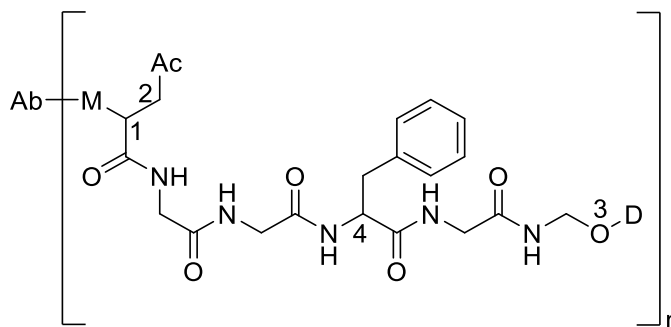


CLAIMS

What is claimed is:

1. A ligand-drug conjugate having a highly stable hydrophilic connecting unit as shown in Formula I, or its pharmaceutically acceptable salt thereof,



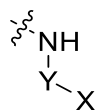
Formula I

wherein:

Ab is a ligand unit, selected from an antibody, antibody fragment, targeting protein, or Fc-fusion protein;

M is a connecting unit connected with Ab;

Ac is a hydrophilic structural unit; wherein Ac has the structure shown in Formula c,



Formula c

wherein X is a hydrophilic carboxyl group;

Y is a scaffold connecting the amino group and X;

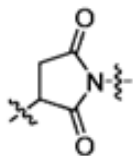
Ac is connected to the position-2 methylene carbon in formula I through the amino group;

D is a camptothecin drug;

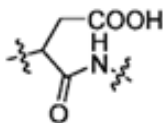
the position-1 carbon and position-4 chiral carbon each has the chirality of R or S configuration;
and

n is selected from an integer of 1-20.

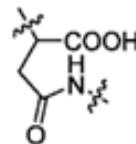
2. The ligand-drug conjugate or its pharmaceutically acceptable salt thereof according to claim 1, wherein the M has a succinimide structure represented by the Formula a, or an open-ringed succinimide structure represented by Formula b1 or b2,



Formula a
(Succinimide)



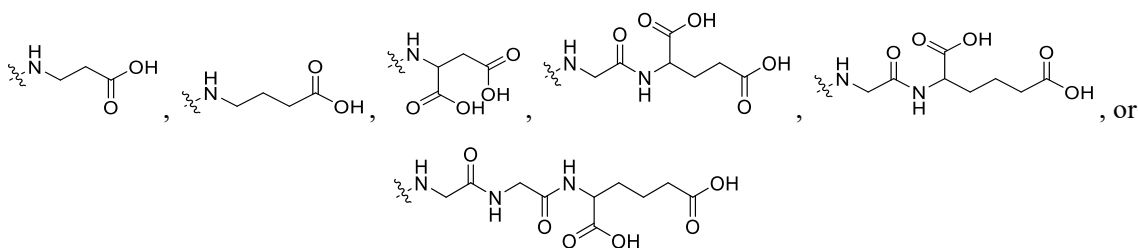
Formula b1 (Open-ringed
succinimide)



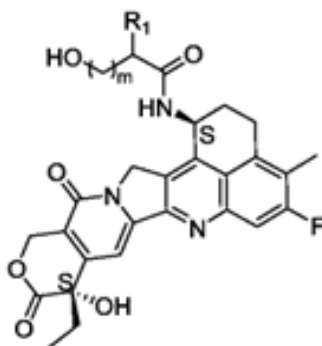
Formula b2 (Open-ringed
succinimide)

wherein, in Formula a, Formula b1, or Formula b2, the wavy line on the left represents the connection to a connection site on Ab, and the wavy line on the right indicates the connection to the position-1 tertiary carbon in formula I.

3. The ligand-drug conjugate or its pharmaceutically acceptable salt thereof according to claim 1, wherein Ac is selected from Glycine, (D/L)-Alanine, (D/L)-Leucine, (D/L)-Isoleucine, (D/L)-Valine, (D/L)-Phenylalanine, (D/L)-Tryptophan, (D/L)-Serine, (D/L)-Tyrosine, (D/L)-Cysteine, (D/L)-Arginine, (D/L)-Histidine, (D/L)-Methionine, (D/L)-Asparagine, (D/L)-Glutamine, (D/L)-Threonine, (D/L)-Aspartic acid, (D/L)-Glutamic acid or the following structures,



4. The ligand-drug conjugate or its pharmaceutically acceptable salt thereof according to claim 1, wherein the camptothecin drug has the structure shown in Formula d;



Formula d

wherein R_1 is selected from hydrogen atom, deuterium atom, halogen, alkyl, deuterated alkyl, haloalkyl, cycloalkyl, cycloalkylalkyl, alkoxyalkyl, heterocyclyl, aryl, substituted aryl, or heteroaryl; alternatively, R_1 and its connected carbon atom form a C_{3-6} cycloalkyl, cycloalkylalkyl or

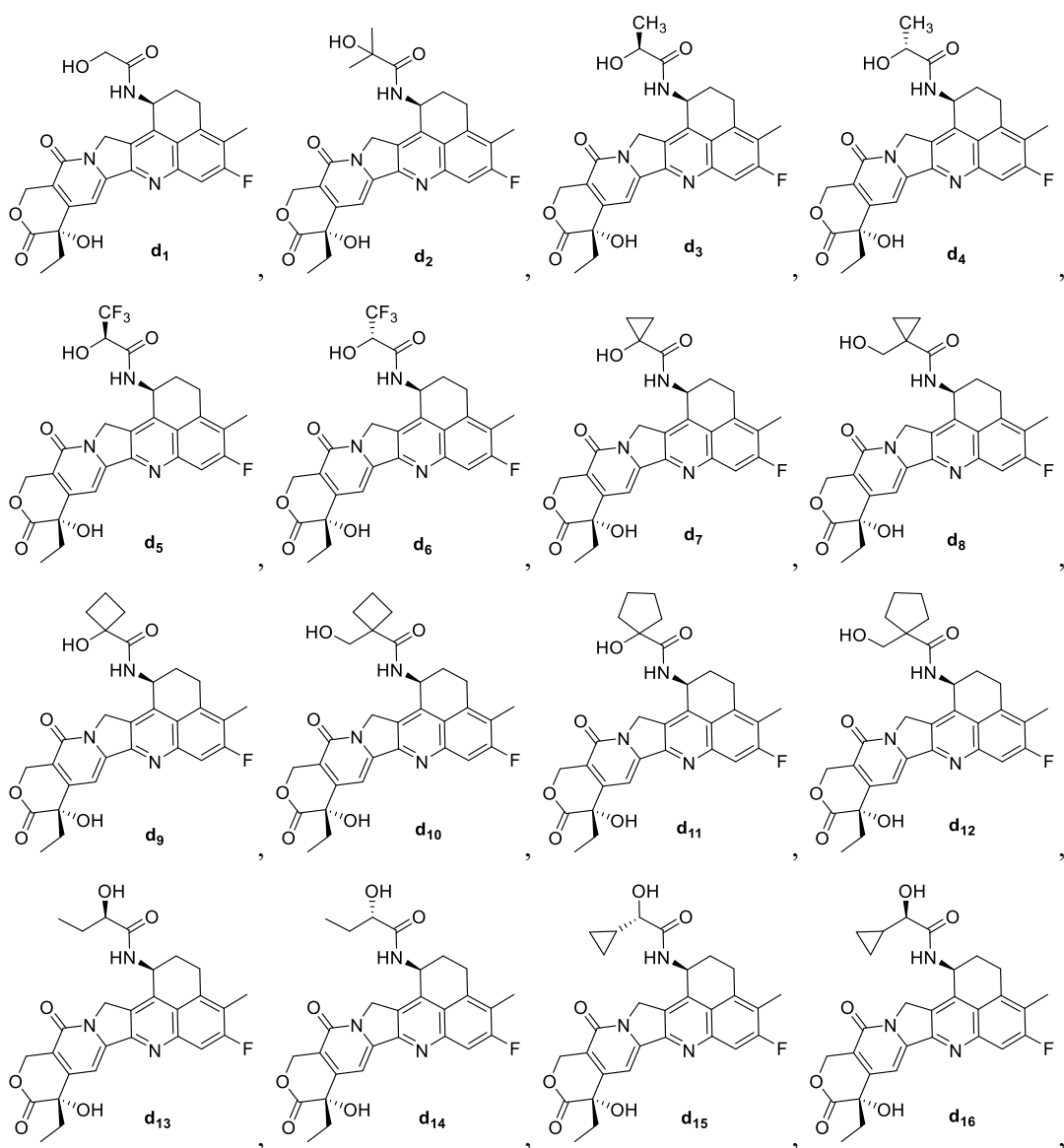
heterocyclic group;

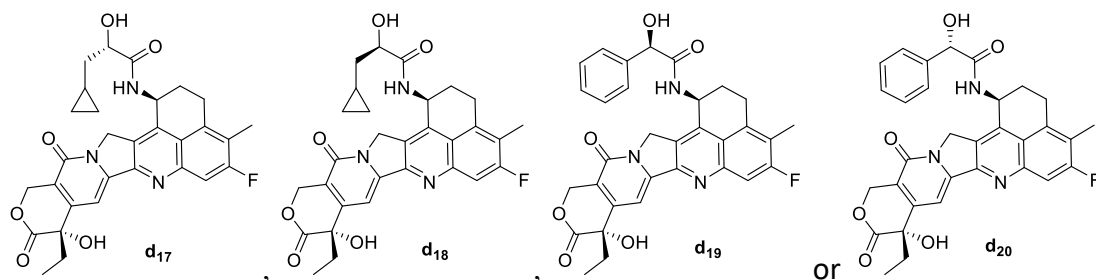
the R1-connected chiral carbon atom has R or S configuration;

m is selected from 0 or 1; and

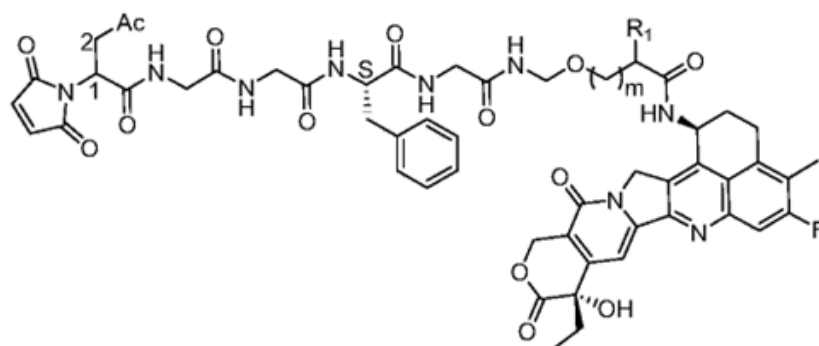
the hydroxyl group linked to the R1-connected chiral carbon in Formula d is configured to conjugate D to Ab as the position-3 oxygen atom in Formula I.

5. The ligand-drug conjugate or its pharmaceutically acceptable salt thereof according to claim 1 or 4, wherein the camptothecin drug is independently selected from the following compounds:





6. A linker-drug compound or a pharmaceutically acceptable salt thereof for coupling with the Ab ligand unit to form the ligand-drug conjugate of Formula I in claim 1, having the following structure shown in Formula II,

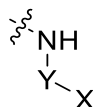


Formula II

wherein R_1 is selected from hydrogen atom, deuterium atom, halogen, alkyl, deuterated alkyl, haloalkyl, cycloalkyl, cycloalkylalkyl, alkoxyalkyl, heterocyclyl, aryl, substituted aryl, or heteroaryl; alternatively, the R_1 and its connected carbon atom form a C_{3-6} cycloalkyl, cycloalkylalkyl or heterocyclic group;

the position-1 chiral carbon has R or S configuration;

Ac is a hydrophilic structural unit; wherein Ac has the structure shown in Formula c,



Formula c

wherein X is a hydrophilic carboxyl group;

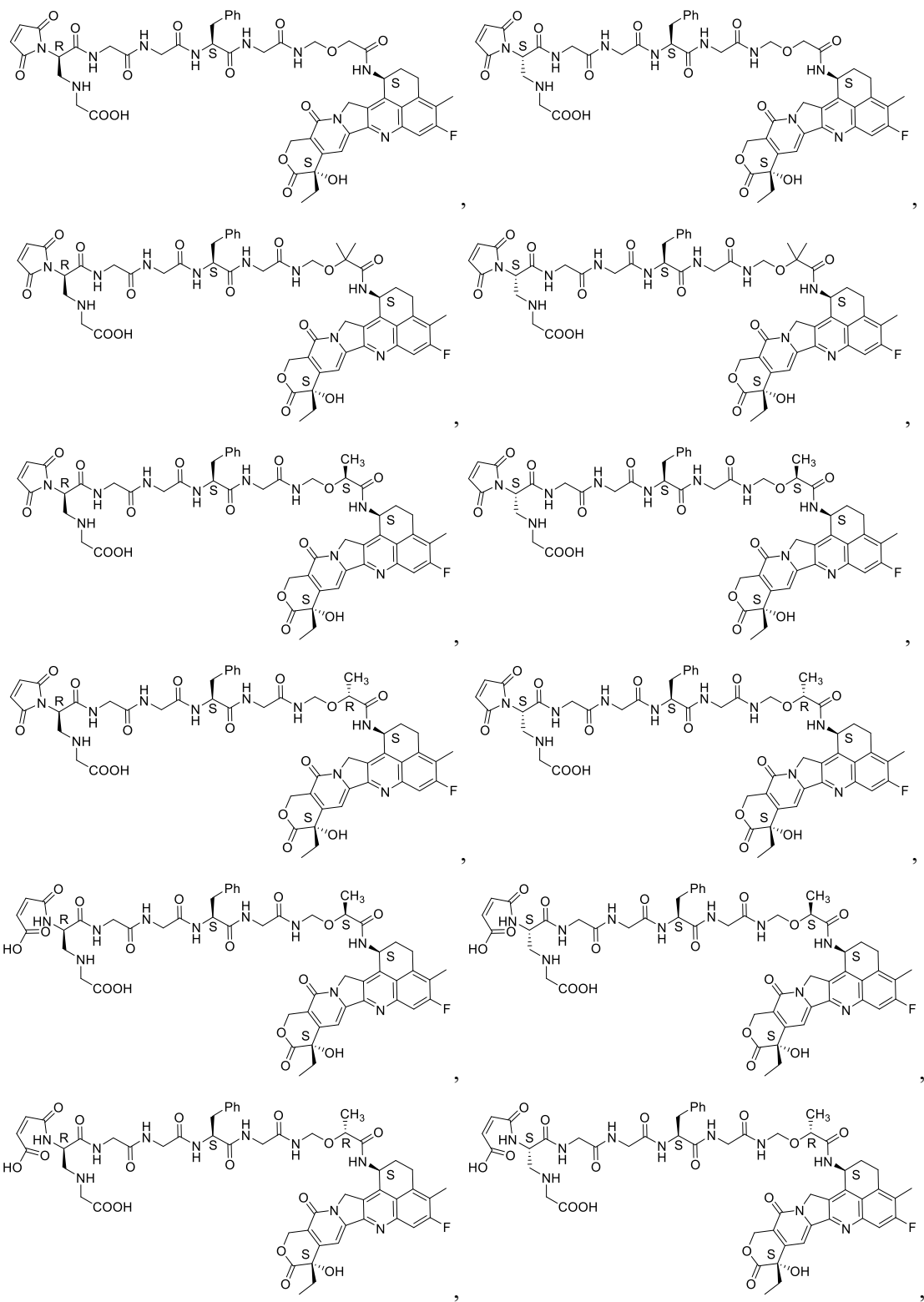
Y is a scaffold connecting the amino group and X;

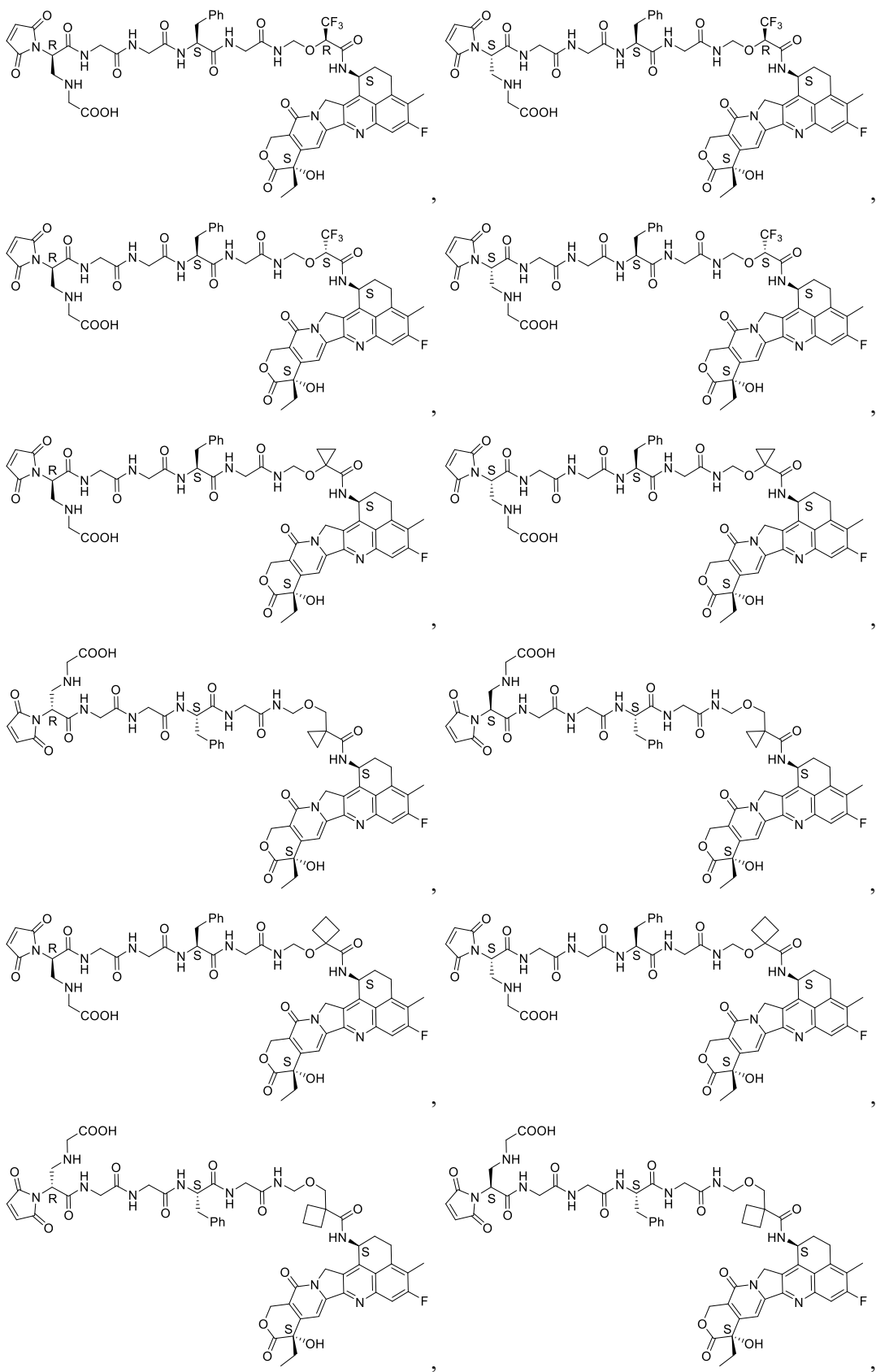
Ac is connected to the position-2 methylene carbon in formula I through the amino group; and m is 0 or 1.

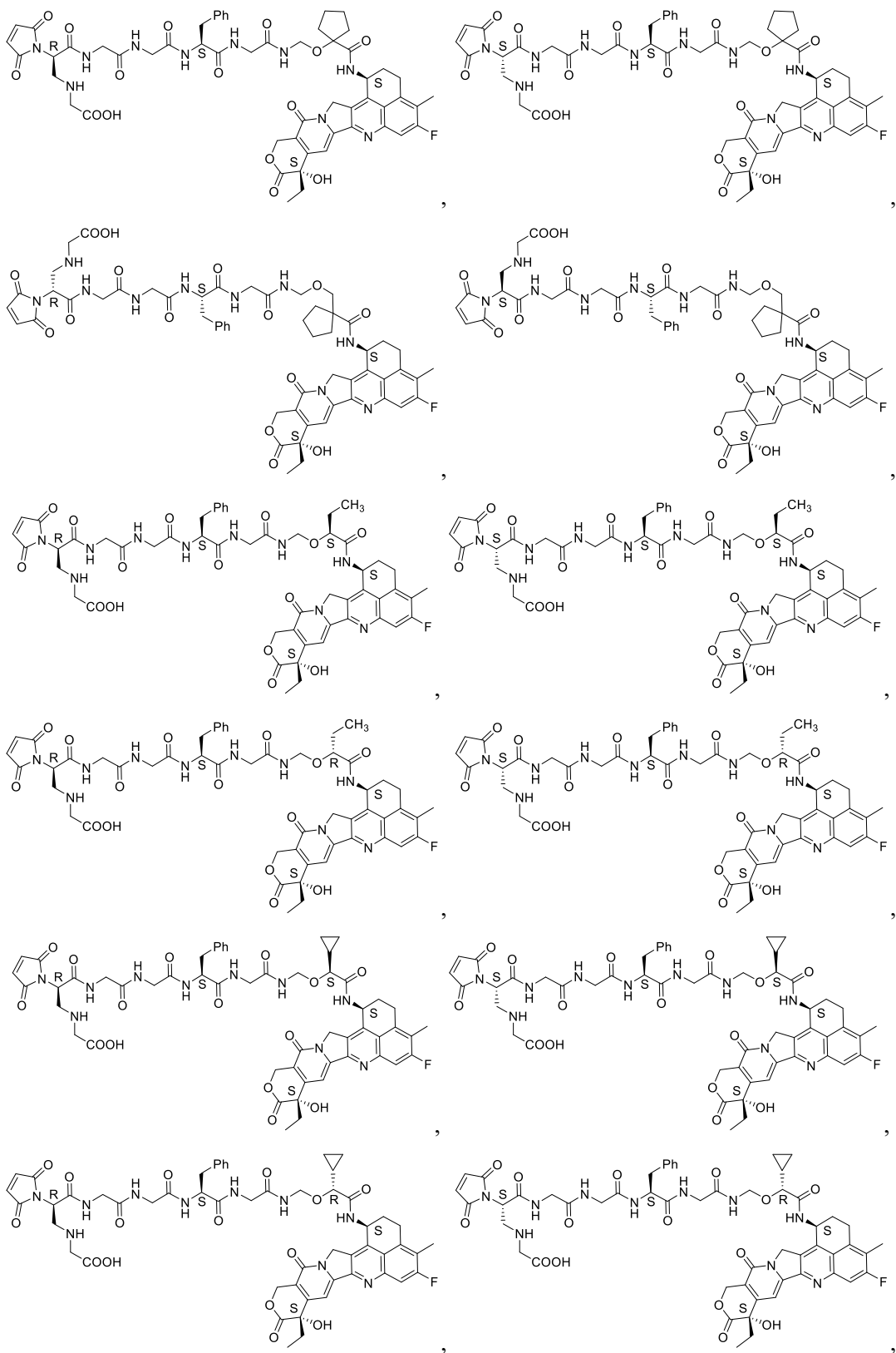
7. The linker-drug compound or its pharmaceutically acceptable salt thereof according to claim 6, wherein Ac is selected from glycine, or (D/L)-glutamic acid.

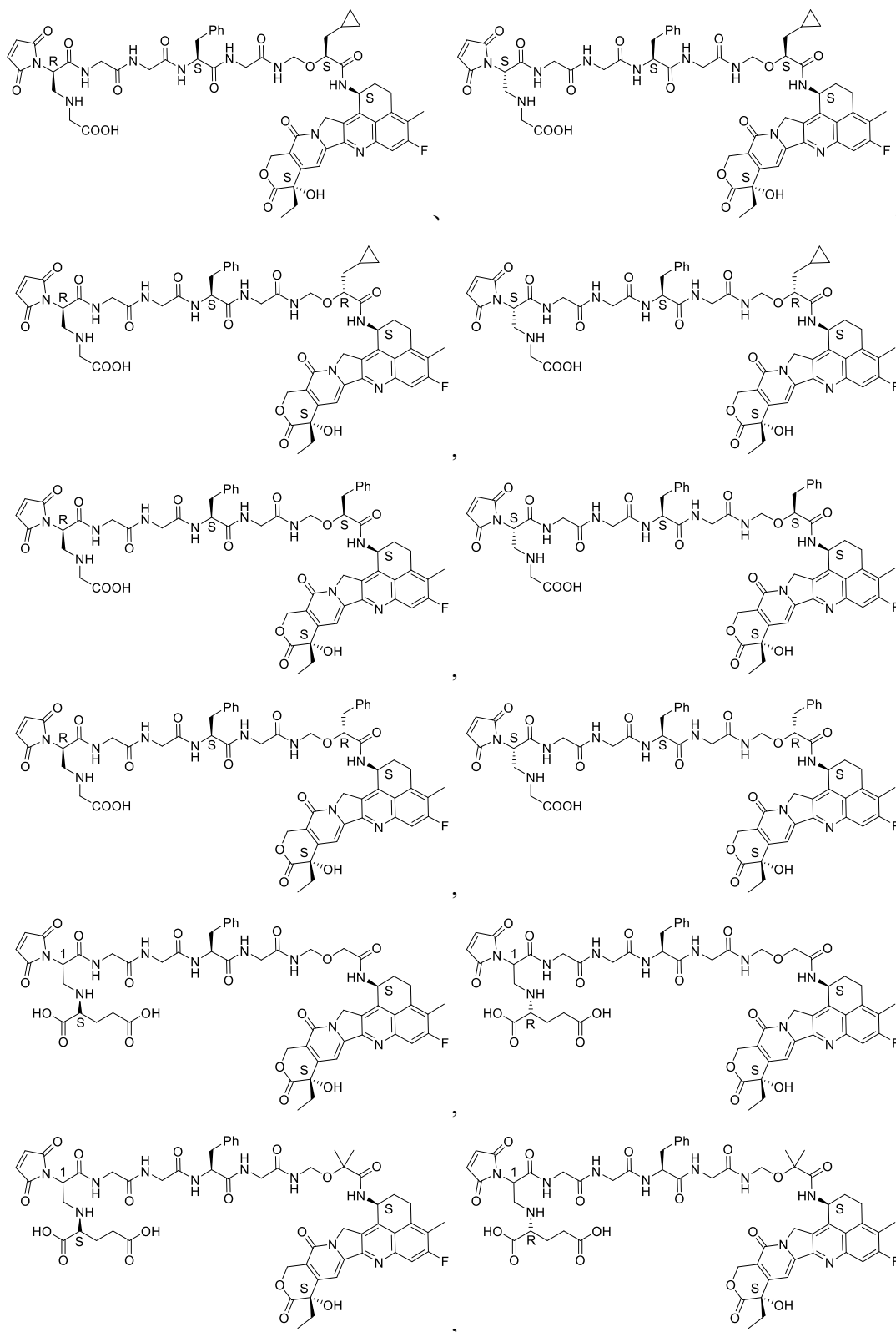
8. The linker-drug compound or its pharmaceutically acceptable salt thereof according to

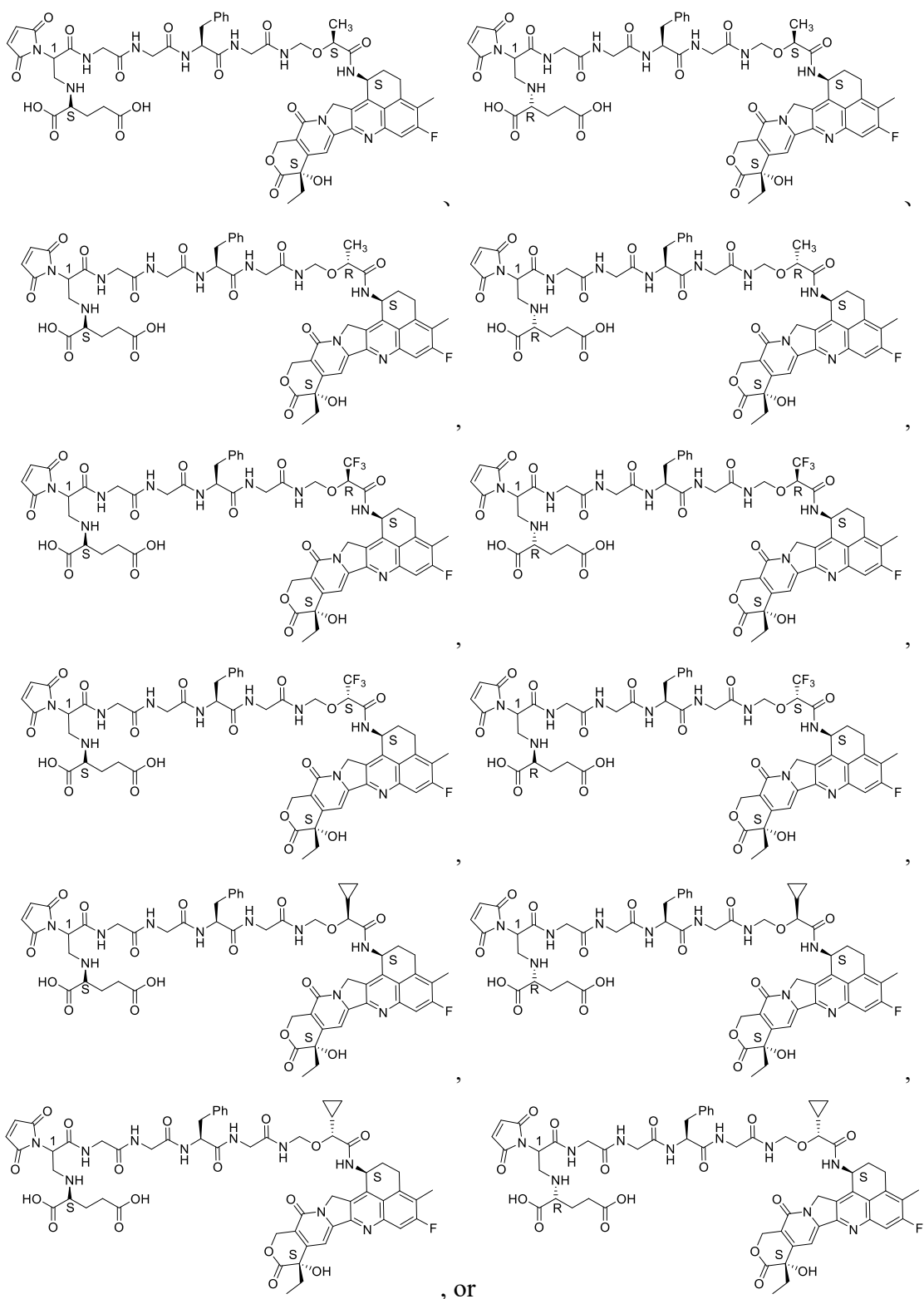
claim 6 or 7, wherein the linker-drug compound is selected from the following structures,







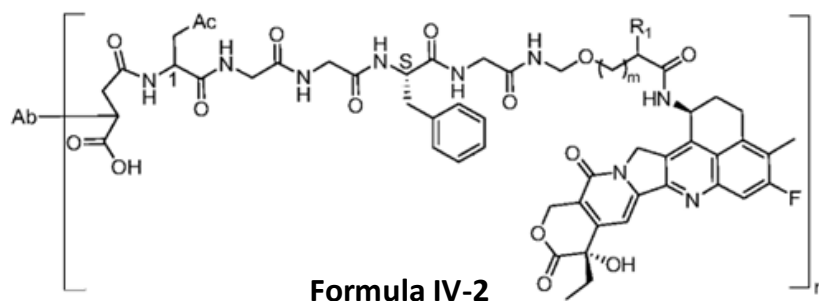
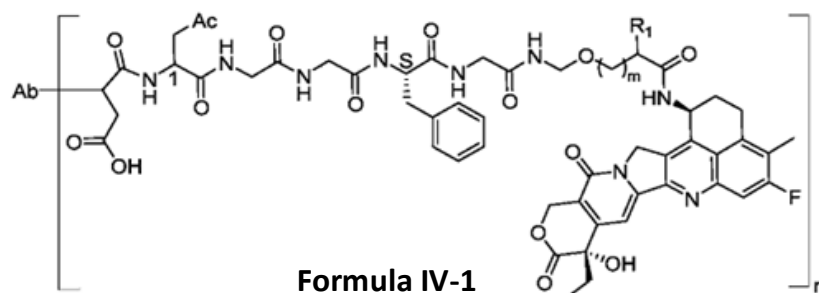
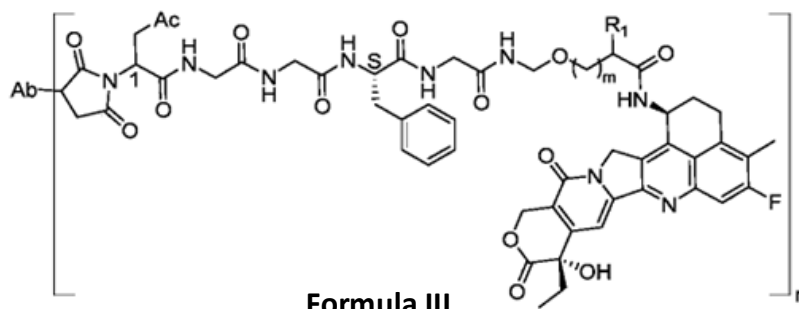




where the position-1 chiral carbon has the chirality of R or S configuration.

9. The ligand-drug conjugate or its pharmaceutically acceptable salt thereof according to any

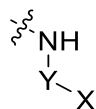
one of claims 1-8, wherein the ligand-drug conjugate or its pharmaceutically acceptable salt thereof has the structure shown in the following Formula III, Formula IV-1 or Formula IV-2,



wherein

Ab is the ligand unit, selected from antibodies, antibody fragments, targeting protein, or Fc-fusion protein;

Ac is the hydrophilic structural unit; wherein Ac has the structure shown in Formula c,



Formula c

wherein X is a hydrophilic carboxyl group;

Y is a scaffold connecting the amino group and X;

Ac is connected to the position-2 methylene carbon in formula I through the amino group; the position-1 chiral carbon has a R or S configuration; and

R₁, and m are as described in Formula II, and n is selected from an integer of 1-20.

10. The ligand-drug conjugate or its pharmaceutically acceptable salt thereof according to claim 9, wherein the ligand unit Ab is selected from an antibody, an antibody fragment, a targeting protein, or a Fc-fusion protein wherein the antibody is selected from murine antibodies, rabbit antibodies, phage display antibodies, yeast display antibodies, chimeric antibodies, humanized antibodies, fully human antibodies, antibody fragments, bispecific antibodies, or multi-specific antibodies.

11. The ligand-drug conjugate or its pharmaceutically acceptable salt thereof according to claim 9, wherein the antibody is a monoclonal antibody, and is selected from the group consisting of anti-EGFRvIII antibody, anti-PD-1 antibody, anti-PD-L1 antibody, anti-DLL-3 antibody, anti-PSMA antibody, anti-CD70 antibody, anti-MUC16 antibody, anti-ENPP3 antibody, anti-TDGF1 antibody, anti-ETBR antibody, anti-MSLN antibody, anti-TIM-1 antibody, Anti-LRRC15 antibody, anti-LIV-1 antibody, anti-CanAg/AFP antibody, anti-cladin 18.2 antibody, anti-Mesothelin antibody, anti-HER2 (ErbB2) antibody, anti-EGFR antibody, anti-c-MET antibody, anti-SLITRK6 antibody, anti-KIT/CD117 Antibody, anti-STEAP1 antibody, anti-SLAMF7/CS1 antibody, anti-NaPi2B/SLC34A2 antibody, anti-GPNMB antibody, anti-HER3 (ErbB3) antibody, anti-MUC1/CD227 antibody, anti-AXL antibody, anti-CD166 antibody, anti-B7-H3 (CD276) Antibody, anti-PTK7/CCK4 antibody, anti-PRLR antibody, anti-EFNA4 antibody, anti-5T4 antibody, anti-NOTCH3 antibody, anti-Nectin 4 antibody, anti-TROP-2 antibody, anti-CD142 antibody, anti-CA6 antibody, anti-GPR20 antibody, anti-CD174 antibody, Anti-CD71 antibody, anti-EphA2 antibody, anti-LYPD3 antibody, anti-FGFR2 antibody, anti-FGFR3 antibody, anti-FR α antibody, anti-CEACAMs antibody, anti-GCC antibody, anti-Integrin Av antibody, anti-CAIX antibody, anti-P-cadherin antibody, anti-GD3 Antibody, anti-Cadherin 6 antibody, anti-LAMP1 antibody, anti-FLT3 antibody, anti-BCMA antibody, anti-CD79b antibody, anti-CD19 antibody, anti-CD33 antibody, anti-CD56 antibody, anti-CD74 antibody, anti-CD22 antibody, anti-CD30 antibody, anti-CD37 antibody, anti-CD47 antibody, anti-CD138 antibody, anti-CD352 antibody, anti-CD25 antibody, and anti-CD123 antibody.

12. The ligand-drug conjugate or its pharmaceutically acceptable salt thereof according to claim 9, wherein the antibody or antigen-binding fragment comprises Trastuzumab having

a light chain comprising:

MDMRVPAQLLGLLLLWLRGARC

DIQMTQSPSSLSASVGDRVTITCRASQDVNTAVAWYQQKPGKAPKLLIYSASFLYSGVPSRFSGSRSG

TDFTLTISLQPEDFATYYCQQHYTTPPTFGQGTKVEIK

RTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYS

LSSTLTLSKADYEKHKVYACEVTHQGLSPVTKSFNRGEC* (SEQ ID NO: 1); and

a heavy chain comprising:

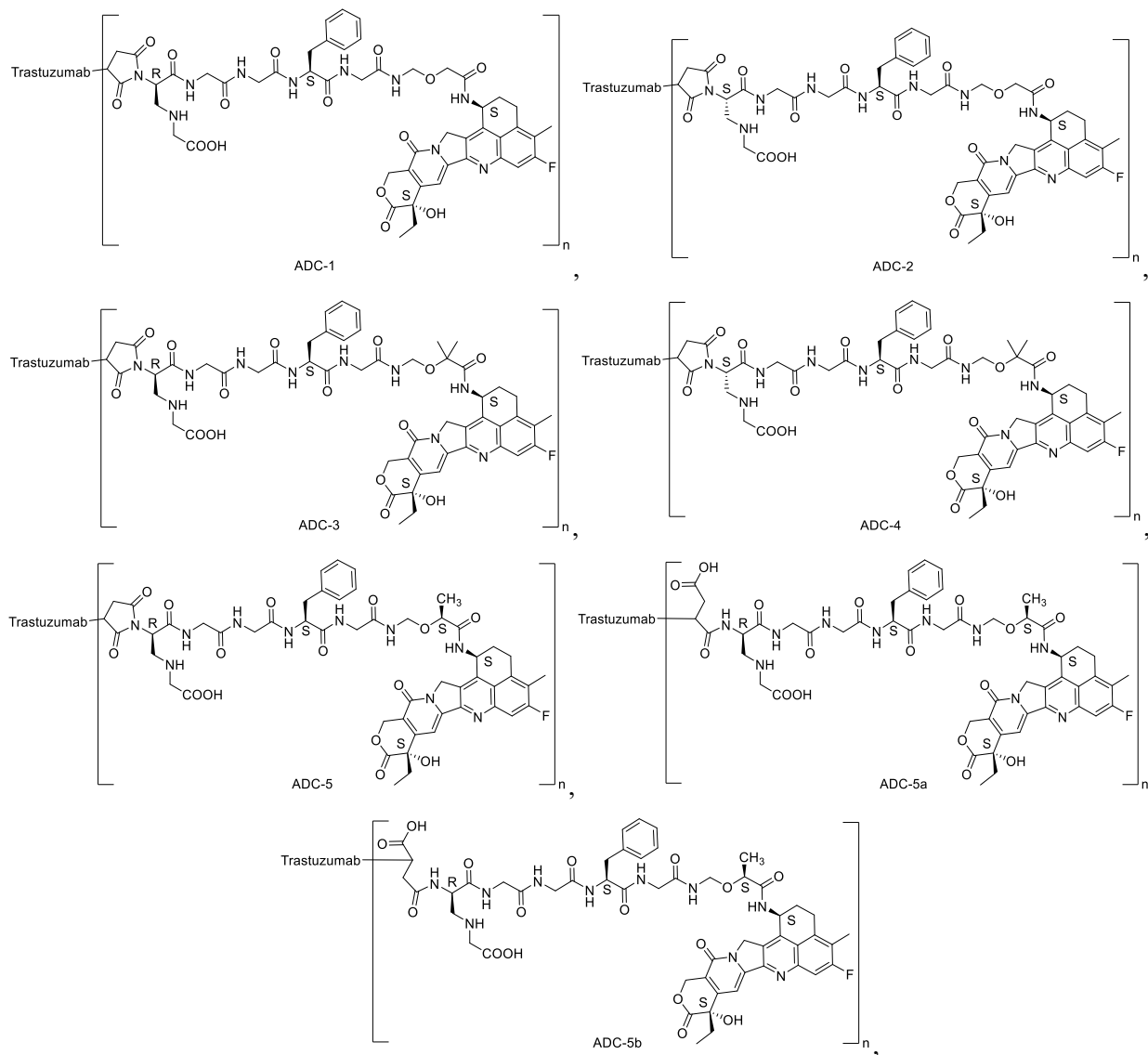
MDMRVPAQLLGLLLLWLRGARC

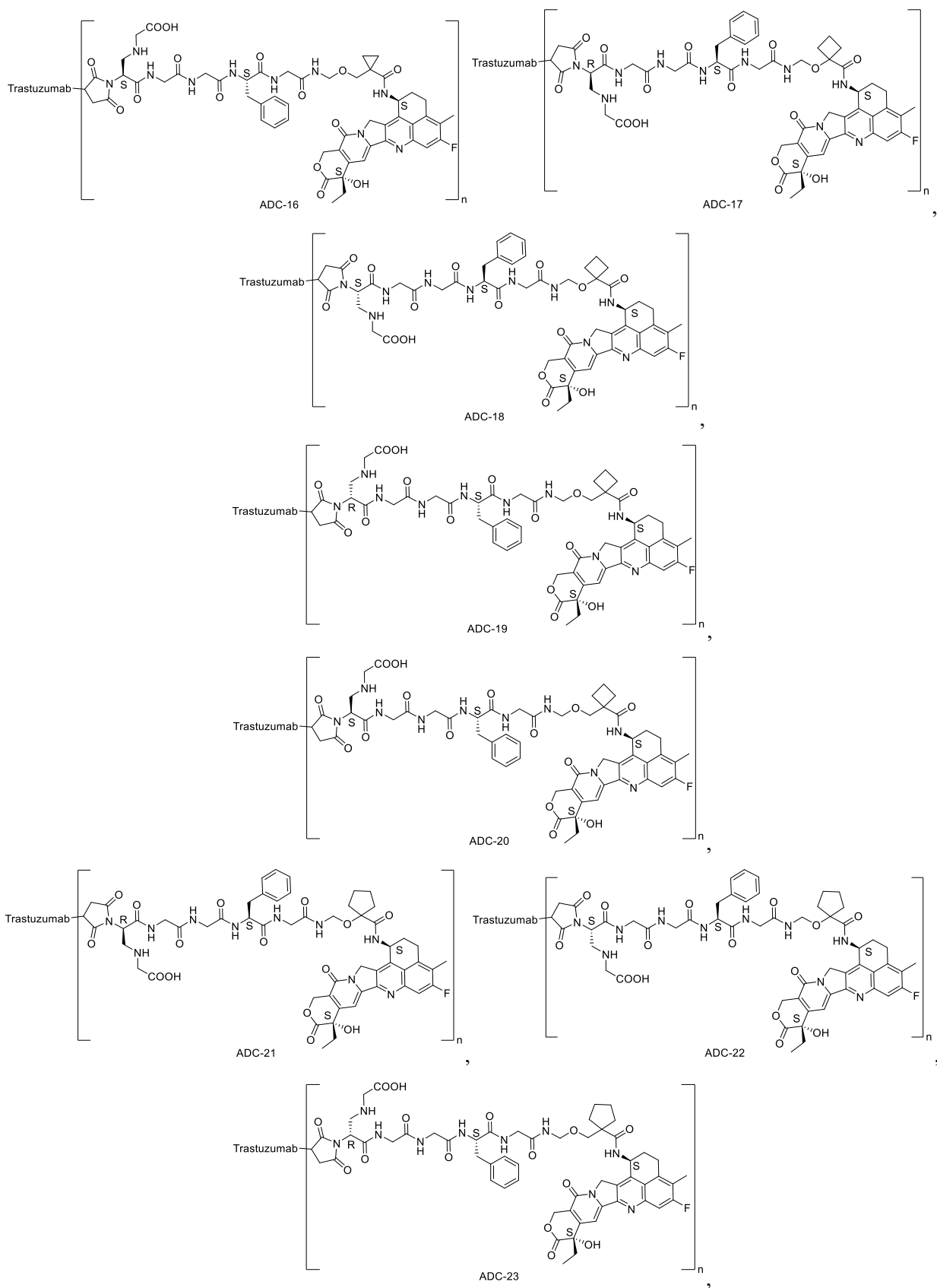
EVQLVESGGGLVQPGGSLRLSCAASGFNIKDTYIHWVRQAPGKGLEWVARIYPTNGYTRYADSVKGR

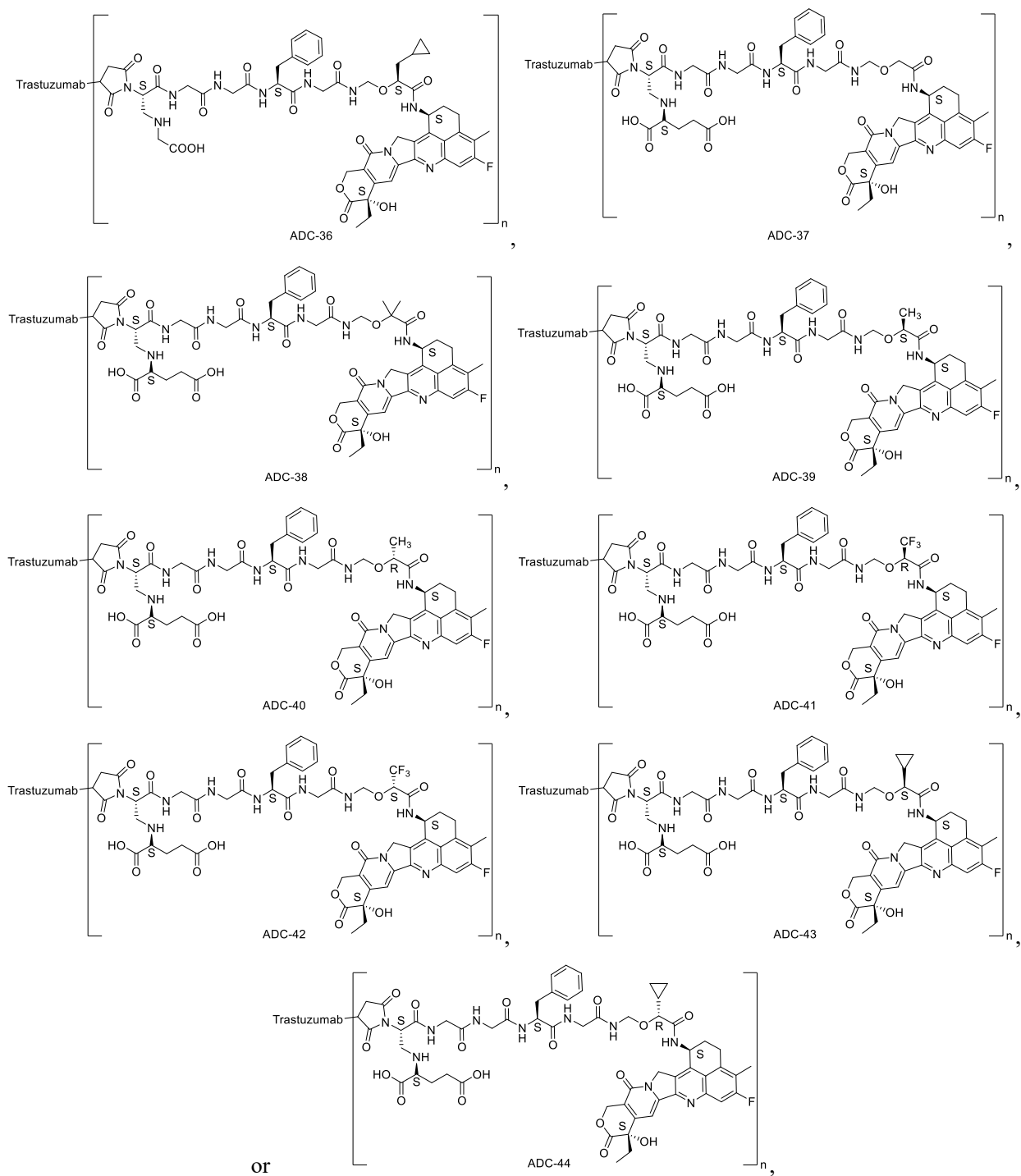
FTISADTSKNTAYLQMNSLRAEDTAVYYCSRWGGDGFYAMDYWGQGLTVTVSS

ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFCFSVMHEALHNHYTQKSLSLSPG (SEQ ID NO: 2).

13. The ligand-drug conjugate or its pharmaceutically acceptable salt thereof according to claim 9, wherein the ligand-drug conjugate or its pharmaceutically acceptable salt thereof is selected from the following succinimide structures or succinimide open-ring structures,

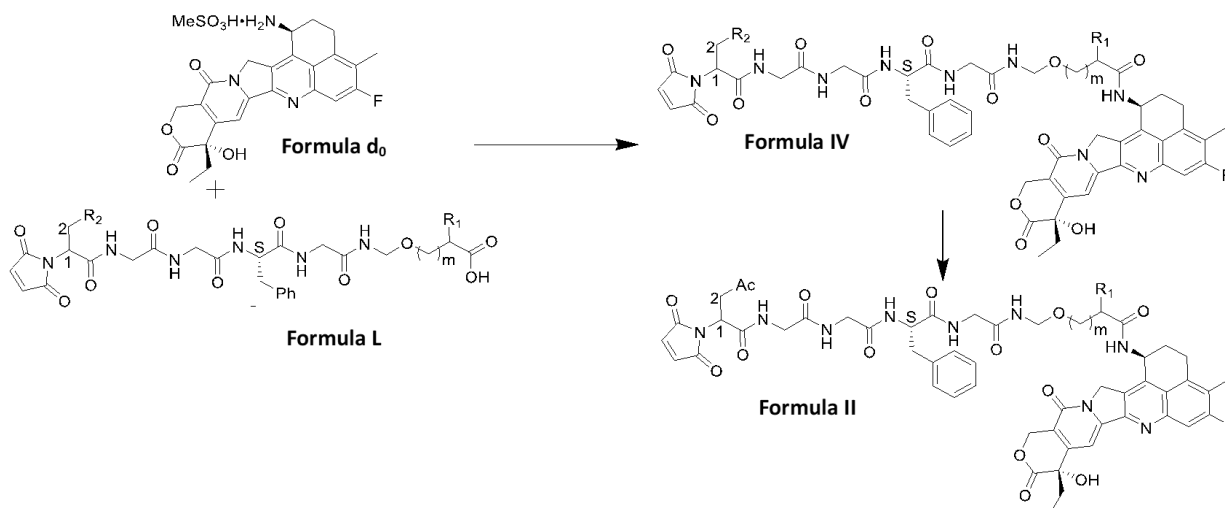






wherein n is selected from an integer of 1-10.

14. A method for preparing the linker-drug compound according to any one of claims 6-8 or its pharmaceutically acceptable salt thereof, comprising the following steps:



reacting a compound having Formula L with Exatecan having a Formula d₀ or its salt in the presence of a condensing agent under an alkaline condition to provide a compound having Formula IV, and

converting the compound having Formula IV to a compound having Formula II;

wherein,

the position-1 carbon and the R₁-connected carbon each has R or S absolute configuration;

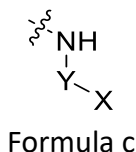
R₂ is configured to form Ac; and

Ac, R₁, and m are as defined in Formula II.

15. The method for preparing the linker-drug compound or its pharmaceutically acceptable salt thereof according to claim 14, wherein converting the compound having Formula IV to a compound having Formula II is carried out with a deprotecting agent and a solvent, wherein the deprotecting agent is zinc bromide, and the solvent is nitromethane.

16. A method for preparing the ligand-drug conjugate or its pharmaceutically acceptable salt thereof according to any one of claims 1-5, comprising the following steps:

Ac comprises a hydrophilic structural unit; wherein Ac has the structure shown in Formula c,



18. Use of the ligand-drug conjugate according to any one of claims 1-13 or its pharmaceutically acceptable salt thereof, in the preparation of a drug for the treatment of cancer, autoimmune diseases, or infectious diseases.

19. The use according to claim 18, wherein the cancer comprises breast cancer, ovarian cancer, cervical cancer, uterine cancer, prostate cancer, kidney cancer, urethral cancer, bladder cancer, liver cancer, gastric cancer, endometrial cancer, salivary gland cancer, esophageal cancer, lung cancer, colon cancer, rectal cancer, colorectal cancer, bone cancer, skin cancer, thyroid cancer, pancreatic cancer, melanoma, glioma, neuroblastoma, glioma multiforme, sarcoma, lymphoma, leukemia, other solid tumors or hematoma drugs.