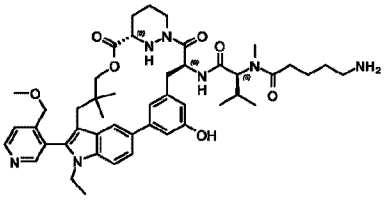
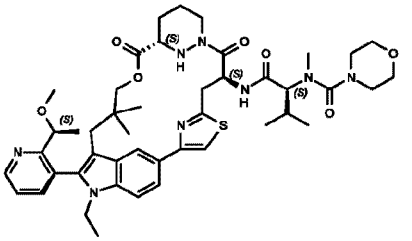
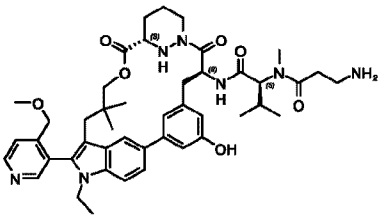
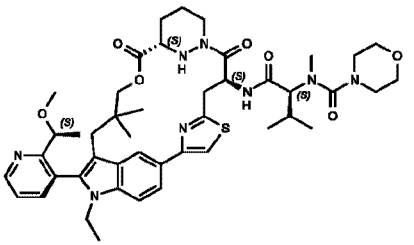
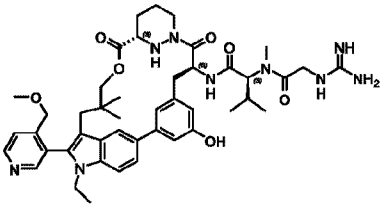
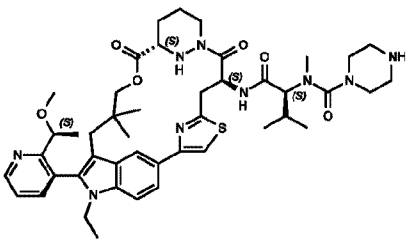
Ex#	Structure	Ex#	Structure
AA 39		AA 346	
AA 40		AA 347	
AA 41		AA 348	
AA 42		AA 349	
AA 43		AA 350	

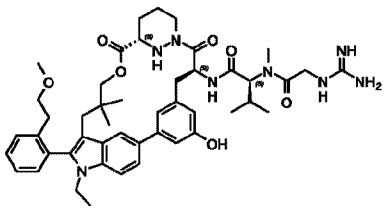
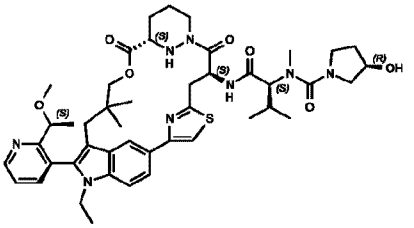
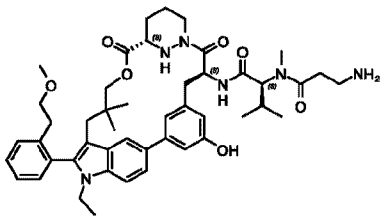
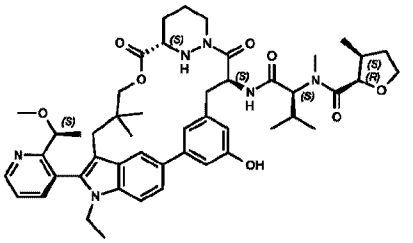
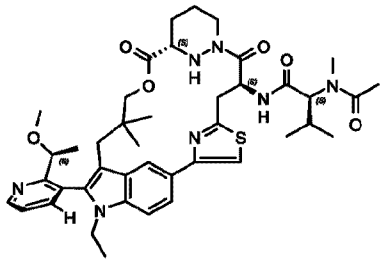
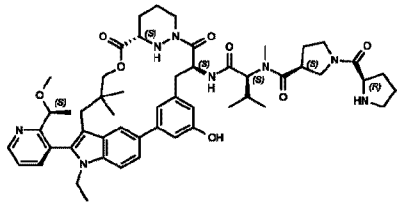
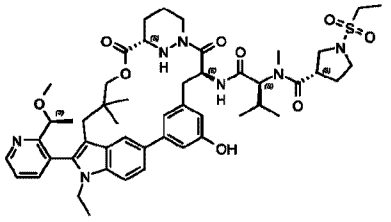
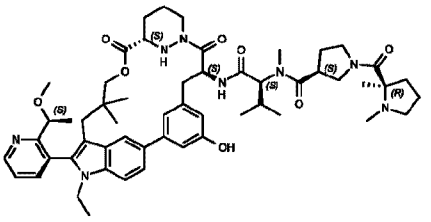
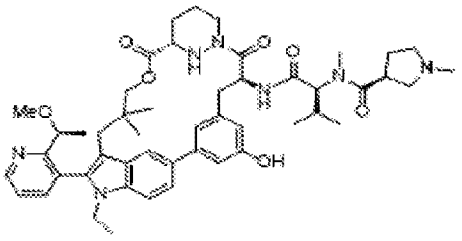
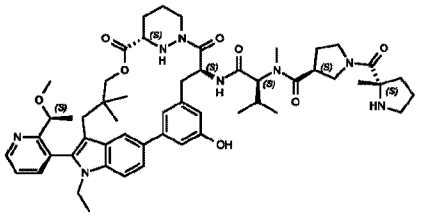
Ex#	Structure	Ex#	Structure
AA 44		AA 351	
AA 45		AA 352	
AA 46		AA 353	
AA 47		AA 354	
AA 48		AA 355	

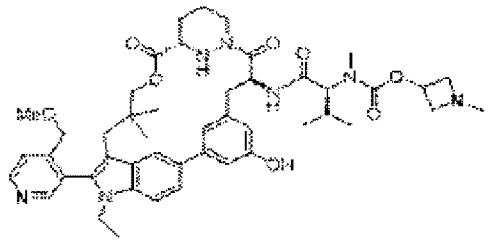
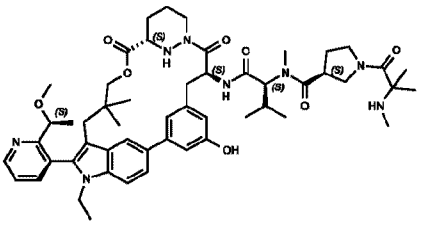
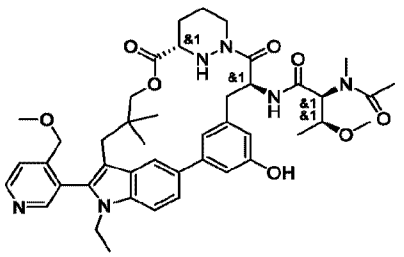
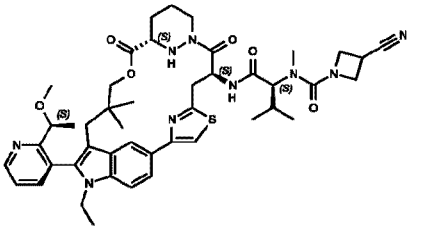
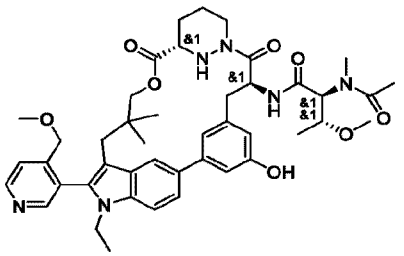
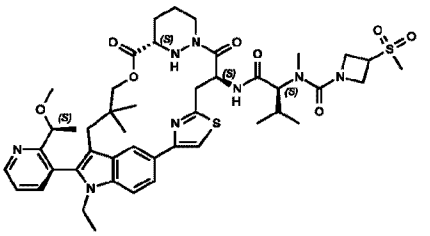
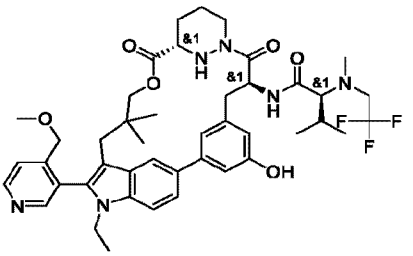
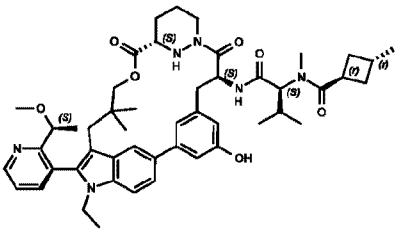
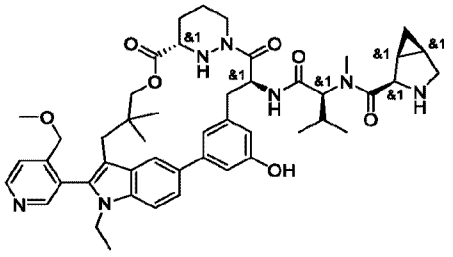
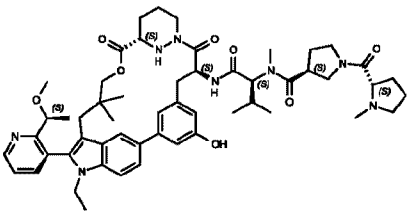
Ex#	Structure	Ex#	Structure
AA 49		AA 356	
AA 50		AA 357	
AA 51		AA 358	
AA 52		AA 359	
AA 53		AA 360	

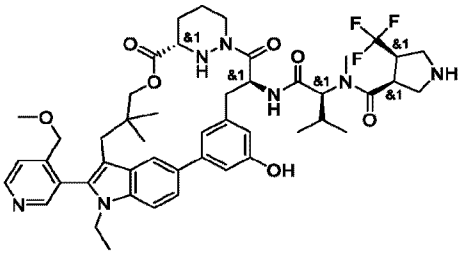
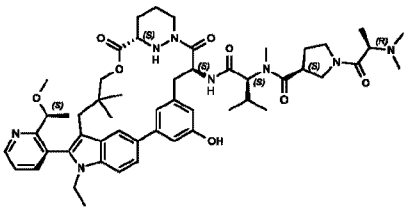
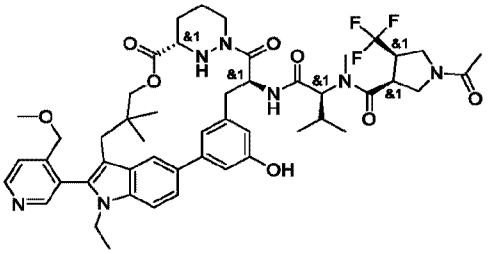
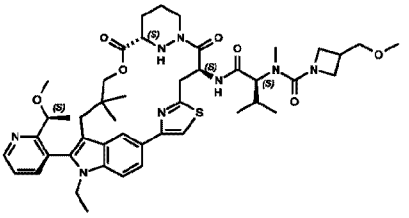
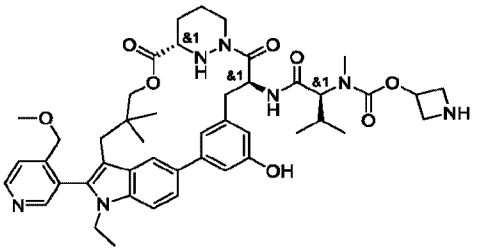
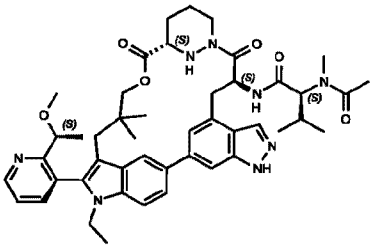
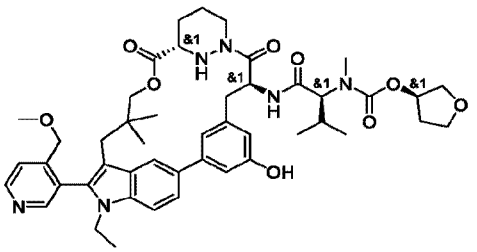
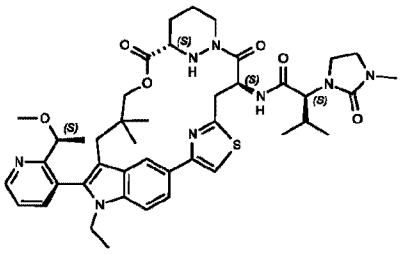
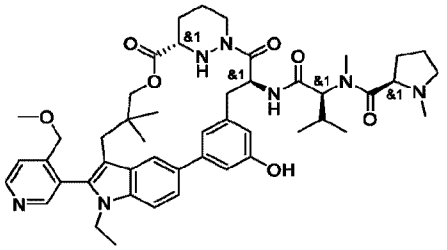
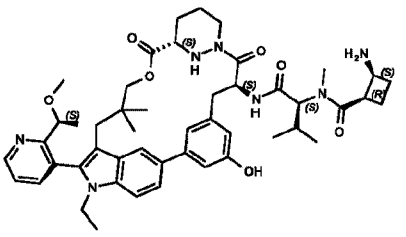
Ex#	Structure	Ex#	Structure
AA 54		AA 361	
AA 55		AA 362	
AA 56		AA 363	
AA 57		AA 364	
AA 58		AA 365	

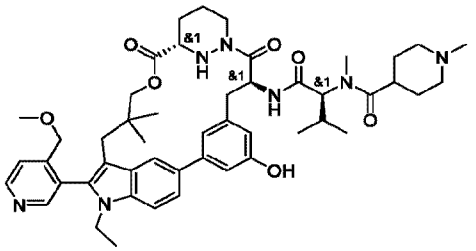
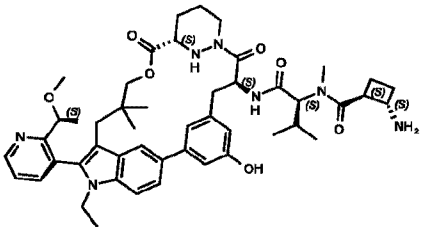
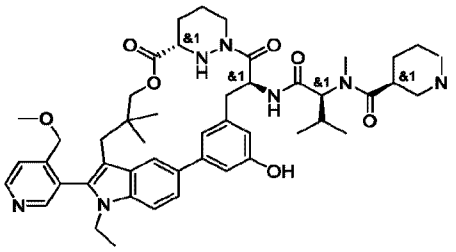
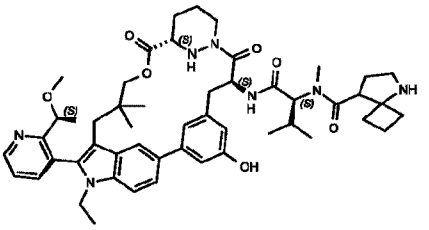
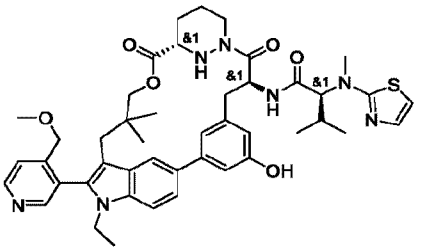
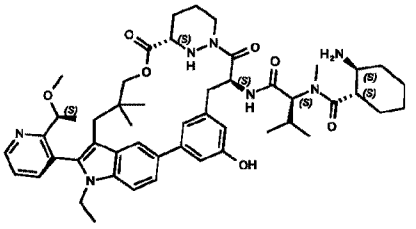
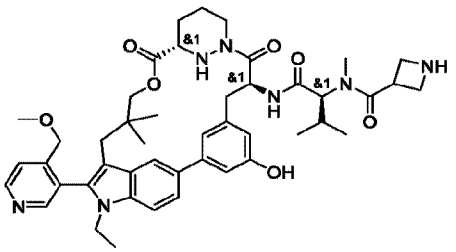
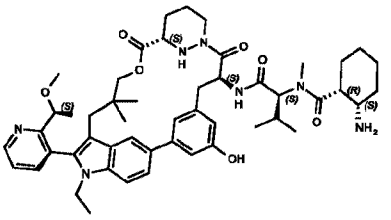
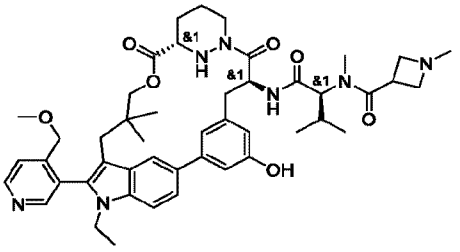
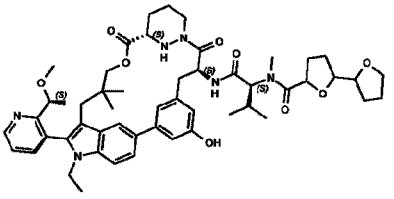
Ex#	Structure	Ex#	Structure
AA 59		AA 366	
AA 60		AA 367	
AA 61		AA 368	
AA 62		AA 369	
AA 63		AA 370	

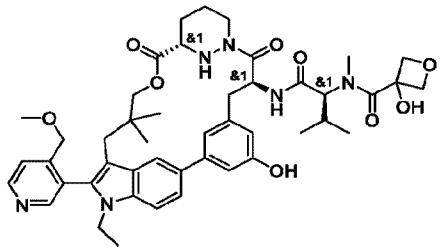
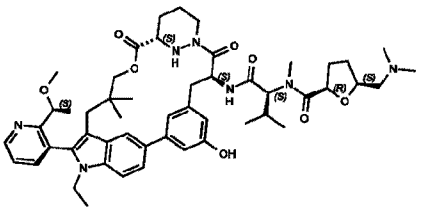
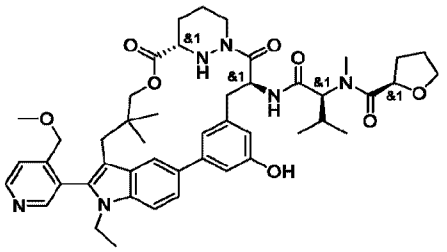
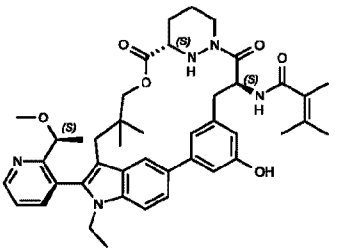
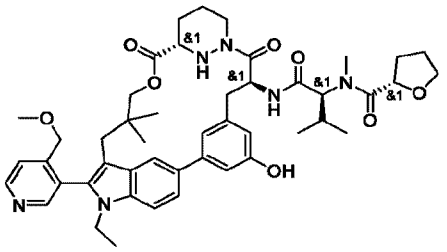
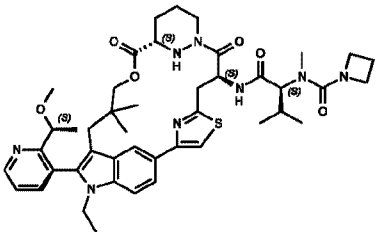
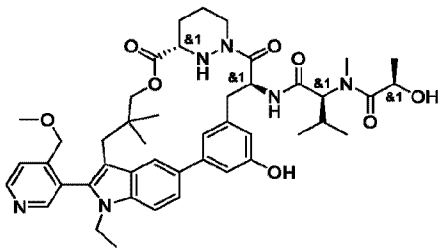
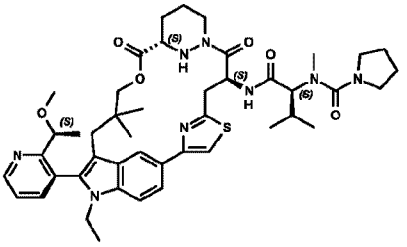
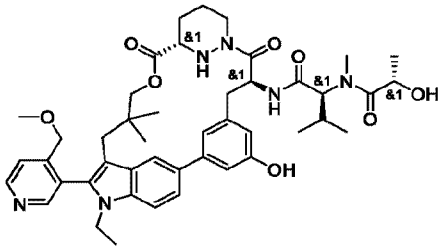
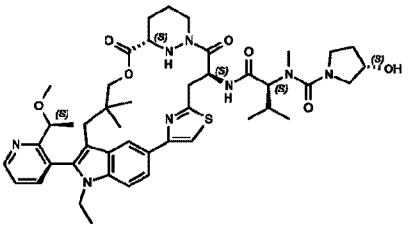
Ex#	Structure	Ex#	Structure
AA 64		AA 371	
AA 65		AA 372	
AA 66		AA 373	
AA 67		AA 374	
AA 68		AA 375	

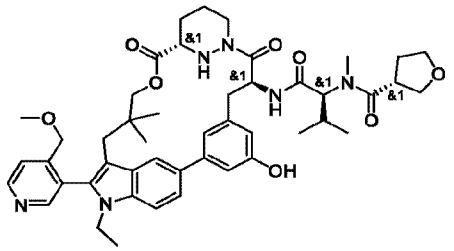
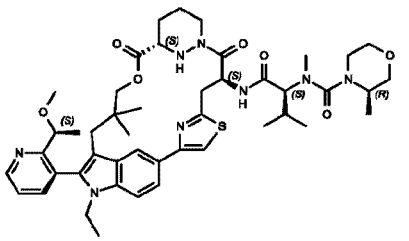
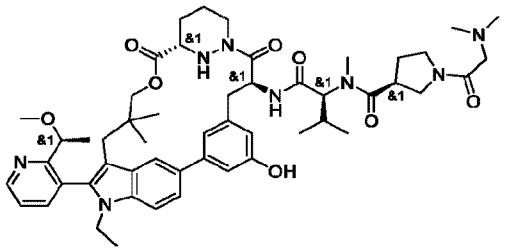
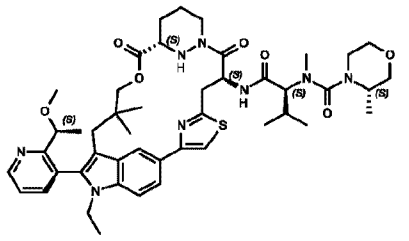
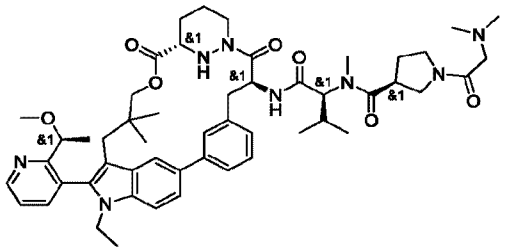
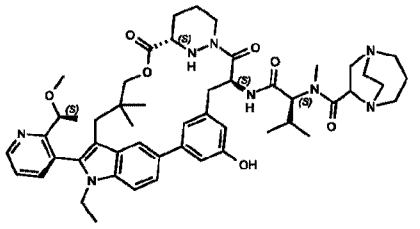
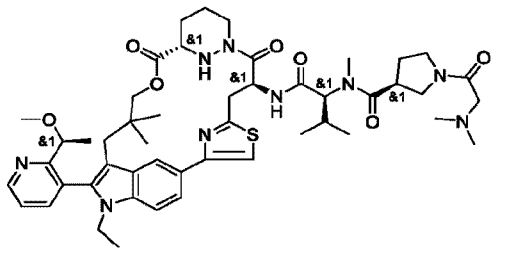
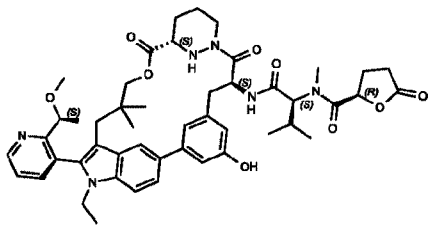
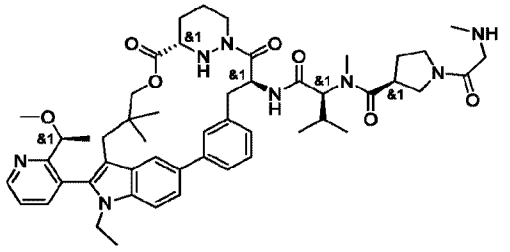
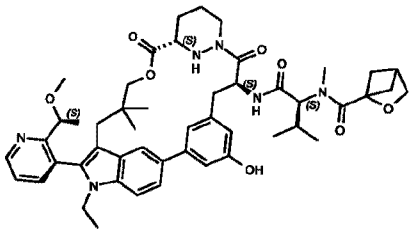
Ex#	Structure	Ex#	Structure
AA 69		AA 376	
AA 70		AA 377	
AA 71		AA 378	
AA 72		AA 379	
AA 73		AA 380	

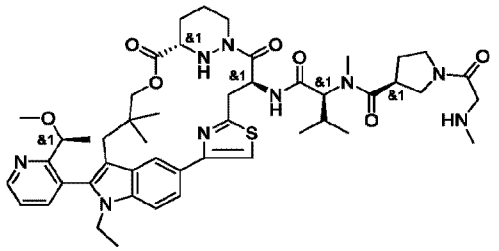
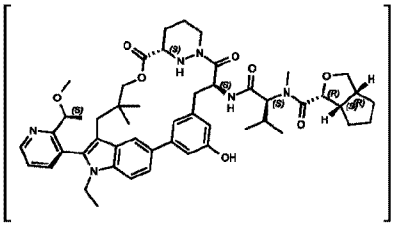
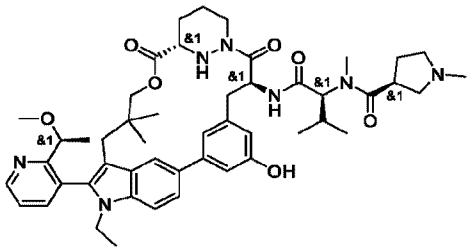
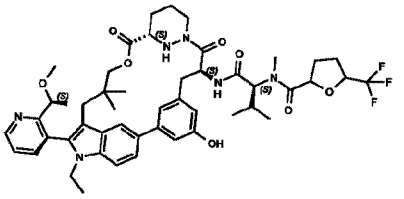
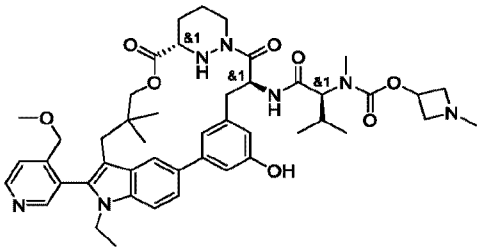
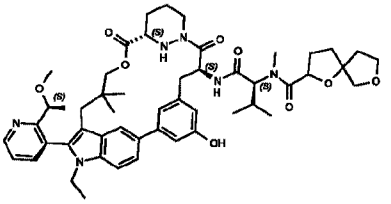
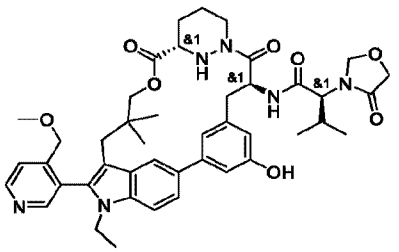
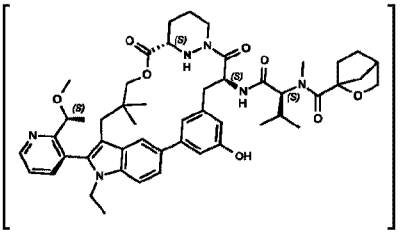
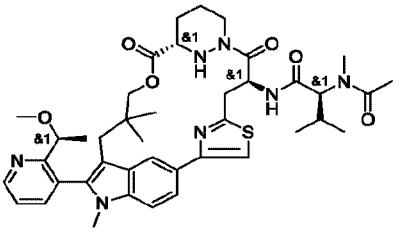
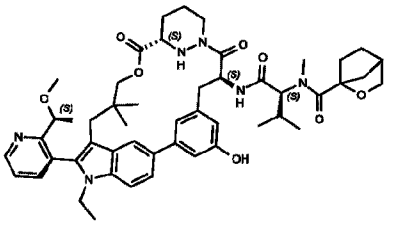
Ex#	Structure	Ex#	Structure
AA 74		AA 381	
AA 75		AA 382	
AA 76		AA 383	
AA 77		AA 384	
AA 78		AA 385	

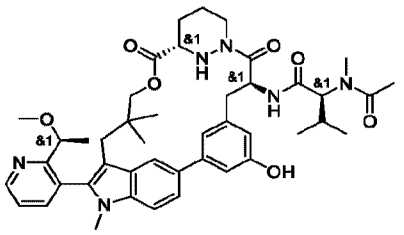
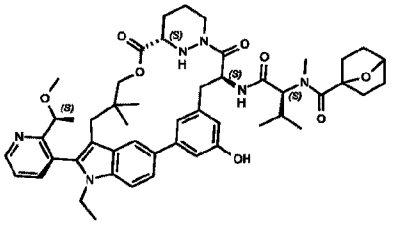
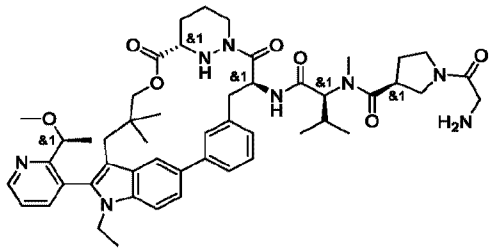
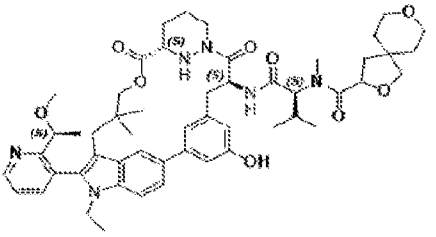
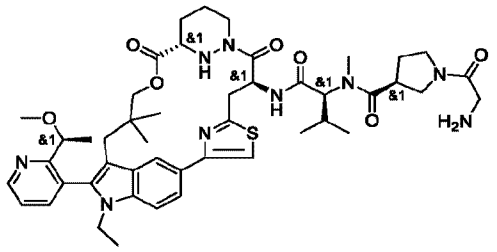
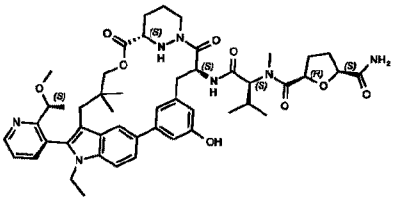
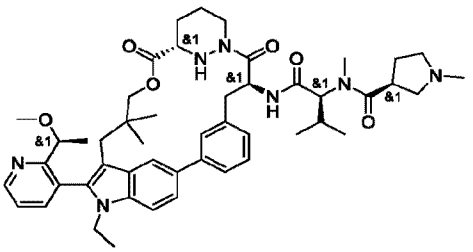
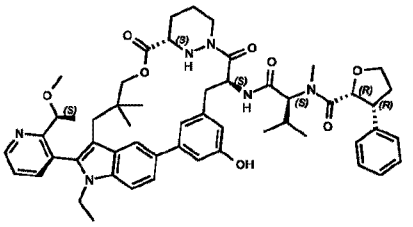
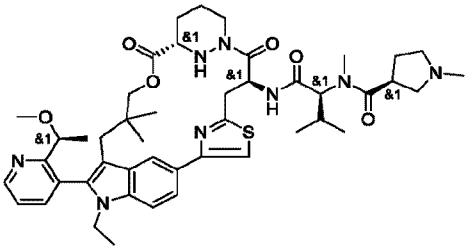
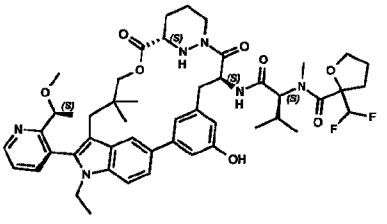
Ex#	Structure	Ex#	Structure
AA 79		AA 386	
AA 80		AA 387	
AA 81		AA 388	
AA 82		AA 389	
AA 83		AA 391	

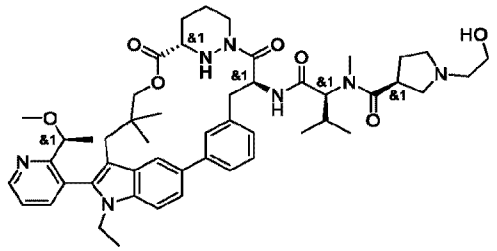
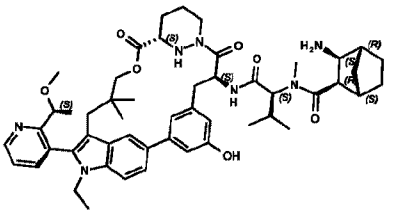
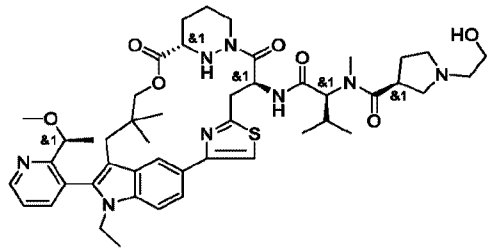
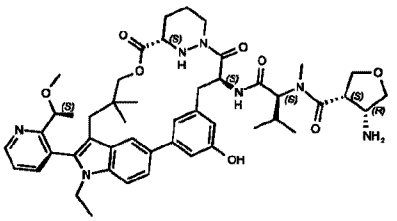
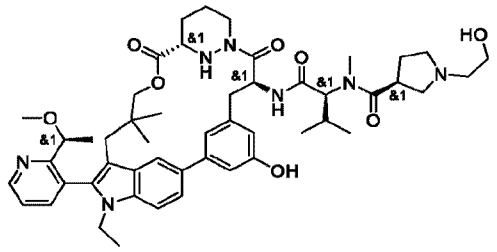
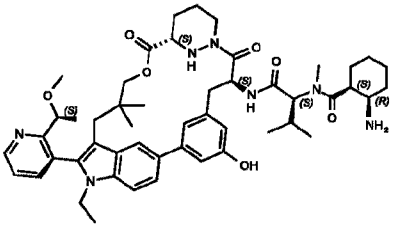
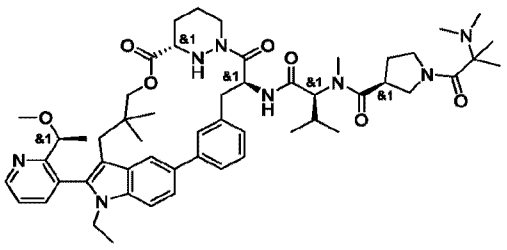
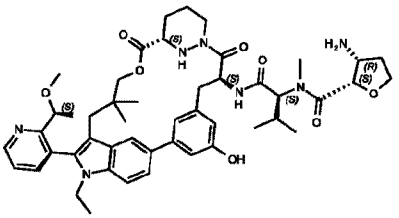
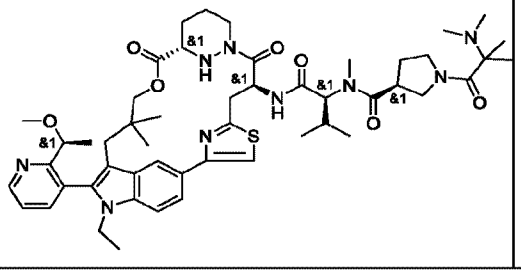
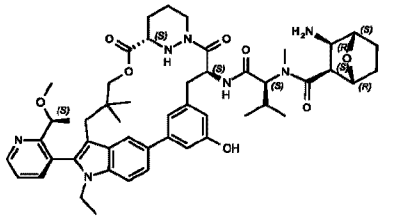
Ex#	Structure	Ex#	Structure
AA 84		AA 392	
AA 85		AA 393	
AA 86		AA 394	
AA 87		AA 395	
AA 88		AA 396	

Ex#	Structure	Ex#	Structure
AA 89		AA 397	
AA 90		AA 398	
AA 91		AA 399	
AA 92		AA 400	
AA 93		AA 401	

Ex#	Structure	Ex#	Structure
AA 94		AA 402	
AA 95		AA 403	
AA 96		AA 404	
AA 97		AA 405	
AA 98		AA 406	

Ex#	Structure	Ex#	Structure
AA 99		AA 407	
AA 100		AA 408	
AA 101		AA 409	
AA 102		AA 410	
AA 103		AA 411	

Ex#	Structure	Ex#	Structure
AA 104		AA 412	
AA 105		AA 413	
AA 106		AA 414	
AA 107		AA 415	
AA 108		AA 416	

Ex#	Structure	Ex#	Structure
AA 109		AA 417	
AA 110		AA 418	
AA 111		AA 419	
AA 112		AA 420	
AA 113		AA 421	

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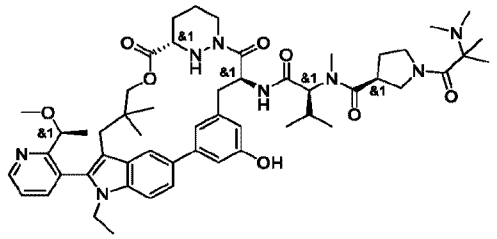
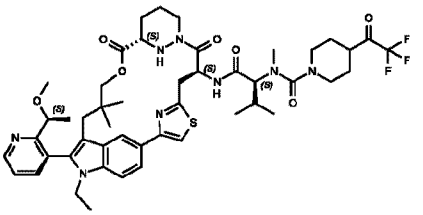
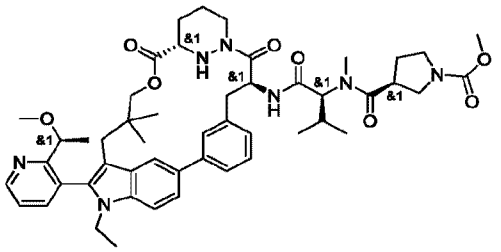
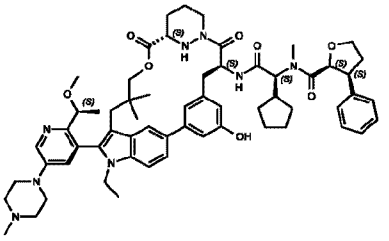
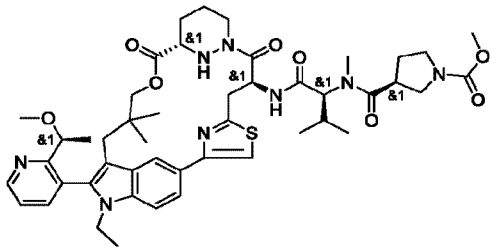
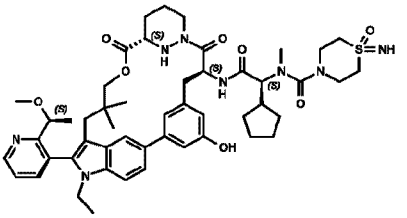
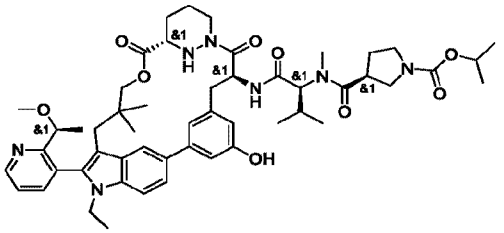
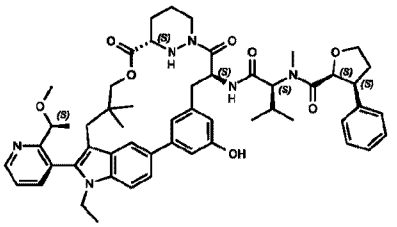
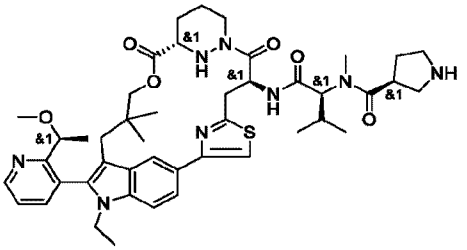
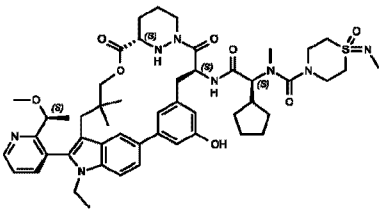
AA 114		AA 422	
AA 115		AA 423	
AA 116		AA 424	
AA 117		AA 425	
AA 118		AA 426	

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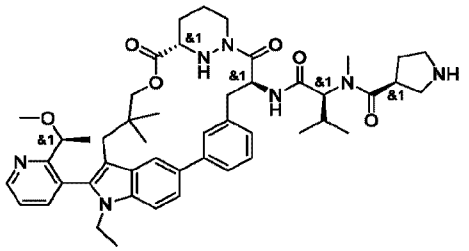
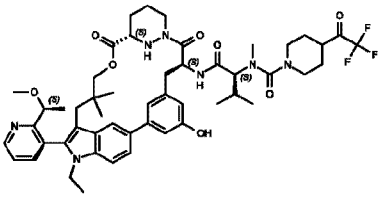
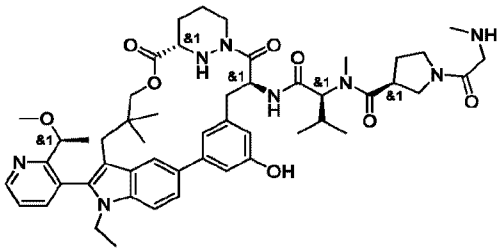
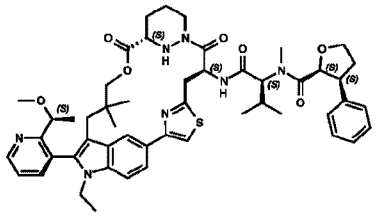
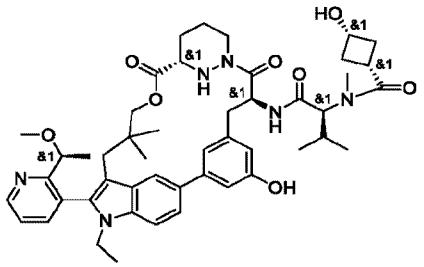
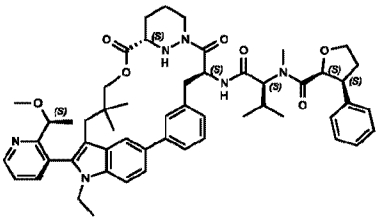
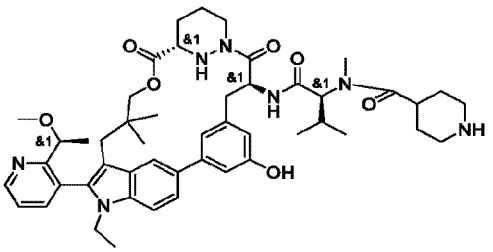
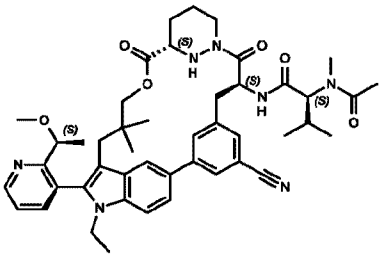
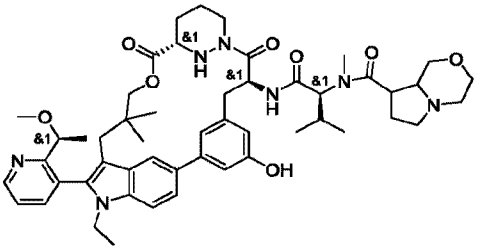
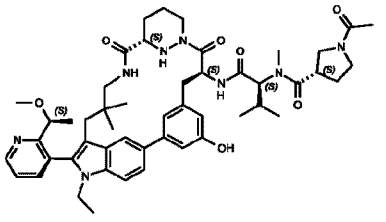
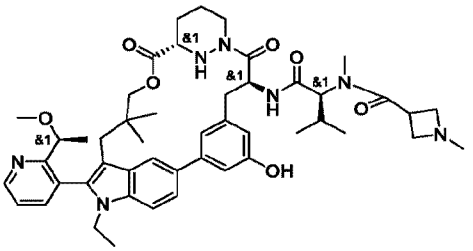
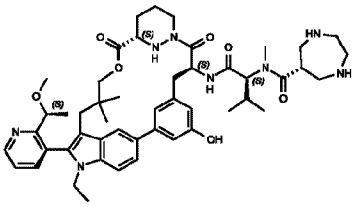
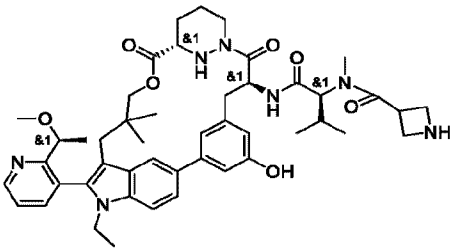
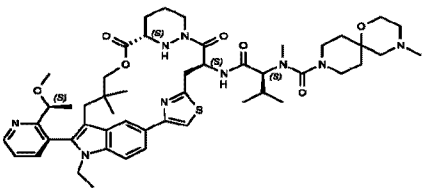
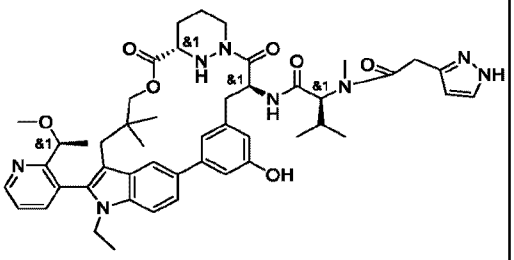
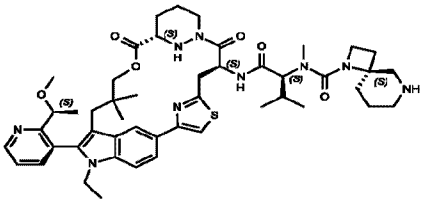
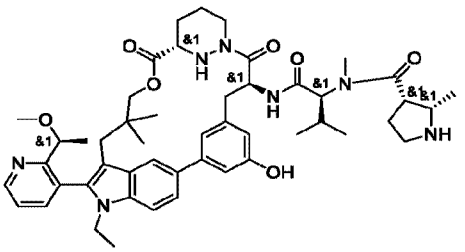
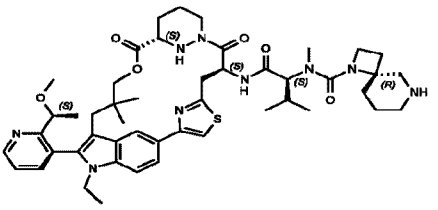
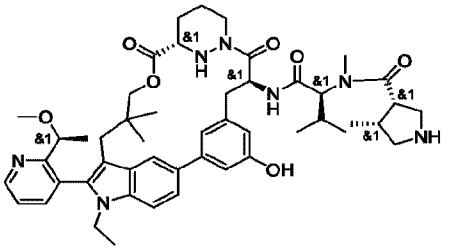
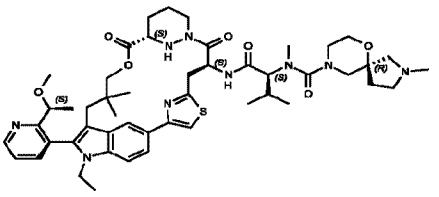
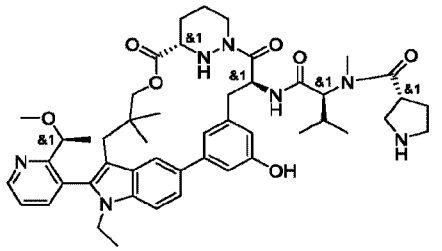
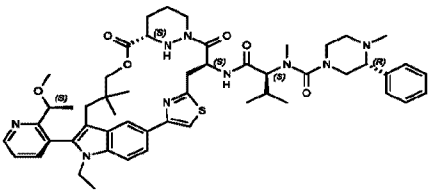
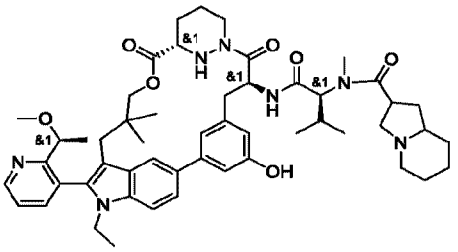
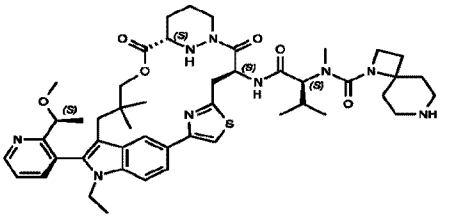
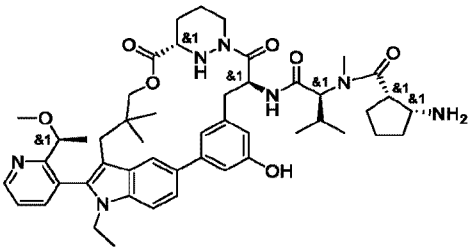
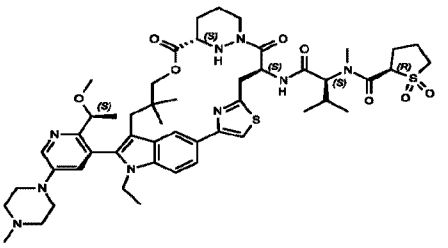
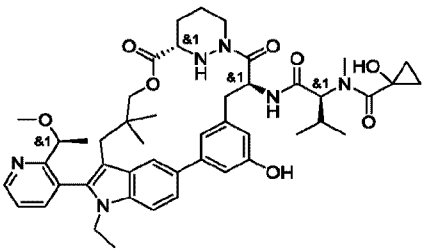
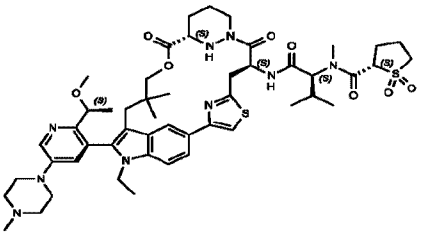
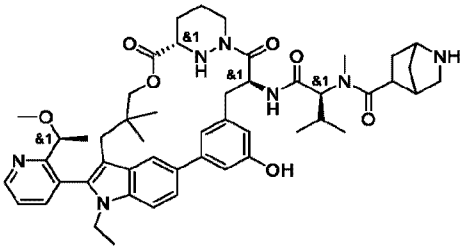
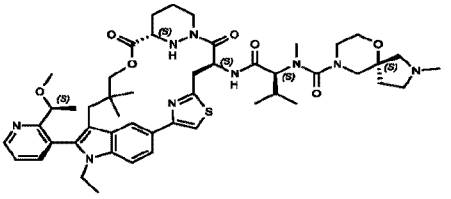
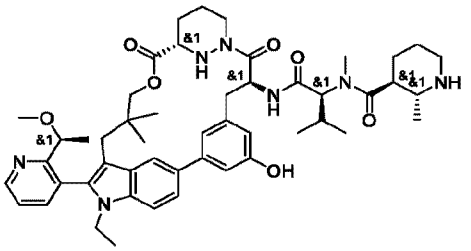
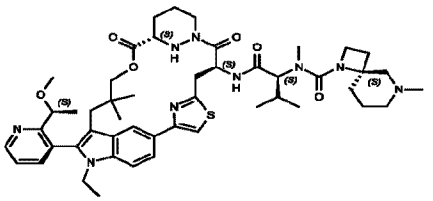
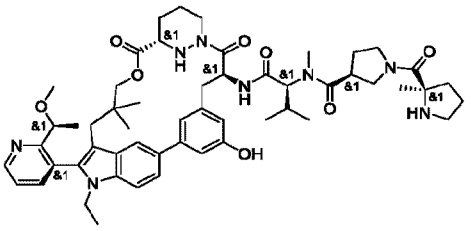
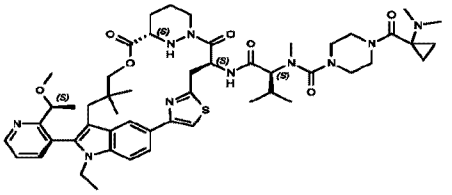
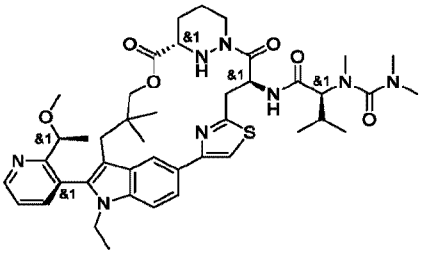
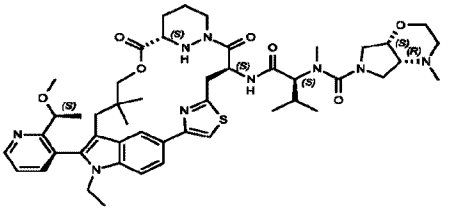
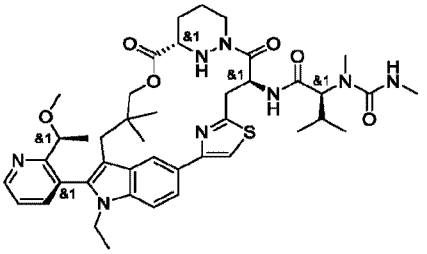
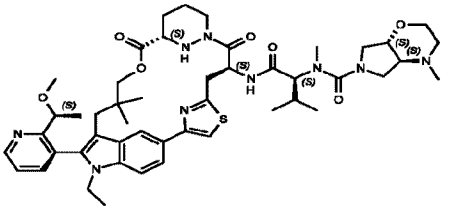
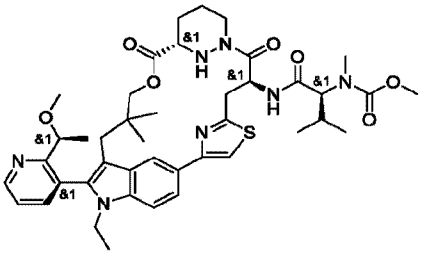
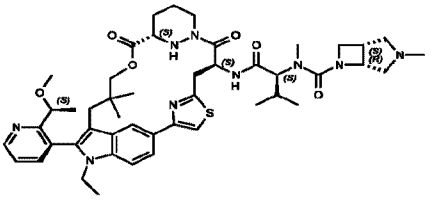
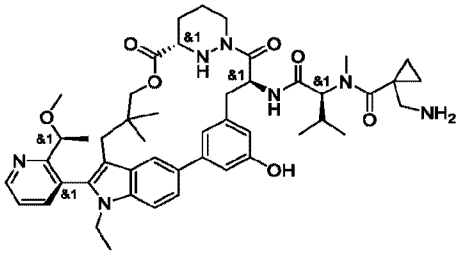
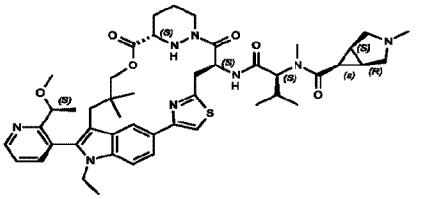
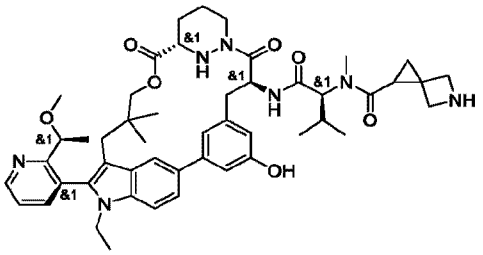
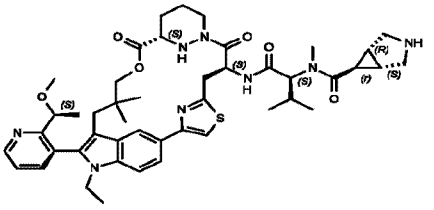
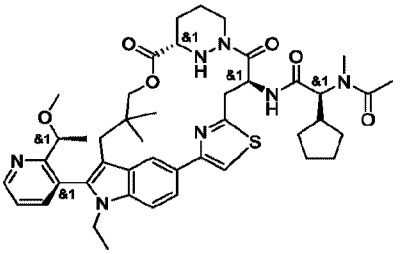
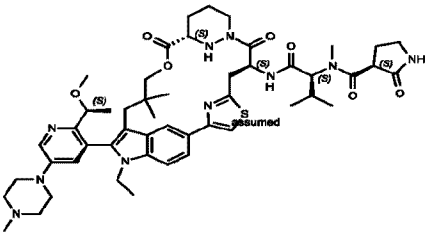
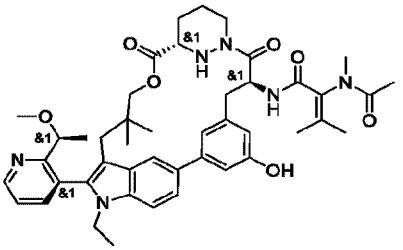
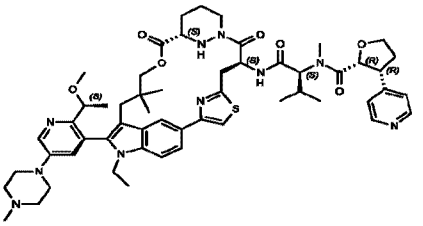
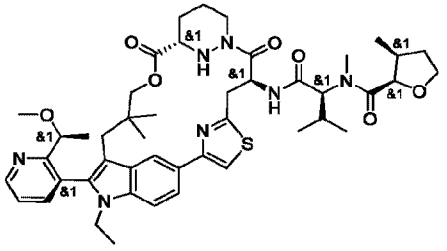
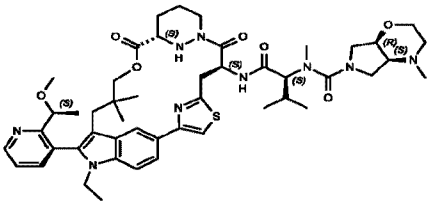
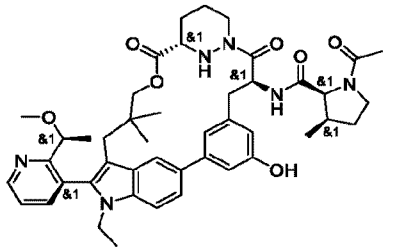
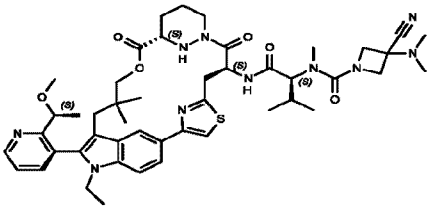
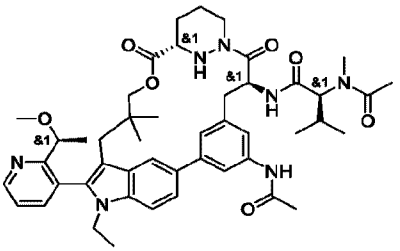
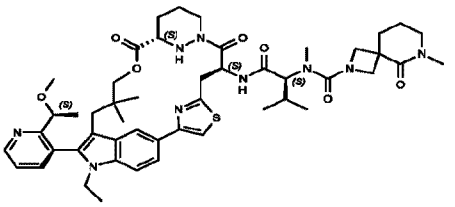
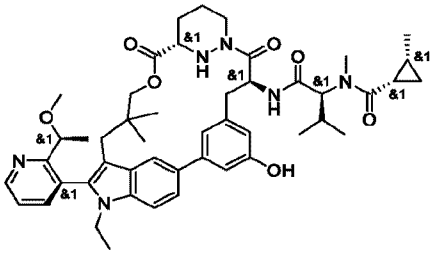
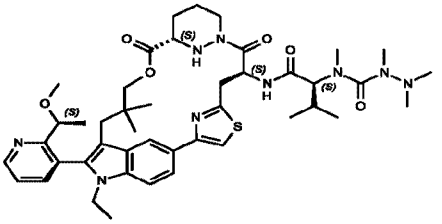
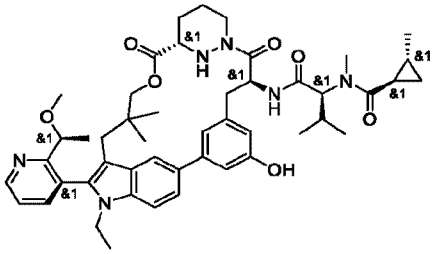
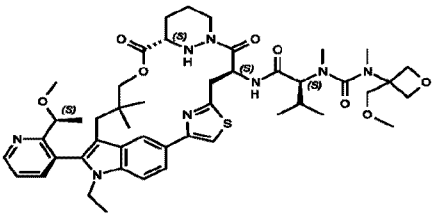
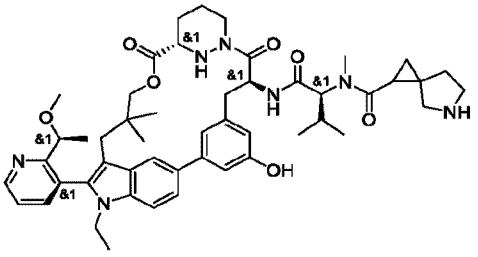
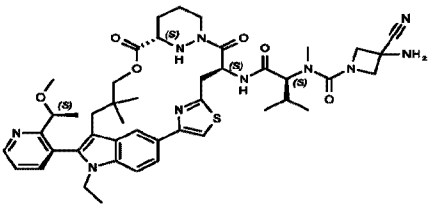
AA 119		AA 427	
AA 120		AA 428	
AA 121		AA 429	
AA 122		AA 430	
AA 123		AA 431	

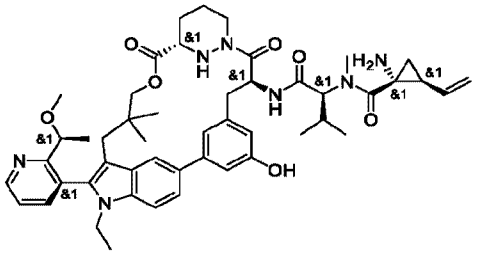
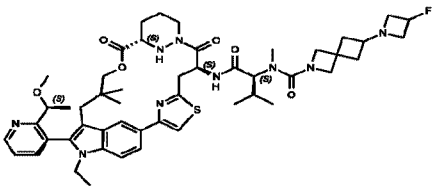
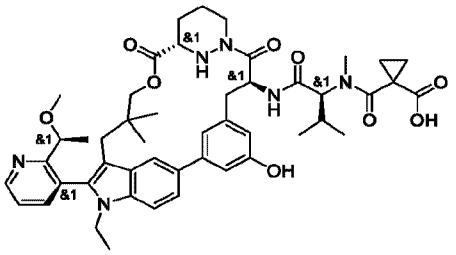
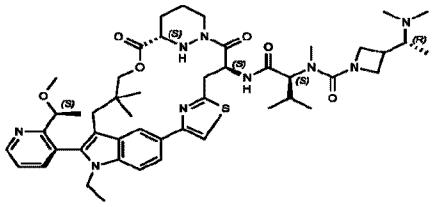
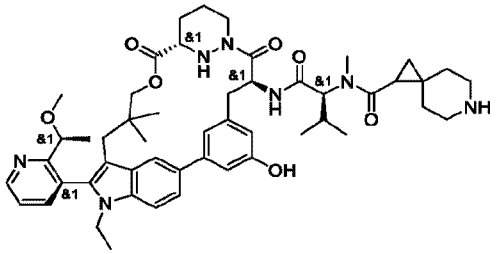
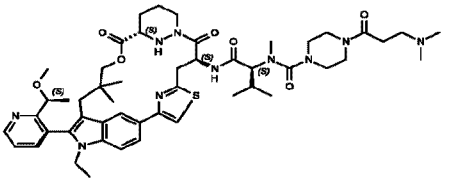
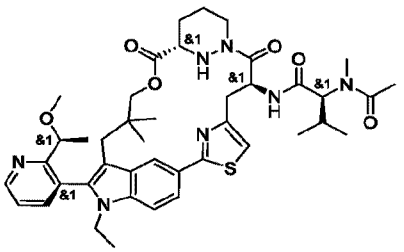
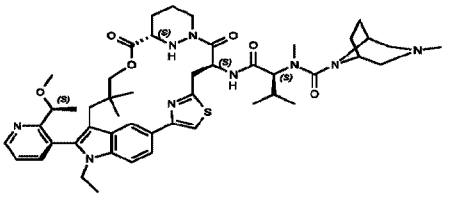
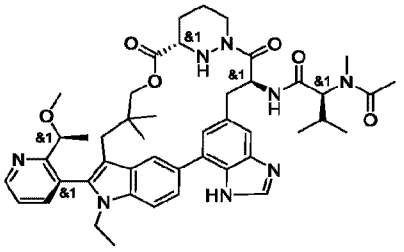
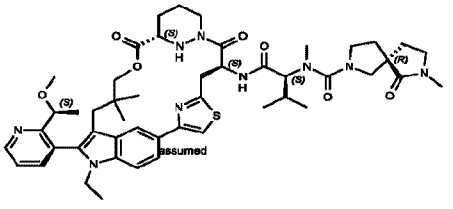
Ex#	Structure	Ex#	Structure
AA 124		AA 432	
AA 125		AA 433	
AA 126		AA 434	
AA 127		AA 435	
AA 128		AA 436	

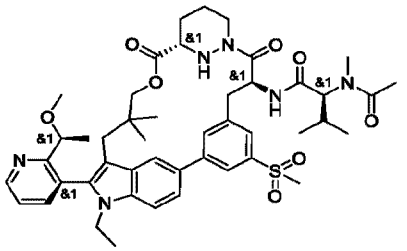
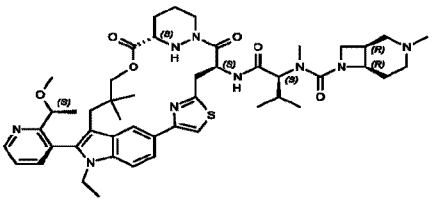
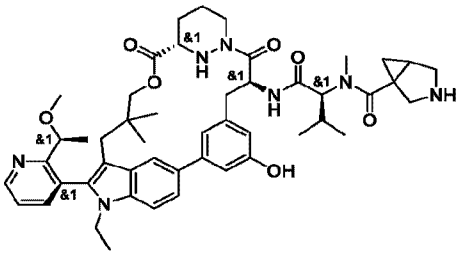
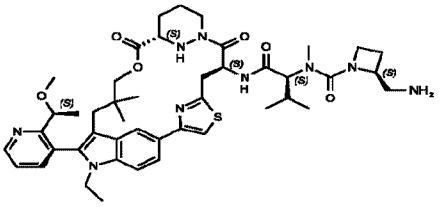
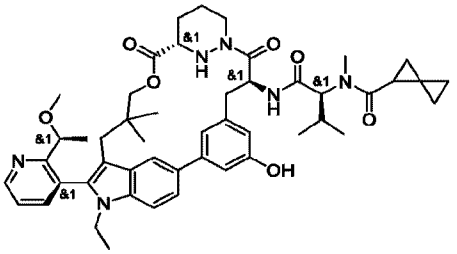
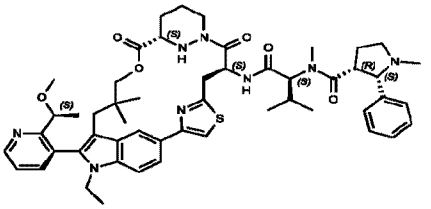
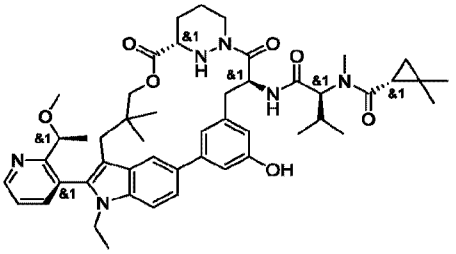
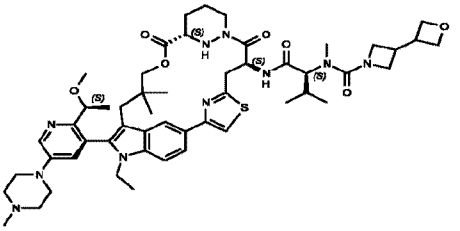
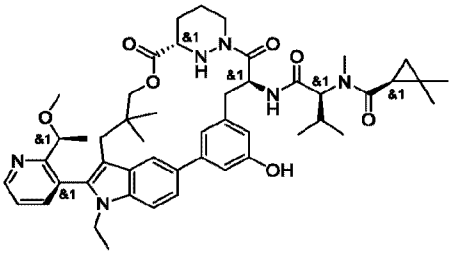
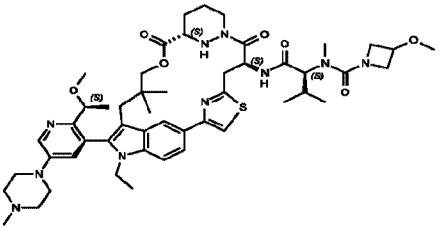
Ex#	Structure	Ex#	Structure
AA 129		AA 437	
AA 130		AA 438	
AA 131		AA 439	
AA 132		AA 440	
AA 133		AA 441	

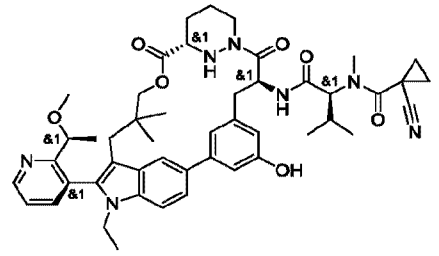
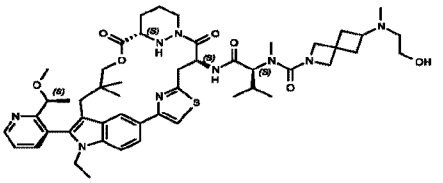
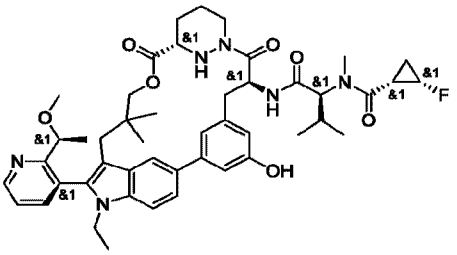
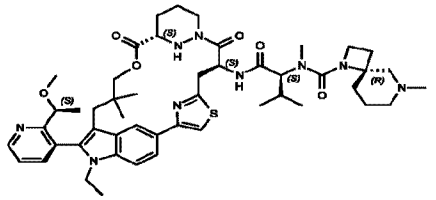
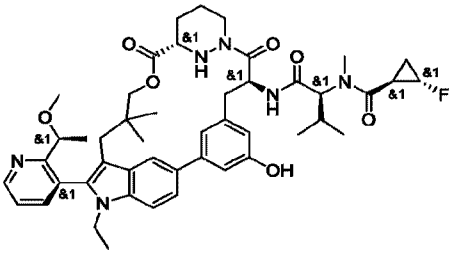
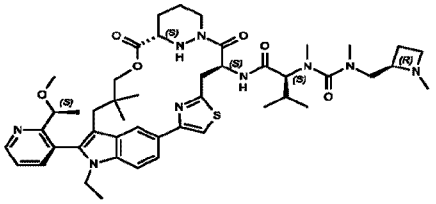
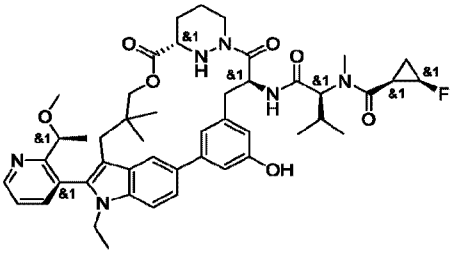
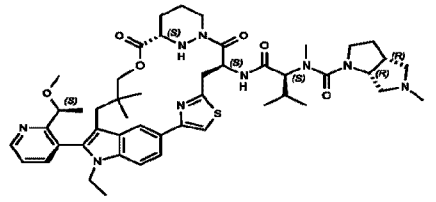
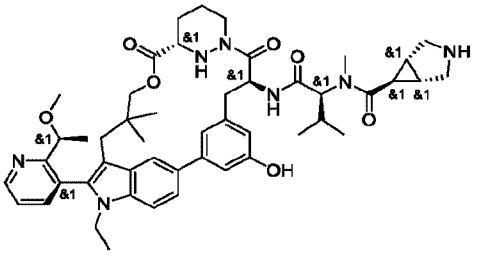
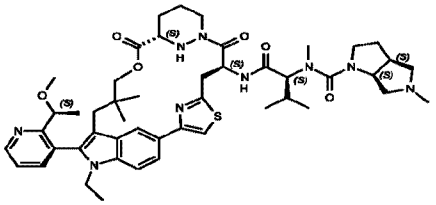
Ex#	Structure	Ex#	Structure
AA 134		AA 442	
AA 135		AA 443	
AA 136		AA 444	
AA 137		AA 445	
AA 138		AA 446	

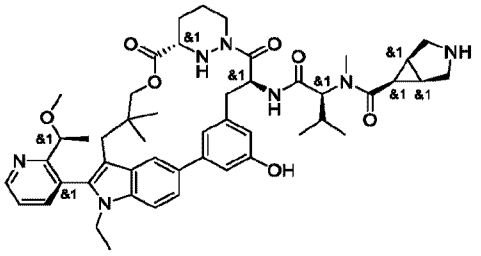
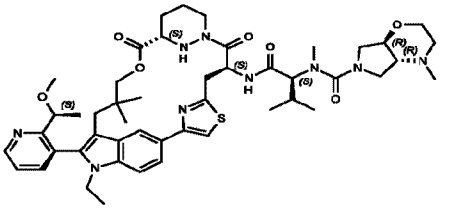
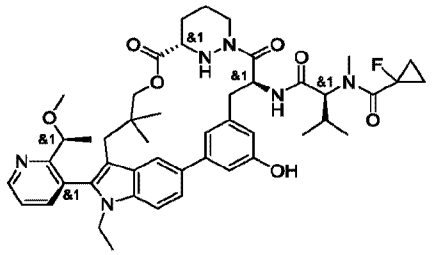
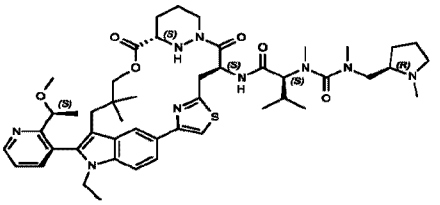
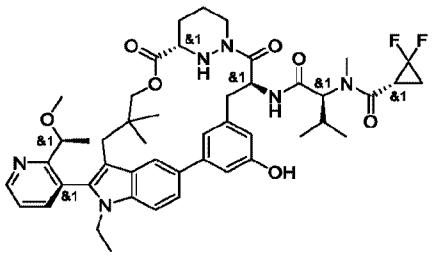
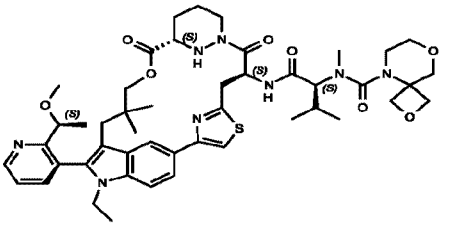
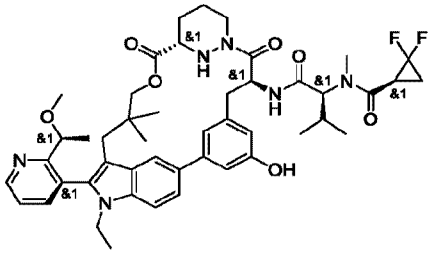
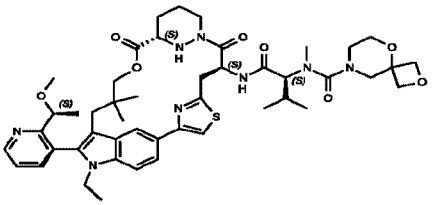
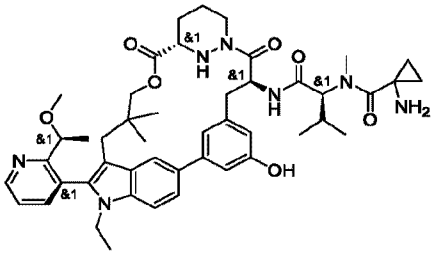
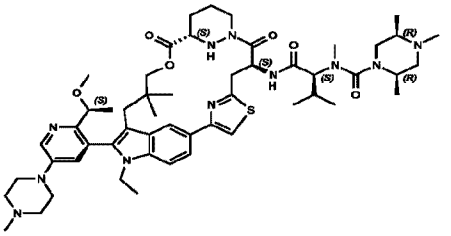
Ex#	Structure	Ex#	Structure
AA 139		AA 447	
AA 140		AA 448	
AA 141		AA 449	
AA 142		AA 450	
AA 143		AA 451	

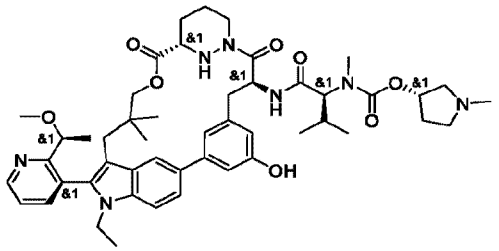
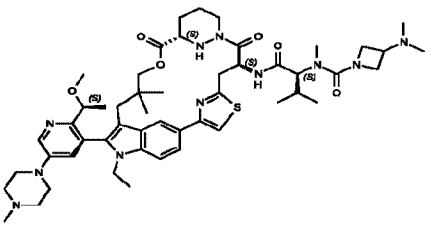
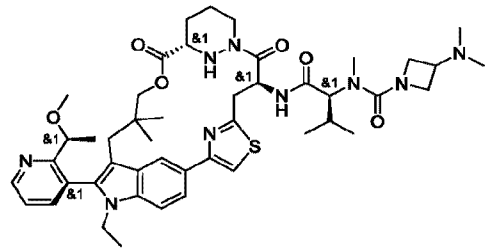
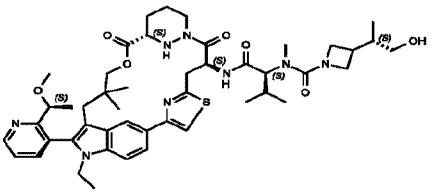
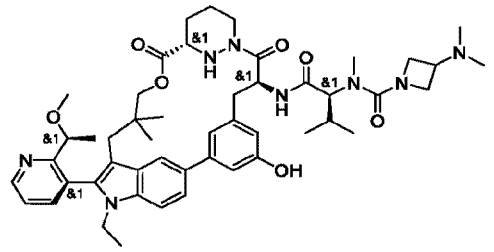
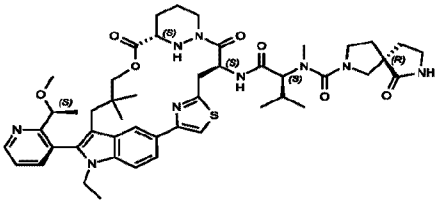
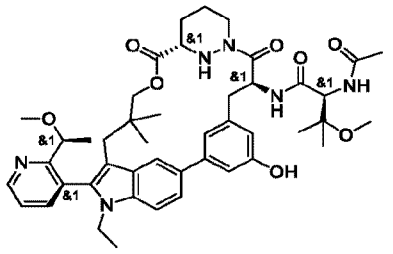
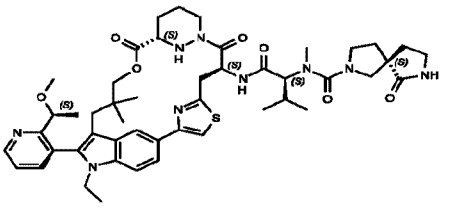
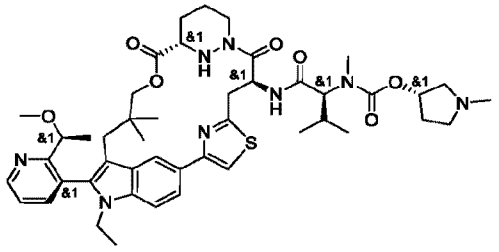
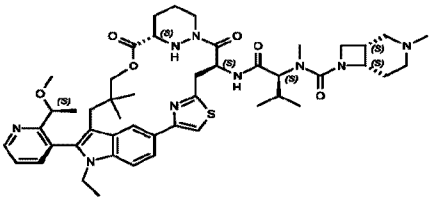
Ex#	Structure	Ex#	Structure
AA 144		AA 452	
AA 145		AA 453	
AA 146		AA 454	
AA 147		AA 455	
AA 148		AA 456	

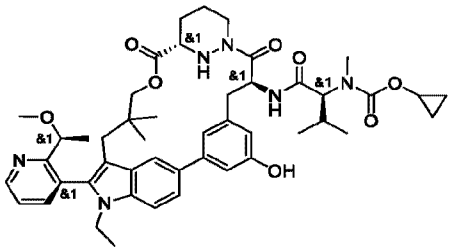
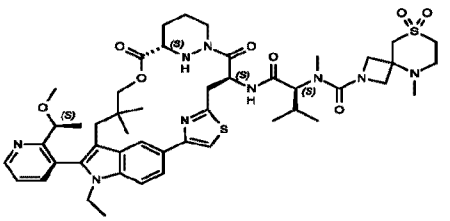
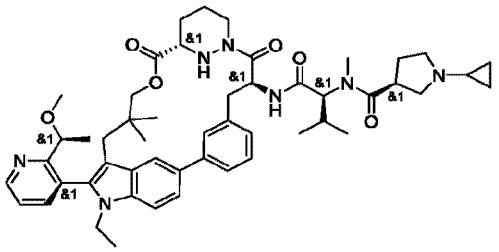
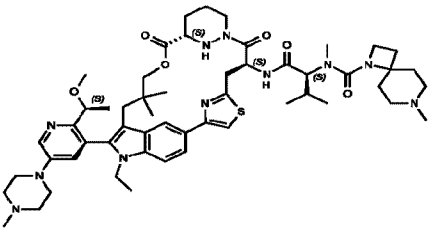
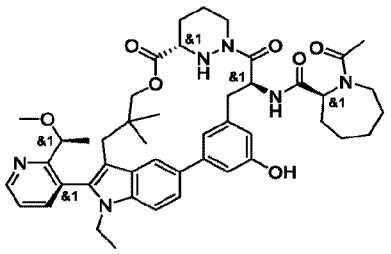
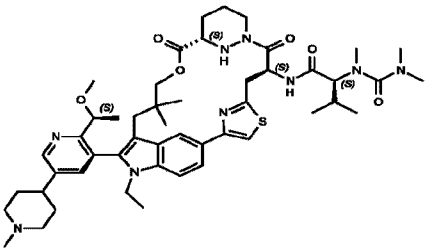
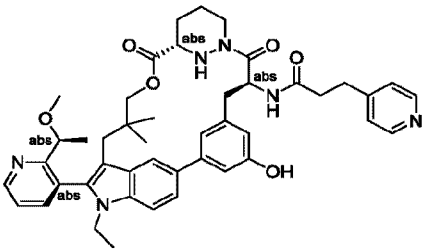
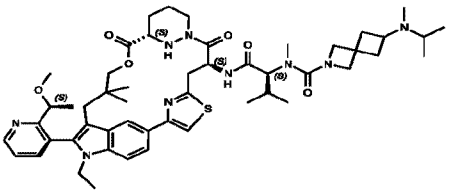
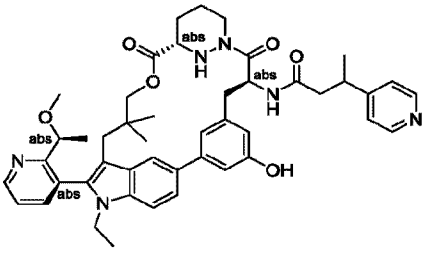
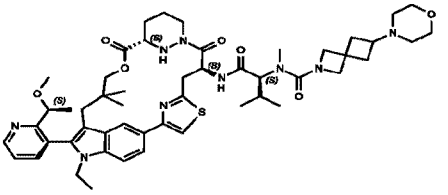
Ex#	Structure	Ex#	Structure
AA 149		AA 457	
AA 150		AA 458	
AA 151		AA 459	
AA 152		AA 460	
AA 153		AA 461	

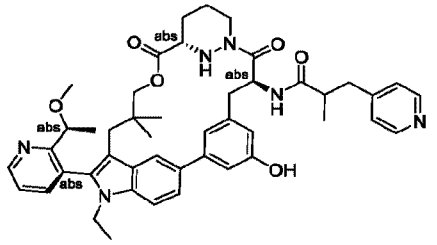
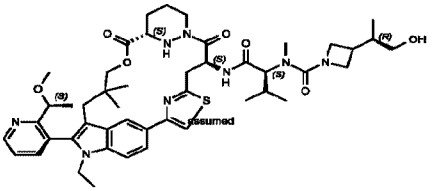
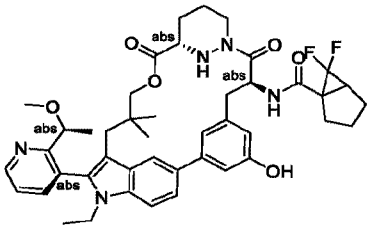
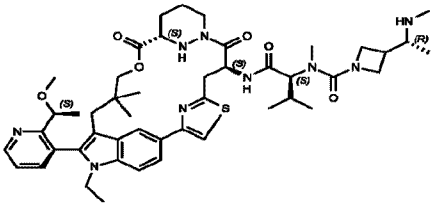
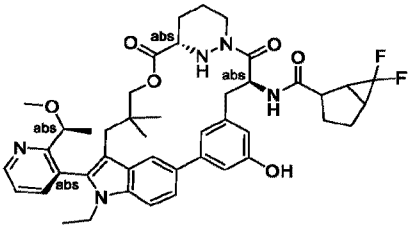
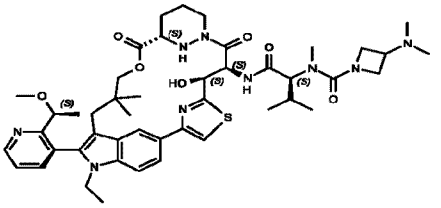
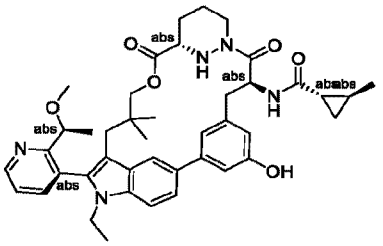
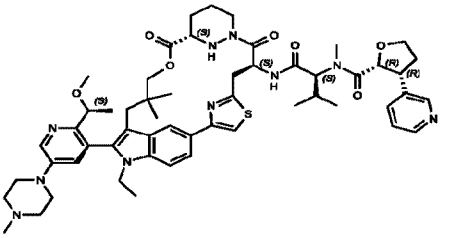
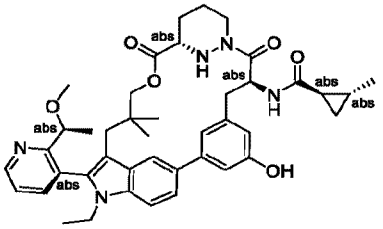
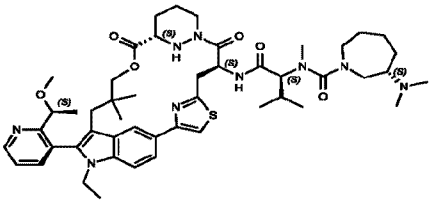
Ex#	Structure	Ex#	Structure
AA 154		AA 462	
AA 155		AA 463	
AA 156		AA 464	
AA 157		AA 465	
AA 158		AA 466	

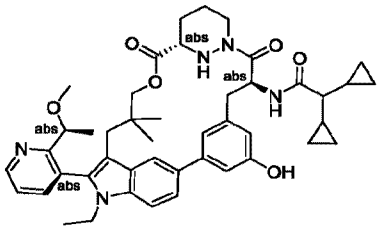
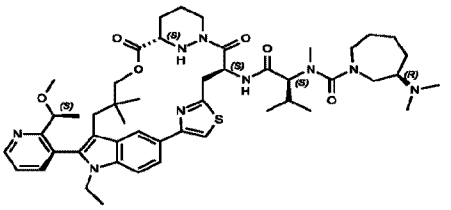
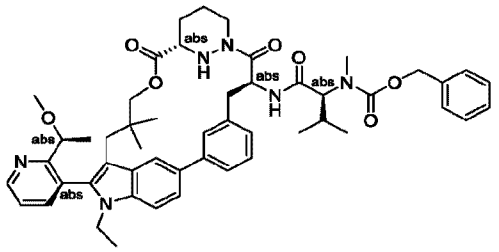
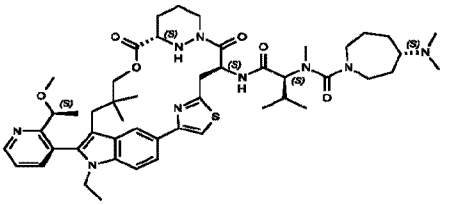
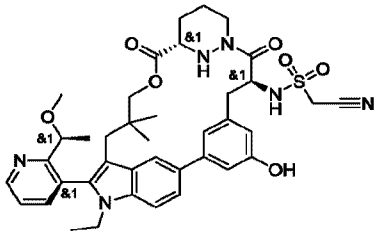
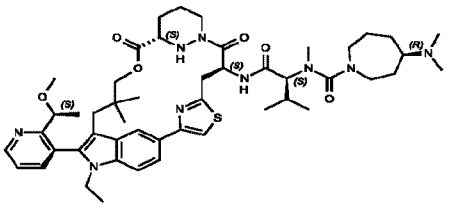
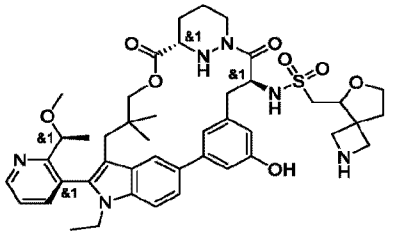
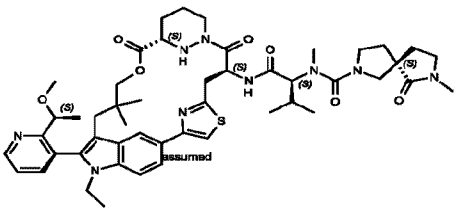
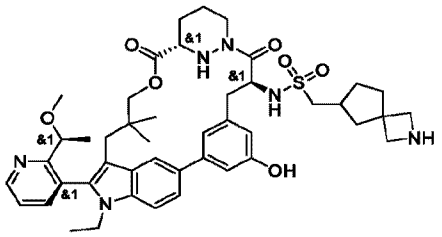
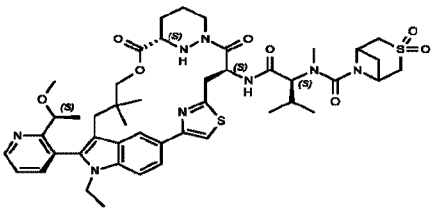
Ex#	Structure	Ex#	Structure
AA 159		AA 467	
AA 160		AA 468	
AA 161		AA 469	
AA 162		AA 470	
AA 163		AA 471	

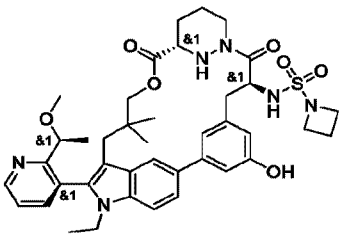
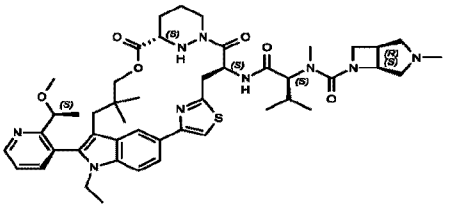
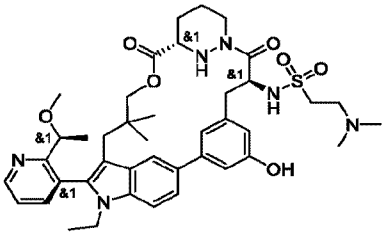
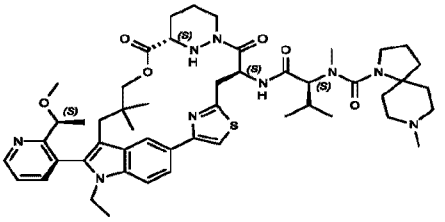
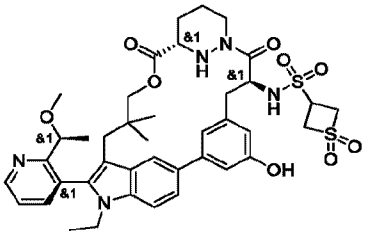
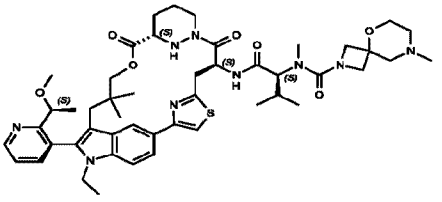
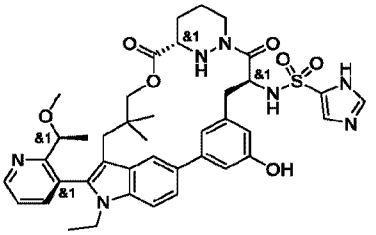
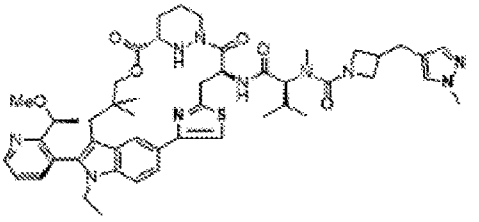
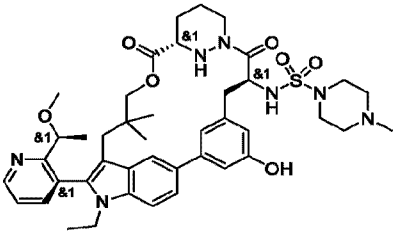
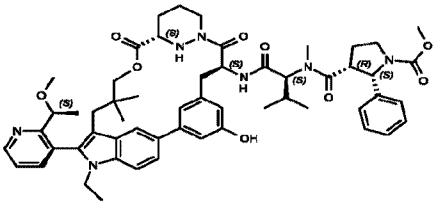
Ex#	Structure	Ex#	Structure
AA 164		AA 472	
AA 165		AA 473	
AA 166		AA 474	
AA 167		AA 475	
AA 168		AA 476	

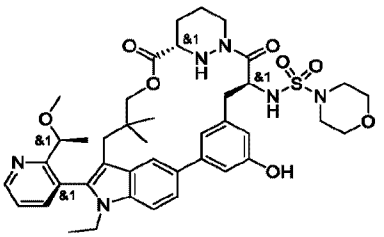
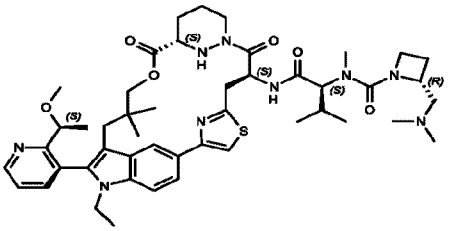
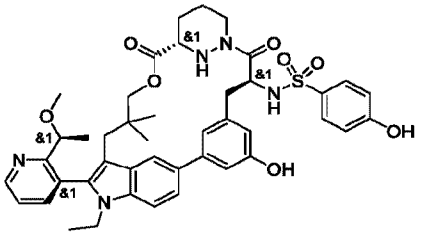
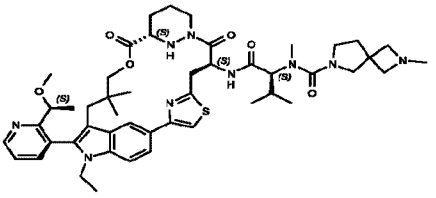
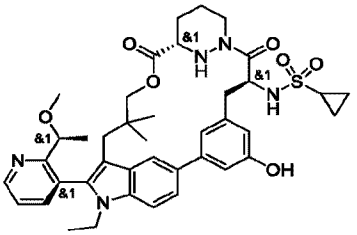
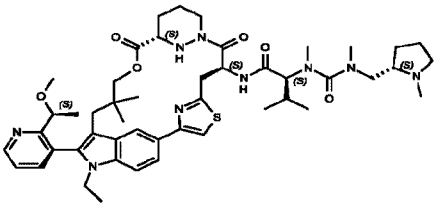
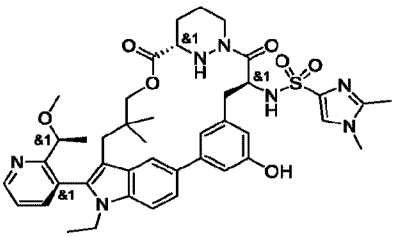
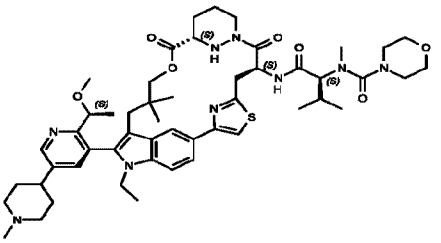
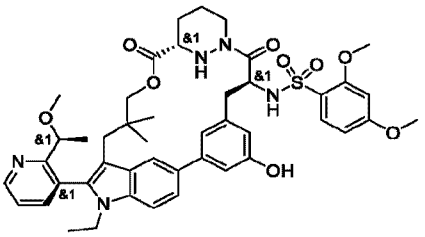
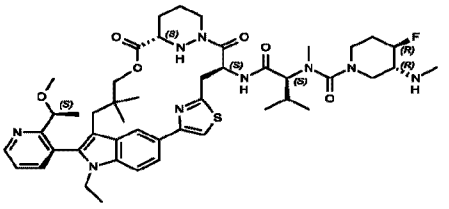
Ex#	Structure	Ex#	Structure
AA 169		AA 477	
AA 170		AA 478	
AA 171		AA 479	
AA 172		AA 480	
AA 173		AA 481	

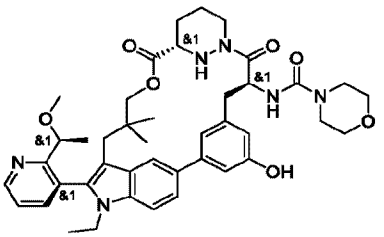
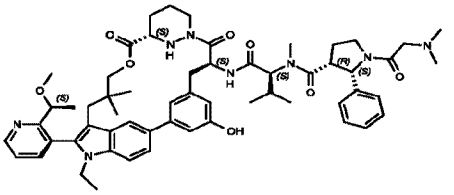
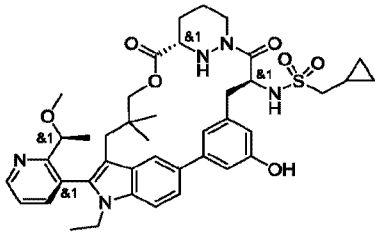
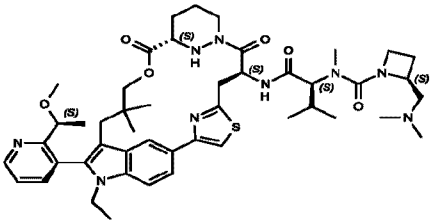
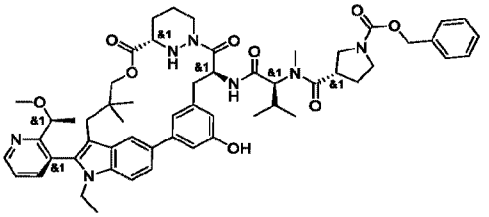
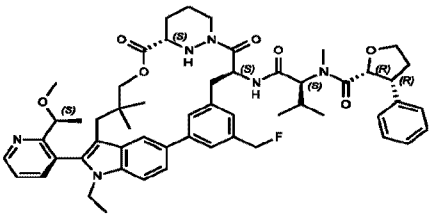
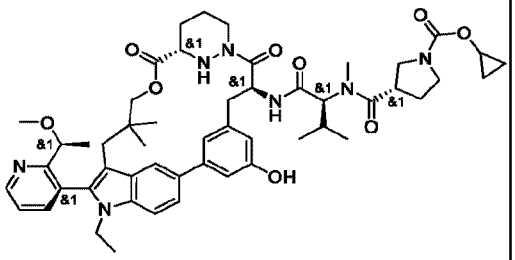
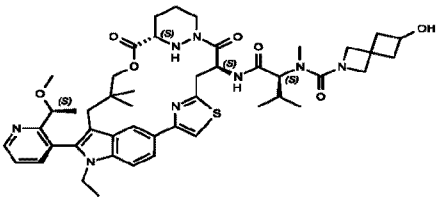
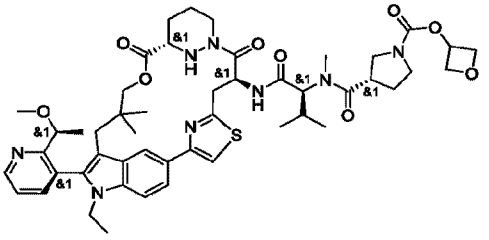
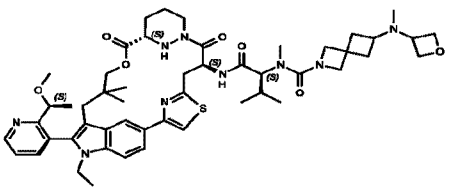
Ex#	Structure	Ex#	Structure
AA 174		AA 482	
AA 175		AA 483	
AA 176		AA 484	
AA 177		AA 485	
AA 178		AA 486	

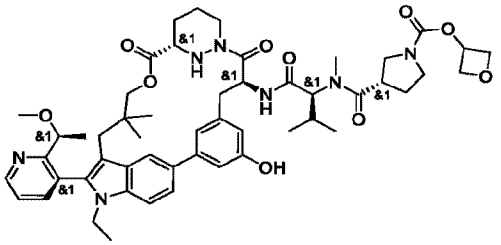
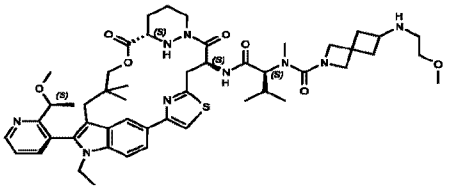
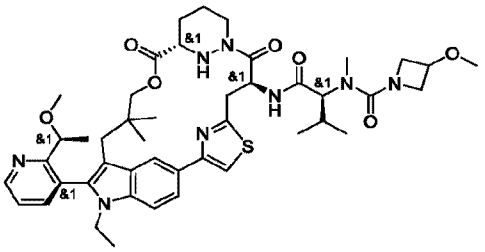
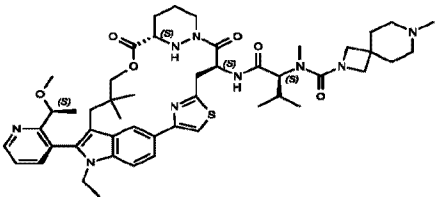
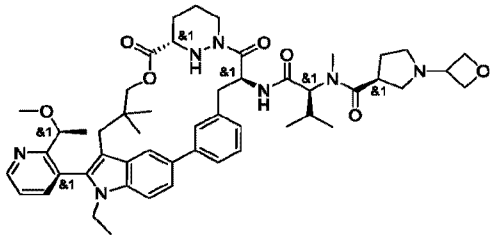
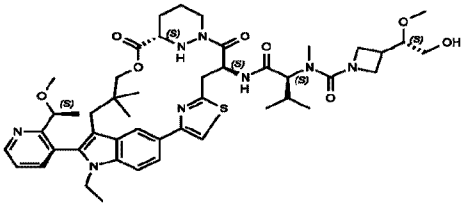
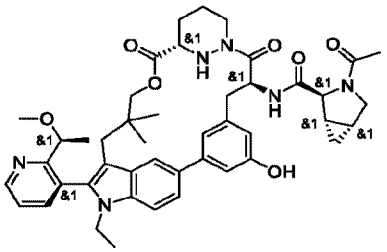
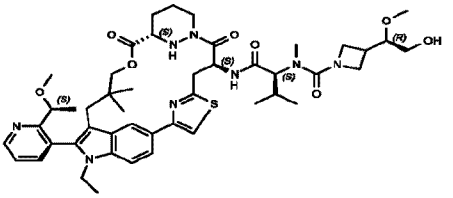
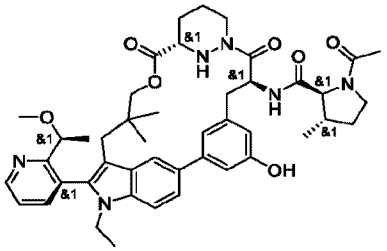
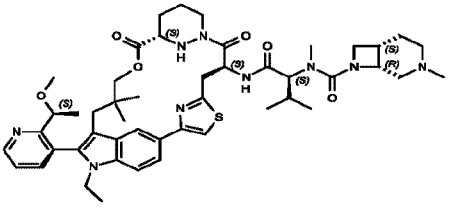
Ex#	Structure	Ex#	Structure
AA 179		AA 487	
AA 180		AA 488	
AA 181		AA 489	
AA 182		AA 490	
AA 183		AA 491	

Ex#	Structure	Ex#	Structure
AA 184		AA 492	
AA 185		AA 493	
AA 186		AA 494	
AA 187		AA 495	
AA 188		AA 496	

Ex#	Structure	Ex#	Structure
AA 189		AA 497	
AA 190		AA 498	
AA 191		AA 499	
AA 192		AA 500	
AA 193		AA 501	

Ex#	Structure	Ex#	Structure
AA 194		AA 502	
AA 195		AA 503	
AA 196		AA 504	
AA 197		AA 505	
AA 198		AA 506	

Ex#	Structure	Ex#	Structure
AA 199		AA 507	
AA 200		AA 508	
AA 201		AA 509	
AA 202		AA 510	
AA 203		AA 511	

Ex#	Structure	Ex#	Structure
AA 204		AA 512	
AA 205		AA 513	
AA 206		AA 514	
AA 207		AA 515	
AA 208		AA 516	

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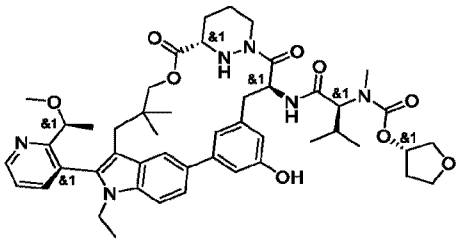
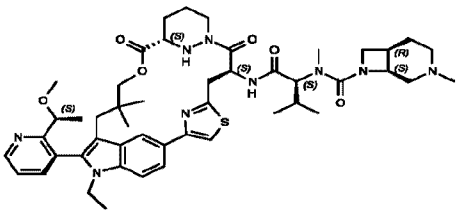
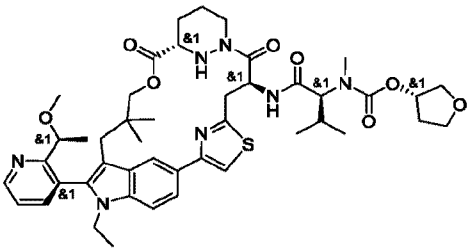
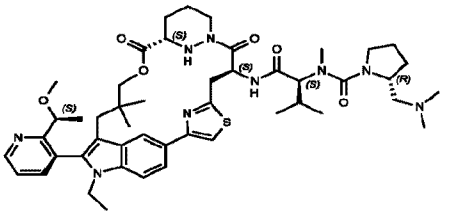
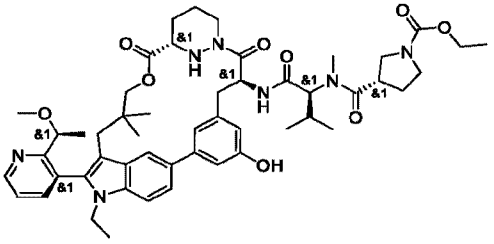
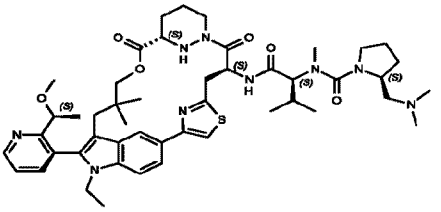
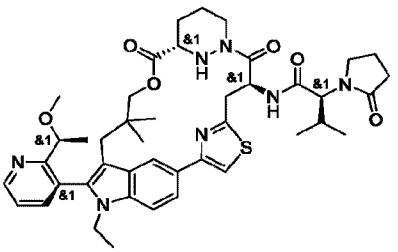
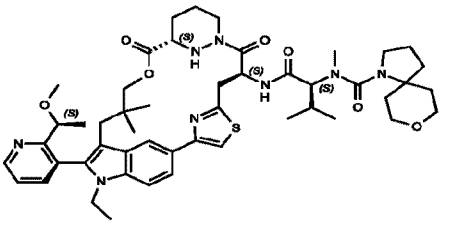
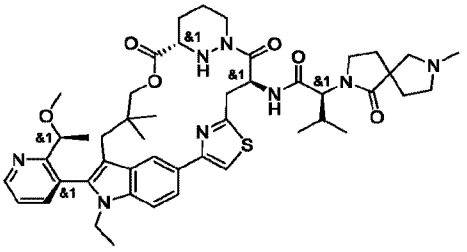
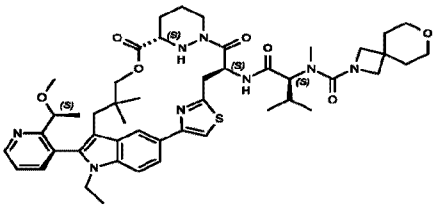
AA 209		AA 517	
AA 210		AA 518	
AA 211		AA 519	
AA 212		AA 520	
AA 213		AA 521	

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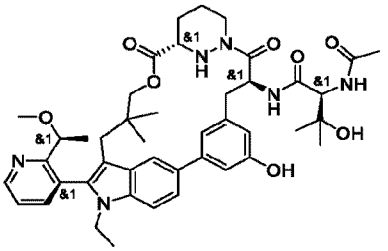
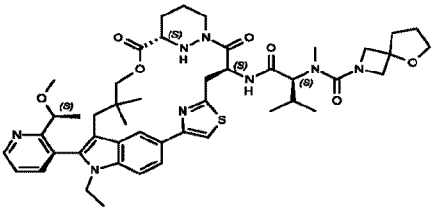
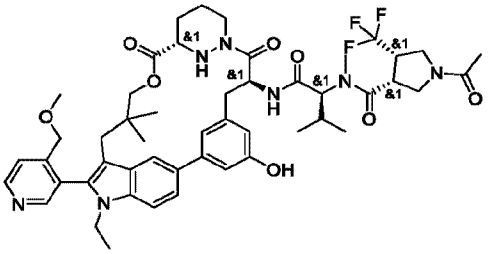
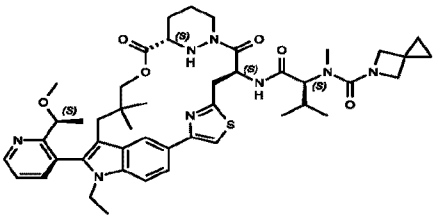
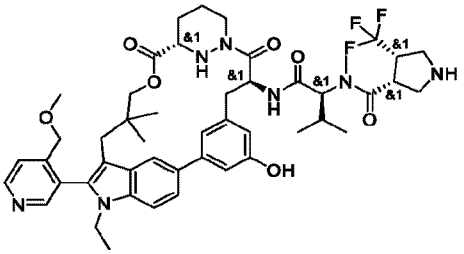
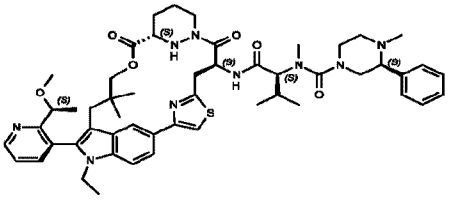
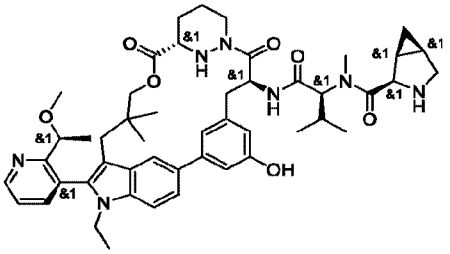
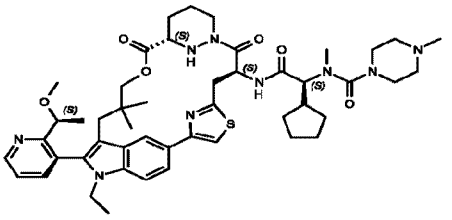
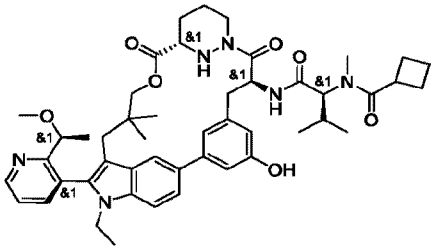
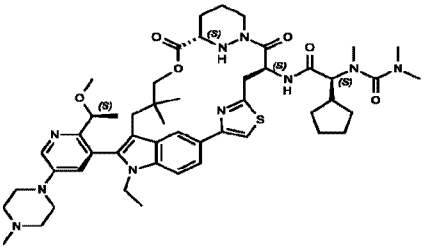
AA 214		AA 522	
AA 215		AA 523	
AA 216		AA 524	
AA 217		AA 525	
AA 218		AA 526	

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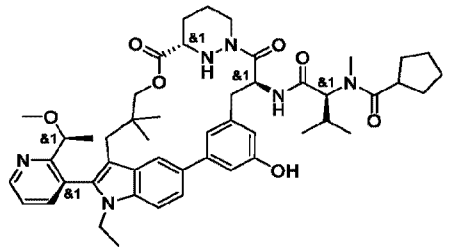
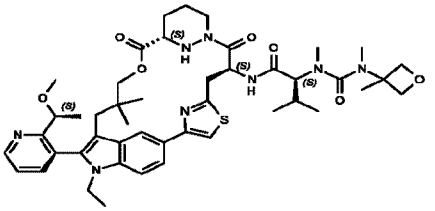
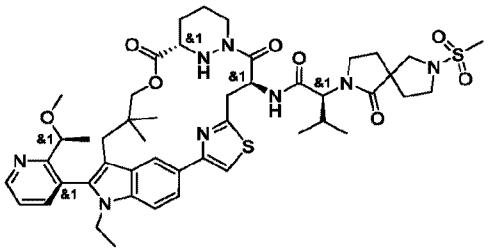
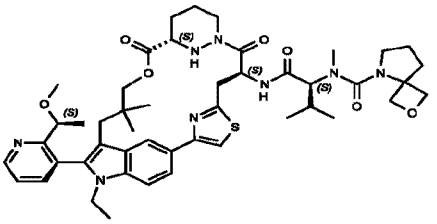
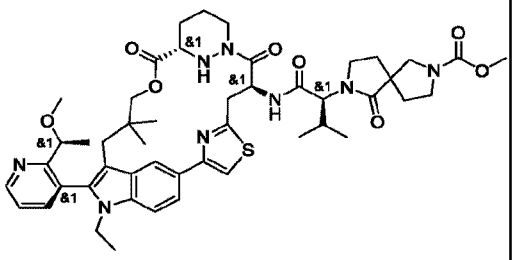
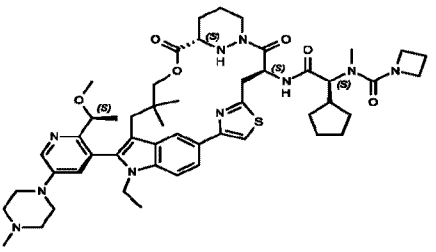
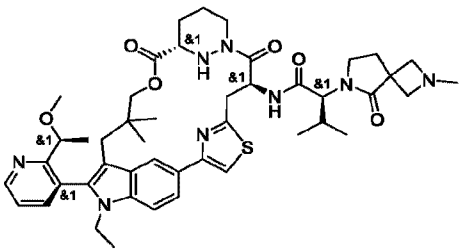
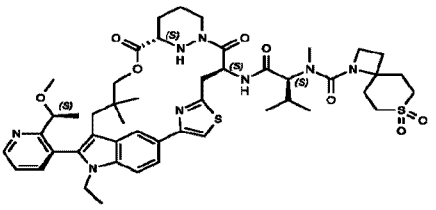
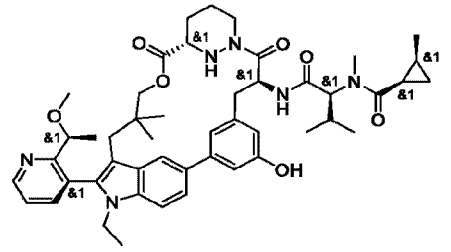
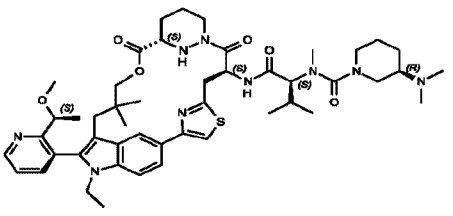
AA 219		AA 527	
AA 220		AA 528	
AA 221		AA 529	
AA 222		AA 530	
AA 223		AA 531	

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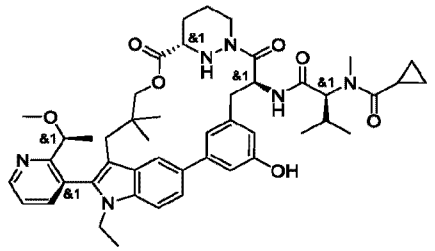
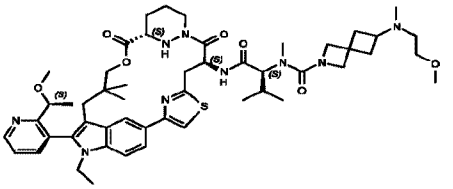
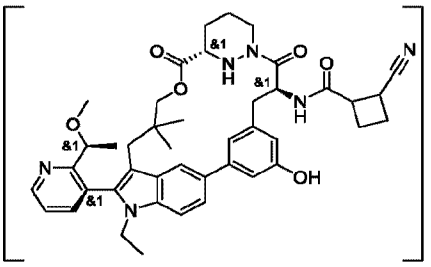
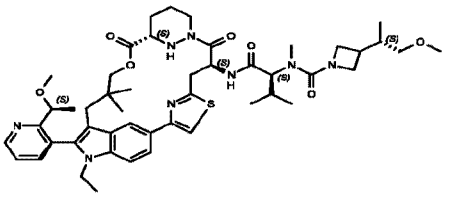
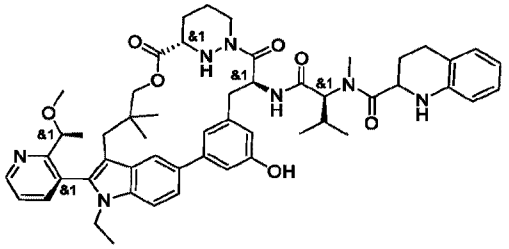
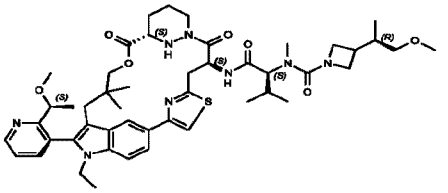
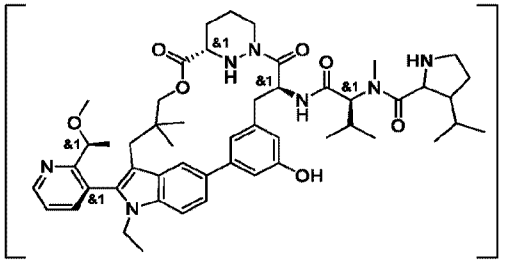
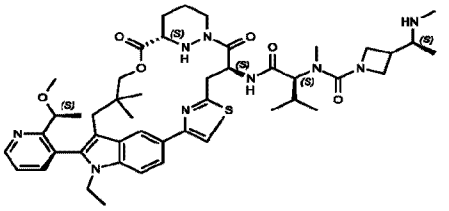
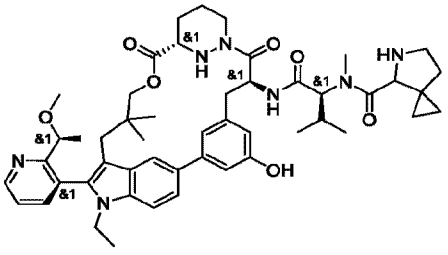
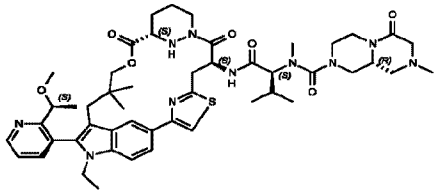
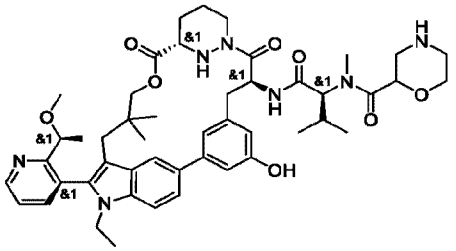
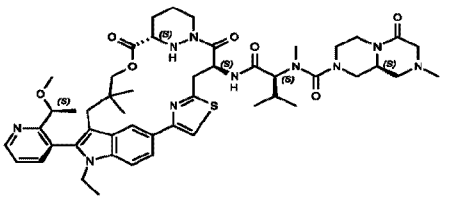
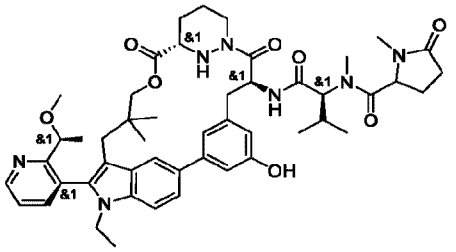
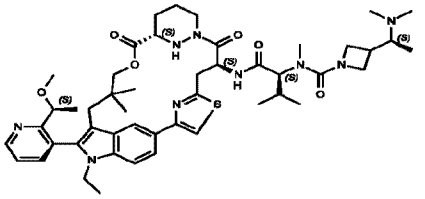
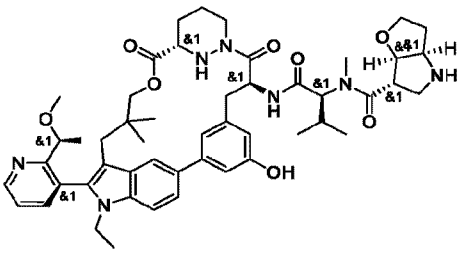
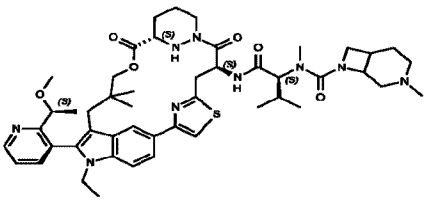
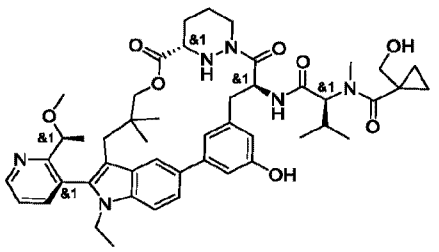
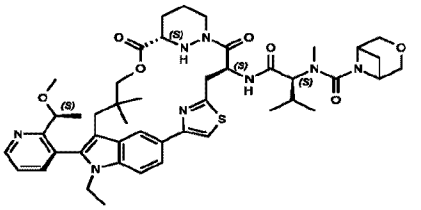
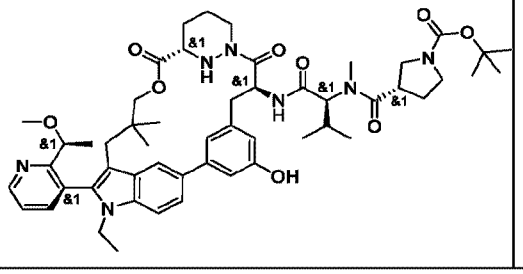
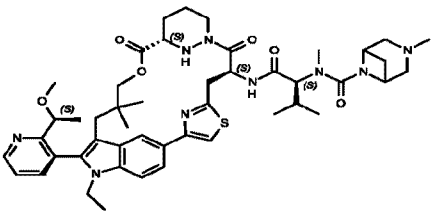
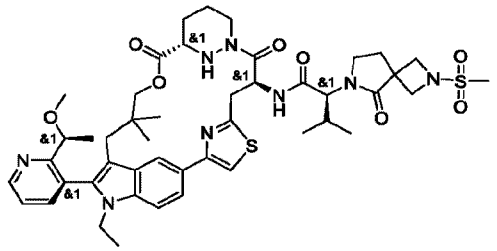
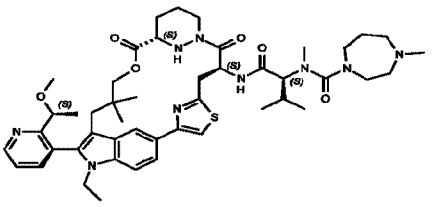
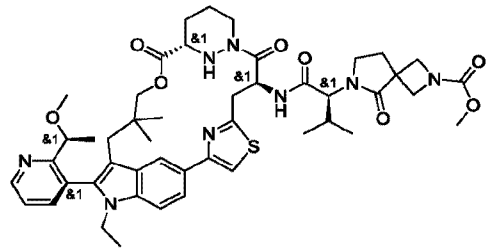
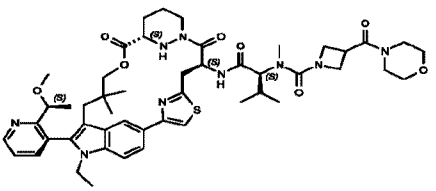
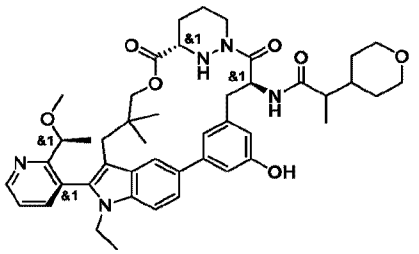
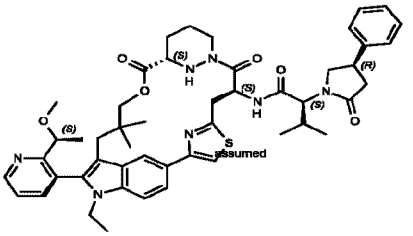
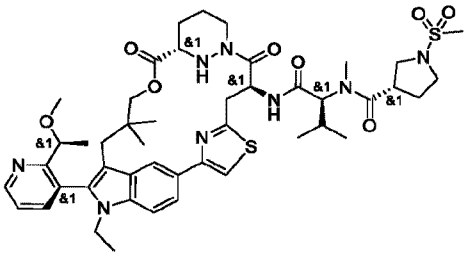
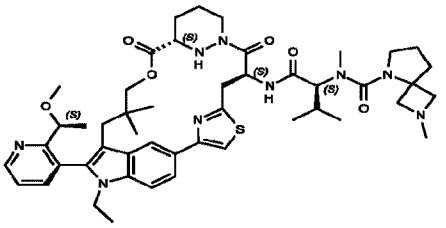
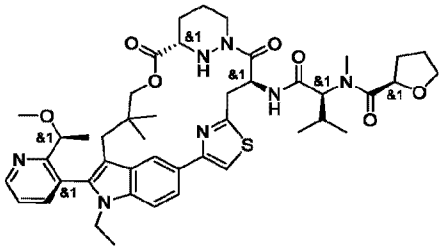
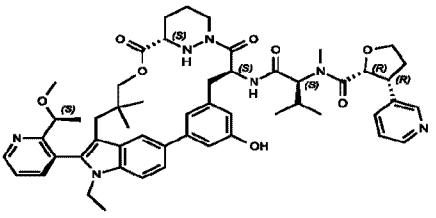
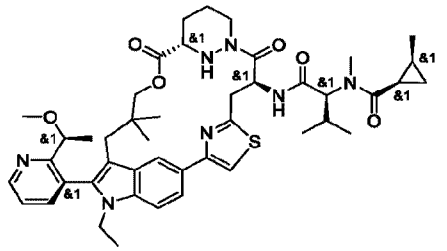
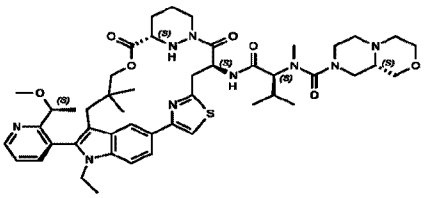
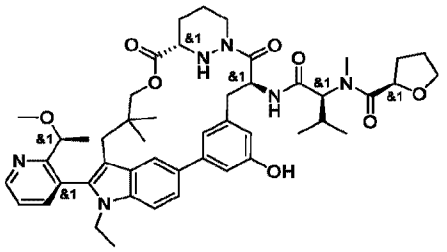
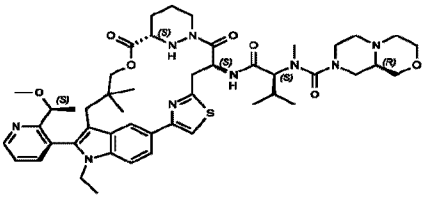
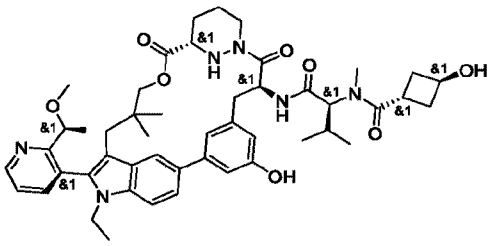
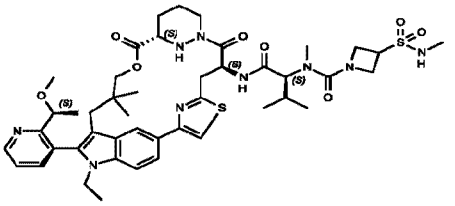
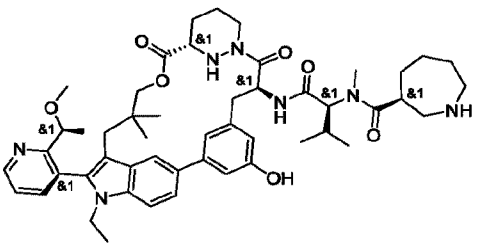
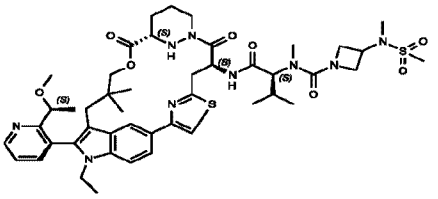
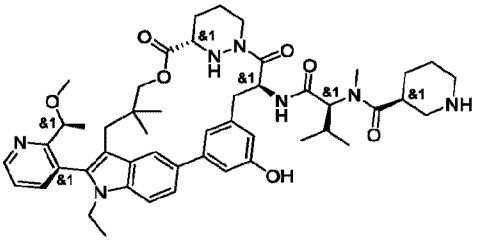
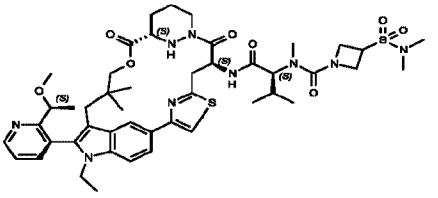
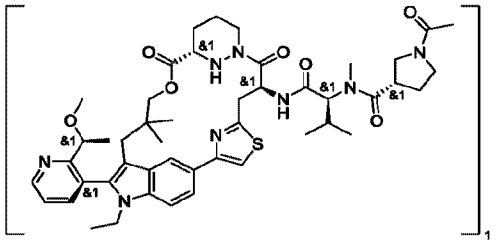
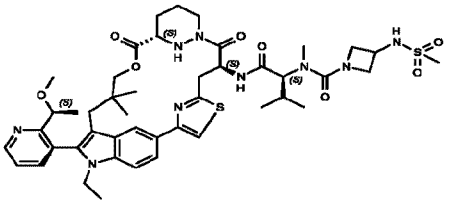
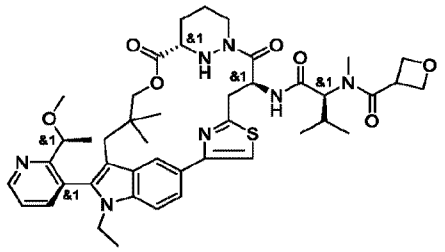
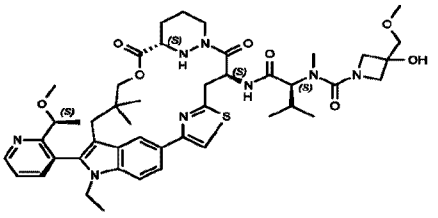
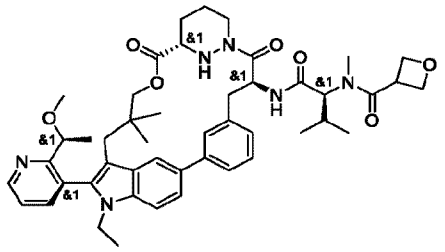
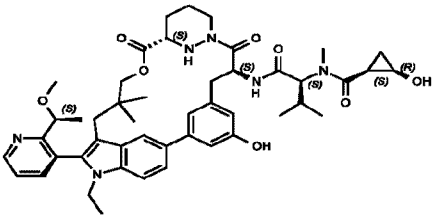
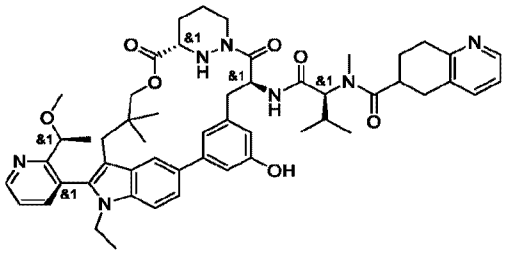
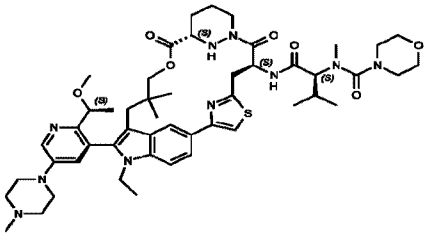
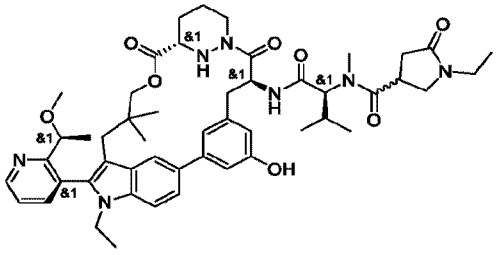
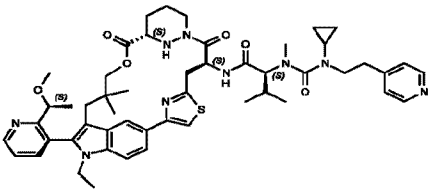
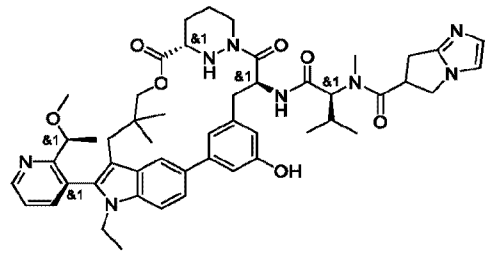
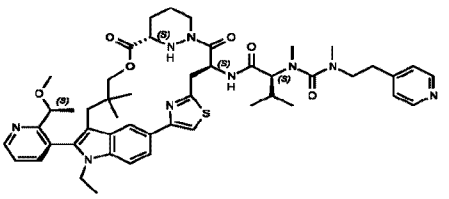
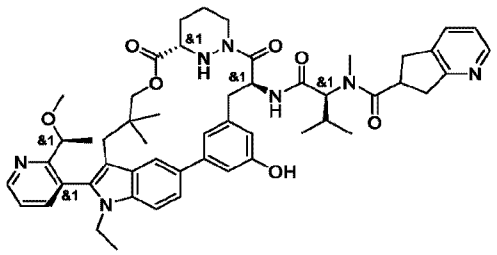
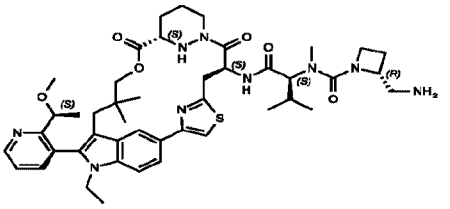
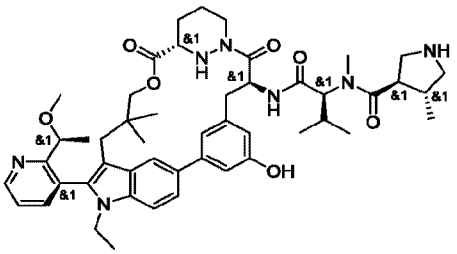
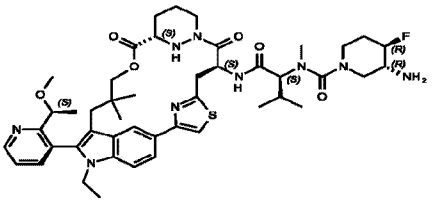
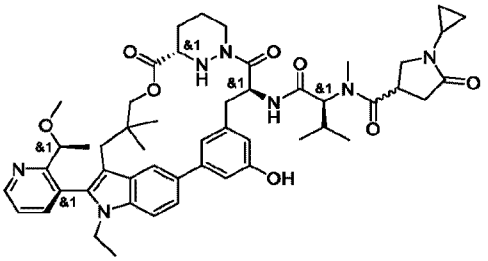
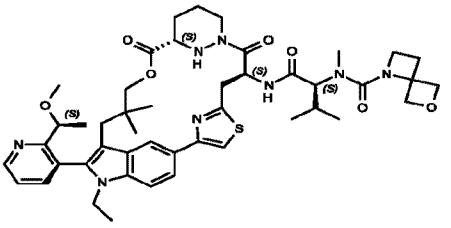
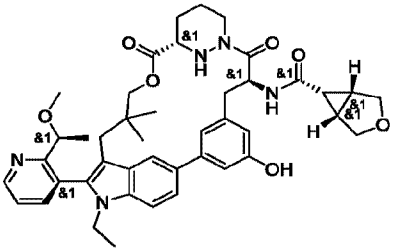
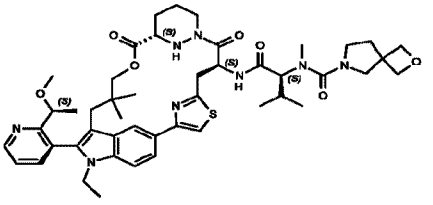
AA 224		AA 532	
AA 225		AA 533	
AA 226		AA 534	
AA 227		AA 535	
AA 228		AA 536	

Ex#	Structure	Ex#	Structure
AA 229		AA 537	
AA 230		AA 538	
AA 231		AA 539	
AA 232		AA 540	
AA 233		AA 541	

Ex#	Structure	Ex#	Structure
AA 234		AA 542	
AA 235		AA 543	
AA 236		AA 544	
AA 237		AA 545	
AA 238		AA 546	

Ex#	Structure	Ex#	Structure
AA 239		AA 547	
AA 240		AA 548	
AA 241		AA 549	
AA 242		AA 550	
AA 243		AA 551	

Ex#	Structure	Ex#	Structure
AA 244		AA 552	
AA 245		AA 553	
AA 246		AA 554	
AA 247		AA 555	
AA 248		AA 556	

Ex#	Structure	Ex#	Structure
AA 249		AA 557	
AA 250		AA 558	
AA 251		AA 559	
AA 252		AA 560	
AA 253		AA 561	

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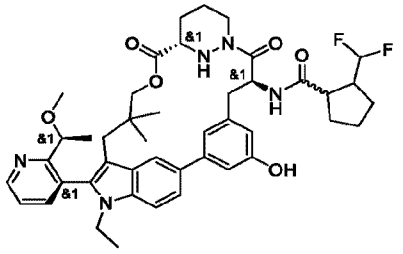
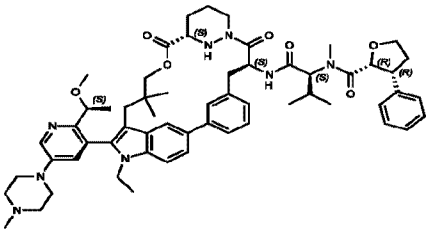
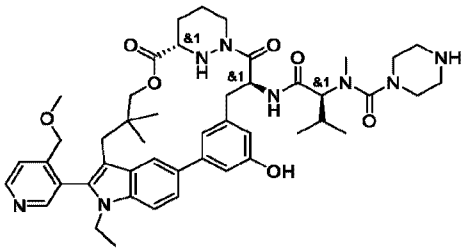
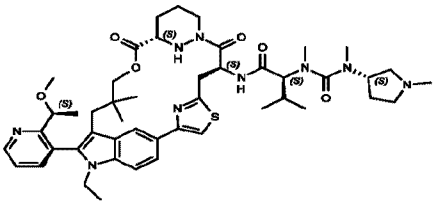
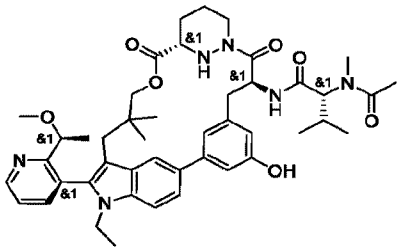
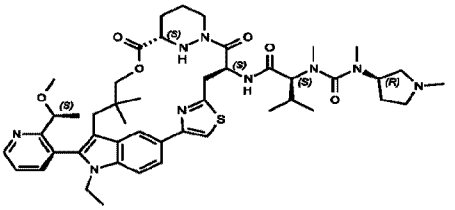
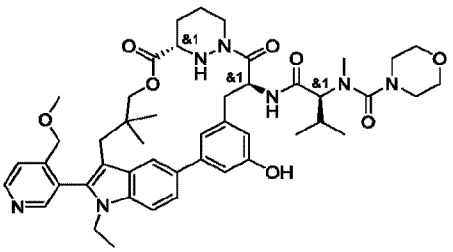
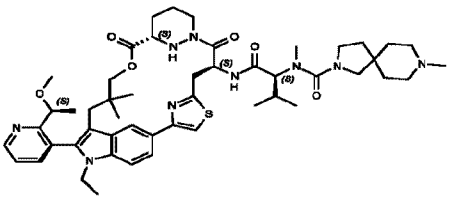
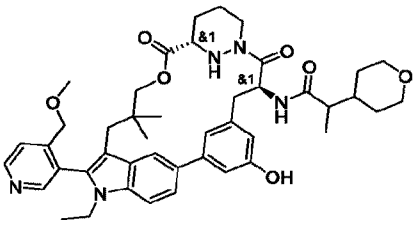
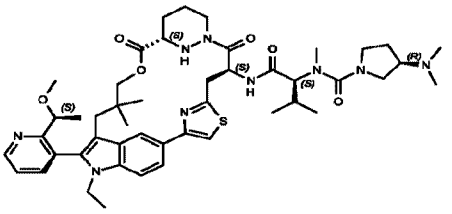
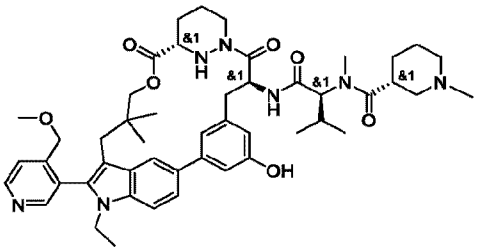
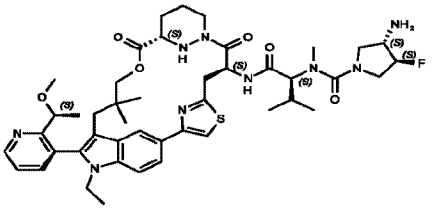
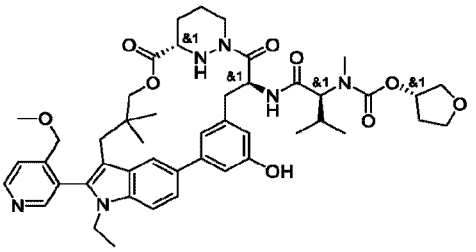
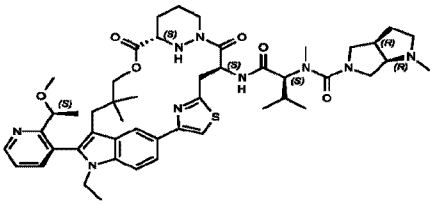
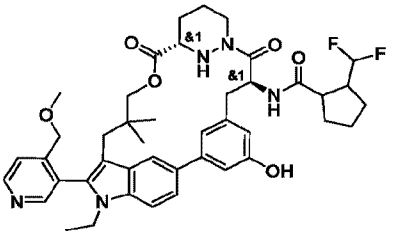
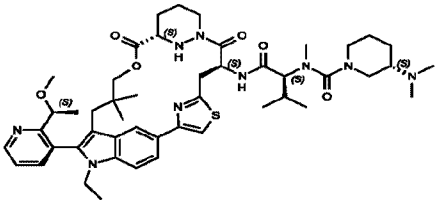
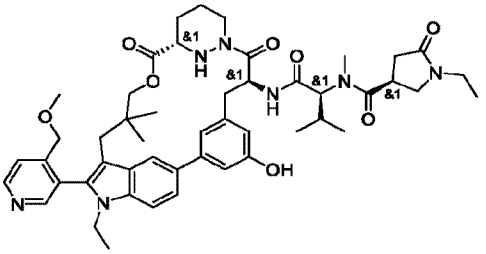
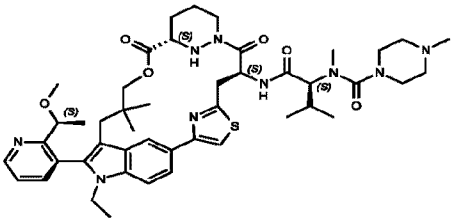
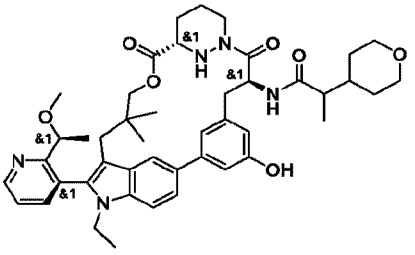
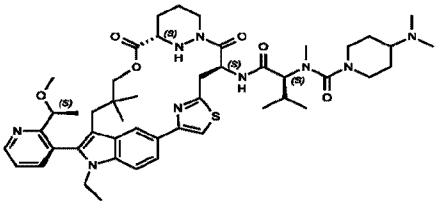
AA 254		AA 562	
AA 255		AA 563	
AA 256		AA 564	
AA 257		AA 565	
AA 258		AA 566	

Ex#	Structure	Ex#	Structure
AA 259		AA 567	
AA 260		AA 568	
AA 261		AA 569	
AA 262		AA 570	
AA 263		AA 571	

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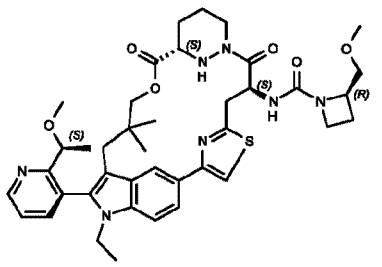
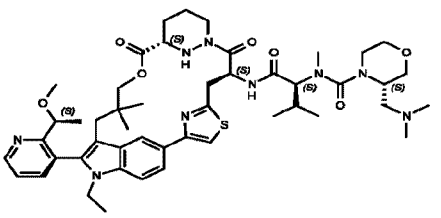
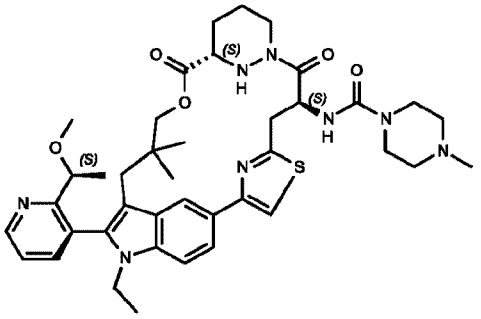
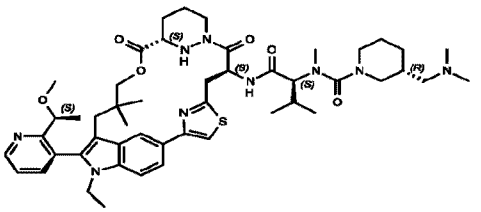
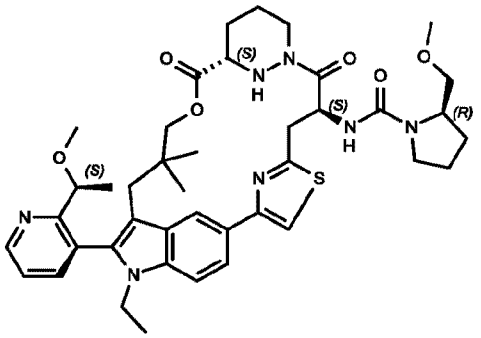
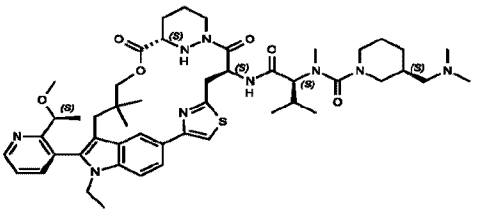
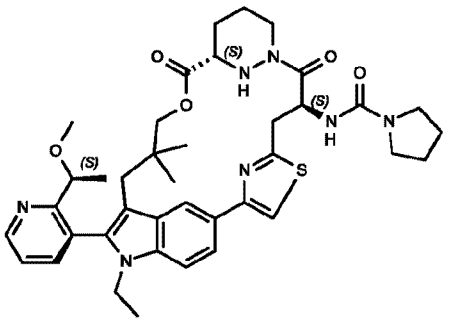
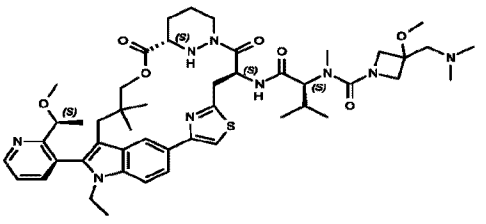
AA 264		AA 572	
AA 265		AA 573	
AA 266		AA 574	
AA 267		AA 575	

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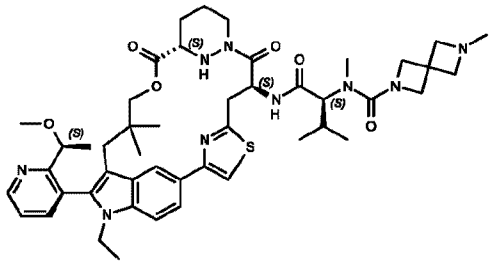
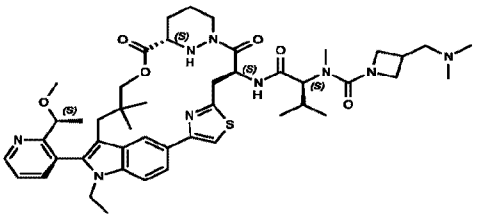
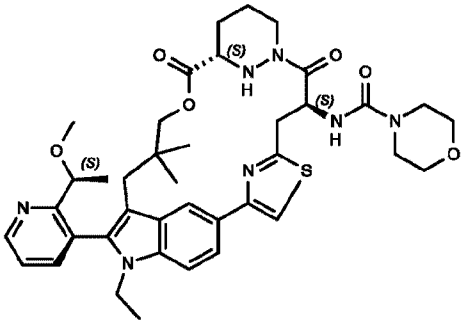
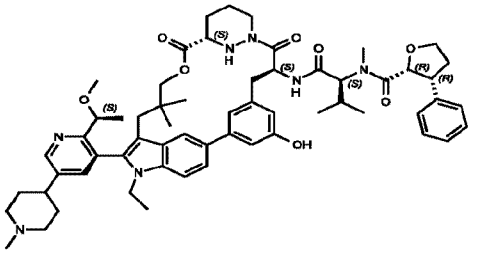
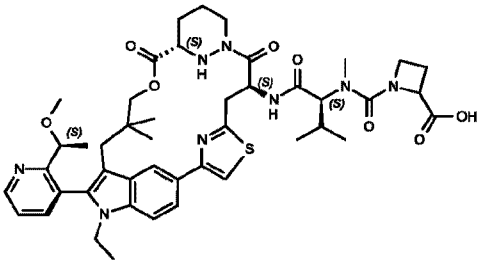
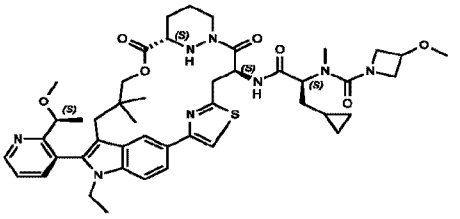
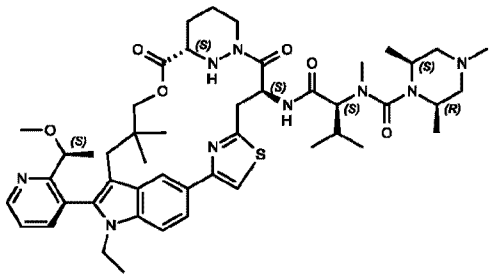
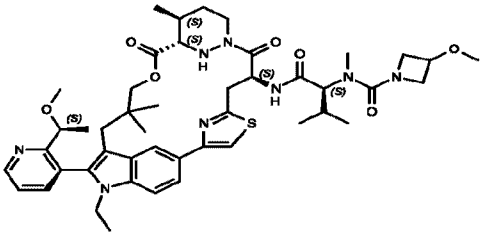
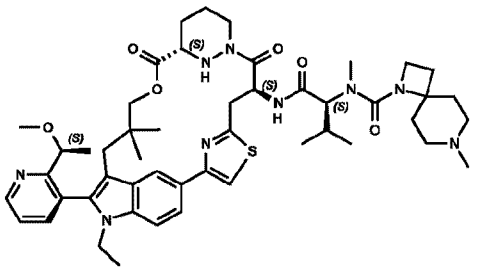
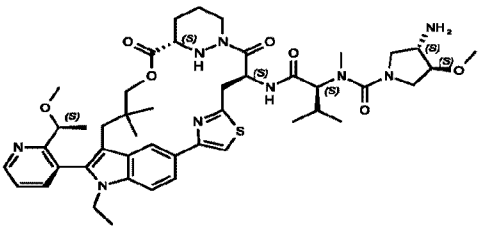
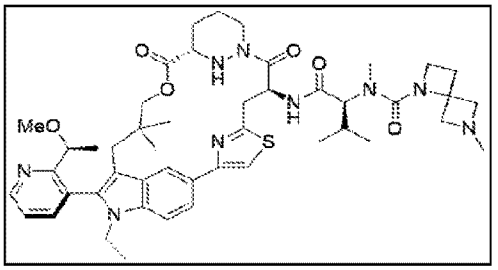
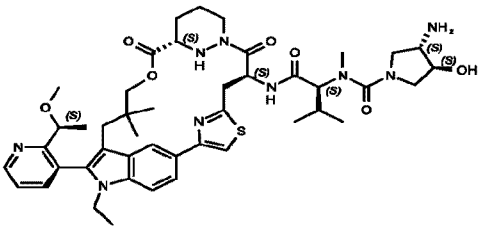
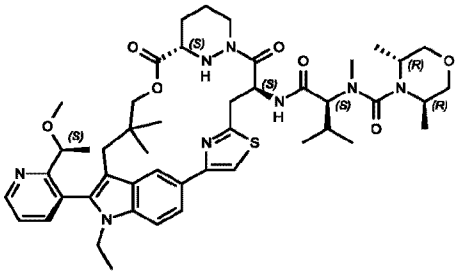
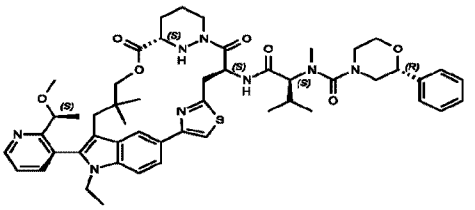
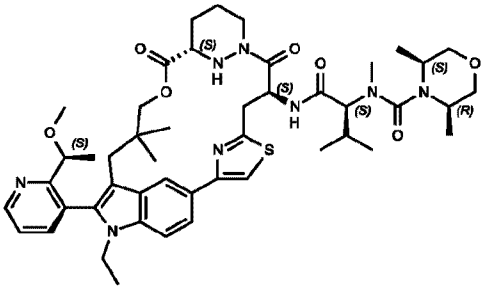
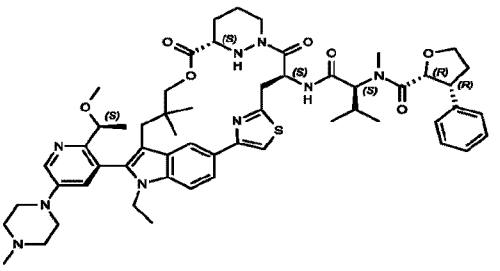
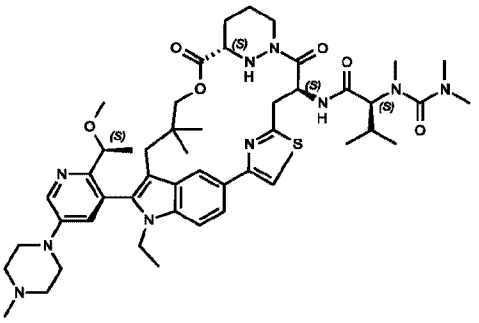
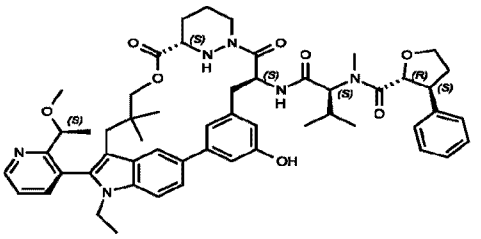
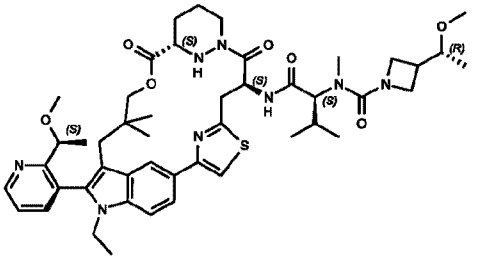
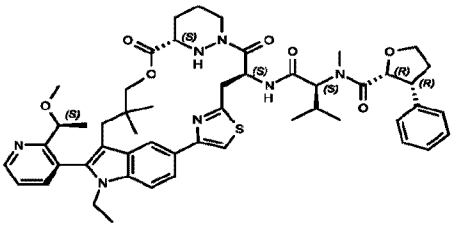
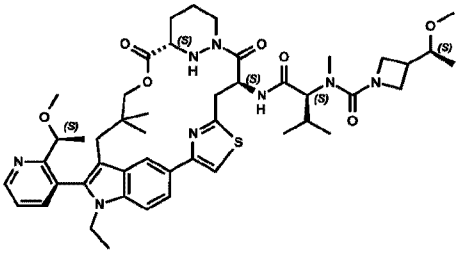
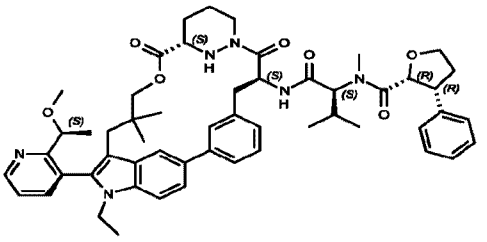
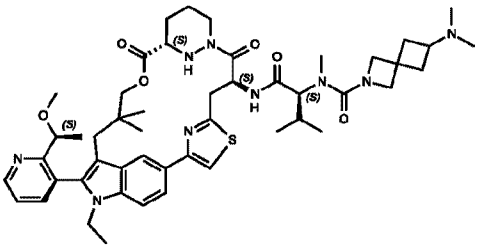
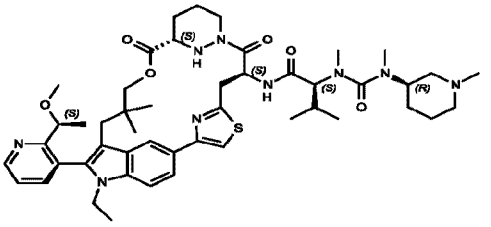
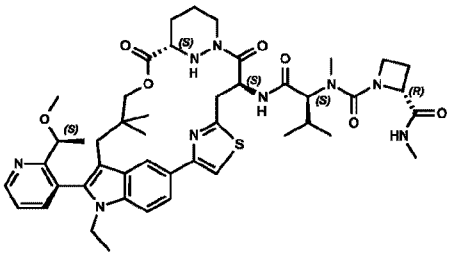
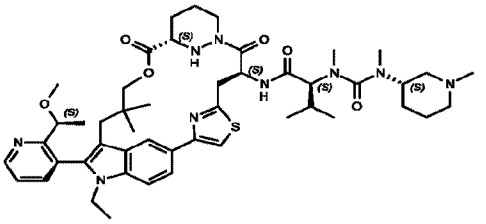
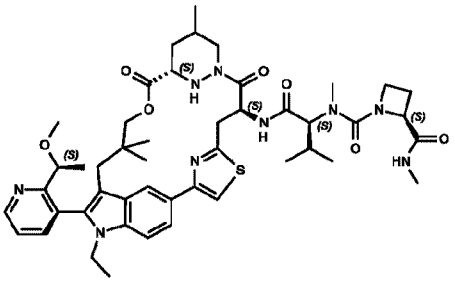
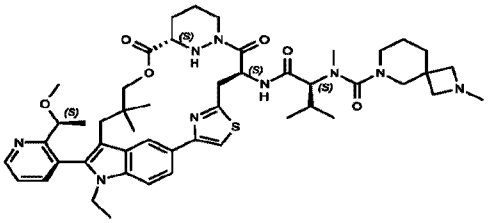
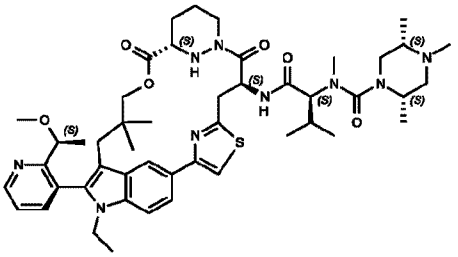
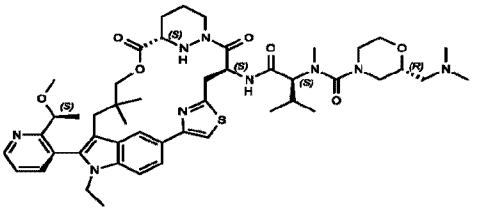
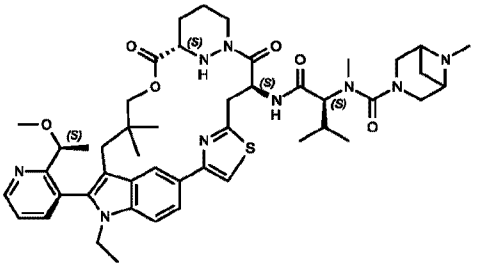
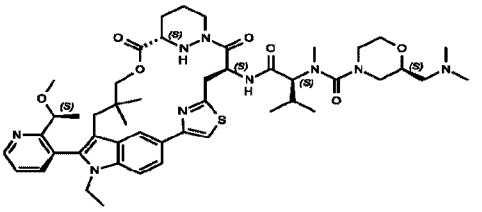
AA 268		AA 576	
AA 270		AA 577	
AA 271		AA 578	
AA 272		AA 579	

Ex#	Structure	Ex#	Structure
AA 273		AA 580	
AA 274		AA 581	
AA 275		AA 582	
AA 276		AA 583	

Ex#	Structure	Ex#	Structure
AA 277		AA 584	
AA 278		AA 585	
AA 279		AA 586	
AA 280		AA 587	

Ex#	Structure	Ex#	Structure
AA 281		AA 588	
AA 282		AA 589	
AA 283		AA 590	
AA 284		AA 591	

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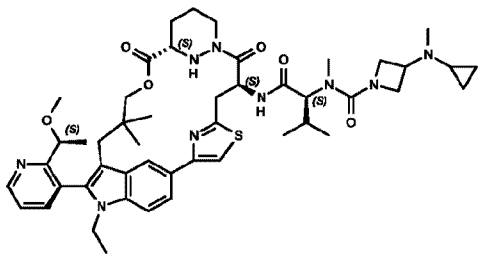
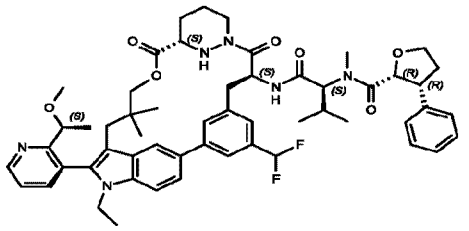
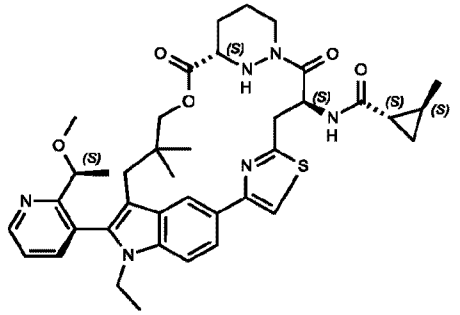
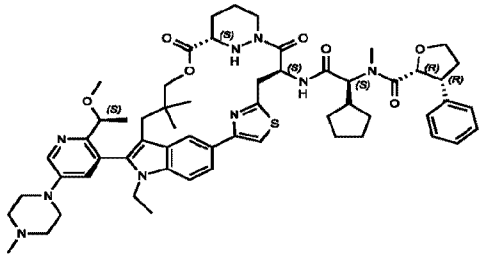
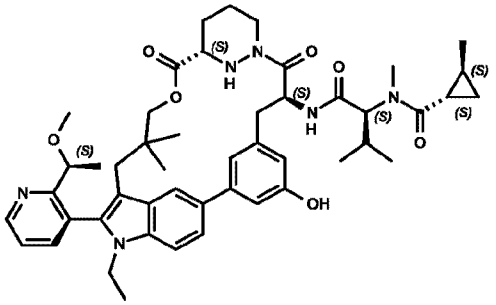
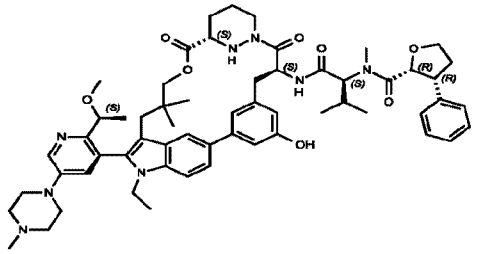
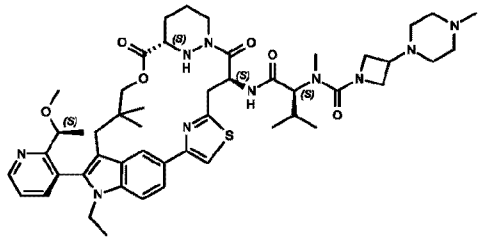
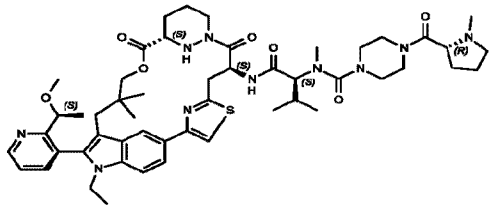
AA 285		AA 592	
AA 286		AA 593	
AA 287		AA 594	
AA 288		AA 595	

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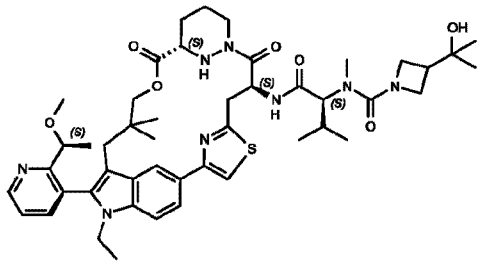
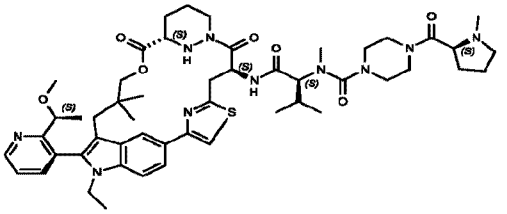
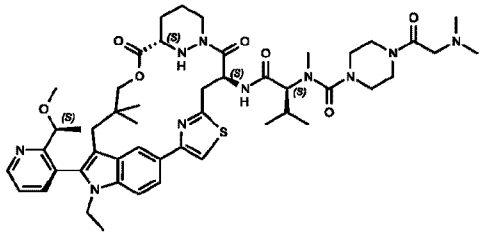
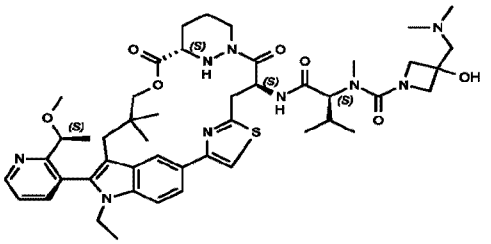
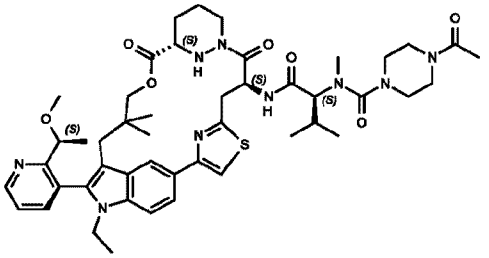
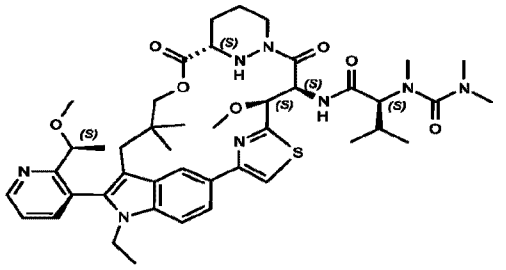
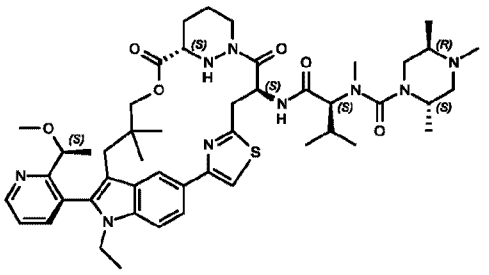
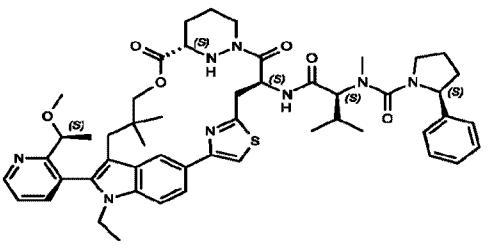
AA 289		AA 596	
AA 290		AA 597	
AA 291		AA 598	
AA 292		AA 599	

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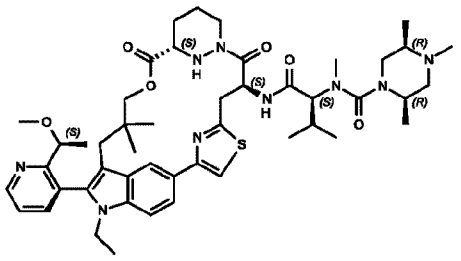
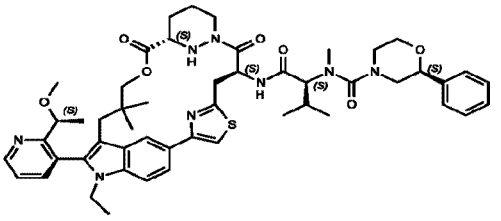
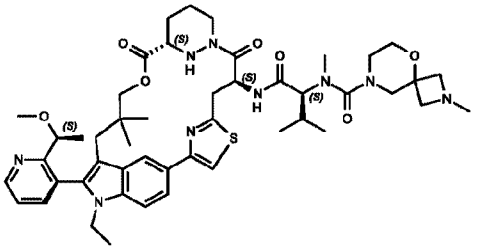
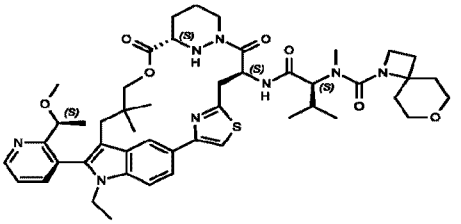
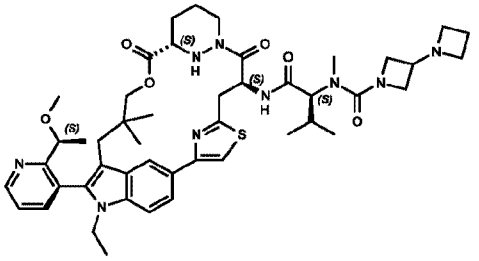
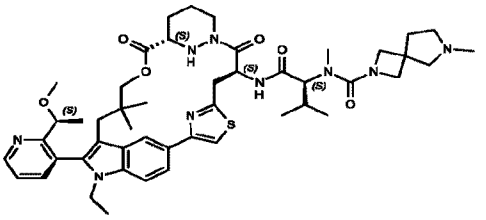
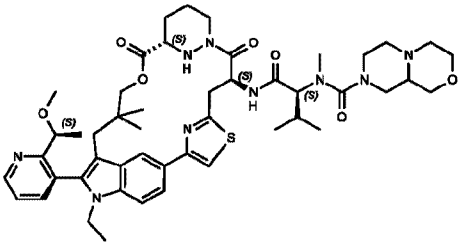
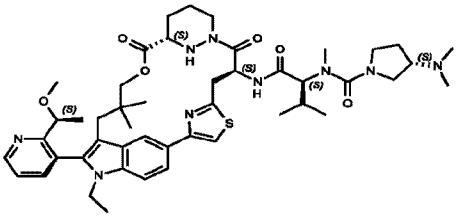
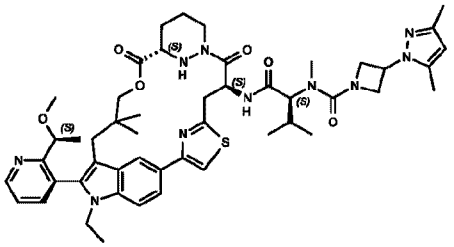
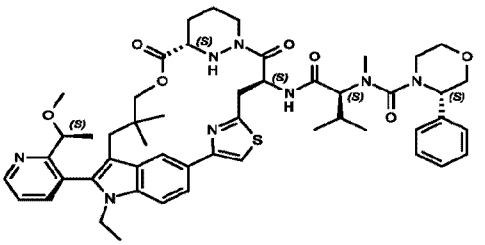
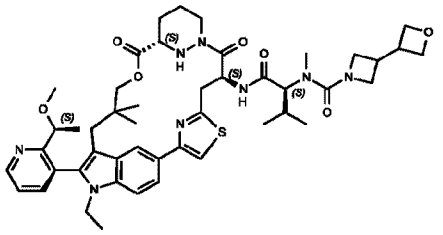
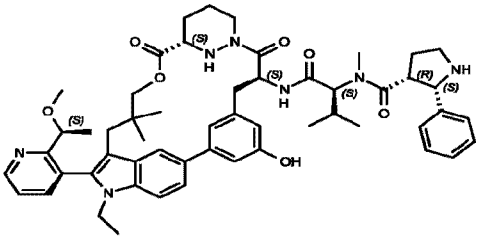
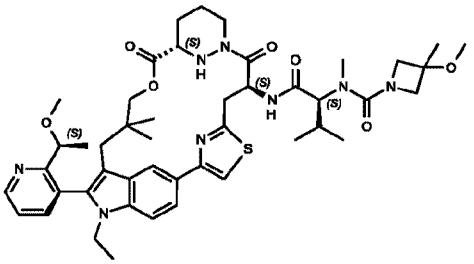
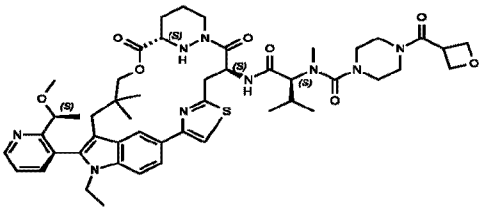
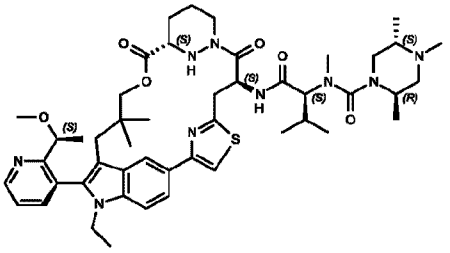
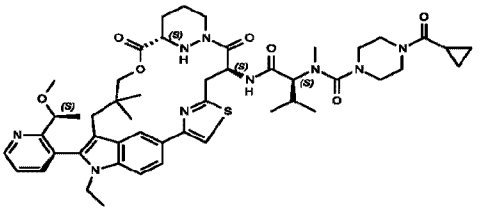
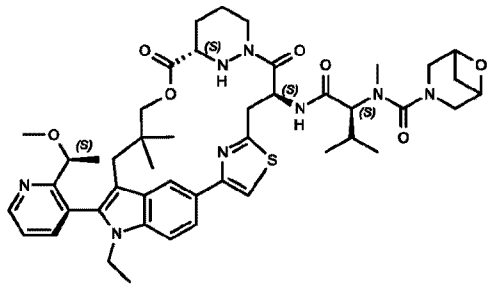
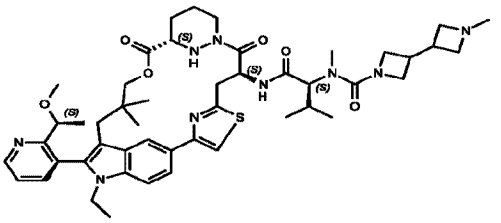
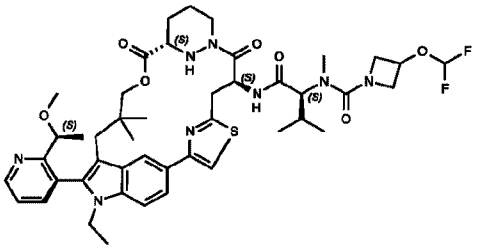
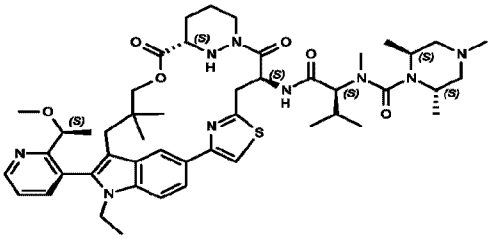
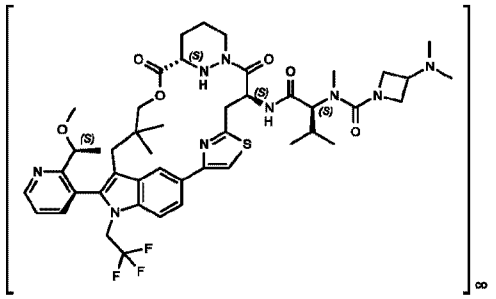
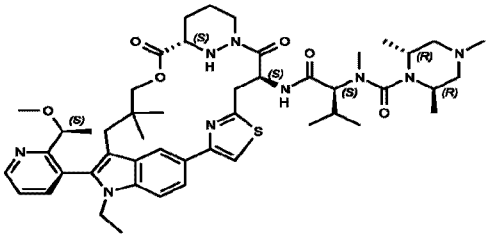
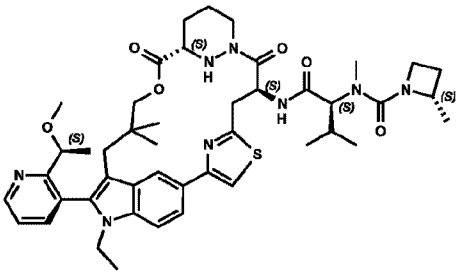
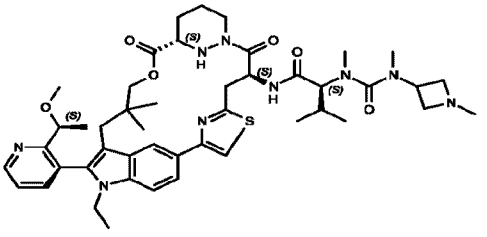
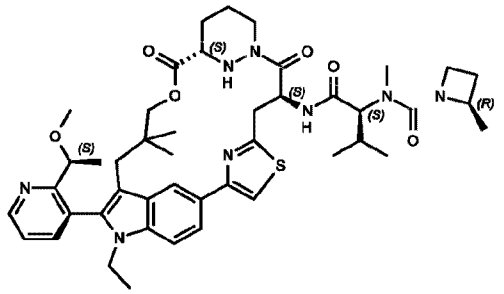
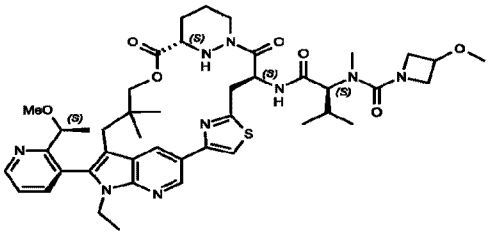
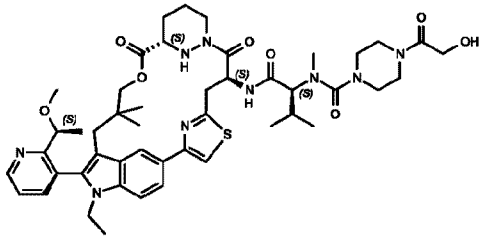
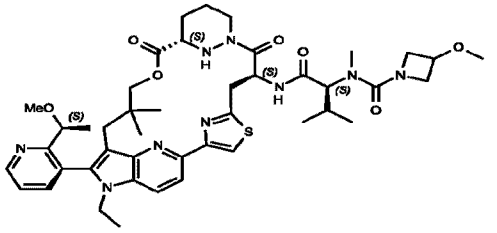
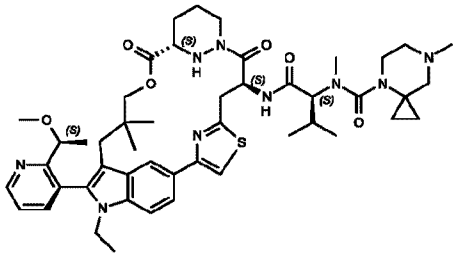
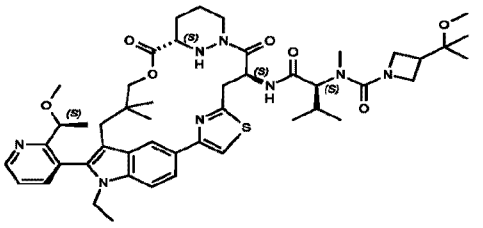
AA 293		AA 600	
AA 294		AA 601	
AA 295		AA 602	
AA 296		AA 603	

Ex#	Structure	Ex#	Structure
AA 297		AA 604	
AA 298		AA 605	
AA 299		AA 606	
AA 300		AA 607	

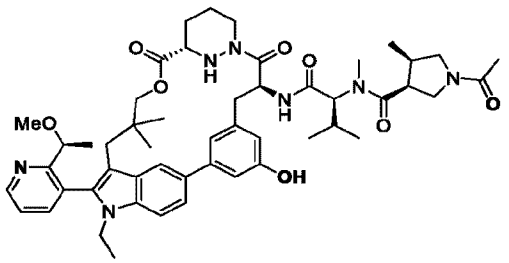
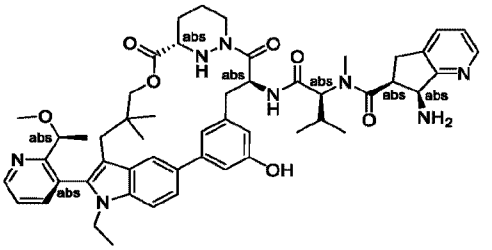
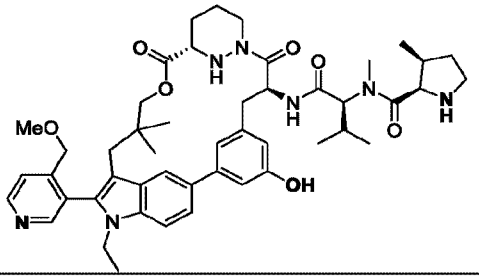
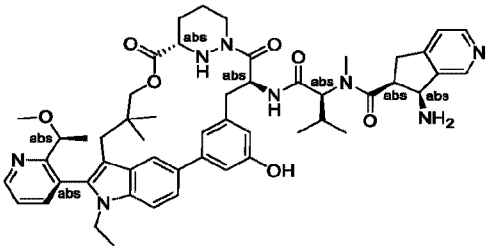
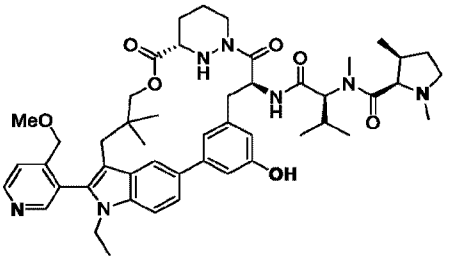
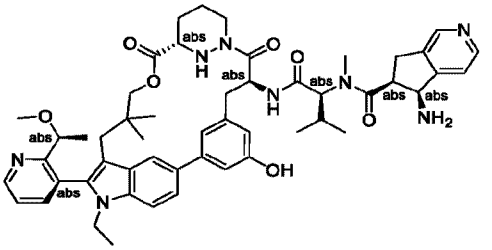
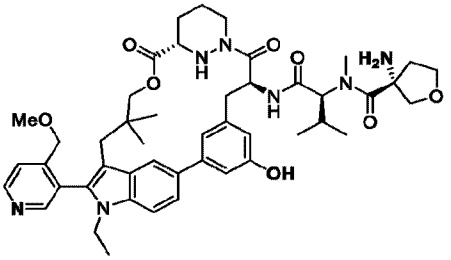
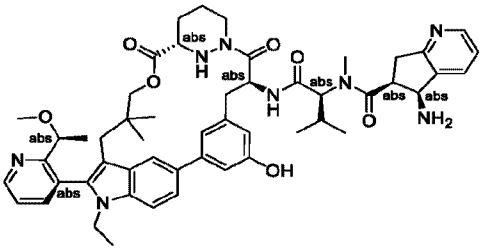
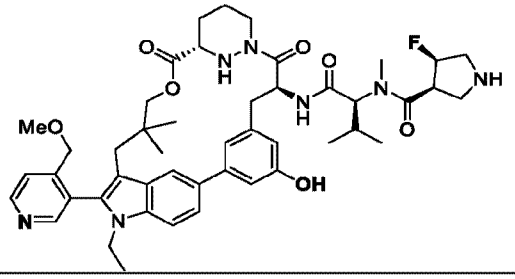
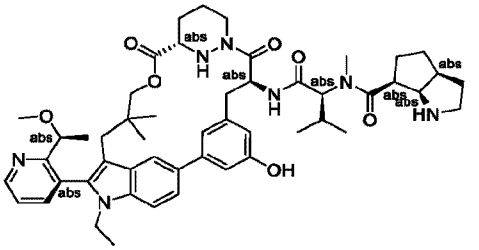
Ex#	Structure	Ex#	Structure
AA 301		AA 608	
AA 302		AA 609	
AA 303		AA 610	
AA 304		AA 611	

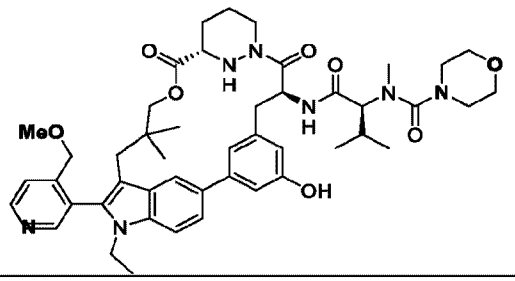
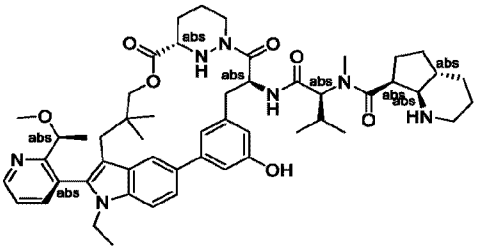
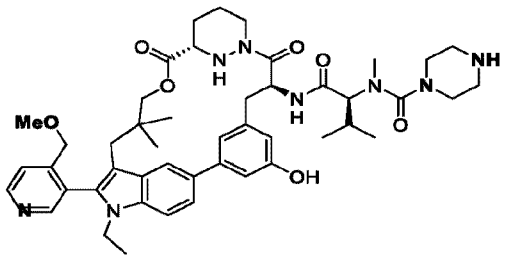
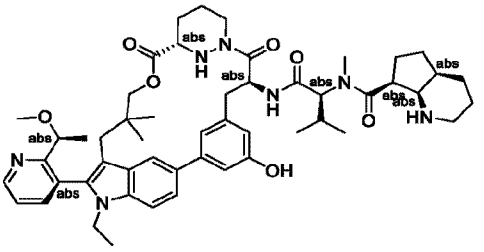
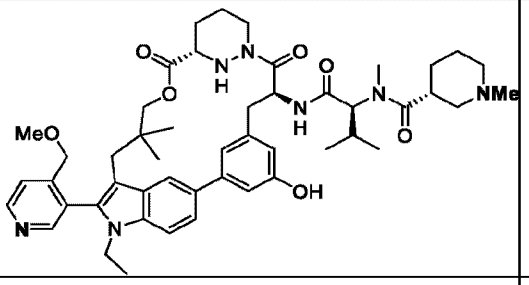
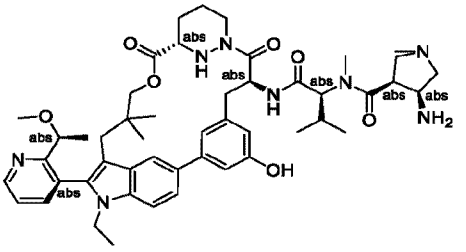
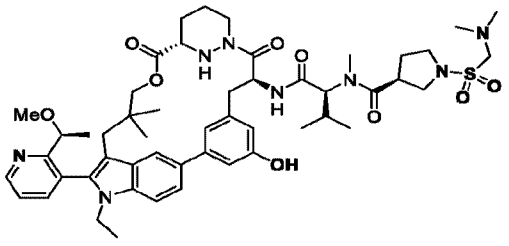
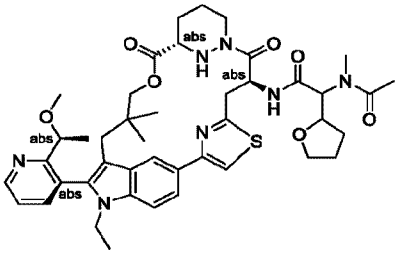
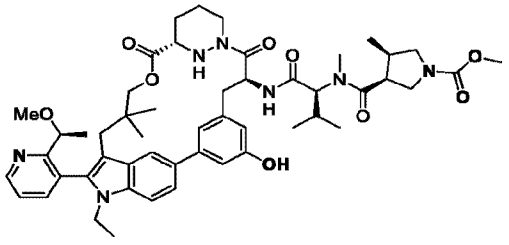
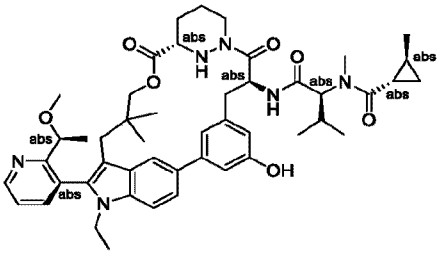
Ex#	Structure	Ex#	Structure
AA 305		AA 612	
AA 306		AA 613	
AA 307		AA 614	

Note that some compounds are shown with bonds as flat or wedged. In some instances, the relative stereochemistry of stereoisomers has been determined; in some instances, the absolute stereochemistry has been determined. In some instances, a single Example number corresponds to a mixture of stereoisomers. All stereoisomers of the compounds of the foregoing table are contemplated by the present invention. In particular embodiments, an atropisomer of a compound of the foregoing table is contemplated. Any compound shown in brackets indicates that the compound is a diastereomer, and the absolute stereochemistry of such diastereomer may not be known.

In some embodiments, a compound of Table A2 is provided, or a pharmaceutically acceptable salt thereof. In some embodiments, the RAS(ON) inhibitor is selected from Table A2, or a pharmaceutically acceptable salt or atropisomer thereof.

Table A2: Certain Compounds of the Present Invention

Ex#	Structure	Ex#	Structure
AB 4		AB 177	
AB 5		AB 178	
AB 6		AB 179	
AB 8		AB 180	
AB 9		AB 181	

Ex#	Structure	Ex#	Structure
AB 12		AB 182	
AB 13		AB 183	
AB 19		AB 184	
AB 44		AB 185	
AB 47		AB 186	

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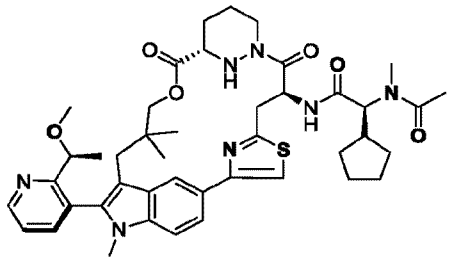
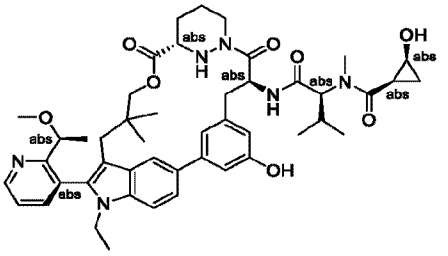
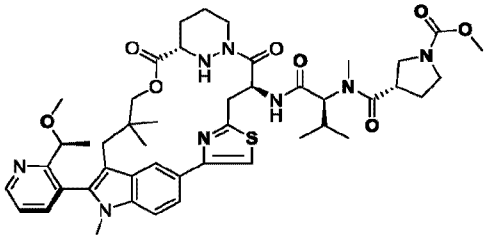
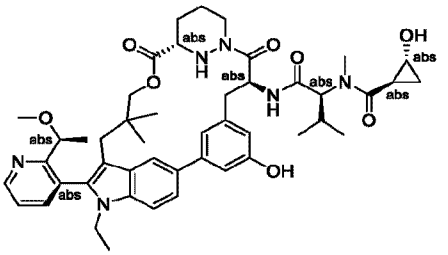
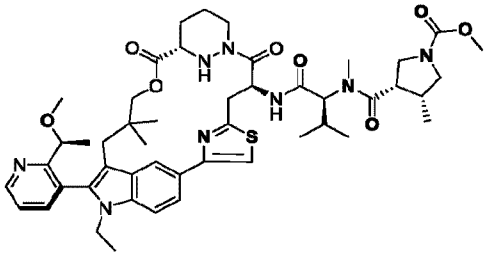
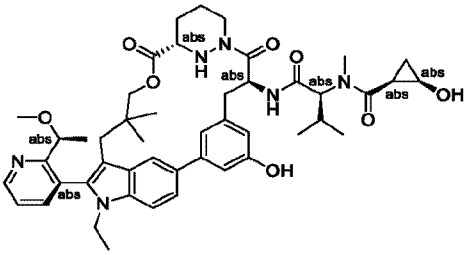
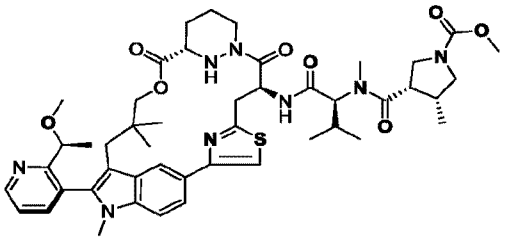
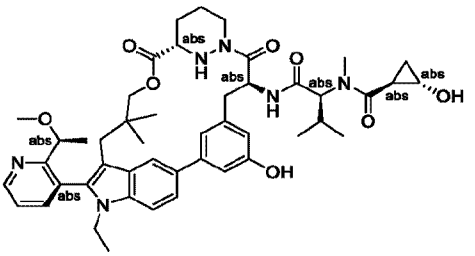
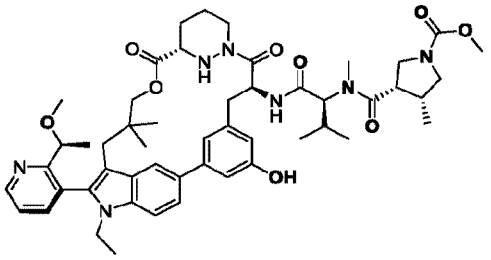
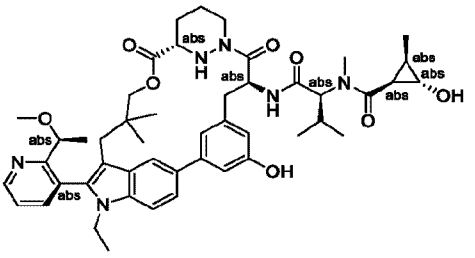
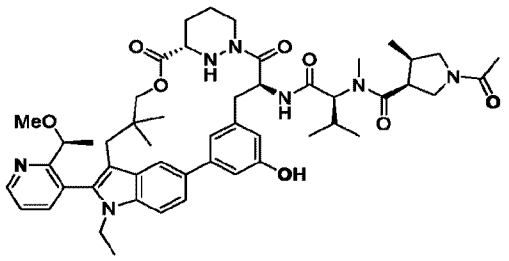
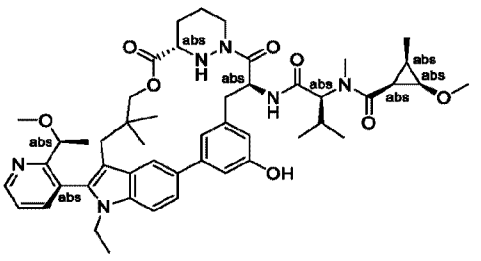
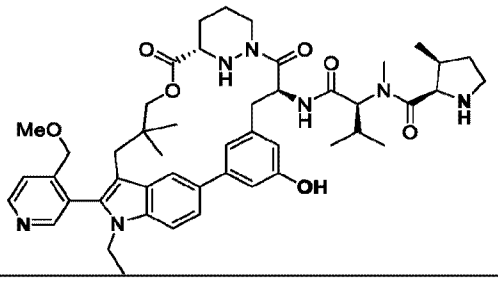
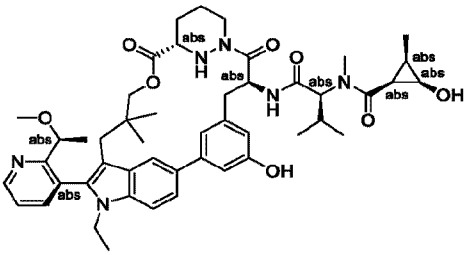
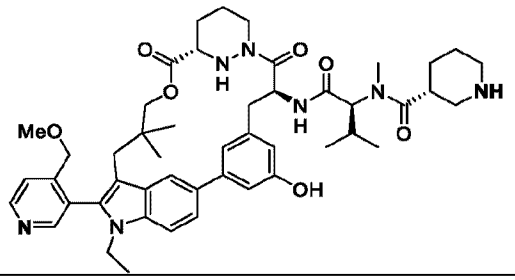
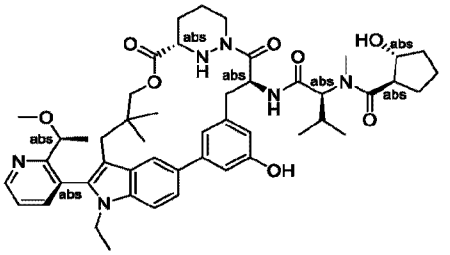
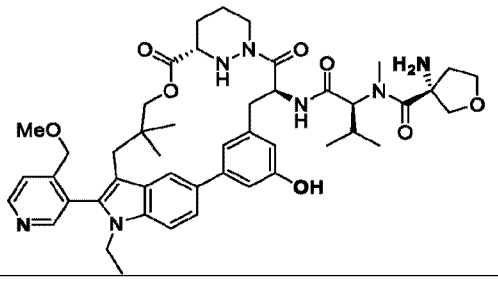
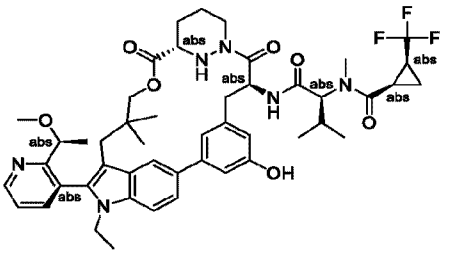
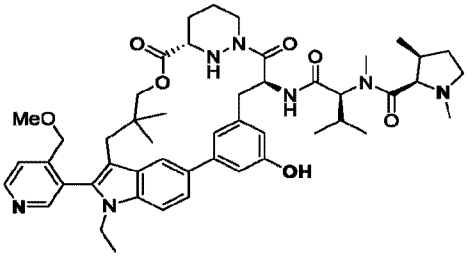
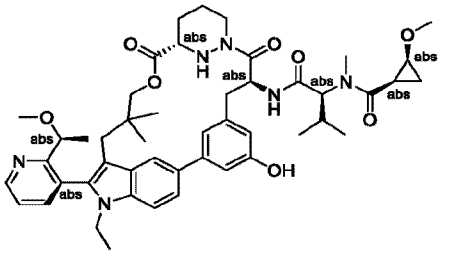
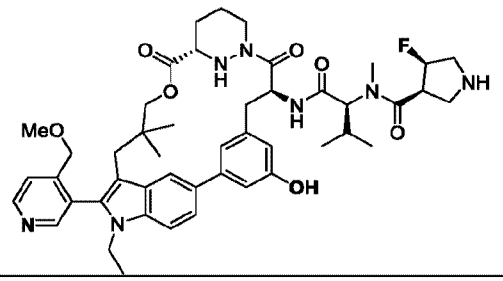
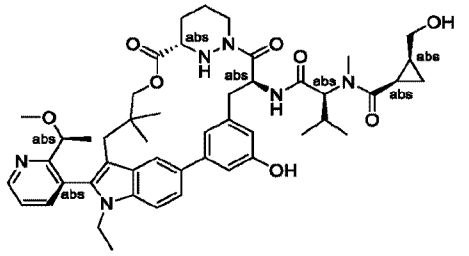
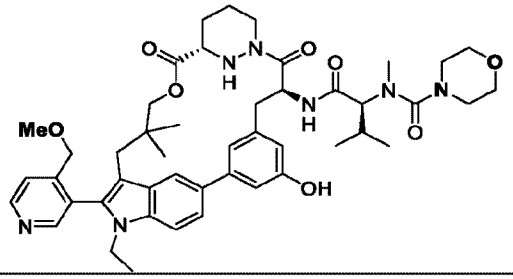
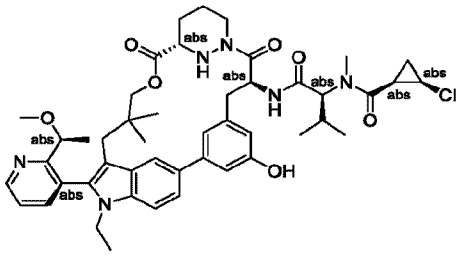
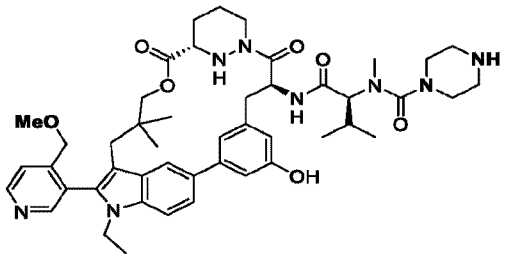
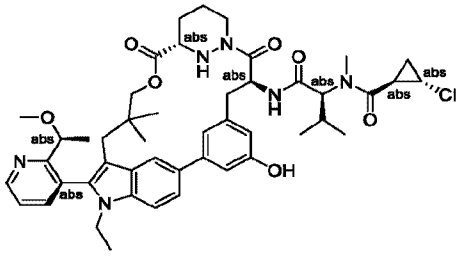
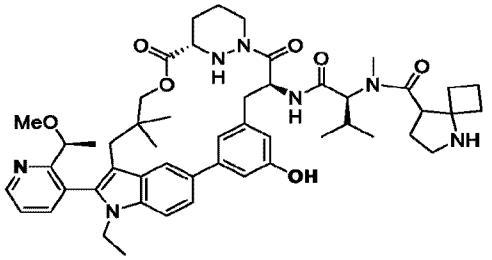
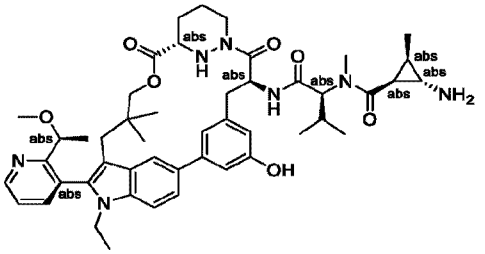
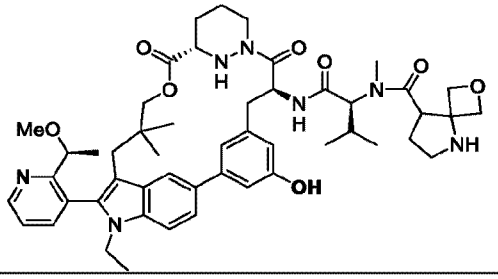
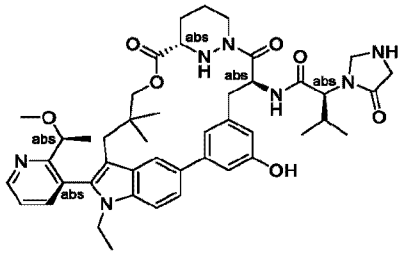
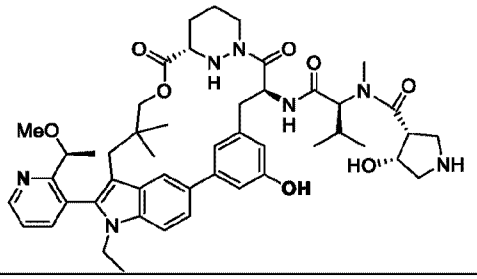
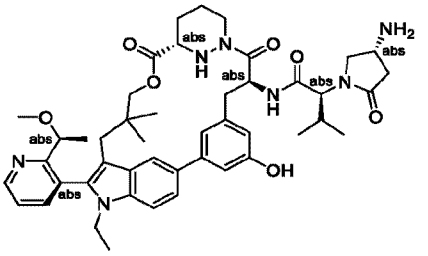
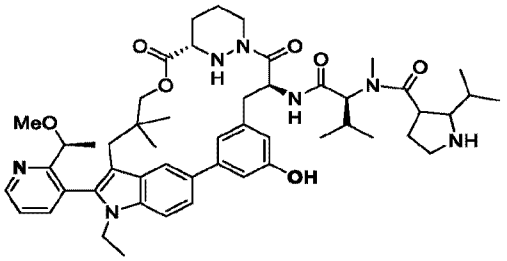
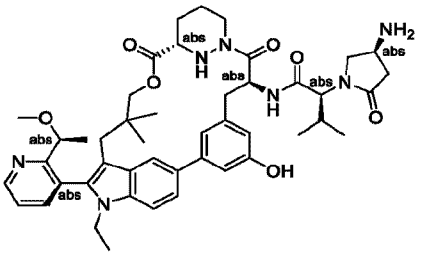
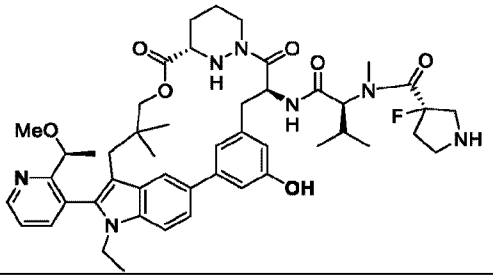
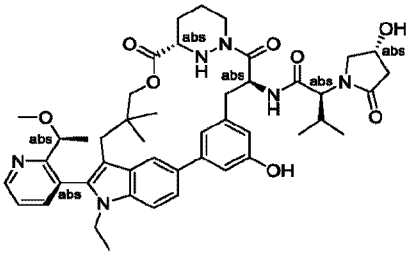
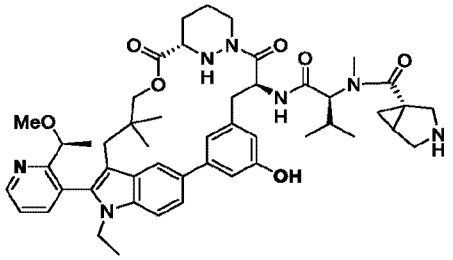
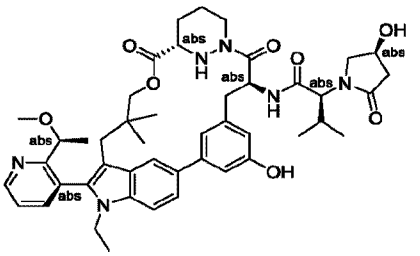
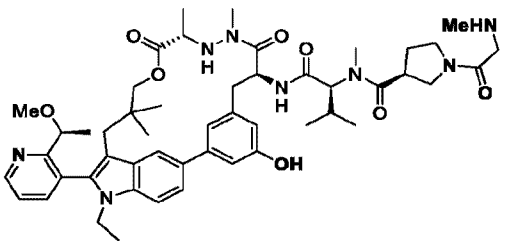
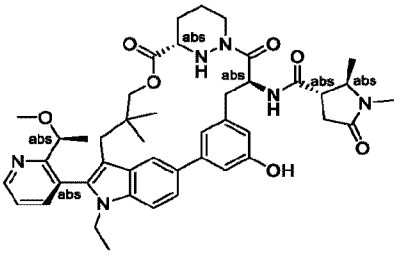
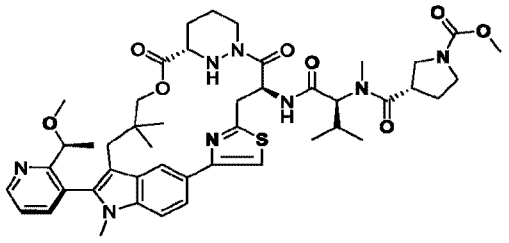
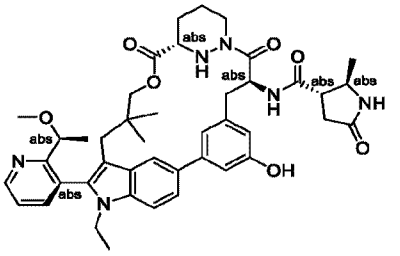
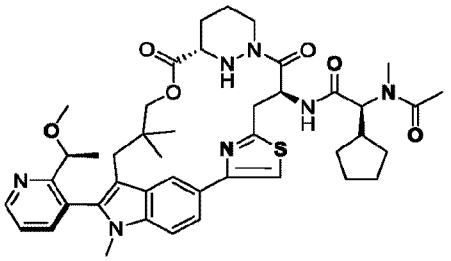
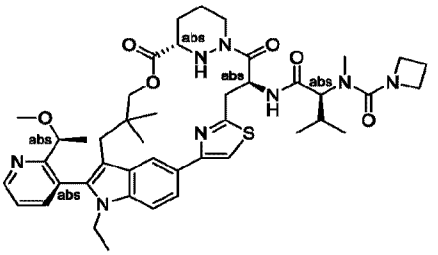
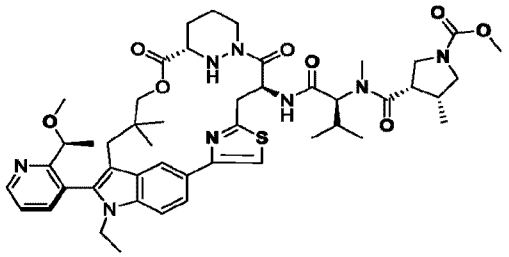
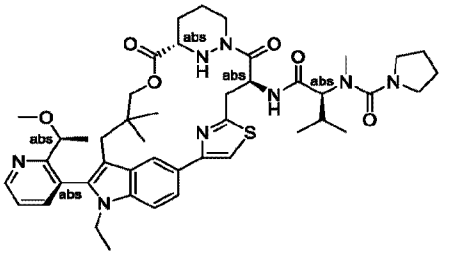
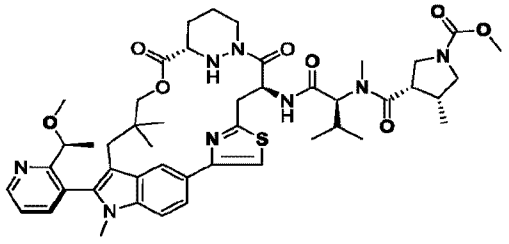
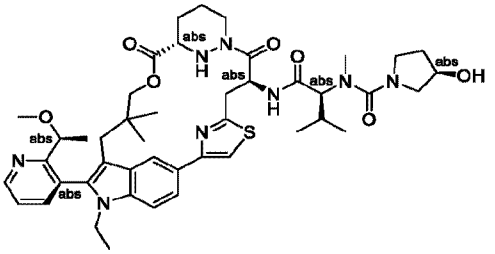
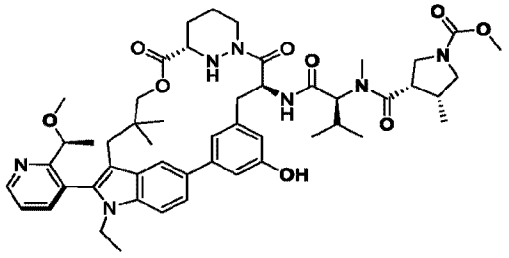
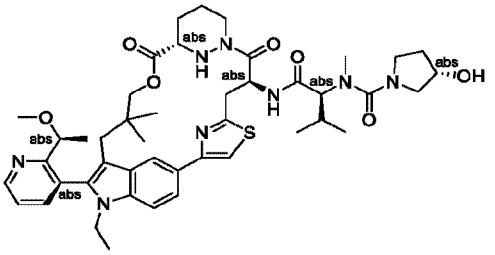
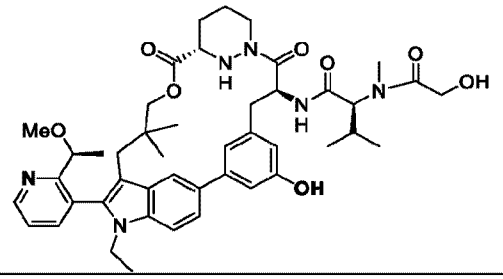
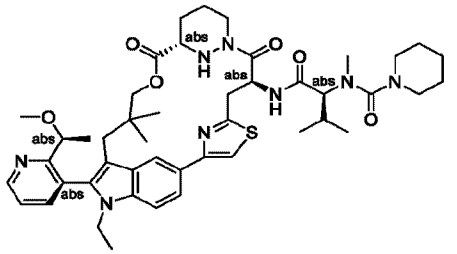
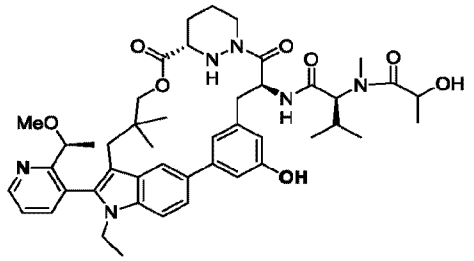
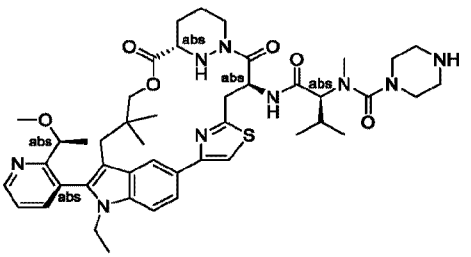
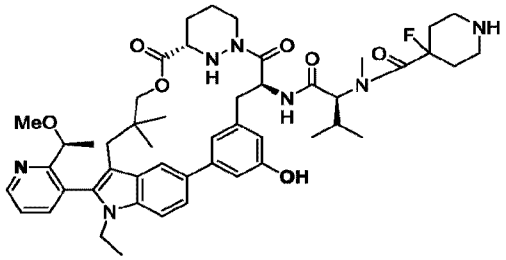
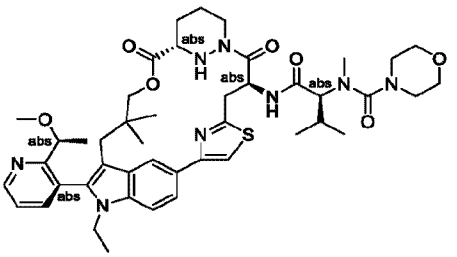
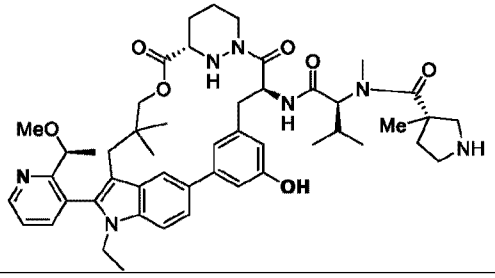
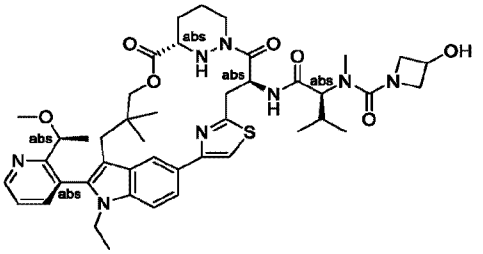
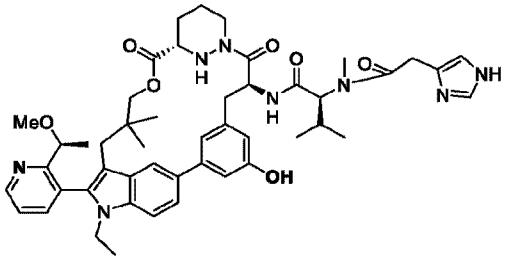
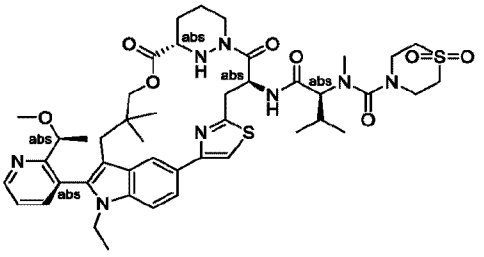
AB 57		AB 187	
AB 58		AB 188	
AB 59		AB 189	
AB 60		AB 190	
AB 61		AB 191	

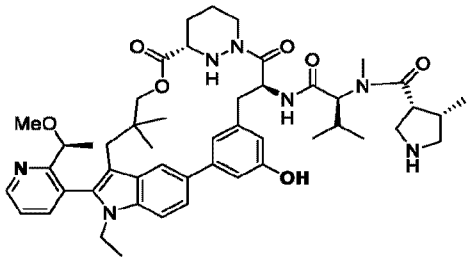
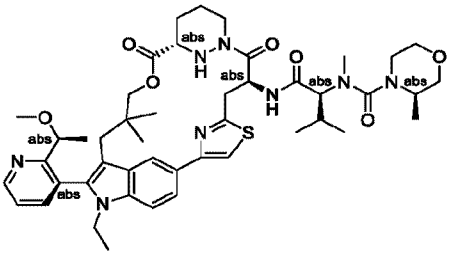
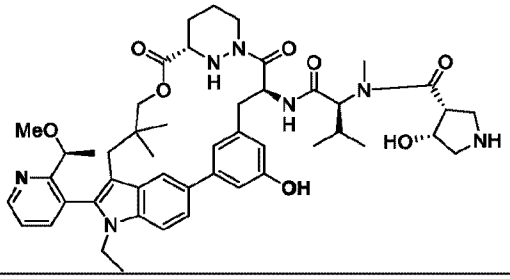
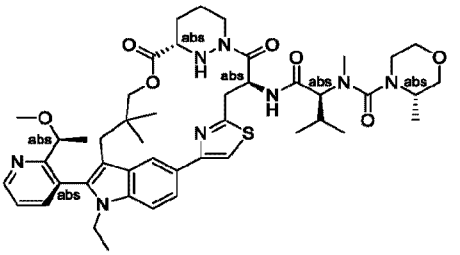
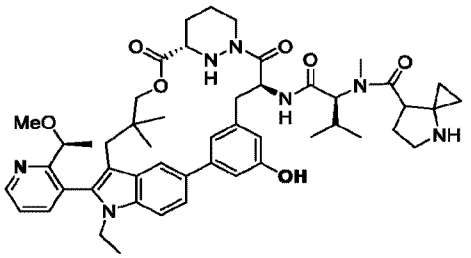
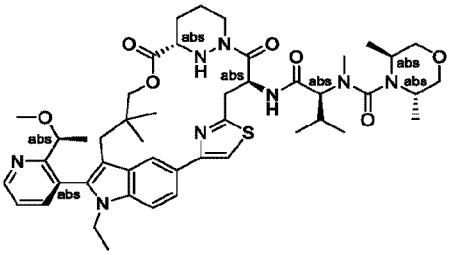
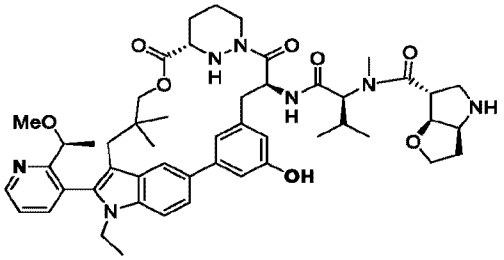
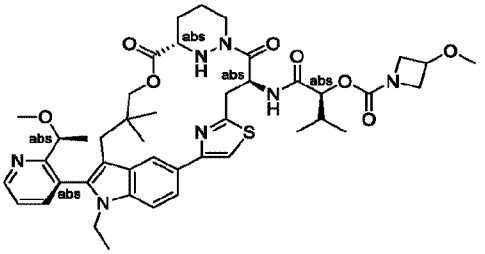
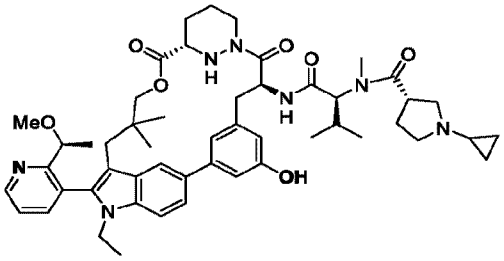
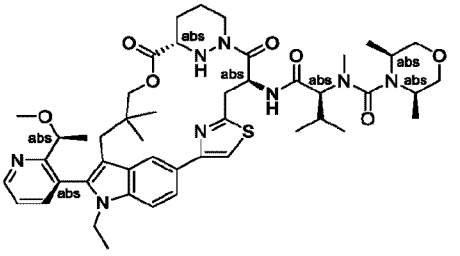
Ex#	Structure	Ex#	Structure
AB 66		AB 192	
AB 67		AB 193	
AB 69		AB 194	
AB 71		AB 195	
AB 73		AB 196	

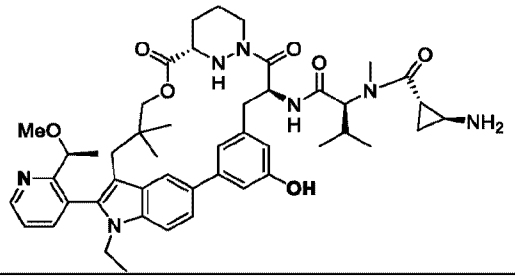
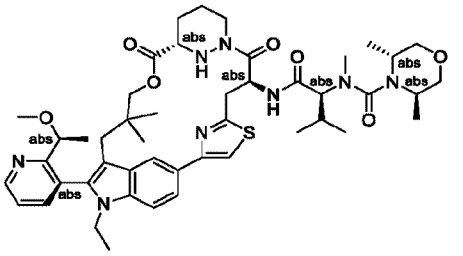
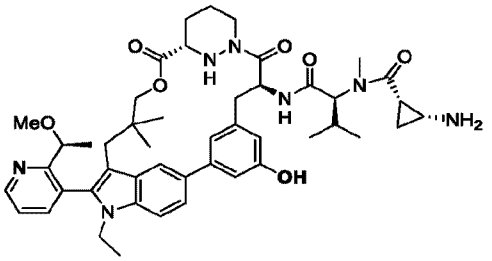
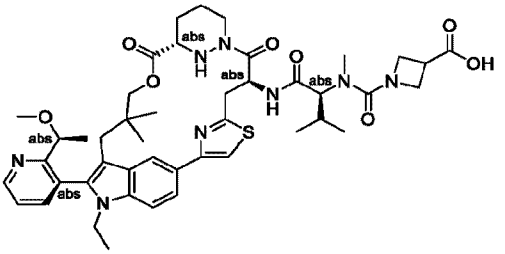
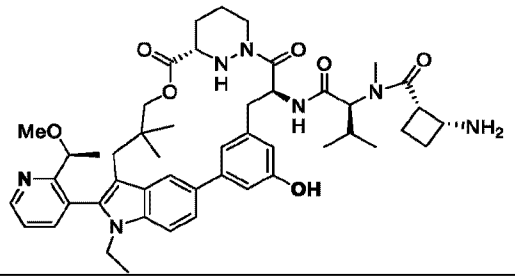
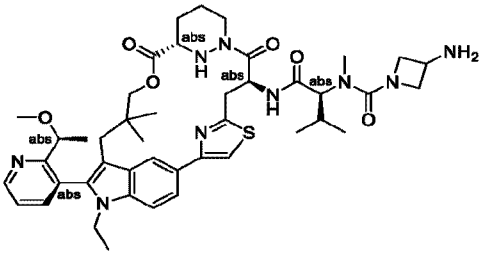
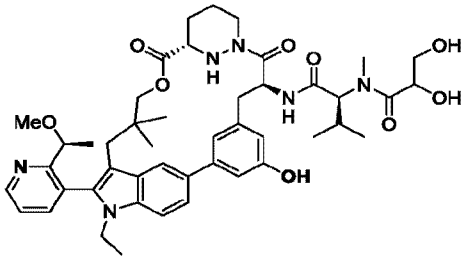
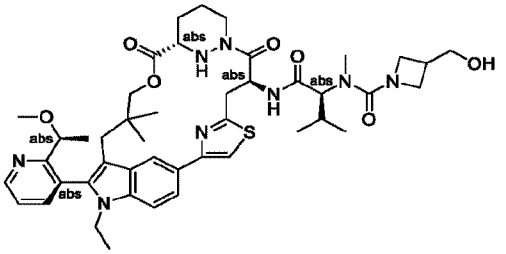
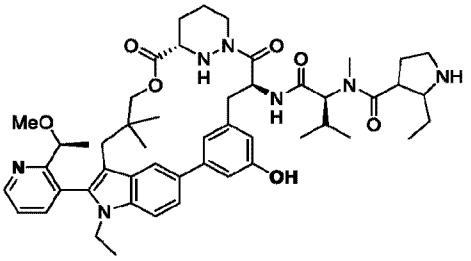
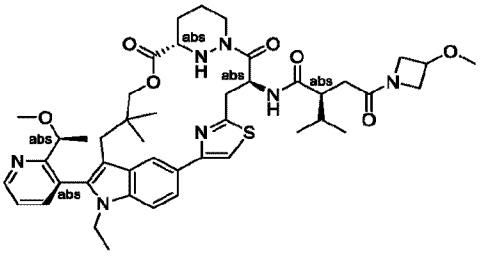
Ex#	Structure	Ex#	Structure
AB 74		AB 197	
AB 80		AB 198	
AB 81		AB 199	
AB 94		AB 200	
AB 95		AB 201	

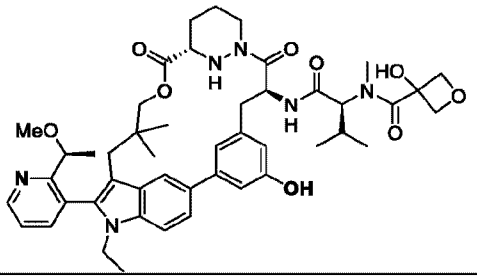
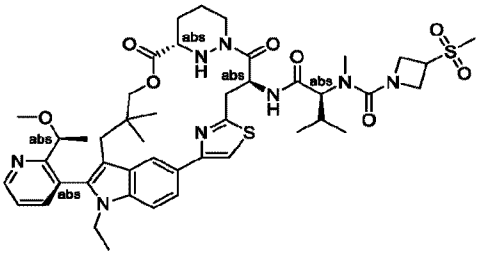
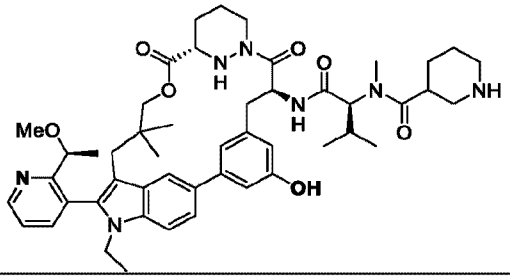
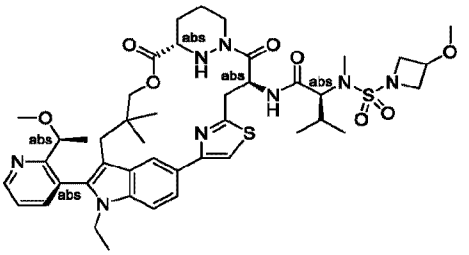
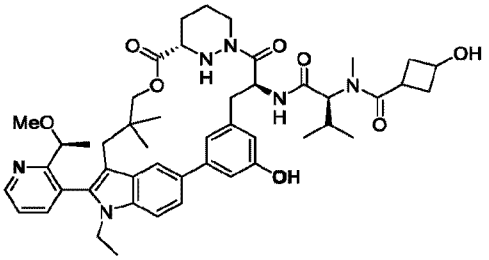
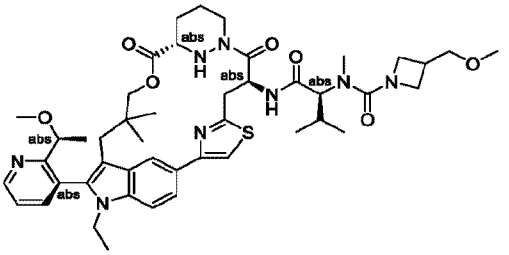
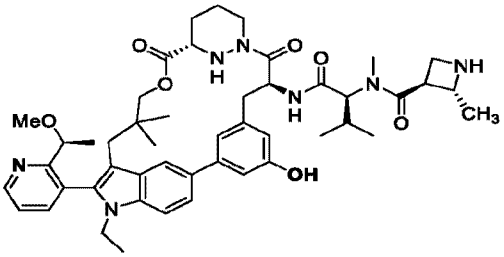
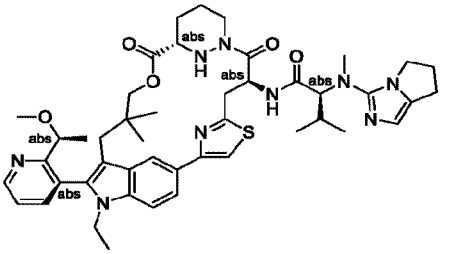
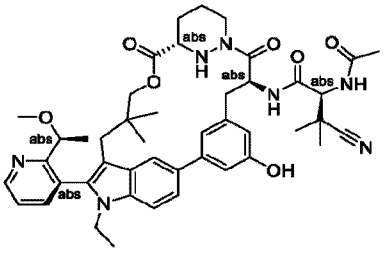
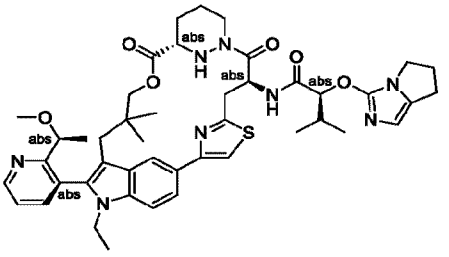
Ex#	Structure	Ex#	Structure
AB 96		AB 202	
AB 97		AB 203	
AB 99		AB 204	
AB 100		AB 205	
AB 104		AB 206	

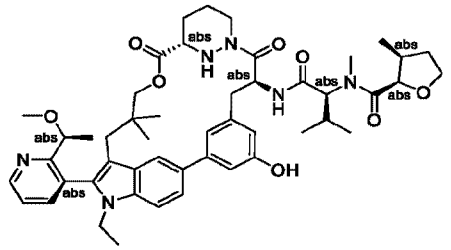
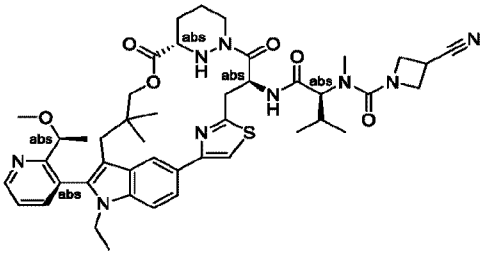
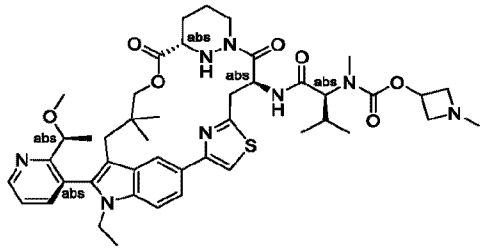
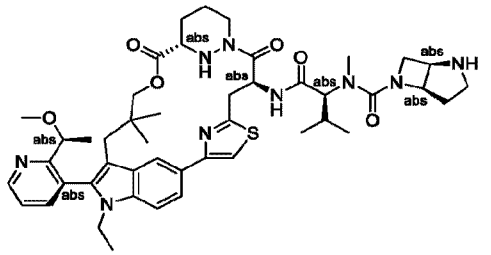
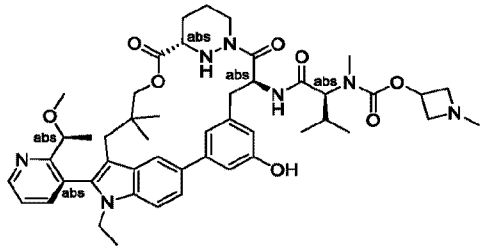
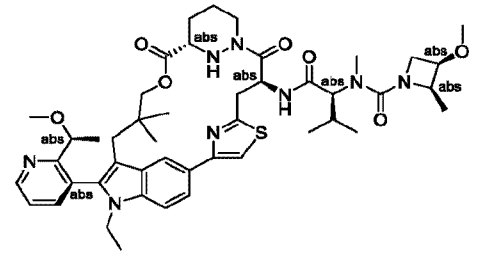
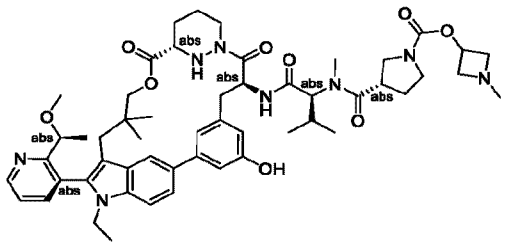
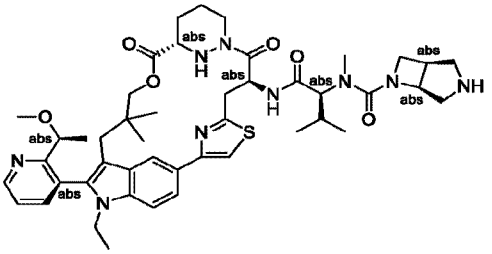
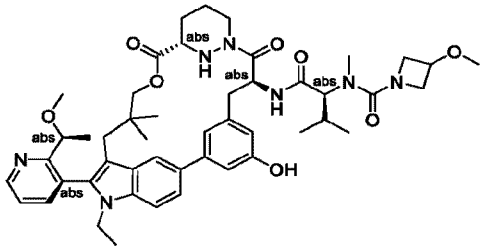
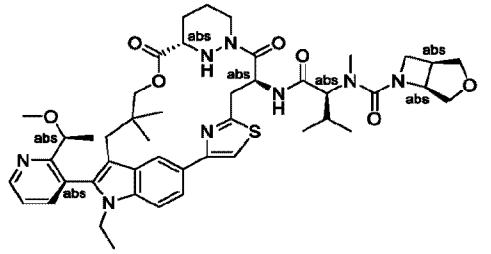
Ex#	Structure	Ex#	Structure
AB 106		AB 207	
AB 107		AB 208	
AB 109		AB 209	
AB 110		AB 210	
AB 111		AB 211	

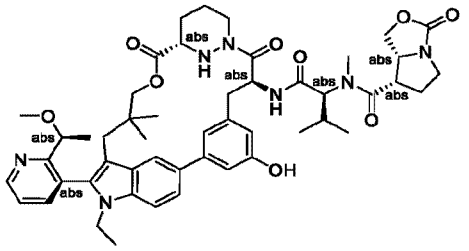
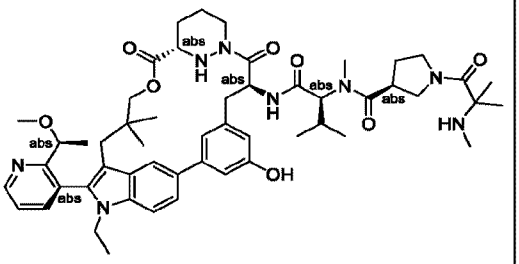
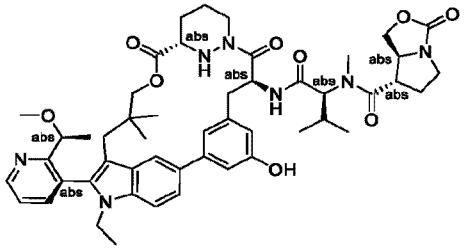
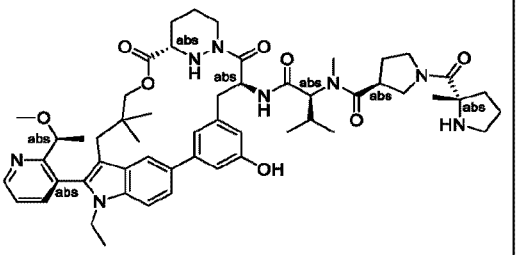
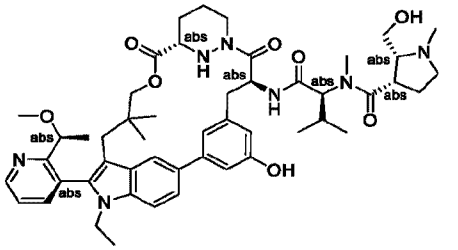
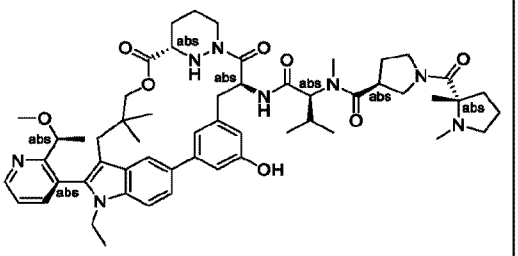
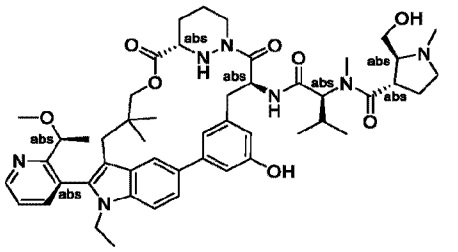
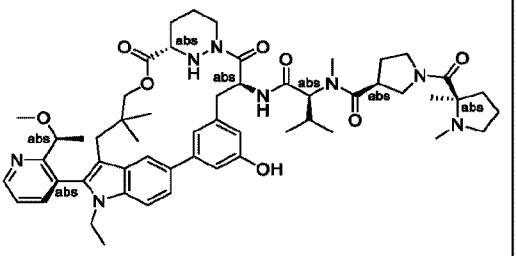
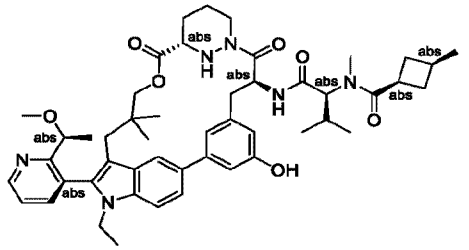
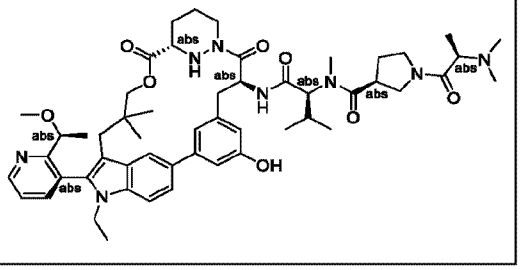
Ex#	Structure	Ex#	Structure
AB 112		AB 212	
AB 113		AB 213	
AB 114		AB 214	
AB 117		AB 215	
AB 119		AB 216	

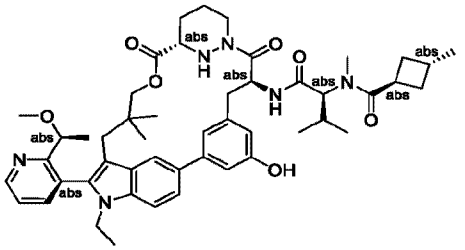
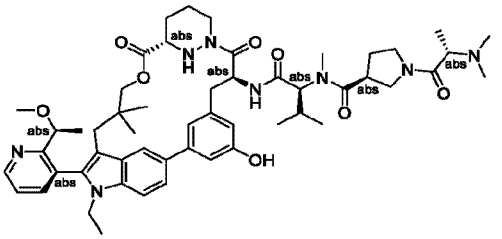
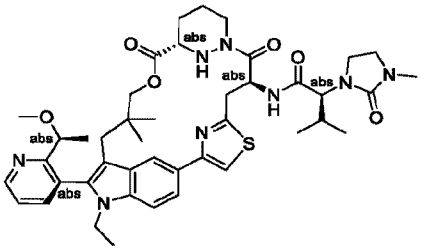
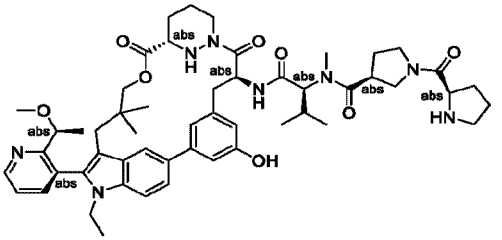
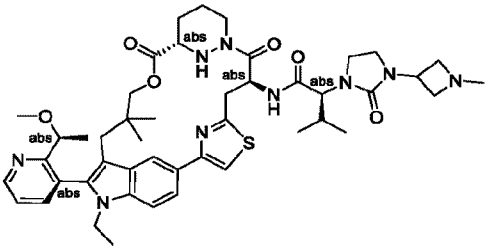
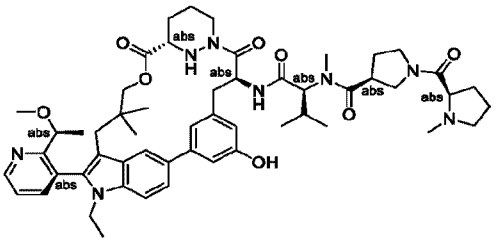
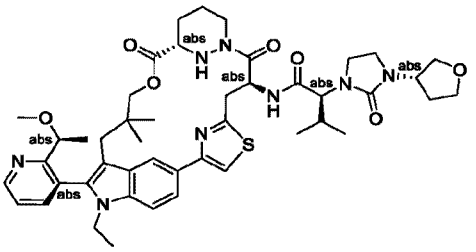
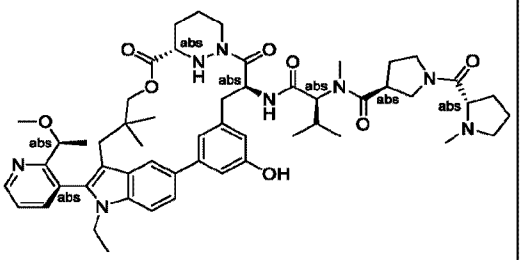
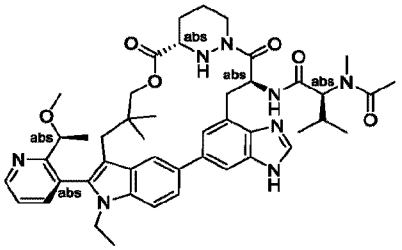
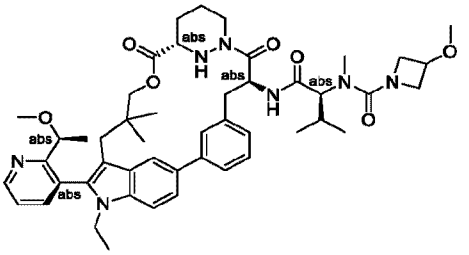
Ex#	Structure	Ex#	Structure
AB 122		AB 217	
AB 123		AB 218	
AB 124		AB 219	
AB 126		AB 220	
AB 128		AB 221	

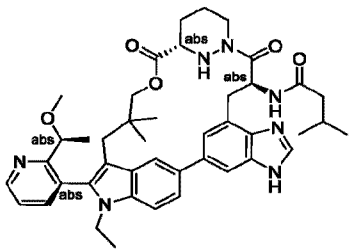
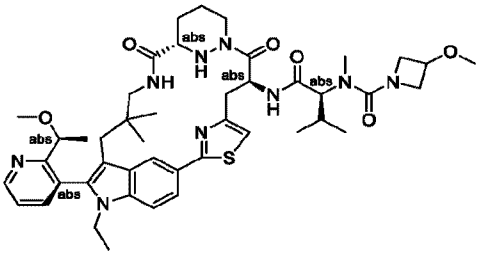
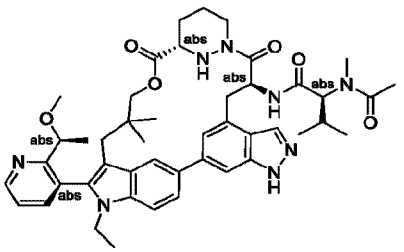
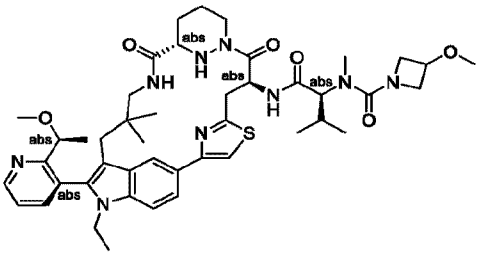
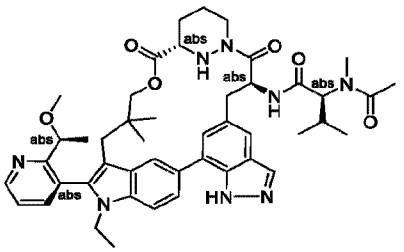
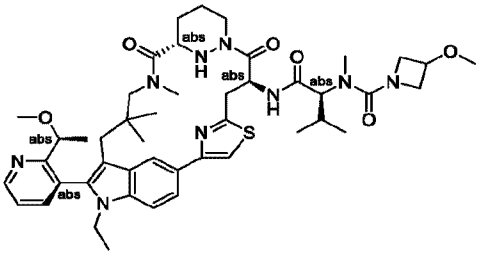
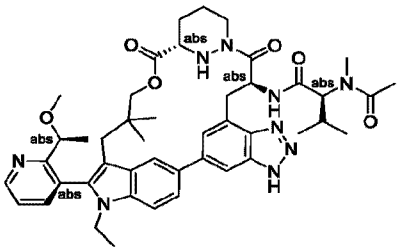
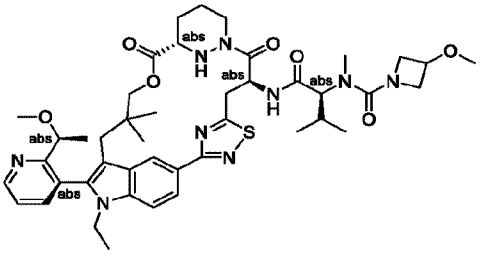
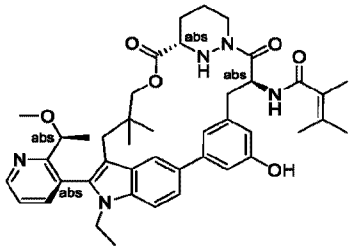
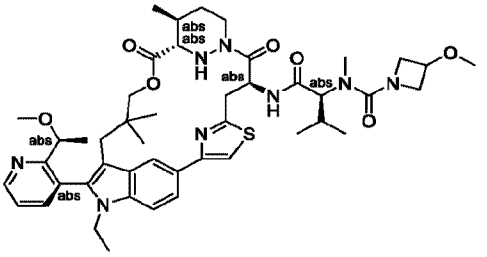
Ex#	Structure	Ex#	Structure
AB 129		AB 222	
AB 130		AB 223	
AB 133		AB 224	
AB 134		AB 225	
AB 135		AB 226	

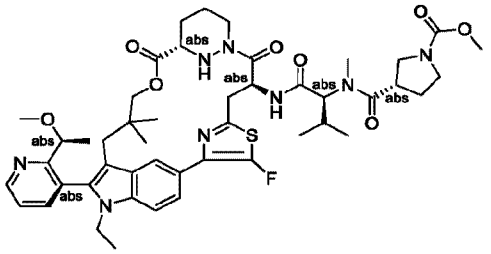
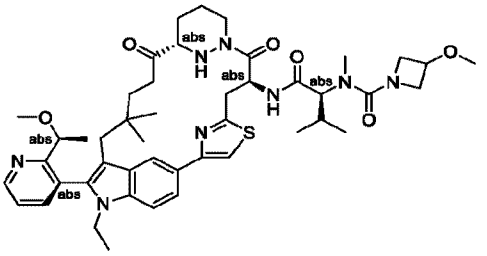
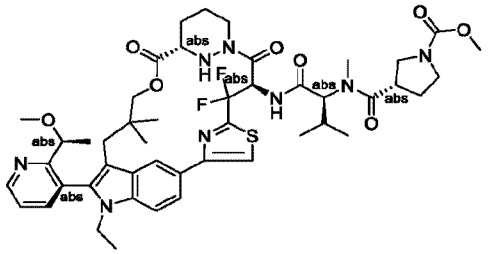
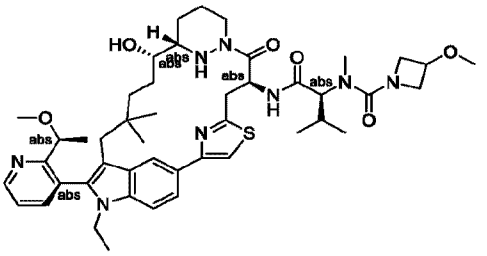
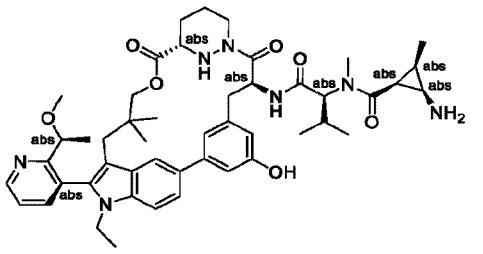
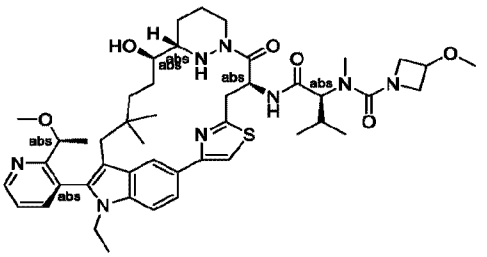
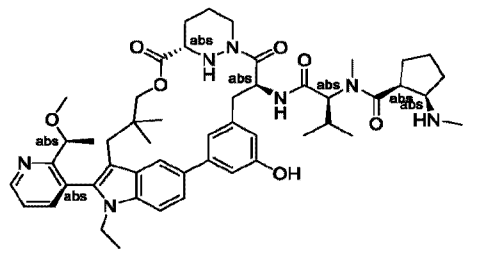
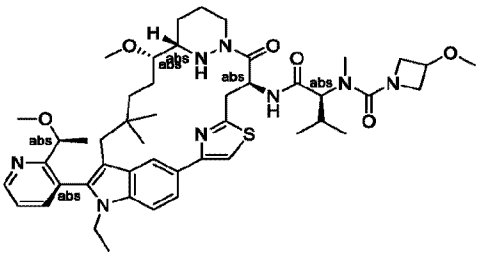
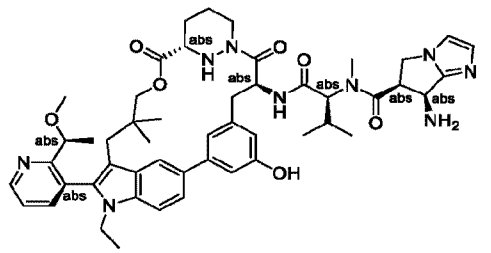
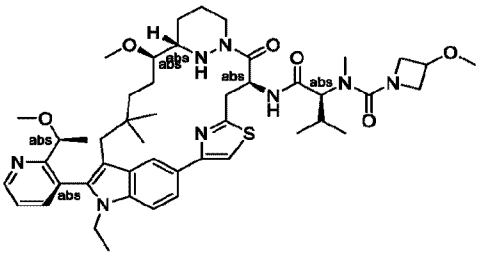
Ex#	Structure	Ex#	Structure
AB 137		AB 227	
AB 138		AB 228	
AB 139		AB 229	
AB 141		AB 230	
AB 143		AB 231	

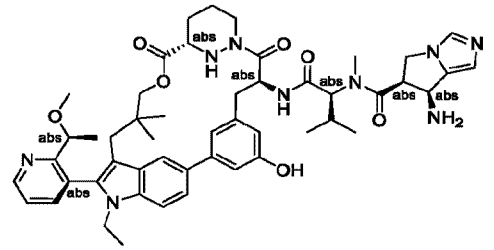
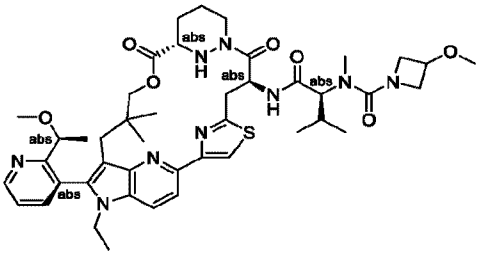
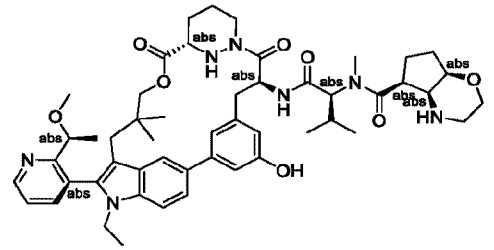
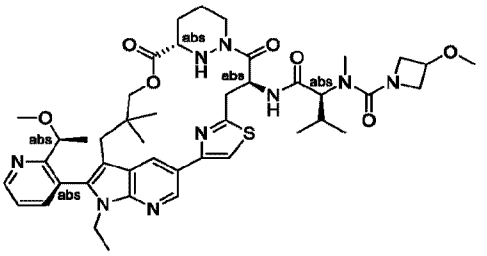
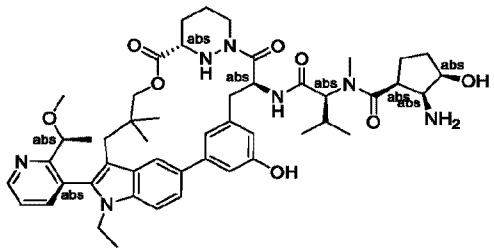
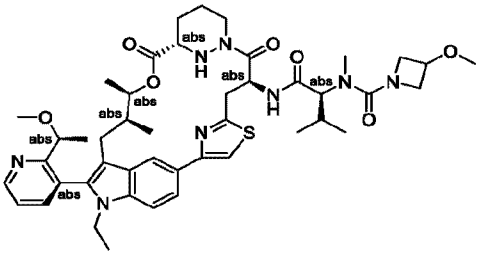
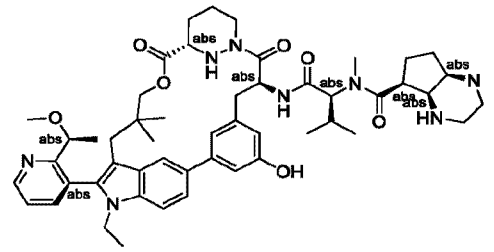
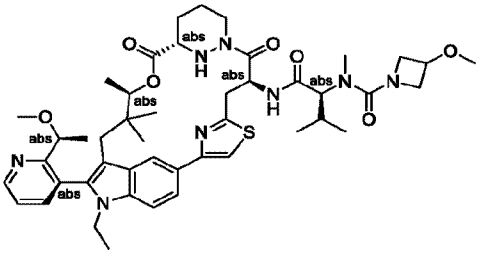
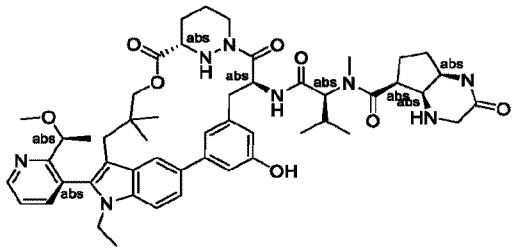
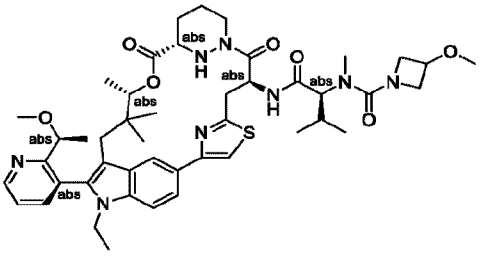
Ex#	Structure	Ex#	Structure
AB 144		AB 232	
AB 145		AB 233	
AB 146		AB 234	
AB 147		AB 235	
AB 148		AB 236	

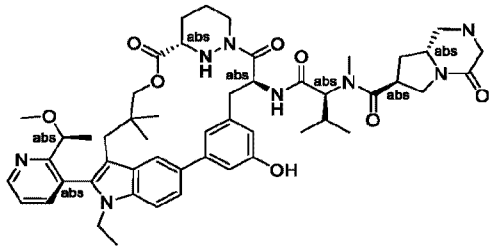
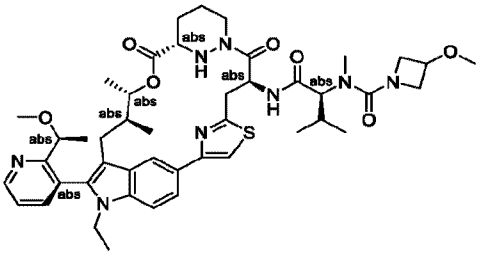
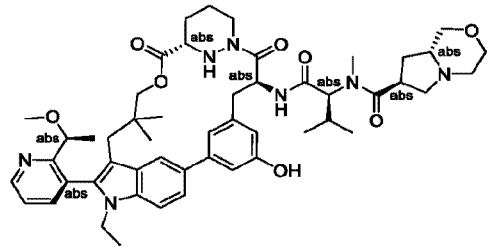
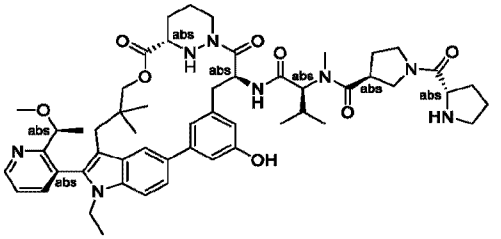
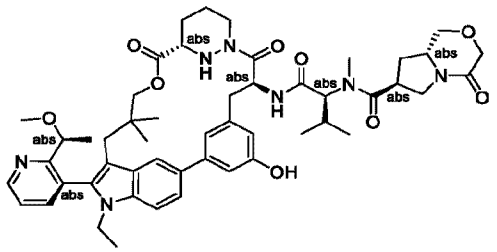
Ex#	Structure	Ex#	Structure
AB 149		AB 237	
AB 150		AB 238	
AB 151		AB 239	
AB 152		AB 240	
AB 153		AB 241	

Ex#	Structure	Ex#	Structure
AB 154		AB 242	
AB 155		AB 243	
AB 156		AB 244	
AB 157		AB 245	
AB 158		AB 246	

Ex#	Structure	Ex#	Structure
AB 159		AB 247	
AB 160		AB 248	
AB 161		AB 249	
AB 162		AB 250	
AB 163		AB 251	

Ex#	Structure	Ex#	Structure
AB 164		AB 252	
AB 165		AB 253	
AB 166		AB 254	
AB 167		AB 255	
AB 168		AB 256	

Ex#	Structure	Ex#	Structure
AB 169		AB 257	
AB 170		AB 258	
AB 171		AB 259	
AB 172		AB 260	
AB 173		AB 261	

Ex#	Structure	Ex#	Structure
AB 174		AB 262	
AB 175		AB 263	
AB 176			

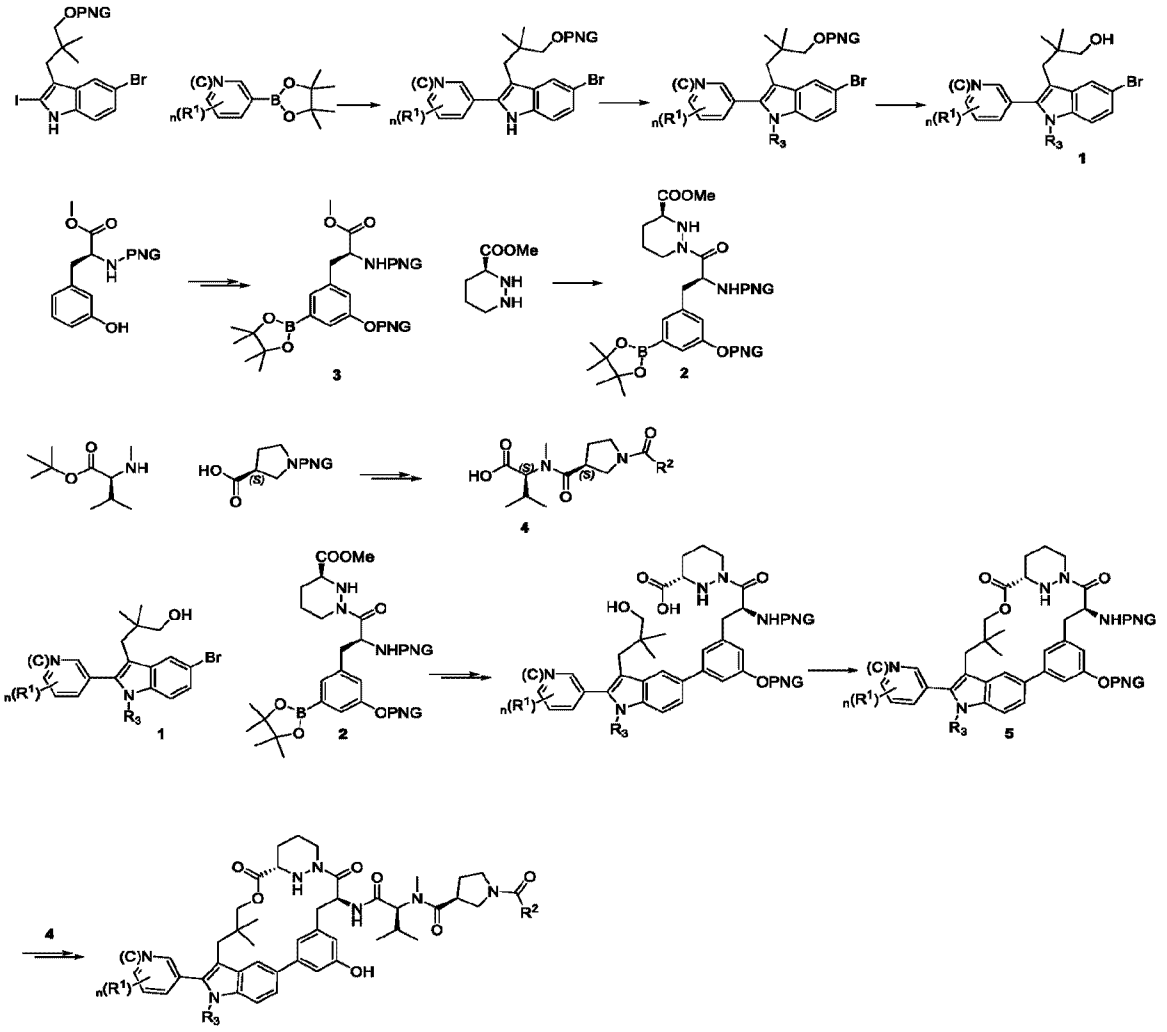
Note that some compounds are shown with bonds as flat or wedged. In some instances, the relative stereochemistry of stereoisomers has been determined; in some instances, the absolute stereochemistry has been determined. All stereoisomers of the compounds of the foregoing table are contemplated by the present invention. In particular embodiments, an atropisomer of a compound of the foregoing table is contemplated.

The compounds described herein may be made from commercially available starting materials or synthesized using known organic, inorganic, or enzymatic processes.

The compounds of the present invention can be prepared in a number of ways well known to those skilled in the art of organic synthesis. By way of example, compounds of the present invention can be synthesized using the methods described in the Schemes below and in WO 2021/091956, together with synthetic methods known in the art of synthetic organic chemistry, or variations thereon as appreciated by those skilled in the art. These methods include but are not limited to those methods described in the Schemes below or as described in WO 2021/091956.

Compounds of Table A1 herein were prepared using methods disclosed herein or were prepared using methods disclosed herein combined with the knowledge of one of skill in the art. Compounds of Table A2 may be prepared using methods disclosed herein or may be prepared using methods disclosed herein combined with the knowledge of one of skill in the art.

Scheme A1. General synthesis of macrocyclic esters



A general synthesis of macrocyclic esters is outlined in Scheme A1. An appropriately substituted Aryl Indole intermediate (**1**) can be prepared in three steps starting from protected 3-(5-bromo-2-iodo-1H-indol-3-yl)-2,2-dimethylpropan-1-ol and appropriately substituted boronic acid, including Palladium mediated coupling, alkylation, and de-protection reactions.

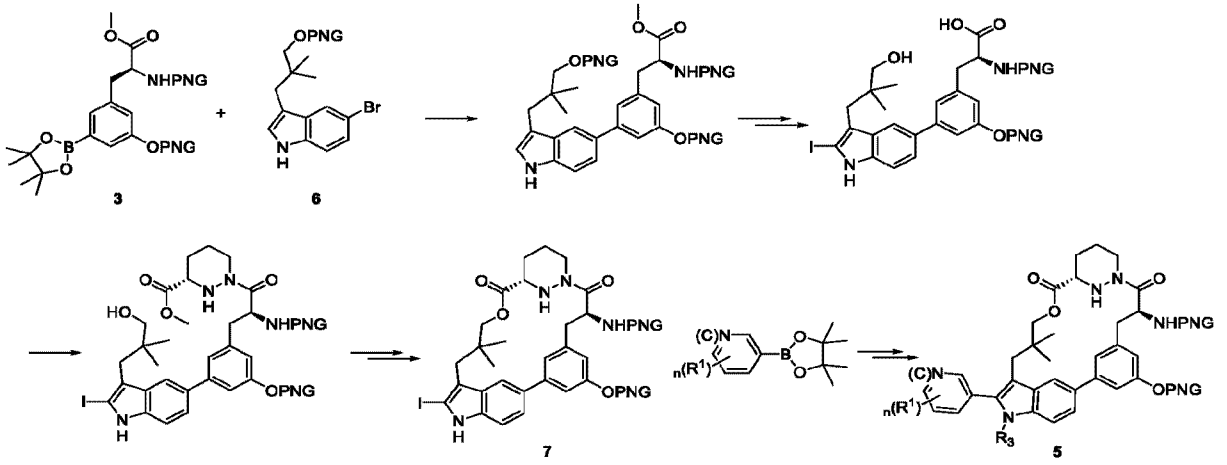
Methyl-amino-hexahydropyridazine-3-carboxylate-boronic ester (**2**) can be prepared in three steps, including protection, Iridium catalyst mediated borylation, and coupling with methyl (*S*)-hexahydropyridazine-3-carboxylate.

An appropriately substituted acetylpyrrolidine-3-carbonyl-N-methyl-L-valine (**4**) can be made by coupling of methyl-L-valinate and protected (*S*)-pyrrolidine-3-carboxylic acid, followed by deprotection, coupling with an appropriately substituted carboxylic acid, and a hydrolysis step.

The final macrocyclic esters can be made by coupling of methyl-amino-hexahydropyridazine-3-carboxylate-boronic ester (**2**) and intermediate (**1**) in the presence of Pd catalyst followed by hydrolysis and macrolactonization steps to result in an appropriately protected macrocyclic intermediate (**5**). Deprotection and coupling with an appropriately substituted acetylpyrrolidine-3-carbonyl-N-methyl-L-valine (**4**) results in a macrocyclic product. Additional deprotection or functionalization steps are be

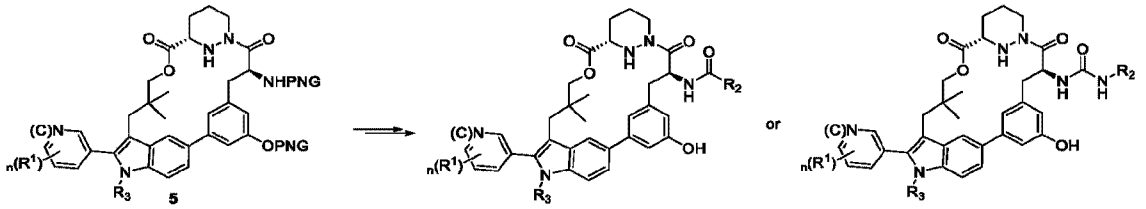
required to produce a final compound. For example, a person of skill in the art would be able to install into a macrocyclic ester a desired -B-L-W group of a compound of Formula (AI), where B, L and W are defined herein, including by using methods exemplified in the Example section herein.

Scheme A2. Alternative general synthesis of macrocyclic esters



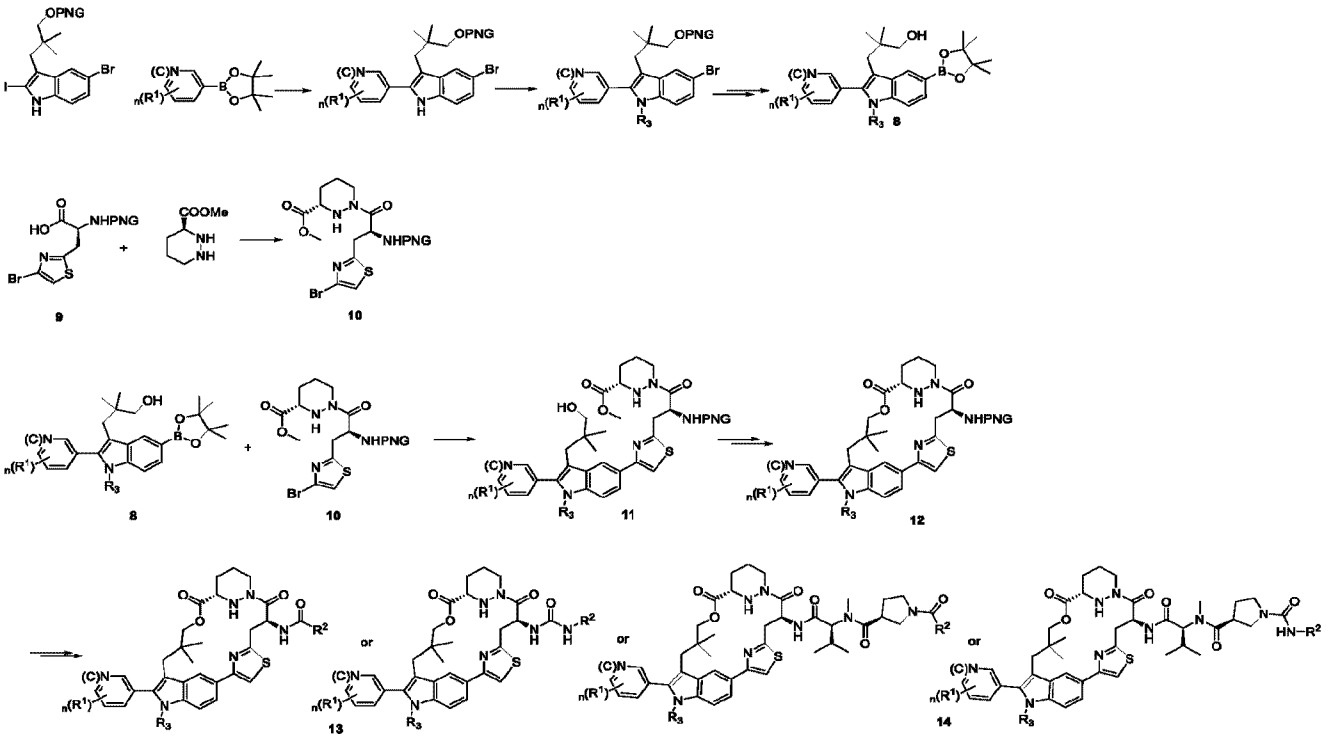
Alternatively, macrocyclic esters can be prepared as described in Scheme 2. An appropriately protected bromo-indolyl (**6**) can be coupled in the presence of Pd catalyst with boronic ester (**3**), followed by iodination, deprotection, and ester hydrolysis. Subsequent coupling with methyl (*S*)-hexahydropyridazine-3-carboxylate, followed by hydrolysis and macrolactonization can result in iodo intermediate (**7**). Coupling in the presence of Pd catalyst with an appropriately substituted boronic ester and alkylation can yield fully a protected macrocycle (**5**). Additional deprotection or functionalization steps are required to produce a final compound. For example, a person of skill in the art would be able to install into a macrocyclic ester a desired -B-L-W group of a compound of Formula (AI), where B, L and W are defined herein, including by using methods exemplified in the Example section herein.

Scheme A3. General synthesis of macrocyclic esters



Alternatively, fully a protected macrocycle (**5**) can be deprotected and coupled with an appropriately substitututed coupling partners, and deprotected to results in a macrocyclic product. Additional deprotection or functionalization steps are be required to produce a final compound. For example, a person of skill in the art would be able to install into a macrocyclic ester a desired -B-L-W group of a compound of Formula (AI), where B, L and W are defined herein, including by using methods exemplified in the Example section herein.

Scheme A4. General synthesis of macrocyclic esters



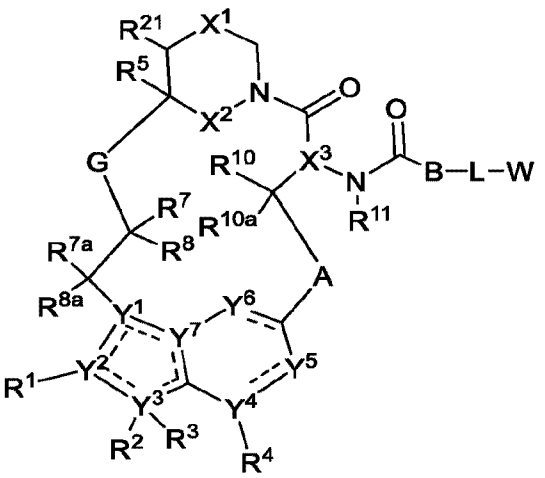
An alternative general synthesis of macrocyclic esters is outlined in Scheme A4. An appropriately substituted indolyl boronic ester (**8**) can be prepared in four steps starting from protected 3-(5-bromo-2-iodo-1H-indol-3-yl)-2,2-dimethylpropan-1-ol and appropriately substituted boronic acid, including Palladium mediated coupling, alkylation, de-protection, and Palladium mediated borylation reactions.

Methyl-amino-3-(4-bromothiazol-2-yl)propanoyl)hexahydropyridazine-3-carboxylate (**10**) can be prepared via coupling of (S)-2-amino-3-(4-bromothiazol-2-yl)propanoic acid (**9**) with methyl (*S*)-hexahydropyridazine-3-carboxylate.

The final macrocyclic esters can be made by coupling of Methyl-amino-3-(4-bromothiazol-2-yl)propanoyl)hexahydropyridazine-3-carboxylate (**10**) and an appropriately substituted indolyl boronic ester (**8**) in the presence of Pd catalyst followed by hydrolysis and macrolactonization steps to result in an appropriately protected macrocyclic intermediate (**11**). Deprotection and coupling with an appropriately substituted carboxylic acid (or other coupling partner) or intermediate **4** can result in a macrocyclic product. Additional deprotection or functionalization steps could be required to produce a final compound **13** or **14**.

In addition, compounds of the disclosure can be synthesized using the methods described in the Examples below, together with synthetic methods known in the art of synthetic organic chemistry, or variations thereon as appreciated by those skilled in the art. These methods include but are not limited to those methods described in the WO 2021/091956. For example, a person of skill in the art would be able to install into a macrocyclic ester a desired -B-L-W group of a compound of Formula (AI), where B, L and W are defined herein, including by using methods exemplified in the Example section herein.

In some embodiments, the RAS(ON) inhibitor is a compound, or a pharmaceutically acceptable salt thereof, having the structure of Formula BI:



Formula BI

wherein the dotted lines represent zero, one, two, three, or four non-adjacent double bonds;

A is -N(H or CH_3)C(O)-(CH_2)- where the amino nitrogen is bound to the carbon atom of -CH(R^{10})-, optionally substituted 3 to 6-membered cycloalkylene, optionally substituted 3 to 6-membered heterocycloalkylene, optionally substituted 6-membered arylene, or optionally substituted 5 to 10-membered heteroarylene;

B is absent, -CH(R^9)-, >C=C$R^9R^{9'}$, or >C$R^9R^{9'}$ where the carbon is bound to the carbonyl carbon of -N(R^{11})C(O)-, optionally substituted 3 to 6-membered cycloalkylene, optionally substituted 3 to 6-membered heterocycloalkylene, optionally substituted 6-membered arylene, or 5 to 6-membered heteroarylene;

G is optionally substituted C_1-C_4 alkylene, optionally substituted C_1-C_4 alkenylene, optionally substituted C_1-C_4 heteroalkylene, -C(O)O-**C**H(R^6)- where **C** is bound to -C(R^7R^8)-, -C(O)NH-**C**H(R^6)- where **C** is bound to -C(R^7R^8)-, optionally substituted C_1-C_4 heteroalkylene, or 3 to 8-membered heteroarylene;

L is absent or a linker;

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

X^1 is optionally substituted C_1-C_2 alkylene, NR, O, or $S(O)_n$;

X^2 is O or NH;

X^3 is N or CH;

n is 0, 1, or 2;

R is hydrogen, cyano, optionally substituted C_1-C_4 alkyl, optionally substituted C_2-C_4 alkenyl, optionally substituted C_2-C_4 alkynyl, C(O)R', C(O)OR', C(O)N(R')$_2$, S(O)R', $S(O)_2$R', or $S(O)_2$N(R')$_2$;

each R' is, independently, H or optionally substituted C_1-C_4 alkyl;

Y^1 is C, CH, or N;

Y^2, Y^3, Y^4, and Y^7 are, independently, C or N;

Y^5 is CH, CH_2, or N;

Y^6 is C(O), CH, CH_2, or N;

R^1 is cyano, 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 cycloalkenyl, optionally

substituted 3 to 6-membered heterocycloalkyl, optionally substituted 6 to 10-membered aryl, or optionally substituted 5 to 10-membered heteroaryl, or

R^1 and R^2 combine with the atoms to which they are attached to form an optionally substituted 3 to 14-membered heterocycloalkyl;

R^2 is absent, hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 alkynyl, optionally substituted 3 to 6-membered cycloalkyl, optionally substituted 3 to 7-membered heterocycloalkyl, optionally substituted 6-membered aryl, optionally substituted 5 or 6-membered heteroaryl; R^3 is absent, or

R^2 and R^3 combine with the atom to which they are attached to form an optionally substituted 3 to 8-membered cycloalkyl or optionally substituted 3 to 14-membered heterocycloalkyl;

R^4 is absent, hydrogen, halogen, cyano, or methyl optionally substituted with 1 to 3 halogens;

R^5 is hydrogen, C_1-C_4 alkyl optionally substituted with halogen, cyano, hydroxy, or C_1-C_4 alkoxy, cyclopropyl, or cyclobutyl;

R^6 is hydrogen or methyl; R^7 is hydrogen, halogen, or optionally substituted C_1-C_3 alkyl, or

R^6 and R^7 combine with the carbon atoms to which they are attached to form an optionally substituted 3 to 6-membered cycloalkyl or optionally substituted 3 to 7-membered heterocycloalkyl;

R^8 is hydrogen, halogen, hydroxy, cyano, optionally substituted C_1-C_3 alkoxy, optionally substituted C_1-C_3 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 alkynyl, optionally substituted 3 to 8-membered cycloalkyl, optionally substituted 3 to 14-membered heterocycloalkyl, optionally substituted 5 to 10-membered heteroaryl, or optionally substituted 6 to 10-membered aryl, or

R^7 and R^8 combine with the carbon atom to which they are attached to form $C=CR^{7'}R^{8'}$; C=N(OH), C=N(O-C_1-C_3 alkyl), C=O, C=S, C=NH, optionally substituted 3 to 6-membered cycloalkyl, or optionally substituted 3 to 7-membered heterocycloalkyl;

R^{7a} and R^{8a} are, independently, hydrogen, halo, optionally substituted C_1-C_3 alkyl, or combine with the carbon to which they are attached to form a carbonyl;

$R^{7'}$ is hydrogen, halogen, or optionally substituted C_1-C_3 alkyl; $R^{8'}$ is hydrogen, halogen, hydroxy, cyano, optionally substituted C_1-C_3 alkoxy, optionally substituted C_1-C_3 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 alkynyl, optionally substituted 3 to 8-membered cycloalkyl, optionally substituted 3 to 14-membered heterocycloalkyl, optionally substituted 5 to 10-membered heteroaryl, or optionally substituted 6 to 10-membered aryl, or

$R^{7'}$ and $R^{8'}$ combine with the carbon atom to which they are attached to form optionally substituted 3 to 6-membered cycloalkyl or optionally substituted 3 to 7-membered heterocycloalkyl;

R^9 is H, F, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted 3 to 6-membered cycloalkyl, or optionally substituted 3 to 7-membered heterocycloalkyl, or

R^9 and L combine with the atoms to which they are attached to form an optionally substituted 3 to 14-membered heterocycloalkyl;

$R^{9'}$ is hydrogen or optionally substituted C_1-C_6 alkyl; or

R^9 and $R^{9'}$, combined with the atoms to which they are attached, form a 3 to 6-membered cycloalkyl or a 3 to 6-membered heterocycloalkyl;

R^{10} is hydrogen, halo, hydroxy, C_1-C_3 alkoxy, or C_1-C_3 alkyl;

R^{10a} is hydrogen or halo;

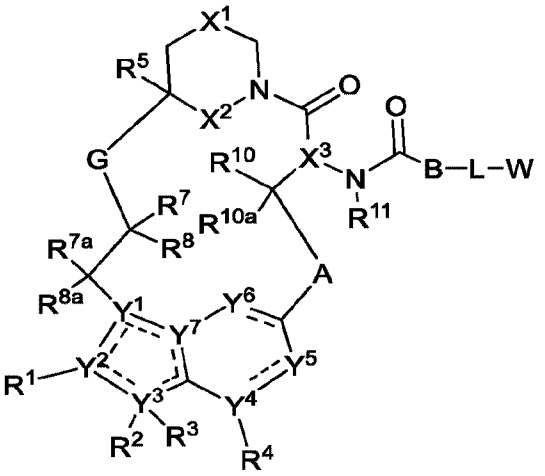
R^{11} is hydrogen or C_1-C_3 alkyl; and

R^{21} is hydrogen or C_1-C_3 alkyl (e.g., methyl).

In some embodiments of Formula BI, R^9 is H, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted 3 to 6-membered cycloalkyl, or optionally substituted 3 to 7-membered heterocycloalkyl.

In some embodiments of Formula BI, R^{21} is hydrogen.

In some embodiments, provided herein is a compound, or pharmaceutically acceptable salt thereof, having the structure of Formula BIa:



Formula BIa

wherein the dotted lines represent zero, one, two, three, or four non-adjacent double bonds;

A is -N(H or CH_3)C(O)-(CH_2)- where the amino nitrogen is bound to the carbon atom of -CH(R^{10})-, optionally substituted 3 to 6-membered cycloalkylene, optionally substituted 3 to 6-membered heterocycloalkylene, optionally substituted 6-membered arylene, or optionally substituted 5 to 10-membered heteroarylene;

B is -CH(R^9)- or >C=C$R^9R^{9'}$ where the carbon is bound to the carbonyl carbon of -N(R^{11})C(O)-, optionally substituted 3 to 6-membered cycloalkylene, optionally substituted 3 to 6-membered heterocycloalkylene, optionally substituted 6-membered arylene, or 5 to 6-membered heteroarylene;

G is optionally substituted C_1-C_4 alkylene, optionally substituted C_1-C_4 alkenylene, optionally substituted C_1-C_4 heteroalkylene, -C(O)O-**C**H(R^6)- where **C** is bound to -C(R^7R^8)-, -C(O)NH-**C**H(R^6)- where **C** is bound to -C(R^7R^8)-, optionally substituted C_1-C_4 heteroalkylene, or 3 to 8-membered heteroarylene;

L is absent or a linker;

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

X^1 is optionally substituted C_1-C_2 alkylene, NR, O, or $S(O)_n$;

X^2 is O or NH;

X^3 is N or CH;

n is 0, 1, or 2;

R is hydrogen, cyano, optionally substituted C_1-C_4 alkyl, optionally substituted C_2-C_4 alkenyl, optionally substituted C_2-C_4 alkynyl, C(O)R', C(O)OR', C(O)N(R')$_2$, S(O)R', S(O)$_2$R', or S(O)$_2$N(R')$_2$;

each R' is, independently, H or optionally substituted C_1-C_4 alkyl;

Y^1 is C, CH, or N;

Y^2, Y^3, Y^4, and Y^7 are, independently, C or N;

Y^5 is CH, CH_2, or N;

Y^6 is C(O), CH, CH_2, or N;

R^1 is cyano, optionally substituted C_1-C_8 alkyl, optionally substituted C_1-C_8 heteroalkyl, optionally substituted 3 to 6-membered cycloalkyl, optionally substituted 3 to 6-membered cycloalkenyl, optionally substituted 3 to 6-membered heterocycloalkyl, optionally substituted 6 to 10-membered aryl, or optionally substituted 5 to 10-membered heteroaryl, or

R^1 and R^2 combine with the atoms to which they are attached to form an optionally substituted 3 to 14-membered heterocycloalkyl;

R^2 is absent, hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 alkynyl, optionally substituted 3 to 6-membered cycloalkyl, optionally substituted 3 to 7-membered heterocycloalkyl, optionally substituted 6-membered aryl, optionally substituted 5 or 6-membered heteroaryl; R^3 is absent, or

R^2 and R^3 combine with the atom to which they are attached to form an optionally substituted 3 to 8-membered cycloalkyl or optionally substituted 3 to 14-membered heterocycloalkyl;

R^4 is absent, hydrogen, halogen, cyano, or methyl optionally substituted with 1 to 3 halogens;

R^5 is hydrogen, C_1-C_4 alkyl optionally substituted with halogen, cyano, hydroxy, or C_1-C_4 alkoxy, cyclopropyl, or cyclobutyl;

R^6 is hydrogen or methyl; R^7 is hydrogen, halogen, or optionally substituted C_1-C_3 alkyl, or

R^6 and R^7 combine with the carbon atoms to which they are attached to form an optionally substituted 3 to 6-membered cycloalkyl or optionally substituted 3 to 7-membered heterocycloalkyl;

R^8 is hydrogen, halogen, hydroxy, cyano, optionally substituted C_1-C_3 alkoxy, optionally substituted C_1-C_3 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 alkynyl, optionally substituted 3 to 8-membered cycloalkyl, optionally substituted 3 to 14-membered heterocycloalkyl, optionally substituted 5 to 10-membered heteroaryl, or optionally substituted 6 to 10-membered aryl, or

R^7 and R^8 combine with the carbon atom to which they are attached to form $C=CR^{7'}R^{8'}$; C=N(OH), C=N(O-C_1-C_3 alkyl), C=O, C=S, C=NH, optionally substituted 3 to 6-membered cycloalkyl, or optionally substituted 3 to 7-membered heterocycloalkyl;

R^{7a} and R^{8a} are, independently, hydrogen, halo, optionally substituted C_1-C_3 alkyl, or combine with the carbon to which they are attached to form a carbonyl;

$R^{7'}$ is hydrogen, halogen, or optionally substituted C_1-C_3 alkyl; $R^{8'}$ is hydrogen, halogen, hydroxy, cyano, optionally substituted C_1-C_3 alkoxy, optionally substituted C_1-C_3 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 alkynyl, optionally substituted 3 to 8-membered cycloalkyl, optionally substituted 3 to 14-membered heterocycloalkyl, optionally substituted 5 to 10-membered heteroaryl, or optionally substituted 6 to 10-membered aryl, or

$R^{7'}$ and $R^{8'}$ combine with the carbon atom to which they are attached to form optionally substituted 3 to 6-membered cycloalkyl or optionally substituted 3 to 7-membered heterocycloalkyl;

R^9 is optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted 3 to 6-membered cycloalkyl, or optionally substituted 3 to 7-membered heterocycloalkyl, or

R^9 and L combine with the atoms to which they are attached to form an optionally substituted 3 to 14-membered heterocycloalkyl;

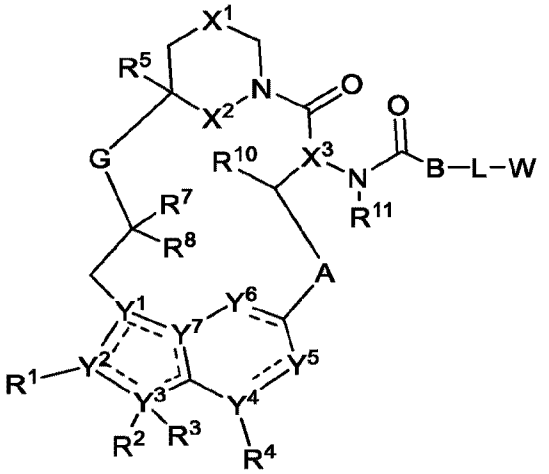
$R^{9'}$ is hydrogen or optionally substituted C_1-C_6 alkyl;

R^{10} is hydrogen, halo, hydroxy, C_1-C_3 alkoxy, or C_1-C_3 alkyl;

R^{10a} is hydrogen or halo; and

R^{11} is hydrogen or C_1-C_3 alkyl.

In some embodiments, the disclosure features a compound, or pharmaceutically acceptable salt thereof, of structural Formula BIb:



Formula BIb

wherein the dotted lines represent zero, one, two, three, or four non-adjacent double bonds;

A is -N(H or CH_3)C(O)-(CH_2)- where the amino nitrogen is bound to the carbon atom of -CH(R^{10})-, optionally substituted 3 to 6-membered cycloalkylene, optionally substituted 3 to 6-membered heterocycloalkylene, optionally substituted 6-membered arylene, or optionally substituted 5 to 6-membered heteroarylene;

B is -CH(R^9)- where the carbon is bound to the carbonyl carbon of -N(R^{11})C(O)-, optionally substituted 3 to 6-membered cycloalkylene, optionally substituted 3 to 6-membered heterocycloalkylene, optionally substituted 6-membered arylene, or 5 to 6-membered heteroarylene;

G is optionally substituted C_1-C_4 alkylene, optionally substituted C_1-C_4 alkenylene, optionally substituted C_1-C_4 heteroalkylene, -C(O)O-**C**H(R^6)- where **C** is bound to -C(R^7R^8)-, -C(O)NH-**C**H(R^6)- where **C** is bound to -C(R^7R^8)-, optionally substituted C_1-C_4 heteroalkylene, or 3 to 8-membered heteroarylene;

L is absent or a linker;

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

X^1 is optionally substituted C_1-C_2 alkylene, NR, O, or $S(O)_n$;

X^2 is O or NH;

X^3 is N or CH;

n is 0, 1, or 2;

R is hydrogen, cyano, optionally substituted C_1-C_4 alkyl, optionally substituted C_2-C_4 alkenyl, optionally substituted C_2-C_4 alkynyl, C(O)R', C(O)OR', C(O)N(R')$_2$, S(O)R', S(O)$_2$R', or S(O)$_2$N(R')$_2$;

each R' is, independently, H or optionally substituted C_1-C_4 alkyl;

Y^1 is C, CH, or N;

Y^2, Y^3, Y^4, and Y^7 are, independently, C or N;

Y^5 and Y^6 are, independently, CH or N;

R^1 is cyano, 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 cycloalkenyl, optionally substituted 3 to 6-membered heterocycloalkyl, optionally substituted 6 to 10-membered aryl, or optionally substituted 5 to 10-membered heteroaryl;

R^2 is hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted 3 to 6-membered cycloalkyl, optionally substituted 3 to 7-membered heterocycloalkyl, optionally substituted 6-membered aryl, optionally substituted 5 or 6-membered heteroaryl; R^3 is absent, or

R^2 and R^3 combine with the atom to which they are attached to form an optionally substituted 3 to 8-membered cycloalkyl or optionally substituted 3 to 14-membered heterocycloalkyl;

R^4 is absent, hydrogen, halogen, cyano, or methyl optionally substituted with 1 to 3 halogens;

R^5 is hydrogen, C_1-C_4 alkyl optionally substituted with halogen, cyano, hydroxy, or C_1-C_4 alkoxy, cyclopropyl, or cyclobutyl;

R^6 is hydrogen or methyl; R^7 is hydrogen, halogen, or optionally substituted C_1-C_3 alkyl, or

R^6 and R^7 combine with the carbon atoms to which they are attached to form an optionally substituted 3 to 6-membered cycloalkyl or optionally substituted 3 to 7-membered heterocycloalkyl;

R^8 is hydrogen, halogen, hydroxy, cyano, optionally substituted C_1-C_3 alkoxy, optionally substituted C_1-C_3 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 alkynyl, optionally substituted 3 to 8-membered cycloalkyl, optionally substituted 3 to 14-membered heterocycloalkyl, optionally substituted 5 to 10-membered heteroaryl, or optionally substituted 6 to 10-membered aryl, or

R^7 and R^8 combine with the carbon atom to which they are attached to form $C=CR^{7'}R^{8'}$; C=N(OH), C=N(O-C_1-C_3 alkyl), C=O, C=S, C=NH, optionally substituted 3 to 6-membered cycloalkyl, or optionally substituted 3 to 7-membered heterocycloalkyl;

$R^{7'}$ is hydrogen, halogen, or optionally substituted C_1-C_3 alkyl; $R^{8'}$ is hydrogen, halogen, hydroxy, cyano, optionally substituted C_1-C_3 alkoxy, optionally substituted C_1-C_3 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 alkynyl, optionally substituted 3 to 8-membered cycloalkyl, optionally substituted 3 to 14-membered heterocycloalkyl, optionally substituted 5 to 10-membered heteroaryl, or optionally substituted 6 to 10-membered aryl, or

$R^{7'}$ and $R^{8'}$ combine with the carbon atom to which they are attached to form optionally substituted 3 to 6-membered cycloalkyl or optionally substituted 3 to 7-membered heterocycloalkyl;

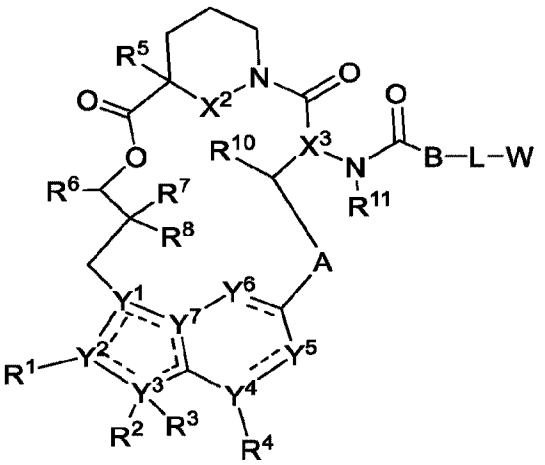
R^9 is optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted 3 to 6-membered cycloalkyl, or optionally substituted 3 to 7-membered heterocycloalkyl;

R^{10} is hydrogen, hydroxy, C_1-C_3 alkoxy, or C_1-C_3 alkyl; and

R^{11} is hydrogen or C_1-C_3 alkyl.

In some embodiments of Formula BI and subformula thereof, G is optionally substituted C_1-C_4 heteroalkylene.

In some embodiments, a compound having the structure of Formula BIc is provided, or a pharmaceutically acceptable salt thereof:



Formula BIc

wherein the dotted lines represent zero, one, two, three, or four non-adjacent double bonds;

A is -N(H or CH_3)C(O)-(CH_2)- where the amino nitrogen is bound to the carbon atom of -CH(R^{10})-, optionally substituted 3 to 6-membered cycloalkylene, optionally substituted 3 to 6-membered heterocycloalkylene, optionally substituted 6-membered arylene, or optionally substituted 5 to 6-membered heteroarylene;

B is -CH(R^9)- where the carbon is bound to the carbonyl carbon of -N(R^{11})C(O)-, optionally substituted 3 to 6-membered cycloalkylene, optionally substituted 3 to 6-membered heterocycloalkylene, optionally substituted 6-membered arylene, or 5 to 6-membered heteroarylene;

L is absent or a linker;

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

X^2 is O or NH;

X^3 is N or CH;

n is 0, 1, or 2;

R is hydrogen, cyano, optionally substituted C_1-C_4 alkyl, optionally substituted C_2-C_4 alkenyl, optionally substituted C_2-C_4 alkynyl, C(O)R', C(O)OR', C(O)N(R')$_2$, S(O)R', S(O)$_2$R', or S(O)$_2$N(R')$_2$;

each R' is, independently, H or optionally substituted C_1-C_4 alkyl;

Y^1 is C, CH, or N;

Y^2, Y^3, Y^4, and Y^7 are, independently, C or N;

Y^5 and Y^6 are, independently, CH or N;

R^1 is cyano, 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 cycloalkenyl, optionally substituted 3 to 6-membered heterocycloalkyl, optionally substituted 6 to 10-membered aryl, or optionally substituted 5 to 10-membered heteroaryl;

R^2 is hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted 3 to 6-membered cycloalkyl, optionally substituted 3 to 7-membered heterocycloalkyl, optionally substituted 6-membered aryl, optionally substituted 5 or 6-membered heteroaryl; R^3 is absent, or

R^2 and R^3 combine with the atom to which they are attached to form an optionally substituted 3 to 8-membered cycloalkyl or optionally substituted 3 to 14-membered heterocycloalkyl;

R^4 is absent, hydrogen, halogen, cyano, or methyl optionally substituted with 1 to 3 halogens;

R^5 is hydrogen, C_1-C_4 alkyl optionally substituted with halogen, cyano, hydroxy, or C_1-C_4 alkoxy, cyclopropyl, or cyclobutyl;

R^6 is hydrogen or methyl; R^7 is hydrogen, halogen, or optionally substituted C_1-C_3 alkyl, or

R^6 and R^7 combine with the carbon atoms to which they are attached to form an optionally substituted 3 to 6-membered cycloalkyl or optionally substituted 3 to 7-membered heterocycloalkyl;

R^8 is hydrogen, halogen, hydroxy, cyano, optionally substituted C_1-C_3 alkoxy, optionally substituted C_1-C_3 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 alkynyl, optionally substituted 3 to 8-membered cycloalkyl, optionally substituted 3 to 14-membered heterocycloalkyl, optionally substituted 5 to 10-membered heteroaryl, or optionally substituted 6 to 10-membered aryl, or

R^7 and R^8 combine with the carbon atom to which they are attached to form $C=CR^{7'}R^{8'}$; C=N(OH), C=N(O-C_1-C_3 alkyl), C=O, C=S, C=NH, optionally substituted 3 to 6-membered cycloalkyl, or optionally substituted 3 to 7-membered heterocycloalkyl;

$R^{7'}$ is hydrogen, halogen, or optionally substituted C_1-C_3 alkyl; $R^{8'}$ is hydrogen, halogen, hydroxy, cyano, optionally substituted C_1-C_3 alkoxy, optionally substituted C_1-C_3 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 alkynyl, optionally substituted 3 to 8-membered cycloalkyl, optionally substituted 3 to 14-membered heterocycloalkyl, optionally substituted 5 to 10-membered heteroaryl, or optionally substituted 6 to 10-membered aryl, or

$R^{7'}$ and $R^{8'}$ combine with the carbon atom to which they are attached to form optionally substituted 3 to 6-membered cycloalkyl or optionally substituted 3 to 7-membered heterocycloalkyl;

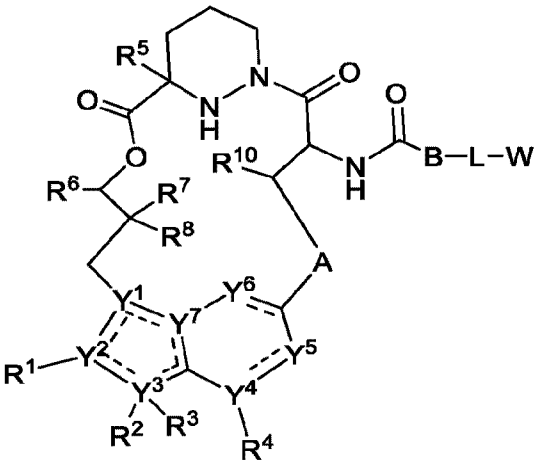
R^9 is optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted 3 to 6-membered cycloalkyl, or optionally substituted 3 to 7-membered heterocycloalkyl;

R^{10} is hydrogen, hydroxy, C_1-C_3 alkoxy, or C_1-C_3 alkyl; and

R^{11} is hydrogen or C_1-C_3 alkyl.

In some embodiments of Formula BI and subformula thereof, X^2 is NH. In some embodiments of Formula BI and subformula thereof, X^3 is CH. In some embodiments of Formula BI and subformula thereof, R^{11} is hydrogen. In some embodiments of Formula BI and subformula thereof, R^{11} is C_1-C_3 alkyl. In some embodiments of Formula BI and subformula thereof, R^{11} is methyl.

In some embodiments, the RAS(ON) inhibitor has the structure of Formula BId, or a pharmaceutically acceptable salt thereof:



Formula BId

wherein the dotted lines represent zero, one, two, three, or four non-adjacent double bonds;

A is -N(H or CH_3)C(O)-(CH_2)- where the amino nitrogen is bound to the carbon atom of -CH(R^{10})-, optionally substituted 3 to 6-membered cycloalkylene, optionally substituted 3 to 6-membered heterocycloalkylene, optionally substituted 6-membered arylene, or optionally substituted 5 to 6-membered heteroarylene;

B is -CH(R^9)- where the carbon is bound to the carbonyl carbon of -NHC(O)-, optionally substituted 3 to 6-membered cycloalkylene, optionally substituted 3 to 6-membered heterocycloalkylene, optionally substituted 6-membered arylene, or 5 to 6-membered heteroarylene;

L is absent or a linker;

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

n is 0, 1, or 2;

R is hydrogen, cyano, optionally substituted C_1-C_4 alkyl, optionally substituted C_2-C_4 alkenyl, optionally substituted C_2-C_4 alkynyl, C(O)R', C(O)OR', C(O)N(R')$_2$, S(O)R', S(O)$_2$R', or S(O)$_2$N(R')$_2$;

each R' is, independently, H or optionally substituted C_1-C_4 alkyl;

Y^1 is C, CH, or N;

Y^2, Y^3, Y^4, and Y^7 are, independently, C or N;

Y^5 and Y^6 are, independently, CH or N;

R^1 is cyano, 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 cycloalkenyl, optionally substituted 3 to 6-membered heterocycloalkyl, optionally substituted 6 to 10-membered aryl, or optionally substituted 5 to 10-membered heteroaryl;

R^2 is hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted 3 to 6-membered cycloalkyl, optionally substituted 3 to 7-membered heterocycloalkyl, optionally substituted 6-membered aryl, optionally substituted 5 or 6-membered heteroaryl; R^3 is absent, or

R^2 and R^3 combine with the atom to which they are attached to form an optionally substituted 3 to 8-membered cycloalkyl or optionally substituted 3 to 14-membered heterocycloalkyl;

R^4 is absent, hydrogen, halogen, cyano, or methyl optionally substituted with 1 to 3 halogens;

R^5 is hydrogen, C_1-C_4 alkyl optionally substituted with halogen, cyano, hydroxy, or C_1-C_4 alkoxy, cyclopropyl, or cyclobutyl;

R^6 is hydrogen or methyl; R^7 is hydrogen, halogen, or optionally substituted C_1-C_3 alkyl, or

R^6 and R^7 combine with the carbon atoms to which they are attached to form an optionally substituted 3 to 6-membered cycloalkyl or optionally substituted 3 to 7-membered heterocycloalkyl;

R^8 is hydrogen, halogen, hydroxy, cyano, optionally substituted C_1-C_3 alkoxy, optionally substituted C_1-C_3 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 alkynyl, optionally substituted 3 to 8-membered cycloalkyl, optionally substituted 3 to 14-membered heterocycloalkyl, optionally substituted 5 to 10-membered heteroaryl, or optionally substituted 6 to 10-membered aryl, or

R^7 and R^8 combine with the carbon atom to which they are attached to form $C=CR^{7'}R^{8'}$; C=N(OH), C=N(O-C_1-C_3 alkyl), C=O, C=S, C=NH, optionally substituted 3 to 6-membered cycloalkyl, or optionally substituted 3 to 7-membered heterocycloalkyl;

$R^{7'}$ is hydrogen, halogen, or optionally substituted C_1-C_3 alkyl; $R^{8'}$ is hydrogen, halogen, hydroxy, cyano, optionally substituted C_1-C_3 alkoxy, optionally substituted C_1-C_3 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 alkynyl, optionally substituted 3 to 8-membered cycloalkyl, optionally substituted 3 to 14-membered heterocycloalkyl, optionally substituted 5 to 10-membered heteroaryl, or optionally substituted 6 to 10-membered aryl, or

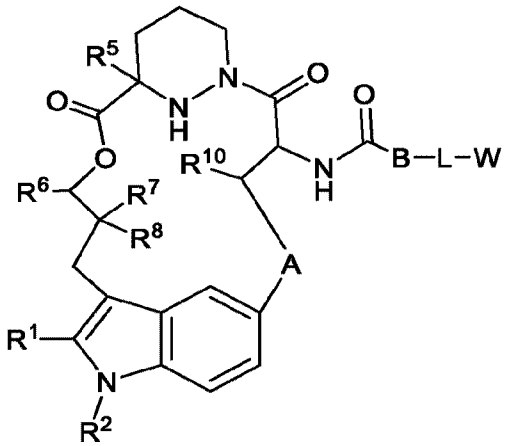
$R^{7'}$ and $R^{8'}$ combine with the carbon atom to which they are attached to form optionally substituted 3 to 6-membered cycloalkyl or optionally substituted 3 to 7-membered heterocycloalkyl;

R^9 is optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted 3 to 6-membered cycloalkyl, or optionally substituted 3 to 7-membered heterocycloalkyl; and

R^{10} is hydrogen, hydroxy, C_1-C_3 alkoxy, or C_1-C_3 alkyl.

In some embodiments of Formula BI and subformula thereof, X^1 is optionally substituted C_1-C_2 alkylene. In some embodiments, X^1 is methylene. In some embodiments of Formula BI and subformula thereof, X^1 is methylene substituted with a C_1-C_6 alkyl group or a halogen. In some embodiments, X^1 is -CH(Br)-. In some embodiments, X^1 is -CH(CH_3)-. In some embodiments of Formula BI and subformula thereof, R^5 is hydrogen. In some embodiments of Formula BI and subformula thereof, R^5 is C_1-C_4 alkyl optionally substituted with halogen. In some embodiments, R^5 is methyl. In some embodiments of Formula BI and subformula thereof, Y^4 is C. In some embodiments of Formula BI and subformula thereof, R^4 is hydrogen. In some embodiments of Formula BI and subformula thereof, Y^5 is CH. In some embodiments of Formula BI and subformula thereof, Y^6 is CH. In some embodiments of Formula BI and subformula thereof, Y^1 is C. In some embodiments of Formula BI and subformula thereof, Y^2 is C. In some embodiments of Formula BI and subformula thereof, Y^3 is N. In some embodiments of Formula BI and subformula thereof, R^3 is absent. In some embodiments of Formula BI and subformula thereof, Y^7 is C.

In some embodiments, the RAS(ON) inhibitor has the structure of Formula BIe, or a pharmaceutically acceptable salt thereof:



Formula BIe

wherein A is -N(H or CH_3)C(O)-(CH_2)- where the amino nitrogen is bound to the carbon atom of -CH(R^{10})-, optionally substituted 3 to 6-membered cycloalkylene, optionally substituted 3 to 6-membered heterocycloalkylene, optionally substituted 6-membered arylene, or optionally substituted 5 to 6-membered heteroarylene;

B is -CH(R^9)- where the carbon is bound to the carbonyl carbon of -NHC(O)-, optionally substituted 3 to 6-membered cycloalkylene, optionally substituted 3 to 6-membered heterocycloalkylene, optionally substituted 6-membered arylene, or 5 to 6-membered heteroarylene;

L is absent or a linker;

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

R^1 is cyano, 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 cycloalkenyl, optionally substituted 3 to 6-membered heterocycloalkyl, optionally substituted 6 to 10-membered aryl, or optionally substituted 5 to 10-membered heteroaryl;

R^2 is hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted 3 to 6-membered cycloalkyl, optionally substituted 3 to 7-membered heterocycloalkyl, optionally substituted 6-membered aryl, optionally substituted 5 or 6-membered heteroaryl; R^3 is absent, or

R^2 and R^3 combine with the atom to which they are attached to form an optionally substituted 3 to 8-membered cycloalkyl or optionally substituted 3 to 14-membered heterocycloalkyl;

R^5 is hydrogen, C_1-C_4 alkyl optionally substituted with halogen, cyano, hydroxy, or C_1-C_4 alkoxy, cyclopropyl, or cyclobutyl;

R^6 is hydrogen or methyl; R^7 is hydrogen, halogen, or optionally substituted C_1-C_3 alkyl, or

R^6 and R^7 combine with the carbon atoms to which they are attached to form an optionally substituted 3 to 6-membered cycloalkyl or optionally substituted 3 to 7-membered heterocycloalkyl;

R^8 is hydrogen, halogen, hydroxy, cyano, optionally substituted C_1-C_3 alkoxy, optionally substituted C_1-C_3 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 alkynyl, optionally

substituted 3 to 8-membered cycloalkyl, optionally substituted 3 to 14-membered heterocycloalkyl, optionally substituted 5 to 10-membered heteroaryl, or optionally substituted 6 to 10-membered aryl, or

R^7 and R^8 combine with the carbon atom to which they are attached to form $C=CR^{7'}R^{8'}$; C=N(OH), C=N(O-C_1-C_3 alkyl), C=O, C=S, C=NH, optionally substituted 3 to 6-membered cycloalkyl, or optionally substituted 3 to 7-membered heterocycloalkyl;

$R^{7'}$ is hydrogen, halogen, or optionally substituted C_1-C_3 alkyl; $R^{8'}$ is hydrogen, halogen, hydroxy, cyano, optionally substituted C_1-C_3 alkoxy, optionally substituted C_1-C_3 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 alkynyl, optionally substituted 3 to 8-membered cycloalkyl, optionally substituted 3 to 14-membered heterocycloalkyl, optionally substituted 5 to 10-membered heteroaryl, or optionally substituted 6 to 10-membered aryl, or

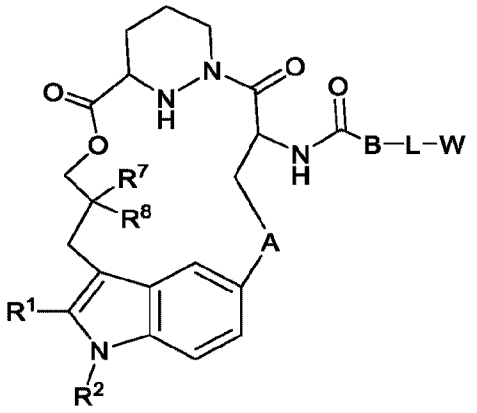
$R^{7'}$ and $R^{8'}$ combine with the carbon atom to which they are attached to form optionally substituted 3 to 6-membered cycloalkyl or optionally substituted 3 to 7-membered heterocycloalkyl;

R^9 is optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted 3 to 6-membered cycloalkyl, or optionally substituted 3 to 7-membered heterocycloalkyl; and

R^{10} is hydrogen, hydroxy, C_1-C_3 alkoxy, or C_1-C_3 alkyl.

In some embodiments of Formula BI and subformula thereof, R^6 is hydrogen. In some embodiments, R^2 is hydrogen, cyano, optionally substituted C_1-C_6 alkyl, optionally substituted 3 to 6-membered cycloalkyl, or optionally substituted 3 to 6-membered heterocycloalkyl. In some embodiments, R^2 is optionally substituted C_1-C_6 alkyl. In some embodiments, R_2 is fluoroalkyl. In some embodiments, R^2 is ethyl. In some embodiments, R_2 is $-CH_2CF_3$. In some embodiments, R_2 is C_2-C_6 alkynyl. In some embodiments, R_2 is -CHC≡CH. In some embodiments, R_2 is $-CH_2C{\equiv}CCH_3$. In some embodiments, R^7 is optionally substituted C_1-C_3 alkyl. In some embodiments, R^7 is C_1-C_3 alkyl. In some embodiments, R^8 is optionally substituted C_1-C_3 alkyl. In some embodiments, R^8 is C_1-C_3 alkyl.

In some embodiments, the RAS(ON) inhibitor has the structure of Formula BIf, or a pharmaceutically acceptable salt thereof:



Formula BIf

wherein A is -N(H or CH_3)C(O)-(CH_2)- where the amino nitrogen is bound to the carbon atom of -CH(R^{10})-, optionally substituted 3 to 6-membered cycloalkylene, optionally substituted 3 to 6-membered heterocycloalkylene, optionally substituted 6-membered arylene, or optionally substituted 5 to 6-membered heteroarylene;

B is -CH(R^9)- where the carbon is bound to the carbonyl carbon of -NHC(O)-, optionally substituted 3 to 6-membered cycloalkylene, optionally substituted 3 to 6-membered heterocycloalkylene, optionally substituted 6-membered arylene, or 5 to 6-membered heteroarylene;

L is absent or a linker;

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

R^1 is cyano, 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 cycloalkenyl, optionally substituted 3 to 6-membered heterocycloalkyl, optionally substituted 6 to 10-membered aryl, or optionally substituted 5 to 10-membered heteroaryl;

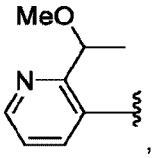
R^2 is C_1-C_6 alkyl or 3 to 6-membered cycloalkyl;

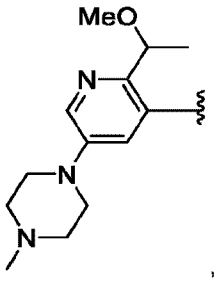
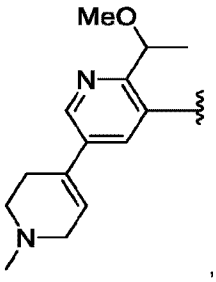
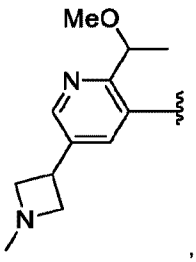
R^7 is C_1-C_3 alkyl;

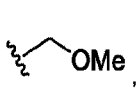
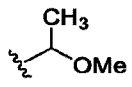
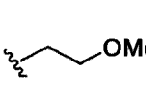
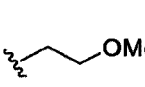
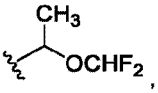
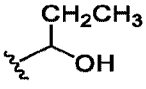
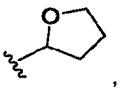
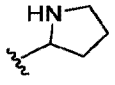
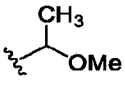
R^8 is C_1-C_3 alkyl; and

R^9 is optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted 3 to 6-membered cycloalkyl, or optionally substituted 3 to 7-membered heterocycloalkyl.

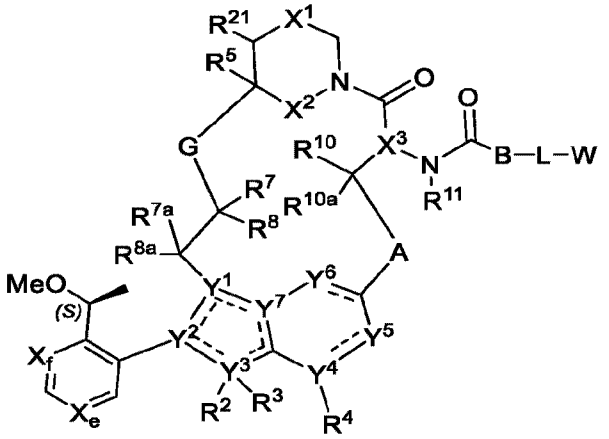
In some embodiments of Formula BI and subformula thereof, R^1 is optionally substituted 6 to 10-membered aryl, optionally substituted 3 to 6-membered cycloalkenyl, or optionally substituted 5 to 10-membered heteroaryl. In some embodiments, R^1 is optionally substituted 6-membered aryl, optionally substituted 6-membered cycloalkenyl, or optionally substituted 6-membered heteroaryl.

In some embodiments of Formula BI and subformula thereof, R_1 is  ,

 ,  ,  . In some embodiments of Formula BI and subformula thereof, R^{12} is optionally substituted C_1-C_6 heteroalkyl. In some embodiments, R^{12} is

 ,  ,  ,  ,  ,  ,  , or  . In some embodiments, R^{12} is  .

In some embodiments, the RAS(ON) inhibitor has the structure of Formula BVI, or a pharmaceutically acceptable salt thereof:



Formula BVI

wherein the dotted lines represent zero, one, two, three, or four non-adjacent double bonds;

A is -N(H or CH_3)C(O)-(CH_2)- where the amino nitrogen is bound to the carbon atom of -CH(R^{10})-, optionally substituted 3 to 6-membered cycloalkylene, optionally substituted 3 to 6-membered heterocycloalkylene, optionally substituted 6-membered arylene (e.g., phenyl or phenol), or optionally substituted 5 to 10-membered heteroarylene;

B is absent, -CH(R^9)-, >C=C$R^9R^{9'}$, or >C$R^9R^{9'}$ where the carbon is bound to the carbonyl carbon of -N(R^{11})C(O)-, optionally substituted 3 to 6-membered cycloalkylene, optionally substituted 3 to 6-membered heterocycloalkylene, optionally substituted 6-membered arylene, or 5 to 6-membered heteroarylene;

G is optionally substituted C_1-C_4 alkylene, optionally substituted C_1-C_4 alkenylene, optionally substituted C_1-C_4 heteroalkylene, -C(O)O-**C**H(R^6)- where **C** is bound to -C(R^7R^8)-, -C(O)NH-**C**H(R^6)- where **C** is bound to -C(R^7R^8)-, optionally substituted C_1-C_4 heteroalkylene, or 3 to 8-membered heteroarylene;

L is absent or a linker;

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

X^1 is optionally substituted C_1-C_2 alkylene, NR, O, or $S(O)_n$;

X^2 is O or NH;

X^3 is N or CH;

n is 0, 1, or 2;

R is hydrogen, cyano, optionally substituted C_1-C_4 alkyl, optionally substituted C_2-C_4 alkenyl, optionally substituted C_2-C_4 alkynyl, C(O)R', C(O)OR', C(O)N(R')$_2$, S(O)R', $S(O)_2$R', or $S(O)_2$N(R')$_2$;

each R' is, independently, H or optionally substituted C_1-C_4 alkyl;

Y^1 is C, CH, or N;

Y^2, Y^3, Y^4, and Y^7 are, independently, C or N;

Y^5 is CH, CH_2, or N;

Y^6 is C(O), CH, CH_2, or N;

R^2 is absent, hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 alkynyl, optionally substituted 3 to 6-membered cycloalkyl, optionally substituted 3 to 7-membered heterocycloalkyl, optionally substituted 6-membered aryl, optionally substituted 5 or 6-membered heteroaryl; R^3 is absent, or

R^2 and R^3 combine with the atom to which they are attached to form an optionally substituted 3 to 8-membered cycloalkyl or optionally substituted 3 to 14-membered heterocycloalkyl;

R^4 is absent, hydrogen, halogen, cyano, or methyl optionally substituted with 1 to 3 halogens;

R^5 is hydrogen, C_1-C_4 alkyl optionally substituted with halogen, cyano, hydroxy, or C_1-C_4 alkoxy, cyclopropyl, or cyclobutyl;

R^6 is hydrogen or methyl; R^7 is hydrogen, halogen, or optionally substituted C_1-C_3 alkyl, or

R^6 and R^7 combine with the carbon atoms to which they are attached to form an optionally substituted 3 to 6-membered cycloalkyl or optionally substituted 3 to 7-membered heterocycloalkyl;

R^8 is hydrogen, halogen, hydroxy, cyano, optionally substituted C_1-C_3 alkoxy, optionally substituted C_1-C_3 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 alkynyl, optionally substituted 3 to 8-membered cycloalkyl, optionally substituted 3 to 14-membered heterocycloalkyl, optionally substituted 5 to 10-membered heteroaryl, or optionally substituted 6 to 10-membered aryl, or

R^7 and R^8 combine with the carbon atom to which they are attached to form $C=CR^{7'}R^{8'}$; C=N(OH), C=N(O-C_1-C_3 alkyl), C=O, C=S, C=NH, optionally substituted 3 to 6-membered cycloalkyl, or optionally substituted 3 to 7-membered heterocycloalkyl;

R^{7a} and R^{8a} are, independently, hydrogen, halo, optionally substituted C_1-C_3 alkyl, or combine with the carbon to which they are attached to form a carbonyl;

$R^{7'}$ is hydrogen, halogen, or optionally substituted C_1-C_3 alkyl; $R^{8'}$ is hydrogen, halogen, hydroxy, cyano, optionally substituted C_1-C_3 alkoxy, optionally substituted C_1-C_3 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 alkynyl, optionally substituted 3 to 8-membered cycloalkyl, optionally substituted 3 to 14-membered heterocycloalkyl, optionally substituted 5 to 10-membered heteroaryl, or optionally substituted 6 to 10-membered aryl, or

$R^{7'}$ and $R^{8'}$ combine with the carbon atom to which they are attached to form optionally substituted 3 to 6-membered cycloalkyl or optionally substituted 3 to 7-membered heterocycloalkyl;

R^9 is H, F, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted 3 to 6-membered cycloalkyl, or optionally substituted 3 to 7-membered heterocycloalkyl; or

R^9 and L combine with the atoms to which they are attached to form an optionally substituted 3 to 14-membered heterocycloalkyl;

$R^{9'}$ is hydrogen or optionally substituted C_1-C_6 alkyl; or

R^9 and $R^{9'}$, combined with the atoms to which they are attached, form a 3 to 6-membered cycloalkyl or a 3 to 6-membered heterocycloalkyl;

R^{10} is hydrogen, halo, hydroxy, C_1-C_3 alkoxy, or C_1-C_3 alkyl;

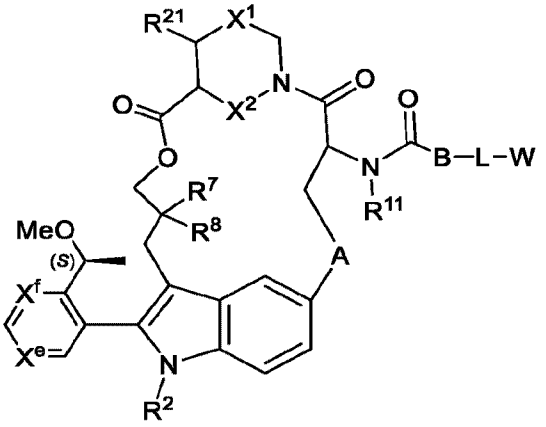
R^{10a} is hydrogen or halo;

R^{11} is hydrogen or C_1-C_3 alkyl;

R^{21} is hydrogen or C_1-C_3 alkyl (e.g., methyl); and

X^e and X^f are, independently, N or CH.

In some embodiments, the RAS(ON) inhibitor has the structure of Formula BVIa, or a pharmaceutically acceptable salt thereof:



Formula BVIa

wherein A optionally substituted 3 to 6-membered cycloalkylene, optionally substituted 3 to 6-membered heterocycloalkylene, optionally substituted 6-membered arylene (e.g., phenyl or phenol), or optionally substituted 5 to 6-membered heteroarylene;

B is -CH(R^9)- where the carbon is bound to the carbonyl carbon of -NHC(O)-, optionally substituted 3 to 6-membered cycloalkylene, optionally substituted 3 to 6-membered heterocycloalkylene, optionally substituted 6-membered arylene, or 5 to 6-membered heteroarylene;

L is absent or a linker;

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

X^1 is optionally substituted C_1-C_2 alkylene, NR, O, or $S(O)_n$;

X^2 is O or NH;

n is 0, 1, or 2;

R is hydrogen, cyano, optionally substituted C_1-C_4 alkyl, optionally substituted C_2-C_4 alkenyl, optionally substituted C_2-C_4 alkynyl, C(O)R', C(O)OR', C(O)N(R')$_2$, S(O)R', $S(O)_2$R', or $S(O)_2$N(R')$_2$;

each R' is, independently, H or optionally substituted C_1-C_4 alkyl;

R^2 is C_1-C_6 alkyl, C_1-C_6 fluoroalkyl, or 3 to 6-membered cycloalkyl;

R^7 is C_1-C_3 alkyl;

R^8 is C_1-C_3 alkyl; and

R^9 is optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted 3 to 6-membered cycloalkyl, or optionally substituted 3 to 7-membered heterocycloalkyl;

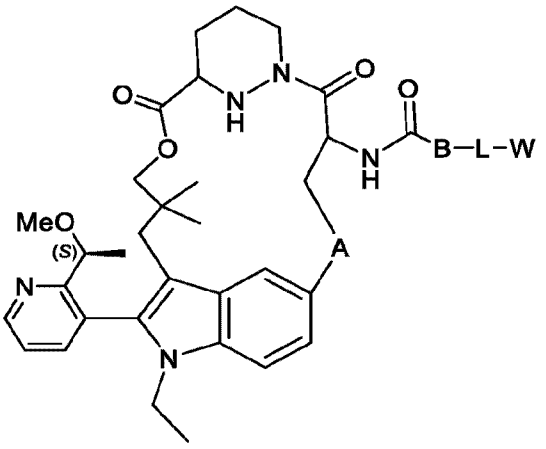
X^e and X^f are, independently, N or CH;

R^{11} is hydrogen or C_1-C_3 alkyl; and

R^{21} is hydrogen or C_1-C_3 alkyl.

In some embodiments of Formula BI and subformula thereof, X^e is N and X^f is CH. In some embodiments, X^e is CH and X^f is N.

In some embodiments, the RAS(ON) inhibitor has the structure of Formula BVIb, or a pharmaceutically acceptable salt thereof:



Formula BVIb

wherein A optionally substituted 3 to 6-membered cycloalkylene, optionally substituted 3 to 6-membered heterocycloalkylene, optionally substituted 6-membered arylene (e.g., phenyl or phenol), or optionally substituted 5 to 6-membered heteroarylene;

B is -CH(R^9)- where the carbon is bound to the carbonyl carbon of -NHC(O)-, optionally substituted 3 to 6-membered cycloalkylene, optionally substituted 3 to 6-membered heterocycloalkylene, optionally substituted 6-membered arylene, or 5 to 6-membered heteroarylene;

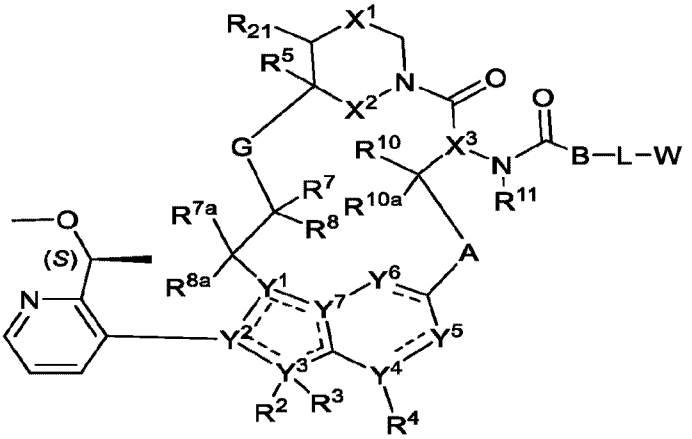
R^9 is optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted 3 to 6-membered cycloalkyl, or optionally substituted 3 to 7-membered heterocycloalkyl;

L is absent or a linker; and

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

In some embodiments of formula BI or subformula thereof, A is optionally substituted 6-membered arylene.

In some embodiments, the RAS(ON) inhibitor has the structure of Formula BVIc, or a pharmaceutically acceptable salt thereof:



Formula BVIc

wherein the dotted lines represent zero, one, two, three, or four non-adjacent double bonds;

A is -N(H or CH_3)C(O)-(CH_2)- where the amino nitrogen is bound to the carbon atom of -CH(R^{10})-, optionally substituted 3 to 6-membered cycloalkylene, optionally substituted 3 to 6-membered heterocycloalkylene, optionally substituted 6-membered arylene (e.g., phenyl or phenol), or optionally substituted 5 to 10-membered heteroarylene;

B is absent, -CH(R^9)-, >C=C$R^9R^{9'}$, or >C$R^9R^{9'}$ where the carbon is bound to the carbonyl carbon of -N(R^{11})C(O)-, optionally substituted 3 to 6-membered cycloalkylene, optionally substituted 3 to 6-membered heterocycloalkylene, optionally substituted 6-membered arylene, or 5 to 6-membered heteroarylene;

G is optionally substituted C_1-C_4 alkylene, optionally substituted C_1-C_4 alkenylene, optionally substituted C_1-C_4 heteroalkylene, -C(O)O-**C**H(R^6)- where **C** is bound to -C(R^7R^8)-, -C(O)NH-**C**H(R^6)- where **C** is bound to -C(R^7R^8)-, optionally substituted C_1-C_4 heteroalkylene, or 3 to 8-membered heteroarylene;

L is absent or a linker;

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

X^1 is optionally substituted C_1-C_2 alkylene, NR, O, or $S(O)_n$;

X^2 is O or NH;

X^3 is N or CH;

n is 0, 1, or 2;

R is hydrogen, cyano, optionally substituted C_1-C_4 alkyl, optionally substituted C_2-C_4 alkenyl, optionally substituted C_2-C_4 alkynyl, C(O)R', C(O)OR', $C(O)N(R')_2$, S(O)R', $S(O)_2R'$, or $S(O)_2N(R')_2$;

each R' is, independently, H or optionally substituted C_1-C_4 alkyl;

Y^1 is C, CH, or N;

Y^2, Y^3, Y^4, and Y^7 are, independently, C or N;

Y^5 is CH, CH_2, or N;

Y^6 is C(O), CH, CH_2, or N;

R^2 is absent, hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 alkynyl, optionally substituted 3 to 6-membered cycloalkyl, optionally substituted 3 to 7-membered heterocycloalkyl, optionally substituted 6-membered aryl, optionally substituted 5 or 6-membered heteroaryl; R^3 is absent, or

R^2 and R^3 combine with the atom to which they are attached to form an optionally substituted 3 to 8-membered cycloalkyl or optionally substituted 3 to 14-membered heterocycloalkyl;

R^4 is absent, hydrogen, halogen, cyano, or methyl optionally substituted with 1 to 3 halogens;

R^5 is hydrogen, C_1-C_4 alkyl optionally substituted with halogen, cyano, hydroxy, or C_1-C_4 alkoxy, cyclopropyl, or cyclobutyl;

R^6 is hydrogen or methyl; R^7 is hydrogen, halogen, or optionally substituted C_1-C_3 alkyl, or

R^6 and R^7 combine with the carbon atoms to which they are attached to form an optionally substituted 3 to 6-membered cycloalkyl or optionally substituted 3 to 7-membered heterocycloalkyl;

R^8 is hydrogen, halogen, hydroxy, cyano, optionally substituted C_1-C_3 alkoxy, optionally substituted C_1-C_3 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 alkynyl, optionally substituted 3 to 8-membered cycloalkyl, optionally substituted 3 to 14-membered heterocycloalkyl, optionally substituted 5 to 10-membered heteroaryl, or optionally substituted 6 to 10-membered aryl, or

R^7 and R^8 combine with the carbon atom to which they are attached to form $C=CR^{7'}R^{8'}$; C=N(OH), C=N(O-C_1-C_3 alkyl), C=O, C=S, C=NH, optionally substituted 3 to 6-membered cycloalkyl, or optionally substituted 3 to 7-membered heterocycloalkyl;

R^{7a} and R^{8a} are, independently, hydrogen, halo, optionally substituted C_1-C_3 alkyl, or combine with the carbon to which they are attached to form a carbonyl;

$R^{7'}$ is hydrogen, halogen, or optionally substituted C_1-C_3 alkyl; $R^{8'}$ is hydrogen, halogen, hydroxy, cyano, optionally substituted C_1-C_3 alkoxy, optionally substituted C_1-C_3 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 alkynyl, optionally substituted 3 to 8-membered cycloalkyl, optionally substituted 3 to 14-membered heterocycloalkyl, optionally substituted 5 to 10-membered heteroaryl, or optionally substituted 6 to 10-membered aryl, or

$R^{7'}$ and $R^{8'}$ combine with the carbon atom to which they are attached to form optionally substituted 3 to 6-membered cycloalkyl or optionally substituted 3 to 7-membered heterocycloalkyl;

R^9 is H, F, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted 3 to 6-membered cycloalkyl, or optionally substituted 3 to 7-membered heterocycloalkyl; or

R^9 and L combine with the atoms to which they are attached to form an optionally substituted 3 to 14-membered heterocycloalkyl;

$R^{9'}$ is hydrogen or optionally substituted C_1-C_6 alkyl; or

R^9 and $R^{9'}$, combined with the atoms to which they are attached, form a 3 to 6-membered cycloalkyl or a 3 to 6-membered heterocycloalkyl;

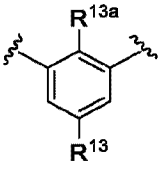
R^{10} is hydrogen, halo, hydroxy, C_1-C_3 alkoxy, or C_1-C_3 alkyl;

R^{10a} is hydrogen or halo;

R^{11} is hydrogen or C_1-C_3 alkyl; and

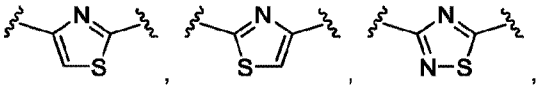
R^{21} is hydrogen or C_1-C_3 alkyl (e.g., methyl).

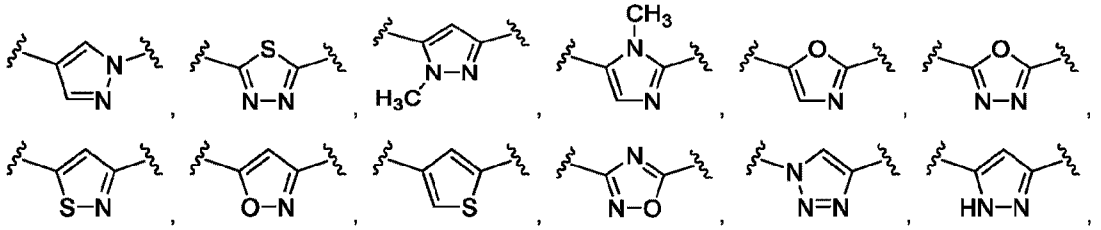
In some embodiments of Formula BI and subformula thereof, A has the structure:

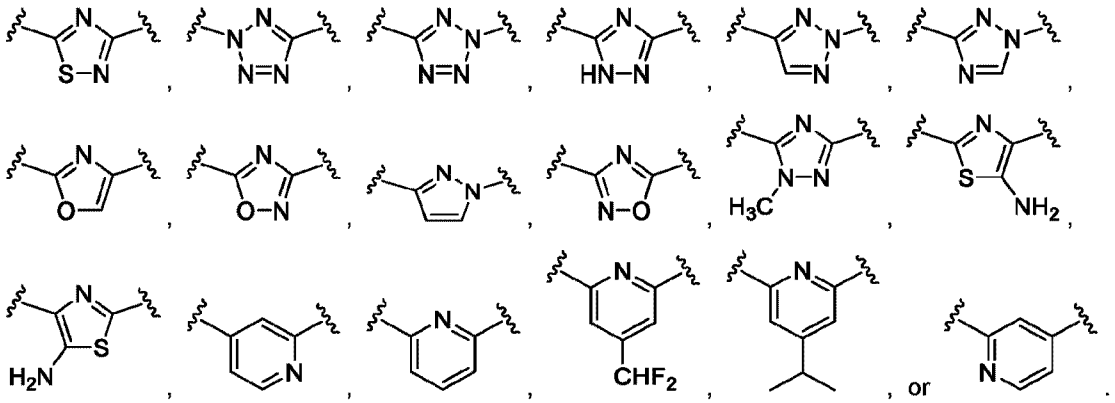


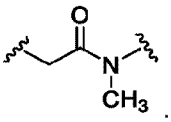
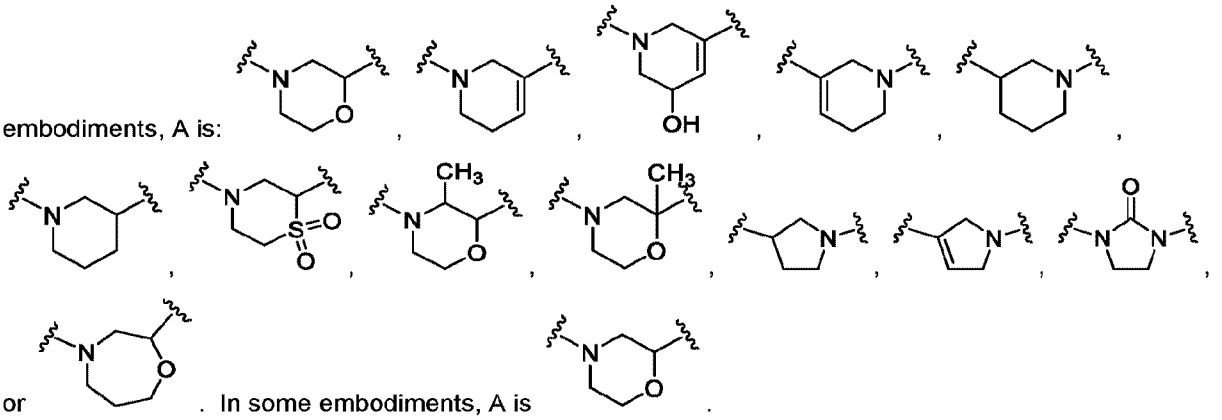
wherein R^{13} is hydrogen, halo, hydroxy, amino, optionally substituted C_1-C_6 alkyl, or optionally substituted C_1-C_6 heteroalkyl; and R^{13a} is hydrogen or halo. In some embodiments, R^{13} is hydrogen. In some embodiments, R^{13} and R^{13a} are each hydrogen. In some embodiments, R^{13} is hydroxy, methyl, fluoro, or difluoromethyl.

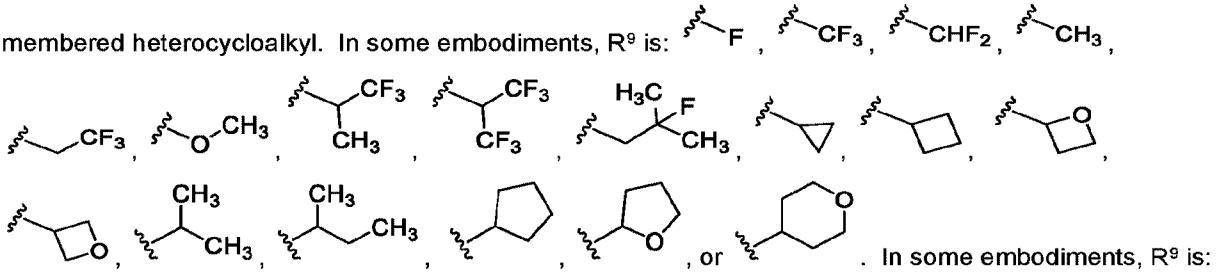
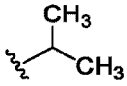
In some embodiments of Formula BI and subformula thereof, A is optionally substituted 5 to 6-membered heteroarylene. In some embodiments, A is:



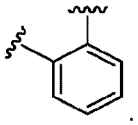




In some embodiments of Formula BI and subformula thereof, A is optionally substituted C_1-C_4 heteroalkylene. In some embodiments, A is:  . In some embodiments of Formula BI and subformula thereof, A is optionally substituted 3 to 6-membered heterocycloalkylene. In some embodiments, A is:  . In some embodiments, A is .

In some embodiments of Formula BI and subformula thereof, B is $-CHR^9-$. In some embodiments of Formula BI and subformula thereof, R^9 is H, F, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted 3 to 6-membered cycloalkyl, or optionally substituted 3 to 7-membered heterocycloalkyl. In some embodiments, R^9 is:  . In some embodiments, R^9 is:  . In some embodiments, R^9 is H, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted 3 to 6-membered cycloalkyl, or optionally substituted 3 to 7-membered heterocycloalkyl.

In some embodiments of Formula BI and subformula thereof, B is optionally substituted 6-membered arylene. In some embodiments, B is 6-membered arylene. In some embodiments, B is:



In some embodiments of Formula BI and subformula thereof, R^7 is methyl.

In some embodiments of Formula BI and subformula thereof, R^8 is methyl.

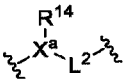
In some embodiments of Formula BI and subformula thereof, R^{21} is hydrogen.

In some embodiments of Formula BI and subformula thereof, the linker is the structure of Formula BII:

$$A^1\text{-}(B^1)_f\text{-}(C^1)_g\text{-}(B^2)_h\text{-}(D^1)\text{-}(B^3)_i\text{-}(C^2)_j\text{-}(B^4)_k\text{–}A^2$$

Formula BII

where A^1 is a bond between the linker and B; A^2 is a bond between W and the linker; B^1, B^2, B^3, and B^4 each, independently, is selected from optionally substituted C_1-C_2 alkylene, optionally substituted C_1-C_3 heteroalkylene, O, S, and NR^N; R^N is hydrogen, optionally substituted C_{1-4} 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; C^1 and C^2 are each, independently, selected from carbonyl, thiocarbonyl, sulphonyl, or phosphoryl; f, g, h, i, j, and k are each, independently, 0 or 1; and D^1 is optionally substituted C_1-C_{10} alkylene, optionally substituted C_2-C_{10} alkenylene, optionally substituted C_2-C_{10} alkynylene, optionally substituted 3 to 14-membered heterocycloalkylene, optionally substituted 5 to 10-membered heteroarylene, optionally substituted 3 to 8-membered cycloalkylene, optionally substituted 6 to 10-membered arylene, optionally substituted C_2-C_{10} polyethylene glycolene, or optionally substituted C_1-C_{10} heteroalkylene, or a chemical bond linking $A^1\text{-}(B^1)_f\text{-}(C^1)_g\text{-}(B^2)_h$- to -$(B^3)_i\text{-}(C^2)_j\text{-}(B^4)_k\text{–}A^2$. In some embodiments, the linker is acyclic. In some embodiments, linker has the structure of Formula BIIa:

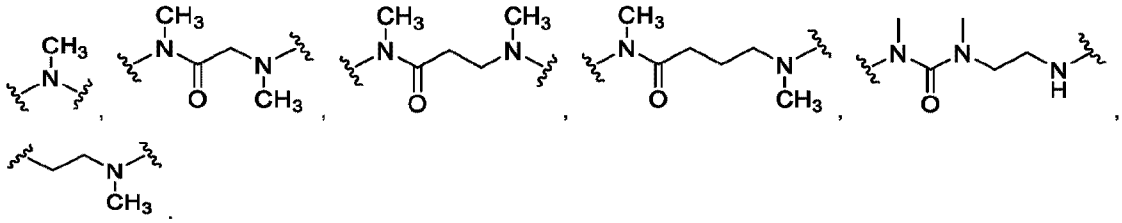


Formula BIIa

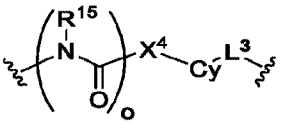
wherein X^a is absent or N;

R^{14} is absent, hydrogen or optionally substituted C_1-C_6 alkyl; and

L^2 is absent, -SO_2-, optionally substituted C_1-C_4 alkylene or optionally substituted C_1-C_4 heteroalkylene, wherein at least one of X^a, R^{14}, or L^2 is present. In some embodiments, the linker has the structure:


, or

In some embodiments of Formula BI and subformula thereof, the linker is or comprises a cyclic moiety. In some embodiments, the linker has the structure of Formula BIIb:



Formula BIIb

wherein o is 0 or 1;

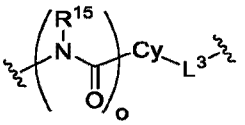
R^{15} is hydrogen or optionally substituted C_1-C_6 alkyl, optionally substituted 3 to 8-membered cycloalkylene, or optionally substituted 3 to 8-membered heterocycloalkylene;

X^4 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 8-membered heterocycloalkylene, optionally substituted 6-10 membered arylene, or optionally substituted 5 to 10-membered heteroarylene; and

L^3 is absent, -SO_2-, optionally substituted C_1-C_4 alkylene or optionally substituted C_1-C_4 heteroalkylene.

In some embodiments of Formula BI and subformula thereof, the linker has the structure of Formula BIIb-1:



Formula BIIb-1

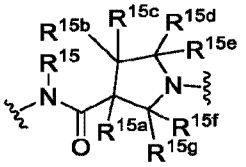
wherein o is 0 or 1;

R^{15} is hydrogen or optionally substituted C_1-C_6 alkyl, optionally substituted 3 to 8-membered cycloalkylene, or optionally substituted 3 to 8-membered heterocycloalkylene;

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

L^3 is absent, -SO_2-, optionally substituted C_1-C_4 alkylene or optionally substituted C_1-C_4 heteroalkylene.

In some embodiments of Formula BI and subformula thereof, the linker has the structure of Formula BIIc:

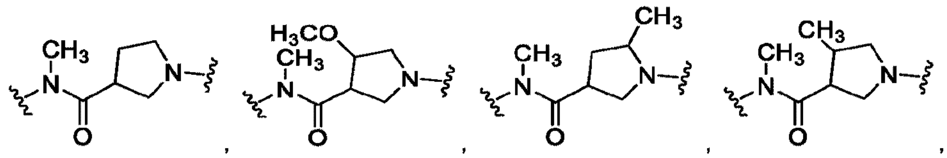


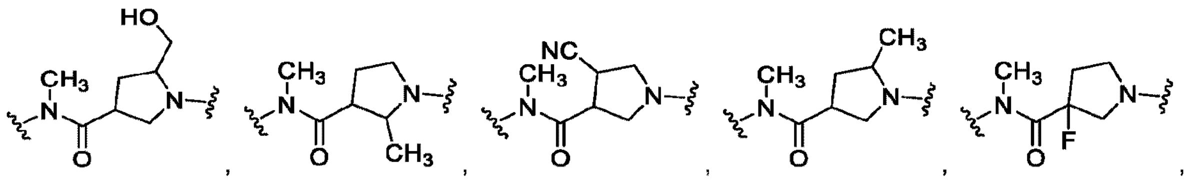
Formula BIIc

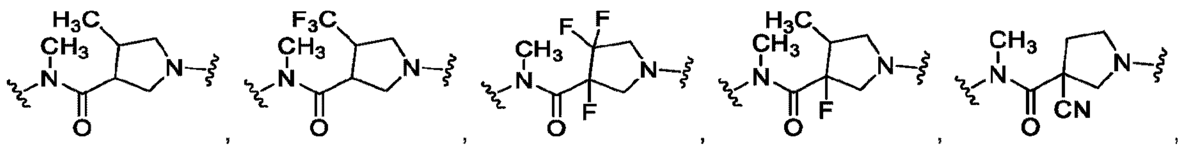
wherein R^{15} is hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted 3 to 8-membered cycloalkylene, or optionally substituted 3 to 8-membered heterocycloalkylene; and

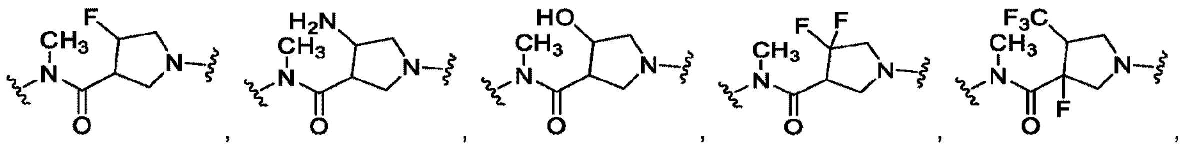
R^{15a}, R^{15b}, R^{15c}, R^{15d}, R^{15e}, R^{15f}, and R^{15g} are, independently, hydrogen, halo, hydroxy, cyano, amino, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 alkoxy, or , or R^{15b} and R^{15d} combine with the carbons to which they are attached to form an optionally substituted 3 to 8-membered cycloalkylene, or optionally substituted 3 to 8-membered heterocycloalkylene.

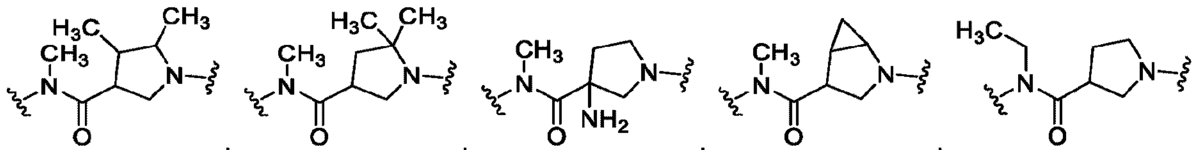
In some embodiments of Formula BI and subformula thereof, the linker has the structure:

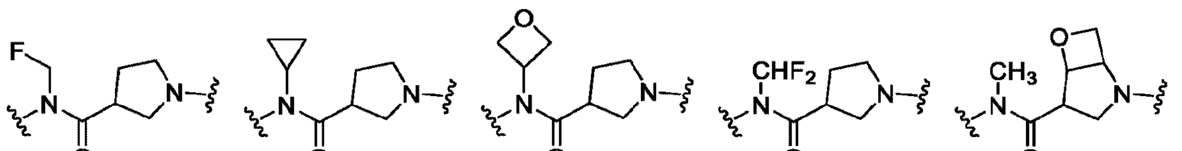


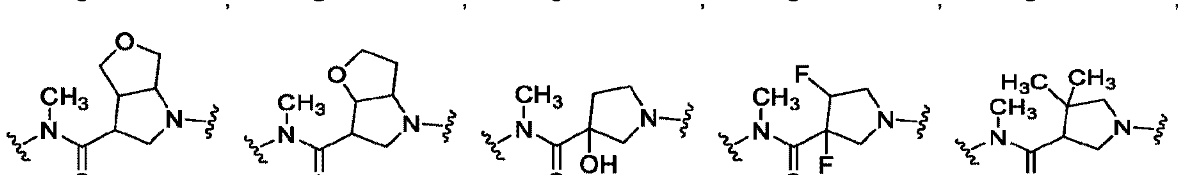


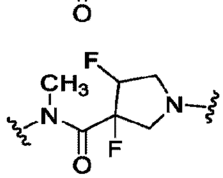
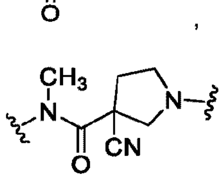




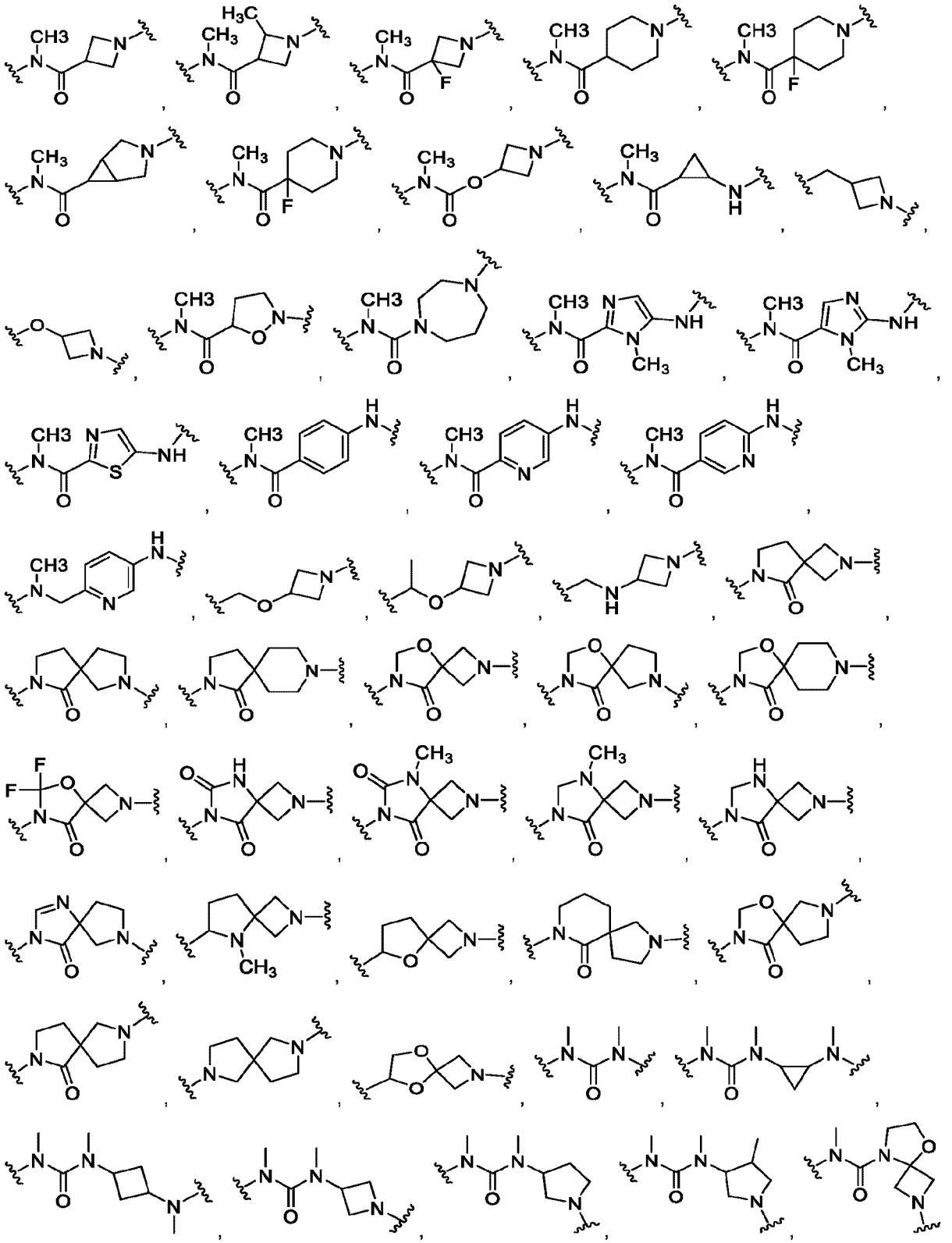


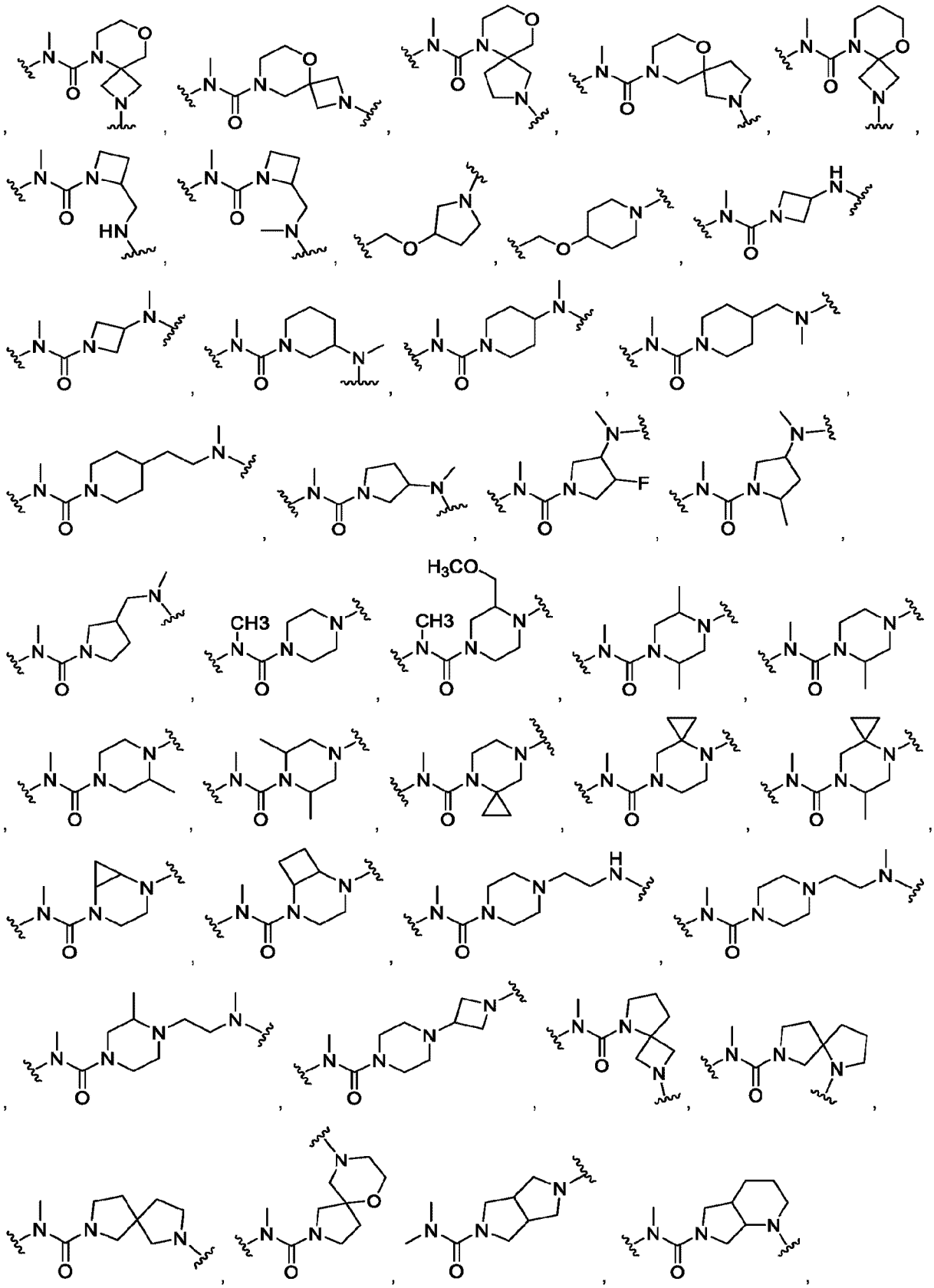


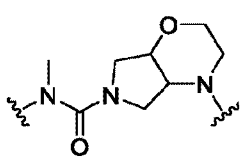
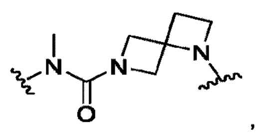
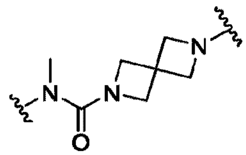
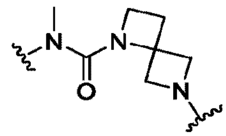


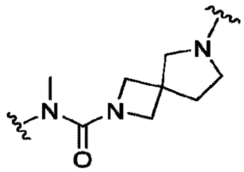
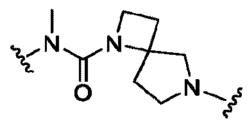
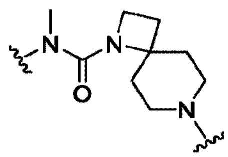
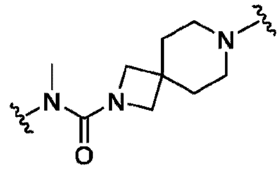
 , or  .

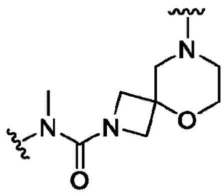
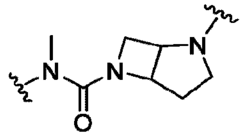
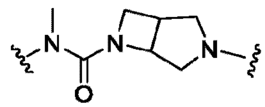
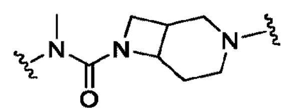
In some embodiments of Formula BI and subformula thereof, the linker has the structure:

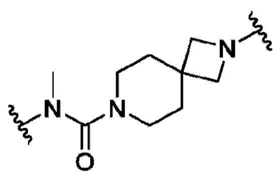
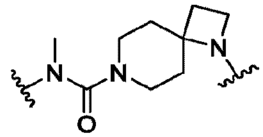
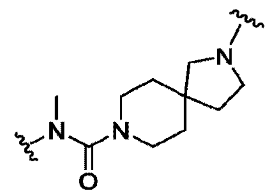
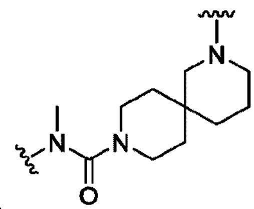


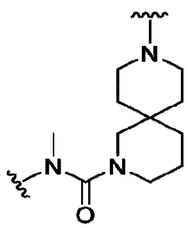
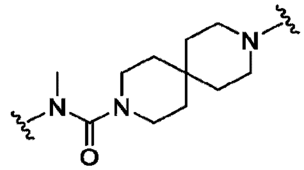
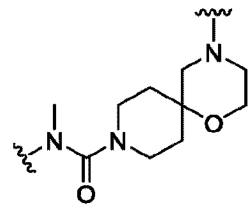
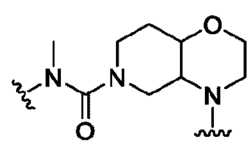


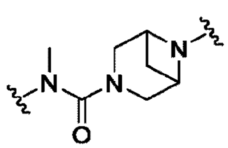
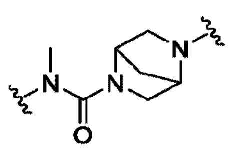
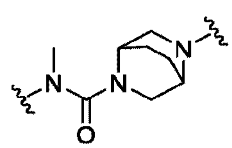
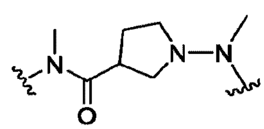
 ,  ,  ,  ,

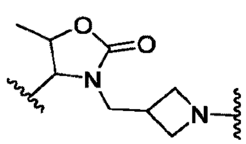
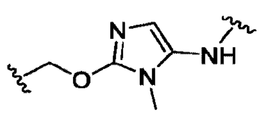
 ,  ,  ,  ,

 ,  ,  ,  ,

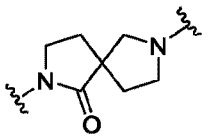
 ,  ,  ,  ,

 ,  ,  ,  ,

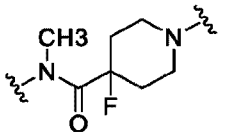
 ,  ,  ,  ,

 , or  .

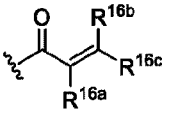
In some embodiments of Formula BI and subformula thereof, the linker has the structure



In some embodiments of Formula BI and subformula thereof, the linker has the structure

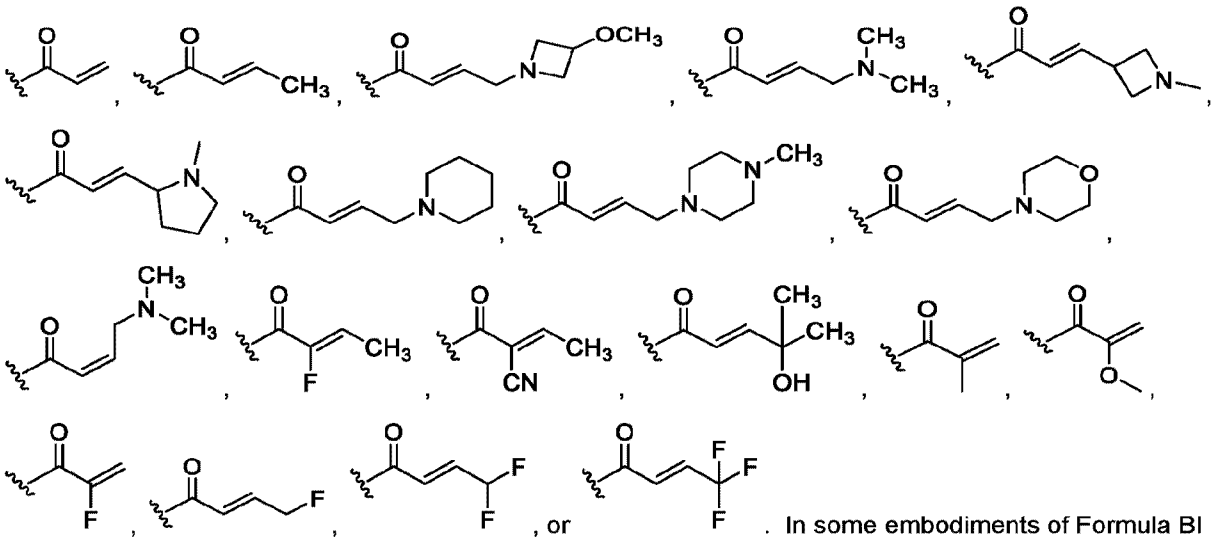


.In some embodiments of Formula BI and subformula thereof, W is a cross-linking group comprising a vinyl ketone. In some embodiments, W has the structure of Formula BIIIa:

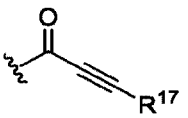


Formula BIIIa

wherein R^{16a}, R^{16b}, and R^{16c} are, independently, hydrogen, -CN, halogen, or -C_1-C_3 alkyl optionally substituted with one or more 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)$_2$, or a 4 to 7-membered saturated heterocycloalkyl. In some embodiments, W is:



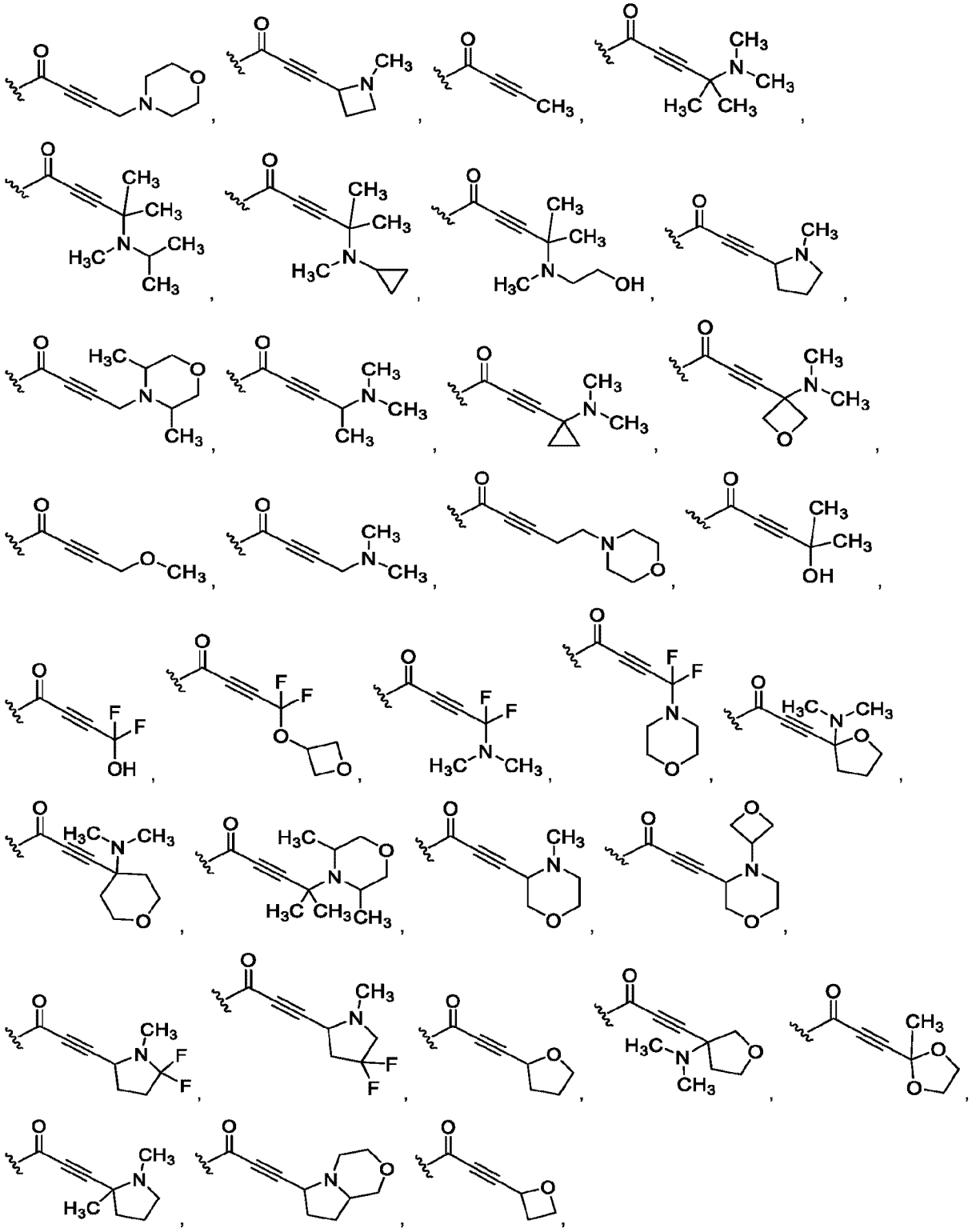
. In some embodiments of Formula BI and subformula thereof, W is a cross-linking group comprising an ynone. In some embodiments, W has the structure of Formula BIIIb:

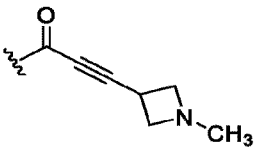
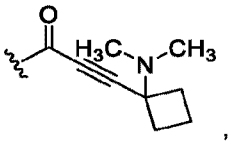
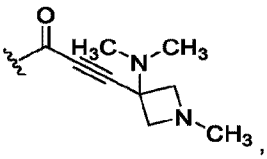
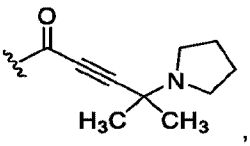
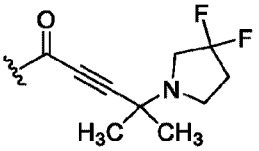
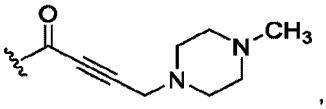
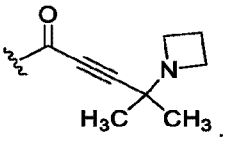
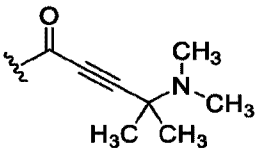


Formula BIIIb

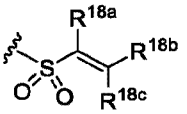
wherein R^{17} is hydrogen, -C_1-C_3 alkyl optionally substituted with one or more substituents independently selected from -OH, -O-C_1-C_3 alkyl, -NH_2, -NH(C_1-C_3 alkyl), -N(C_1-C_3 alkyl)$_2$, or a 4 to 7-

membered saturated heterocycloalkyl, or a 4 to 7-membered saturated heterocycloalkyl. In some embodiments, W is:



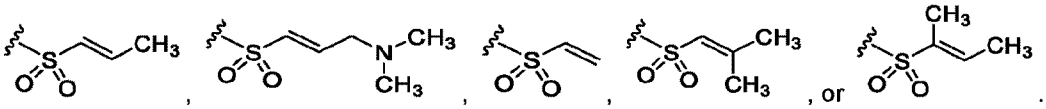









In some embodiments of Formula BI and subformula thereof, W is a cross-linking group comprising a vinyl sulfone. In some embodiments, W has the structure of Formula BIIIc:

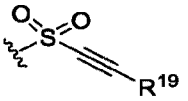


Formula BIIIc

wherein R^{18a}, R^{18b}, and R^{18c} are, independently, hydrogen, -CN, or -C_1-C_3 alkyl optionally substituted with one or more 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)$_2$, or a 4 to 7-membered saturated heterocycloalkyl. In some embodiments, W is:

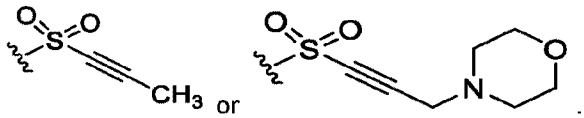


In some embodiments of Formula BI and subformula thereof, W is a cross-linking group comprising an alkynyl sulfone. In some embodiments, W has the structure of Formula BIIId:

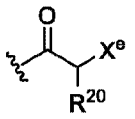


Formula BIIId

wherein R^{19} is hydrogen, -C_1-C_3 alkyl optionally substituted with one or more 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)$_2$, or a 4 to 7-membered saturated heterocycloalkyl, or a 4 to 7-membered saturated heterocycloalkyl. In some embodiments, W is:



In some embodiments of Formula BI and subformula thereof, W has the structure of Formula BIIIe:



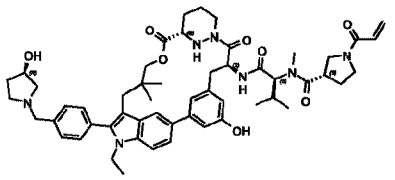
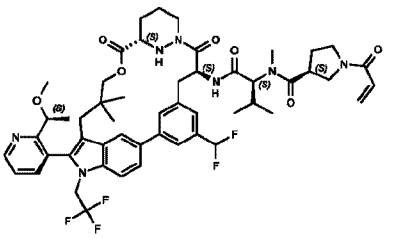
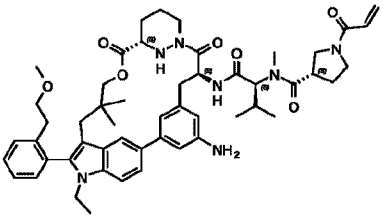
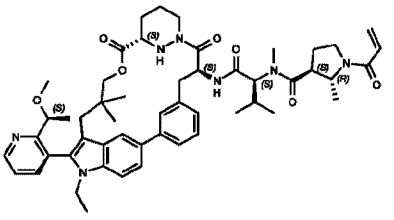
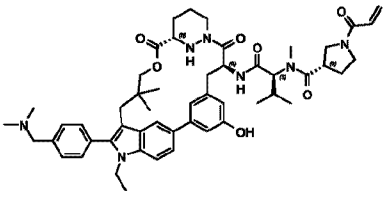
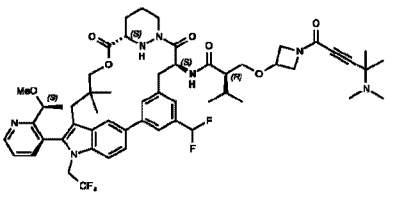
Formula BIIIe

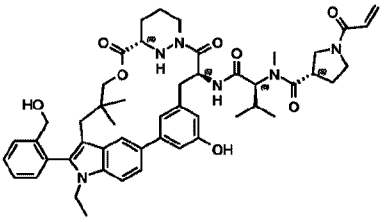
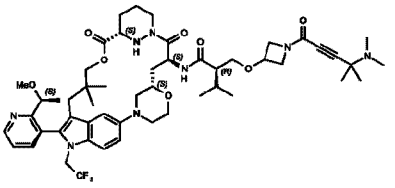
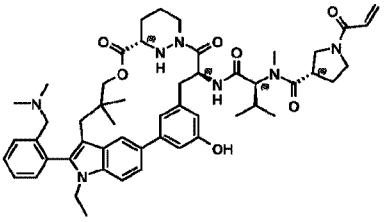
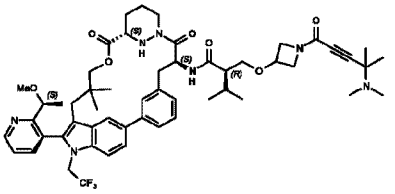
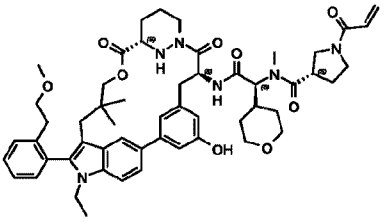
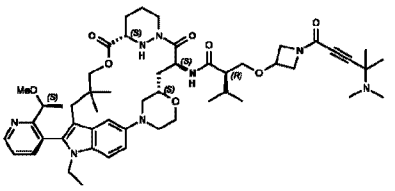
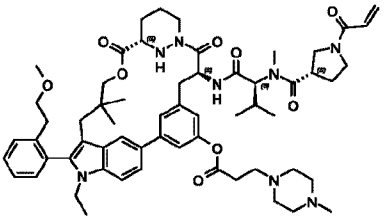
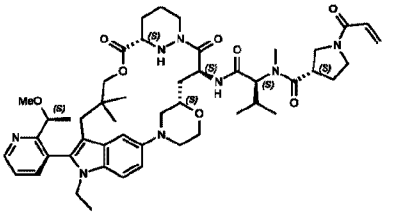
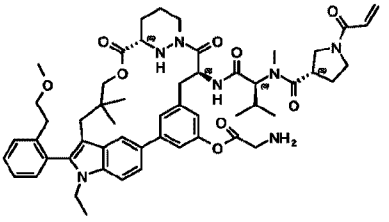
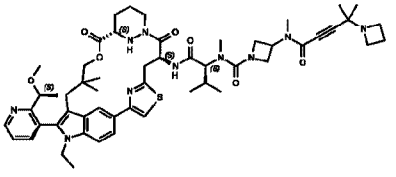
wherein X^e is a halogen; and

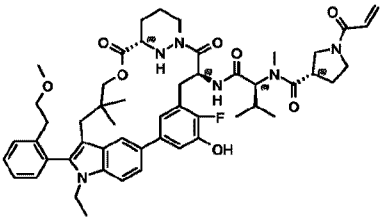
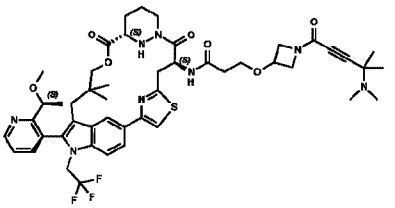
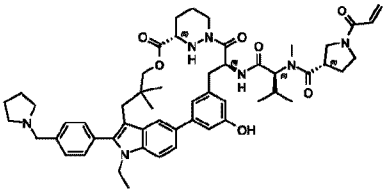
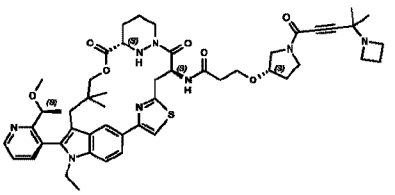
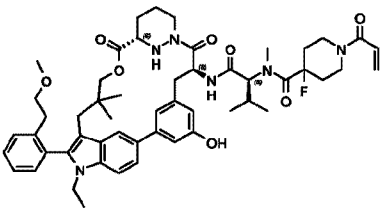
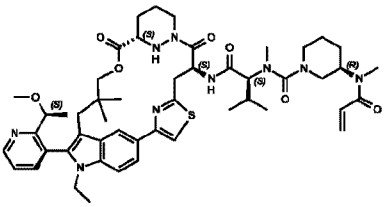
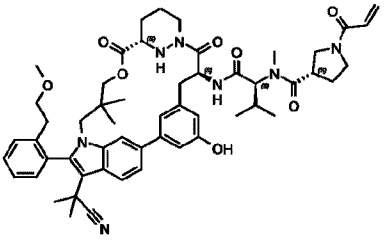
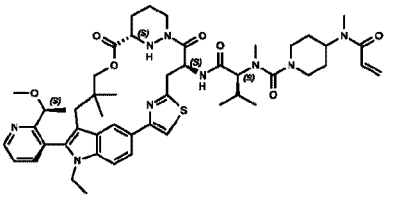
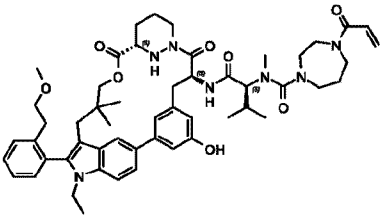
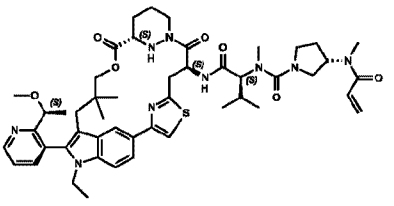
R^{20} is hydrogen, -C_1-C_3 alkyl optionally substituted with one or more substituents independently selected from -OH, -O-C_1-C_3 alkyl, -NH_2, -NH(C_1-C_3 alkyl), -N(C_1-C_3 alkyl)$_2$, or a 4 to 7-membered saturated heterocycloalkyl. In some embodiments of Formula BI and subformula thereof, W is haloacetyl. In some embodiments of Formula BI and subformula thereof, W is not haloacetyl.

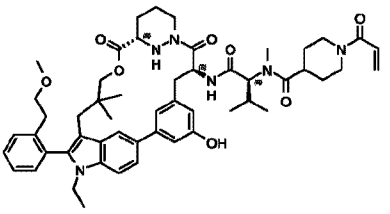
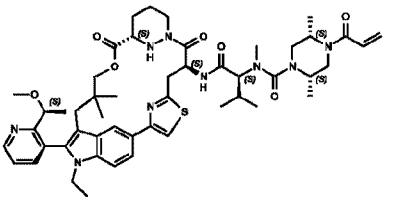
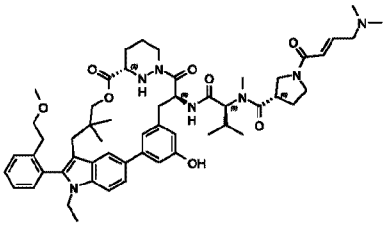
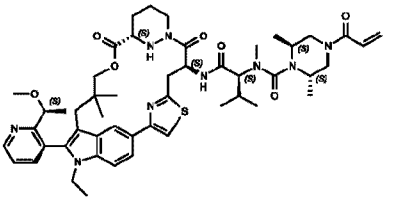
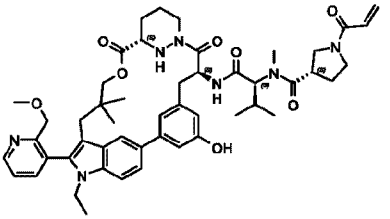
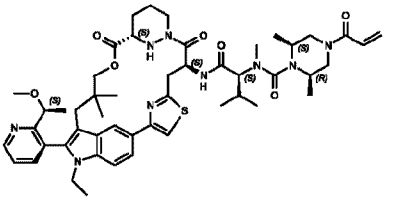
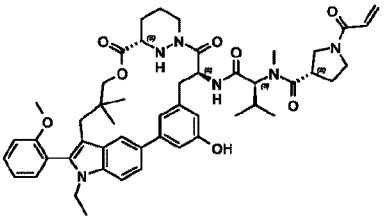
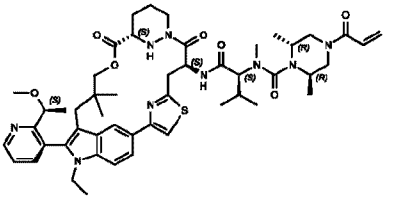
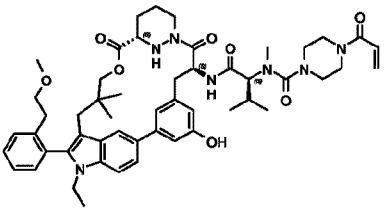
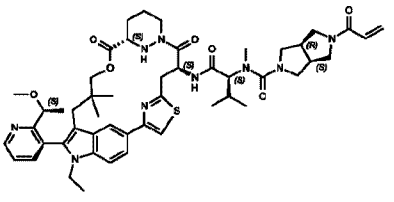
In some embodiments, the RAS(ON) inhibitor is selected from Table B1, or a pharmaceutically acceptable salt or stereoisomer thereof. In some embodiments, the RAS(ON) inhibitor is selected from Table B1, or a pharmaceutically acceptable salt or atropisomer thereof.

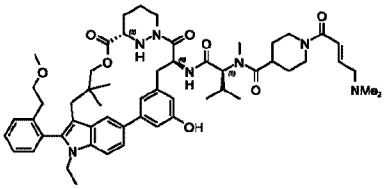
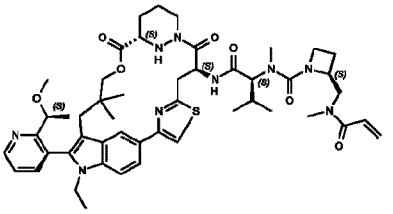
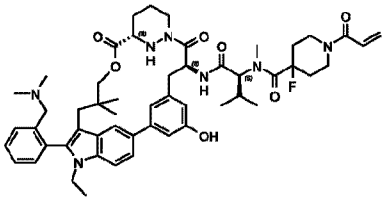
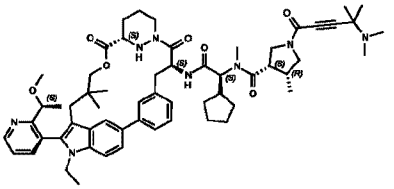
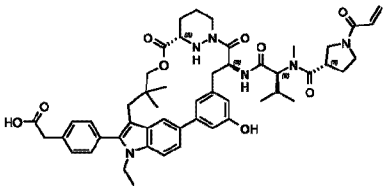
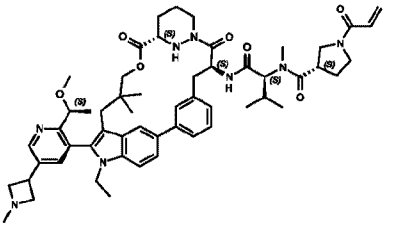
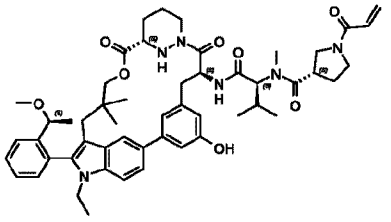
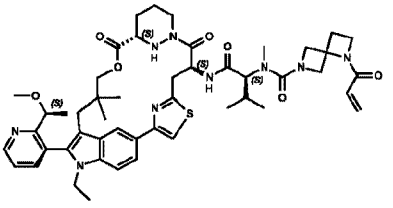
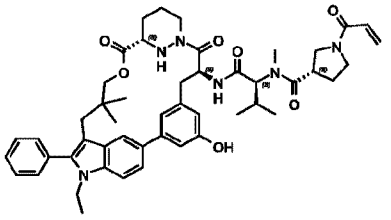
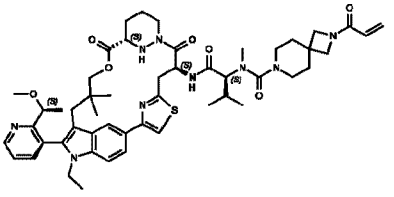
Table B1: Certain Compounds of the Present Invention

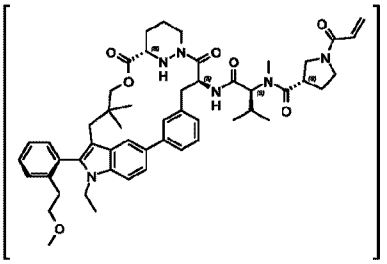
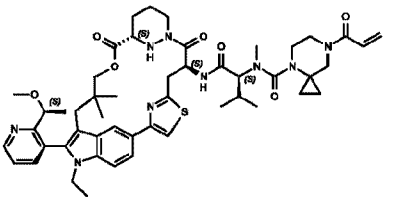
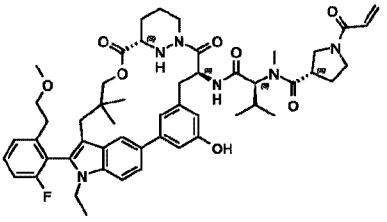
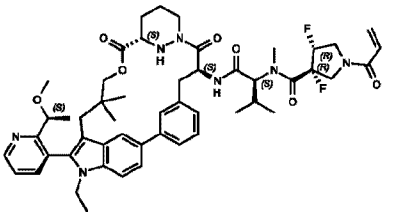
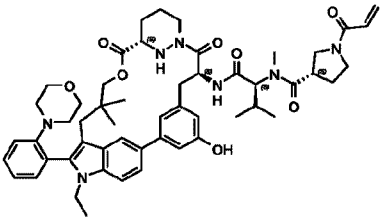
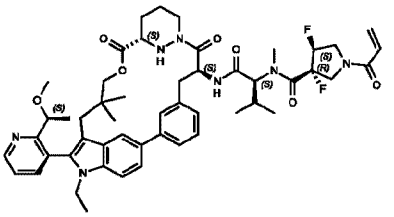
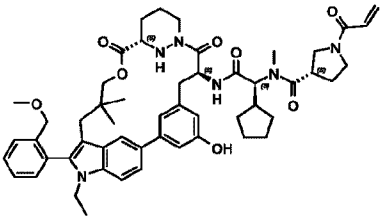
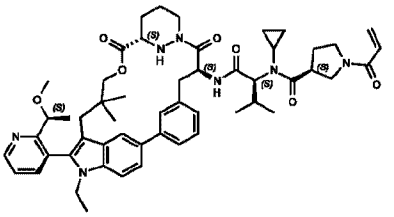
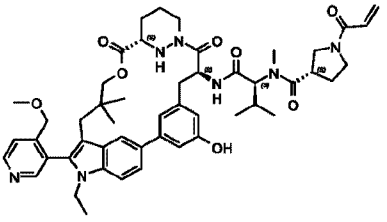
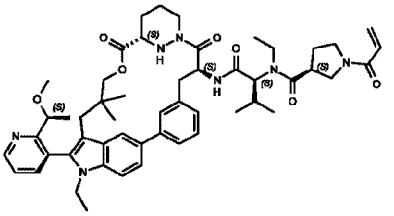
Ex#	Structure	Ex#	Structure
BA 1		BA 372	
BA 2		BA 373	
BA 3		BA 374	

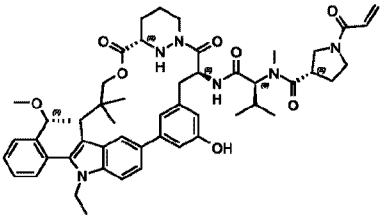
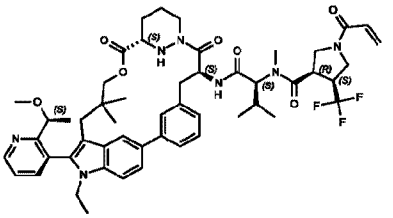
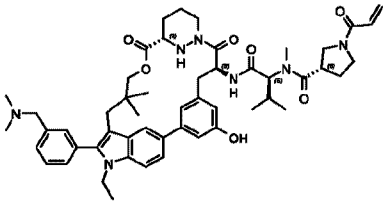
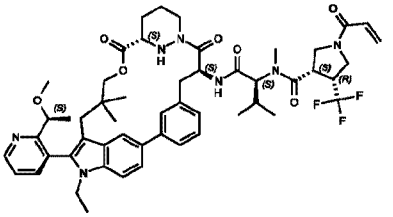
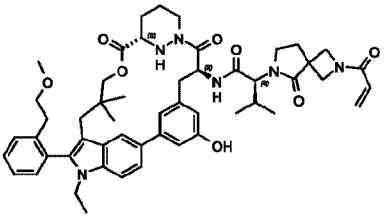
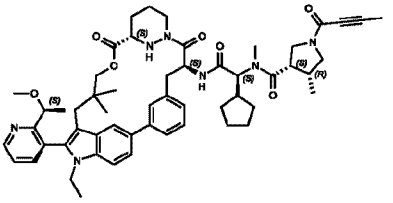
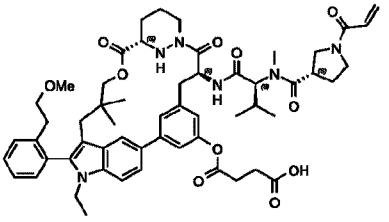
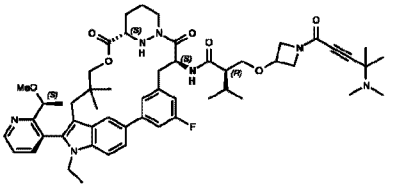
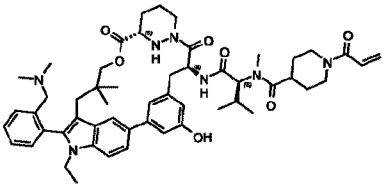
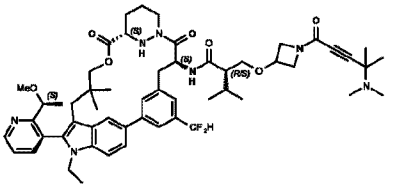
Ex#	Structure	Ex#	Structure
BA 4		BA 375	
BA 5		BA 376	
BA 6		BA 377	
BA 7		BA 378	
BA 8		BA 379	

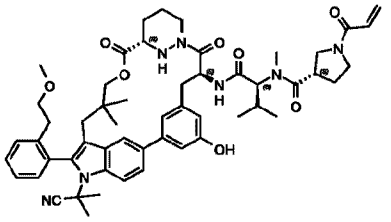
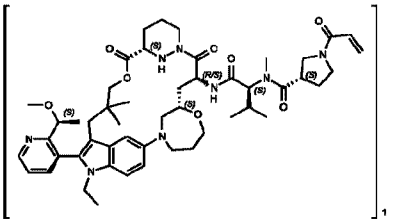
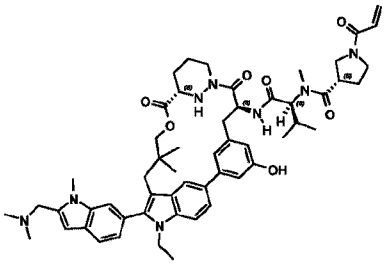
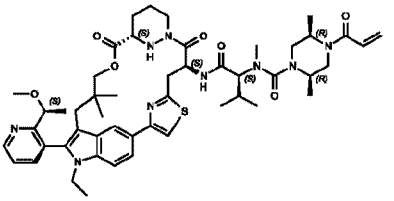
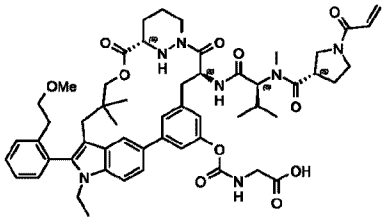
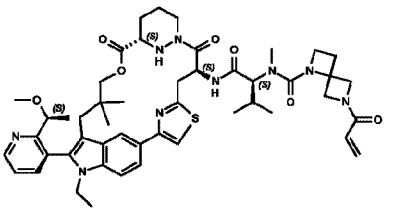
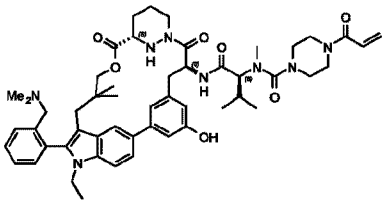
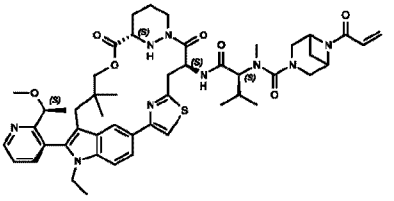
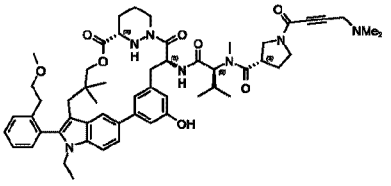
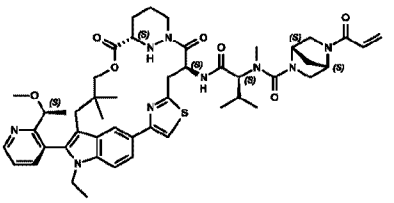
Ex#	Structure	Ex#	Structure
BA 9		BA 380	
BA 10		BA 381	
BA 11		BA 382	
BA 12		BA 383	
BA 13		BA 384	

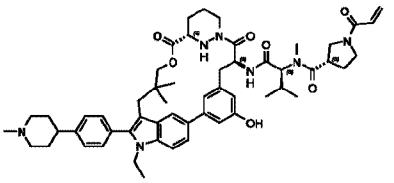
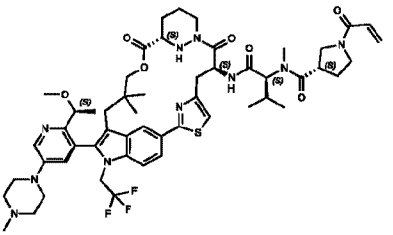
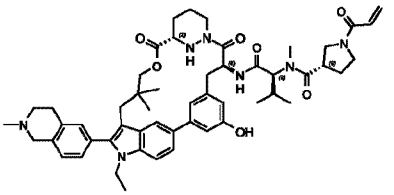
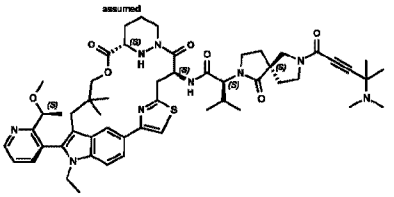
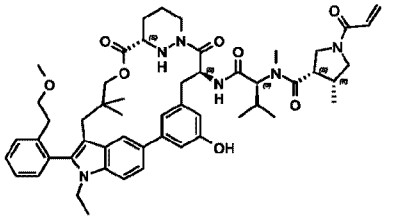
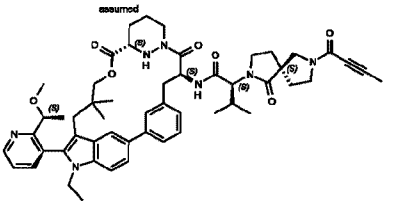
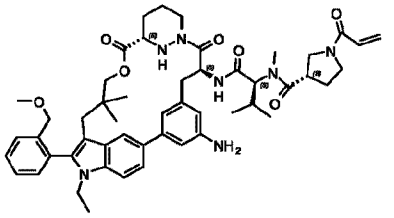
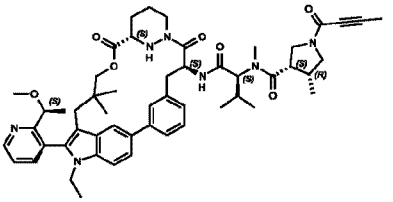
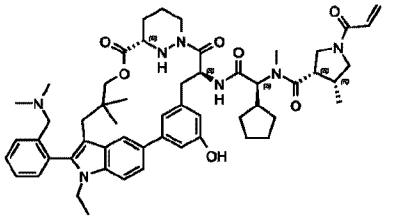
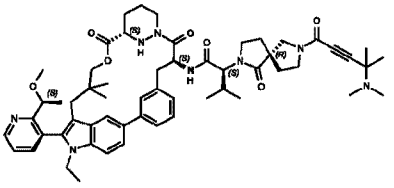
Ex#	Structure	Ex#	Structure
BA 14		BA 385	
BA 15		BA 386	
BA 16		BA 387	
BA 17		BA 388	
BA 18		BA 389	

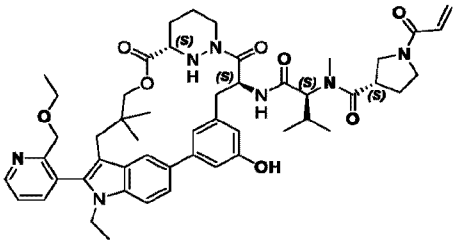
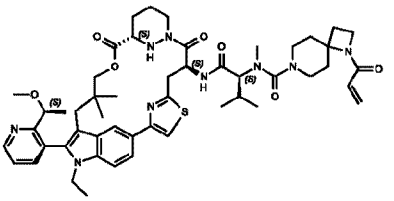
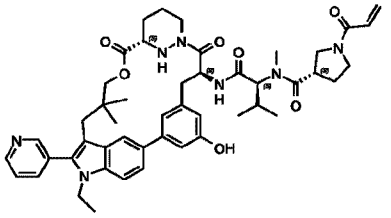
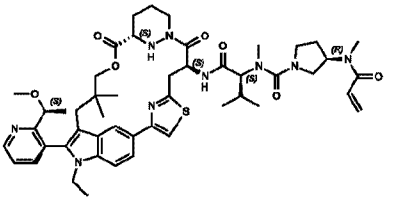
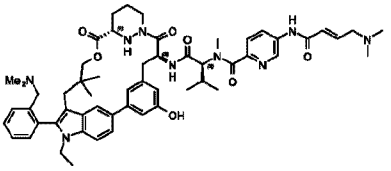
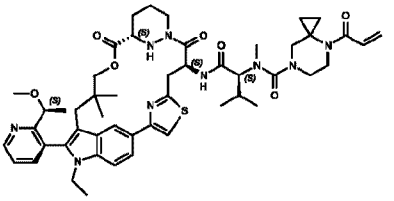
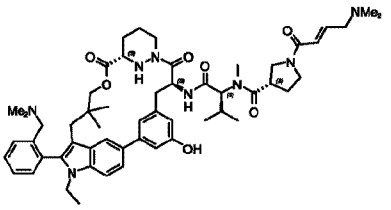
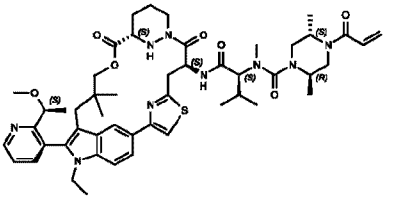
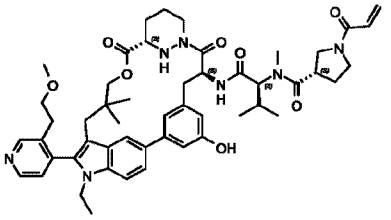
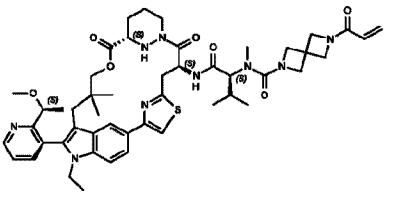
Ex#	Structure	Ex#	Structure
BA 19		BA 390	
BA 20		BA 391	
BA 21		BA 392	
BA 22		BA 393	
BA 23		BA 394	

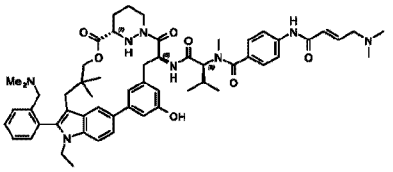
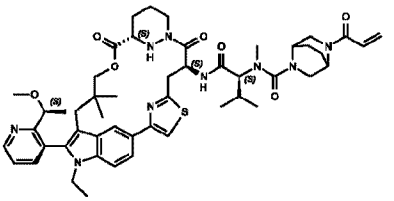
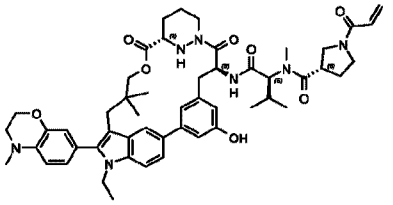
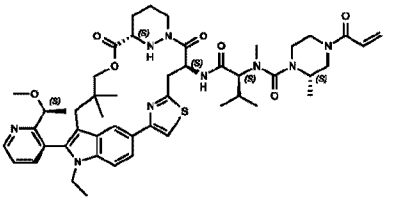
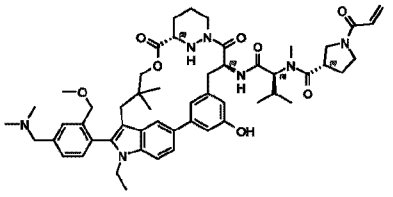
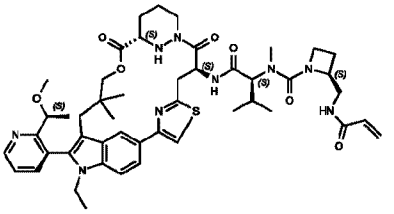
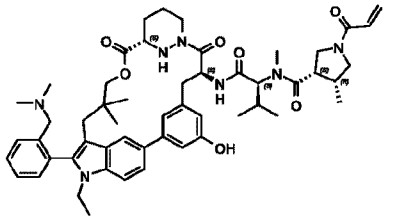
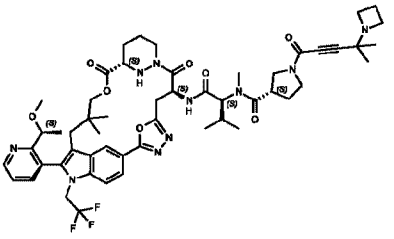
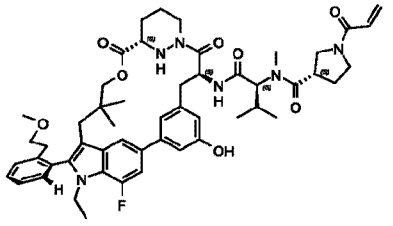
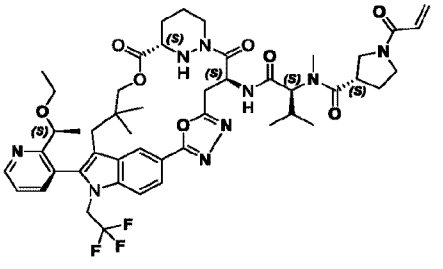
Ex#	Structure	Ex#	Structure
BA 24		BA 395	
BA 25		BA 396	
BA 26		BA 397	
BA 27		BA 398	
BA 28		BA 399	

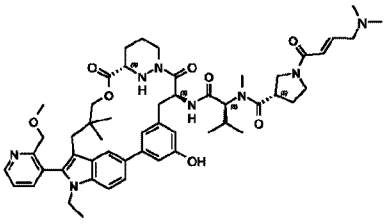
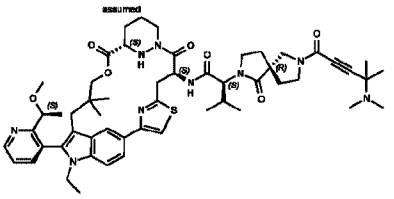
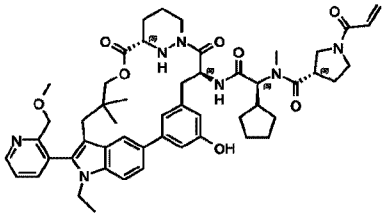
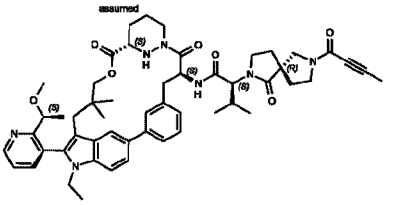
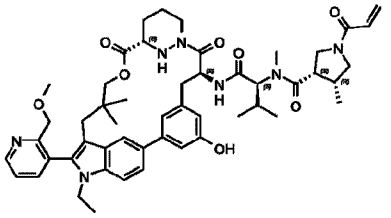
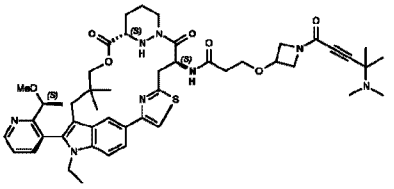
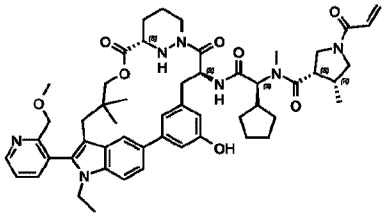
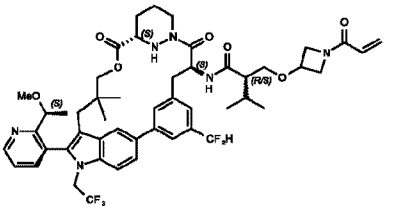
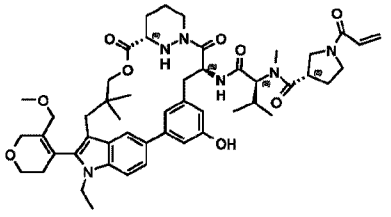
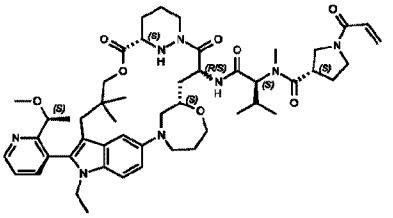
Ex#	Structure	Ex#	Structure
BA 29		BA 400	
BA 30		BA 401	
BA 31		BA 402	
BA 32		BA 403	
BA 33		BA 404	

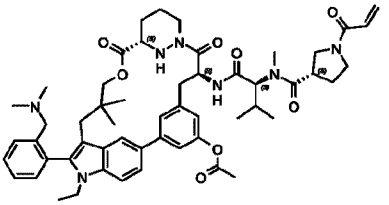
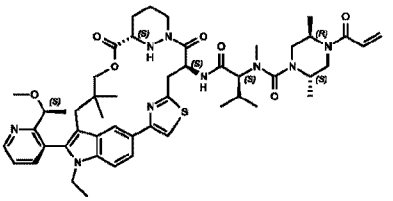
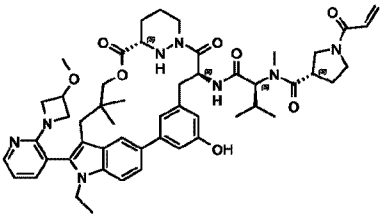
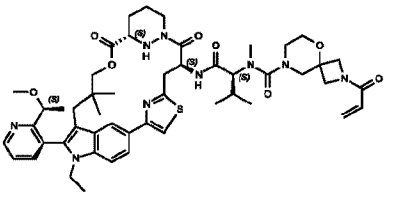
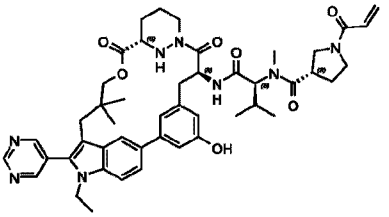
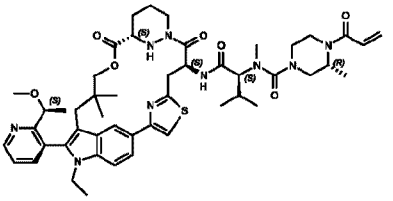
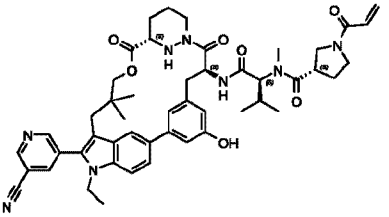
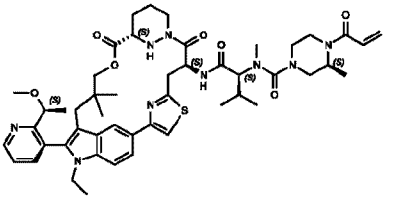
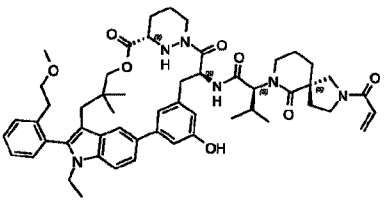
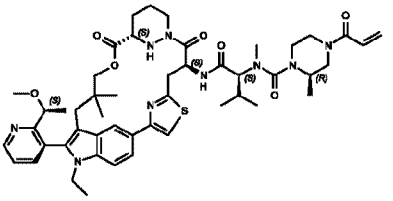
Ex#	Structure	Ex#	Structure
BA 34		BA 405	
BA 35		BA 406	
BA 36		BA 407	
BA 37		BA 408	
BA 38		BA 409	

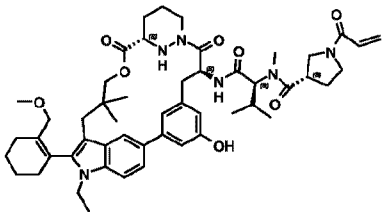
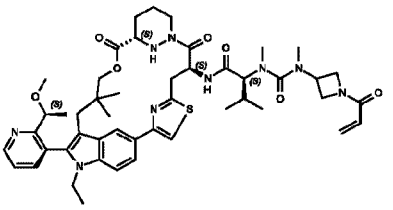
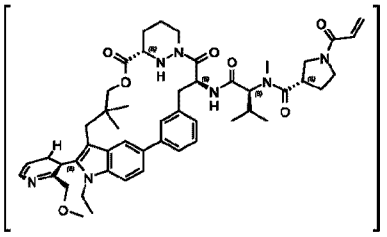
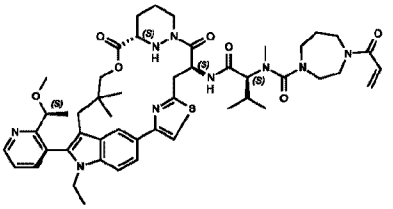
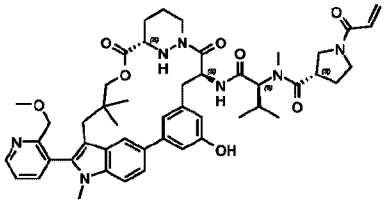
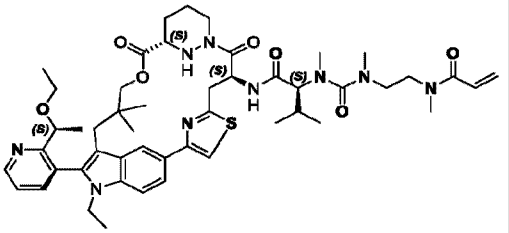
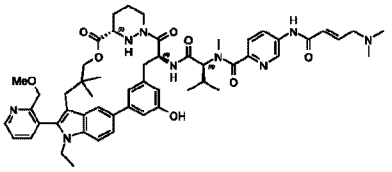
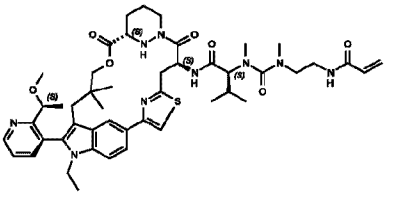
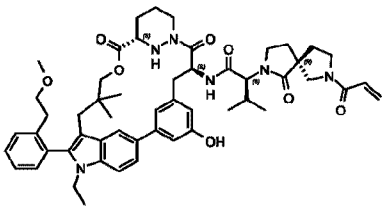
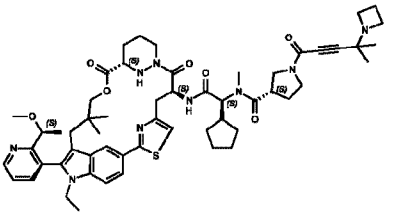
Ex#	Structure	Ex#	Structure
BA 39		BA 410	
BA 40		BA 411	
BA 41		BA 412	
BA 42		BA 413	
BA 43		BA 414	

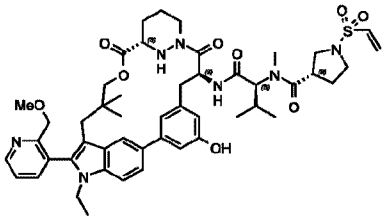
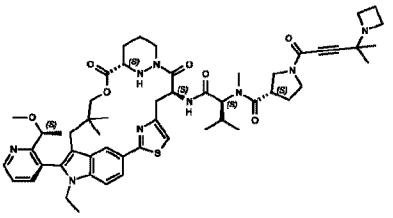
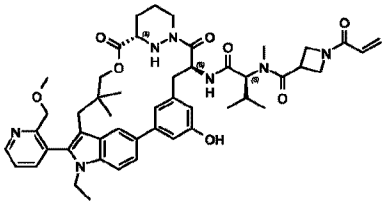
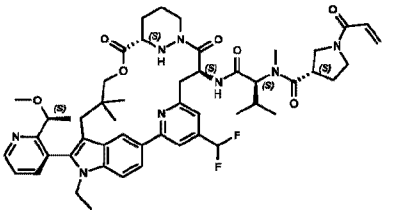
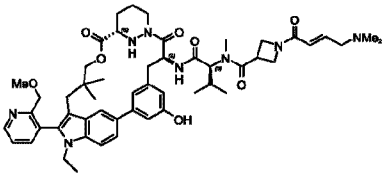
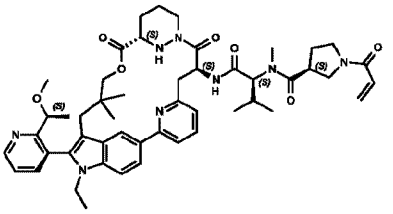
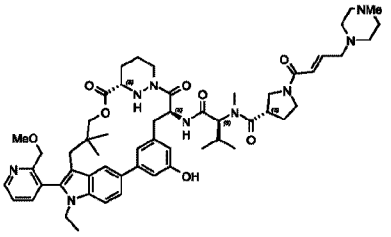
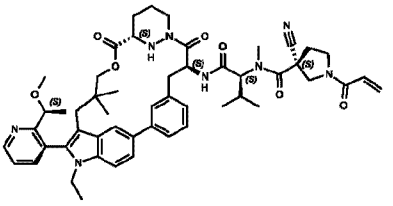
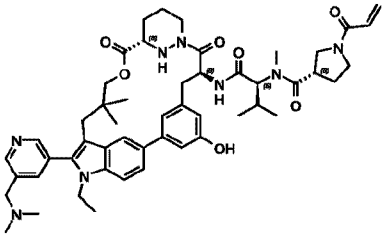
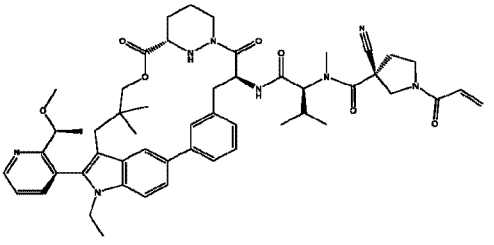
Ex#	Structure	Ex#	Structure
BA 44		BA 415	
BA 45		BA 416	
BA 46		BA 417	
BA 47		BA 418	
BA 48		BA 419	

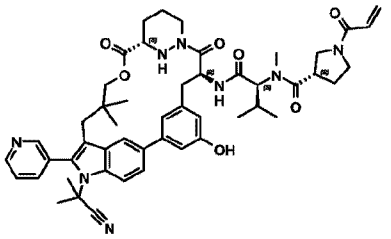
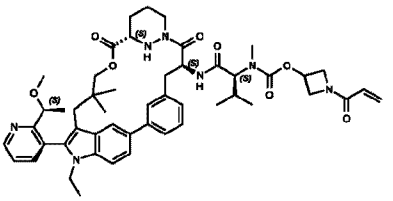
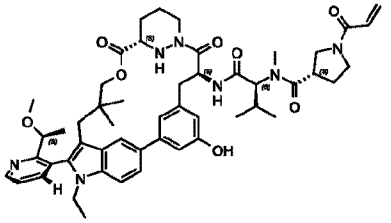
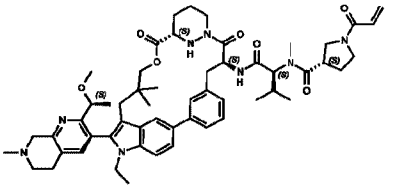
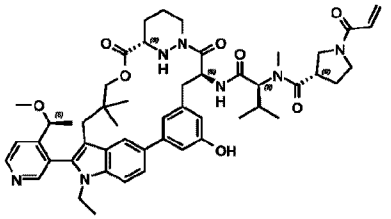
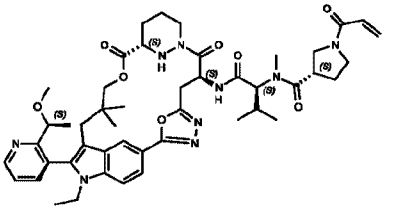
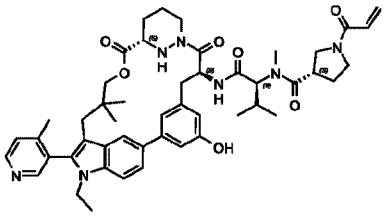
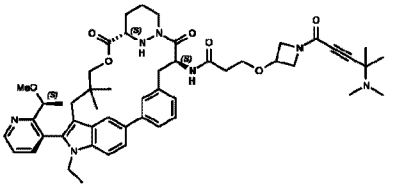
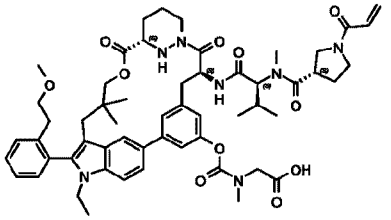
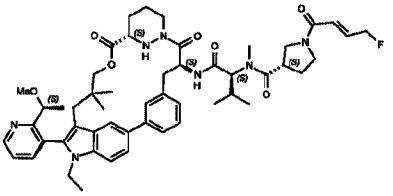
Ex#	Structure	Ex#	Structure
BA 49		BA 420	
BA 50		BA 421	
BA 51		BA 422	
BA 52		BA 423	
BA 53		BA 424	

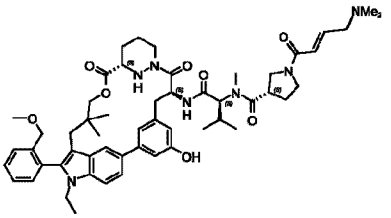
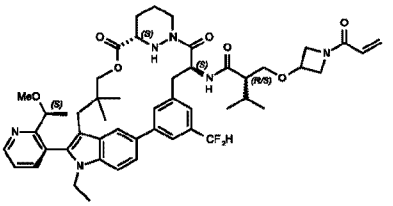
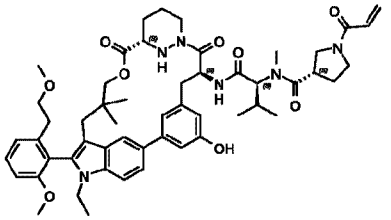
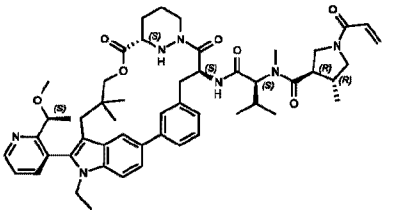
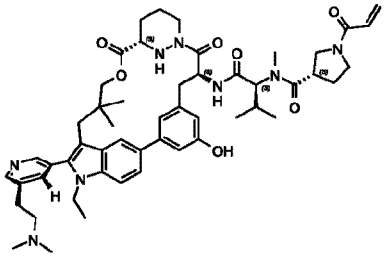
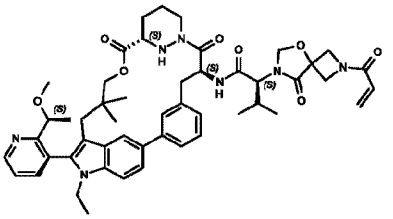
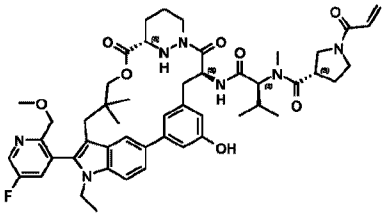
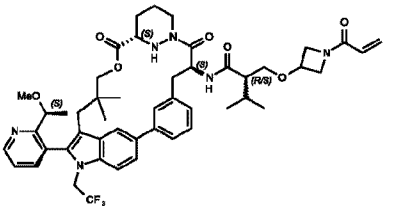
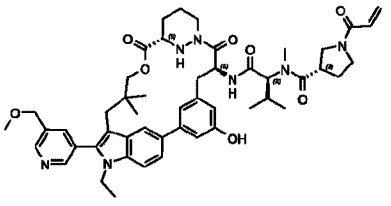
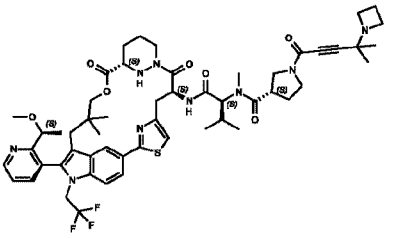
Ex#	Structure	Ex#	Structure
BA 54		BA 425	
BA 55		BA 426	
BA 56		BA 427	
BA 57		BA 428	
BA 58		BA 429	

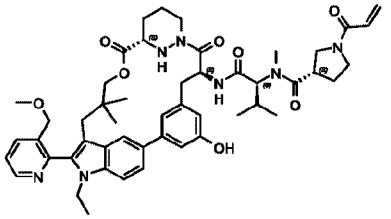
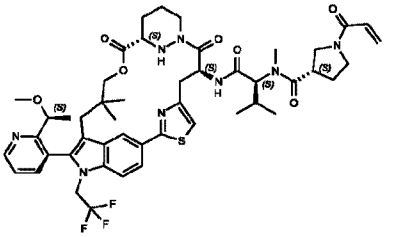
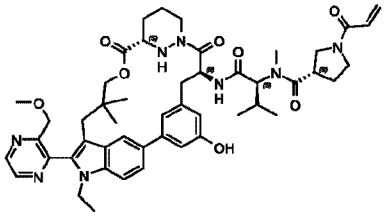
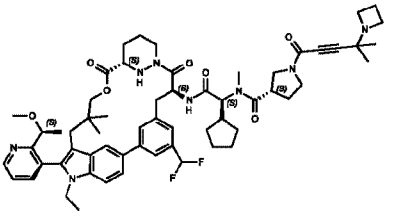
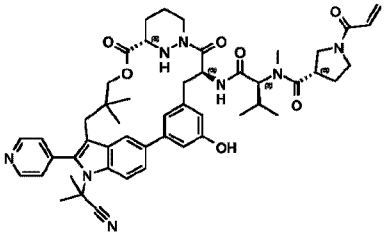
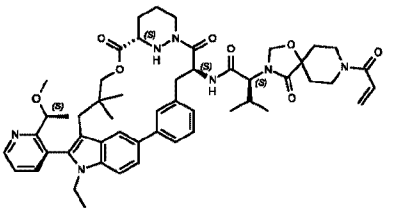
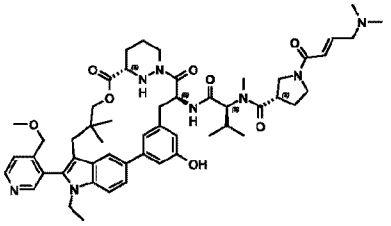
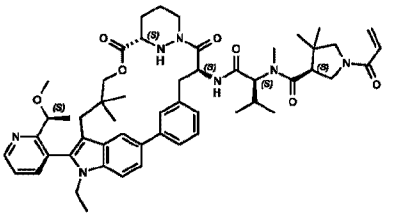
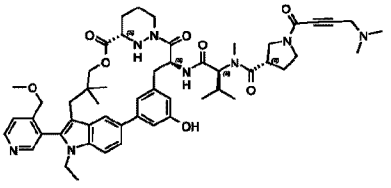
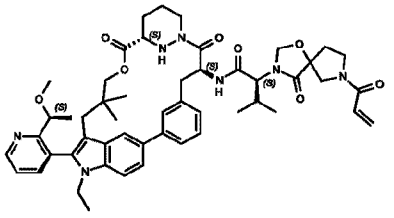
Ex#	Structure	Ex#	Structure
BA 59		BA 430	
BA 60		BA 431	
BA 61		BA 432	
BA 62		BA 433	
BA 63		BA 334	

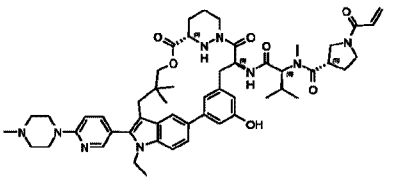
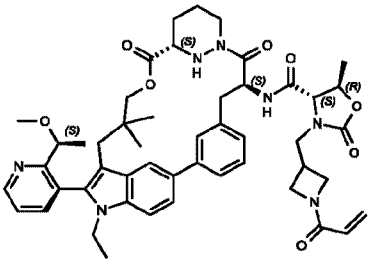
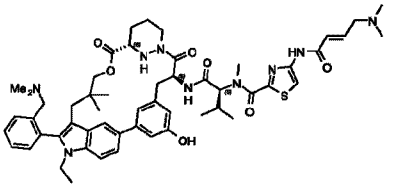
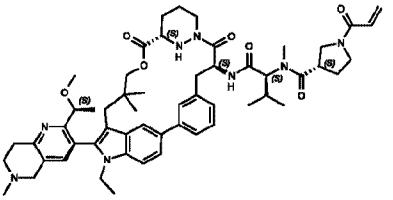
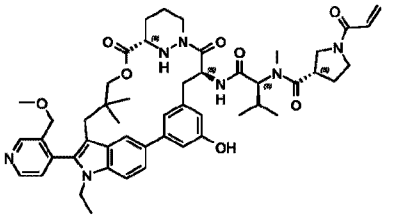
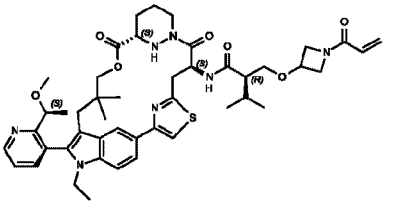
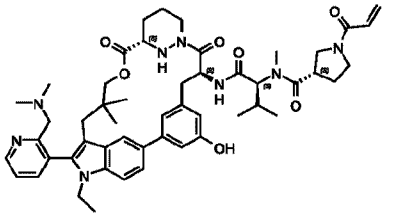
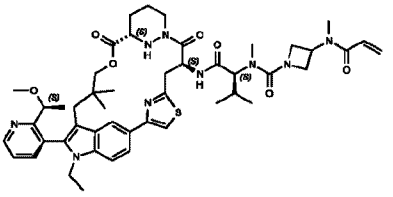
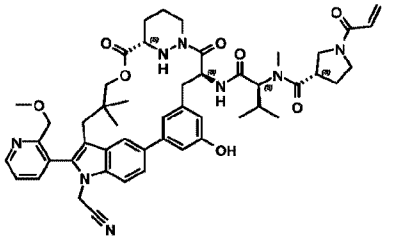
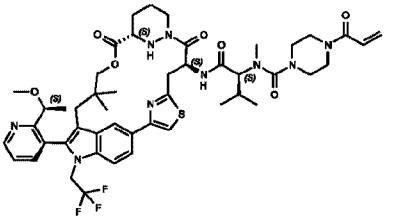
Ex#	Structure	Ex#	Structure
BA 64		BA 435	
BA 65		BA 436	
BA 66		BA 437	
BA 67		BA 438	
BA 68		BA 439	

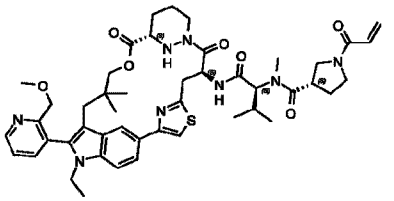
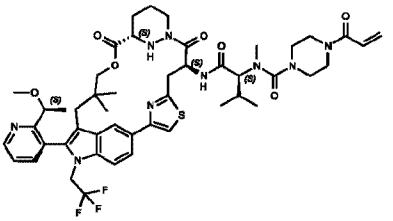
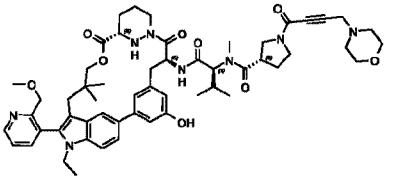
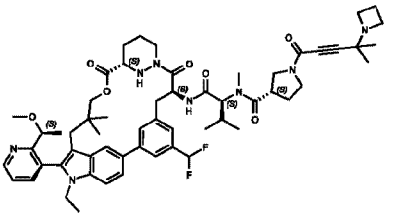
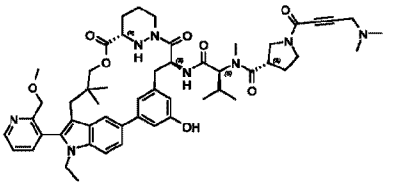
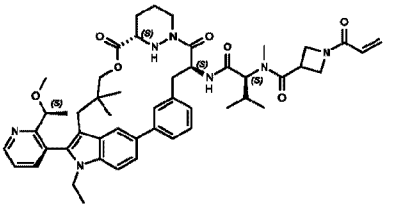
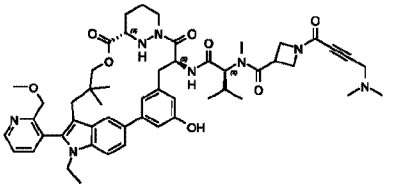
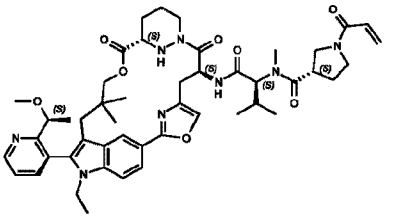
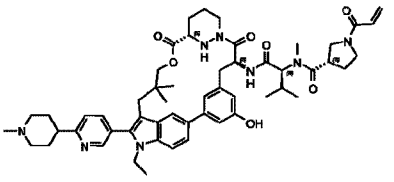
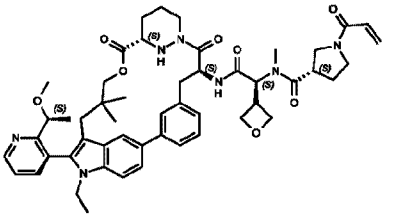
Ex#	Structure	Ex#	Structure
BA 69		BA 440	
BA 70		BA 441	
BA 71		BA 442	
BA 72		BA 443	
BA 73		BA 444	

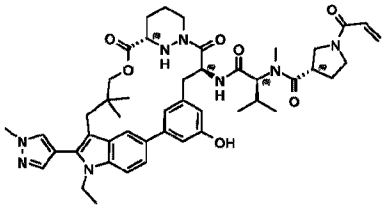
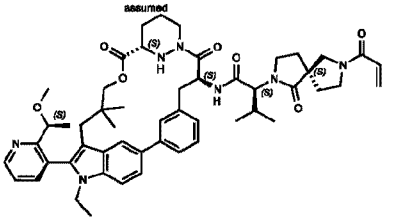
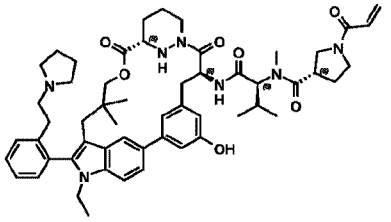
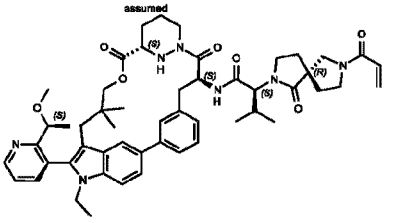
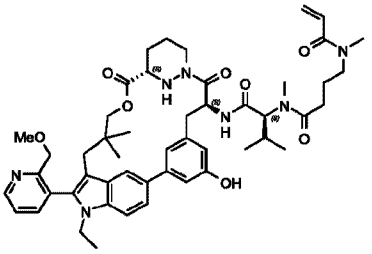
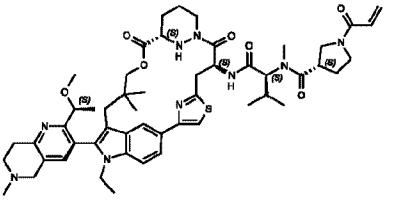
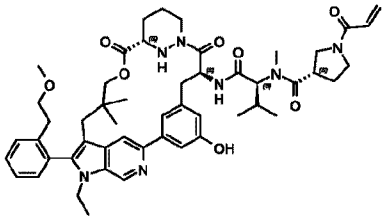
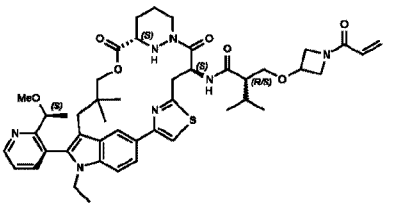
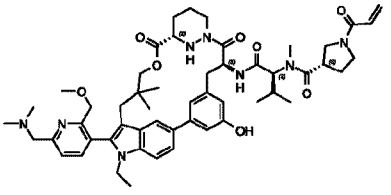
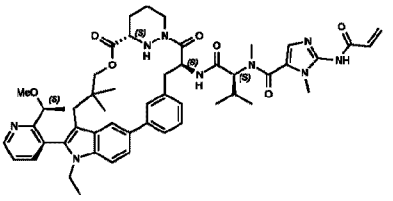
Ex#	Structure	Ex#	Structure
BA 74		BA 445	
BA 75		BA 446	
BA 76		BA 447	
BA 77		BA 448	
BA 78		BA 449	

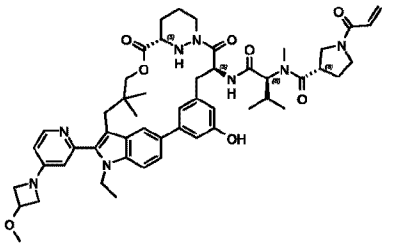
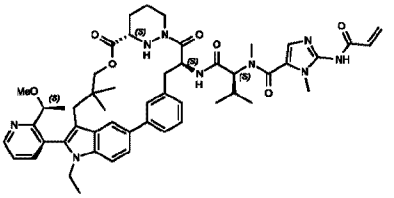
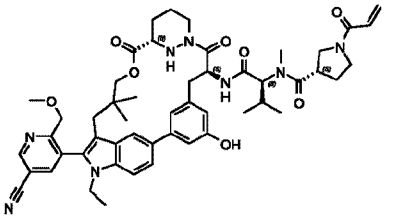
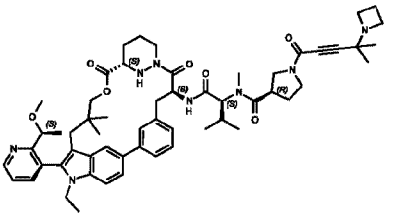
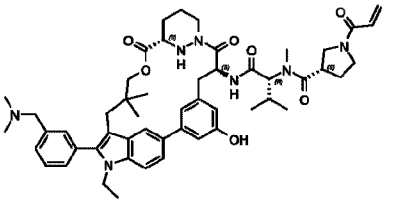
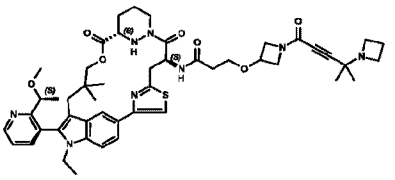
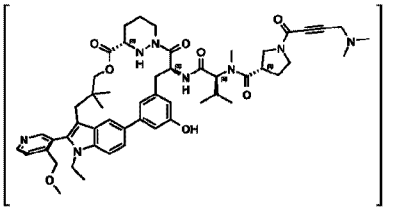
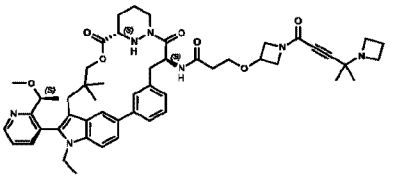
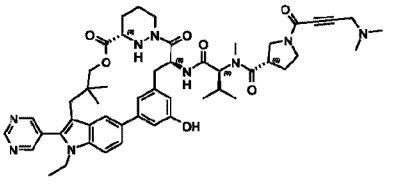
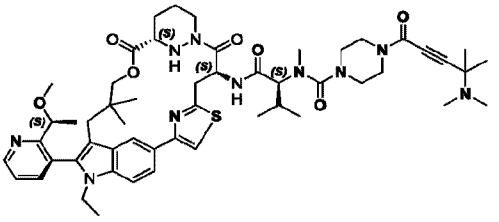
Ex#	Structure	Ex#	Structure
BA 79		BA 450	
BA 80		BA 451	
BA 81		BA 452	
BA 82		BA 453	
BA 83		BA 454	

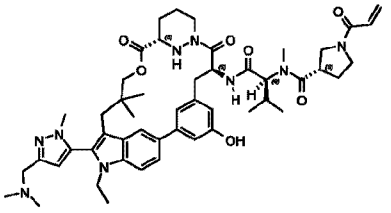
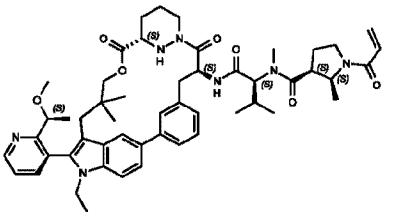
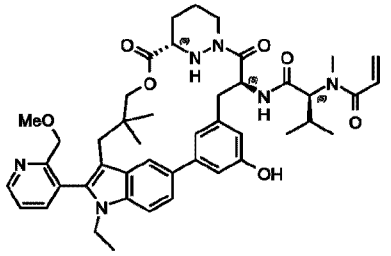
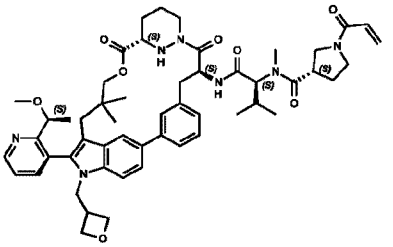
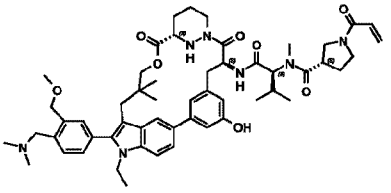
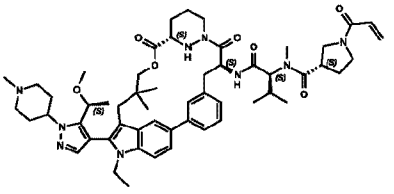
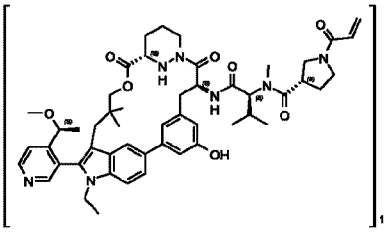
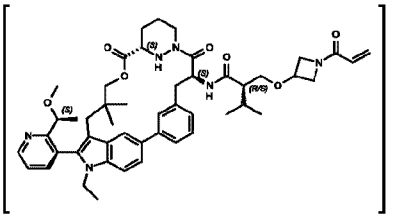
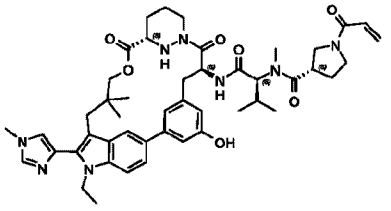
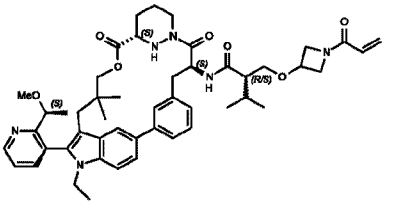
Ex#	Structure	Ex#	Structure
BA 84		BA 455	
BA 85		BA 456	
BA 86		BA 457	
BA 87		BA 458	
BA 88		BA 459	

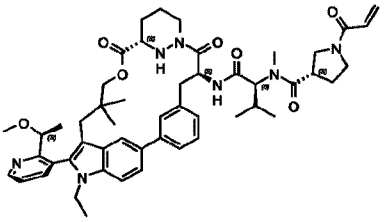
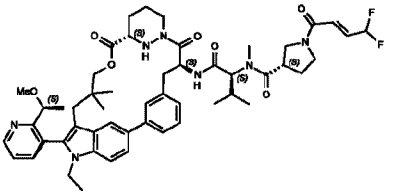
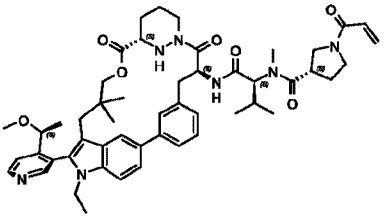
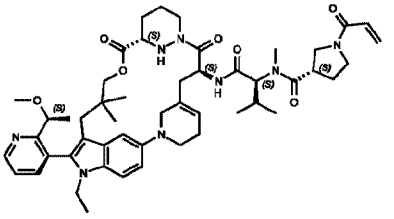
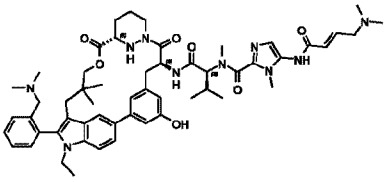
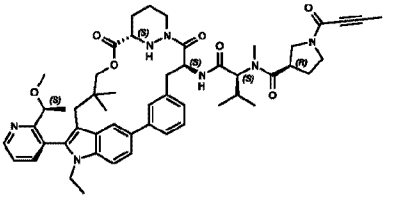
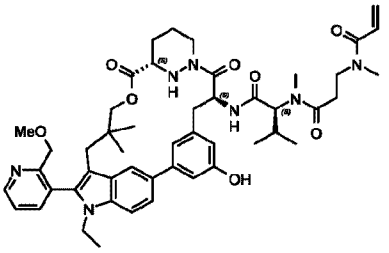
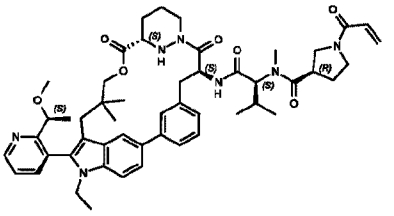
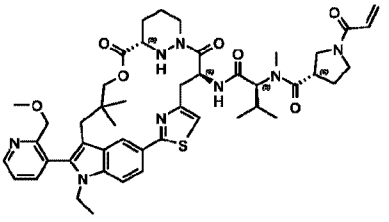
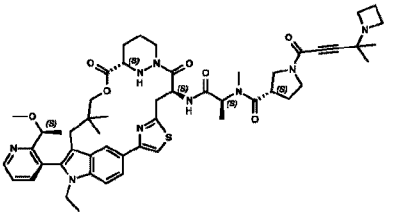
Ex#	Structure	Ex#	Structure
BA 89		BA 460	
BA 90		BA 461	
BA 91		BA 462	
BA 92		BA 463	
BA 93		BA 464	

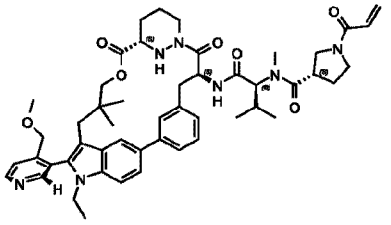
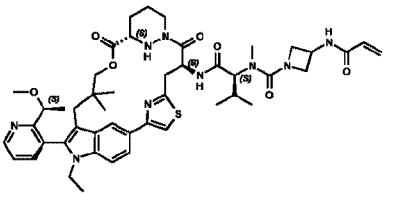
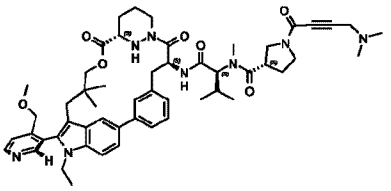
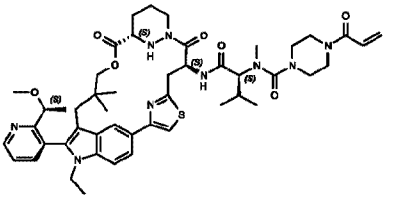
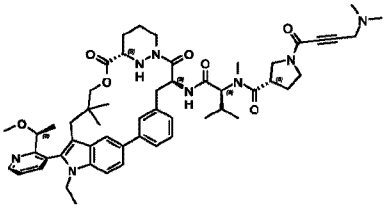
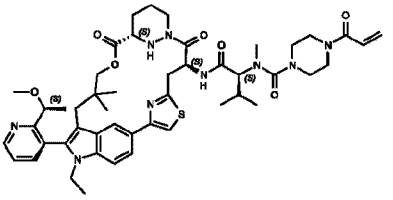
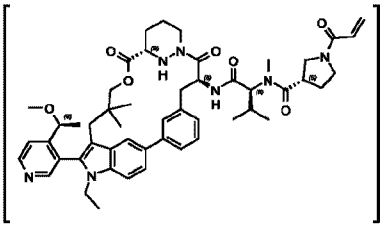
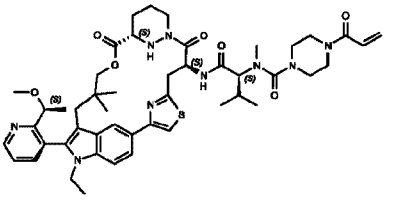
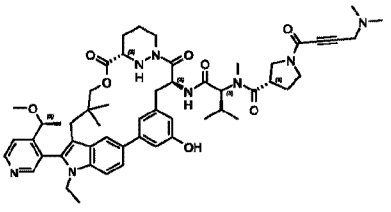
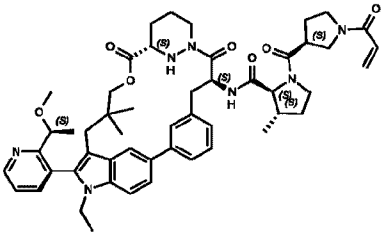
Ex#	Structure	Ex#	Structure
BA 94		BA 465	
BA 95		BA 466	
BA 96		BA 467	
BA 97		BA 468	
BA 98		BA 469	

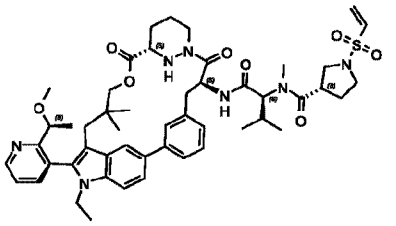
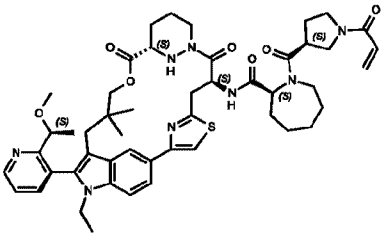
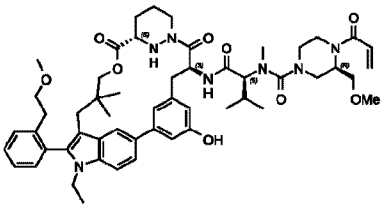
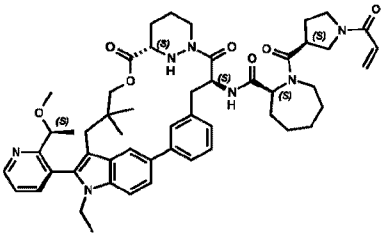
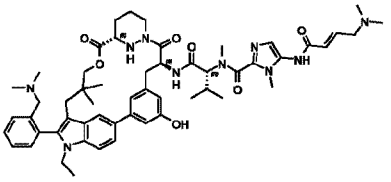
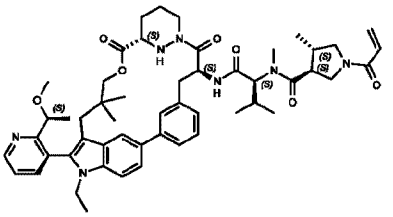
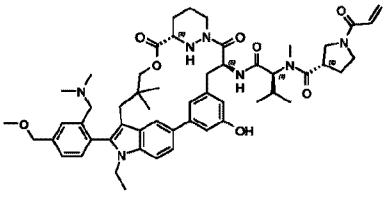
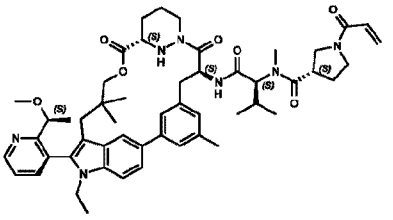
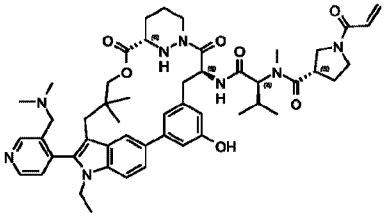
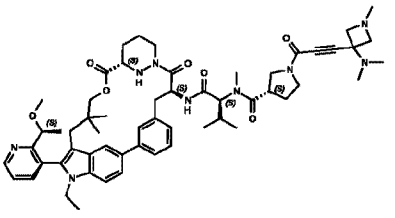
Ex#	Structure	Ex#	Structure
BA 99		BA 470	
BA 100		BA 471	
BA 101		BA 472	
BA 102		BA 473	
BA 103		BA 474	

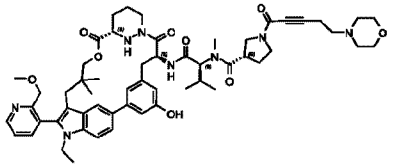
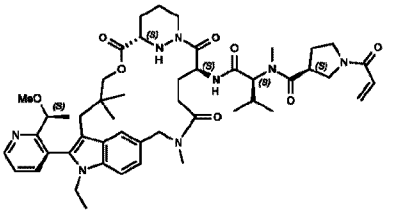
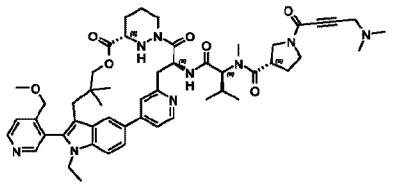
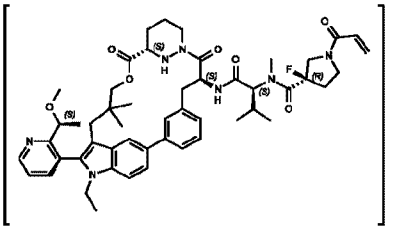
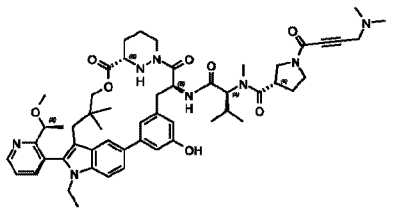
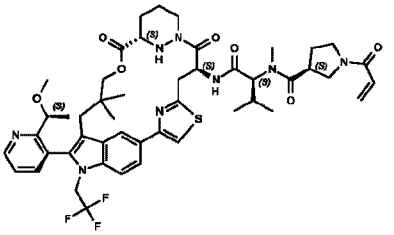
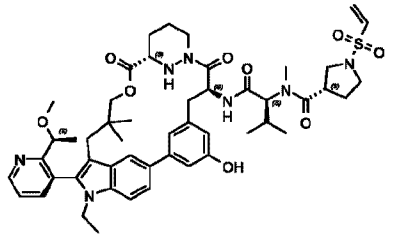
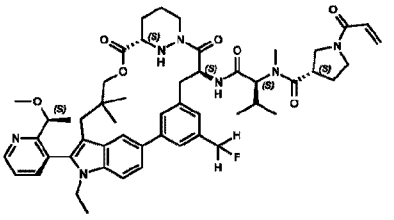
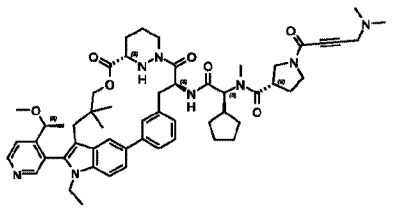
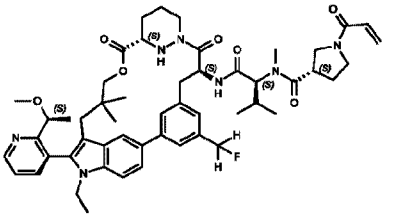
Ex#	Structure	Ex#	Structure
BA 104		BA 475	
BA 105		BA 476	
BA 106		BA 477	
BA 107		BA 478	
BA 108		BA 479	

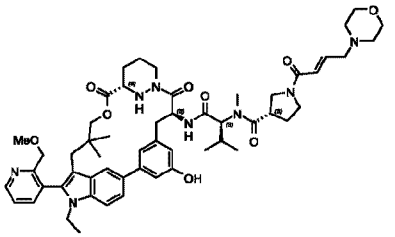
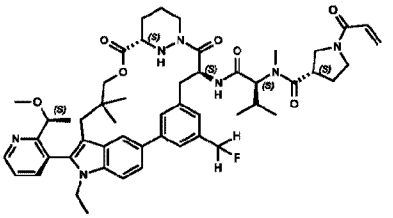
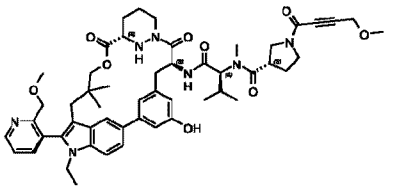
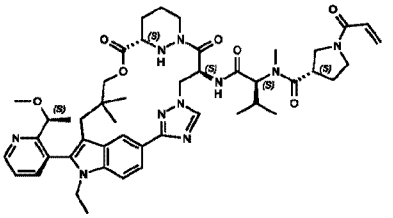
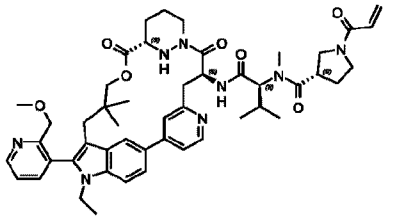
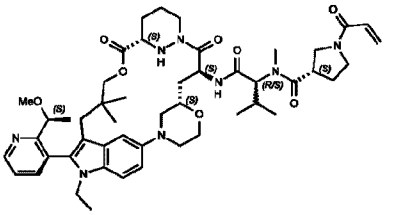
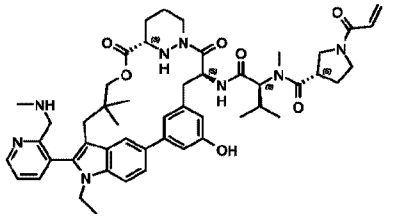
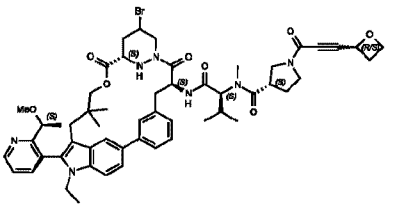
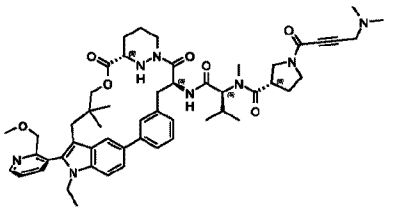
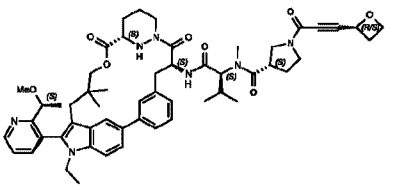
Ex#	Structure	Ex#	Structure
BA 109		BA 480	
BA 110		BA 481	
BA 111		BA 482	
BA 112		BA 483	
BA 113		BA 484	

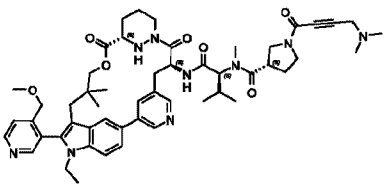
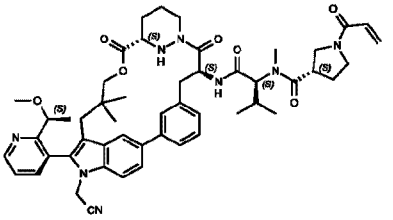
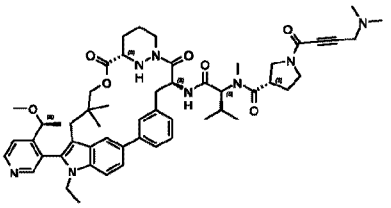
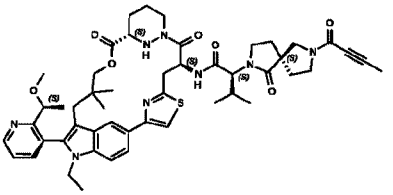
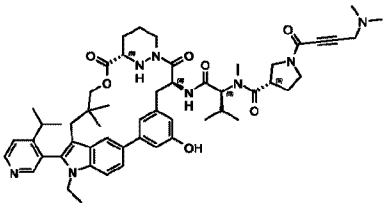
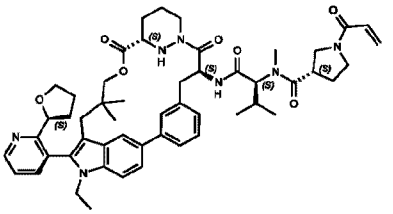
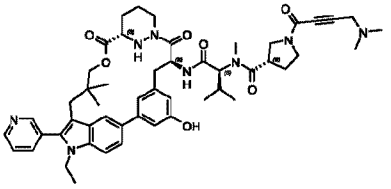
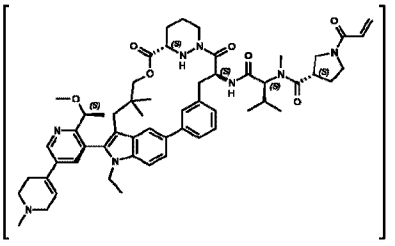
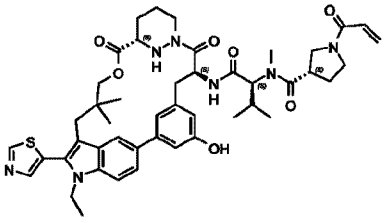
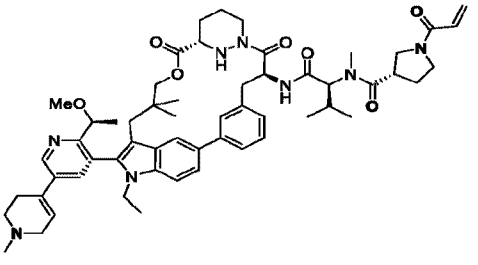
Ex#	Structure	Ex#	Structure
BA 114		BA 485	
BA 115		BA 486	
BA 116		BA 487	
BA 117		BA 488	
BA 118		BA 489	

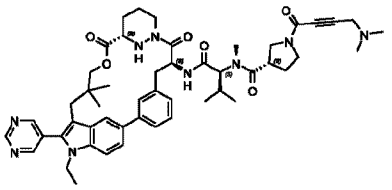
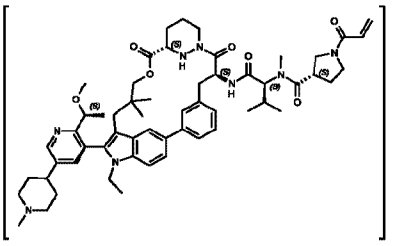
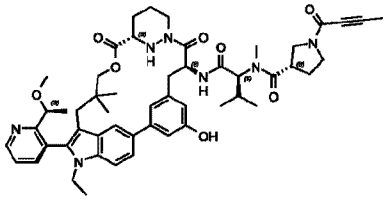
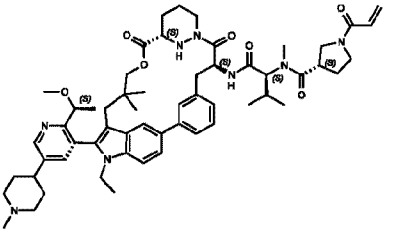
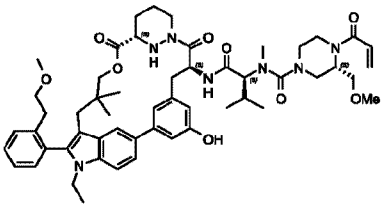
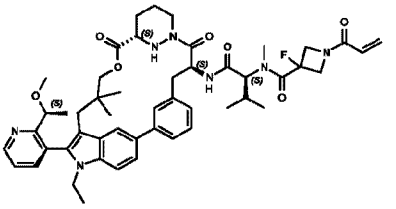
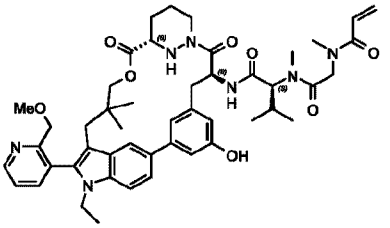
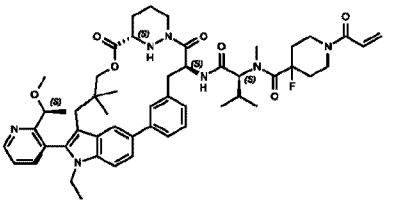
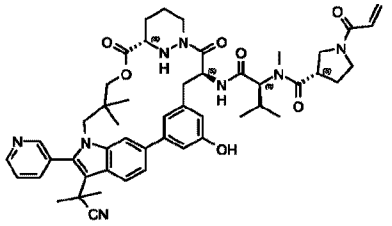
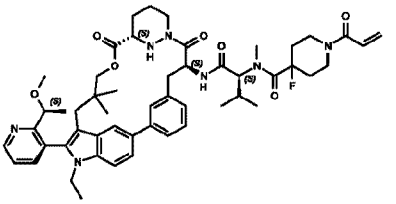
Ex#	Structure	Ex#	Structure
BA 119		BA 490	
BA 120		BA 491	
BA 121		BA 492	
BA 122		BA 493	
BA 123		BA 494	

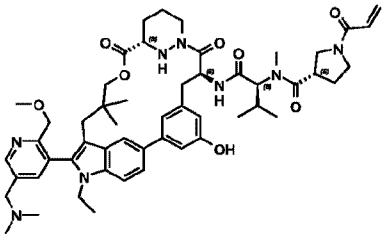
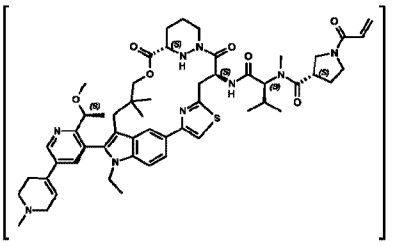
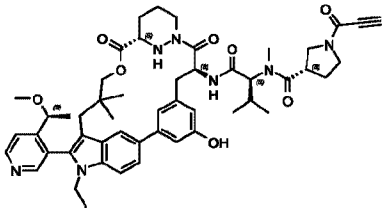
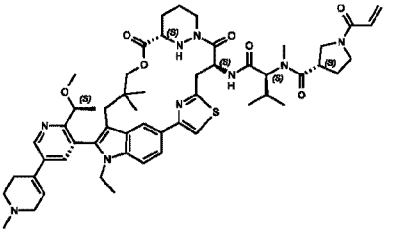
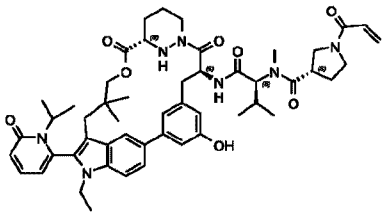
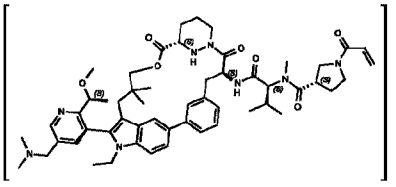
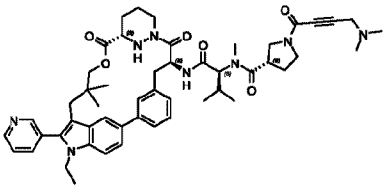
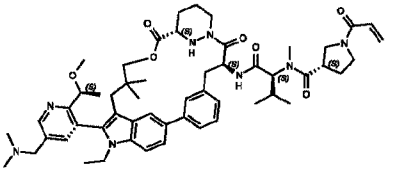
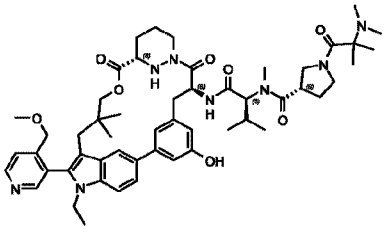
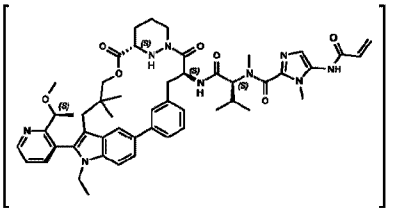
Ex#	Structure	Ex#	Structure
BA 124		BA 495	
BA 125		BA 496	
BA 126		BA 497	
BA 127		BA 498	
BA 128		BA 499	

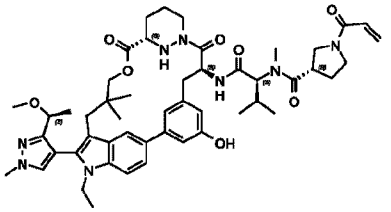
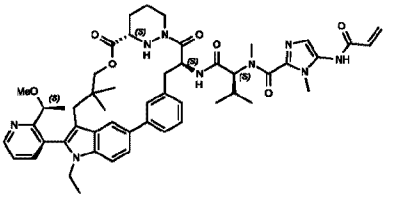
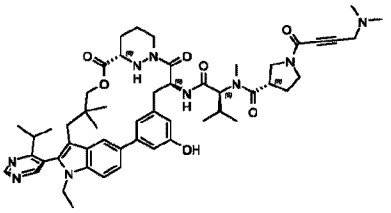
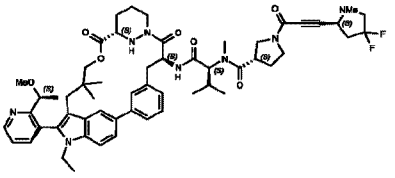
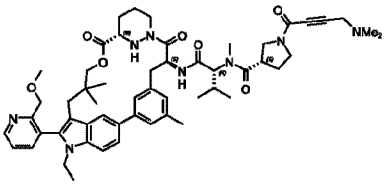
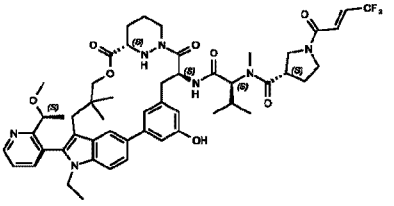
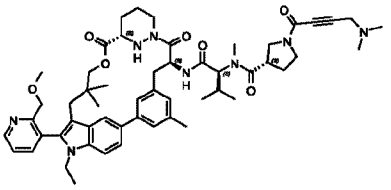
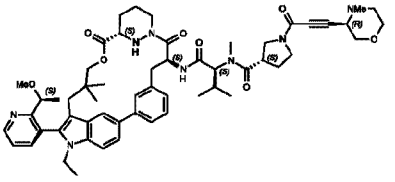
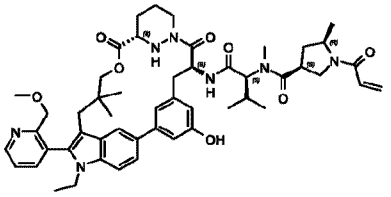
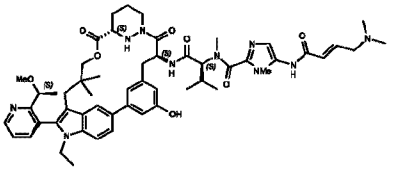
Ex#	Structure	Ex#	Structure
BA 129		BA 500	
BA 130		BA 501	
BA 131		BA 502	
BA 132		BA 503	
BA 133		BA 504	

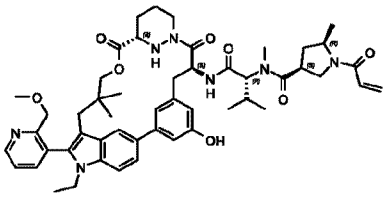
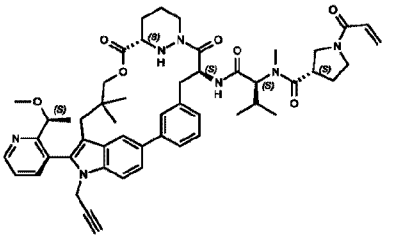
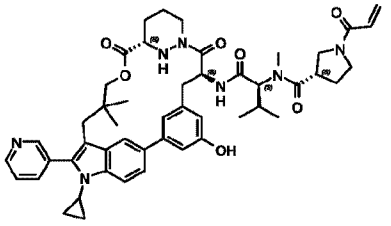
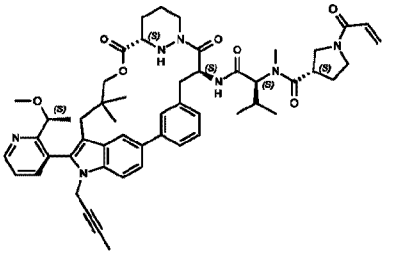
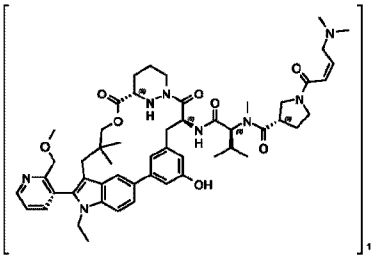
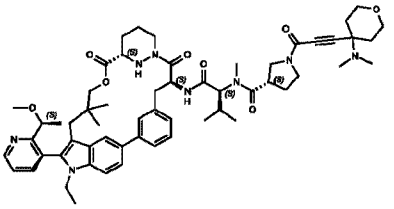
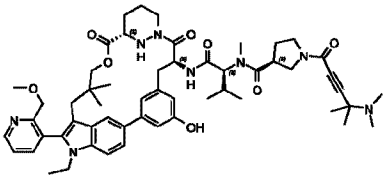
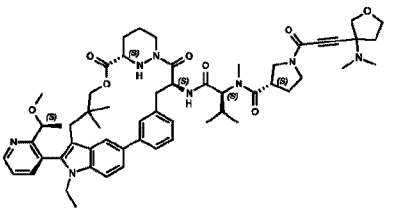
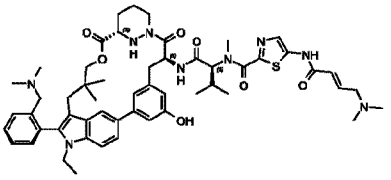
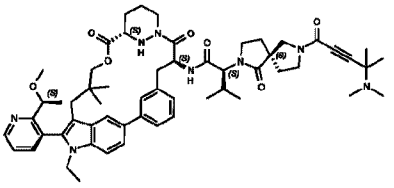
Ex#	Structure	Ex#	Structure
BA 134		BA 505	
BA 135		BA 506	
BA 136		BA 507	
BA 137		BA 508	
BA 138		BA 509	

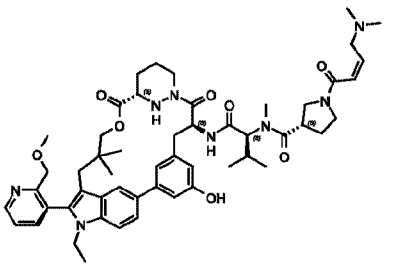
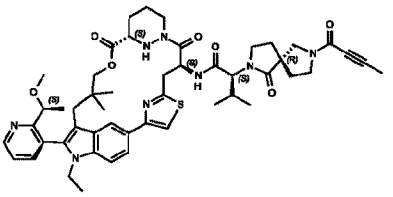
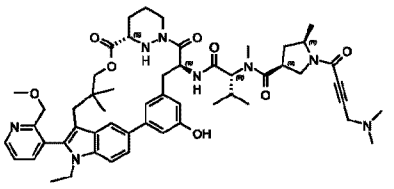
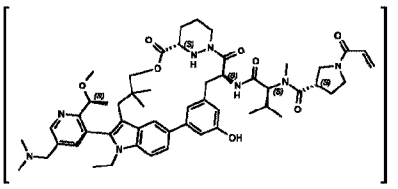
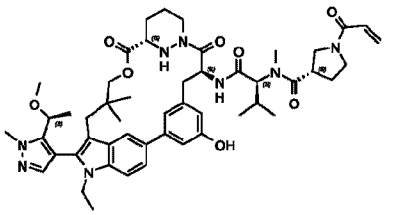
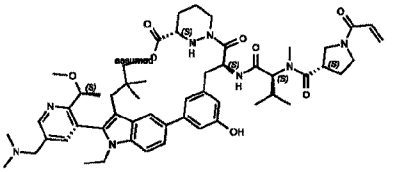
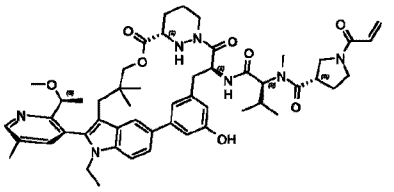
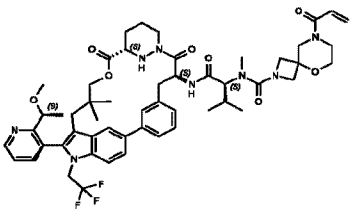
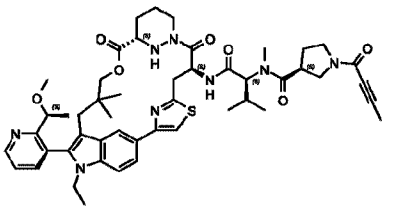
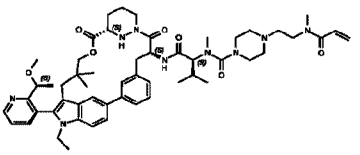
Ex#	Structure	Ex#	Structure
BA 139		BA 510	
BA 140		BA 511	
BA 141		BA 512	
BA 142		BA 513	
BA 143		BA 514	

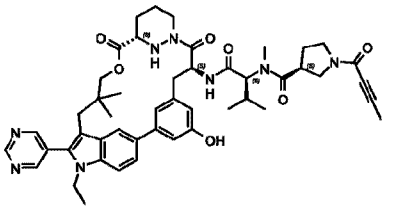
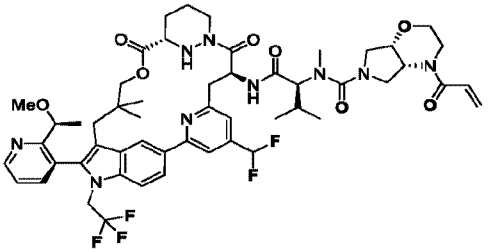
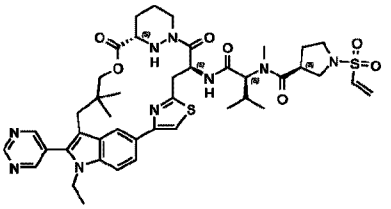
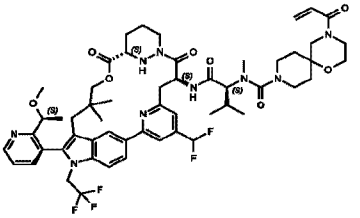
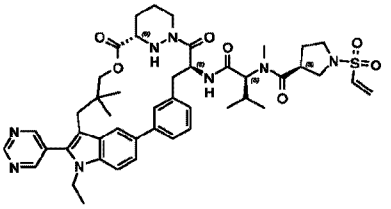
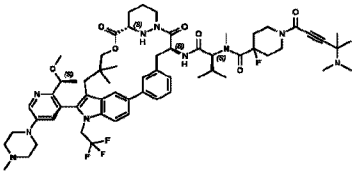
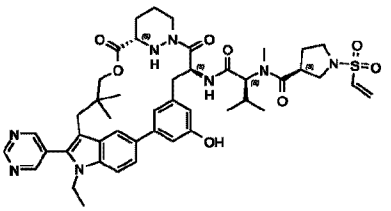
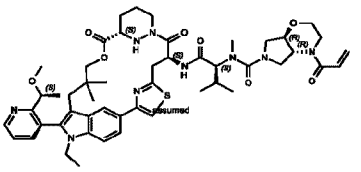
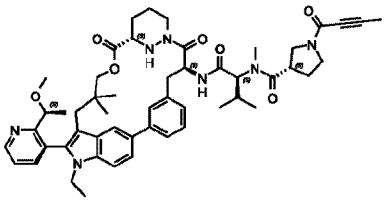
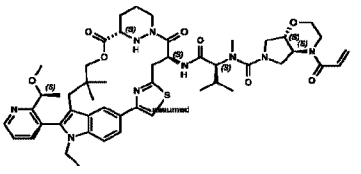
Ex#	Structure	Ex#	Structure
BA 144		BA 515	
BA 145		BA 516	
BA 146		BA 517	
BA 147		BA 518	
BA 148		BA 519	

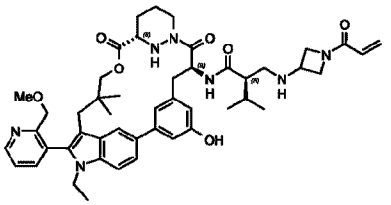
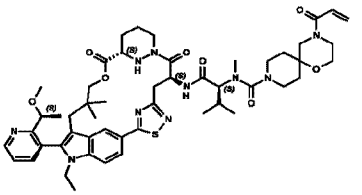
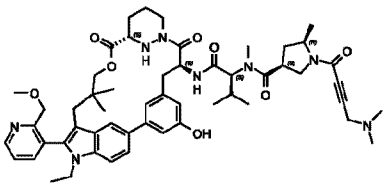
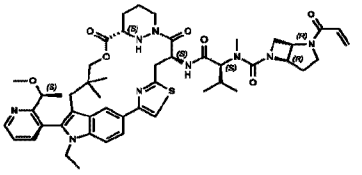
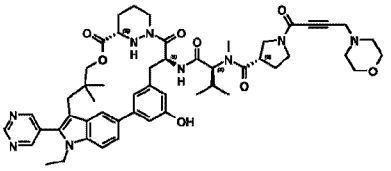
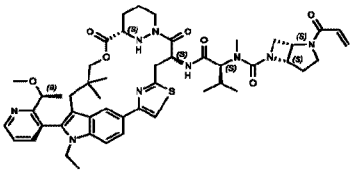
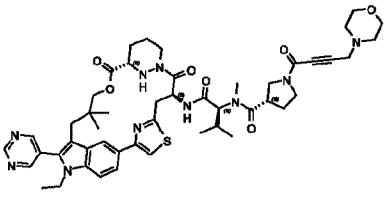
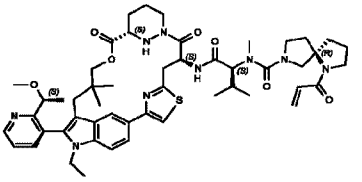
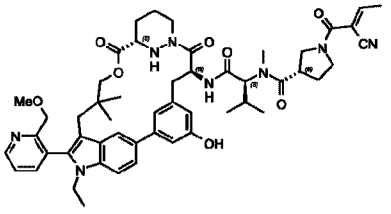
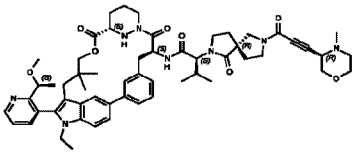
Ex#	Structure	Ex#	Structure
BA 149		BA 520	
BA 150		BA 521	
BA 151		BA 522	
BA 152		BA 523	
BA 153		BA 524	

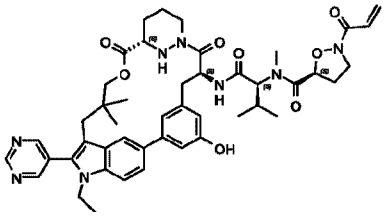
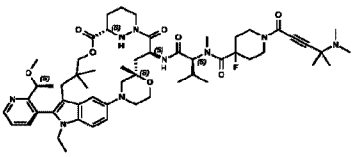
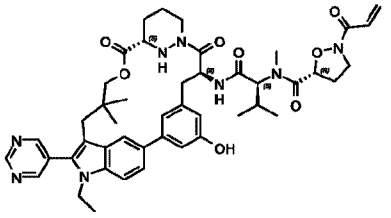
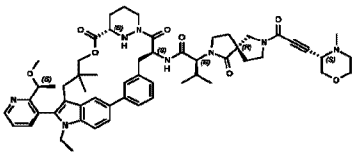
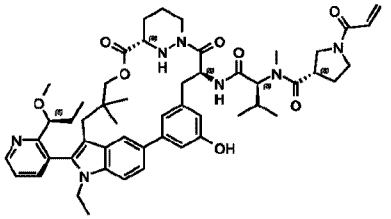
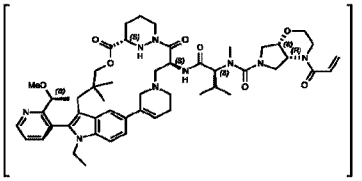
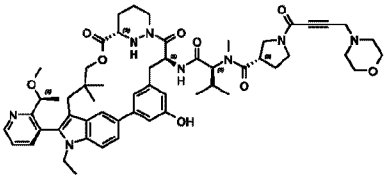
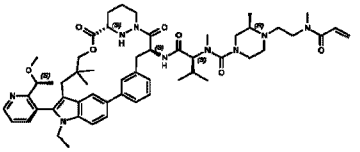
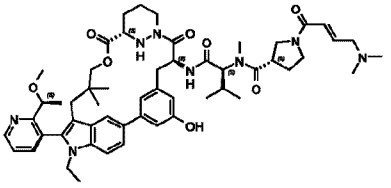
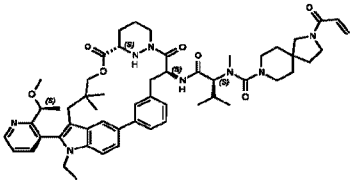
Ex#	Structure	Ex#	Structure
BA 154		BA 525	
BA 155		BA 526	
BA 156		BA 527	
BA 157		BA 528	
BA 158		BA 529	

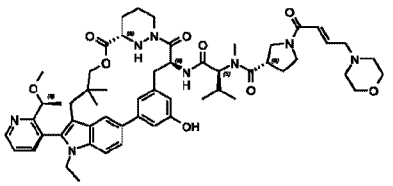
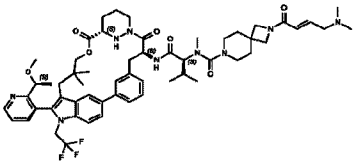
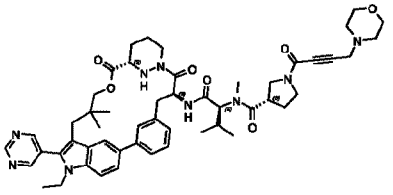
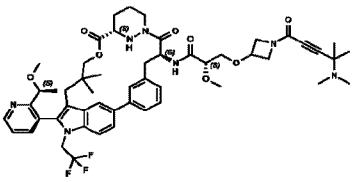
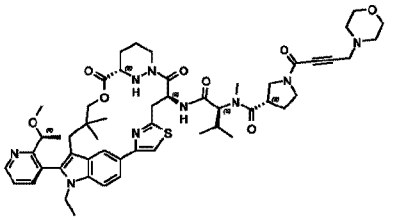
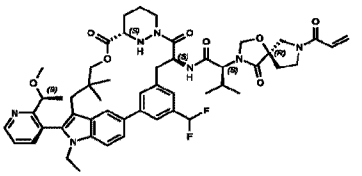
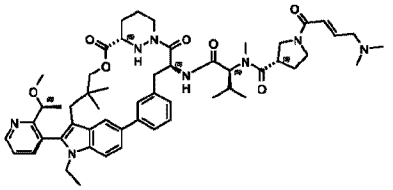
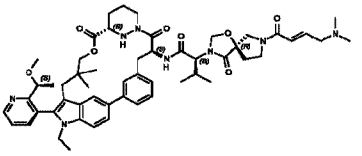
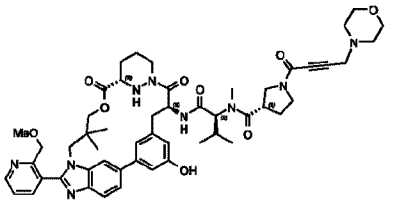
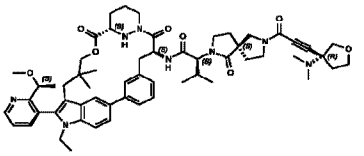
Ex#	Structure	Ex#	Structure
BA 159		BA 530	
BA 160		BA 531	
BA 161		BA 532	
BA 162		BA 533	
BA 163		BA 534	

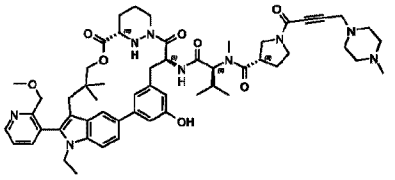
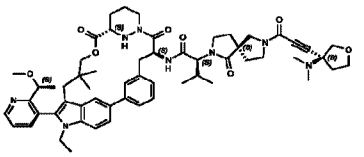
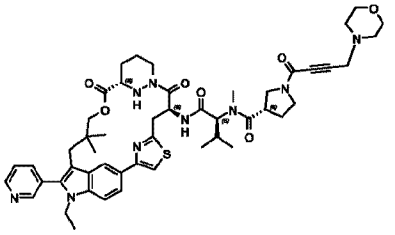
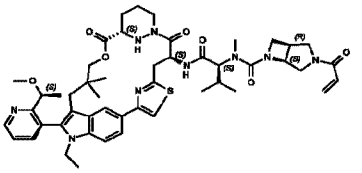
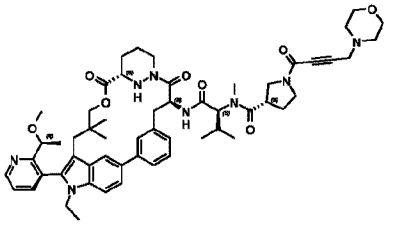
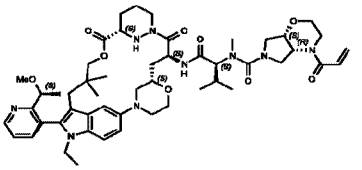
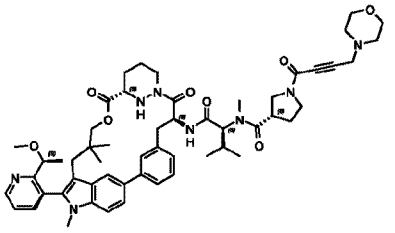
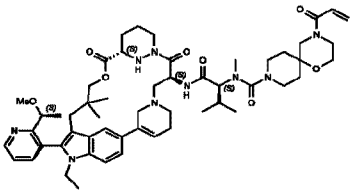
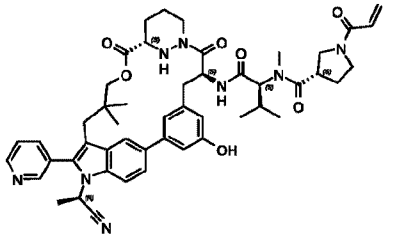
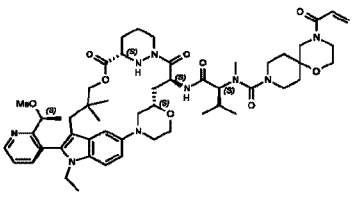
Ex#	Structure	Ex#	Structure
BA 164		BA 535	
BA 165		BA 536	
BA 166		BA 537	
BA 167		BA 538	
BA 168		BA 539	

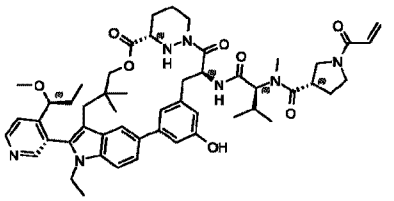
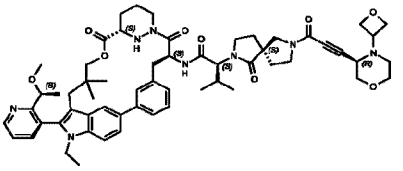
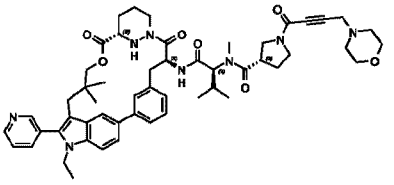
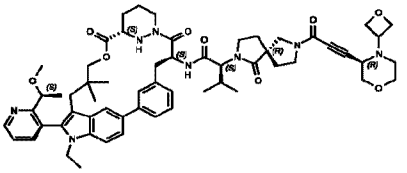
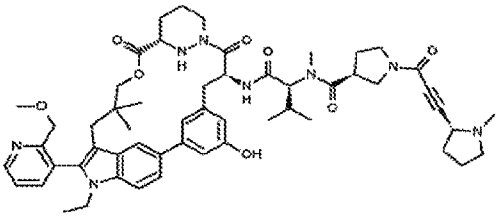
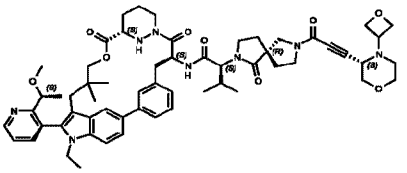
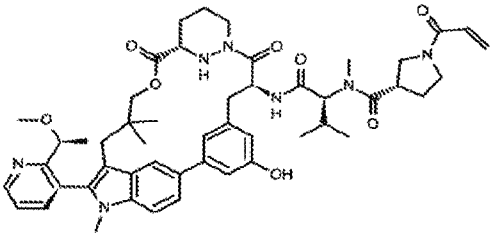
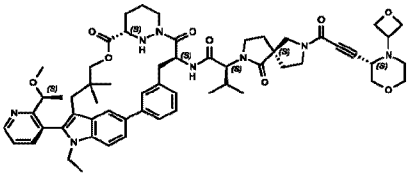
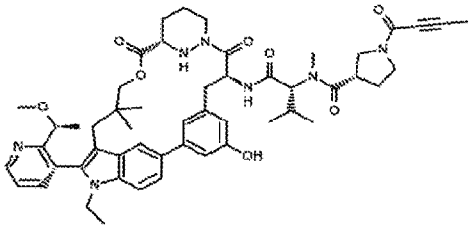
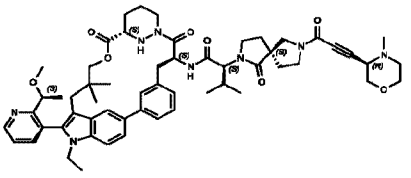
Ex#	Structure	Ex#	Structure
BA 169		BA 540	
BA 170		BA 541	
BA 171		BA 542	
BA 172		BA 543	
BA 173		BA 544	

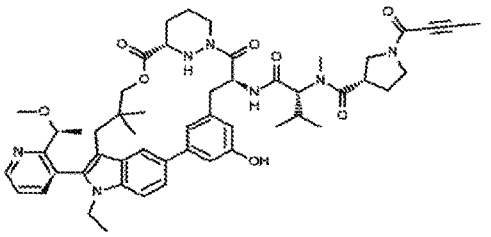
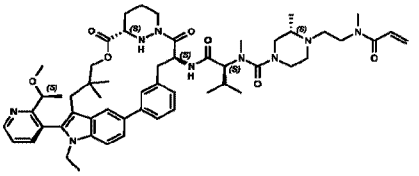
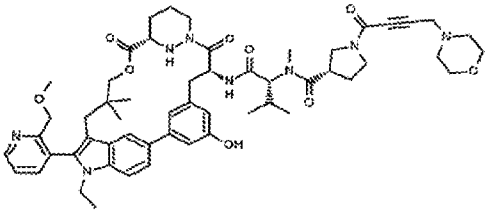
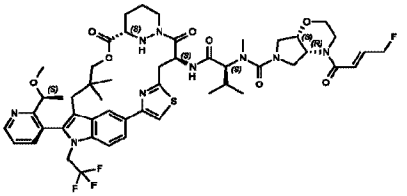
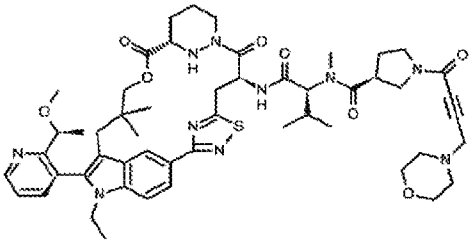
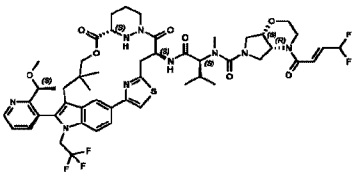
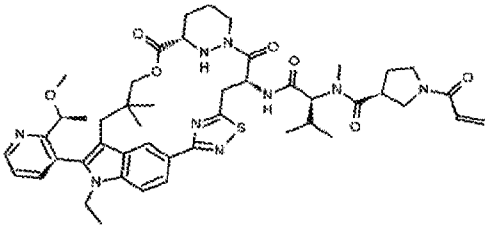
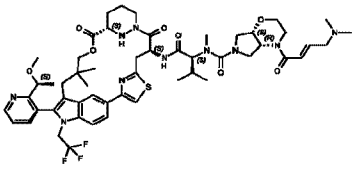
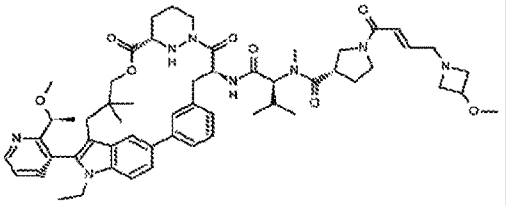
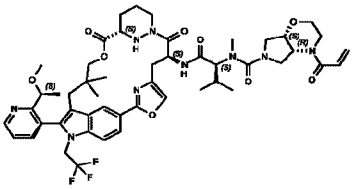
Ex#	Structure	Ex#	Structure
BA 174		BA 545	
BA 175		BA 546	
BA 176		BA 547	
BA 177		BA 548	
BA 178		BA 549	

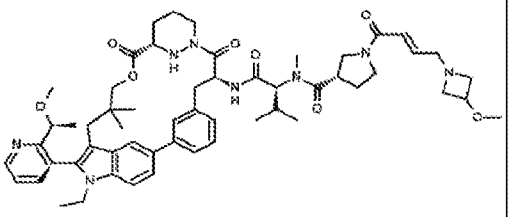
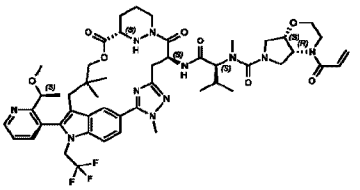
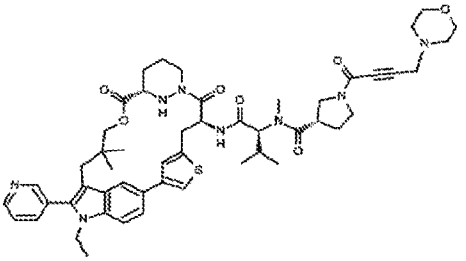
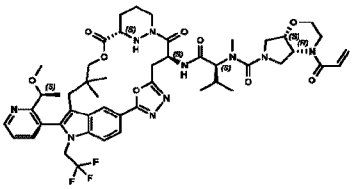
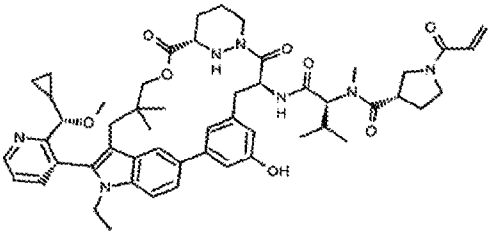
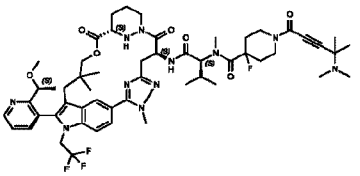
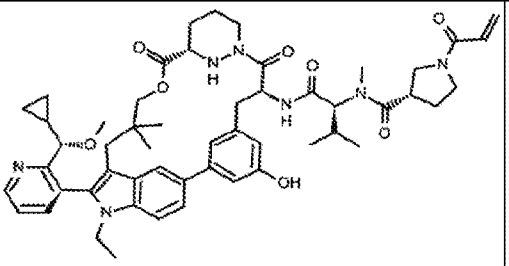
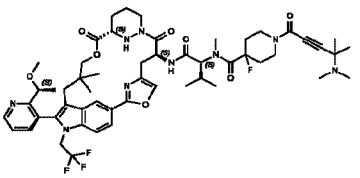
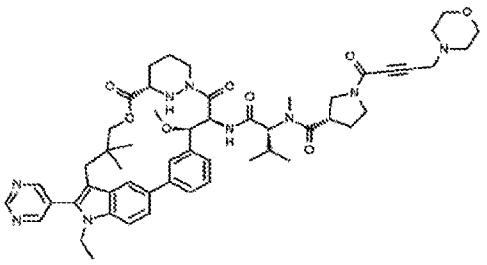
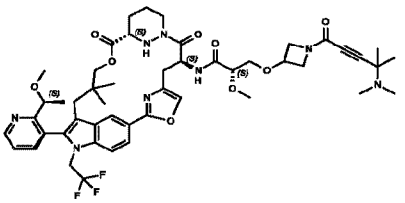
Ex#	Structure	Ex#	Structure
BA 179		BA 550	
BA 180		BA 551	
BA 181		BA 552	
BA 182		BA 553	
BA 183		BA 554	

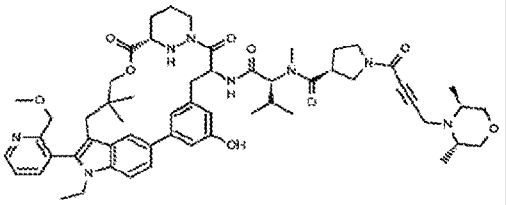
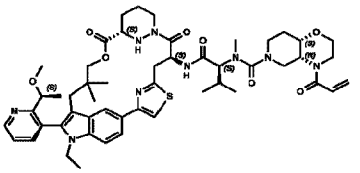
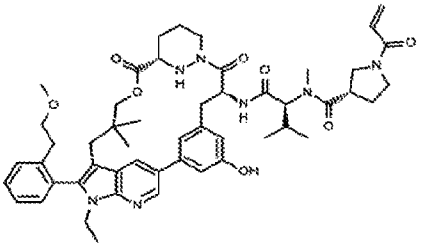
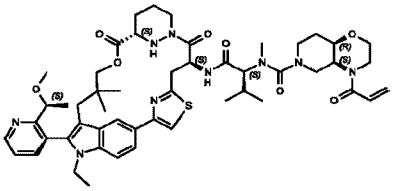
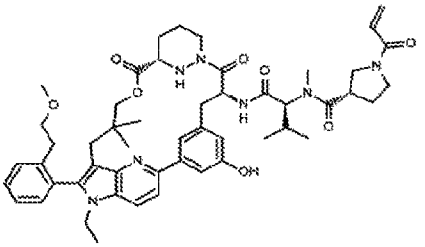
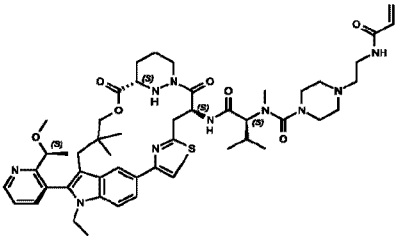
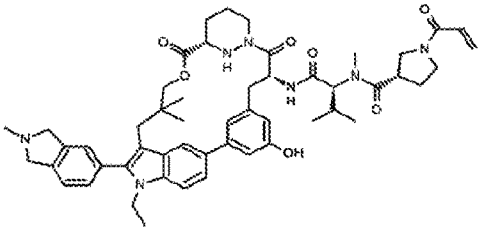
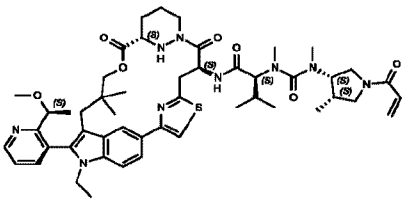
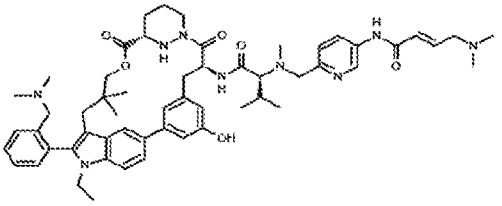
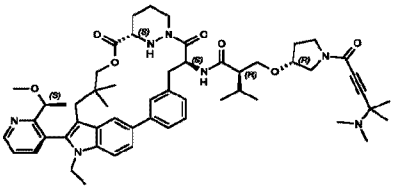
Ex#	Structure	Ex#	Structure
BA 184		BA 555	
BA 185		BA 556	
BA 186		BA 557	
BA 187		BA 558	
BA 188		BA 559	

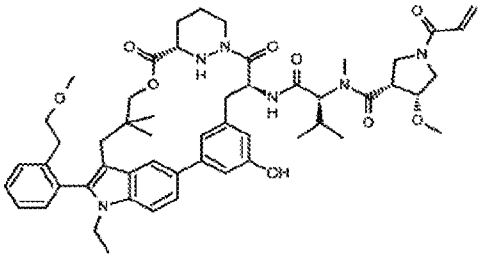
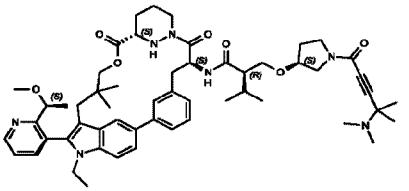
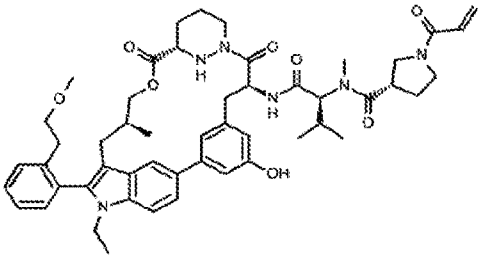
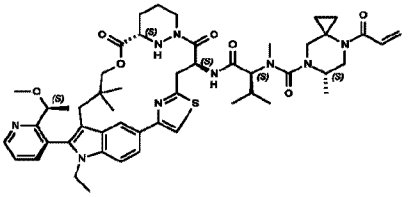
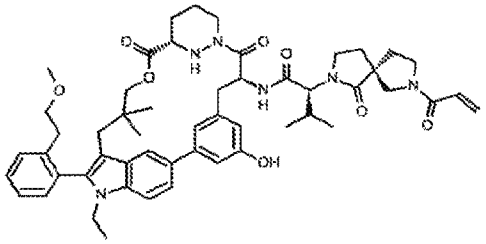
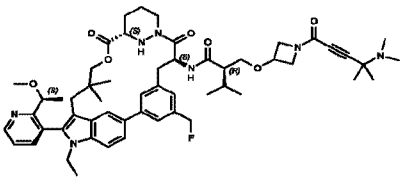
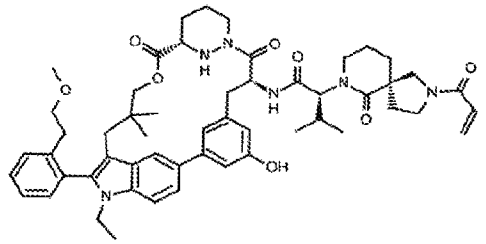
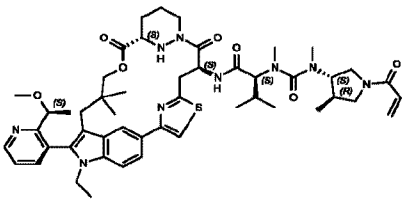
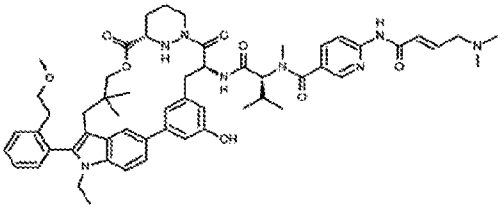
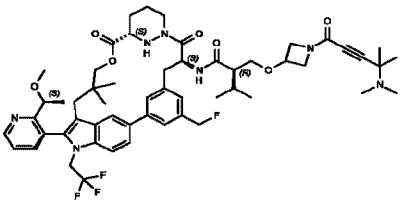
Ex#	Structure	Ex#	Structure
BA 189		BA 560	
BA 190		BA 561	
BA 191		BA 562	
BA 192		BA 563	
BA 193		BA 564	

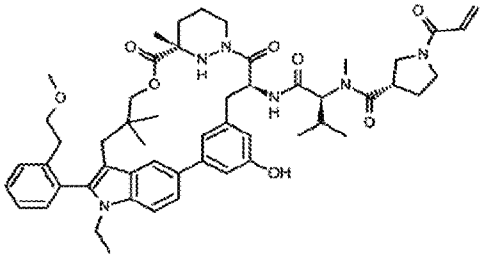
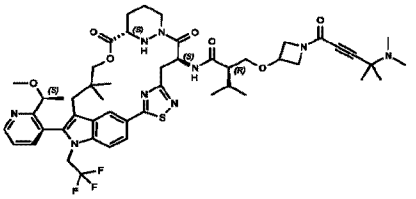
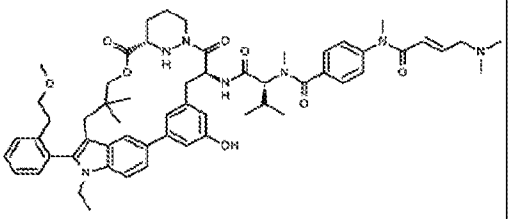
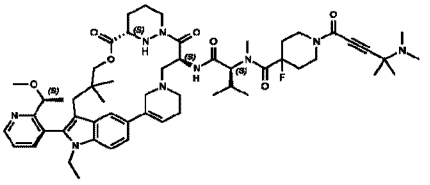
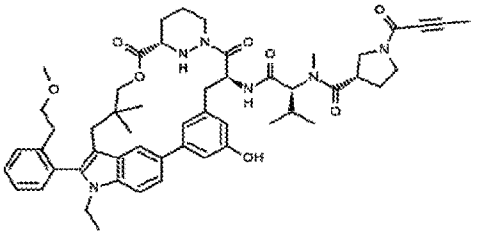
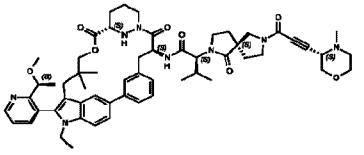
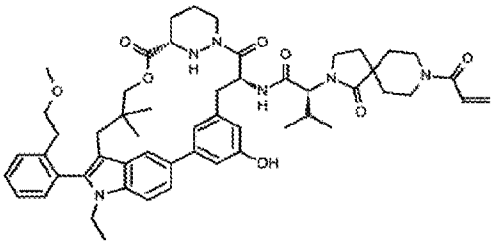
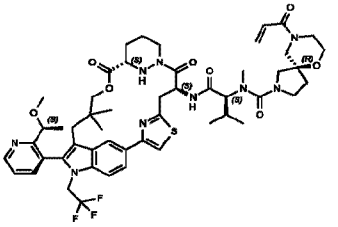
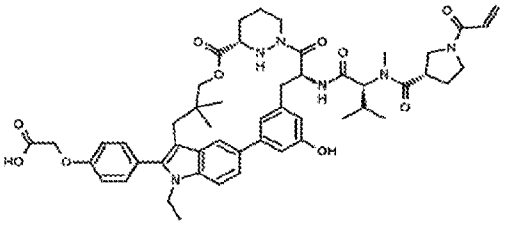
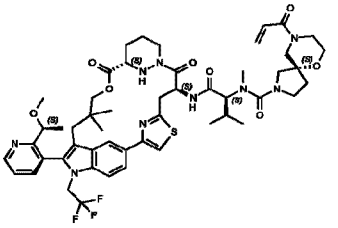
Ex#	Structure	Ex#	Structure
BA 194		BA 565	
BA 195		BA 566	
BA 196		BA 567	
BA 197		BA 568	
BA 198		BA 569	

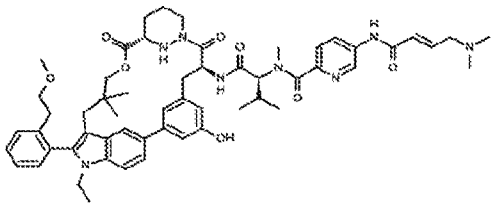
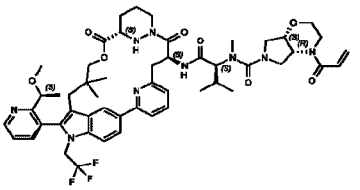
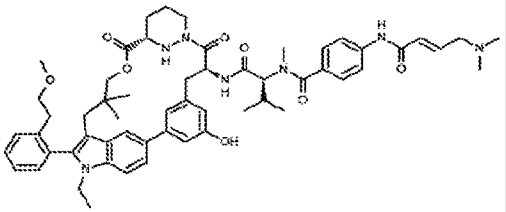
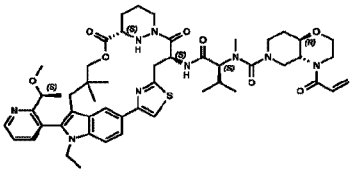
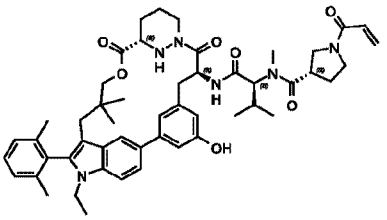
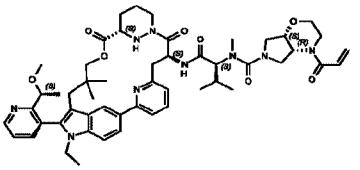
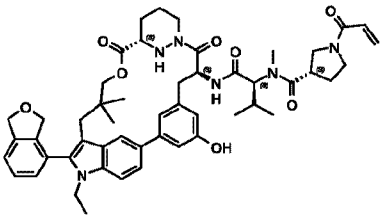
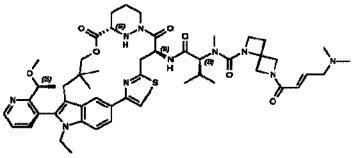
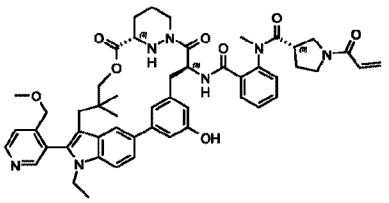
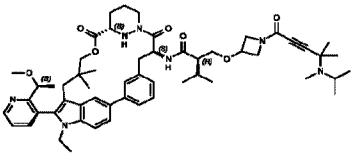
Ex#	Structure	Ex#	Structure
BA 199		BA 570	
BA 200		BA 571	
BA 201		BA 572	
BA 202		BA 573	
BA 203		BA 574	

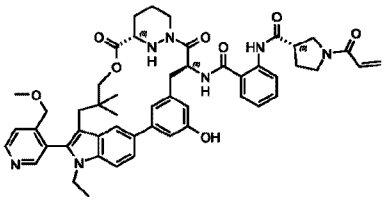
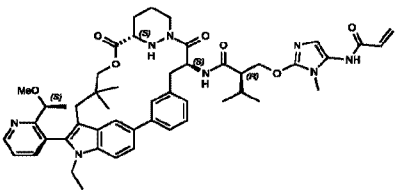
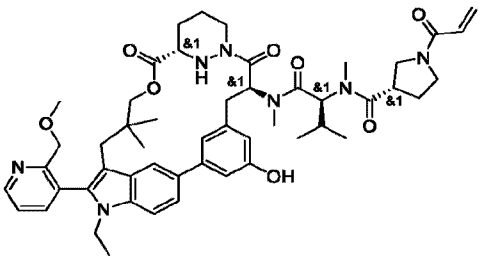
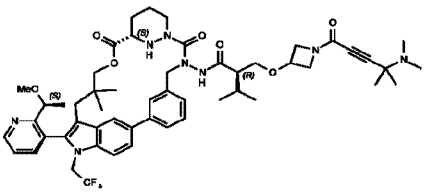
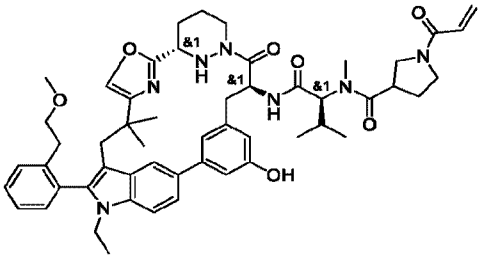
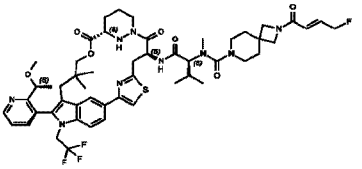
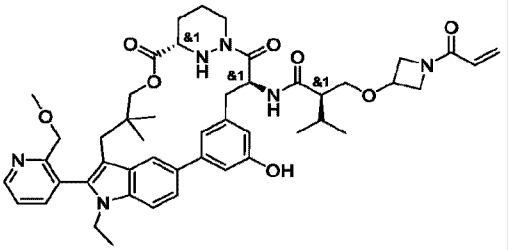
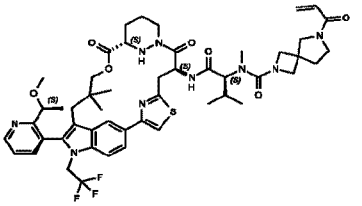
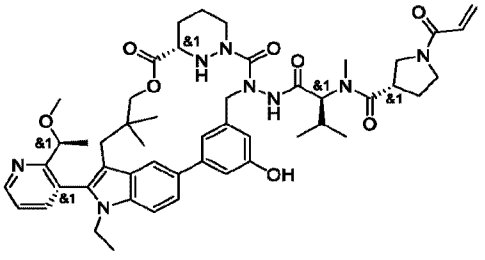
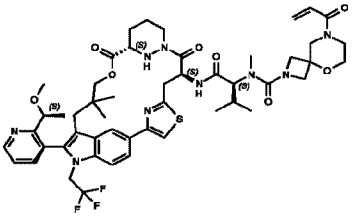
Ex#	Structure	Ex#	Structure
BA 204		BA 575	
BA 205		BA 576	
BA 206		BA 577	
BA 207		BA 578	
BA 208		BA 579	

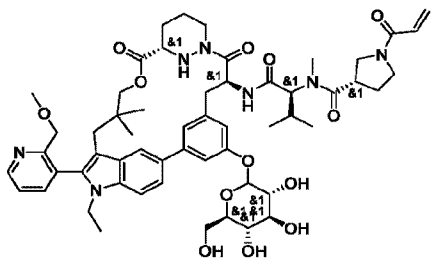
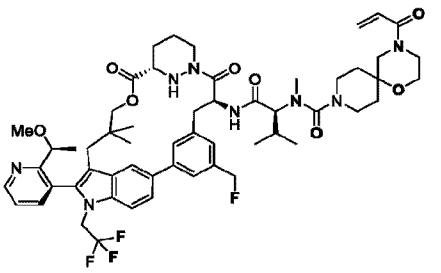
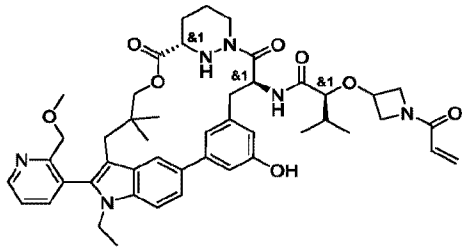
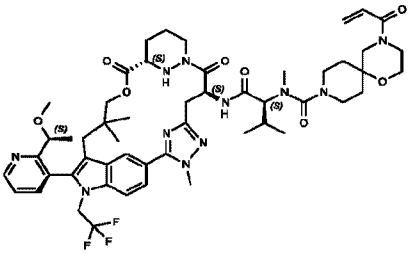
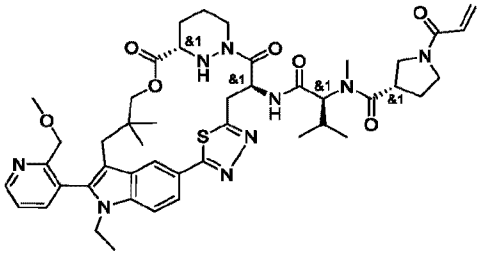
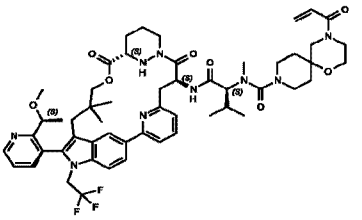
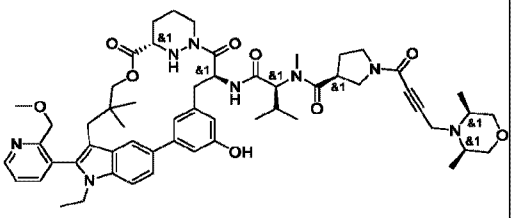
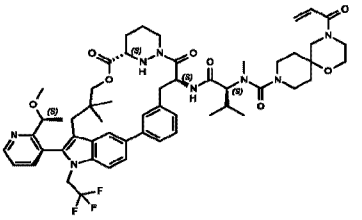
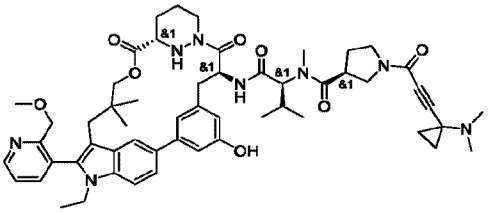
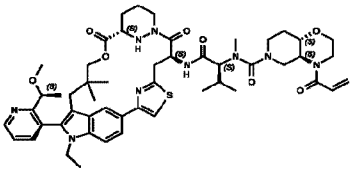
Ex#	Structure	Ex#	Structure
BA 209		BA 580	
BA 210		BA 581	
BA 211		BA 582	
BA 212		BA 583	
BA 213		BA 584	

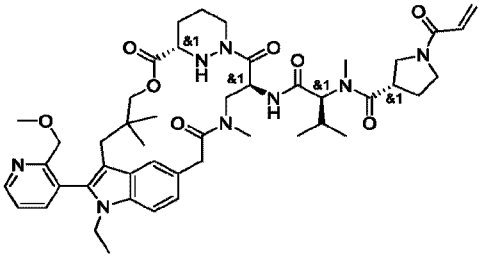
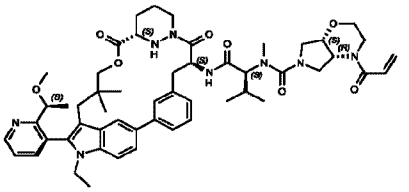
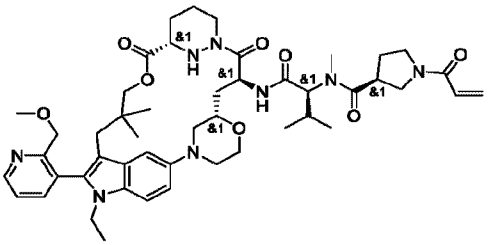
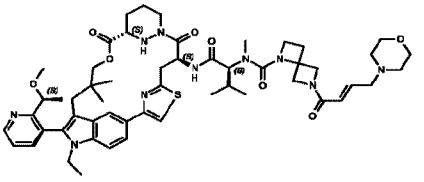
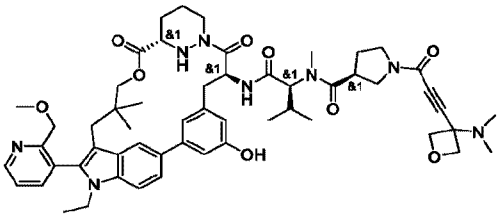
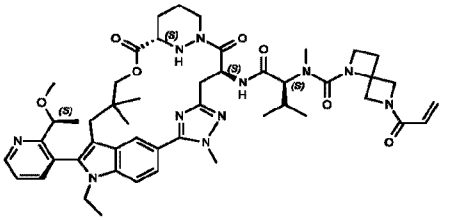
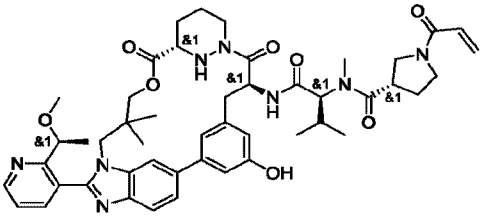
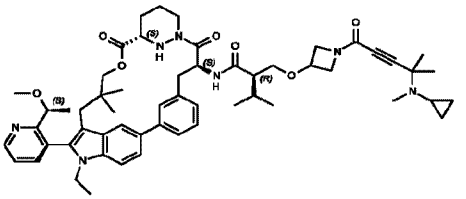
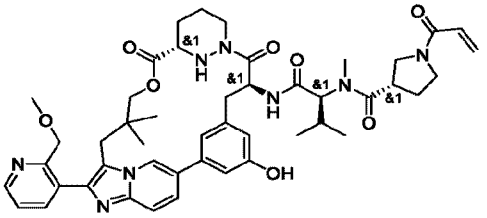
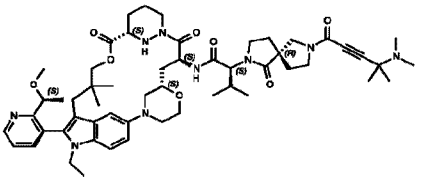
Ex#	Structure	Ex#	Structure
BA 214		BA 585	
BA 215		BA 586	
BA 216		BA 587	
BA 217		BA 588	
BA 218		BA 589	

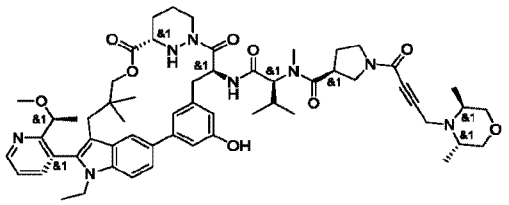
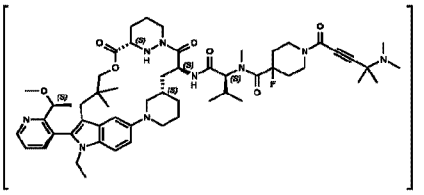
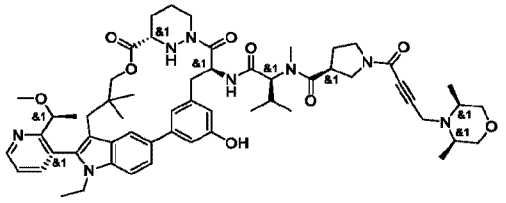
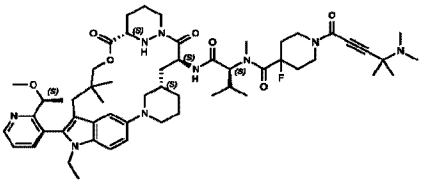
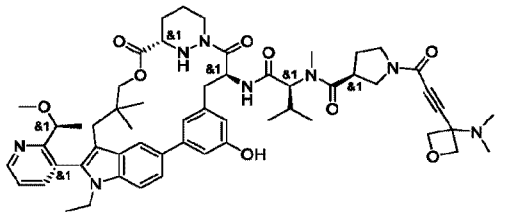
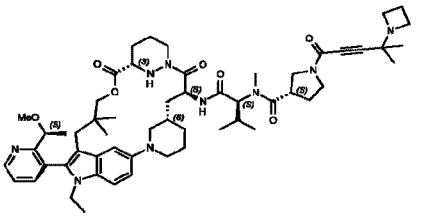
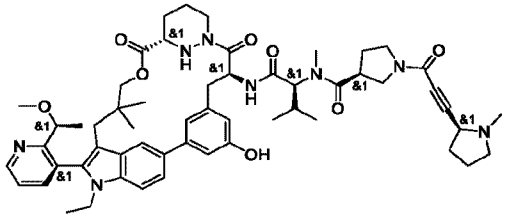
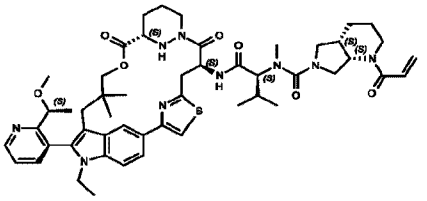
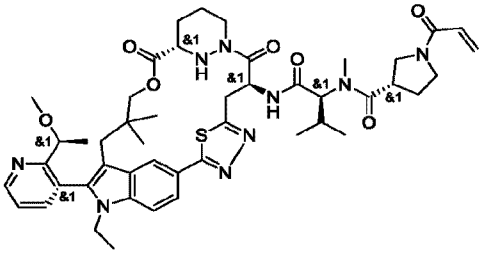
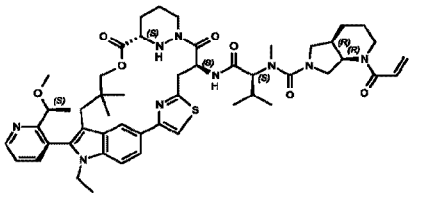
Ex#	Structure	Ex#	Structure
BA 219		BA 590	
BA 220		BA 591	
BA 221		BA 592	
BA 222		BA 593	
BA 223		BA 594	

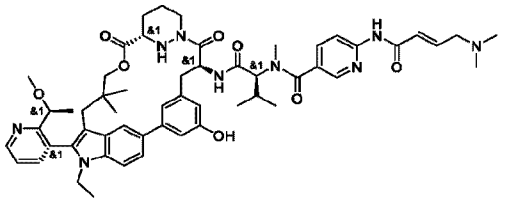
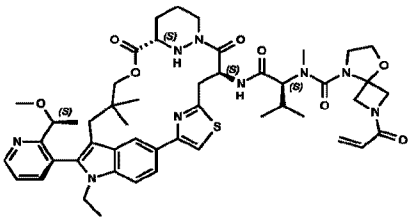
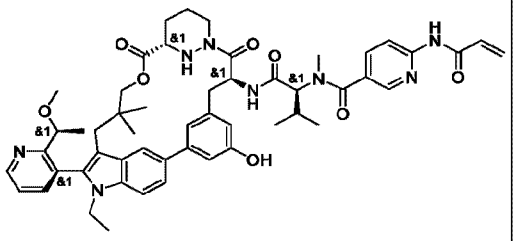
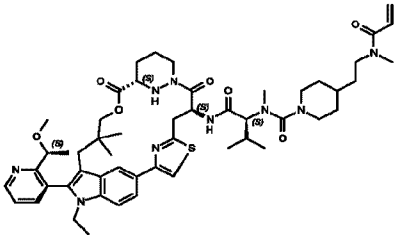
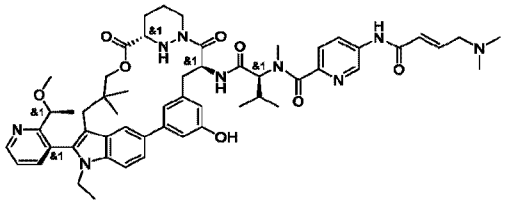
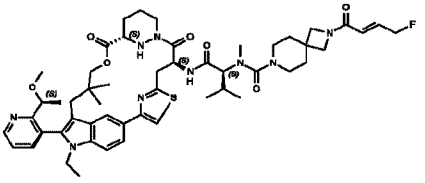
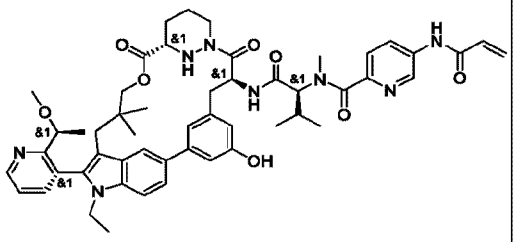
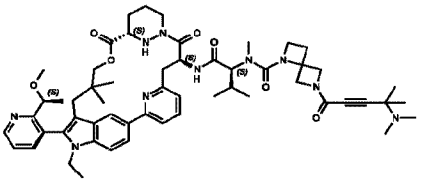
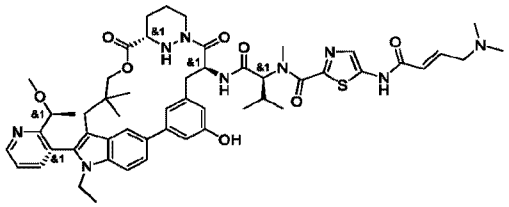
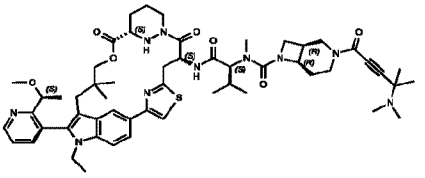
Ex#	Structure	Ex#	Structure
BA 224		BA 595	
BA 225		BA 596	
BA 226		BA 597	
BA 227		BA 598	
BA 228		BA 599	

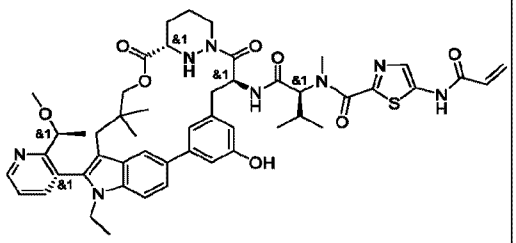
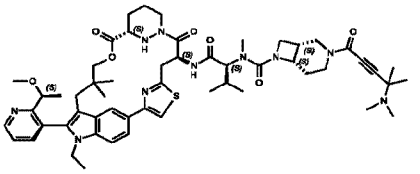
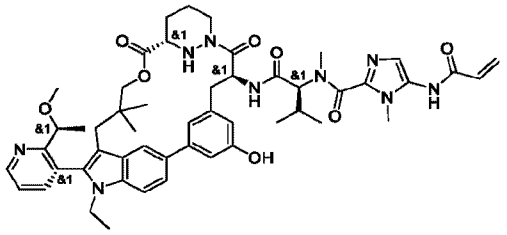
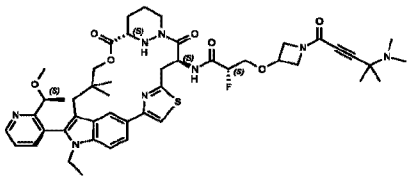
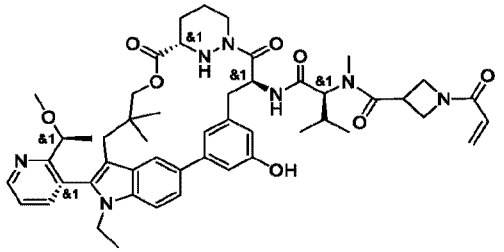
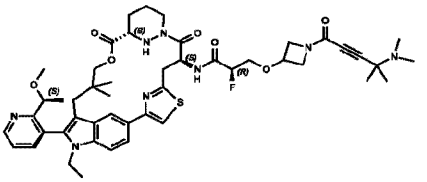
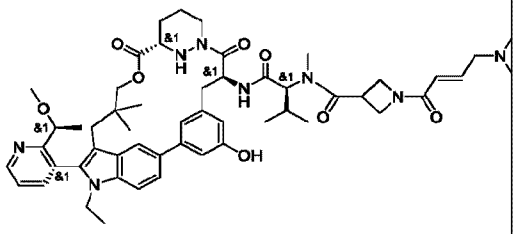
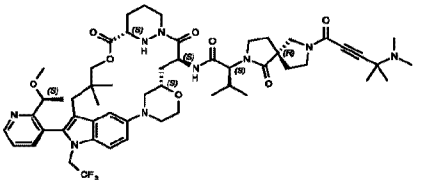
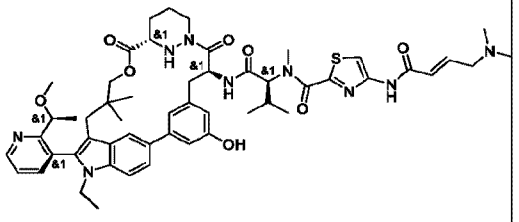
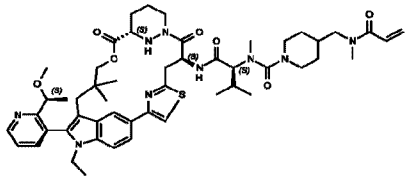
Ex#	Structure	Ex#	Structure
BA 229		BA 600	
BA 230		BA 601	
BA 231		BA 602	
BA 232		BA 603	
BA 233		BA 604	

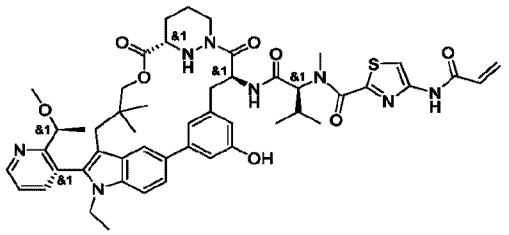
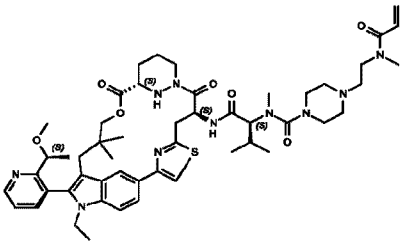
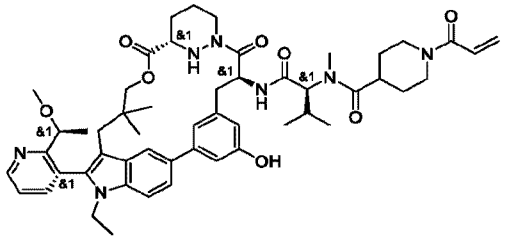
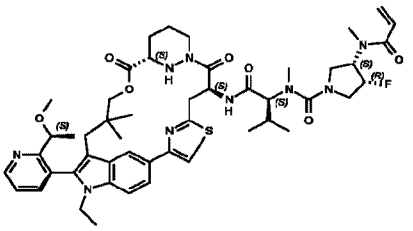
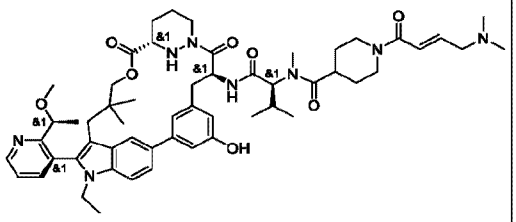
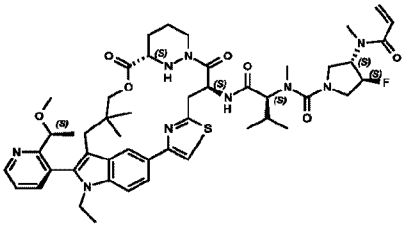
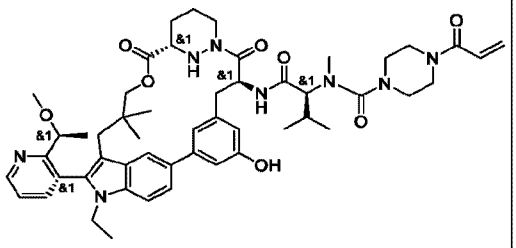
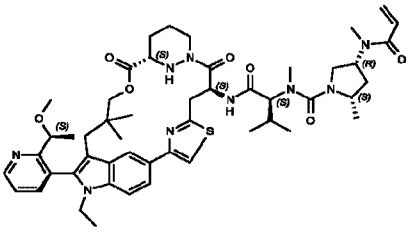
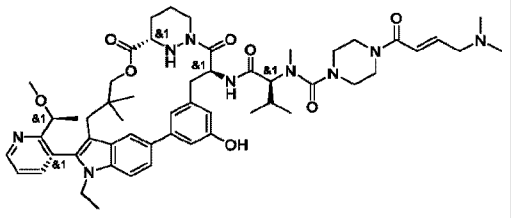
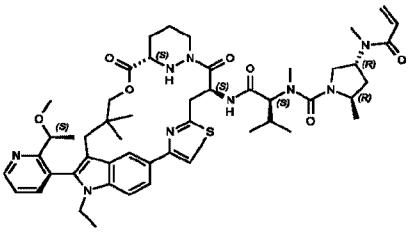
Ex#	Structure	Ex#	Structure
BA 234		BA 605	
BA 235		BA 606	
BA 236		BA 607	
BA 237		BA 608	
BA 238		BA 609	

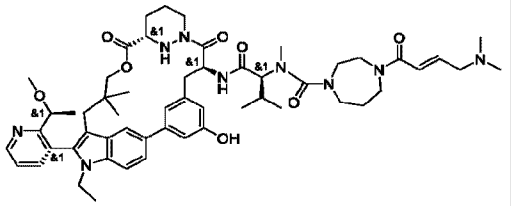
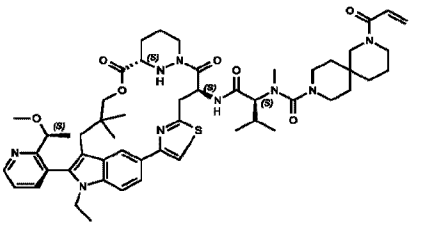
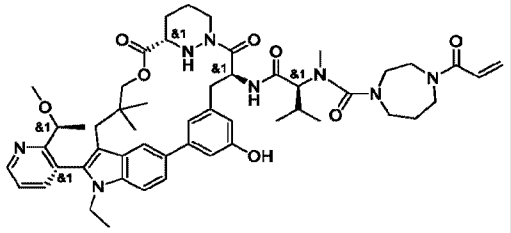
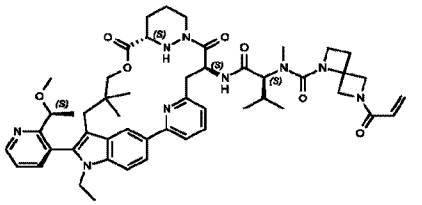
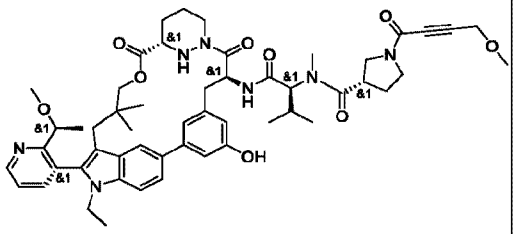
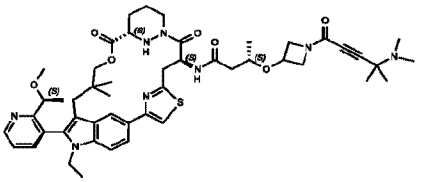
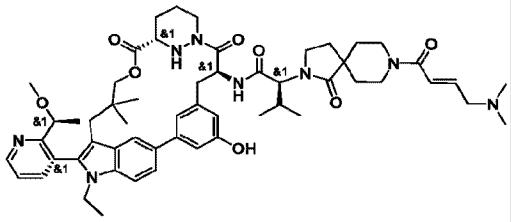
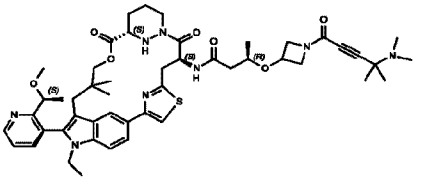
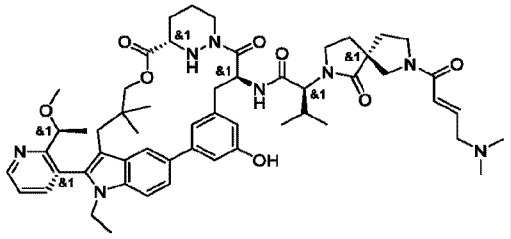
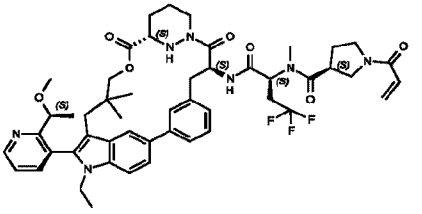
Ex#	Structure	Ex#	Structure
BA 239		BA 610	
BA 240		BA 611	
BA 241		BA 612	
BA 242		BA 613	
BA 243		BA 614	

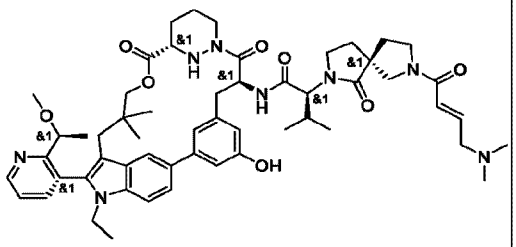
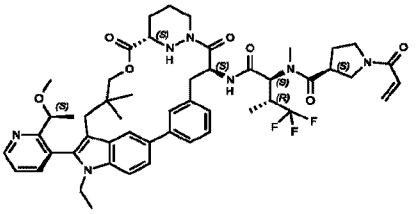
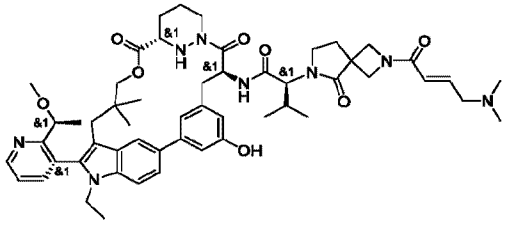
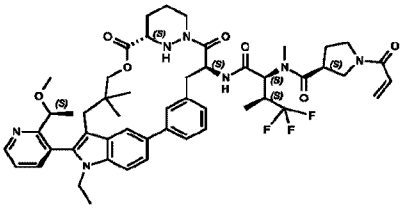
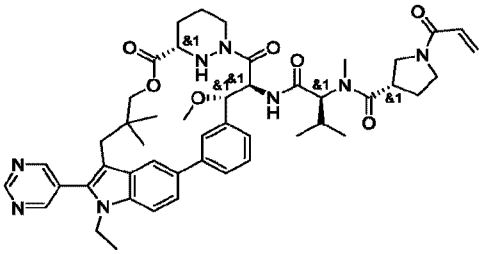
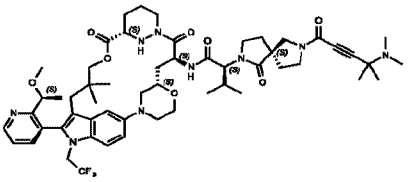
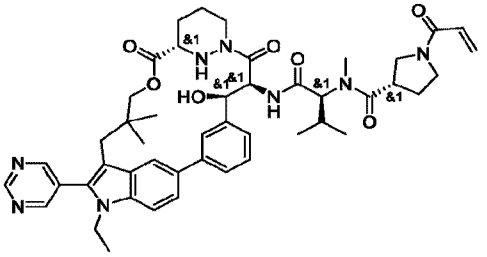
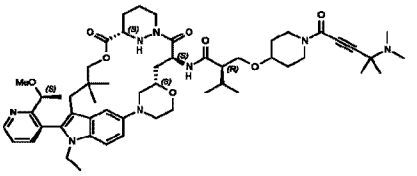
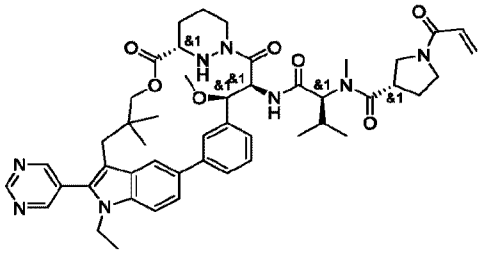
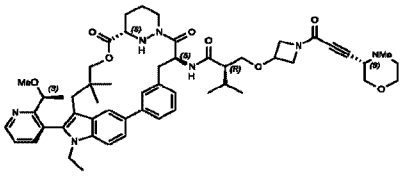
Ex#	Structure	Ex#	Structure
BA 244		BA 615	
BA 245		BA 616	
BA 246		BA 617	
BA 247		BA 618	
BA 248		BA 619	

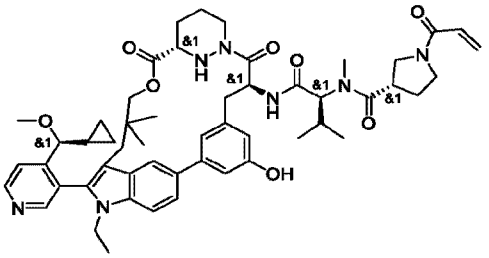
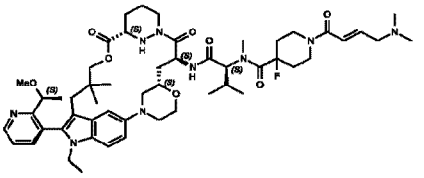
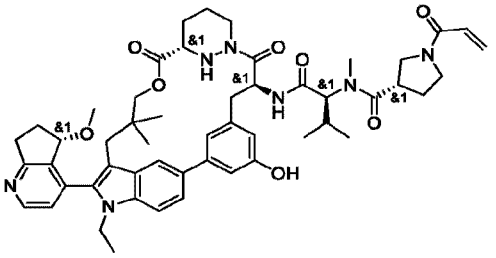
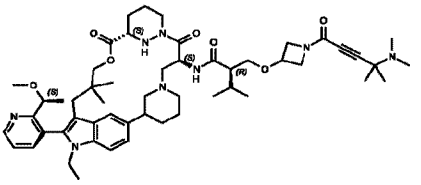
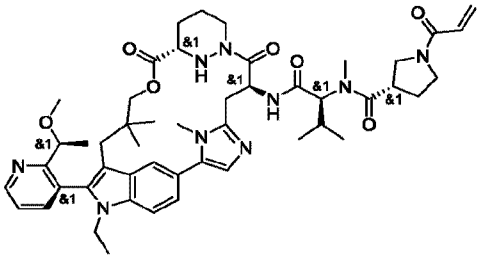
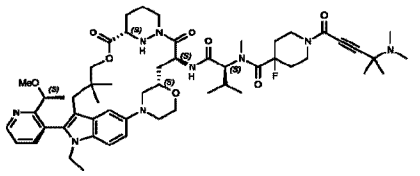
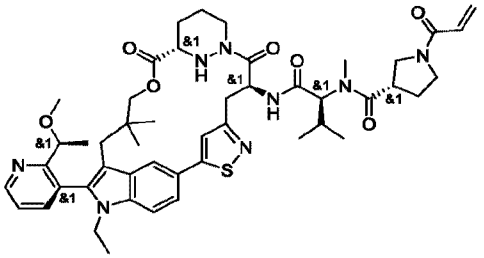
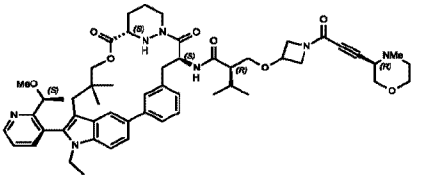
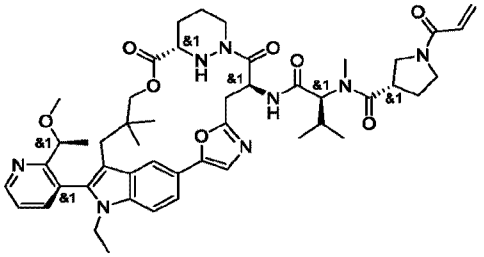
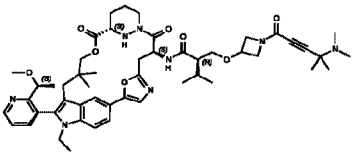
Ex#	Structure	Ex#	Structure
BA 249		BA 620	
BA 250		BA 621	
BA 251		BA 622	
BA 252		BA 623	
BA 253		BA 624	

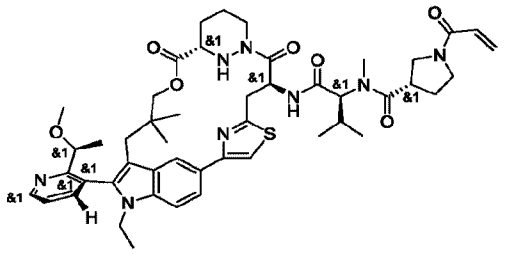
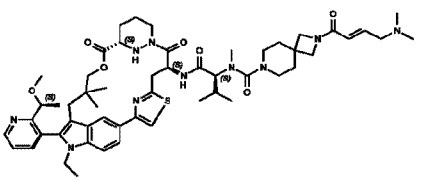
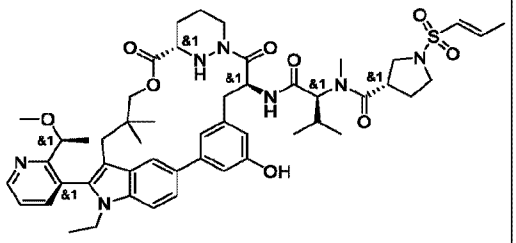
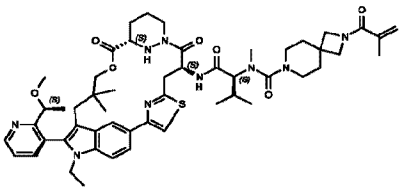
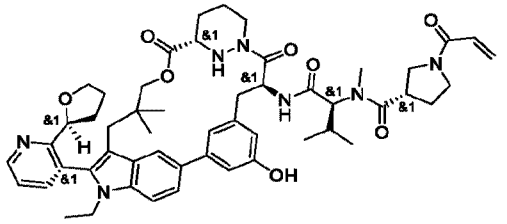
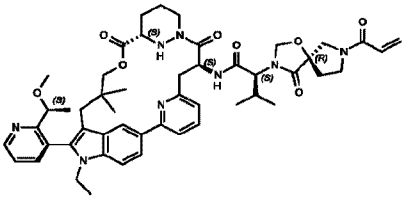
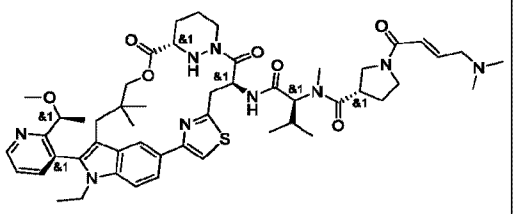
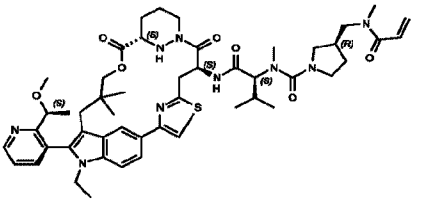
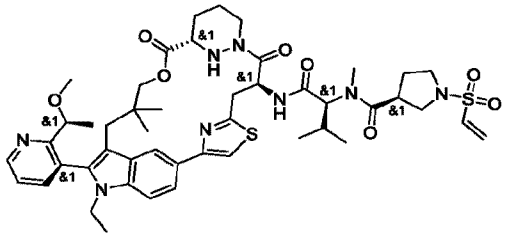
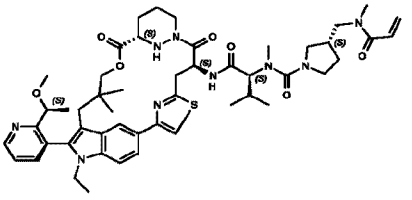
Ex#	Structure	Ex#	Structure
BA 254		BA 625	
BA 255		BA 626	
BA 256		BA 627	
BA 257		BA 628	
BA 258		BA 629	

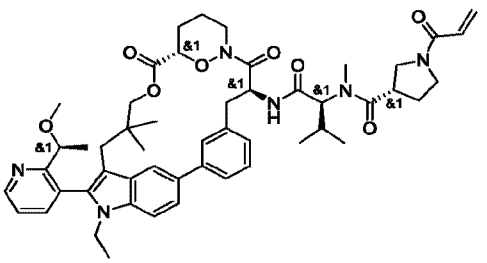
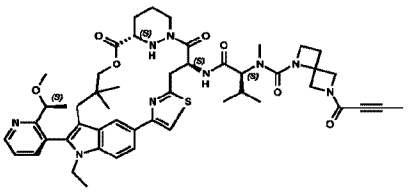
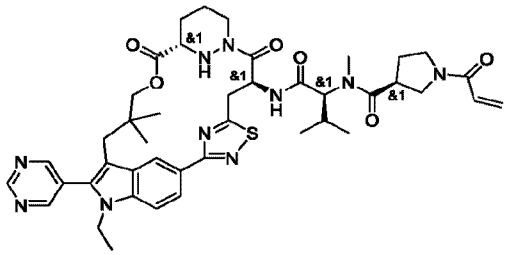
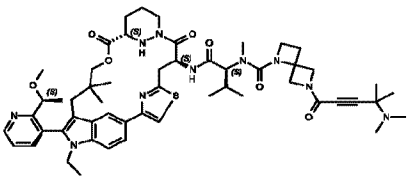
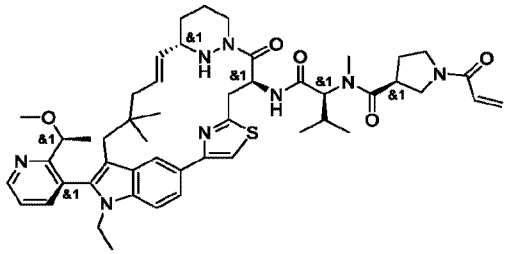
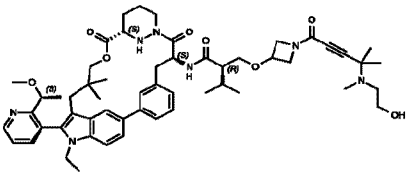
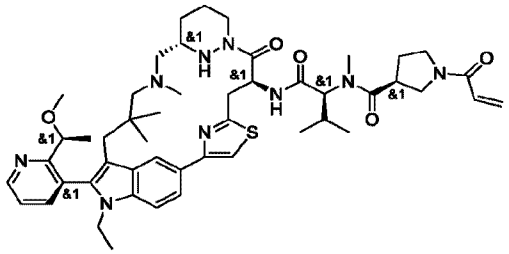
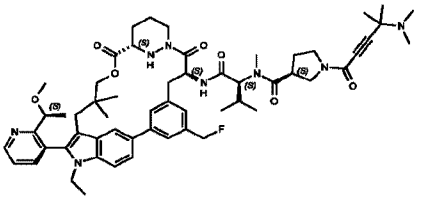
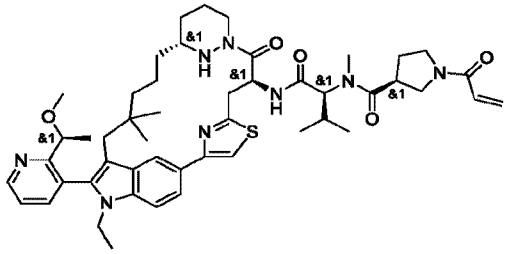
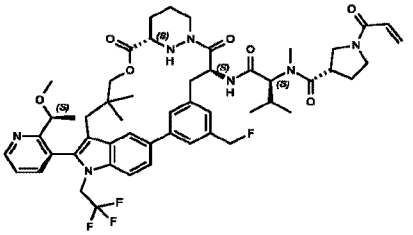
Ex#	Structure	Ex#	Structure
BA 259		BA 630	
BA 260		BA 631	
BA 261		BA 632	
BA 262		BA 633	
BA 263		BA 634	

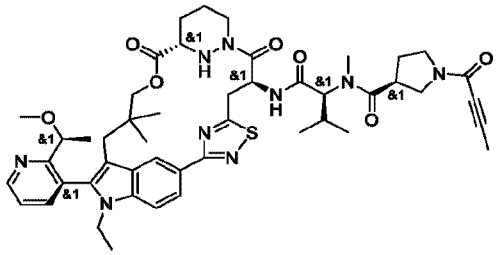
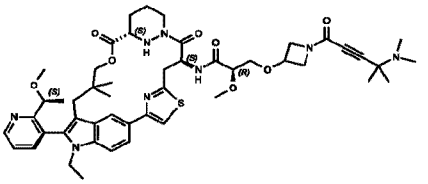
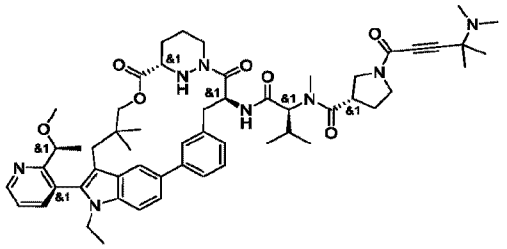
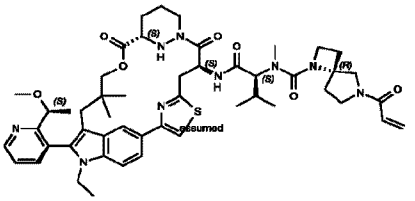
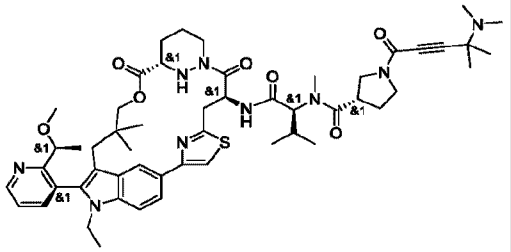
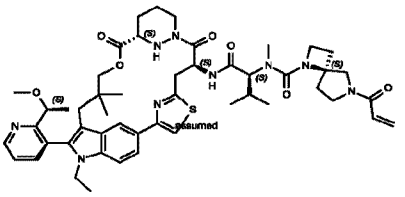
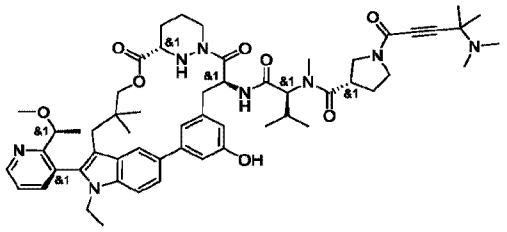
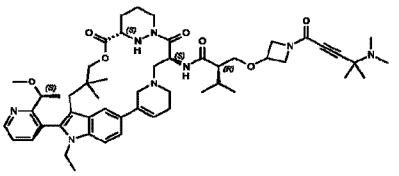
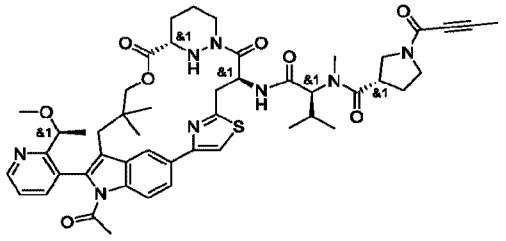
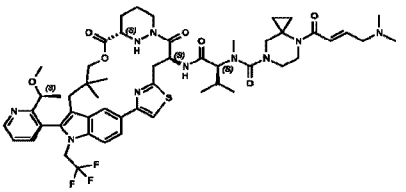
Ex#	Structure	Ex#	Structure
BA 264		BA 635	
BA 265		BA 636	
BA 266		BA 637	
BA 267		BA 638	
BA 268		BA 639	

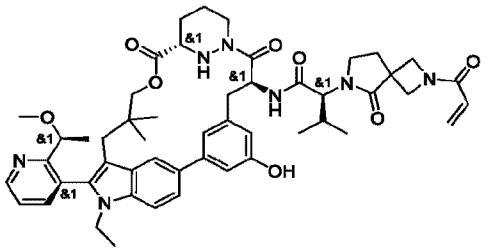
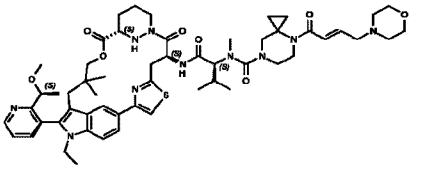
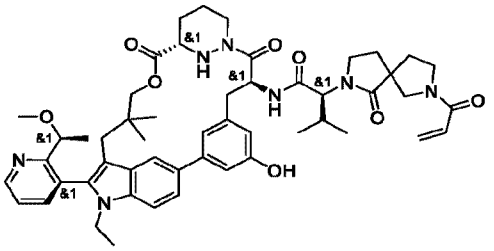
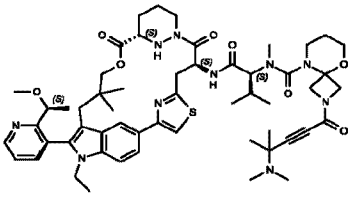
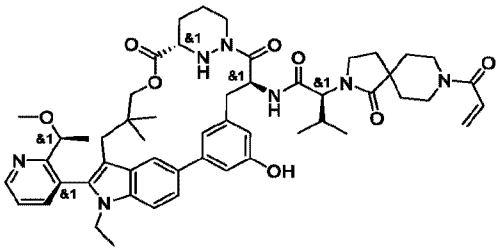
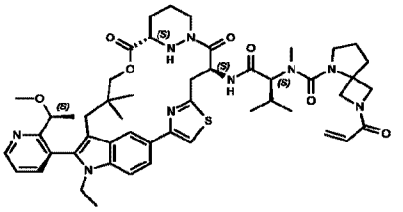
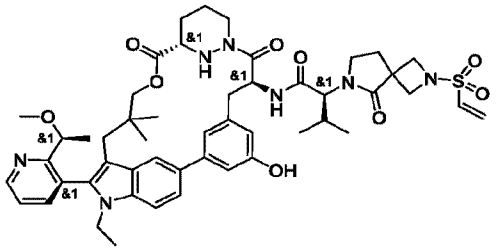
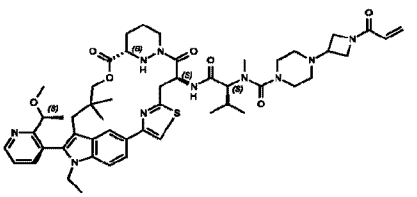
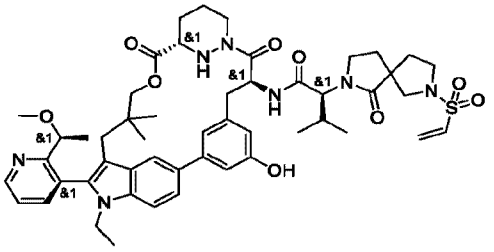
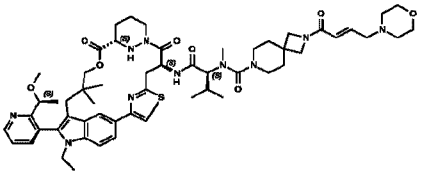
Ex#	Structure	Ex#	Structure
BA 269		BA 640	
BA 270		BA 641	
BA 271		BA 642	
BA 272		BA 643	
BA 273		BA 644	

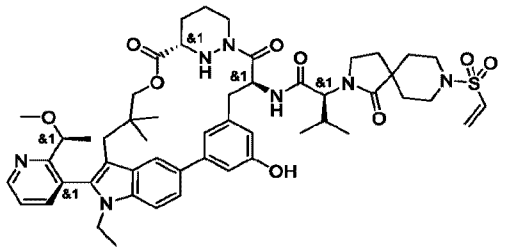
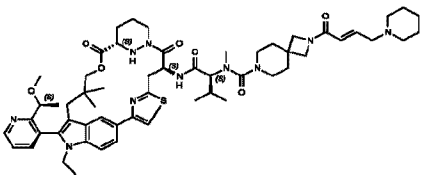
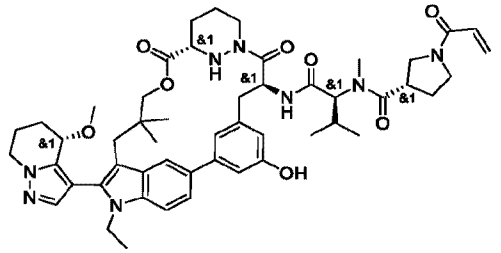
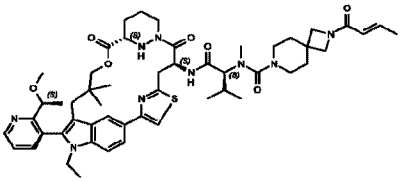
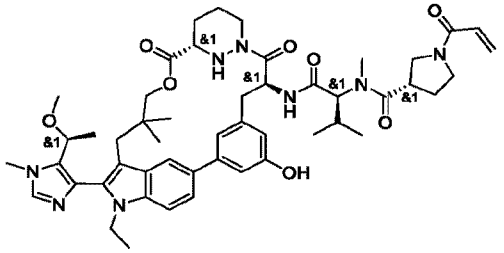
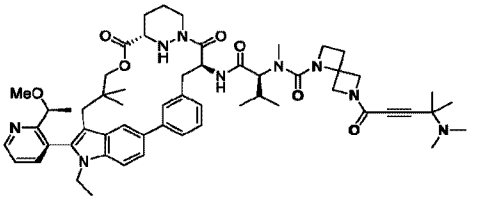
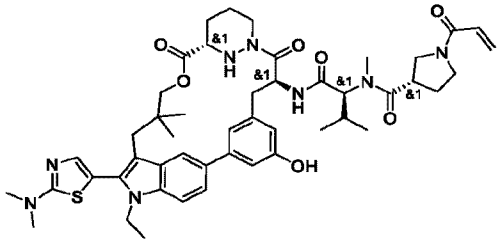
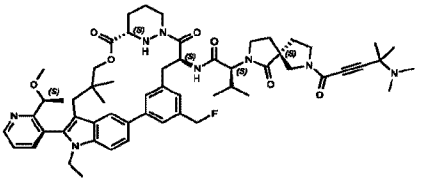
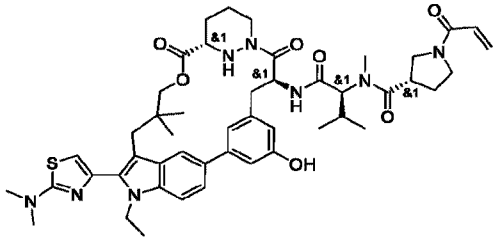
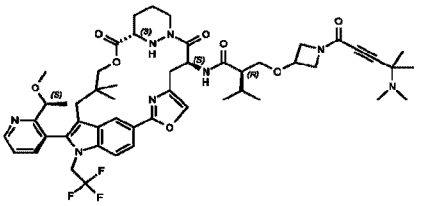
Ex#	Structure	Ex#	Structure
BA 274		BA 645	
BA 275		BA 646	
BA 276		BA 647	
BA 277		BA 648	
BA 278		BA 649	

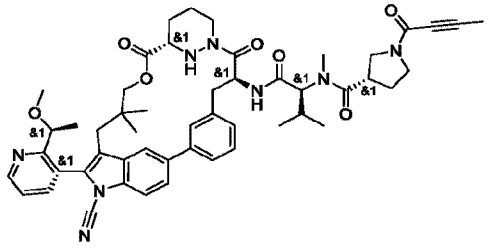
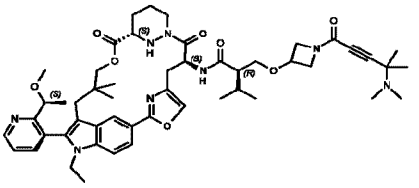
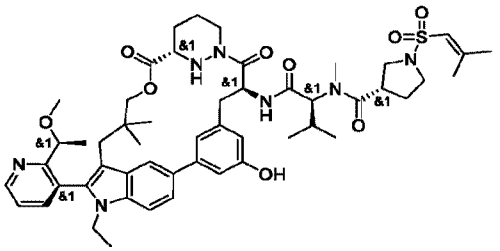
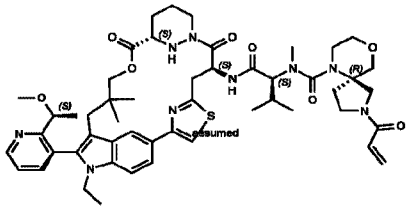
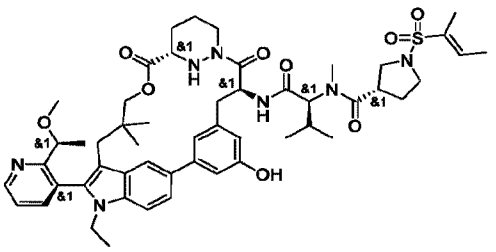
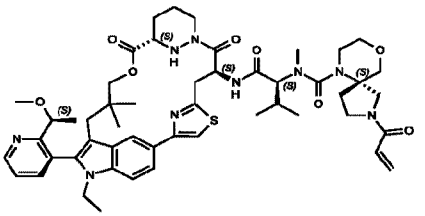
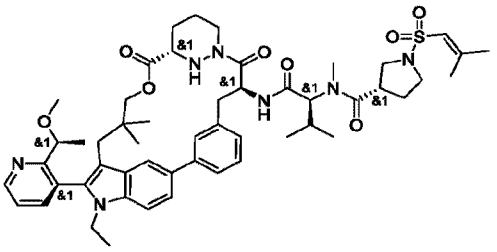
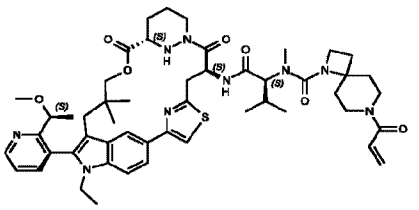
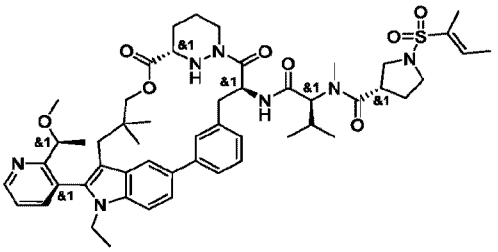
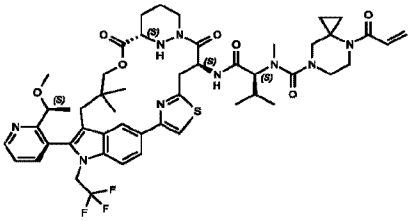
Ex#	Structure	Ex#	Structure
BA 279		BA 650	
BA 280		BA 651	
BA 281		BA 652	
BA 282		BA 653	
BA 283		BA 654	

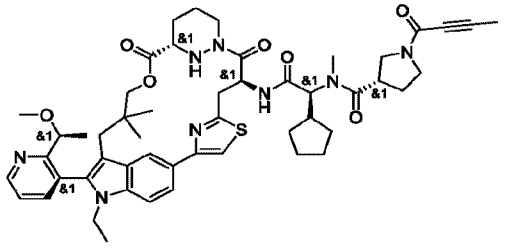
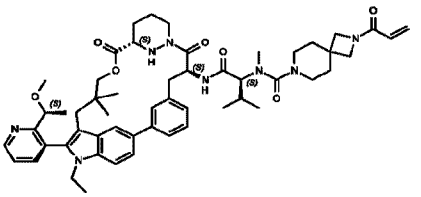
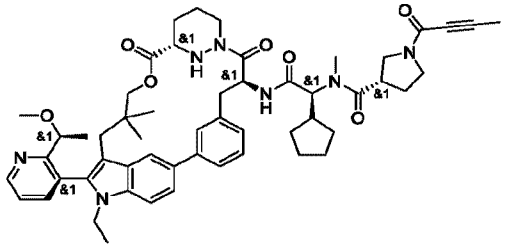
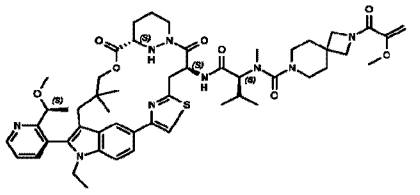
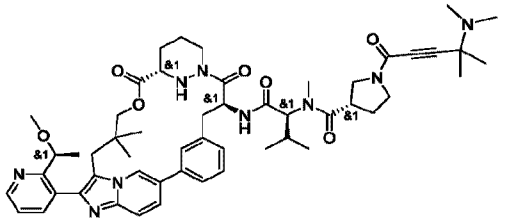
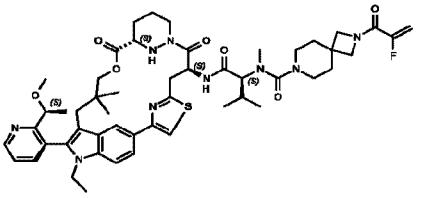
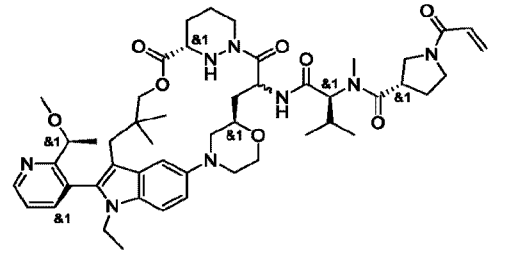
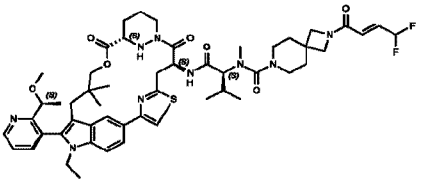
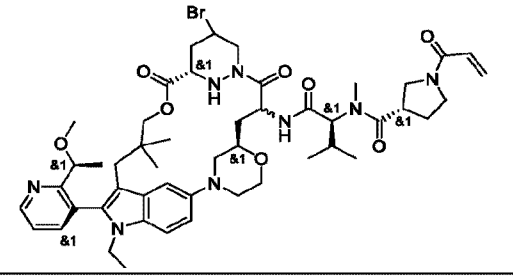
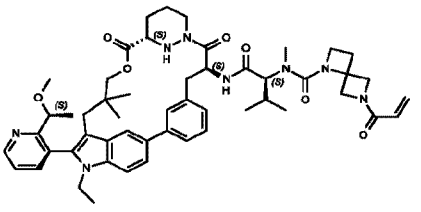
Ex#	Structure	Ex#	Structure
BA 284		BA 655	
BA 285		BA 656	
BA 286		BA 657	
BA 287		BA 658	
BA 288		BA 659	

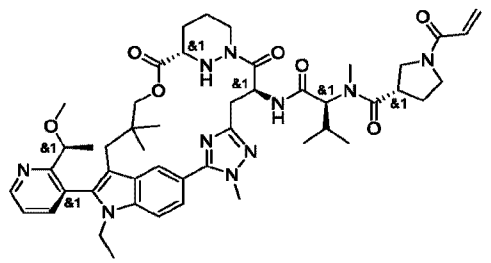
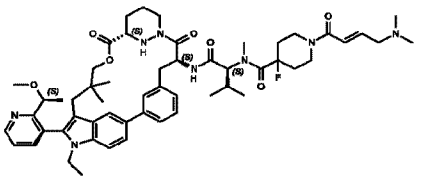
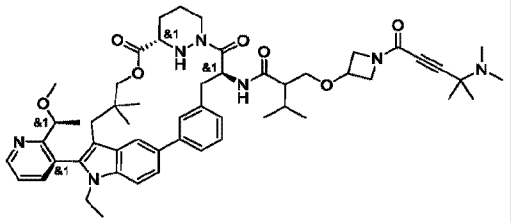
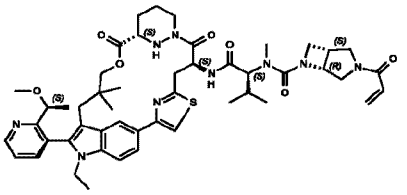
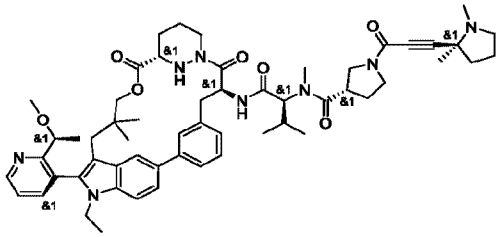
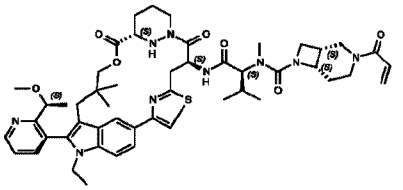
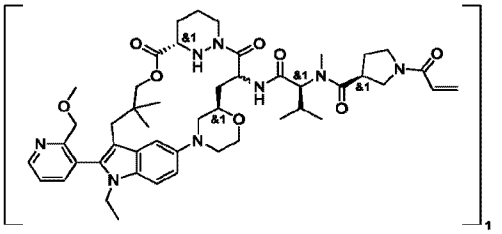
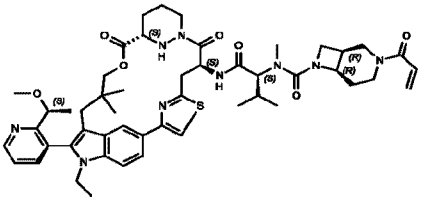
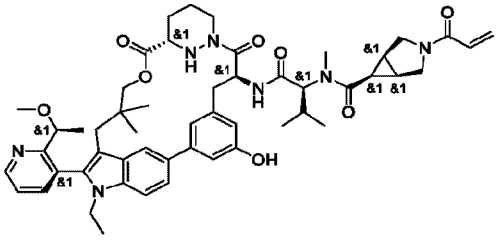
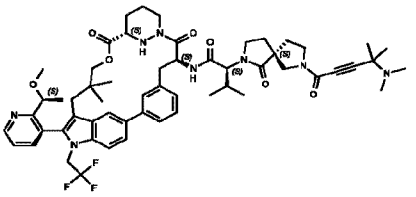
Ex#	Structure	Ex#	Structure
BA 289		BA 660	
BA 290		BA 661	
BA 291		BA 662	
BA 292		BA 663	
BA 293		BA 664	

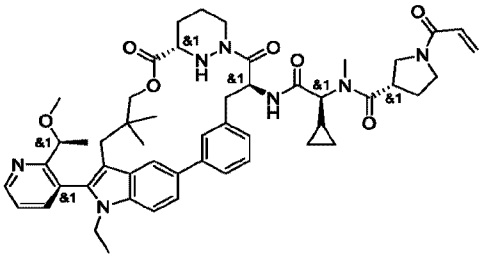
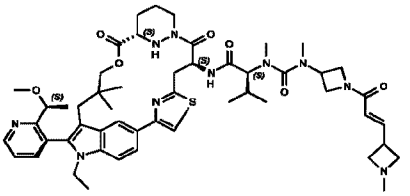
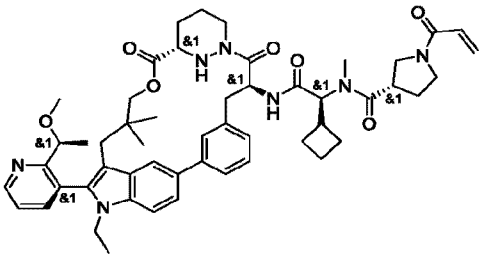
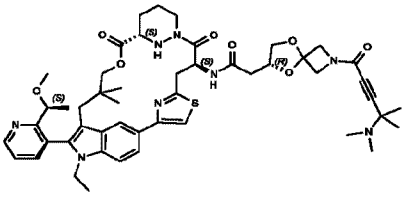
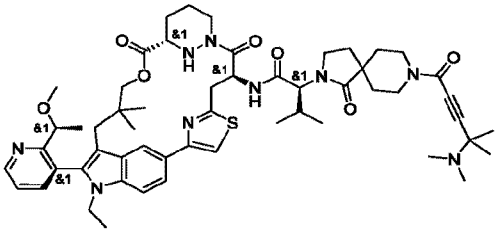
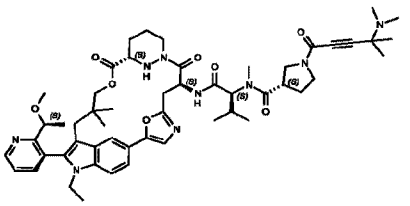
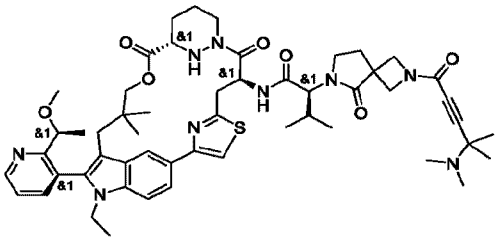
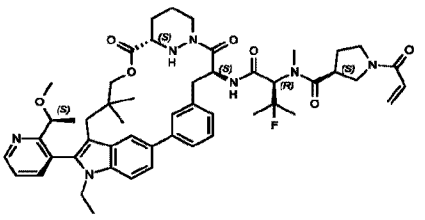
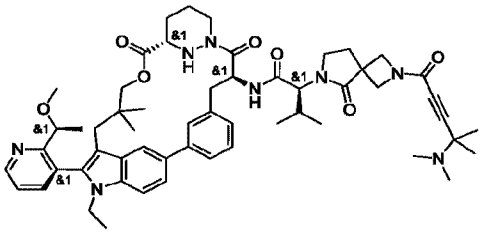
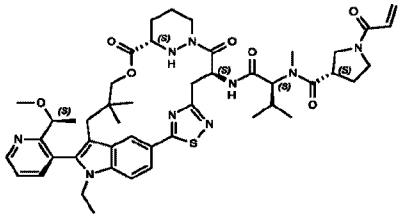
Ex#	Structure	Ex#	Structure
BA 294		BA 665	
BA 295		BA 666	
BA 296		BA 667	
BA 297		BA 668	
BA 298		BA 669	

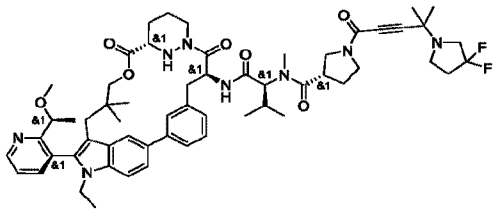
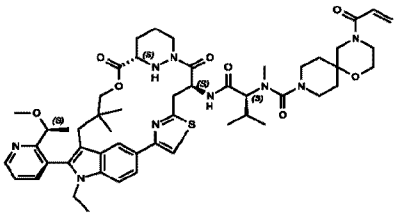
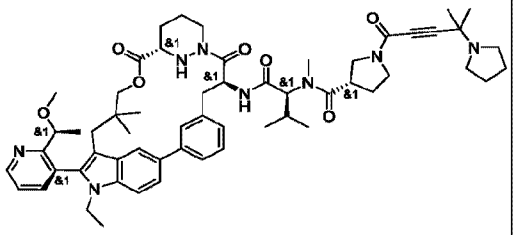
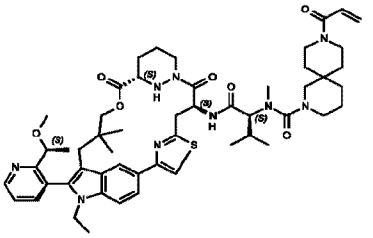
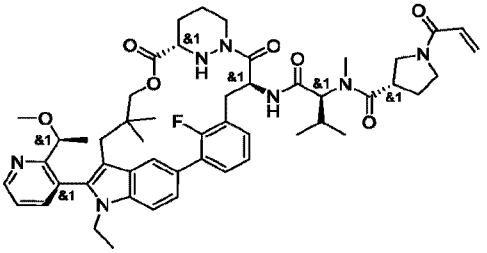
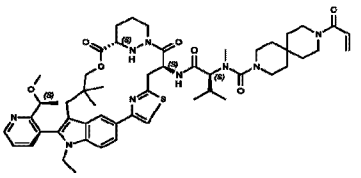
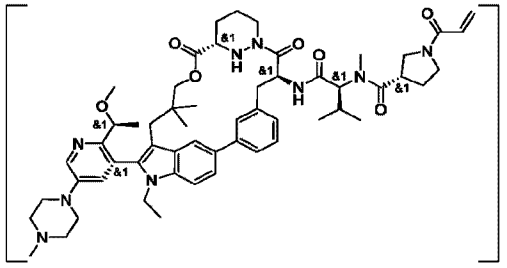
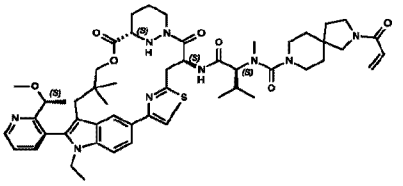
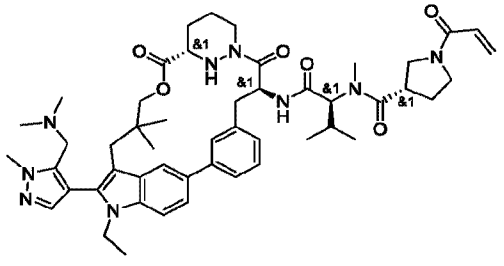
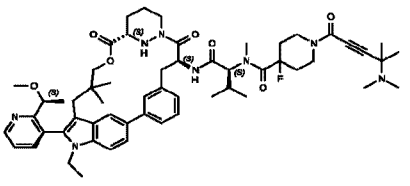
Ex#	Structure	Ex#	Structure
BA 299		BA 670	
BA 300		BA 671	
BA 301		BA 672	
BA 302		BA 673	
BA 303		BA 674	

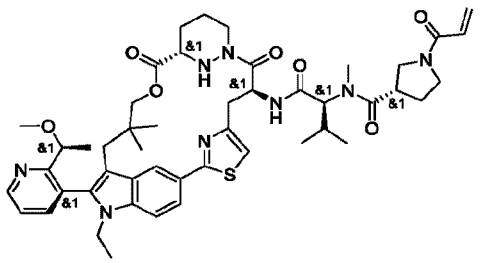
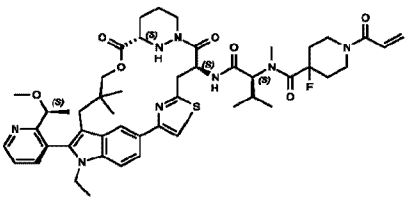
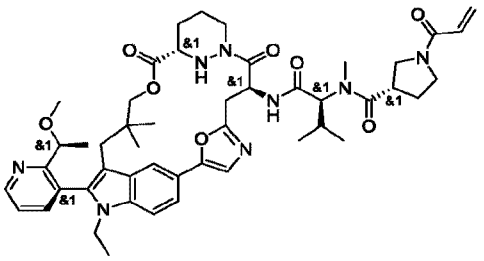
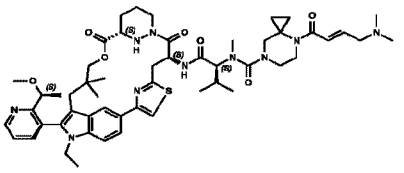
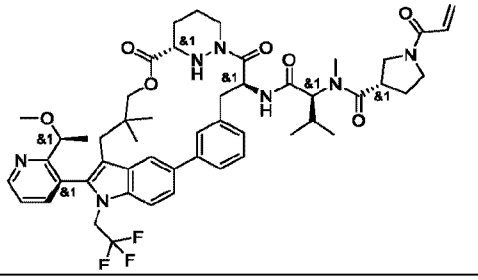
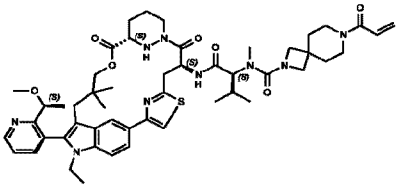
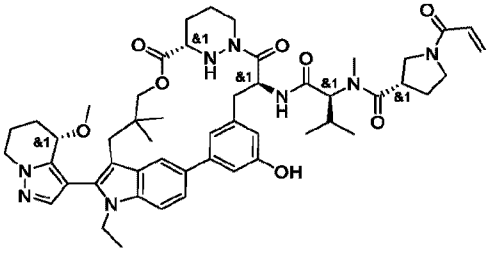
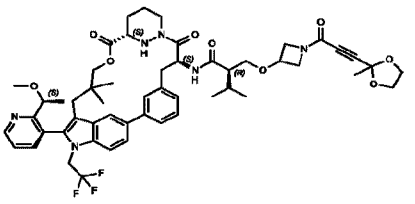
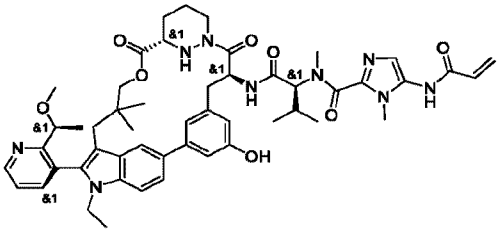
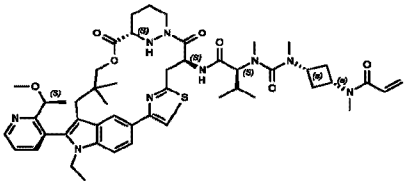
Ex#	Structure	Ex#	Structure
BA 304		BA 675	
BA 305		BA 676	
BA 306		BA 677	
BA 307		BA 678	
BA 308		BA 679	

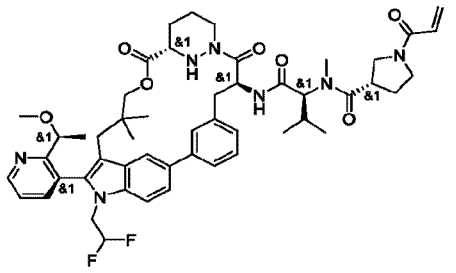
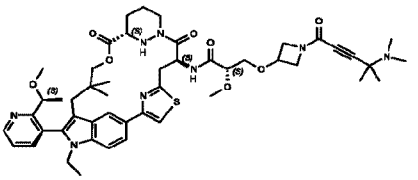
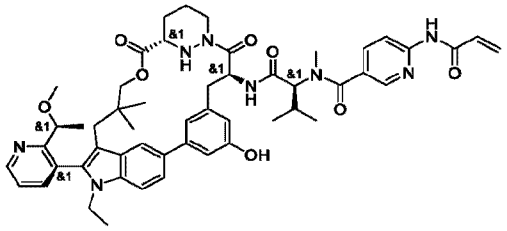
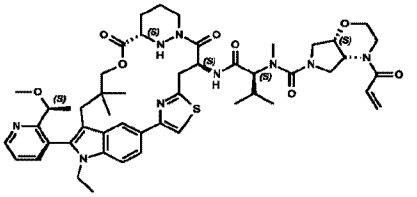
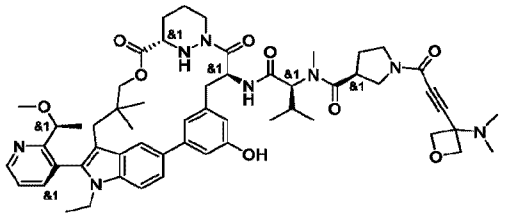
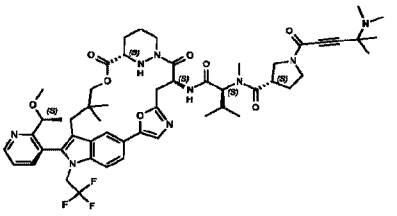
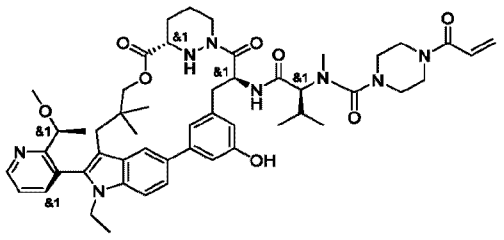
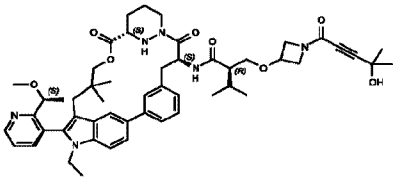
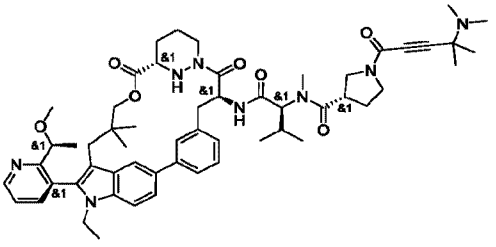
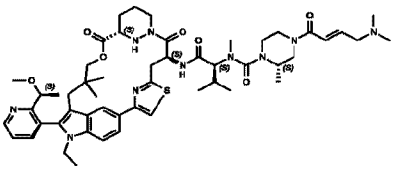
Ex#	Structure	Ex#	Structure
BA 309		BA 680	
BA 310		BA 681	
BA 311		BA 682	
BA 312		BA 683	
BA 313		BA 684	

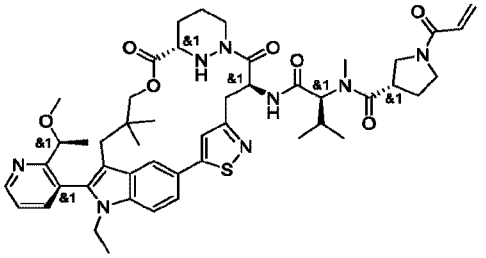
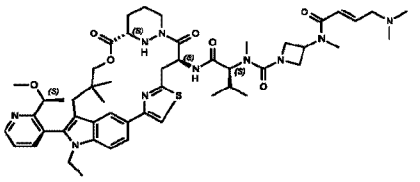
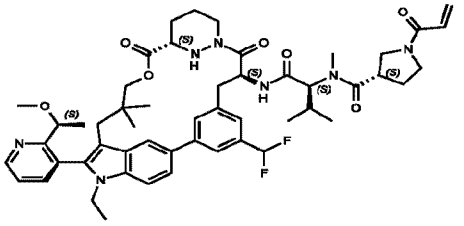
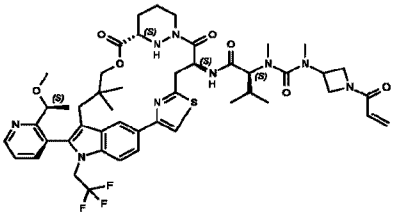
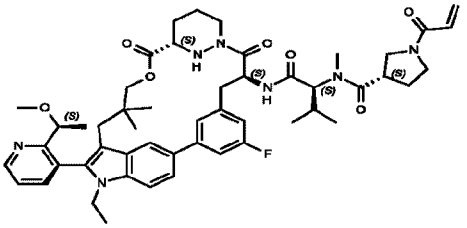
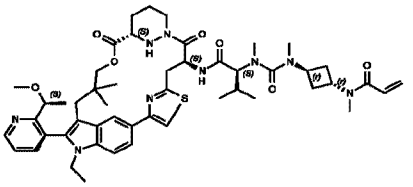
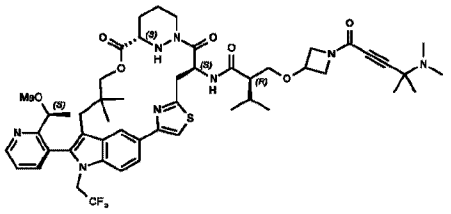
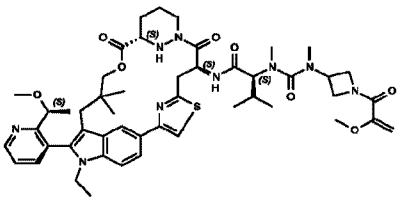
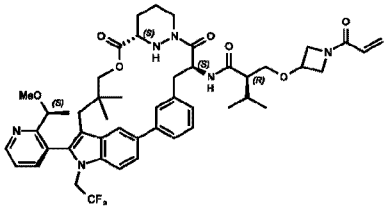
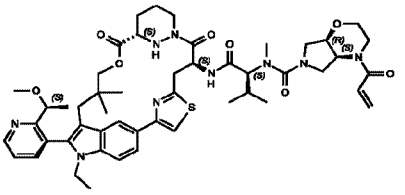
Ex#	Structure	Ex#	Structure
BA 314		BA 685	
BA 316		BA 686	
BA 317		BA 687	
BA 318		BA 688	
BA 319		BA 689	

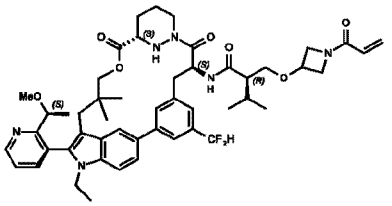
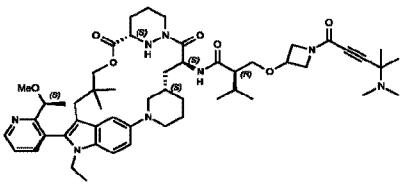
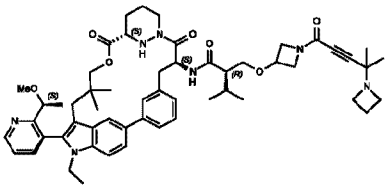
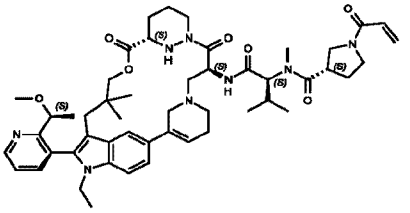
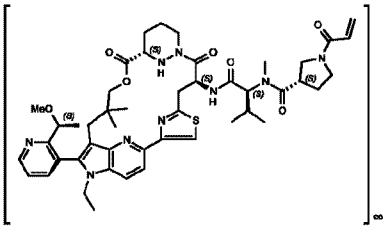
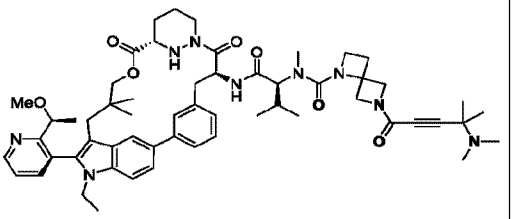
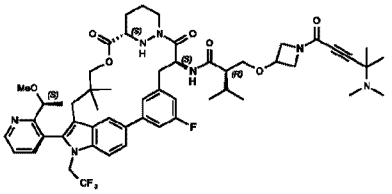
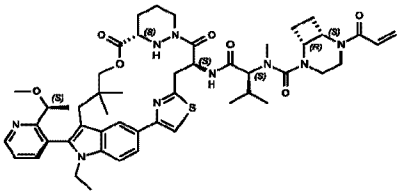
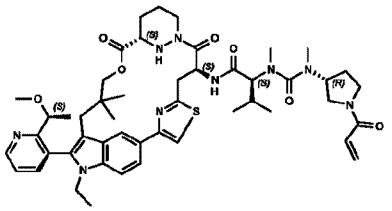
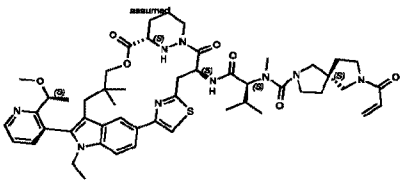
Ex#	Structure	Ex#	Structure
BA 320		BA 690	
BA 321		BA 691	
BA 322		BA 692	
BA 323		BA 693	
BA 324		BA 694	

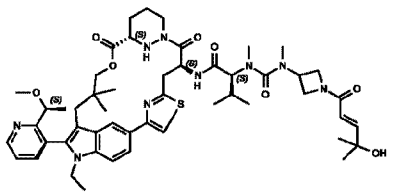
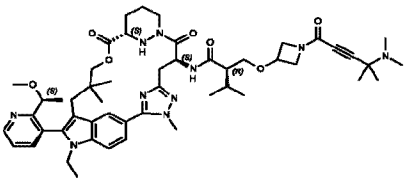
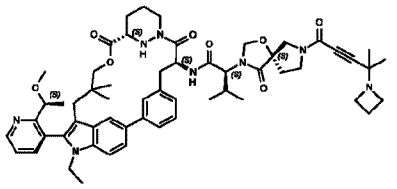
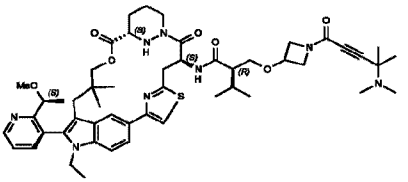
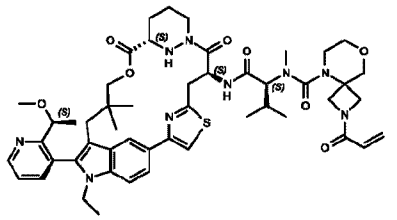
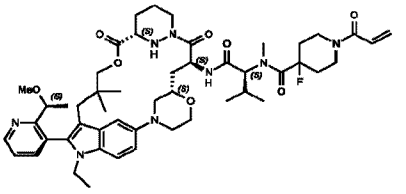
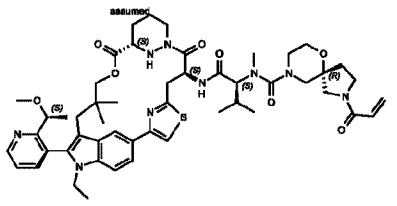
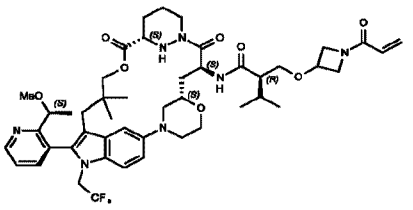
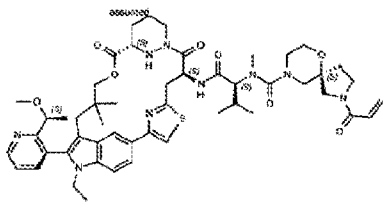
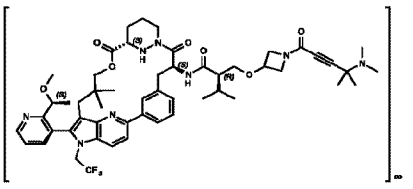
Ex#	Structure	Ex#	Structure
BA 325		BA 695	
BA 326		BA 696	
BA 327		BA 697	
BA 328		BA 698	
BA 329		BA 699	

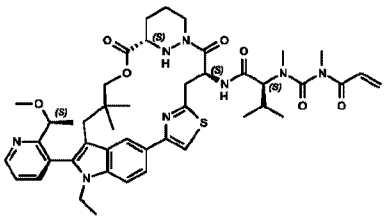
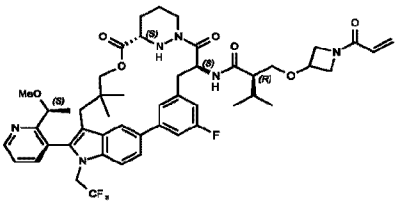
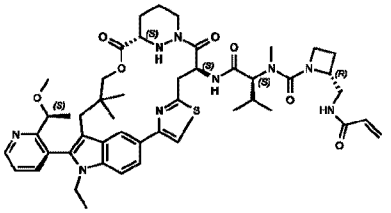
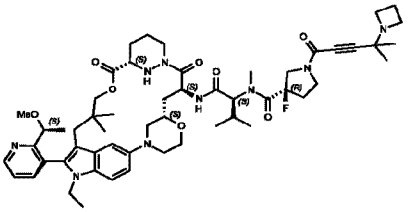
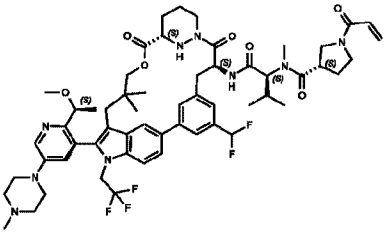
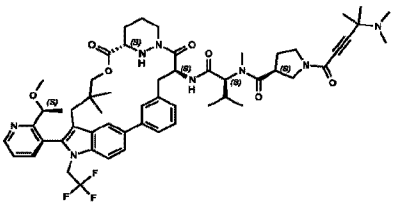
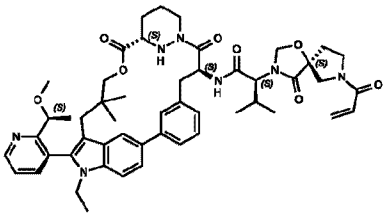
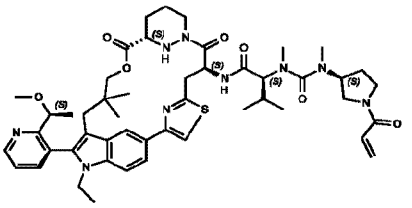
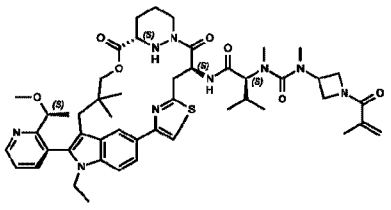
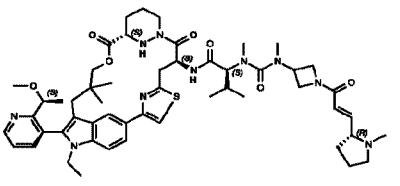
Ex#	Structure	Ex#	Structure
BA 330		BA 700	
BA 331		BA 701	
BA 332		BA 702	
BA 333		BA 703	
BA 334		BA 704	

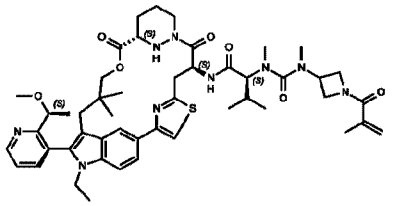
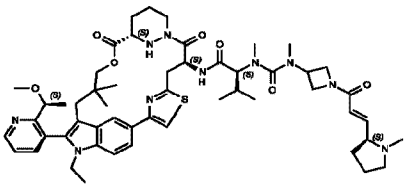
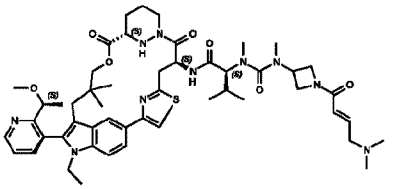
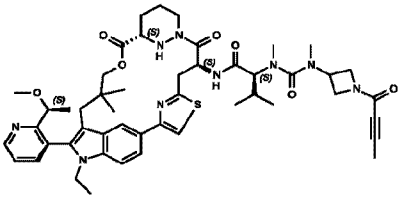
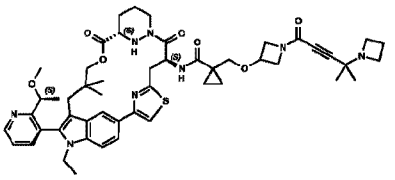
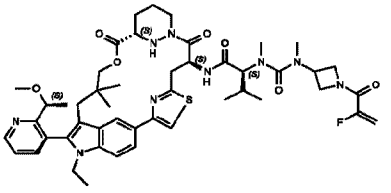
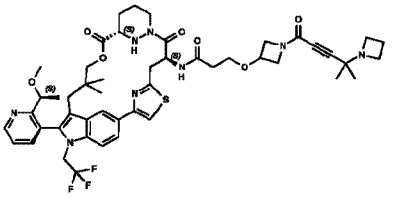
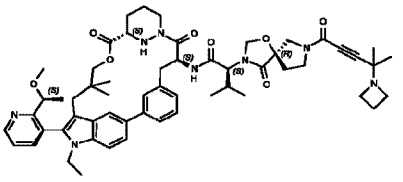
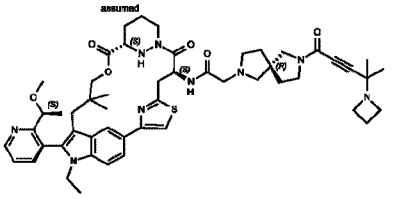
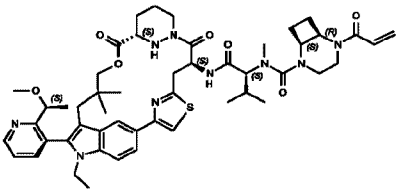
Ex#	Structure	Ex#	Structure
BA 335		BA 705	
BA 336		BA 706	
BA 337		BA 707	
BA 338		BA 708	
BA 339		BA 709	

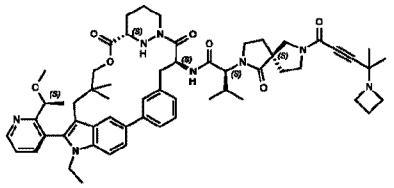
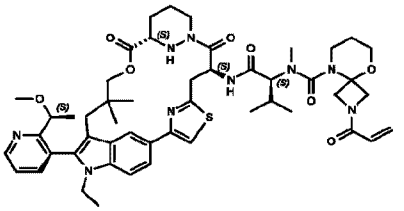
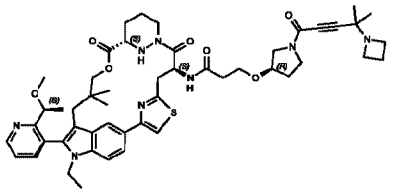
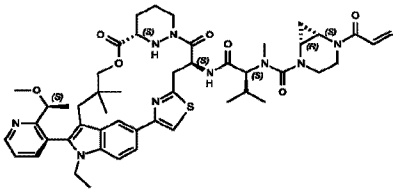
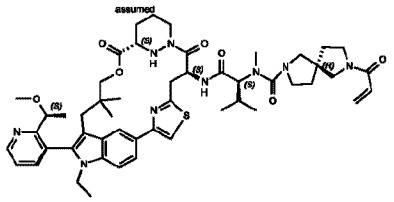
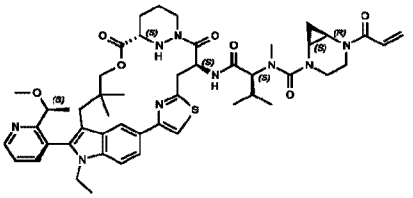
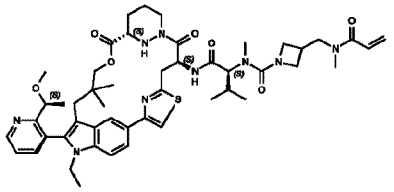
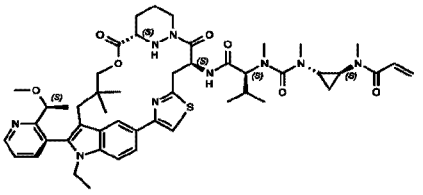
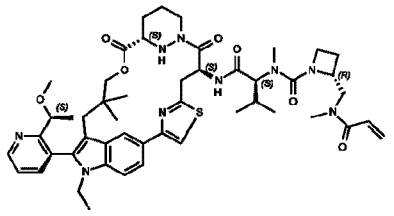
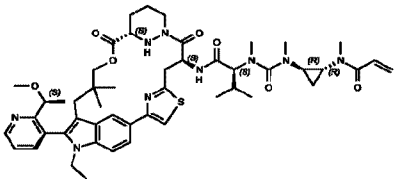
Ex#	Structure	Ex#	Structure
BA 340		BA 710	
BA 341		BA 711	
BA 342		BA 712	
BA 343		BA 713	
BA 344		BA 714	

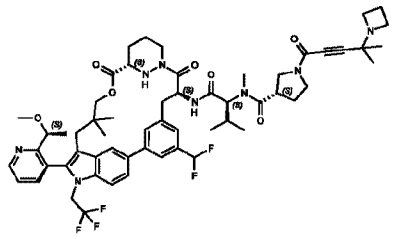
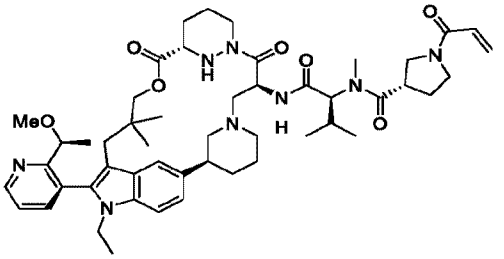
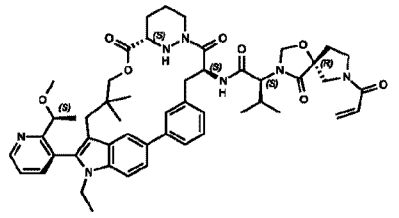
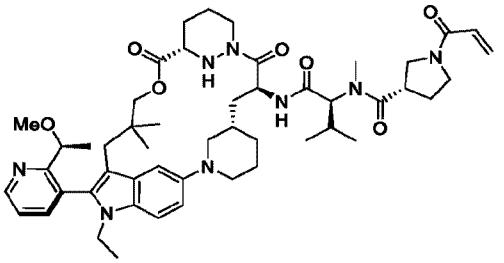
Ex#	Structure	Ex#	Structure
BA 345		BA 715	
BA 346		BA 716	
BA 347		BA 717	
BA 348		BA 718	
BA 349		BA 719	

Ex#	Structure	Ex#	Structure
BA 350		BA 720	
BA 351		BA 721	
BA 352		BA 722	
BA 353		BA 723	
BA 354		BA 724	

Ex#	Structure	Ex#	Structure
BA 355		BA 725	
BA 356		BA 726	
BA 357		BA 727	
BA 358		BA 728	
BA 359		BA 729	

Ex#	Structure	Ex#	Structure
BA 360		BA 730	
BA 361		BA 731	
BA 362		BA 732	
BA 363		BA 733	
BA 364		BA 734	

Ex#	Structure	Ex#	Structure
BA 365		BA 735	
BA 366		BA 736	
BA 367		BA 737	
BA 368		BA 738	
BA 369		BA 739	

Ex#	Structure	Ex#	Structure
BA 370		BA 740	
BA 371		BA 741	

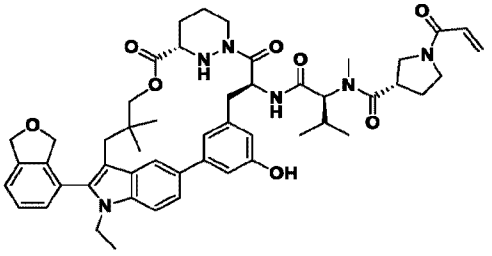
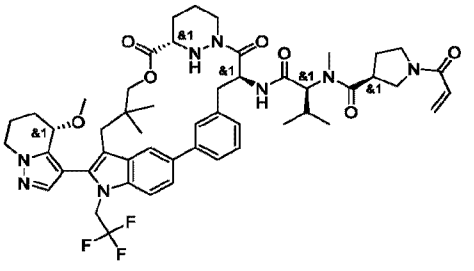
Note that some compounds are shown with bonds as flat or wedged. In some instances, the relative stereochemistry of stereoisomers has been determined; in some instances, the absolute stereochemistry has been determined. In some instances, a single Example number corresponds to a mixture of stereoisomers. All stereoisomers of the compounds of the foregoing table are contemplated by the present invention. In particular embodiments, an atropisomer of a compound of the foregoing table is contemplated.

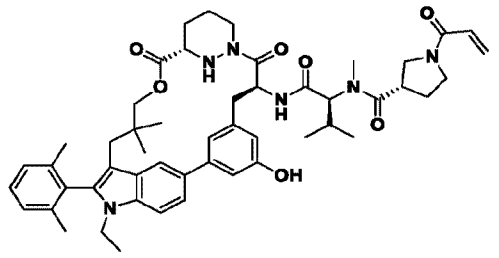
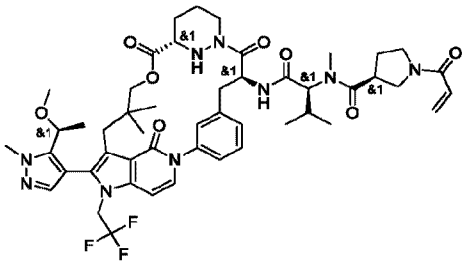
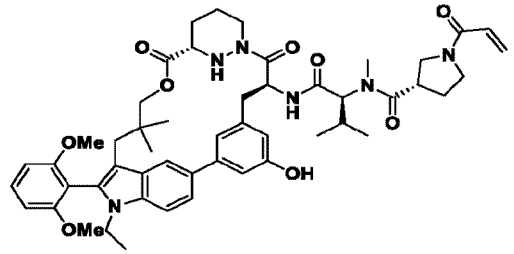
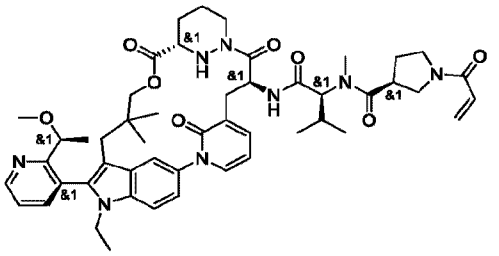
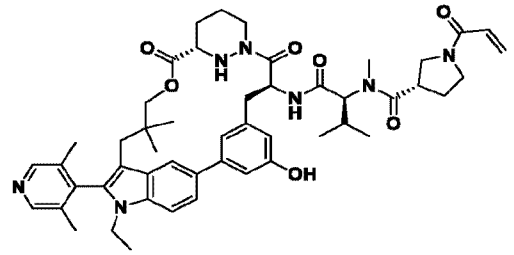
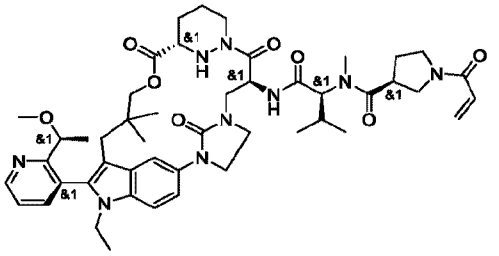
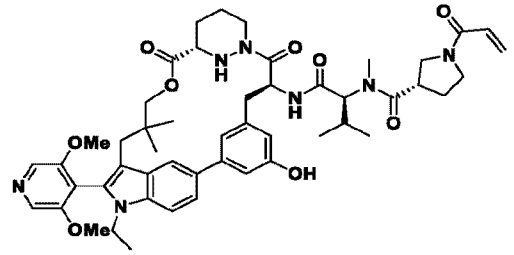
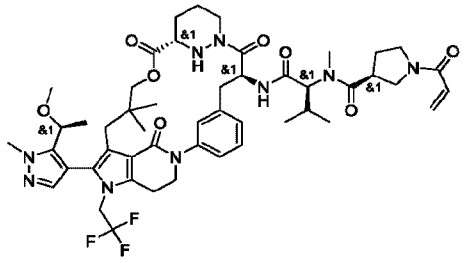
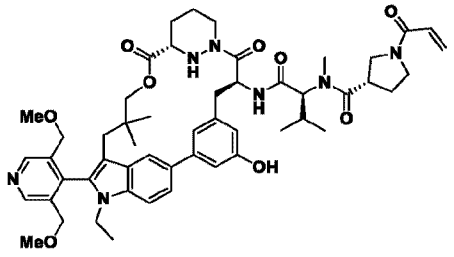
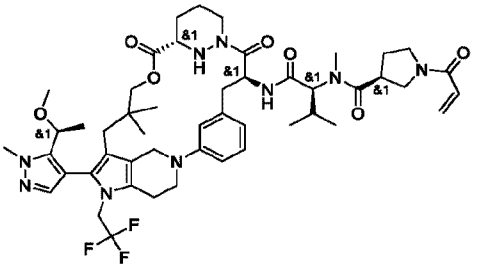
Brackets are to be ignored.

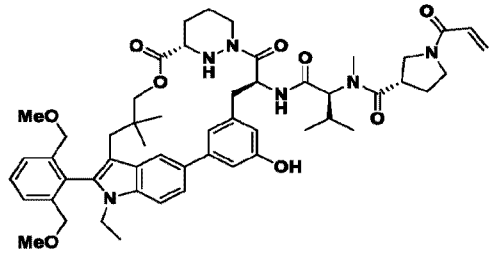
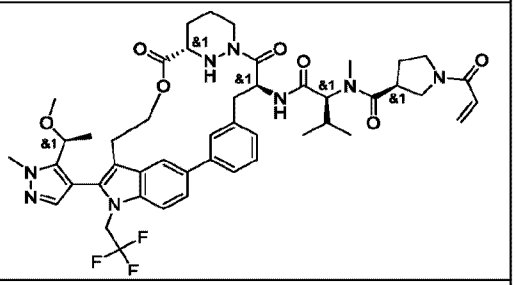
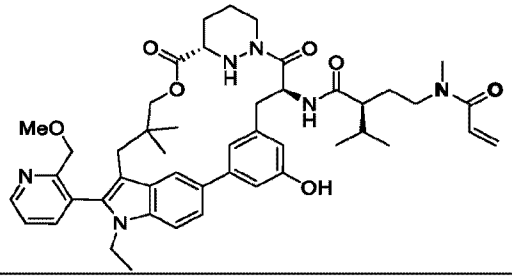
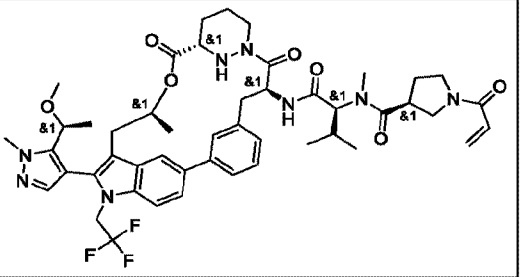
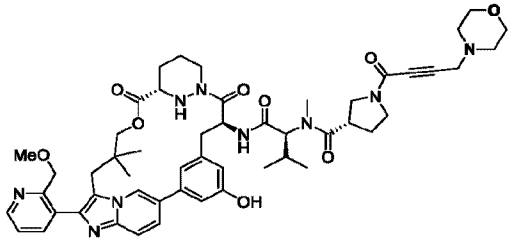
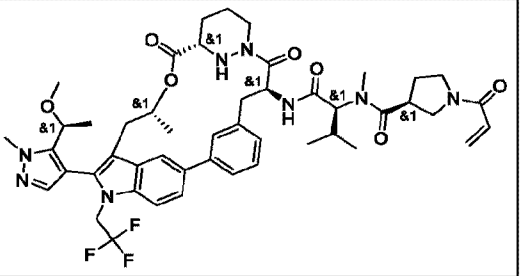
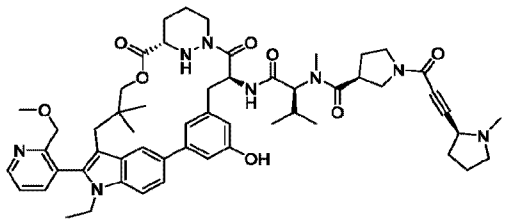
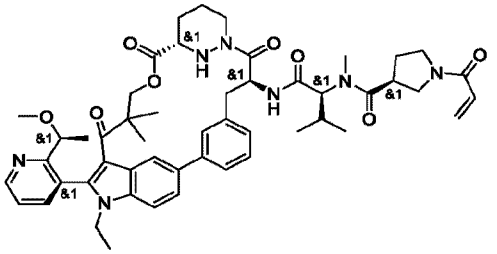
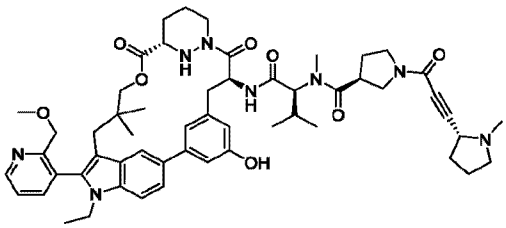
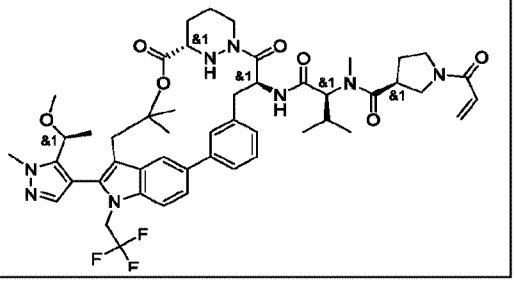
*The activity of this stereoisomer may, in fact, be attributable to the presence of a small amount of the stereoisomer with the (S) configuration at the -NC(O)-CH(CH_3)$_2$-N(CH_3)- position.

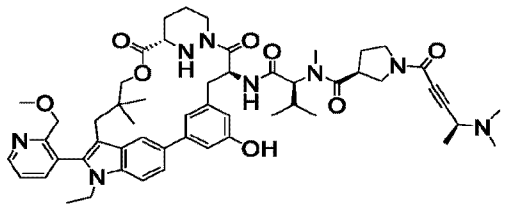
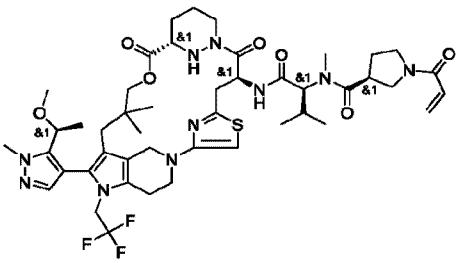
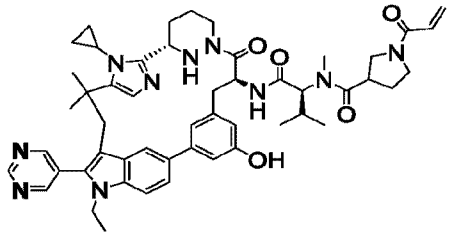
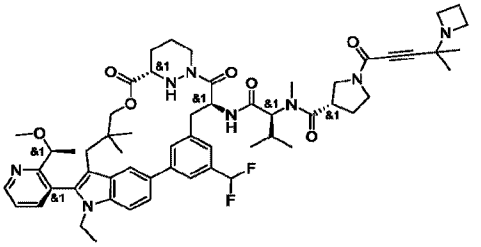
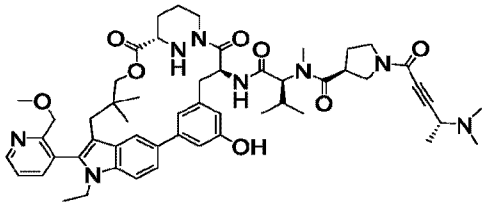
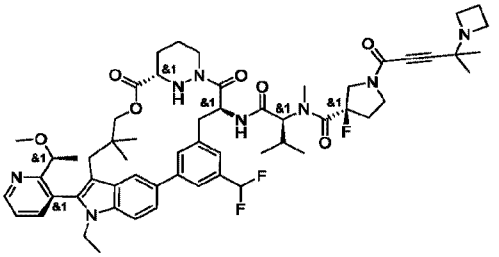
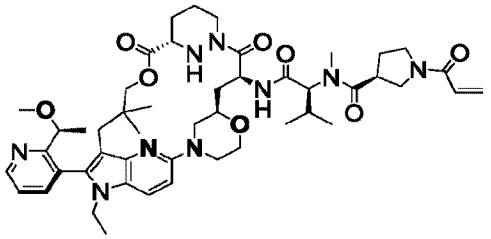
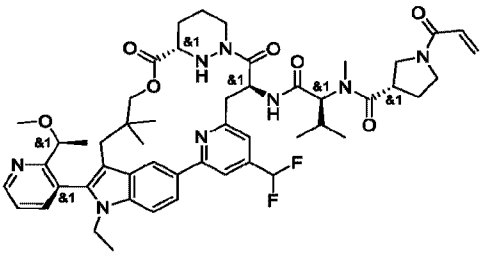
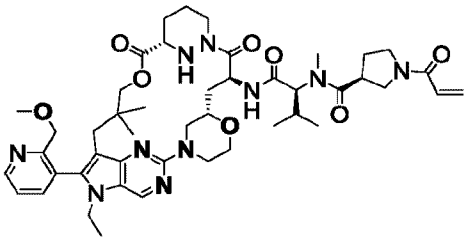
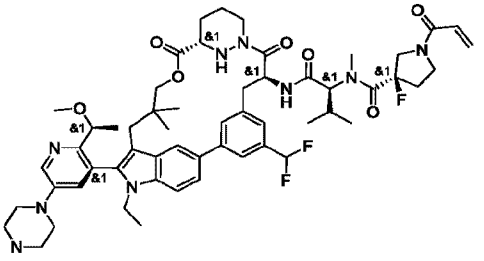
In some embodiments, a compound of Table B2 is provided, or a pharmaceutically acceptable salt thereof. In some embodiments, the RAS(ON) inhibitor is selected from Table B2, or a pharmaceutically acceptable salt or atropisomer thereof.

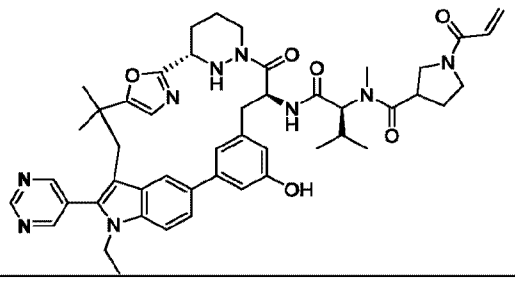
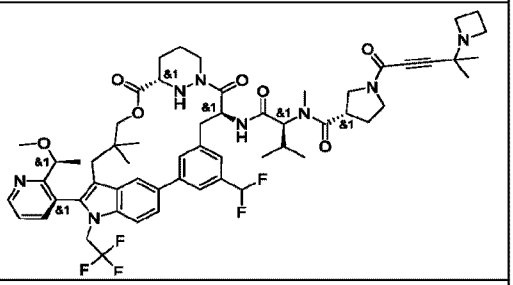
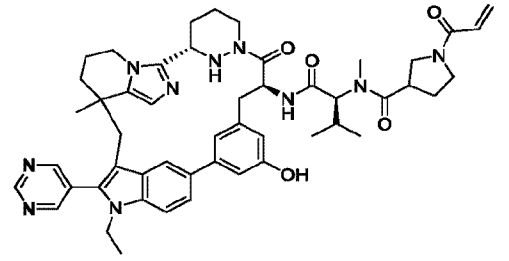
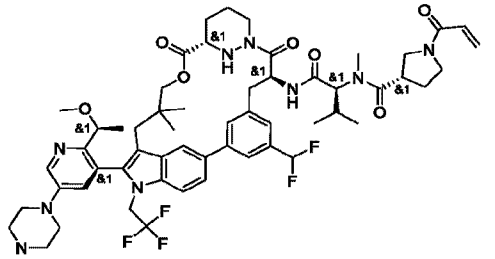
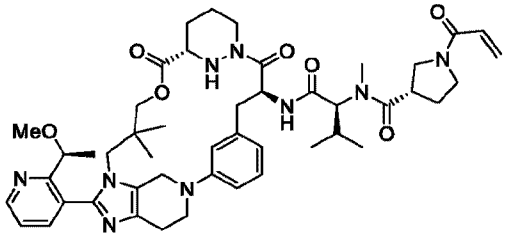
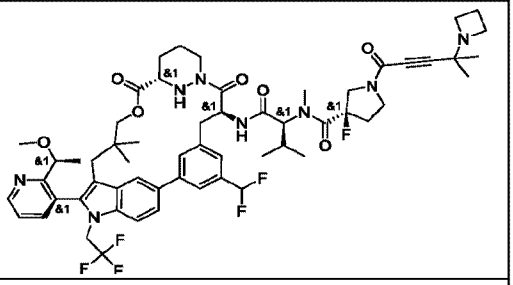
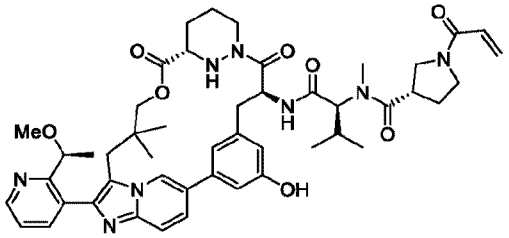
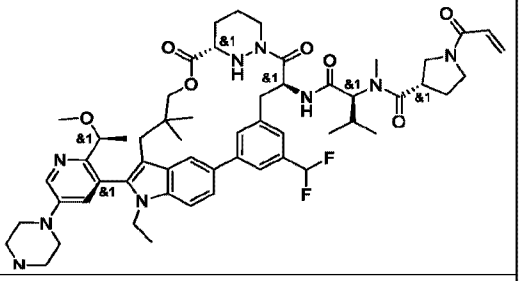
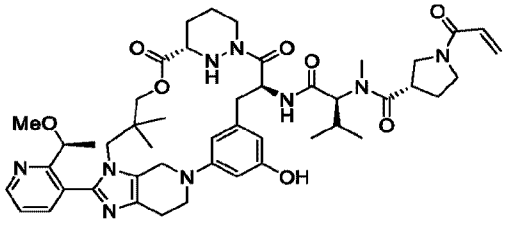
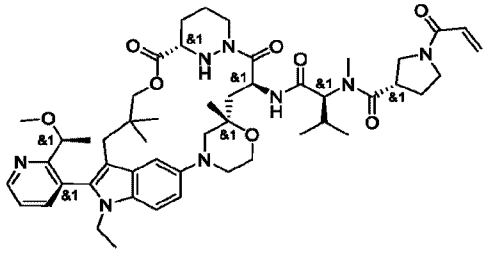
Table B2: Certain Compounds of the Present Invention

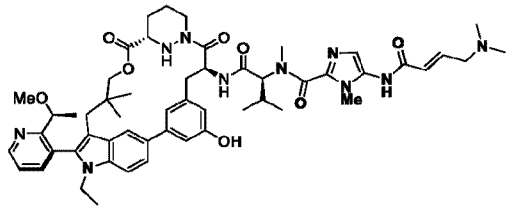
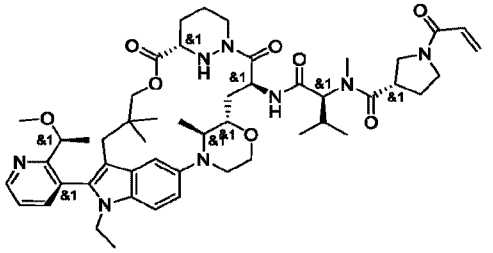
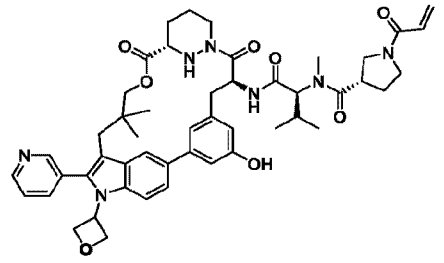
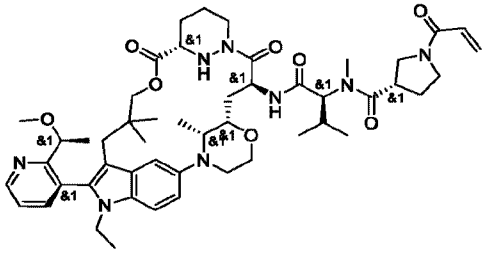
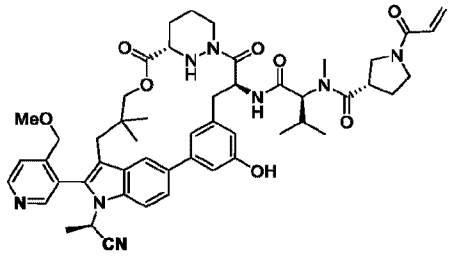
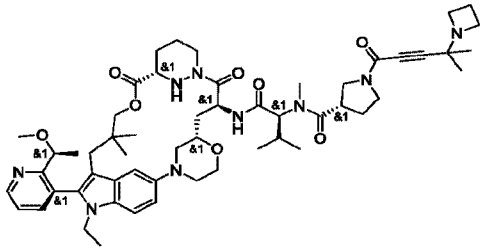
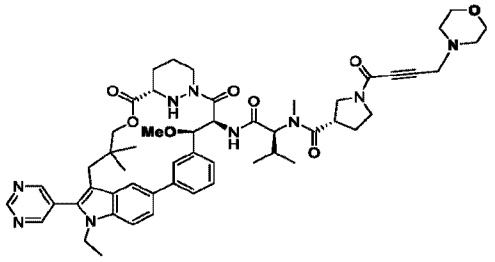
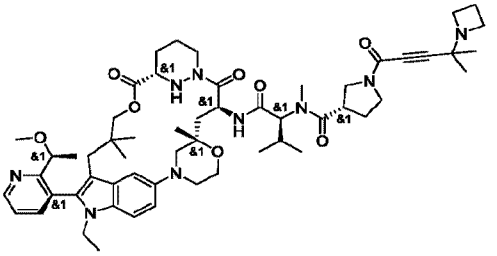
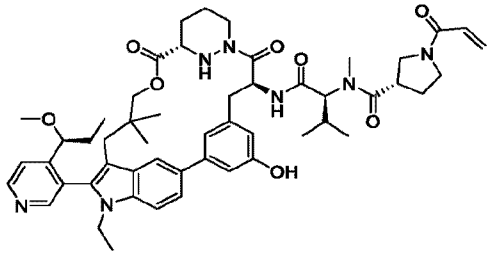
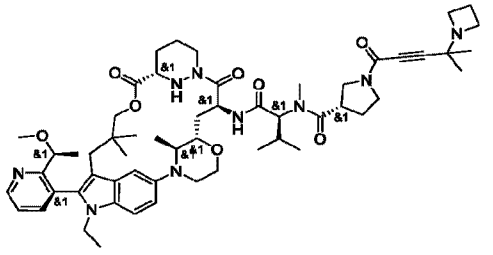
Ex#	Structure	Ex#	Structure
BB 1		BB 254	

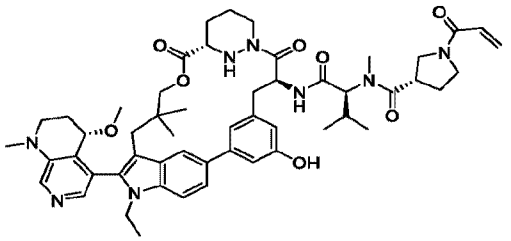
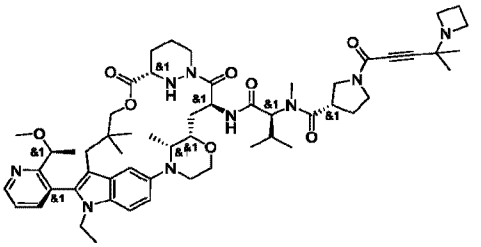
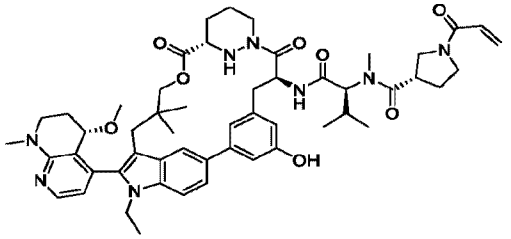
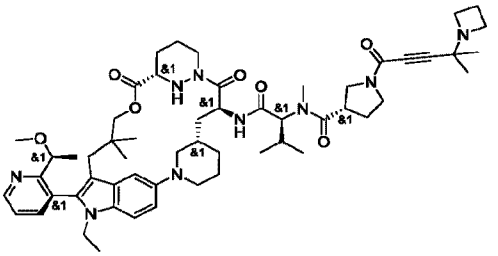
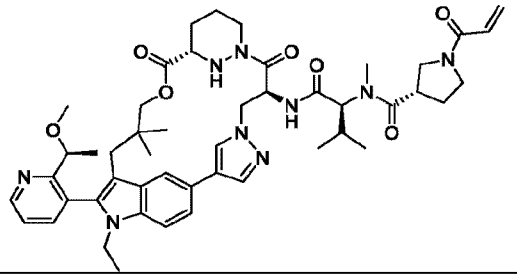
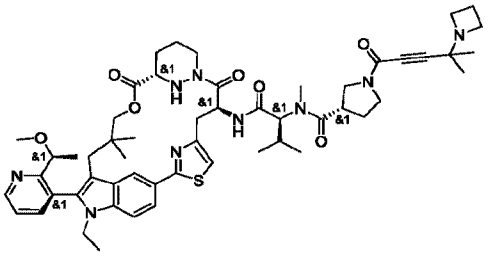
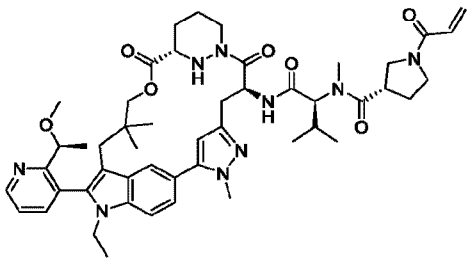
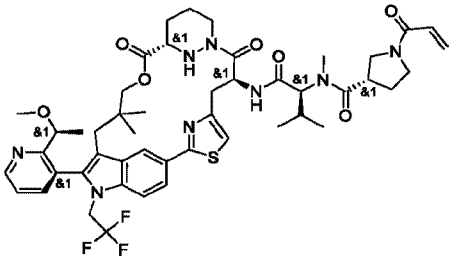
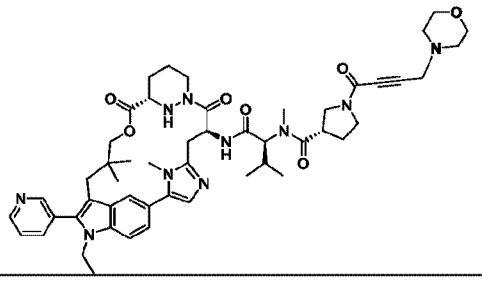
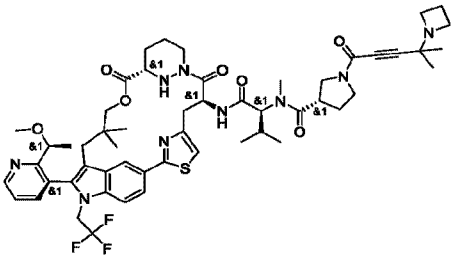
Ex#	Structure	Ex#	Structure
BB 2		BB 255	
BB 3		BB 256	
BB 4		BB 257	
BB 5		BB 258	
BB 6		BB 259	

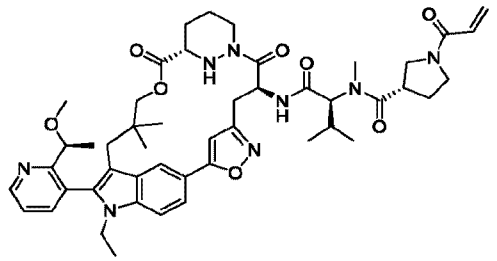
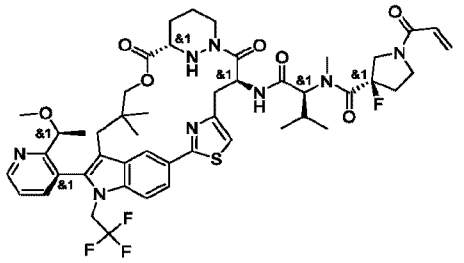
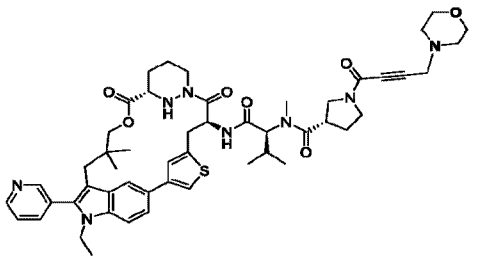
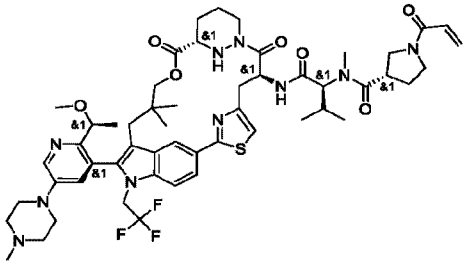
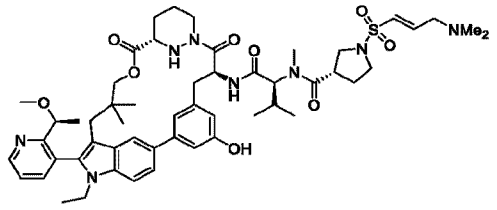
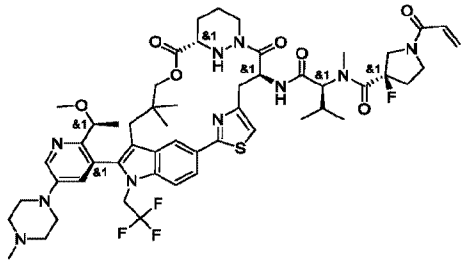
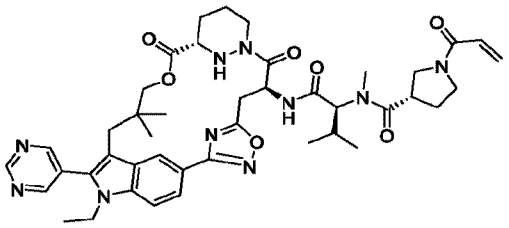
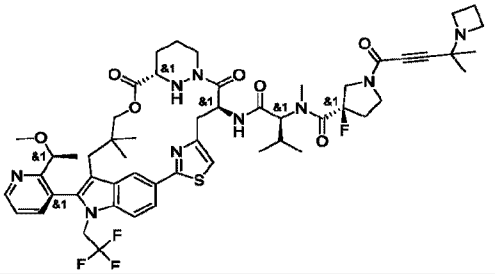
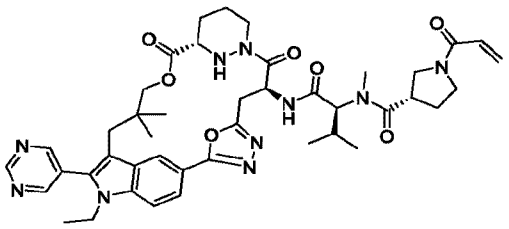
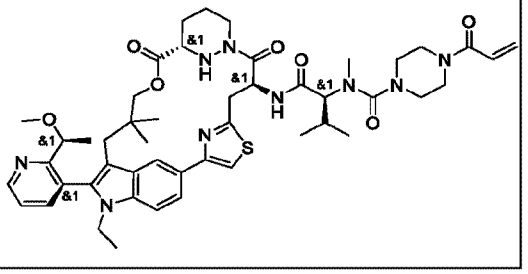
Ex#	Structure	Ex#	Structure
BB 7		BB 260	
BB 11		BB 261	
BB 12		BB 262	
BB 13		BB 263	
BB 18		BB 264	

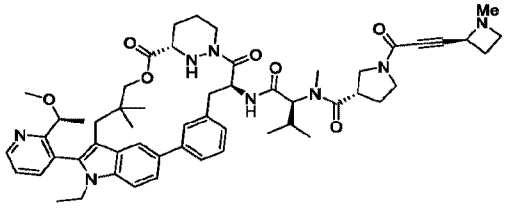
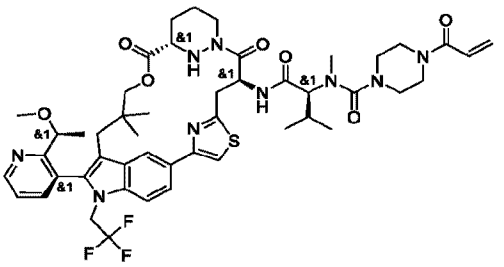
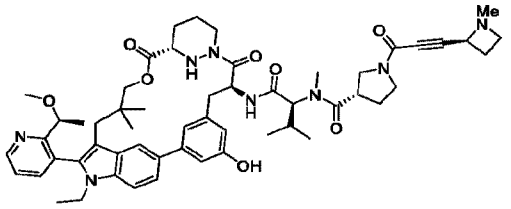
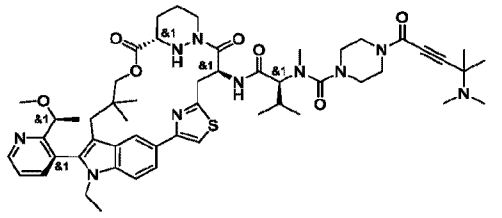
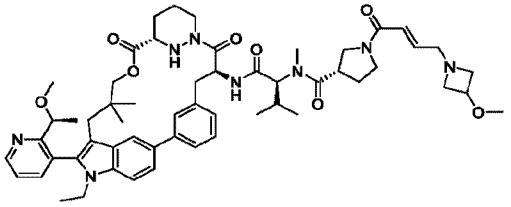
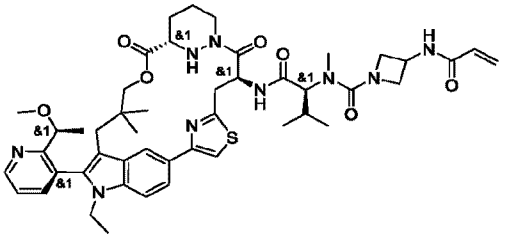
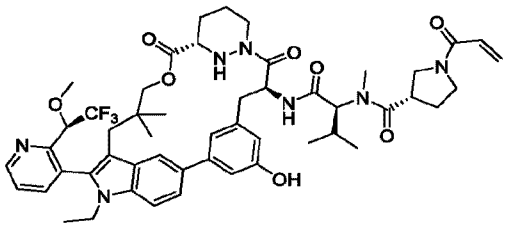
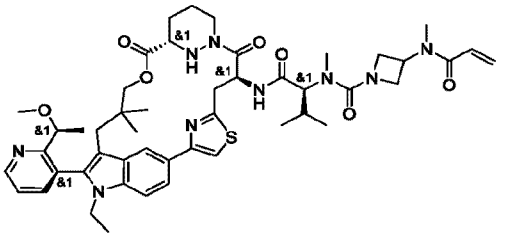
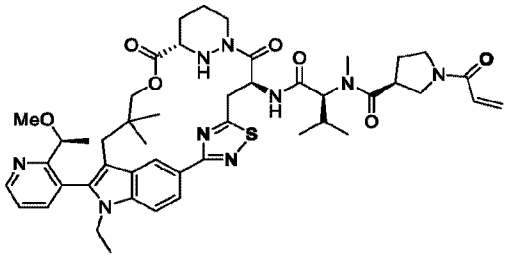
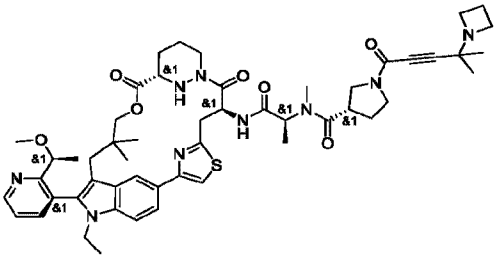
Ex#	Structure	Ex#	Structure
BB 21		BB 265	
BB 22		BB 266	
BB 25		BB 267	
BB 27		BB 268	
BB 28		BB 269	

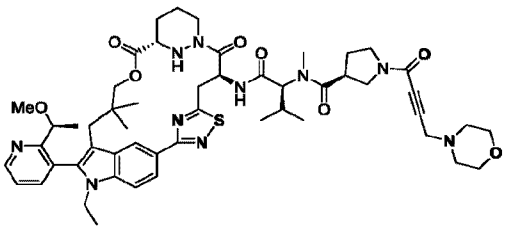
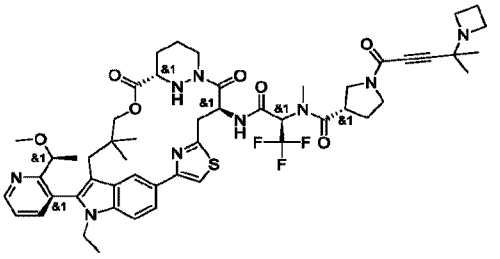
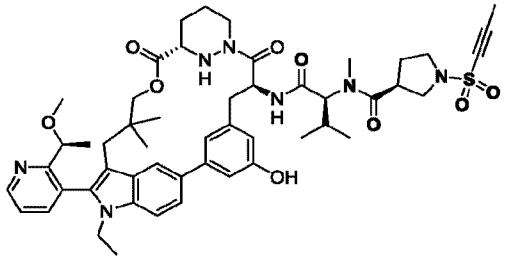
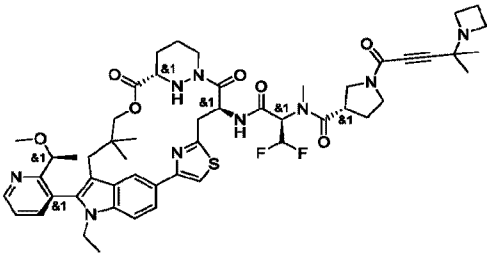
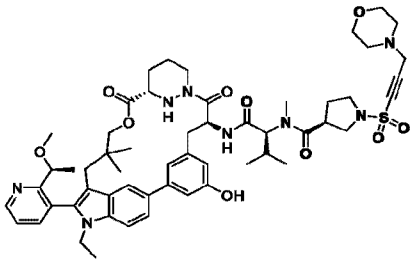
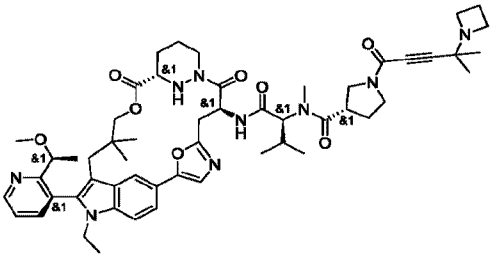
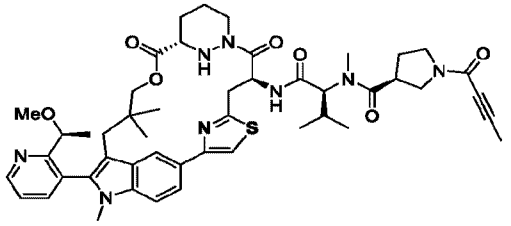
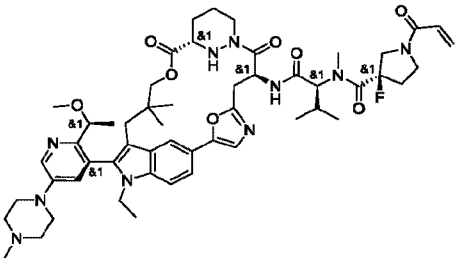
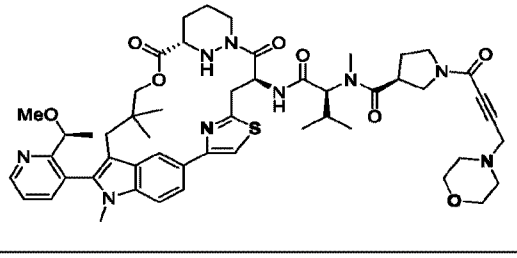
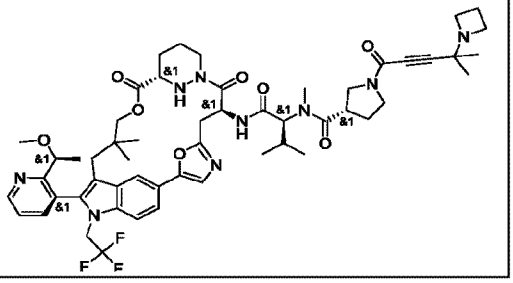
Ex#	Structure	Ex#	Structure
BB 29		BB 270	
BB 30		BB 271	
BB 32		BB 272	
BB 34		BB 273	
BB 38		BB 274	

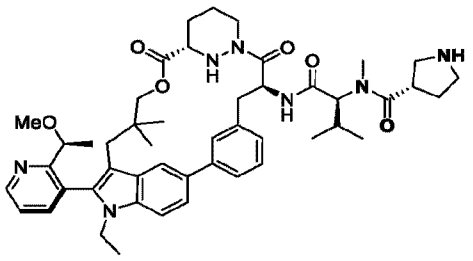
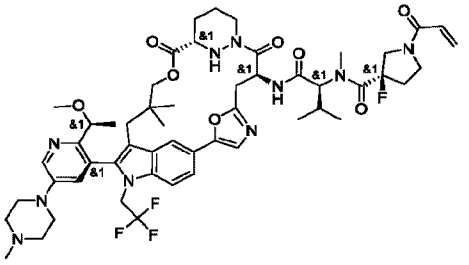
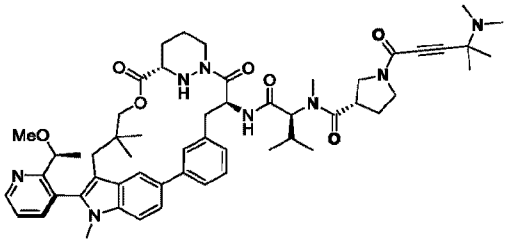
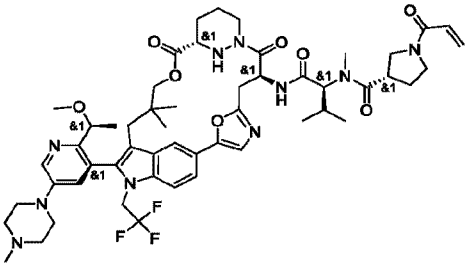
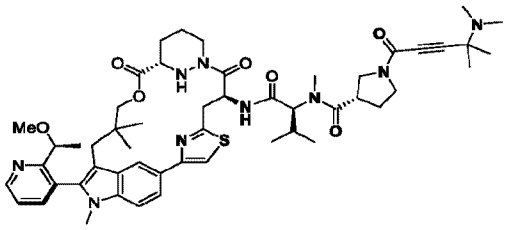
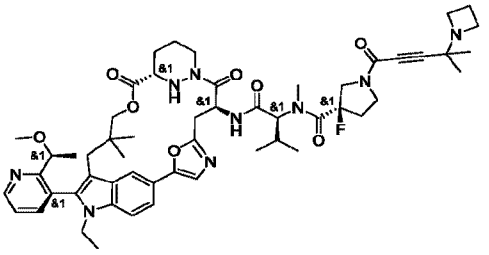
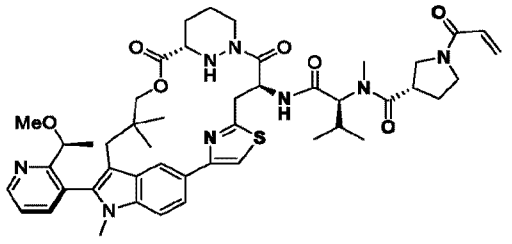
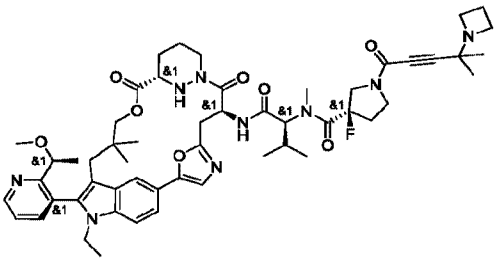
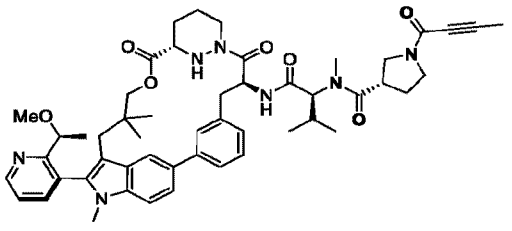
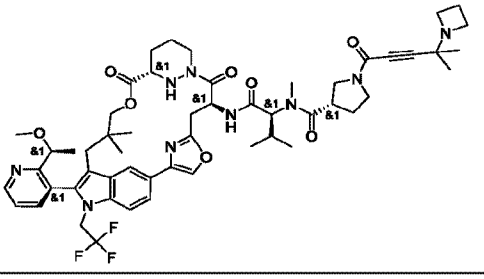
Ex#	Structure	Ex#	Structure
BB 47		BB 275	
BB 64		BB 276	
BB 65		BB 277	
BB 66		BB 278	
BB 70		BB 279	

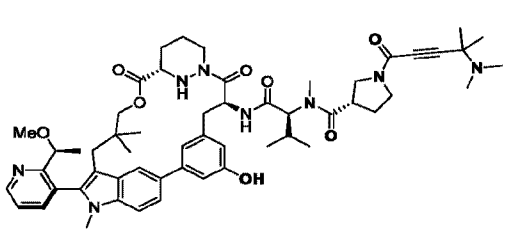
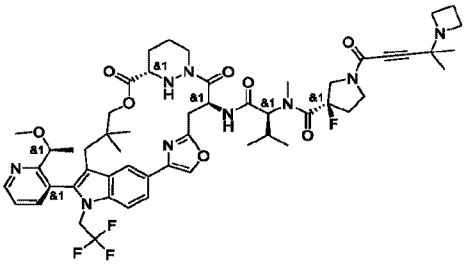
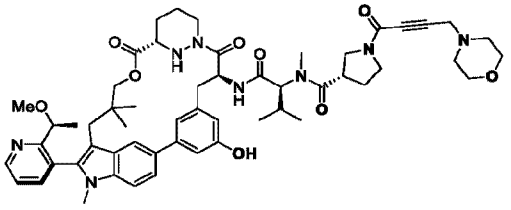
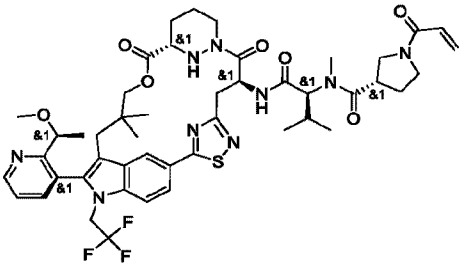
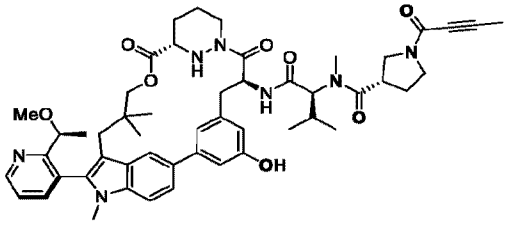
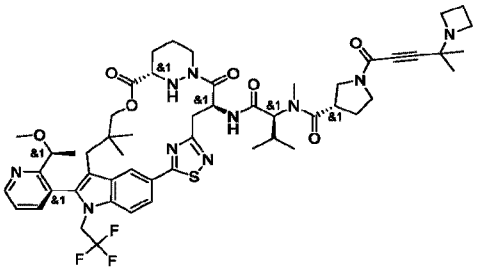
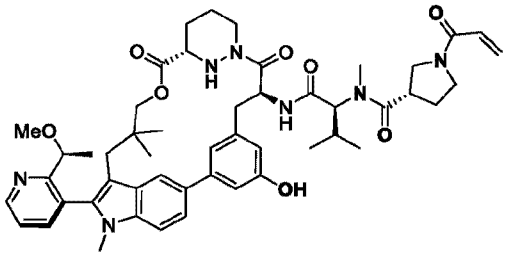
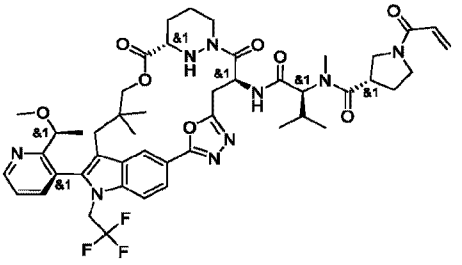
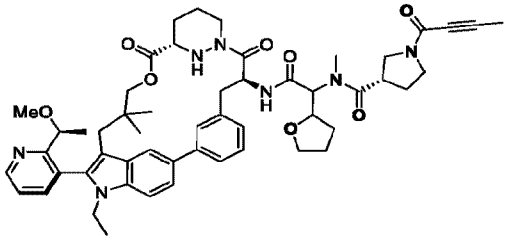
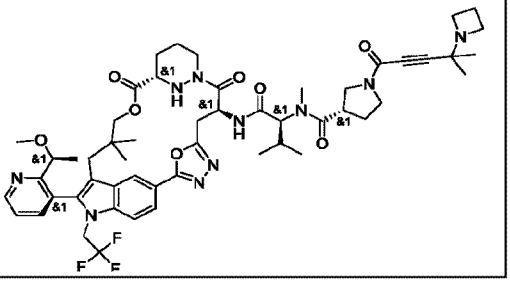
Ex#	Structure	Ex#	Structure
BB 73		BB 280	
BB 74		BB 282	
BB 75		BB 283	
BB 76		BB 284	
BB 77		BB 285	

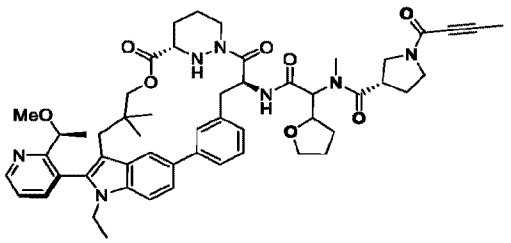
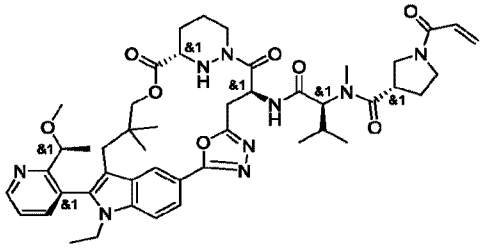
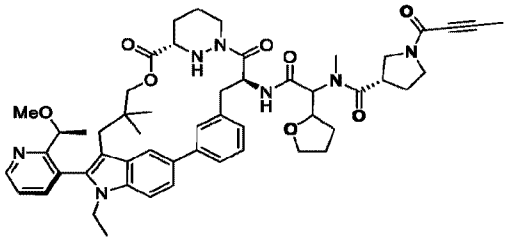
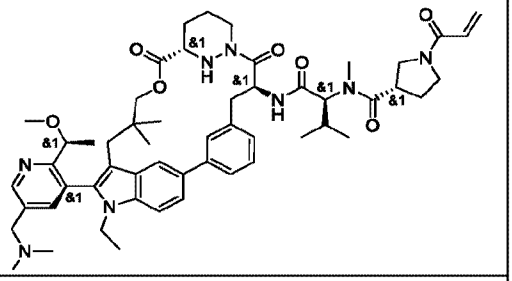
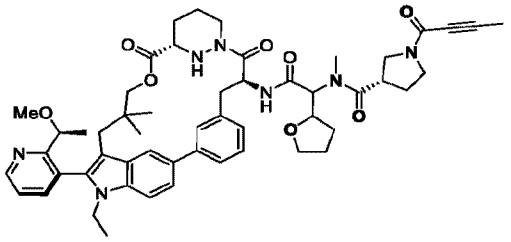
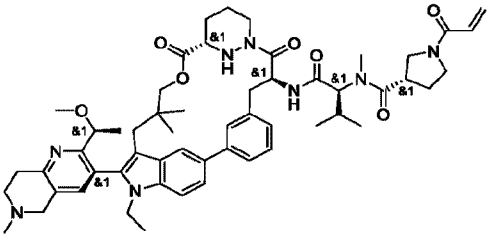
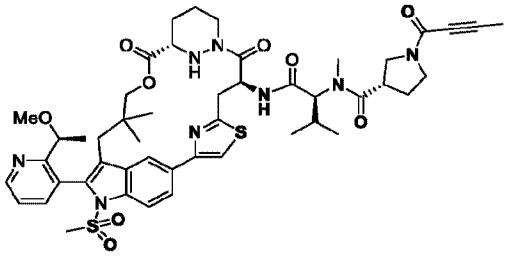
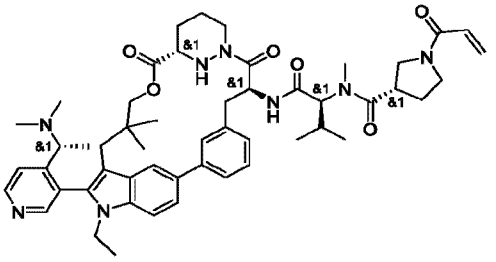
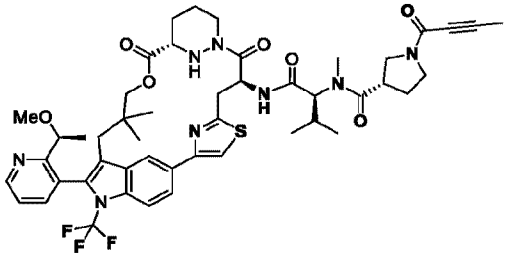
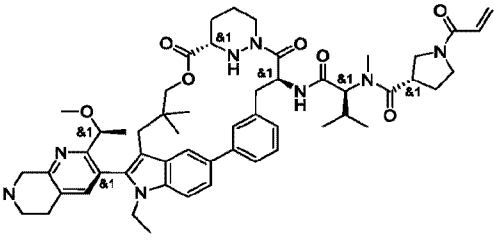
Ex#	Structure	Ex#	Structure
BB 81		BB 286	
BB 83		BB 287	
BB 85		BB 288	
BB 86		BB 289	
BB 87		BB 290	

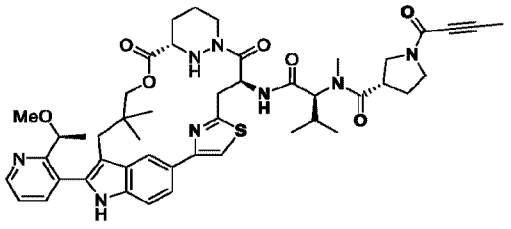
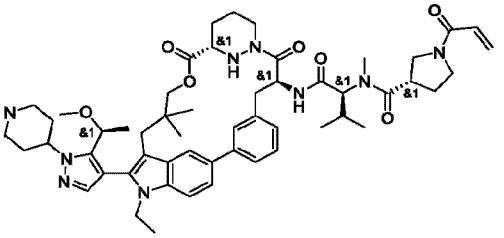
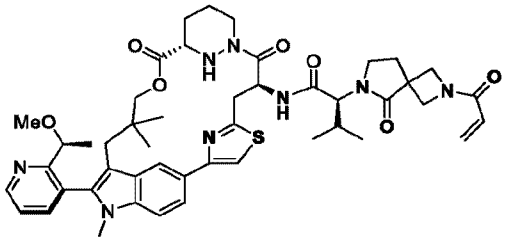
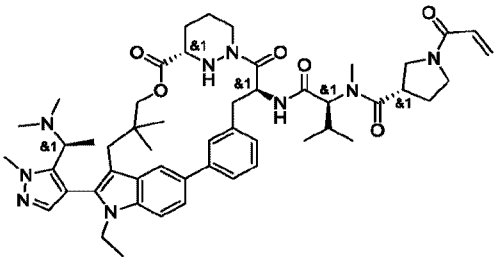
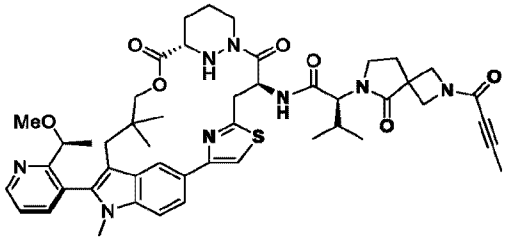
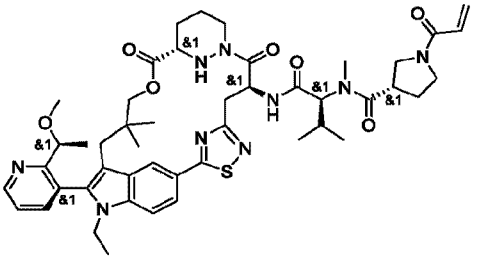
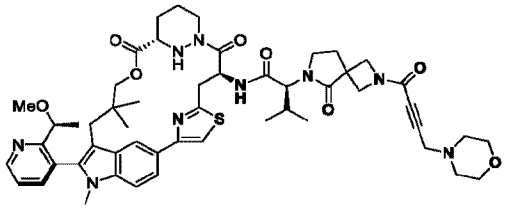
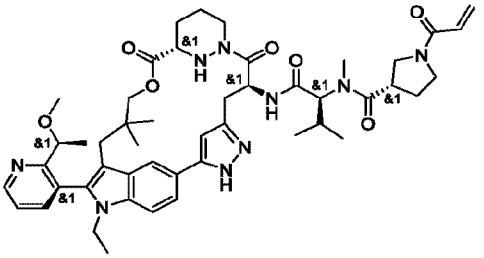
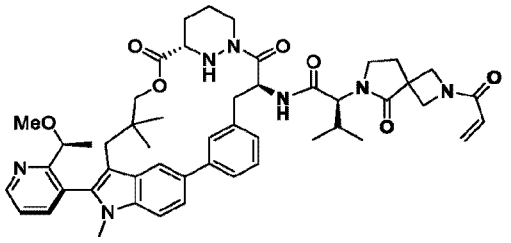
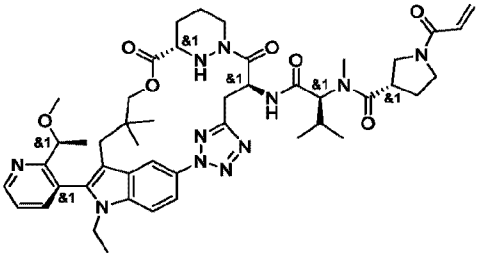
Ex#	Structure	Ex#	Structure
BB 88		BB 291	
BB 89		BB 292	
BB 90		BB 293	
BB 91		BB 294	
BB 96		BB 295	

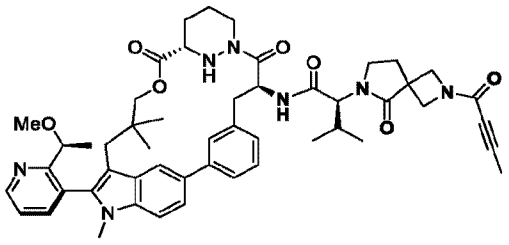
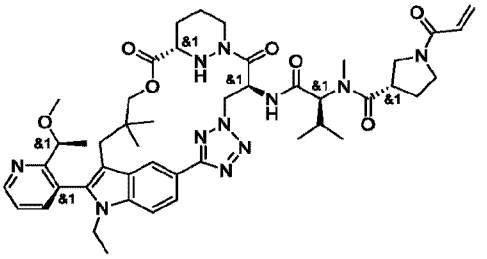
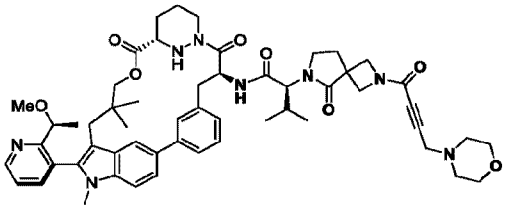
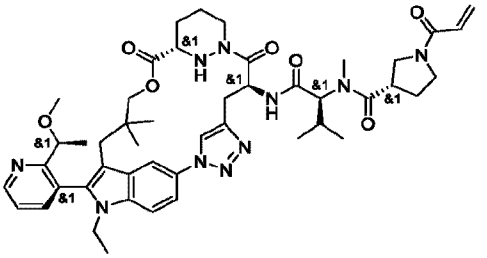
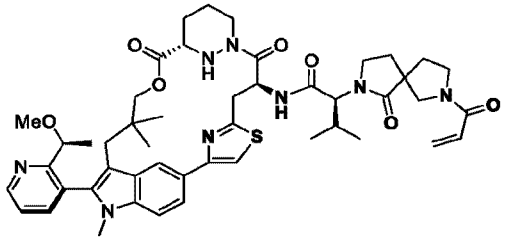
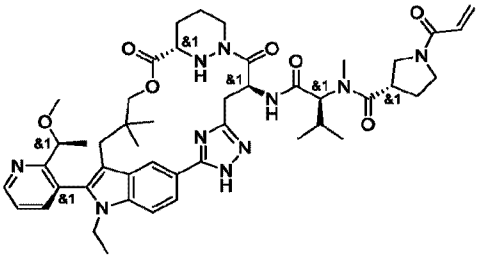
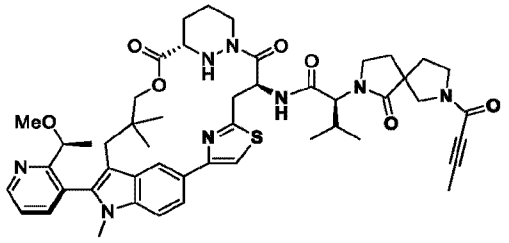
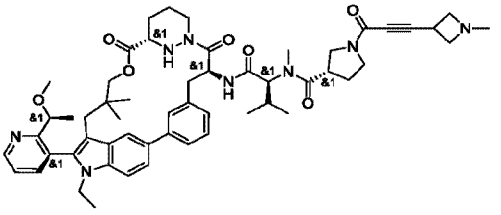
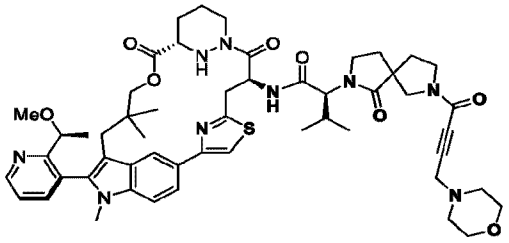
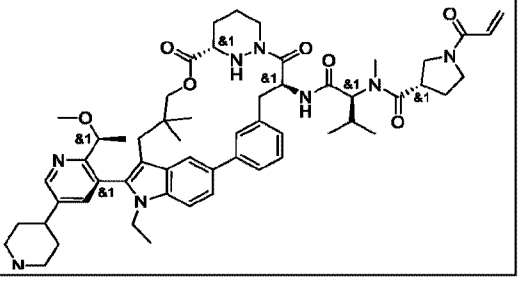
Ex#	Structure	Ex#	Structure
BB 97		BB 296	
BB 102		BB 297	
BB 103		BB 298	
BB 104		BB 299	
BB 106		BB 300	

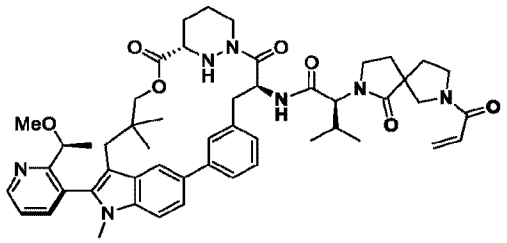
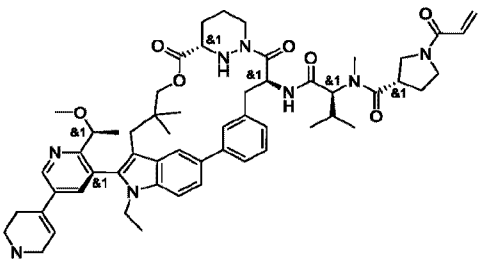
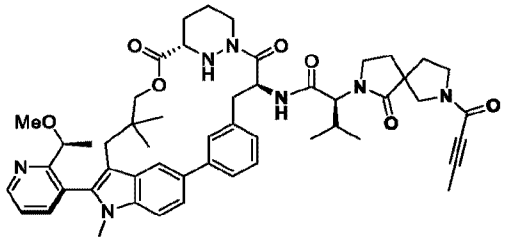
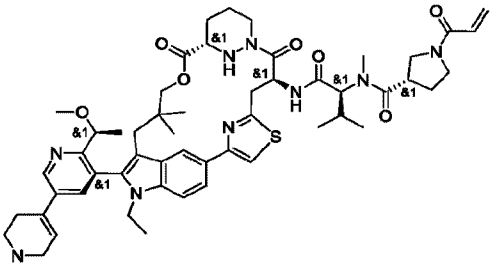
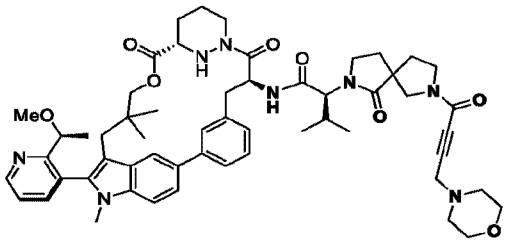
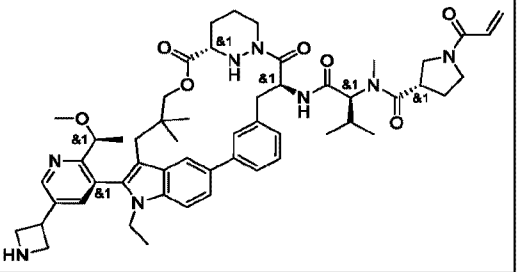
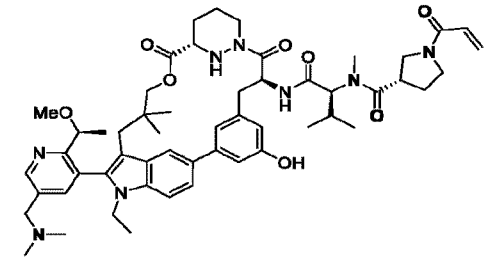
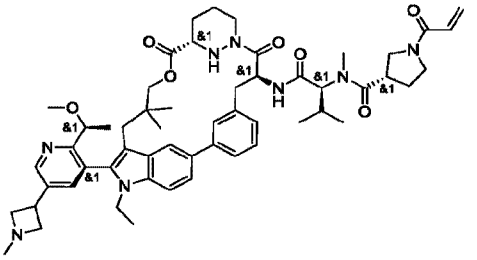
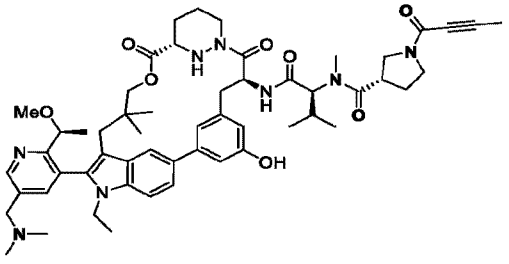
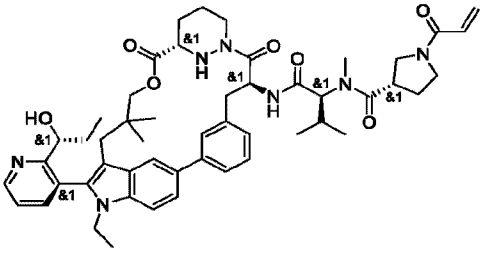
Ex#	Structure	Ex#	Structure
BB 107		BB 301	
BB 109		BB 302	
BB 111		BB 303	
BB 112		BB 304	
BB 113		BB 305	

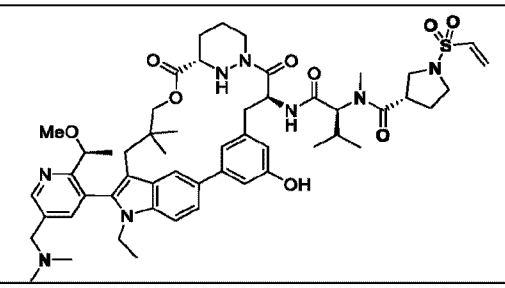
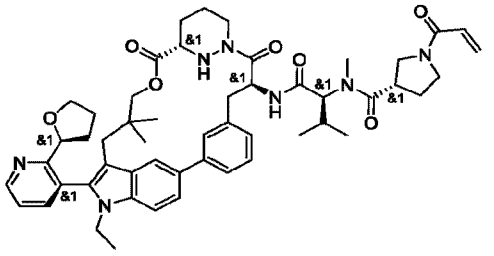
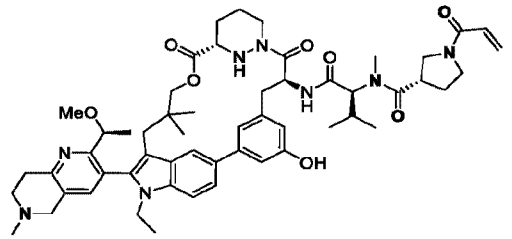
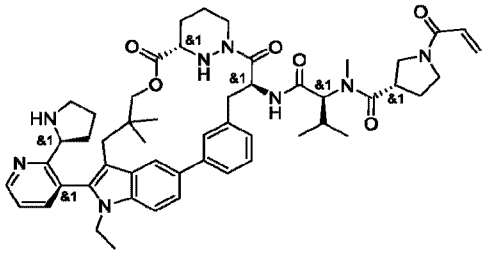
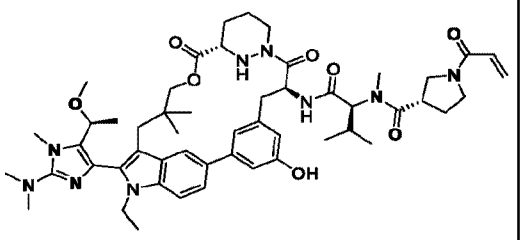
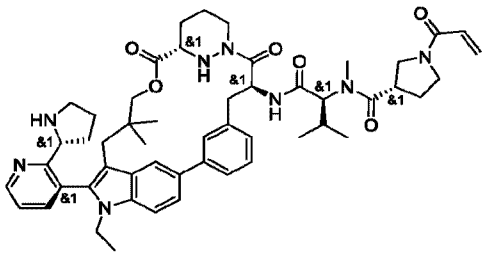
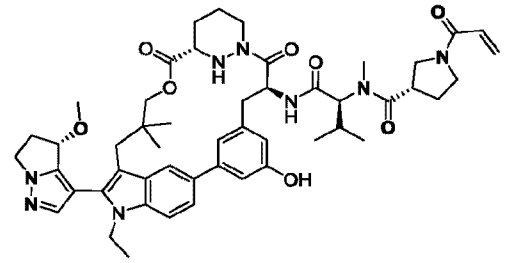
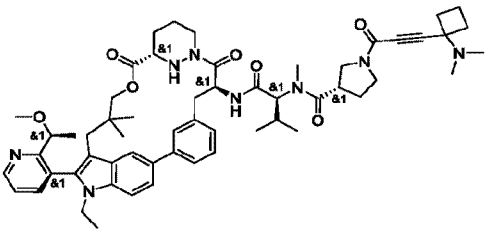
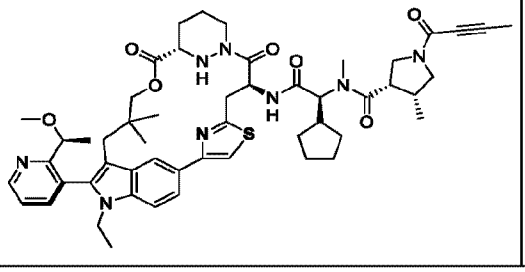
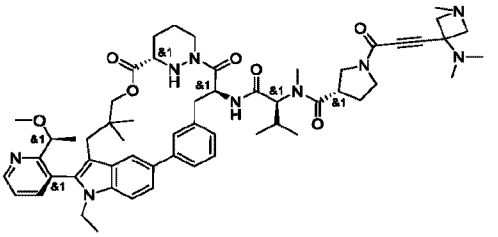
Ex#	Structure	Ex#	Structure
BB 115		BB 306	
BB 116		BB 307	
BB 117		BB 308	
BB 118		BB 309	
BB 119		BB 310	

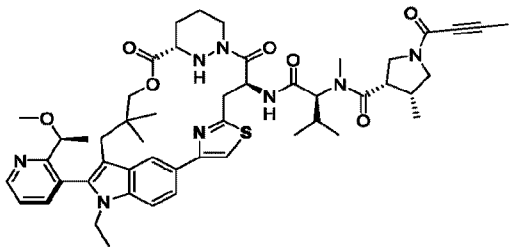
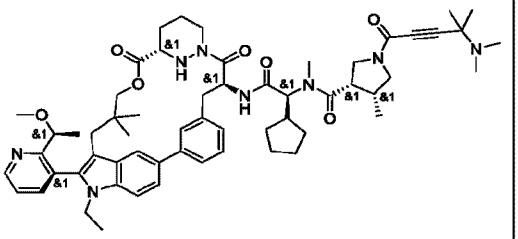
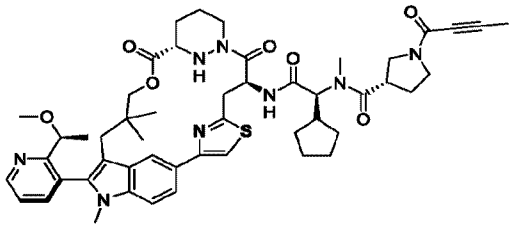
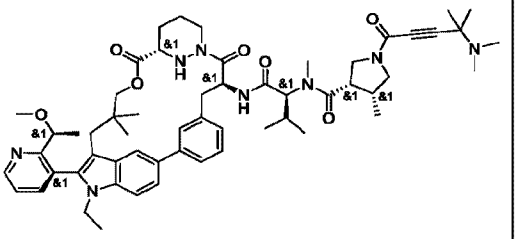
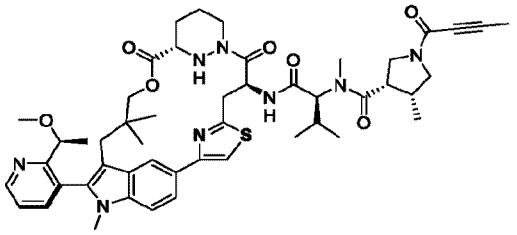
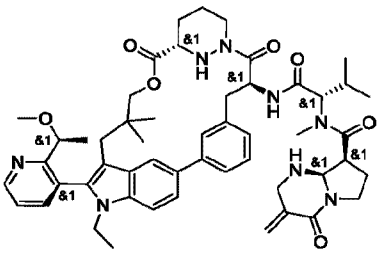
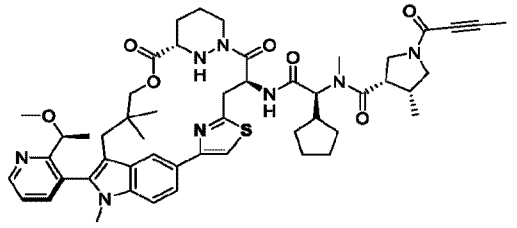
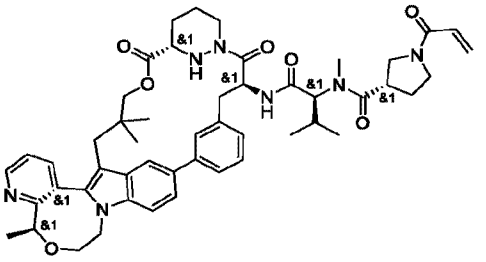
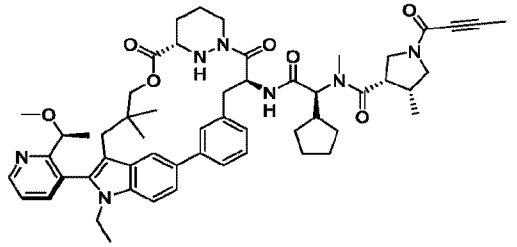
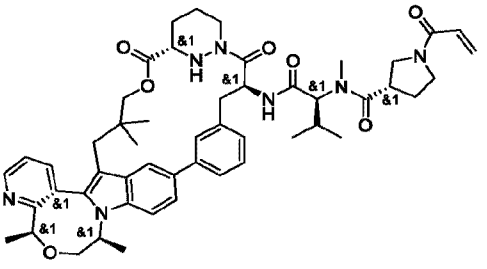
Ex#	Structure	Ex#	Structure
BB 120		BB 311	
BB 121		BB 312	
BB 122		BB 313	
BB 123		BB 314	
BB 124		BB 315	

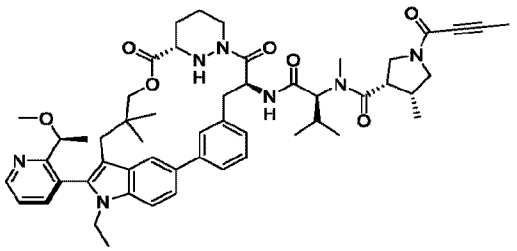
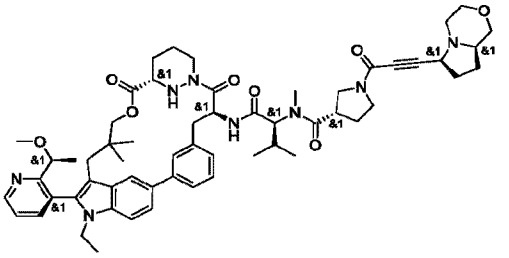
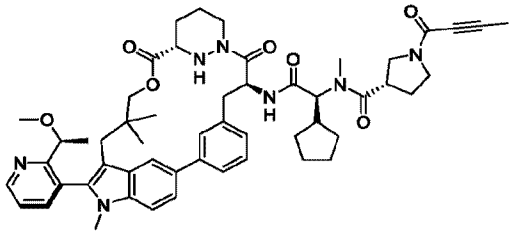
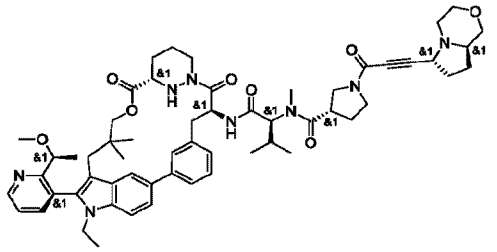
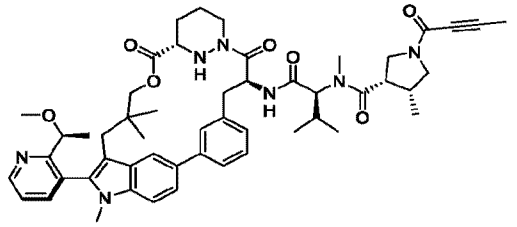
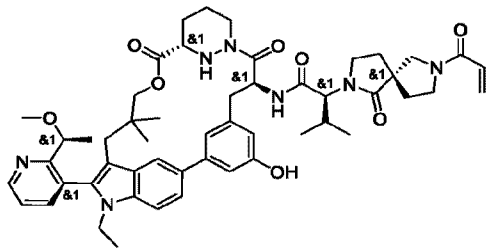
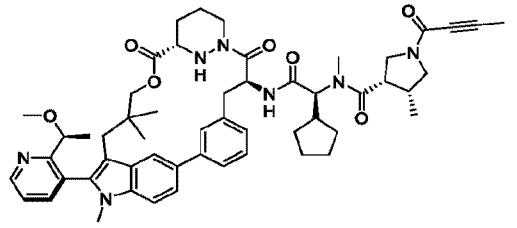
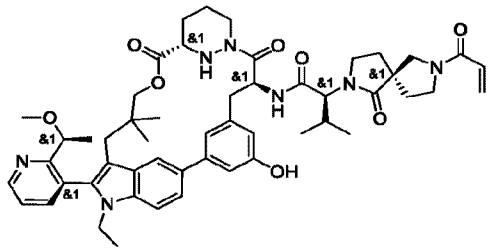
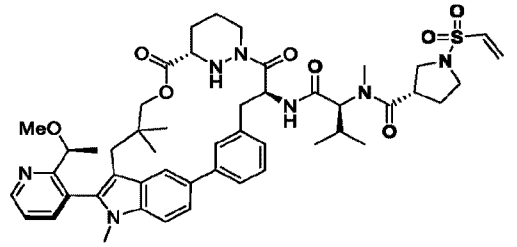
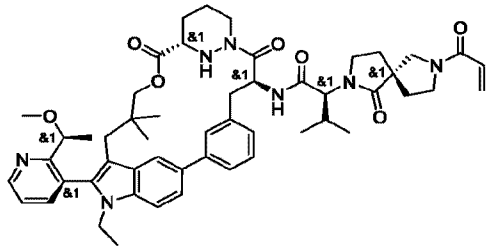
Ex#	Structure	Ex#	Structure
BB 126		BB 316	
BB 127		BB 317	
BB 128		BB 318	
BB 129		BB 319	
BB 130		BB 320	

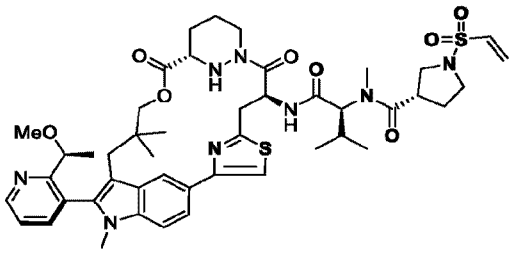
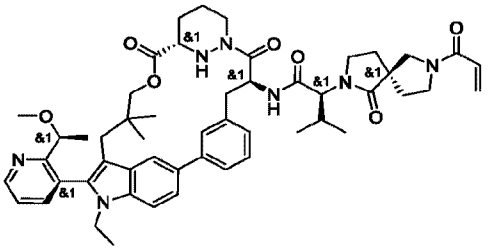
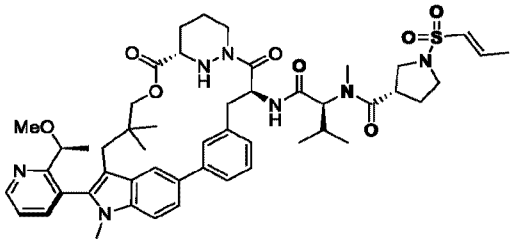
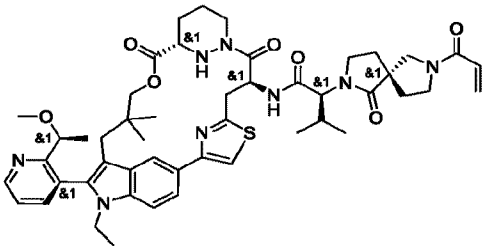
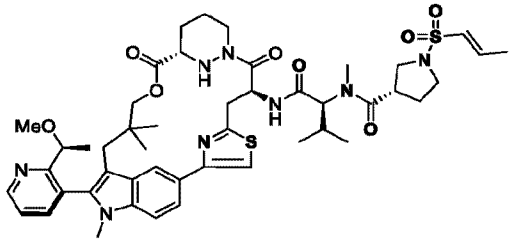
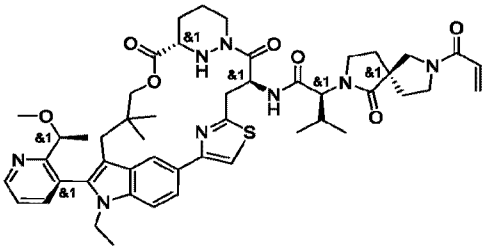
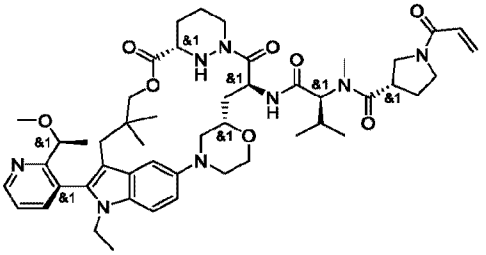
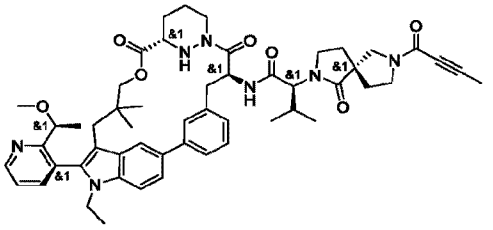
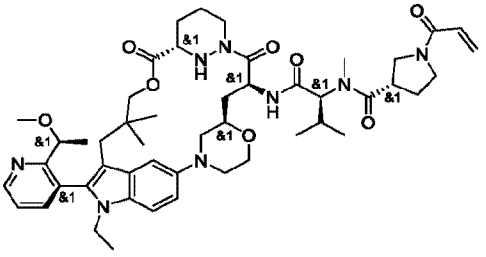
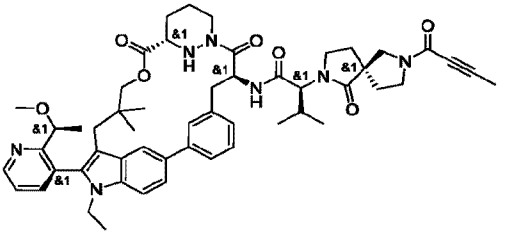
Ex#	Structure	Ex#	Structure
BB 131		BB 321	
BB 132		BB 322	
BB 139		BB 323	
BB 140		BB 324	
BB 141		BB 325	

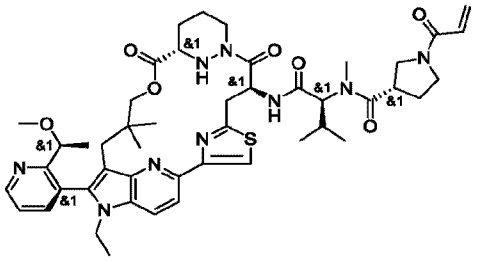
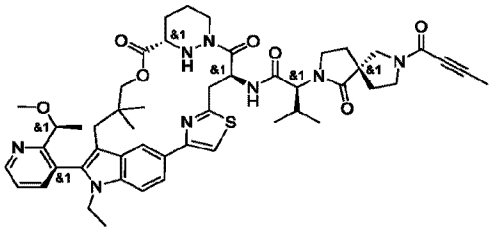
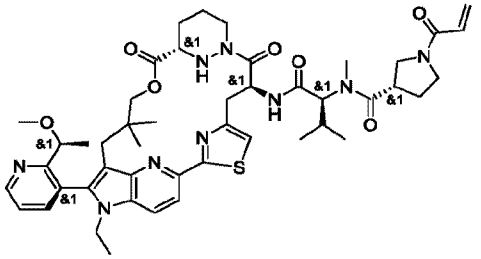
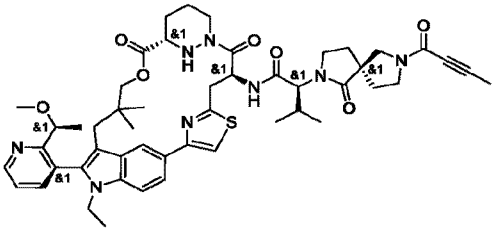
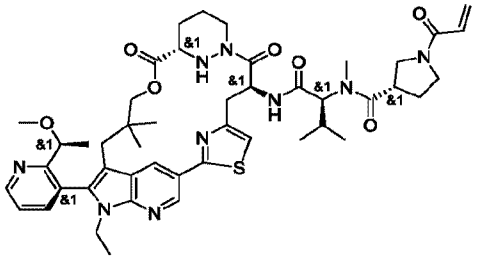
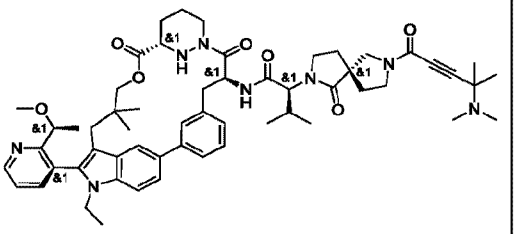
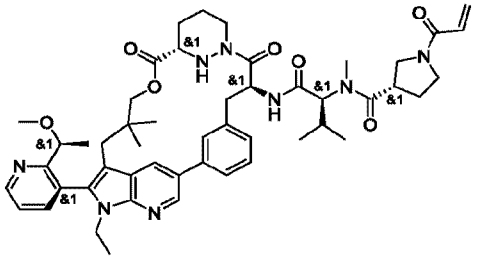
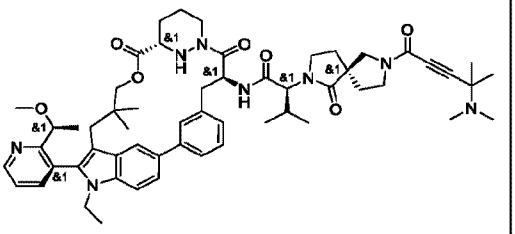
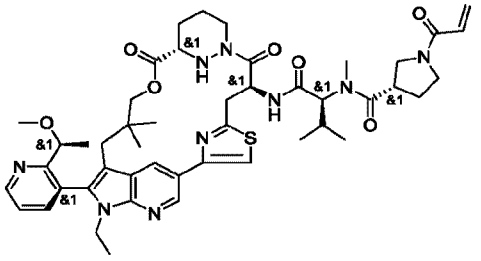
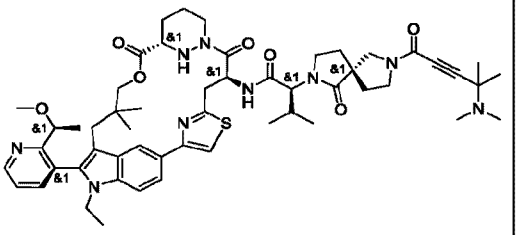
Ex#	Structure	Ex#	Structure
BB 142		BB 326	
BB 143		BB 327	
BB 144		BB 328	
BB 145		BB 329	
BB 146		BB 330	

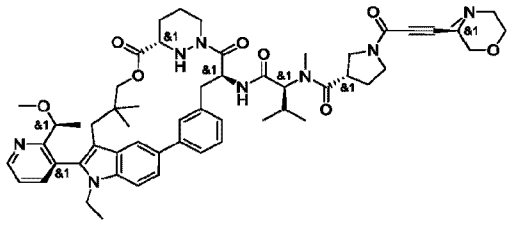
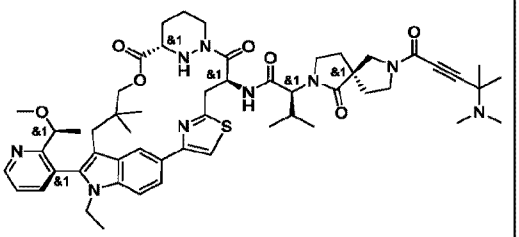
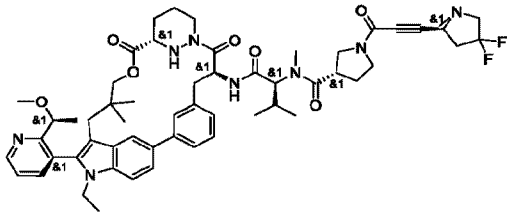
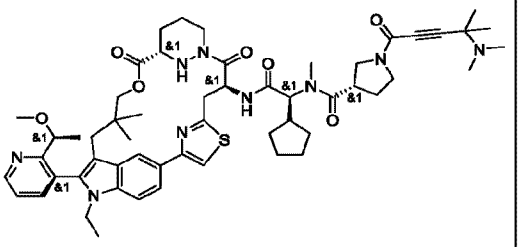
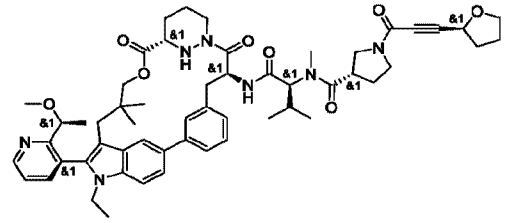
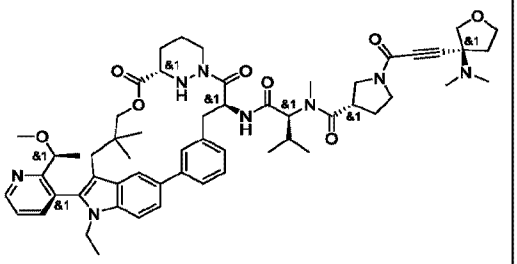
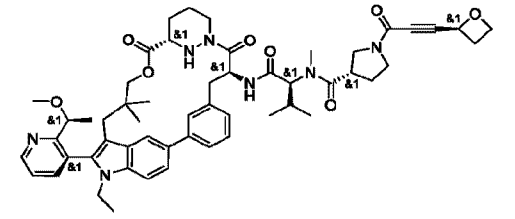
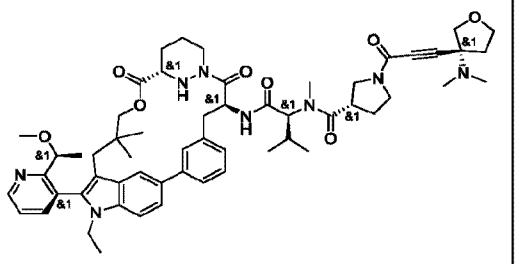
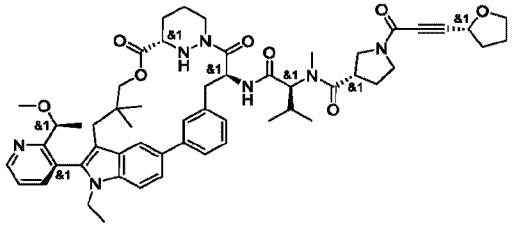
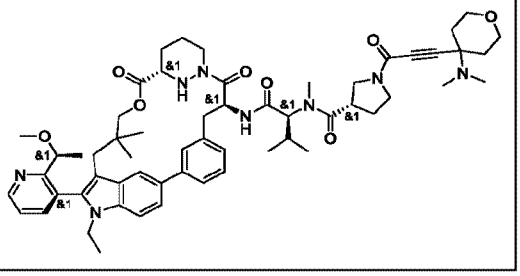
Ex#	Structure	Ex#	Structure
BB 147		BB 331	
BB 148		BB 332	
BB 149		BB 333	
BB 150		BB 334	
BB 161		BB 335	

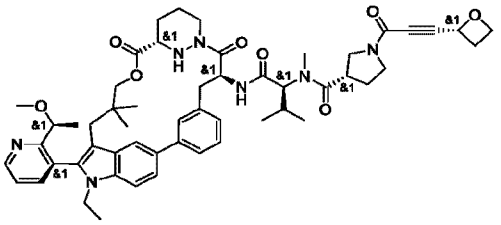
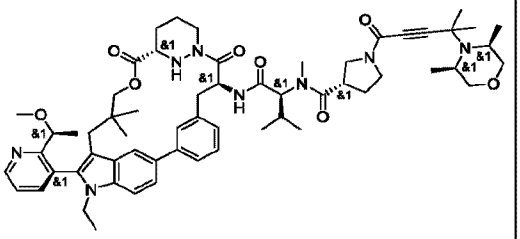
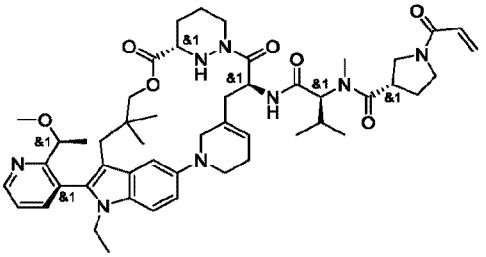
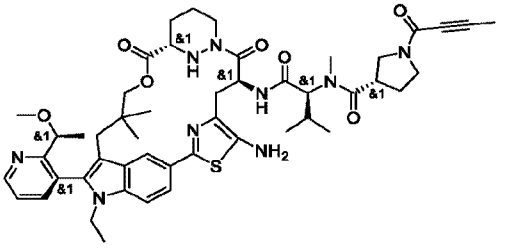
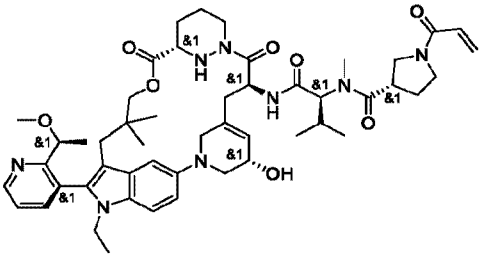
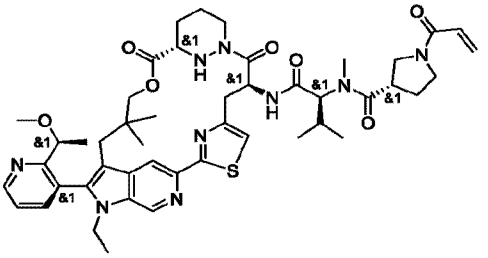
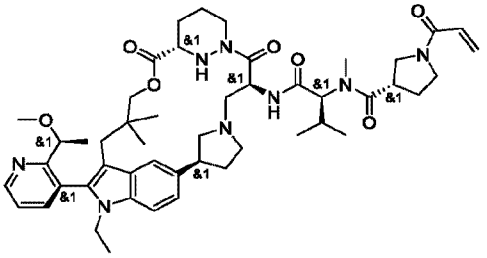
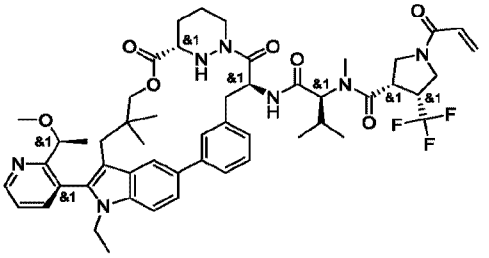
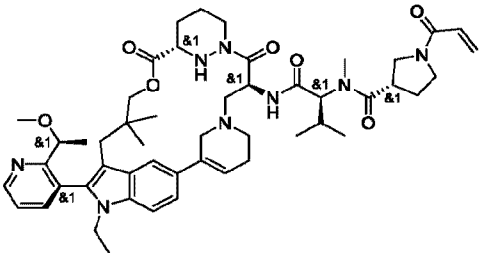
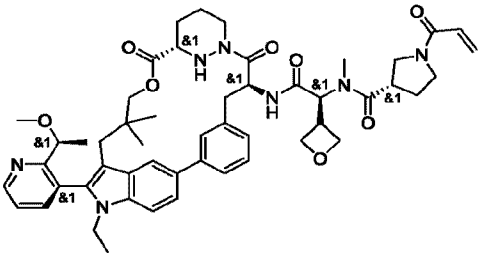
Ex#	Structure	Ex#	Structure
BB 162		BB 336	
BB 163		BB 337	
BB 164		BB 338	
BB 165		BB 339	
BB 167		BB 340	

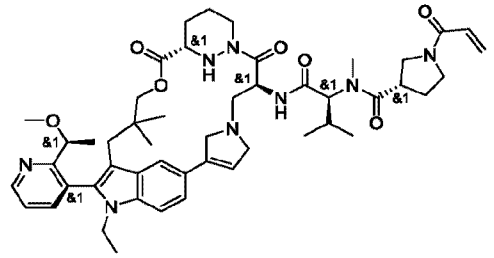
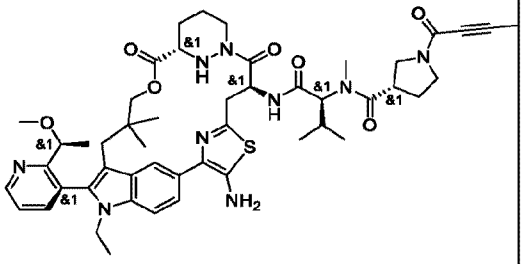
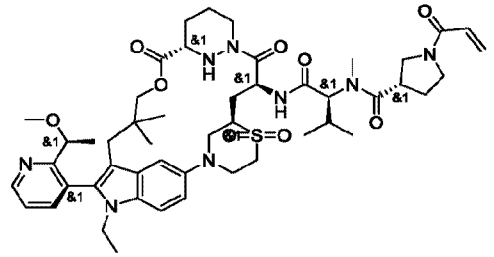
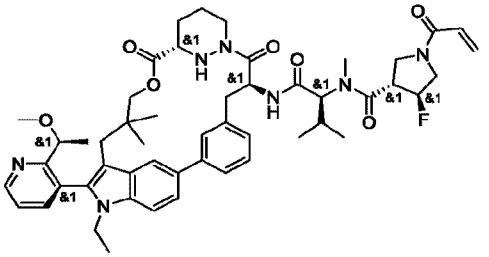
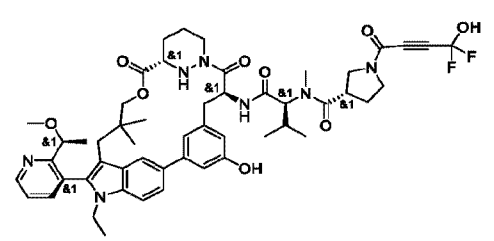
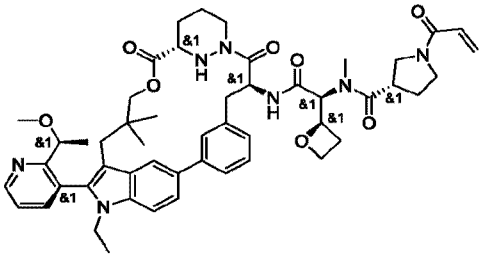
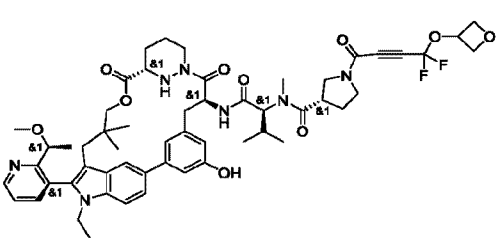
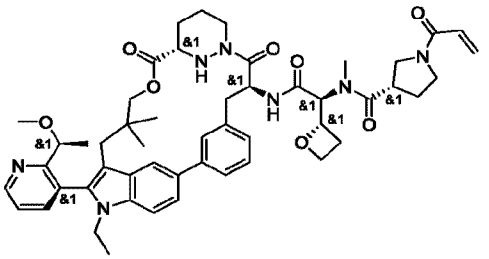
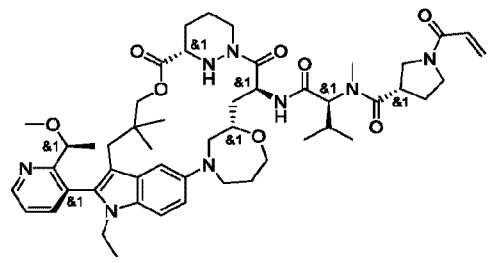
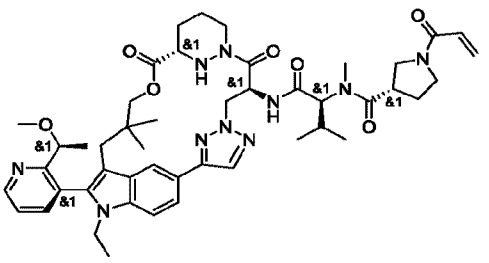
Ex#	Structure	Ex#	Structure
BB 168		BB 341	
BB 169		BB 342	
BB 170		BB 343	
BB 171		BB 344	
BB 172		BB 345	

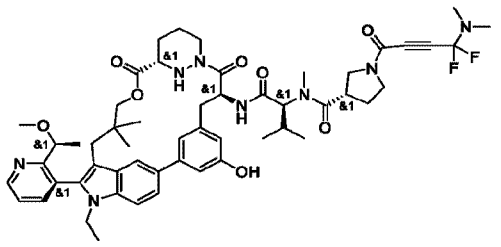
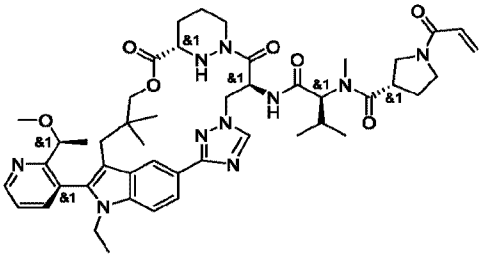
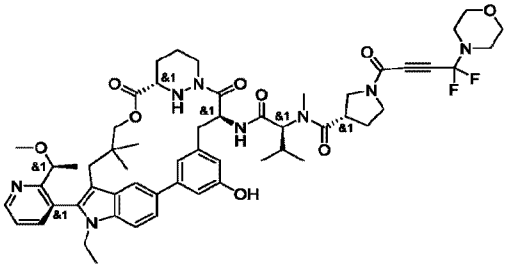
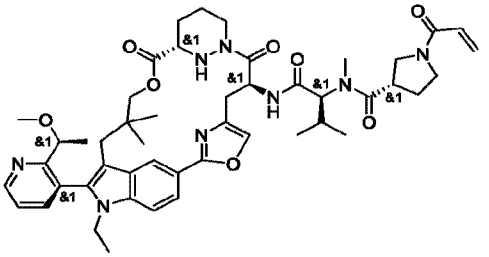
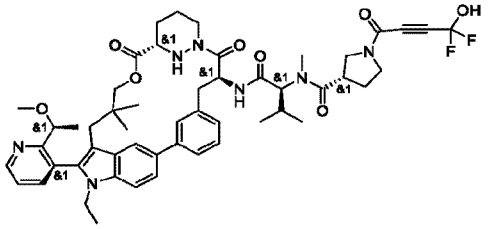
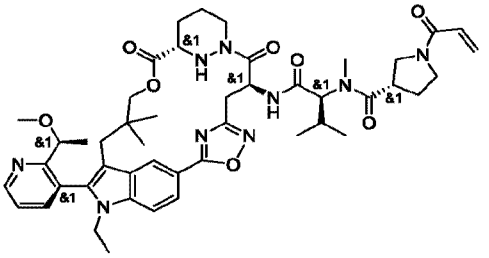
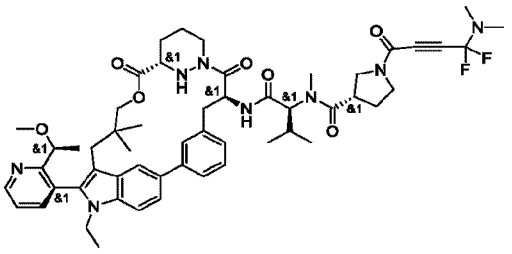
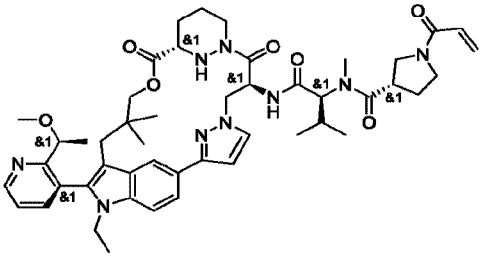
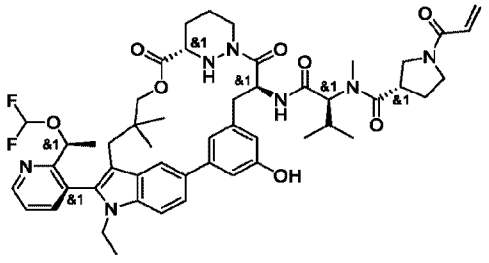
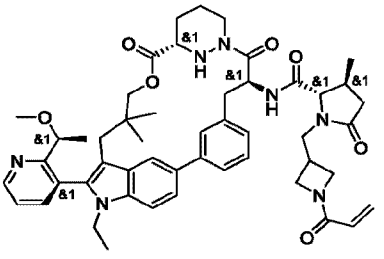
Ex#	Structure	Ex#	Structure
BB 173		BB 346	
BB 174		BB 347	
BB 175		BB 348	
BB 176		BB 349	
BB 177		BB 350	

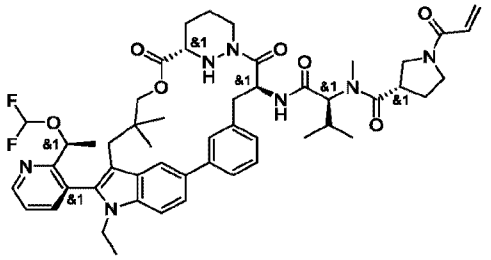
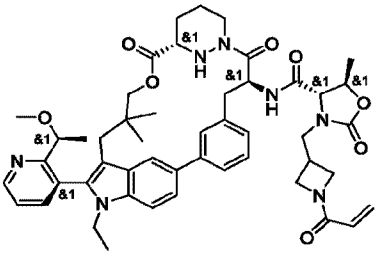
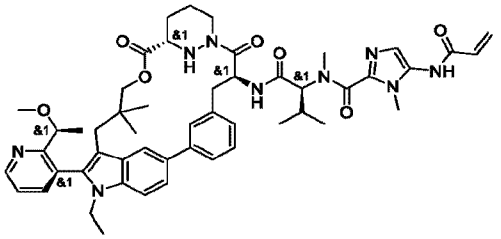
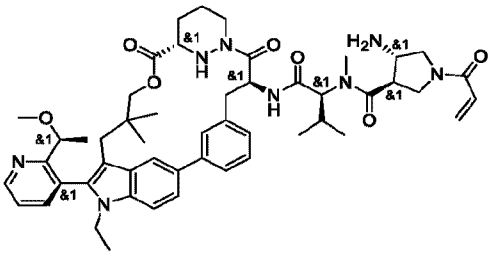
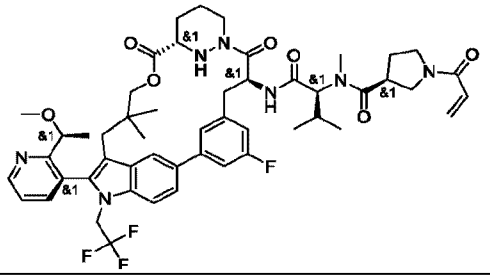
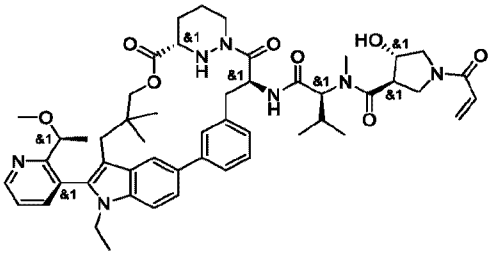
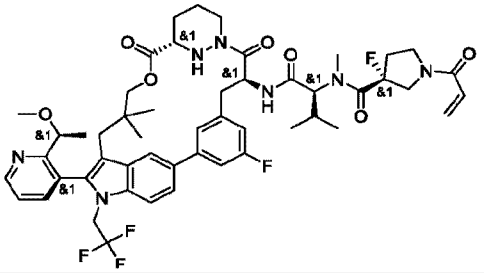
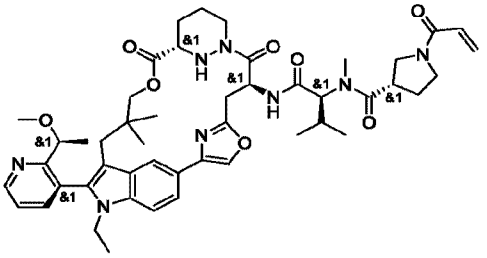
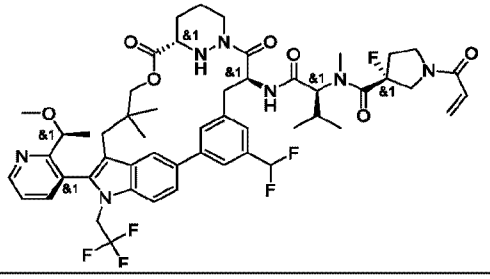
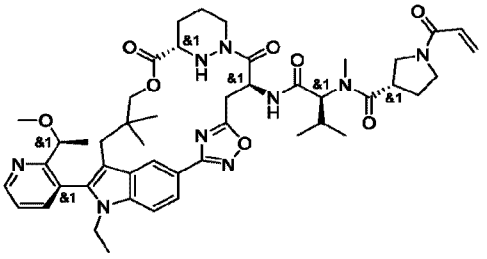
Ex#	Structure	Ex#	Structure
BB 178		BB 351	
BB 179		BB 352	
BB 180		BB 353	
BB 181		BB 354	
BB 182		BB 355	

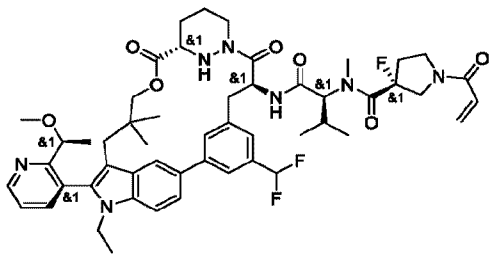
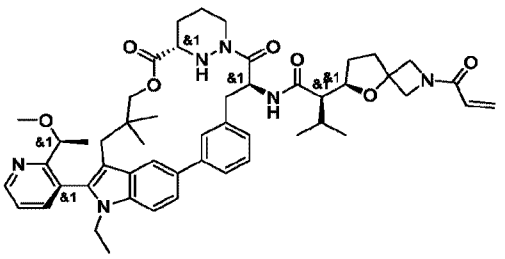
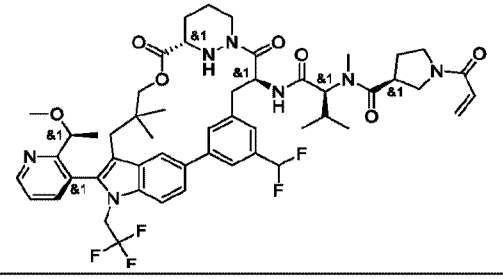
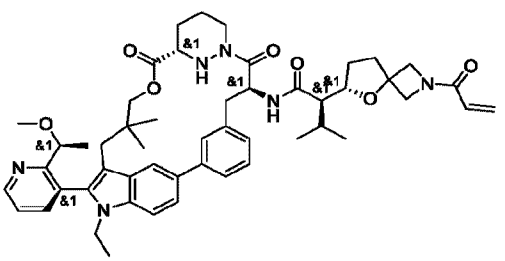
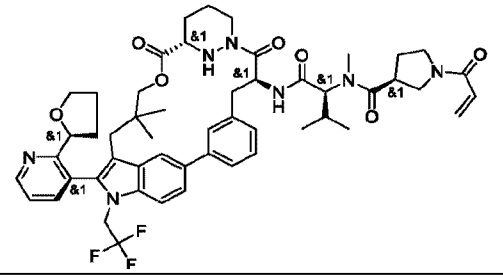
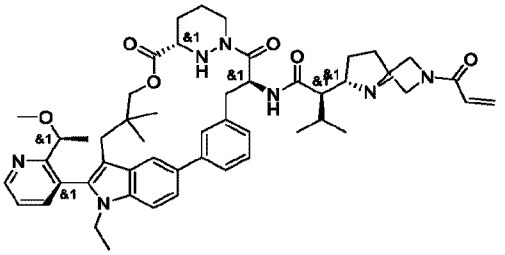
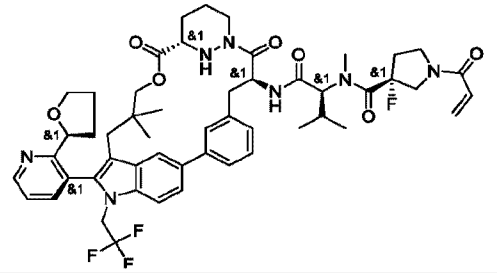
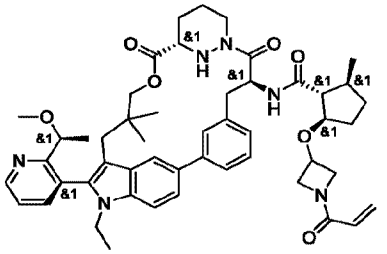
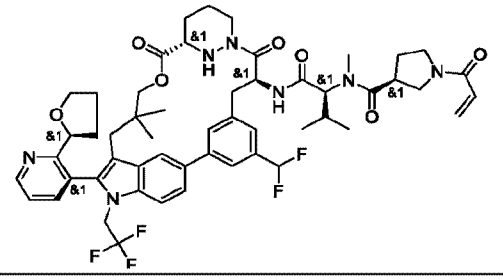
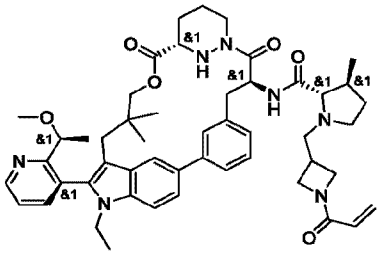
Ex#	Structure	Ex#	Structure
BB 183		BB 356	
BB 184		BB 357	
BB 185		BB 358	
BB 186		BB 359	
BB 187		BB 360	

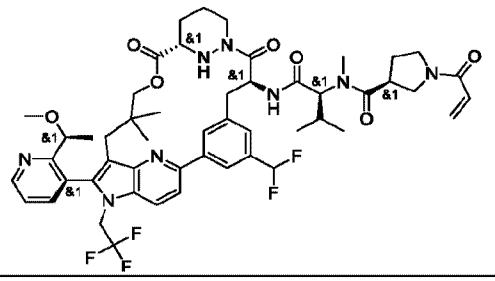
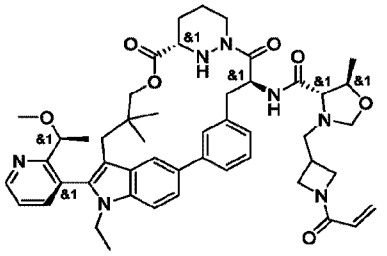
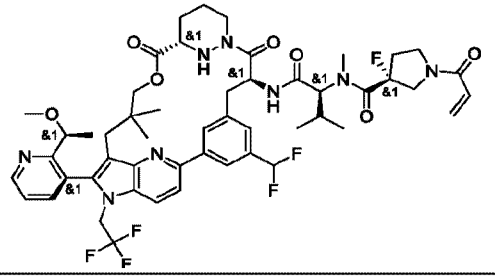
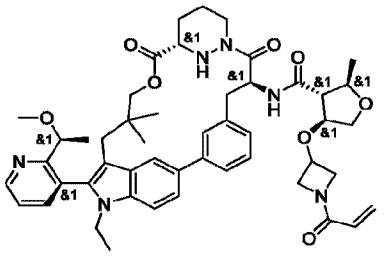
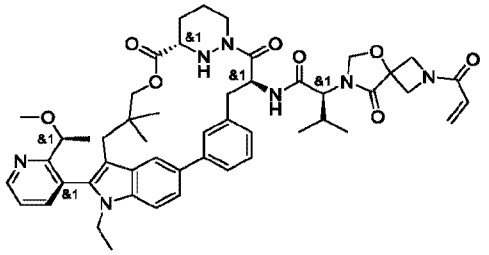
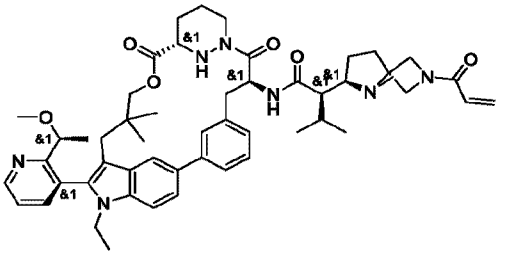
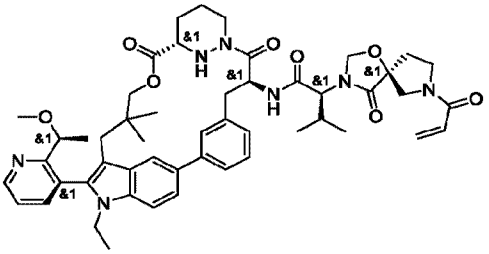
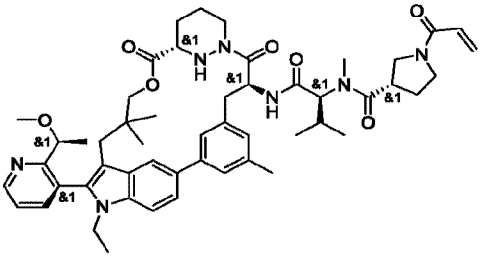
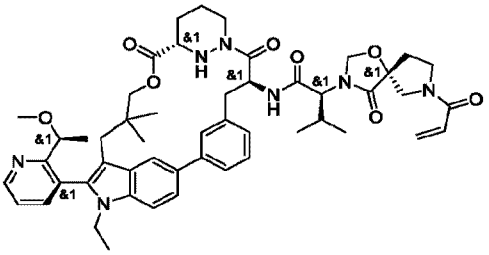
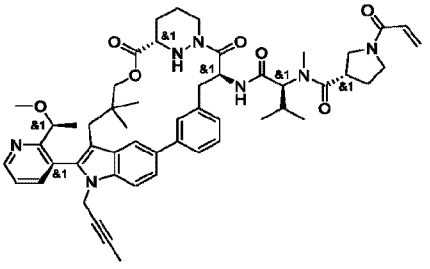
Ex#	Structure	Ex#	Structure
BB 188		BB 361	
BB 189		BB 362	
BB 190		BB 363	
BB 191		BB 364	
BB 192		BB 365	

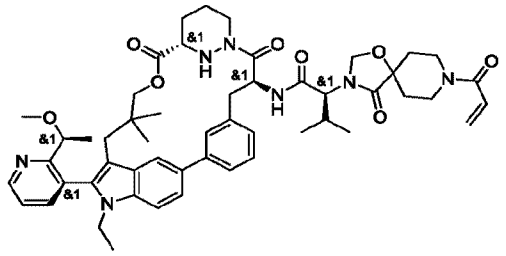
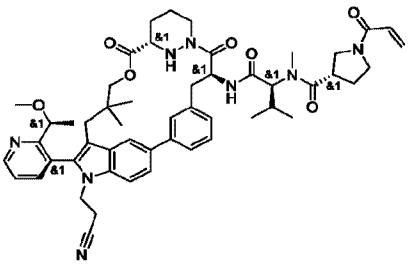
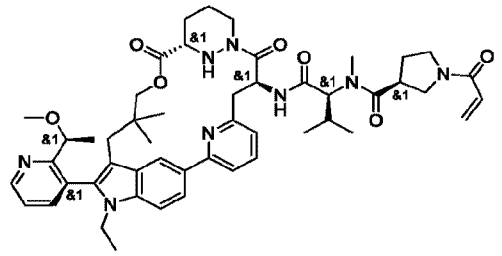
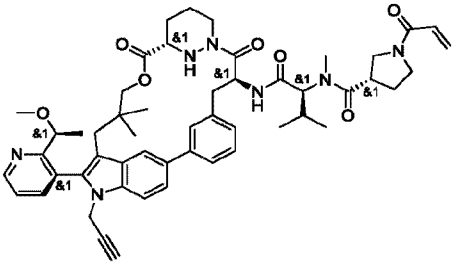
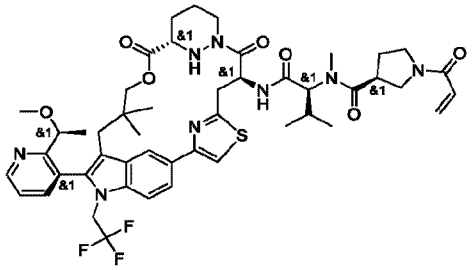
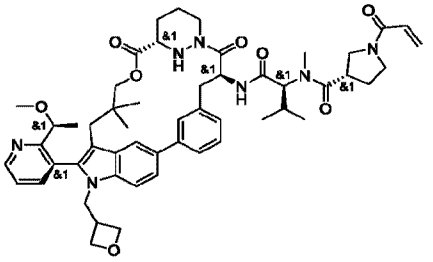
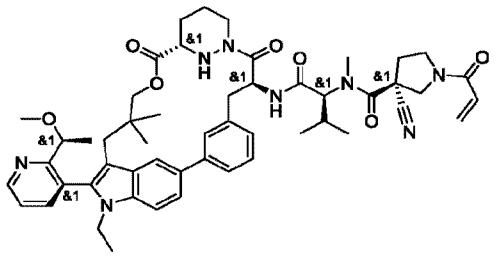
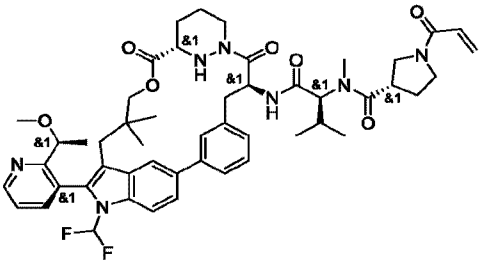
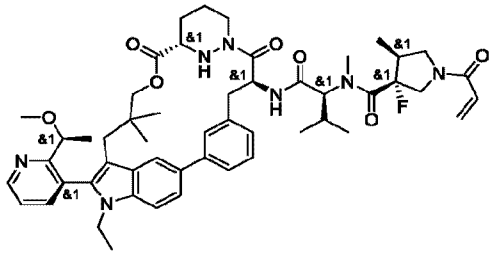
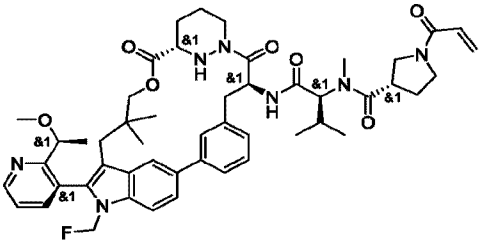
Ex#	Structure	Ex#	Structure
BB 194		BB 366	
BB 195		BB 367	
BB 196		BB 368	
BB 197		BB 369	
BB 198		BB 370	

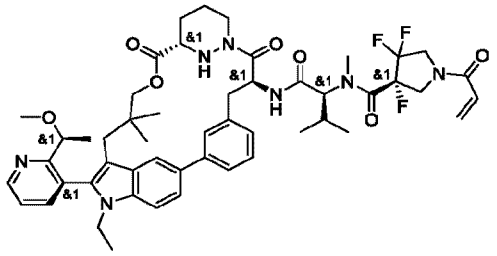
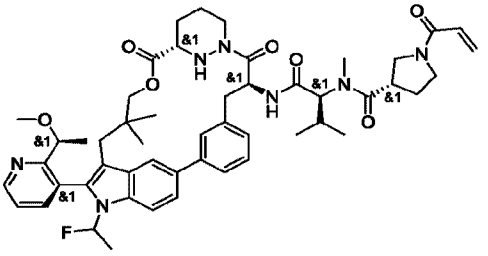
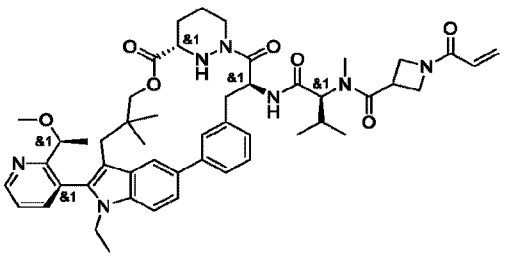
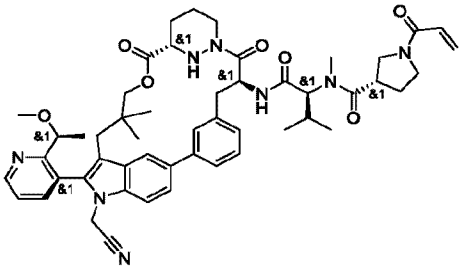
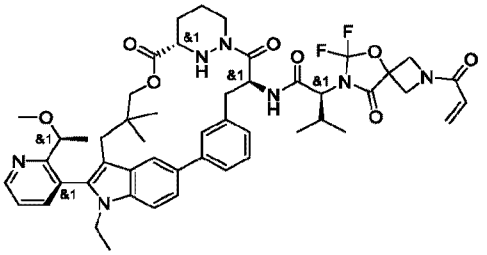
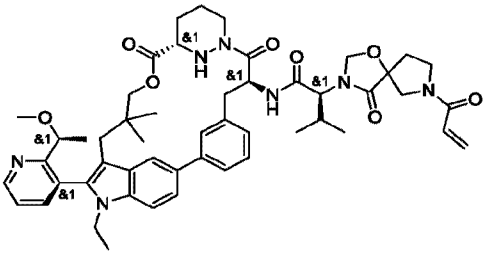
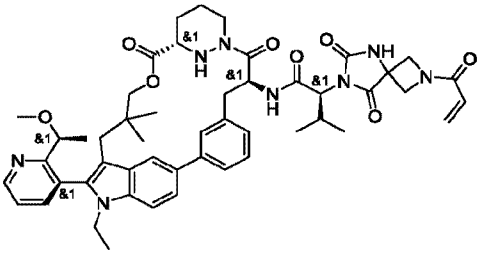
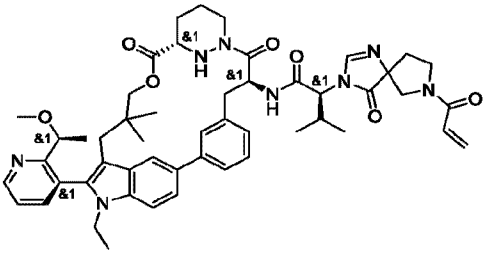
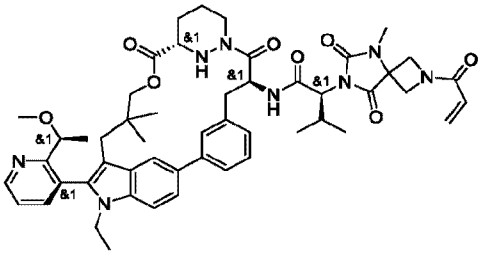
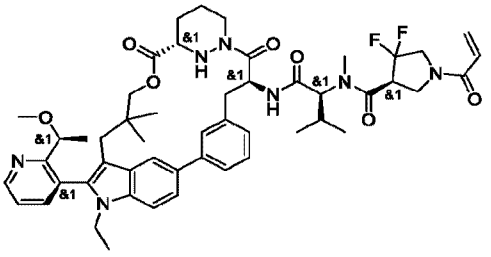
Ex#	Structure	Ex#	Structure
BB 199		BB 371	
BB 200		BB 372	
BB 201		BB 373	
BB 202		BB 374	
BB 203		BB 375	

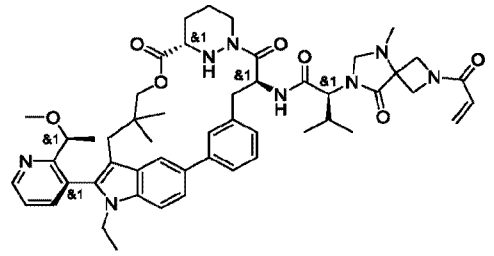
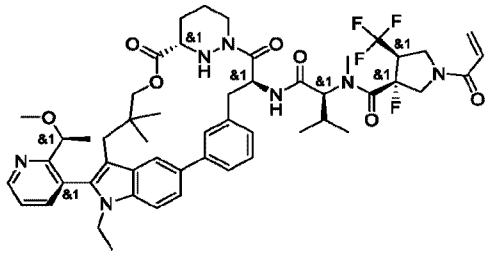
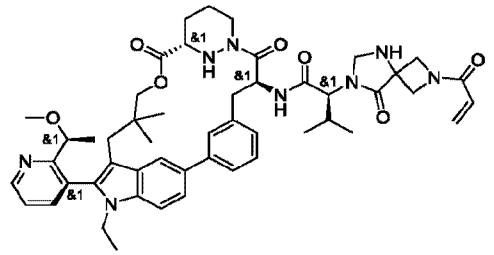
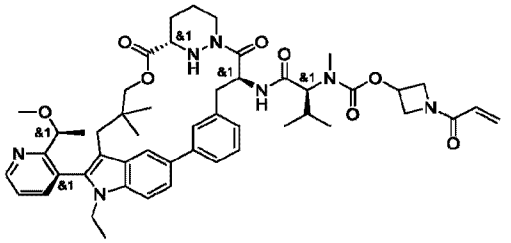
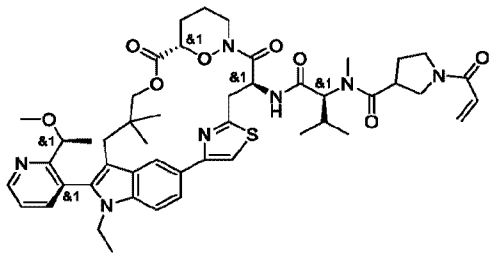
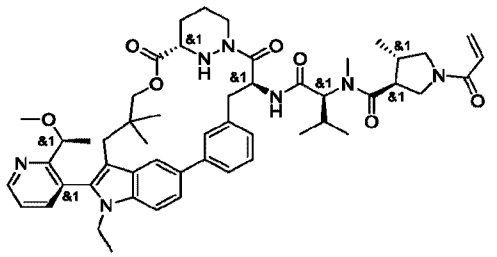
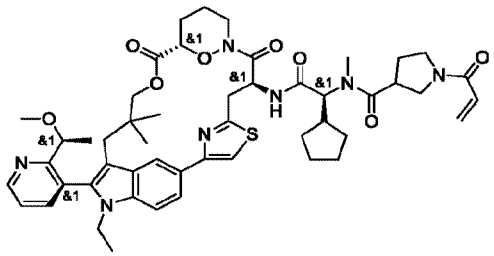
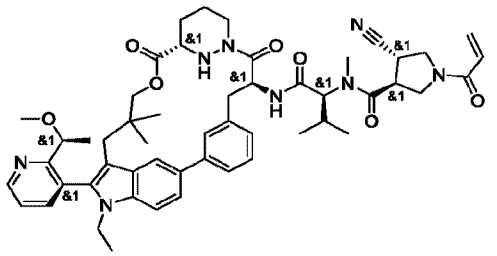
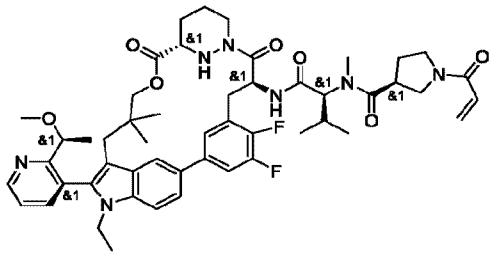
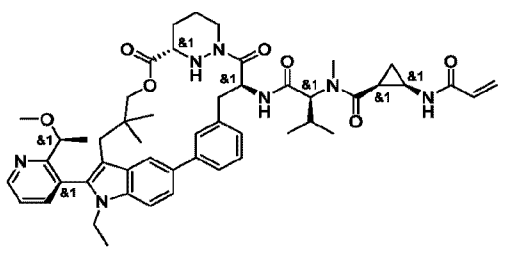
Ex#	Structure	Ex#	Structure
BB 204		BB 376	
BB 205		BB 377	
BB 206		BB 378	
BB 207		BB 379	
BB 208		BB 380	

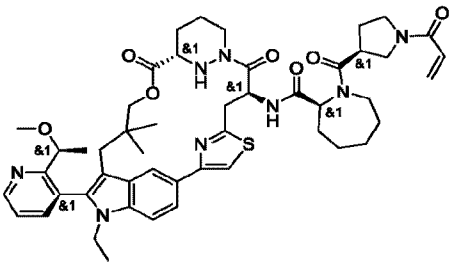
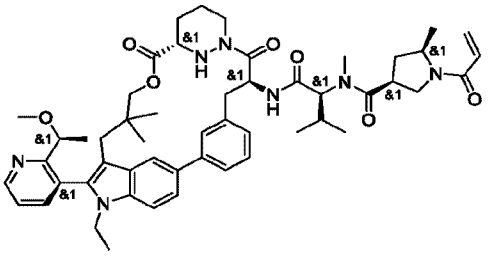
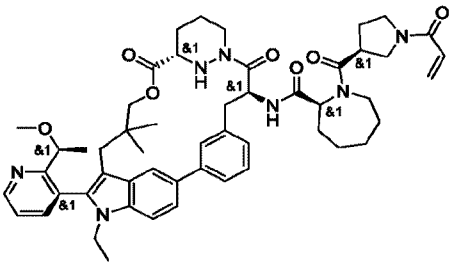
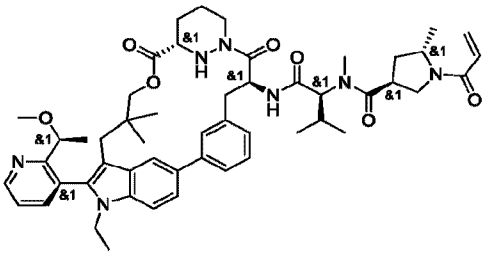
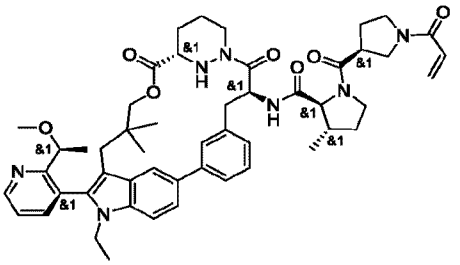
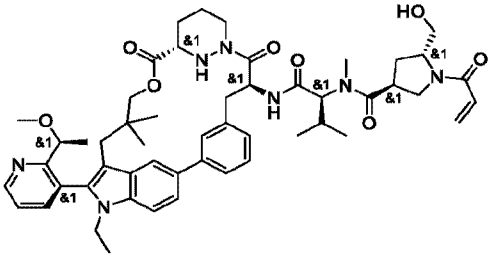
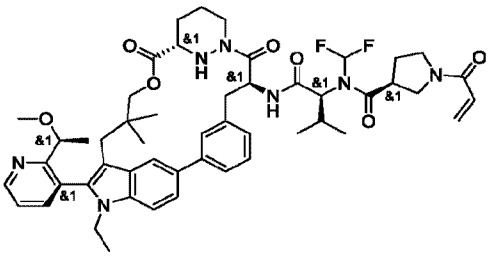
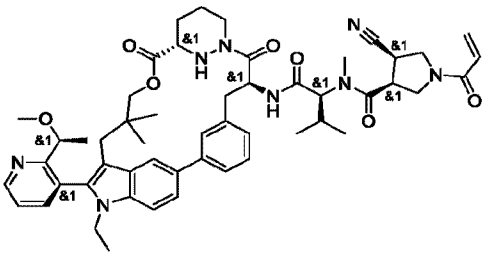
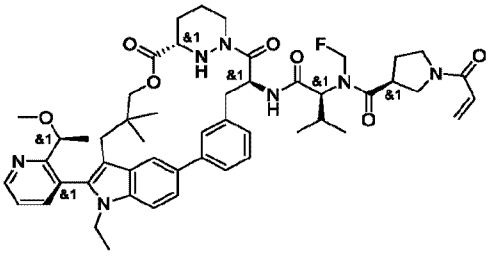
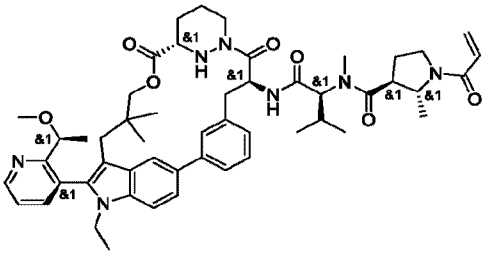
Ex#	Structure	Ex#	Structure
BB 209		BB 381	
BB 210		BB 382	
BB 211		BB 383	
BB 212		BB 384	
BB 213		BB 385	

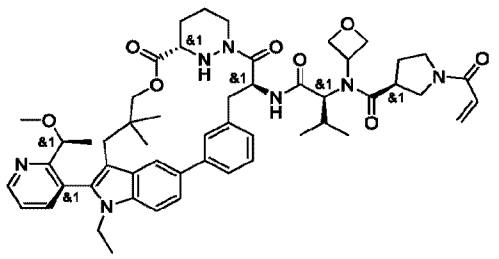
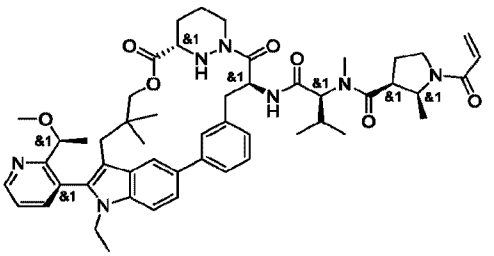
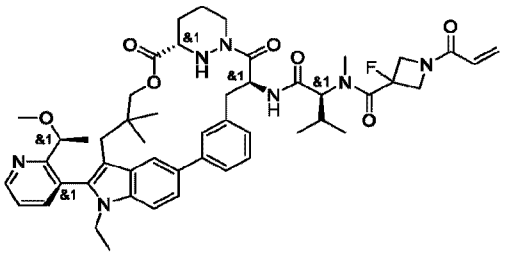
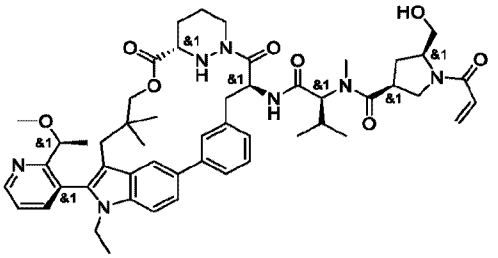
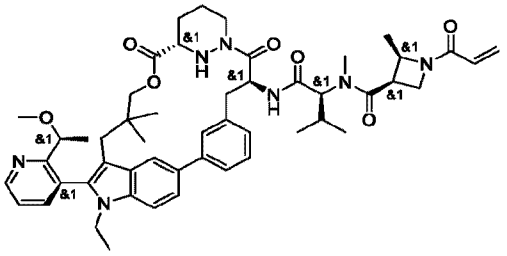
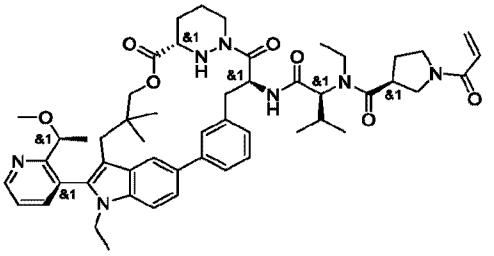
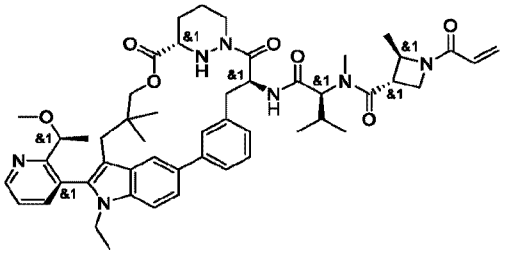
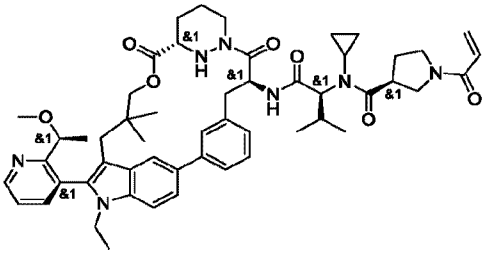
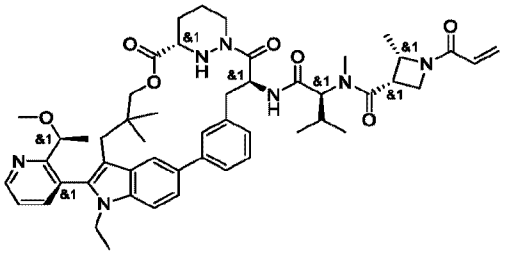
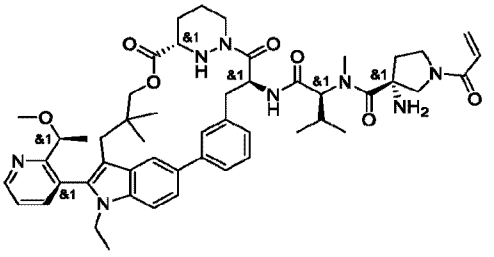
Ex#	Structure	Ex#	Structure
BB 214		BB 386	
BB 215		BB 387	
BB 216		BB 388	
BB 217		BB 389	
BB 218		BB 390	

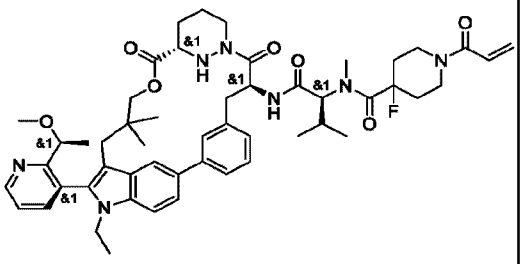
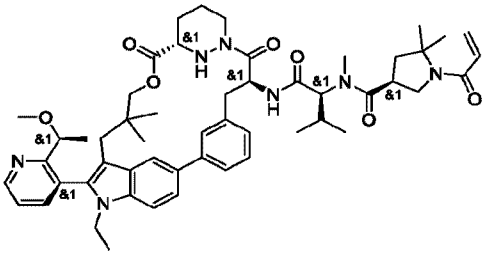
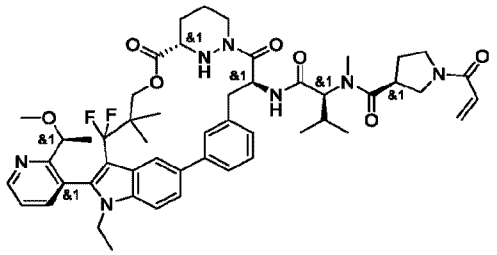
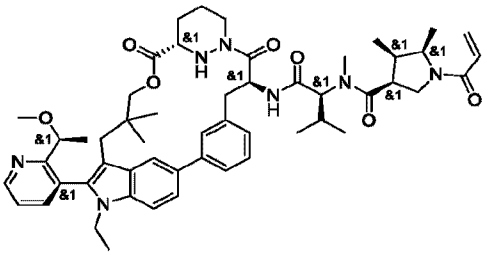
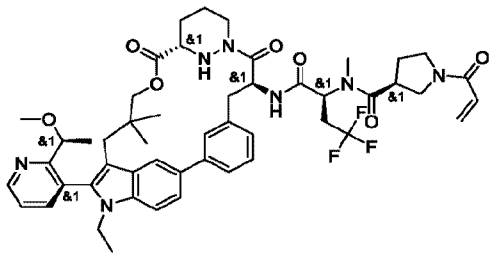
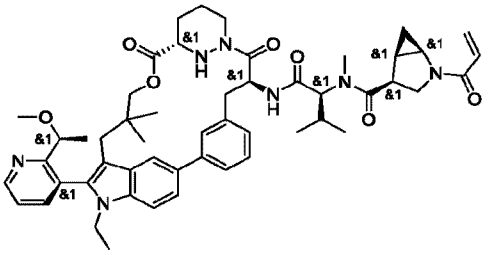
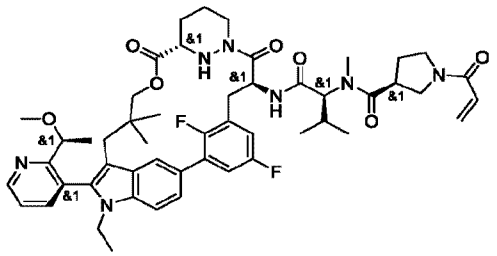
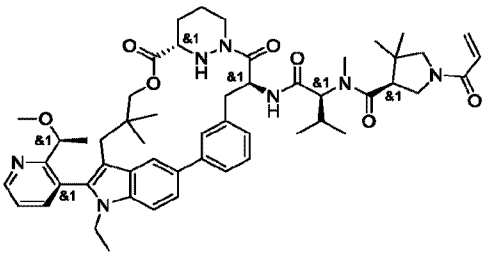
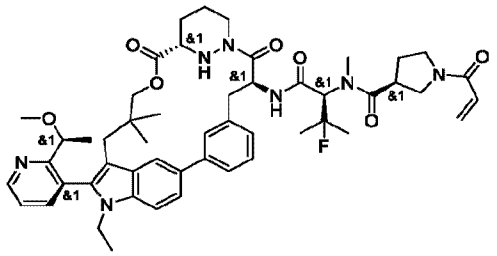
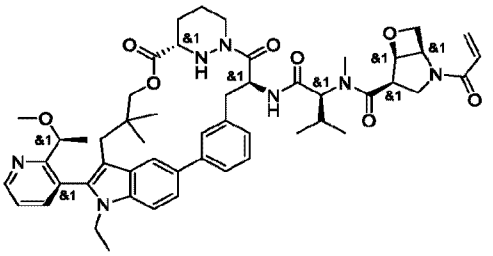
Ex#	Structure	Ex#	Structure
BB 219		BB 391	
BB 220		BB 392	
BB 221		BB 393	
BB 222		BB 394	
BB 223		BB 395	

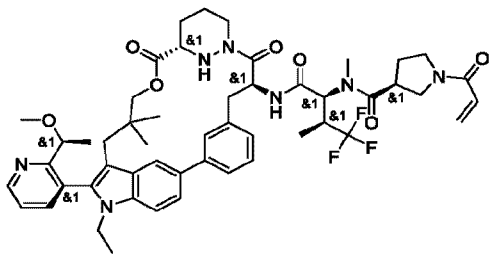
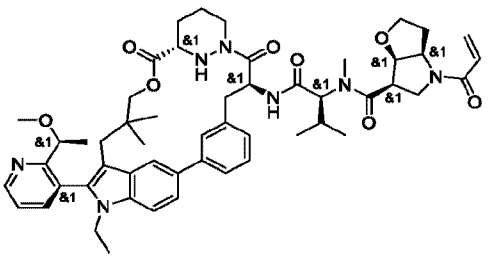
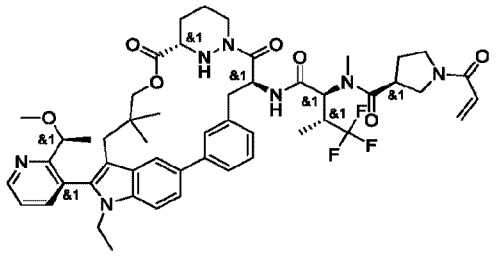
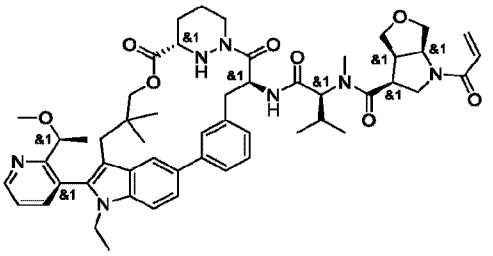
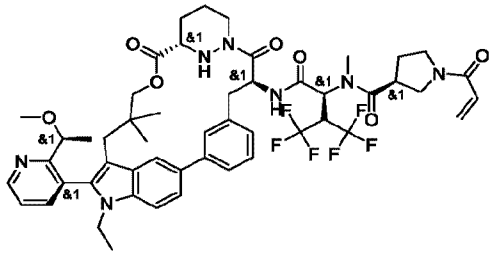
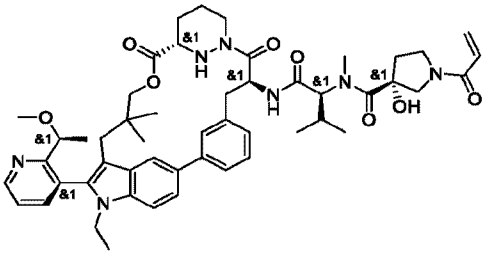
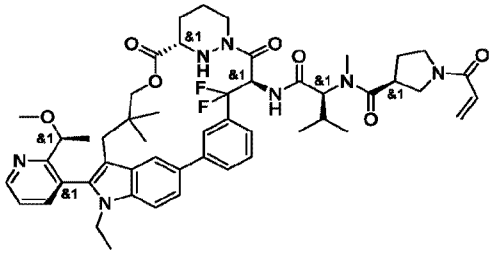
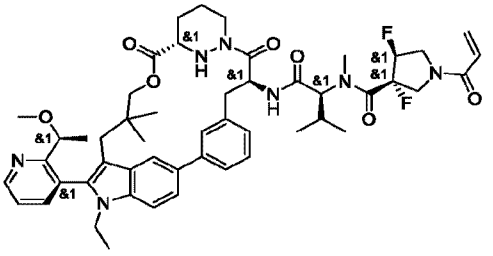
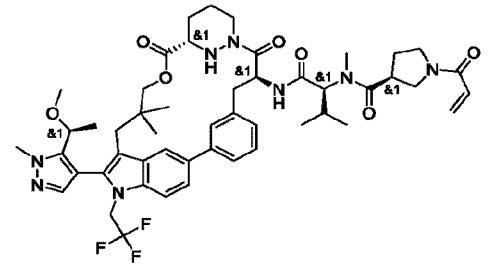
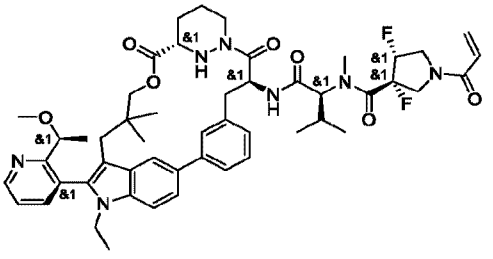
Ex#	Structure	Ex#	Structure
BB 224		BB 396	
BB 225		BB 397	
BB 226		BB 398	
BB 227		BB 399	
BB 228		BB 400	

Ex#	Structure	Ex#	Structure
BB 229		BB 401	
BB 230		BB 402	
BB 231		BB 403	
BB 232		BB 404	
BB 233		BB 405	

Ex#	Structure	Ex#	Structure
BB 234		BB 406	
BB 235		BB 407	
BB 236		BB 408	
BB 237		BB 409	
BB 238		BB 410	

Ex#	Structure	Ex#	Structure
BB 239		BB 411	
BB 240		BB 412	
BB 241		BB 413	
BB 242		BB 414	
BB 243		BB 415	

Ex#	Structure	Ex#	Structure
BB 244		BB 416	
BB 245		BB 417	
BB 246		BB 418	
BB 247		BB 419	
BB 248		BB 420	

Ex#	Structure	Ex#	Structure
BB 249		BB 421	
BB 250		BB 422	
BB 251		BB 423	
BB 252		BB 424	
BB 253		BB 425	

Note that some compounds are shown with bonds as flat or wedged. In some instances, the relative stereochemistry of stereoisomers has been determined; in some instances, the absolute stereochemistry has been determined. All stereoisomers of the compounds of the foregoing table are contemplated by the present invention. In particular embodiments, an atropisomer of a compound of the foregoing table is contemplated.

In some embodiments, the RAS(ON) inhibitor is or acts as a prodrug, such as with respect to administration to a cell or to a subject in need thereof.

Also provided are pharmaceutical compositions comprising a compound of the present invention, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

In some embodiments, the RAS(ON) inhibitor is provided as a conjugate, or salt thereof, comprising the structure of Formula BIV:

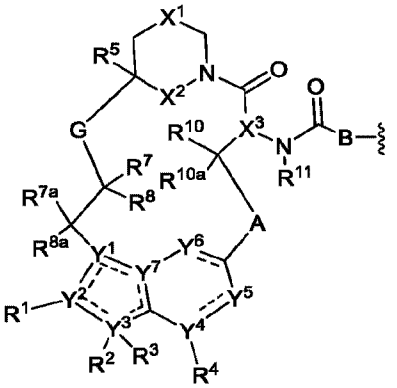
M-L-P

Formula BIV

wherein L is a linker;

P is a monovalent organic moiety; and

M has the structure of Formula BVa:



Formula BVa

wherein the dotted lines represent zero, one, two, three, or four non-adjacent double bonds;

A is -N(H or CH_3)C(O)-(CH_2)- where the amino nitrogen is bound to the carbon atom of -CH(R^{10})-, optionally substituted 3 to 6-membered cycloalkylene, optionally substituted 3 to 6-membered heterocycloalkylene, optionally substituted 6-membered arylene, or optionally substituted 5 to 6-membered heteroarylene;

B is absent, -CH(R^9)-, >C=C$R^9R^{9'}$, or >C$R^9R^{9'}$ where the carbon is bound to the carbonyl carbon of -N(R^{11})C(O)-, optionally substituted 3 to 6-membered cycloalkylene, optionally substituted 3 to 6-membered heterocycloalkylene, optionally substituted 6-membered arylene, or 5 to 6-membered heteroarylene;

G is optionally substituted C_1-C_4 alkylene, optionally substituted C_1-C_4 alkenylene, optionally substituted C_1-C_4 heteroalkylene, -C(O)O-**C**H(R^6)- where **C** is bound to -C(R^7R^8)-, -C(O)NH-**C**H(R^6)- where **C** is bound to -C(R^7R^8)-, optionally substituted C_1-C_4 heteroalkylene, or 3 to 8-membered heteroarylene;

X^1 is optionally substituted C_1-C_2 alkylene, NR, O, or $S(O)_n$;

X^2 is O or NH;

X^3 is N or CH;

n is 0, 1, or 2;

R is hydrogen, cyano, optionally substituted C_1-C_4 alkyl, optionally substituted C_2-C_4 alkenyl, optionally substituted C_2-C_4 alkynyl, C(O)R', C(O)OR', C(O)N(R')$_2$, S(O)R', $S(O)_2$R', or $S(O)_2$N(R')$_2$;

each R' is, independently, H or optionally substituted C_1-C_4 alkyl;

Y^1 is C, CH, or N;

Y^2, Y^3, Y^4, and Y^7 are, independently, C or N;

Y^5 is CH, CH_2, or N;

Y^6 is C(O), CH, CH_2, or N;

R^1 is cyano, 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 cycloalkenyl, optionally substituted 3 to 6-membered heterocycloalkyl, optionally substituted 6 to 10-membered aryl, or optionally substituted 5 to 10-membered heteroaryl, or

R^1 and R^2 combine with the atoms to which they are attached to form an optionally substituted 3 to 14-membered heterocycloalkyl;

R^2 is absent, hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 alkynyl, optionally substituted 3 to 6-membered cycloalkyl, optionally substituted 3 to 7-membered heterocycloalkyl, optionally substituted 6-membered aryl, optionally substituted 5 or 6-membered heteroaryl; R^3 is absent, or

R^2 and R^3 combine with the atom to which they are attached to form an optionally substituted 3 to 8-membered cycloalkyl or optionally substituted 3 to 14-membered heterocycloalkyl;

R^4 is absent, hydrogen, halogen, cyano, or methyl optionally substituted with 1 to 3 halogens;

R^5 is hydrogen, C_1-C_4 alkyl optionally substituted with halogen, cyano, hydroxy, or C_1-C_4 alkoxy, cyclopropyl, or cyclobutyl;

R^6 is hydrogen or methyl; R^7 is hydrogen, halogen, or optionally substituted C_1-C_3 alkyl, or

R^6 and R^7 combine with the carbon atoms to which they are attached to form an optionally substituted 3 to 6-membered cycloalkyl or optionally substituted 3 to 7-membered heterocycloalkyl;

R^8 is hydrogen, halogen, hydroxy, cyano, optionally substituted C_1-C_3 alkoxy, optionally substituted C_1-C_3 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 alkynyl, optionally substituted 3 to 8-membered cycloalkyl, optionally substituted 3 to 14-membered heterocycloalkyl, optionally substituted 5 to 10-membered heteroaryl, or optionally substituted 6 to 10-membered aryl, or

R^7 and R^8 combine with the carbon atom to which they are attached to form $C=CR^{7'}R^{8'}$; C=N(OH), C=N(O-C_1-C_3 alkyl), C=O, C=S, C=NH, optionally substituted 3 to 6-membered cycloalkyl, or optionally substituted 3 to 7-membered heterocycloalkyl;

R^{7a} and R^{8a} are, independently, hydrogen, halo, optionally substituted C_1-C_3 alkyl, or combine with the carbon to which they are attached to form a carbonyl;

$R^{7'}$ is hydrogen, halogen, or optionally substituted C_1-C_3 alkyl; $R^{8'}$ is hydrogen, halogen, hydroxy, cyano, optionally substituted C_1-C_3 alkoxy, optionally substituted C_1-C_3 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 alkynyl, optionally substituted 3 to 8-membered cycloalkyl, optionally substituted 3 to 14-membered heterocycloalkyl, optionally substituted 5 to 10-membered heteroaryl, or optionally substituted 6 to 10-membered aryl, or

$R^{7'}$ and $R^{8'}$ combine with the carbon atom to which they are attached to form optionally substituted 3 to 6-membered cycloalkyl or optionally substituted 3 to 7-membered heterocycloalkyl;

R^9 is H, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted 3 to 6-membered cycloalkyl, or optionally substituted 3 to 7-membered heterocycloalkyl, or

R^9 and L combine with the atoms to which they are attached to form an optionally substituted 3 to 14-membered heterocycloalkyl;

$R^{9'}$ is hydrogen or optionally substituted C_1-C_6 alkyl; or

R^9 and $R^{9'}$, combined with the atoms to which they are attached, form a 3 to 6-membered cycloalkyl or a 3 to 6-membered heterocycloalkyl;

R^{10} is hydrogen, halo, hydroxy, C_1-C_3 alkoxy, or C_1-C_3 alkyl;

R^{10a} is hydrogen or halo; and

R^{11} is hydrogen or C_1-C_3 alkyl.

In some embodiments the conjugate, or salt thereof, comprises the structure of Formula BIV:

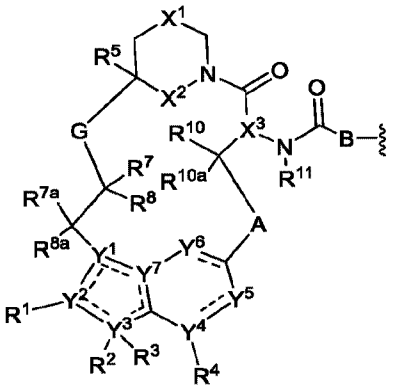
M-L-P

Formula BIV

wherein L is a linker;

P is a monovalent organic moiety; and

M has the structure of Formula BVb:



Formula BVb

wherein the dotted lines represent zero, one, two, three, or four non-adjacent double bonds;

A is -N(H or CH_3)C(O)-(CH_2)- where the amino nitrogen is bound to the carbon atom of -CH(R^{10})-, optionally substituted 3 to 6-membered cycloalkylene, optionally substituted 3 to 6-membered heterocycloalkylene, optionally substituted 6-membered arylene, or optionally substituted 5 to 6-membered heteroarylene;

B is -CH(R^9)- or >C=C$R^9R^{9'}$ where the carbon is bound to the carbonyl carbon of -N(R^{11})C(O)-, optionally substituted 3 to 6-membered cycloalkylene, optionally substituted 3 to 6-membered heterocycloalkylene, optionally substituted 6-membered arylene, or 5 to 6-membered heteroarylene;

G is optionally substituted C_1-C_4 alkylene, optionally substituted C_1-C_4 alkenylene, optionally substituted C_1-C_4 heteroalkylene, -C(O)O-**C**H(R^6)- where **C** is bound to -C(R^7R^8)-, -C(O)NH-**C**H(R^6)- where **C** is bound to -C(R^7R^8)-, optionally substituted C_1-C_4 heteroalkylene, or 3 to 8-membered heteroarylene;

X^1 is optionally substituted C_1-C_2 alkylene, NR, O, or $S(O)_n$;

X^2 is O or NH;

X^3 is N or CH;

n is 0, 1, or 2;

R is hydrogen, cyano, optionally substituted C_1-C_4 alkyl, optionally substituted C_2-C_4 alkenyl, optionally substituted C_2-C_4 alkynyl, C(O)R', C(O)OR', C(O)N(R')$_2$, S(O)R', S(O)$_2$R', or S(O)$_2$N(R')$_2$;

each R' is, independently, H or optionally substituted C_1-C_4 alkyl;

Y^1 is C, CH, or N;

Y^2, Y^3, Y^4, and Y^7 are, independently, C or N;

Y^5 is CH, CH_2, or N;

Y^6 is C(O), CH, CH_2, or N;

R^1 is cyano, 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 cycloalkenyl, optionally substituted 3 to 6-membered heterocycloalkyl, optionally substituted 6 to 10-membered aryl, or optionally substituted 5 to 10-membered heteroaryl, or

R^1 and R^2 combine with the atoms to which they are attached to form an optionally substituted 3 to 14-membered heterocycloalkyl;

R^2 is absent, hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 alkynyl, optionally substituted 3 to 6-membered cycloalkyl, optionally substituted 3 to 7-membered heterocycloalkyl, optionally substituted 6-membered aryl, optionally substituted 5 or 6-membered heteroaryl; R^3 is absent, or

R^2 and R^3 combine with the atom to which they are attached to form an optionally substituted 3 to 8-membered cycloalkyl or optionally substituted 3 to 14-membered heterocycloalkyl;

R^4 is absent, hydrogen, halogen, cyano, or methyl optionally substituted with 1 to 3 halogens;

R^5 is hydrogen, C_1-C_4 alkyl optionally substituted with halogen, cyano, hydroxy, or C_1-C_4 alkoxy, cyclopropyl, or cyclobutyl;

R^6 is hydrogen or methyl; R^7 is hydrogen, halogen, or optionally substituted C_1-C_3 alkyl, or

R^6 and R^7 combine with the carbon atoms to which they are attached to form an optionally substituted 3 to 6-membered cycloalkyl or optionally substituted 3 to 7-membered heterocycloalkyl;

R^8 is hydrogen, halogen, hydroxy, cyano, optionally substituted C_1-C_3 alkoxy, optionally substituted C_1-C_3 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 alkynyl, optionally substituted 3 to 8-membered cycloalkyl, optionally substituted 3 to 14-membered heterocycloalkyl, optionally substituted 5 to 10-membered heteroaryl, or optionally substituted 6 to 10-membered aryl, or

R^7 and R^8 combine with the carbon atom to which they are attached to form $C=CR^{7'}R^{8'}$; C=N(OH), C=N(O-C_1-C_3 alkyl), C=O, C=S, C=NH, optionally substituted 3 to 6-membered cycloalkyl, or optionally substituted 3 to 7-membered heterocycloalkyl;

R^{7a} and R^{8a} are, independently, hydrogen, halo, optionally substituted C_1-C_3 alkyl, or combine with the carbon to which they are attached to form a carbonyl;

$R^{7'}$ is hydrogen, halogen, or optionally substituted C_1-C_3 alkyl; $R^{8'}$ is hydrogen, halogen, hydroxy, cyano, optionally substituted C_1-C_3 alkoxy, optionally substituted C_1-C_3 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 alkynyl, optionally substituted 3 to 8-membered cycloalkyl, optionally substituted 3 to 14-membered heterocycloalkyl, optionally substituted 5 to 10-membered heteroaryl, or optionally substituted 6 to 10-membered aryl, or

$R^{7'}$ and $R^{8'}$ combine with the carbon atom to which they are attached to form optionally substituted 3 to 6-membered cycloalkyl or optionally substituted 3 to 7-membered heterocycloalkyl;

R^9 is optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted 3 to 6-membered cycloalkyl, or optionally substituted 3 to 7-membered heterocycloalkyl, or

R^9 and L combine with the atoms to which they are attached to form an optionally substituted 3 to 14-membered heterocycloalkyl;

$R^{9'}$ is hydrogen or optionally substituted C_1-C_6 alkyl;

R^{10} is hydrogen, halo, hydroxy, C_1-C_3 alkoxy, or C_1-C_3 alkyl;

R^{10a} is hydrogen or halo; and

R^{11} is hydrogen or C_1-C_3 alkyl.

In some embodiments, the conjugate has the structure of Formula BIV:

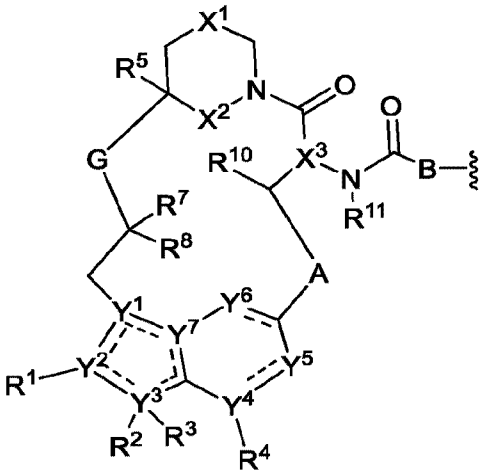
M-L-P

Formula BIV

wherein L is a linker;

P is a monovalent organic moiety; and

M has the structure of Formula BVc:



Formula BVc

wherein the dotted lines represent zero, one, two, three, or four non-adjacent double bonds;

A is -N(H or CH_3)C(O)-(CH_2)- where the amino nitrogen is bound to the carbon atom of -CH(R^{10})-, optionally substituted 3 to 6-membered cycloalkylene, optionally substituted 3 to 6-membered heterocycloalkylene, optionally substituted 6-membered arylene, or optionally substituted 5 to 6-membered heteroarylene;

B is -CH(R^9)- where the carbon is bound to the carbonyl carbon of -N(R^{11})C(O)-, optionally substituted 3 to 6-membered cycloalkylene, optionally substituted 3 to 6-membered heterocycloalkylene, optionally substituted 6-membered arylene, or 5 to 6-membered heteroarylene;

G is optionally substituted C_1-C_4 alkylene, optionally substituted C_1-C_4 alkenylene, optionally substituted C_1-C_4 heteroalkylene, -C(O)O-**C**H(R^6)- where **C** is bound to -C(R^7R^8)-, -C(O)NH-**C**H(R^6)- where **C** is bound to -C(R^7R^8)-, optionally substituted C_1-C_4 heteroalkylene, or 3 to 8-membered heteroarylene;

X^1 is optionally substituted C_1-C_2 alkylene, NR, O, or $S(O)_n$;

X^2 is O or NH;

X^3 is N or CH;

n is 0, 1, or 2;

R is hydrogen, cyano, optionally substituted C_1-C_4 alkyl, optionally substituted C_2-C_4 alkenyl, optionally substituted C_2-C_4 alkynyl, C(O)R', C(O)OR', C(O)N(R')$_2$, S(O)R', S(O)$_2$R', or S(O)$_2$N(R')$_2$;

each R' is, independently, H or optionally substituted C_1-C_4 alkyl;

Y^1 is C, CH, or N;

Y^2, Y^3, Y^4, and Y^7 are, independently, C or N;

Y^5 and Y^6 are, independently, CH or N;

R^1 is cyano, 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 cycloalkenyl, optionally substituted 3 to 6-membered heterocycloalkyl, optionally substituted 6 to 10-membered aryl, or optionally substituted 5 to 10-membered heteroaryl;

R^2 is hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted 3 to 6-membered cycloalkyl, optionally substituted 3 to 7-membered heterocycloalkyl, optionally substituted 6-membered aryl, optionally substituted 5 or 6-membered heteroaryl; R^3 is absent, or

R^2 and R^3 combine with the atom to which they are attached to form an optionally substituted 3 to 8-membered cycloalkyl or optionally substituted 3 to 14-membered heterocycloalkyl;

R^4 is absent, hydrogen, halogen, cyano, or methyl optionally substituted with 1 to 3 halogens;

R^5 is hydrogen, C_1-C_4 alkyl optionally substituted with halogen, cyano, hydroxy, or C_1-C_4 alkoxy, cyclopropyl, or cyclobutyl;

R^6 is hydrogen or methyl; R^7 is hydrogen, halogen, or optionally substituted C_1-C_3 alkyl, or

R^6 and R^7 combine with the carbon atoms to which they are attached to form an optionally substituted 3 to 6-membered cycloalkyl or optionally substituted 3 to 7-membered heterocycloalkyl;

R^8 is hydrogen, halogen, hydroxy, cyano, optionally substituted C_1-C_3 alkoxy, optionally substituted C_1-C_3 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 alkynyl, optionally substituted 3 to 8-membered cycloalkyl, optionally substituted 3 to 14-membered heterocycloalkyl, optionally substituted 5 to 10-membered heteroaryl, or optionally substituted 6 to 10-membered aryl, or

R^7 and R^8 combine with the carbon atom to which they are attached to form $C=CR^{7'}R^{8'}$; C=N(OH), C=N(O-C_1-C_3 alkyl), C=O, C=S, C=NH, optionally substituted 3 to 6-membered cycloalkyl, or optionally substituted 3 to 7-membered heterocycloalkyl;

$R^{7'}$ is hydrogen, halogen, or optionally substituted C_1-C_3 alkyl; $R^{8'}$ is hydrogen, halogen, hydroxy, cyano, optionally substituted C_1-C_3 alkoxy, optionally substituted C_1-C_3 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 alkynyl, optionally substituted 3 to 8-membered cycloalkyl, optionally substituted 3 to 14-membered heterocycloalkyl, optionally substituted 5 to 10-membered heteroaryl, or optionally substituted 6 to 10-membered aryl, or

$R^{7'}$ and $R^{8'}$ combine with the carbon atom to which they are attached to form optionally substituted 3 to 6-membered cycloalkyl or optionally substituted 3 to 7-membered heterocycloalkyl;

R^9 is optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted 3 to 6-membered cycloalkyl, or optionally substituted 3 to 7-membered heterocycloalkyl;

R^{10} is hydrogen, hydroxy, C_1-C_3 alkoxy, or C_1-C_3 alkyl; and

R^{11} is hydrogen or C_1-C_3 alkyl.

In some embodiments, the RAS(ON) inhibitor has the structure of of Formula BIV:

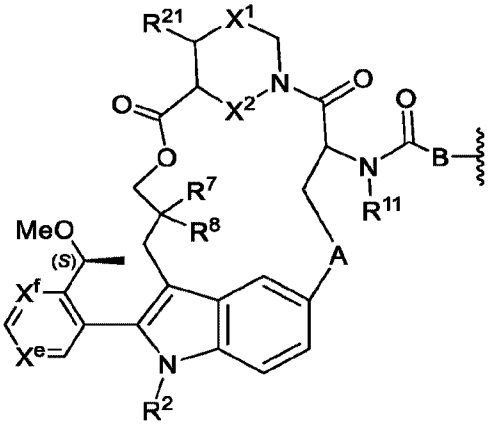
M-L-P

Formula BIV

wherein L is a linker;

P is a monovalent organic moiety; and

M has the structure of Formula BVd:



Formula BVd

wherein A optionally substituted 3 to 6-membered cycloalkylene, optionally substituted 3 to 6-membered heterocycloalkylene, optionally substituted 6-membered arylene (e.g., phenyl or phenol), or optionally substituted 5 to 6-membered heteroarylene;

B is -CH(R^9)- where the carbon is bound to the carbonyl carbon of -NHC(O)-, optionally substituted 3 to 6-membered cycloalkylene, optionally substituted 3 to 6-membered heterocycloalkylene, optionally substituted 6-membered arylene, or 5 to 6-membered heteroarylene;

X^1 is optionally substituted C_1-C_2 alkylene, NR, O, or $S(O)_n$;

X^2 is O or NH;

n is 0, 1, or 2;

R is hydrogen, cyano, optionally substituted C_1-C_4 alkyl, optionally substituted C_2-C_4 alkenyl, optionally substituted C_2-C_4 alkynyl, C(O)R', C(O)OR', $C(O)N(R')_2$, S(O)R', $S(O)_2R'$, or $S(O)_2N(R')_2$;

each R' is, independently, H or optionally substituted C_1-C_4 alkyl;

R^2 is C_1-C_6 alkyl, C_1-C_6 fluoroalkyl, or 3 to 6-membered cycloalkyl;

R^7 is C_1-C_3 alkyl;

R^8 is C_1-C_3 alkyl; and

R^9 is optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted 3 to 6-membered cycloalkyl, or optionally substituted 3 to 7-membered heterocycloalkyl;

X^e and X^f are, independently, N or CH;

R^{11} is hydrogen or C_1-C_3 alkyl; and

R^{21} is hydrogen or C_1-C_3 alkyl.

In some embodiments of formula BI and subformula thereof, X^e is N and X^f is CH. In some embodiments, X^e is CH and X^f is N.

In some embodiments, the RAS(ON) inhibitor has the structure of of Formula BIV:

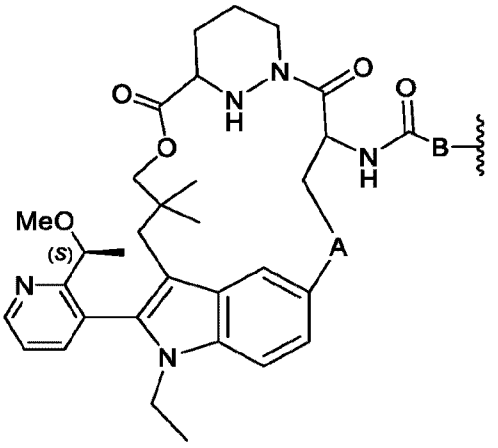
M-L-P

Formula BIV

wherein L is a linker;

P is a monovalent organic moiety; and

M has the structure of Formula BVe:



Formula BVe

wherein A is optionally substituted 3 to 6-membered cycloalkylene, optionally substituted 3 to 6-membered heterocycloalkylene, optionally substituted 6-membered arylene (e.g., phenyl or phenol), or optionally substituted 5 to 6-membered heteroarylene;

B is -CH(R^9)- where the carbon is bound to the carbonyl carbon of -NHC(O)-, optionally substituted 3 to 6-membered cycloalkylene, optionally substituted 3 to 6-membered heterocycloalkylene, optionally substituted 6-membered arylene, or 5 to 6-membered heteroarylene; and

R^9 is optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted 3 to 6-membered cycloalkyl, or optionally substituted 3 to 7-membered heterocycloalkyl.

In some embodiments of a conjugate of Formula BIV, the linker has the structure of Formula BII:

$$A^1\text{-}(B^1)_f\text{-}(C^1)_g\text{-}(B^2)_h\text{-}(D^1)\text{-}(B^3)_i\text{-}(C^2)_j\text{-}(B^4)_k\text{–}A^2$$

Formula BII

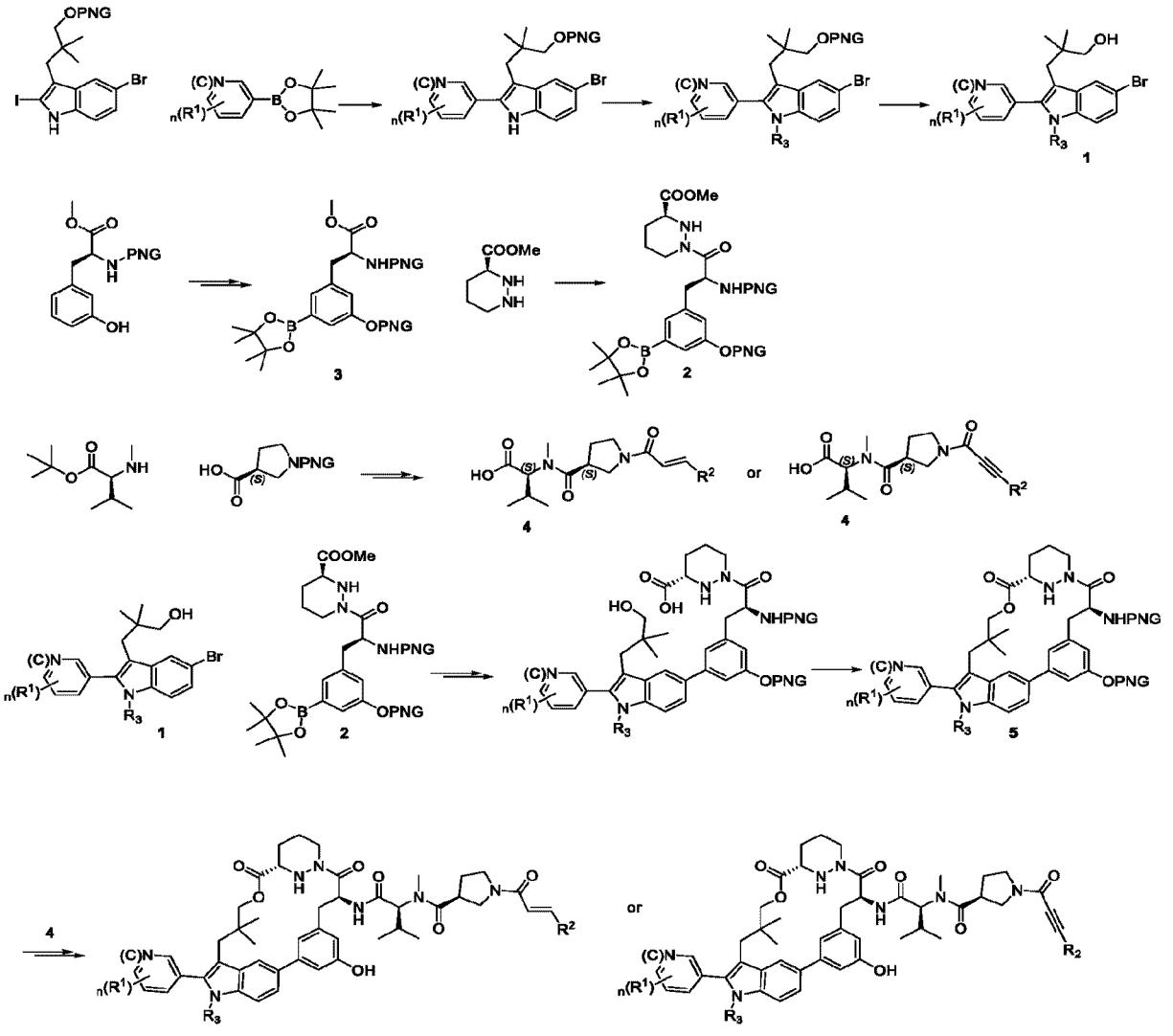
where A^1 is a bond between the linker and B; A^2 is a bond between P and the linker; B^1, B^2, B^3, and B^4 each, independently, is selected from optionally substituted C_1-C_2 alkylene, optionally substituted C_1-C_3 heteroalkylene, O, S, and NR^N; R^N is hydrogen, optionally substituted C_1-C_4 alkyl, 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; C^1 and C^2 are each, independently, selected from carbonyl, thiocarbonyl, sulphonyl, or phosphoryl; f, g, h, i, j, and k are each, independently, 0 or 1; and D^1 is optionally substituted C_1-C_{10} alkylene, optionally substituted C_2-C_{10} alkenylene, optionally substituted C_2-C_{10} alkynylene, optionally substituted 3 to 14-membered heterocycloalkylene, optionally substituted 5 to 10-membered heteroarylene, optionally substituted 3 to 8-membered cycloalkylene, optionally substituted 6 to 10-membered arylene, optionally substituted C_2-C_{10} polyethylene glycolene, or optionally substituted C_1-C_{10} heteroalkylene, or a chemical bond linking $A^1\text{-}(B^1)_f\text{-}(C^1)_g\text{-}(B^2)_h$- to -$(B^3)_i\text{-}(C^2)_j\text{-}(B^4)_k\text{–}A^2$.

In some embodiments of a conjugate of formula BIV, the monovalent organic moiety is a protein, such as a Ras protein. In some embodiments, the Ras protein is K-Ras G12C, K-Ras G13C, H-Ras G12C, H-Ras G13C, N-Ras G12C, or N-Ras G13C. Other Ras proteins are described herein. In some embodiments, 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. In some embodiments, the linker is bound to

the monovalent organic moiety through a bond to a carboxyl group of an amino acid residue of the monovalent organic moiety.

The compounds described in Tables B1 and B2 may be made from commercially available starting materials or synthesized using known organic, inorganic, or enzymatic processes. The compounds of the present invention can be prepared in a number of ways well known to those skilled in the art of organic synthesis. By way of example, compounds of the present invention can be synthesized using the methods described in the Schemes below, together with synthetic methods known in the art of synthetic organic chemistry, or variations thereon as appreciated by those skilled in the art. These methods include but are not limited to those methods described in the Schemes below or as described in WO 2021/091982.

Scheme B1. General synthesis of macrocyclic esters



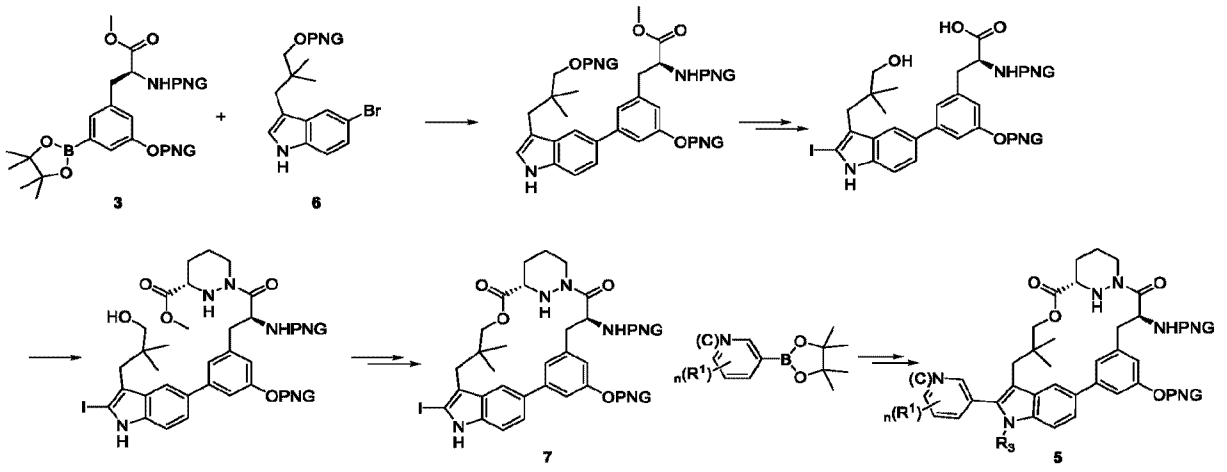
A general synthesis of macrocyclic esters is outlined in Scheme B1. An appropriately substituted aryl-3-(5-bromo-1-ethyl-1H-indol-3-yl)-2,2-dimethylpropan-1-ol (**1**) can be prepared in three steps starting

from protected 3-(5-bromo-2-iodo-1H-indol-3-yl)-2,2-dimethylpropan-1-ol and appropriately substituted boronic acid, including palladium mediated coupling, alkylation, and de-protection reactions. Methyl-amino-hexahydropyridazine-3-carboxylate-boronic ester (**2**) can be prepared in three steps, including protection, iridium catalyst mediated borylation, and coupling with methyl methyl (*S*)-hexahydropyridazine-3-carboxylate.

An appropriately substituted acetylpyrrolidine-3-carbonyl-N-methyl-L-valine (or an alternative aminoacid derivative (**4**) can be made by coupling of methyl-L-valinate and protected (*S*)-pyrrolidine-3-carboxylic acid, followed by deprotection, coupling with a carboxylic acid containing an appropriately substituted Michael acceptor, and a hydrolysis step.

The final macrocyclic esters can be made by coupling of methyl-amino-hexahydropyridazine-3-carboxylate-boronic ester (**2**) and aryl-3-(5-bromo-1-ethyl-1H-indol-3-yl)-2,2-dimethylpropan-1-ol (**1**) in the presence of a Pd catalyst followed by hydrolysis and macrolactonization steps to result in an appropriately protected macrocyclic intermediate (**5**). Deprotection and coupling with an appropriately substituted intermediate **4** results in a macrocyclic product. Additional deprotection and/or functionalization steps can be required to produce the final compound.

Scheme B2. Alternative general synthesis of macrocyclic esters



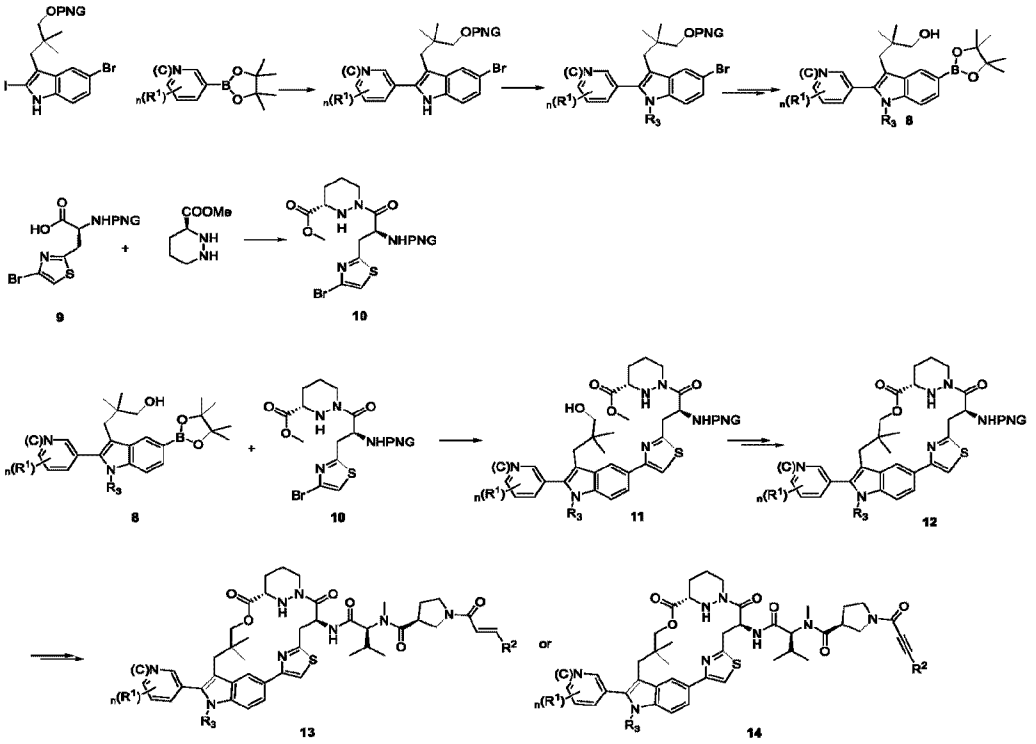
Alternatively, macrocyclic ester can be prepared as described in Scheme B2. An appropriately protected bromo-indolyl (**6**) coupled in the presence of a Pd catalyst with boronic ester (**3**), followed by iodination, deprotection, and ester hydrolysis. Subsequent coupling with methyl (*S*)-hexahydropyridazine-3-carboxylate, followed by hydrolysis and macrolactonization can result in iodo intermediate (**7**). Coupling in the presence of a Pd catalyst with an appropriately substituted boronic ester and alkylation can yield fully protected macrocycle (**5**). Additional deprotection or functionalization steps are required to produce the final compound.

In addition, compounds of the disclosure can be synthesized using the methods described in the Examples below or as described in WO 2021/091982, together with synthetic methods known in the art of synthetic organic chemistry, or variations thereon as appreciated by those skilled in the art. These methods include but are not limited to those methods described in the Examples below. For example, a

person of skill in the art would be able to install into a macrocyclic ester a desired -B-L-W group of a compound of Formula (BI), where B, L and W are defined herein, including by using methods exemplified in the Example section herein and in WO 2021/091982.

Compounds of Table B1 herein were prepared using methods disclosed herein or were prepared using methods disclosed herein combined with the knowledge of one of skill in the art. Compounds of Table B2 may be prepared using methods disclosed herein or may be prepared using methods disclosed herein combined with the knowledge of one of skill in the art.

Scheme B3. General synthesis of macrocyclic esters

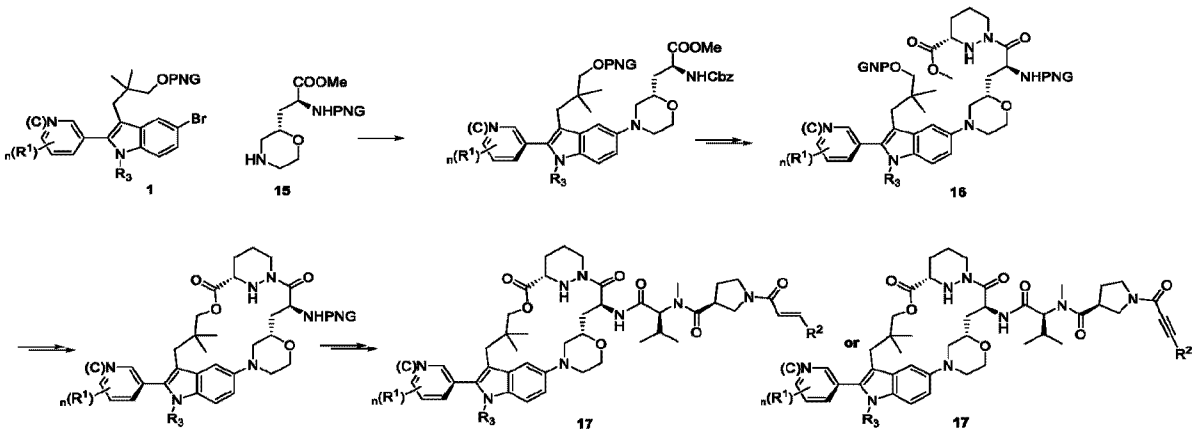


An alternative general synthesis of macrocyclic esters is outlined in Scheme B3. An appropriately substituted indolyl boronic ester (**8**) can be prepared in four steps starting from protected 3-(5-bromo-2-iodo-1H-indol-3-yl)-2,2-dimethylpropan-1-ol and appropriately substituted boronic acid, including Palladium mediated coupling, alkylation, de-protection, and Palladium mediated borylation reactions.

Methyl-amino-3-(4-bromothiazol-2-yl)propanoyl)hexahydropyridazine-3-carboxylate (**10**) can be prepared via coupling of (S)-2-amino-3-(4-bromothiazol-2-yl)propanoic acid (**9**) with methyl (*S*)-hexahydropyridazine-3-carboxylate.

The final macrocyclic esters can be made by coupling of Methyl-amino-3-(4-bromothiazol-2-yl)propanoyl)hexahydropyridazine-3-carboxylate (**10**) and an appropriately substituted indolyl boronic ester (**8**) in the presence of Pd catalyst followed by hydrolysis and macrolactonization steps to result in an appropriately protected macrocyclic intermediate (**11**). Deprotection and coupling with an appropriately substituted intermediate **4** can result in a macrocyclic product. Additional deprotection or functionalization steps could be required to produce a final compound **13 or 14**.

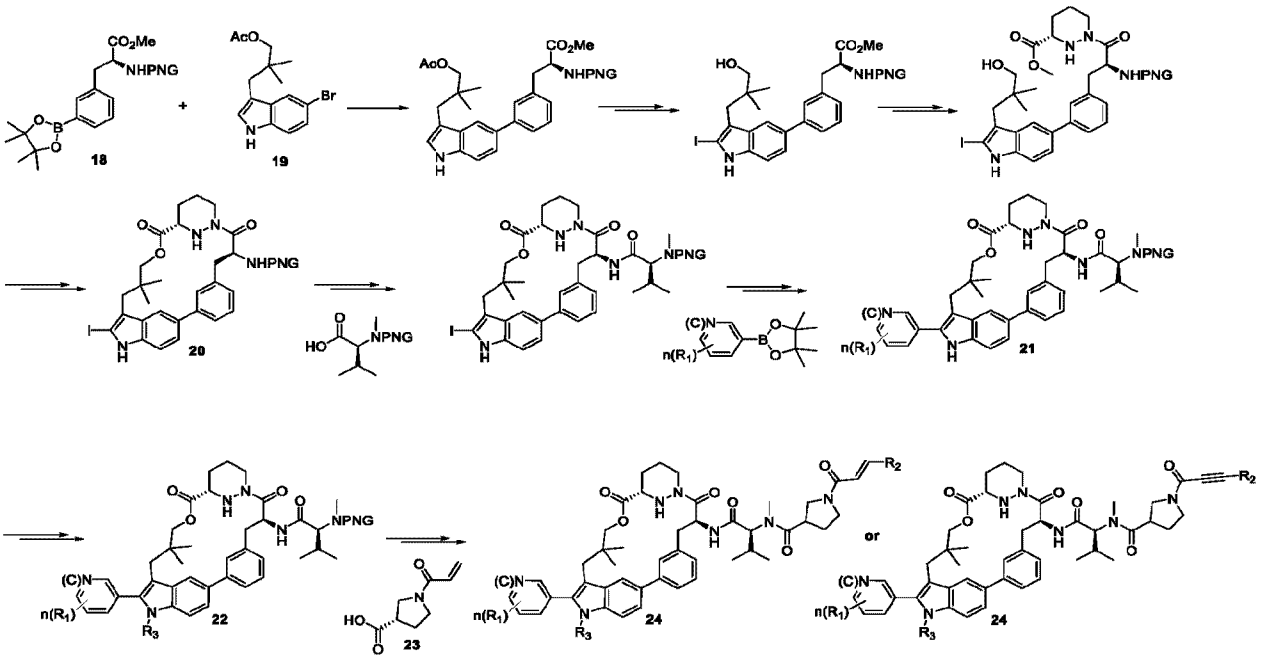
Scheme B4. General synthesis of macrocyclic esters



An alternative general synthesis of macrocyclic esters is outlined in Scheme B4. An appropriately substituted morpholine or an alternative heterocyclic intermediate (**15**) can be coupled with appropriately protected Intermediate **1** via Palladium mediated coupling. Subsequent ester hydrolysis, and coupling with piperazoic ester results in intermediate **16**.

The macrocyclic esters can be made by hydrolysis, deprotection and macrocyclization sequence. Subsequent deprotection and coupling with Intermediate **4** (or analogs) result in an appropriately substituted final macrocyclic products. Additional deprotection or functionalization steps could be required to produce a final compound **17**.

Scheme B5. General synthesis of macrocyclic esters

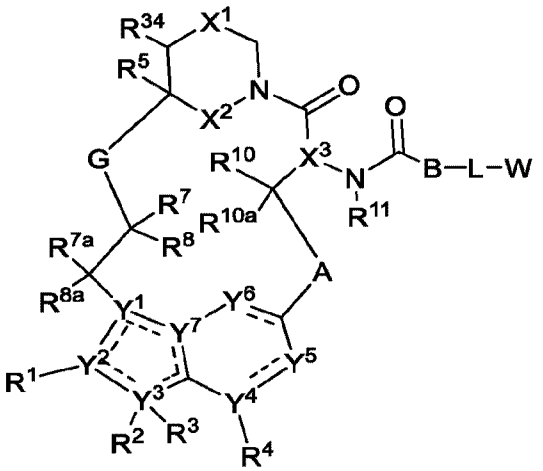


An alternative general synthesis of macrocyclic esters is outlined in Scheme B5. An appropriately substituted macrocycle (**20**) can be prepared starting from an appropriately protected boronic ester **18** and bromo indolyl intermediate (**19**), including Palladium mediated coupling, hydrolysis, coupling with piperazoic ester, hydrolysis, de-protection, and macrocyclizarion steps. Subsequent coupling with an appropriately substituted protected amino acid followed by palladium mediated coupling yiels intermediate **21**. Additional deprotection and derivatization steps, including alkylation may be required at this point.

The final macrocyclic esters can be made by coupling of intermediate (**22**) and an appropriately substituted carboxylic acid intermediate (**23**). Additional deprotection or functionalization steps could be required to produce a final compound (**24**).

In addition, compounds of the disclosure can be synthesized using the methods described in the Examples below and in WO 2021/091982, together with synthetic methods known in the art of synthetic organic chemistry, or variations thereon as appreciated by those skilled in the art. These methods include but are not limited to those methods described in the Examples below. For example, a person of skill in the art would be able to install into a macrocyclic ester a desired -B-L-W group of a compound of Formula (BI), where B, L and W are defined herein, including by using methods exemplified in the WO 2021/091982.

In some embodiments, the RAS(ON) inhibitor is a compound, or a pharmaceutically acceptable salt thereof, having the structure of Formula CI:



Formula CI

wherein the dotted lines represent zero, one, two, three, or four non-adjacent double bonds;

A is -N(H or CH_3)C(O)-(CH_2)- where the amino nitrogen is bound to the carbon atom of -CH(R^{10})-, optionally substituted 3 to 6-membered cycloalkylene, optionally substituted 3 to 6-membered heterocycloalkylene, optionally substituted 6-membered arylene, or optionally substituted 5 to 10-membered heteroarylene;

B is -CH(R^9)- or >C=C$R^9R^{9'}$ where the carbon is bound to the carbonyl carbon of -N(R^{11})C(O)-, optionally substituted 3 to 6-membered cycloalkylene, optionally substituted 3 to 6-membered heterocycloalkylene, optionally substituted 6-membered arylene, or 5 to 6-membered heteroarylene;

G is optionally substituted C_1-C_4 alkylene, optionally substituted C_1-C_4 alkenylene, optionally substituted C_1-C_4 heteroalkylene, -C(O)O-**C**H(R^6)- where **C** is bound to -C(R^7R^8)-, -C(O)NH-**C**H(R^6)- where **C** is bound to -C(R^7R^8)-, optionally substituted C_1-C_4 heteroalkylene, or 3 to 8-membered heteroarylene;

L is absent or a linker;

W is a cross-linking group comprising a carbodiimide, an oxazoline, a thiazoline, a chloroethyl urea, a chloroethyl thiourea, a chloroethyl carbamate, a chloroethyl thiocarbamate, an aziridine, a trifluoromethyl ketone, a boronic acid, a boronic ester, an *N*-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline (EEDQ), an iso-EEDQ or other EEDQ derivative, an epoxide, an oxazolium, or a glycal;

X^1 is optionally substituted C_1-C_2 alkylene, NR, O, or $S(O)_n$;

X^2 is O or NH;

X^3 is N or CH;

n is 0, 1, or 2;

R is hydrogen, cyano, optionally substituted C_1-C_4 alkyl, optionally substituted C_2-C_4 alkenyl, optionally substituted C_2-C_4 alkynyl, C(O)R', C(O)OR', $C(O)N(R')_2$, S(O)R', $S(O)_2R'$, or $S(O)_2N(R')_2$;

each R' is, independently, H or optionally substituted C_1-C_4 alkyl;

Y^1 is C, CH, or N;

Y^2, Y^3, Y^4, and Y^7 are, independently, C or N;

Y^5 is CH, CH_2, or N;

Y^6 is C(O), CH, CH_2, or N;

R^1 is cyano, 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 cycloalkenyl, optionally substituted 3 to 6-membered heterocycloalkyl, optionally substituted 6 to 10-membered aryl, or optionally substituted 5 to 10-membered heteroaryl, or

R^1 and R^2 combine with the atoms to which they are attached to form an optionally substituted 3 to 14-membered heterocycloalkyl;

R^2 is absent, hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 alkynyl, optionally substituted 3 to 6-membered cycloalkyl, optionally substituted 3 to 7-membered heterocycloalkyl, optionally substituted 6-membered aryl, optionally substituted 5 or 6-membered heteroaryl; R^3 is absent, or

R^2 and R^3 combine with the atom to which they are attached to form an optionally substituted 3 to 8-membered cycloalkyl or optionally substituted 3 to 14-membered heterocycloalkyl;

R^4 is absent, hydrogen, halogen, cyano, or methyl optionally substituted with 1 to 3 halogens;

R^5 is hydrogen, C_1-C_4 alkyl optionally substituted with halogen, cyano, hydroxy, or C_1-C_4 alkoxy, cyclopropyl, or cyclobutyl;

R^6 is hydrogen or methyl; R^7 is hydrogen, halogen, or optionally substituted C_1-C_3 alkyl, or

R^6 and R^7 combine with the carbon atoms to which they are attached to form an optionally substituted 3 to 6-membered cycloalkyl or optionally substituted 3 to 7-membered heterocycloalkyl;

R^8 is hydrogen, halogen, hydroxy, cyano, optionally substituted C_1-C_3 alkoxyl, optionally substituted C_1-C_3 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 alkynyl, optionally substituted 3 to 8-membered cycloalkyl, optionally substituted 3 to 14-membered heterocycloalkyl, optionally substituted 5 to 10-membered heteroaryl, or optionally substituted 6 to 10-membered aryl, or

R^7 and R^8 combine with the carbon atom to which they are attached to form $C=CR^{7'}R^{8'}$; C=N(OH), C=N(O-C_1-C_3 alkyl), C=O, C=S, C=NH, optionally substituted 3 to 6-membered cycloalkyl, or optionally substituted 3 to 7-membered heterocycloalkyl;

R^{7a} and R^{8a} are, independently, hydrogen, halo, optionally substituted C_1-C_3 alkyl, or combine with the carbon to which they are attached to form a carbonyl;

$R^{7'}$ is hydrogen, halogen, or optionally substituted C_1-C_3 alkyl; $R^{8'}$ is hydrogen, halogen, hydroxy, cyano, optionally substituted C_1-C_3 alkoxyl, optionally substituted C_1-C_3 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 alkynyl, optionally substituted 3 to 8-membered cycloalkyl, optionally substituted 3 to 14-membered heterocycloalkyl, optionally substituted 5 to 10-membered heteroaryl, or optionally substituted 6 to 10-membered aryl, or

$R^{7'}$ and $R^{8'}$ combine with the carbon atom to which they are attached to form optionally substituted 3 to 6-membered cycloalkyl or optionally substituted 3 to 7-membered heterocycloalkyl;

R^9 is hydrogen, F, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted 3 to 6-membered cycloalkyl, or optionally substituted 3 to 7-membered heterocycloalkyl, or

R^9 and L combine with the atoms to which they are attached to form an optionally substituted 3 to 14-membered heterocycloalkyl;

$R^{9'}$ is hydrogen or optionally substituted C_1-C_6 alkyl;

R^{10} is hydrogen, halo, hydroxy, C_1-C_3 alkoxy, or C_1-C_3 alkyl;

R^{10a} is hydrogen or halo; and

R^{11} is hydrogen or C_1-C_3 alkyl; and

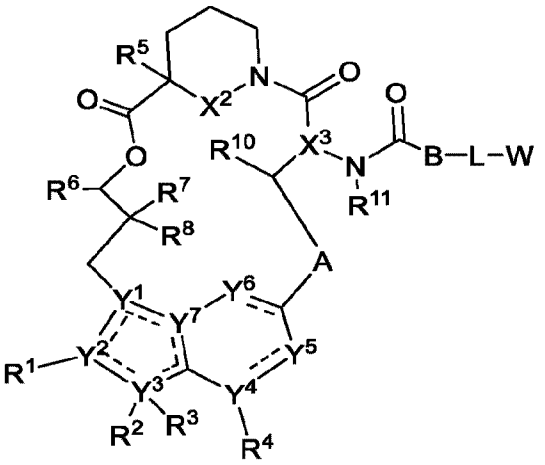
R^{34} is hydrogen or C_1-C_3 alkyl (e.g., methyl).

In some embodiments of Formula CI and subformula thereof, R^9 is optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted 3 to 6-membered cycloalkyl, or optionally substituted 3 to 7-membered heterocycloalkyl.

In some embodiments of Formula CI and subformula thereof, R^{34} is hydrogen.

In some embodiments of Formula CI and subformula thereof, G is optionally substituted C_1-C_4 heteroalkylene.

In some embodiments, the RAS(ON) inhibitor has the structure of Formula CIa, or a pharmaceutically acceptable salt thereof:



Formula CIa

wherein the dotted lines represent zero, one, two, three, or four non-adjacent double bonds;

A is -N(H or CH_3)C(O)-(CH_2)- where the amino nitrogen is bound to the carbon atom of -CH(R^{10})-, optionally substituted 3 to 6-membered cycloalkylene, optionally substituted 3 to 6-membered heterocycloalkylene, optionally substituted 6-membered arylene, or optionally substituted 5 to 6-membered heteroarylene;

B is -CH(R^9)- where the carbon is bound to the carbonyl carbon of -N(R^{11})C(O)-, optionally substituted 3 to 6-membered cycloalkylene, optionally substituted 3 to 6-membered heterocycloalkylene, optionally substituted 6-membered arylene, or 5 to 6-membered heteroarylene;

L is absent or a linker;

W is a cross-linking group comprising a carbodiimide, an oxazoline, a thiazoline, a chloroethyl urea, a chloroethyl thiourea, a chloroethyl carbamate, a chloroethyl thiocarbamate, an aziridine, a trifluoromethyl ketone, a boronic acid, a boronic ester, an *N*-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline (EEDQ), an iso-EEDQ or other EEDQ derivative, an epoxide, an oxazolium, or a glycal;

X^2 is O or NH;

X^3 is N or CH;

n is 0, 1, or 2;

R is hydrogen, cyano, optionally substituted C_1-C_4 alkyl, optionally substituted C_2-C_4 alkenyl, optionally substituted C_2-C_4 alkynyl, C(O)R', C(O)OR', C(O)N(R')$_2$, S(O)R', S(O)$_2$R', or S(O)$_2$N(R')$_2$;

each R' is, independently, H or optionally substituted C_1-C_4 alkyl;

Y^1 is C, CH, or N;

Y^2, Y^3, Y^4, and Y^7 are, independently, C or N;

Y^5 and Y^6 are, independently, CH or N;

R^1 is cyano, 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 cycloalkenyl, optionally substituted 3 to 6-membered heterocycloalkyl, optionally substituted 6 to 10-membered aryl, or optionally substituted 5 to 10-membered heteroaryl;

R^2 is hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted 3 to 6-membered cycloalkyl, optionally substituted 3 to 7-membered heterocycloalkyl, optionally substituted 6-membered aryl, optionally substituted 5 or 6-membered heteroaryl; R^3 is absent, or

R^2 and R^3 combine with the atom to which they are attached to form an optionally substituted 3 to 8-membered cycloalkyl or optionally substituted 3 to 14-membered heterocycloalkyl;

R^4 is absent, hydrogen, halogen, cyano, or methyl optionally substituted with 1 to 3 halogens;

R^5 is hydrogen, C_1-C_4 alkyl optionally substituted with halogen, cyano, hydroxy, or C_1-C_4 alkoxy, cyclopropyl, or cyclobutyl;

R^6 is hydrogen or methyl; R^7 is hydrogen, halogen, or optionally substituted C_1-C_3 alkyl, or

R^6 and R^7 combine with the carbon atoms to which they are attached to form an optionally substituted 3 to 6-membered cycloalkyl or optionally substituted 3 to 7-membered heterocycloalkyl;

R^8 is hydrogen, halogen, hydroxy, cyano, optionally substituted C_1-C_3 alkoxyl, optionally substituted C_1-C_3 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 alkynyl, optionally

substituted 3 to 8-membered cycloalkyl, optionally substituted 3 to 14-membered heterocycloalkyl, optionally substituted 5 to 10-membered heteroaryl, or optionally substituted 6 to 10-membered aryl, or

R^7 and R^8 combine with the carbon atom to which they are attached to form $C=CR^{7'}R^{8'}$; C=N(OH), C=N(O-C_1-C_3 alkyl), C=O, C=S, C=NH, optionally substituted 3 to 6-membered cycloalkyl, or optionally substituted 3 to 7-membered heterocycloalkyl;

$R^{7'}$ is hydrogen, halogen, or optionally substituted C_1-C_3 alkyl; $R^{8'}$ is hydrogen, halogen, hydroxy, cyano, optionally substituted C_1-C_3 alkoxyl, optionally substituted C_1-C_3 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 alkynyl, optionally substituted 3 to 8-membered cycloalkyl, optionally substituted 3 to 14-membered heterocycloalkyl, optionally substituted 5 to 10-membered heteroaryl, or optionally substituted 6 to 10-membered aryl, or

$R^{7'}$ and $R^{8'}$ combine with the carbon atom to which they are attached to form optionally substituted 3 to 6-membered cycloalkyl or optionally substituted 3 to 7-membered heterocycloalkyl;

R^9 is optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted 3 to 6-membered cycloalkyl, or optionally substituted 3 to 7-membered heterocycloalkyl;

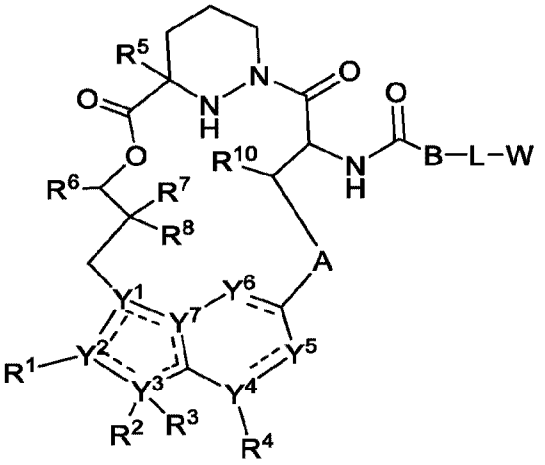
R^{10} is hydrogen, hydroxy, C_1-C_3 alkoxy, or C_1-C_3 alkyl; and

R^{11} is hydrogen or C_1-C_3 alkyl.

In some embodiments of Formula CI and subformula thereof, X^2 is NH. In some embodiments, X^3 is CH.

In some embodiments of Formula CI and subformula thereof, R^{11} is hydrogen. In some embodiments, R^{11} is C_1-C_3 alkyl, such as methyl.

In some embodiments, the RAS(ON) inhibitor has the structure of Formula CIb, or a pharmaceutically acceptable salt thereof:



Formula CIb

wherein the dotted lines represent zero, one, two, three, or four non-adjacent double bonds;

A is -N(H or CH_3)C(O)-(CH_2)- where the amino nitrogen is bound to the carbon atom of -CH(R^{10})-, optionally substituted 3 to 6-membered cycloalkylene, optionally substituted 3 to 6-membered heterocycloalkylene, optionally substituted 6-membered arylene, or optionally substituted 5 to 6-membered heteroarylene;

DEMANDE OU BREVET VOLUMINEUX

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CECI EST LE TOME 1 DE 4
CONTENANT LES PAGES 1 À 298

NOTE : Pour les tomes additionels, veuillez contacter le Bureau canadien des brevets

JUMBO APPLICATIONS/PATENTS

THIS SECTION OF THE APPLICATION/PATENT CONTAINS MORE THAN ONE VOLUME

THIS IS VOLUME 1 OF 4
CONTAINING PAGES 1 TO 298

NOTE: For additional volumes, please contact the Canadian Patent Office

NOM DU FICHIER / FILE NAME :

NOTE POUR LE TOME / VOLUME NOTE:

Claims

1. A method of treating cancer in a subject in need thereof, wherein the cancer comprises:

(a) a first RAS mutation that is G12C and a second RAS mutation at a position selected from the group consisting of H95, R68, G13 and Q61, or a second RAS mutation that is selected from the group consisting of Y96C, Y96F, Y96H, Y96N, Y96S; or

(b) a first RAS mutation at position G12 selected from the group consisting of G12H, G12I, G12K, G12M, G12N, G12P, G12Q, G12T, G12W and G12Y,

wherein the cancer is resistant to treatment with a RAS(OFF) inhibitor, the method comprising administering to the subject a RAS(ON) inhibitor.

FIG. 1A

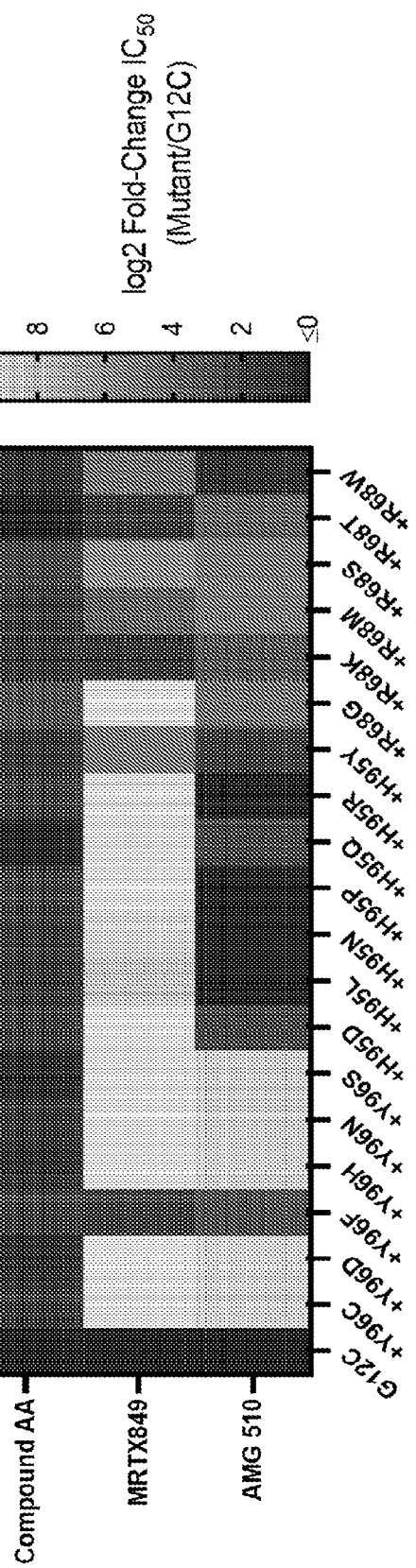

FIG. 1B

	G12C	+Y96C	+Y96D	+Y96F	+Y96H	+Y96N	+Y96S	+H95D	+H95L	+H95N	+H95P	+H95Q	+H95R	+H95Y	+R68G	+R68K	+R68M	+R68S	+R68T	+R68W
AMG 510	0.00	8.83	8.83	1.87	8.83	8.83	8.83	1.29	<0.00	0.06	0.10	1.32	<0.00	0.99	3.92	2.14	4.14	4.42	2.55	0.32
MRTX849	0.00	9.78	9.78	0.87	9.78	9.78	9.78	9.78	8.14	9.17	9.78	9.78	9.78	3.96	9.78	0.77	2.38	5.37	0.85	3.77
Compound AA	0.00	0.85	0.32	0.94	0.45	0.63	0.20	0.91	0.66	0.76	0.87	<0.00	0.90	0.86	1.60	0.81	0.80	1.37	0.04	0.48

FIG. 2A

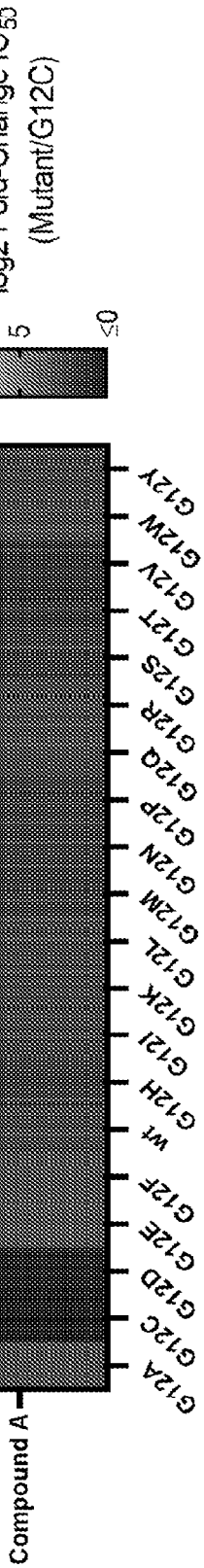

FIG. 2B

	G12A	G12C	G12D	G12E	G12F	wt	G12H	G12I	G12K	G12L	G12M	G12N	G12P	G12Q	G12R	G12S	G12T	G12V	G12W	G12Y
Compound A	1.72	0.00	0.23	1.62	1.00	1.44	1.02	1.20	1.47	1.40	0.87	0.88	1.00	1.39	1.33	1.04	0.78	0.70	1.39	1.54

FIG. 3