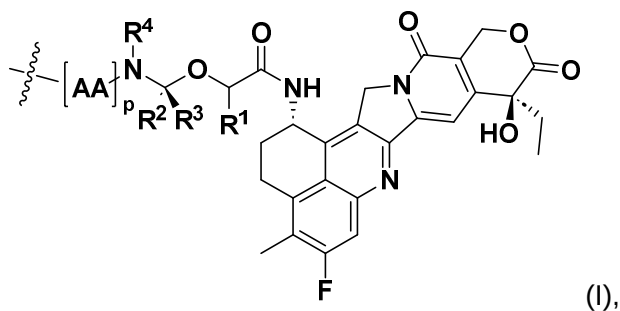


WHAT IS CLAIMED IS:

1. An antibody-drug conjugate comprising an antibody or an antigen-binding fragment thereof conjugated to a compound having Formula (I)



or a pharmaceutically acceptable salt thereof,

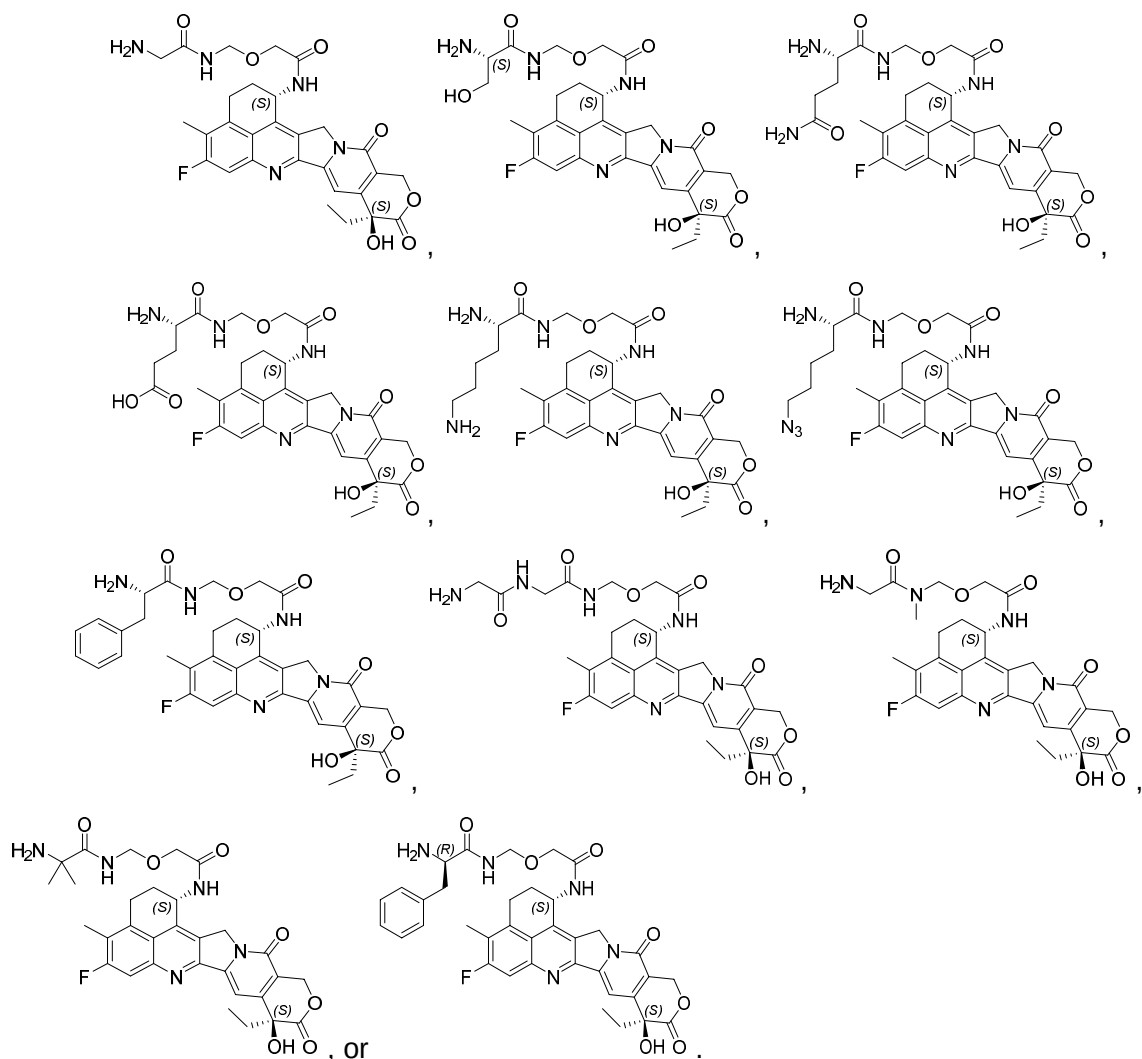
wherein R¹, R², R³, and R⁴ are independently hydrogen, a C₁₋₅ alkyl, or aryl;

AA is a natural or a nonnatural amino acid;

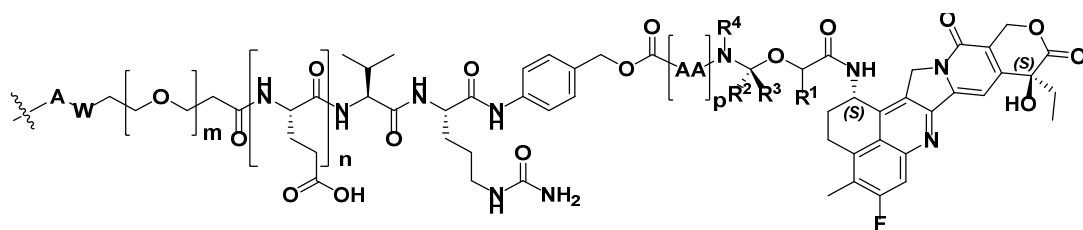
p is an integer from 1 to 6, and

 indicates the point of attachment to the antibody or the antigen-binding fragment thereof, directly or via a linker.

2. The antibody-drug conjugate according to claim 1, wherein said compound of Formula (I) comprises



3. The antibody-drug conjugate according to claim 1, wherein said antibody or said antigen-binding fragment thereof is conjugated to a compound having a structure according to Formula (II)



(II),

or a pharmaceutically acceptable salt thereof, wherein R¹, R², R³, and R⁴ are independently hydrogen or a C₁₋₅ alkyl;
A is a Click chemistry adduct;

W is NH, O, CO, CH₂, a phenyl, or a combination of two or more thereof;

AA is a natural or a nonnatural amino acid;

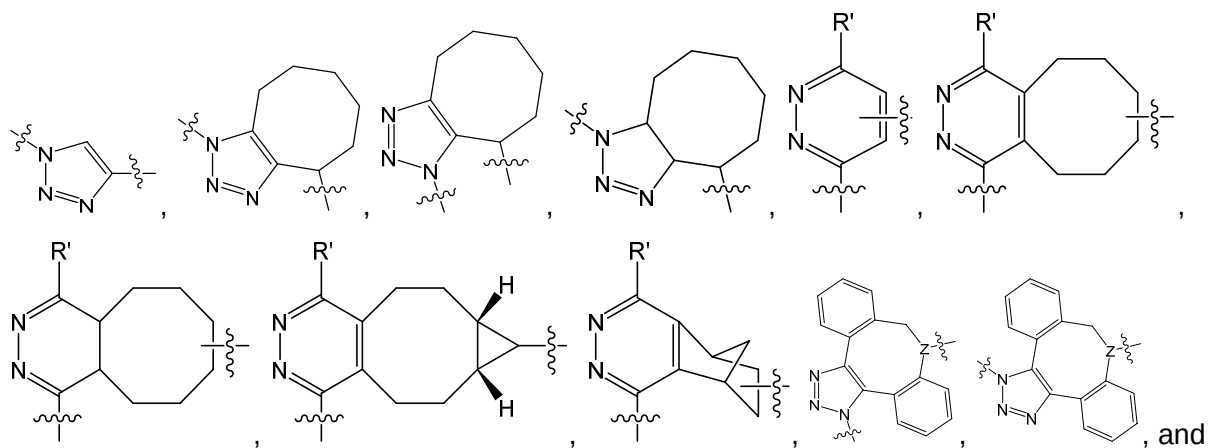
m is an integer from 0 to 8;

n is 0 or 1;

p is an integer from 1 to 6, and

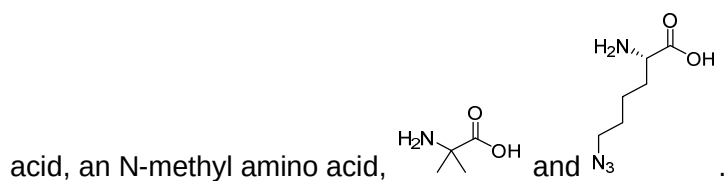
 indicates the point of attachment to the antibody or the antigen-binding fragment thereof, directly or via a linker.

4. The antibody-drug conjugate according to claim 3, wherein the click chemistry adduct is a product of a copper-free click chemistry reaction selected from: (a) strain-promoted azide/dibenzocyclooctyne-amine (DBCO) click chemistry; (b) inverse electron demand Diels-Alder (IED-DA) tetrazine/trans-cyclooctene (TCO) click chemistry; (c) inverse electron demand Diels-Alder (IED-DA) tetrazine/norbornene click chemistry; (d) Diels-Alder maleimide/furan click-chemistry; (e) Staudinger ligation; and (f) nitrile-oxide/norbornene cycloaddition click chemistry.
5. The antibody-drug conjugate according to claims 3 or 4, wherein the click chemistry adduct comprises a triazole or a diazine.
6. The antibody-drug conjugate according to any one of claims 3-5, wherein the click chemistry adduct is selected from the group consisting of:

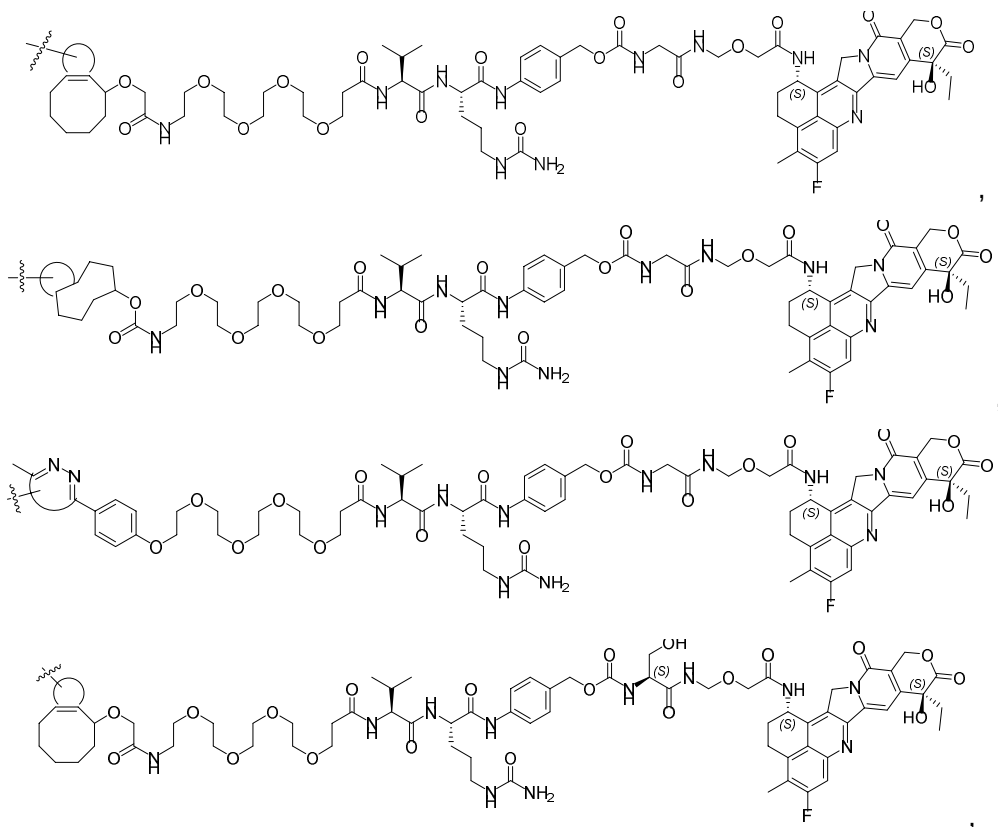


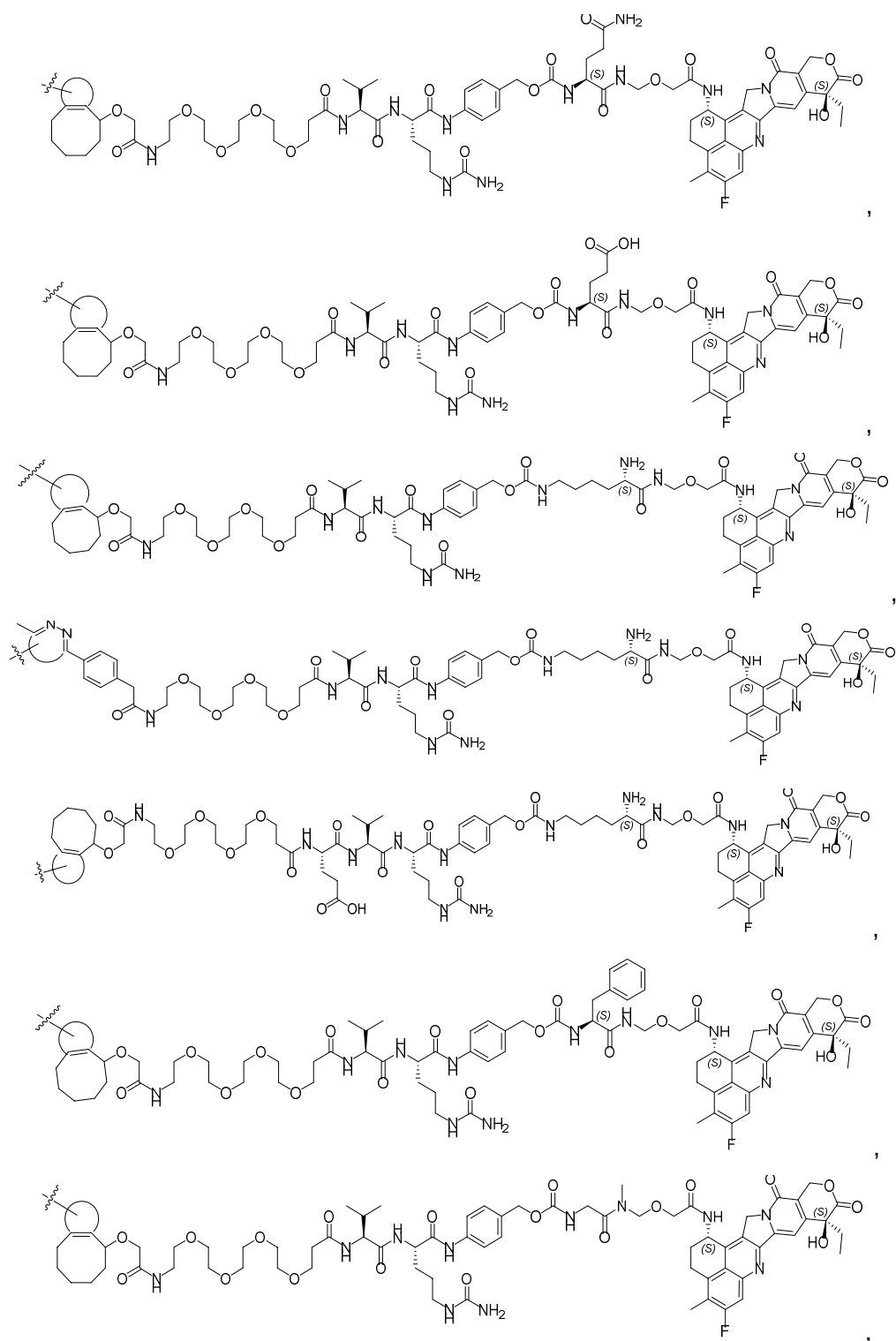
any regio-isomers or enantiomers thereof, where R' is H or a C₁₋₃ alkyl and Z is C or N.

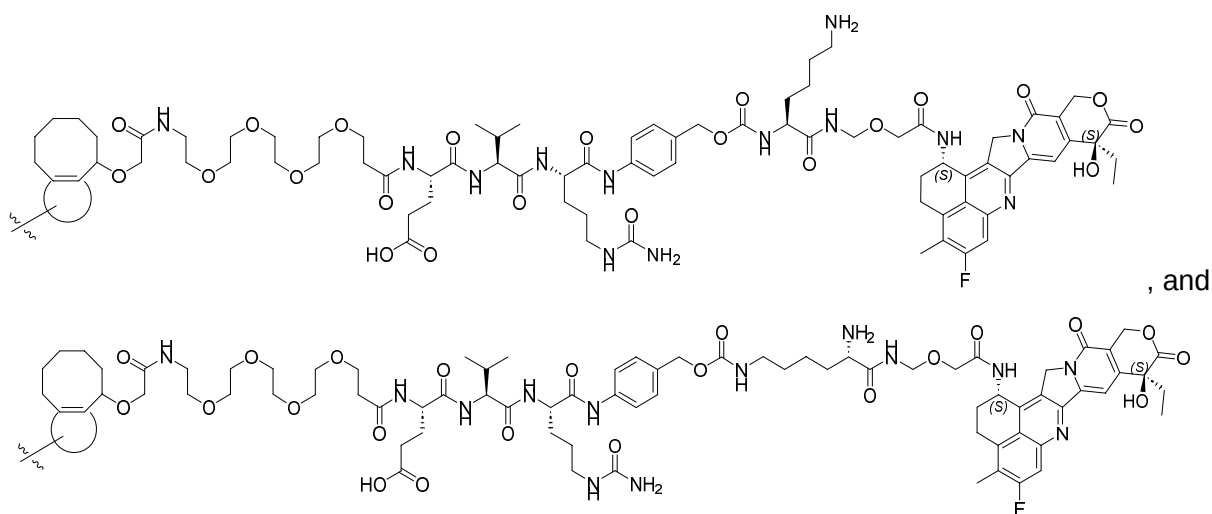
7. The antibody-drug conjugate according to any one of claims 3-6, wherein AA comprises a natural amino acid selected from glycine, alanine, valine, leucine, isoleucine, phenylalanine, tyrosine, threonine, lysine, asparagine, glutamine, aspartic acid, and glutamic acid.
8. The antibody-drug conjugate according to any one of claims 3-6, wherein AA comprises a nonnatural amino acid selected from the group consisting of an R-amino



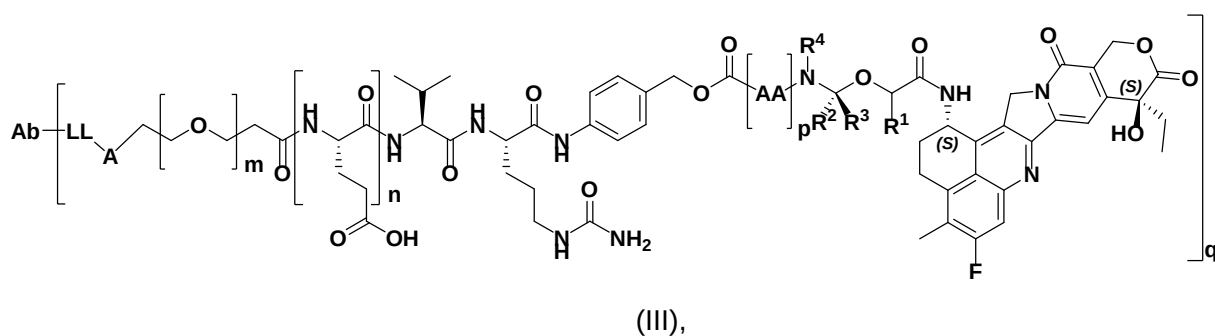
9. The antibody-drug conjugate according to any one of claims 3-6, wherein said compound of Formula (II) comprises







10. An antibody-drug conjugate having a structure according to Formula (III)



or a pharmaceutically acceptable salt thereof, wherein

Ab is an antibody or an antigen-binding fragment thereof;

R^1 , R^2 , R^3 , and R^4 are independently hydrogen or a C_{1-5} alkyl;

A is a Click chemistry adduct;

LL is a linker or a bond connecting said Ab and said A;

AA is a natural or a nonnatural amino acid;

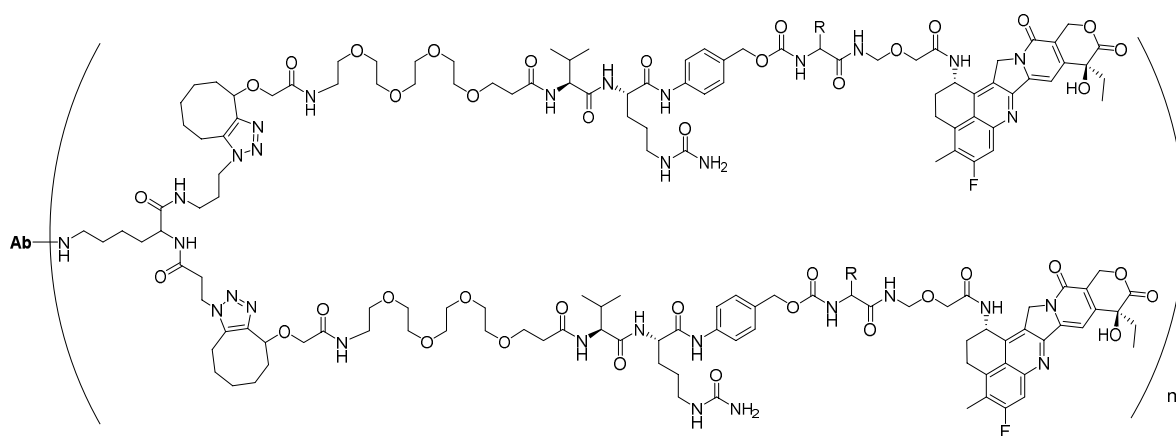
m is an integer from 0 to 8;

n is 0 or 1;

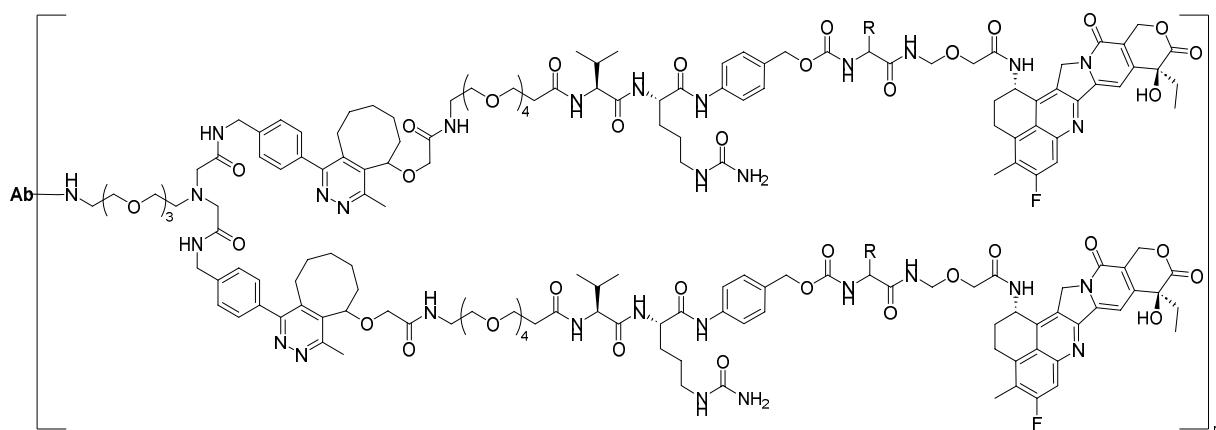
p is an integer from 1 to 6;

and q is an integer from 1 to 10.

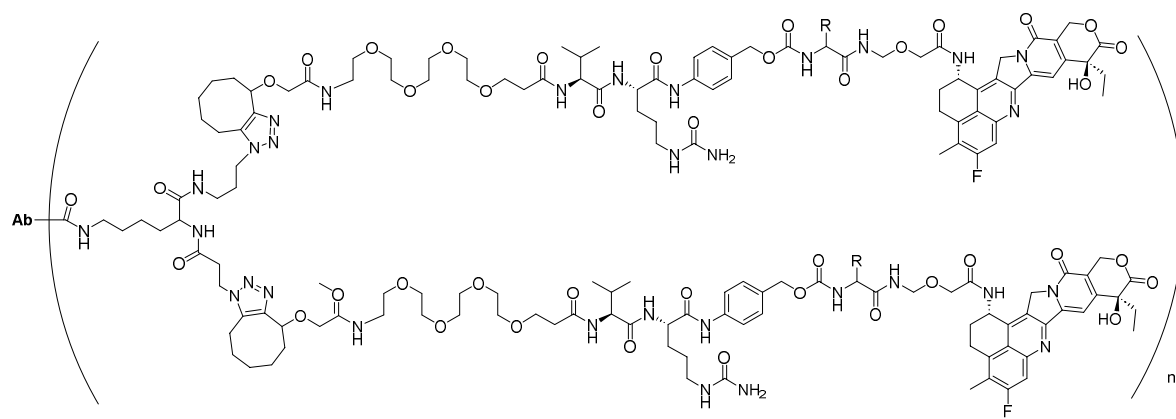
11. An antibody-drug conjugate having a structure according to Formula (IVa, IVb, IVc, IVd, IVe, IVf, IVg, IVh, IVi, IVj, or IVk)



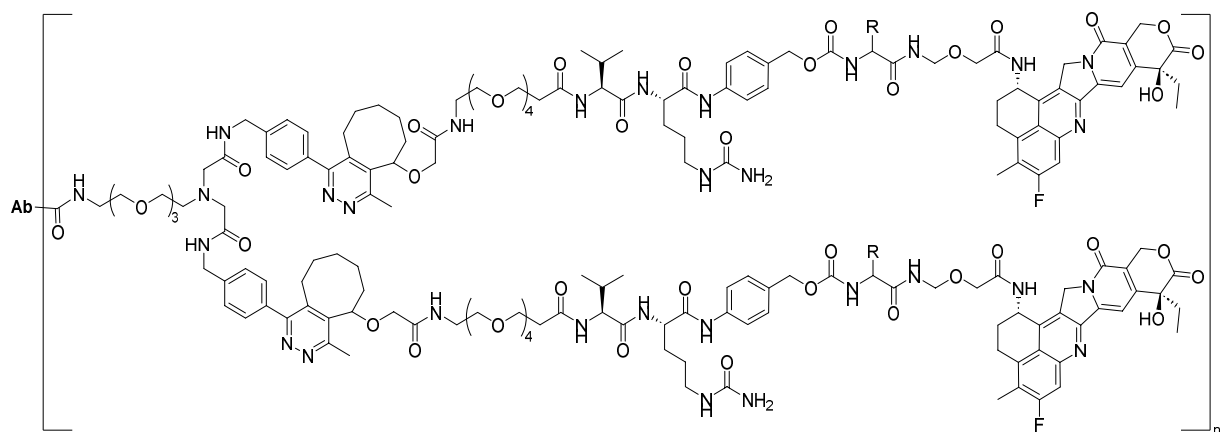
(IVa),



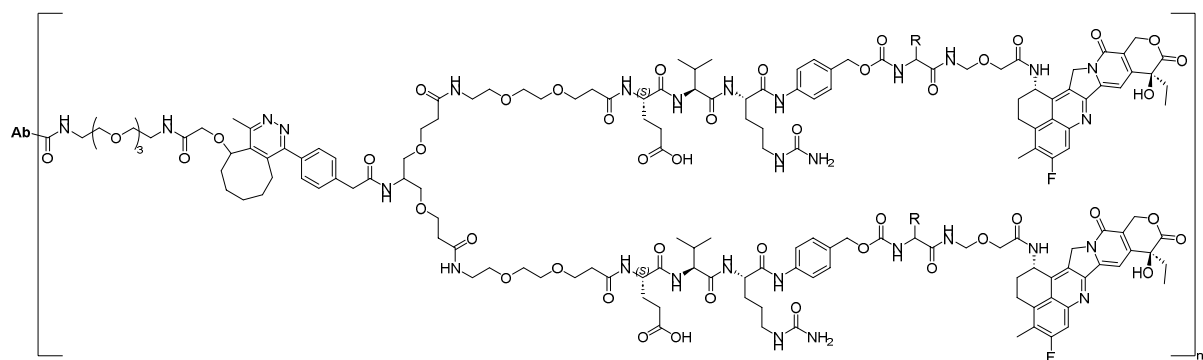
(IVb),



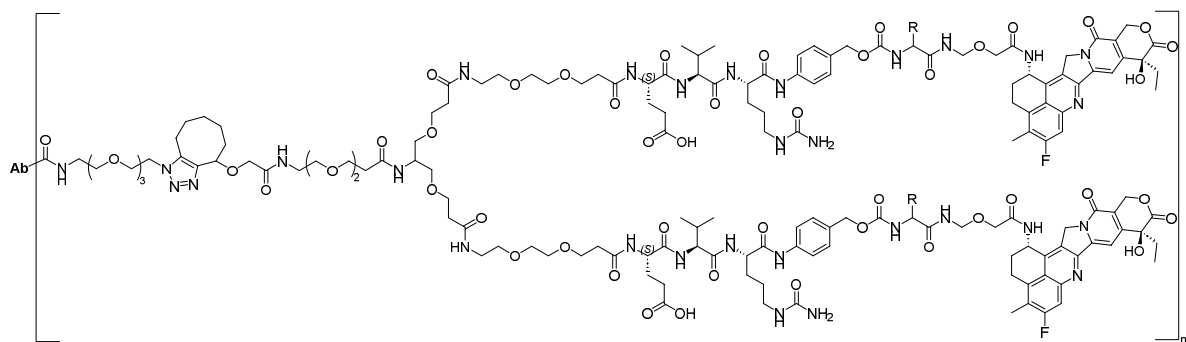
(IVc),



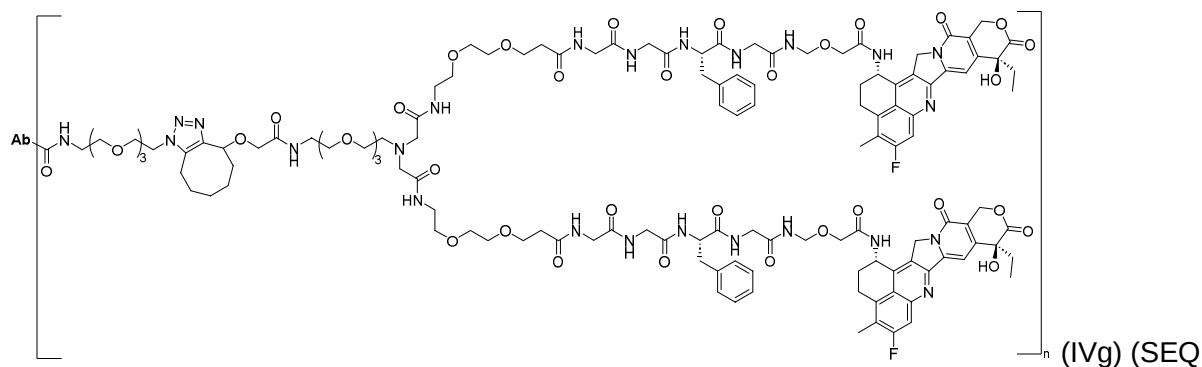
(IVd),



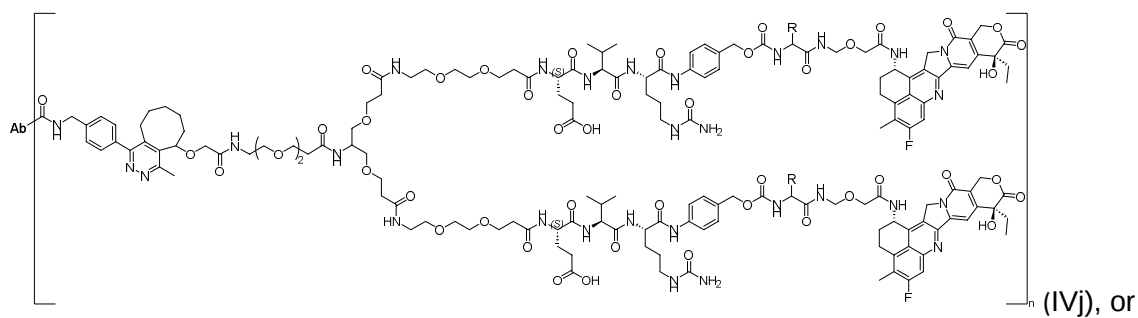
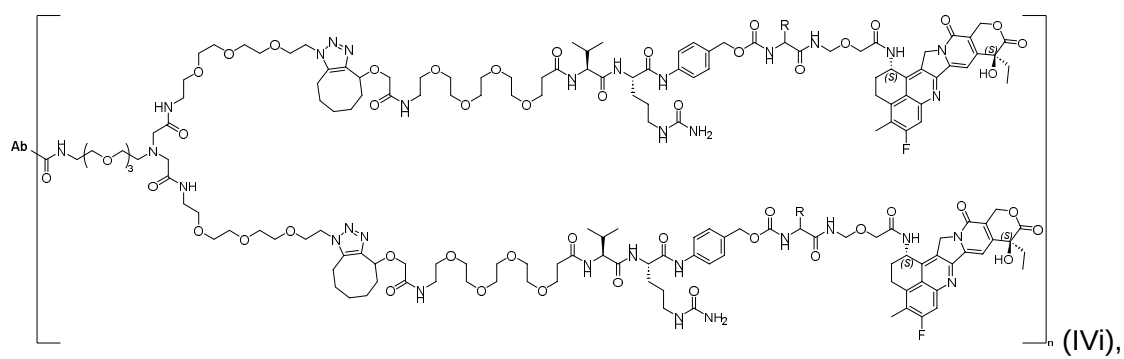
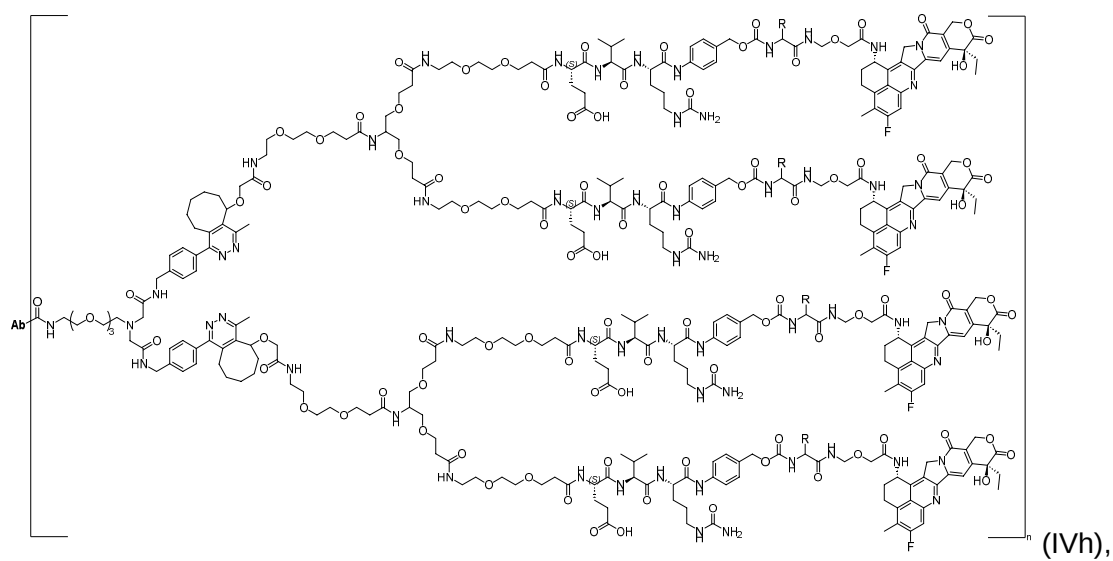
(IVe),

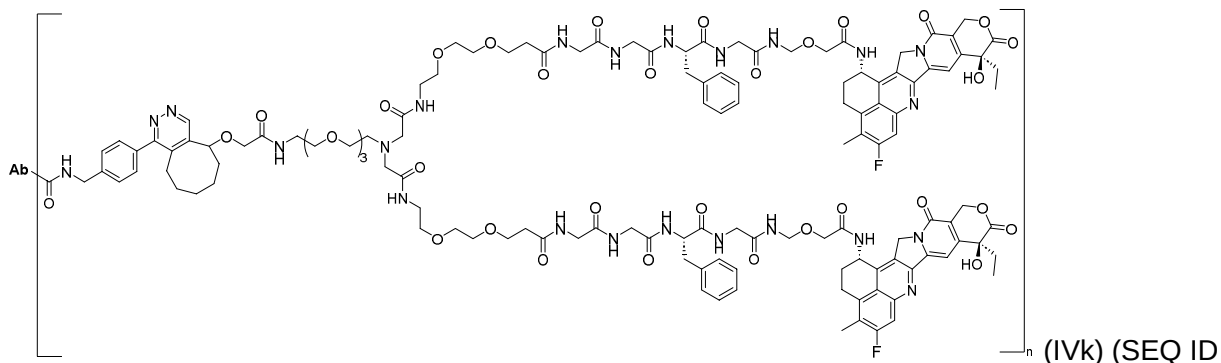


(IVf),



ID NOS 2115 and 2115, respectively), or





or a pharmaceutically acceptable salt thereof, wherein

Ab is an antibody or an antigen-binding fragment thereof;

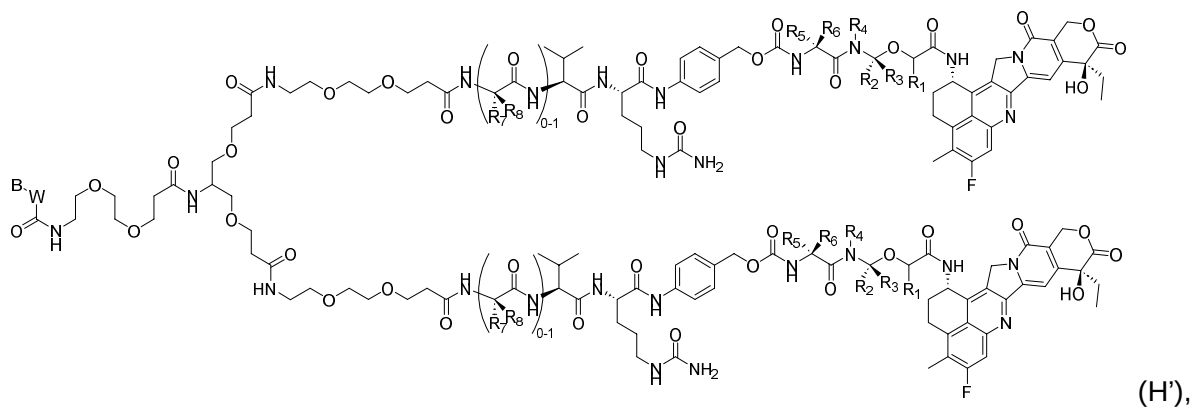
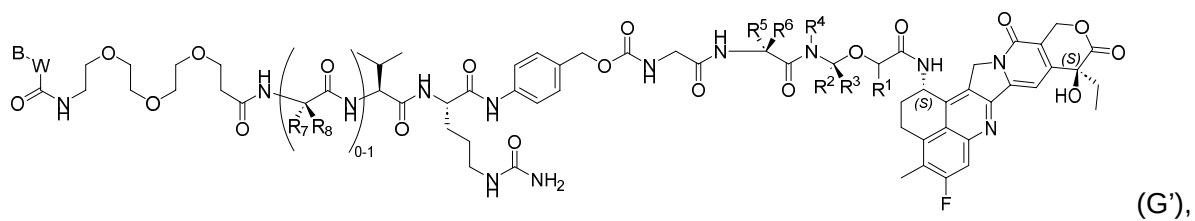
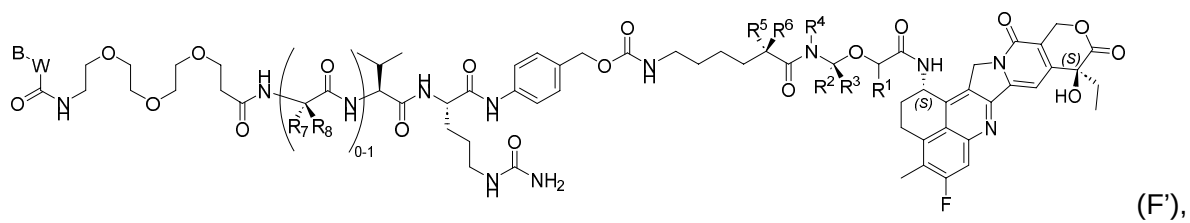
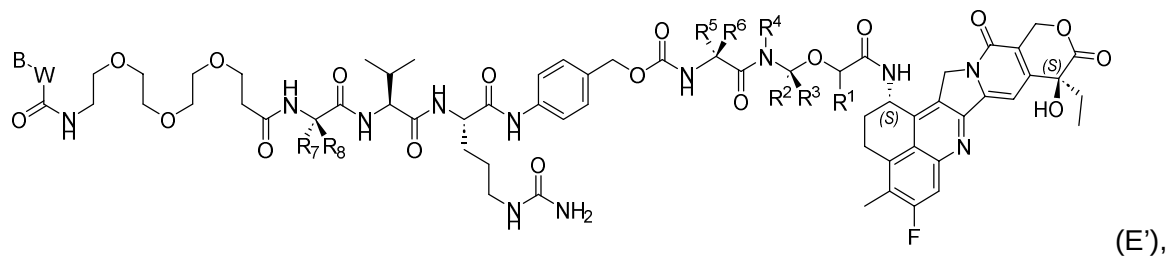
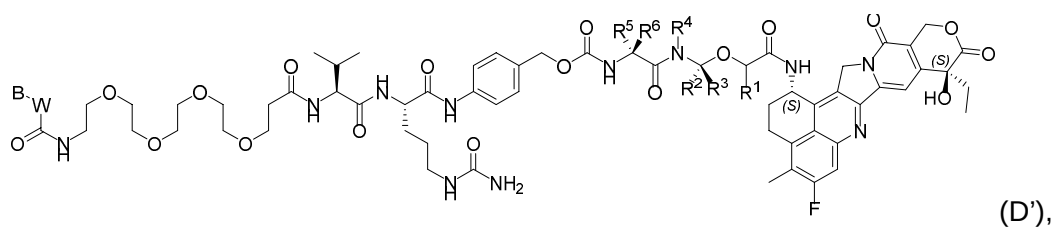
R is a side chain of any natural or nonnatural amino acid;

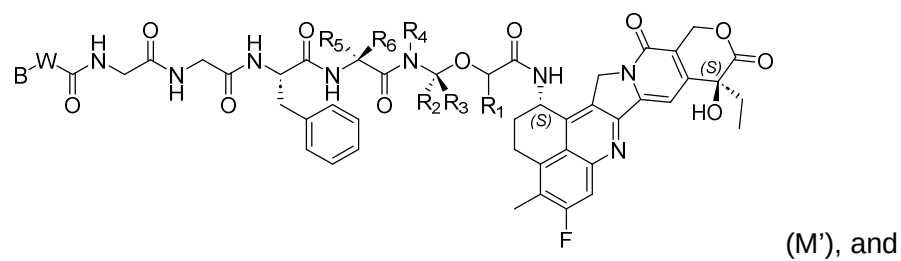
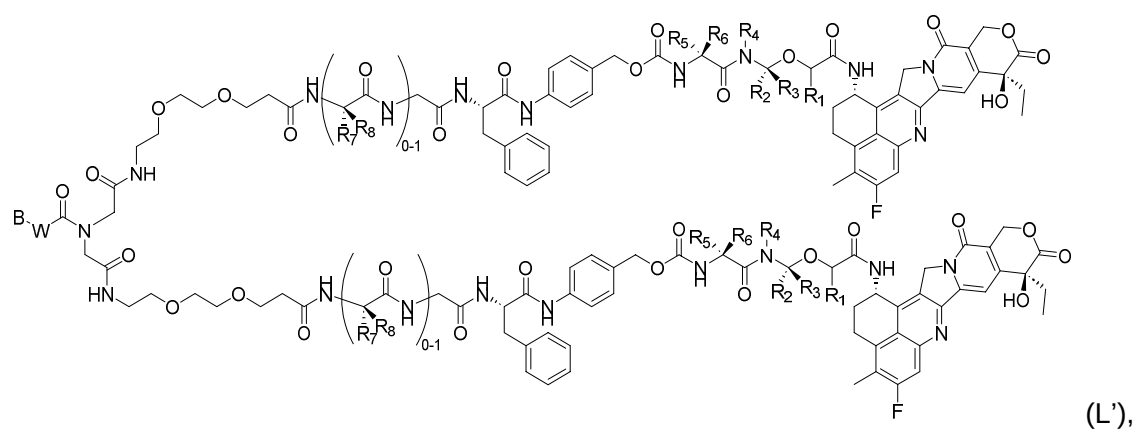
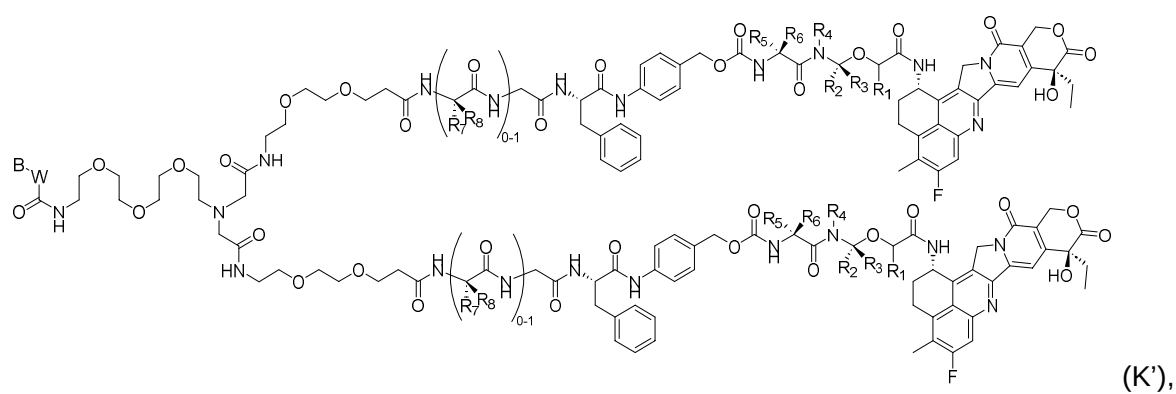
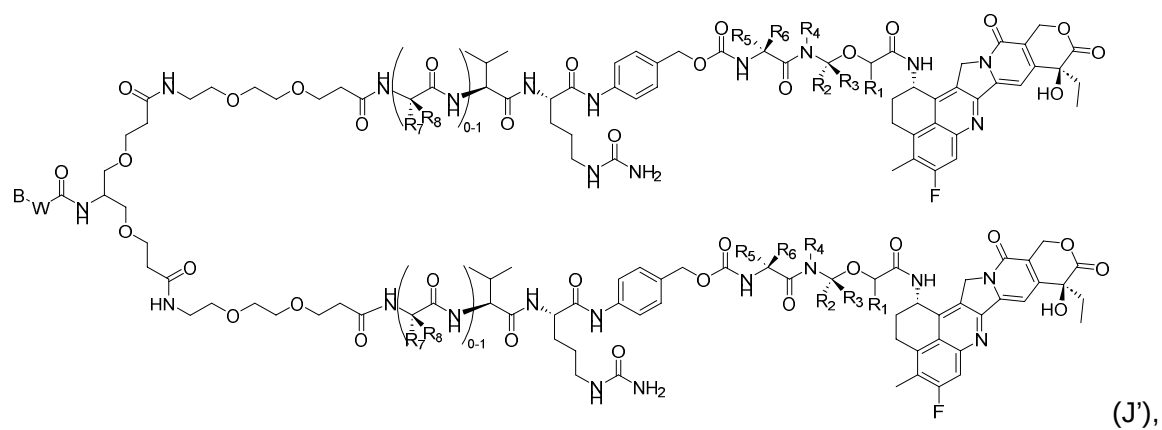
and n is an integer from 1 to 5.

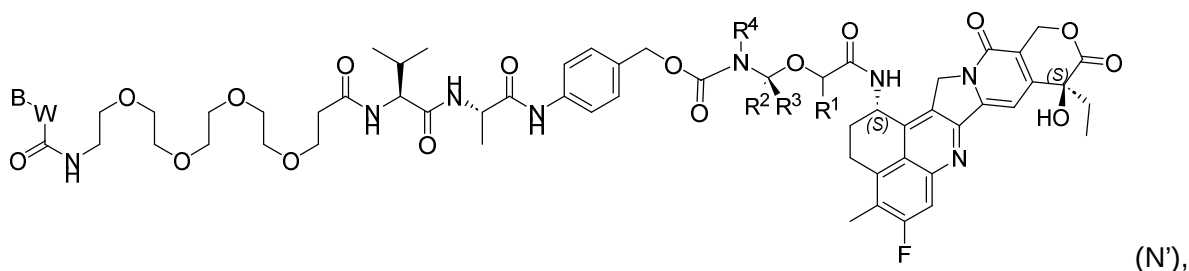
12. The antibody-drug conjugate according to claim 11, wherein said antibody or said antigen-binding fragment thereof comprises Gln295 and/or Gln297, and wherein the drug payload is conjugated to said antibody or antigen-binding fragment through the side chains of Gln295 and/or Gln297.
13. The antibody-drug conjugate according claims 1-12, wherein said antibody or said antigen-binding fragment thereof is selected from an anti-HER2 antibody, an anti-STEAP2 antibody, an anti-MET antibody, an anti-EGFRVIII antibody, an anti-MUC16 antibody, an anti-PRLR antibody, an anti-PSMA antibody, an anti-FGFR2 antibody, an anti-FOLR1 antibody, an anti-HER2/HER2 bispecific antibody, an anti-MET/MET bispecific antibody, or an antigen-binding fragment thereof.
14. The antibody-drug conjugate of any of claims 1-13, wherein the antibody or antigen-binding fragment thereof is an anti-HER2/HER2 bispecific antibody.
15. The antibody-drug conjugate of any of claims 13 or 14, wherein the anti-HER2/HER2 bispecific antibody comprises:
 - a first antigen-binding domain (D1); and
 - a second antigen-binding domain (D2);

wherein D1 specifically binds a first epitope of human HER2; and
wherein D2 specifically binds a second epitope of human HER2.

16. The antibody-drug conjugate of any claims 1-15, wherein said antibody and linker-drug payload is conjugated site-specifically by using a transglutaminase.
17. The antibody-drug conjugate of claim 16, wherein said transglutaminase is a microbial transglutaminase.
18. A pharmaceutical composition comprising an antibody-drug conjugate according to any one of claims 1-17, co-formulated together with one or more pharmaceutically acceptable diluents, excipients, and/or additives.
19. A composition comprising a population of the antibody-drug conjugates according to any one of claims 1-17, having a drug-antibody ratio (DAR) of about 0.5 to about 30.0.
20. The composition of claim 19 having a DAR of about 1.0 to about 2.5.
21. The composition of claim 20 having a DAR of about 2.
22. The composition of claim 19 having a DAR of about 3.0 to about 4.5.
23. The composition of claim 22 having a DAR of about 4.
24. The composition of claim 19 having a DAR of about 6.5 to about 8.5.
25. The composition of claim 24 having a DAR of about 8.
26. Use of the antibody-drug conjugate according to any one of claims 1-17, or the pharmaceutical composition of claim 18, in the manufacture of a medicament for treating cancer in a subject in need thereof .
27. A process for manufacturing a linker-payload compound having the formula selected from the group consisting of (D') to (N'):







or a pharmaceutically acceptable salt thereof,

wherein R^1 , R^2 , R^3 , and R^4 are independently hydrogen or a C_{1-5} alkyl;

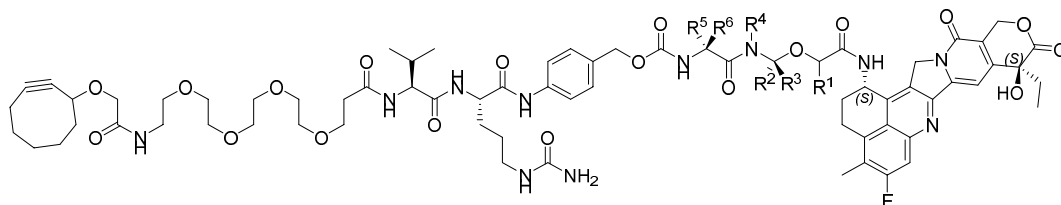
B is selected from the group consisting of ;

W is NH, O, CO, CH_2 , a phenyl, or a combination of two or more thereof; and

R^5 , R^6 , R^7 and R^8 are independently hydrogen, $-NH_2$, or a side chain of any natural or non-natural amino acid,

the method comprising a step of exposing a payload having an amino group to an activated intermediate having a para-nitro-phenyl carbonate in the presence of a base and a coupling catalyst to afford said linker-payload compound (D')-(G'), wherein said coupling catalyst is 4-Hydroxy-2-methylquinoline (MeHYQ).

28. A process for manufacturing a linker-payload compound having the formula (D-1)



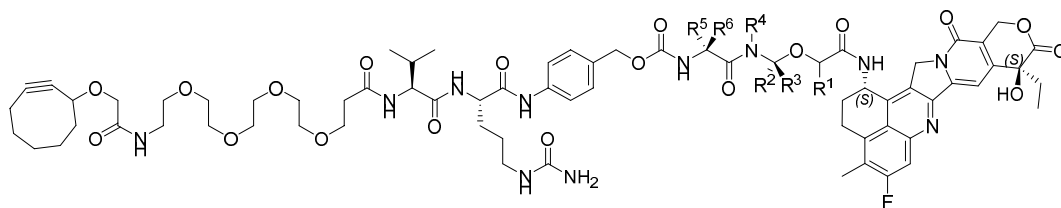
(D-1), or a pharmaceutically acceptable salt thereof,

wherein R^1 , R^2 , R^3 , and R^4 are independently hydrogen or a C_{1-5} alkyl, and

R^5 and R^6 are independently hydrogen, $-NH_2$, or a side chain of any natural or non-natural amino acid,

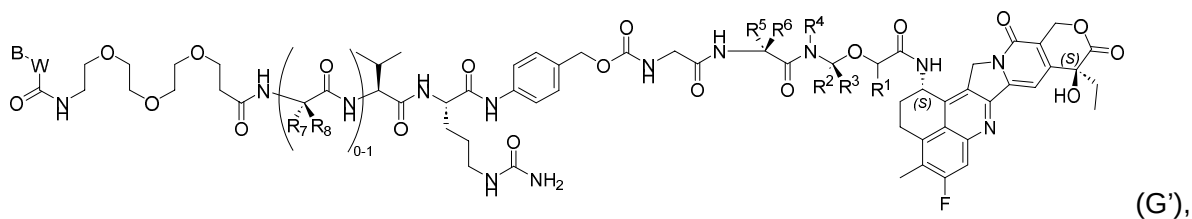
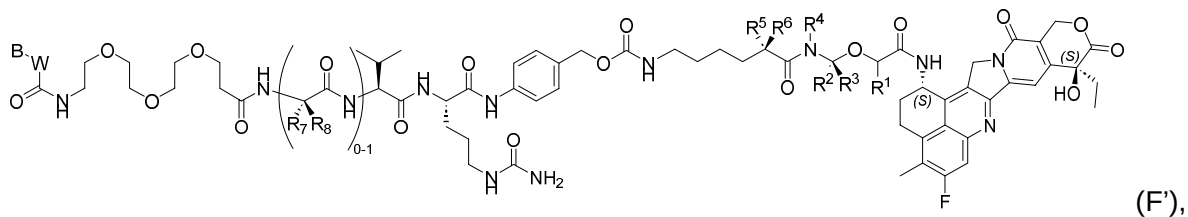
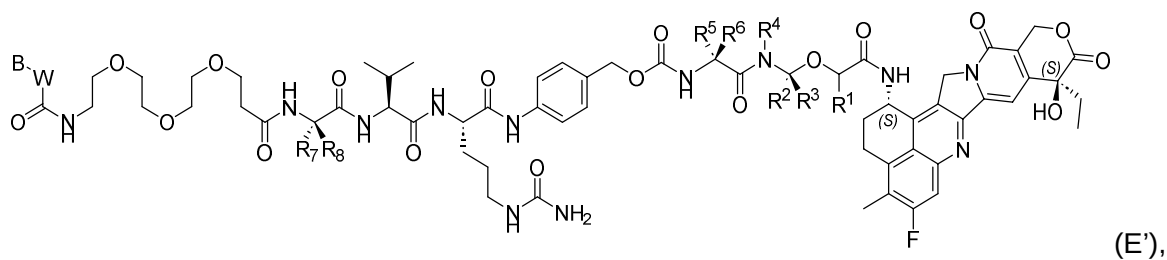
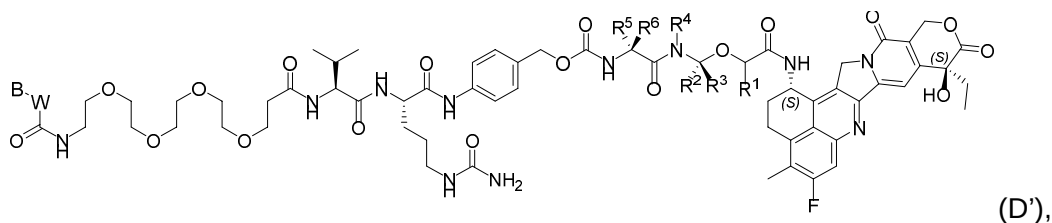
the method comprising a step of exposing a drug payload having an amino group to an activated intermediate having a para-nitro-phenyl carbonate in the presence of a base and a coupling catalyst to afford said linker-payload compound (D), wherein said coupling catalyst is 4-Hydroxy-2-methylquinoline (MeHYQ).

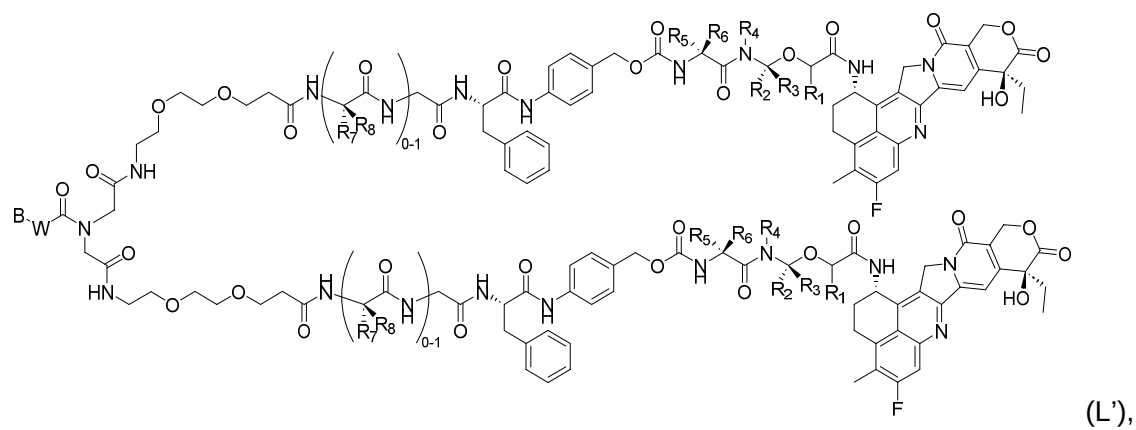
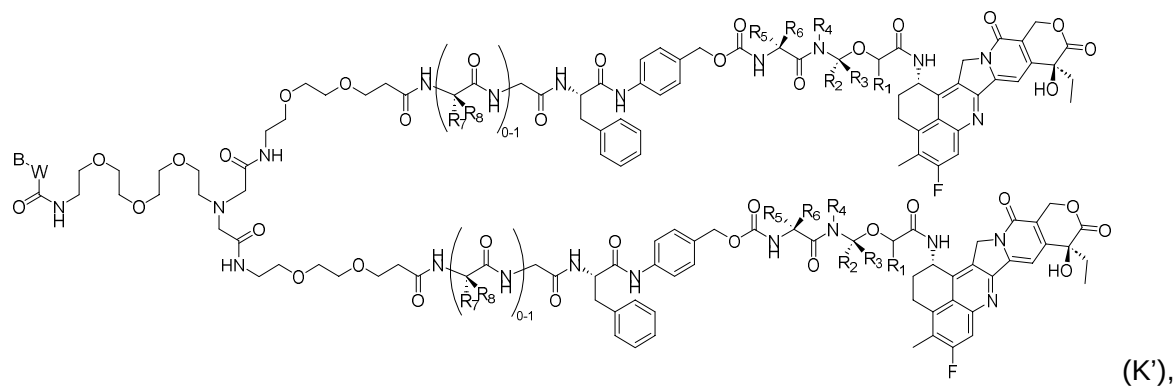
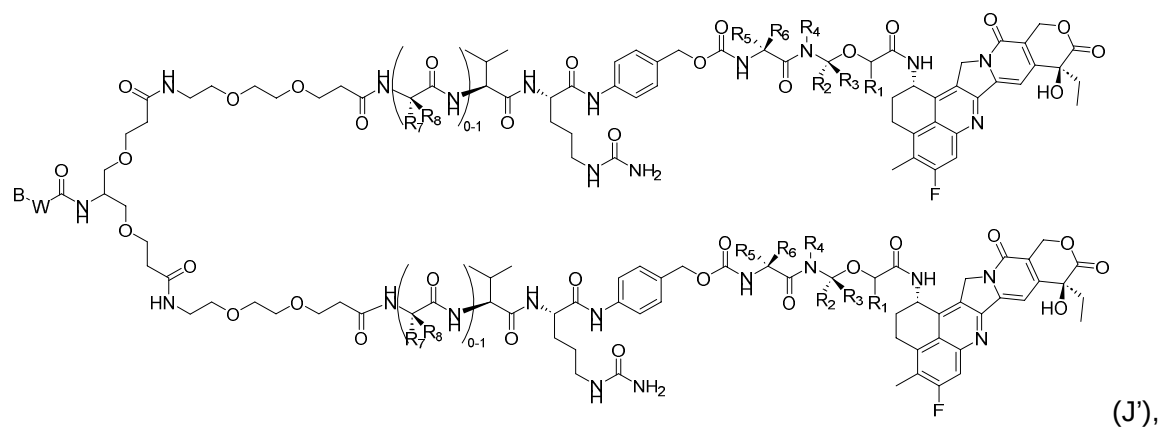
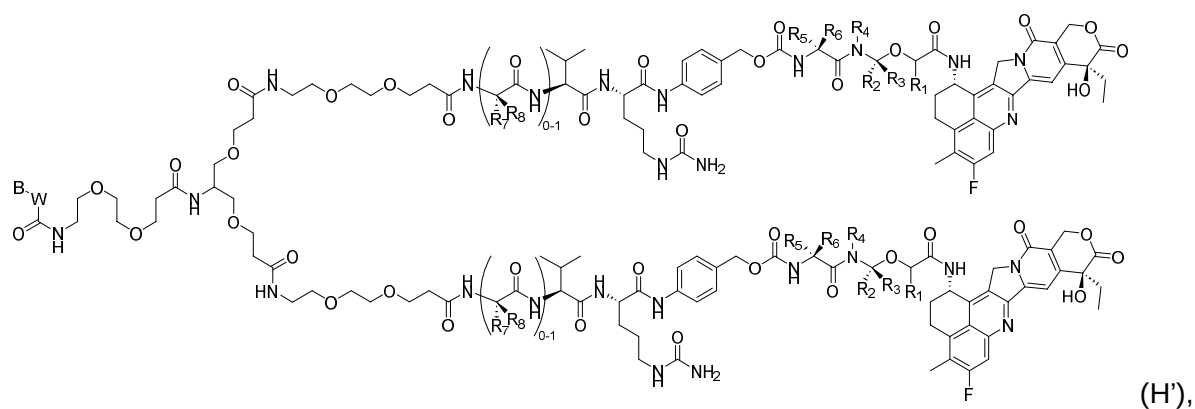
29. A linker-payload compound of formula (D),

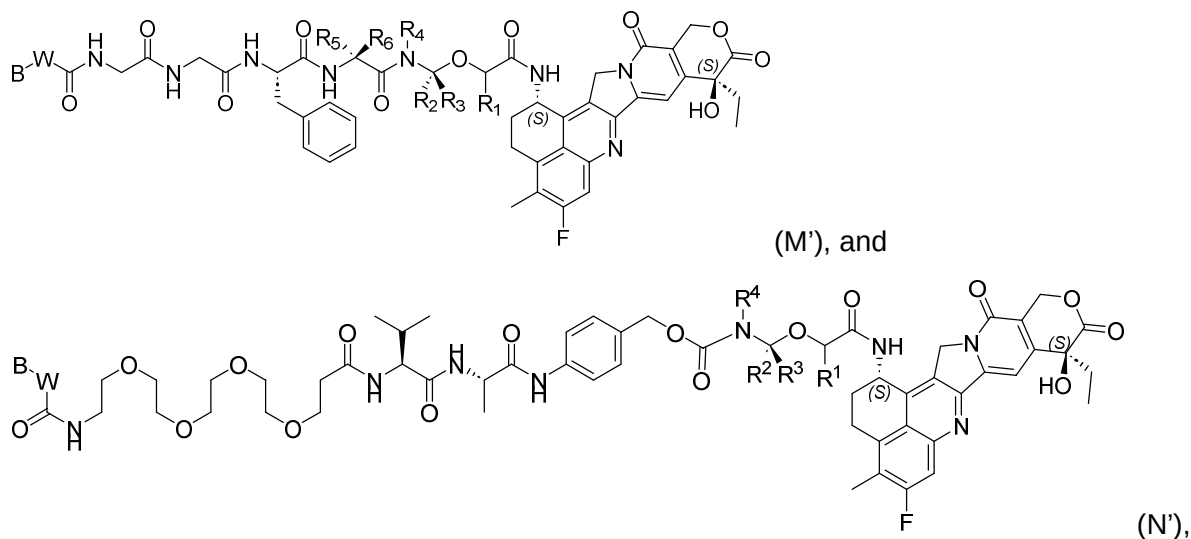


(D), or a pharmaceutically acceptable salt thereof,
 wherein R^1 , R^2 , R^3 , and R^4 are independently hydrogen or a C_{1-5} alkyl, and
 R^5 and R^6 are independently hydrogen, $-NH_2$, or a side chain of any natural or non-natural amino acid.

30. A linker-payload compound having the formula selected from the group consisting of (D') to (N'):







or a pharmaceutically acceptable salt thereof,

wherein R^1 , R^2 , R^3 , and R^4 are independently hydrogen or a C_{1-5} alkyl;

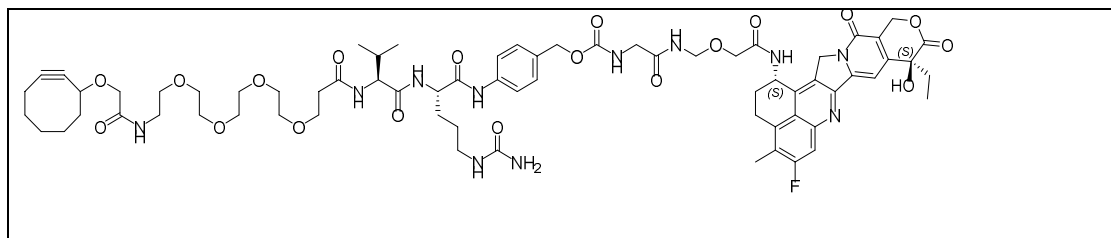
B is selected from the group consisting of , , and ;

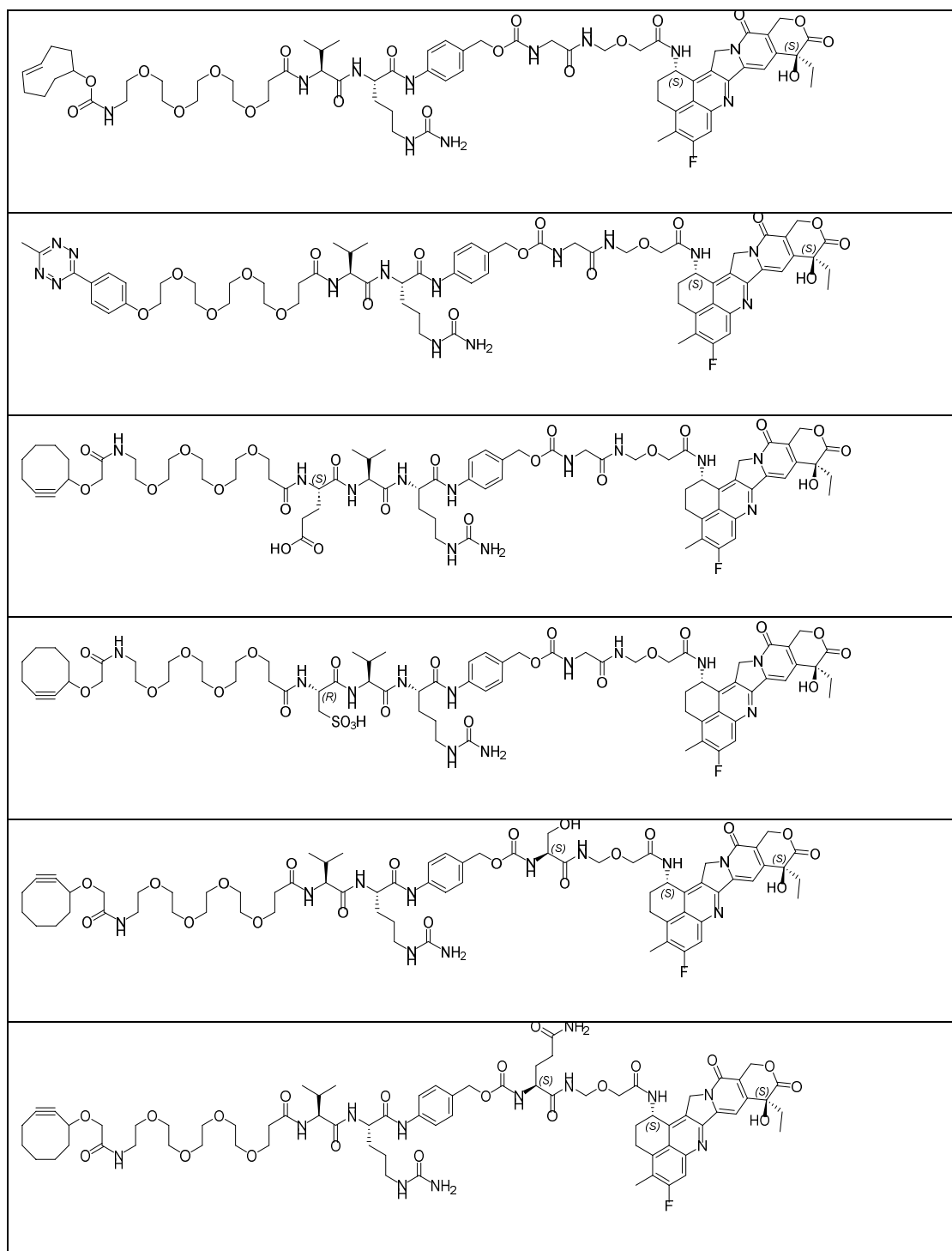
W is NH, O, CO, CH_2 , a phenyl, or a combination of two or more thereof; and

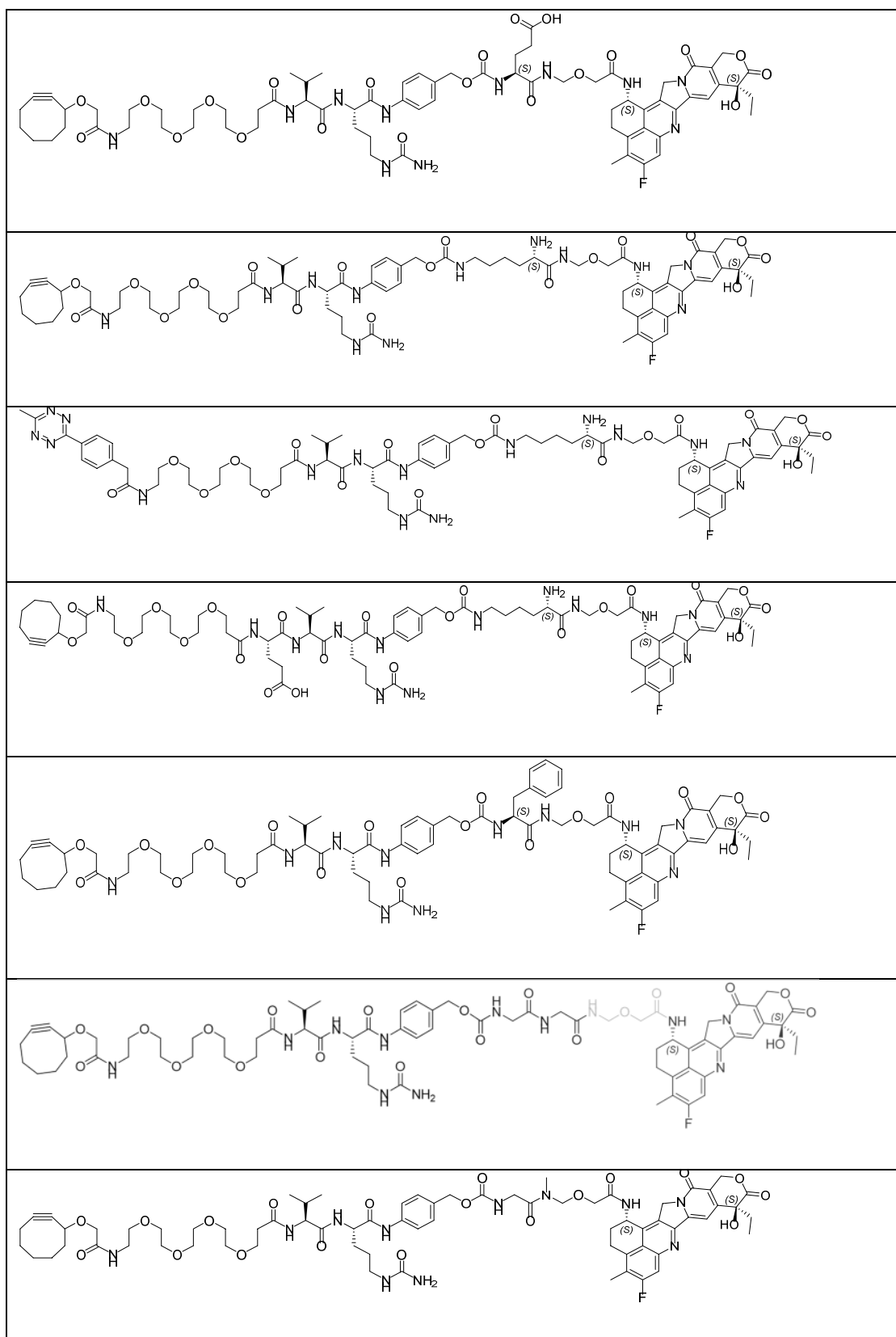
R^5 , R^6 , R^7 and R^8 are independently hydrogen, $-NH_2$, or a side chain of any natural or non-natural amino acid,

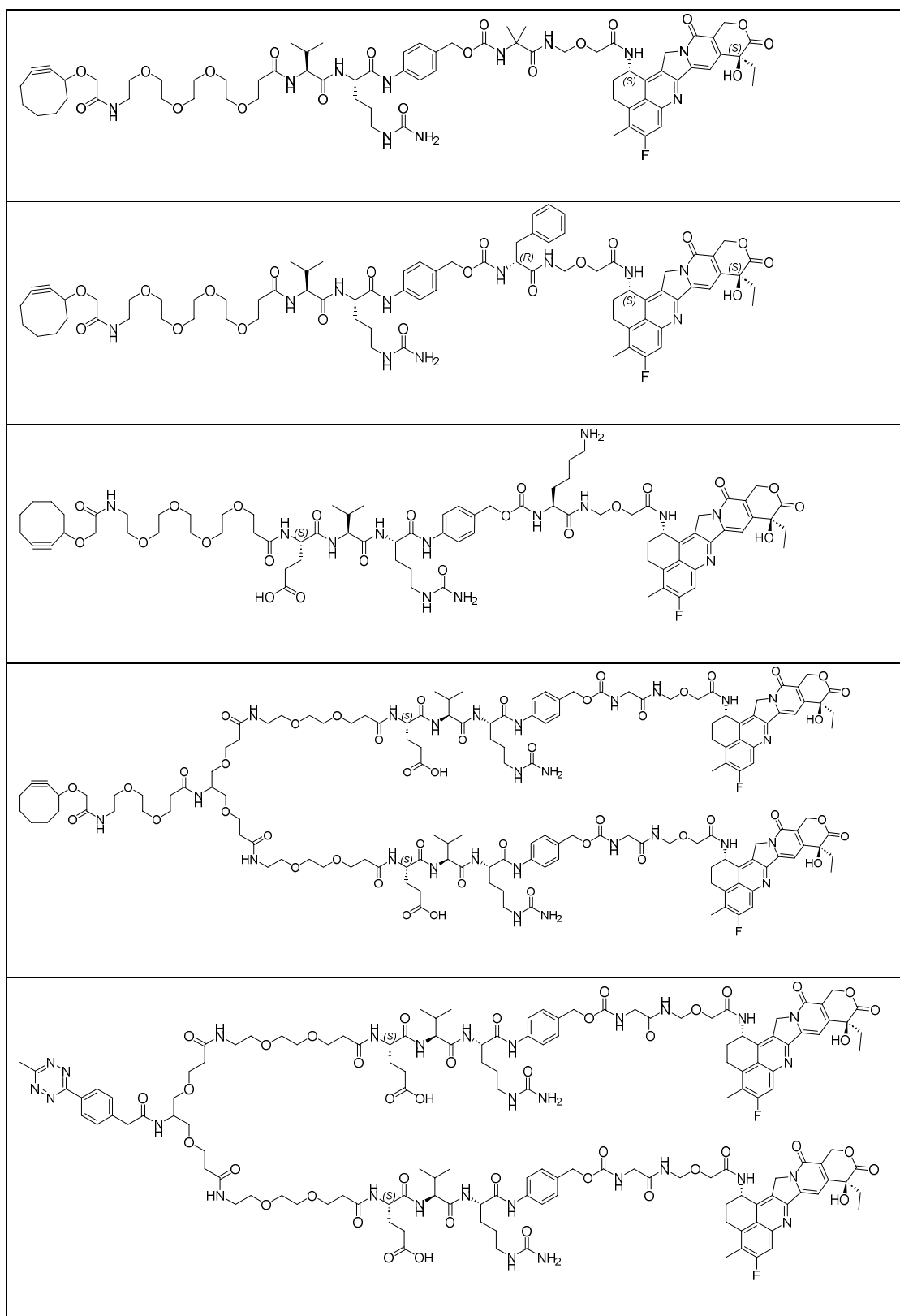
the method comprising a step of exposing a payload having an amino group to an activated intermediate having a para-nitro-phenyl carbonate in the presence of a base and a coupling catalyst to afford said linker-payload compound (D')-(G'), wherein said coupling catalyst is 4-Hydroxy-2-methylquinoline (MeHYQ).

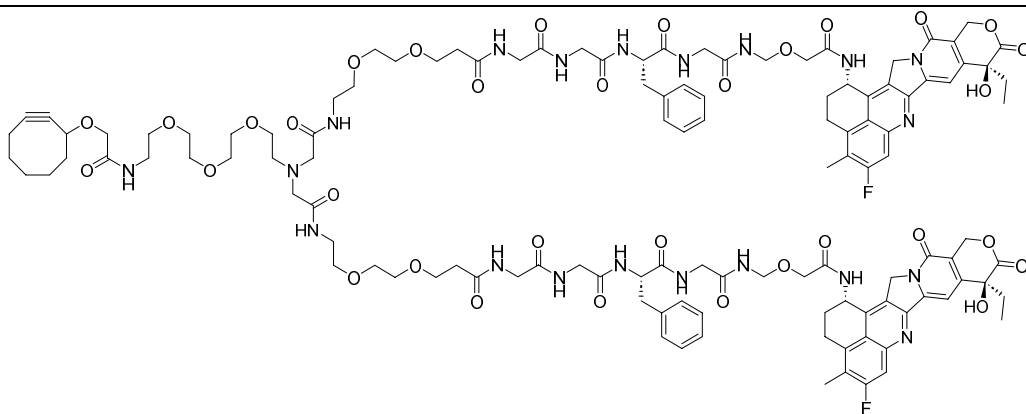
31. The linker-payload compound of claim 30 having the structure selected from the group consisting of:



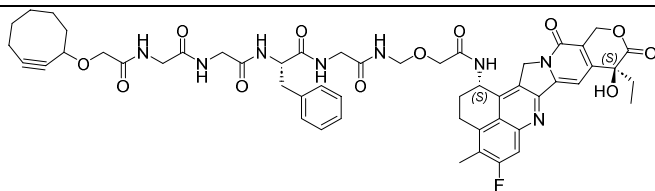




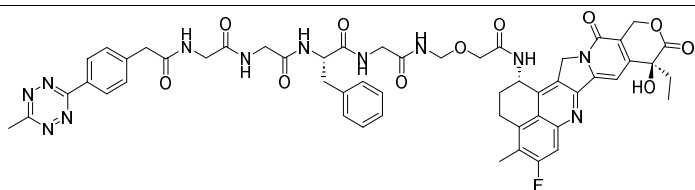




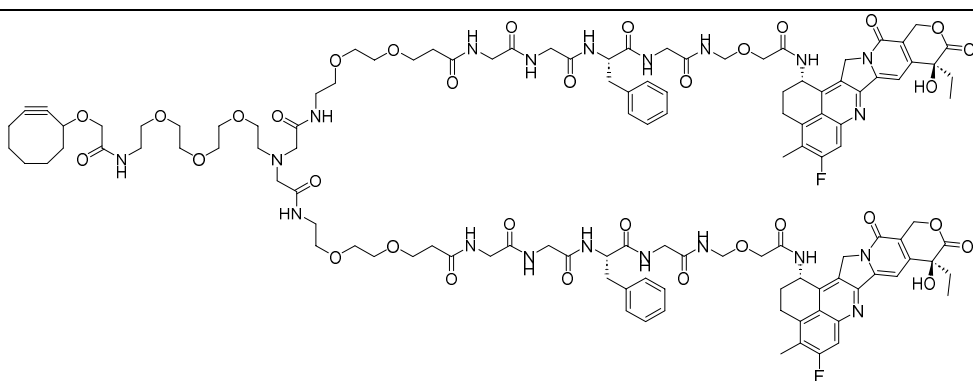
(SEQ ID NOS 2119 and 2119, respectively)



(SEQ ID NO: 2117)

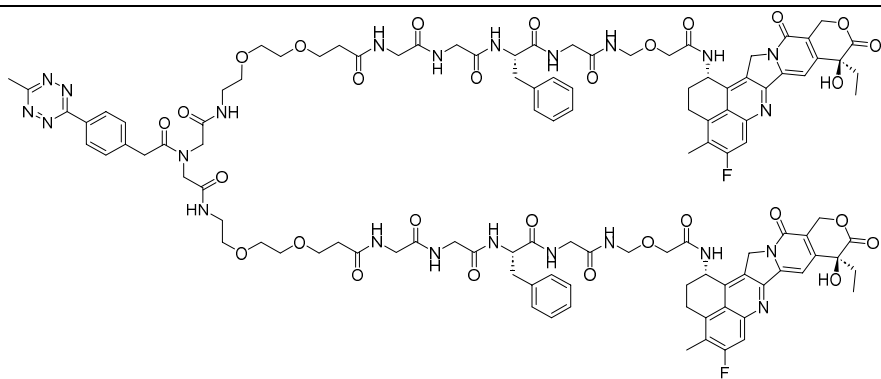


(SEQ ID NO: 2118)



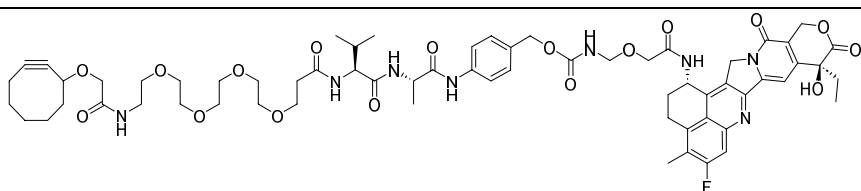
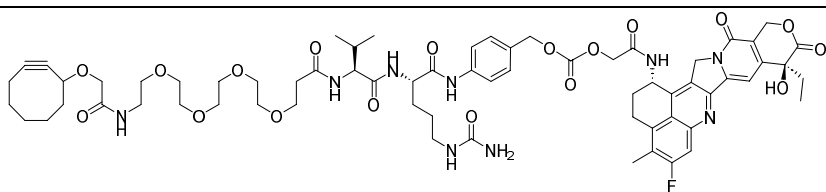
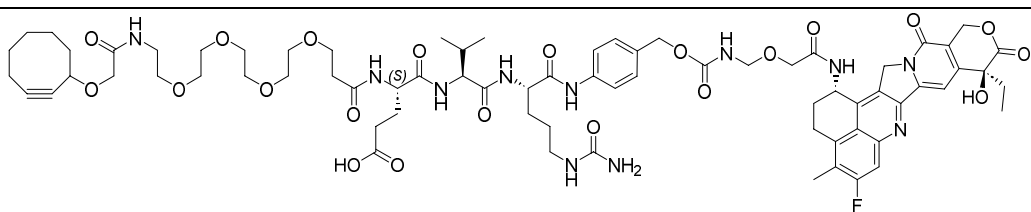
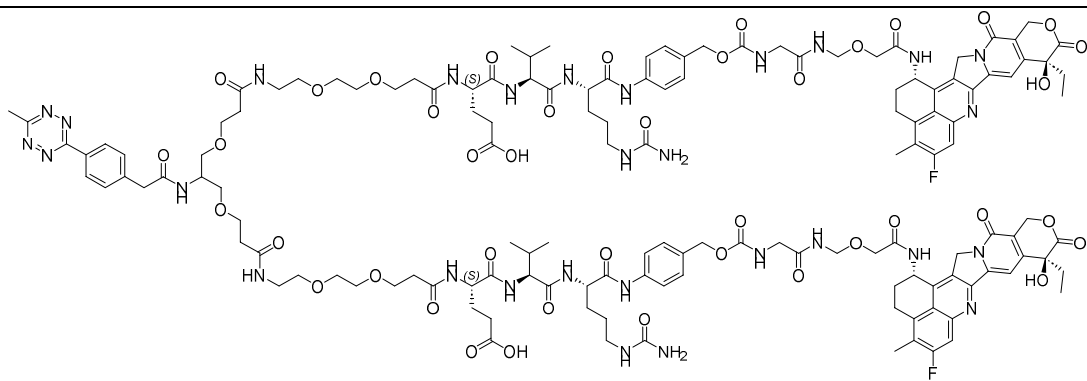
(SEQ

ID NOS 2119 and 2119, respectively)

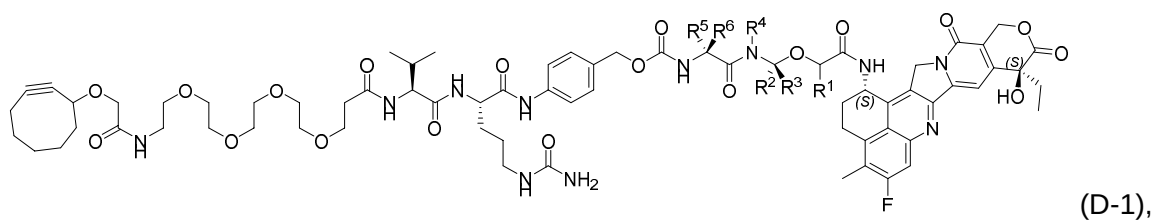


(SEQ ID NOS

2120 and 2120, respectively)



32. A process for preparation of a compound of Formula (D-1):



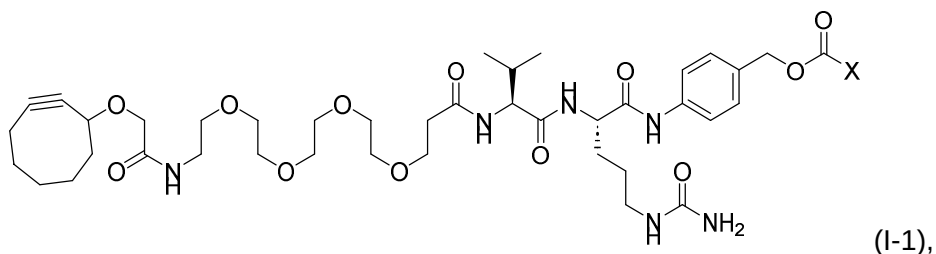
or a pharmaceutically acceptable salt thereof,

wherein R^1 , R^2 , R^3 , and R^4 are independently hydrogen or a C_{1-5} alkyl, and

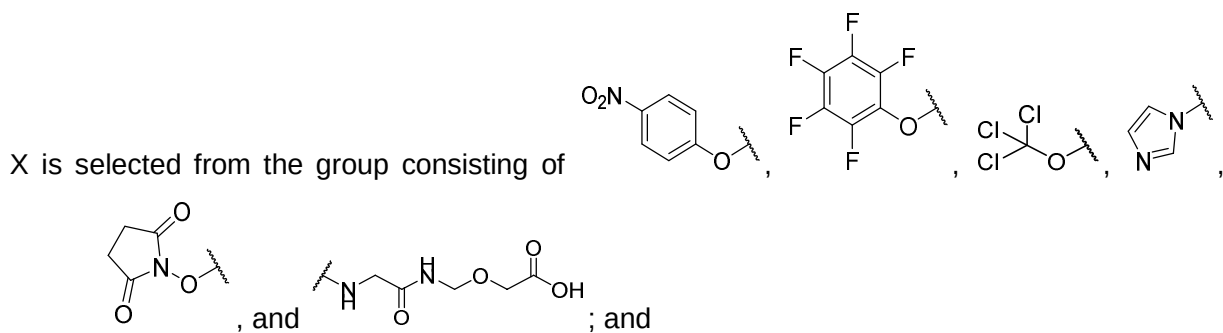
R^5 and R^6 are independently hydrogen, $-NH_2$, or a side chain of any natural or non-natural amino acid,

said process comprising:

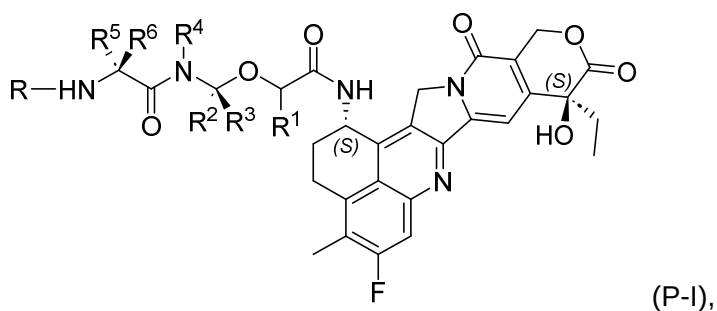
(a) providing a compound of Formula (I-1) having the structure:



wherein



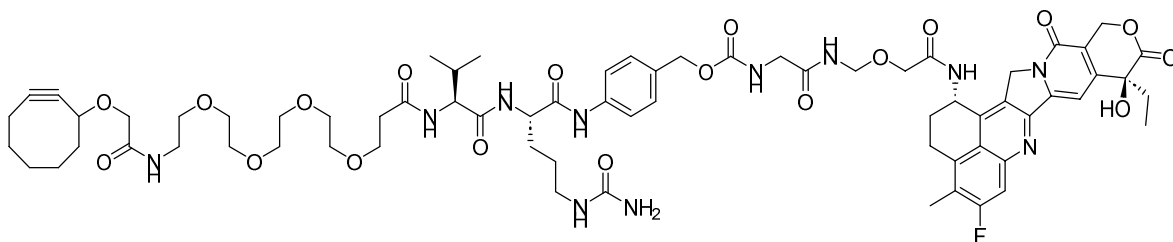
(b) reacting the compound of Formula (I-1) with a compound of Formula (P-I):



wherein

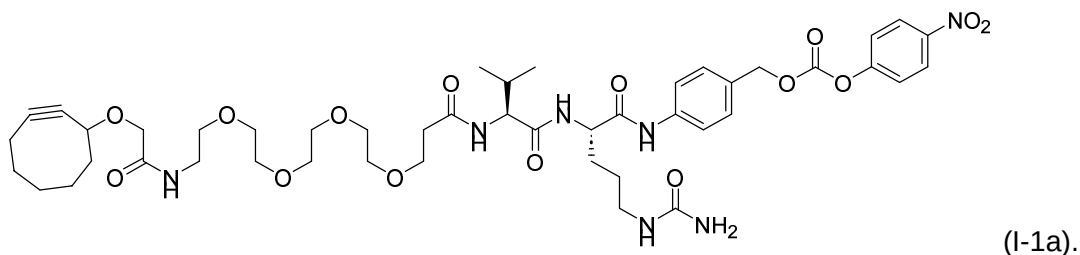
PG is a suitable protecting group;

33. The process of claim 32, wherein the compound of Formula (D-1) has the following structure:

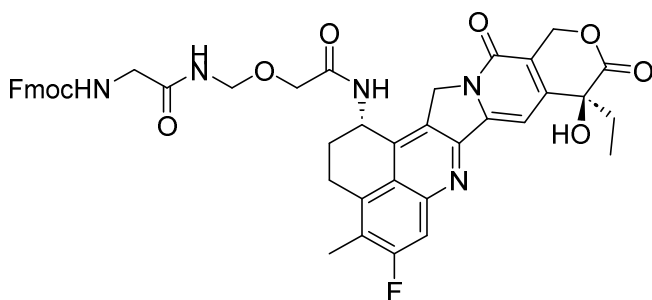


reacting the compound of Formula (P-I), wherein R is PG, with a protecting group removing agent prior to said reacting with the compound of Formula (I-1).

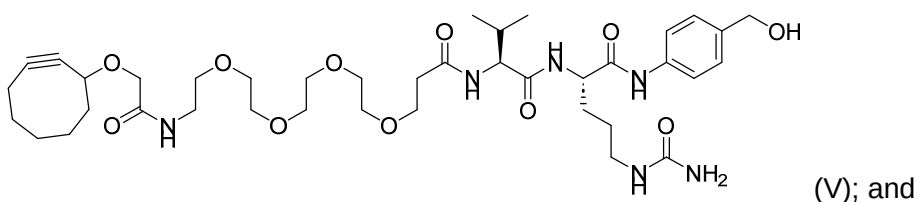
36. The process of claim 32, wherein the compound of Formula (I-1) has the following structure:



302

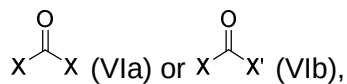


38. The process according to claim 32 further comprising the steps of:
providing a compound of Formula (V) having the structure:



forming the compound of Formula (I-1) from the compound of Formula (V) prior to the step (a).

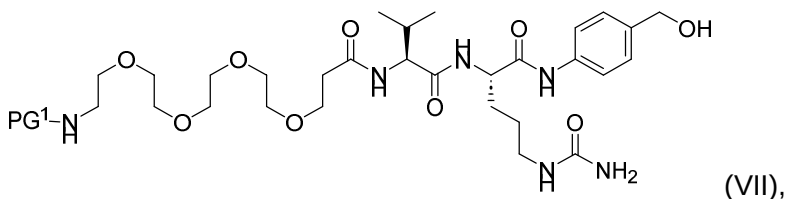
39. The process according to claim 38, wherein said step of forming the compound of Formula (I-1) comprises:
reacting the compound of Formula (V) with a compound of Formula (VIa) or Formula (VIb):



wherein X' is halogen,

to produce the compound of Formula (I-1).

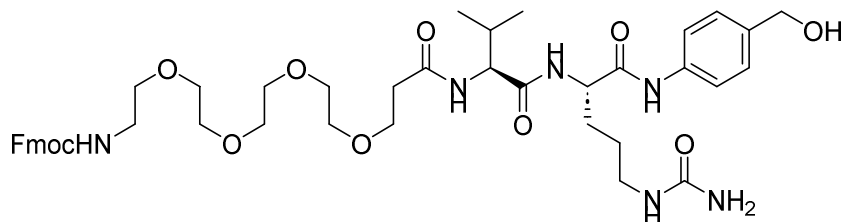
40. The process according to claim 38 further comprising the steps of:
providing a compound of Formula (VII) having the structure:



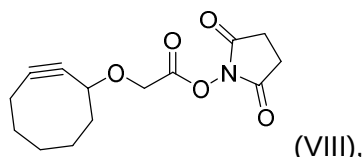
wherein PG^1 is a suitable protecting group, and

forming the compound of Formula (V) from the compound of Formula (VII).

41. The process of claim 40, wherein the compound of Formula (VII) has the following structure:

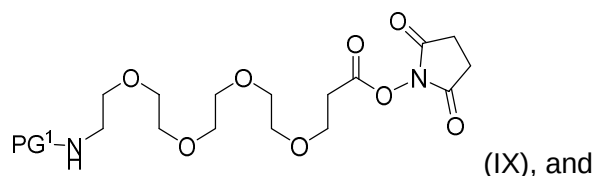


42. The process according to claim 40, wherein said step of forming the compound of Formula (V) comprises:
reacting the compound of Formula (VII) with a compound of Formula (VIII):



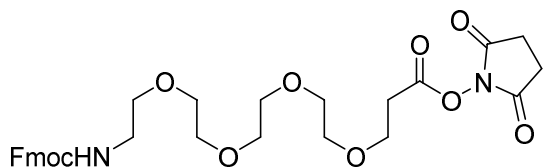
to produce the compound of Formula (V).

43. The process according to claim 40 further comprising the steps of:
providing a compound of Formula (IX) having the structure:

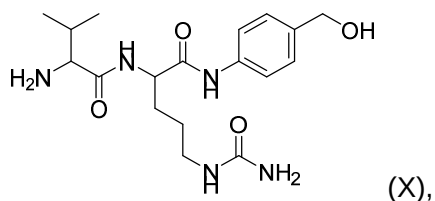


forming the compound of Formula (VII) from the compound of Formula (IX).

44. The process of claim 43, wherein the compound of Formula (IX) has the following structure:

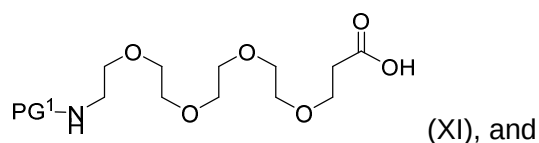


45. The process according to claim 43, wherein said step of forming the compound of Formula (VII) comprises:
reacting the compound of Formula (IX) with a compound of Formula (X):



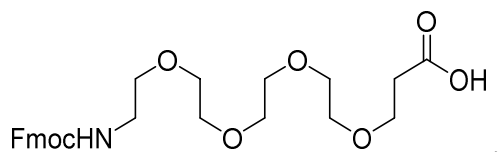
to produce the compound of Formula (VII).

46. The process according to claim 43 further comprising the steps of:
providing a compound of Formula (XI) having the structure:

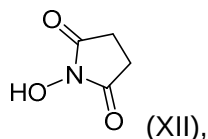


forming the compound of Formula (IX) from the compound of Formula (XI).

47. The process of claim 46, wherein the compound of Formula (XI) has the following structure:

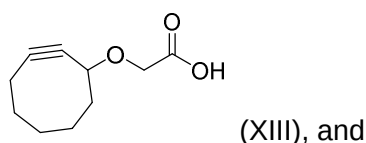


48. The process according to claim 46, wherein said step of forming the compound of Formula (IX) comprises:
reacting the compound of Formula (XI) with a compound of Formula (XII):



to produce the compound of Formula (IX).

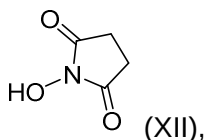
49. The process according to claim 42 further comprising the steps of:
providing a compound of Formula (XIII) having the structure:



forming the compound of Formula (VIII) from the compound of Formula (XIII).

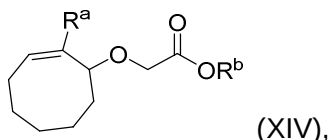
50. The process according to claim 49, wherein said step of forming the compound of Formula (VIII) comprises:

reacting the compound of Formula (XIII) with a compound of Formula (XII):



to produce the compound of Formula (VIII).

51. The process according to claim 49 further comprising the steps of:
providing a compound of Formula (XIV) having the structure:

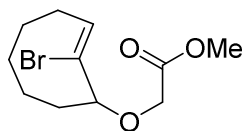


wherein R^a is halogen;

R^b is C₁₋₆ alkyl; and

forming the compound of Formula (XIII) from the compound of Formula (XIV).

52. The process of claim 51, wherein the compound of Formula (XIV) has the following structure:

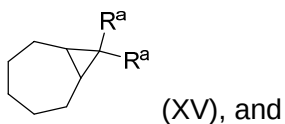


53. The process according to claim 51, wherein said step of forming the compound of Formula (XIII) comprises:

reacting the compound of Formula (XIV) with a base to produce the compound of Formula (XIII).

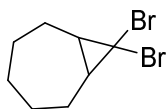
54. The process according to claim 53, wherein the base is selected from the group consisting of NaOMe, t-BuOK, NaH, and LDA.

55. The process according to claim 51 further comprising the steps of:
providing a compound of Formula (XV) having the structure:



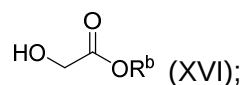
forming the compound of Formula (XIV) from the compound of Formula (XV).

56. The process of claim 55, wherein the compound of Formula (XV) has the following structure:



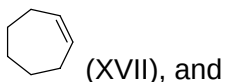
57. The process according to claim 55, wherein said step of forming the compound of Formula (XIV) comprises:

reacting the compound of Formula (XV) with a compound of Formula (XVI):



to produce the compound of Formula (XIV).

58. The process according to claim 55 further comprising the steps of:
providing a compound of Formula (XVII) having the structure:



forming the compound of Formula (XV) from the compound of Formula (XVII).

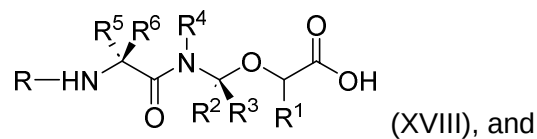
59. The process according to claim 58, wherein said step of forming the compound of Formula (XV) comprises:

reacting the compound of Formula (XVII) with a bromination agent to produce the compound of Formula (XVII).

60. The process according to claim 59, wherein the bromination agent is CHBr_3 .

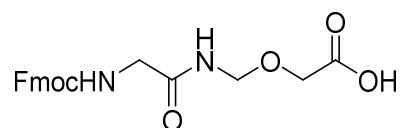
61. The process according to claim 32, further comprising the steps of:

providing a compound of Formula (XVIII) having the structure:

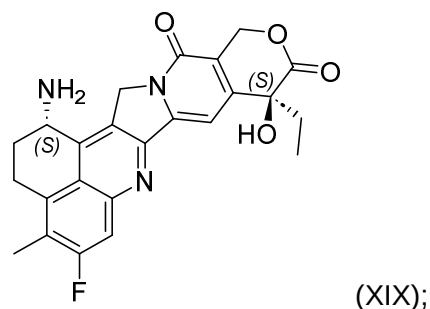


forming the compound of Formula (P-I) from the compound of Formula (XVIII).

62. The process of claim 61, wherein the compound of Formula (XVIII) has the following structure:

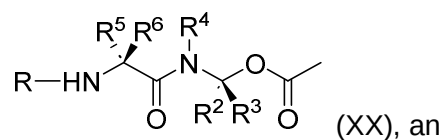


63. The process according to claim 61, wherein the step of forming the compound of Formula (P-I) comprises:
reacting the compound of Formula (XVIII) with a compound of Formula (XIX):



to produce the compound of Formula (P-I).

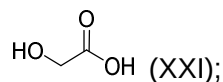
64. The process according to claim 61, further comprising the steps of:
providing a compound of Formula (XX) having the structure:



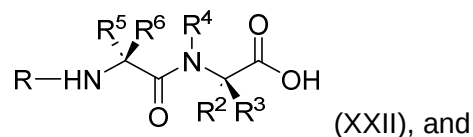
forming the compound of Formula (XVIII) from the compound of Formula (XX).

65. The process of claim 64, wherein the compound of Formula (XX) has the following structure:
g.

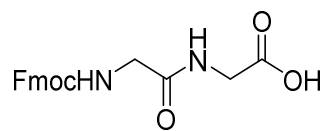
- reacting the compound of Formula (XX) with a compound of Formula (XXI):



67. The process according to claim 64, further comprising the steps of:
providing a compound of Formula (XXII) having the structure:

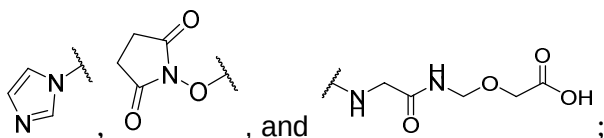


68. The process of claim 67, wherein the compound of Formula (XXII) has the following structure:

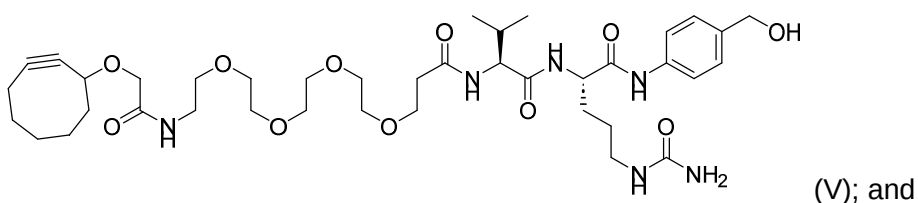


- CC(C)[C@H](NC(=O)NCCCNC(=O)Nc1ccc(COC(=O)X)cc1)C(=O)NCCOCOCOCOCOC(=O)Nc2c3ccccc3oc2
- (I-1),

309



(a) providing a compound of Formula (V) having the structure:



70. The process according to claim 69, wherein said step (b) of forming the compound of Formula (I-1) comprises:

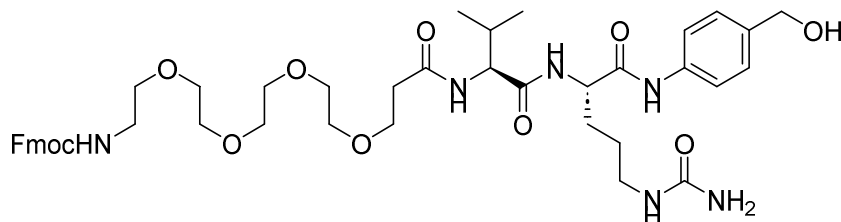
$$X-\overset{\overset{O}{\parallel}}{C}-X \text{ (VIa) or } X-\overset{\overset{O}{\parallel}}{C}-X' \text{ (VIb),}$$

X' is halogen,

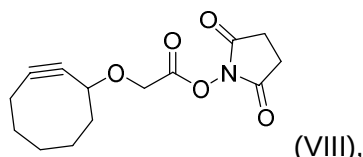
71. The process according to claim 69 further comprising the steps of:

forming the compound of Formula (V) from the compound of Formula (VII).

72. The process of claim 71, wherein the compound of Formula (VII) has the following structure:

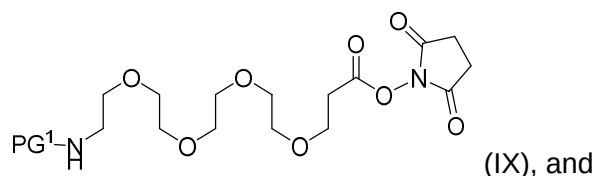


73. The process according to claim 71, wherein said step of forming the compound of Formula (V) comprises:
reacting the compound of Formula (VII) with a compound of Formula (VIII):



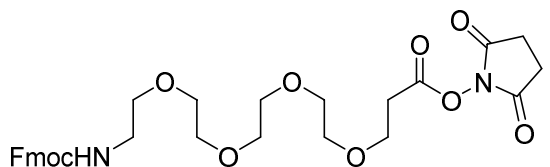
to produce the compound of Formula (V).

74. The process according to claim 71 further comprising the steps of:
providing a compound of Formula (IX) having the structure:

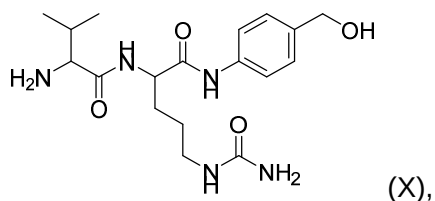


forming the compound of Formula (VII) from the compound of Formula (IX).

75. The process of claim 74, wherein the compound of Formula (IX) has the following structure:

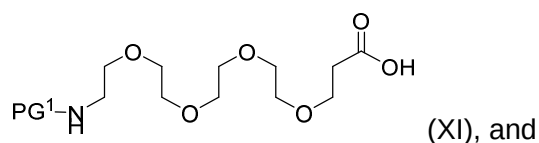


76. The process according to claim 74, wherein said step of forming the compound of Formula (VII) comprises:
reacting the compound of Formula (IX) with a compound of Formula (X):



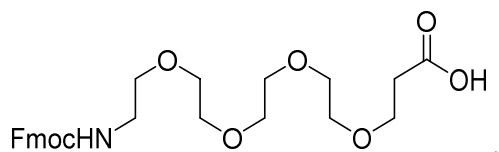
to produce the compound of Formula (VII).

77. The process according to claim 74 further comprising the steps of:
providing a compound of Formula (XI) having the structure:

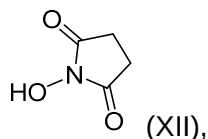


forming the compound of Formula (IX) from the compound of Formula (XI).

78. The process of claim 77, wherein the compound of Formula (XI) has the following structure:

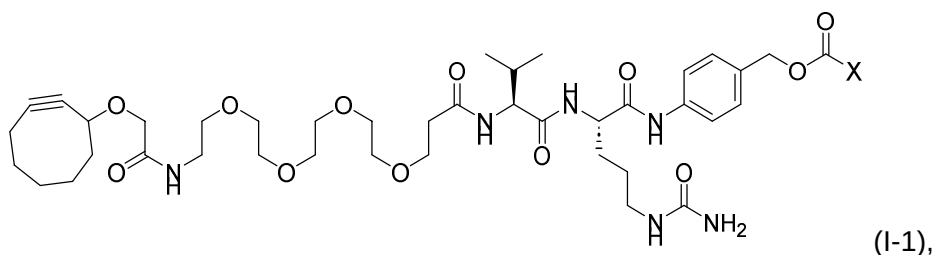


79. The process according to claim 77, wherein said step of forming the compound of Formula (IX) comprises:
reacting the compound of Formula (XI) with a compound of Formula (XII):

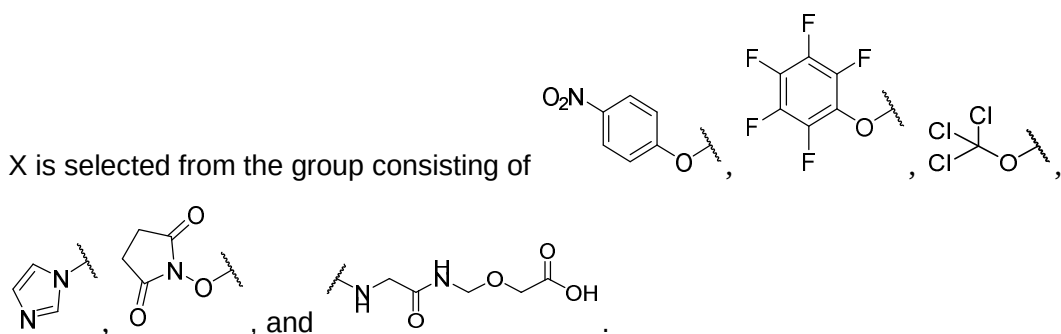


to produce the compound of Formula (IX).

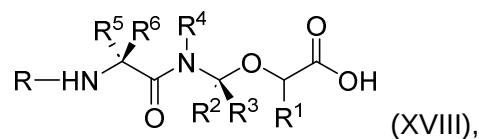
80. A compound of Formula (I-1):



or a pharmaceutically acceptable salt thereof,
wherein

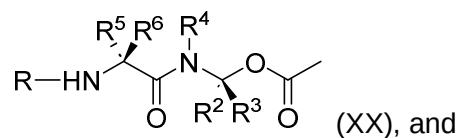


81. A process for preparation of a compound of Formula (XVIII):



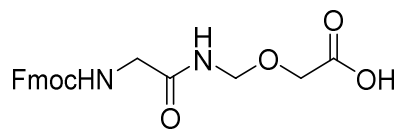
or a pharmaceutically acceptable salt thereof,
wherein R^1 , R^2 , R^3 , and R^4 are independently hydrogen or a C_{1-5} alkyl, and
 R^5 and R^6 are independently hydrogen, $-NH_2$, or a side chain of any natural or non-natural amino acid,
said process comprising:

- (a) providing a compound of Formula (XX) having the structure:

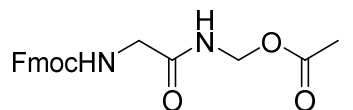


- (b) forming the compound of Formula (XVIII) from the compound of Formula (XX).

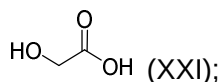
82. The process of claim 81, wherein the compound of Formula (XVIII) has the following structure:



83. The process of claim 81, wherein the compound of Formula (XX) has the following structure:

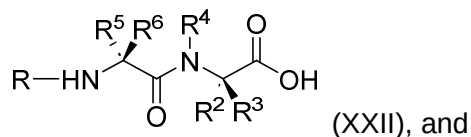


84. The process according to claim 81, wherein the step of forming the compound of Formula (XVIII) comprises:
reacting the compound of Formula (XX) with a compound of Formula (XXI):



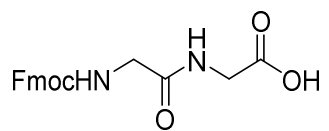
to produce the compound of Formula (XVIII).

85. The process according to claim 81, further comprising the steps of:
providing a compound of Formula (XXII) having the structure:

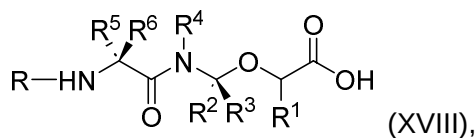


forming the compound of Formula (XX) from the compound of Formula (XXII).

86. The process of claim 85, wherein the compound of Formula (XXII) has the following structure:

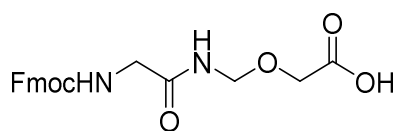


87. A compound of Formula (XVIII):

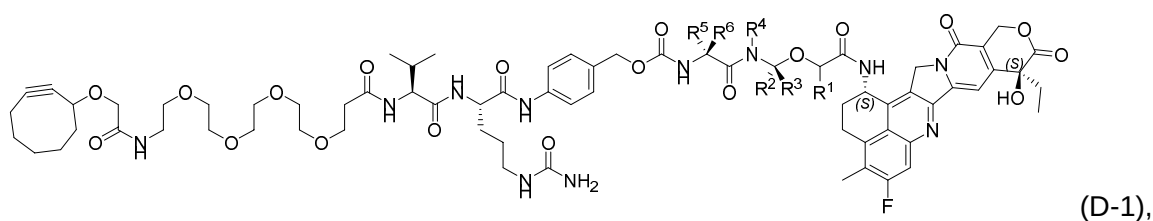


or a pharmaceutically acceptable salt thereof,
 wherein R^1 , R^2 , R^3 , and R^4 are independently hydrogen or a C_{1-5} alkyl, and
 R^5 and R^6 are independently hydrogen, $-NH_2$, or a side chain of any natural or non-natural amino acid.

88. The compound of claim 87, wherein the compound has the following structure:

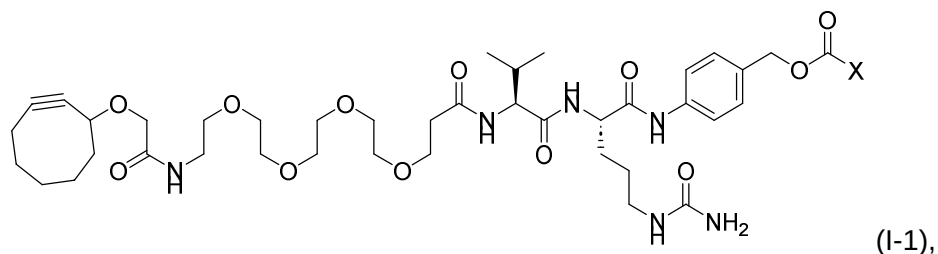


89. A process for preparation of a compound of Formula (D-1):

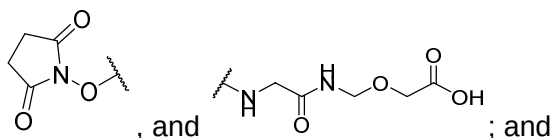


or a pharmaceutically acceptable salt thereof,
 wherein R^1 , R^2 , R^3 , and R^4 are independently hydrogen or a C_{1-5} alkyl, and
 R^5 and R^6 are independently hydrogen, $-NH_2$, or a side chain of any natural or non-natural amino acid,
 said process comprising:

- (a) providing a compound of Formula (I-1) having the structure:



wherein



(P-I),

to produce the compound of Formula (D-1).

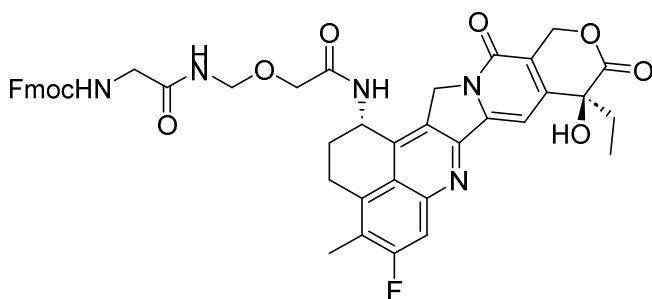
CN(C)C(=O)N[C@@H](CCCCNC(=O)N)C(=O)NCCOC(=O)NCCOC(=O)NCCOC(=O)NCCOC(=O)NCCOC(=O)Nc1ccc(cc1)COC(=O)NCC(=O)NCOCC(=O)Nc2nc3cc(F)c(C)ccc3[nH]2Cc4c(O)c(C)oc(=O)n4

316

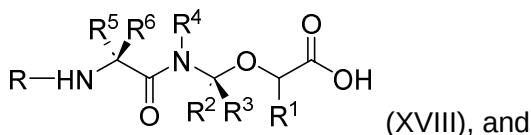
92. The process according to claim 89, wherein the PG is selected from the group consisting of allyloxycarbonyl (Alloc), benzyloxycarbonyl (Cbz), tert-butyloxycarbonyl (Boc), and 9-fluorenylmethoxycarbonyl (Fmoc).

93. The process according to claim 91, wherein the protecting group removing agent is selected from the group consisting of Pd(PPh)_3 , PhSiH_3 , H_2 , piperidine, and trifluoroacetic acid (TFA).

94. The process of claim 89, wherein the compound of Formula (P-I) has the following structure:

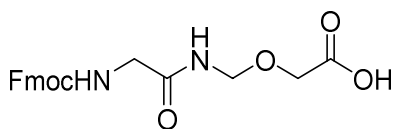


95. The process according to claim 89, further comprising the steps of:
providing a compound of Formula (XVIII) having the structure:

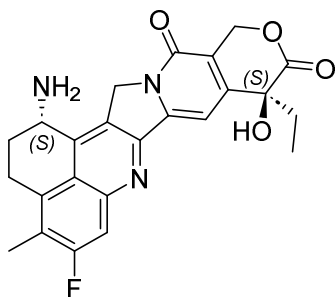


forming the compound of Formula (P-I) from the compound of Formula (XVIII).

96. The process of claim 95, wherein the compound of Formula (XVIII) has the following structure:



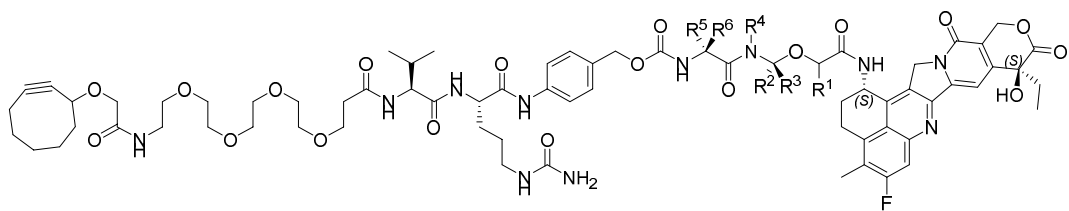
97. The process according to claim 95, wherein the step of forming the compound of Formula (P-I) comprises:
reacting the compound of Formula (XVIII) with a compound of Formula (XIX):



(XIX);

to produce the compound of Formula (P-I).

98. A process for preparation of a compound of Formula (D-1):



(D-1),

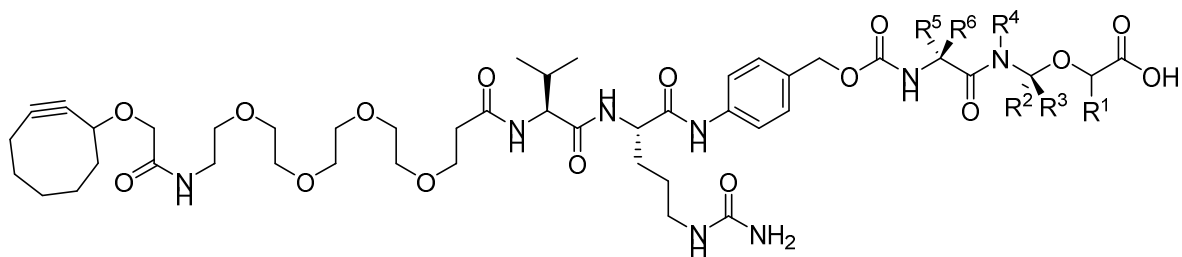
or a pharmaceutically acceptable salt thereof,

wherein R^1 , R^2 , R^3 , and R^4 are independently hydrogen or a C_{1-5} alkyl, and

R^5 and R^6 are independently hydrogen, $-NH_2$, or a side chain of any natural or non-natural amino acid,

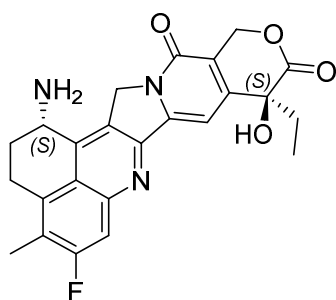
said process comprising:

(a) providing a compound of Formula (XXIII):



(XXIII); and

(b) reacting the compound of Formula (XXIII) with a compound having the structure:



in the presence of an activating reagent and a base to produce the compound of Formula (D-1).

99. The process of claim 98, wherein the compound of Formula (D-1) has the following structure:

