

METHODS AND COMPOSITIONS FOR TREATING TUMORS USING ANTIBODY CAMPTOTHECIN DRUG CONJUGATES

CROSS REFERENCE TO RELATED APPLICATIONS

This application claims the benefit of the filing date of U.S. Provisional Application Ser. No. 63/591,214 filed October 18, 2023, under 35 U.S.C. 119(e), the entire disclosures of which are incorporated by reference herein.

TECHNICAL FIELD

10 The present application relates to the field of biopharmaceuticals, and specifically to methods of treating cancer or a tumor using antibody-drug conjugates.

BACKGROUND

Unless otherwise indicated herein, the materials described in this section are not prior art to the claims in this application and are not admitted being prior art by inclusion in this section.

Epidermal Growth Factor Receptor (EGFR) and human epidermal growth factor receptor 3 (also known as HER3 and ErbB3) are receptor protein tyrosine kinases and belong to the epidermal growth factor receptor (EGFR) subfamily of receptor protein tyrosine kinases, which includes EGFR (ErbB-1), HER2/c-neu (ErbB-2), HER 3 (ErbB-3) and HER 4 (ErbB-4).

20 The epidermal growth factor receptor is a glycoprotein with a molecular weight of 170 kDa that crosses cell membranes and is activated by binding to ligands. Upon activation, EGFR is converted from a monomer to an auto-dimer or to a heterodimer with other EGFR family members. Dimer formation activates intracellular kinase pathways that direct the phosphorylation of downstream pathways, including the MAPK, Akt, and JNK pathways, to induce cell proliferation. Studies have shown that high expression of EGFR is associated with tumor cell proliferation, angiogenesis, tumor invasion, etc. EGFR-related signaling pathways play a very important role in the maintenance and growth of epidermal tissues. Especially in breast cancer, malignant glioma and lung cancer, EGFR promotes tumorigenesis. In lung cancer tissues, the EGFR signaling pathway shows a stimulated state, and there is a positive correlation between the expression level of EGFR and the stage of cancer development. Meanwhile, more and more studies are using EGFR as a biomarker of tumor drug resistance due to the finding of secondary mutations of EGFR under drug stress.

30 Epidermal growth factor receptor 3 (HER3 or ErbB3) also has the structure of a typical epidermal growth factor receptor, but HER3 lacks the structural domain of the intracellular protein tyrosine kinase and thus cannot autophosphorylate. HER3 can bind to ligand proteins and promote their heterodimerization with other epidermal growth factor receptor family members to activate receptor-mediated signaling pathways, which not only acts as a signal diversification means, but also plays a role in signal amplification and accelerates tumor progression. Heregulins (glial cell growth factor, neudifferentiation factor) can activate intracellular kinase-dependent multistep signaling pathway responses upon binding to the transmembrane receptors HER3 and HER4. Down-regulation of this signaling pathway often leads to Alzheimer's disease, heart failure, atherosclerosis, and cancer, etc. Up-regulation of HER3 expression promotes tumorigenesis and growth by interacting with receptor tyrosine kinases (RTKs). Also, since 40 HER3 is a heterodimeric molecular chaperone for other EGFR family members, it has the potential to modulate EGFR/HER2 signaling pathway-mediated drug resistance in cancer cells. Studies have also shown that HER3 fails cancer therapy by activating the PI3K/AKT, MAPK/ERK and JAK/STAT signaling pathways.

Overexpression/dysregulation of EGFR and HER3 has been closely associated with the development

of a variety of tumors. EGFR and HER3 have been shown to drive tumor progression in solid tumors such as breast, lung, gastric, and pancreatic cancers. Several studies have shown that high expression of HER3 is associated with clinical failure of EGFR antibodies and inhibitors. Several combination drug therapies targeting EGFR and HER3 are already underway in the clinic.

Monoclonal antibodies have been widely used in anti-tumor therapy in recent years, but their efficacy leaves much to be desired. A larger number of tumor patients have poor clinical responses, and some patients with clinical responses develop resistance after a sustained period of monoclonal antibody therapy, leading to tumor recurrence. Bispecific monoclonal antibody refers to a monoclonal antibody molecule with two different antigen recognition sequences, which can bind protein molecules of two antigenic epitopes, and thus be able to achieve, for example, a variety of new and unique anti-tumor mechanisms, such as mediating the killing of tumor cells by immune cells, mediating the killing of tumor cells by toxic small molecules, or blocking the signaling pathways that play a promotional role in the growth of tumors. The development of bispecific monoclonal antibodies is mainly in consideration of the fact that multiple mediators are involved in the pathogenesis of tumors through specific or overlapping mechanisms, and if multiple targets are blocked at the same time, it will produce better therapeutic effects than inhibition of a single target, and at the same time, the action of multiple targets makes the probability of drug resistance greatly reduced. Currently, two bispecific antibodies, Catumaxomab and Blinatumomab, have been approved for marketing in the U.S., and more than fifty bispecific antibody molecules are in clinical trials.

Antibody-Drug Conjugates (ADCs) are molecules with specifically targeted killing effects obtained by attaching small molecule toxins with cell-killing effects to antibodies and are mainly used in the treatment of tumors and other diseases. Antibody-drug coupled drugs use antibodies that specifically bind to proteins on the surface of tumor cells, and therefore have tumor specificity and potential not achieved by traditional drugs. Currently, 12 ADC drugs have received marketing approval worldwide, and hundreds of programs are in clinical trials. However, most ADC programs currently on the market or in the clinic are directed at a single target and cannot achieve the synergistic benefits of dual-target therapy.

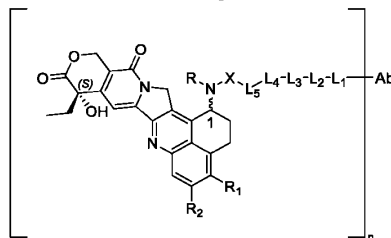
SUMMARY

The following summary is illustrative only and is not intended to be in any way limiting. In addition to the illustrative aspects, embodiments, and features described above, further aspects, embodiments, and features will become apparent by reference to the drawings and the following detailed description.

The application provides pharmaceutical compositions, method of treating cancer or a tumor using the pharmaceutical compositions, methods of making the pharmaceutical compositions, and the treatments kits comprising the pharmaceutical compositions.

In one aspect, the application provides methods of treating cancer or a tumor. In one embodiment, the method includes the step of administering to a subject in need thereof a ligand-camptothecin conjugate of Formula I, or a pharmaceutically acceptable salt or solvate thereof.

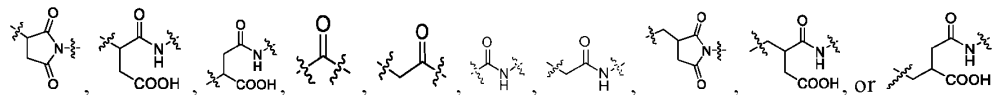
In one embodiment, the Formula I have the following structure:



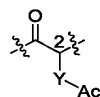
Formula I

In one embodiment, Ab is a bispecific antibody or antigen-binding fragment thereof that simultaneously targets two different epitopes or targets. In one embodiment, Ab has a binding affinity to EGFR and HER3.

L₁ is:



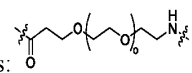
L₂ has the structure shown in Formula A,



Formula A

wherein Y is a scaffold selected from C1-C6 alkyl, substituted C1-C6 alkyl, or C3-C8 cycloalkyl; in one embodiment, Y is C1-C6 alkyl; Ac is a hydrophilic structural unit; and the carbon 2 attached to Y is absolutely chiral in either the R configuration or the S configuration;

L₃ is present or absent, and when present, L₃ is selected from PEG hydrophilic units:



o is selected from an integer of 1-10, in one embodiment, an integer of 2-8;

L₄ is an enzymatically cleavable unit;

L₅ is a connection unit;

the chiral carbon atom No. 1 attached to N in Formula I has absolute chirality in either the R configuration or the S configuration;

R is selected from hydrogen atom, deuterium atom, halogen, C1-C6 alkyl, substituted C1-C6 alkyl, deuterated C1-C6 alkyl, C3-C8 cycloalkyl C1-C6 alkyl, C1-C6 alkoxy C1-C6 alkyl, C6-C10 aryl, substituted C6-C10 aryl, 5-10 heteroaryl, substituted 5-10 heteroaryl;

R₁ is selected from hydrogen atom, deuterium atom, halogen, C1-C6 alkyl, substituted C1-C6 alkyl, deuterated C1-C6 alkyl, C3-C8 cycloalkyl C1-C6 alkyl, C1-C6 alkoxy C1-C6 alkyl, carboxyl, 3-7 heterocyclic, substituted 3-7 heterocyclic, C6-C10 aryl, substituted C6-C10 aryl, 5-10 heteroaryl, substituted 5-10 heteroaryl;

R₂ is selected from hydrogen atom, deuterium atom, halogen, C1-C6 alkyl, substituted C1-C6 alkyl, deuterated C1-C6 alkyl, C3-C8 cycloalkyl C1-C6 alkyl, C1-C6 alkoxy C1-C6 alkyl, carboxyl, 3-7 heterocyclic, substituted 3-7 heterocyclic, C6-C10 aryl, substituted C6-C10 aryl, 5-10 heteroaryl, substituted 5-10 heteroaryl;

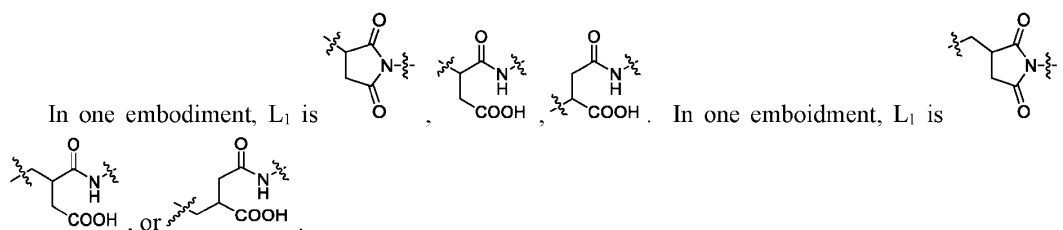
X selected from -C(O)-CR_aR_b-(CR₃R₄)_m-O-, -C(O)-CR_aR_b-(CR₃R₄)_m-NH- or -C(O)-CR_aR_b-(CR₃R₄)_m-S-;

R_a and R_b are each independently selected from hydrogen atoms, deuterium atom, halogens, C1-C6 alkyl, deuterated C1-C6 alkyl, halogenated C1-C6 alkyl, C3-C8 cycloalkyl, C3-C8 cycloalkyl C1-C6 alkyl, C6-C10 aryl C1-C6 alkyl, C1-C6 alkoxy C1-C6 alkyl, 3-7 heterocyclic group, substituted 3-7 heterocyclic group, C6-C10 aryl, substituted C6-C10 aryl, 5-10 heteroaryl, substituted 5-10 heteroaryl;

R₃, R₄ are the same or different and are independently hydrogen atoms, deuterium atoms, halogens, C1-C6 alkyl, halogenated C1-C6 alkyl, deuterated C1-C6 alkyl, C1-C6 alkoxy, hydroxyl, amino, cyano, nitro, hydroxy C1-C6 alkyl, C3-C8 cycloalkyl, 3-7 heterocyclic, substituted 3-7 heterocyclic, respectively;

m is selected from integers 0-4 (e.g., 0, 1, 2, 3, or 4. In one embodiment, m is 0, 1.

n is selected from integers 1-10 (e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10).



In one embodiment, R is selected from a hydrogen atom or a C1-C6 alkyl group.

In one embodiment, R_1 is selected from a hydrogen atom or a C1-C6 alkyl group. In one embodiment, R_1 is selected from C1-C6 alkyl.

In one embodiment, R_2 is selected from a hydrogen atom, a halogen or a C1-C6 alkyl group. In one embodiment, R_2 is selected from halogen.

In one embodiment, X is selected from $-C(O)-CR_aR_b-(CR_3R_4)_m-O-$. In one embodiment, R_a and R_b are each independently selected from hydrogen atoms, C1-C6 alkyl, halo-C1-C6 alkyl, C3-C8 cycloalkyl C1-C6 alkyl or C6-C10 aryl C1-C6 alkyl. In one embodiment, R_a , R_b and the carbon atoms to which they are attached constitute C3-C8 cycloalkyl, C3-C8 cycloalkyl C1-C6 alkyl, 3-7 heterocycloalkyl, substituted 3-7 heterocycloalkyl. In one embodiment, R_a , R_b and the carbon atoms to which they are attached constitute a C3-C8 cycloalkyl group.

In one embodiment, R_3 , R_4 are independently hydrogen or C1-C6 alkyl groups. In one embodiment, R_3 , R_4 and the carbon atoms attached thereto constitute C3-C8 cycloalkyl group, C3-C8 cycloalkyl C1-C6 alkyl group, 3-7 heterocyclic group, substituted 3-7 heterocyclic group

In one embodiment, L_1 is , Y is C1-C6 alkyl, and the carbon 2 attached to Y is absolutely chiral in the S configuration, R is hydrogen, R_1 is C1-C6 alkyl, R_2 is halogen, and X selected from $-C(O)-CR_aR_b-(CR_3R_4)_m-O-$, wherein R_a and R_b are each independently selected from hydrogen and C1-C6 alkyl, and wherein m is 0.

In one embodiment, R_1 is methyl, R_2 is F, R_a and R_b are H and methyl.

In one embodiment, the method includes the step of administering to the subject at a treatment dose per administration from about 0.1 mg/kg to 15.0 mg/kg. In one embodiment, the treatment dose per administration is not more than about 2.2mg, 2.5mg/kg, 3mg/kg, 4mg/kg, 4.5mg/kg, 5mg/kg, 6mg/kg, or 9mg/kg. In one embodiment, the treatment dose per administration is not more than about 0.5mg/kg, 1.5mg/kg, 2.5mg/kg, 3mg/kg, 4.5mg/kg, 6mg/kg, 9mg/kg, or 10mg/kg.

In one embodiment, the treatment dose per administration is from about 0.1 mg/kg to 9.0 mg/kg, from about 1.5 mg/kg to 4.5 mg/kg, from about 2.5 mg/kg to 4.5 mg/kg, from about 2.5 mg/kg to 3 mg/kg, or from about 2.5mg/kg to about 10mg/kg. In one embodiment, the treatment dose per administration is about 2mg/kg, 2.2mg/kg, 2.5mg/kg, 2.75mg/kg, 3 mg/kg, 3.5mg/kg, 4.5mg/kg, 5mg/kg, or 9mg/kg.

The method comprises one or more treatment cycles. In one embodiment, the treatment cycle comprises a 4-week period, comprising weekly dosing. In one embodiment, the treatment dose per administration for the weekly dosing is from about 0.1 mg/kg to about 9.0 mg/kg, 2.0mg/kg to 5mg/kg, 2.2mg/kg to 8mg/kg, 2.5mg/kg to 6mg/kg or a combination thereof. In one embodiment, the treatment dose per administration for the weekly dosing is about 0.1 mg/kg, about 0.27 mg/kg, about 0.5 mg/kg, about 1.0 mg/kg, about 1.5 mg/kg, about 2.0 mg/kg, about 2.2mg/kg, about 2.5mg/kg, about 2.75mg/kg, about 3 mg/kg, about 3.5mg/kg, about 4mg/kg, about 4.5mg/kg, or about 5mg/kg.

In one embodiment, the treatment cycle comprises a 4-weeks period, comprising dosing on the first day of the first, second, and third weeks, and no dosing in the fourth week. In one embodiment, the treatment dose per administration is from about 0.1 mg/kg to 5.0 mg/kg. In one embodiment, the treatment dose per administration is about 0.1 mg/kg, 0.27 mg/kg, 0.5 mg/kg, 1.0 mg/kg, 1.5 mg/kg, 2.0 mg/kg, 2.5 mg/kg, 3.0 mg/kg, 3.5 mg/kg, 4.0 mg/kg, 5.0 mg/kg or a combination thereof.

10 In one embodiment, the treatment cycle comprises a 4-week period, comprising biweekly dosing. In one embodiment, the treatment dose per administration for the biweekly dosing is from about 0.1 mg/kg to about 15.0 mg/kg. In one embodiment, the treatment dose per administration is about 0.1 mg/kg, about 0.27 mg/kg, about 0.5 mg/kg, about 1.0 mg/kg, about 1.5 mg/kg, about 2.0 mg/kg, about 2.2mg/kg, about 2.5 mg/kg, about 2.75mg/kg, about 3.0 mg/kg, about 3.5 mg/kg, about 4.0 mg/kg, about 4.5 mg/kg, about 5.0 mg/kg, about 5.5 mg/kg or about 6.0 mg/kg or a combination thereof.

In one embodiment, the treatment cycle comprises 3-week period, comprising weekly dosing. In one embodiment, the treatment dose per administration for the weekly dosing is from about 0.1 mg/kg to about 9.0 mg/kg, about 1.5 mg/kg to about 9 mg/kg, 2.5 mg/kg to about 6 mg/kg, 3 mg/kg to about 6 mg/kg, from about 4.5mg/kg to about 5mg/kg, or a combination thereof. In one embodiment, the treatment dose per administration is about 0.1 mg/kg, 0.27 mg/kg, about 0.5 mg/kg, about 1.0 mg/kg, about 1.5 mg/kg, about 2.0 mg/kg, about 2.2mg/kg, about 2.5 mg/kg, about 2.75mg/kg, about 3.0 mg/kg, or about 3.5mg/kg or a combination thereof.

20 In one embodiment, the treatment cycle comprises a 3-week period, comprising dosing on the first day of the first week and no dosing in the second and third weeks (D1Q3W). In one embodiment, the treatment dose per administration for the treatment cycle is from about 0.1 mg/kg to about 4.5 mg/kg, 1.5 mg/kg to about 9 mg/kg, 2.5 mg/kg to about 15 mg/kg, 2.5 mg/kg to about 6 mg/kg, 3 mg/kg to about 6 mg/kg, from about 4.5mg/kg to about 5mg/kg, or a combination thereof. In one embodiment, the treatment dose per administration is about 0.1 mg/kg, about 0.27 mg/kg, about 0.5 mg/kg, about 1.0 mg/kg, about 1.5 mg/kg, about 2.0 mg/kg, about 2.2mg/kg, about 2.5 mg/kg, about 2.75mg/kg, about 3.0 mg/kg, about 3.5 mg/kg, about 4.0 mg/kg, about 4.5mg/kg, or about 5mg/kg.

30 In one embodiment, the treatment cycle comprises a 3-week period, comprising dosing on the first day of the first and second weeks and no dosing in the third week (D1D8Q3W). In one embodiment, the treatment dose per administration for the treatment cycle is from about 0.1 mg/kg to about 9.0 mg/kg, about 0.1 mg/kg, about 0.27 mg/kg, about 0.5 mg/kg, about 1.0 mg/kg, about 1.5 mg/kg, about 2.0 mg/kg, about 2.2mg/kg, about 2.5 mg/kg, about 2.75mg/kg, about 3.0 mg/kg, about 3.5 mg/kg, about 4.0 mg/kg, about 4.5 mg/kg, about 5.0 mg/kg, about 5.5 mg/kg, about 6.0 mg/kg kg, about 3.0 mg/kg, about 3.5 mg/kg, about 4.0 mg/kg, about 4.5 mg/kg, about 5.0 mg/kg, about 5.5 mg/kg, about 6.0 mg/kg, about 6.5 mg/kg, about 7.0 mg/kg, about 7.5 mg/kg, about 8.0 mg/kg, about 8.5 mg/kg or about 9.0 mg/kg or a combination thereof. In one embodiment, the treatment dose per administration is from about 2.5mg/kg to about 3mg/kg. In one embodiment, the treatment dose per administration is about 2mg/kg, 2.2mg/kg, 2.5mg/kg, 2.75mg/kg, about 3mg/kg, about 3.5mg/kg, about 4mg/kg, about 4.5mg/kg, or about 5mg/kg.

40 In one embodiment, the method includes a combination of the treatment cycles as described herein. In one embodiment, the method comprises one or more treatment cycles, such as 2, 3, 4, 5, 6, 7 or 8 treatment cycles.

In one embodiment, the cancer or tumor comprises a cancer expressing EGFR and/or HER3. In one embodiment, the cancer or tumor comprises a locally advanced or metastatic solid tumor. In one embodiment, the cancer or tumor comprises lung cancer, nasopharyngeal cancer, head and neck cancer, urological tumors, gastrointestinal tumors, bladder cancer, biliary cancer, esophageal cancer, or breast

cancer. In one embodiment, the cancers or tumor comprises adenocarcinoma, ovarian cancer, cervical cancer, uterine cancer, prostate cancer, renal cancer, hepatocellular carcinoma, gastric cancer, endometrial cancer, salivary gland cancer, bone cancer, skin cancer, thyroid cancer, pancreatic cancer, melanoma, glioma, neuroblastoma, glioblastoma multiforme, sarcoma, lymphoma, or leukemia.

In one embodiment, the cancers or tumor may include a combination of the cancers/tumors.

In one embodiment, the cancer or tumor comprises non-small cell lung cancer or small cell lung cancer. In one embodiment, the cancer or tumor comprises EGFR wild-type non-small cell lung cancer or EGFR mutant non-small cell lung cancer. In one embodiment, the cancer or tumor comprises head and neck squamous carcinoma. In one embodiment, the cancer or tumor comprises head and neck squamous carcinoma. In one embodiment, the cancers or tumor comprises triple negative breast cancer, bladder cancer, esophageal squamous cell carcinoma (ESCC), metastatic biliary tract carcinoma (BTC), or a combination thereof.

In one embodiment, the subject is a human. In one embodiment, the subject is a patient with a recurrent or metastatic tumor. In one embodiment, the subject is a patient with cancer who has previously undergone systemic therapy. In one embodiment, the subject is a patient with cancer who has previously undergone systemic treatment.

In one embodiment, the subject is a patient with non-small cell lung cancer, a patient with EGFR wild-type non-small cell lung cancer, a patient with EGFR mutant non-small cell lung cancer, a patient with small cell lung cancer, a patient with nasopharyngeal cancer, or a patient with head and neck cancer, or a patient with a combination of the cancers thereof.

In one embodiment, the subject is a patient with EGFR wild-type non-small cell lung cancer who has not previously undergone systemic therapy or a patient with EGFR wild-type non-small cell lung cancer who has previously undergone systemic therapy. In one embodiment, the subject is a patient with EGFR mutant non-small cell lung cancer who has not previously undergone systemic therapy, or a patient with EGFR mutant non-small cell lung cancer who has previously undergone systemic therapy.

In one embodiment, the subject is a patient with small cell lung cancer who has not previously undergone systemic treatment, or a patient with small cell lung cancer who has previously undergone systemic treatment. In one embodiment, the subject is a patient with nasopharyngeal cancer who has not previously undergone systemic treatment, or a patient with nasopharyngeal cancer who has previously undergone systemic treatment.

In one embodiment, the subject is a patient with head and neck cancer who has not previously undergone systemic treatment, or a patient with head and neck cancer who has previously undergone systemic treatment.

In one embodiment, the ligand-camptothecin derivative conjugate or a pharmaceutically acceptable salt or solvent compound thereof is administered to the subject in the form of an injection.

In one embodiment, the injection is carried out using an injectable solution derived from a lyophilized powder injection formula. In one embodiment, the method comprises the steps of combining the lyophilized powder injection formula with water to provide the injection solution, and administering the injection solution to the subject. Example administering step includes without limitation intravenous injection, intramuscular injection, subcutaneous injection, or a combination thereof. In one embodiment, the injection is given to the subject by intravenous drip. In one embodiment, the duration of the intravenous drip is $(60 \text{ to } 120 \text{ min}) \pm 10 \text{ min}$.

In one embodiment, the lyophilized powder injection formula comprises the ligand-camptothecin derivative conjugate or a pharmaceutically acceptable salt and a pharmaceutical carrier composition. In

one embodiment, the lyophilized powder injection formula comprises the ligand-camptothecin derivative conjugate or a pharmaceutically acceptable salt or solvate thereof in an amount not less than about 10%, 12%, 15%, 18%, 20%, 30%, 50% w/w. In one embodiment, the lyophilized powder injection formula comprises the ligand-camptothecin derivative conjugate or a pharmaceutically acceptable salt or solvate thereof in an amount from about 5% to about 30% w/w, from about 10% to about 20% w/w, from about 12% to about 18% w/w, from about 14% to about 16% w/w, from about 10% to about 18% w/w, from about 14% to about 18% w/w, or from about 13% to about 16% w/w.

10 The therapeutic methods disclosed herein can be used as first-line treatments (i.e., the first treatment after a definitive tumor diagnosis) or as non-first-line treatments. The treatments may be used in combination with other treatments.

In one embodiment, the method further includes the step of administering a second treatment to the subject before, after, or concurrently with the administration of the ligand-camptothecin derivative conjugate or a pharmaceutically acceptable salt or solvate thereof. In one embodiment, the second treatment comprises hormonal treatment, chemotherapy, immunotherapy, a targeted therapy, or a combination thereof.

In one embodiment, the second treatment comprises chemotherapy, immune checkpoint inhibitor therapy, EGFR-TKI (epidermal growth factor receptor-lysine kinase inhibitor) therapy, or a combination thereof.

20 In one embodiment, the chemotherapy comprises administering a platinum-containing or platinum-free chemotherapeutic agent. In one embodiment, the immune checkpoint inhibitor therapy comprises administering an immune checkpoint inhibitor. In one embodiment, the immune checkpoint inhibitor comprises anti-PD-1 mAb, anti-PD-L1 mAb, a combination of anti-PD-1 mAb, anti-PD-L1 mAb, anti-CTLA-4 mAb, anti-LAG3 mAb, anti-TIGIT mAb, or a combination thereof.

In one embodiment, the subject is a patient with EGFR wild-type non-small cell lung cancer and wherein the second treatment comprises the chemotherapy comprising administering platinum-containing or non-platinum-containing chemotherapeutic agents, the immune checkpoint inhibitor therapy comprising administering anti-PD-1 mAb, anti-PD-L1 mAb, a combination of anti-PD-1 mAb, anti-CTLA-4 mAb, anti-LAG3 mAb, or anti-TIGIT mAb, or a combination thereof.

30 In one embodiment, the subject is a patient with EGFR-mutant non-small cell lung cancer, and wherein the second treatment comprises the EGFR-TKI therapy, the chemotherapy comprising administering platinum-containing or non-platinum-containing chemotherapeutic agents, the immune checkpoint inhibitor therapy comprising administering anti-PD-1 mAb, anti-PD-L1 mAb, a combination of anti-PD-1 mAb, anti-CTLA-4 mAb, anti-LAG3 mAb, or anti-TIGIT mAb, or a combination thereof.

In one embodiment, the subject is a patient with small cell lung cancer, and wherein the second treatment comprises the chemotherapy comprising administering platinum-containing or non-platinum-containing chemotherapeutic agents, the immune checkpoint inhibitor therapy comprising administering anti-PD-1 mAb, anti-PD-L1 mAb, a combination of anti-PD-1 mAb, anti-CTLA-4 mAb, anti-LAG3 mAb, or anti-TIGIT mAb, or a combination thereof.

40 In one embodiment, the subject is a patient with nasopharyngeal cancer, and wherein the second treatment comprises the chemotherapy comprising administering platinum-containing or non-platinum-containing chemotherapeutic agents, the immune checkpoint inhibitor (e.g., anti-PD-1/PD-L1 mAb, dual antibody, anti-CTLA-4 mAb, anti-LAG3 mAb, anti-TIGIT mAb) therapy, or a combination thereof.

In one embodiment, the subject is a patient with head and neck cancer, and the second treatment comprises the chemotherapy comprising administering platinum-containing or non-platinum-containing

chemotherapeutic agents, the immune checkpoint inhibitor therapy comprising administering anti-PD-1/PD-L1 mAb, and dual-antibody, anti-CTLA-4 mAb, anti-LAG3 mAb, anti-TIGIT mAb) therapy, or a combination thereof.

10 In one embodiment, the subject is a patient with EGFR wild-type non-small cell lung cancer, e.g., a patient with EGFR wild-type non-small cell lung cancer who has not previously undergone systemic therapy, or a patient with EGFR wild-type non-small cell lung cancer who has previously undergone systemic therapy, and the method is used in conjunction with chemotherapy (e.g., using platinum-containing or non-platinum-containing chemotherapeutic agents) and/or immune checkpoint inhibitors (e.g., anti-PD-1/PD-L1 mAb, dual antibody, anti-CTLA-4 mAb, anti-LAG3 mAb, anti-TIGIT mAb) therapy in combination.

In one embodiment, the subject is a patient with EGFR-mutant non-small cell lung cancer, such as a patient with EGFR-mutant non-small cell lung cancer who has not previously undergone systemic therapy, or a patient with EGFR-mutant non-small cell lung cancer who has previously undergone systemic therapy, and that the methods of the application can be used in conjunction with EGFR-TKI therapy and/or chemotherapy (e.g., using platinum-containing or non-platinum-containing chemotherapeutic agents) and/or immune checkpoint inhibitor (e.g., anti-PD-1/PD-L1 mono- and dual-antibody, anti-CTLA-4 mAb, anti-LAG3 mAb, anti-TIGIT mAb) therapy in combination.

20 In one embodiment, the subject is a patient with small cell lung cancer, such as a patient with small cell lung cancer who has not previously undergone systemic therapy, or a patient with small cell lung cancer who has previously undergone systemic therapy, and the methods of the present application may be used in conjunction with chemotherapy (e.g., using platinum-containing or non-platinum-containing chemotherapeutic agents) and/or immune checkpoint inhibitor (e.g., PD-1/PD-L1 mAb, dual antibody, anti-CTLA-4 mAb, anti-LAG3 mAb, anti-TIGIT mAb) therapy in combination.

In one embodiment, the subject is a patient with nasopharyngeal cancer, such as a patient with nasopharyngeal cancer who has not previously undergone systemic treatment, or a patient with nasopharyngeal cancer who has previously undergone systemic treatment, and the methods of the application may be used in conjunction with chemotherapy (e.g., using platinum-containing or non-platinum-containing chemotherapeutic agents) and/or immune checkpoint inhibitor (e.g., anti-PD-1/PD-L1 mAb, dual antibody, anti-CTLA-4 mAb, anti-LAG3 mAb, anti-TIGIT mAb) therapy in combination.

30 In one embodiment, the subject is a patient with head and neck cancer, such as a patient with head and neck cancer who has not previously undergone systemic therapy, or a patient with head and neck cancer who has previously undergone systemic therapy, the methods of the application may be used in conjunction with chemotherapy (e.g., using platinum-containing or non-platinum-containing chemotherapeutic agents) and/or immune checkpoint inhibitor (e.g., PD-1/PD-L1 mono- and dual-antibody, anti-CTLA-4 mAb, anti-LAG3 mAb, anti-TIGIT mAb) therapy in combination.

In one embodiment, Ab is a bispecific antibody or antigen-binding fragment thereof that simultaneously targets two different epitopes or targets. In one embodiment, Ab is a bispecific antibody or antigen-binding fragment thereof that simultaneously targets EGFR and HER3 in one embodiment, a bispecific antibody or antigen-binding fragment thereof targeting both EGFR and HER3.

40 In one embodiment, Ab comprises an IgG1 heavy chain (HC), a κ light chain (LC), and a single-chain Fv (scFv) domain, the IgG1 HC and κ LC form an IgG portion (i.e. a Fab region) having a binding specificity for EGFR, and the scFv domain has a binding specificity for HER3, wherein the scFv domain is connected to the IgG1 HC or the κ LC through a linker, wherein the linker is attached to the C-terminus or the N-terminus of the IgG1 HC or the C-terminus or the N-terminus of the κ LC, and wherein the scFv

domain has a structural order of N-terminus-HC variable region-joint-LC variable region-C-terminus, or N-terminus-LC variable region-joint-HC variable region-C-terminus.

In one embodiment, the linker comprises an amino acid sequence of (gly-gly-gly-gly-ser)_n, and wherein n is an integer from 1 to 10. In one embodiment, the joint comprises an amino acid sequence of (gly-gly-gly-gly-ser)_m, wherein m is 3, 4, 5, or 6.

In one embodiment, the κ LC comprises a CDR having at least 90%, 95%, 98%, or 99% sequence identity to SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, the IgG1 HC comprises a CDR having at least 90%, 95%, 98%, or 99% sequence identity to SEQ ID NO: 8, SEQ ID NO: 9, SEQ ID NO: 10, and the scFv domains comprises HC variable region CDRs having at least 90%, 95%, 98%, or 99% sequence identity to SEQ ID NO: 16, SEQ ID NO: 17, SEQ ID NO: 18, and LC variable region CDRs having at least 90%, 95%, 98%, or 99% sequence identity to SEQ ID NO: 12, SEQ ID NO: 13, SEQ ID NO: 14.

In one embodiment, the Ab comprises the κ LC variable region having at least 90%, 95%, 98%, or 99% sequence identity to SEQ ID NO: 2, the IgG1 HC comprises a variable region having at least 90%, 95%, 98%, or 99% sequence identity to SEQ ID NO: 7, and the scFv domain contains a HC variable region having at least 90%, 95%, 98%, or 99% sequence identity to SEQ ID NO: 15 and a LC variable region having at least 90%, 95%, 98%, or 99% sequence identity to SEQ ID NO: 11.

In one embodiment, the Ab comprises the κ LC having an amino acid sequence having at least 90%, 95%, 98%, or 99% sequence identity to SEQ ID NO: 1, and the IgG1 HC-linker-scFv comprising an amino acid sequence having at least 90%, 95%, 98%, or 99% sequence identity to SEQ ID NO: 6.

In one embodiment, the Ab comprises the κ LC comprises CDRs having at least 90%, 95%, 98%, or 99% sequence identity to SEQ ID NO: 29, SEQ ID NO: 30, SEQ ID NO: 31, the IgG1 HC comprises CDRs having at least 90%, 95%, 98%, or 99% sequence identity to SEQ ID NO: 34, SEQ ID NO: 35, SEQ ID NO: 36 shown, and the scFv domain contains the HC variable region CDRs having at least 90%, 95%, 98%, or 99% sequence identity to SEQ ID NO: 16, SEQ ID NO: 17, SEQ ID NO: 18, as the LC variable region CDRs having at least 90%, 95%, 98%, or 99% sequence identity to SEQ ID NO: 12, SEQ ID NO: 13, SEQ ID NO: 14.

In one embodiment, the Ab comprises the κ LC comprises a variable region having at least 90%, 95%, 98%, or 99% sequence identity to SEQ ID NO: 28, the IgG1 HC comprises a variable region having at least 90%, 95%, 98%, or 99% sequence identity to SEQ ID NO: 33, and the scFv domain comprising a heavy chain variable region having at least 90%, 95%, 98%, or 99% sequence identity to SEQ ID NO: 15 and a light chain variable region having at least 90%, 95%, 98%, or 99% sequence identity to SEQ ID NO: 11.

In one embodiment, the Ab comprises the κ LC having an amino acid sequence having at least 90%, 95%, 98%, or 99% sequence identity to SEQ ID NO: 27, and the IgG1 HC-linker-scFv having an amino acid sequence having at least 90%, 95%, 98%, or 99% sequence identity to SEQ ID NO: 32. In one embodiment, the Ab comprises the κ LC having a variable region having at least 90%, 95%, 98%, or 99% sequence identity to SEQ ID NO: 20, the IgG1 HC having a variable region having at least 90%, 95%, 98%, or 99% sequence identity to SEQ ID NO: 24, and the scFv domain comprising a HC variable region having at least 90%, 95%, 98%, or 99% sequence identity to SEQ ID NO: 22 and a LC variable region having at least 90%, 95%, 98%, or 99% sequence identity to SEQ ID NO: 21.

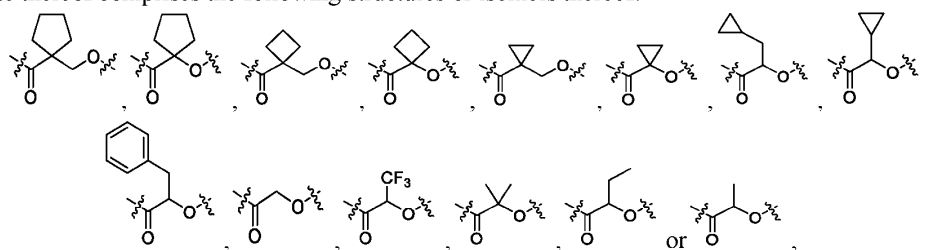
In one embodiment, the Ab comprises the IgG1 HC comprising an amino acid sequence having at least 90%, 95%, 98%, or 99% sequence identity to SEQ ID NO: 23, and the κ LC-linker-scFv comprising an amino acid sequence having at least 90%, 95%, 98%, or 99% sequence identity to SEQ ID NO: 19. In one embodiment, the Ab comprises the κ LC comprising an amino acid sequence having at least 90%, 95%, 98%, or 99% sequence identity to SEQ ID NO: 25, and the IgG1 HC-linker- scFv comprises an amino acid

sequence having at least 90%, 95%, 98%, or 99% sequence identity to SEQ ID NO: 26. In one embodiment, the Ab comprises the IgG1 HC comprising an amino acid sequence having at least 90%, 95%, 98%, or 99% sequence identity to SEQ ID NO: 38, and the κ LC-linker-the scFv comprising an amino acid sequence having at least 90%, 95%, 98%, or 99% sequence identity to SEQ ID NO: 37.

In one embodiment, the Ab comprises a variable region having at least 90%, 95%, 98%, or 99% sequence identity to SEQ ID NO: 40, the IgG1 HC comprising a variable region having at least 90%, 95%, 98%, or 99% sequence identity to SEQ ID NO: 42, and the scFv domain comprising a heavy chain variable region having at least 90%, 95%, 98%, or 99% sequence identity to SEQ ID NO: 50 and a light chain variable region having at least 90%, 95%, 98%, or 99% sequence identity to SEQ ID NO: 21. In one embodiment, the Ab comprises the IgG1 HC comprising an amino acid sequence having at least 90%, 95%, 98%, or 99% sequence identity to SEQ ID NO: 41, and the κ LC-linker-the scFv comprising an amino acid sequence having at least 90%, 95%, 98%, or 99% sequence identity to SEQ ID NO: 39.

In one embodiment, the Ab comprises two IgG1 heavy chains, two κ light chains, and two single chain scFv domains, wherein each scFv domain is connected to each of IgG heavy chain or κ light chain through a linker.

In one embodiment, X in the ligand-camptothecin conjugate of or a pharmaceutically acceptable salt or solvate thereof comprises the following structures or isomers thereof:



where the left wavy line is connected to the camptothecin derivative, and the right wavy line is connected to L_5 .

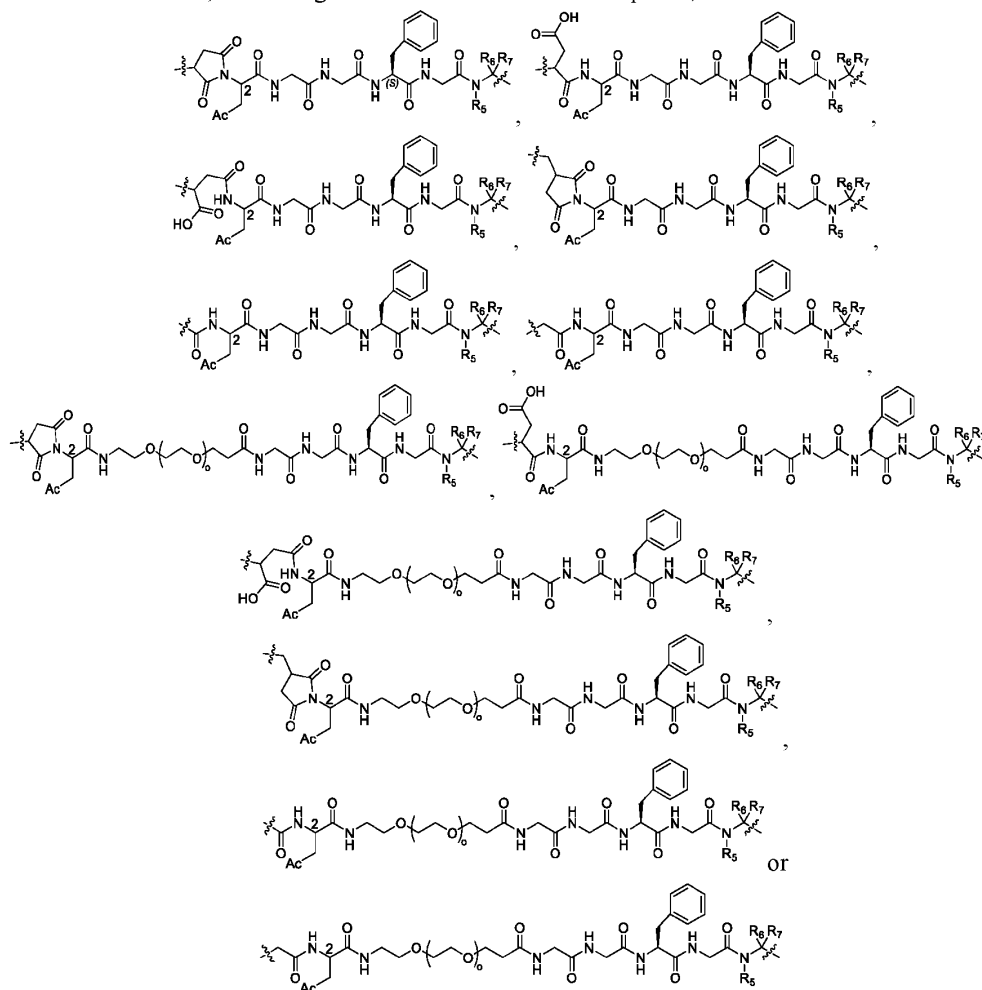
In one embodiment, L_4 is selected from peptide residues consisting of amino acids. In one embodiment, the amino acid is further substituted with one or more substituents selected from one or more of deuterium atoms, halogens, hydroxyl, cyano, amino, nitro, carboxyl, C1-C6 alkyl, substituted C1-C6 alkyl, C1-C6 alkoxy and C3-C8 cycloalkyl or substituted C3-C8 cycloalkyl.

In one embodiment, the peptide residue is a peptide residue formed from one, two or more amino acids selected from among phenylalanine (F), glycine (G), valine (V), lysine (K), citrulline (C), serine (S), glutamic acid (E) or aspartic acid (D). In one embodiment, the peptide residue is a tetrapeptide residue comprising glycine (G) -glycine (G) -phenylalanine (F) -glycine (G). In one embodiment, peptide residue is -GGFG-.

In one embodiment, L_5 is selected from $-NR_5 (CR_6R_7)_q-$ or a chemical bond, and q is selected from integers 0-6; and

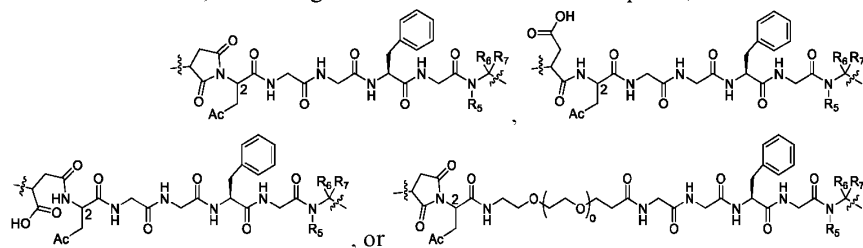
In one embodiment, R_5 , R_6 and R_7 are the same or different and are each independently selected from hydrogen atoms, deuterium atoms, halogens, C1-C6 alkyl group, substituted C1-C6 alkyl group, deuterated C1-C6 alkyl group, C3-C8 cycloalkyl group, C3-C8 cycloalkyl C1-C6 alkyl group, C1-C6 alkoxy C1-C6 alkyl group, 3-7 heterocycloheteroaryl group, substituted 3-7 heterocycloheteroaryl group, C6-C10 aryl group, substituted C6-C10 aryl, 5-10 heteroaryl, substituted 5-10 heteroaryl, or a combination thereof. In one embodiment, R_5 , R_6 and R_7 are each independently selected from hydrogen atoms or C1-C6 alkyl group. In one embodiment, R_5 , R_6 and R_7 are each independently selected from hydrogen atoms.

In one embodiment, the linking unit -L₁ -L₂ -L₃ -L₄ -L₅ - comprises,



10

In one embodiment, the linking unit -L₁ -L₂ -L₃ -L₄ -L₅ - comprises,



wherein:

Ac is a hydrophilic structural unit,

R₅, R₆ and R₇ are the same or different and are each independently selected from hydrogen atom, deuterium atom, halogen, C1-C6 alkyl, substituted C1-C6 alkyl, deuterated C1-C6 alkyl, C3-C8 cycloalkyl, C3-C8 cycloalkyl C1-C6 alkyl, C1-C6 alkoxy C1-C6 alkyl, 3-7 heterocyclic, substituted 3-7 heterocyclic,

C6-C10 aryl, substituted C6-C10 aryl, 5-10 heteroaryl, substituted 5-10 heteroaryl,

the carbon atom #2 attached to N has absolute chirality in either the R configuration or the S configuration,

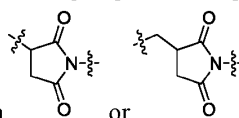
the left wavy line is connected to the antibody or its antigen-binding fragment portion, and the right wavy line is connected to the X; and

o is selected from integers 1-10 (e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10).

In one embodiment, R₅, R₆ and R₇ are each independently selected from a hydrogen atom or a C1-C6 alkyl group. In one embodiment, R₅, R₆ and R₇ are each independently selected from a hydrogen atom.

10 In one embodiment, L₁ may comprise a succinimide moiety. In these embodiments, the ligand-drug coupling may undergo hydrolysis under readily hydrolyzable conditions, with the site of hydrolysis being the butanediimide moiety of the linker unit. When the ligand contains multiple linker-drugs, the following scenarios can occur with varying degrees of hydrolysis.

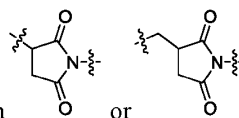
In one embodiment, the succinimide groups are completely non-hydrolyzed, i.e., the succinimide



groups are all in the closed ring form

or

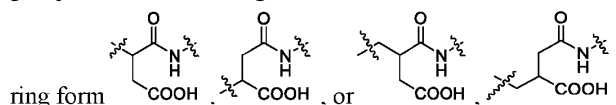
In one embodiment, incomplete hydrolysis of the butanediimide group, i.e., some of the butanediimide



group is in the closed ring form

or

and some of the butanediimide group is in the open



ring form

, or

, or

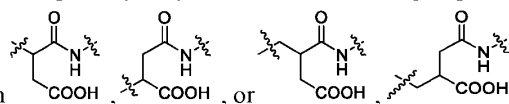
, or

, or

, or

, or

In one embodiment, complete hydrolysis of the succinimide groups, i.e., the succinimide groups are all



in the ring-opened form

, or

, or

, or

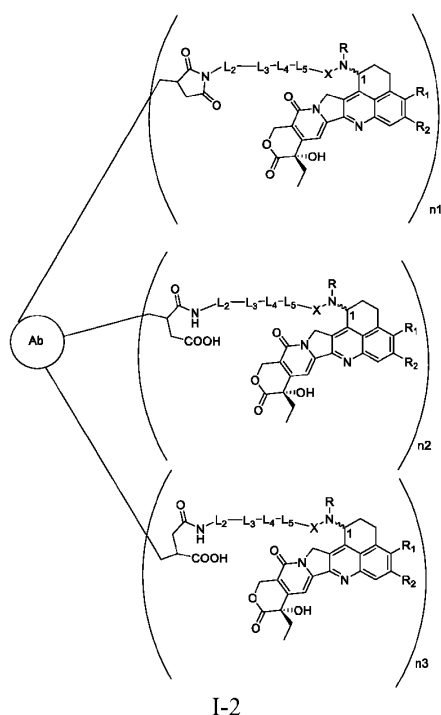
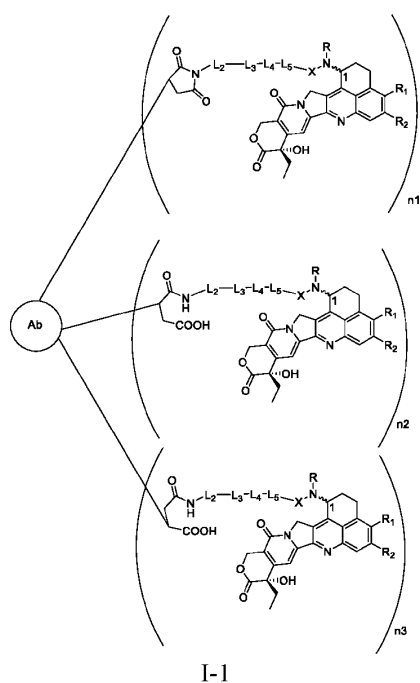
, or

, or

20 Thus, when multiple L₁ containing succinimide moieties (i.e., Ab is connected to multiple drug-linkers containing succinimide moieties) are present in the ADC at the same time, all these succinimide moieties can be in a closed-loop form, partially in an open-loop form, or fully in an open-loop form.

It is to be understood that the present application, even though the butanediimide moiety appearing in the chemical structural formula of the ADC is in the closed ring form, covers the three cases of butanediimide fully closed, partially open and fully open.

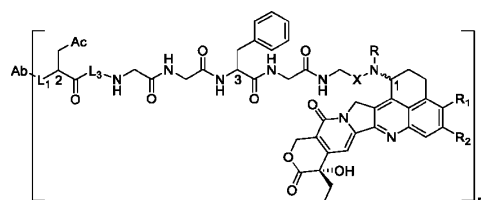
Thus, in one embodiment, the ligand-camptothecin derivative conjugate or pharmaceutically acceptable salt or solvate thereof has a structure as shown in Formula I-1 or I-2.



wherein n1, n2, n3 are each independently selected from any integer or any decimal number from 0-10

(e.g., 0, 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 2, 2.1, 2.2, 2.3, 2.4, 2.5, 2.6, 2.7, 2.8, 2.9, 3, 3.1, 3.2, 3.3, 3.4, 3.5, 3.6, 3.7, 3.8, 3.9, 4, 4.1, 4.2, 4.3, 4.4, 4.5, 4.6, 4.7, 4.8, 4.9, 5, 5.1, 5.2, 5.3, 5.4, 5.5, 5.6, 5.7, 5.8, 5.9, 6, 6.1, 6.2, 6.3, 6.4, 6.5, 6.6, 6.7, 6.8, 6.9, 7, 7.1, 7.2, 7.3, 7.4, 7.5, 7.6, 7.7, 7.8, 7.9, 8, 8.1, 8.2, 8.3, 8.4, 8.5, 8.6, 8.7, 8.8, 8.9, 9, 9.1, 9.2, 9.3, 9.4, 9.5, 9.6, 9.7, 9.8, 9.9, or 10), n_1, n_2, n_3 are not simultaneously 0, and $1 \leq n_1 + n_2 + n_3 \leq 10$.

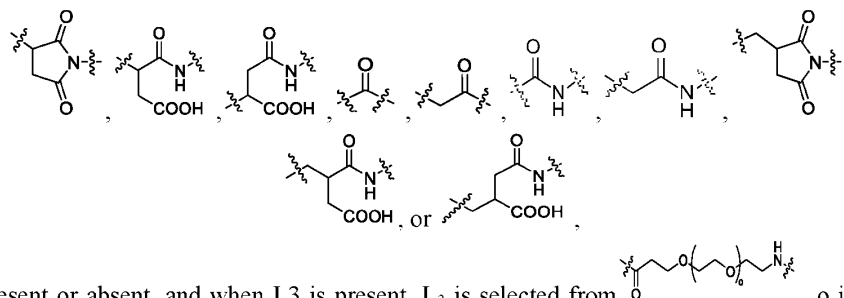
In one embodiment, the ligand-camptothecin derivative conjugate, or pharmaceutically acceptable salt or solvate thereof has a structure as shown in Formula II:



II

10 wherein:

L₁ is the connection unit connected to Ab, comprising:



L₃ is present or absent, and when L₃ is present, L₃ is selected from $\{0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10\}$, o is selected from an integer from 1-10 (e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10). In one embodiment, o is an integer from 2-8.

Ac is a hydrophilic structural unit.

the 1-position, 2-position and 3-position chiral carbon atoms have two chiral configurations, the R-absolute configuration or the S-absolute configuration,

20 R is selected from hydrogen atoms, deuterium atoms, halogens, C1-C6 alkyl, substituted C1-C6 alkyl, deuterated C1-C6 alkyl, C3-C8 cycloalkyl C1-C6 alkyl, C1-C6 alkoxy C1-C6 alkyl, C6-C10 aryl, substituted C6-C10 aryl, 5-10 heteroaryl, substituted 5-10 heteroaryl,

R₁ is selected from hydrogen atoms, deuterium atoms, halogens, C1-C6 alkyl, substituted C1-C6 alkyl, deuterated C1-C6 alkyl, C3-C8 cycloalkyl C1-C6 alkyl, C1-C6 alkoxy C1-C6 alkyl, carboxyl, 3-7 heterocyclic, substituted 3-7 heterocyclic, C6-C10 aryl, substituted C6-C10 aryl, 5-10 heteroaryl, substituted 5-10 heteroaryl.

R₂ is selected from hydrogen atoms, deuterium atoms, halogens, C1-C6 alkyl, substituted C1-C6 alkyl, deuterated C1-C6 alkyl, C3-C8 cycloalkyl C1-C6 alkyl, C1-C6 alkoxy C1-C6 alkyl, carboxyl, 3-7 heterocyclic, substituted 3-7 heterocyclic, C6-C10 aryl, substituted C6-C10 aryl, 5-10 heteroaryl, substituted 5-10 heteroaryl.

X selected from -C(O)-CR_aR_b-(CR₃R₄)_m-O-, -C(O)-CR_aR_b-(CR₃R₄)_m-NH- or -C(O)-CR_aR_b-(CR₃R₄)_m-S-,

R_a and R_b are each independently selected from a hydrogen atom, a deuterium atom, a halogen, a C1-C6 alkyl, a deuterated C1-C6 alkyl, a halogenated C1-C6 alkyl, a C3-C8 cycloalkyl, a C3-C8 cycloalkyl C1-C6 alkyl, a C1-C6 alkoxy C1-C6 alkyl, a 3-7 heterocyclic group, a substituted 3-7 heterocyclic group, a C6-C10 aryl, a substituted C6-C10 aryl, a 5-10 heteroaryl, substituted 5-10 heteroaryl,

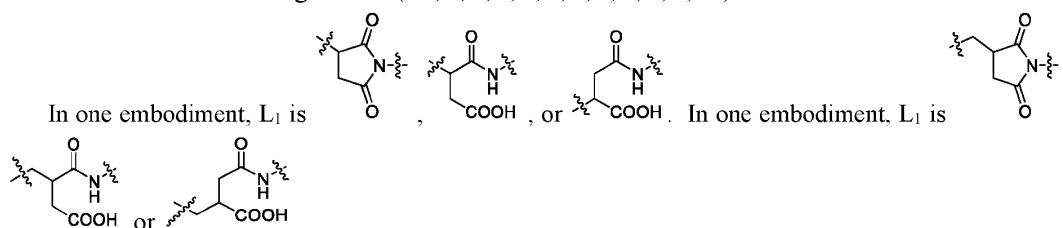
R_3 , R_4 are the same or different and are independently hydrogen atoms, deuterium atoms, halogens, C1-C6 alkyl, halogenated C1-C6 alkyl, deuterated C1-C6 alkyl, C1-C6 alkoxy, hydroxyl, amino, cyano, nitro, hydroxy C1-C6 alkyl, C3-C8 cycloalkyl, 3-7 heterocyclic, substituted 3-7 heterocyclic, respectively,

m is selected from the integers 0-4 (i.e., 0, 1, 2, 3, 4). In one embodiment, m is 0 or 1, and

n is chosen from the integers 1-10 (i.e., 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10).

10

In one embodiment, L_1 is



In one embodiment, R is hydrogen or C1-C6 alkyl.

In one embodiment, R_1 is hydrogen or C1-C6 alkyl. In one embodiment, R_1 is C1-C6 alkyl.

In one embodiment, R_2 is hydrogen, halogen, or C1-C6 alkyl. In one embodiment, R_2 is halogen.

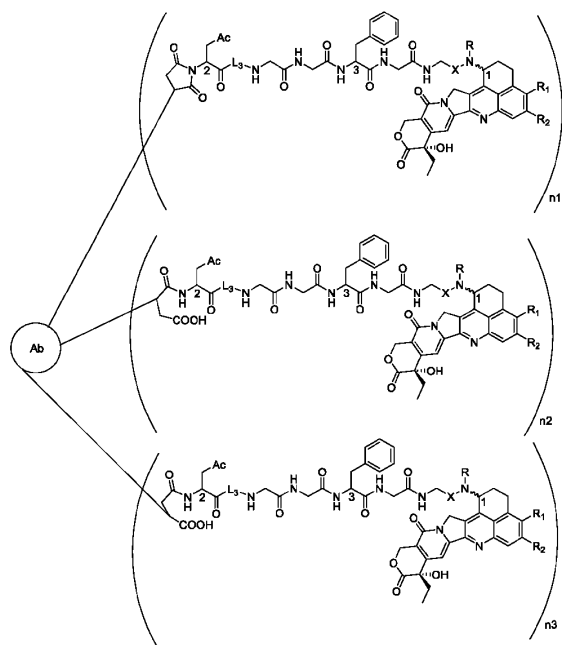
In one embodiment, X is $-C(O)-CR_aR_b-(CR_3R_4)_m-O-$,

In one embodiment, R_a and R_b are each independently selected from a hydrogen atom, a C1-C6 alkyl, a halo-C1-C6 alkyl, a C3-C8 cycloalkyl C1-C6 alkyl or a C6-C10 aryl C1-C6 alkyl, or wherein R_a , R_b and the carbon atoms to which they are attached constitute C3-C8 cycloalkyl group, C3-C8 cycloalkyl C1-C6 alkyl group, 3-7 heterocycloalkyl group, substituted 3-7 heterocycloalkyl group; in one embodiment, R_a , R_b and the carbon atoms to which they are attached constitute C3-C8 cycloalkyl group.

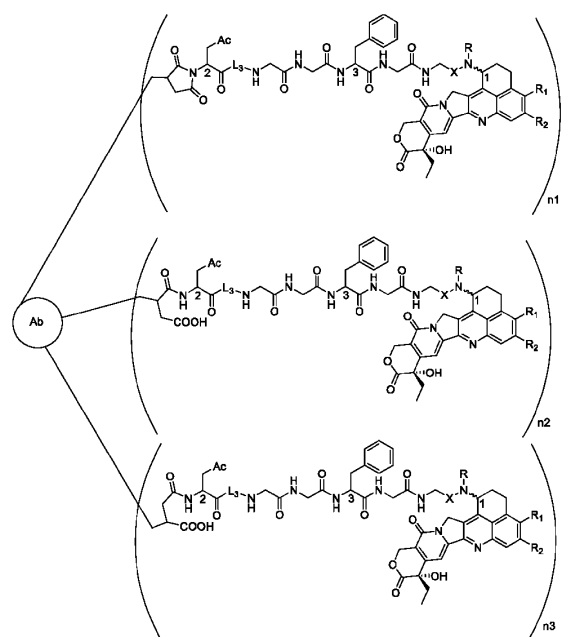
20

In one embodiment, R_3 , R_4 are independently hydrogen or C1-C6 alkyl, or wherein R_3 , R_4 and the carbon atoms attached thereto constitute a C3-C8 cycloalkyl group, a C3-C8 cycloalkyl C1-C6 alkyl group, a 3-7 heterocyclic group, a substituted 3-7 heterocyclic group.

In one embodiment, the ligand-camptothecin derivative coupling or pharmaceutically acceptable salt or solvate thereof having a structure as shown in Formula II-1 or II-2:



II-1

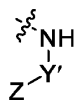


II-2

wherein $n1$, $n2$, and $n3$ are each independently selected from any integer or any decimal number from

0 to 10 (e.g. 0, 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 2, 2.1, 2.2, 2.3, 2.4, 2.5, 2.6, 2.7, 2.8, 2.9, 3, 3.1, 3.2, 3.3, 3.4, 3.5, 3.6, 3.7, 3.8, 3.9, 4, 4.1, 4.2, 4.3, 4.4, 4.5, 4.6, 4.7, 4.8, 4.9, 5, 5.1, 5.2, 5.3, 5.4, 5.5, 5.6, 5.7, 5.8, 5.9, 6, 6.1, 6.2, 6.3, 6.4, 6.5, 6.6, 6.7, 6.8, 6.9, 7, 7.1, 7.2, 7.3, 7.4, 7.5, 7.6, 7.7, 7.8, 7.9, 8, 8.1, 8.2, 8.3, 8.4, 8.5, 8.6, 8.7, 8.8, 8.9, 9, 9.1, 9.2, 9.3, 9.4, 9.5, 9.6, 9.7, 9.8, 9.9, or 10), n_1 , n_2 , and n_3 are not simultaneously 0, and $1 \leq n_1 + n_2 + n_3 \leq 10$.

In one embodiment, the Ac has the structure shown in Formula B below.



Formula B

wherein:

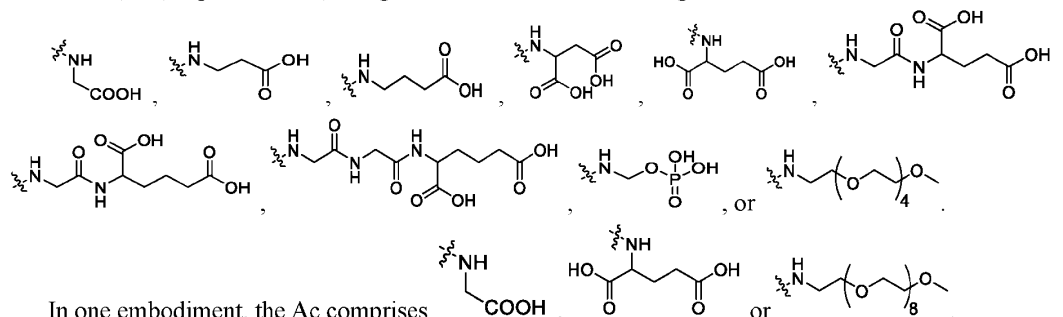
- 10 Z comprises one or more of hydrophilic structural carboxyl group, phosphoric acid, polyphosphoric acid, phosphite, sulfonic acid, sulfidic acid, or polyethylene glycol (PEG),

Y' is optionally a scaffold connecting the amino group to Z; in one embodiment, Y' is C1-C6 alkyl (e.g. methylene); and

Ac is connected to the 2-position carbon that has been labeled in structural formula I by means of a bracket Y.

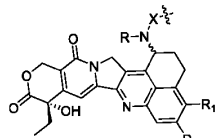
In one embodiment, Z is selected from hydrophilic structural carboxylates and phosphoric acid or polyethylene glycol (PEG).

- 20 In one embodiment, the Ac comprises natural or non-natural amino acid or their derivatives. Example amino acids may include without limitation glycine, (D/L) alanine, (D/L) leucine, (D/L) isoleucine, (D/L) valine, (D/L) phenylalanine, (D/L) proline, (D/L) tryptophan, (D/L) serine, (D/L) tyrosine, (D/L) cysteine, (D/L) cystine, (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 or isomers thereof:

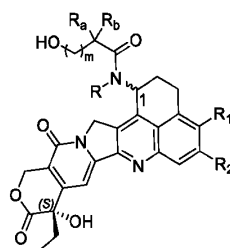


In one embodiment, the Ac comprises

In one embodiment, the Ac comprises a glycine, phosphoric acid, (D/L) glutamic acid, or polyethylene glycol hydrophilic structure.



In one embodiment, the has the structure shown in Formula D below:



Formula D

wherein:

R is selected from hydrogen atom, deuterium atom, halogen, C1-C6 alkyl, substituted C1-C6 alkyl, deuterated C1-C6 alkyl, C3-C8 cycloalkyl C1-C6 alkyl, C1-C6 alkoxy C1-C6 alkyl, C6-C10 aryl, substituted C6-C10 aryl, 5-10 heteroaryl, substituted 5-10 heteroaryl,

R₁ is selected from hydrogen atoms, deuterium atoms, halogens, C1-C6 alkyl, substituted C1-C6 alkyl, deuterated C1-C6 alkyl, C3-C8 cycloalkyl C1-C6 alkyl, C1-C6 alkoxy C1-C6 alkyl, carboxyl, 3-7 heterocyclic, substituted 3-7 heterocyclic, C6-C10 aryl, substituted C6-C10 aryl, 5-10 heteroaryl, substituted 5-10 heteroaryl,

R₂ is selected from hydrogen atoms, deuterium atoms, halogens, C1-C6 alkyl, substituted C1-C6 alkyl, deuterated C1-C6 alkyl, C3-C8 cycloalkyl C1-C6 alkyl, C1-C6 alkoxy C1-C6 alkyl, carboxyl, 3-7 heterocyclic, substituted 3-7 heterocyclic, C6-C10 aryl, substituted C6-C10 aryl, 5-10 heteroaryl, substituted 5-10 heteroaryl,

R_a and R_b are each independently selected from a hydrogen atom, a deuterium atom, a halogen, a C1-C6 alkyl, a deuterated C1-C6 alkyl, a halogenated C1-C6 alkyl, a C3-C8 cycloalkyl, a C3-C8 cycloalkyl C1-C6 alkyl, a C1-C6 alkoxy C1-C6 alkyl, a 3-7 heterocyclic group, a substituted 3-7 heterocyclic group, a C6-C10 aryl, a substituted C6-C10 aryl, a 5-10 heteroaryl, substituted 5-10 heteroaryl,

the 1-position chiral carbon atom has two chiral configurations, the R absolute configuration or the S absolute configuration, and

m is selected from 0 or 1.

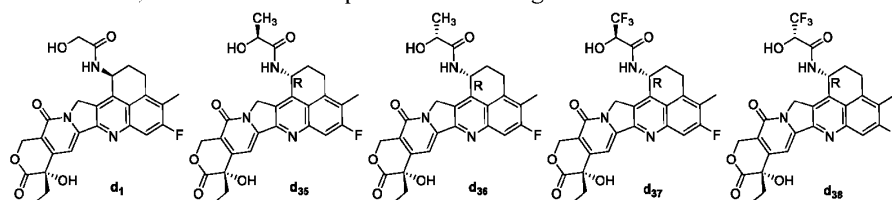
In one embodiment, R is hydrogen atom or C1-C6 alkyl.

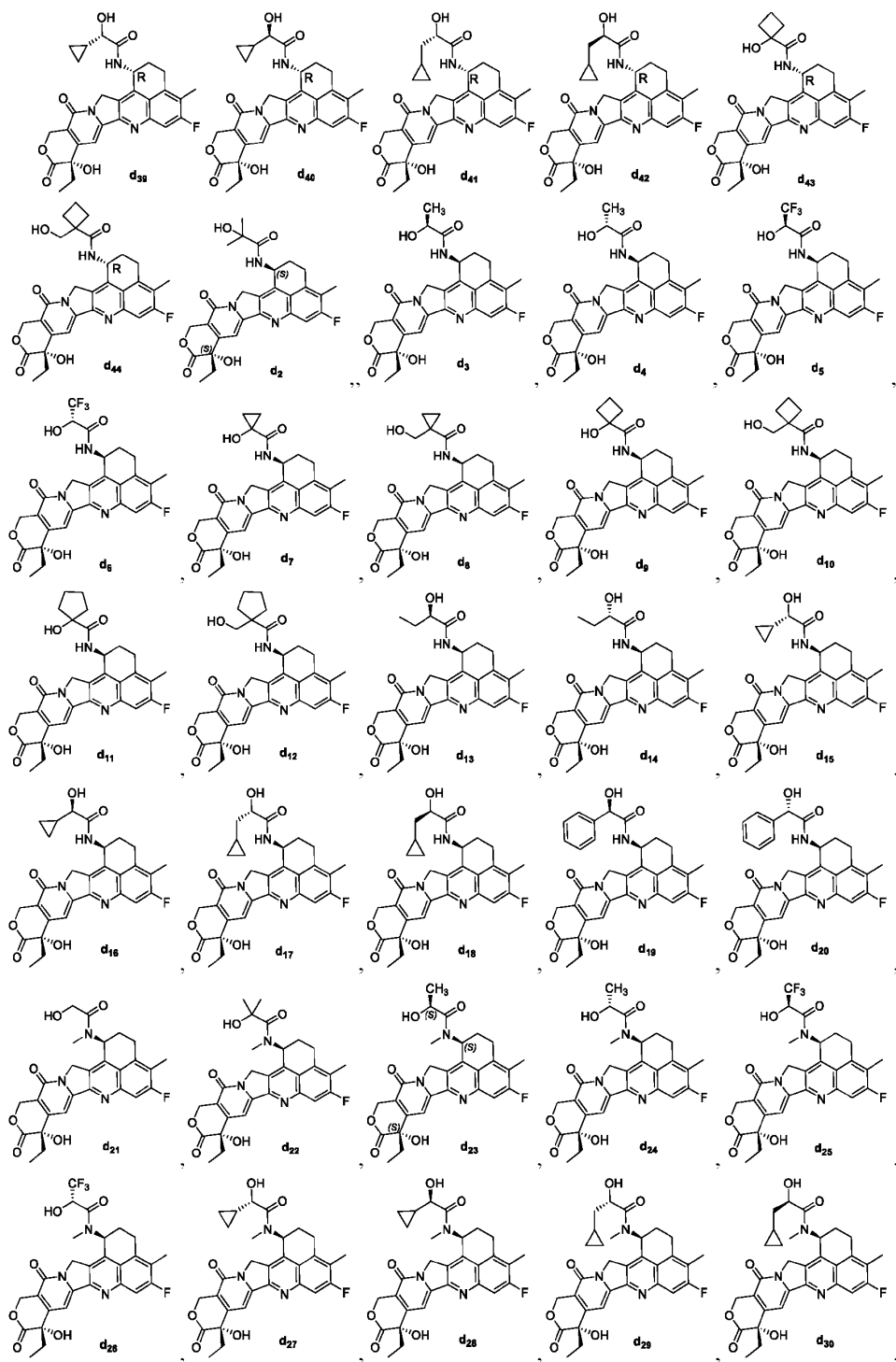
In one embodiment, R₁ is hydrogen atom or C1-C6 alkyl. In one embodiment, R₁ is C1-C6 alkyl.

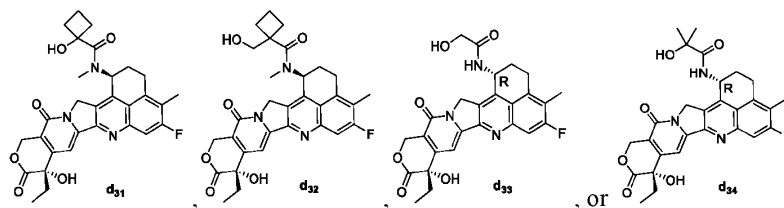
In one embodiment, R₂ is hydrogen, halogen or C1-C6 alkyl. In one embodiment, R₂ is halogen.

In one embodiment, R_a and R_b are each independently selected from a hydrogen atom, a C1-C6 alkyl group, a halo-C1-C6 alkyl group, a C3-C8 cycloalkyl C1-C6 alkyl group, a C6-C10 aryl group, or wherein R_a, R_b and the carbon atoms to which they are attached constitute a C3-C8 cycloalkyl group, a C3-C8 cycloalkyl C1-C6 alkyl group, a 3-7 heterocycloalkyl group, a substituted 3-7 heterocycloalkyl group; in one embodiment, R_a, R_b and the carbon atoms to which they are attached constitute a C3-C8 cycloalkyl group.

In one embodiment, the Formula D comprises the following:

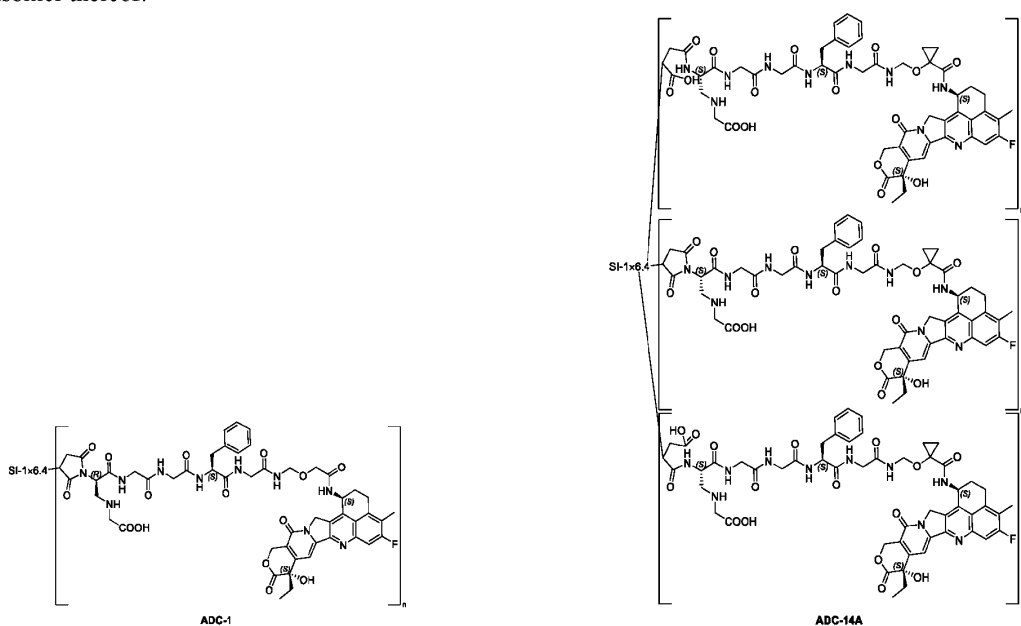


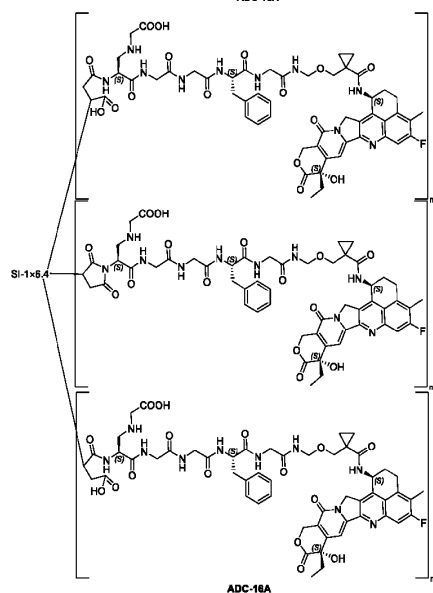
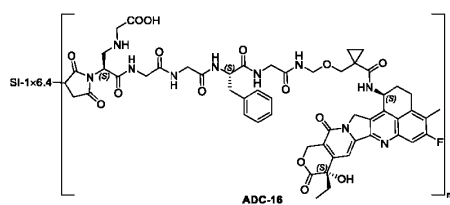
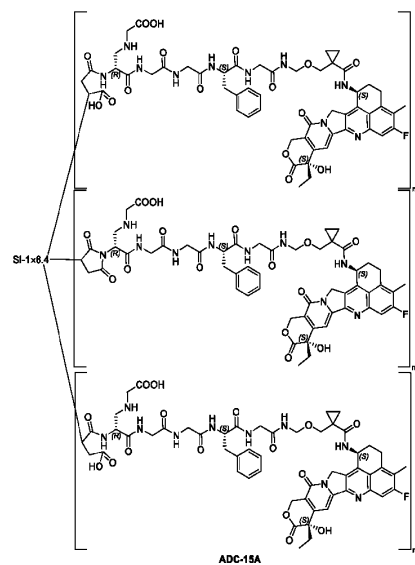
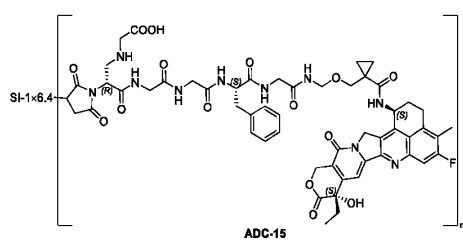


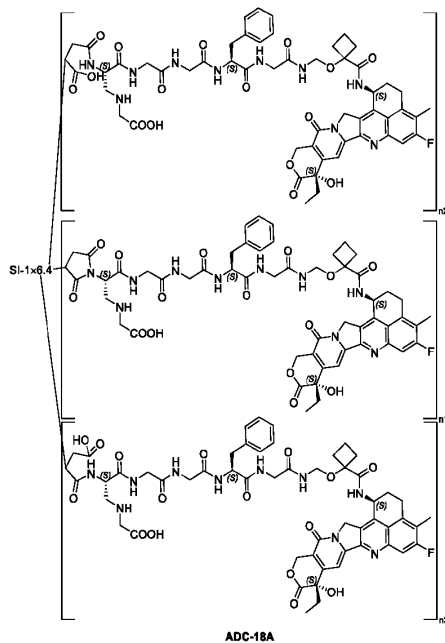
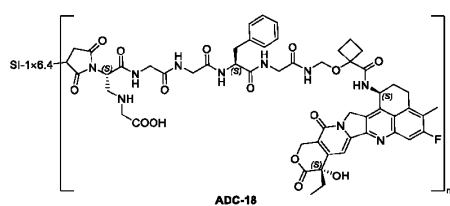
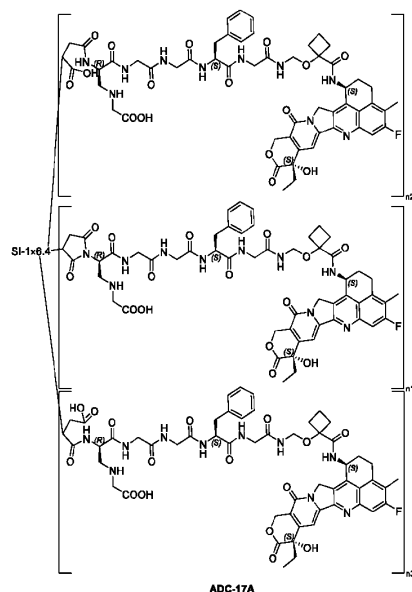


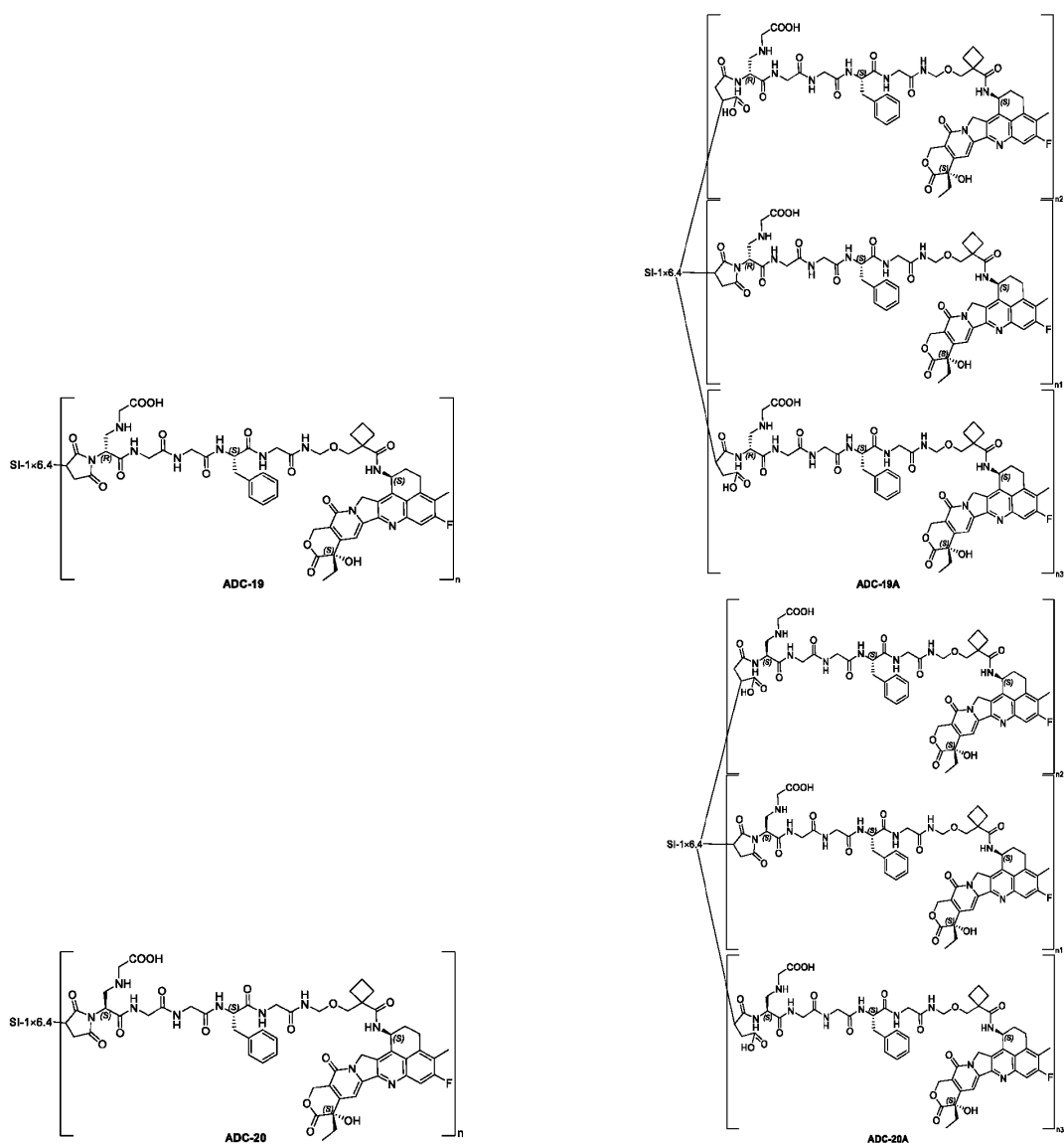
Methods for the preparation of the ligand-camptothecin derivative couplings shown above in General Formula I or General Formula II, or pharmaceutically acceptable salts or solvates thereof, can be found in WO 2023/083381, incorporated herein by reference in its entirety.

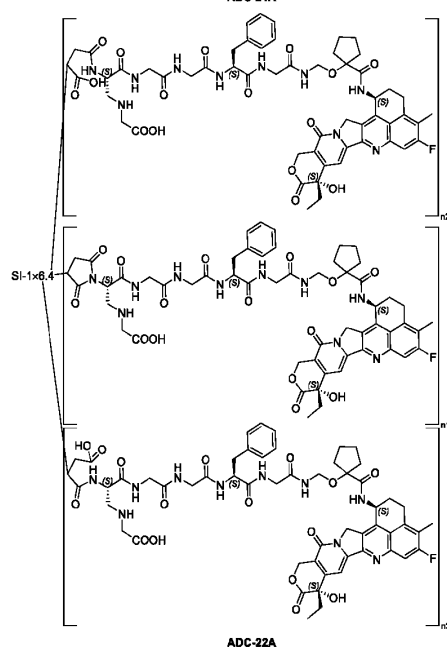
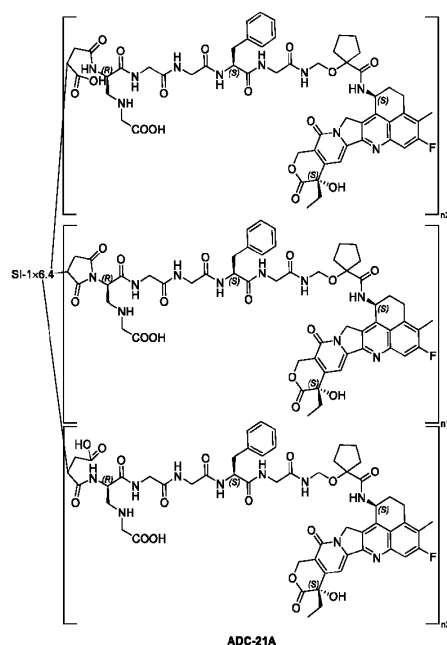
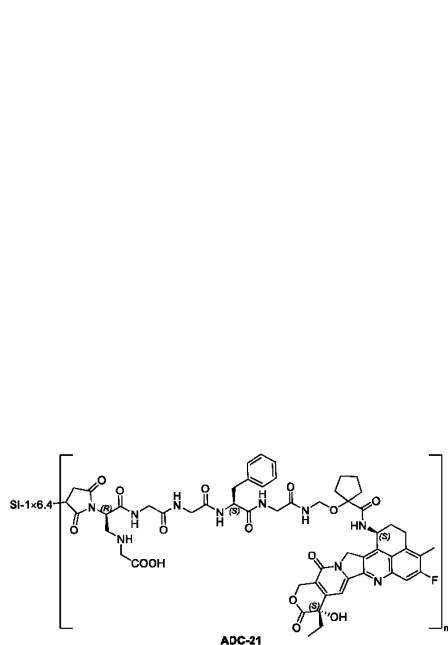
In one embodiment, the ligand-camptothecin derivative conjugate or pharmaceutically acceptable salt or solvate thereof comprises the following structure or a butanediimide ring-opening structure thereof or an isomer thereof:

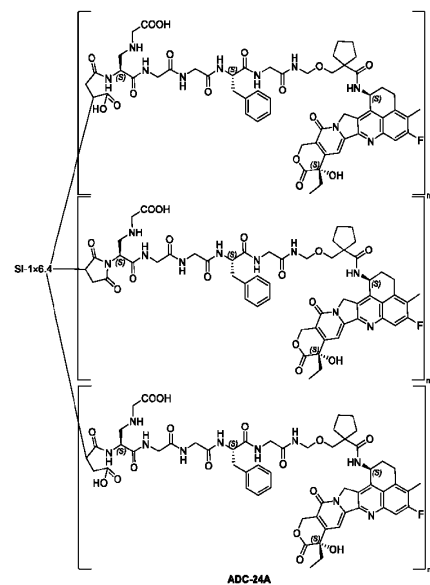
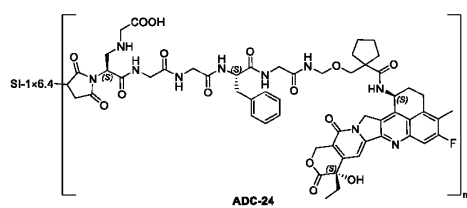
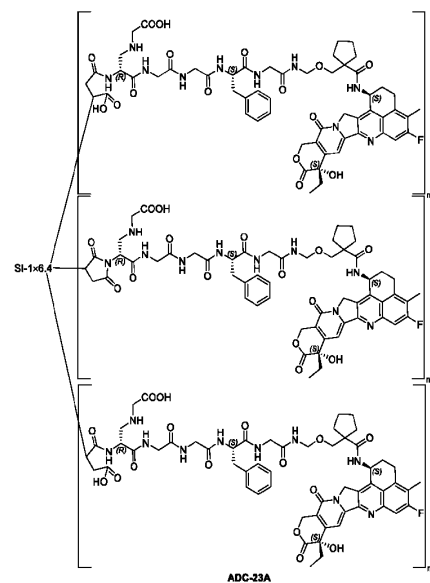
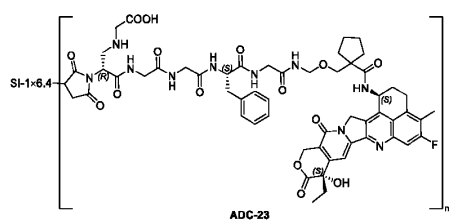


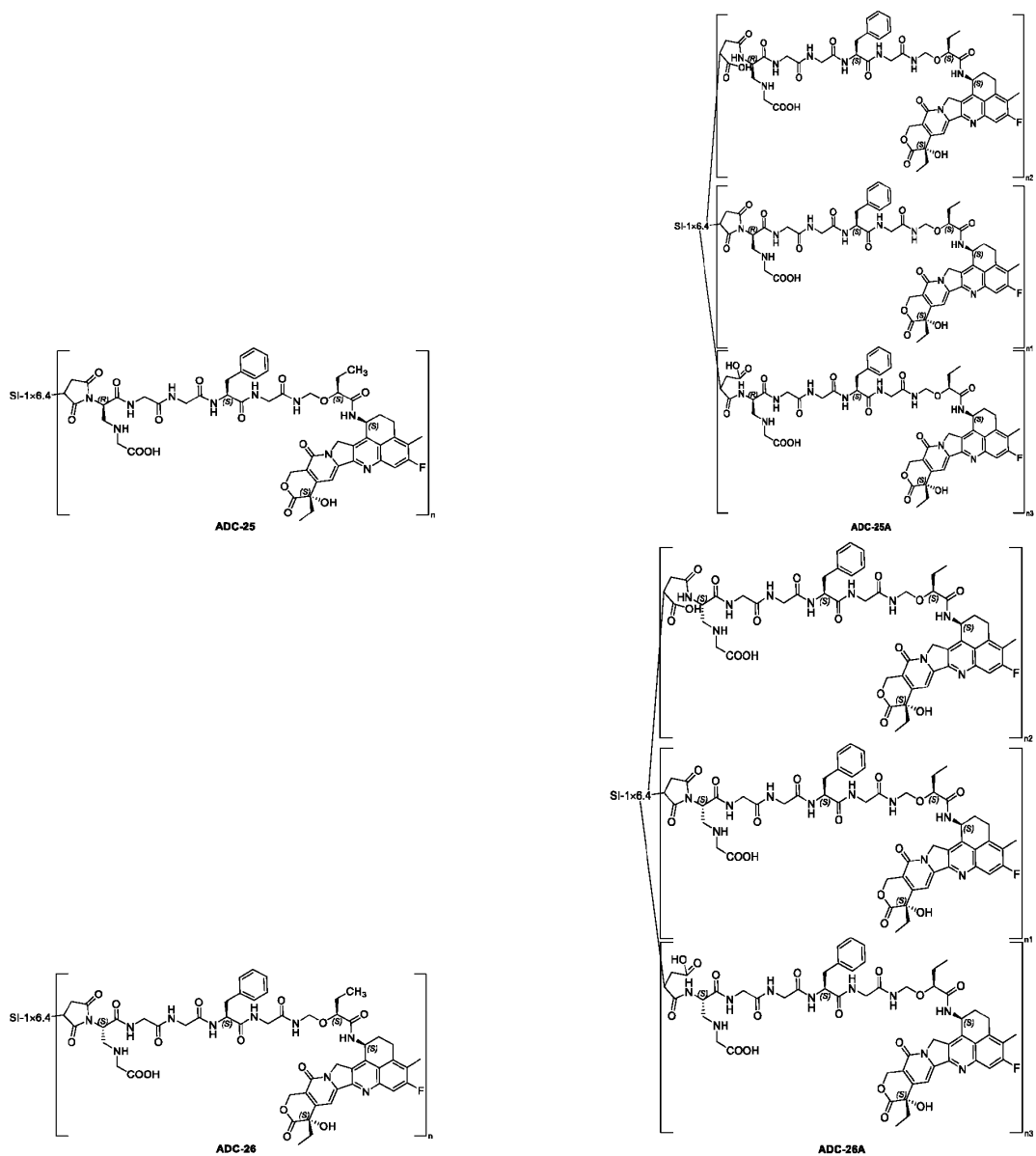


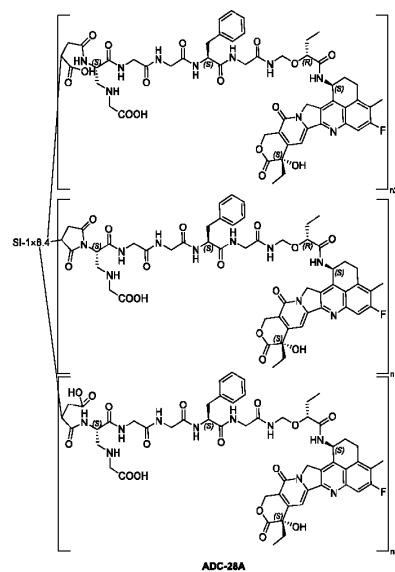
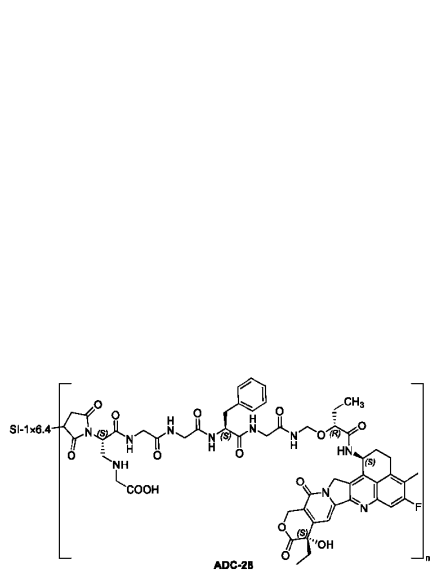
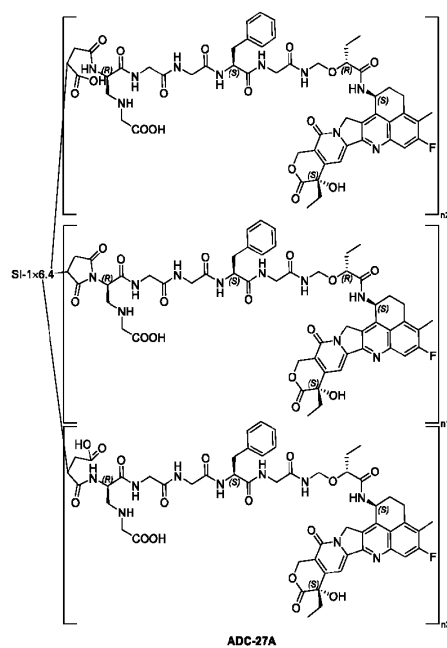
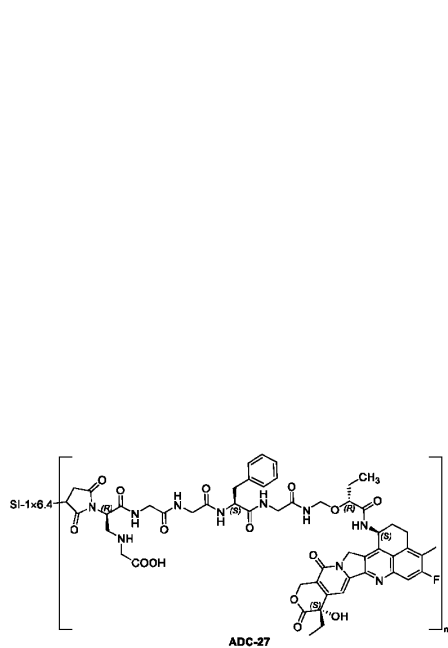


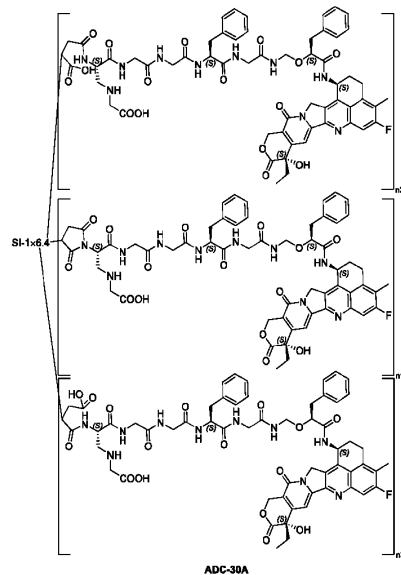
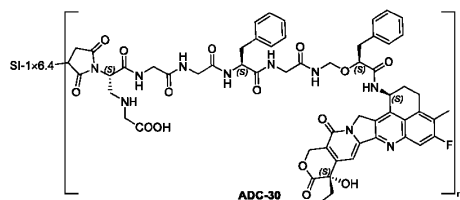
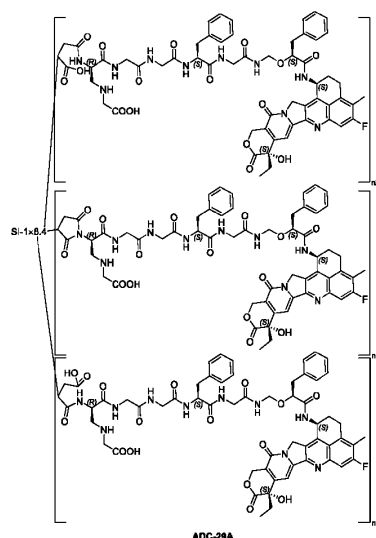


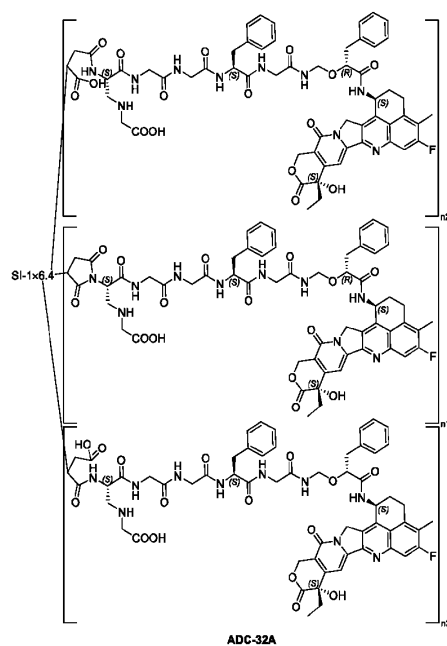
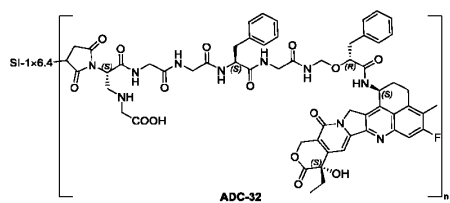
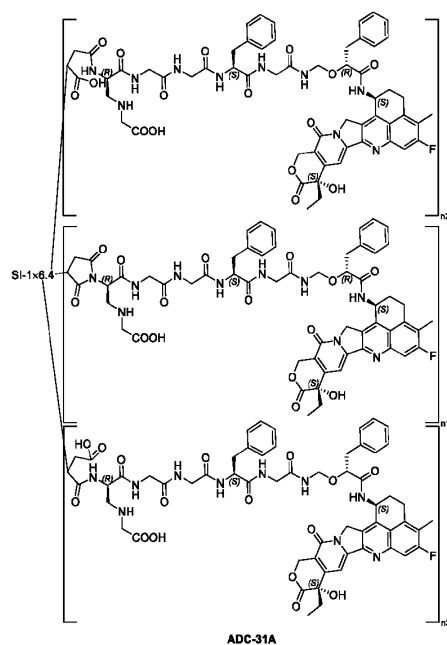
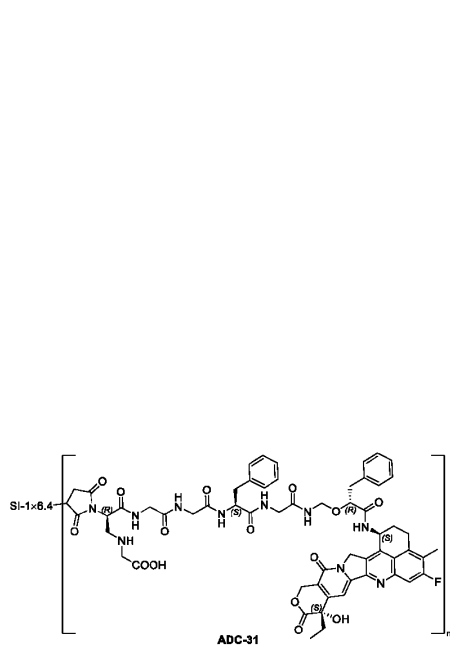


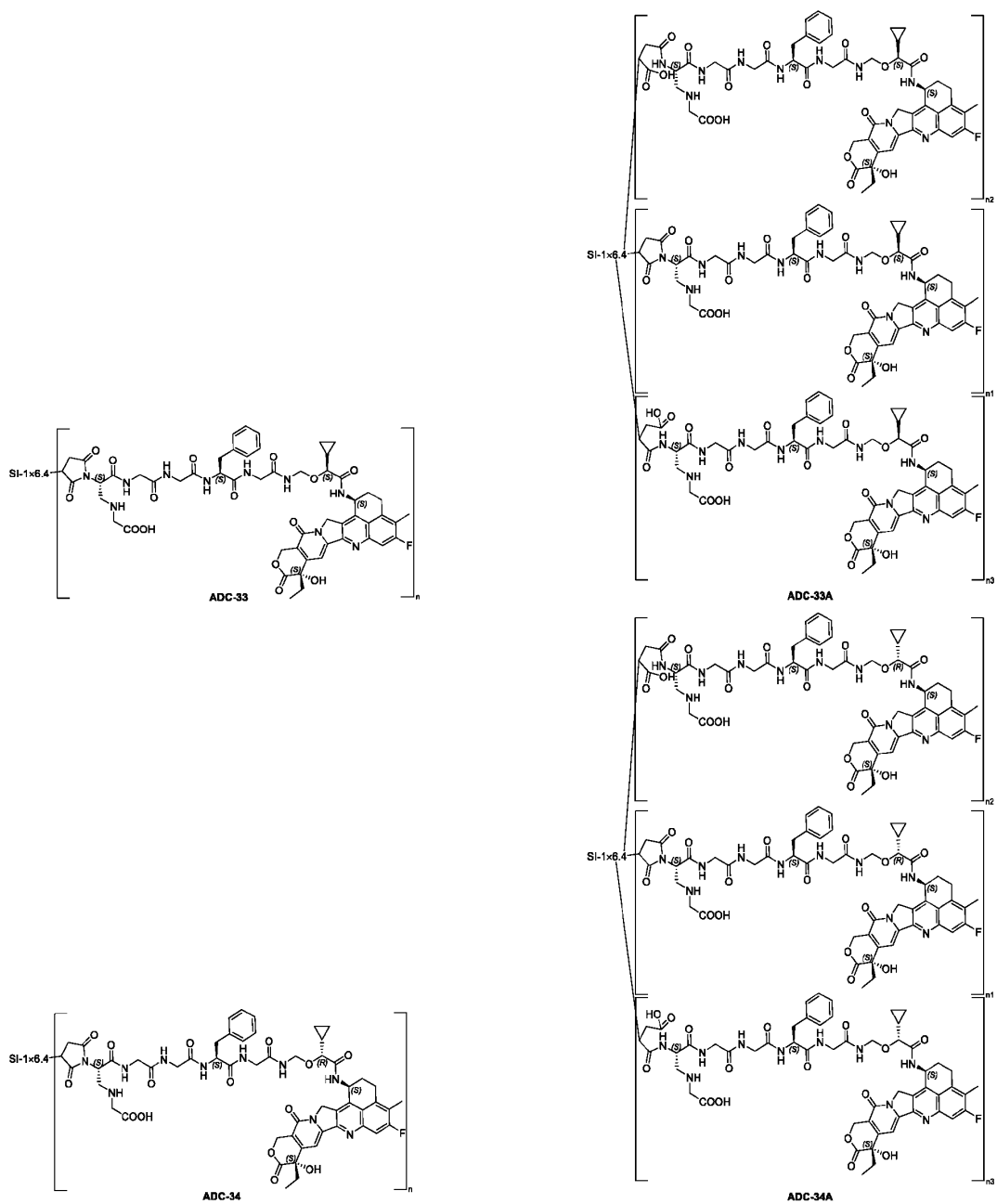




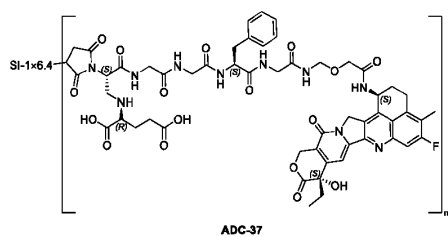




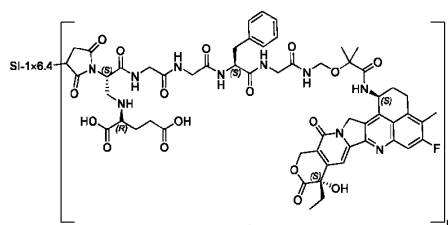




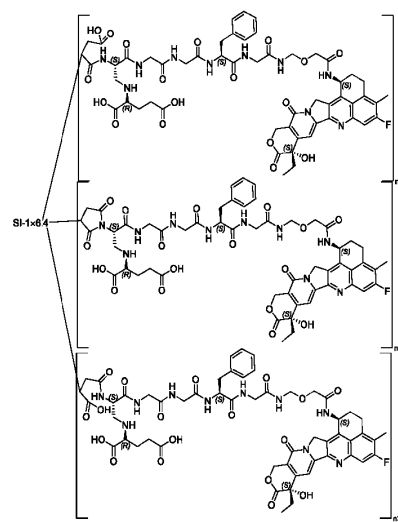




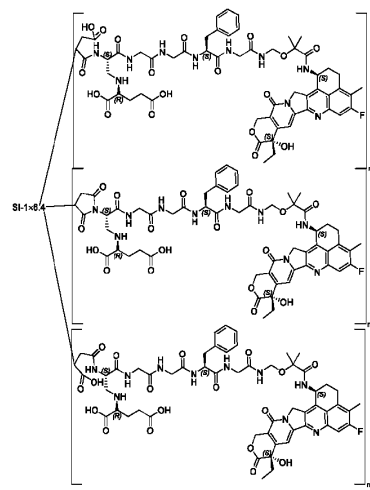
ADC-37



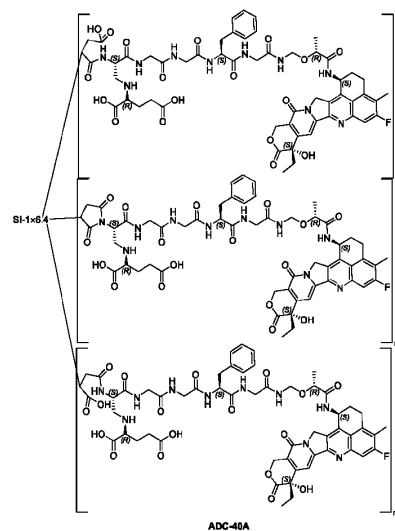
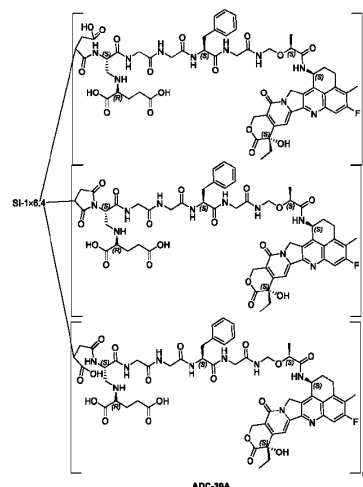
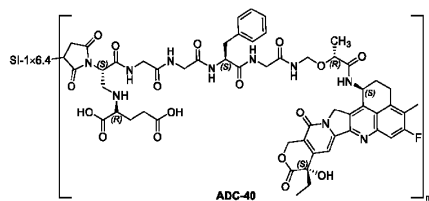
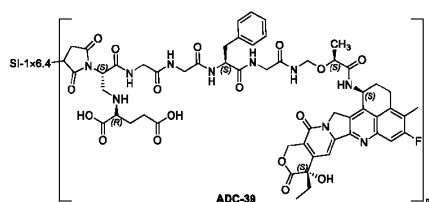
ADC-38

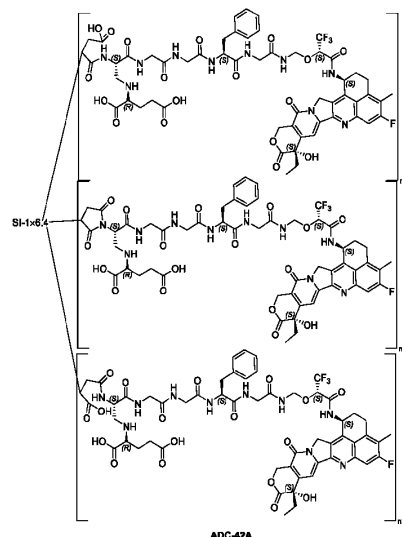
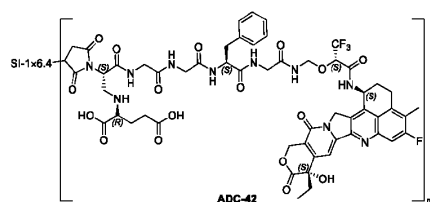
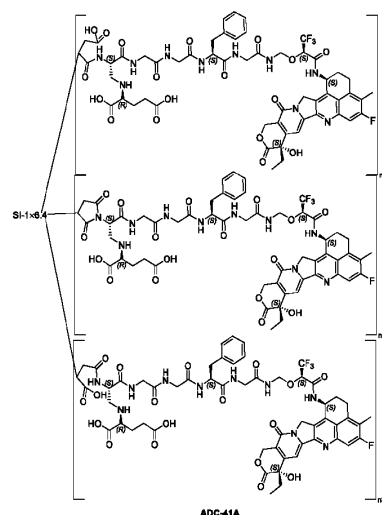
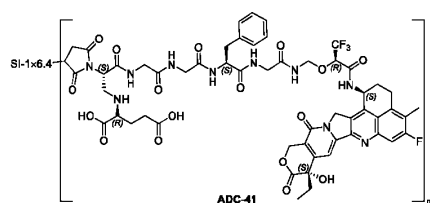


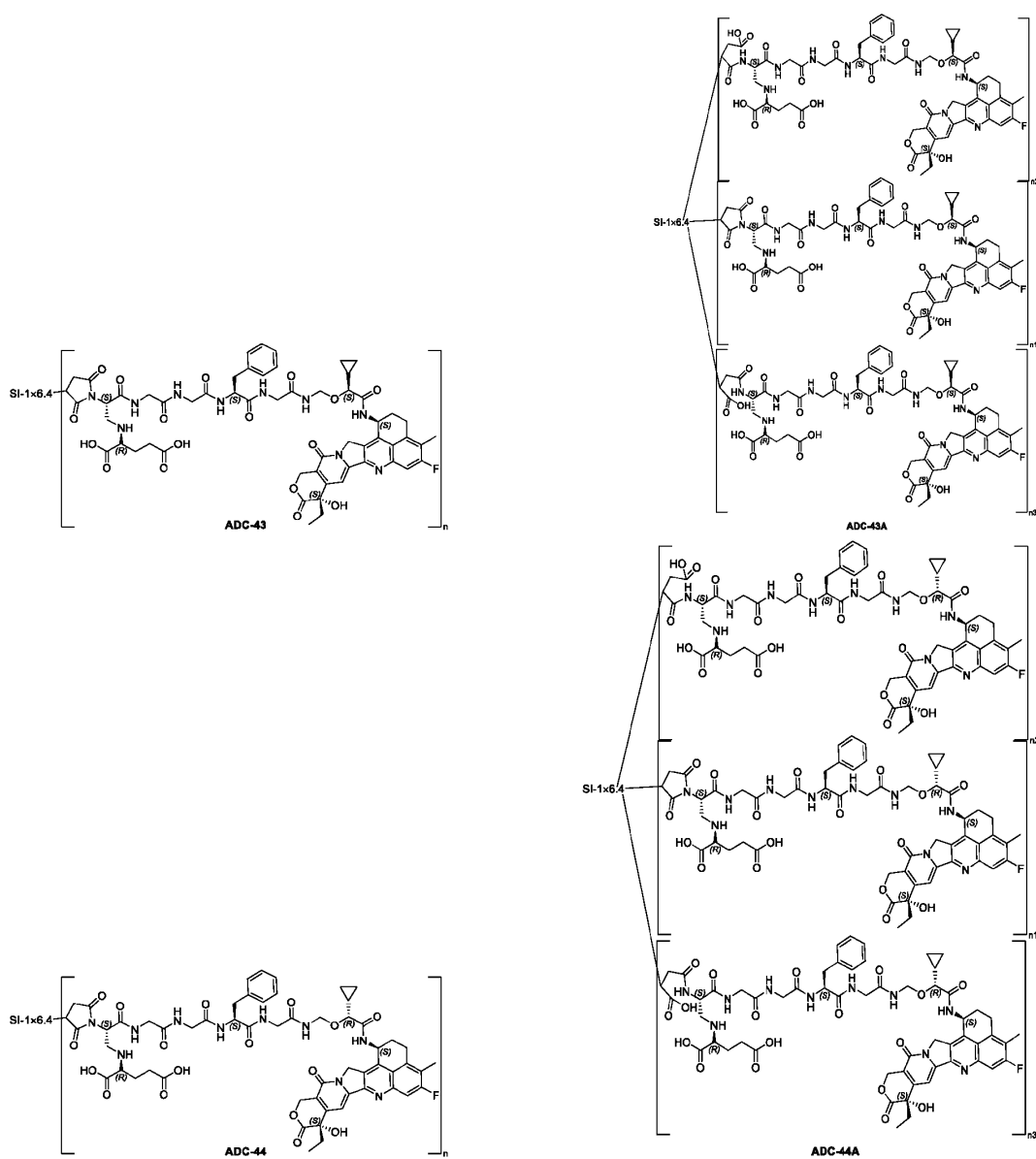
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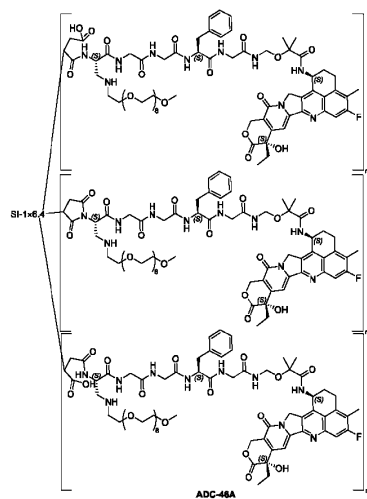
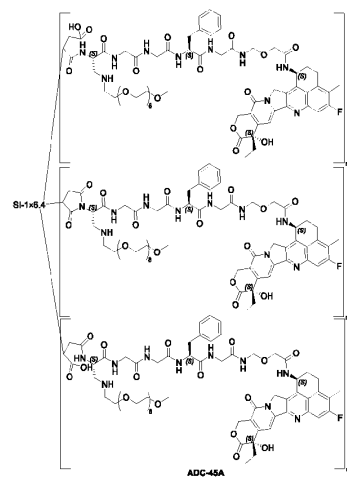
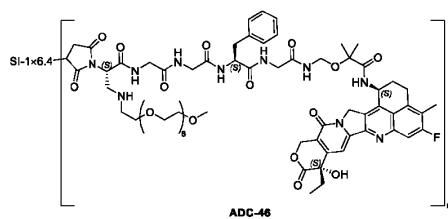
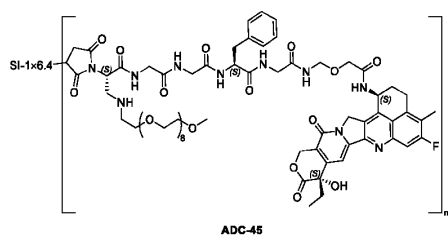


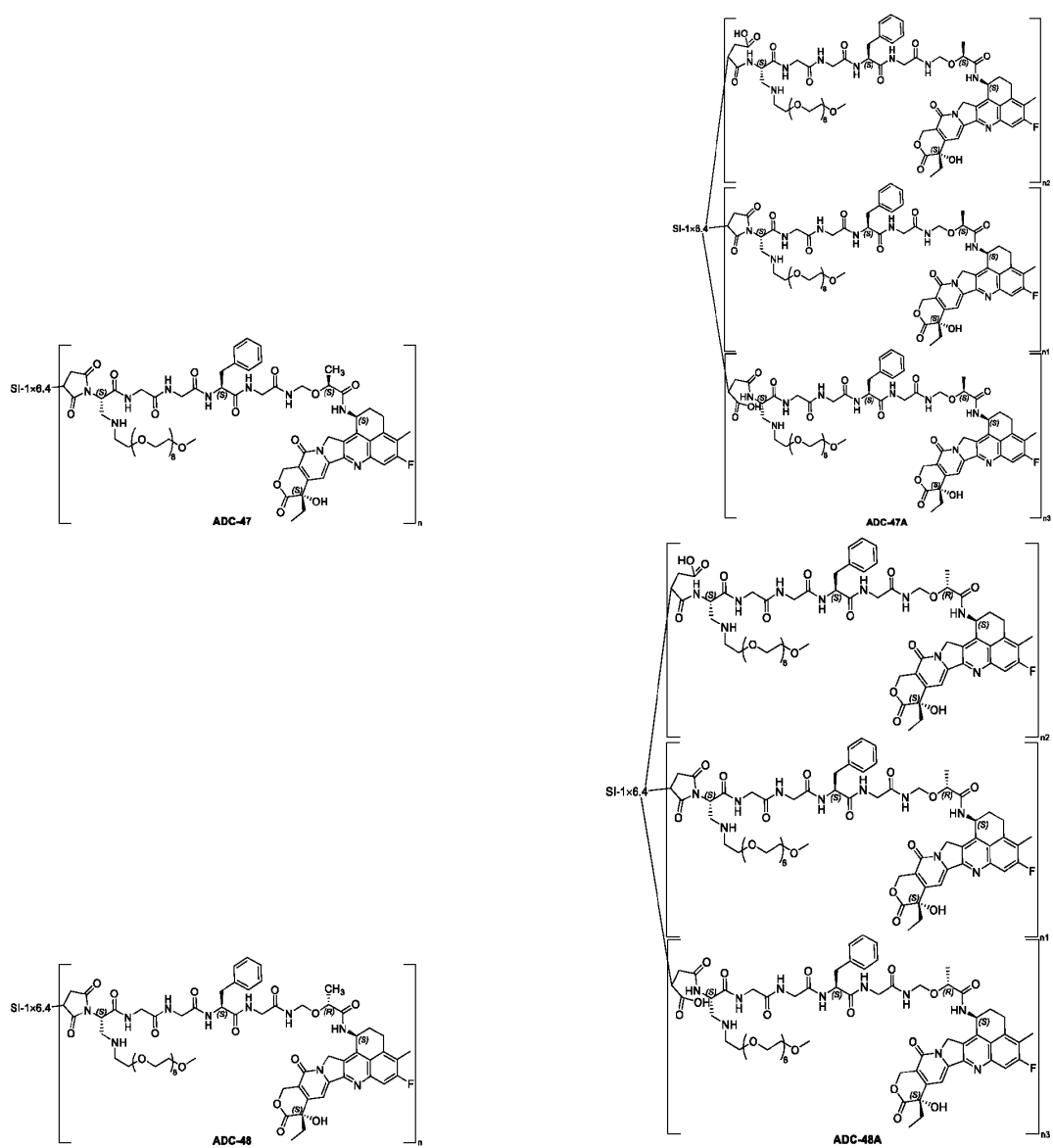
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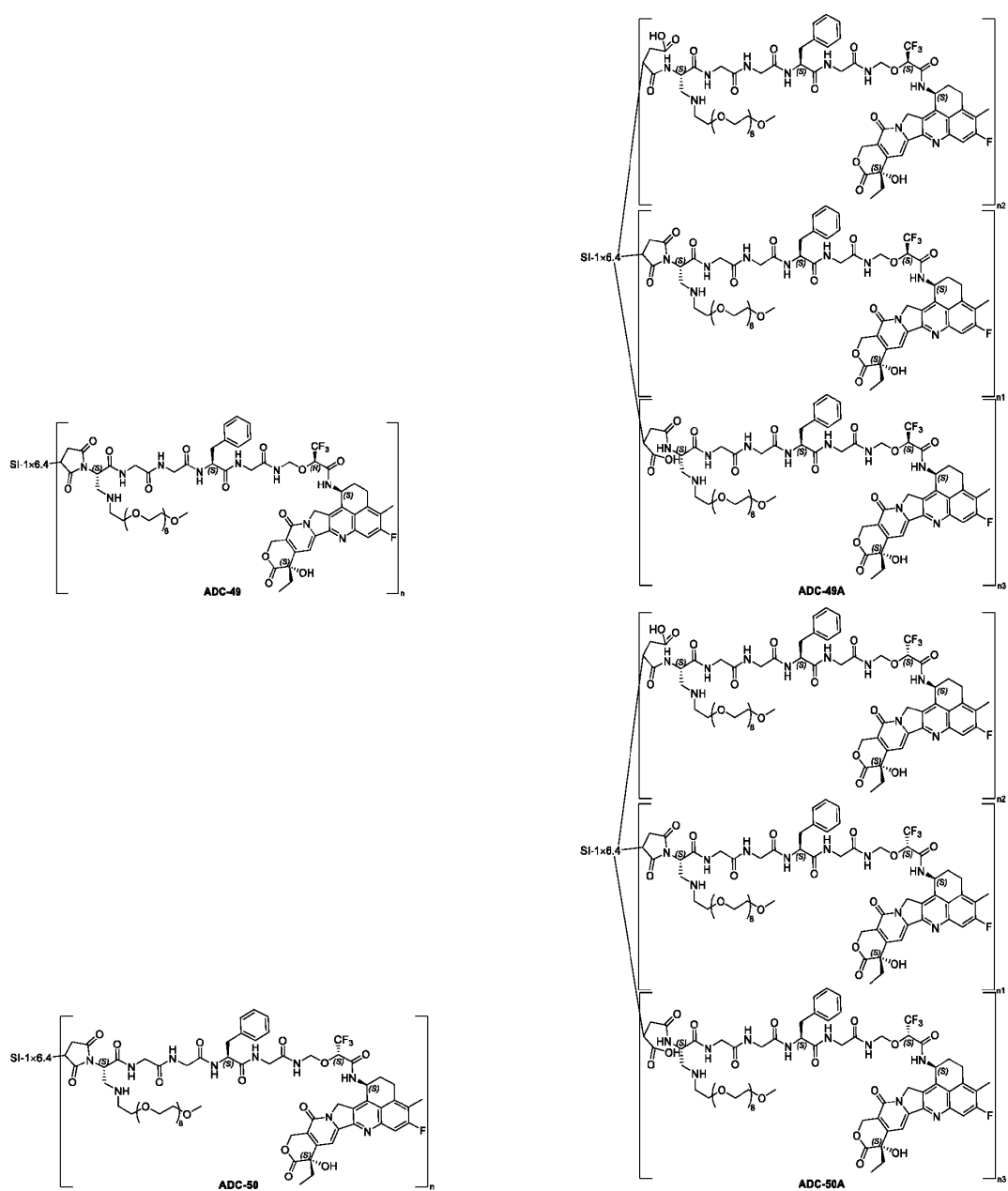


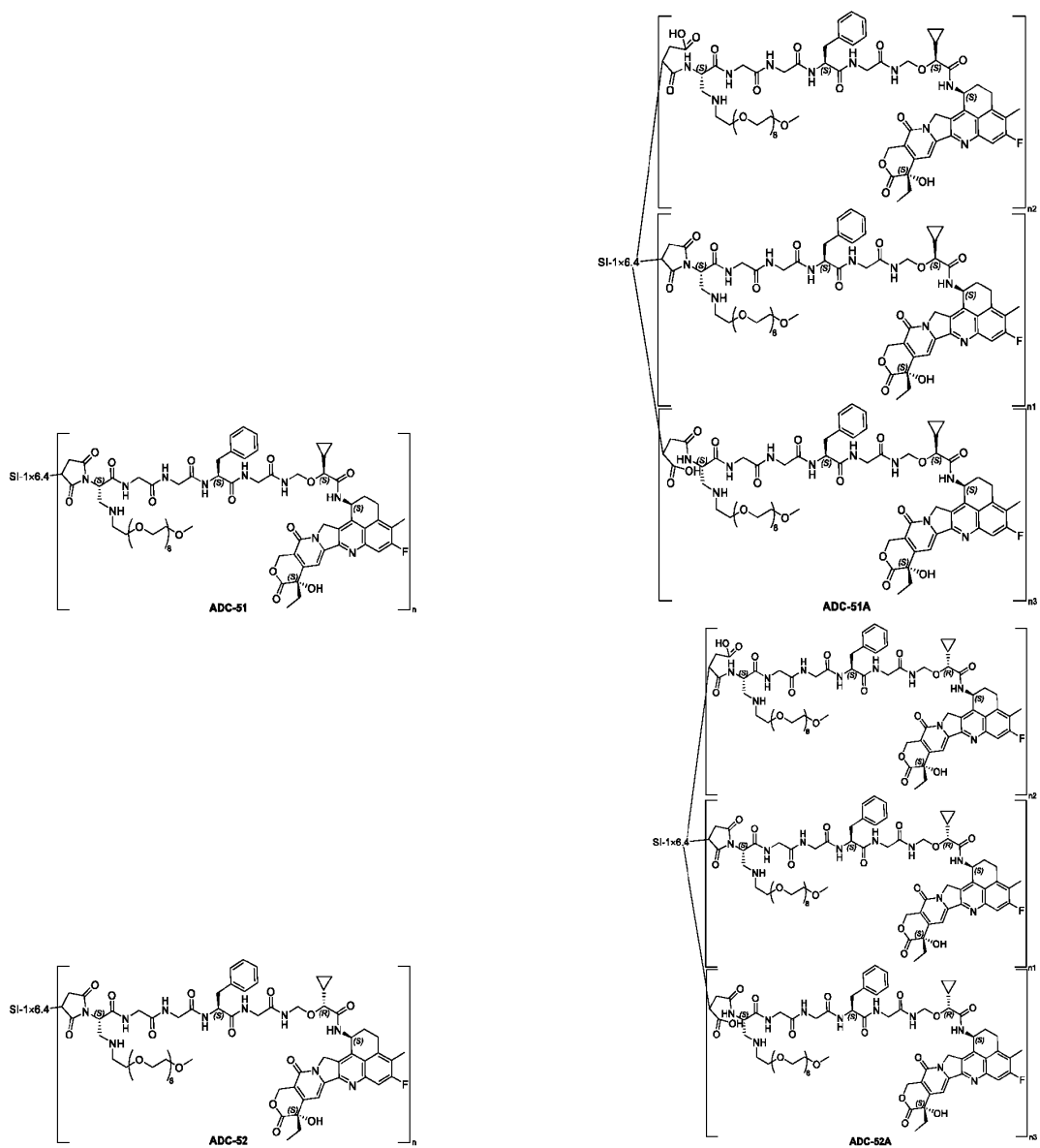


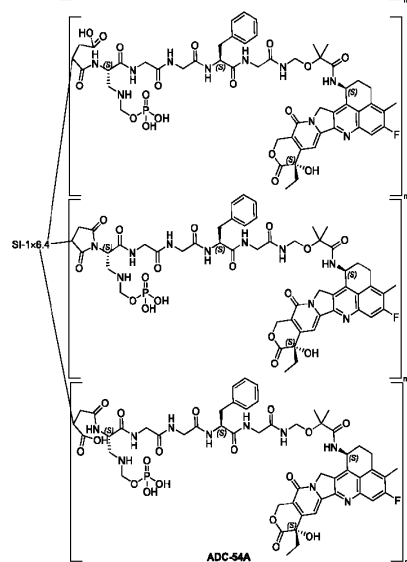
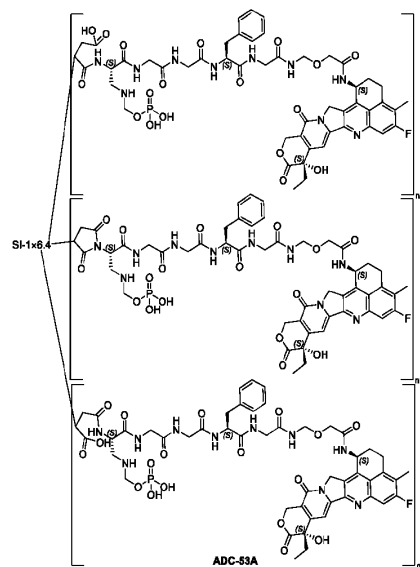
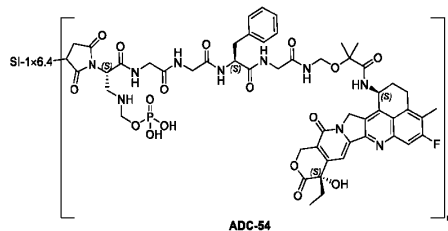
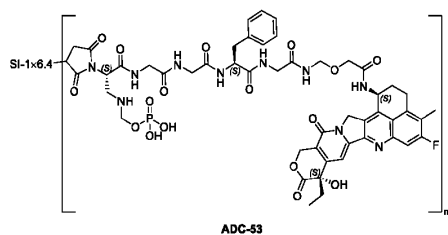


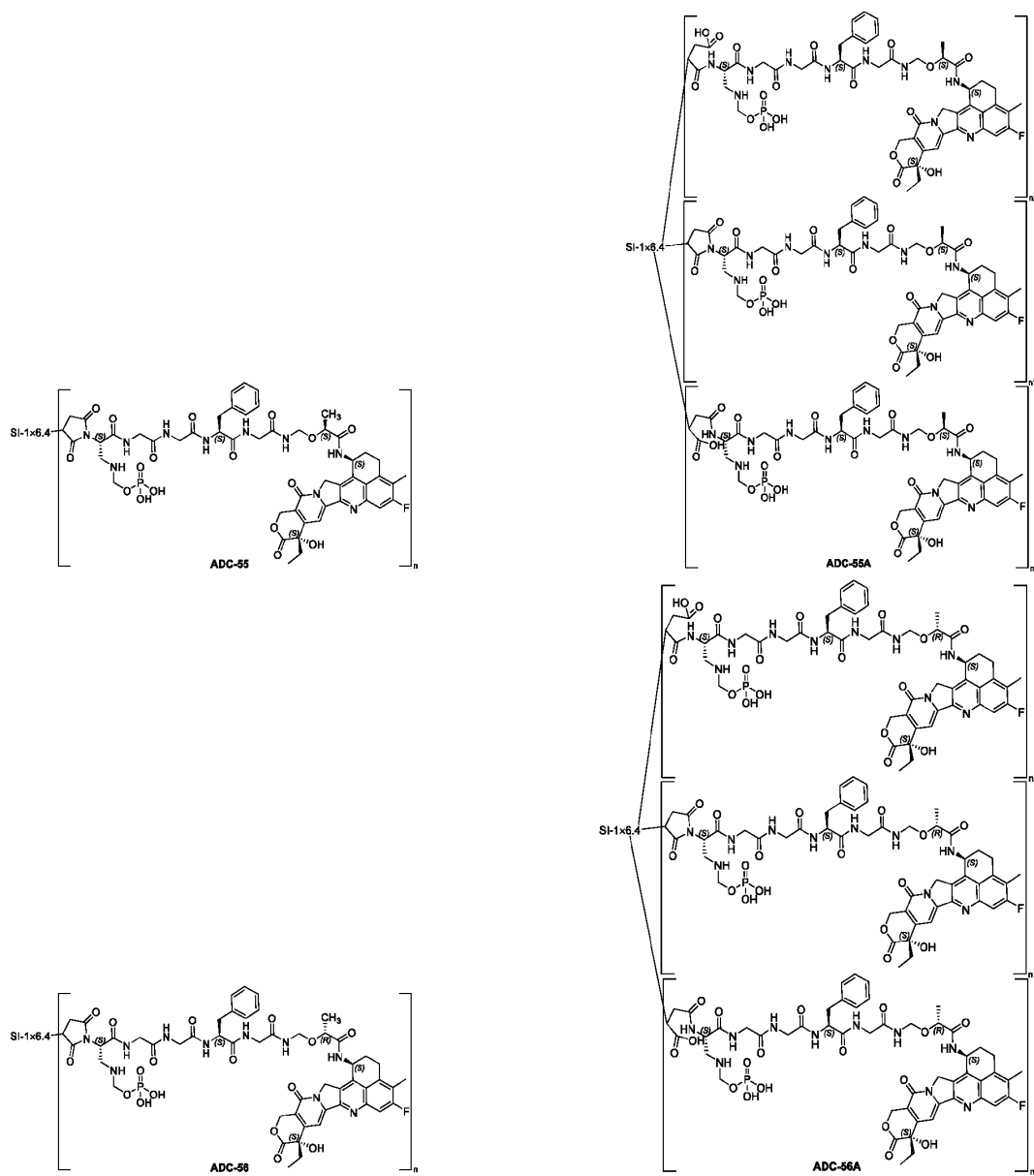


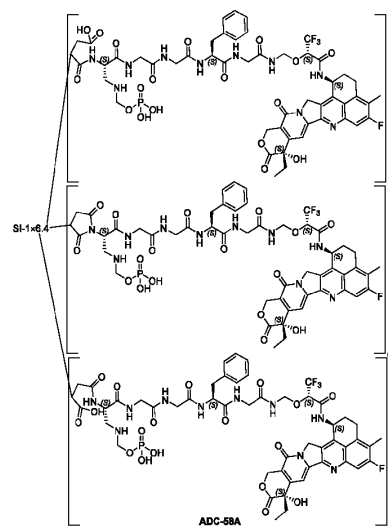
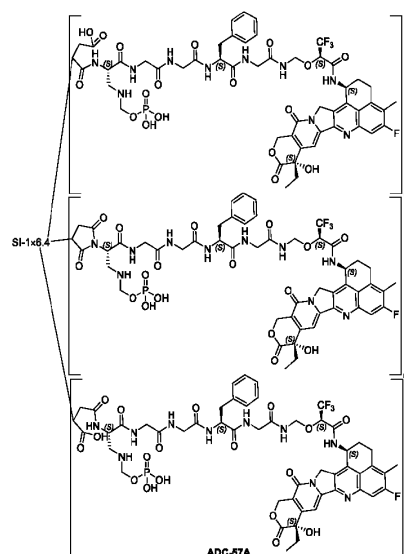
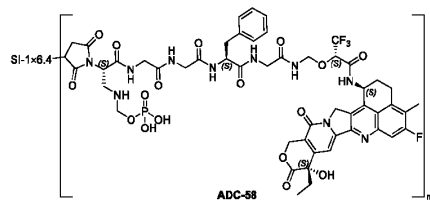
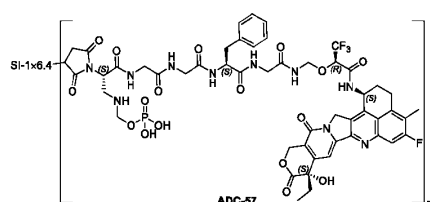


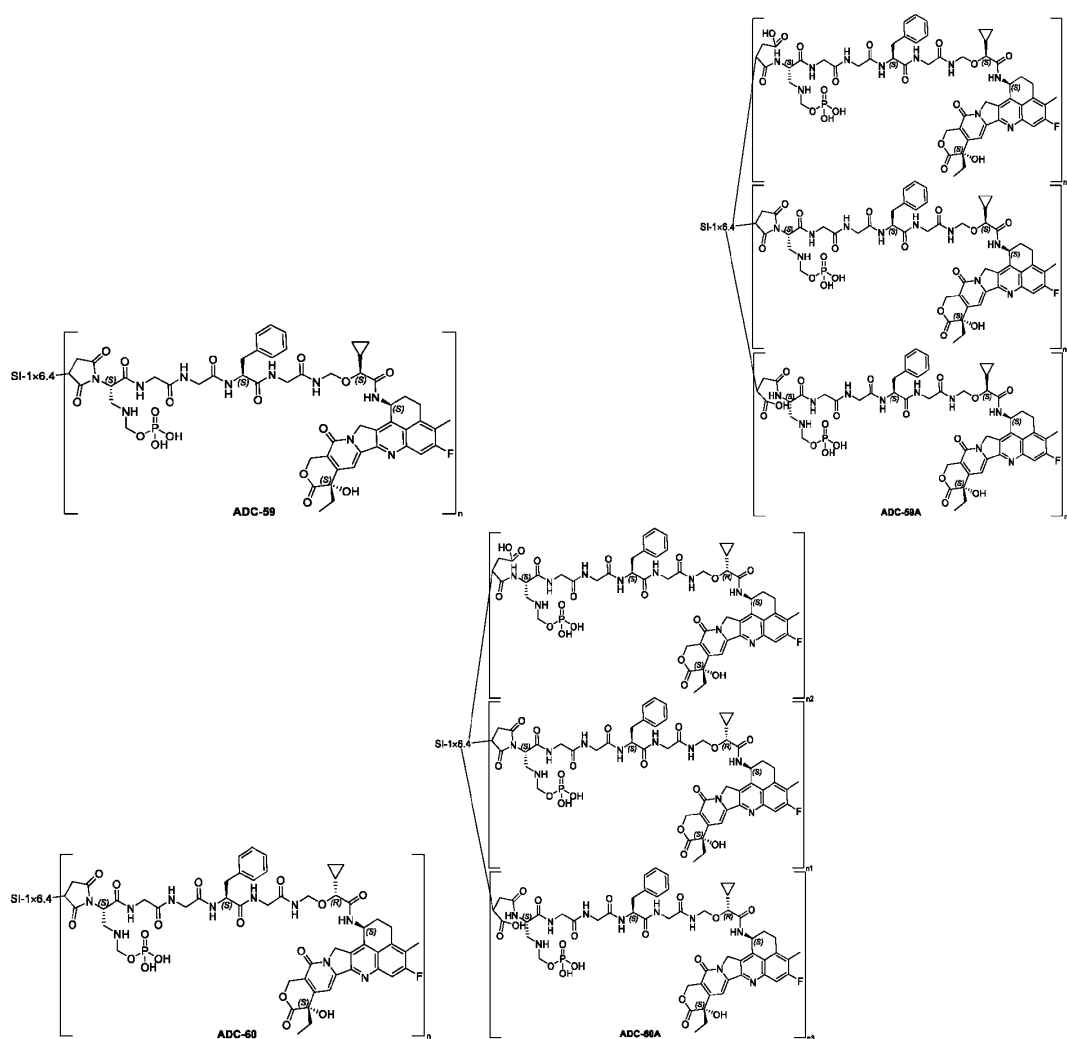


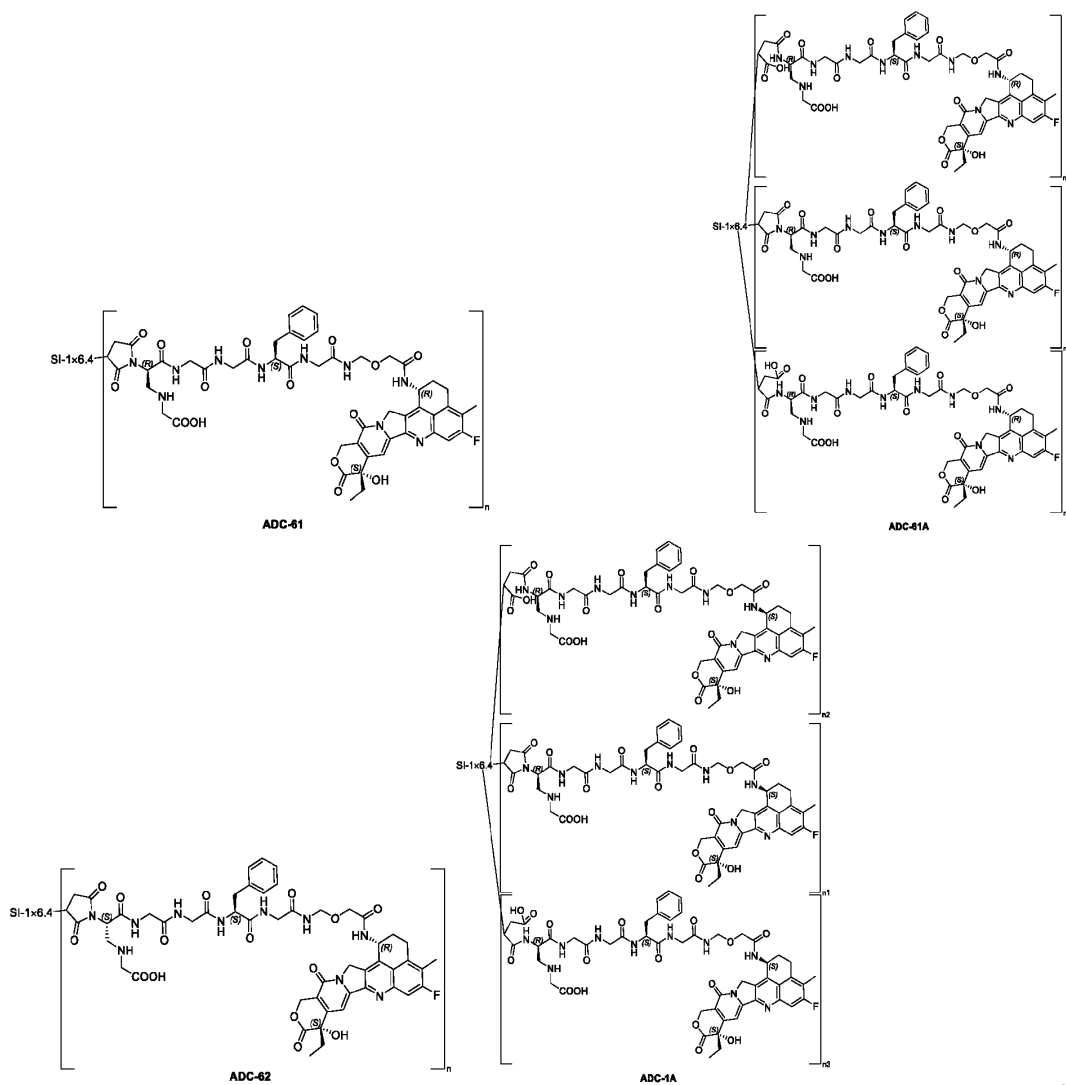


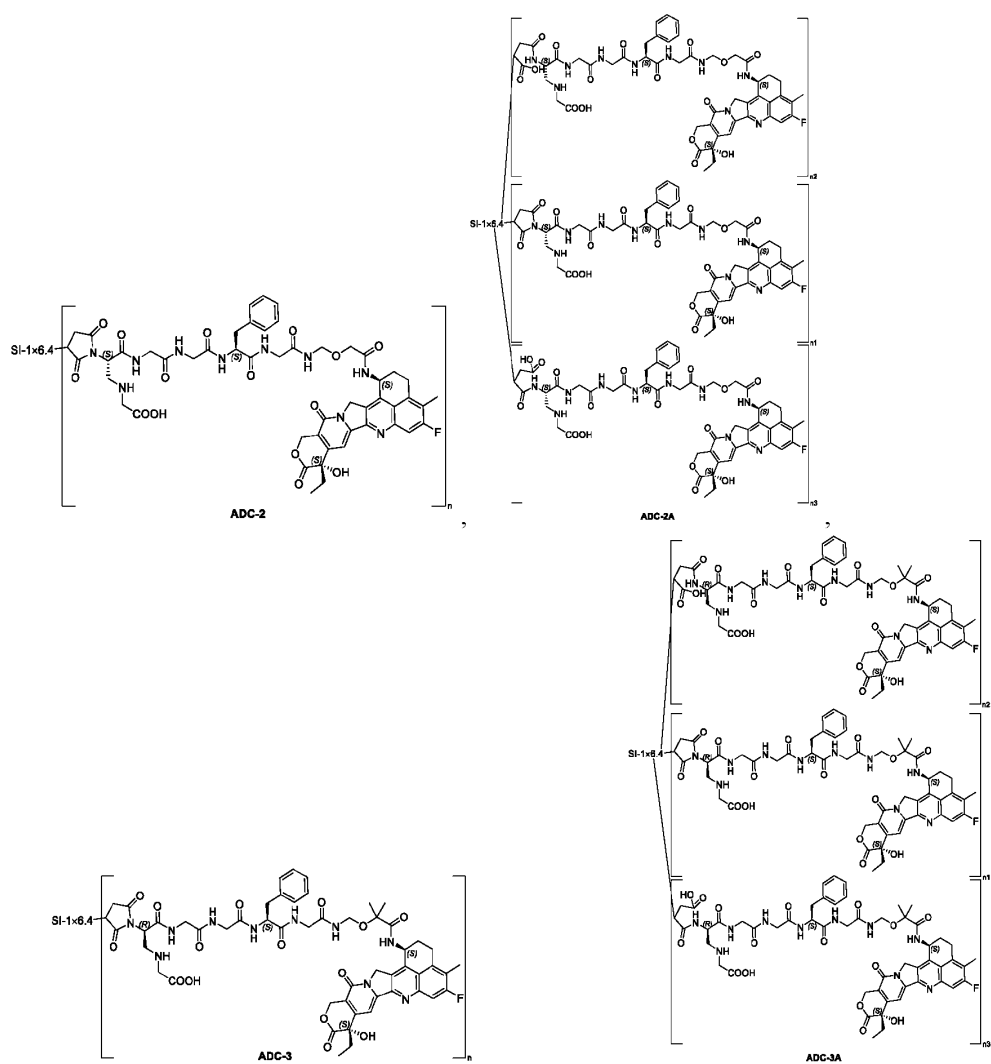


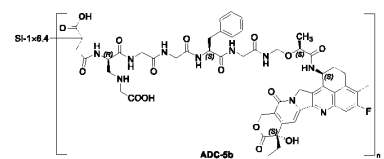
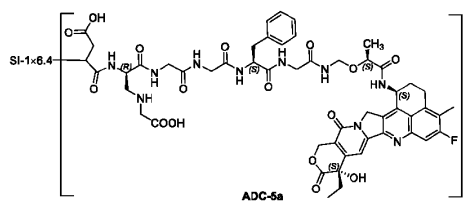
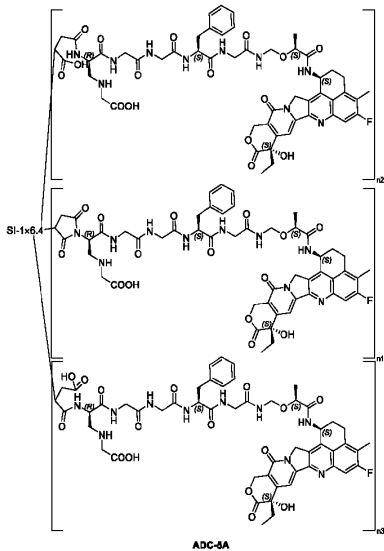
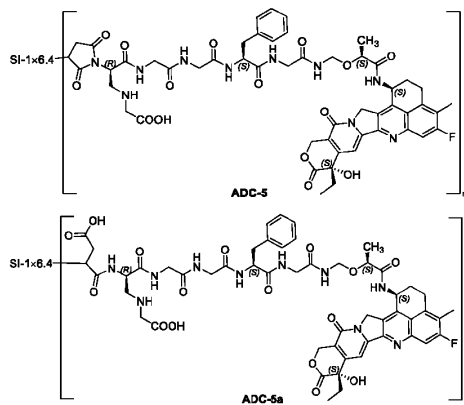
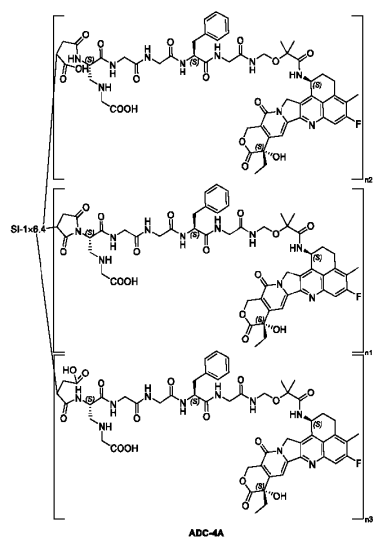
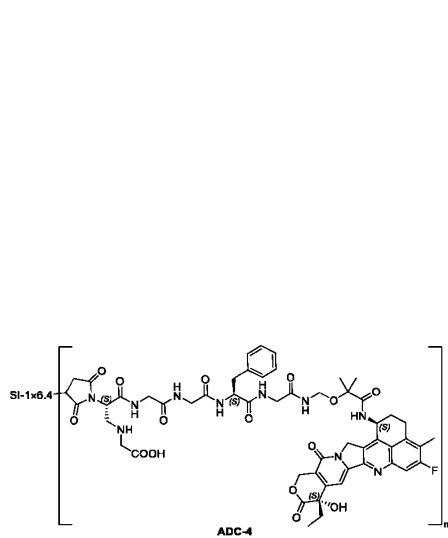




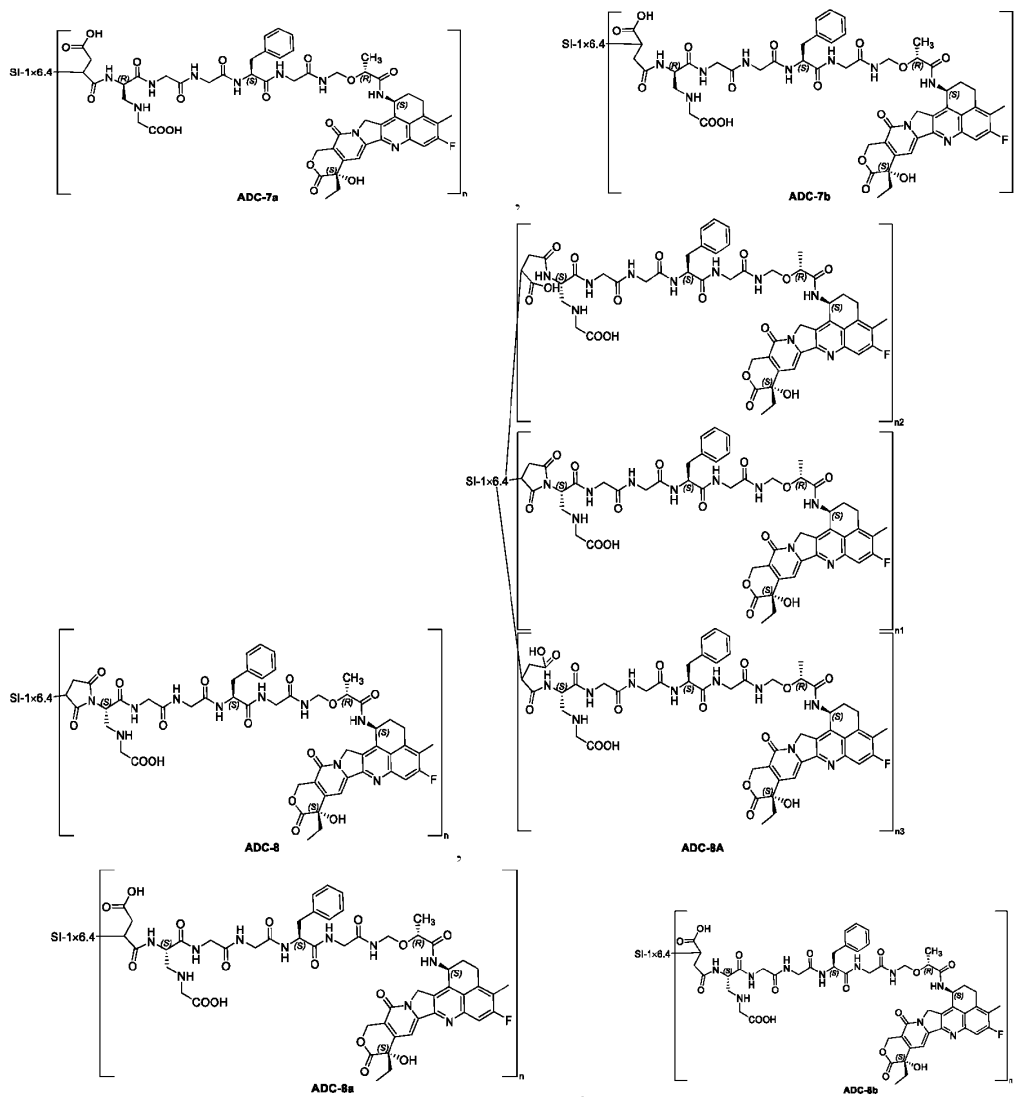


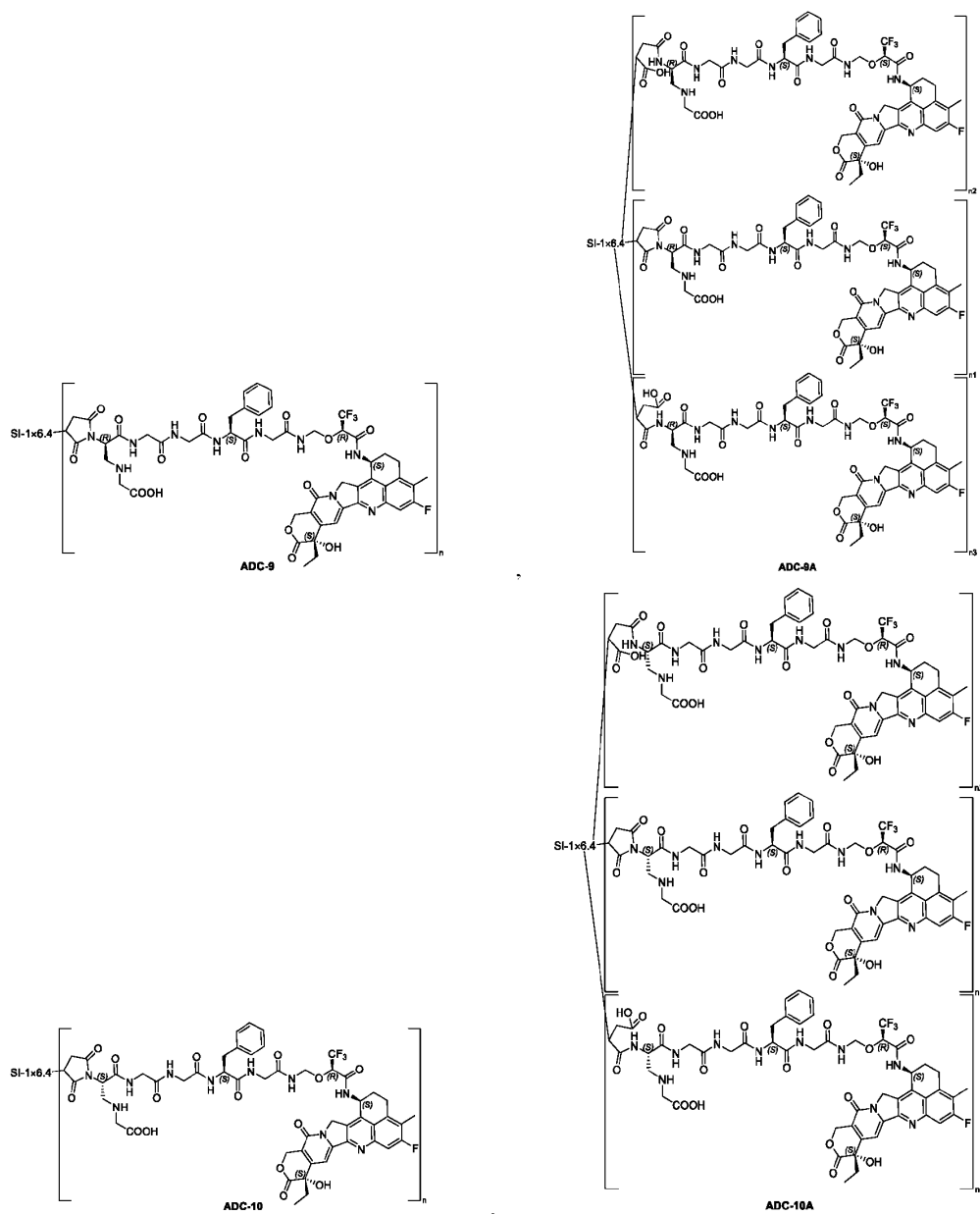


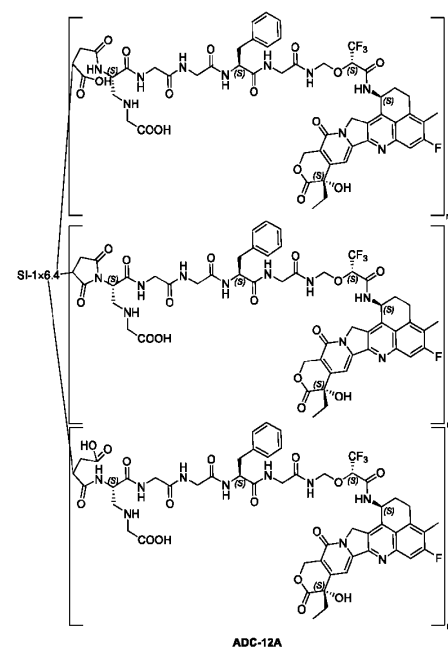
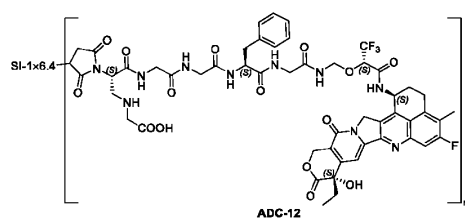
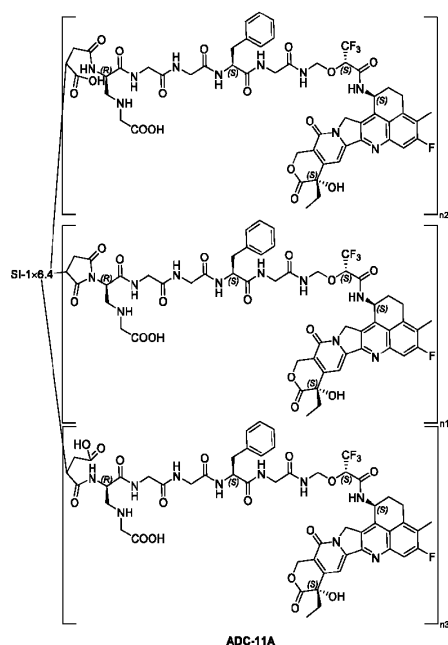
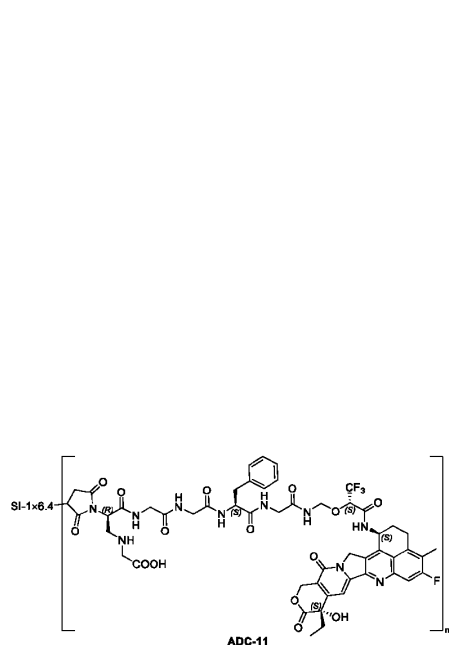


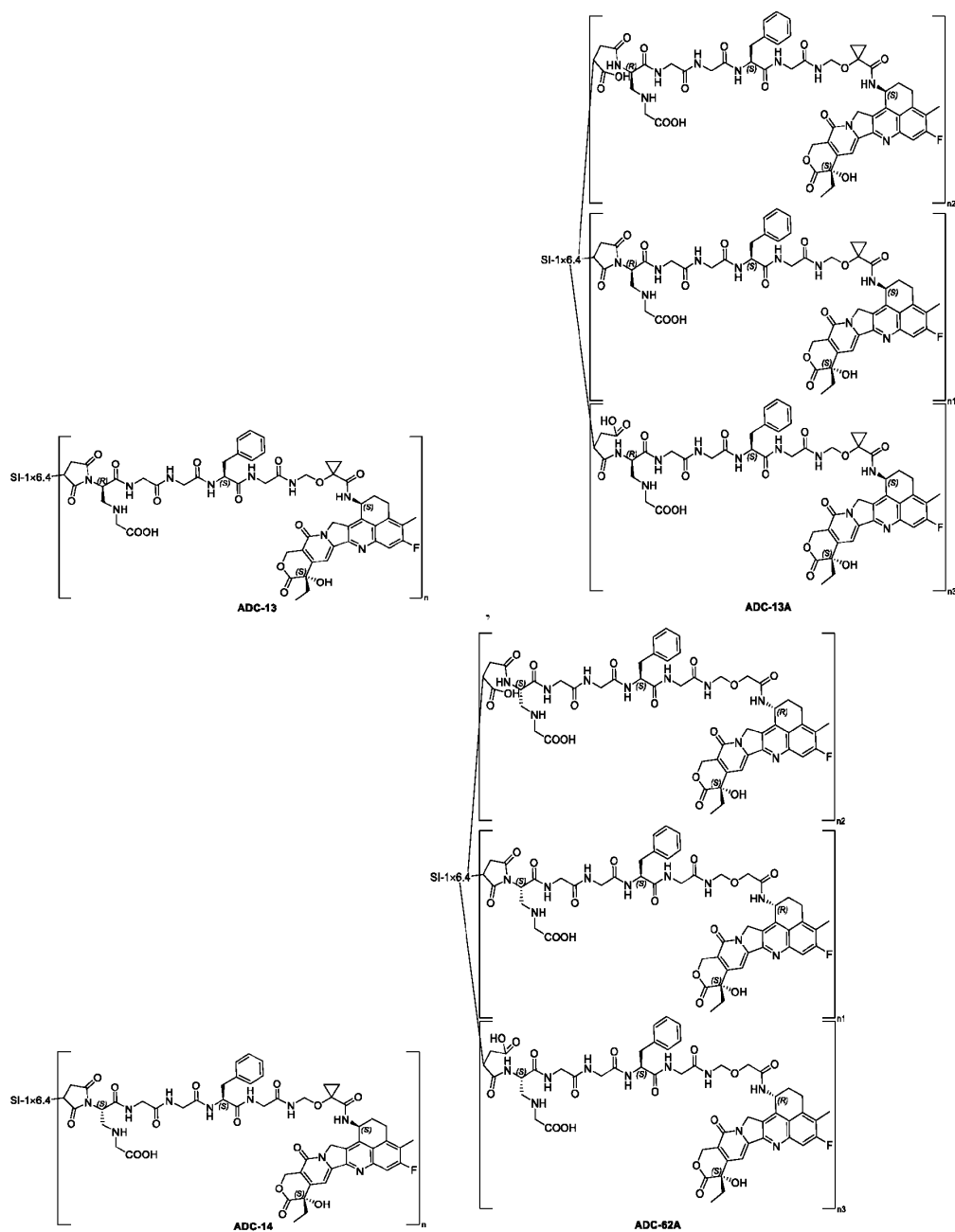


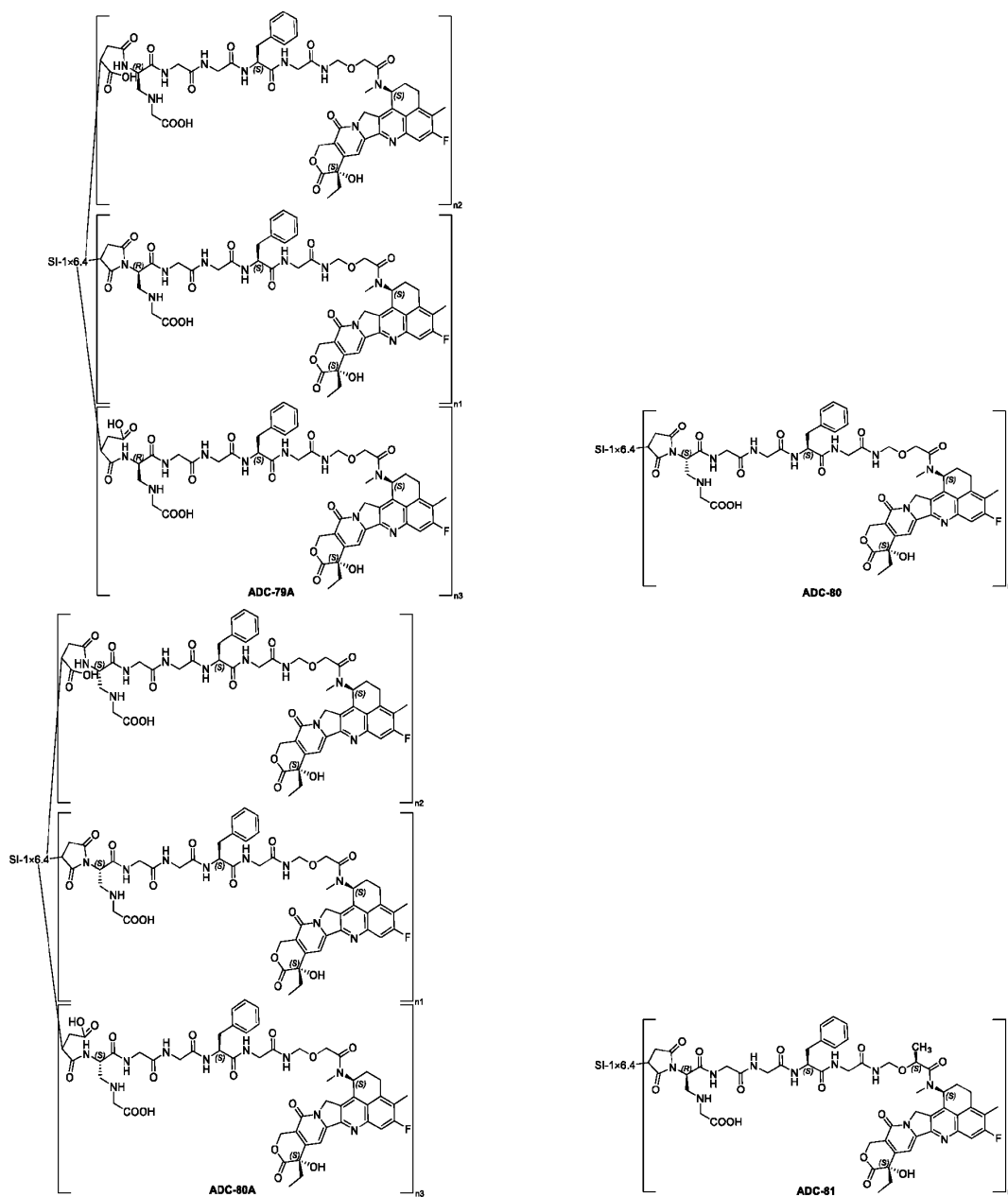


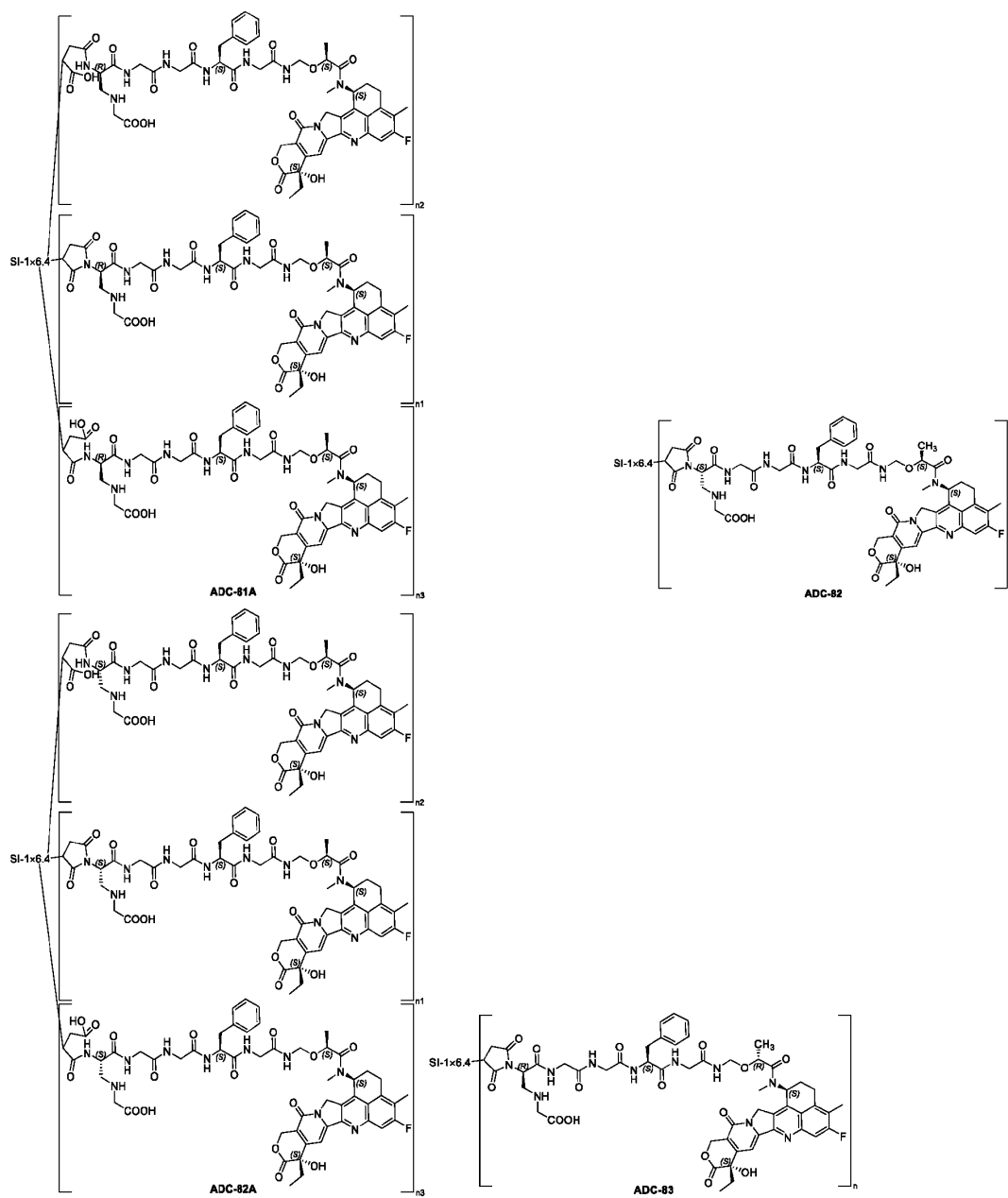


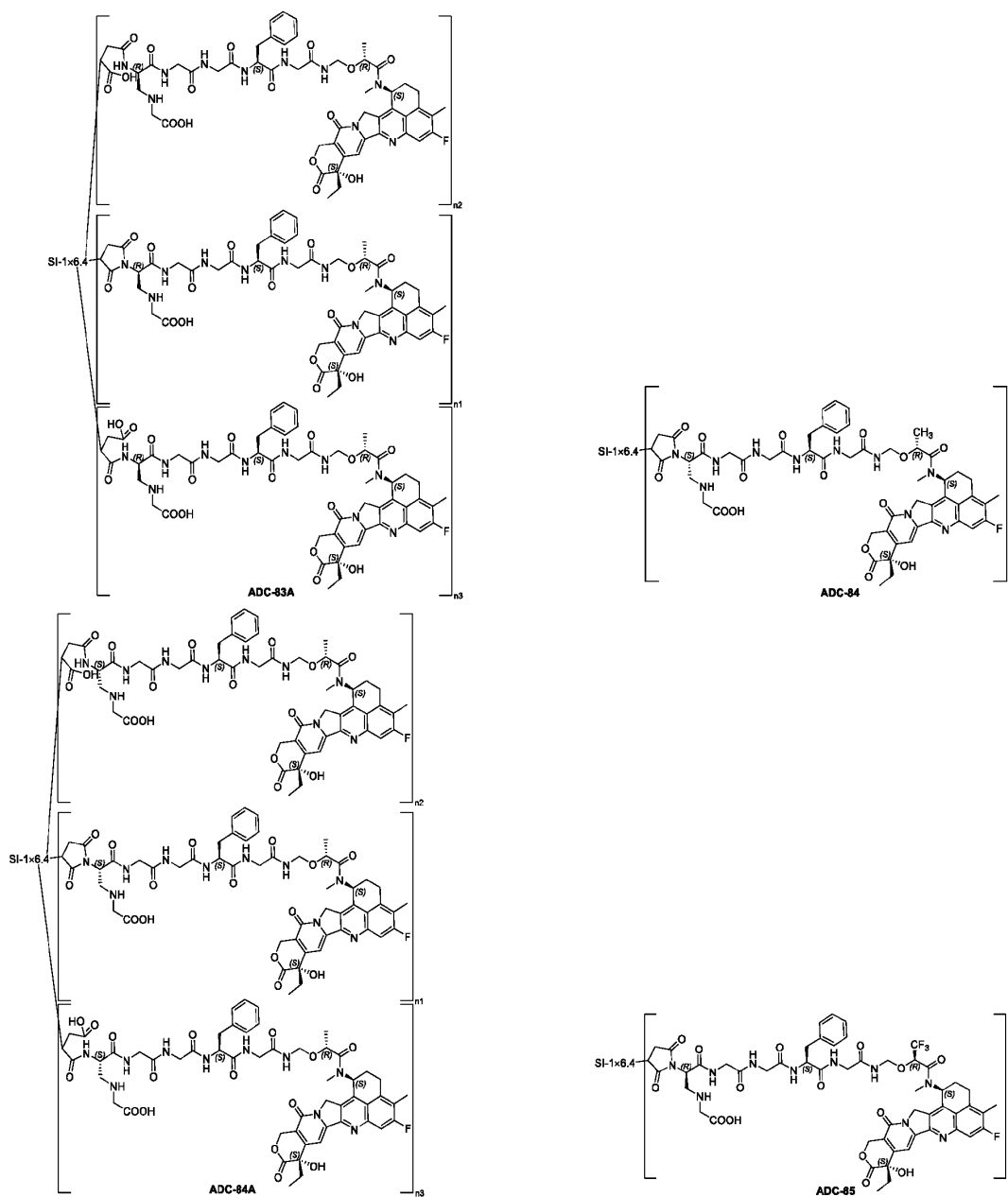


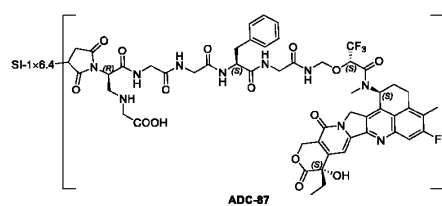
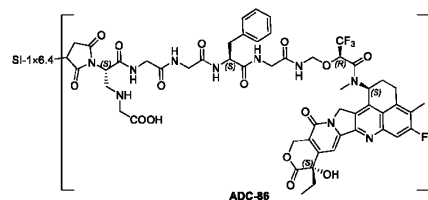
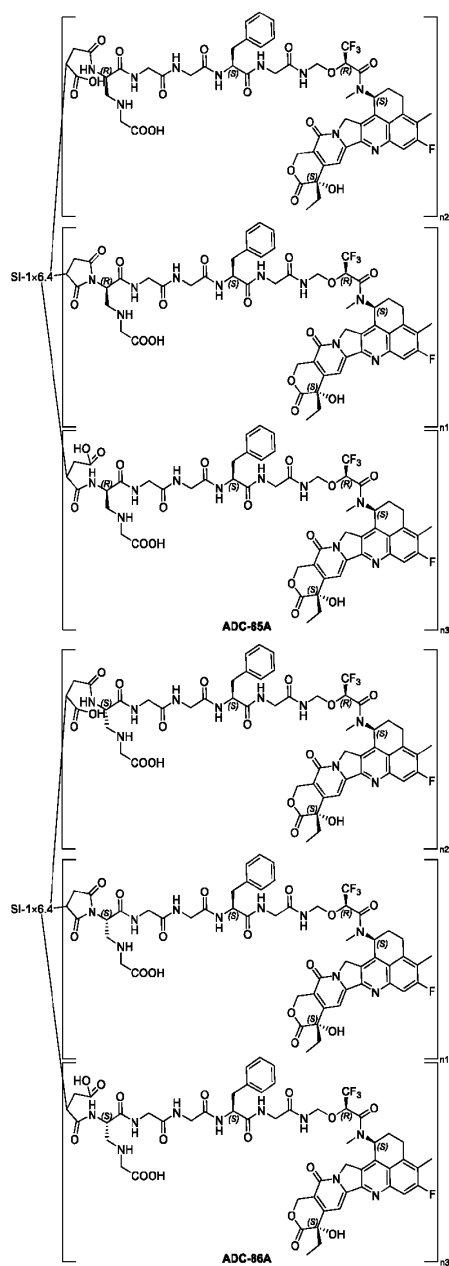


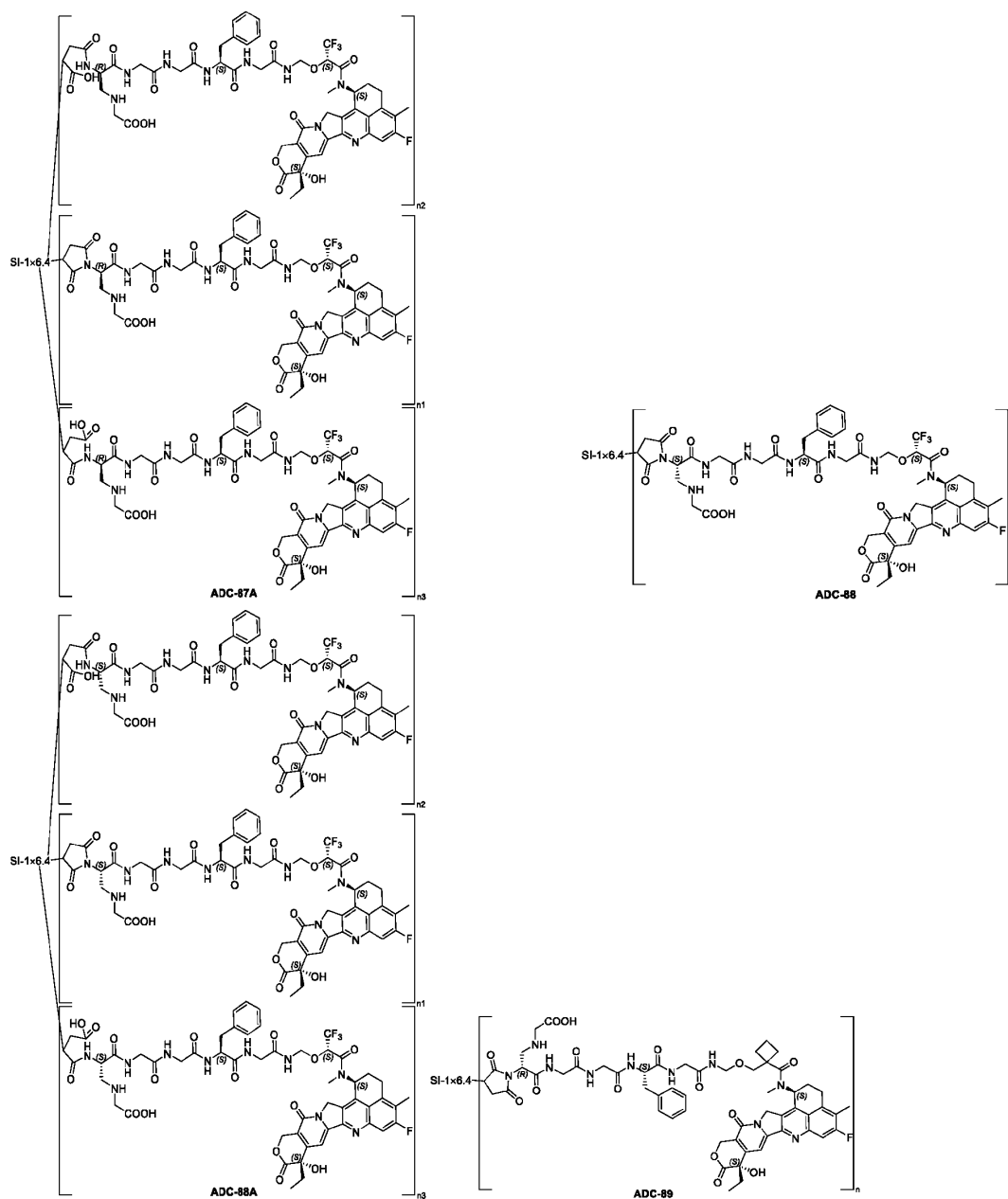


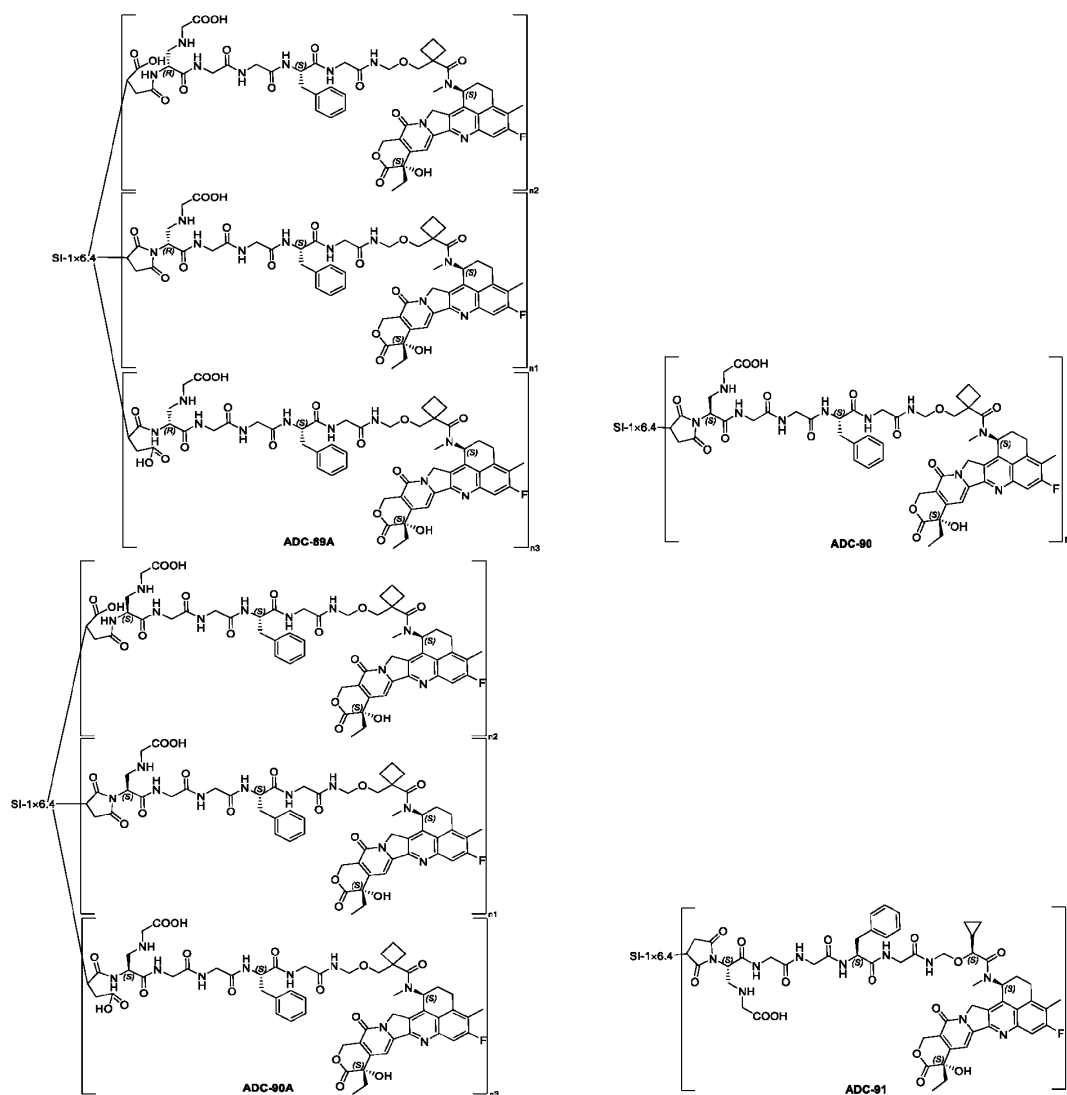


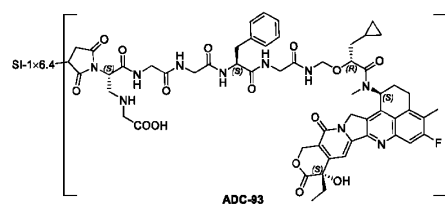
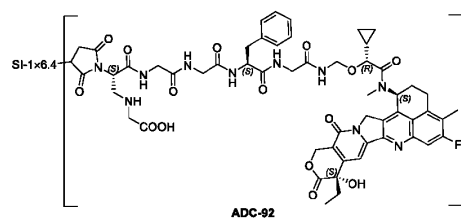
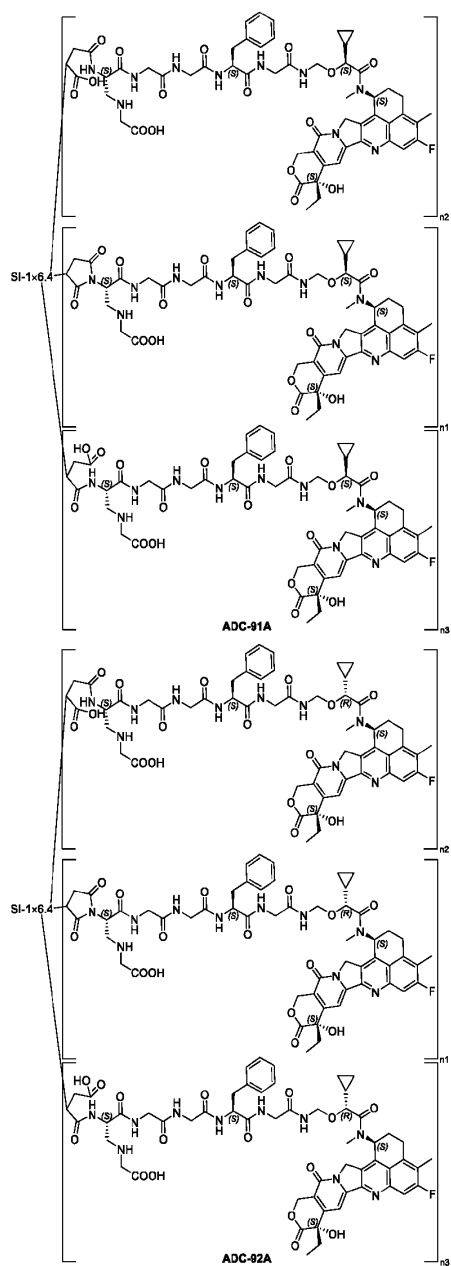


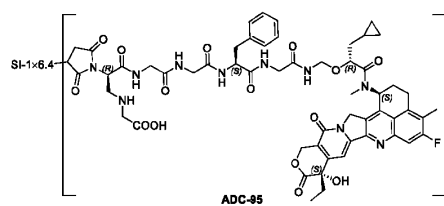
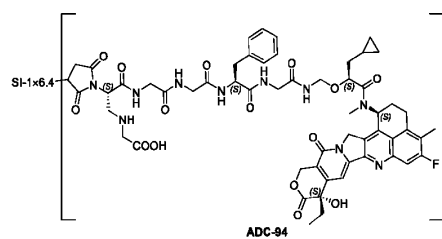
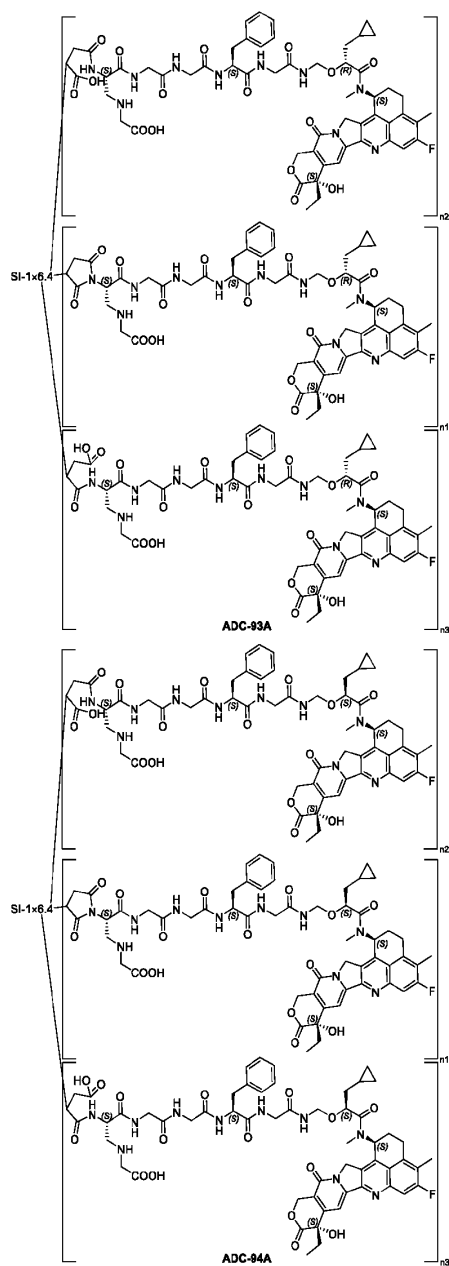


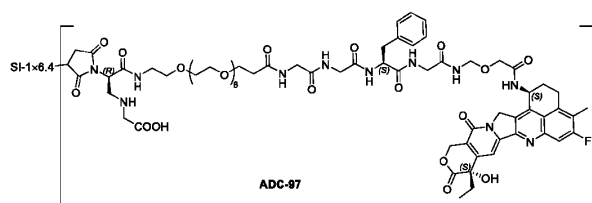
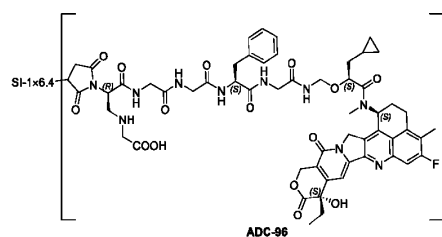
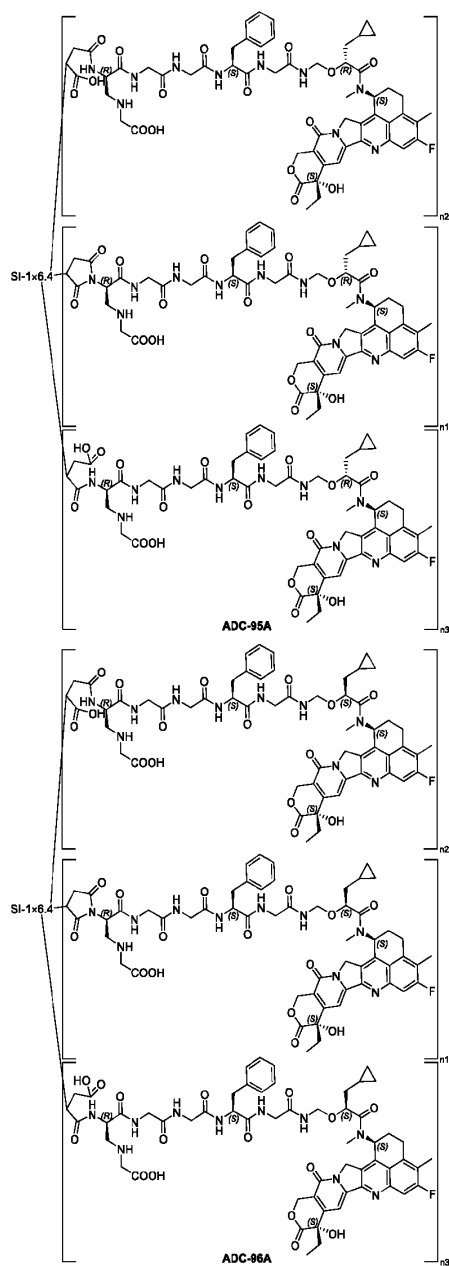


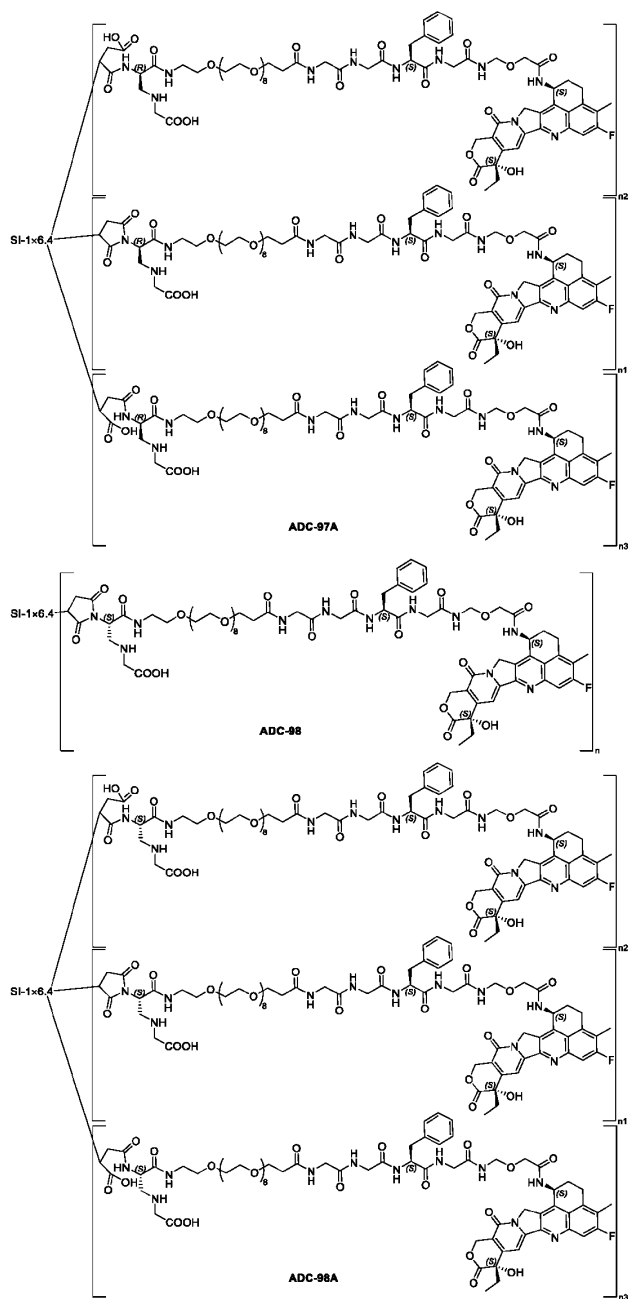


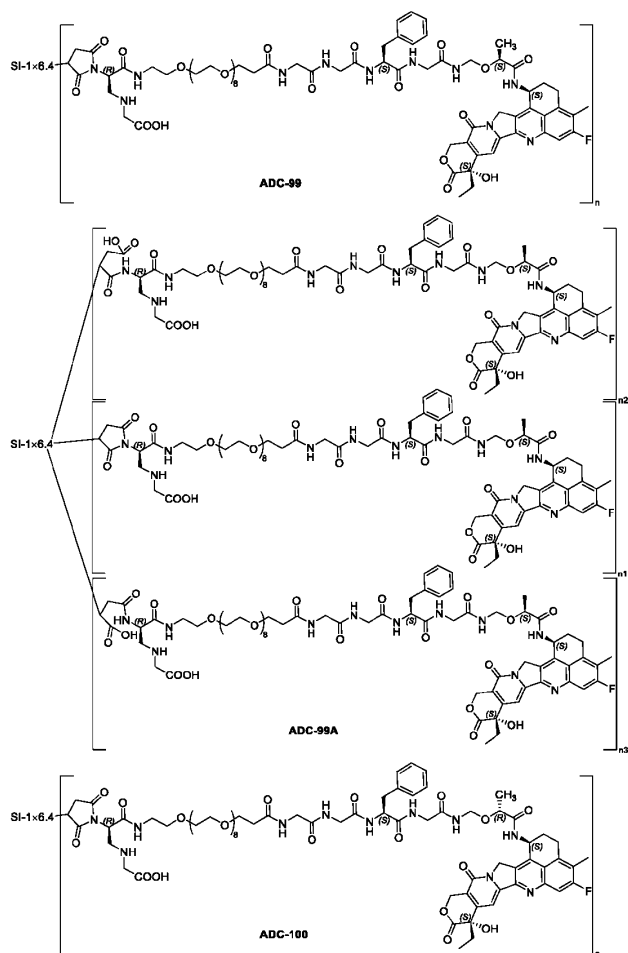


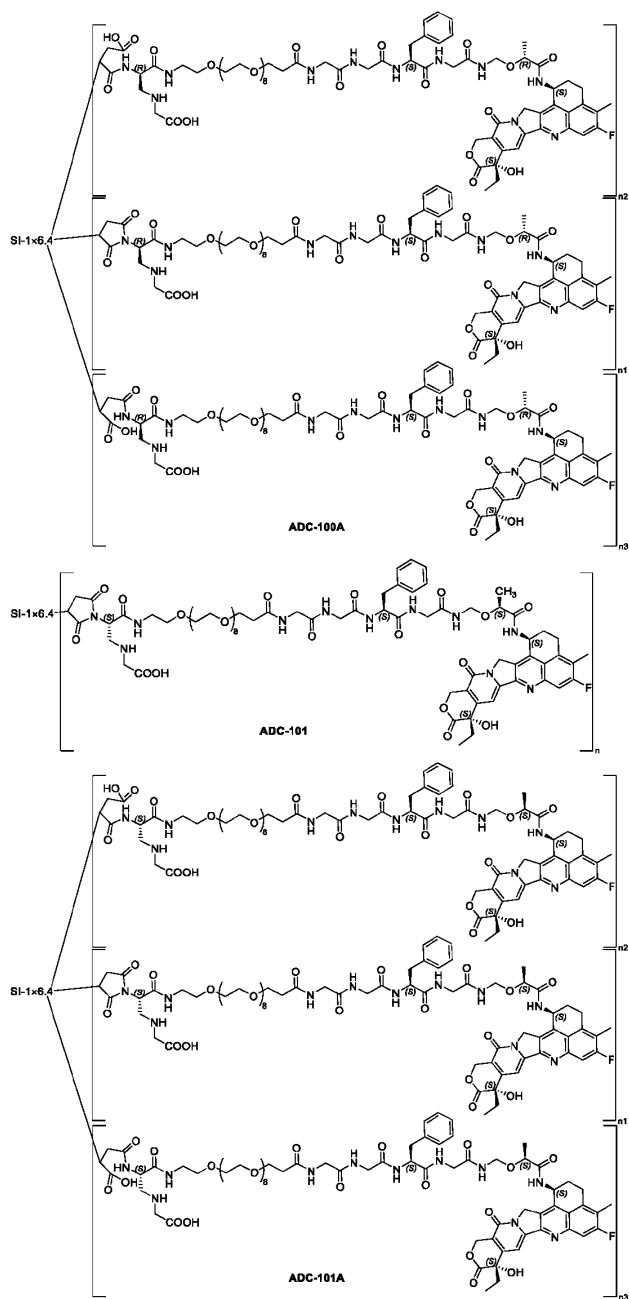


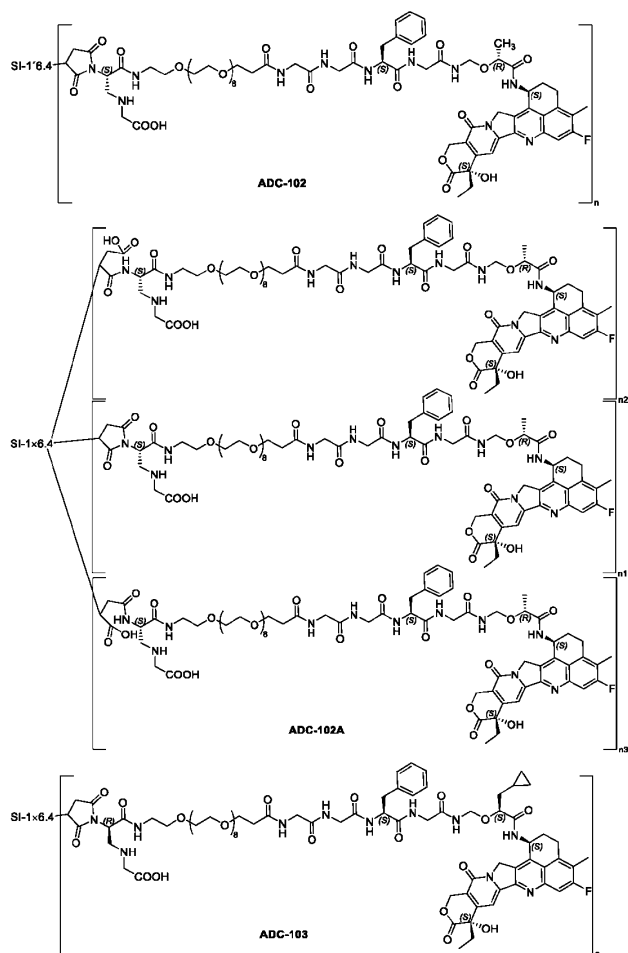


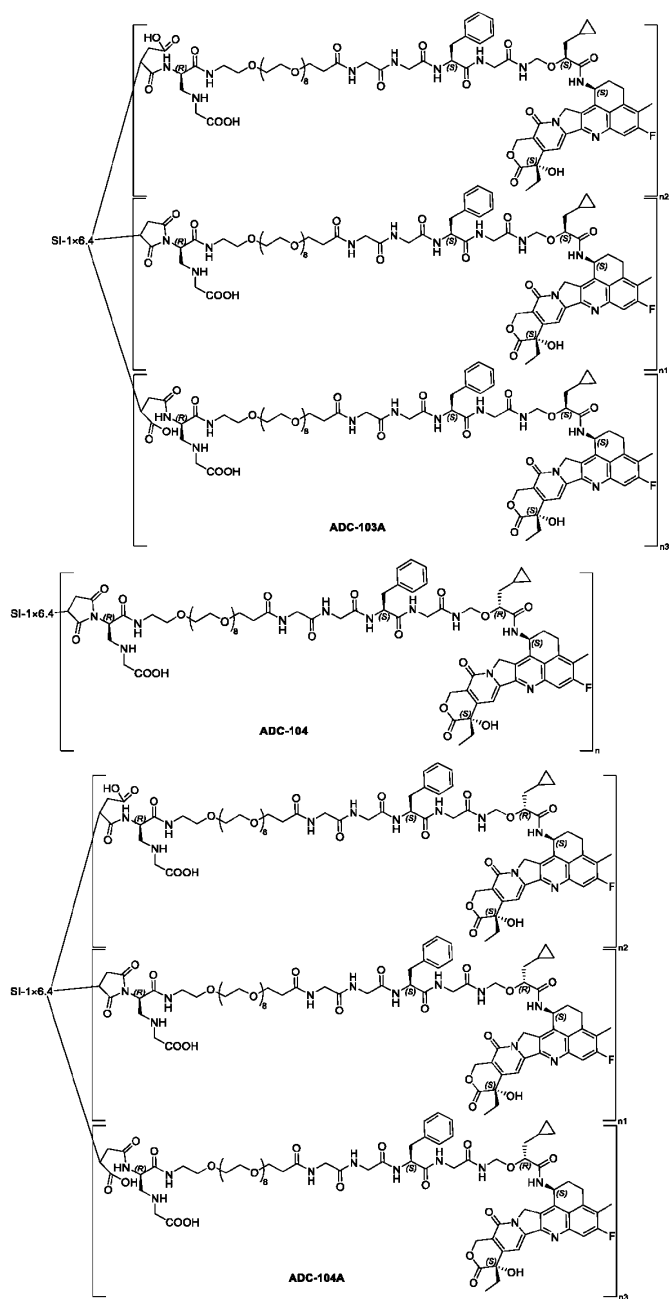


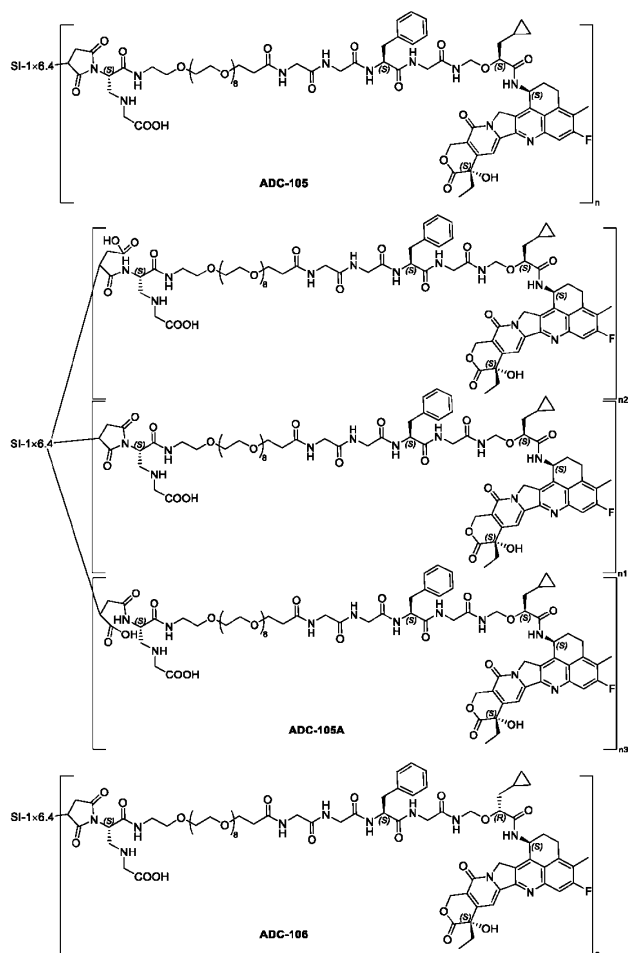


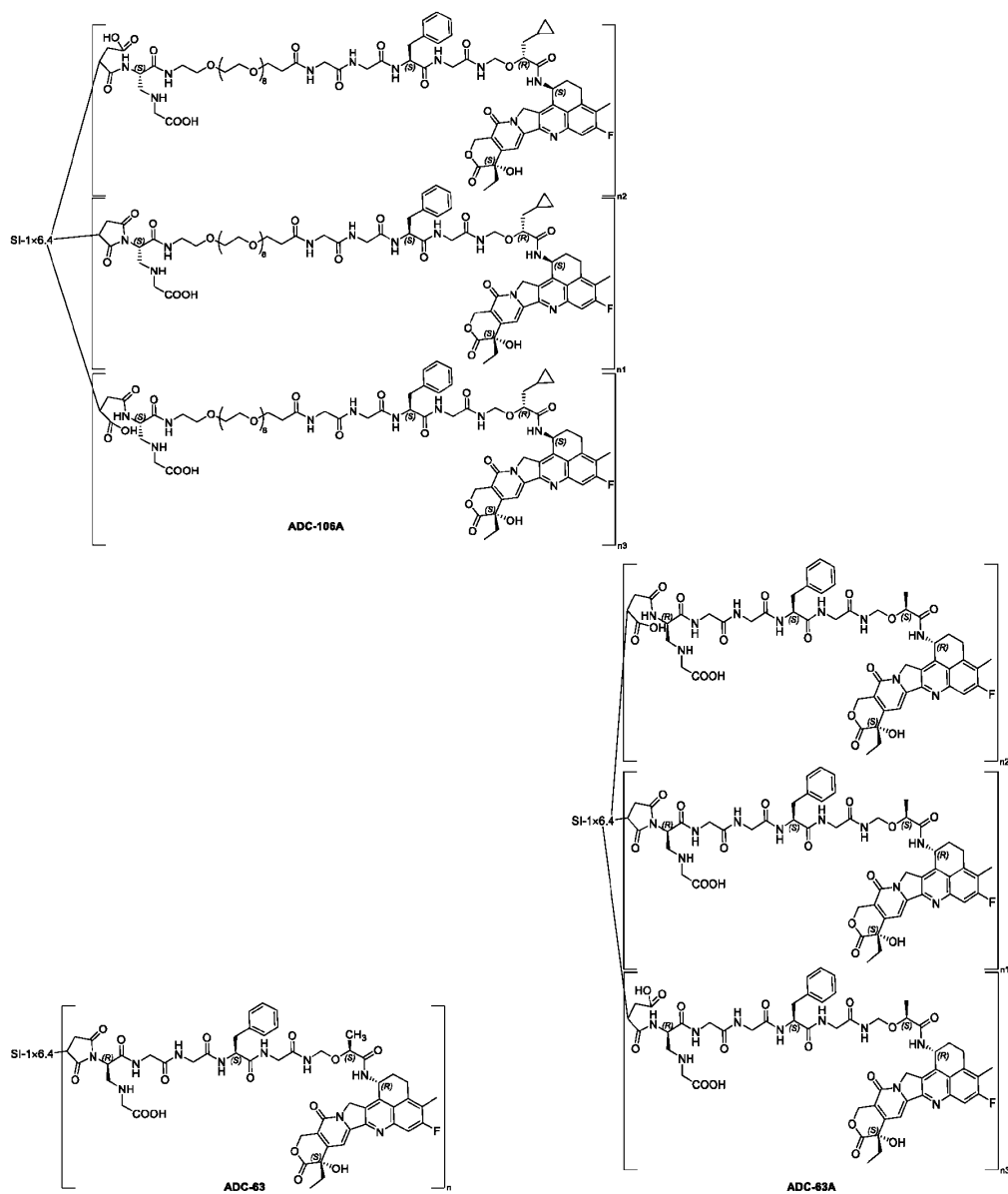


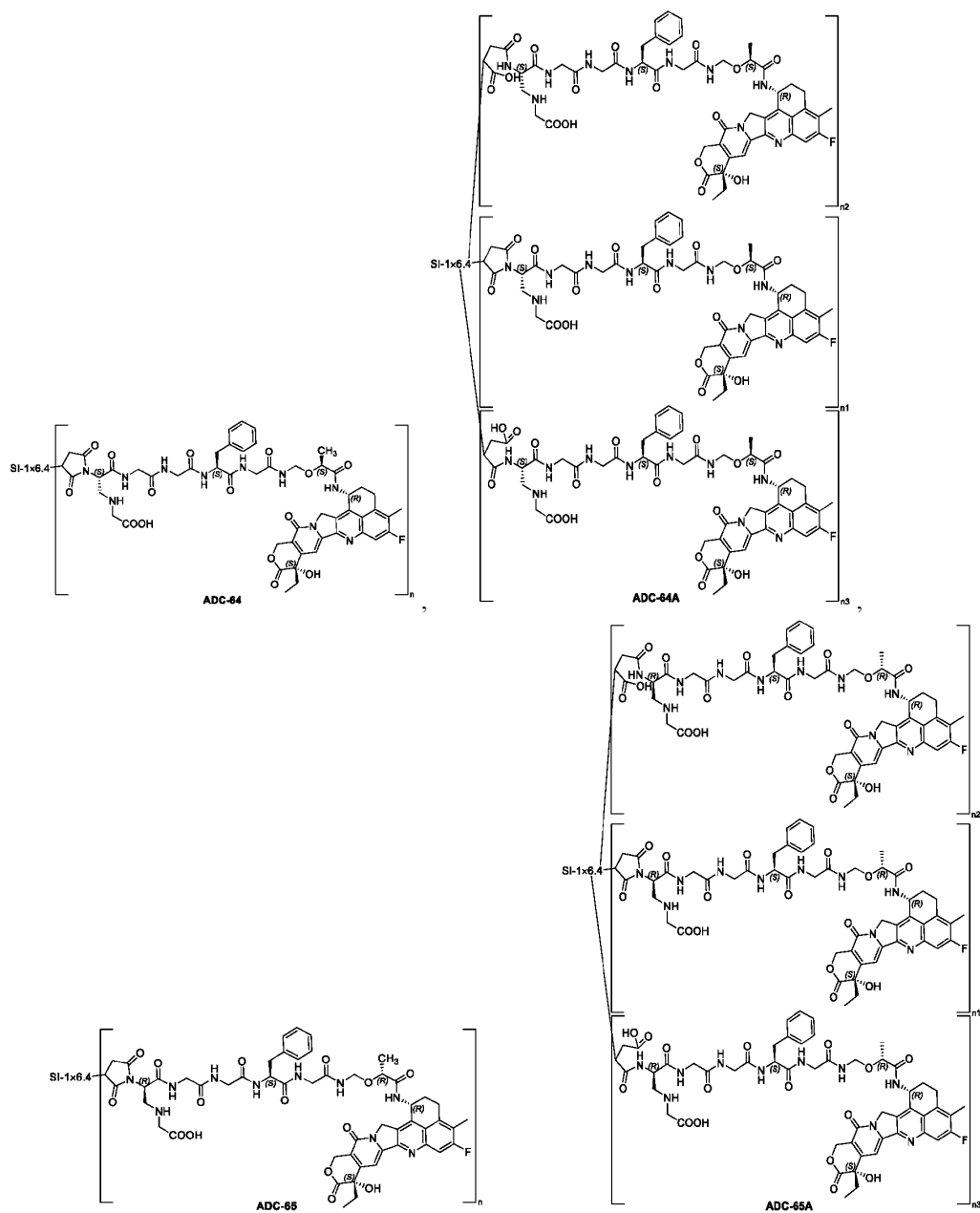


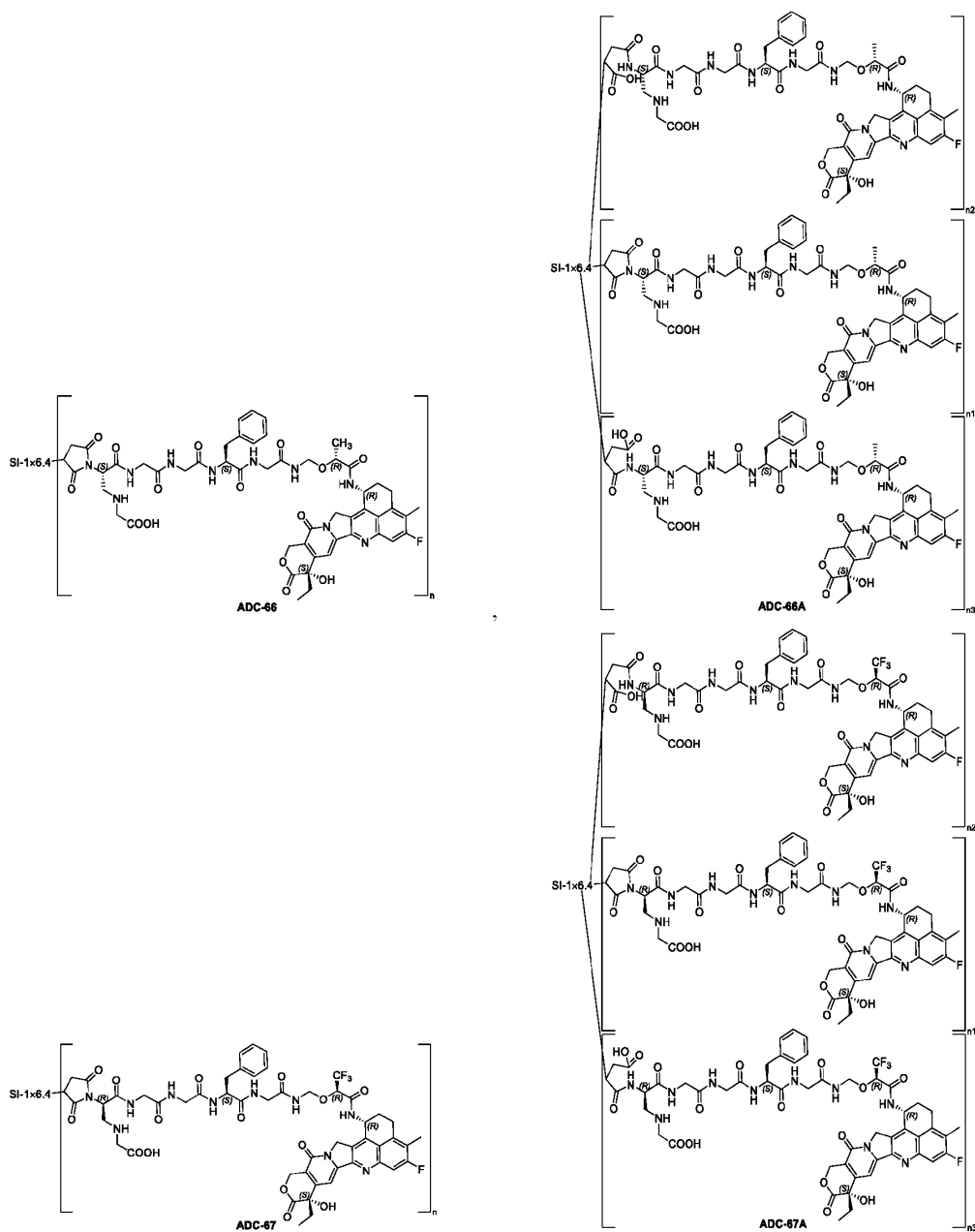


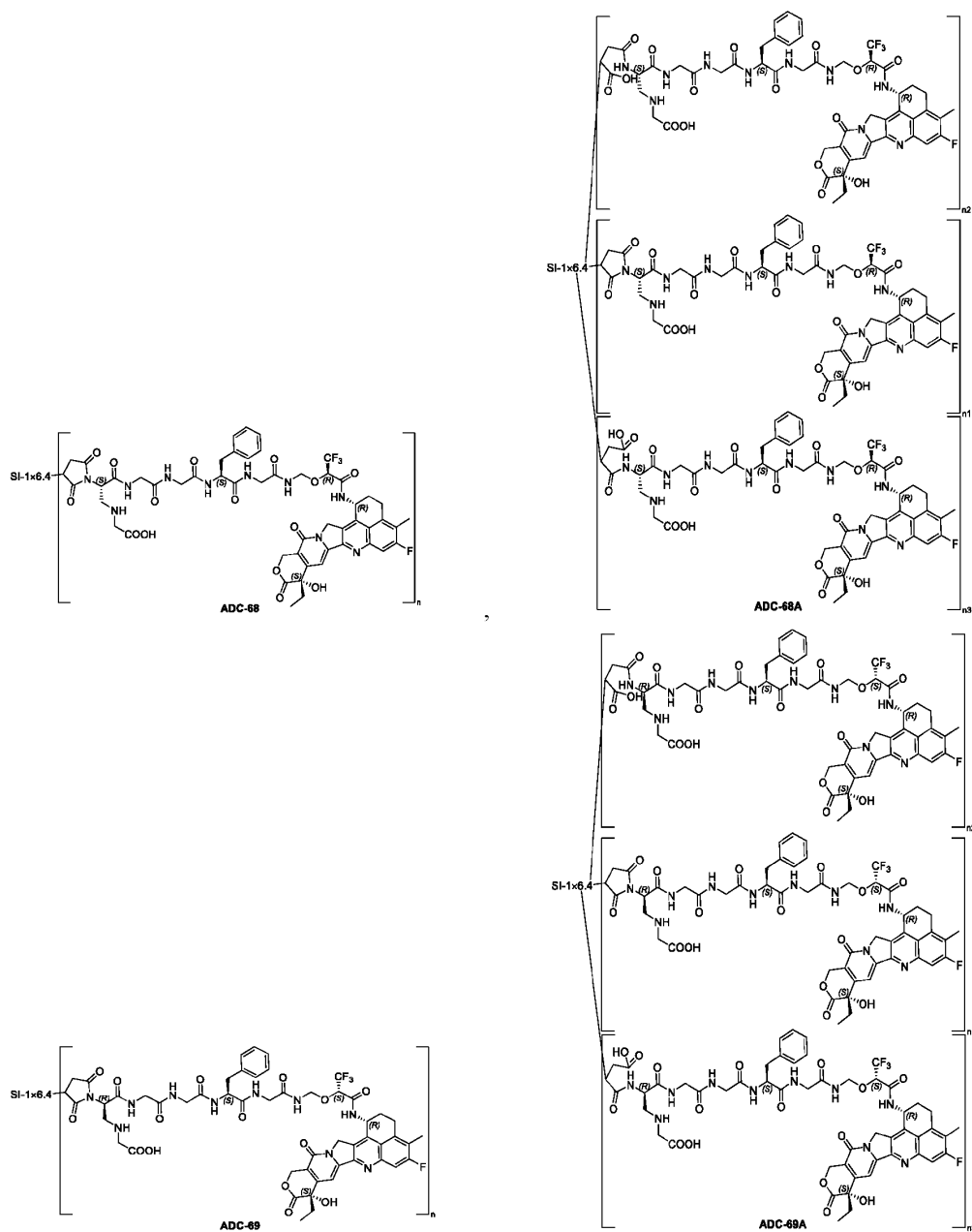


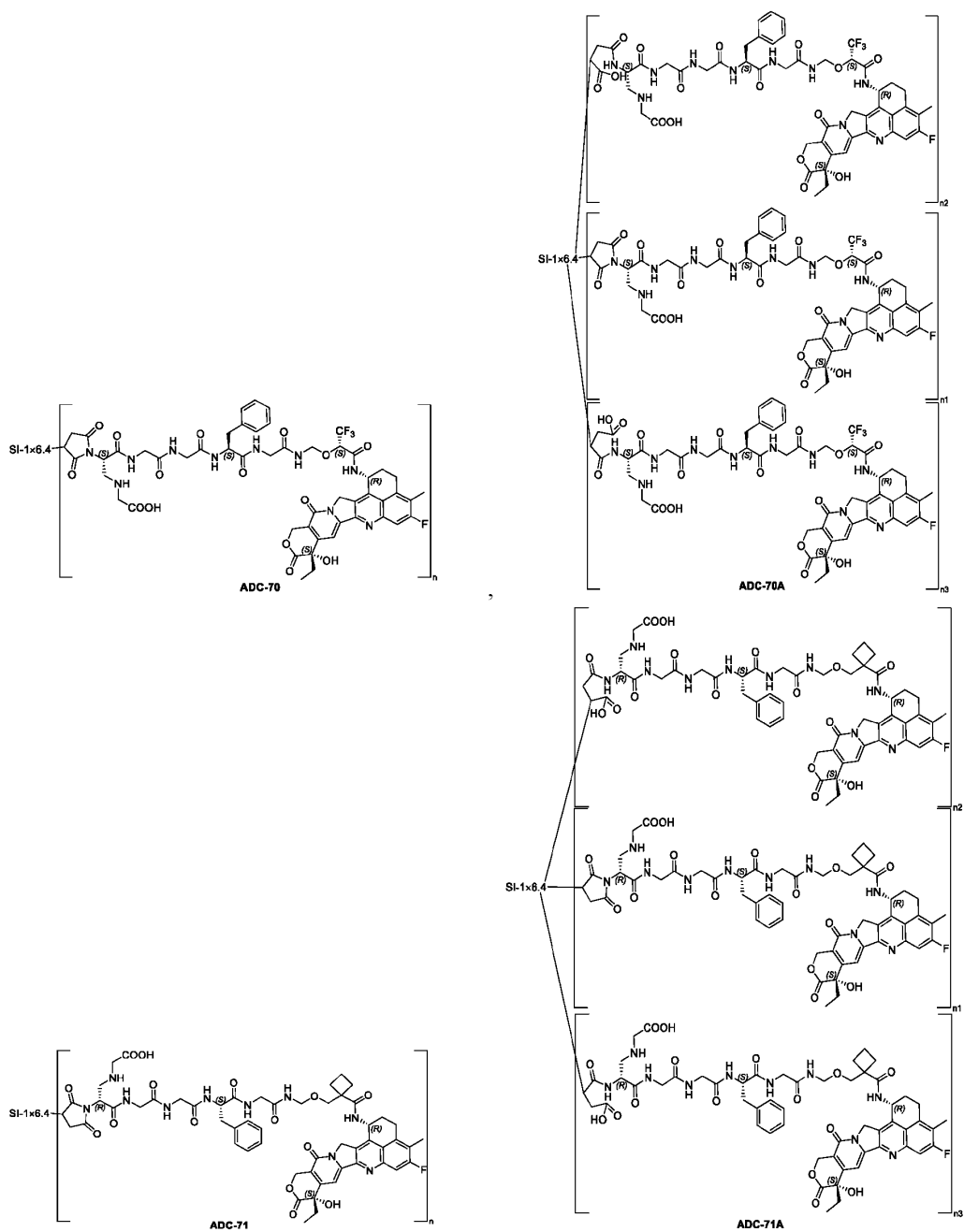


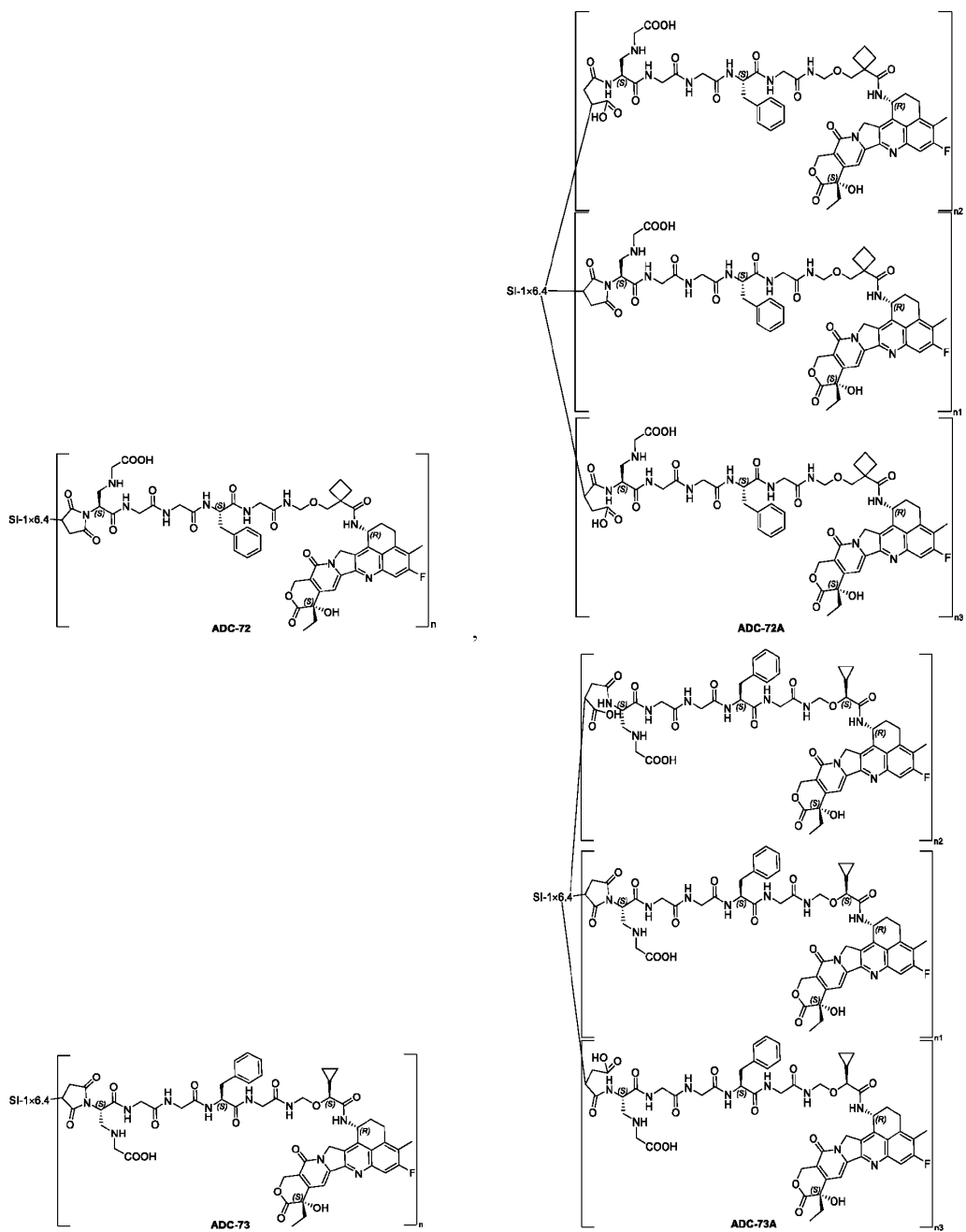


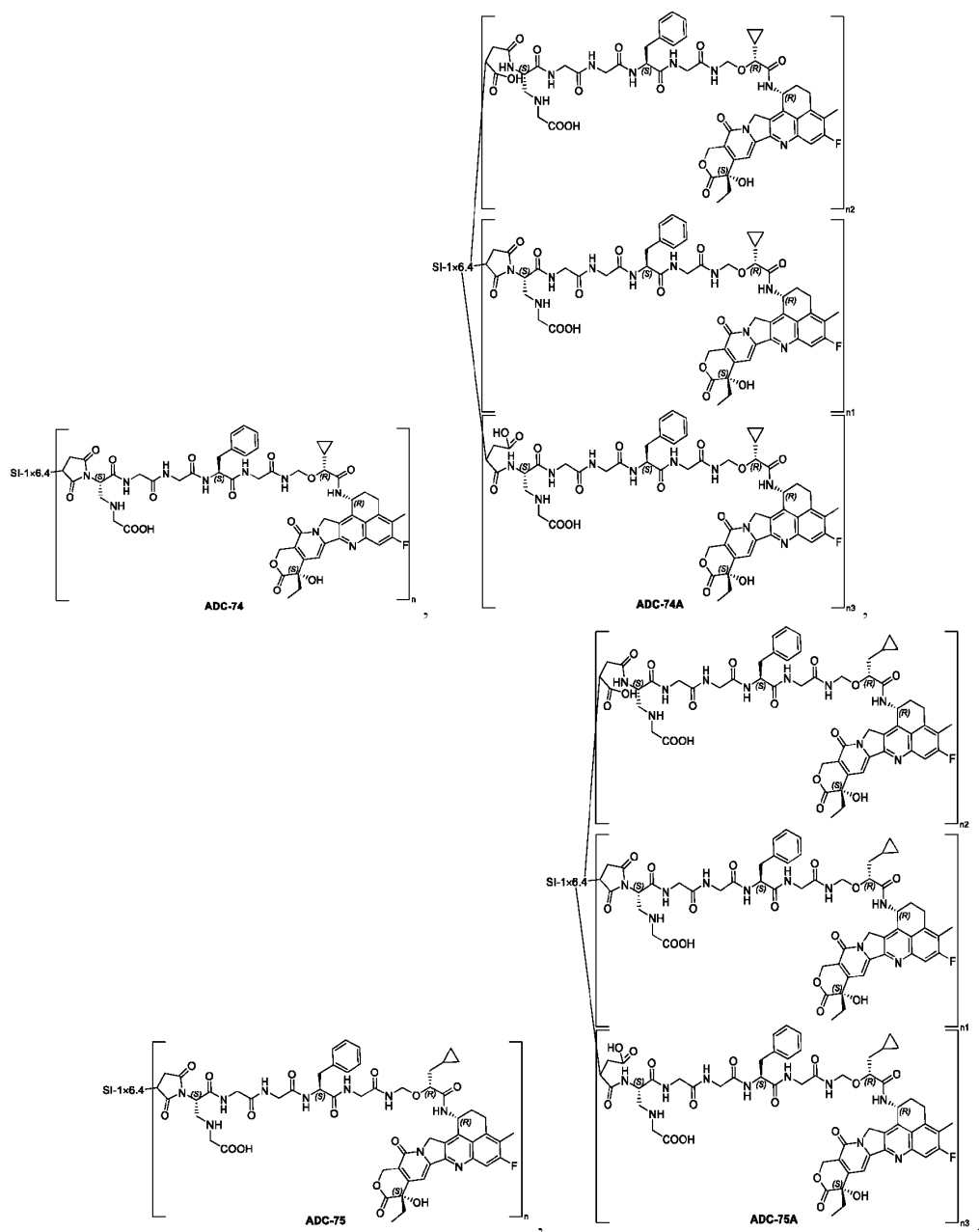


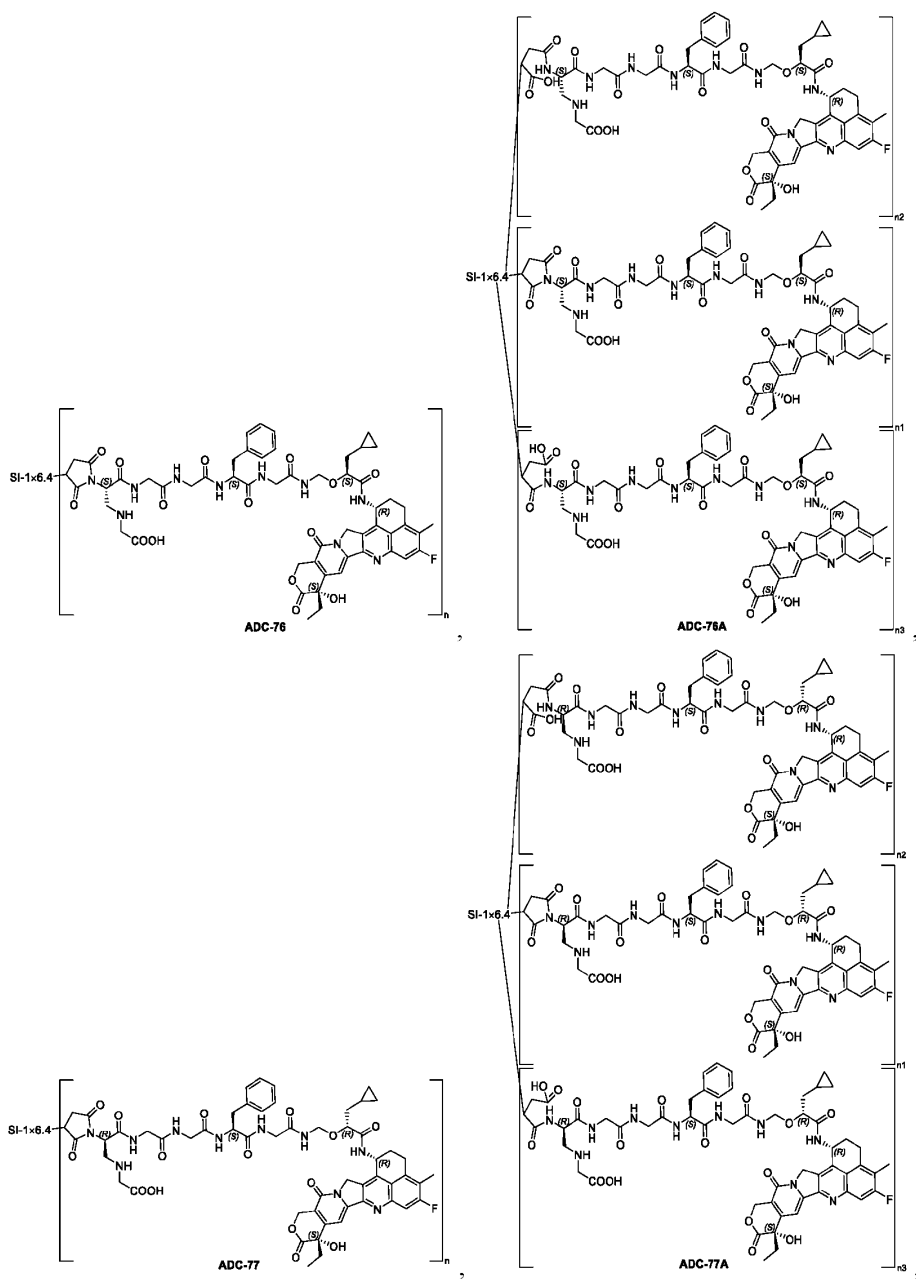


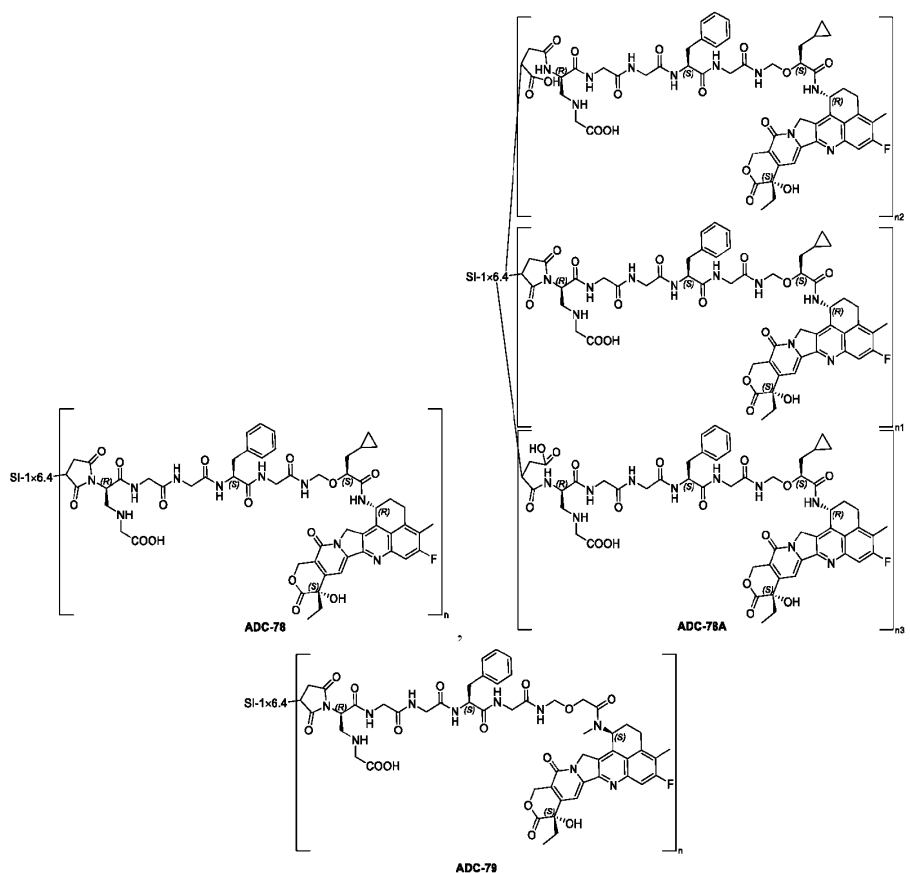










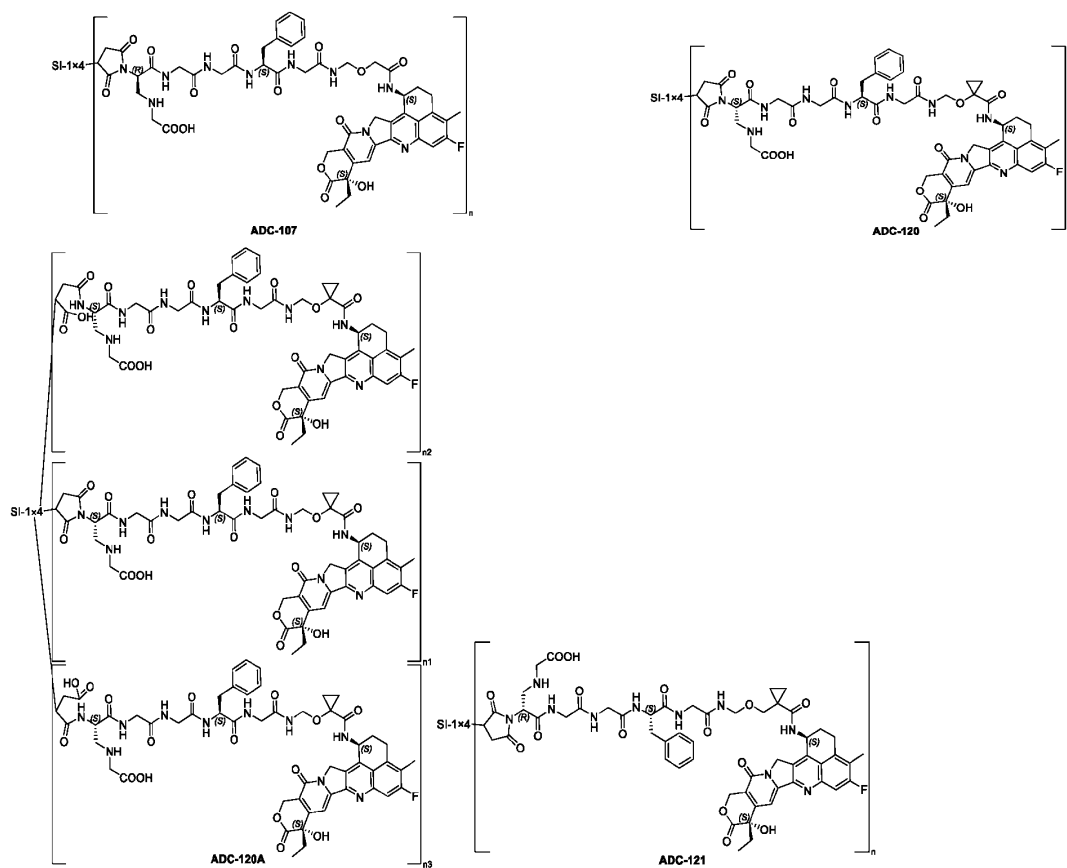


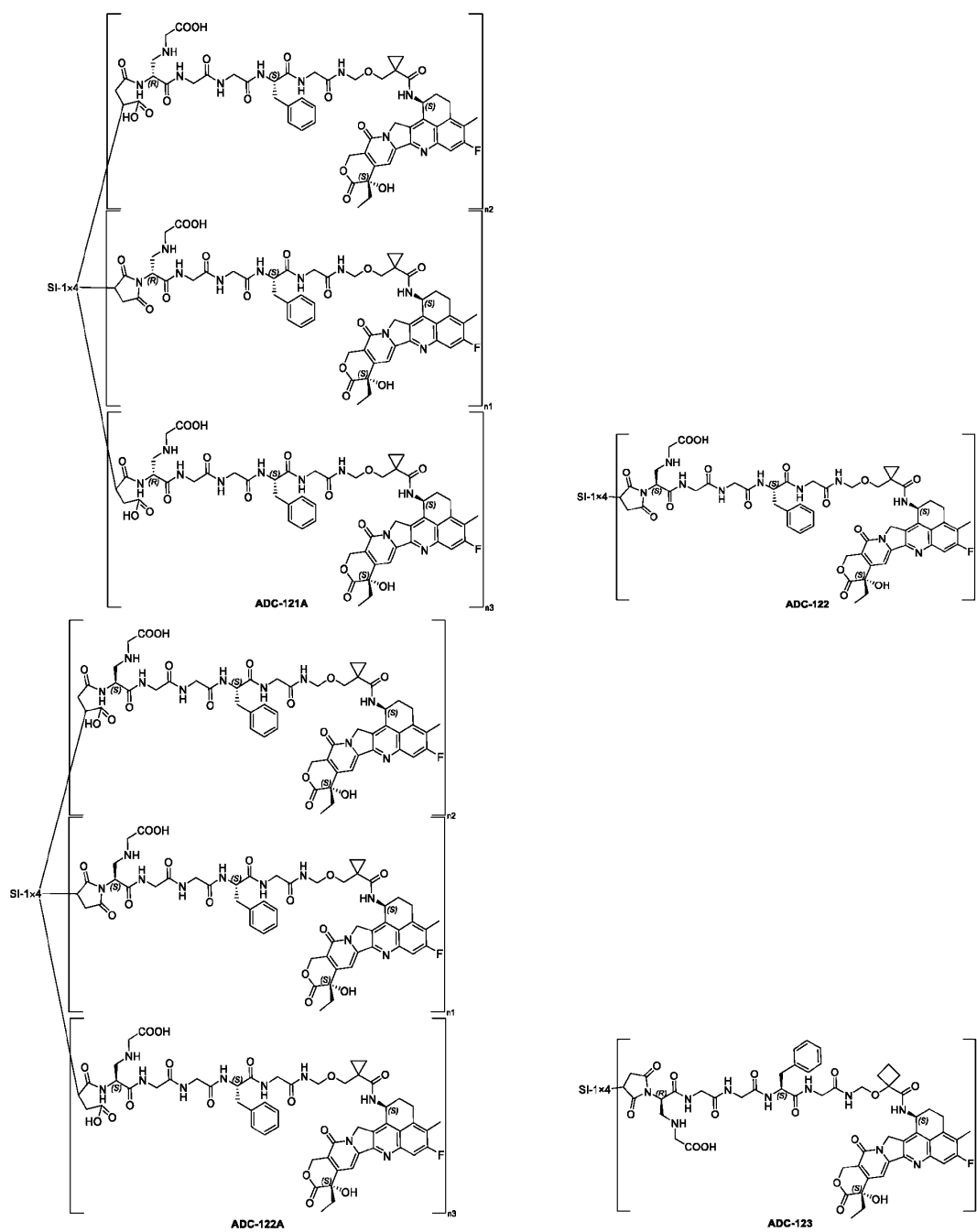
wherein:

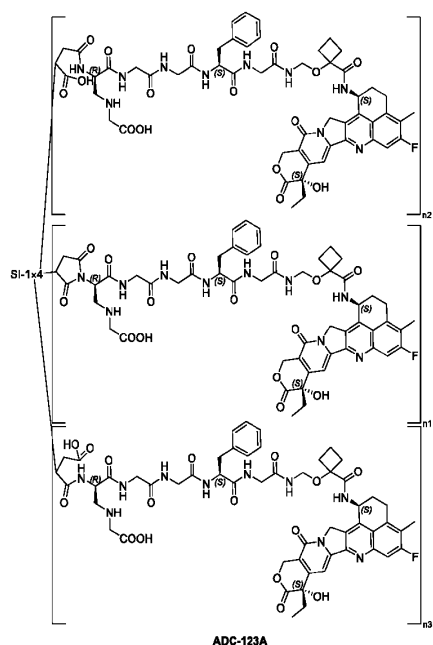
SI-1 x 6.4 is a bispecific antibody or antigen-binding fragment thereof having a binding affinity to EGFR and HER3,

n is an integer of 1-10 (e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10), wherein $n1$, $n2$, and $n3$ are each independently chosen from any integer or any decimal number from 0-10 (e.g., 0, 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 2, 2.1, 2.2, 2.3, 2.4, 2.5, 2.6, 2.7, 2.8, 2.9, 3, 3.1, 3.2, 3.3, 3.4, 3.5, 3.6, 3.7, 3.8, 3.9, 4, 4.1, 4.2, 4.3, 4.4, 4.5, 4.6, 4.7, 4.8, 4.9, 5, 5.1, 5.2, 5.3, 5.4, 5.5, 5.6, 5.7, 5.8, 5.9, 6, 6.1, 6.2, 6.3, 6.4, 6.5, 6.6, 6.7, 6.8, 6.9, 7, 7.1, 7.2, 7.3, 7.4, 7.5, 7.6, 7.7, 7.8, 7.9, 8, 8.1, 8.2, 8.3, 8.4, 8.5, 8.6, 8.7, 8.8, 8.9, 9, 9.1, 9.2, 9.3, 9.4, 9.5, 9.6, 9.7, 9.8, 9.9, or 10), $n1$, $n2$, and $n3$ are not simultaneously 0, and $1 \leq n1 + n2 + n3 \leq 10$.

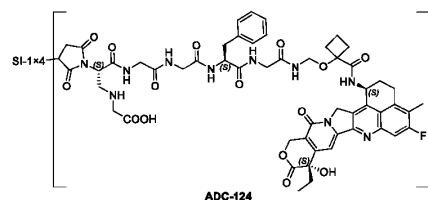
In one embodiment, the ligand-camptothecin derivative conjugate, or a pharmaceutically acceptable salt or solvate thereof, comprises the following structure, or a butanediimide ring-opening structure thereof, or an isomer thereof:



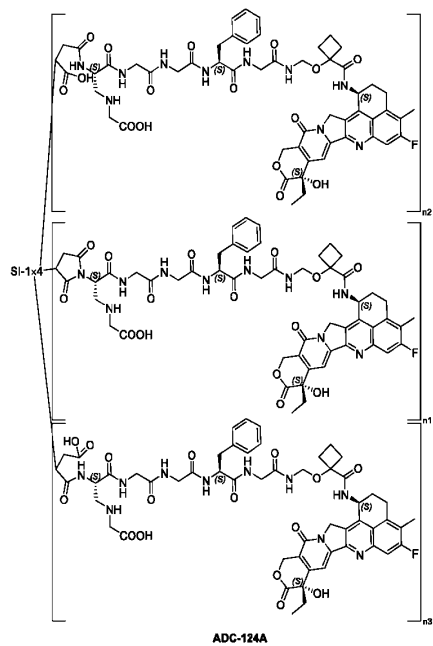




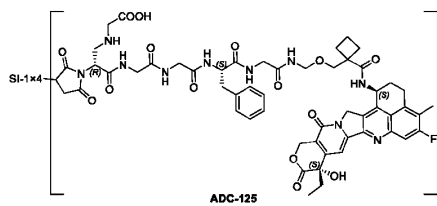
ADC-123A



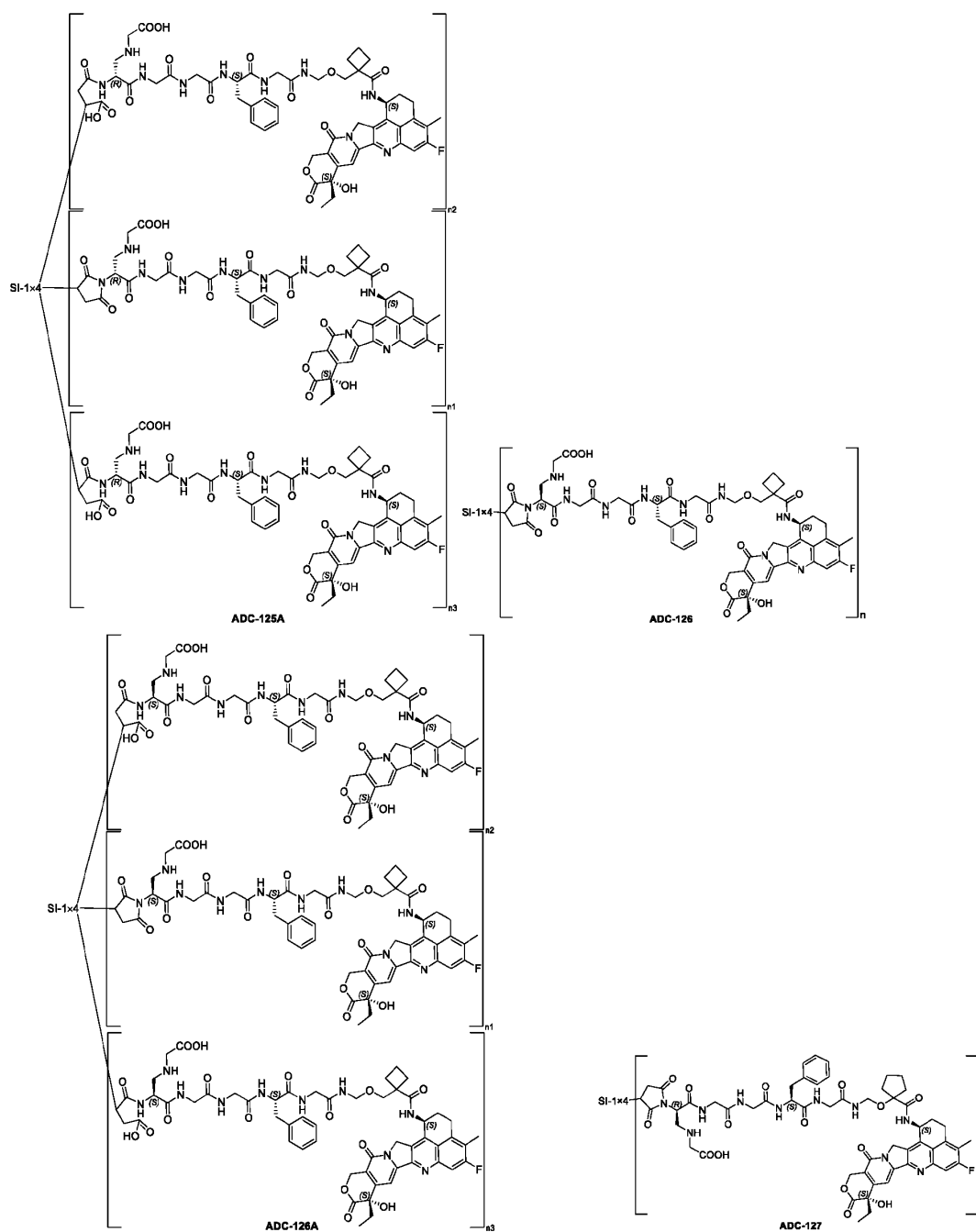
ADC-124

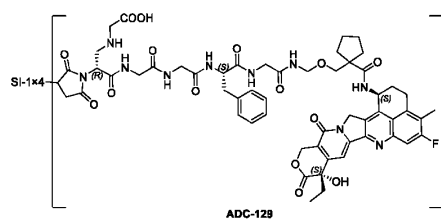
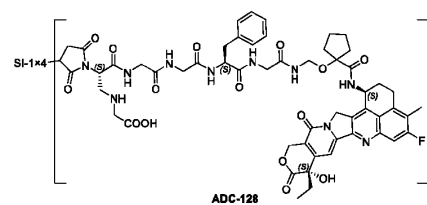
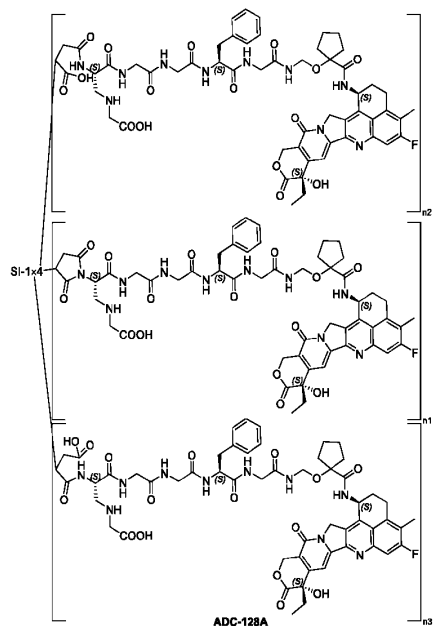
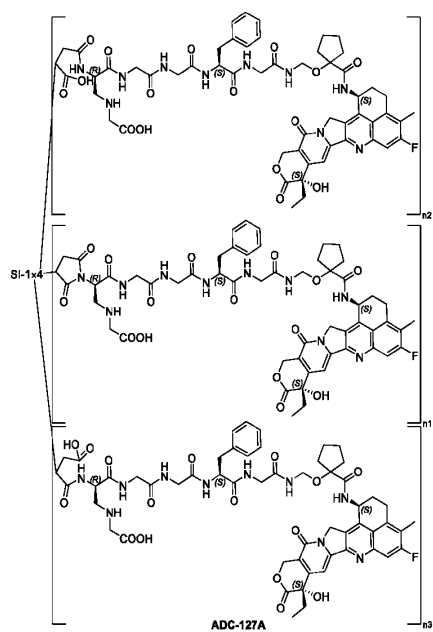


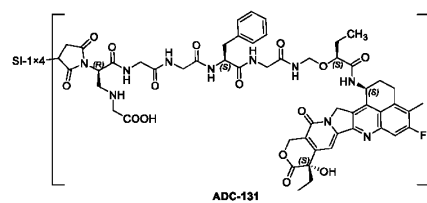
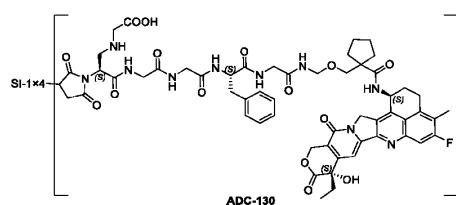
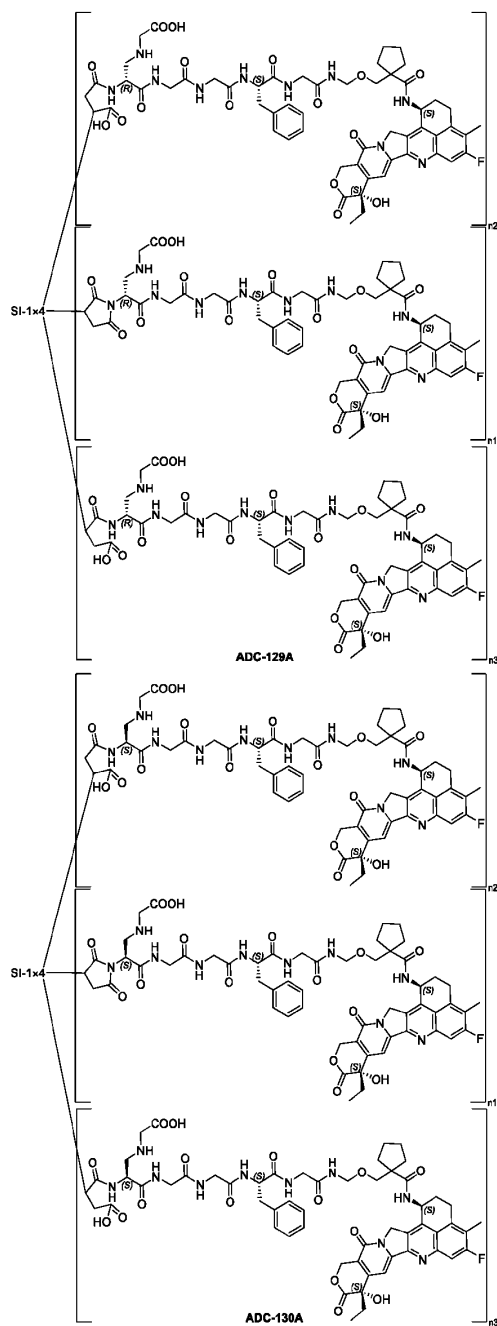
ADC-124A

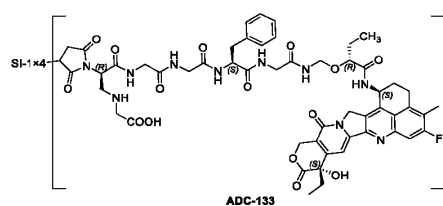
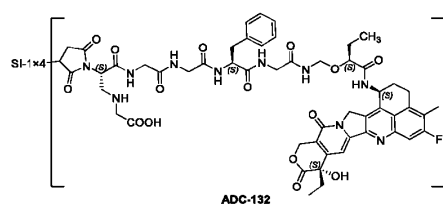
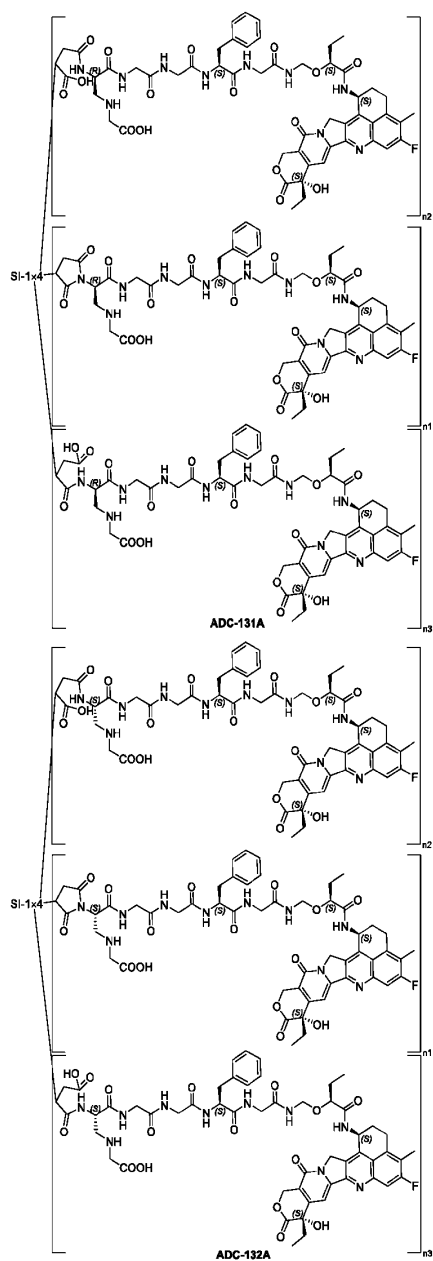


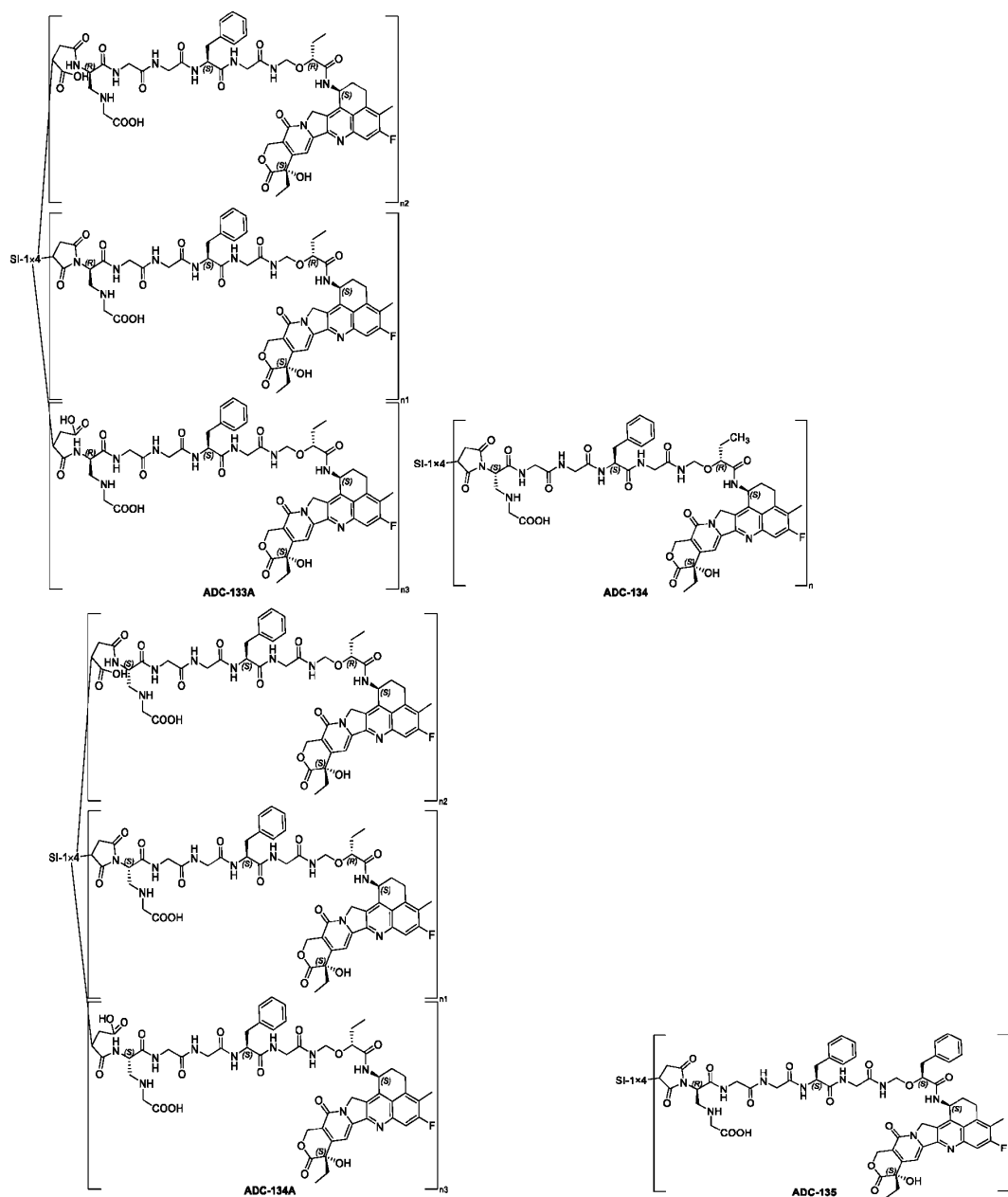
ADC-125

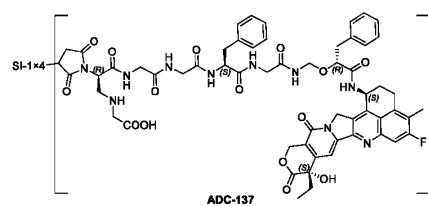
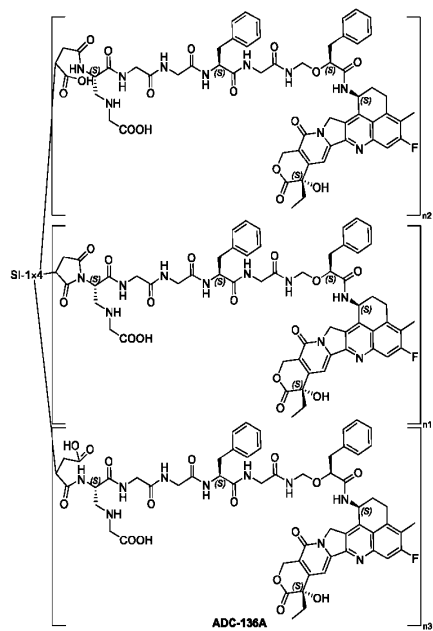
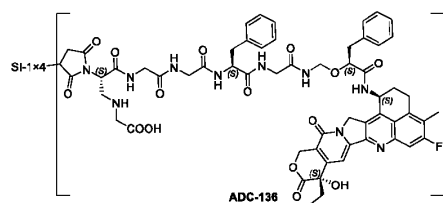
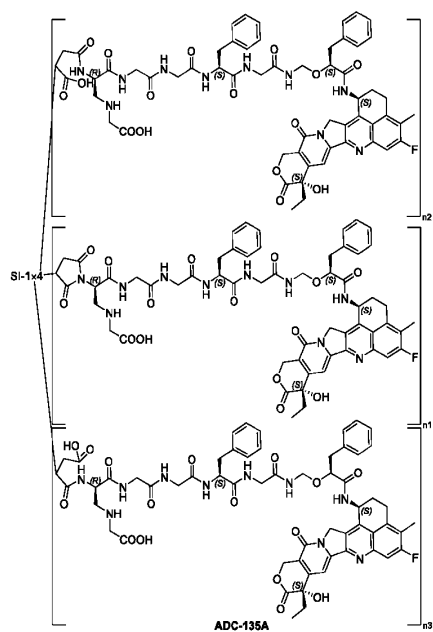


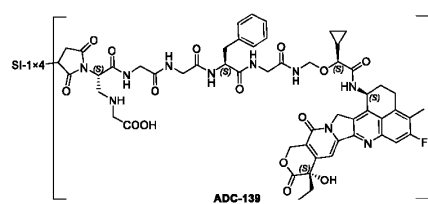
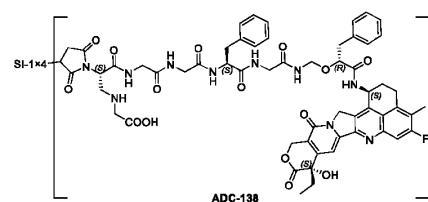
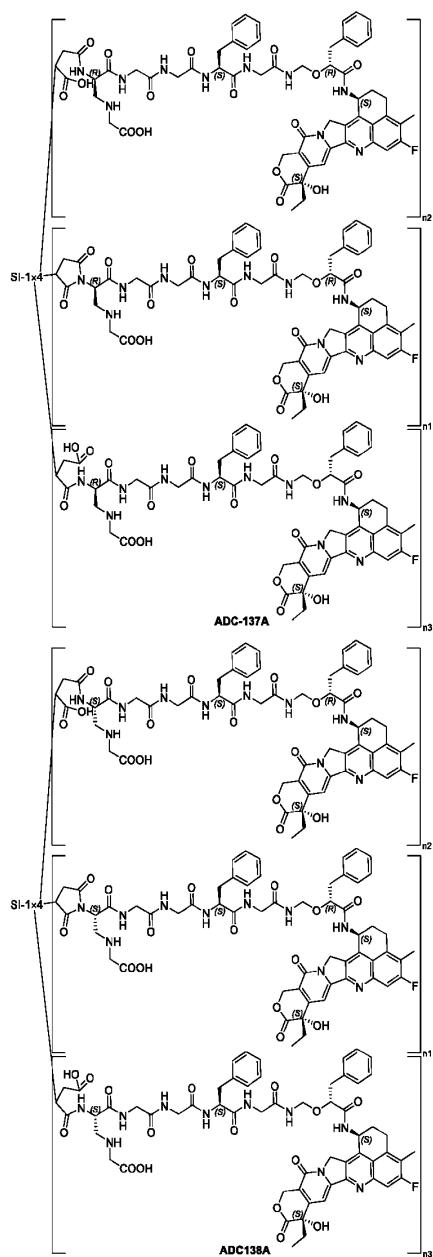


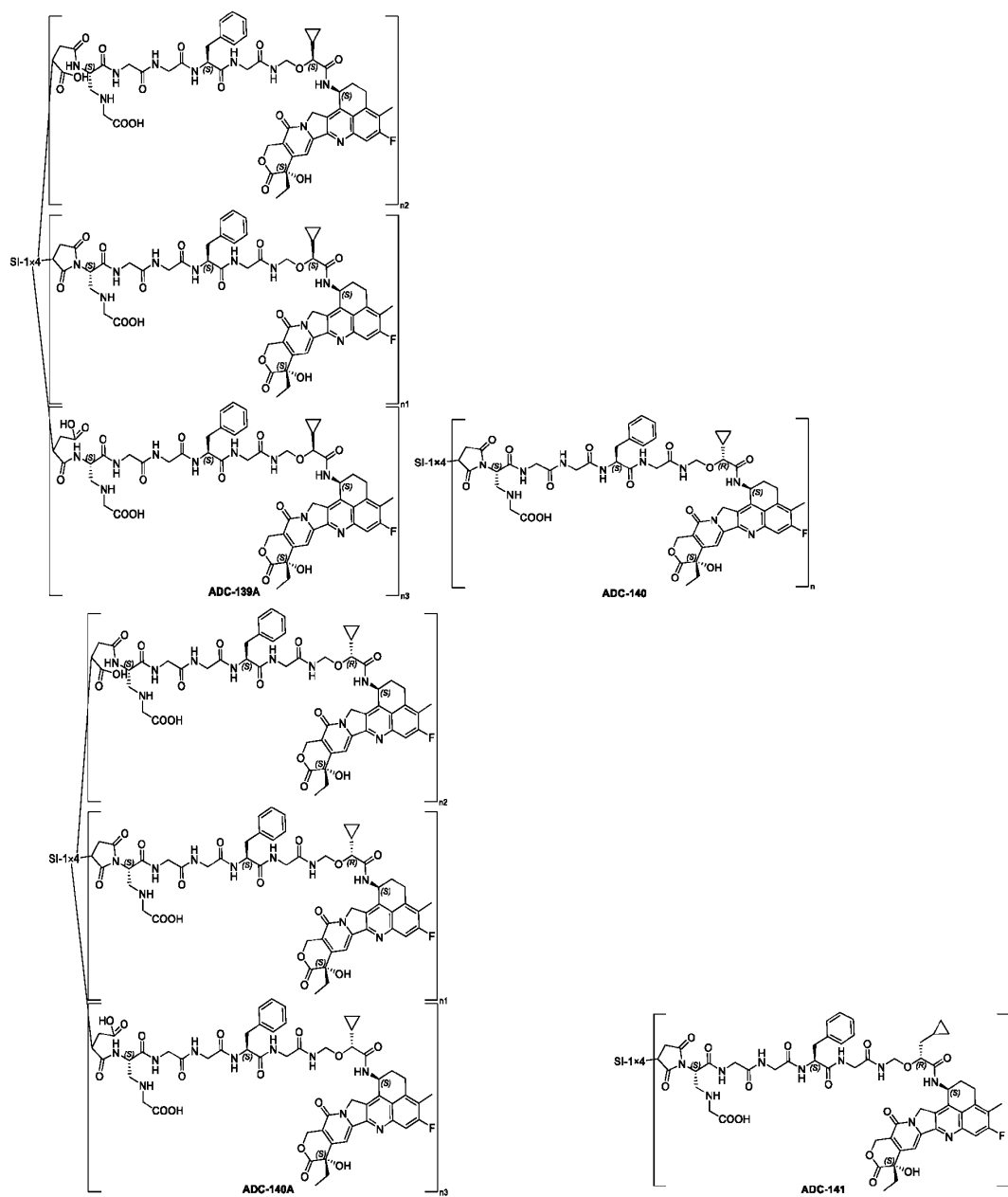


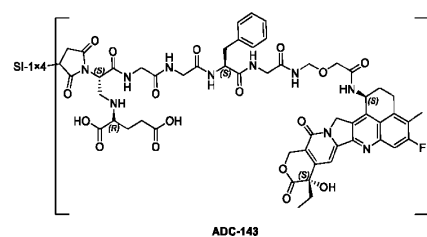
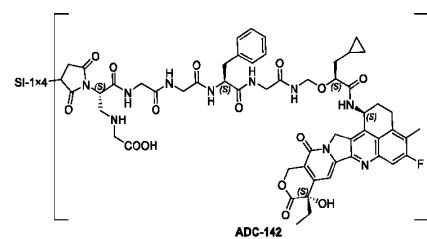
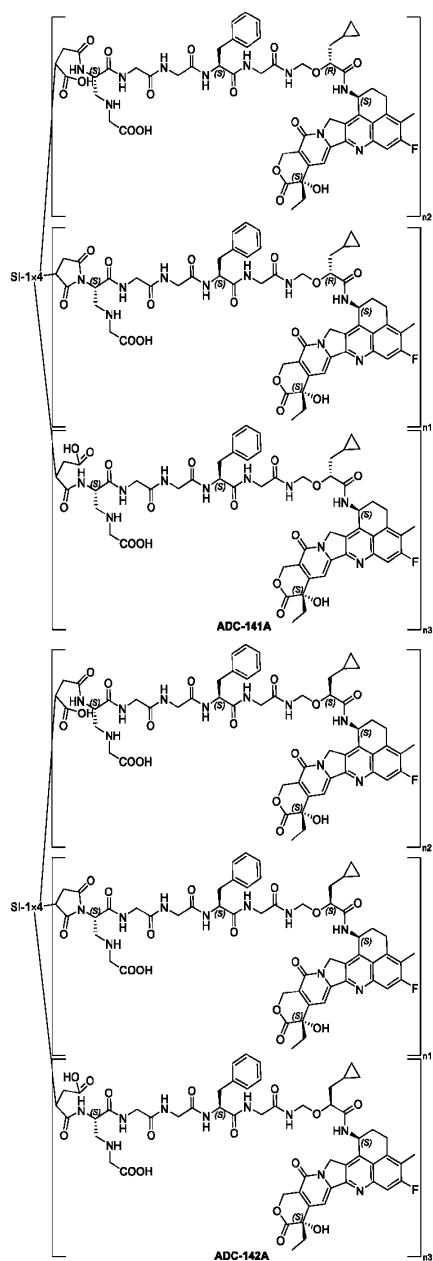


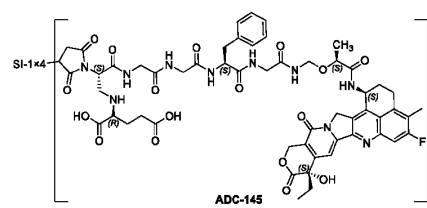
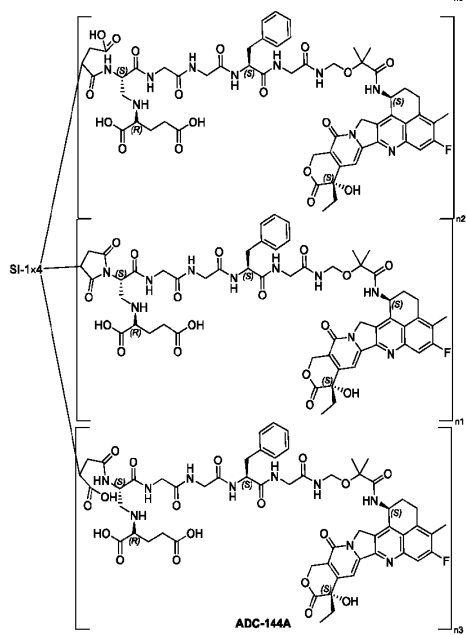
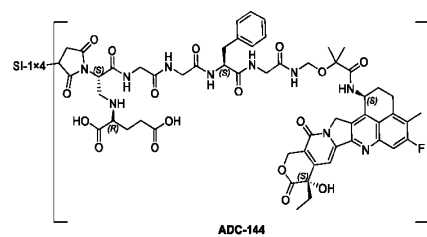
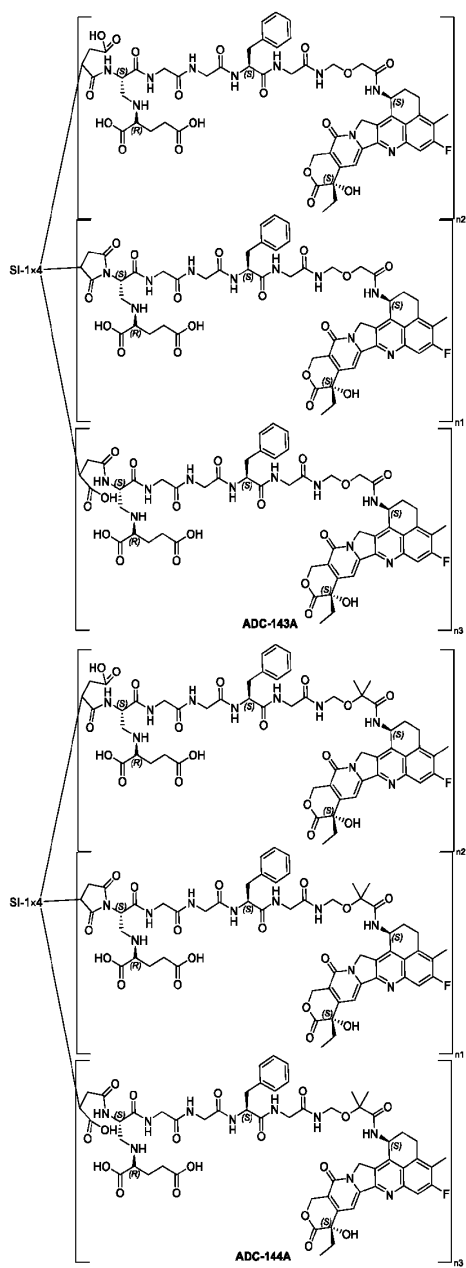


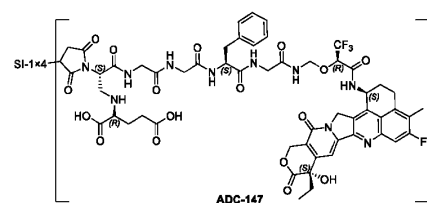
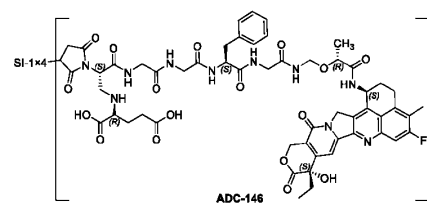
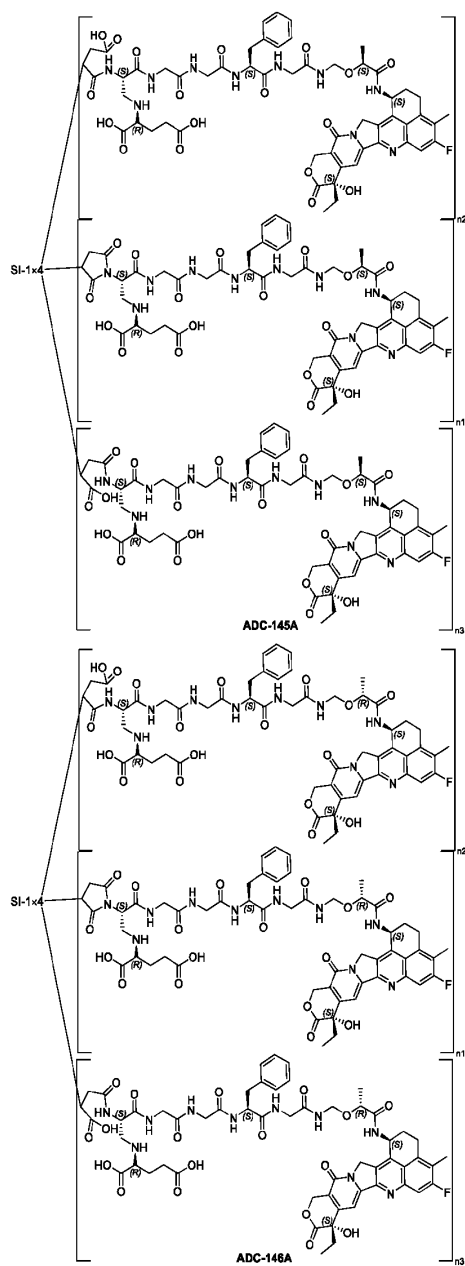


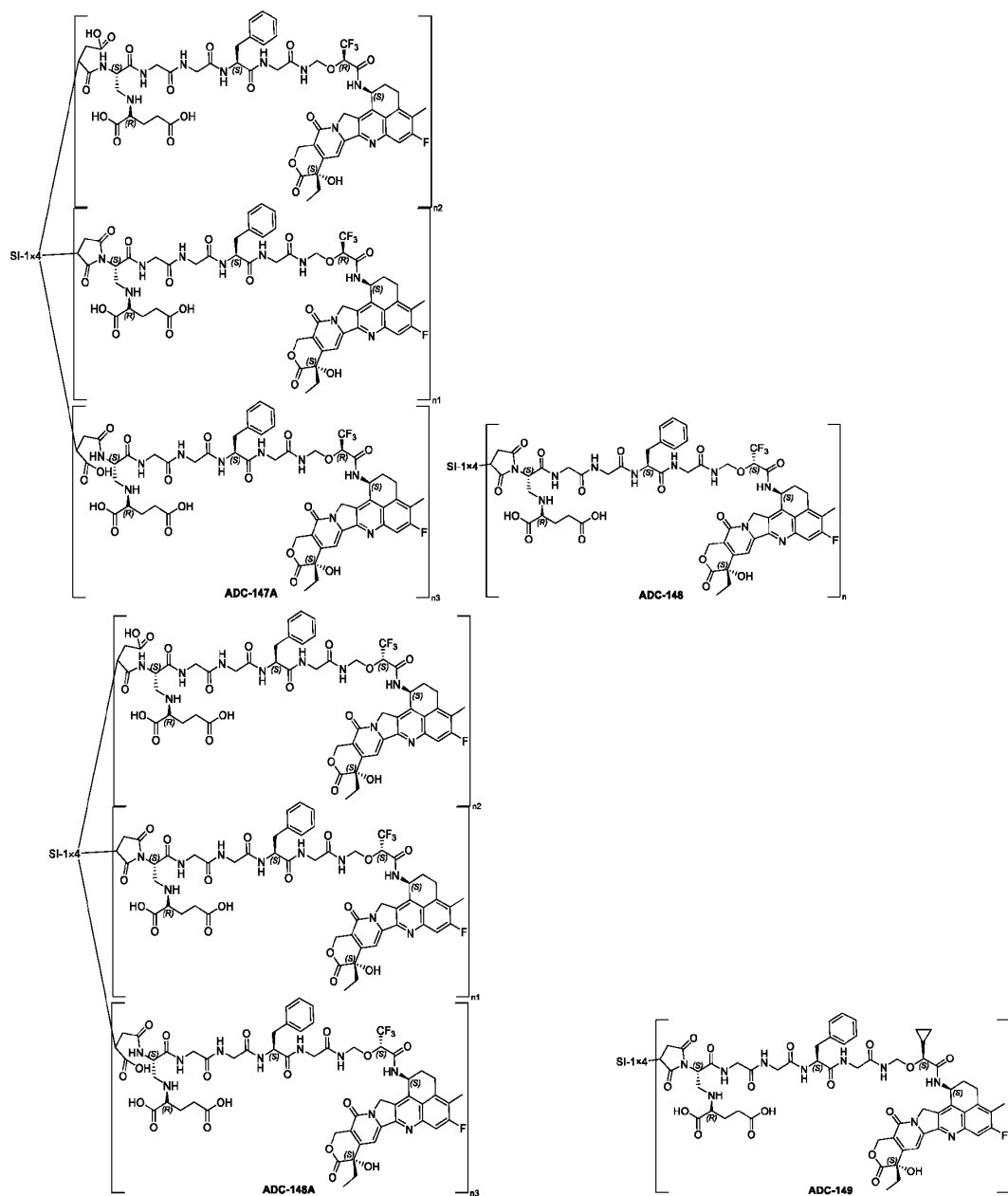


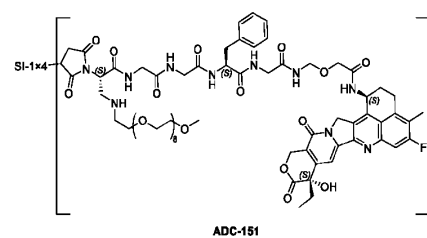
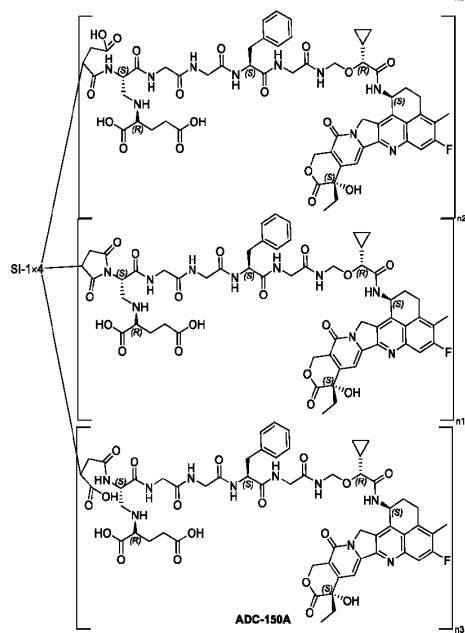
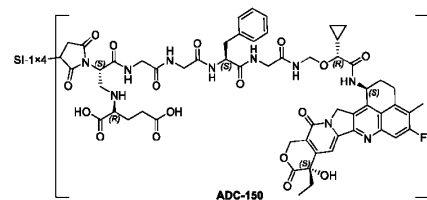
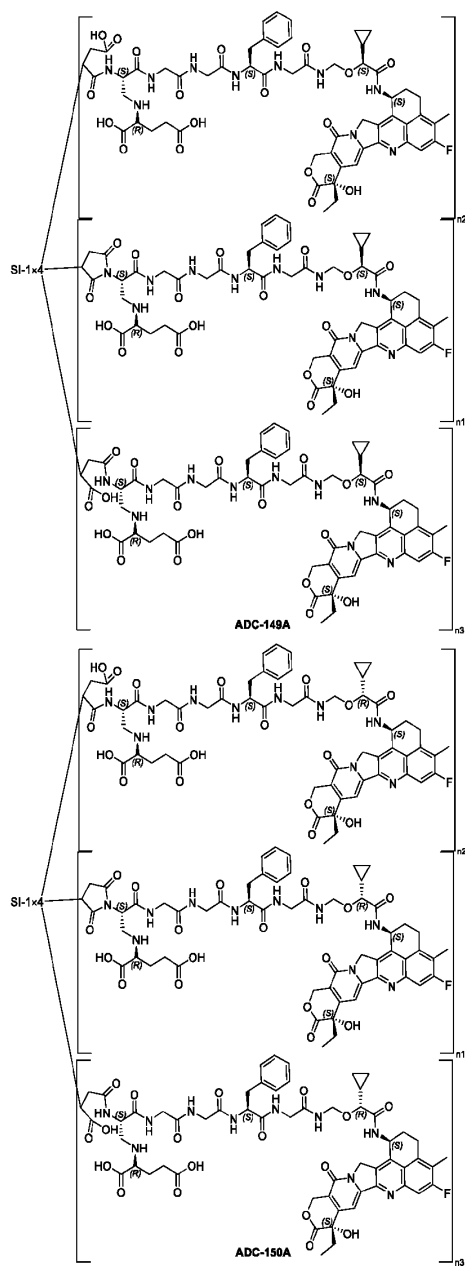


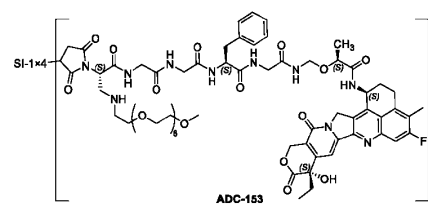
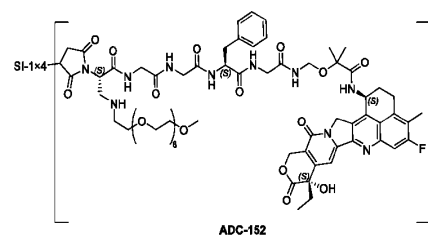
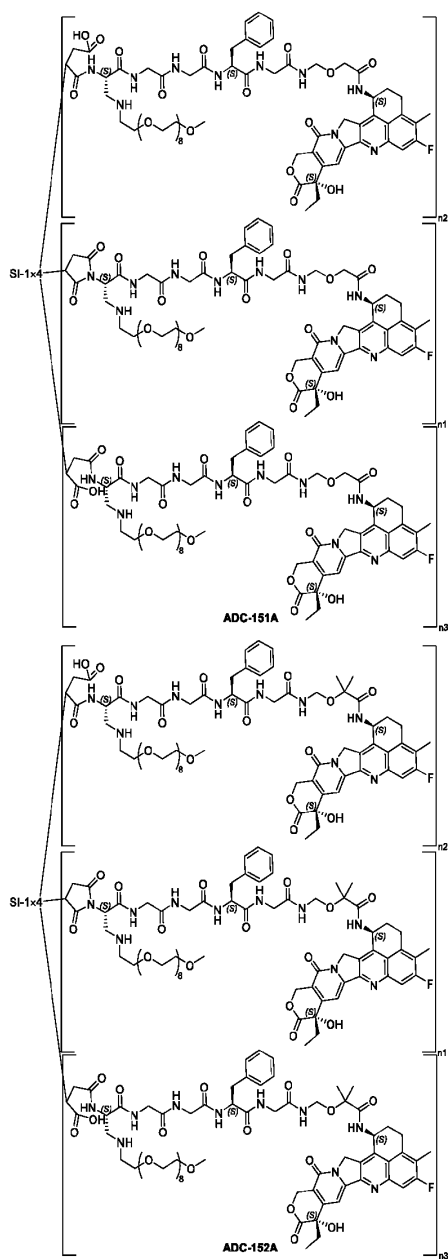


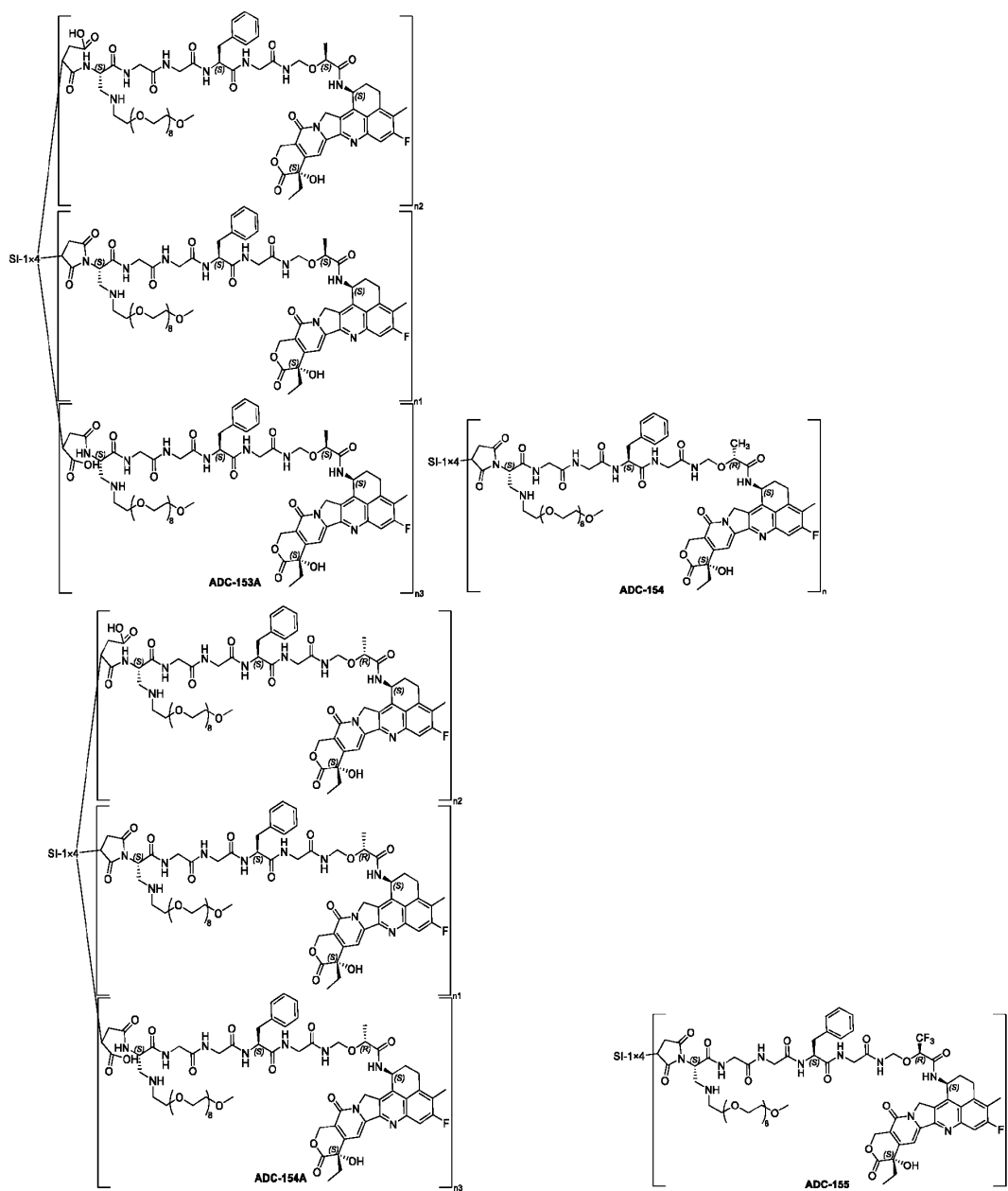


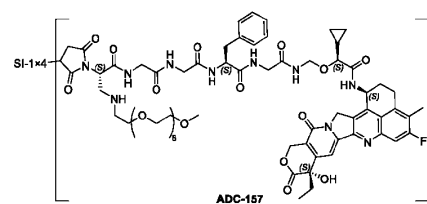
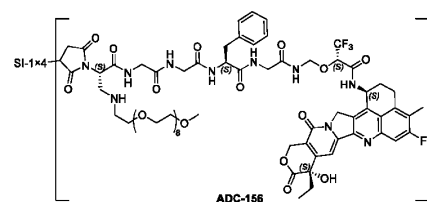
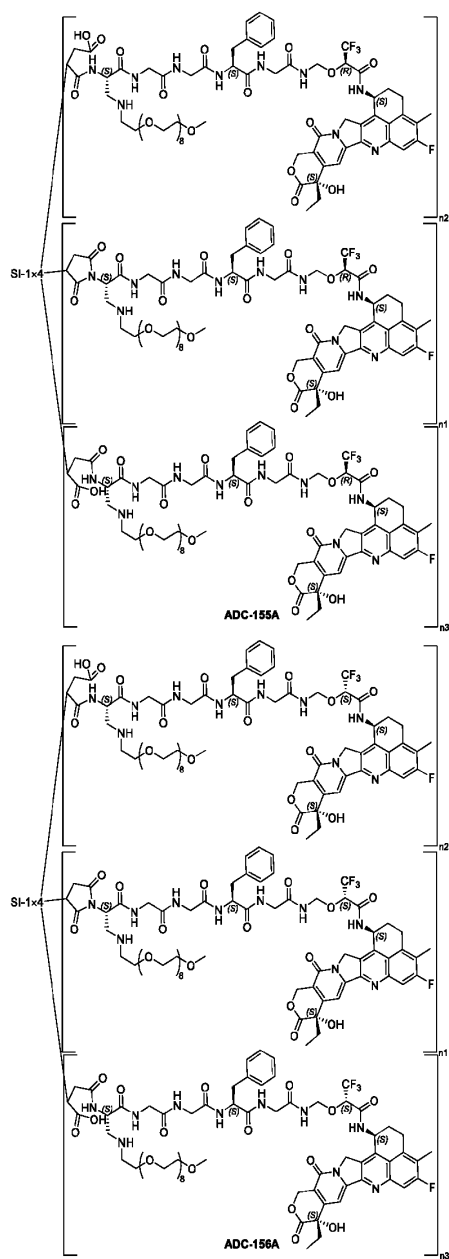


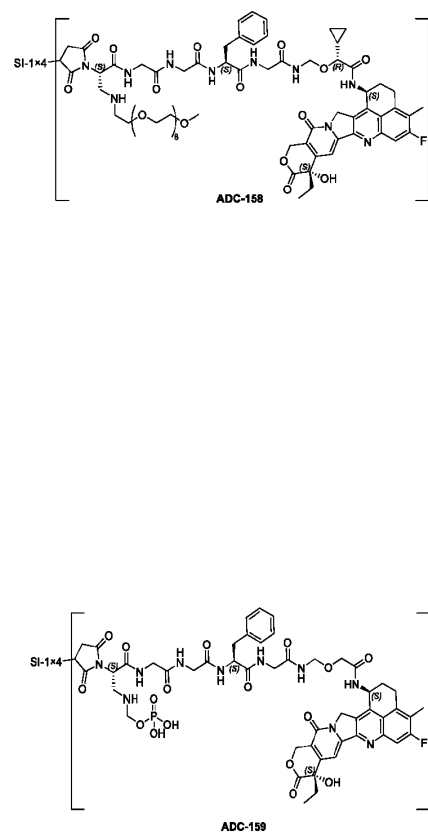


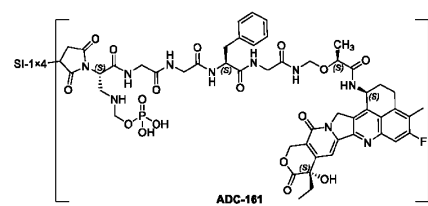
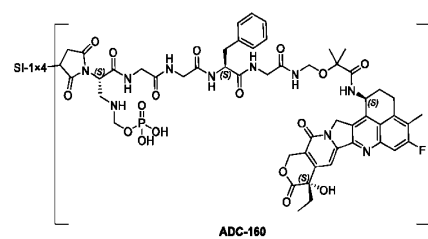
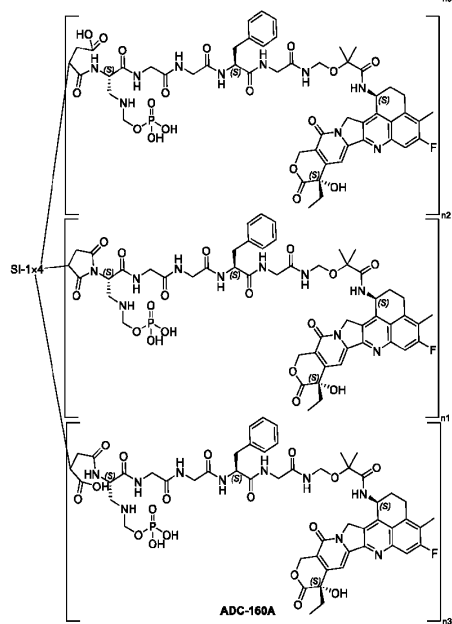
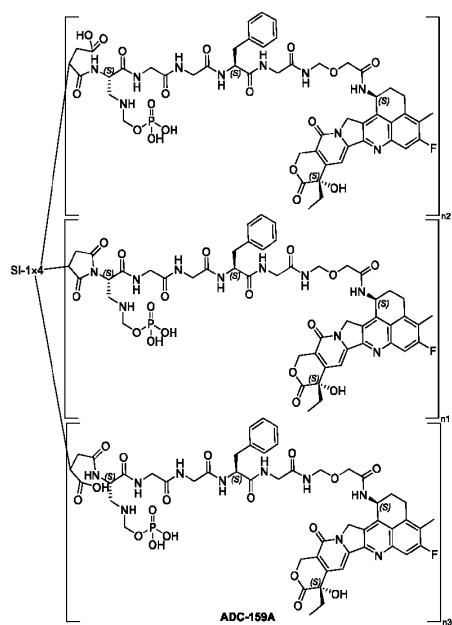


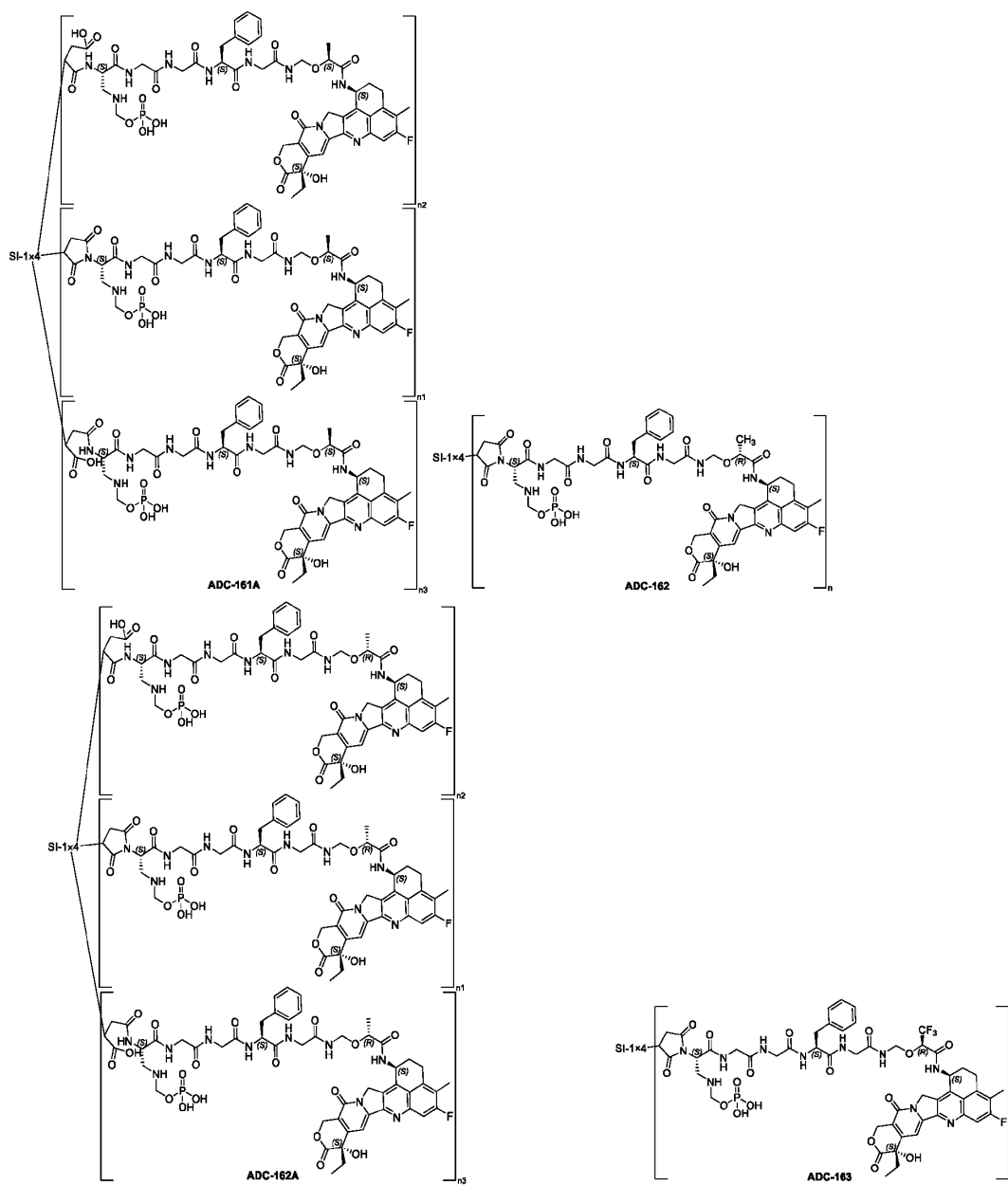


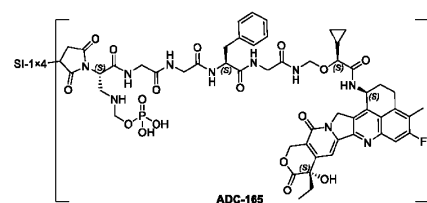
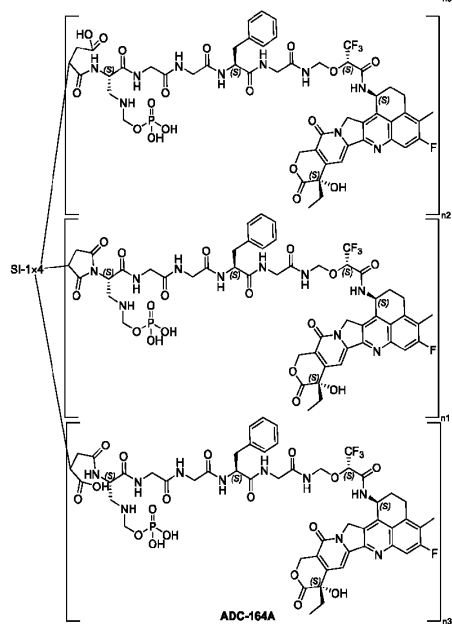
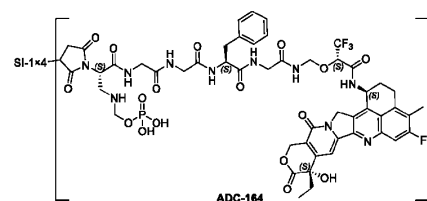
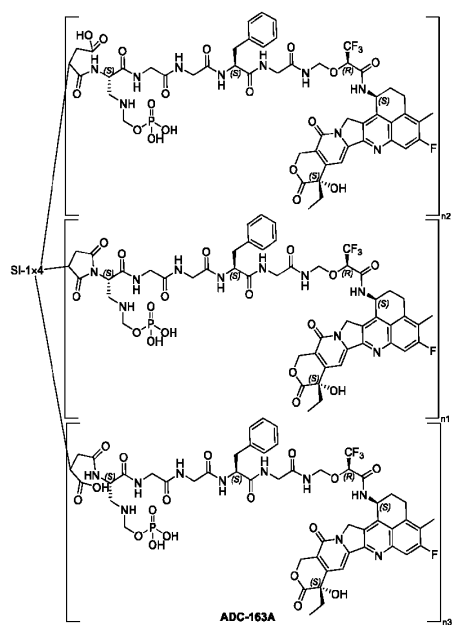


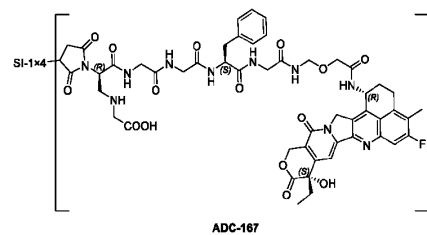
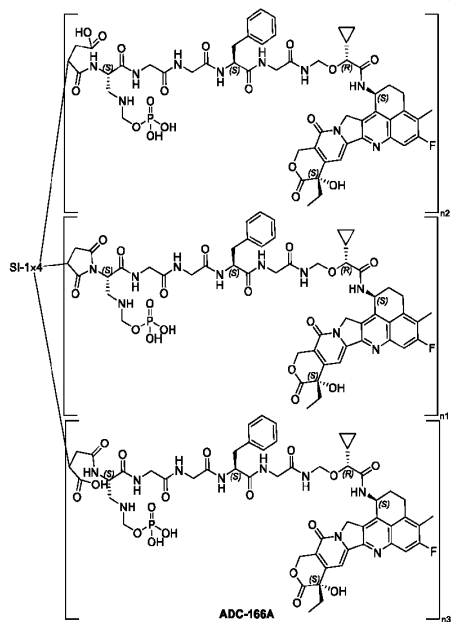
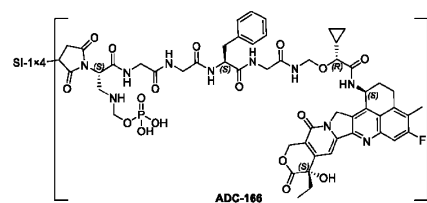
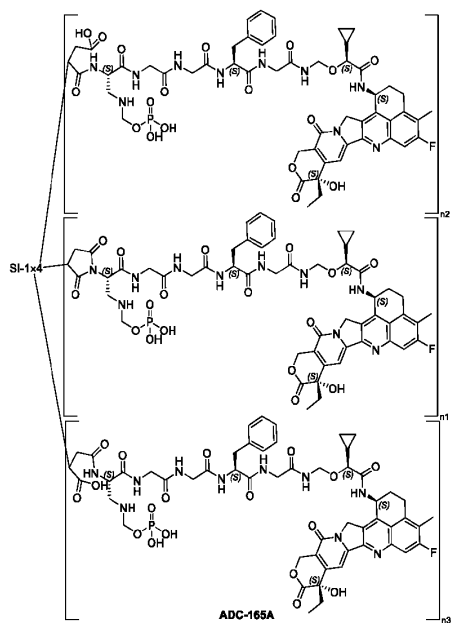


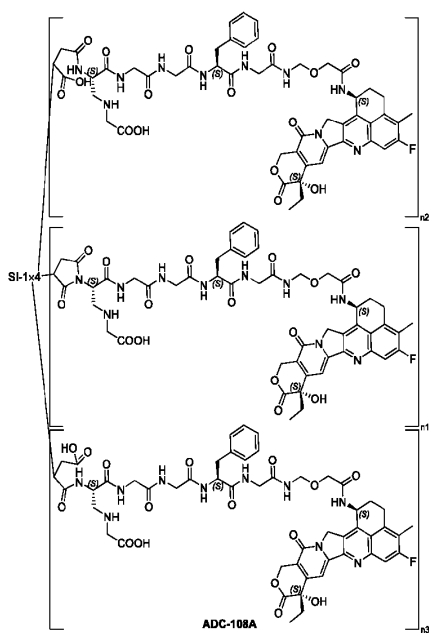
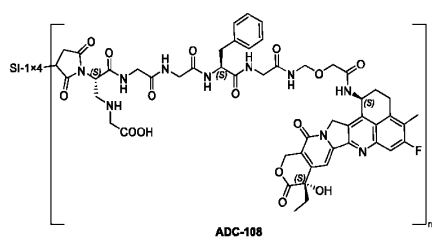
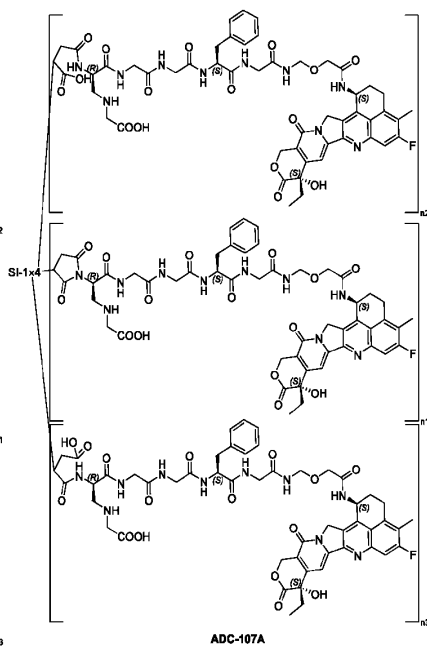
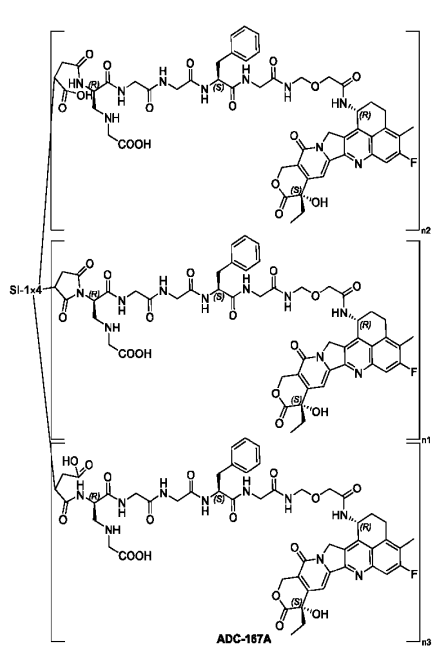


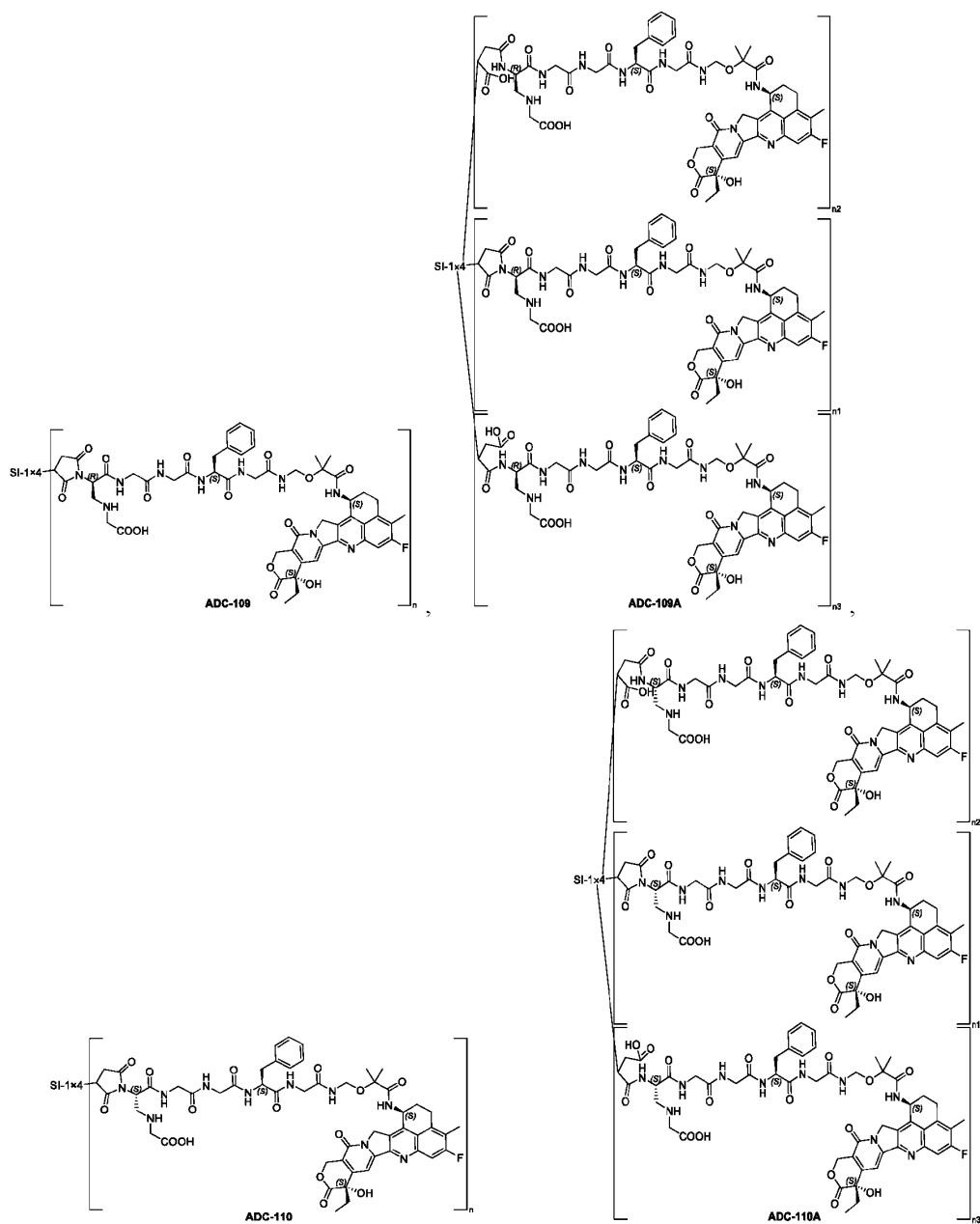


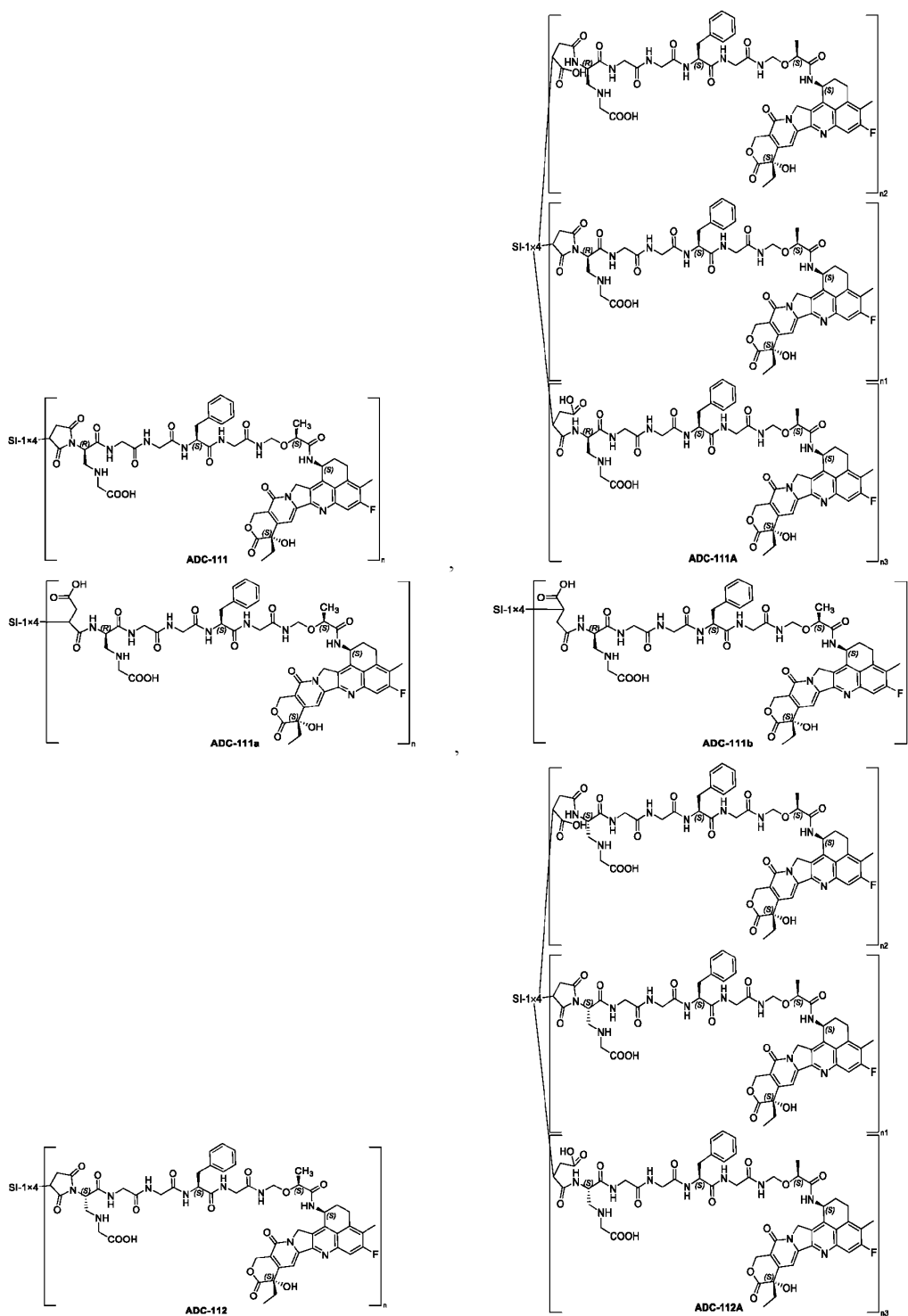


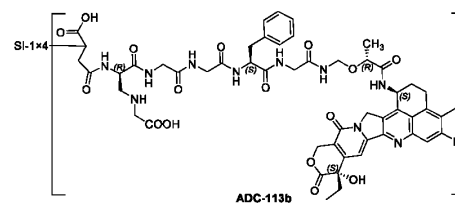
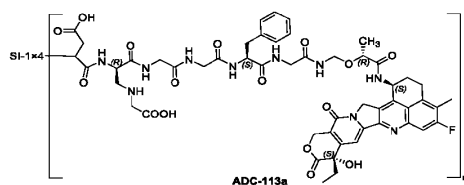
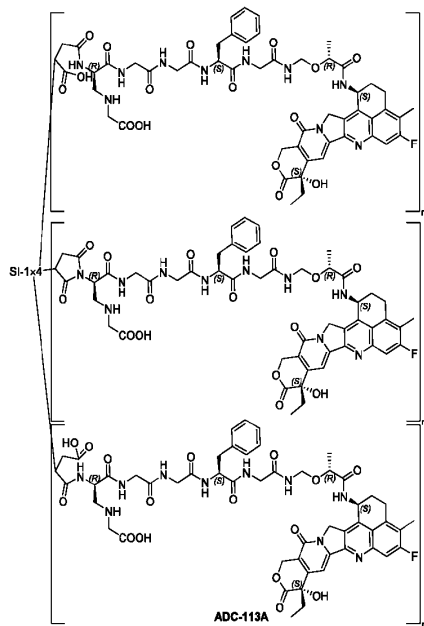
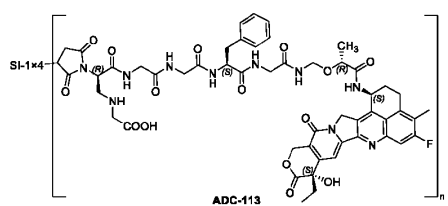
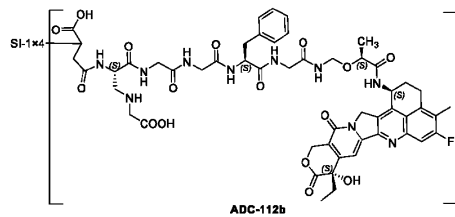
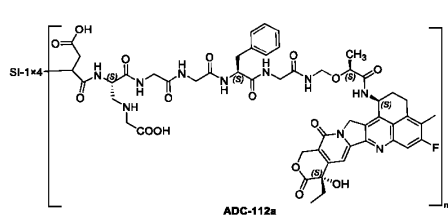


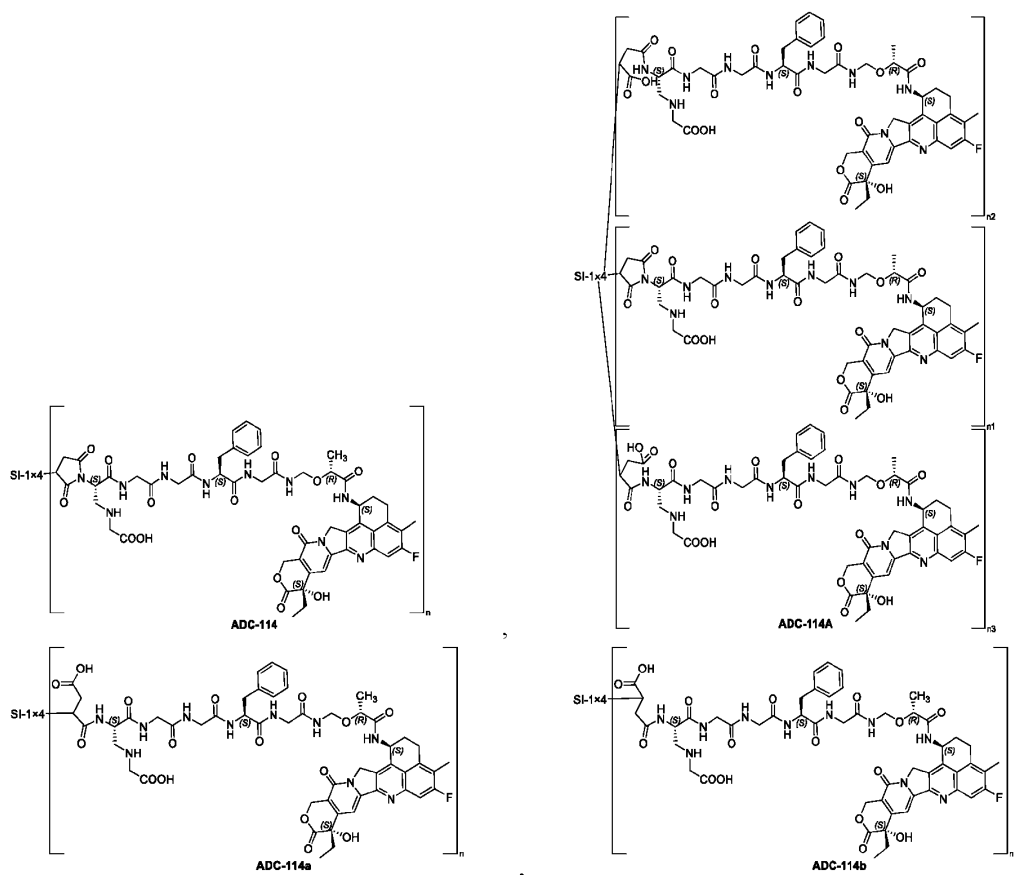


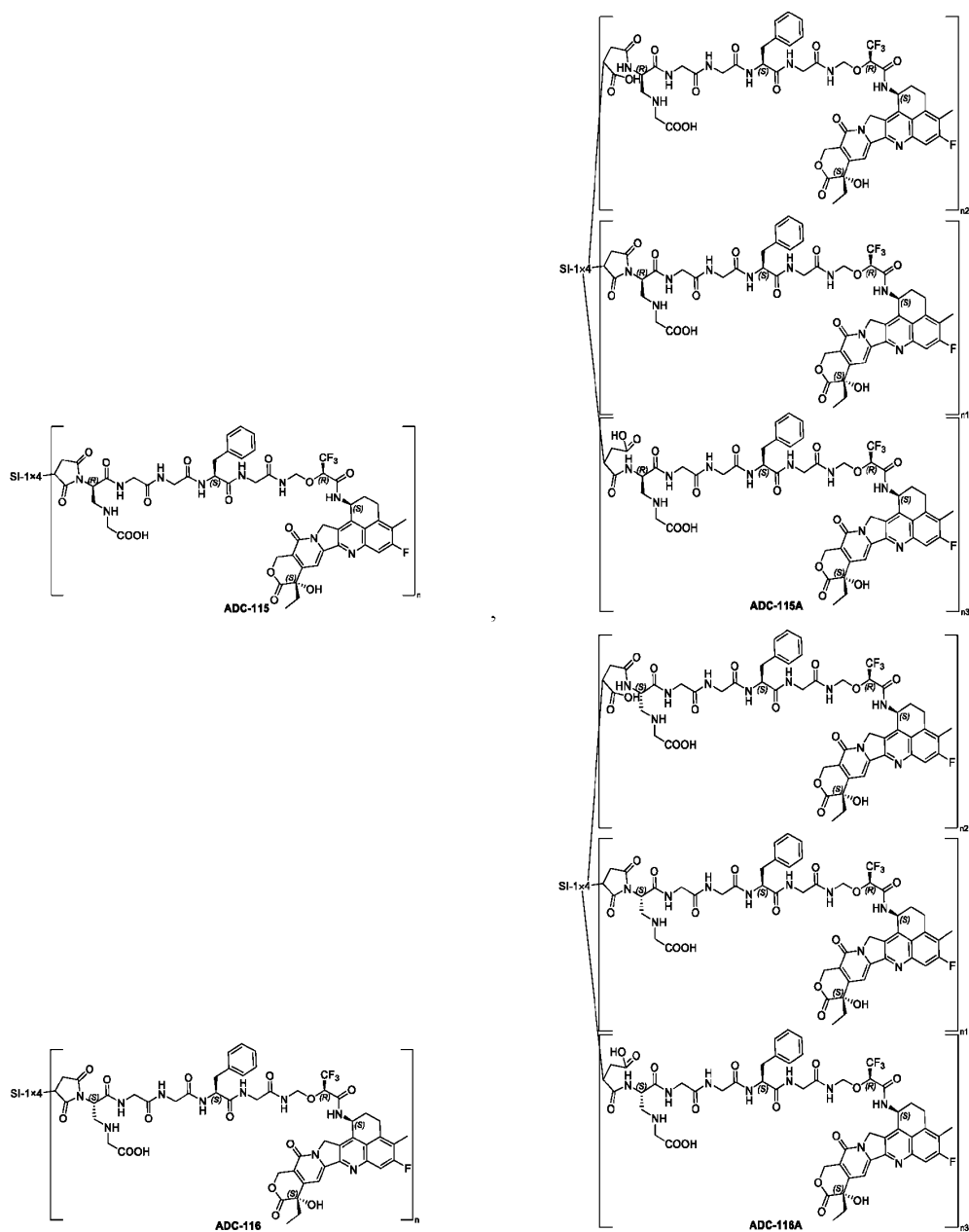


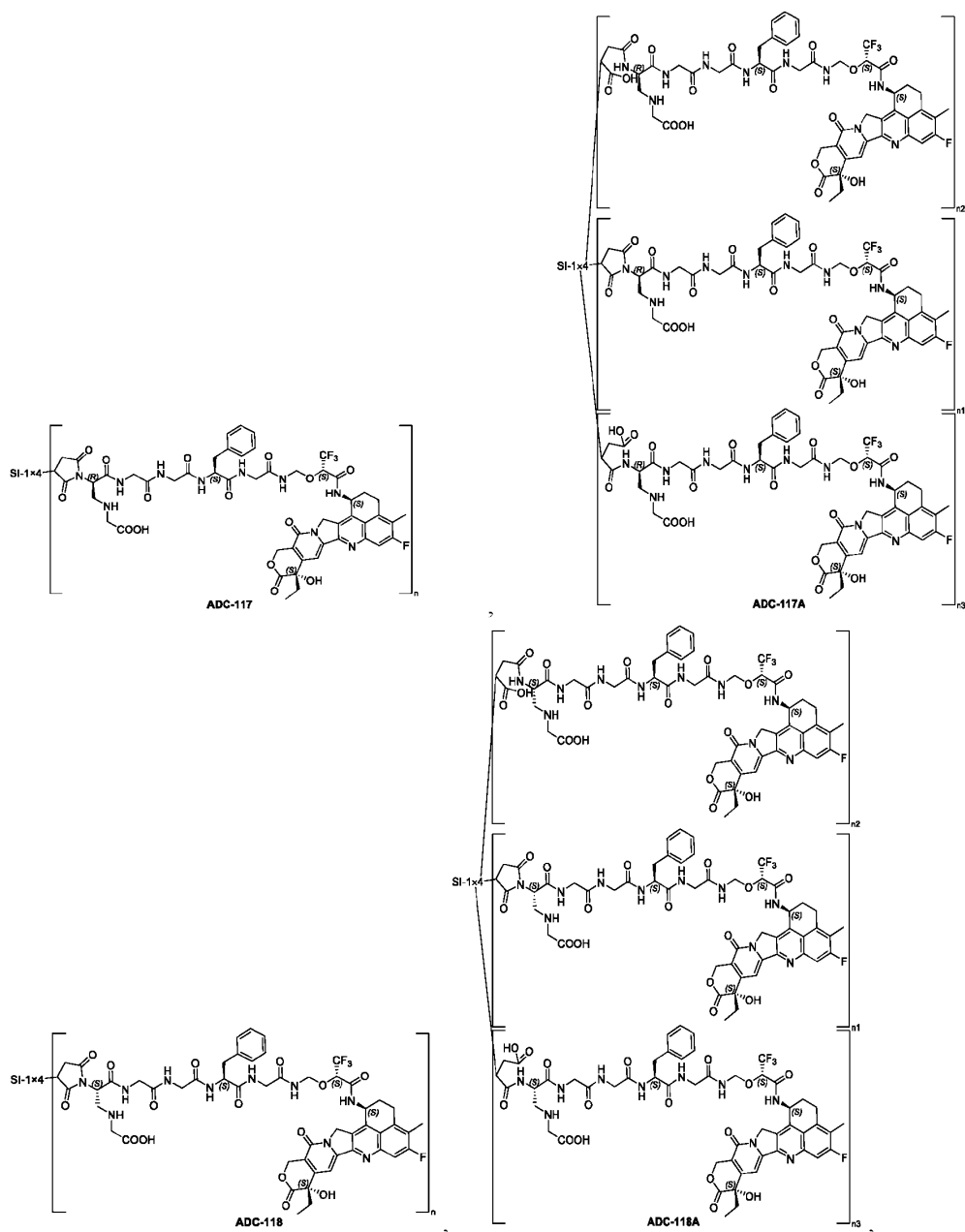


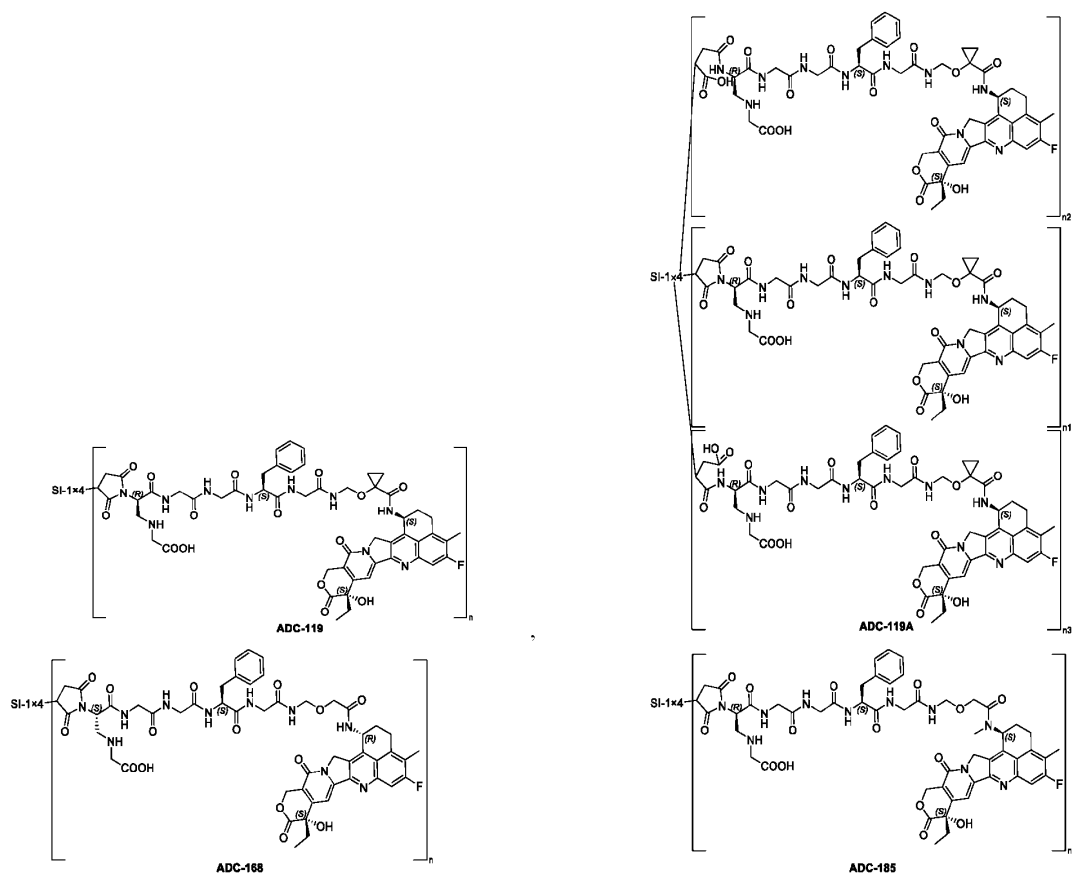


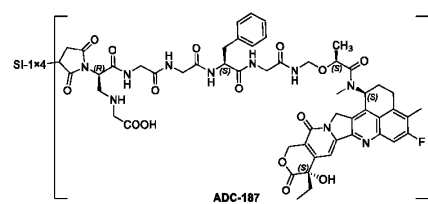
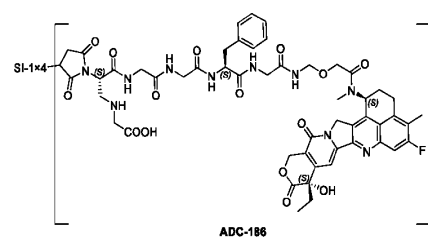
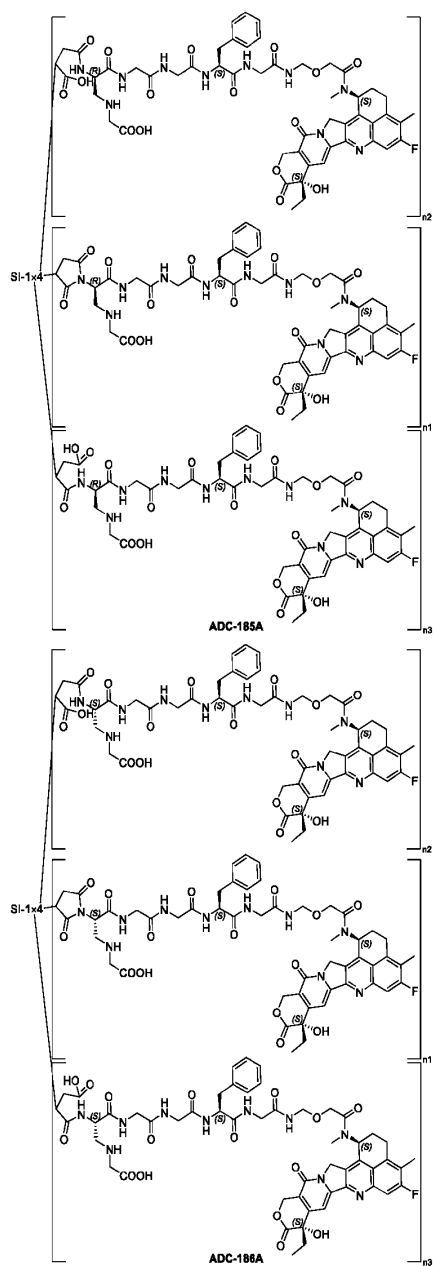




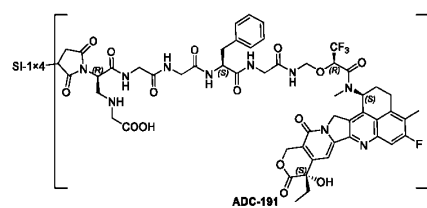
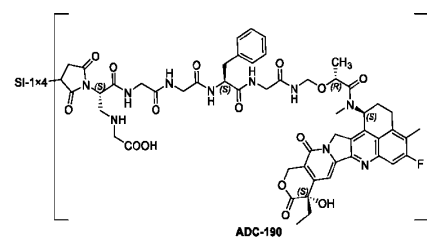
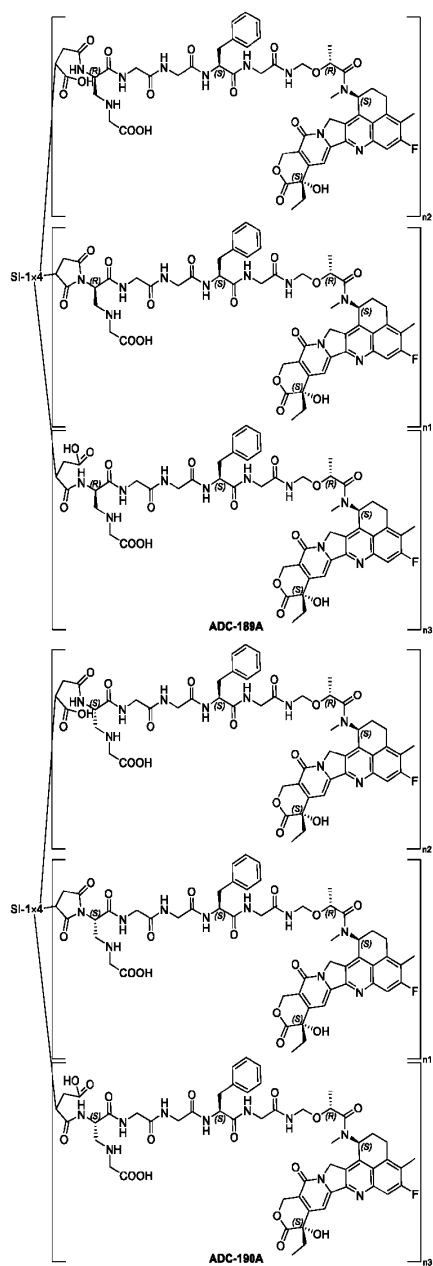


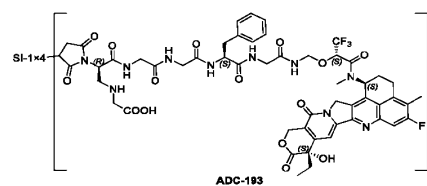
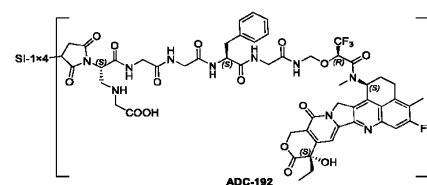
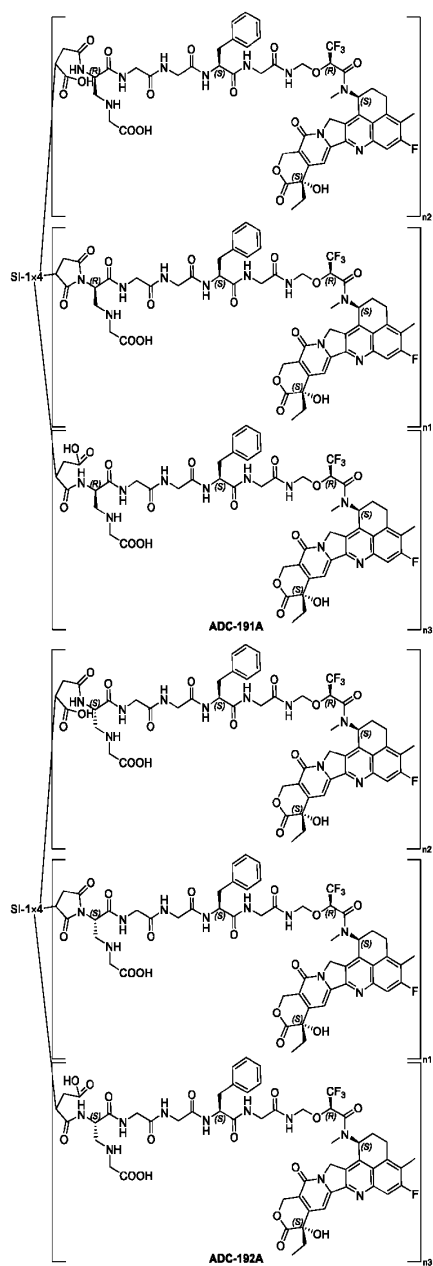


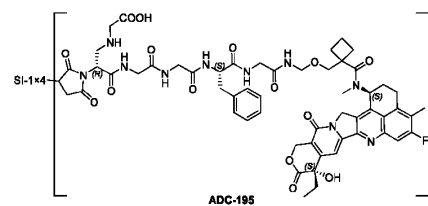
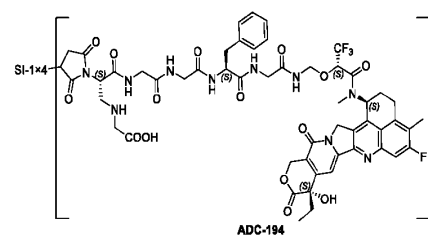
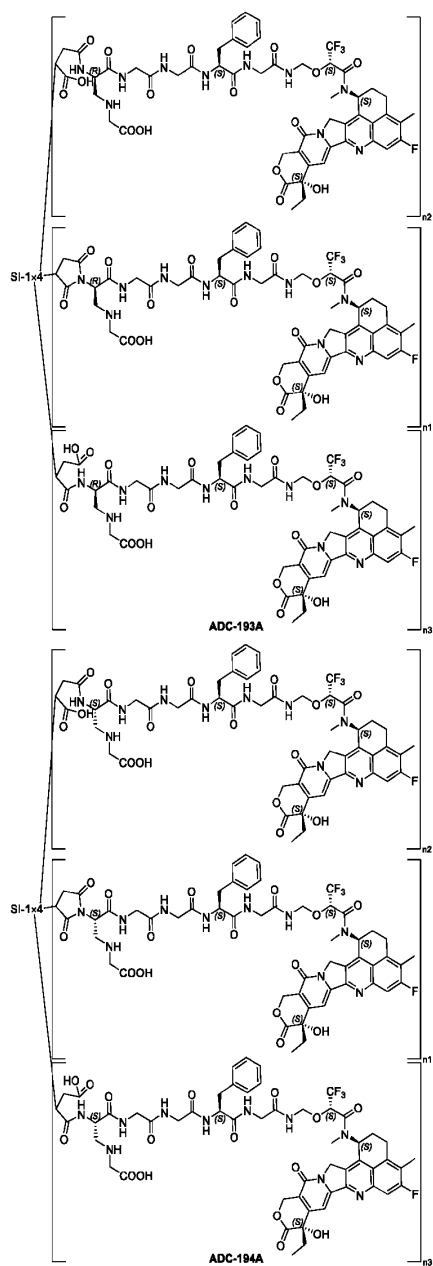


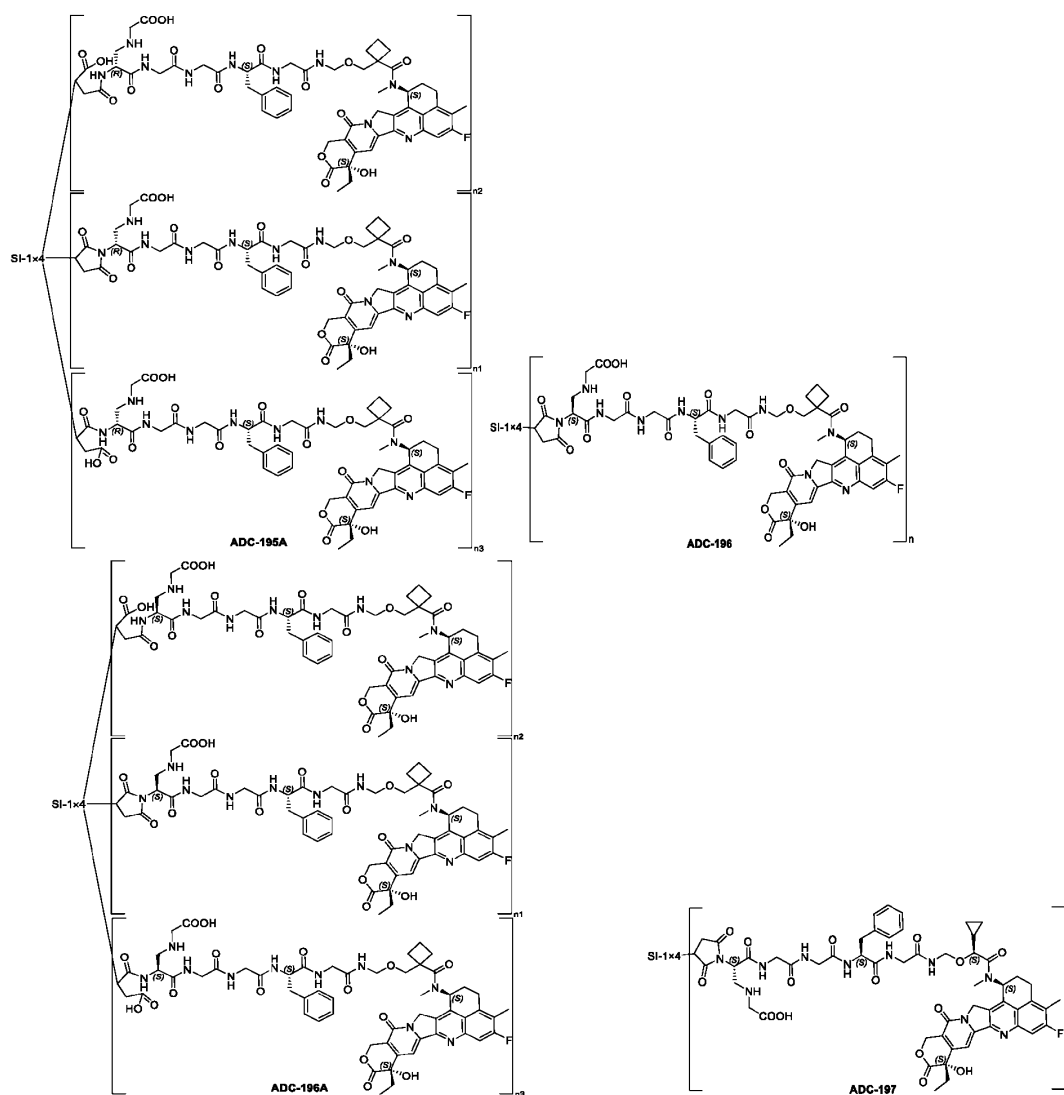


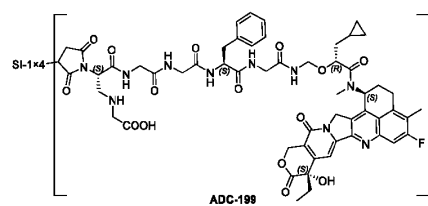
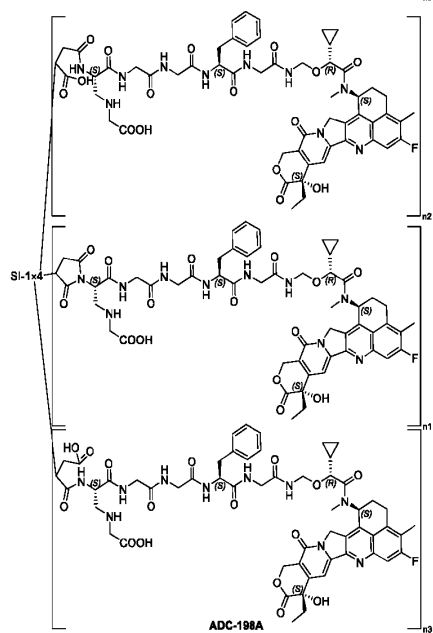
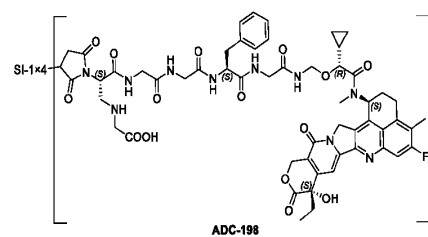
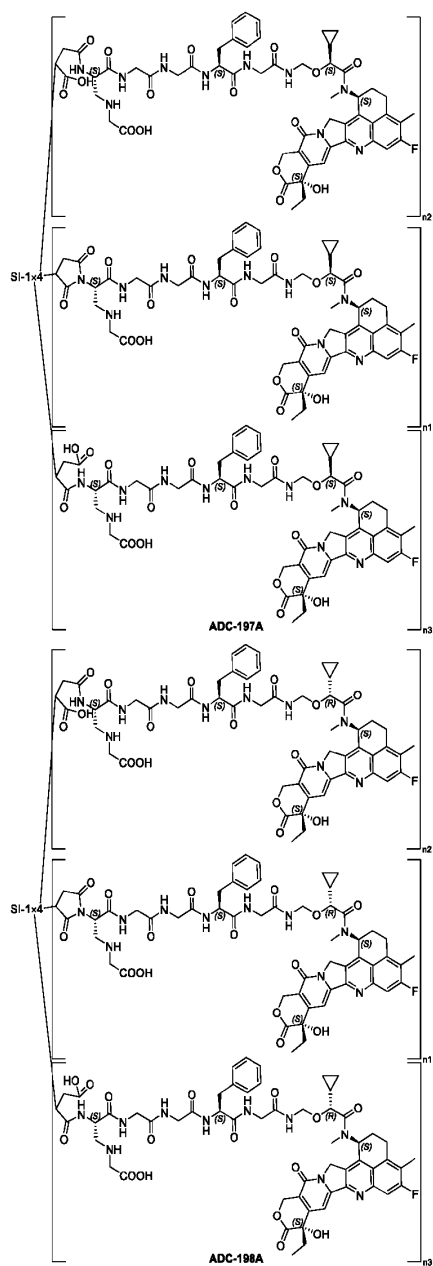


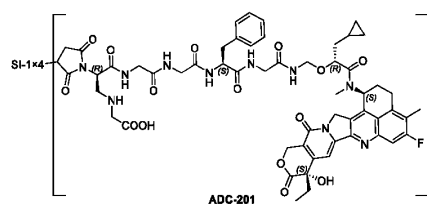
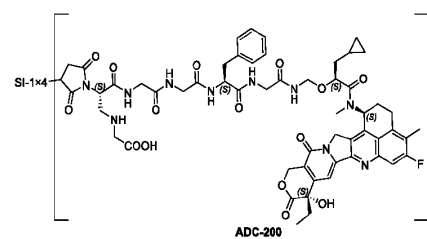
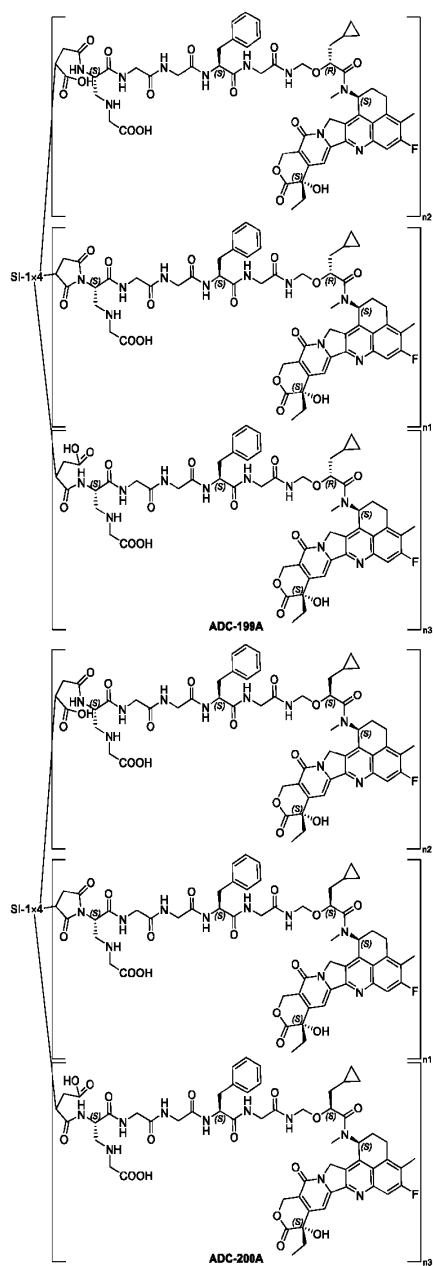




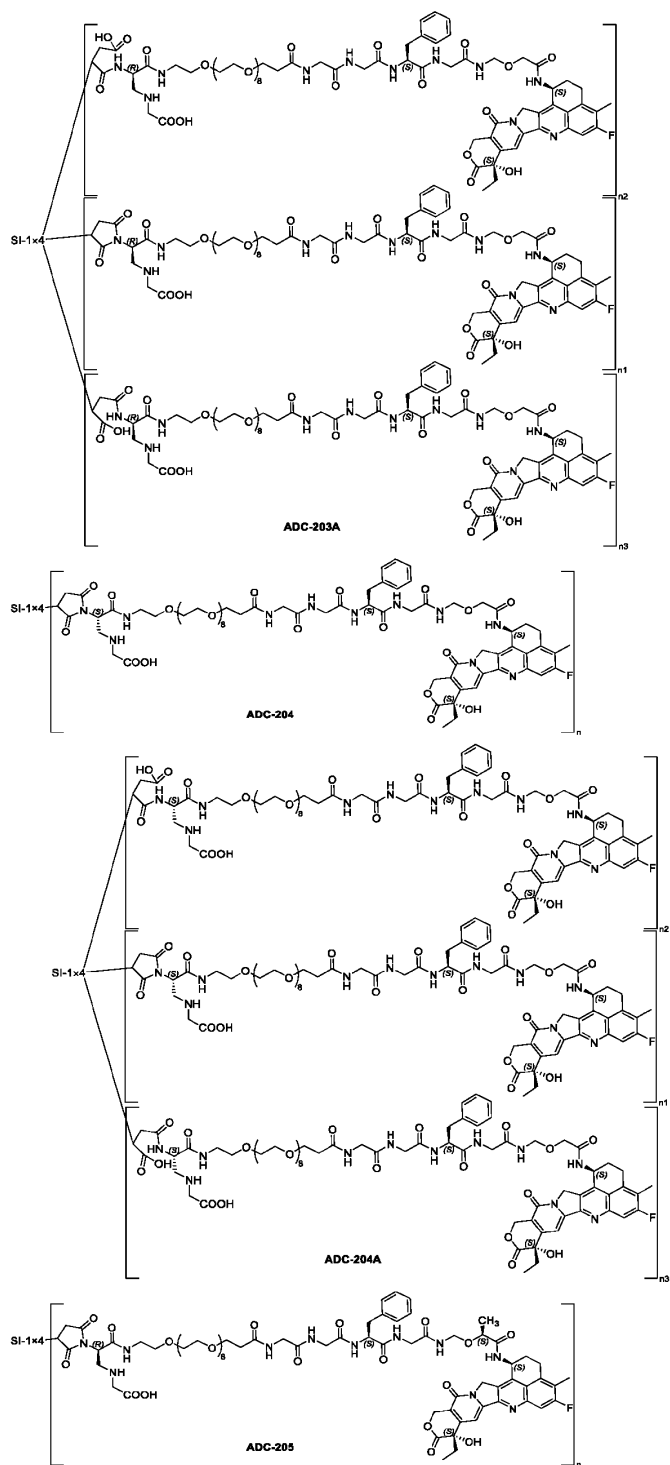


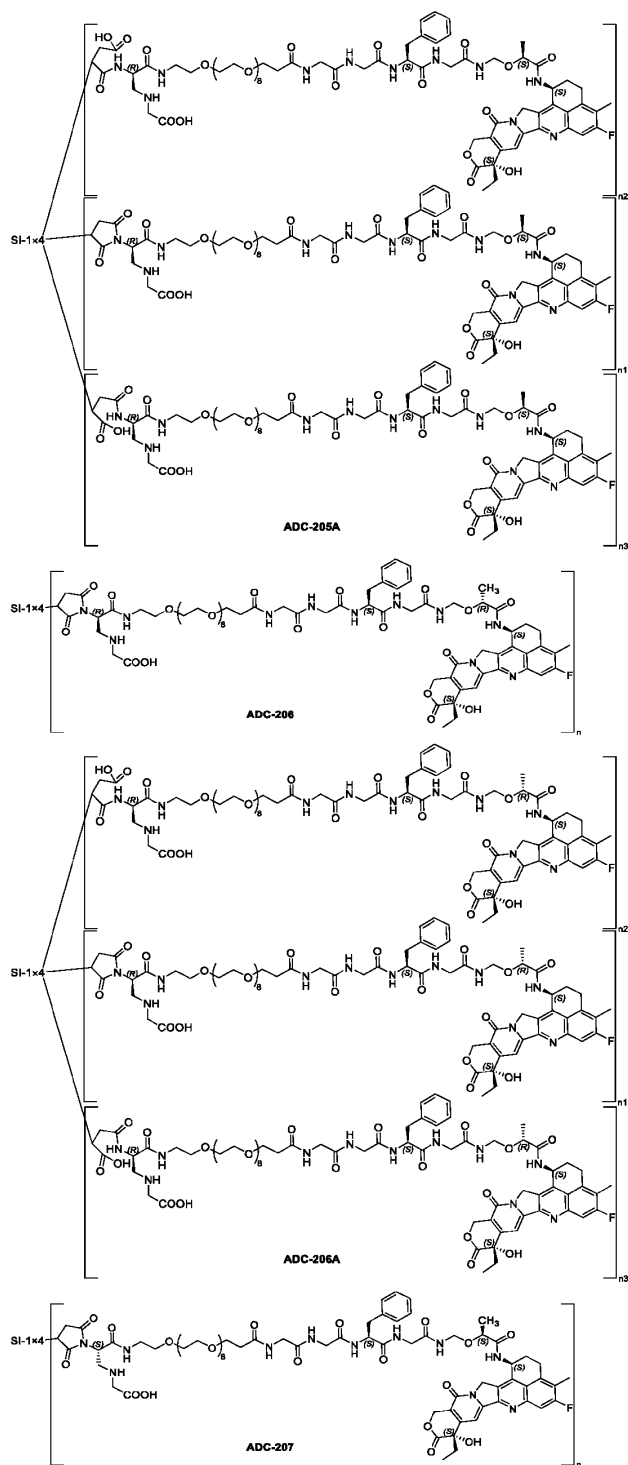


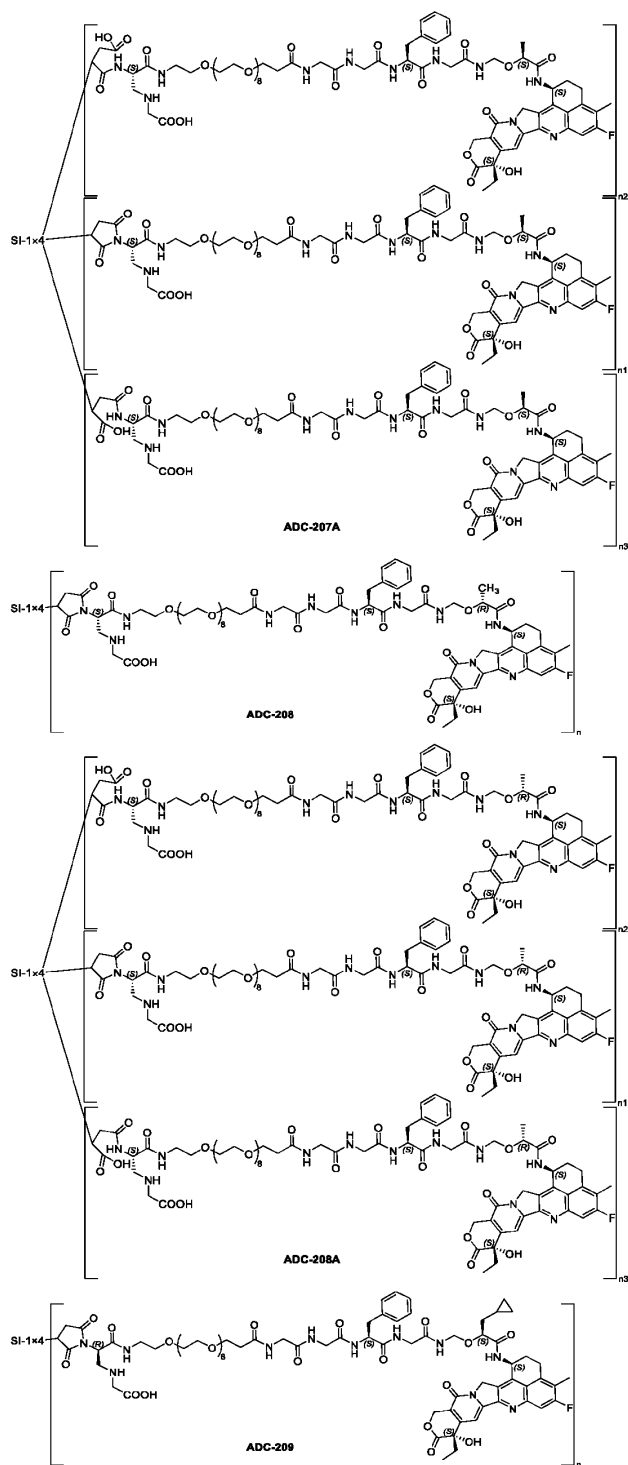


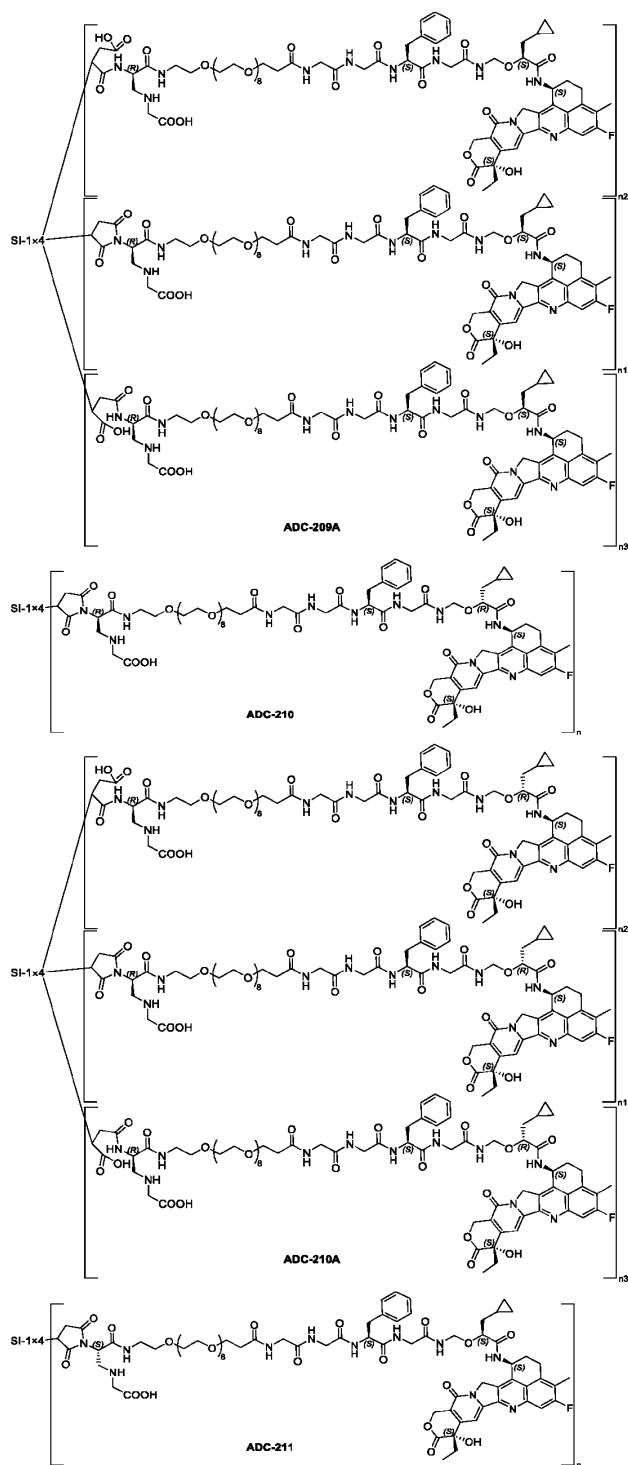


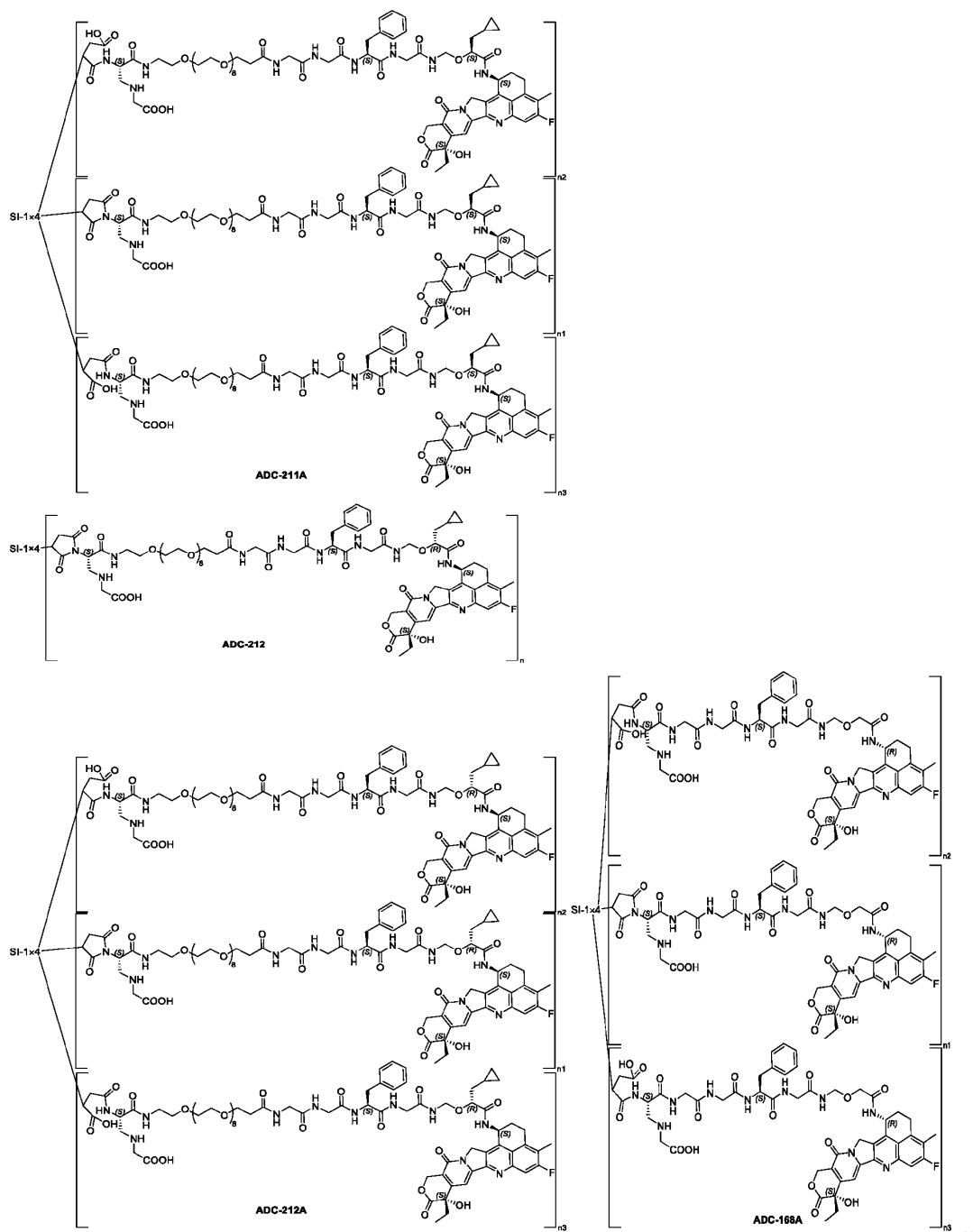


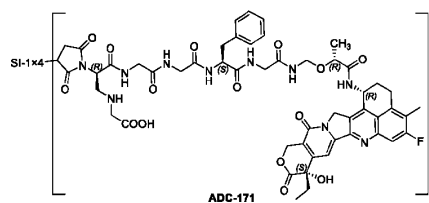
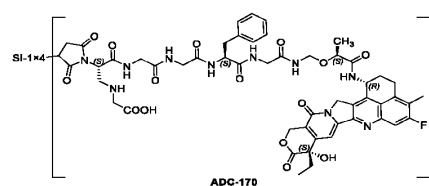
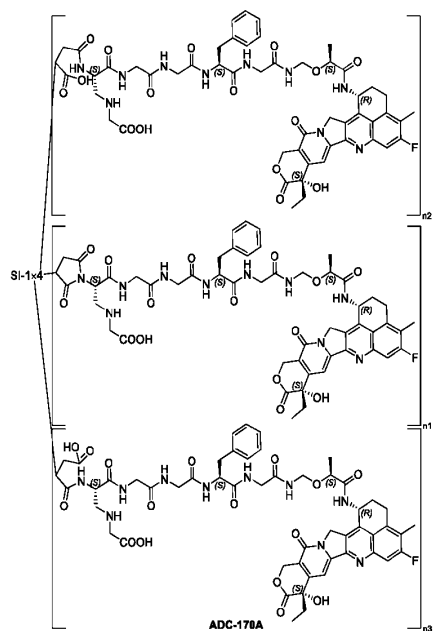
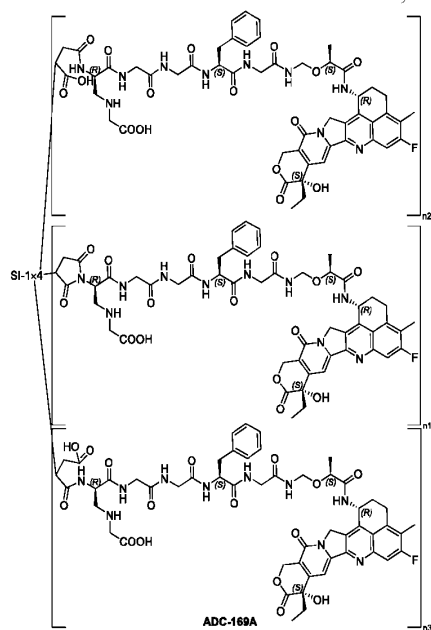
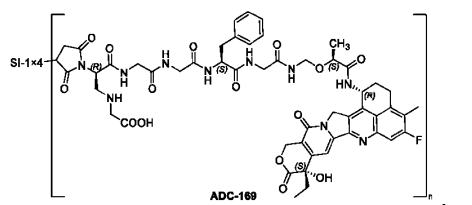


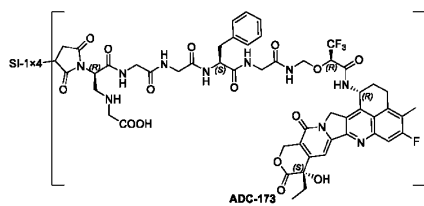
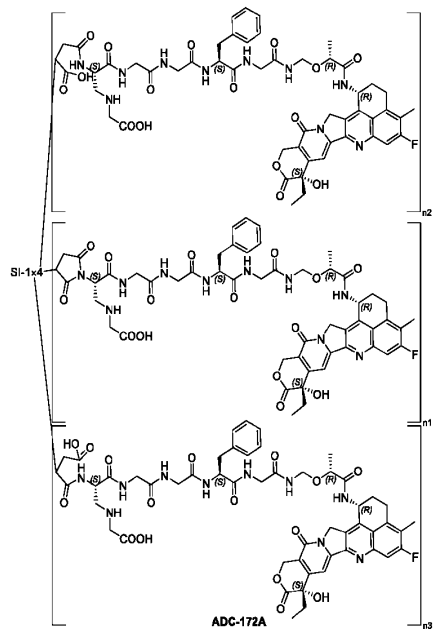
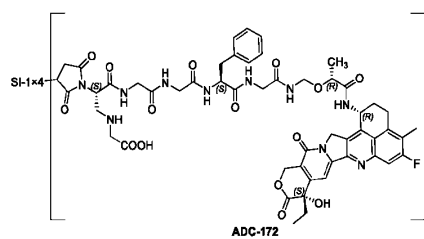
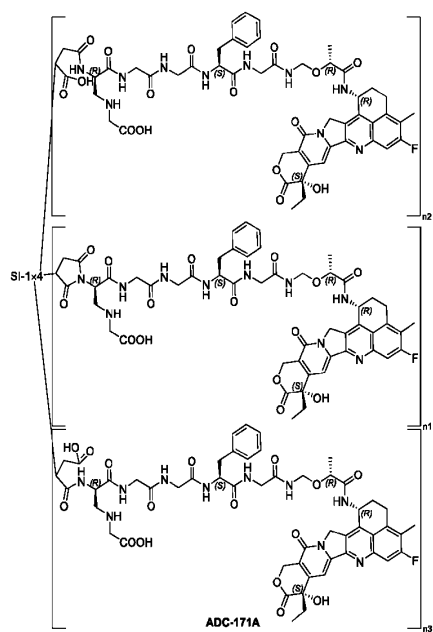


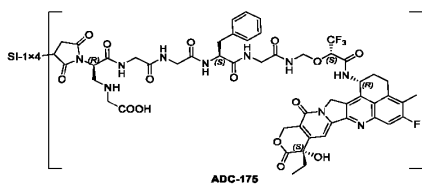
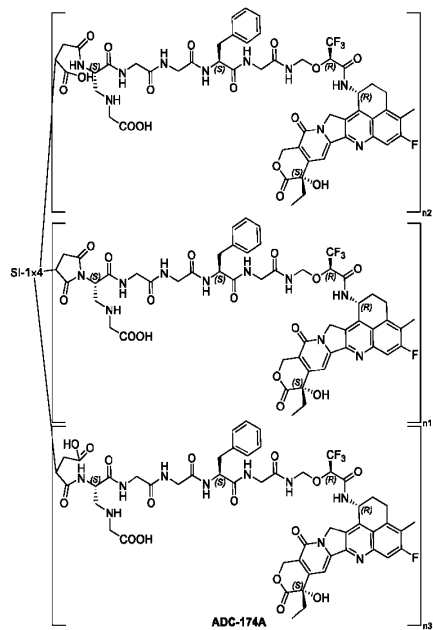
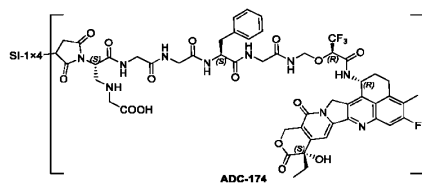
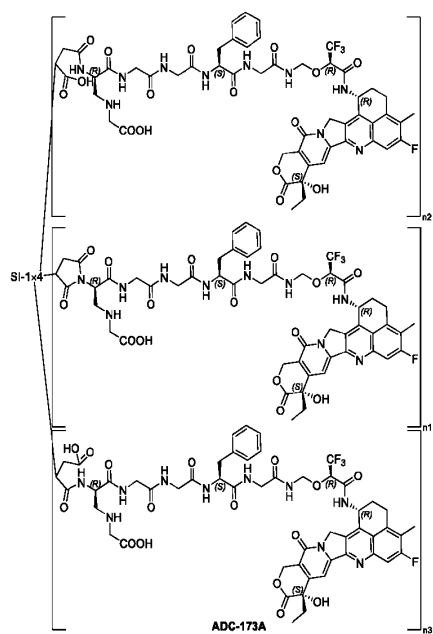


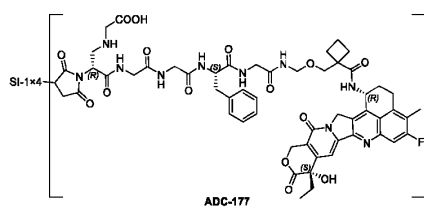
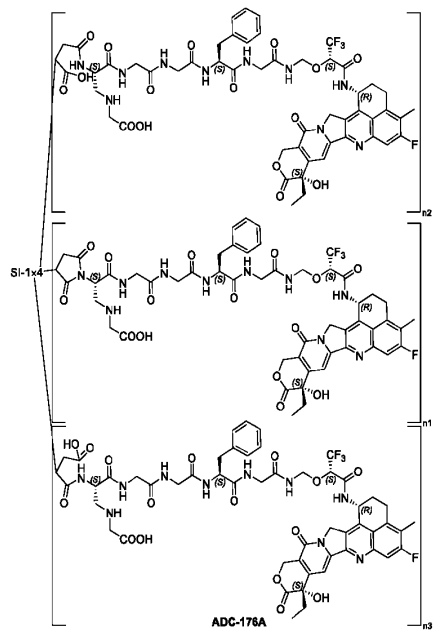
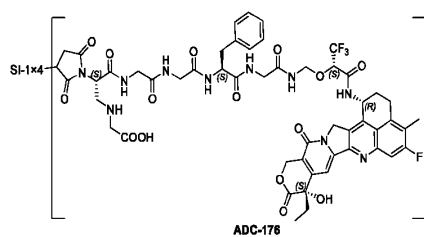
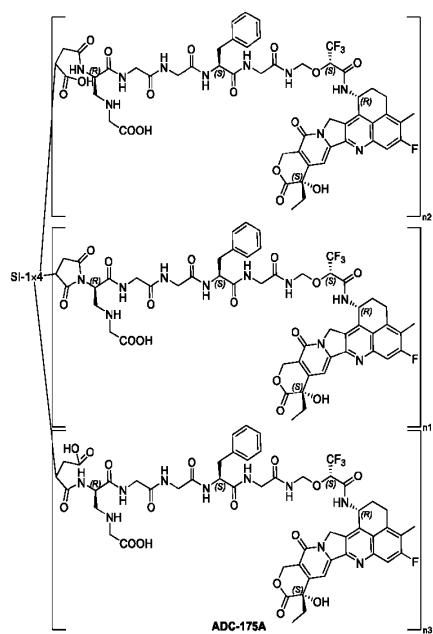


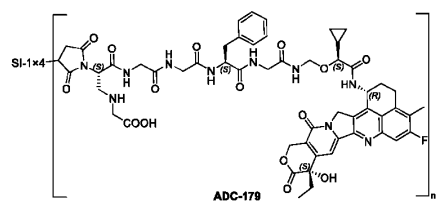
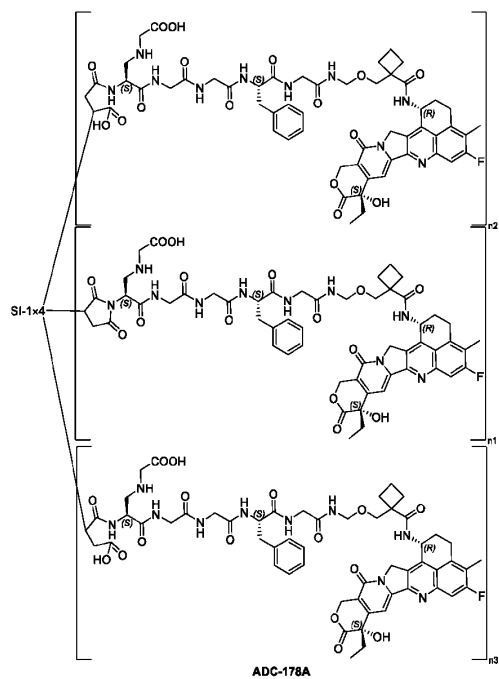
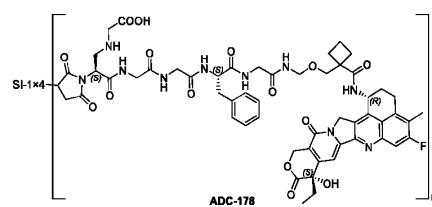
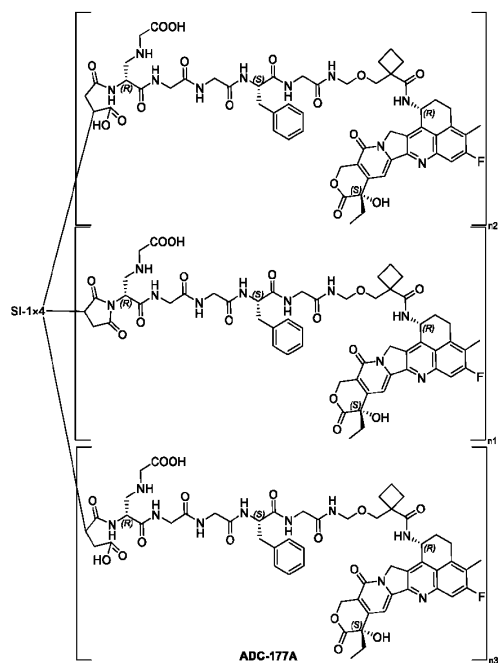


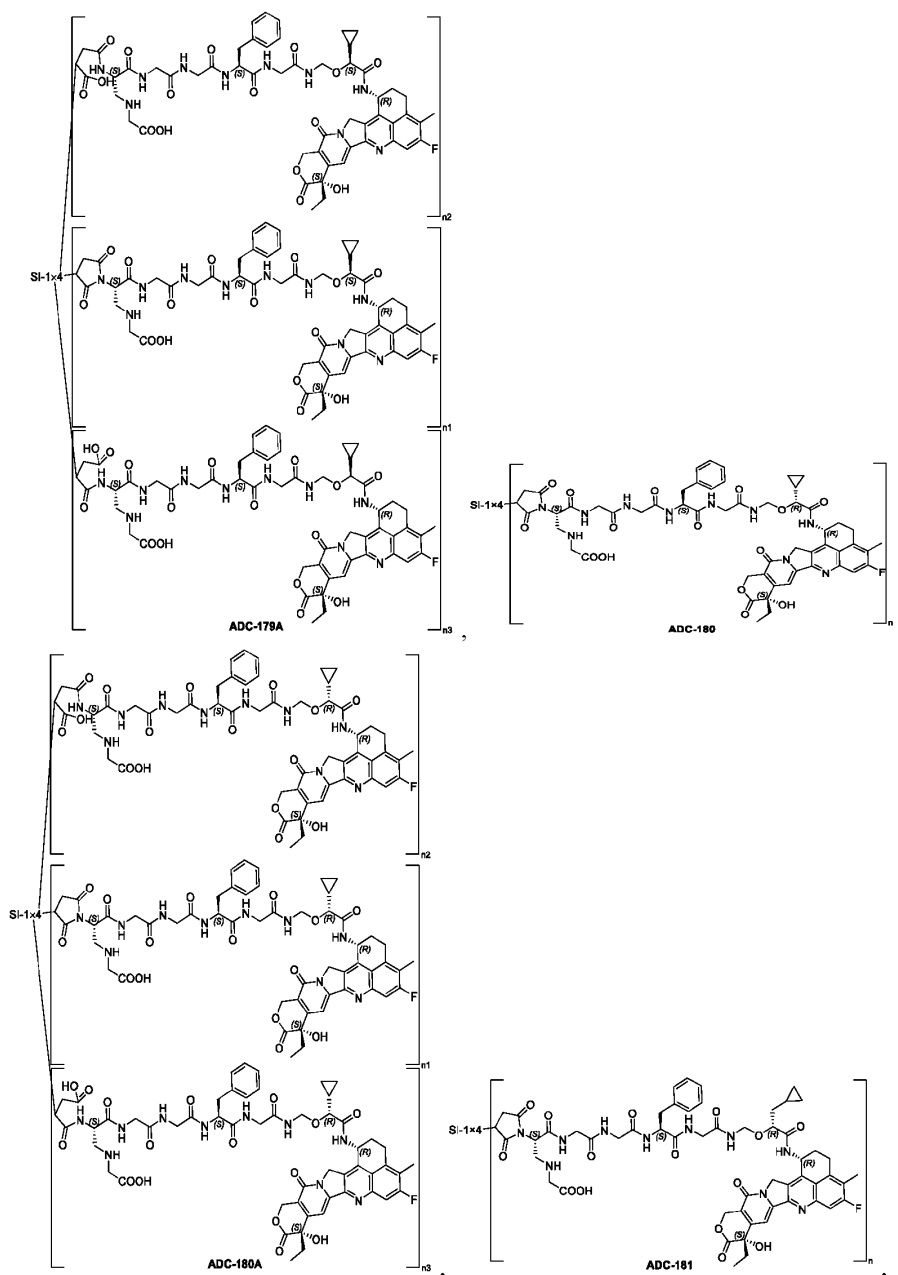


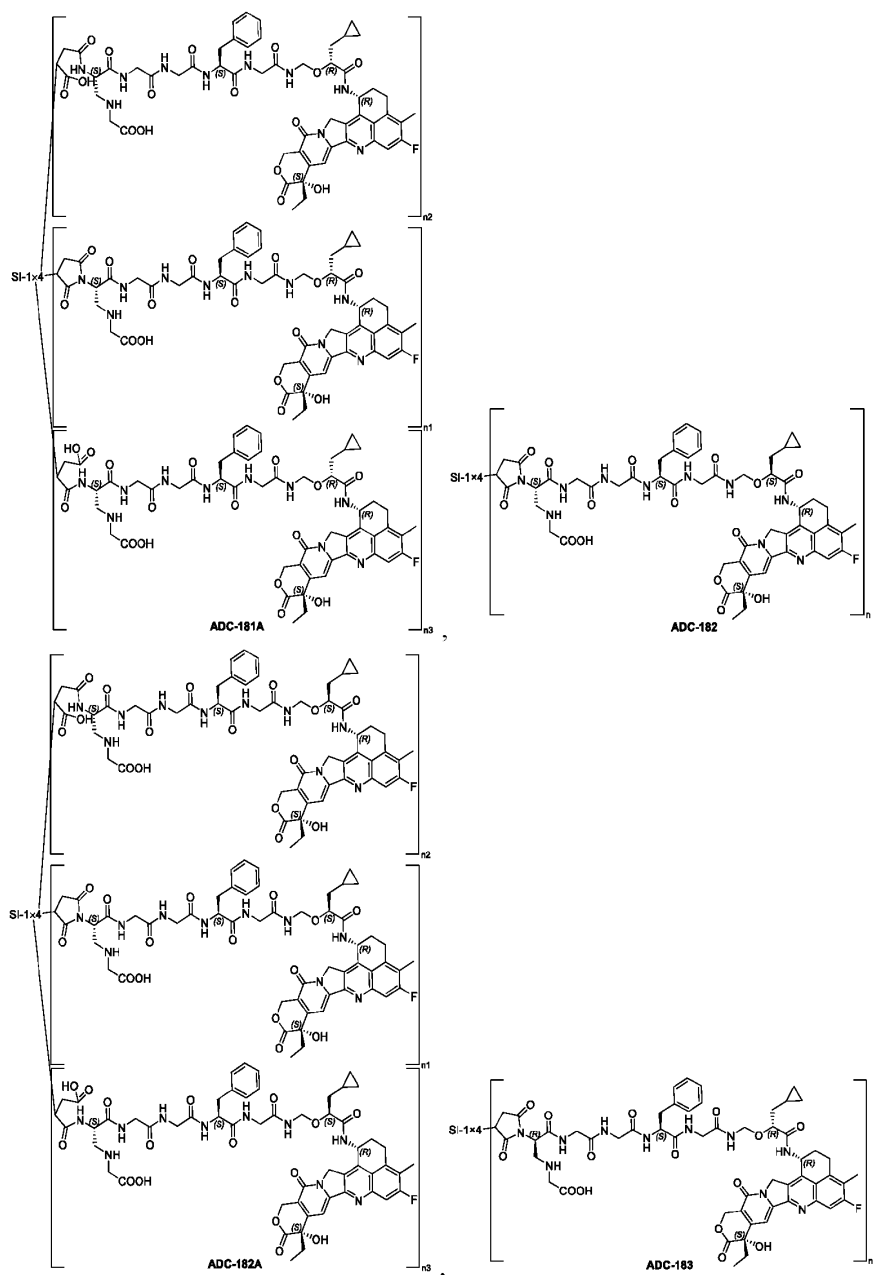


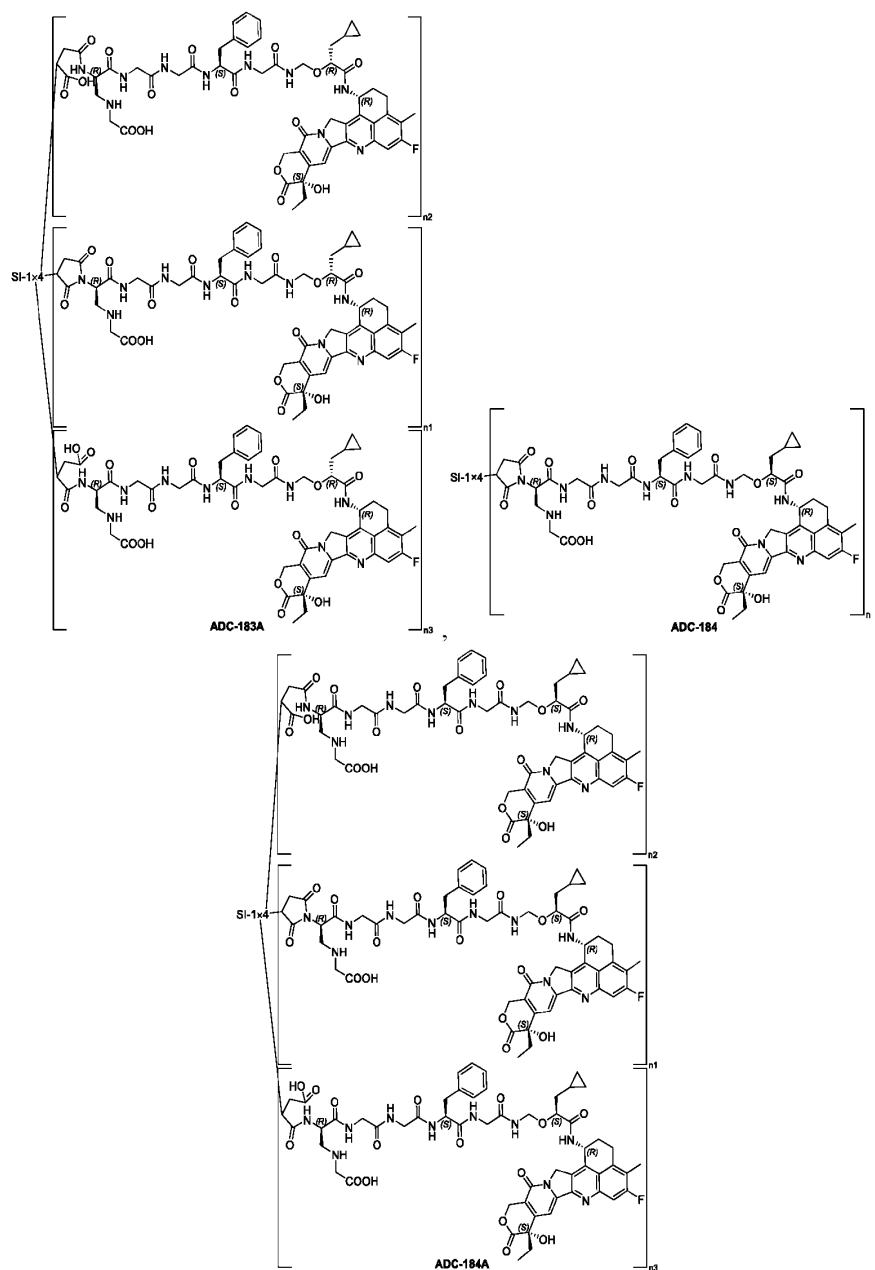










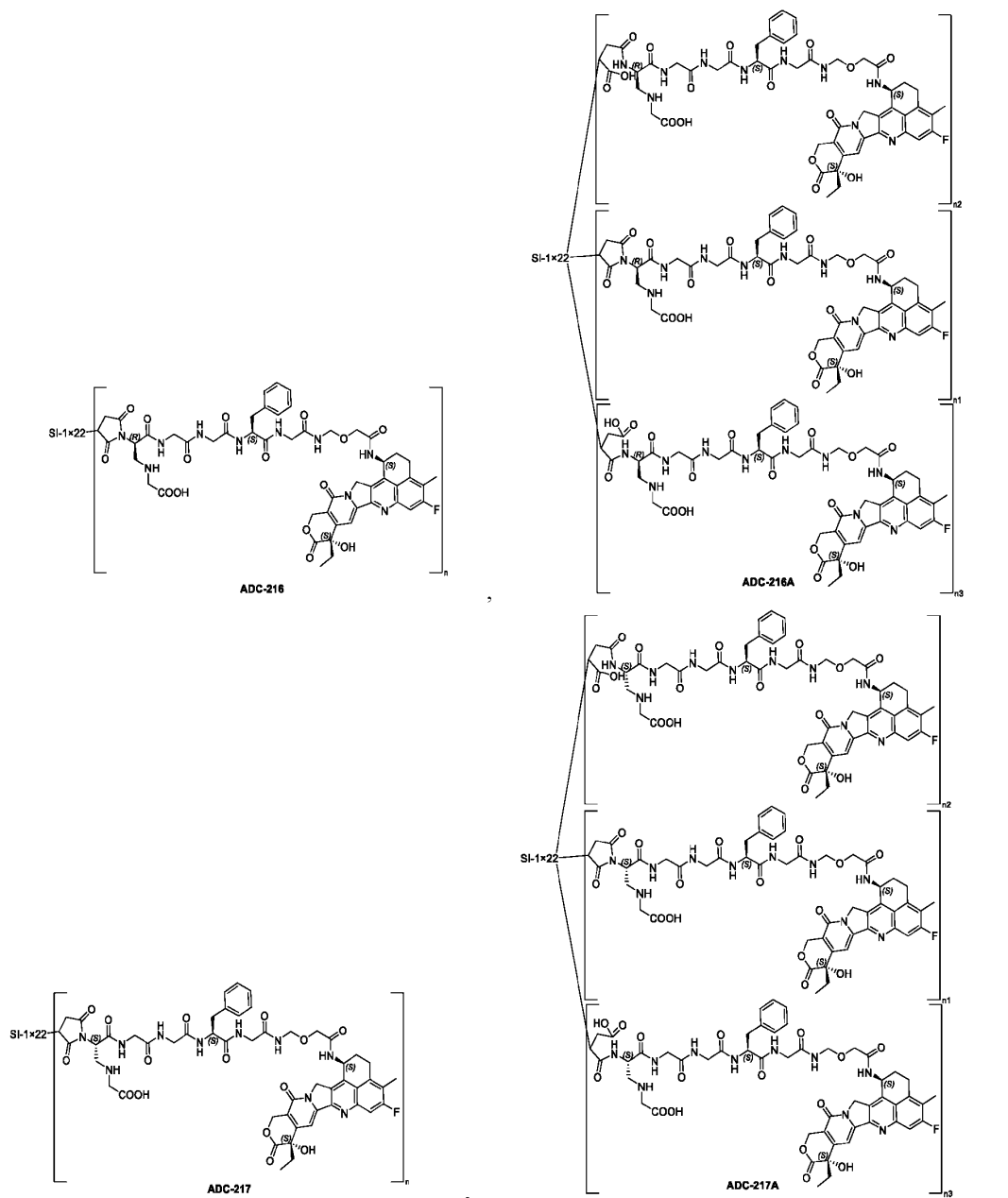


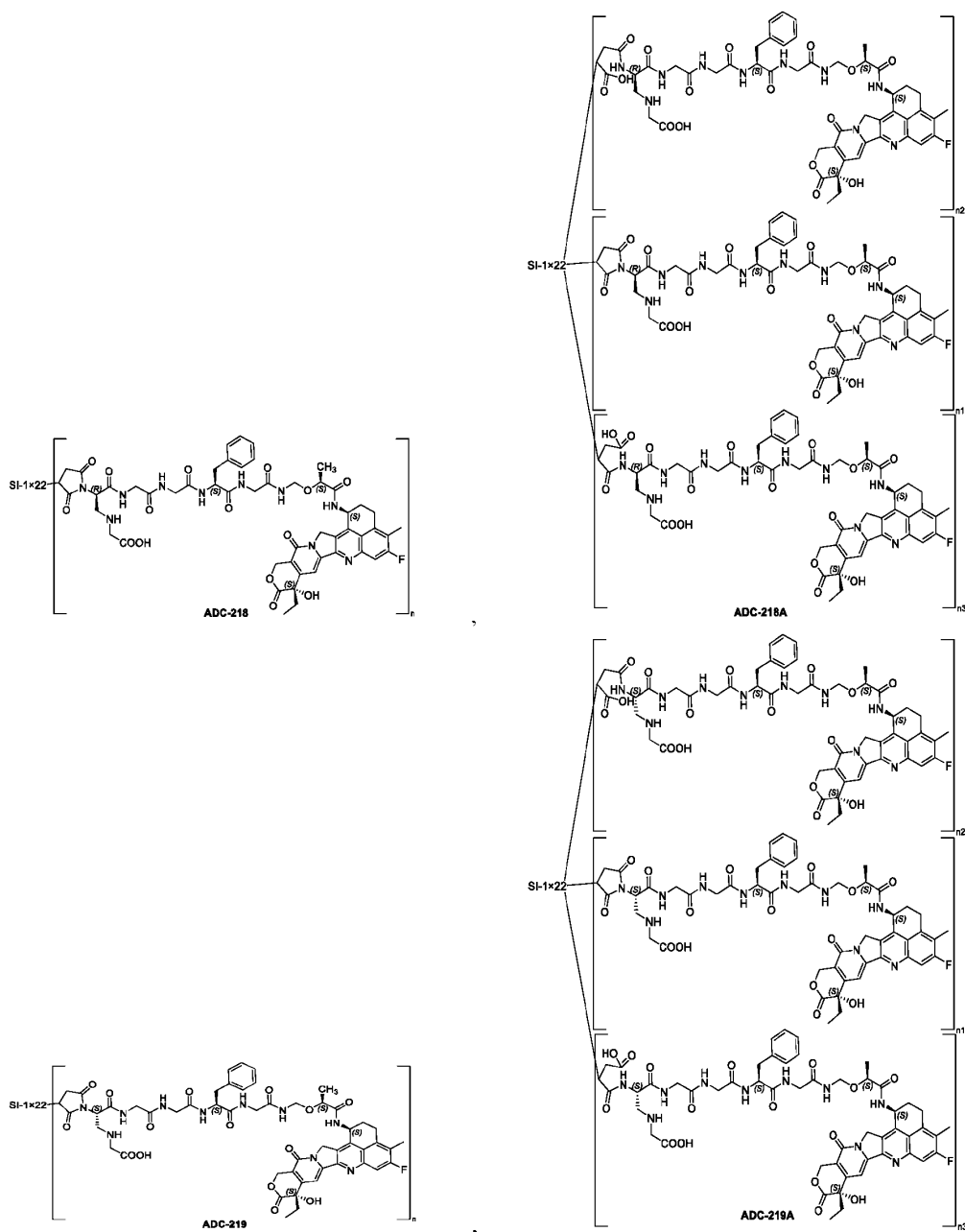
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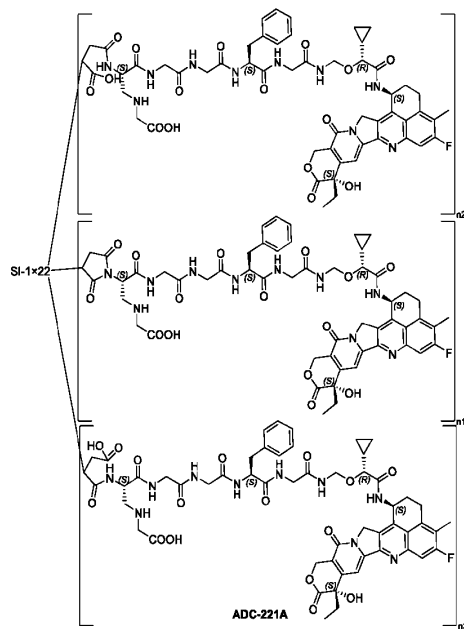
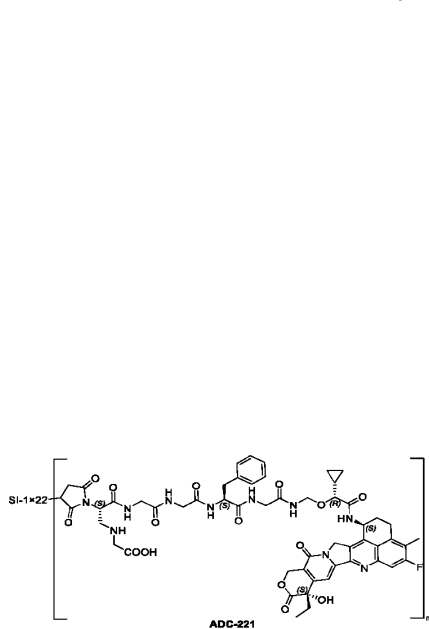
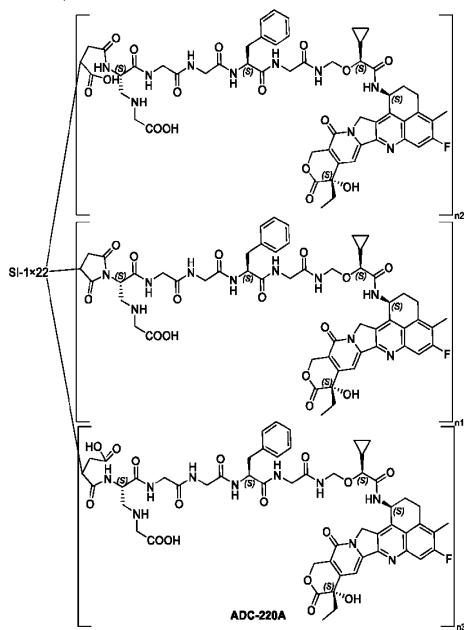
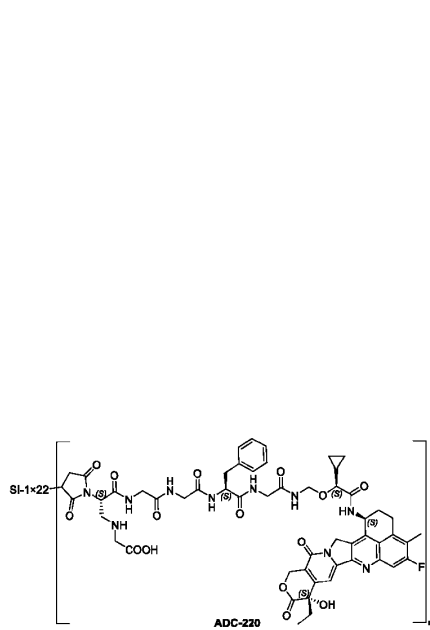
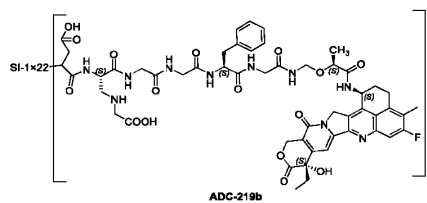
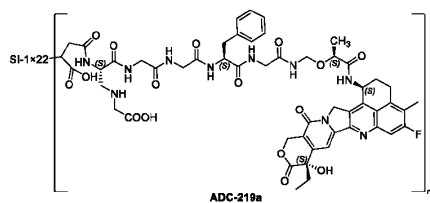
SI-1 x 4 is a bispecific antibody or antigen-binding fragment thereof having a binding specificity to both EGFR and HER3,

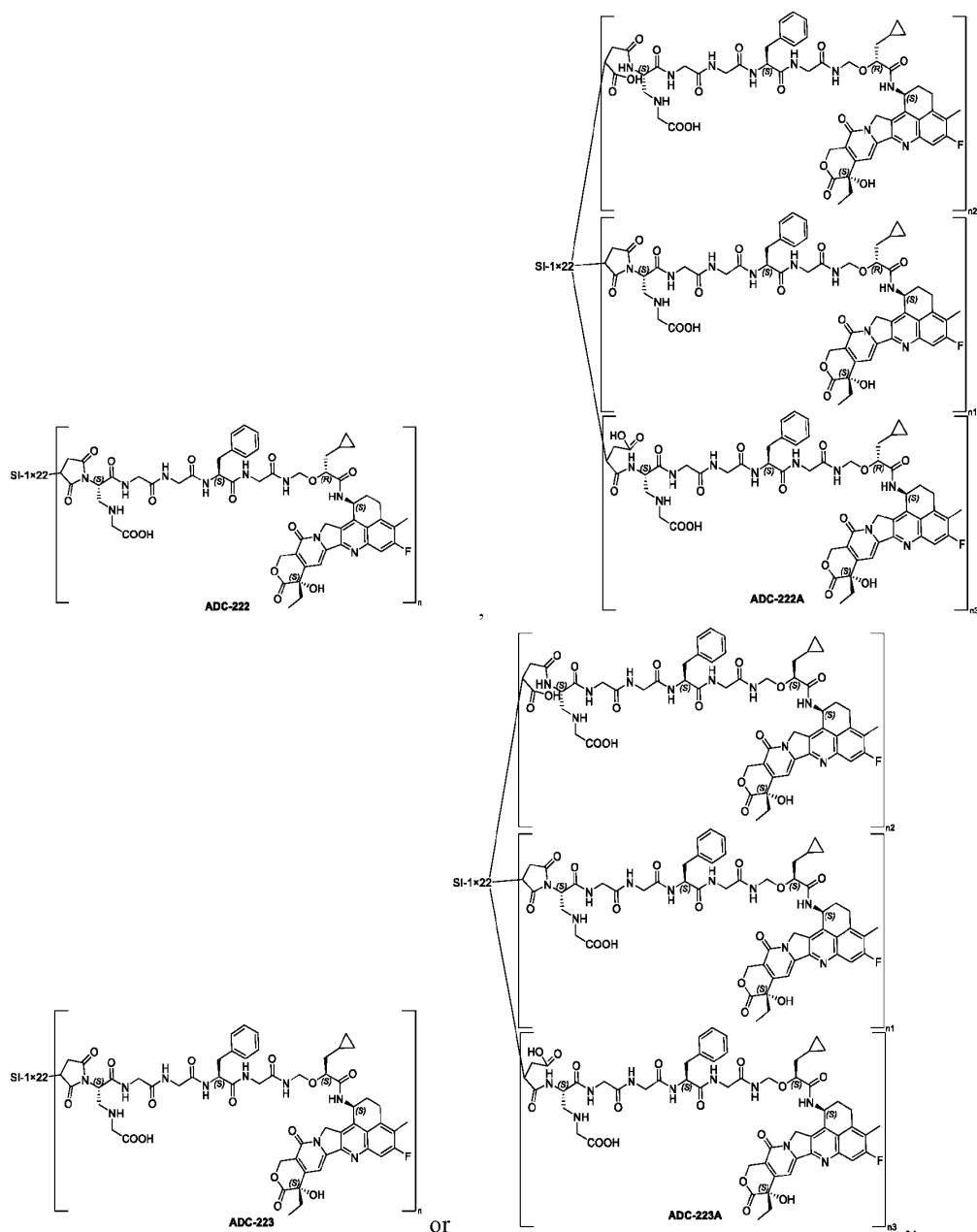
n is an integer of 1-10, wherein n_1 , n_2 , and n_3 are each independently chosen from any integer or any decimal number from 0-10, n_1 , n_2 , and n_3 are not simultaneously 0, and $1 \leq n_1 + n_2 + n_3 \leq 10$.

In one embodiment, the ligand-camptothecin derivative conjugate, or a pharmaceutically acceptable salt or solvate thereof, comprises the following structure, or a butanediimide ring-opening structure thereof, or an isomer thereof:







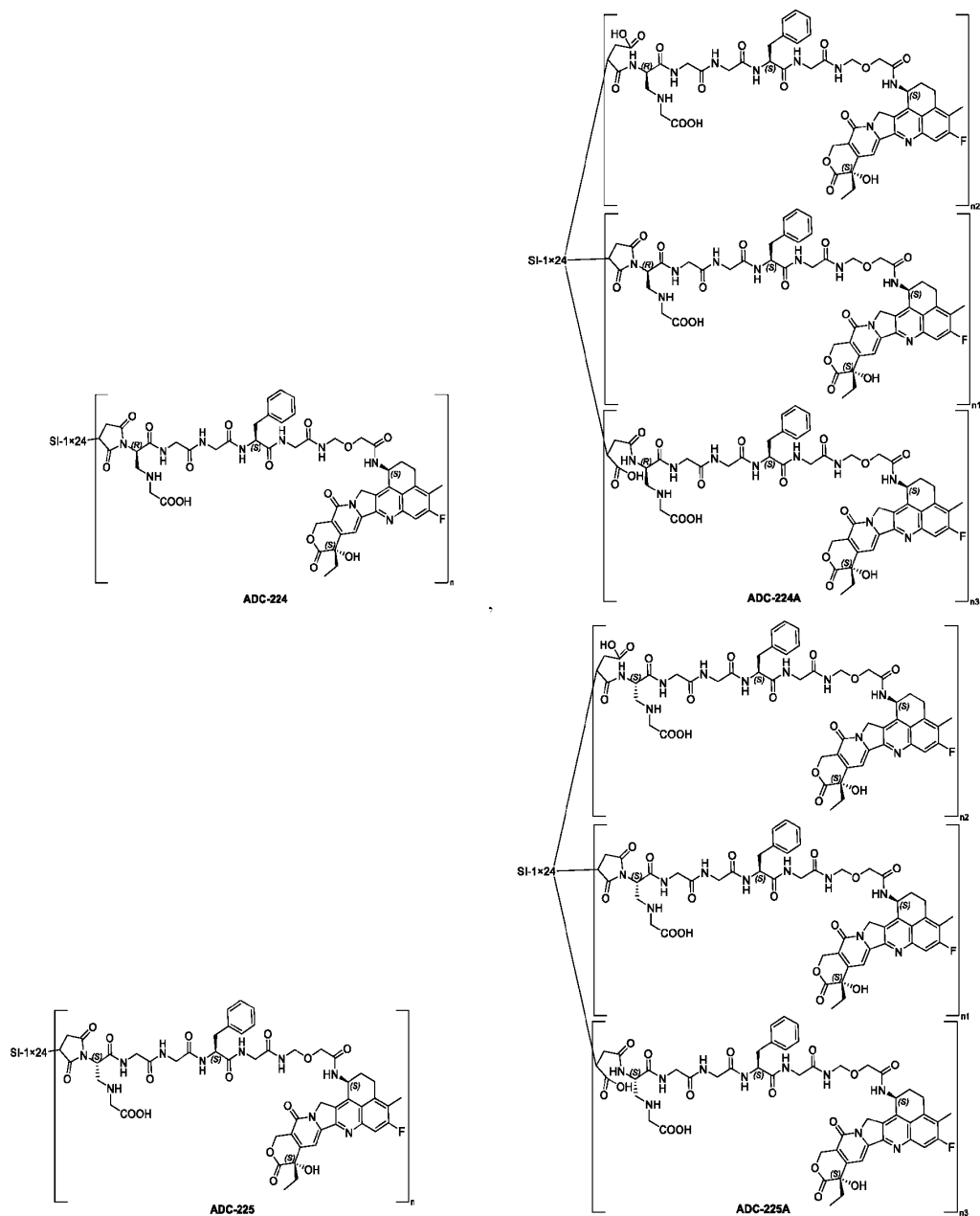


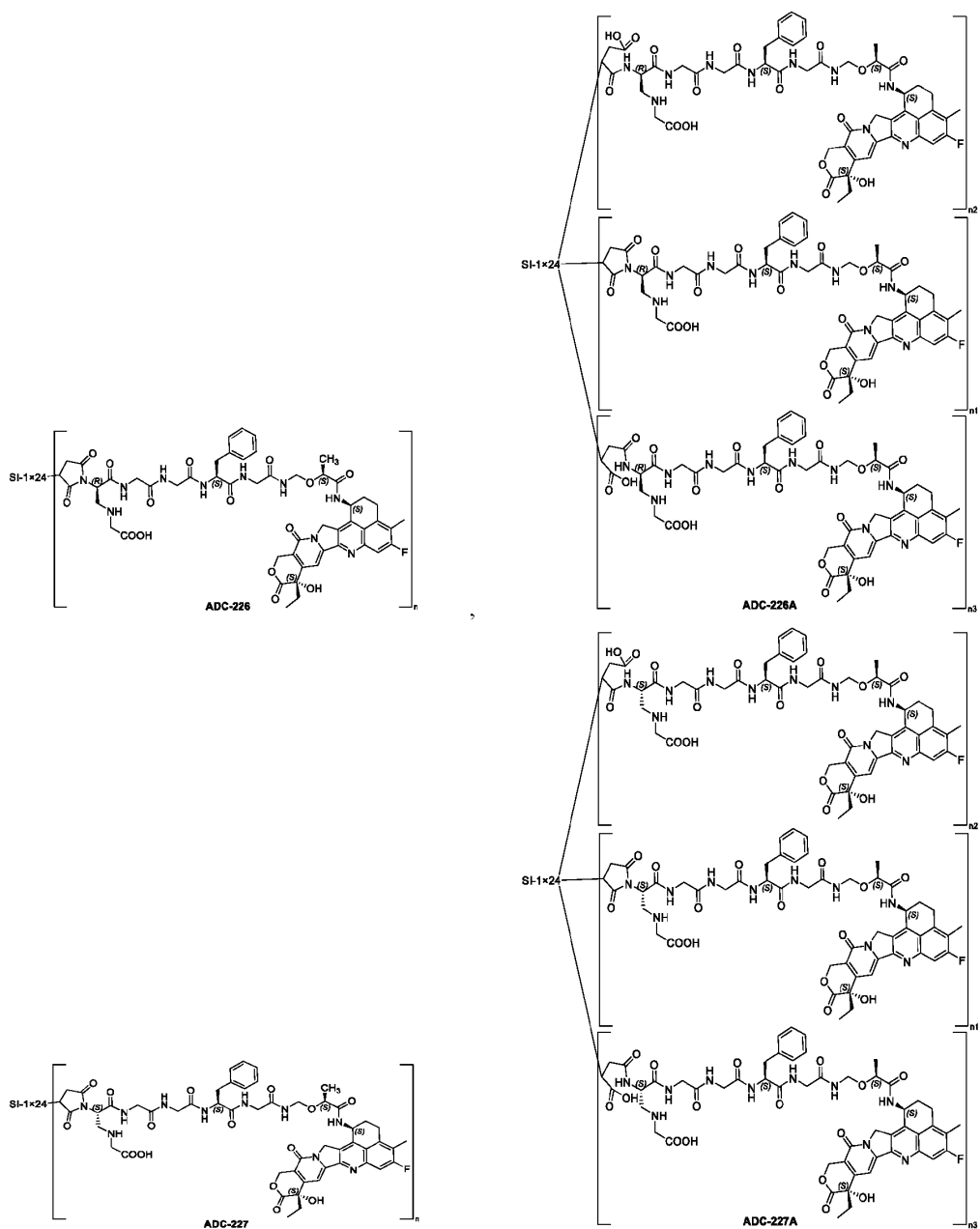
wherein:

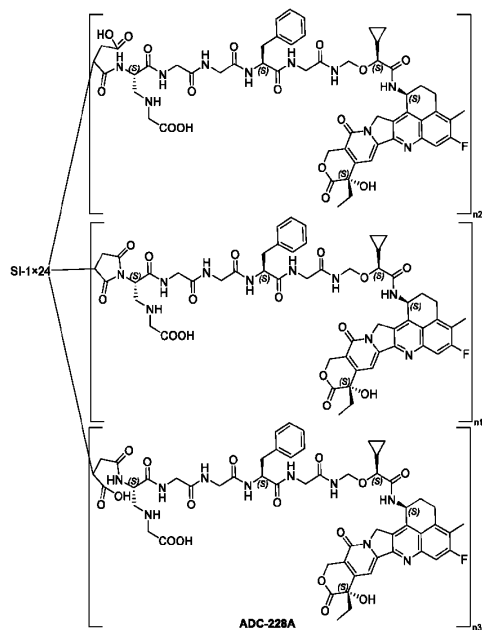
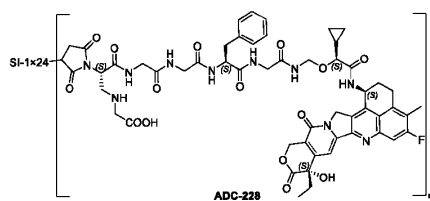
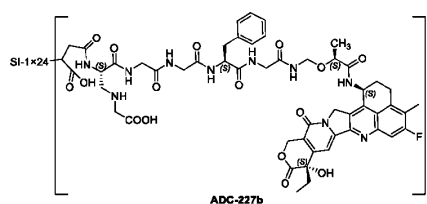
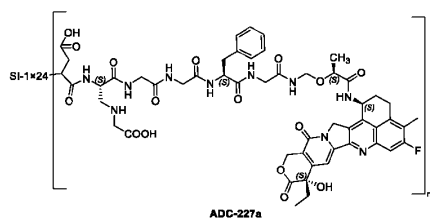
SI-1 x 22 is a bispecific antibody or antigen-binding fragment thereof having a binding specificity to both EGFR and HER3;

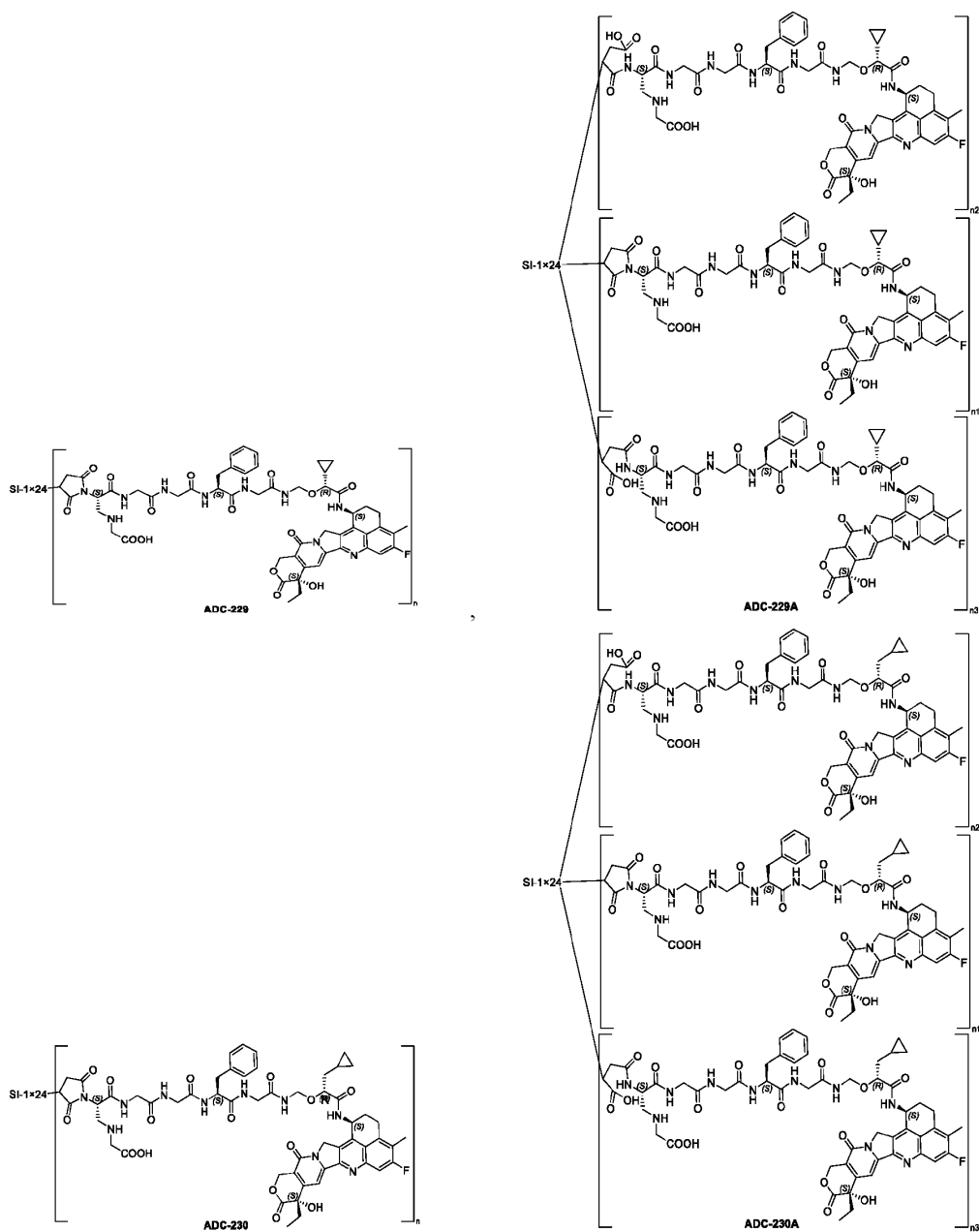
n is an integer of 1-10, wherein n1, n2, and n3 are each independently chosen from any integer or any decimal number from 0-10, n1, n2, and n3 are not simultaneously 0, and $1 \leq n1 + n2 + n3 \leq 10$.

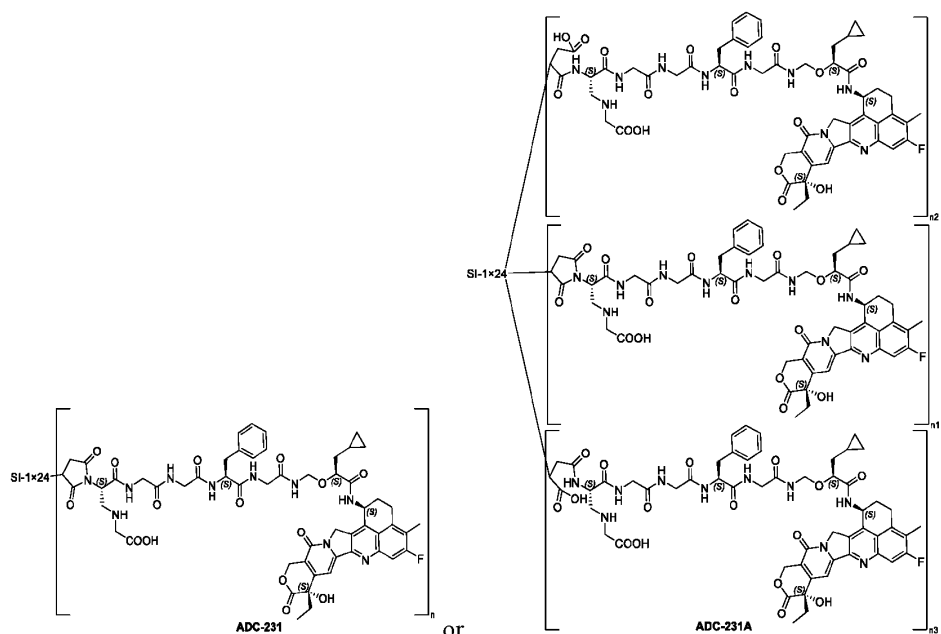
In one embodiment, the ligand-camptothecin derivative coupling, or a pharmaceutically acceptable salt or solvate thereof, comprises the following structure, or a butanediimide ring-opening structure thereof, or an isomer thereof:









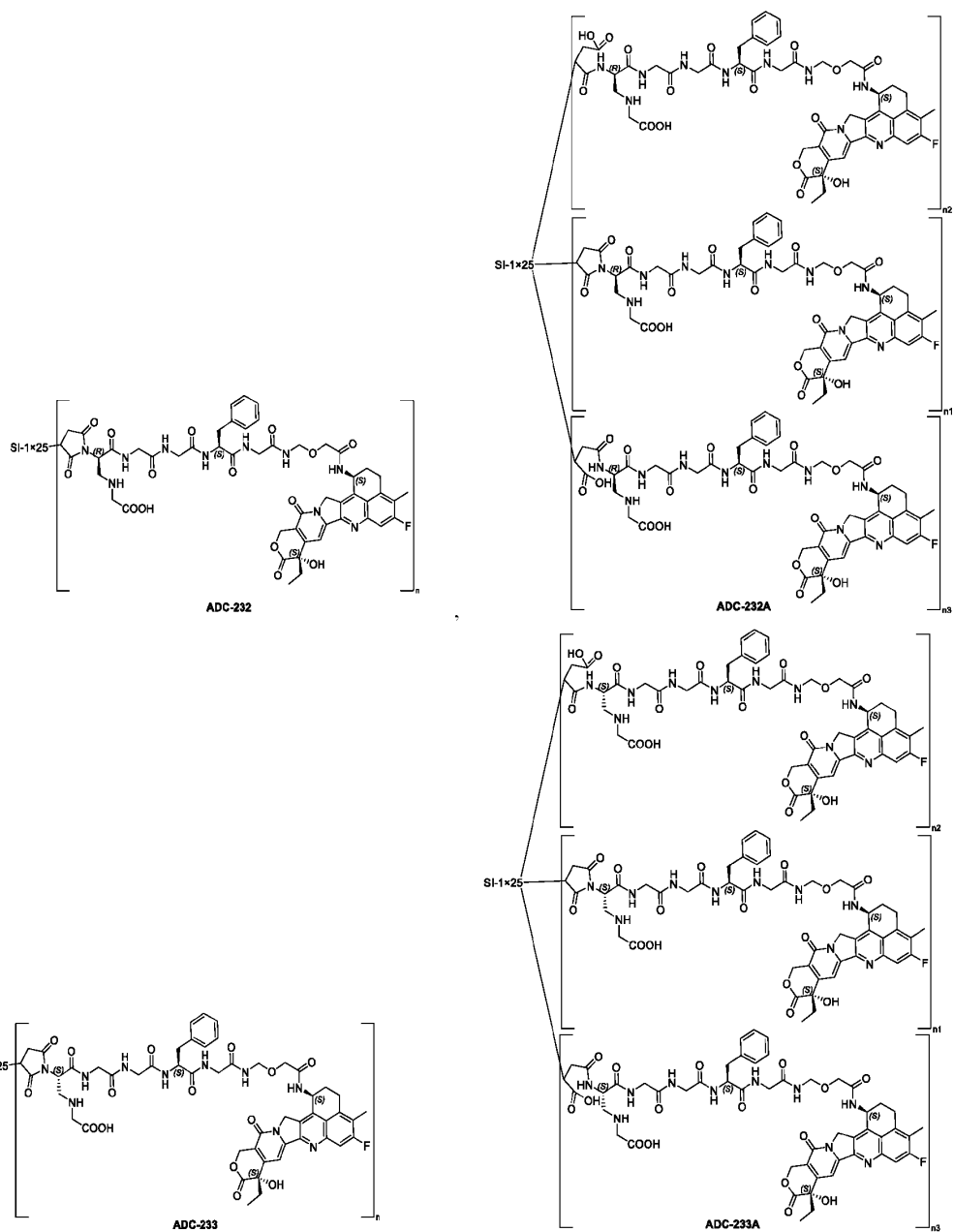


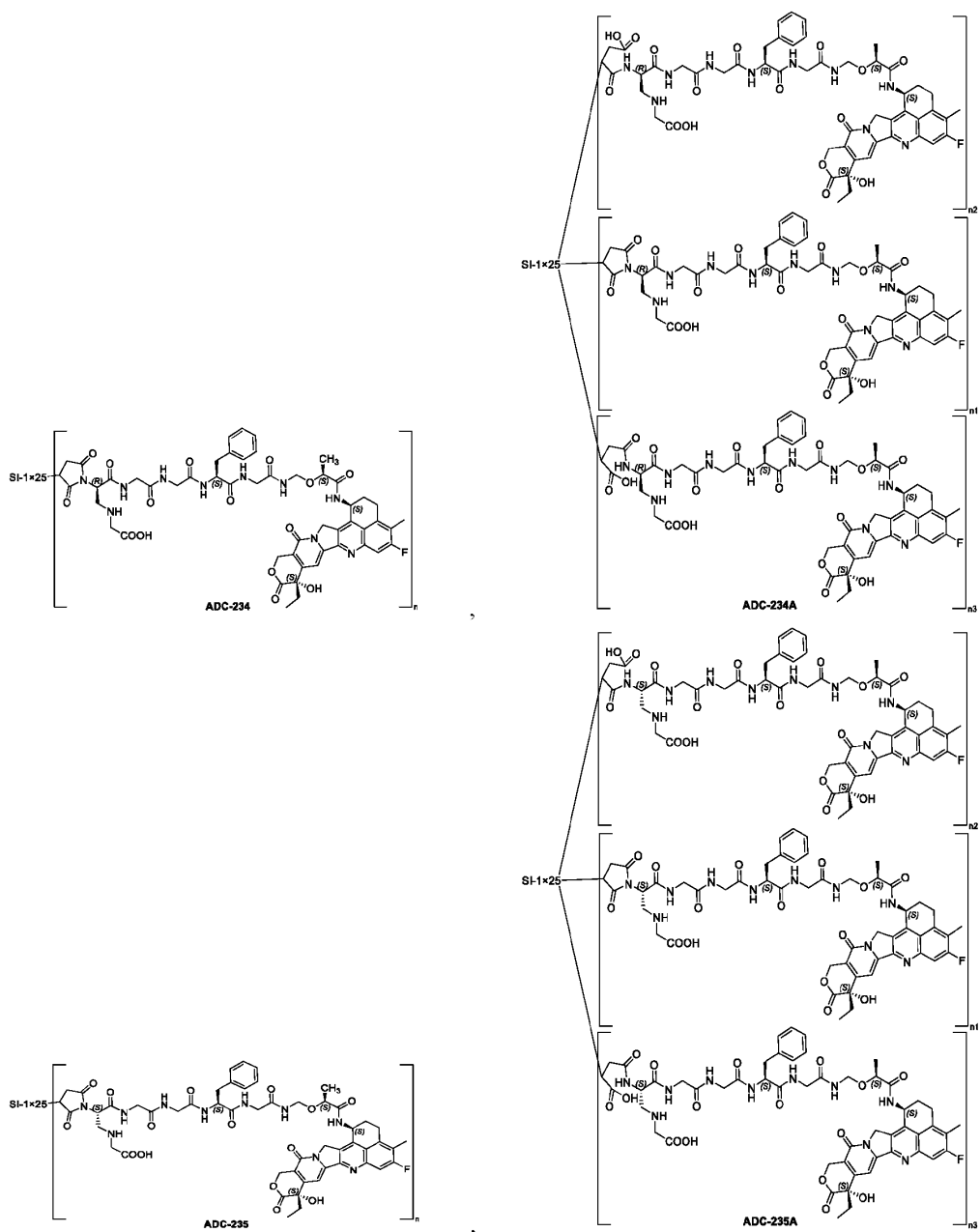
wherein:

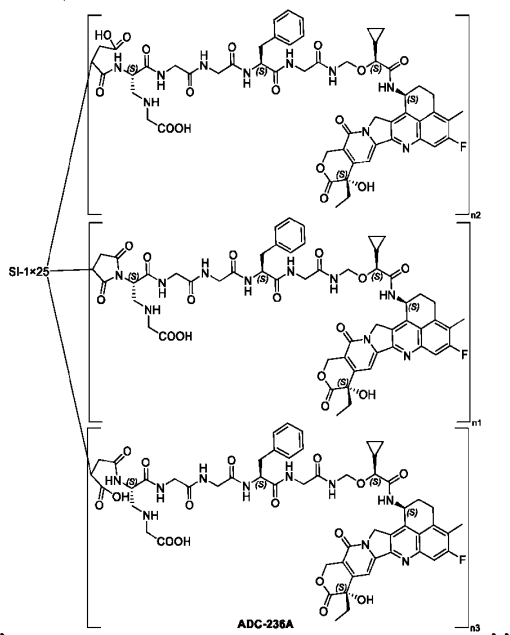
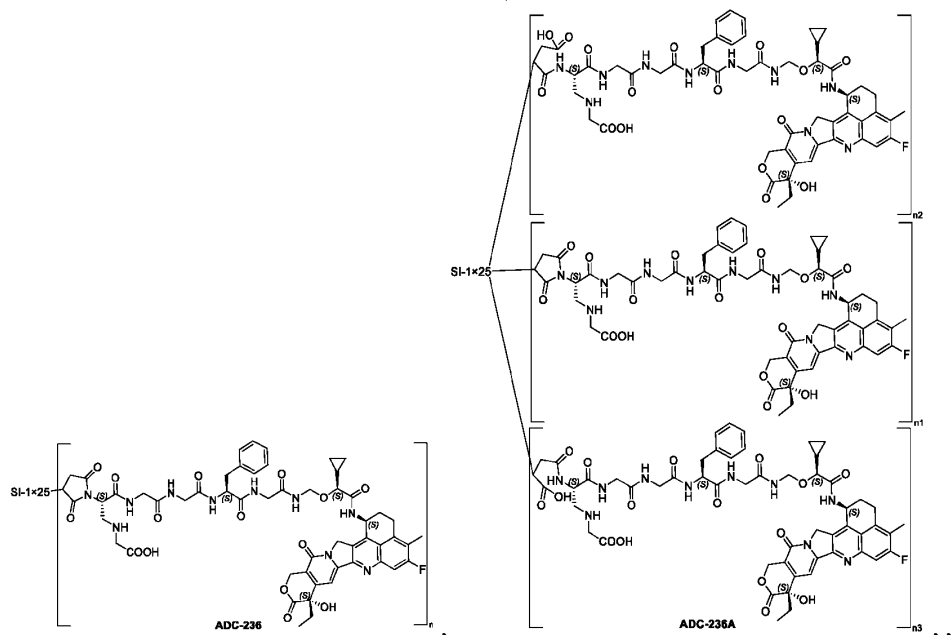
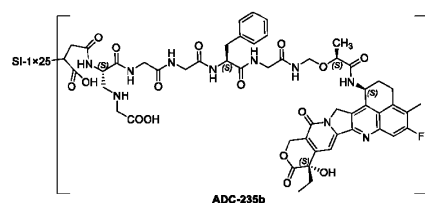
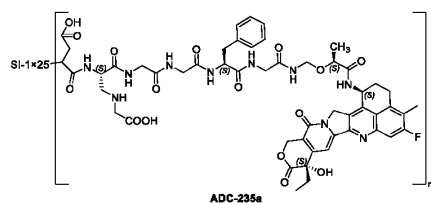
SI-1 x 24 is a bispecific antibody or antigen-binding fragment thereof having a binding specificity to both EGFR and HER3;

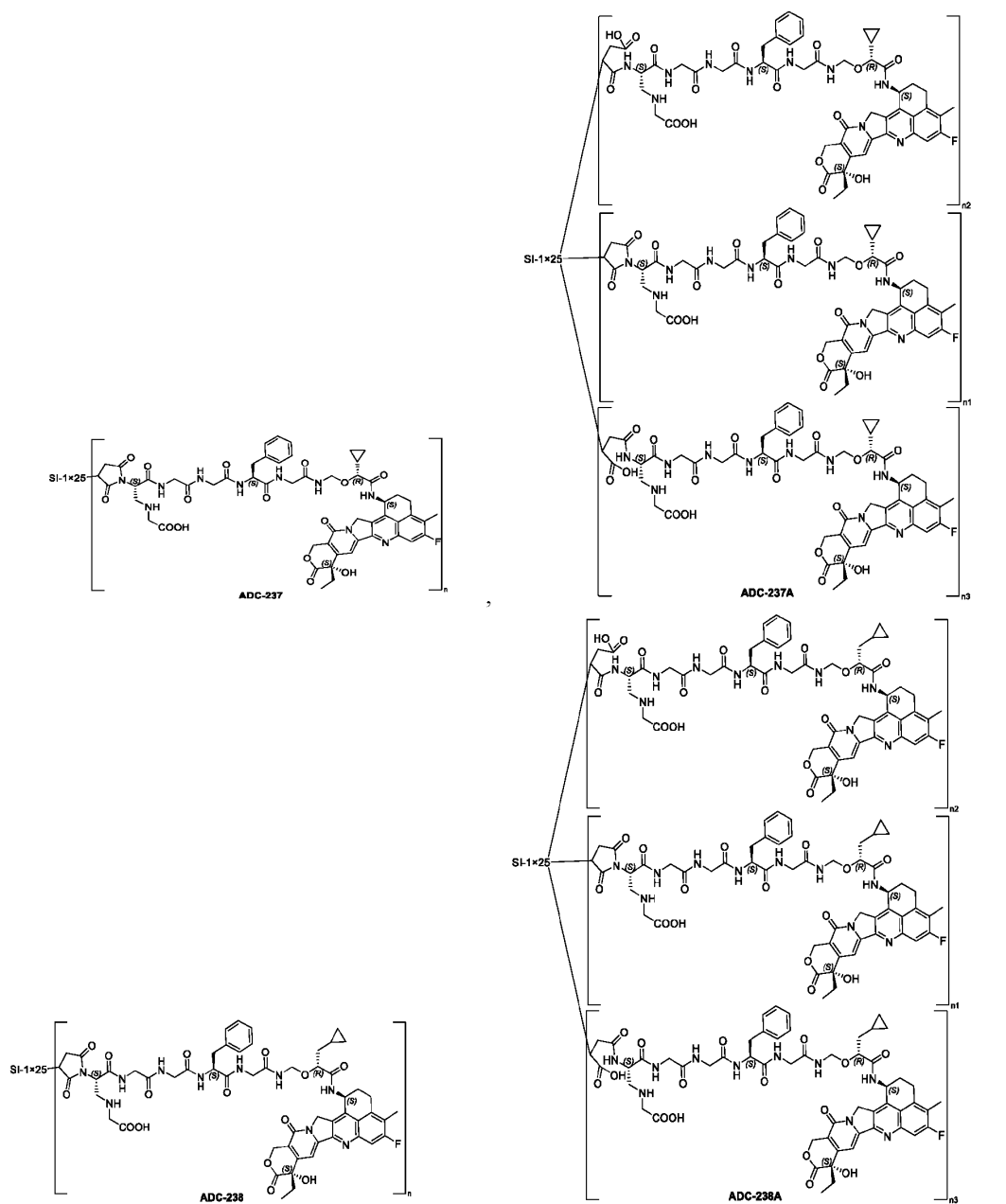
n is an integer of 1-10, wherein n1, n2, and n3 are each independently chosen from any integer or any decimal number from 0-10, n1, n2, and n3 are not simultaneously 0, and $1 \leq n1 + n2 + n3 \leq 10$.

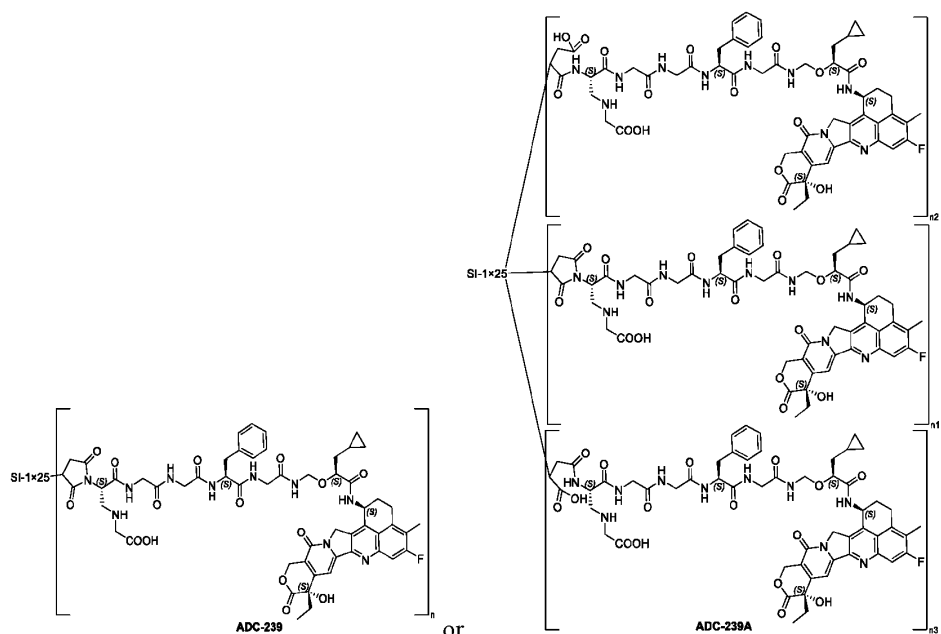
In one embodiment, the ligand-camptothecin derivative conjugate, or a pharmaceutically acceptable salt or solvate thereof, comprises the following structure, or a butanediimide ring-opening structure thereof, or an isomer thereof.











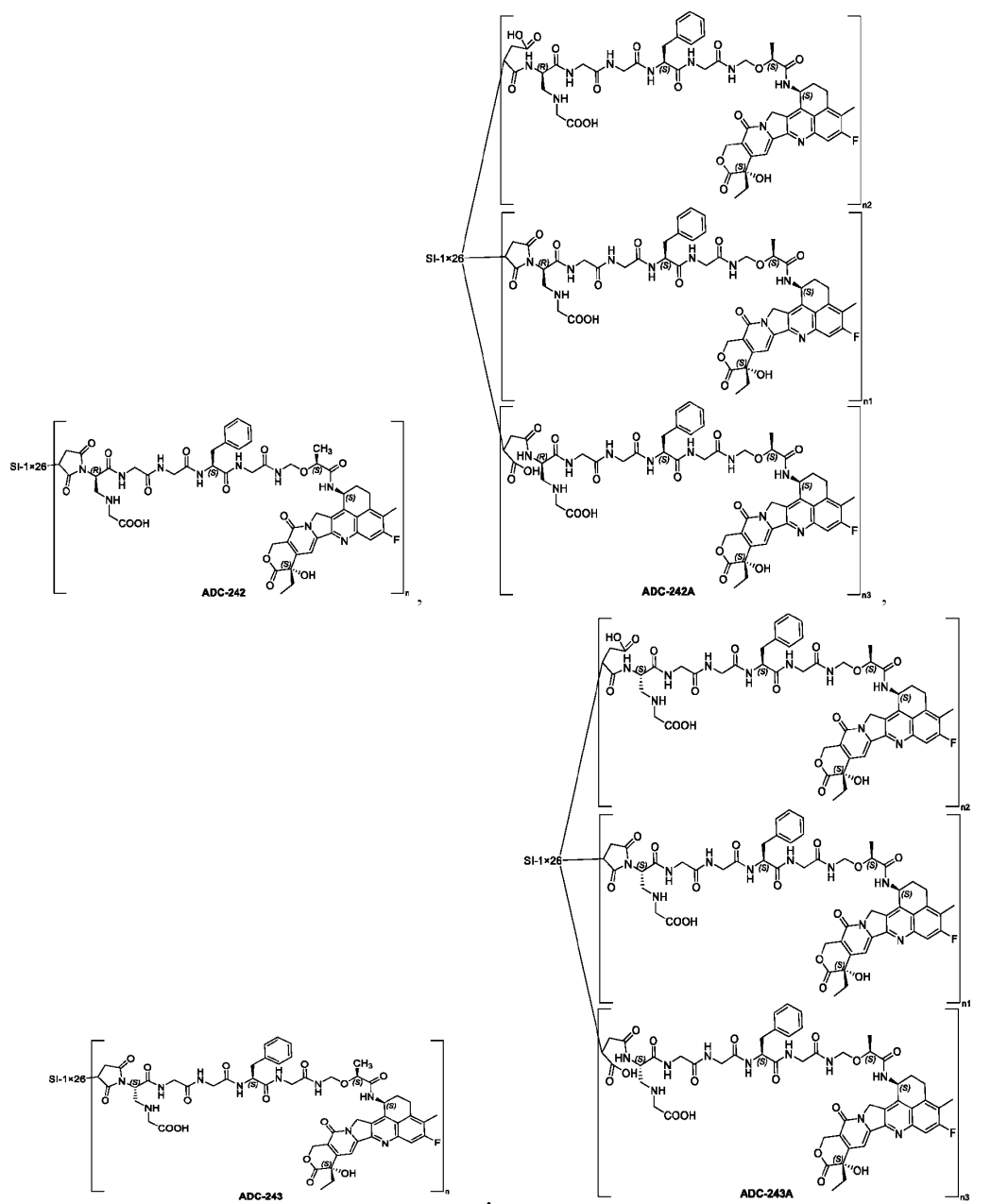
wherein:

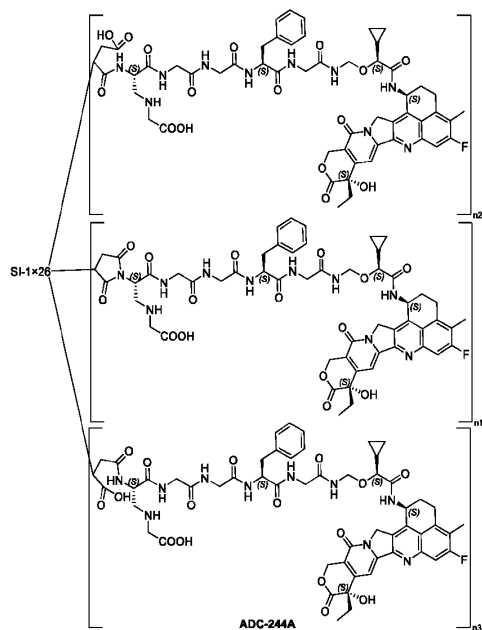
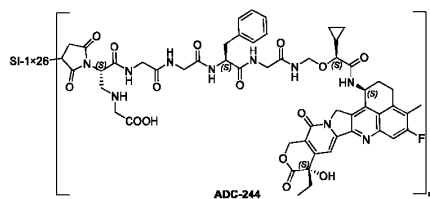
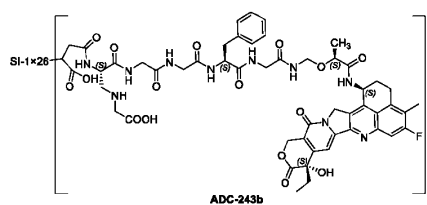
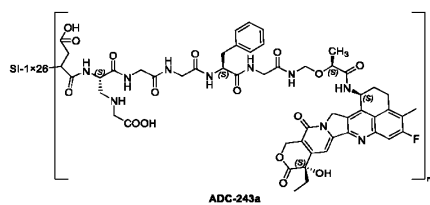
SI-1 x 25 is a bispecific antibody or antigen-binding fragment thereof having a binding specificity to both EGFR and HER3,

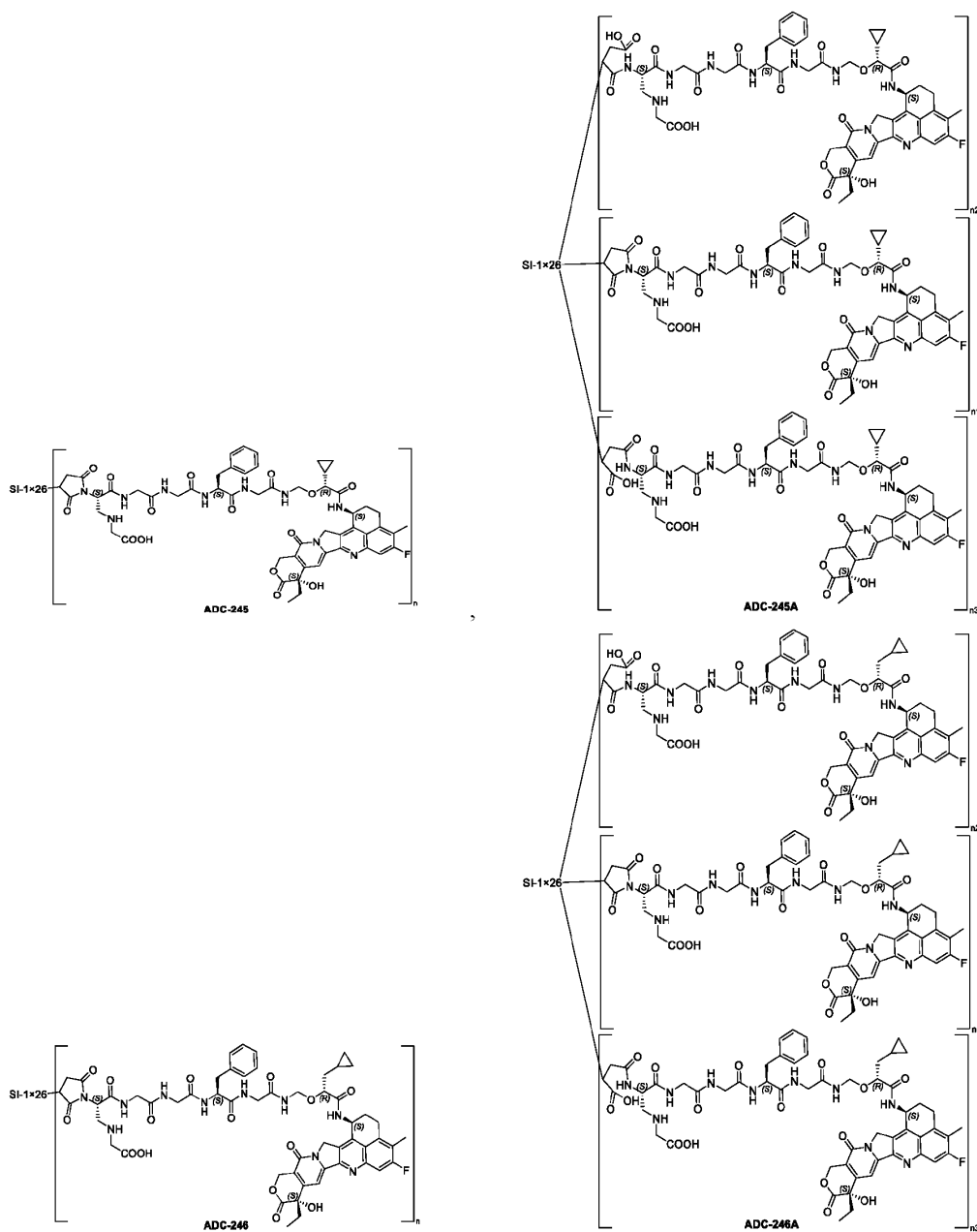
n is an integer of 1-10, wherein n1, n2, and n3 are each independently chosen from any integer or any decimal number from 0-10, n1, n2, and n3 are not simultaneously 0, and $1 \leq n1 + n2 + n3 \leq 10$.

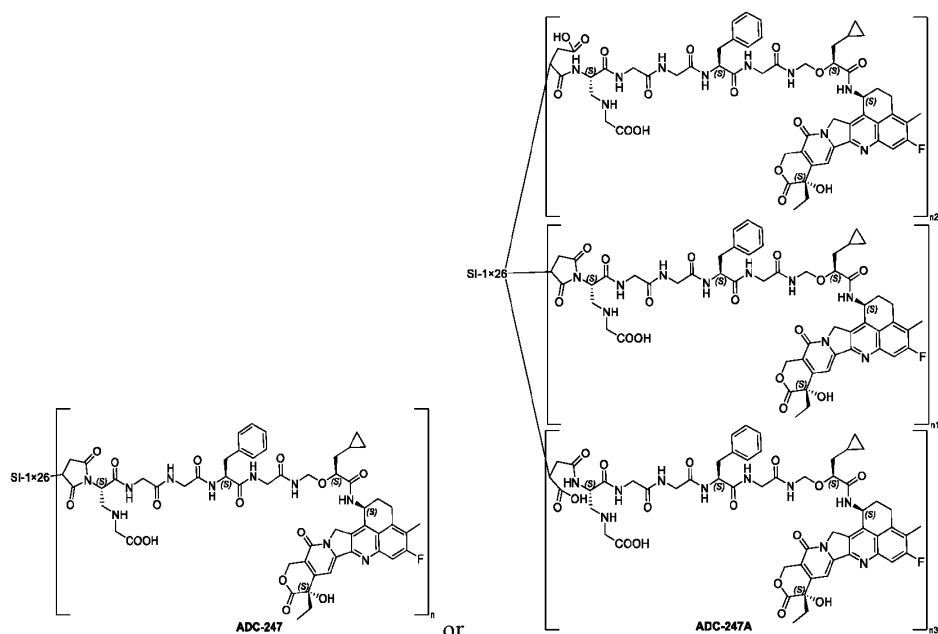
In one embodiment, the ligand-camptothecin derivative conjugate, or a pharmaceutically acceptable salt or solvate thereof, comprises the following structure, or a butanediimide ring-opening structure thereof, or an isomer thereof:











wherein:

SI-1 x 26 is a bispecific antibody or antigen-binding fragment thereof targeting having a binding specificity to both EGFR and HER3,

n is an integer of 1-10, wherein n1, n2, and n3 are each independently chosen from any integer or any decimal number from 0-10, n1, n2, and n3 are not simultaneously 0, and $1 \leq n1 + n2 + n3 \leq 10$.

In one embodiment, the pharmaceutically acceptable salt comprises a sodium, potassium, calcium, or magnesium salt formed with an acidic functional group in the structural formula, and acetate, trifluoroacetate, citrate, oxalate, tartrate, malate, nitrate, chloride, bromide, iodide, sulphate, bisulfate, phosphate, lactate, oleate, ascorbate, salicylic acid, tartrate, malate, nitrate, chloride, bromide, iodide, sulfate, bisulfate, phosphate, lactate, oleate, ascorbate, salicylate, formate, glutamate, methanesulfonate, ethanesulfonate, benzenesulfonate or p-toluenesulfonate, or a combination thereof.

In one aspect, the application provides pharmaceutical compositions. In one embodiment, the pharmaceutical composition comprises a lyophilized powder injection formula. In one embodiment, the lyophilized powder injection formula comprises the ligand-camptothecin derivative conjugate or a pharmaceutically acceptable salt or solvent compound thereof and a pharmaceutical carrier composition.

In one embodiment, the lyophilized powder injection formula comprises the ligand-camptothecin derivative conjugate or a pharmaceutically acceptable salt or solvate thereof in an amount from about 10% to about 20% w/w, from about 12% to about 16% w/w, from about 14% to about 15% w/w, from about 12% to about 18% w/w, from about 5% to about 15% w/w, from about 10% to about 16% w/w, or from about 14% to about 18% w/w.

In one embodiment, the pharmaceutical carrier composition comprises a buffer composition, an excipient, an emulsifier, or a combination thereof.

Any pharmaceutically suitable pH buffer system may be used as the buffer composition. Examples include an amino acid and its salt(s), citrate buffer system, PBS buffer system, or tris buffer system. In one embodiment, the lyophilized powder injection formula comprises from about 1% to about 10%, from about

2% to about 8%, about 4%, 6%, 8%, or 10% w/w of the buffer composition. In one embodiment, the molar ratio of the ADC and the buffer composition is from about 200:1 to about 10:1, from about 160:1 to about 20:1, from about 120:1 to about 60:1, from about 100:1 to about 500:1, or from about 150:1 to about 30:1. In one embodiment, the buffer composition comprises histidine, histidine HCl, or a combination thereof. In one embodiment, the molar ratio of the ADC and histidine is from about 800:1 to about 100:1, from about 800:1 to about 300:1, from about 600:1 to about 300:1, from about 600:1 to about 400:1, or from about 500:1 to about 200:1.

10 In one embodiment, the pharmaceutical composition has a pH from about 5 to about 7, from 4 to about 6, from about 4.5 to about 6.2, from about 4.7 to about 5.7, from about 5.5 to about 6.5, from about 5.2 to about 6.2. In one embodiment, the pharmaceutical composition has a pH of about 5, about 5.2, about 5.7, about 6, about 6.2, about 6.5, or about 6.7. In one embodiment, the pharmaceutical composition has a pH not less than 5. In one embodiment, the pharmaceutical composition has a pH not more than 6.7.

The excipient may be a pharmaceutically suitable excipient. The excipient may serve as a stabilizer to stabilize the pharmaceutical composition. Example excipients include without limitation sugar alcohols, mono- or di-saccharides, amino acids, or a combination thereof. Example sugar alcohols include without limitation mannitol, erythritol, maltitol, xylitol, isomalt, glycerol, or sorbitol. Example mono- or di-saccharides include without limitation fructose, glucose, maltose, or sucrose. Amino acids may be essentially amino acids, nonessential amino acids, common amino acids, or uncommon amino acids. Example amino acids include histidine, methionine, glycine, arginine, or a combination thereof. In one
20 embodiment, the excipient may include mannitol, sucrose, glycine, arginine, methionine, or a combination thereof. In one embodiment, the lyophilized powder injection formula comprises from about 60% to about 85%, from about 70% to about 80%, about 75%, 78%, 79%, or 80% w/w of the excipient.

The emulsifier may be a pharmaceutically suitable emulsifier. Examples include without limitation polysorbates, surfactants, lecithin, sodium stearyl lactylate (SSL), carbomer, cellulose and its derivatives thereof, sodium lauryl sulfate, or a combination thereof. In one embodiment, the emulsifier comprises polysorbate 80. In one embodiment, the lyophilized powder injection formula comprises from about 0.2% to about 1.5%, from about 0.5% to about 1%, about 0.5%, 0.6%, or 0.7% of the emulsifier.

In one embodiment, the pharmaceutical carrier composition consists essentially of histidine, histidine hydrochloride, mannitol, sucrose, and polysorbate 80(II). In one embodiment, the lyophilized powder
30 injection formula comprises from about 1% to about 1.5% of histidine, from about 4% to about 5% of histidine hydrochloride, from about 15% to about 16% of mannitol, from about 62% to about 64% of sucrose, and from about 0.5% to about 0.7% polysorbate 80(II).

In one embodiment, the lyophilized powder injection formula comprises about 14.85% the ligand-camptothecin derivative conjugate or a pharmaceutically acceptable salt or solvate thereof, about 1.41% of histidine, about 4.59% of histidine hydrochloride, about 15.46% of mannitol, about 63.08% of sucrose, and f about 0.62% of polysorbate 80(II). In one embodiment, each minimal packaging unit of the lyophilized powder injection contains 120 mg of ADC-6A, 11.4 mg of histidine, 37.12 mg of histidine hydrochloride, 125 mg of mannitol, 510 mg of sucrose, and 5 mg of polysorbate 80(II).

40 In one embodiment, the pharmaceutical composition comprises water. In one embodiment, the pharmaceutical composition comprises water solution of the lyophilized powder injection formula.

In one aspect, the application provides methods for making the pharmaceutical compositions. In one embodiment, the pharmaceutical composition comprises the lyophilized powder injection formula. In one embodiment, the method includes the step of combining the ligand-camptothecin derivative conjugate or a pharmaceutically acceptable salt or solvent compound thereof and a pharmaceutical carrier composition to

provide a pharmaceutical mixture and lyophilizing the pharmaceutical mixture to provide the lyophilized powder injection formula. In one embodiment, the method further comprises the step of combining water with the lyophilized powder injection formula to provide an injection solution.

In one aspect, the application provides treatment kits. In one embodiment, the treatment kit comprises a first container and a package insert. In one embodiment, the first container comprises at least one dose of the pharmaceutical composition as disclosed herein. In one embodiment, the package insert comprises instructions for treating the subject using the pharmaceutical composition.

10 In one embodiment, the treatment kit comprises a second container, wherein the second container comprises at least one dose of a second treatment composition. In one embodiment, the packaging insert further comprises instructions for using the second treatment composition.

In one embodiment, the second treatment composition comprises a therapeutic agent. In one embodiment, the second treatment composition comprises a platinum-containing or platinum-free chemotherapeutic agent, an immune checkpoint inhibitor, an EGFR-TKI, or a combination thereof. In one embodiment, the immune checkpoint inhibitor comprises anti-PD-1 mAb, anti-PD-L1 mAb, a combination of anti-PD-1 mAb, anti-PD-L1 mAb, anti-CTLA-4 mAb, anti-LAG3 mAb, anti-TIGIT mAb, or a combination thereof.

20 In one embodiment, the instructions state that the treatment kit is intended for use in treating the subject having cancer or tumor that tests positive for EGFR, HER3 or both. In one embodiment, the instructions state that the treatment kit is intended for use in treating the subject having non-small cell lung cancer or small cell lung cancer. In one embodiment, the instructions state that the treatment kit is intended for use in treating the subject having EGFR wild-type non-small cell lung cancer or EGFR mutant non-small cell lung cancer.

In one embodiment, the instructions state that the treatment kit is intended for use in treating the subject having head and neck squamous carcinoma. In one embodiment, the instructions state that the treatment kit is intended for use in treating the subject having nasopharyngeal cancer.

30 In each of the above embodiments, the "C1-C6 alkyl" and various composite groups involving "C1-C6 alkyl" (e.g., "C1-C6 alkyl-substituted," "C1-C6 alkyl" in "C1-C6 alkyl" (e.g., "C1-C6 alkyl-substituted," "C1-C6 alkyl-deuterated")) can be replaced with "C1-C20 alkyl," "C1-C12 alkyl C1-C12 alkyl" or "C1-C10 alkyl;" the "C3-C8 cycloalkyl" and various composite groups involving "C3-C8 cycloalkyl" in which "C3-C8 cycloalkyl" may be replaced by "C3-C20 cycloalkyl" or "C3-C10 cycloalkyl;" the "C1-C6 alkoxy" and "C1-C6 alkoxy" can be replaced with "C1-C20 alkoxy" in various compound groups thereof, "C1-C12 alkoxy" or "C1-C10 alkoxy;" the "C6-C10 aryl" can be replaced with "C6-C12 aryl" in "C6-C10 aryl" and various composite groups thereof; and the "3-7 heterocyclic group" and various complex groups thereof may be replaced with "3-20 heterocyclic group," "3-12 heterocyclic group" or "3-10 heterocyclic group."

BRIEF DESCRIPTION OF THE DRAWINGS

The foregoing and other features of this disclosure will become more fully apparent from the following description and appended claims, taken in conjunction with the accompanying drawings. Understanding that these drawings depict only several embodiments arranged in accordance with the disclosure and are, therefore, not to be considered limiting of its scope, the disclosure will be described with additional specificity and detail through use of the accompanying drawings, in which:

Figure 1 depicts the primary prevention pathways to prevent the development of neutropenia in patients with malignant tumors;

Figure 2 depicts the secondary prevention pathways to prevent the development of neutropenia in patients with malignant tumors;

Figure 3.1 depicts the waterfall chart of 85 subjects with Non-Small Cell Lung Cancer (NSCLC) showing change in tumor size and the best efficacy;

Figure 3.2 depicts the waterfall chart of 37 subjects with NSCLC showing change in tumor size and the best efficacy in the 2.5 mg/kg D1D8 Q3W;

Figure 3.3 depicts the waterfall chart of 21 subjects with NSCLC showing change in tumor size and the best efficacy in the 4.5 mg/kg D1D3 Q3W dose group;

Figure 3.4 depicts the waterfall chart of 47 subjects with EGFRwt NSCLC showing change in tumor size and the best efficacy;

Figure 3.5 depicts the waterfall chart of 38 subjects with EGFRmut NSCLC showing change in tumor size and the best efficacy;

Figure 3.6 shows brain metastasis stratified PFS K-M plot for NSCLC patients;

Figure 3.7 shows PFS K-M plot for NPC patients;

Figure 3.8 depicts the waterfall chart of Nasopharyngeal Cancer Subjects showing change in tumor size and the best efficacy;

Figure 4.1 shows single dose ADC and TAB semi-log concentration-time plots;

Figure 4.2 shows C_{max} trend for ADC-6A multiple dosing ADCs;

Figure 4.3 shows trend of C_{max} for ADC-6A multiple doses of TAB;

Figure 4.4 shows trend plot of immediate post-administration points for multiple ADC-6A toxin administrations;

Figure 4.5 shows C_{trough} trend plot for ADC-6A multiple dosing ADCs;

Figure 4.6 shows C_{trough} trend plot of ADC-6A multiple doses of TAB;

Figure 4.7 shows trend of C_{trough} for multiple administrations of toxin in ADC-6A;

Figure 4.8 shows incidence of ADC-6A characteristic hematological toxicity vs dose;

Figure 4.9 shows ADC-6A characteristic hematological toxicity severity vs dose (2.5 mg/kg D1D8Q3W vs 4.5 mg/kg D1Q3W);

Figure 4.10 shows the ADC-6A dose-ORR relationship;

Figure 4.11 shows the ADC-6A dose-ORR relationship;

Figure 5.1 shows the study profile with notes: a) ten patients withdrew their informed consent forms due to the COVID-19 pandemic; b) 25 patients withdrew from the study for compliance-related reasons, among them, six due to voluntary alteration to alternative treatment options, five due to lack of caregiver, five due to personal issues, four due to excessive blood collection, three due to frequent follow-up visits, one due to treatment of pre-existing comorbidity, one due to frequent follow-up visits and pandemic concern; and c) three patients who died after discontinuation of treatment due to adverse events were considered treatment-related deaths;

Figure 5.2 depicts tumor response in the waterfall plot showing the best overall responses in all evaluable patients (n=174), wherein dashed lines indicate 20% increase in tumour size and 30% decrease in tumour size and * denotes partial response pending confirmation;

Figure 5.3 shows single dose ADC-6A concentration over time at different doses (Bars represent 95%

Cis);

Figure 5.4 shows the Kaplan-Meier curves of progression-free survival of all patients (A), as well as patients with EGFR mutant NSCLC (B), EGFR wild type NSCLC (C), NPC (D), SCLC (E), and HNSCC (F);

Figure 5.5 shows the Kaplan-Meier curves of overall survival of all patients (A), as well as patients with EGFR mutant NSCLC (B), EGFR wild type NSCLC (C), NPC (D), SCLC (E), and HNSCC (F);

Figure 5.6 depicts the best overall response in the waterfall plot concerning the tumor subtype and size in patients with EGFR wild type NSCLC (A), EGFR mutant NSCLC (B), and NPC (C), wherein dashed lines indicate 20% increase in tumor size and 30% decrease in tumor size, partial response pending confirmation (*), confirmed the best of response (cBOR), confirmed partial response (cPR), stable disease (SD), and progressive disease (PD);

Figure 5.7 shows the Kaplan-Meier curves of duration of response of all patients (A), EGFR mutant NSCLC patients (B), and EGFR wild type NSCLC patients (C), nasopharyngeal carcinoma patients (D), small cell lung cancer (E), and head and neck squamous cell carcinoma (F);

Figure 5.8 depicts the swimmer plot showing the time to tumor response in all patients (A), as well as patients with EGFR mutant NSCLC (B), EGFR wild type NSCLC (C), and NPC (D);

Figure 5.9 shows Grade 3 or worse treatment-related hematological toxicity in the different dose groups, wherein QW: one dose per week with 4 weeks per cycle, D1D8 Q3W: one dose on days 1 and 8 every 3 weeks per cycle, and D1 Q3W: one dose on day 1 every 3 weeks per cycle;

Figure 6.1 shows the best percentage change from baseline and ctDNA detection results of EGFR mutant NSCLC patients, wherein documented EGFR mutations were tumor genomic alterations before the BL-B01D1 treatment; ctDNA analysis was available in 24 patients with EGFR mutation; the mutations detected by ctDNA were shown in the last three rows, and median (interquartile range) line of prior treatment was 3 (2-5);

Figure 6.2 depicts heatmap showing the baseline mutation landscape in patients with advanced NSCLC defined by ctDNA, including a total of 69 NSCLC patients (26 with EGFR mutations and 43 with EGFR wildtype), and displaying the top 35 mutated genes, with the patient identifier shown at the bottom, the prevalence of mutations at the top bar, the number of mutations in each patient under the bar, the proportion of mutations in all patients illustrated at the right column, and patient characteristics and tumor efficacy shown below the heatmap;

Figure 6.3 shows the response based on the levels of HER3 or EGFR expression in patients as measured by H-score;

Figure 7.1 depicts the waterfall chart of 96 subjects with previously treated locally advanced or metastatic breast cancer showing a spectrum of changes in tumor size;

Figure 7.2 depicts the waterfall chart of 22 subjects with previously treated locally advanced or metastatic breast cancer showing immunohistochemistry (IHC) staining of the levels of EGFR and HER3 expression;

Figure 7.3 depicts the waterfall chart of 52 subjects with previously treated locally advanced or metastatic esophageal squamous cell carcinoma (ESCC) showing a spectrum of changes in tumor size;

Figure 7.4 shows PFS K-M plot of the evaluable efficacy among 52 patients in 2.5mg/kg D1D8 Q3W regimen;

Figure 7.5 shows the waterfall chart of 25 subjects with previously treated locally advanced or metastatic biliary tract carcinoma (BTC) showing a spectrum of changes in tumor size;

Figure 7.6 shows PFS K-M plot of the evaluable efficacy among 72 patients in 2.5mg/kg D1D8 Q3W regimen;

Figure 7.7 shows the waterfall chart of 27 subjects with locally advanced or metastatic urothelial carcinoma (UC) (A) and 12 UC subjects with 1 prior line of chemo (B), showing maximum change from baseline in response to the regimen of 2.2 mg/kg D1D8 Q3W; and

Figure 7.8 shows progress-free survival probability of subjects with locally advanced or metastatic urothelial carcinoma (UC) in response to 2.2mg/kg D1D8 Q3W regimen.

DETAILED DESCRIPTION

In the following detailed description, reference is made to the accompanying drawings, which form a part hereof. In the drawings, similar symbols typically identify similar components, unless context dictates otherwise. The illustrative embodiments described in the detailed description, drawings, and claims are not meant to be limiting. Other embodiments may be utilized, and other changes may be made, without departing from the spirit or scope of the subject matter presented herein. It will be readily understood that the aspects of the disclosure, as generally described herein, and illustrated in the Figures, can be arranged, substituted, combined, separated, and designed in a wide variety of different configurations, all of which are explicitly contemplated herein.

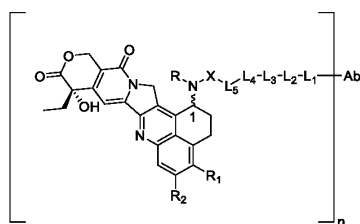
This disclosure is generally drawn, inter alia, to methods, compositions, and kits for treating cancers using a combination therapy including an antibody and an additional therapeutic agent.

Tyrosine kinase inhibitors (TKIs) are preferred targeted therapy for treating patients with non-small cell lung cancer (NSCLC) with EGFR-sensitive mutations, and there is no systematic first-line treatment option with breakthrough efficacy at home and abroad after EGFR-TKI treatment failure, and the CSCO/NCCN guideline recommends the use of platinum-containing chemotherapy, such as "pemetrexed + platinum", after EGFR-TKI treatment failure. The CSCO/NCCN guidelines recommend the use of "pemetrexed + platinum" and other platinum-containing chemotherapy-based regimens after EGFR-TKI treatment failure. For recurrent or metastatic nasopharyngeal cancer patients treated with anti-PD-1 monoclonal antibody + platinum-containing chemotherapy in the first line, there is no second-line systemic treatment option with prospective evidence-based medicine at home and abroad after treatment failure. There is a significant unmet clinical need in all of the above target populations.

BL-B01D1 is an anti-EGFR/HER Antibody-Drug Conjugate (ADC) comprised of a bispecific antibody against EGFRxHER3 (SI-B001), a cathepsin B cleavable linker, and a novel topoisomerase I inhibitor agent (Ed-04), which is a derivative of the alkaloid camptothecin (see WO 2023/083381, incorporated herein by reference in its entirety). Such ADCs can specifically bind to EGFR and/or HER3 on the surface of tumor cells prior to internalization via endocytosis, culminating in the release of the comedoine derivative in the lysosome, which in turn leads to tumor cell death by inhibiting DNA replication and RNA synthesis.

EGFRxHER3 bispecific ADCs have a favorable safety profile, tolerability and encouraging clinical anti-tumor activity in a variety of advanced solid tumors. The present application provides therapeutic compositions and methods for the treatment of non-small cell lung cancer, nasopharyngeal carcinoma, and other solid tumor species using a specific dosage regimen of EGFRxHER3 bispecific ADCs, which can be used as a systemic therapeutic regimen for the treatment of the aforementioned solid tumor species.

The present application discloses methods for treating a cancer or tumor comprising administering to a subject in need thereof, for a certain period of time, a ligand-camptothecin derivative conjugate (ADC) as shown in General Formula I or a pharmaceutically acceptable salt or solvate thereof according to one of the following dosage regimens.



I

Abbreviations and Definitions

Unless otherwise indicated, the following terms and phrases, as used herein, are intended to have the meanings set forth below. When a trade name is used herein, unless otherwise indicated in the context, the trade name includes the product formulation, generic drug and active ingredient of said trade name product.

Unless stated to the contrary, terms used in the claims and specification herein have the meanings set forth below.

10 The term "ligand" refers to a macromolecular compound that recognizes and binds to an antigen or receptor associated with a target cell. The ligand serves to present a drug to a target cell population bound to a ligand, which includes, but is not limited to, a protein-like hormone, a lectin, a growth factor, an antibody, or other molecule that binds to the cell. In this embodiment of the application, the ligand is denoted as Ab, and the ligand may form a linkage bond with a linkage unit via a heteroatom on the ligand, preferably an antibody or an antigen-binding fragment thereof, said antibody being selected from chimeric, humanized, fully human, or murine antibodies, preferably monoclonal antibodies.

A ligand unit is a targeting agent that binds specifically to a target component. Said ligand is capable of binding specifically to a cellular fraction or to a cellular component or to other target molecules of interest. The target portion or target is typically on the surface of the cell. In some aspects, the ligand unit serves to deliver the drug unit to a specific target cell population with which the ligand unit interacts. Ligands include, but are not limited to, proteins, polypeptides and peptides, and non-proteins such as sugars. Suitable ligand units include, for example, antibodies, such as full-length (intact) antibodies and antigen-binding fragments thereof. In embodiments where the ligand unit is a non-antibody targeting reagent, it may be a peptide or polypeptide, or a non-protein molecule. Examples of such targeting reagents include interferons, lymphokines, hormones, growth and colony stimulating factors, vitamins, nutrient transporter molecules, or any other cell-binding molecule or substance. In some embodiments, the linker is covalently attached to the sulfur atom of the ligand. In some aspects, the sulfur atom is a sulfur atom of a cysteine residue that forms an interchain disulfide bond of the antibody. In another aspect, the sulfur atom is a sulfur atom of a cysteine residue that has been imported into the ligand unit, which forms an interchain disulfide bond of the antibody. In another aspect, the sulfur atom is a sulfur atom that has been introduced into a cysteine residue of the ligand unit (e.g., by targeted mutagenesis or chemical reaction). In other aspects, the linker-bound sulfur atom is selected from a cysteine residue that forms the interchain disulfide bond of the antibody or a cysteine residue that has been introduced into the ligand unit (e.g., by targeted mutagenesis or chemical reaction). In some embodiments, the EU index numbering system in accordance with Kabat {[Kabat E.A et al, (1991)] Sequences of proteins of Immunological Interest, Fifth Edition, NIH Publication 91-3242}.

As used herein, "antibody" or "antibody unit" includes, to the extent thereof, any part of an antibody structure. This unit may bind, reactively associate, or complex with a receptor, antigen, or other receptor unit possessed by the target cell population. The antibody may be any protein or protein-like molecule that binds, complexes, or reacts with a portion of the cell population to be treated or biologically modified. The antibodies comprising the antibody-drug coupling compounds of the

present application maintain their original antigen-binding capacity in the wild. Thus, the antibodies of the present application are capable of binding exclusively to antigens. Antigens involved include, for example, tumor-associated antigens (TAA), cell surface receptor proteins and other cell surface molecules, cell survival regulators, cell proliferation regulators, molecules associated with tissue growth and differentiation (such as are known or foreseen to be functional), lymphokines, cytokines, molecules involved in the regulation of cellular cycling, molecules involved in angiogenic molecules (if known or predicted to be functional). Tumor-associated factors may be cluster differentiation factors (e.g., CD proteins).

- Antibodies applied in antibody drug couplings include, but are not limited to, antibodies directed against cell surface receptors and tumor-associated antigens. Such tumor-associated antigens are well known in the industry and can be prepared by methods and information for antibody preparation well known in the industry. To develop effective cellular level targets that can be used for cancer diagnosis and treatment, researchers seek to find transmembrane or other tumor-associated peptides. These targets can be specifically expressed on the surface of one or more cancer cells with little or no expression on the surface of one or more non-cancer cells. Typically, such tumor-associated polypeptides are more overexpressed on the surface of cancer cells relative to the surface of non-cancer cells. Identification of such tumor-associated factors can greatly enhance the specific targeting properties of antibody-based cancer therapies. For convenience, information related to antigens known to the industry is labeled below, including name, other names, and GenBank accession number.
- Nucleic acid and protein sequences corresponding to the tumor-associated antigens can be found in publicly available databases, such as GenBank, and the antibody-targeted tumor-associated antigens include all amino acid sequence variants and isoforms having at least 70%, 80%, 85%, 90%, or 95% homology to the sequences identified in the references, or possessing biological properties and characteristics that are identical to the tumor-associated antigen sequences of the cited literature. biological properties and characteristics of the tumor-associated antigen.

The term "inhibition" or "inhibition" means that a detectable amount is reduced or completely prevented.

The term "cancer" refers to a physiological condition or disease characterized by dysregulated cell growth. "Tumor" includes cancer cells.

- The term "autoimmune disease" refers to diseases or disorders that originate in tissues or proteins that target an individual's own body.

The term "drug" refers to cytotoxic drugs, denoted by d, which are chemical molecules that have a strong ability to disrupt normal growth in tumor cells. Cytotoxic drugs can in principle kill tumor cells at sufficiently high concentrations, but due to a lack of specificity, they can kill tumor cells while causing apoptosis of normal cells, leading to serious side effects. The term includes toxins, such as small molecule toxins or enzymatically active toxins of bacterial, fungal, plant or animal origin, radioisotopes (e.g., radioisotopes of At211, I131, I125, Y90, Re186, Re188, Sm153, Bi212, P32 and Lu176), toxic drugs, chemotherapeutic drugs, antibiotics and nucleolytic enzymes, preferably toxic drugs.

- The term "linker" or "linker fragment" or "linker unit" refers to a fragment or bond of a chemical structure that is attached to a ligand at one end and to the drug at the other end or may be attached to other connectors and then to the drug, or to other connectors and then to the drug. Junctions, including extensions, spacers and amino acid units, can be synthesized by methods known in the art, such as those described in US20050238649A1. The junctions can be "cleavable junctions" that facilitate the release of the drug in the cell. For example, acid-unstable junctions (e.g., hydrazone), protease-sensitive (e.g., peptidase-sensitive) junctions, photo-unstable junctions, dimethyl junctions, or disulfide-containing junctions can be used (Chari et al. Cancer Research 52:127-131, 1992); U.S. Patent No. 5, 208, 020.

According to the mechanism of intracellular drug release, as used herein, "linkers" or "linkers of

antibody-drug couplers" can be categorized into two types: unbreakable linkers and breakable linkers. For antibody-drug couplers containing an unbreakable linker, the mechanism of drug release is as follows: after the coupler binds to the antigen and is endocytosed by the cell, the antibody is cleaved enzymatically in lysosomes, releasing an active molecule consisting of the small molecule of drug, the linker, and amino acid residues of the antibody. The resulting change in the structure of the drug molecule does not diminish its cytotoxicity, but because the active molecule is electrically charged (amino acid residues), it cannot penetrate neighboring cells. Therefore, such active drugs cannot kill neighboring tumor cells that do not express the targeted antigen (antigen-negative cells) (bystander effect) (Ducry et al., 2010, *Bioconjugate Chem.* 21: 5-13). For antibody-drug couplings containing a breakable linker, the mechanism of drug release is that after the coupling binds to the antigen and is endocytosed by the cell, the coupling breaks and releases the active ingredient (the small-molecule drug itself) in the target cell. Breakable linkers are mainly categorized into chemical-sensitive linkers and enzyme-sensitive linkers. Chemically sensitive linkers can be selectively broken due to differences in the nature of the plasma and cytoplasm or tumor microenvironment. Such properties include pH, glutathione concentration, etc. pH-sensitive linkers, which are relatively stable in the neutral or weakly alkaline environment of blood (pH 7.3-7.5), will be hydrolyzed within the weakly acidic tumor microenvironment (pH 5.0-6.5) and lysosomes (pH 4.5-5.0), e.g., stilbenes, carbonates acetals, and ketones. Antibody-drug couplings based on such linkers typically have a short half-life (2-3 days) due to the limited plasma stability of acid breakage linkers. This shorter half-life has somewhat limited the use of pH-sensitive linkers in the new generation of antibody-drug couplers. For glutathione-sensitive linkers, also known as disulfide-bonded linkers. Drug release is based on the difference between the high intracellular glutathione concentration (millimolar range) and the relatively low glutathione concentration in the blood (micromolar range). This is particularly true for tumor cells, whose low oxygen content leads to enhanced reductase activity and thus to higher glutathione concentrations. Disulfide bonds are thermodynamically stable and therefore have better stability in plasma. Enzyme destabilizing linkers, such as peptide linkers, provide better control of drug release. Peptide linkers can be efficiently severed by lysosomal proteases such as tissue protease (Cathepsin B). This peptide linkage is thought to be very stable in the plasma circulation due to the unfavorable extracellular pH and serum protease inhibitors resulting in proteases that are normally inactive outside the cell. In view of the high plasma stability and good intracellular break selectivity and effectiveness, enzyme-unstable linkers are widely used as breakable linkers for antibody-drug couplings.

The term "antibody-drug conjugate" refers to the attachment of an antibody to a biologically active drug by means of a stabilized linkage unit. In the present application "ligand-drug coupling", preferably antibody-drug conjugate (ADC), refers to the attachment of a monoclonal antibody or antibody fragment to a biologically active toxic drug by means of a stabilized linkage unit.

The three-letter codes and single-letter codes for amino acids used in this disclosure are as described in *J. boil. chem.* 1968, 243, 3558.

The term "alkyl" refers to a saturated aliphatic hydrocarbon group, which is a straight or branched chain group containing 1 to 20 carbon atoms (i.e., "C1-C20 alkyl"), preferably an alkyl group containing 1 to 12 carbon atoms (i.e., "C1-C12 alkyl"), more preferably an alkyl group containing 1 to 10 carbon atoms (i.e., "C1-C10 alkyl"), and most preferably an alkyl group containing 1 to 6 carbon atoms (i.e., "C1-C6 alkyl"). Non-limiting examples include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, sec-butyl, n-pentyl, 1, 1-dimethylpropyl, 1, 2-dimethylpropyl, 2, 2-dimethylpropyl, 1-ethylpropyl, 2-methylbutyl, 3-methylbutyl, n-hexyl, 1-ethyl-2-methylpropyl, 1, 1, 2-trimethylpropyl, 1, 1-dimethylbutyl, 1, 2-dimethylbutyl, 2, 2-dimethylbutyl, 1, 3-dimethylbutyl, 2-ethylbutyl, 2-methylpentyl, 3-methylpentyl, 4-methylpentyl, 2, 3-dimethylbutyl, n-heptyl, 2-methylhexyl, 3-methylhexyl, 4-methylhexyl, 5-methylhexyl, 2, 3-dimethylpentyl, 2, 4-dimethylpentyl, 2, 2-dimethylpentyl, 2, 3-dimethylpentyl, 3, 3-dimethylpentyl, 2-ethylpentyl, 3-ethylpentyl, n-octyl, 2, 3-

dimethylhexyl, 2, 4-dimethylhexyl, 2, 5-dimethylhexyl, 2, 2-dimethylhexyl, 3, 3-dimethylhexyl, 4, 4-dimethylhexyl, 2-ethylhexyl, 3-ethylhexyl, 4-ethylhexyl, 2-methyl-2-ethylpentyl, 2-methyl-3-ethylpentyl, n-nonyl, n-ethylpentyl, 2, 2-dimethylpentyl, n-nonyl, 2, 2-dimethylpentyl, n-nonyl, 2, 2-dimethylpentyl, 2, 2-methylpentyl, 2, 2-methylpentyl ethylpentyl, n-nonyl, 2-methyl-2-ethylhexyl, 2-methyl-3-ethylhexyl, 2, 2-diethylpentyl, n-decyl, 3, 3-diethylhexyl, 2, 2-diethylhexyl, and their various branched isomers, and the like. More preferred are lower alkyl groups containing from 1 to 6 carbon atoms, and non-limiting embodiments include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, sec-butyl, n-pentyl, 1, 1-dimethylpropyl, 1, 2-dimethylpropyl, 2, 2-dimethylpropyl, 1-ethylpropyl, 2-methylbutyl, 3-methylbutyl, hexyl, 1-ethyl-2-methylpropyl, 1, 1, 2-trimethylpropyl, 1, 1-dimethylbutyl, 1, 2-dimethylbutyl, 2, 2-dimethylbutyl, 1, 3-dimethylbutyl, 2-ethylbutyl, 2-methylpentyl, 3-methylpentyl, 4-methylpentyl, 2, 3-dimethylbutyl, and the like. The alkyl group may be substituted or non-substituted, and when substituted, the substituent group may be substituted at any available point of attachment, said substituent group preferably being one or more of the following groups independently selected from alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylamino, halogen, mercapto, hydroxy, nitro, cyano, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, cycloalkoxy, heterocycloalkoxy, cycloalkylthio, heterocycloalkylthio, oxo.

The term "substituted alkyl" means that the hydrogen in the alkyl group has been replaced by a substituent group. Unless otherwise indicated in the text, the substituent group of the alkyl group may be a variety of groups selected from the following group: -halogen, -OR', -NR'R'', -SR', -SiR'R''R''', -OC(O)R'', -SR', -SiR'R''R''', -OC(O)R', -C(O)R', -CO₂R', -CONR'R'', -OC(O)NR'R'', -NR'C(O)R'', -NR'C(O)NR'R''', -NR'C(O)2R'', -NH-C(NH₂)=NH, -NR'C(NH₂)=NH, -NH-C(NH₂)=NR', -S(O)R', -S(O)2R', -S(O)2NR'R'', -NR'S(O)2R'', -CN and -NO₂, the number of substituents is from 0 to (2m'+1), where m' is the total number of carbon atoms in the group. R', R'' and R''' each independently refer to hydrogen, unsubstituted C1-8 alkyl, unsubstituted C6-C12 aryl (or C6-C10 aryl), C6-C12 aryl (or C6-C10 aryl) substituted by 1-3 halogens, unsubstituted C 1-8alkyl, C1-8 alkoxy or C1-8 thioalkoxy, or unsubstituted C6-C12 aryl (or C6-C10 aryl)-C1-4 alkyl. When R' and R'' are attached to the same nitrogen atom, they may form a 3-, 4-, 5-, 6-, or 7-membered ring together with that nitrogen atom. For example, -NR'R'' includes 1-pyrrolidinyl and 4-morpholinyl.

The term "alkylene" refers to a saturated straight or branched aliphatic hydrocarbon group having two residues derived from the same carbon atom or two different carbon atoms of a parent alkane by removing two hydrogen atoms and is a straight or branched group containing 1 to 20 carbon atoms, preferably 1 to 12 carbon atoms, and more preferably 1 to 6 carbon atoms. Non-limiting examples of alkylene include, but are not limited to, methylene (-CH₂-), 1,1-ethylene (-CH(CH₃)-), 1,2-ethylene (-CH₂CH₂-), 1,1-propylene (-CH(CH₂CH₃)-), 1,2-propylene (-CH₂CH(CH₃)-), 1,3-propylene (-CH₂CH₂CH₂-), 1,4-butylene (-CH₂CH₂CH₂CH₂-), and 1,5-butylene (-CH₂CH₂CH₂CH₂CH₂-), etc. Alkylene may be substituted or unsubstituted, and when substituted, the substituent may be substituted at any available attachment point, and the substituent is preferably independently selected from one or more substituents of alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylamino, halogen, mercapto, hydroxyl, nitro, cyano, cycloalkyl, heterocyclyl, aryl, heteroaryl, cycloalkyloxy, heterocycloalkyloxy, cycloalkylthio, heterocycloalkylthio and oxo.

The term "alkoxy" refers to -O-(alkyl) and -O-(cycloalkyl), wherein the definition of alkyl or cycloalkyl is as described above. Non-limiting examples of C1-C6 alkoxy include: methoxy, ethoxy, propoxy, butoxy, cyclopropyloxy, cyclobutyloxy, cyclopentyloxy, cyclohexyloxy. Alkoxy can be optionally substituted or unsubstituted, and when substituted, substituents are preferably one or more of the following groups, which are independently selected from alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylamino, halogen, sulfhydryl, hydroxyl, nitro, cyano, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, cycloalkyloxy, heterocycloalkyloxy, cycloalkylthio, heterocycloalkylthio.

The term "cycloalkyl" refers to a saturated or partially unsaturated monocyclic or polycyclic cyclic

hydrocarbon substituent, wherein the cycloalkyl ring comprises from 3 to 20 carbon atoms (i.e. "C3-C20 cycloalkyl"), preferably from 3 to 12 carbon atoms (i.e. "C3-C12 cycloalkyl"), more preferably comprising 3 to 10 carbon atoms (i.e., "C3-C10 cycloalkyl"), most preferably comprising 3 to 8 carbon atoms (i.e., "C3-C8 cycloalkyl"). Non-limiting examples of monocyclic cycloalkyl groups (e.g., "C3-C8 cycloalkyl") include cyclopropyl, cyclobutyl, cyclopentyl, cyclopentenyl, cyclohexyl, cyclohexenyl, cyclohexadienyl, cycloheptenyl, cycloheptatrienyl, cyclooctyl, and the like; and multi-cyclic cycloalkyl groups include cycloalkyl groups of spirocycles, thickened rings, and bridged rings.

The term "heterocyclyl" refers to a saturated or partially unsaturated monocyclic or polycyclic cyclic hydrocarbon substituent containing 3 to 20 ring atoms (i.e., "3-20 membered heterocyclyl"), wherein one or more ring atoms are heteroatoms selected from nitrogen, oxygen or S(O)_m (wherein m is an integer from 0 to 2), but excluding the ring portion of -O-O-, -O-S- or -S-S-, and the remaining ring atoms are carbon. Preferably, it contains 3 to 12 ring atoms (i.e., "3-12 membered heterocyclyl"), wherein 1 to 4 are heteroatoms; more preferably, the cycloalkyl ring contains 3 to 10 ring atoms (i.e., "3-10 membered heterocyclyl"). Non-limiting examples of monocyclic heterocyclyls (e.g., 3-7 membered heterocyclyls) include pyrrolidiny, piperidiny, piperaziny, morpholiny, thiomorpholiny, homopiperaziny, etc. Polycyclic heterocyclyls include spirocyclic, fused ring, and bridged heterocyclyls.

The term "cycloalkylalkyl" means that the alkyl group is substituted with one or more cycloalkyl groups, preferably with a cycloalkyl group, wherein alkyl is as defined above and wherein cycloalkyl is as defined above. For example, C3-C8 cycloalkyl C1-C6 alkyl.

The term "alkyl halide" means an alkyl group substituted with one or more halogens, wherein the alkyl group is as defined above. For example, C1-C6 alkyl halides.

The term "deuteroalkyl" means an alkyl group substituted with one or more deuterium atoms, wherein the alkyl group is as defined above. For example, C1-C6 alkyl is deuterated.

The term "C6-C12 aryl" refers to groups of carbocyclic aromatic systems having 6-12 carbon atoms.

The term "C6-C10 aryl" refers to carbocyclic aromatic system groups with 6-10 carbon atoms, such as phenyl, naphthalene, etc.

The term "5-10 heteroaryl" refers to an aromatic heterocyclic ring, usually 5-, 6-, 7-, 8-, 9- having 1 to 3 heteroatoms selected from N, O or S, 10 heterocycles; heteroaryl rings may optionally be further fused or attached to aromatic and nonaromatic carbocyclic and heterocyclic rings. Non-limiting examples of the 5-10 heteroaryl group are, for example, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, indolyl, imidazolyl, thiazolyl, isothiazolyl, thioxazolyl, Pyrrolyl, phenyl-pyrrolyl, furyl, phenyl-furyl, oxazolyl, isoxazolyl, pyrazolyl, thienyl, benzofuryl, benzothienyl, benzo-1,3-dioxolane (benzodioxin), isoindolyl, benzimidazolyl, indazolyl, quinolyl, isoquinolyl, 1,2,3-triazolyl, 1-phenyl-1,2,3-triazolyl, 2,3-dihydroindolyl, 2,3-dihydrobenzofuranyl, 2,3-dihydrobenzothienyl, benzopyranyl, 2,3-dihydrobenzoxazinyl, 2,3-dihydroquinoxalinyl, etc.

The term "substituted C6-C10 aryl" or "substituted 5-10 heteroaryl" or "substituted 3-7 heterocyclyl" means that the hydrogen in the aryl, heteroaryl or heterocyclyl is replaced by a substituent group. Unless otherwise specified in the text, the substituent of the aryl, heteroaryl or heterocyclyl can be a variety of groups selected from the following groups: -halogen, -OR', -NR'R'', -SR', -SiR'R''R''', -OC(O)R', -C(O)R', -CO₂R', -CONR'R'', -OC(O)R', -)NR'R'', -NR''C(O)R', -NR'-C(O)NR''R''', -NR''C(O)2R', -NH-C(NH₂)=NH, -NR'C(NH₂)=NH, -NH-C(NH₂)=NR', -S(O)R', -S(O)2R', -S(O)2NR'R''', -NR'S(O)2R'', -CN and -NO₂, and the number of substituents is 0 to (2m'+1), where m' is the total number of carbon atoms in the group. R', R'' and R''' independently represent hydrogen, unsubstituted C1-8 alkyl, unsubstituted C6-C12 aryl (or C6-C10 aryl), C6-C12 aryl (or C6-C10 aryl) substituted by 1-3 halogens, unsubstituted C1-8 alkyl, C1-8 alkoxy or C1-8 thioalkoxy, or unsubstituted C6-C12 aryl (or C6-C10 aryl)-C1-4 alkyl. When R' and R'' are attached to the same nitrogen atom, they may form a 3-, 4-, 5-, 6- or 7 ring together with the nitrogen atom. For example, -NR'R'' includes

1-pyrrolidinyl and 4-morpholinyl. The term "hydroxyl" refers to the -OH group.

The term "halogen" means fluorine, chlorine, bromine or iodine.

The term "amino" means -NH₂. The term "nitro" means -NO₂.

The term "amide group" means -C(O)N(alkyl) or (cycloalkyl), wherein alkyl, cycloalkyl is as defined above.

The term "carboxylate group" means -C(O)O(alkyl) or (cycloalkyl), wherein alkyl, cycloalkyl is as defined above.

The present application also includes various deuterated forms of Formula I. Each of the available hydrogen atoms attached to the carbon atom may be independently replaced by a deuterium atom. A person skilled in the art can synthesize the deuterated form of Formula I with reference to the relevant literature. Commercially available deuterated starting materials may be used in the preparation of the deuterated form of Formula I, or they may be synthesized by conventional techniques using deuterated reagents, non-limiting examples of deuterated reagents include: deuteroborane, trideuteroborane tetrahydrofuran solution, lithium-aluminum deuterohydride, ethyl iodine deuteride, and methylene iodide deuteride, and the like.

The term "antibody" refers to immunoglobulin, which is a tetrapeptide chain structure composed of two identical heavy chains and two identical light chains connected by interchain disulfide bonds. The amino acid composition and arrangement order of the constant region of the immunoglobulin heavy chain are different, so their antigenicity is also different. Based on this, immunoglobulins can be divided into five categories, or isotypes of immunoglobulins, namely IgM, IgD, IgG, IgA and IgE, and their corresponding heavy chains are μ chain, δ chain, γ chain, α chain and ϵ chain respectively. The same class of Ig can be divided into different subclasses according to the difference in the amino acid composition of its hinge region and the number and position of disulfide bonds in the heavy chain. For example, IgG can be divided into IgG1, IgG2, IgG3, and IgG4. Light chains are divided into κ chains or λ chains according to the difference in constant regions. Each of the five classes of Ig can have κ chains or λ chains. The antibody of the present application is preferably a specific antibody against a cell surface antigen on a target cell, and non-limiting examples are the following antibodies: anti-EGFRvIII 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-CD138 antibody, anti-CD352 antibody, anti-CD25 antibody or anti-CD123 antibody. The term "solvent compound" or "solvent compound" refers to the formation of a pharmaceutically usable solvent compound of the ligand-drug coupling of the present application with one or more solvent molecules, non-limiting examples of solvent molecules include water, ethanol, acetonitrile, isopropanol, DMSO, ethyl acetate.

The term "drug load" refers to the average amount of cytotoxic drug loaded on each antibody in Formula I. It can also be expressed as a ratio of drug amount to antibody amount, and the drug load

can range from 0-12, preferably 1-10 cytotoxic drugs (D) per antibody (Ab). In embodiments of the application, the drug load is denoted as n, which exemplarily may be the mean value of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10. The average amount of drug per ADC molecule after coupling reaction can be identified by conventional methods such as UV/visible spectroscopy, mass spectrometry, ELISA tests and HPLC characterization.

In one embodiment of the present application, the cytotoxic drug is coupled to the open cysteine sulfhydryl-SH and/or the sulfhydryl-SH of the fixed-point mutated cysteine residue between the antibody chains by a linker unit, and generally the number of drug molecules that can be coupled to the antibody in the coupling reaction will be less than or equal to a theoretical maximum.

- 10 The loading of ligand cytotoxic drug couplers can be controlled by non-limiting methods including:
- (1) controlling the molar ratio of the linking reagent to the monoclonal antibody,
 - (2) control of reaction time and temperature, and
 - (3) selection of different reaction reagents.

The term "pharmaceutically acceptable salt" or "pharmaceutically usable salt" means a salt of a ligand-drug coupling compound of the present application, or a salt of a compound described in the present application, which is safe and efficacious when used in a mammal and is biologically active as desired. The ligand-drug coupling compounds of the present application contain at least one carboxyl group so that they can form salts with bases, and non-limiting examples of pharmaceutically acceptable salts include, for example, sodium, potassium, calcium or magnesium salts.

- 20 The term "pharmaceutically acceptable salt" or "pharmaceutically usable salt" means a salt of an antibody-drug coupling compound of the present application, or a salt of a compound described herein, which is safe and efficacious when used in a mammal and is biologically active as desired. The ligand-drug coupling compounds of the present application contain at least one amino group and can therefore form salts with acids, non-limiting examples of pharmaceutically acceptable salts, including hydrochloride, hydrobromide, hydriodate, sulfate, bisulfate, citrate, acetate, succinate, ascorbate, oxalate, nitrate, pyrite, hydrophosphate, dihydrophosphate, salicylate, citric acid hydrochloride, tartaric acid salt, maleate, fumarate, formate, benzoate, methanesulfonate, ethanesulfonate, benzenesulfonate, p-toluenesulfonate.

- 30 "Acidic amino acid" refers to amino acids with an isoelectric point of less than 7. Acidic amino acid molecules tend to have one or more acidic groups, such as carboxyl groups, which can be effectively ionized into negative ionic forms in the structure to increase hydrophilicity. Acidic amino acids can be natural or unnatural.

The term "natural amino acids" refers to biologically synthesized amino acids. Natural amino acids are generally of the L-type, but there are a few exceptions, such as glycine, both natural and synthesized by living organisms.

The term "Unnatural amino acids" means amino acids obtained by synthetic means.

- 40 The abbreviations frequently used to describe the clinical study of the present application include, but not limited to, AE: Adverse Event; AUC: Area Under the Curve; $AUC_{0-\infty}$: Area Under the Curve (0- ∞); AUC_{0-t} : Area Under the Curve (0-t); C_{max} : Maximum Drug Concentration; CI: Confidence Interval; CR: Complete Response; CTCAE: Common Terminology Criteria for Adverse Events; DCR: Disease Control Rate; DLT: Dose Limiting Toxicity; DOR: Duration of Response; EGFR Epidermal Growth Factor Receptor; FAS: Full Analysis Set; HNSTD: Highest Non-Severely Toxic Dose; MedDRA: Medical Dictionary for Regulatory Activities; MTD: Maximum Tolerated Dose; NSCLC: Non-Small Cell Lung Cancer; ORR: Objective Response Rate; PD: Progressive Disease; PFS: Progression-Free-Survival; PK: Pharmacokinetics; PR: Partial Response; Q2W: Every 2 week; QW: Every 1 week; RECIST: Response Evaluation Criteria in Solid Tumors; SAE: Serious Adverse Event; SAP: Statistical Analysis Plan; SD: Stable Disease; TEAE: Treatment Emergent Adverse Event; and TLF: Table Listing Figure; WBC: White Blood Cell.

Based on the FAS, statistical analyses of efficacy parameters are performed by dose level, sub-type of tumor type and all subjects. Such analyses often use these terms and definitions, including but not limited to, "ORR", "DCR", and "DOR. ORR is defined as the proportion of patients with complete response (CR) or partial response (PR) (i.e., CR+PR) from initiation of study drug to withdrawal/EOT/EOS as evaluated by investigator according to the Response Evaluation Criteria in Solid Tumors (RECIST v1.1). Tumor response evaluated after the initiation of new anti-tumor therapy should not be included into the evaluation of the best response. The Clopper-Pearson method is used to calculate 95% CI for their percentages. DCR is defined as the proportion of patients with responses of CR, PR, and stable disease (SD) (i.e., CR+PR+SD) from initiation of study drug to withdrawal/EOT/EOS, as evaluated by RECIST 1.1 criteria. Tumor response evaluated after the initiation of new anti-tumor therapy should not be included into the evaluation of response at the optimal time point. The Clopper-Pearson method is used to calculate 95% CI for their percentages. DOR defined as the time from the first documentation of objective response to the first documentation of PD or death from any cause before PD, reflecting the duration of ORR.

The present application is further described below in conjunction with specific examples. It should be understood that these examples are only used to illustrate the present application and are not used to limit the scope of the present application. The test methods in the following examples where specific conditions are not specified are usually carried out under conventional conditions or under conditions recommended by the manufacturer. Unless otherwise specified, all percentages, proportions, ratios, or parts are by weight.

The ligand-camptothecin derivative conjugate ADC-6A used in the following examples can be obtained by the preparation method described in patent application WO 2023/083381, incorporated herein by reference in its entirety.

The amino acid sequence information of ADC-6A is shown below:

light chain amino acid sequence

SEQ ID NO: 1

DILLTQSPVILSVSPGERVSFSCRASOSIGTNIHWYQORTNGSPRLLIKYASESISGIPSRFSGSGSGT
DFTLSINSVESEDIADYYCQONNNWPTTFGAGTKLELKKRTVAAPSVFIFPPSDEQLKSGTASVVCL
LNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDESTYSLSTLTLSKADYEKHKVYACEV
THQGLSSPVTKSFNRGEC

wherein the variable area is:

SEQ ID NO: 2

DILLTQSPVILSVSPGERVSFSCRASOSIGTNIHWYQORTNGSPRLLIKYASESISGIPSRFSGSGSGT
DFTLSINSVESEDIADYYCQONNNWPTTFGAGTKLELK

wherein the underlined portions are CDR1 (SEQ ID NO: 3), CDR2 (SEQ ID NO: 4), and CDR3 (SEQ ID NO: 5), respectively, from left to right.

Amino acid sequences of constructs with heavy chain and single chain Fv (scFv) structural domains

SEQ ID NO: 6

QVOLKQSGPGLVQPSQSLSITCTVSGFSLTNYGVHWRQSPGKGLEWLGVIWSGGNTDYNTPFT
SRLSINKDNSKSQVFFKMNSLQSNDAIYYCARALTYDYEFAYWGQGLTVTVSSASTKGPSVFPL
APSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSSS
LGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRT
PEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNG
KEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVE
WESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKSRWQQGNVVFSCSVMHEALHNHYTQKSL
SLSPGGGGGGSGGGGSQVOLQESGGGLVPGGSLRLSCAASGFTFSSYWM~~SWVRQAPGKGLEWV~~
ANINRDGSASYVDSVKGRFTISRDDAKNSLYLOMNSLRAEDTAVYYCARDRGVGYFDLWGRGTL

VTVSSGGGSGGGSGGGSGGGSGSQSALTPASVSGSPGOSITISCTGTSSDVGGYNFVSWYQOHPGKA
PKLMIYDVSDRPSGVSDRFSGSKSGNTASLIISGLQADDEADYYCSSYGSSSTHVIFGGGTKVTVL

wherein the variable region of the heavy chain is:

SEQ ID NO: 7

QVQLKQSGPGLVQPSQSLSITCTVSGFSLTNYGVHWVRQSPGKGLEWLGVIWSGGNTDYNTPFT
SRLSINKDNSKSQVFFKMNSLQSNDAIYYCARALTYDYEFAYWGQGLTVTVSS

wherein the underlined portions are CDR1 (SEQ ID NO: 8), CDR2 (SEQ ID NO: 9), and CDR3 (SEQ ID NO: 10), respectively, from left to right.

The variable region of the light chain in the single-chain Fv (scFv) structural domain is:

10 SEQ ID NO: 11

QSALTPASVSGSPGQSITISCTGTSSDVGGYNFVSWYQOHPGKAPKLMYDVSDRPSGVSDRFSG
SKSGNTASLIISGLQADDEADYYCSSYGSSSTHVIFGGGTKVTVL

wherein the underlined portions are CDR1 (SEQ ID NO: 12), CDR2 (SEQ ID NO: 13), and CDR3 (SEQ ID NO: 14), respectively, from left to right.

The variable region of the heavy chain in the structural domain of the single chain Fv (scFv) is:

SEQ ID NO: 15

QVQLQESGGGLVKPGGSLRLSCAASGFTFSSSYWMSWVRQAPGKGLEWVANINRDGSASYYVDSV
KGRFTISRDDAKNSLYLQMNSLRAEDTAVYYCARDRGVGYFDLWGRGTLTVTVSS

20 wherein the underlined portions are CDR1 (SEQ ID NO:16), CDR2 (SEQ ID NO: 17), and CDR3 (SEQ ID NO: 18), respectively, from left to right.

Some of the abbreviations related to frequency of administration have the following meanings:

Abbreviation	Meaning
QW	Weekly dosing
D1D8D22 Q4W	4-week cycle, administered on the first day of the first, second, and third weeks and not on the fourth week
Q2W	2-week cycle, dose every two weeks
D1 Q3W	3-week cycle, administered on the first day of the first week, not on the second or third week
D1D8 Q3W	3-week cycle, administered on the first day of the first and second week, not on the third week

EXAMPLES

The treatment method provided in the present application has shown the potential to be superior to the existing standard treatment such as platinum-containing chemotherapy and has excellent safety in patients with locally advanced or metastatic non-small cell lung cancer with EGFR sensitive mutations and has the potential to achieve unexpected breakthrough efficacy and bring significant clinical benefits to patients when compared to existing treatments.

30 The treatment method provided in the present application has shown superior efficacy to existing systemic treatments and good safety in patients with recurrent or metastatic nasopharyngeal carcinoma and has the potential to achieve breakthrough efficacy and bring clinical benefits to patients.

Example 1. Clinical Study: Design and Protocols

Research Topic	Project ADC-6A-101 is a phase I clinical study to evaluate the safety, tolerability, pharmacokinetic characteristics and preliminary efficacy of ADC-6A for injection in patients with locally advanced or metastatic solid tumors
Product	ADC-6A for injection (abbreviated as ADC-6A), each vial contains 120 mg of ADC-6A (BL-B01D1), 11.4 mg of histidine, 37.12 mg of histidine hydrochloride, 125 mg of

	mannitol, 510 mg of sucrose, and 5 mg of polysorbate 80 (II), in the form of lyophilized powder for injection.
Research Centers and Planned Enrollment:	The clinical study was divided into 2 phases: 1. Dose-escalation phase (Ia) is a combination of accelerated titration plus i3+3 design, enrolling approximately 26 patients with locally advanced or metastatic solid tumors (as determined by the progress of the study), planned to be carried out at one to three study centers. 2. Dose-expansion phase (Ib) is divided into two parts: the Dose Expansion Cohort and the Indication Expansion Cohort. The Dose Expansion Cohort will select 1 or more doses for cohort expansion to further evaluate the safety and efficacy of ADC-6A at different doses. The Indication Expansion Cohort will select multiple tumors to further evaluate the safety and efficacy of ADC-6A on different indications. Initial tumor lines, including but are not limited to: non-small cell lung cancer (NSCLC), small cell lung cancer (SCLC), nasopharyngeal carcinoma (NPC), head and neck cancer (HNC), and other solid tumors. The actual enrollment for each indication will be adjusted based on efficacy and safety and is planned to be conducted at 10-20 study centers.
Target Population	This includes, but is not limited to, patients with locally advanced or metastatic non-small cell lung cancer (NSCLC), small cell lung cancer (SCLC), nasopharyngeal carcinoma (NPC), head and neck cancer (HNC), and other solid tumors, who have failed or are unable to access standard treatment.
Purpose of the Trial.	Dose-escalation phase (Ia) 1. Main purpose • To observe the safety and tolerability of ADC-6A in patients with locally advanced or metastatic solid tumors to determine the maximum tolerated dose (MTD) and dose-limiting toxicity (DLT) of ADC-6A. 2. Secondary purpose • To evaluate the pharmacokinetic profile of ADC-6A in patients with locally advanced or metastatic solid tumors. • To evaluate the immunogenicity of ADC-6A in patients with locally advanced or metastatic solid tumors. 3. Exploratory purpose • To detect EGFR or/and HER3 protein expression or gene amplification, expression of related ligands in tumor pathology tissues, and to exploratively investigate their correlation with ADC-6A effectiveness indicators. Dose-expansion phase (Ib) 1. Main purpose • Further observe the safety and tolerability of ADC-6A at the recommended dose in Phase Ia and determine the recommended dose (RP2D) for the Phase II clinical study. 2. Secondary purpose • To evaluate the preliminary efficacy of ADC-6A in patients with locally advanced or metastatic solid tumors. • To further evaluate the pharmacokinetic profile of ADC-6A in patients with locally advanced or metastatic solid tumors.

	- To evaluate the immunogenicity of ADC-6A in patients with locally advanced or metastatic solid tumors. 3. Exploratory purpose - Based on the results of Phase Ia, the biomarkers were prioritized, and the selected biomarkers were further studied for correlation with preliminary efficacy.
Endpoints:	Under the D1D8 Q3W dosing regimen, two DLTs were seen in the 3.5 mg/kg D1 Q3W dose group with a maximum tolerated dose (MTD) of 3.0 mg/kg D1D8 Q3W. Dose-escalation phase (Ia) - Primary endpoints Dose-limiting toxicity (DLT), maximum tolerated dose (MTD). - Secondary endpoints - Type, frequency, and severity of treatment-emergent adverse events (TEAE); - Pharmacokinetic (PK) parameters: C_{max}, T_{max}, $T_{1/2}$, AUC_{0-t}, CL, C_{trough}, and others; - Immunogenicity: incidence of anti-ADC-6A antibodies; - Exploratory endpoints - Protein expression and/or gene amplification of EGFR and/or HER3, and expression of related ligands, as biomarkers to predict ADC-6A efficacy. - Neutralizing activity of anti-ADC-6A antibody. Dose-expansion Phase (Ib) - Primary endpoints - Recommended Dose for Phase II Clinical Studies (RP2D). - Secondary endpoints - Type, frequency, and severity of treatment-emergent adverse events (TEAE); - Objective remission rate (ORR), disease control rate (DCR), and duration of remission (DOR); - Pharmacokinetic (PK) parameters: C_{max}, T_{max}, $T_{1/2}$, AUC_{0-t}, CL, C_{trough}, and others; - Immunogenicity: incidence of anti-ADC-6A antibodies. - Exploratory endpoints - Progression-free survival (PFS), overall survival (OS); - Protein expression and/or gene amplification of EGFR and/or HER3, and expression of related ligands, as biomarkers for predicting efficacy; - Neutralizing activity of anti-ADC-6A antibody.
Design of Trial.	This study is an open, multicenter, dose-escalation and expanded-enrollment, non-randomized Phase I clinical study evaluating the safety, tolerability, pharmacokinetic profile, and preliminary efficacy of ADC-6A for injection in locally advanced or metastatic solid tumors in two phases: a dose-escalation phase (Phase Ia) and an expanded-enrollment phase (Phase Ib). This study is an open, multicenter, dose-escalation and expanded enrollment non-randomized Phase I clinical study to evaluate the safety, tolerability, pharmacokinetic characteristics and preliminary efficacy of ADC-6A for injection in locally advanced or metastatic solid tumors. The study is divided into two phases: dose escalation phase (Phase Ia) and expansion phase (Phase Ib).

	1. Dose-escalation phase (Phase Ia) a. The original dose-escalation program: A combined accelerated titration and i3+3 design was used to enroll approximately 26 patients with locally advanced or metastatic solid tumors (as determined by the progress of the study) and is planned to be conducted at one to three study centers. The initial preset dose groups for the study drug ADC-6A were 0.27 mg/kg, 1.5 mg/kg, 3.0 mg/kg, 6.0 mg/kg, 9.0 mg/kg, 12.0 mg/kg, and 15.0 mg/kg. Starting at 3.0 mg/kg, the preset default increment was 3.0 mg/kg. Dose increments are adjusted as follows (see Table 1.1, the original climbing dose adjustment table for details). b. The current dose-escalation program: Because patients in the <u>3mg/kg, QW, 4-week cycle</u> dose group experienced significant myelosuppressive toxicity after 3 consecutive weeks of dosing, now, for the sake of subject safety and the need for recovery from myelosuppression after dosing, the ramping protocol was adjusted to two ramping cohorts, and the existing total dose administered every 3 weeks was adjusted downward from 9mg/kg to 5mg/kg, as described in the protocol below (see Table 1.2). Cohort A: A total dose of 5 mg/kg every 3 weeks, with 2.5 mg/kg given to D1 and D8 respectively, i.e., <u>D1 and D8 administered at 2.5 mg/kg every 3-week cycle</u>, and their subsequent climbing doses simultaneously adjusted downward relative to the original climbing dose to: D1 and D8 administered at 3.0 mg/kg, 3.5 mg/kg, 4.0 mg/kg, and 4.5 mg/kg; 2.0 mg/kg, 1.5 mg/kg if dose reductions are required according to the ramp-up rule or for other safety considerations; Cohort B: A total dose of 5 mg/kg every 3 weeks and 5 mg/kg given for D1, i.e., <u>D1 administered, 5 mg/kg, every 3-week cycle</u>, with subsequent ramp-down doses relative to the original ramp-up dose simultaneously adjusted downward as follows: 6.0 mg/kg, 7.0 mg/kg, 8.0 mg/kg, and 9.0 mg/kg for D1 administered, every 3-week cycle; if dose reductions are required according to the ramp-up rule or for 4.0 mg/kg and 3.0 mg/kg if dose reductions are required under the climb rule or for other safety considerations. For subjects who have completed DLT observation and accelerated titration, in order to maximize the benefits to the subject, the investigator and the sponsor will discuss, and the dose of the drug administered to the subject may be adjusted upward to a higher safe and effective dose to maximize the benefits to the subject. If dose adjustment is required according to the climbing rules or for other safety considerations, the investigator and the sponsor will discuss and, at the current climbing dose, select another appropriate dose or dosing regimen to conduct a climbing study. ADC-6A requires a complete blood count (CBC) test prior to each dose, and neutrophils and platelets are required to meet the following criteria prior to each dose, except for the first dose (Cohort B will be administered D1 only, see Table 1.3). Prophylactic treatment for neutropenia is as follows: Neutropenia prophylaxis (Stage Ia: no prophylaxis allowed during the DLT observation period), based on the patient's tolerance of prior antineoplastic therapy, long-acting G-CSF primary prophylaxis may be given at the investigator's discretion if there has been
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	a high-risk factor such as febrile neutropenia or grade 4 neutropenia, and long-acting G-CSF secondary prophylaxis may be given at the investigator's discretion based on the tolerance of the first or prior administration if there has been a high-risk factor such as febrile neutropenia or grade ≥ 3 neutropenia. neutropenia or grade ≥ 3 neutropenia, secondary prophylactic treatment with G-CSF after the next dose (at least the second cycle), with either short- or long-acting G-CSF depending on the dosing interval or clinical practice; the decision pathway for treatment (with reference to [the Chinese Society of Clinical Oncology (CSCO) Guidelines for the Standardized Management of Oncology Radiotherapy-Associated Neutropenia (2021)], <i>see Figure 1</i>). Supportive treatment for neutropenia and thrombocytopenia after the first dose is as follows: 1. Neutropenia supportive treatment refers to the granulocyte colony-stimulating factor (G-CSF) drug manual, that is, when the ANC is $<1.0 \times 10^9 /L$. 2. Thrombocytopenia supportive treatment refers to the thrombopoietin drug manual, that is, when the platelets are $<50 \times 10^9 /L$. 3. Hemoglobin supportive treatment refers to the EPO, that is, when the hemoglobin is $<100g/L$. Dose creep is a combination of accelerated titration and i3+3 design, with dose escalation in cohorts of 2 to 4 individuals. For the first 2 dose cohorts an accelerated titration design will be used (only 1 subject will be enrolled): 1. If a DLT or two drug-related AEs greater than or equal to Grade 2 (except infusion-related reactions) are observed in either accelerated titration dose group, an additional 2 to 3 subjects will be added at the current dose level, and the design of the subsequent trial will be automatically changed to an i3+3 design in groups of 2 to 4; 2. If no DLT was observed in the first 2 dose cohorts of accelerated titration and the number of drug-related AEs greater than or equal to grade 2 occurred less than twice, the dose was incremented using an i3+3 design with groups of 2 to 4 starting in the 3rd dose cohort. 3. If a safety event is observed in any of the accelerated titration dose groups, it is assessed by the investigator that it is necessary to increase the number of subjects to continue the observation of drug toxicity at the current dose level. The i3+3 design uses a Bayesian statistical framework and a Beta-Bernoulli model to pre-compute decision rules for dose escalation. A target DLT rate of 28% and an equivalence interval of 23% to 33% (i.e., target DLT rate $\pm 5\%$) will be used to parameterize the i3+3 design in this study. During the dose-escalation phase, the dosing interval between the two subjects enrolled was at least 24 hours to allow for a preliminary assessment of tolerability and toxicity. If any of the following conditions are met, the climb is stopped: 1. Maximum sample size was reached (approximately 38 cases in total); 2. Sample size ≥ 9 individuals treated at the same dose and this dose was adjudicated as MTD. Note: The maximum sample size prediction is based on the number of cases of subjects assumed to have climbed to the highest dose group and terminated the climb after full exposure to toxicity.
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	Based on the i3+3 design, the detailed rules for dose escalation/decrease are shown in Table 1.4 and 1.5. After the dose-escalation phase has stopped climbing, the probability of DLT in each dose group is estimated by the PAVA algorithm (Pool Adjacent Violators Algorithm) that implements Isotonic Regression, and the DLT rate estimate that is closest to the target DLT rate, but does not exceed the DLT rate equivalence interval, is then selected as the MTD. The highest dose with the upper threshold value was used as the MTD. Within the dose range interval expected to be effective, the investigator, in communication with the sponsor's medical staff, may adjust the magnitude of the dose increment, increase the intermediate dose with the rate of increment, or perform a lower dose creep. If a subject withdraws from the study or voluntarily withdraws from the study for non-DLT reasons during Cycle 1 treatment, (i) the subject is considered an evaluable subject if the subject has completed the total anticipated dosage for the DLT period and has completed the 21 days of observation for the DLT period; and (ii) the subject is considered a non-evaluable subject if the subject has not completed the total dosage for the DLT period or has not completed the 21 days of observation for the DLT period. Subjects were considered evaluable if they developed DLT in Cycle 1 and withdrew from the study. Additional rules for non-evaluable subjects are listed below: 1. If the number of evaluable subjects and the number of DLTs occurring at the current dose are determined to be "dose escalated" or "reduced to the previous dose" or "reduced to the previous dose and all doses above this are canceled" according to the Dose Escalation/Decrease Rulebook, then the subject does not need to be supplemented at the current dose. "Reduce to previous dose and eliminate all doses above", then the subject does not need to be supplemented at the current dose; and 2. If the number of evaluable subjects and the number of DLT occurrences in the current dose is determined to be "Maintain Current Dose" according to the "Dose Escalation/Decrease Rule Sheet", then it is necessary to replenish the subject at the current dose or continue enrolling subjects in groups of two to four. Dose-expansion phase (phase Ib) The Phase Ib trial was divided into two parts: (i) a dose expansion cohort and (ii) an indication expansion cohort. 1. Dose Expansion Cohort: Based on safety, pharmacokinetic, and preliminary efficacy data obtained in Phase Ia, select 1 or more doses (including preliminary RP2D and other dose levels of interest, or different frequencies of administration with similar exposure) for cohort expansion to further evaluate the safety and efficacy of ADC-6A at different doses. Now that ADC-6A Cohort A: 2.5 mg/kg, 3.0 mg/kg and Cohort B: 5.0 mg/kg, 6.0 mg/kg have completed the climb, are generally tolerated and all show signals of efficacy, an expansion can be performed in Cohort A: 3.0 mg/kg and below dose groups and Cohort B: 6.0 mg/kg and below dose groups, which can be decided by the sponsor in discussion with the investigator to decide after discussion; and 2. Expanded Indication Cohort: Based on the safety, pharmacokinetic and preliminary efficacy data obtained in Phase Ia, multiple tumor types will be selected to further evaluate the safety and efficacy of ADC-6A in different
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	indications. Preliminary tumor types include but are not limited to: non-small cell lung cancer (NSCLC), small cell lung cancer (SCLC), nasopharyngeal carcinoma (NPC), head and neck cancer (HNC) and other solid tumors. The actual enrollment for each indication will be adjusted based on efficacy and safety and is planned to be conducted at 10-20 study centers.
Inclusion Criteria	1. Voluntarily sign an informed consent form and follow program requirements; 2. Gender is not limited; 3. Age: ≥ 18 and ≤ 75 years (Stage Ia); ≥ 18 years (Stage Ib); 4. Expected survival time ≥ 3 months; 5. Locally advanced or metastatic solid tumors diagnosed by pathohistology and/or cytology that are incurable or for which there is no current standard of care; 6. Agree to provide an archived tumor tissue specimen or fresh tissue sample within 2 years of the primary focus or metastasis; if the subject is unable to provide a tumor tissue sample, he/she may be enrolled after evaluation by the investigator if other enrollment criteria are met; 7. Must have at least one measurable lesion that meets the definition of RECIST v1.1; 8. Physical condition score ECOG 0 or 1; 9. Toxicity of prior antineoplastic therapy that has recovered to $\leq$ grade 1 as defined by the NCI-CTCAE v5.0 (except for asymptomatic laboratory test abnormalities considered by the investigator, such as elevated ALP, hyperuricemia, and elevated glucose; except for toxicities judged by the investigator to be of no safety risk, such as alopecia, grade 2 peripheral neurotoxicity; or except for hemoglobin that is reduced but ≥ 90 g/L); 10. No serious cardiac abnormalities and left ventricular ejection fraction $\geq 50\%$; 11. The level of organ function must meet the following requirements to the following standards: a. Bone marrow function: absolute neutrophil count (ANC) $\geq 1.5 \times 10^9$ /L, platelet count $\geq 90 \times 10^9$ /L, hemoglobin ≥ 90 g/L; b. Liver function: total bilirubin (TBIL) ≤ 1.5 ULN, both AST and ALT ≤ 2.5 ULN in the absence of liver metastases, and both AST and ALT ≤ 5.0 ULN in the presence of liver metastases; c. Renal function: creatinine (Cr) ≤ 1.5 ULN, or creatinine clearance (Ccr) ≥ 50 mL/min (according to the Cockcroft and Gault formula). 12. Coagulation: international normalized ratio (INR) ≤ 1.5 and activated partial thromboplastin time (APTT) ≤ 1.5 ULN; 13. Urine protein $\leq 2+$ or ≤ 1000mg/24h; and 14. For premenopausal women of childbearing potential, a pregnancy test must be performed within 7 days prior to initiation of treatment, must be negative for serum or urine pregnancy, and must be non-lactating; all enrolled patients (whether male or female) should use adequate barrier contraception throughout the treatment cycle and for 6 months after completion of treatment.
Exclusion Criteria	1. Screened patients presenting with any of the following conditions will not be enrolled in the study: 2. Antineoplastic treatments such as chemotherapy, biologic therapy, immunotherapy, radical radiotherapy, major surgery (investigator-defined), and

	targeted therapies (including small-molecule tyrosine kinase inhibitors) were used within 4 weeks or 5 half-lives (whichever is shorter) prior to the first administration of the drug; mitomycin and nitrosoureas within 6 weeks prior to the first administration of the drug; oral drugs such as Tegretol, capecitabine in the fluorouracil group, or palliative radiotherapy is within 2 weeks before the first dose; 3. History of severe cardiac disease, e.g., history of symptomatic congestive heart failure (CHF) $\geq$ grade 2 (CTCAE 5.0), New York Heart Association (NYHA) class $\geq$ grade 2 heart failure, history of transmural myocardial infarction, unstable angina pectoris; 4. Prolonged QT interval (QTc > 450 msec in men or QTc > 470 msec in women), complete left bundle branch block, and third-degree AV block; 5. Active autoimmune and inflammatory diseases, e.g., systemic lupus erythematosus, psoriasis requiring systemic therapy, rheumatoid arthritis, inflammatory bowel disease, and Hashimoto's thyroiditis; except for type I diabetes mellitus, hypothyroidism that can be controlled by substitution therapy only, and dermatologic disorders (e.g., vitiligo, psoriasis) that do not require systemic therapy; 6. Diagnosis of another malignancy within 5 years prior to the first dose, with the following exceptions: radically treated basal cell carcinoma of the skin, squamous cell carcinoma of the skin, and/or radically resected carcinoma in situ; 7. Hypertension (systolic blood pressure >150 mmHg or diastolic blood pressure >100 mmHg) not well controlled by two antihypertensive medications; 8. Patients with current or history of interstitial lung disease (ILD) with lung disease defined as $\geq$ grade 3 according to CTCAE v5.0; 9. Thrombotic events such as unstable deep vein thrombosis, arterial thrombosis, and pulmonary artery embolism requiring therapeutic intervention within 6 months prior to screening; with the exception of infuser-associated thrombosis; 10. Symptoms of active CNS metastases. However, patients with stable brain parenchymal metastases may be enrolled. Stable is defined as: a. Seizure-free status epilepticus lasting >12 weeks with or without antiepileptic drugs; b. Glucocorticoids are not required; and c. Multiple consecutive MRIs (at least 8 weeks between scans) are shown to 11. be stable on imaging; 12. Patients with a history of hypersensitivity to recombinant humanized or human-mouse chimeric antibodies or to any of the excipient components of ADC-6A; 13. Prior organ transplantation or allogeneic hematopoietic stem cell transplantation (Allo-HSCT); 14. Cumulative anthracycline dose >360 mg/m² in prior anthracycline (neo)adjuvant therapy; 15. Human immunodeficiency virus antibody (HIVAb) positivity, active tuberculosis, active hepatitis B virus infection (HBV-DNA copy number >10³ IU/ml) or active hepatitis C virus infection (HCV antibody positivity and HCV-RNA > lower limit of detection); 16. Active infections requiring systemic therapy, such as severe pneumonia, bacteremia, and sepsis;
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	17. Participation in another clinical trial within 4 weeks prior to the first dose (counting from the time of the last dose); and 18. Other conditions that the investigator believes are not appropriate to adopt for participation in this clinical trial.
Drug Delivery Program	Phase Ia: ADC-6A was administered by intravenous drip, Cohort A: D1 and D8 administered every 3 weeks; Cohort B: D1 administered every 3 weeks. The first administration was titrated to 120 min $\pm$ 10 min, and subsequent administrations could be infused in 60-120 min $\pm$ 10 min if the infusion response during the first administration was tolerable. The DLT observation period was followed by a window of 3 days (+3 days) allowed for the dosing interval specified by the plan. Dosing was administered until disease progression or intolerable toxicity or other reasons for termination of dosing (e.g., withdrawal of informed consent or death). During the Phase Ia dose-escalation phase, the dosing regimen (including changes in dosing frequency, shock dose settings, etc.) and dosing dose may be adjusted based on available safety, tolerability, PK/PD, and other data. Phase Ib: Selection of appropriate dose groups and dosing regimens for Phase Ib studies based on safety, pharmacokinetic and preliminary efficacy data from Phase Ia.
Definition of MTD	During the dose-escalation phase, the highest dose for which the DLT rate estimate is closest to the target DLT rate but does not exceed the upper bound of the DLT rate equivalence interval, is selected as the MTD. If there are multiple dose groups for which the DLT rate estimate meets the above conditions: - If this DLT rate estimate is less than the target DLT rate, select the highest of these doses as the MTD; and - If this DLT rate estimate is greater than the target DLT rate, select the lowest of these doses as the MTD.
Definition of DLT	The DLT observation period is the first treatment cycle (first 3 weeks of treatment) at each dose level. Toxicity should be graded according to NCI-CTCAE version v5.0; all prophylactic medications prior to study drug infusion that affect DLT judgment are not permitted during the DLT Observation Period. However, initiation of supportive therapy is permissible in the event of CTCAE v5.0-defined grade ≥ 3 hematologic toxicity after study drug infusion. DLT is defined as: Hematological toxicity: - Grade 4 neutropenia lasting >7 days after supportive therapy; Grade ≥ 3 febrile neutropenia (absolute neutrophil count $<1.0 \times 10^9 / L$ and a single temperature $>38.3^\circ C$ or sustained temperature $\geq 38^\circ C$ for more than 1 hour); - Grade 4 thrombocytopenia persisting for >7 days after supportive therapy or $\geq$ Grade 3 thrombocytopenia with significant bleeding; - Grade 4 anemia persisting for >7 days after supportive care. Hepatotoxicity: - Grade 4 Elevated blood bilirubin, AST and/or ALT; $\geq$ Grade 3 AST and/or ALT elevation lasting > 7 days; $\geq$ Grade 3 blood bilirubin elevation lasting > 7 days;

	• $\geq$ Grade 2 AST and/or ALT elevation with $\geq$ Grade 2 blood bilirubin elevation for > 7 days. • $\geq$ Grade 3 non-hematologic non-hepatotoxicity, except for the following: • Grade 3 Skin toxicity, constipation, nausea, vomiting, anorexia, electrolyte abnormalities, recovery to CTCAE v5.0 defined as $\leq$ Grade 2 in ≤ 7 days with symptomatic supportive therapy; • Grade 3 diarrhea with recovery to CTCAE v5.0 defined as $\leq$ Grade 2 after 3 days of symptomatic supportive treatment; • Grade 3 fatigue that recovers to $\leq$ Grade 1 within 7 days of treatment; • Grade 3/4 asymptomatic laboratory test abnormalities (elevated ALP, hyperuricemia, elevated blood glucose, etc.); • Any grade of hair loss; • Infusion-Related Reactions (IRR). Infusion-related reactions are generally symptoms of adverse reactions that commonly occur during intravenous infusion of blood products, protein products, and biologics and are not considered DLTs; however, patients experiencing a Grade 3 or 4 infusion reaction would require an additional patient in that dose group if they could not continue to be treated with the study drug.
PK Research	Cohort A: Administered in dose-escalation phases D1 and D8, the blood collection points were designed as follows for every 3-week cycle: Cycle 1: For the first infusion of the test drug, a PK blood sample will be collected at the following time points: • Prior to the first infusion of the test drug (within -4h) • Immediately after infusion (within +15 min) • 2h$\pm$30 min, 4h$\pm$30 min, 6h$\pm$30 min after the end of infusion • Day 2 of administration (24 h $\pm$ 1 h after end of infusion) • Day 3 of administration (48 h $\pm$ 2 h after end of infusion) • Day 5 of administration (96 h $\pm$ 4 h after end of infusion) • Day 8 of administration (within 168 h-4 h of the end of infusion) If the patient receives the second dose of the first cycle, the blood collection prior to the second dose of the first cycle is duplicated at the same point as the blood collection on day 8 (within 168 h-4 h of the end of the infusion) of the first dose of the cycle and only needs to be collected once, and if the patient no longer receives the second dose of the first cycle, the PK collection on day 8 (within 168 h-4 h of the end of the infusion) of the first dose of the cycle needs to be completed. For the second infusion of the test drug, PK blood samples will be collected at the following time points: • Day 8 (before - within 4h of second infusion of test drug) • Immediately + 15 min from end of infusion • 2h$\pm$30 min, 4h$\pm$30 min, 6h$\pm$30 min after the end of infusion • Day 9 of administration (24 h $\pm$ 1 h after end of infusion) • Day 10 of administration (48 h $\pm$ 2 h after end of infusion) • Day 12 of administration (96 h $\pm$ 4 h after end of infusion) • Day 15 of administration (168h$\pm$4h after the end of administration) • Day 22 of administration (within 336h-4h of the end of administration) Follow-up cycle:

	PK blood sampling was performed at the first infusion of the test drug in each cycle, and the blood collection points were designed: • Prior to infusion of test drug (within -4h) • Immediately after infusion (within +15 min) For the second infusion of the test drug, the blood collection point was designed: • Prior to infusion of test drug (within -4h) • Immediately after infusion (within +15 min) • Day 22 of administration (within 336h-4h of the end of administration) If the patient receives the next cycle of administration, the next cycle of D1 pre-administration blood collection is duplicated at the D22 blood collection point for that cycle and need only be collected once, and if the patient is no longer receiving the next cycle of treatment, the PK blood collection for that cycle of D22 will need to be completed. Cohort B: Administered in dose-escalation phase D1, every 3 weeks blood collection points were designed as follows: Cycle 1: For infusion of the test drug, PK blood samples will be collected at the following time points: • Prior to the first infusion of the test drug (within -4h) • Immediately after infusion (within +15 min) • 2h±30 min, 4h±30 min, 6h±30 min after the end of infusion • Day 2 of administration (24 h ± 1 h after end of infusion) • Day 3 of administration (48 h ± 2 h after end of infusion) • Day 5 of administration (96 h ± 4 h after end of infusion) • Day 8 of administration (168 h ± 4 h after end of infusion) • Day 15 of administration (336 h ± 4 h after the end of infusion) • Day 22 of administration (within 504h-4 h of the end of infusion) Cycle 2: • D1 Before infusion of test drug (within -4h) • Immediately after infusion (within +15 min) • Day 8 of administration (168 h ± 4 h after end of infusion) • Day 15 of administration (336 h ± 4 h after the end of infusion) • Day 22 of administration (within 504h-4 h of the end of infusion) Follow-up cycle: • D1 Before infusion of test drug (within -4h) • Immediately after infusion (within +15 min) • Day 22 of administration (within 504h-4 h of the end of infusion) If the patient receives the next cycle of administration, the next cycle of D1 pre-administration blood collection is duplicated at the D22 blood collection point for that cycle and need only be collected once, and if the patient is no longer receiving the next cycle of treatment, the PK blood collection for that cycle of D22 will need to be completed. Each PK sample required 4 ml of blood. During the dose-escalation phase, based on preliminary pharmacokinetic data obtained from the completed dose groups, the time of blood collection for subsequent patients may be adjusted accordingly. The time points for blood collection in the enrollment-expansion phase are referenced to the PK study in the dose-escalation phase,
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	where subjects in each dose group of the Team Leader Unit, 10-15 subjects are required to collect all the time points for blood collection in the PK study, while other Team Leader Unit subjects and sub-center subjects are reserved for only the two time points for blood collection, within -4h prior to dosing, and immediately after dosing (within +15min). Blood collection time points for the cohort-expansion phase will likely be adjusted based on the results of the dose-escalation phase.
Immuno-genicity Evaluation	Serum ADA and neutralizing antibody (Nab) production were detected at the following time points: • Prior to the first dose of Cycle 1; • Cycle 2 onwards, before (within -4h) the first infusion of test drug in each even-numbered cycle; • Within 0-7 days after termination of treatment. • Approximately 3 mL of blood was collected from each at a time.
Research Indicators	Safety indicators. All subjects will be assessed at the end of Cycle 1 (initial 3 weeks) and DLT will be assessed after each dose in Cycle 1 and graded and tabulated according to NCI-CTCAE v5.0. Patient safety and tolerability assessments were based on analysis of physical examination, adverse events (including DLT), vital signs, physical status ECOG score, echocardiography, electrocardiogram, laboratory tests, and coadministration. Evaluate adverse events and serious adverse events based on NCI-CTCAE v5.0 criteria. The investigator should determine the relationship of the adverse event to the study drug. Indicators of immunogenicity: Anti-ADC-6A antibody and neutralizing antibody. PK Parameters: Blood concentration-area under the timeline (AUC_{0-t} and AUC_{0-inf}), time to peak (T_{max}), peak concentration (C_{max}), half-life ($T_{1/2}$), and trough concentration (C_{trough}). Indicators of efficacy: Clinical efficacy was assessed by the investigator according to RECIST v1.1 criteria to determine the course of patient treatment. Anti-tumor effects were assessed by the following parameters: • Objective remission rate (ORR); • Progression-free survival (PFS); • Overall survival (OS); • Disease Control Rate (DCR); and • Duration of remission (DOR).
Statistical Methods	In this trial, descriptive statistical analyses of safety indicators, efficacy indicators, PK parameters, immunogenicity indicators, and biomarker measurements will be performed without statistical tests, and these data will be presented in summary charts or tables. Descriptive statistics for continuous variables included the number of instances, mean, standard deviation, median, quartiles, minimum and maximum values. Descriptive statistics for categorical variables were frequency counts and percentages. DLT: The number of cases and percentage of patients presenting with DLT were summarized by dosing regimen and dose level.

	Safety Parameters: All AEs were judged for severity using NCI-CTCAE v5.0 criteria, and the number of cases and incidence were summarized according to system organ classification (SOC) and preferred terminology (PT). Pharmacokinetic parameters: Based on the blood concentration-time data measured in the trial for each patient, the drug-time curves for each patient and the average drug-time curves for each dose group (including semi-log plots) were plotted, and the estimation of pharmacokinetic parameters was analyzed by using a non-atrial model to find the main metabolic kinetic parameters of the drug. Therapeutic parameters: Objective remission rate (ORR), disease control rate (DCR), duration of remission (DOR), progression-free survival (PFS), and overall survival (OS) will be statistically described. 95% CI will be calculated using Clopper-Pearson intervals.DOR, PFS, and OS will be estimated using the Kaplan-Meier method for median survival time.
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Example 2. Analysis of Clinical Safety and Tolerability Data

1.1. Dose Creep and DLT profile

A total of 25 subjects were enrolled in the climb phase of the ADC-6A single-agent phase I solid tumor program (ADC-6A-101). ADC-6A was dose-climbed in the first QW dosing regimen, and in the 3.0 mg/kg QW dose group, 2 DLTs were seen, while the frequency of dosing was then reduced and dose-climbing continued in the D1D8 Q3W and D1 Q3W dosing regimens.

Under the D1D8 Q3W dosing regimen, two DLTs were seen in the 3.5 mg/kg D1 Q3W dose group with a maximum tolerated dose (MTD) of 3.0 mg/kg D1D8 Q3W.

Under the D1 Q3W dosing regimen, there were no DLTs in the 6.0 mg/kg D1 Q3W dose group, however, two DLTs occurred in the 3.5 mg/kg D1D8 Q3W dose group (equivalent to the 7.0 mg/kg D1 Q3W dose group based on a 3-week total dose). Thus, in order to minimize the risk to subjects, the applicant did not proceed with the ramp-up to a higher dose group, after full discussion with the investigator. At the current dose, 6.0 mg/kg D1 Q3W is the maximum administered dose (MAD).

DLT subjects are detailed in **Table 2.1**.

1.2. Overall Safety

A total of 169 subjects were enrolled in the ADC-6A monotherapy Phase I solid tumor project (ADC-6A-101). Approximately 5% (8/169) and 23% (39/169) of the subjects discontinued or reduced the dose due to adverse events, respectively. Approximately 3% (5/169) and 23% (39/169) of the subjects discontinued or reduced the dose due to drug-related adverse events, respectively. The safety of the 2.5 mg/kg D1D8 Q3W and 4.5 mg/kg D1 Q3W dose groups was relatively optimal, as shown in **Table 2.2**. The safety characteristics of 104 subjects with non-small cell lung cancer and 36 subjects with nasopharyngeal carcinoma were basically consistent with those of the general population, as shown in **Tables 2.3 and 2.4**.

Example 3. Clinical Efficacy Data Analysis

3.1. Tumor Assessment Method

The subjects enrolled in the ADC-6A -101 project are: locally advanced or metastatic solid tumors that are incurable or currently have no standard treatment confirmed by pathological histology and/or cytology.

The classification of tumor efficacy evaluation will be carried out according to the RECIST v1.1 efficacy criteria.

Imaging examinations will be performed once every 6 weeks $\pm$ 7 days in the first year of medication from the start of medication; once every 12 weeks $\pm$ 7 days in the second year of medication. According to the protocol, additional imaging examinations can be performed at any time during the study if progression is suspected.

3.2. Efficacy Analysis

There were 144 subjects with at least one tumor assessment. Existing efficacy data show that ADC-6A has shown clear efficacy signals in solid tumors such as non-small cell lung cancer, small cell lung cancer, nasopharyngeal carcinoma, and head and neck squamous cell carcinoma.

3.2.1. Effectiveness by dose group

10 Six subjects in the QW dose group underwent at least one tumor evaluation, and the best efficacy was SD in 6/6 cases. Among them, 1 subject with nasopharyngeal carcinoma was enrolled in the 0.27mg/kg QW dose group, 1 subject with lung adenocarcinoma was enrolled in the 1.5mg/kg QW dose group, and 2 subjects with lung squamous cell carcinoma, 1 subject with lung lymphoepithelioma-like carcinoma, and 1 subject with nasopharyngeal carcinoma were enrolled in the 3mg/kg QW dose group. The efficacy data were analyzed according to different QW dose groups (see **Table 3.1** for details).

138 subjects in the Q3W dose group underwent at least one tumor assessment. In each Q3W dose group, ADC-6A showed clear efficacy signals. Efficacy data were analyzed by different dose groups (see **Table 3.2** for details).

3.2.2. Effectiveness of Q3W dose group to each tumor type

20 Among the 138 subjects with at least one tumor assessment in the Q3W dose group, 85 were non-small cell lung cancer, 29 were nasopharyngeal carcinoma, 15 were head and neck squamous cell carcinoma, 7 were small cell lung cancer, and 2 were other rare tumors. The efficacy data of each cancer type are detailed in **Table 3.3**.

For the aforementioned 85 subjects with non-small cell lung cancer, the median line of treatment was 3 lines, the objective response rate (ORR) was 54.1% (46/85), the disease control rate (DCR) was 92.9% (79/85), and the median progression-free survival (mPFS) of the subjects was not yet mature, but a good, sustained response could be observed.

30 For the aforementioned 29 subjects with nasopharyngeal carcinoma, the median previous line of treatment was 3, the objective response rate (ORR) was 51.7% (15/29), the disease control rate (DCR) was 100% (29/29), and the median progression-free survival (mPFS) of the subjects had not yet been reached, but good sustained responses were observed.

3.2.3. Effectiveness of Q3W dose group in non-small cell lung cancer (NSCLC)

For the aforementioned 85 NSCLC subjects, each dose group showed a high response rate; the overall effectiveness of the 2.5mg/kg D1D8 Q3W dose group and the 4.5mg/kg D1 Q3W dose group was comparable; the effectiveness data of other effective dose groups are detailed in **Table 3.4**, and the waterfall charts of the best efficacy of the subjects are shown in **Figures 3.1, 3.2, and 3.3**.

40 During the trial, 9 of the 85 NSCLC subjects had their medication severely affected by the COVID-19 pandemic, specifically defined as the number of medications that actually produced efficacy during the first and second tumor assessments due to COVID-19-related factors, which was $\geq 25\%$ less than the planned number of medications, ultimately resulting in SD results for the first and second tumor assessments of the subjects. After excluding this part of the subjects, the ORR of the subjects not affected by the COVID-19 pandemic was 60.5% (46/76), and the DCR was 92.1% (70/76); among them, 31 patients in the 2.5mg/kg D1D8 Q3W dose group who were not affected by the COVID-19 had a total tumor evaluation, with an ORR of 58.1% (18/31) and a DCR of 93.5% (29/31); 19 patients in the 4.5mg/kg D1 Q3W dose group who were not affected by the COVID-19 had a total tumor evaluation, with an ORR of 52.6% (10/19) and a DCR of 89.5% (17/19).

Based on the above data, each effective dose of ADC-6A monotherapy showed potential breakthrough efficacy in patients with non-small cell lung cancer.

Among the aforementioned 85 NSCLC subjects, 47 subjects were EGFR wild-type, with a median line of treatment of 2, an ORR of 46.8% (22/47), a DCR of 95.7% (45/47), and mPFS of the subjects had not yet been reached; among them, 43 (91.4%) subjects had received PD-1/PD-L1 monoclonal antibody treatment and at least 1 line of platinum-containing chemotherapy, that is, patients who had received PD-1/PD-L1 monoclonal antibody treatment and ≥ 1 line of platinum-containing chemotherapy, with a median line of treatment of 2, an ORR of 48.8% (21/43), DCR was 95.3% (41/43), and the mPFS of the subjects had not yet been achieved; among them, 31 subjects (66%) had received PD-1/PD-L1 monoclonal antibody treatment and at least 2 lines of chemotherapy (including 1 line of platinum-containing chemotherapy) as the frontline, that is, patients who had received PD-1/PD-L1 monoclonal antibody treatment and ≥ 2 lines of platinum-containing chemotherapy, with a median line of treatment of 3 lines, ORR was 48.4% (15/31), DCR was 96.8% (30/31), and the mPFS of the subjects had not yet been achieved.

Among the aforementioned 85 NSCLC subjects, 38 subjects had EGFR mutant non-squamous NSCLC, all of whom had received TKI treatment in the front line, with a median of 3 lines of treatment, an ORR of 63.2% (24/38), a DCR of 89.5% (34/38), and mPFS of the subjects was not yet mature; among them, 29 (76.3%) subjects had received sufficient TKI treatment in the front line (treated with 3rd generation TKI or treated with 1st or 2nd generation TKI with clear negative evidence of T790M mutation) and at least 1 line of platinum-containing chemotherapy, that is, they had been fully treated with TKI and contained For patients who had received ≥ 1 line of platinum chemotherapy, the median line of treatment was 4, the ORR was 58.6% (17/29), the DCR was 88.7% (26/29), and the mPFS of the subjects was not yet mature; among them, 19 subjects (50%) had been fully treated with TKI and platinum-containing chemotherapy and other subsequent treatments, that is, patients who had been fully treated with TKI and ≥ 2 lines of platinum-containing chemotherapy, the median line of treatment was 5, the ORR was 63.2% (12/19), the DCR was 93.7% (18/19), and the mPFS of the subjects had not yet been achieved (**Table 3.5**).

The waterfall charts of the subjects' best efficacy are shown in **Figures 3.4 and 3.5**, respectively.

Among 85 subjects with NSCLC, 28 subjects had brain metastases at baseline, of which 26 subjects had not received treatment for brain lesions, and 2 subjects had received radiotherapy, with an ORR of 50% (14/28), a DCR of 85.7% (24/28), and a mPFS of 4.3 (3.9~NR) months; 57 subjects had no brain metastases at baseline, and in the subgroup without brain metastases, the ORR was 56.1% (32/57), the DCR was 96.5% (55/57), and the mPFS of the subjects had not yet been reached. It can be seen that patients with non-small cell lung cancer with brain metastases at baseline and without targeted treatment also have a good response to ADC-6A monotherapy, but compared with patients without brain metastases at baseline, the mPFS is significantly shorter (**Table 3.6 and Figure 3.6**).

3.2.4. Effectiveness of Q3W dose group in nasopharyngeal carcinoma (NPC)

Among the aforementioned 29 subjects with nasopharyngeal carcinoma, the 2.5mg/kg D1D8 Q3W, 4.5mg/kg D1 Q3W, and 5.0mg/kg D1 Q3W dose groups all showed high response rates (**Table 3.4**), and the PFS K-M plots of the subjects and the best efficacy waterfall plots are shown in **Figure 3.1 and Figure 3.2**.

Among the aforementioned 29 NPC subjects, the medication of 5 subjects was severely affected by the COVID-19 pandemic, which was specifically defined as the subjects' actual number of medications that produced efficacy during the first and second tumor assessments was reduced by $\geq 25\%$ compared with the planned number of medications due to COVID-19-related factors, which ultimately resulted in SD results for the subjects' first and second tumor assessments. After excluding these subjects, the ORR of subjects not affected by the COVID-19 pandemic was 62.5% (15/24), and the DCR was 100% (24/24).

Among the aforementioned 29 NPC subjects, 19 patients were evaluated in the 2.5 mg/kg D1D8 Q3W dose group, with a median of 3 (1-9) lines of treatment, an ORR of 52.6% (10/19), a DCR of

100%, and mPFS of the subjects was not reached. A total of 15 patients who were not affected by COVID-19 were evaluated, with an ORR of 66.7% (10/15), and a DCR of 100% (15/15).

Based on the above data, the ADC-6A monotherapy 2.5 mg/kg D1D8 Q3W dose group showed potential breakthrough efficacy in late-line NPC patients.

Example 4. Analysis of Clinical Pharmacology Trial Data

4.1. Characterisation of Pharmacokinetic of ADC-6A

In the ADC-6A-101 project, patients underwent complete intensive blood sampling before and after the first dose (C1D1) to detect the concentrations of ADC, Total Antibody (TAB) and small molecule toxins in plasma after a single dose, and to perform pharmacokinetic analysis.

10 Within the dose range of 0.27mg/kg to 6.0mg/kg, there was no significant difference in the concentrations of ADC and TAB of ADC-6A at various blood collection time points (**Figure 4.1**), demonstrating the role of ADC-6A in the human body good stability in plasma. This result is also consistent with the preclinical pharmacokinetic results of ADC-6A.

Within this dose range, ADC-6A's ADC and TAB overall exhibit nonlinear pharmacokinetic characteristics similar to those of its naked anti-SI-B001^[1] and EGFR antibody Cetuximab^[2] (**Figure 4.1**). As the dose increases, clearance slows.

4.1.1. Parameters of pharmacokinetics

20 The pharmacokinetic parameters of ADC-6A after a single administration are shown in **Tables 4.1-4.3**. In the dose proportional analysis, the C_{max} of ADC and TAB has an approximately linear relationship with dose, which is manifested as dose-proportionality characteristics; the AUC_{0-t} and AUC_{0-inf} of ADC and TAB have a superlinear relationship with dose changes, as shown below the super proportionality characteristics (**Table 4.4**) are generally consistent with the dose proportional characteristics of its naked anti-SI-B001^[1] and EGFR antibody Cetuximab^[2]. The C_{max}, AUC_{0-t} and AUC_{0-inf} of small molecule toxins all show dose proportional characteristics.

30 The half-lives (t_{1/2}) of ADC and TAB after a single dose of ADC-6A are similar, and both become longer as the dose increases. No plateau is observed within the current dose range, compared with its naked antibody (about 9~12 mg /kg has entered the half-life plateau ^[1]), which is in line with the applicant's expectations. The half-life of toxin after a single dose of ADC-6A is slightly longer than that of ADC and TAB. At the dose of 3.0 mg/kg and above, the half-life does not change significantly with the increase in dose. The clearance rate (CL) of ADC and TAB after a single administration of ADC-6A decreases with increasing dose, and no plateau is observed within the current dose range. Compared with its naked antibody (the clearance rate enters at about 6~9 mg/kg plateau period), in line with the applicant's expectations. The volume of distribution (Vd) of ADC and TAB of ADC-6A is basically constant (about 3L) and does not change with changes in dose. The overall clearance characteristics of ADC-6A are similar to those of its naked anti-SI-B001^[1] and the EGFR antibody Cetuximab.

4.1.2. Concentration-time plots of pharmacokinetics

40 Within this dose range, after multiple administrations, there was no significant trend change in C_{max} and C_{trough} of ADC-6A (ADC and TAB) (**Figures 4.2 to 4.7**), indicating drug accumulation is not obvious. The blood concentration of ADC-6A toxin immediately after administration decreases with the increase in the number of administrations (e.g. **Figure 4.4**), which may indicate that subjects will increase their tolerance to the drug after multiple administrations.

4.2. Analysis of Quantitative Effectiveness of ADC-6A

4.2.1. Analysis of drug exposure and safety

In the dose escalation phase of the Phase I clinical trial of ADC-6A, DLT (all hematological toxicity) was observed in 2 subjects in the 3.0 mg/kg QW dose group. After the protocol was revised, the dosing method was changed to D1D8Q3W and D1Q3W. In further dose escalation, DLT (all hematological toxicity) was observed in 2 subjects in the 3.5 mg/kg dose group with the D1D8Q3W

dosing method, and no DLT occurred in the D1Q3W dosing method until the 6.0 mg/kg dose group. Based on the current safety data, the MTD of ADC-6A is 3.0 mg/kg D1D8Q3W under the D1D8D3W dosing method, and the MAD is 6.0 mg/kg D1QW under the D1Q3W dosing method. The target toxicity of ADC-6A is not obvious, and the non-target toxicity is manifested as obvious hematological toxicity, including anemia, decreased white blood cell count, decreased neutrophil count, decreased platelet count, decreased lymphocyte count, febrile neutropenia, etc.

The characteristic hematological toxicity of ADC-6A has a significant dose-effect relationship. Under the two administration methods of D1D8Q3W and D1Q3W, the frequency of hematological toxicity increased with the increase of dose (**Figure 4.8** and **Table 4.5**). Except for 2.5mg/kg D1D8Q3W, other dose groups all had different frequencies of febrile neutropenia with a significant dose-effect relationship. In general, the drug toxicity of 2.5mg/kg D1D8Q3W and 4.5mg/kg D1Q3W is low and safe.

Further comparison of the severity of hematological toxicity in the two dose groups of 2.5 mg/kg D1D8Q3W and 4.5 mg/kg D1Q3W showed that the severity of hematological toxicity in 2.5 mg/kg D1D8Q3W was generally lower than that of 4.5 mg/kg D1Q3W (**Figure 4.9** and **Table 4.6**).

G3+ white blood count decreased, G3+ neutrophil count decreased, and G3+ lymphocyte count decreased. The incidence rate in the 2.5 mg/kg D1D8Q3W dose group was significantly lower than that in the 4.5 mg/kg D1Q3W dose group, and at the 4.5 mg/kg D1Q3W dose group febrile neutropenia was observed in 8.6% of the 2.5 mg/kg D1D8Q3W group and no febrile neutropenia was observed in the 2.5 mg/kg D1D8Q3W group. There was no significant difference in the decrease in G3+ platelet count between the two dose groups, but the incidence of G1/G2 platelet count decrease in the 2.5 mg/kg D1D8Q3W dose group was significantly lower than that in the 4.5 mg/kg D1Q3W dose group. The incidence of G3+ anemia, the 2.5mg/kg D1D8Q3W dose group was slightly higher than the 4.5mg/kg D1Q3W dose group; the incidence of G2 anemia, the 2.5mg/kg D1D8Q3W dose group was higher than the 4.5mg/kg D1Q3W dose group.

In summary, the hematological toxicity of ADC-6A has a significant dose-response relationship. Among the two administration methods, the hematological toxicity of 2.5 mg/kg D1D8Q3W and 4.5 mg/kg D1Q3W was lower, and the safety of the 2.5 mg/kg D1D8Q3W dose group was relatively better.

4.2.2. Analysis of drug exposure and efficacy

In the ADC-6A-101 project, partial responses (PR) were observed in the 2.5mg/kg D1D8Q3W, 3.0mg/kg D1D8Q3W, 3.5mg/kg D1D8D3W, 4.5mg/kg D1Q3W, 5.0mg/kg D1Q3W, and 6.0mg/kg D1Q3W dose groups. The objective response rate (ORR) and disease control rate (DCR) tended to increase with increasing doses within the above dose range and in the two administration methods (D1D8Q3W and D1Q3W), and there was a certain dose-effect relationship (**Figure 4.10** and **Figure 4.11** for ORR and DCR, respectively). Among them, the ORR of 6.0mg/kg D1Q3W was lower than that of 4.5mg/kg D1Q3W and 5.0mg/kg D1Q3W, and there were factors of drug toxicity leading to delayed medication, dose reduction, and discontinuation.

Overall, the effectiveness and dosage of ADC-6A are within the dosage range of two administration methods: 2.5~3.5mg/kg D1D8Q3W and 4.5~6.0mg/kg D1Q3W. There is a certain dose-effect relationship. However, due to the relatively large sample size, few to no statistically significant difference. 2.5mg/kg D1D8Q3W and 4.5mg/kg D1Q3W are presumed to be the lowest effective doses of ADC-6A.

4.3. Dose Determination for Pivotal Clinical Trials

4.3.1. Non-small cell lung cancer (NSCLC)

Taking into account the dose-effect relationship of ADC-6A's effectiveness and safety, the applicant believes that 2.5mg/kg D1D8Q3W is an effective dose of ADC-6A, and that the safety is good, and the toxicity is controllable at this dose. Therefore, the applicant chose to use 2.5 mg/kg

D1D8Q3W as the dose for the registrational pivotal clinical study for the treatment of non-small cell lung cancer.

4.3.2. Nasopharyngeal cancer (NPC)

Taking into account the dose-effect relationship of ADC-6A's effectiveness and safety, the applicant believes that 2.5 mg/kg D1D8Q3W is the effective dose of ADC-6A, and at this dose, it has good safety and controllable toxicity. Therefore, the applicant chose 2.5 mg/kg D1D8Q3W as the dose for the registration-based pivotal clinical study of nasopharyngeal carcinoma treatment.

Example 5. Further Analysis of Clinical Study

5.1. Overview

10 Overall, 276 patients were screened for eligibility and 195 patients (133 [68%] men and 62 [32%] women; all were Asian; **Table 5.1**) were enrolled (25 in the phase 1a dose escalation and 170 in the phase 1b dose expansion), including 113 patients with NSCLC, 13 with small cell lung cancer (SCLC), 42 with nasopharyngeal carcinoma (NPC), 25 with head and neck squamous cell carcinoma (HNSCC), one with thymic squamous cell carcinoma, and one with submandibular lymphoepithelioma-like carcinoma. At the data cutoff, 50 patients were still on treatment (Ma, Yuxiang et al. *The Lancet Oncology*, Volume 25, Issue 7, 901–911, including its supplemental appendix 1 and 2, incorporated herein by reference in its entirety). All enrolled patients had an ECOG performance status of 0 or 1, progressed or could not tolerate previous standard therapy with multiple metastases, and 98 (50%) had received three or more previous lines of therapy. Median follow-up was 9.5 months (IQR 7.7–12.2) 20 for phase 1a and 6.6 months (4.3–8.6) for phase 1b. 145 (74%) patients discontinued treatment due to disease progression (82 [57%]), adverse events (six [4%]), death (12 [8%]; with three deaths considered drug related), withdrawal (25 [17%]), and other reasons (20 [14%], with four related to COVID-19 (**Figure 5.1**)).

189 (97%) of the 195 patients experienced at least one treatment related adverse event (**Table 5.4**). The median duration of drug exposure was 4.1 months (IQR 1.8–6.8). The most common any grade treatment related adverse events were hematological events (anemia in 157 [81%] of 195 patients, leukopenia in 140 [72%], neutropenia in 130 [67%], and thrombocytopenia in 121 [62%]), gastrointestinal events (nausea in 81 [42%], decreased appetite in 67 [34%], and vomiting in 66 [34%]), and dermatological events (alopecia in 63 [32%], **Table 5.2**). 139 (71%) of 195 patients had Grade 3 30 or worse treatment related adverse events; the most common were neutropenia (91 [47%]), anemia (76 [39%]), leukopenia (76 [39%]), and thrombocytopenia (63 [32%]). Adverse events that occurred in the different dose groups are shown in **Table 5.4**. 71 (36%) of 195 patients had a treatment related serious adverse events. Of 195 patients, five (3%, including two deaths) discontinued treatment and 52 (27%) had dose reductions due to treatment related adverse events. 21 patients (20%) received dose reduction and two (2%) of them discontinued treatment due to treatment related adverse events at 2.5 mg on days 1 and 8 of each cycle every 3 weeks. 11 (6%) of 195 patients died due to treatment emergent adverse events (Grade 5), due to pneumonia (n=3), COVID19 infected pneumonia (n=1), pleural effusion (n=1), pericardial effusion (n=1), death of unknown cause (n=2), septic shock (n=1), tumor hemorrhage (n=1), and myelosuppression (n=1, **Table 5.5**). Three (2%) deaths (pneumonia, 40 septic shock, and myelosuppression) were considered related to BL-B01D1 treatment (**Table 5.4**). No patients withdrew from the therapy due to cardiac toxicity. One patient (<1%) discontinued the therapy due to interstitial lung disease. All treatment emergent adverse events occurring in more than 10% of patients and those with Grade 3 or worse treatment emergent adverse events are summarised in **Tables 5.4, 5.6**). The most common treatment emergent adverse events in all 195 patients were anemia (165 [85%]), leukopenia (140 [72%]), and neutropenia (130 [67%]).

In all 195 patients, all four (2%) dose limiting toxicities were febrile neutropenia, with two (1%) occurring in the 3.0 mg/kg weekly dose group and two (1%) in the 3.5 mg/kg on days 1 and 8 every 3 weeks group (**Table 5.7**). No dose limiting toxicity was observed in the 6.0 mg/kg on day 1 every 3

weeks dose group. Due to the presence of two cases of dose limiting toxicity in the 3.5 mg/kg on days 1 and 8 every 3 weeks group, the researchers discussed thoroughly and decided not to increase to a higher dose in the day 1 every 3 weeks schedule to minimize the risk to participants. Accordingly, the maximum tolerated dose was determined to be 3.0 mg/kg on days 1 and 8 every 3 weeks and 6.0 mg/kg on day 1 every 3 weeks.

174 patients were evaluable for antitumor activity (21 were excluded, including six who received the weekly regimen, nine who withdrew voluntarily, and six who dropped out) with a median follow-up of 6.9 months (IQR 4.5–8.9). Patient demographics of the activity analysis population are in **Table 5.8**. 60 (34%) of 174 patients had a partial response, 75 (43%) had stable disease, 12 (7%) experienced progressive disease, and seven (7%) were not evaluated (**Table 5.3**). 60 (34%; 95% CI 27–42) patients had an objective response, median duration of response was 8.5 months (95% CI 5.4–NE), median progression free survival was 5.7 months (4.2–6.8), and 155 patients had disease control (89%; 83–93; **Tables 5.3; Figures 5.1; and Table 5.9**). For progression free survival, 75 (43%) of 174 patients were censored, comprising 42 (24%) still under treatment and 33 (19%) who discontinued due to reasons other than progression or death (**Figure 5.1**). Overall survival data were not mature with only 24 (18%) overall survival events (deaths) observed as of data cutoff, and the median overall survival was not reached (**Figure 5.2**). Post hoc analyses of antitumor activity in different dose groups and tumor types, and in patients with NSCLC with or without brain metastases at baseline and who had previous EGFR tyrosine kinase inhibitor treatment or at least one line of platinum based chemotherapy are shown in **Figures 5.1–5.5 and Tables 5.9–5.12**.

53 patients were included in the pharmacokinetics analysis. The maximum concentration of total antibody, antibody–drug conjugates, and toxin (Ed04) increased with the increasing dose (**Figure 5.3, Table 5.13, and 5.14**). The concentration–time curves of total antibody and antibody–drug conjugates were nearly identical across all dose levels. Non-linear clearance kinetics were indicated by the concentration time characteristics (**Figure 5.3**) and the increase in terminal half-life with dose. The half-life of BLB01D1 ranged from 10 h to 40 h across doses from 0.27 mg/kg to 6.0 mg/kg single dose (data from dose-escalation phase). Drug accumulation was minimal; the 5-fold half lifetime was shorter than the dosing interval in the one dose on days 1 and 8 every 3 weeks schedule (7 days or 14 days).

Details of Grade 3 or worse treatment related hematological toxicity in the different dose groups are shown (**Figure 5.6; Table 5.15**). The 2.5 mg/kg on days 1 and 8 every 3 weeks group had the lowest incidence of Grade 3 or worse treatment related adverse events as well as total Grade 3 or worse hematological toxicity (**Figure 5.6; Table 5.15**).

Considering the pharmacokinetic profile, the half-life of BL-B01D1 ranged from 11 to 37.4 h, and the 5-fold half lifetime was approximately 7 days (data from dose-escalation phase and dose-expansion phase). Based on a collaborative assessment of safety, antitumor activity (**Table 5.11**), and pharmacological analysis, the recommended phase 2 dose for BL-B01D1 in Chinese patients was determined as a dose of 2.5 mg/kg administered on a Days 1 and 8 every 3 weeks schedule.

Example 6. Therapeutics Effects

6.1. Analysis of Blood Samples

Blood samples for pharmacokinetics (PK) analysis were collected at specific time points. Dense PK included pre-infusion (within 4 hours), post-infusion (15 minutes after infusion), 2, 4, 6, 24, 48, 96, and 168 hours after the administration of the first dose and second dose. Total antibody (TAB), antibody–drug conjugates (ADC), and toxin were assessed separately in the pharmacokinetics assessments. TAB refers to the antibody molecule of BL-B01D1, including antibody with or without conjugated payload in peripheral blood. Toxin refers to free toxin without linker which is released from BL-B01D1 into peripheral blood through cellular endocytosis. The serum concentrations of BL-B01D1 and total antibody were measured by validated Ligand binding assay methods. Briefly, anti-

idiotype mAb #6A10 served as a capture, biotinylated anti-ED04 mAb #6C8 or anti-idiotypic mAb #10F4 were used as a detection reagent to detect BL-B01D1 or total antibody, respectively. For Ed04 concentration determination, serum samples were deproteinized with ethyl acetate and analyzed using validated liquid chromatography-tandem mass spectrometry methods (LC-MS/MS) (MS: ABSCIEX, Qtrap5500; LC: Shimadzu, LC-20AD) with an internal standard method.

Blood samples for DNA sequencing were collected before the first cycle of BL-B01D1 during the screening period. The panels used in this study covered 73 or 1021 cancer-related genes (Geneplus-Beijing). Ten milliliters of blood samples were collected in EDTA tubes and separated by centrifugation at $1,600 \times g$ for 10 minutes. The supernatant was transferred to microcentrifuge tubes, centrifuged again at $16,000 \times g$ for 10 minutes to remove cell debris, and then frozen at -80°C . Cell-free DNA (cfDNA) and circulating tumor DNA (ctDNA) were extracted from 4 to 5 mL of plasma using the Enhanced Magnetic Circulating DNA Kit. Genomic DNA was isolated from peripheral blood lymphocytes using the CWE9600 Blood DNA Kit. The concentration and fragment length of DNA were determined using Labchip. Plasma and its paired genomic germline DNA libraries were hybridized to a custom-designed biotinylated oligonucleotide probe. The indexed libraries were sequenced using a 100-bp paired-end configuration on a DNBSEQ-T7RS sequencer (MGI Tech). The sequenced reads were mapped to the reference human genome (GRCh37) using the default parameters in BWA version 0.6.2 after removing the adaptor and low-quality reads. For cfDNA, duplicated reads were identified by UID and the position of template fragments to eliminate errors introduced by PCR or sequencing using realSeq (v3.1.0 Geneplus-Beijing, in-house). Local realignment around SNVs and indels, as well as quality control assessment, were performed using GATK (version 3.4.46; Broad Institute). Tumor somatic SNVs and small indels were profiled using real-Dcaller (Geneplus-Beijing, in-house) and TNscope. CNVKit was used to detect copy-number alterations. The structural variations were analyzed using the self-developed algorithm NCsv (Geneplus-Beijing, in-house.)

Analyses of HER3 and EGFR expression were performed in available pretreatment tumor tissues by immunohistochemistry assay. Paraffin sections were dewaxed, and were autoclaved with Tris-EDTA repair solution. Primary antibodies anti-HER3 (Abcam, ab93739, 1:50 dilution), and Anti-EGFR (Abcam, ab52894, 1:1600 dilution) were added on slides, and a drop of PBS was added as blank control for background assessment. After washing, the biotinylated detection reagent was added dropwise, followed by the addition of DAB colorant. The samples were re-stained with hematoxylin, dehydrated, clarified, and sealed with neutral resin. Then the protein expression was detected by the OptiView DAB IHC Detection Kit. The score result was obtained by multiplying the cell staining intensity with the percentage of positive cells. H score was calculated using the following formula: $H\text{ Score} = 1 * (1\%) + 2 * (2\%) + 3 * (3\%)$. Details were as follows: 0 (absence of staining), 1+ (weak staining), 2+ (moderate-intensity staining), and 3+ (strong staining); (1+%), (2+%) and (3+%) are the values of percentages of positive cells in three intensity level.

6.2. Analysis of EGFRwt, EGFRmut, and the Expression of EGFR and HER3

Among the 40 patients with documented EGFR mutations, most had the common EGFR-activating mutations exon 19del (n=22) or L858R (n=14), one had exon 20 insertion, one had EGFR G719X as well as L861Q mutation, one had EGFR L747P mutation, and one had EGFR-SHC1 fusion. Thirteen patients were also with T790M mutation and eight of them had a PR. Twelve patients experienced a PR in those with EGFR mutations exon 19del (n=22), while seven patients had a PR in those with L858R (n=14). There was no significant difference in the ORR between the two groups ($p = 0.79$) (Figure 6.1). Baseline ctDNA samples were analyzed using a custom NGS panel in 69 NSCLC patients (26 with EGFR mutations, 43 with EGFR wt) (Figure 6.2). In patients with known secondary EGFR mutation (n=4, including L718Q and C797S), one achieved a PR; in patients with bypass activation (n=10, including AGK-BRAF fusion MET amplification, ROS1 fusion and others), seven showed a PR; in patients with an unknown resistance mechanism, four had a PR. One patient with

EGFR L747P mutation combined with EPHA6-ROS1 fusion, previously treated with 1st/2nd generation EGFR-TKI, had a PR. In EGFRwt patients, those with baseline concurrent mutations (including TP53, PIK3CA, and others) also benefited from ADC-6A treatment (**Figure 6.2**). Posthoc, exploratory biomarker analyses are presented. In 35 patients with pre treatment specimens available, nearly all tumors expressed detectable EGFR and HER3 by immunohistochemistry (**Figure 6.3**). No relationship was observed between EGFR or HER3 expression and antitumor response.

6.3. Mechanism of Therapeutics

EGFR is overexpressed, dysregulated, or mutated in many epithelial malignancies, and EGFR activation appears important in tumor growth and progression, while increased HER3 expression is associated with a poor prognosis in multiple solid tumors. EGFR therapies include both small molecules and anti-EGFR antibodies, approved for treatment of colorectal cancer, pancreatic cancer, head and neck cancer, and non-small cell lung cancer (NSCLC). EGFR tyrosine kinase inhibitors (TKI) are commonly used as 2nd line therapies for non small cell lung cancer (NSCLC), but often stop working within twelve months due to resistance pathways.

HER3-mediated signaling has adverse consequences for tumor progression; upregulation of HER3 is associated with resistance to anti-HER2 and anti-EGFR therapy and solid tumors refractory to anti-PD-1 therapy have been shown to have higher HER3 expression compared to those that respond to anti-PD-1 therapy.

BL-B01D1 is a recombinant bispecific antibody conjugated drug with anti-tumor activity. Without being limited by theory, BL-B01D1 related mechanism of killing tumors involves at least one or more of the following combinations: a) the antibody part of BL-B01D1 (EGFR×HER3 bispecific antibody) can bind to EGFR and HER3 on the surface of tumor cells simultaneously, simultaneously blocking two tumor-associated targets and inhibiting the tumor growth; b) once the body binds to the tumor cell, the Fc segment of the EGFR×HER3 bispecific antibody can mediate antibody-dependent cellular cytotoxicity (ADCC) that kills the tumor cell; and/or c) when BL-B01D1 binds to EGFR and/or HER3 on the surface of tumor cells, it enters into tumor cells through endocytosis, releases the toxin Ed-04 (a camptothecin derivative can act as a topoisomerase I inhibitor) in lysosomes, and blocks the DNA replication and RNA synthesis of tumor cells.

Example 7. Treating EGFR- and/or HER3-expressing cancer or tumors

In addition to non-small cell lung carcinoma (NSCLC), nasopharyngeal cancer (NPC), and head and neck squamous cell carcinoma (HNSCC), tumors prone to the effects of EGFR dysregulation also include breast cancer, bladder cancer, glioblastoma, cervical cancer, uterine cancer, colon and colorectal cancer, esophageal cancer, ovarian cancer, pancreatic cancer, and renal cell carcinoma, squamous cell carcinoma, and thyroid cancer.

7.1. Breast Cancer

Further embodiments of the methods of treating breast cancer using pharmaceutical compositions incorporating ADC as disclosed herein are described in NCI05470348, all of which are incorporated herein by references in their entirety.

To investigate the safety and tolerability of ADC-06A in patients with locally advanced or metastatic breast cancer and other solid tumors, a total of 127 patients were treated with at least one dose regardless of the EGFR/HER3 expression, including 126 breast cancer patients and 1 non-small cell lung cancer (NSCLC) patient (**Table 7.1**). Among the 127 patients, 5 patients received 5.0 mg/kg D1 Q3W and 122 patients were treated with 2.5 mg/kg on the D1D8 Q3W schedule. This Phase Ia study aims to observe the safety and tolerability of BL-B01D1 in patients with locally advanced or metastatic breast cancer and other solid tumors to determine the maximum tolerated dose (MTD) and dose-limiting toxicity (DLT) of ADC-6A. At a cut-off timepoint, the result indicates most common Grade ≥3 treatment-related adverse events (TRAEs) were leukopenia (32%), neutropenia (44%), anemia (29%), and thrombocytopenia (20%) (**Table 7.2**). The most common adverse events of ADC-6A were

hematological toxicity which was deemed to be manageable and tolerable, and the incidence and severity of toxicity related to EGFR/HER3 targeting of BL-B01D1 were relatively low, demonstrating a favorable safety profile.

At the cut-off timepoint and among the 127 enrolled patients, 96 breast cancer patients had at least one post-baseline tumor assessment and revealed a spectrum of change in tumor size from baseline (**Figure 7.1**), indicative of favorable efficacy by subtypes of breast cancer below:

35 patients with triple-negative breast cancer (TNBC), had at least one post-baseline tumor assessment, the ORR (n/N, [95%CI]) was 31.4% (11/35, [16.9-49.3]), cORR (n/N, [95%CI]) was 22.9% (8/35, [10.4-40.1]), DCR was 91.4% (32/35, [76.9-98.2]) (**Table 7.3**). The mPFS and mDOR have not reached at this cutoff timepoint;

38 patients with hormone receptor-positive (HR+), HER2 negative (HER2) breast cancer (BC) had at least one post-baseline tumor assessment, the ORR (n/N, [95%CI]) was 44.7% (17/38, [28.6-61.7]), cORR (n/N, [95%CI]) was 18.4% (7/38, [7.7-34.3]), DCR was 94.7% (336/38, [82.3-99.4]) (**Table 7.3**). The mPFS and mDOR have not reached at this cutoff timepoint; and

23 patients with HER2 positive (HER2+) BC, had at least one post-baseline tumor assessment, the ORR (n/N, [95%CI]) was 39.1% (9/23, [19.7-61.5]), cORR (n/N, [95%CI]) was 21.7% (5/23, [10.2-48.4]), DCR was 87.0% (20/23, [66.4-97.2]) (**Table 7.3**). The mPFS and mDOR have not reached at this cutoff timepoint.

22 breast cancer patients who had at least one post-baseline tumor assessment were further tested for the EGFR and HER3 expression in archival biopsy by using immunohistochemistry (IHC) staining. The result of this biomarker study showed activity in patients who had some levels of expression of either EGFR or HER3 in tumor (**Figure 7.2**), supporting the heterogeneity nature of solid tumors, such as breast cancer.

Thus, ADC-6A exhibited anti-tumor activity in patients who had some level of expression of either EGFR or HER3 and exhibited promising preliminary antitumor activity in different subtypes of breast cancer patients. The result from Phase Ia demonstrated the safety and tolerability of BL-B01D1, which helped determine the recommended Phase II dose (RP2D) at 2.5 mg/kg on the D1D8 Q3W schedule.

7.2. Esophageal Squamous Cell Carcinoma

Further embodiments of the methods of treating gastrointestinal cancer using pharmaceutical compositions incorporating ADC as disclosed herein are described in NCT05194982, NCT05262491, and NCT06304974, all of which are incorporated herein by references in their entirety.

A Phase I study was designed to enroll patients with locally advanced or metastatic esophageal squamous cell carcinoma (ESCC) and other solid tumors. Other key eligibility criteria included locally advanced or metastatic ESCC; previously treated with at least one line of therapy; ECOG performance status of 0-1; at least one measurable lesion per RECIST v1.1, and adequate organ and marrow function. This open-label trial aimed to evaluate ADC-6A safety, tolerability, pharmacokinetic characteristics, and preliminary efficacy in patients with locally advanced or metastatic gastrointestinal cancer and other solid tumors. Dose-escalation phase referred to ADC-6A study and dose-expansion phase was being investigated. During dose-expansion, subjects with different tumor types were treated with BL-B01D1 at 2.0, 2.5, 3.0, 3.5mg/kg D1D8 Q3W and 3.0, 5.0mg/kg D1 Q3W.

83 previously treated patients with esophageal squamous cell carcinoma (ESCC) were enrolled in Q3W D1D8 regimens with 22 patients treated at 2.0 mg/kg, 60 patients at 2.5mg/kg and 1 patient at 3.0mg/kg (**Table 7.4**). Among the enrolled ESCC patients, 97.6% (81/83) had received anti-PD-1/L1 and platinum-based chemotherapy (PBC) in combination or sequentially. More than half of the patients received at least 2 prior lines of systemic treatment, and the median follow up was 10.5 months.

At the time of cut-off, no new safety signals were observed (**Table 7.5**). The most common $\geq$ Grade 3 treatment-related adverse events (TRAEs) at the regimen of 2.5 mg/kg D1D8 Q3W were anemia (28.3%), leukopenia (18.3%), thrombocytopenia (18.3%), neutropenia (16.7%), etc. Two cases (1/2 G2, 1/2 G3) of interstitial lung disease (ILD) by investigator's adjudication were observed at 2.5mg/kg D1D8 Q3W dose level.

Among the enrolled patients, 74 patients were evaluable for efficacy. As shown in **Table 7.6**, the ORR was 35.1% (26/74), cORR was 32.4% (24/74), DCR was 73.6% (53/74), mPFS was 4.3 months, mDOR was 6.5 months. A total of 52 patients were evaluable for efficacy in 2.5mg/kg D1D8 Q3W regimen. The ORR was 44.2% (23/52), cORR was 40.4% (21/52), DCR was 80.8% (42/52), mPFS was 5.4 months, and mDOR was 6.6 months.

At the cut-off time, 52 patients with previously treated locally advanced or metastatic esophageal squamous cell carcinoma (ESCC) showed a spectrum of changes in tumor size from baseline (**Figure 7.3**) and the evaluable efficacy in 2.5mg/kg D1D8 Q3W (**Figure 7.4**).

Thus, this clinical study demonstrated that in patients with heavily pretreated ESCC, ADC-6A demonstrated manageable safety with encouraging antitumor activity.

7.3. Biliary Tract Carcinoma

Further embodiments of the methods of treating gastrointestinal cancer or tumors using pharmaceutical compositions incorporating ADC as disclosed herein are described in NCT NCT05194982 and NCT05262491, all of which are incorporated herein by references in their entirety.

A Phase I study was designed to enroll patients with locally advanced or metastatic biliary tract carcinoma (BTC) and other solid tumors. Other key eligibility criteria included locally advanced or metastatic BTC, previously treated with at least one line of therapy, ECOG performance status of 0-1, at least one measurable lesion per RECIST v1.1, and adequate organ and marrow function.

This open-label, Phase I study was designed to evaluate BL-B01D1 safety, tolerability, pharmacokinetic characteristics, and preliminary efficacy in patients with locally advanced or metastatic gastrointestinal cancer and other solid tumors. Dose-escalation phase referred to BL-B01D1 study and dose-expansion phase is being investigated. During dose-expansion, subjects with different tumor types were treated with BL-B01D1 at 2.0, 2.5, 3.0, 3.5mg/kg D1D8 Q3W and 3.0, 5.0mg/kg D1 Q3W. The primary endpoints of the study are dose limiting toxicities (DLT), maximum tolerated dose (MTD), and recommended phase 2 dose (RP2D). Secondary endpoints are treatment emergent adverse events (TEAE), pharmacokinetics parameters, objective response rate (ORR), disease control rate (DCR), and duration of response (DOR).

At the time of cut-off, 44 BTC patients were enrolled in D1D8 Q3W regimens, with 31 patients treated at 2.5mg/kg, 3 patients treated at 3.0 mg/kg and 10 patients treated at 3.5 mg/kg (**Table 7.7**). More than half of the patients received at least 2 prior lines of systemic treatment. The median follow up was 5.9 months.

At the cutoff time, no interstitial lung disease (ILD) was observed, nor any new safety signals were observed (**Table 7.8**). The most common $\geq$ Grade 3 treatment-related adverse events (TRAEs) were thrombocytopenia (31.8%), anemia (27.3%), leukopenia (20.5%) and neutropenia (18.2%).

Among the 44 enrolled patients, 36 were evaluable for efficacy. The ORR was 38.9% (14/36), cORR was 22.2% (8/36), DCR was 88.9% (32/36), mPFS was 4.3 months, and mDOR was 7.3 months (**Table 7.9**). A total of 25 patients were evaluable for efficacy in the 2.5 mg/kg D1D8 Q3W regimen and showed a spectrum of changes in tumor size from baseline (**Figure 7.5**). The ORR was 32.0% (8/25), cORR was 20.0% (5/25), DCR was 88.9% (22/25), mPFS was 4.3 months, and mDOR was 7.3 months (**Figure 7.6**).

Thus, to the patients with locally advanced or metastatic BTC, ADC-6A exhibited manageable safety TRAEs with encouraging antitumor activity.

7.4. Urothelial Carcinoma

Further embodiments of the methods of treating urothelial carcinoma or tumors such as bladder cancer using pharmaceutical compositions incorporating ADC as disclosed herein are described in NCT05785039, all of which are incorporated herein by references in their entirety.

This non-randomized phase II study was designed to observe the safety and tolerability of ADC-6A in patients with multiple solid tumors, including locally advanced or metastatic urinary system tumors at the recommended dose of Phase Ia and determine the recommended Phase II dose (RP2D).

At the time of cut-off, 41 BTC patients were enrolled in D1D8 Q3W regimens, with 34 patients treated at 2.2mg/kg, 4 patients treated at 2.5 mg/kg and 3 patients treated at 2.75 mg/kg (**Table 7.10**). 12 patients received at least 1 prior lines of systemic treatment. The major key inclusion criteria included locally advanced or metastatic urothelial carcinoma, failed standard therapy or without feasible treatment.

Results for safety, tolerability and preliminary efficacy in previously treated patients with locally advanced or metastatic urothelial carcinoma (UC) in phase II study showed no treatment related deaths, and the most common TRAEs were hematological toxicities (**Table 7.11-7.13**). The non-hematological toxicities were mostly Grade 1 or 2. No interstitial lung disease (ILD) was observed. No new safety signals were observed.

While the incidence and severity of toxicities related to EGFR and HER3 targeting were relatively low, EGFR and HER3 remain highly expressed in urothelial carcinoma. 27 patients with locally advanced or metastatic urothelial carcinoma and 12 UC patients with at least one line of prior chemo showed maximum change from baseline in response to the regimen of 2.2 mg/kg D1D8 Q3W (**Figure 7.7**). Furthermore, the latter group displayed the progress-free survival probability (**Figure 7.8**). The biomarker analysis indicated that clinical activity was seen across various levels of EGFR and HER3 expression.

Thus, ADC-6A showed encouraging preliminary efficacy and favorable safety profile at 2.2 mg/kg D1D8 Q3W in previously treated urothelial carcinoma, especially at second line. The most common TRAEs were hematological toxicities, which were manageable, and no new safety signals were observed.

TABLES

Table 1.1. The original climbing dose adjustment table

Dose group in which the first DLT occurred	Climbing Dosage Group
3.0mg/kg	0.27, 1.5, 3.0, 4.5, 6.0, 7.5, 9.0, 10.5 mg/kg
6.0mg/kg	0.27, 1.5, 3.0, 6.0, 7.5, 9.0, 10.5 mg/kg
9.0mg/kg	0.27, 1.5, 3.0, 6.0, 9.0, 10.5 mg/kg
12.0mg/kg or 15.0mg/kg	0.27, 1.5, 3.0, 6.0, 9.0, 12.0, 15.0 mg/kg

Note:

- ① Starting at 3.0 mg/kg, the subsequent dose increment (ADJUSTED increment) for the dose at which the first DLT occurs is adjusted to 1.5 mg/kg, the maximum dose is 10.5 mg/kg, if the first DLT occurs only at 12.0 mg/kg, no adjustment is made.
- ② Multiple DLTs at the same dose, or subsequent DLTs at different doses, the preset dose increments are no longer adjusted. However, the increments may be adjusted, or intermediate doses may be added in consultation with the investigator.

Table 1.2. The current climbing dose adjustment table

Dose level	Cohort A: D1, D8	Cohort B: D1
-2	1.5	3
-1	2	4
<u>0</u>	<u>2.5</u>	<u>5</u>
+1	3	6
+2	3.5	7
+3	4	8
+4	4.5	9

Table 1.3. The white blood cell counts prior to each administration

	Neutrophils $\geq$	Platelets $\geq$
D 0 or 1	$1.5 \times 10^9 / L$	$75 \times 10^9 / L$
D 7 or 8	$1.5 \times 10^9 / L$	$75 \times 10^9 / L$

Note: Cohort B only performs D1 administration

Table 1.4. i3+3 Dose escalation/decrease rules (by 3-person cohort).

Total number of patients treated at current dose	3	6	9	12
The dose increases if the number of DLTs $\leq$	0	1	2	2
The dose is reduced if the number of DLTs $\geq$	2	3	4	4
Terminate dosing if the number of DLT $\geq$	3	4	5	6

Note:

1. Termination of dosing represents the removal of the current dose, as well as all higher doses, from the trial for the purpose of subject protection. When termination of administration occurs, the dose is automatically reduced to the next dose at the same time. If termination of dosing occurs at the lowest dose, the entire trial is stopped and no MTD can be confirmed;
2. If neither dose increase, dose decrease, nor termination of administration occurs, maintain the dose; and
3. If the current dose is the lowest dose, but a dose decrease is indicated in **Table 2a**, the trial is stopped and no MTD can be confirmed. If the current dose is the highest dose, but a dose increase is indicated in the table, subsequent patients are maintained at the current highest dose administered until the stopping condition is met.

Table 1.5. Detailed dose escalation/decrease rule for i3+3.

		Number of Patients											
Number of DLTs		1	2	3	4	5	6	7	8	9	10	11	12
	0	E	E	E	E	E	E	E	E	E	E	E	E
	1	E	E	E	S	S	S	S	S	S	S	S	S
	2		DU	D	D	S	S	S	S	S	S	S	S
	3			DU	DU	D	D	D	D	S	S	S	S
	4				DU	DU	DU	DU	D	D	D	D	D
	5					DU	DU	DU	DU	DU	D	D	D
	6						DU	DU	DU	DU	DU	DU	DU
	7							DU	DU	DU	DU	DU	DU
	8								DU	DU	DU	DU	DU
	9									DU	DU	DU	DU
	10										DU	DU	DU
	11											DU	DU
	12												DU

Note 1: Target DLT rate $p_T = 0.28$, $\epsilon_1 = 0.05$, $\epsilon_2 = 0.05$, with an equivalence interval of 0.23 to 0.33.
Note 2: E Dose increase; S Maintain current dose; D Decrease to previous dose; DU Decrease to previous dose and cancel all doses above this. The dose increase is triggered only if the number of subjects in the group is greater than or equal to 3, otherwise the current dose is maintained.

Table 2.1. Summary of ADC-6A -101 Project DLTs

Serial number	Dose	AE Name	Start date	End date	Grade	SAE	Relevance	Conclusion
01007	3.0mg/kg QW	Febrile neutropenia	3/16/2022	3/17/2022	G3	No	Possibly relevant	fully recovered
01010	3.0mg/kg QW	Decreased platelet count	3/19/2022	3/28/2022	G4	Yes	Possibly relevant	fully recovered
		Febrile neutropenia	3/22/2022	3/22/2022	G3	No	Possibly relevant	fully recovered
01024	3.5mg/kg D1D8 Q3W	Febrile neutropenia	7/31/2022	8/02/2022	G3	Yes	Possibly relevant	fully recovered
01026	3.5mg/kg D1D8 Q3W	Decreased feverish neutrophil count	7/21/2022	7/25/2022	G4	Yes	Possibly relevant	fully recovered

Note: DLT for hematologic toxicity is defined as Grade 4 neutropenia lasting >7 days after supportive therapy; Grade ≥ 3 febrile neutropenia (absolute neutrophil count $<1.0 \times 10^9 / L$ with a single temperature $>38.3^\circ C$ or a sustained temperature $\geq 38^\circ C$ for more than 1 hour); Grade 4 thrombocytopenia lasting >7 days or ≥ 3 Grade thrombocytopenia with significant bleeding after supportive therapy; Grade 4 anemia lasting >7 days after supportive therapy. Grade 4 thrombocytopenia with significant bleeding; Grade 4 anemia lasting >7 days after supportive therapy.

Table 2.2. Overall Safety Analysis of All Subjects in the ADC-6A -101 Program

TEAEs, n (%)	All Patients (N=169)									
	ALL Patient s (n=169)	QW- 0.27 mg/kg (n=1)	QW- 1.5 mg/kg (n=1)	QW- 3.0 mg/kg (n=4)	D1D8Q3 W- 2.5mg/k g (n=80)	D1D8Q3 W-3.0 mg/kg (n=7)	D1D8Q3 W- 3.5mg/k g (n=5)	D1Q3 W- 4.5mg/ kg (n=35)	D1Q3 W-5.0 mg/kg (n=24)	D1Q3 W-6.0 mg/kg (n=12)
Any TEAE	164 (97%)	1 (100%)	1 (100%)	4 (100%)	75 (94%)	7 (100%)	5 (100%)	35 (100%)	24 (100%)	12 (100%)
Associated with treatment discontinuation	8 (5%)	0	0	1 (25%)	5 (6%)	0	1 (20%)	0	0	1 (8%)
Associated with dose reduction	39 (23%)	0	0	1 (25%)	13 (16%)	1 (14%)	3 (60%)	4 (11%)	7 (29%)	10 (83%)
Associated with death	10 (6%)	0	0	0	5 (6%)	1 (14%)	2 (40%)	1(3%)	1(4%)	0
Grade ≥3 TEAE	108 (64%)	1 (100%)	0	4 (100%)	41 (51%)	6 (86%)	5 (100%)	22 (63%)	17 (71%)	12 (100%)
Treatment Related TEAE (TREA)	156 (92%)	1 (100%)	1 (100%)	4 (100%)	71 (89%)	6 (86%)	5 (100%)	32 (91%)	24 (100%)	12 (100%)
Associated with treatment discontinuation	5 (3%)	0	0	1 (25%)	3(4%)	0	0	0	0	1 (8%)
Associated with dose reduction	39 (23%)	0	0	1 (25%)	13 (16%)	1 (14%)	3 (60%)	4 (11%)	7 (29%)	10 (83%)
Associated with death	3 (2%)	0	0	0	2 (3%)	1 (14%)	0	0	0	0
Grade ≥3 TRAE	98 (58%)	1 (100%)	0	3 (75%)	37 (46%)	5 (71%)	4 (80%)	19 (54%)	17 (71%)	12 (100%)
SAE	63 (37%)	0	0	4 (100%)	23 (29%)	5 (71%)	4 (80%)	6 (17%)	11 (46%)	10 (83%)
TR-SAE	50 (30%)	0	0	3 (75%)	17 (21%)	3 (43%)	3 (60%)	4 (11%)	11 (46%)	9 (75%)

Table 2.3. Overall Safety Analysis of NSCLC Subjects on the ADC-6A -101 Program

TEAEs, n (%)	NSCLC Patients (N=104)									
	ALL NSCLC Patients (n=104)	QW- 0.27 mg/kg (n=0)	QW- 1.5 mg/kg (n=1)	QW- 3.0 mg/kg (n=3)	D1D8Q 3W- 2.5mg/ kg (n=45)	D1D8Q 3W-3.0 mg/kg (n=5)	D1D8Q 3W- 3.5mg/ kg (n=4)	D1Q3 W-4.5 mg/kg (n=23)	D1Q3 W-5.0 mg/kg (n=15)	D1Q3 W-6.0 mg/kg (n=8)
Any TEAE	101 (97%)	0	1 (100%)	3 (100%)	42 (93%)	5 (100%)	4 (100%)	23 (100%)	15 (100%)	8 (100%)
Associated with treatment discontinuation	6 (6%)	0	0	1 (33%)	3 (7%)	0	1 (25%)	0	0	1 (13%)
Associated with dose reduction	27 (26%)	0	0	0	10 (22%)	1 (20%)	2 (50%)	2 (9%)	4 (27%)	8 (100%)
Associated with death	6 (6%)	0	0	0	3 (7%)	0	2 (50%)	1(4%)	0	0
Grade ≥3 TEAE	66 (63%)	0	0	3 (100%)	23 (51%)	4 (80%)	4 (100%)	15 (65%)	9 (60%)	8 (100%)
Treatment Related TEAE (TREA)	97 (93%)	0	1 (100%)	3 (100%)	40 (89%)	5 (100%)	4 (100%)	21 (91%)	15 (100%)	8 (100%)
Associated with treatment discontinuation	5 (5%)	0	0	1 (33%)	3 (7%)	0	0	0	0	1 (13%)
Associated with dose reduction	27 (26%)	0	0	0	10 (22%)	1 (20%)	2 (50%)	2 (9%)	4 (27%)	8 (100%)
Associated with death	2 (2%)	0	0	0	2(4%)	0	0	0	0	0
Grade ≥3 TRAE	61 (59%)	0	0	2 (67%)	22 (49%)	4 (80%)	3 (75%)	13 (57%)	9 (60%)	8 (100%)
SAE	37 (36%)	0	0	3 (100%)	10 (22%)	3 (60%)	4 (100%)	5 (22%)	5 (33%)	7 (88%)
TR-SAE	32 (31%)	0	0	2 (67%)	9 (20%)	2 (40%)	3 (75%)	4 (17%)	5 (33%)	7 (88%)

Table 2.4. Overall Safety Analysis of NPC Subjects in the ADC-6A -101 Program

TEAEs, n (%)	NPC Patients (N=36)									
	ALL NPC Patients (n=36)	QW- 0.27 mg/kg (n=1)	QW- 1.5 mg/kg (n=0)	QW- 3.0mg/ kg (n=1)	D1D8Q 3W- 2.5mg/ kg (n=22)	D1D8Q 3W-3.0 mg/kg (n=0)	D1D8Q 3W- 3.5mg/ kg (n=1)	D1Q3 W-4.5 mg/kg (n=6)	D1Q3 W-5.0 mg/kg (n=3)	D1Q3 W-6.0 mg/kg (n=2)
Any TEAE	34 (94%)	1 (100%)	0	1 (100%)	20 (91%)	0	1 (100%)	6 (100%)	3 (100%)	2 (100%)
Associated with treatment discontinuation	0	0	0	0	0	0	0	0	0	0
Associated with dose reduction	9 (25%)	0	0	1 (100%)	2 (9%)	0	1 (100%)	2 (33%)	1 (33%)	2 (100%)
Associated with death	0	0	0	0	0	0	0	0	0	0
Grade ≥3 TEAE	21 (58%)	1 (100%)	0	1 (100%)	10 (45%)	0	1 (100%)	4 (67%)	2 (67%)	2 (100%)
Treatment Related TEAE (TREA)	32 (89%)	1 (100%)	0	1 (100%)	19 (86%)	0	1 (100%)	5 (83%)	3 (100%)	2 (100%)
Associated with treatment discontinuation	0	0	0	0	0	0	0	0	0	0
Associated with dose reduction	9 (25%)	0	0	1 (100%)	2 (9%)	0	1 (100%)	2 (33%)	1 (33%)	2 (100%)
Associated with death	0	0	0	0	0	0	0	0	0	0
Grade ≥3 TRAE	20 (56%)	1 (100%)	0	1 (100%)	10 (45%)	4 (80%)	1 (100%)	3 (50%)	2 (67%)	2 (100%)
SAE	12 (33%)	0	0	1 (100%)	6 (27%)	3 (60%)	0	1 (17%)	2 (67%)	2 (100%)
TR-SAE	10 (28%)	0	0	1 (100%)	6 (27%)	2 (40%)	0	0	2 (67%)	1 (50%)

Table 3.1. Best Efficacy for Tumor Evaluation in ADC-6A -101 Program Subjects (4 Week One Cycle, QW Administration)

Best efficacy, n	0.27 mg/kg	1.5 mg/kg	3.0 mg/kg
	(N=1)	(N=1)	(N=4)
PR	0	0	0
SD	1 (100%)	1 (100%)	4 (100%)
PD	0	0	0
NE	0	0	0
ORR	0	0	0
DCR	100%	100%	100%

Table 3.2. Best Efficacy for Tumor Assessment in ADC-6A -101 Project Subjects (Q3W Cohort Grouped by Dose)

Best efficacy, n	Q3W D1D8			Q3W D1		
	2.5mg/kg N=65	3.0mg/kg N=4	3.5mg/kg N=4	4.5mg/kg N=32	5.0mg/kg N=21	6.0mg/kg N=12
PR	29	2	0	14	12	4
SD	31	1	2	16	7	8
PD	5	1	0	2	2	0
ORR (95% CI)	44.6% (32.3-57.5)	50.0% (6.8-93.2)	50.0% (6.8-93.2)	43.8% (21.9-57.8)	57.1% (32.2-75.6)	33.3% (10.0-65.1)
DCR (95% CI)	92.3% (83.0-97.5)	75.0% (17.4-99.4)	75.0% (17.4-99.4)	93.8% (83.3-99.9)	90.5% (70.8-98.9)	100%

Table 3.3. Best Efficacy for Tumor Assessment of ADC-6A-101 Project Subjects (Q3W Cohort Grouped by Tumor Type)

	NSCLC (n=85)	SCLC (n=7)	NPC (n=29)	HNSCC (n=15)	Other (n=2)
Median meridian number (range)	3(1-8)	2 (1-2)	3 (1-9)	3 (1-7)	3(2-4)
Best efficacy, n					
PR	46	1	15	1	0
SD	33	5	14	11	2
PD	6	1	0	3	0
ORR (95% CI)	54.1% (43.0-65.0)	14.3% (0.36-57.9)	51.7% (32.5-70.6)	6.7% (0.19-36.03)	0%
DCR (95% CI)	92.9% (85.3-97.4)	85.7% (42.1-99.6)	100%	80% (46.19-94.96)	100%

Table 3.4. Analysis of Effectiveness for Subjects in Non-Small Cell Lung Cancer Dose Groups of the ADC-6A -101 Program

	full dose group N=85	4.5mg/kg D1 Q3W N=21	2.5mg/kg D1D8 Q3W N=37	5.0mg/kg D1 Q3W N=12	3.0mg/kg D1D8 Q3W N=4	6.0mg/kg D1 Q3W N=8	3.5mg/kg D1D8 Q3W N=3
Median number of meridian lines (range)	3(1-8)	3 (1-7)	2(1-7)	2(1-8)	6 (1-6)	4 (1-7)	2 (1-5)
Best efficacy							
PR	46	10	18	10	2	4	2
SD	33	9	17	1	1	4	1
PD	6	2	2	1	1	0	0
ORR (95% CI)	54.1% (43.0-65.0)	47.6% (31.9-65.6)	48.6% (6.8-93.2)	83.3% (9.4-99.2)	50.0% (25.7-70.2)	50.0% (51.6-97.9)	66.7% (15.7-84.3)
DCR (95% CI)	92.9% (85.3-97.4)	90.5% (81.8-99.3)	94.6% (19.4-99.4)	91.7% (29.2-)	75.0% (69.6-98.8)	100.0% -	100.0% -
Number of patients affected by the new crown outbreak	9	2	6	0	0	1	0
Exclusion of new crowns affects ORR (95% CI)	60.5% (48.7-71.6)	52.6% (39.1-75.5)	58.1% (6.8-93.2)	83.3% (9.4-99.2)	50.0% (28.9-75.6)	57.1% (51.6-97.9)	66.7% (18.4-90.1)
Removal of new crowns affects DCR (95% CI)	92.1% (83.6-97.1)	89.5% (78.6-99.2)	93.5% (19.4-99.4)	91.7% (29.2-)	75.0% (66.9-98.7)	100.0% -	100.0% -

Table 3.5. Fractionated Treatment Line Efficacy Analysis of Non-Small Cell Lung Cancer Subjects in the Full Dose Group of the ADC-6A -101 Project

	Total	EGFRwt PD-1 is treated and PBC after treatment ≥1L N=43 (91.5%)	PD-1 is treated and PBC after treatment ≥2L N=31 (66.0%)	Total	EGFRmut TKI treated and PBC after treatment ≥1L N=29 (76.3%)	TKI treated and PBC after treatment ≥2L N=19 (50%)
Median number of meridian lines (range)	2(1-8)	2(1-8)	3(1-8)	3 (1-7)	4 (2-7)	5 (3-7)
optimal efficacy						
PR	22	21	15	24	17	12
SD	23	20	15	10	9	6
PD	2	2	1	4	3	1
ORR (95% CI)	46.8% (32.1-61.9)	48.8% (33.3-64.5)	48.4% (30.2-66.9)	63.2% (46.0-78.2)	58.6% (38.9-76.5)	63.2% (38.4-83.7)
DCR (95% CI)	95.7% (85.5-99.5)	95.3% (84.2-99.4)	96.8% (83.3-99.9)	89.5% (75.2-97.1)	89.7% (7.7-97.8)	94.7% (74.0-99.9)
Number of patients affected by the new crown outbreak	5	4	2	4	4	2
Exclusion of new crowns affects ORR (95% CI)	52.4% (36.4-68.0)	53.8% (37.2-69.9)	51.7% (32.5-70.6)	70.6% (52.5-84.9)	68.0% (46.5-85.1)	70.6% (44.0-90.0)
Removal of new crowns affects DCR (95% CI)	95.2% (83.8-99.4)	94.9% (82.7-99.4)	96.6% (82.2-99.9)	88.2% (72.6-96.7)	88.0% (68.8-97.5)	94.1% (71.3-99.9)

Table 3.6. Analysis of Brain Metastasis Efficacy in Non-Small Cell Lung Cancer Subjects in the ADC-6A -101 Project

	population (statistics) N=85	Brain metastases at baseline N=28	No brain metastases at baseline N=57
median rule Number of lines (range)	3(1-8)	3 (1-7)	2(1-8)
best efficacy			
PR	46	14	32
SD	33	10	23
PD	6	4	2
ORR (95% CI)	54.1% (43.0-65.0)	50.0% (30.7-69.4)	56.1% (42.4-69.3)
DCR (95% CI)	92.9% (85.3-97.4)	85.7% (67.3-96.0)	96.5% (87.9-99.6)

Table 3.7. Analysis of Effectiveness for Subjects in Nasopharyngeal Carcinoma by Dose Group for the ADC-6A -101 Program

	full dose group N=29	4.5mg/kg D1 Q3W N=5	2.5mg/kg D1D8 Q3W N=19	5.0mg/kg D1 Q3W N=2	6.0mg/kg D1 Q3W N=2	3.5mg/kg D1D8 Q3W N=1
Median number of meridian lines (range)	3 (1-9)	2 (1-5)	3 (1-9)	1 (1)	5-9	3
best efficacy						
PR	15	3	10	2	0	0
SD	14	2	9	0	2	1
PD	0	0	0	0	0	0
ORR	51.7%	60.0%	52.6%	100.0%	0.0%	0.0%
(95% CI)	(32.5- 70.6)	(14.7- 94.7)	(28.9-75.6)	-	-	-
DCR	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%
(95% CI)	-	-	-	-	-	-
Number of patients affected by the new crown outbreak [#]	5	1	4	0	0	0
Exclusion of new crowns affects ORR	62.5%	75.0%	66.7%	100.0%	0.0%	0.0%
(95% CI)	(40.6- 81.2)	(19.4- 99.4)	(38.4-88.2)	-	-	-
Removal of new crowns affects DCR	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%
(95% CI)	-	-	-	-	-	-

[#]Subjects affected by the New Crown Epidemic were defined as subjects with a $\geq 25\%$ reduction in the number of doses that actually produced efficacy compared to the planned number of doses due to epidemic-related factors such as epidemic closure or nucleic acid positivity during the first and second tumor evaluations, resulting in a result of SD and failure to achieve a PR on the subject's previous first and second tumor evaluations.

Table 4.1. ADC-6A Non-Cavity Model (NCA) Pharmacokinetic Parameters for a Single ADC Administration

Parameters Dose levels	k_z (1/hr)	$t_{1/2}$ (hr)	T_{max} (hr)	C_{max} (ng/mL)	AUC_{0-4} (hr*ng/mL)	$AUC_{0-\infty}$ (hr*ng/mL)	Vd SD (L)	CL SD (L/hr)
0.27 mg/kg (n=1)	0.059	11.7	2.0	3007	37040	47727	6.259	0.386
1.5 mg/kg (n=1)	0.032	21.5	2.0	28746	659918	813538	4.551	0.147
2.5 mg/kg (n=13)	0.041 (0.015)	19.3 (7.4)	2.8 (1.3)	51132 (16408)	1513279 (620031)	1613659 (685342)	2.947 (0.972)	0.116 (0.045)
3.0 mg/kg (n=11)	0.032 (0.008)	23.3 (6.1)	2.4 (1.2)	56026 (13603)	1659555 (615577)	1815956 (698102)	3.890 (0.851)	0.122 (0.041)
3.5 mg/kg (n=5)	0.027 (0.004)	26.0 (3.3)	3.2 (1.8)	98600 (41417)	3012539 (1389173)	3198930 (1372129)	3.446 (1.056)	0.093 (0.029)
4.5 mg/kg (n=5)	0.030 (0.010)	25.0 (7.1)	2.4 (0.9)	116348 (46101)	3984244 (2011025)	4157185 (1895349)	2.435 (0.417)	0.075 (0.039)
5.0 mg/kg (n=5)	0.019 (0.005)	37.4 (7.9)	2.4 (0.9)	96165 (28603)	3600917 (1168130)	3880831 (1203152)	4.102 (0.977)	0.081 (0.035)
6.0 mg/kg (n=13)	0.022 (0.006)	33.9 (11.2)	3.2 (2.4)	147016 (48553)	5714516 (2186027)	6639116 (2363515)	3.114 (1.148)	0.067 (0.025)

Table 4.2. Non-Cavity Model (NCA) Pharmacokinetic Parameters for ADC-6A Single Administration of TAB

Parameters Dose levels	k_z (1/hr)	$t_{1/2}$ (hr)	T_{max} (hr)	C_{max} (ng/mL)	AUC_{0-t} (hr*ng/mL)	$AUC_{0-\infty}$ (hr*ng/mL)	Vd SD (L)	CL SD (L/hr)
0.27 mg/kg (n=1)	0.069	10.0	2.0	3423	39654	47771	5.563	0.385
1.5 mg/kg (n=)	0.031	22.2	2.0	32756	729419	918587	4.171	0.130
2.5 mg/kg (n=13)	0.039 (0.016)	21.5 (10.5)	2.0 (0)	51765 (11804)	1574460 (542004)	1715802 (659843)	2.938 (1.004)	0.107 (0.040)
3.0 mg/kg (n=11)	0.029 (0.008)	25.2 (6.1)	2.0 (0)	58712 (18148)	1805377 (682936)	2009571 (773835)	3.756 (0.648)	0.108 (0.029)
3.5 mg/kg (n=5)	0.024 (0.003)	29.0 (3.9)	2.8 (1.1)	95930 (38594)	3303728 (1383455)	3579879 (1340133)	3.355 (0.958)	0.080 (0.020)
4.5 mg/kg (n=5)	0.027 (0.007)	27.3 (6.7)	2.0 (0)	99488 (29039)	3898300 (1969903)	4180492 (1719465)	2.606 (0.729)	0.068 (0.022)
5.0 mg/kg (n=5)	0.018 (0.006)	40.9 (10.2)	2.4 (0.9)	89273 (27815)	3750096 (1332352)	4143527 (1447332)	4.273 (1.385)	0.077 (0.032)
6.0 mg/kg (n=13)	0.021 (0.006)	36.5 (12.7)	3.2 (2.4)	143690 (46378)	5836452 (2125931)	6896191 (2434488)	3.189 (1.145)	0.065 (0.024)

Table 4.3. Non-Cavity Model (NCA) Pharmacokinetic Parameters of ADC-6A Single Administration of Toxin

Parameters Cohorts	λ_z (1/hr)	$t_{1/2}$ (hr)	T_{max} (hr)	C_{max} (ng/mL)	AUC_{0-t} (hr*ng/mL)	$AUC_{0-\infty}$ (hr*ng/mL)
0.27 mg/kg (n=1)	0.024	29.3	4.0	0.9	20.0	29.1
1.5 mg/kg (n=1)	0.022	31.0	8.0	2.4	132.6	151.1
2.5 mg/kg (n=13)	0.019 (0.006)	41.0 (15.3)	6.0 (6.1)	8.2 (2.7)	334.6 (228.0)	378.8 (224.0)
3.0 mg/kg (n=11)	0.014 (0.006)	57.9 (21.9)	5.1 (1.6)	9.2 (5.5)	456.3 (370.0)	639.6 (596.0)
3.5 mg/kg (n=5)	0.015 (0.004)	50.8 (15.0)	5.2 (1.8)	10.7 (3.1)	483.2 (193.0)	526.5 (189.0)
4.5 mg/kg (n=5)	0.019 (0.011)	44.0 (18.2)	8.4 (9.4)	14.8 (8.5)	541.1 (335.0)	621.5 (375.0)
5.0 mg/kg (n=5)	0.011 (0.006)	76.8 (31.2)	4.4 (0.9)	8.7 (2.5)	480.4 (189.0)	574.3 (41.0)
6.0 mg/kg (n=12)	0.012 (0.002)	59.0 (9.2)	11.1 (10.5)	14.9 (11.4)	689.7 (486.0)	779.2 (489.0)

Table 4.4. ADC-6A Single Dose-Proportionality Analysis for Single Dose Administration

Analyte	PK Parameters	Adj R2	Interception (95% CI)	Slope (95% CI)
TAB	C_{max} (ng/mL)	0.6574	9.82 (9.668, 9.972)	1.096 (0.975, 1.217)
	AUC_{0-t} (hr*ng/ml)	0.7806	12.758 (12.454, 13.062)	1.532 (1.309, 1.756)
	$AUC_{0-\infty}$ (hr*ng/ml)	0.8186	12.849 (12.575, 13.123)	1.558 (1.356, 1.76)
ADC	C_{max} (ng/mL)	0.6794	9.731 (9.577, 9.884)	1.163 (1.04, 1.285)
	AUC_{0-t} (hr*ng/ml)	0.7716	12.663 (12.344, 12.981)	1.566 (1.332, 1.8)
	$AUC_{0-\infty}$ (hr*ng/ml)	0.795	12.757 (12.458, 13.055)	1.573 (1.353, 1.792)
TOX	C_{max} (ng/mL)	0.2136	0.837 (0.471, 1.204)	0.78 (0.502, 1.058)
	AUC_{0-t} (hr*ng/ml)	0.4774	4.757 (4.385, 5.129)	0.959 (0.685, 1.233)
	$AUC_{0-\infty}$ (hr*ng/ml)	0.4676	4.975 (4.608, 5.342)	0.924 (0.653, 1.196)

Table 4.5. Incidence of ADC-6A Characteristic Hematological Toxicity vs Dose

PT Name	ALL	QW_ 0.27mg/kg	QW_ 3.0mg/kg	D1D8Q3W_ 2.5mg/kg	D1D8Q3W_ 3.0mg/kg	D1D8Q3W_ 3.5mg/kg	D1Q3W_ 4.5mg/kg	D1Q3W_ 5.0mg/kg	D1Q3W_ 6.0mg/kg
Decreased white blood cell count	54/169 (32%)	0/1 (0%)	3/4 (75%)	14/80 (17.5%)	2/7 (28.6%)	4/5 (80%)	10/35 (28.6%)	13/24 (54.2%)	8/12 (66.7%)
Febrile neutropenia	13/169 (8%)	0/1 (0%)	2/4 (50%)	0/80 (0%)	1/7 (14.3%)	2/5 (40%)	3/35 (8.6%)	3/24 (12.5%)	2/12 (16.7%)
Decreased lymphocyte count	4/169 (2%)	0/1 (0%)	2/4 (50%)	1/80 (1.3%)	0/7 (0%)	0/5 (0%)	1/35 (2.9%)	0/24 (0%)	0/12 (0%)
Anemic	44/169 (26%)	1/1 (100%)	3/4 (75%)	20/80 (25%)	4/7 (57.1%)	2/5 (40%)	7/35 (20%)	6/24 (25%)	1/12 (8.3%)
Decreased platelet count	37/169 (22%)	0/1 (0%)	3/4 (75%)	13/80 (16.3%)	2/7 (28.6%)	2/5 (40%)	5/35 (14.3%)	7/24 (29.2%)	5/12 (41.7%)
Decreased neutrophil count	62/169 (37%)	0/1 (0%)	3/4 (75%)	18/80 (22.5%)	2/7 (28.6%)	2/5 (40%)	12/35 (34.3%)	14/24 (58.3%)	11/12 (91.7%)

Table 4.6. ADC-6A Characteristic Hematological Toxicity Severity vs Dose (2.5 mg/kg D1D8Q3W vs 4.5 mg/kg D1Q3W)

PT Name	AE classification	D1D8Q3W_	D1Q3W_
		2.5mg/kg	4.5mg/kg
Decreased white blood cell count	Level 1	4/80 (5%)	3/35 (8.6%)
	Level 2	18/80 (22.5%)	13/35 (37.1%)
	Level 3	10/80 (12.5%)	5/35 (14.3%)
	Level 4	4/80 (5%)	5/35 (14.3%)
	Level 5	0/80 (0%)	0/35 (0%)
Febrile neutropenia	Level 1	0/80 (0%)	0/35 (0%)
	Level 2	0/80 (0%)	0/35 (0%)
	Level 3	0/80 (0%)	1/35 (2.9%)
	Level 4	0/80 (0%)	2/35 (5.7%)
	Level 5	0/80 (0%)	0/35 (0%)
Decreased lymphocyte count	Level 1	1/80 (1.3%)	0/35 (0%)
	Level 2	1/80 (1.3%)	0/35 (0%)
	Level 3	0/80 (0%)	1/35 (2.9%)
	Level 4	1/80 (1.3%)	0/35 (0%)
	Level 5	0/80 (0%)	0/35 (0%)
anemic	Level 1	10/80 (12.5%)	8/35 (22.9%)
	Level 2	20/80 (25%)	3/35 (8.6%)
	Level 3	19/80 (23.8%)	6/35 (17.1%)
	Level 4	1/80 (1.3%)	1/35 (2.9%)
	Level 5	0/80 (0%)	0/35 (0%)
Decreased platelet count	Level 1	11/80 (13.8%)	3/35 (8.6%)
	Level 2	9/80 (11.3%)	10/35 (28.6%)
	Level 3	4/80 (5%)	2/35 (5.7%)
	Level 4	8/80 (10%)	3/35 (8.6%)
	Level 5	1/80 (1.3%)	0/35 (0%)
Decreased neutrophil count	Level 1	4/80 (5%)	6/35 (17.1%)
	Level 2	8/80 (10%)	5/35 (14.3%)
	Level 3	9/80 (11.3%)	4/35 (11.4%)
	Level 4	9/80 (11.3%)	8/35 (22.9%)
	Level 5	0/80 (0%)	0/35 (0%)

Table 5.1. Patient characteristics at baseline by different tumor type

	ALL (N=195)	NSCLC (EGFR wt) (N=72)	NSCLC (EGFR mt) (N=41)	NPC (N=42)	HNSCC (N=25)	SCLC (N=13)	Other (N=2)
Age (years)	53.5 (11.5)	55.4 (9.4)	56.1 (12.5)	45.7 (11.0)	54.6 (12.1)	58.0 (9.0)	49.5 (13.4)
Sex							
Male	133 (68)	53 (74)	11 (27)	33 (79)	25 (100)	10 (77)	1 (50)
Female	62 (32)	19 (26)	30 (73)	9 (21)	0	3 (23)	1 (50)
Smoking History							
Never	107 (55)	32 (44)	35 (85)	29 (69)	4 (16)	5 (38)	2 (100)
Yes	83 (43)	39 (54)	5 (12)	13 (31)	18 (72)	8 (62)	0
UNK	5 (3)	1 (1)	1 (2)	0	3 (12)	0	0
ECOG							
0	16 (8)	6 (8)	5 (12)	3 (7)	0	1 (8)	1 (50)
1	179 (92)	66 (92)	36 (88)	39 (93)	25 (100)	12 (92)	1 (50)
Histology							
Squamous carcinoma	57 (29)	25 (35)	0	6 (14)	25 (100)	0	1 (50)
non-squamous carcinoma	138 (71)	47 (65)	41 (100)	36 (86)	0	13 (100)	1 (100)
Brain Metastasis at Screening	35 (18)	11 (15)	21 (41)	0	0	3 (23)	0
# of metastasis organ	3 (1.3)	3 (1.4)	3 (1.3)	3 (1.3)	2 (1.2)	3 (1.4)	2 (1.4)
# of prior treatment line							
1	39 (20)	21 (29)	1 (2)	7 (17)	4 (16)	6 (46)	0
2	58 (30)	23 (32)	12 (29)	8 (19)	10 (40)	4 (31)	1 (50)
3+	98 (50)	28 (39)	28 (68)	27 (64)	11 (44)	3 (23)	1 (50)
Prior TKI	44 (23)	2 (3)	41 (100)	0	1 (4)	0	0
Prior 3 rd -generation TKI	40 (21)	2 (3)	37 (90)	0	1 (4)	0	0
Prior Osimertinib	33 (17)	2 (3)	30 (73)	1 (2)	0	0	0
Prior PBC	177 (91)	70 (97)	30 (73)	39 (93)	25 (100)	11 (85)	2 (100)
Prior CI*	159 (82)	68 (94)	14 (34)	39 (93)	23 (92)	13 (100)	2 (100)
Prior anti-PD-1/PD-L1**	158 (81)	68 (94)	14 (34)	39 (93)	23 (92)	12 (92)	2 (100)
Prior ADC	6 (3)	0	0	2 (5)	4 (16)	0	0

Prior TOP1 ADC	1 (1)	0	0	0	0	1 (4)	0	0
Note: Data are n (%) or Mean (SD). All participants in this study were Asians. NSCLC, non-small-cell lung cancer; NPC, nasopharyngeal carcinoma; HNSCC, head and neck squamous cell carcinoma; SCLC, small cell lung cancer. UNK, unknown; ECOG, Eastern Cooperative Oncology Group; wt, wild type; mt, mutant; SD, standard deviation; TKI, tyrosine kinase inhibitor; PBC, platinum-based chemotherapy; ICI, immune checkpoint inhibitors; anti-PD-1/PD-L1, including anti-PD-1/PD-L1 monoclonal and bispecific antibody; ADC, antibody-drug conjugate; TOP1, topoisomerase I. *Prior ICIs include prior PD-1/PD-L1 monoclonal antibodies, bispecific antibodies or triple antibodies targeting PD-1/PD-L1 or other immune checkpoints. **Prior anti-PD-1/PD-L1 include prior PD-1/PD-L1 monoclonal antibodies, bispecific antibodies or triple antibodies contained PD-1/PD-L1 blockade.								

Table 5.2. Treatment-related adverse events

TRAE in ≥10% of patients and all grade 3-5 TRAEs	ALL (N=195)				2.5mg/kg on days 1 and 8 every 3 weeks (N=106)			
	G1-G2	G3	G4	G5	G1-G2	G3	G4	G5
Anaemia	81 (42%)	73 (37%)	3 (2%)		44 (42%)	40 (38%)	2 (2%)	
Nausea	80 (41%)	1 (<1%)			41 (39%)	1 (<1%)		
Asthenia	66 (34%)	1 (<1%)			31 (29%)	1 (<1%)		
Decreased appetite	65 (33%)	2 (1%)			32 (30%)	2 (2%)		
Leukopenia	64 (33%)	46 (24%)	30 (15%)		37 (35%)	21 (20%)	10 (9%)	
Alopecia	63 (32%)				27 (25%)			
Vomiting	63 (32%)	3 (2%)			31 (29%)	2 (2%)		
Stomatitis	60 (31%)	1 (<1%)			28 (26%)			
Thrombocytopenia	58 (30%)	28 (14%)	35 (18%)		30 (28%)	17 (16%)	15 (14%)	
Diarrhoea	43 (22%)	3 (2%)			22 (21%)	1 (<1%)		
Skin related disorder *	43 (22%)	2 (1%)			22 (21%)	1 (<1%)		
Neutropenia	39 (20%)	36 (18%)	55 (28%)		24 (23%)	17 (16%)	19 (18%)	
Hypophagia	31 (16%)				15 (14%)			
Hypoalbuminaemia	27 (14%)				18 (17%)			
Alanine aminotransferase increased	24 (12%)		1 (<1%)		7 (7%)			
Hypokalaemia	24 (12%)	3 (2%)	2 (1%)		17 (16%)			
Constipation	21 (11%)				12 (11%)			
Hyponatraemia	21 (11%)		2 (1%)		14 (13%)		2 (2%)	
Pyrexia	19 (10%)				6 (6%)			
Aspartate aminotransferase increased	18 (9%)	1 (<1%)	2 (1%)		6 (6%)		1 (<1%)	
Abdominal Pain	13 (7%)	1 (<1%)			9 (8%)	1 (<1%)		
Proteinuria	11 (6%)	1 (<1%)			6 (6%)	1 (<1%)		
Chest discomfort	5 (3%)	1 (<1%)			4 (4%)	1 (<1%)		
Cough	5 (3%)	1 (<1%)			2 (2%)			

Hypertriglyceridaemia	6 (3%)	1 (<1%)			4 (4%)	1 (<1%)	
Hypoaesthesia	5 (3%)	2 (1%)			4 (4%)	1 (<1%)	
Pneumonia	6 (3%)	4 (2%)	1 (<1%)	1 (<1%)	2 (2%)	2 (2%)	1 (<1%)
Lymphocyte count decreased	3 (2%)	2 (1%)	2 (1%)		2 (2%)		1 (<1%)
Bilirubin conjugated increased	2 (1%)	1 (<1%)			1 (<1%)	1 (<1%)	
Dyspnoea	1 (<1%)	1 (<1%)			1 (<1%)	1 (<1%)	
Gastrointestinal infection		1 (<1%)				1 (<1%)	
Granulocyte count decreased	1 (<1%)	1 (<1%)			1 (<1%)		
Herpes zoster	1 (<1%)	1 (<1%)			1 (<1%)		
Monocyte count decreased			1 (<1%)				1 (<1%)
Myelosuppression	1 (<1%)		6 (3%)	1 (<1%)			4 (4%)
Myositis		1 (<1%)					
Septic shock	1 (<1%)		1 (<1%)	1 (<1%)		1 (<1%)	1 (<1%)
Troponin T increased	1 (<1%)	1 (<1%)			1 (<1%)	1 (<1%)	
White blood cell counts increased		1 (<1%)				1 (<1%)	

Data are n (%). *Skin related disorders: acne, dermatitis allergic, dry skin, eczema, lichenoid keratosis, palmar-plantar erythrodysesthesia syndrome, papule, pruritus, rash, maculopapular rash, skin exfoliation, skin fissures, skin hyperplasia, skin ulcer

Table 5.3 Efficacy results of BL-B01D1 in different tumor types

	Total (n=174)	NSCLC (EGFR mut) (n=40)	NSCLC (EGFR wt) (n=62)	NPC (n=37)	SCLC (n=13)	HNSCC (n=20)	Other (n=2)
Median prior treatment line (range)	3 (1-9)	3 (1-7)	2 (1-8)	3 (1-9)	2 (1-4)	3 (1-9)	3 (2-4)
BOR, n (%)							
PR (confirmed and pending confirmation)	80 (46%)	27 (68%)	25 (40%)	22 (59%)	3 (23%)	3 (15%)	0 (0%)
PR	60 (34%)	21 (53%)	19 (31%)	14 (38%)	3 (23%)	3 (15%)	0 (0%)
SD	75 (43%)	8 (20%)	29 (47%)	15 (41%)	8 (62%)	13 (65%)	2 (100%)
PD	12 (7%)	4 (10%)	3 (5%)	0 (0%)	2 (15%)	3 (15%)	0 (0%)
NE	7 (4%)	1 (3%)	5 (8%)	0 (0%)	0 (0%)	1 (5%)	0 (0%)
ORR (confirmed and pending confirmation), % (95% CI)	46.0 (38.4-53.7)	67.5 (50.9-81.4)	40.3 (28.1-53.6)	59.5 (42.1-75.2)	23.1 (5.0-53.8)	15.0 (3.2-37.9)	0
ORR, % (95% CI)	34.5 (27.5-42.1)	52.5 (36.1-68.5)	30.6 (19.6-43.7)	37.8 (22.5-55.2)	23.1 (5.0-53.8)	15.0 (3.2-37.9)	0
DCR, % (95% CI)	89.1 (83.5-93.3)	87.5 (73.2-95.8)	87.1 (76.1-94.3)	100	84.6 (54.6-98.1)	80.0 (56.3-94.3)	100
mDOR (95%CI), mo	8.5 (5.4-NE)	8.5 (2.8-NE)	NE (5.4-NE)	NE (4.0-NE)	4.4 (4.3-NE)	NE	/
mPFS (95%CI), mo	5.7 (4.2-6.8)	5.6 (3.9-9.7)	5.4 (4.0-6.8)	6.8 (4.1-NE)	5.5 (1.5-7.9)	NE (1.6-NE)	7.6 (6.8-NE)

Note: NSCLC, non-small-cell lung cancer; wt, wild type; mt, mutant; NPC, nasopharyngeal carcinoma; HNSCC, head and neck squamous cell carcinoma; SCLC, small cell lung cancer. UNK, unknown; ECOG, Eastern Cooperative Oncology Group; BOR, best of response; PR, partial responses; SD, stable diseases; PD, progressive diseases; NE, not estimated; ORR, overall response rate; DCR, disease control rate; CI, confidence interval; mDOR, median duration of

response; mPFS, median progression-free survival.

Table 5.4. Adverse events in different dose groups

	ALL									
	weekly			On days 1 and 8 every 3 weeks			On day 1 every 3 weeks			
	0.27mg/kg (n=1)	1.5mg/kg (n=1)	3.0mg/kg (n=4)	2.5mg/kg (n=106)	3.0mg/kg (n=7)	3.5mg/kg (n=5)	4.5mg/kg (n=35)	5.0mg/kg (n=24)	6.0mg/kg (n=12)	
TEAEs, n (%) ^a	1 (100)	1 (100)	4 (100)	104 (98)	7 (100)	5 (100)	35 (100)	24 (100)	12 (100)	
Associated with treatment discontinuation	0	0	1 (25)	6 (6)	1 (14)	1 (20)	2 (6)	0	1 (8)	
Associated with dose reduction	0	0	1 (25)	21 (20)	1 (14)	3 (60)	6 (17)	10 (42)	10 (83)	
Associated with death	0	0	0	6 (6)	1 (14)	2 (40)	1 (3)	1 (4)	0	
Grade >=3 TEAE	1 (100)	0	4 (100)	75 (71)	6 (86)	5 (100)	29 (83)	21 (88)	12 (100)	
Treatment Related TEAE (TRAE)	1 (100)	1 (100)	4 (100)	103 (97)	7 (100)	5 (100)	32 (91)	24 (100)	12 (100)	
Associated with treatment discontinuation	0	0	1 (25)	2 (2)	1 (14)	0	0	0	1 (8)	
Associated with dose reduction	0	0	1 (25)	21 (20)	1 (14)	3 (60)	6 (17)	10 (42)	10 (83)	
Associated with death	0	0	0	2 (1)	1 (14)	0	0	0	0	
Grade >=3 TRAE	1 (100)	0	3 (75)	68 (64)	6 (86)	4 (80)	24 (69)	21 (88)	12 (100)	
SAE	0	0	4 (100)	46 (43)	5 (71)	4 (80)	11 (31)	13 (54)	11 (92)	
TR-SAE	0	0	3 (75)	33 (31)	3 (43)	3 (60)	5 (14)	13 (54)	10 (83)	

TEAEs, Treatment emergent adverse event; SAE, severe adverse event; TR-SAE, treatment related SAE.

Table 5.5. Numbers and reasons for all deaths

Patient No.	Age	Sex	Dose level	Tumor type	Adverse event	Drug Related
01012	60	Male	D1D8Q3W-2.5mg/kg	NSCLC_EGFRwt	Pericardial effusion	Possibly irrelevant
01015	32	Male	D1D8Q3W-2.5mg/kg	HNSCC	Pneumonia	Possibly irrelevant
01024	39	Male	D1D8Q3W-3.5mg/kg	NSCLC_EGFRmt	Pleural effusion	Possibly irrelevant
01033	53	Male	D1D8Q3W-3.5mg/kg	NSCLC_EGFRwt	Death of unknown cause	Unable to evaluate
01087	51	Male	D1D8Q3W-2.5mg/kg	NSCLC_EGFRwt	Pulmonary, COVID-19-infected pneumonia	Pulmonary (Possibly relevant); COVID-19-infected pneumonia (Possibly irrelevant)
01093	60	Male	D1D8Q3W-2.5mg/kg	NSCLC_EGFRwt	Septic shock	Possibly relevant
01125	64	Male	D1Q3W-4.5mg/kg	NSCLC_EGFRwt	Pneumonia	Possibly irrelevant
01175	63	Male	D1D8Q3W-2.5mg/kg	NSCLC_EGFRwt	Death of unknown cause	Unable to evaluate
03001	64	Male	D1Q3W-5.0mg/kg	HNSCC	Tumor hemorrhage	Possibly irrelevant
03002	47	Male	D1D8Q3W-3.0mg/kg	HNSCC	Myelosuppression	Relevant
06001	51	Male	D1D8Q3W-2.5mg/kg	HNSCC	Pneumonia	Possibly irrelevant

D1D8 Q3W, one dose on days 1 and 8 of each cycle every 3 weeks; D1 Q3W, one dose on day 1 of each cycle every 3 weeks; NSCLC, non-small cell lung cancer; HNSCC, head and neck squamous cell carcinoma

Table 5.6. Treatment-emergent adverse events summary

TEAE in ≥10% of patients and all grade 3-5 TRAEs, n (%)	ALL (N=195)				2.5mg/kg on days 1 and 8 every 3 weeks (N=106)			
	G1-G2	G3	G4	G5	G1-G2	G3	G4	G5
Anaemia	87 (45%)	75 (38%)	3 (2%)		48 (45%)	40 (38%)	2 (2%)	
Nausea	81 (42%)	1 (<1%)			42 (40%)	1 (<1%)		
Asthenia	69 (35%)	1 (<1%)			33 (31%)	1 (<1%)		
Decreased appetite	69 (35%)	2 (1%)			32 (30%)	2 (2%)		
Alopecia	66 (34%)				29 (27%)			
Vomiting	66 (34%)	3 (2%)			33 (31%)	2 (2%)		
Leukopenia	64 (33%)	46 (24%)	30 (15%)		37 (35%)	21 (20%)	10 (9%)	
Stomatitis	61 (31%)	2 (1%)			29 (27%)	1 (<1%)		
Thrombocytopenia	59 (30%)	28 (14%)	35 (18%)		31 (29%)	17 (16%)	15 (14%)	
COVID-19	57 (29%)				25 (24%)			
Diarrhoea	54 (28%)	3 (2%)			28 (26%)	1 (<1%)		
Hypoalbuminaemia	49 (25%)				31 (29%)			
Constipation	46 (24%)				25 (24%)			
Hypokalaemia	46 (24%)	7 (4%)	3 (2%)		25 (24%)	2 (2%)		
Pyrexia	44 (23%)	1 (<1%)			17 (16%)	1 (<1%)		
Skin related disorder*	45 (23%)	2 (1%)			23 (22%)	1 (<1%)		
Hyponatraemia	43 (22%)	1 (<1%)	2 (1%)		28 (26%)		2 (2%)	
Neutropenia	38 (19%)	36 (18%)	56 (29%)		24 (23%)	17 (16%)	19 (18%)	
Proteinuria	38 (19%)	1 (<1%)			13 (12%)	1 (<1%)		
Hypophagia	31 (16%)				15 (14%)			
Alanine aminotransferase increased	30 (15%)		1 (<1%)		10 (9%)			
Cough	30 (15%)	1 (<1%)			16 (15%)			
Hyperuricaemia	29 (15%)				16 (15%)			
Productive cough	30 (15%)				15 (14%)			
Dizziness	27 (14%)				17 (16%)			
Abdominal Pain	26 (13%)	2 (1%)			15 (14%)	1 (<1%)		
Aspartate aminotransferase increased	25 (13%)	1 (<1%)	2 (1%)		9 (8%)		1 (<1%)	
Hypertriglyceridaemia	23 (12%)	1 (<1%)			15 (14%)	1 (<1%)		

Epistaxis	20 (10%)				9 (8%)	
Hyperglycaemia	19 (10%)				12 (11%)	
Chest discomfort	15 (8%)	1 (<1%)			7 (7%)	1 (<1%)
Headache	15 (8%)	1 (<1%)			8 (8%)	
Urinary tract infection	16 (8%)	1 (<1%)			9 (8%)	
Hypocalcaemia	14 (7%)	2 (1%)			6 (6%)	
Upper respiratorytract infection	13 (7%)	2 (1%)			5 (5%)	1 (<1%)
Abdominal distension	11 (6%)	1 (<1%)			5 (5%)	
Hypoesthesia	10 (5%)	2 (1%)			6 (6%)	1 (<1%)
Pneumonia	10 (5%)	14 (7%)	1 (<1%)	4 (2%)	4 (4%)	1 (<1%) 3 (3%)
Dyspnoea	8 (4%)	3 (2%)			4 (4%)	2 (2%)
Pain	8 (4%)	1 (<1%)			2 (2%)	1 (<1%)
Bilirubin conjugated increased	3 (2%)	1 (<1%)			2 (2%)	1 (<1%)
Herpes zoster	3 (2%)	1 (<1%)			1 (<1%)	
Interleukin level increased	4 (2%)		1 (<1%)		1 (<1%)	
Lymphocyte count decreased	4 (2%)	2 (1%)	2 (1%)		2 (2%)	1 (<1%)
Haemorrhoids	2 (1%)	1 (<1%)			2 (2%)	1 (<1%)
Hypercalcaemia	2 (1%)	1 (<1%)	1 (<1%)		2 (2%)	1 (<1%)
Pleural effusion	2 (1%)	3 (2%)		1 (<1%)	1 (<1%)	
C-reactive protein increased	1 (<1%)		1 (<1%)		1 (<1%)	1 (<1%)
COVID-19 pneumonia	1 (<1%)			1 (<1%)	1 (<1%)	1 (<1%)
Chronic kidney disease		1 (<1%)				
Death				2 (1%)		1 (<1%)
Gastrointestinal infection		1 (<1%)				
Generalised oedema		1 (<1%)				1 (<1%)
Granulocyte count decreased	1 (<1%)	1 (<1%)			1 (<1%)	
Hyperglycaemic hyperosmolar nonketotic syndrome		1 (<1%)				
Hypermagnesaemia		1 (<1%)				1 (<1%)
Infection		1 (<1%)				
Monocyte count decreased			1 (<1%)			1 (<1%)
Myelosuppression	1 (<1%)		6 (3%)	1 (<1%)		4 (4%)

Myocardial ischaemia	1 (<1%)	1 (<1%)	1 (<1%)	1 (<1%)
Myositis	1 (<1%)	1 (<1%)		
PO2 decreased	1 (<1%)	1 (<1%)		
Pericardial effusion	1 (<1%)	1 (<1%)	1 (<1%)	1 (<1%)
Pharyngeal haemorrhage	1 (<1%)	1 (<1%)		
Red blood cell sedimentation rate increased		1 (<1%)		1 (<1%)
Septic shock	1 (<1%)	1 (<1%)	1 (<1%)	1 (<1%)
Serum amyloid A protein increased		1 (<1%)		1 (<1%)
Troponin T increased	1 (<1%)	1 (<1%)	1 (<1%)	1 (<1%)
Tumour haemorrhage		1 (<1%)	1 (<1%)	1 (<1%)
Type 2 diabetes mellitus		1 (<1%)		1 (<1%)
White blood cell counts increased		1 (<1%)		1 (<1%)

¹Skin disorders: acne, dermatitis allergic, dry skin, eczema, lichenoid keratosis, palmar-plantar erythrodysesthesia syndrome, papule, pruritus, rash, maculopapular rash, skin exfoliation, skin fissures, skin hyperplasia, skin ulcer

Table 5.7. Details of patients with drug limited toxicity

Patient. No.	Age	Sex	Tumor type	Dose level	DLT detail	Time of occurrence	Time of recovery
01007	40	Male	NSCLC_EGF Rwt	QW-3.0 mg/kg	Grade 3 Febrile neutropenia	2022-03-16	2022-03-17
01010	56	Male	NPC	QW-3.0 mg/kg	Grade 3 Febrile neutropenia	2022-03-22	2022-03-22
01024	39	Male	NSCLC_EGF Rmt	D1D8Q3W-3.5 mg/kg	Grade 3 Febrile neutropenia	2022-07-31	2022-08-07
01026	39	Female	NSCLC_EGF Rmt	D1D8Q3W-3.5 mg/kg	Grade 4 Febrile neutropenia	2022-07-21	2022-07-25

DLT, drug limited toxicity; NSCLC, non-small cell lung cancer; NPC, nasopharyngeal carcinoma; QW, one dose weekly; D1D8 Q3W, one dose on days 1 and 8 of each cycle every 3 weeks; D1 Q3W, one dose on day 1 of each cycle every 3 weeks.

Table 5.8. Patient characteristics of the activity analysis population at baseline by different tumor type

	ALL (N=174)	NSCLC (EGFR wt) (N=62)	NSCLC (EGFR mt) (N=40)	NPC (N=37)	HNSCC (N=20)	SCLC (N=13)	Other (N=2)
Age (years), Mean (SD)	53.4 (11.5)	55.1 (9.3)	55.7 (12.3)	45.2 (11.5)	56.2 (11.0)	58.0 (9.0)	49.5 (13.4)
Sex (Male), n (%)	116 (67)	44 (71)	11 (28)	30 (81)	20 (100)	10 (77)	1 (50)
Smoking History, n (%)							
Never	98 (56)	29 (47)	34 (85)	25 (68)	3 (15)	5 (38)	2 (100)
Yes	71 (41)	32 (51)	5 (13)	12 (33)	14 (70)	8 (61)	0
UNK	5 (3)	1 (2)	1 (3)	0	3 (15)	0	0
ECOG, n (%)							
0	14 (8)	3 (5)	5 (13)	3 (8)	0	1 (8)	1 (50)
1	160 (92)	59 (95)	35 (88)	34 (92)	20 (100)	12 (92)	1 (50)
Histology							
SCC	46 (26)	20 (32)	0	5 (14)	20 (100)	0	1 (50)
Non-SCC	128 (74)	42 (68)	40 (100)	32 (86)	0	13 (100)	1 (50)
Brain Metastasis at	29 (17)	9 (15)	17 (43)	0	0	3 (23)	0
Screening, n (%)							
# of metastasis organs, Mean (SD)	3 (1.4)	3 (1.4)	3 (1.3)	3 (1.3)	2 (1.3)	3 (1.4)	2 (1.4)
# of prior treatment line, n (%)							
1	35 (20)	18 (29)	1 (2)	7 (19)	3 (15)	6 (46)	0
2	50 (29)	20 (32)	11 (28)	8 (22)	6 (30)	4 (31)	1 (50)
3+	89 (51)	24 (39)	28 (70)	22 (59)	11 (55)	3 (23)	1 (50)
Prior TKI, n (%)	43 (25)	2 (3)	40 (100)	0	1 (5)	0	0
Prior 3 rd -generation TKI, n (%)	39 (22)	2 (3)	36 (90)	0	1 (5)	0	0
Prior Osimertinib, n (%)	32 (18)	2 (3)	29 (73)	1 (3)	0	0	0
Prior PBC, n (%)	158 (91)	62 (100)	29 (73)	34 (92)	20 (100)	11 (85)	2 (100)
Prior ICI, n (%)*	140 (80)	58 (94)	14 (35)	35 (95)	18 (90)	13 (100)	2 (100)
Prior anti-PD-1/PD-L1**	139 (80)	58 (94)	14 (35)	35 (95)	18 (90)	12 (92)	2 (100)
Prior ADC, n (%)	6 (3)	0	0	2 (5)	4 (20)	0	0
Prior TOP1 ADC, n (%)	1 (1)	0	0	0	1 (4)	0	0

Note: Data are n (%) or Mean (SD). All participants in this study were Asians. NSCLC, non-small-cell lung cancer; NPC, nasopharyngeal carcinoma; HNSCC, head and neck squamous cell carcinoma; SCLC, small cell lung cancer. UNK, unknown; ECOG, Eastern Cooperative Oncology Group; wt, wild type; mt, mutant; SD, standard deviation; TKI, tyrosine kinase inhibitor; PBC, platinum-based chemotherapy; ICI, immune checkpoint inhibitors; ADC, antibody-drug conjugate; TOP1, topoisomerase I. * Prior ICIs include prior PD-1/PD-L1 monoclonal antibodies; bispecific antibodies or triple antibodies targeting PD-1/PD-L1 or other immune checkpoints. ** Prior anti-PD-1/PD-L1 include prior PD-1/PD-L1 monoclonal antibodies; bispecific antibodies or triple antibodies contained PD-1/PD-L1 blockade.

Table 5.9. Efficacy results of BL-B01D1 in different tumor types

	NSCLC (EGFR mut) (n=40)	NSCLC (EGFR wt) (n=62)	NPC (n=37)	SCLC (n=13)	HNSCC (n=20)	Other (n=2)
BOR, n (%)						
PR (confirmed and pending confirmation)	27 (68%)	25 (40%)	22 (59%)	3 (23%)	3 (15%)	0 (0%)
SD	21 (53%)	19 (31%)	14 (38%)	3 (23%)	3 (15%)	0 (0%)
PD	8 (20%)	29 (47%)	15 (41%)	8 (62%)	13 (65%)	2 (100%)
NE	4 (10%)	3 (5%)	0 (0%)	2 (15%)	3 (15%)	0 (0%)
	1 (3%)	5 (8%)	0 (0%)	0 (0%)	1 (5%)	0 (0%)
ORR (confirmed and pending confirmation), % (95% CI)	67.5 (50.9-81.4)	40.3 (28.1-53.6)	59.5 (42.1-75.2)	23.1 (5.0-53.8)	15.0 (3.2-37.9)	0
ORR, % (95% CI)	52.5 (36.1-68.5)	30.6 (19.6-43.7)	37.8 (22.5-55.2)	23.1 (5.0-53.8)	15.0 (3.2-37.9)	0
DCR, % (95% CI)	87.5 (73.2-95.8)	87.1 (76.1-94.3)	100	84.6 (54.6-98.1)	80.0 (56.3-94.3)	100
mDOR (95%CI), mo	8.5 (2.8- NE)	NE (5.4- NE)	NE (4.0- NE)	4.4 (4.3- NE)	NE	/
mPFS (95%CI), mo	5.6 (3.9-9.7)	5.4 (4.0-6.8)	6.8 (4.1- NE)	5.5 (1.5-7.9)	NE (1.6- NE)	7.6 (6.8- NE)

Note: NSCLC, non-small-cell lung cancer; wt, wild type; mt, mutant; NPC, nasopharyngeal carcinoma; HNSCC, head and neck squamous cell carcinoma; SCLC, small cell lung cancer. UNK, unknown; ECOG, Eastern Cooperative Oncology Group; BOR, best of response; PR, partial responses; SD, stable diseases; PD, progressive diseases; NE, not estimated; ORR, overall response rate; DCR, disease control rate; CI, confidence interval; mDOR, median duration of response; mPFS, median progression-free survival.

Table 5.10. Efficacy results of BL-B01D1 in different tumor types (Wilson score)^a

	Total (N=174)	NSCLC (EGFR mut) (n=40)	NSCLC (EGFR wt) (n=62)	NPC (n=37)	SCLC (n=13)	HNSCC (n=20)	Other (n=2)
BOR, n (%)							
PR (confirmed and pending confirmation)	80 (46%)	27 (68%)	25 (40%)	22 (59%)	3 (23%)	3 (15%)	0 (0%)
PR	60 (34%)	21 (53%)	19 (31%)	14 (38%)	3 (23%)	3 (15%)	0 (0%)
SD	75 (43%)	8 (20%)	29 (47%)	15 (41%)	8 (62%)	13 (65%)	2 (100%)
PD	12 (7%)	4 (10%)	3 (5%)	0 (0%)	2 (15%)	3 (15%)	0 (0%)
NE	7 (4%)	1 (3%)	5 (8%)	0 (0%)	0 (0%)	1 (5%)	0 (0%)
ORR (confirmed and pending confirmation), % (95% CI)	46.0 (38.7-53.4)	67.5 (52.0-79.9)	40.3 (29.0-52.8)	59.5 (43.5-73.7)	23.1 (8.2-50.3)	15.0 (5.2-36.0)	0
ORR, % (95% CI)	34.5 (27.8-41.8)	52.5 (37.5-67.1)	30.6 (20.6-43.0)	37.8 (24.1-53.9)	23.1 (8.2-50.3)	15.0 (5.2-36.0)	0
DCR, % (95% CI)	89.1 (83.6-92.9)	87.5 (73.9-94.5)	87.1 (76.6-93.3)	100	84.6 (57.8-95.7)	80.0 (58.4-91.9)	100
mDOR (95%CI), mo	8.5 (5.4- NR)	8.5 (2.8- NR)	NR (5.4- NR)	NR (4.0- NR)	4.4 (4.3- NR)	NR (1.6- NR)	/
mPFS (95%CI), mo	5.7 (4.2-6.8)	5.6 (3.9-9.7)	5.4 (4.0-6.8)	6.8 (4.1- NR)	5.5 (1.5-7.9)	NR (1.6- NR)	7.6 (6.8- NR)

^a Wilson score method was also used as a post-hoc analysis to calculate 95% CIs. Note: NSCLC, non-small-cell lung cancer; wt, wild type; mt, mutant; NPC, nasopharyngeal carcinoma; HNSCC, head and neck squamous cell carcinoma; SCLC, small cell lung cancer. UNK, unknown; ECOG, Eastern Cooperative Oncology Group; BOR, best of response; PR, partial responses; SD, stable diseases; PD, progressive diseases; NE, not estimated; ORR, overall response rate; DCR, disease control rate; CI, confidence interval; mDOR, median duration of response; mPFS, median progression-free survival.

Table 5.11. Efficacy results in different dose groups

BOR, n (%)	D1D8 Q3W (N=105)			D1 Q3W (N=68)			Q3W Total (N=174)
	2.5 mg/kg (N=97)	3.0 mg/kg (N=5)	3.5 mg/kg (N=4)	4.5 mg/kg (N=33)	5.0 mg/kg (N=23)	6.0 mg/kg (N=12)	
PR (confirmed and pending confirmation)	43 (44%)	2 (40%)	2 (50%)	17 (52%)	11 (48%)	5 (42%)	80 (46%)
PR	30 (31%)	1 (20%)	2 (50%)	14 (42%)	8 (35%)	5 (42%)	60 (34%)
SD	44 (45%)	1 (20%)	2 (50%)	13 (39%)	8 (35%)	7 (58%)	75 (43%)
PD	7 (7%)	1 (20%)	0	2 (6%)	2 (9%)	0	12 (7%)
NE	3 (3%)	1 (20%)	0	1 (3%)	2 (9%)	0	7 (3%)
ORR (confirmed and pending confirmation), % (95% CI)	44.3 (34.2-54.8)	40.0 (6.8-93.2)	50.0 (6.8-93.2)	51.5 (33.5-69.2)	47.8 (26.8-69.4)	41.7 (15.2-72.3)	46.2 (38.6-54.0)
ORR (95% CI)	30.9 (21.9-41.1)	20.0 (0.5-71.6)	50.0 (6.8-93.2)	42.4 (25.5-60.8)	34.8 (16.4-57.3)	41.7 (15.2-57.3)	34.5 (27.5-42.1)
DCR, % (95% CI)	89.7 (81.9-94.9)	60.0 (17.4-99.4)	100.0	90.9 (75.7-98.1)	82.6 (61.2-95.0)	100	89.6 (84.1-93.7)
mDOR (95%CI), mo	6.9 (4.8- NE)	3.0 (NE)	4.0 (2.4- NE)	NE (3.0- NE)	NE (2.7- NE)	NE (NE)	8.5 (5.4- NE)
mPFS (95%CI), mo	5.5 (4.1-6.8)	1.8 (0.4- NE)	3.3 (2.6- NE)	6.4 (4.1- NE)	5.7 (2.6- NE)	NE (3.1- NE)	5.7 (4.2-6.8)

Note: BOR, best of response; D1D8 Q3W, one dose on days 1 and 8 of each cycle every 3 weeks; D1 Q3W, one dose on day 1 of each cycle every 3 weeks; PR, partial response; SD, stable disease; PD, progressive disease; NE, not estimated; ORR, overall response rate; DCR, disease control rate; CI, confidence interval; mDOR, median duration of response; mPFS, median progression-free survival.

Table 5.12. Subgroup analysis of BL-B01D1 efficacy in NSCLC patients

Subgroup	EGFRmut NSCLC (N=40)			EGFRwt NSCLC (N=62)		
	Treated/no CNS metastasis	Untreated CNS metastasis	Prior TKI + at least 1 line of PBC ^b	treated/no CNS metastasis	Untreated CNS metastasis	Prior PD-1/L1 + at least 1 line of PBC ^b
Number of Patients	23	17	27	52	10	58
BOR, n (%)						
PR (confirmed and pending confirmation)	17	10	18	22	3	24
PR	14	7	15	17	2	18
SD	4	4	7	22	7	26
PD	1	3	2	3	0	3
NE	1	0	0	5	0	5
ORR (confirmed and pending confirmation), % (95% CI)	73.9 (51.6, 89.8)	58.8 (32.9, 81.6)	66.7 (46.0,83.5)	42.3 (28.7,56.8)	30.0 (6.7,65.2)	41.4 (28.6,55.1)
ORR, % (95% CI)	60.9 (38.5- 80.3)	41.2 (18.4,67.1)	55.6 (35.3,74.5)	32.7 (20.3,47.1)	20.0 (2.5,55.6)	31.0 (19.5,44.5)
DCR, % (95% CI)	91.3 (72.0, 98.9)	100	92.6 (75.7,99.1)	84.6 (71.9,93.1)	100	86.2 (74.6,93.9)

^aCNS: central nervous system. ^bPBC: platinum-based chemotherapy

TKI, tyrosine kinase inhibitors; BOR, best of response; PR, partial response; SD, stable disease; PD, progressive disease; NE, not evaluated; ORR, overall response rate; DCR, disease control rate; CI, confidence interval.

Table 5.13. BL-B01D1 single dose noncompartmental pharmacokinetic parameters

Parameters	λ_z	T_{max}	C_{max}	AUC_{0-t}	$AUC_{0-\infty}$	Vd_{SD}	CL_{SD}
Dose levels	(1/hr)	(hr)	(ng/mL)	(hr*ng/mL)	(hr*ng/mL)	(L)	(L/hr)
0.27 mg/kg (n=1)	0.059	2.0	3007	37040	47727	6.259	0.386
1.5 mg/kg (n=1)	0.032	2.0	28746	659918	813538	4.551	0.147
2.5 mg/kg (n=13)	0.041 (0.015)	2.8 (1.3)	51132 (16408)	1513279 (620031)	1613659 (685342)	2.947 (0.972)	0.116 (0.045)
3.0 mg/kg (n=11)	0.032 (0.008)	2.4 (1.2)	56026 (13603)	1659555 (615577)	1815956 (698102)	3.890 (0.851)	0.122 (0.041)
3.5 mg/kg (n=5)	0.027 (0.004)	3.2 (1.8)	98600 (41417)	3012539 (1389173)	3198930 (1372129)	3.446 (1.056)	0.093 (0.029)
4.5 mg/kg (n=5)	0.030 (0.010)	2.4 (0.9)	116348 (46101)	3984244 (2011025)	4157185 (1895349)	2.435 (0.417)	0.075 (0.039)
5.0 mg/kg (n=5)	0.019 (0.005)	2.4 (0.9)	96165 (28603)	3600917 (1168130)	3880831 (1203152)	4.102 (0.977)	0.081 (0.035)
6.0 mg/kg (n=13)	0.022 (0.006)	3.2 (2.4)	147016 (48553)	5714516 (2186027)	6639116 (2363515)	3.114 (1.148)	0.067 (0.025)

$AUC_{0-\infty}$, area under the blood concentration-time curve from 0 to infinite; AUC_{0-t} area under the blood concentration-time curve from 0 to the last detectable concentration collection time t; C_{max} , maximum concentration; T_{max} , time at which the maximum drug concentration occurs; λ_z , terminal elimination rate, lambda; Vd , volume of distribution; CL , clearance. Noncompartmental analysis was used. Individual values are presented where $n \leq 2$. Geometric means (SD) are presented where $n > 2$.

Table 5.14. BL-B01D1 single dose total antibody and toxin pharmacokinetic parameters

Parameters	λ_z	T_{max}	C_{max}	AUC_{0-4}	$AUC_{0-\infty}$	V_d	CL_{SD}	λ_z	T_{max}	C_{max}	AUC_{0-4}	$AUC_{0-\infty}$
Dose levels	(1/hr)	(hr)	(ng/mL)	(hr*ng/mL)	(hr*ng/mL)	(L)	(L/hr)	(1/hr)	(hr)	(ng/mL)	(hr*ng/mL)	(hr*ng/mL)
0.27 mg/kg	0.069 n=1	2 n=1	3423 n=1	39654 n=1	47771 n=1	5.563 n=1	0.385 n=1	0.024 n=1	4 n=1	0.9 n=1	20 n=1	29.1 n=1
1.5 mg/kg	0.031 n=1	2 n=1	32756 n=1	729419 n=1	918587 n=1	4.171 n=1	0.13 n=1	0.022 n=1	8 n=1	2.4 n=1	132.6 n=1	151.1 n=1
2.5 mg/kg	0.039 (0.016) n=13	2 0 n=13	51765 (11804) n=13	1574460 (542004) n=13	1715802 (659843) n=13	2.938 (1.004) n=13	0.107 (0.04) n=13	0.019 (0.006) n=13	6 (6.1) n=13	8.2 (2.7) n=13	334.6 (228) n=13	378.8 (224) n=13
3.0 mg/kg	0.029 (0.008) n=11	2 0 n=11	58712 (18148) n=11	1805377 (682936) n=11	2009571 (773835) n=11	3.756 (0.648) n=11	0.108 (0.029) n=11	0.014 (0.006) n=11	5.1 (1.6) n=11	9.2 (5.5) n=11	456.3 (370) n=11	639.6 (596) n=11
3.5 mg/kg	0.024 (0.003) n=5	2.8 (1.1) n=5	95930 (38594) n=5	3303728 (1383455) n=5	3579879 (1340133) n=5	3.355 (0.958) n=5	0.08 (0.020) n=5	0.015 (0.004) n=5	5.2 (1.8) n=5	10.7 (3.1) n=5	483.2 (193) n=5	526.5 (189) n=5
4.5 mg/kg	0.027 (0.007) n=5	2 0 n=5	99488 (29039) n=5	3898300 (1969903) n=5	4180492 (1719465) n=5	2.606 (0.729) n=5	0.068 (0.022) n=5	0.019 (0.011) n=5	8.4 (9.4) n=5	14.8 (8.5) n=5	541.1 (335) n=5	621.5 (375) n=5
5.0 mg/kg	0.018 (0.006) n=13	2.4 (0.9) n=13	89273 (27815) n=13	3750096 (1332352) n=13	4143527 (1447332) n=13	4.273 (1.385) n=13	0.077 (0.032) n=13	0.011 (0.006) n=13	4.4 (0.9) n=12	8.7 (2.5) n=12	480.4 (189) n=12	574.3 (41) n=12
6.0 mg/kg	0.021 (0.006) n=13	3.2 (2.4) n=13	143690 (46378) n=13	5836452 (2125931) n=13	6896191 (2434488) n=13	3.189 (1.145) n=13	0.065 (0.024) n=13	0.012 (0.002) n=12	11.1 (10.5) n=12	14.9 (11.4) n=12	689.7 (486) n=12	779.2 (489) n=12

$AUC_{0-\infty}$, area under the blood concentration-time curve from 0 to infinite; AUC_{0-4} area under the blood concentration-time curve from 0 to the last detectable concentration collection time t; C_{max} , maximum concentration; T_{max} , time at which the maximum drug concentration occurs; λ_z , terminal elimination rate, lambda; V_d , volume of distribution; CL , clearance. Noncompartmental analysis was used. Individual values are presented where $n \leq 2$. Geometric means (SD) are presented where $n > 2$

Table 5.15. Details of Grade ≥3 Treated Related Hematological Toxicity of Different Dose Groups

pt_term	ALL	QW		D1D8Q3W		D1D8Q3W		D1D8Q3W		D1Q3W		D1Q3W	
		0.27mg/kg	3.0mg/kg	3.0mg/kg	2.5mg/kg	3.0mg/kg	3.0mg/kg	3.5mg/kg	4.5mg/kg	5.0mg/kg	6.0mg/kg	5.0mg/kg	6.0mg/kg
Anaemia	76/195 (39%)	1/1 (100%)	3/4 (75%)	42/106 (39.6%)	5/7 (71.4%)	2/5 (40%)	9/35 (25.7%)	11/24 (45.8%)	3/12 (25%)				
Leukopenia	76/195 (39%)	0/1 (0%)	3/4 (75%)	31/106 (29.2%)	2/7 (28.6%)	4/5 (80%)	13/35 (37.1%)	14/24 (58.3%)	9/12 (75%)				
Neutropenia	91/195 (47%)	0/1 (0%)	3/4 (75%)	36/106 (34%)	2/7 (28.6%)	4/5 (80%)	17/35 (48.6%)	18/24 (75%)	11/12 (91.7%)				
Thrombocytopenia	63/195 (32%)	0/1 (0%)	3/4 (75%)	32/106 (30.2%)	2/7 (28.6%)	2/5 (40%)	9/35 (25.7%)	9/24 (37.5%)	6/12 (50%)				
Total		1/1 (100%)	3/4 (75%)	68/106 (64.2%)	6/7 (85.7%)	4/5 (80%)	24/35 (68.6%)	21/24 (87.5%)	12/12 (100%)				

QW, one dose weekly; D1D8 Q3W, one dose on days 1 and 8 of each cycle every 3 weeks; D1 Q3W, one dose on day 1 of each cycle every 3 weeks.

Table 7.1. Enrollment of patients with previously treated locally advanced or metastatic breast cancer

	ALL (N=127)	D1D8Q3W 2.5mg/kg (N=122)	D1Q3W 5.0mg/kg (N=5)
Age (Median, Range)	53 (26.0 - 79.0)	53 (26.0 - 79.0)	54 (38.0 - 66.0)
Sex (Male)	1/127 (1%)	1/122 (1%)	0/5 (0%)
BMI (Mean, Range)	23.7 (16.9 - 36.8)	23.8 (16.9 - 36.8)	21.4 (18.9 - 23.6)
BSA (Mean, Range)	1.6 (1.3 - 1.9)	1.6 (1.3 - 1.9)	1.6 (1.5 - 1.7)
	ECOG		
0	15/127 (12%)	15/122 (12%)	0/5 (0%)
1	109/127 (86%)	104/122 (85%)	5/5 (100%)
UNK (0 or 1)	3/127 (2%)	3/122 (2%)	0/5 (0%)
	Tumor type		
Breast cancer	126/127 (99%)	121/122 (99%)	5/5 (100%)
HER2+*	24/127 (19%)	22/122 (18%)	2/5 (20%)
HR+ HER2-#	56/127 (44%)	56/122 (46%)	0/5 (0%)
TNBC	46/127 (36%)	43/122 (35%)	3/5 (60%)
NSCLC	1/127 (1%)	1/122 (1%)	0/5 (0%)
	Prior treatment line		
0	1/127 (1%)	1/122 (1%)	0/5 (0%)
1	19/127 (15%)	18/122 (15%)	1/5 (20%)
2	20/127 (16%)	19/122 (16%)	1/5 (20%)
≥3	87/127 (69%)	84/122 (69%)	3/5 (60%)

* HER2+ defined as IHC 3+ or IHC 2+/in situ hybridization (ISH)+;

HER2- defined as IHC 0, 1+, 2+/ISH-.

**Table 7.2. Summary of treatment-related adverse events (TRAE frequency $\geq$ 20%)
BL-B01D1-104 (N=127)**

PT Term	G1	G2	$\geq$ G3+	All Grade
Leukopenia¹	16 (13%)	39 (31%)	41 (32%)	98 (77%)
Anemia²	18 (14%)	41 (32%)	37 (29%)	96 (76%)
Neutropenia³	11 (9%)	24 (19%)	56 (44%)	91 (72%)
Thrombocytopenia⁴	30 (24%)	22 (17%)	26 (20%)	78 (61%)
Nausea	48 (38%)	13 (10%)	4 (3%)	65 (51%)
Stomatitis⁵	17 (13%)	31 (24%)	3 (2%)	51 (40%)
Vomiting	26 (20%)	23 (18%)	1 (<1%)	50 (39%)
Asthenia	23 (18%)	21 (17%)	1 (<1%)	45 (35%)
ALT increased	38 (30%)	0	0	39 (31%)
Decreased appetite	30 (24%)	8 (6%)	1 (<1%)	39 (31%)
Alopecia	23 (18%)	13 (10%)	NA	36 (28%)
AST increased	35 (28%)	0	1 (<1%)	36 (28%)
Hypokalemia	22 (17%)	7 (6%)	2 (2%)	31 (24%)
Hypertriglyceridemia	26 (20%)	3 (2%)	0	29 (23%)
Hyponatremia	28 (22%)	0	0	28 (22%)

¹ Leukopenia combined white blood cell count decreased and leukopenia;

² Neutropenia combined neutrophil count decreased, neutropenia, and febrile neutropenia;

³ Anemia combined anemia and hemoglobin count decreased;

⁴ Thrombocytopenia combined platelet count decreased and thrombocytopenia;

⁵ Stomatitis combined stomatitis, aphthous stomatitis, mouth ulceration, oral mucosa erosion, and oral mucosal blistering.

Table 7.3. Efficacy in patients with subtypes of breast cancer

BOR, n	TNBC (n=35)	HR+ HER2- (n=38)	HER2+ (n=23)
Prior treatment line median (range)	3 (1-9)	4 (1-13)	4 (0-8)
CR	0	0	0
PR	11	17	9
cPR	8	7	6
PR*	2	5	1
SD	21	19	11
SD#	12	12	7
PD	3	2	3
ORR, % (95% CI)	31.40% (16.9-49.3)	44.70% (28.6-61.7)	39.10% (19.7-61.5)
cORR, % (95% CI)	22.90% (10.4-40.1)	18.40% (7.7-34.3)	26.10% (10.2-48.4)
DCR, % (95% CI)	91.40% (76.9-98.2)	94.70% (82.3-99.4)	87.00% (66.4-97.2)

TNBC: triple negative breast cancer; *Confirmation pending; #On-going with shrinkage

Table 7.4. Enrollment of patients with previously treated locally advanced or metastatic esophageal squamous cell carcinoma (ESCC)

	Total (N=83*)	2.0mg/kg (N =22)	2.5mg/kg (N =60)
Age, median (range)	62 (45~75)	63.5 (51~73)	61 (45~75)
Sex (Male), n (%)	73/83 (88.0%)	21/22 (95.5%)	51/60 (85.0)
BMI, mean (range)	20 (13.2 - 31.6)	20.6 (15.9, 26.4)	19.8 (13.2, 31.6)
ECOG, n (%)			
0	15/83 (18.10%)	4/22 (18.20%)	10/60 (16.70%)
1	68/83 (81.90%)	18/22 (81.80%)	50/60 (83.30%)
Prior line of therapy, n (%)			
1	31/83 (37.30%)	8/22 (36.40%)	23/60 (38.30%)
2	27/83 (32.50%)	4/22 (18.20%)	23/60 (38.30%)
≥3	25/83 (30.10%)	10/22 (45.50%)	14/60 (23.30%)
Prior anti-PD(L)-1, n(%)	81/83 (97.60%)	22/22 (100%)	58/60 (96.70%)

* Including one patient treated at 3.0mg/kg D1D8Q3W.

Table 7.5. Summary of treatment-related adverse events (TRAE frequency $\geq 15\%$)

ESCC at 2.5mg/kg D1D8 Q3W (N=60)		
Preferred Term (PT), n (%)	All Grade	$\geq G3$
Hematological AE		
Anemia	50 (83.3)	17 (28.3)
Leukopenia	34 (56.7)	11 (18.3)
Thrombocytopenia	35 (58.3)	11 (18.3)
Neutropenia	28 (46.7)	10 (16.7)
Lymphocyte count decreased	18 (30.0)	9 (15.0)
Non-Hematological AE		
Nausea	28 (46.7)	0
Asthenia	23 (38.3)	1 (1.7)
Decreased appetite	15 (25.0)	0
Vomiting	14 (23.3)	0
Weight decreased	13 (21.7)	0
Hypoalbuminemia	13 (21.7)	0
Hyponatremia	13 (21.7)	0
Hypokalemia	12 (20.0)	2 (3.3)
Blood alkaline phosphatase increased	12 (20.0)	0
Alanine aminotransferase increased	10 (16.7)	1 (1.7)
Albumin urine present	9 (15.0)	0
Stomatitis	9 (15.0)	0

Table 7.6. Efficacy in patients with different regimens

	Total	2.0mg/kg D1D8Q3W	2.5mg/kg D1D8Q3W
	(N=74)	(N=22)	(N=52)
Prior treatment line, median (range)	2 (1-7)	2 (1-7)	2 (1-4)
Best overall response (BOR), n			
CR	1	1	0
PR	25	2	23
Confirmed PR	23	2	21
SD	26	7	19
PD	19	9	10
NE	3	3	0
ORR, 95%CI (%)	35.10% (24.4, 47.1)	13.60% (2.9, 34.9)	44.20% (30.5, 58.7)
cORR, 95%CI (%)	32.40% (22.0, 44.3)	13.60% (2.9, 34.9)	40.40% (27.0, 54.9)
DCR, 95%CI (%)	70.30% (58.5, 80.3)	45.50% (24.4, 67.8)	80.80% (67.5, 90.4)
Median PFS (months)	4.3	2.7	5.4
(95% CI)	(3.3, 5.5)	(1.4, 3.6)	(4.0, 6.8)
Median DOR	6.5	4.5	6.6
(months) (95% CI)	(4.5, 12.4)	(2.8, NR)	(5.6, 12.4)

Table 7.7. Enrollment of patients with previously treated locally advanced or metastatic biliary tract carcinoma (BTC)

	ALL	2.5mg/kg	3.0mg/kg	3.5mg/kg
	(N=44)	(N=31)	(N =3)	(N =10)
Age, median (range)	60.0 (31~75)	59 (31~70)	70 (61~75)	60 (44~73)
Sex (Male), n(%)	29/44 (65.9%)	22/31 (71.0%)	3/3 (100%)	4/10 (40.00%)
BMI, mean (range)	23 (16.4~33.8)	23.6 (17.4~33.8)	24.1 (20.9~27.5)	20.7 (16.4~24.2)
ECOG, n (%)				
0	6/44 (13.60%)	6/31 (19.40%)	0	0
1	38/44 (86.4%)	25/31 (80.6%)	3/3 (100%)	10/10 (100%)
Prior line of therapy, n (%)				
0	1/44 (2.30%)	0	0	1/10 (10.00%)
1	20/44 (45.50%)	16/31 (51.6%)	0	4/10 (40.00%)
2	10/44 (22.70%)	7/31 (22.60%)	1/3 (33.30%)	2/10 (20.00%)
≥3	13/44 (29.50%)	8/31 (25.80%)	2/3 (66.70%)	3/10 (30.00%)
Prior anti-PD(L)-1, n (%)	35/44 (79.5%)	23/31 (75.20%)	3/3 (100%)	9/10 (90.00%)

Table 7.8. Summary of treatment-related adverse events (TRAE frequency $\geq 20\%$)

BTC (N=44)		
Preferred Term (PT), n(%)	All Grade	$\geq G3$
Hematological AE		
Anemia	36 (81.8)	12 (27.3)
Thrombocytopenia	33 (75.0)	14 (31.8)
Leukopenia	26 (59.1)	9 (20.5)
Neutropenia	17 (38.6)	8 (18.2)
Lymphocyte count decreased	10 (22.7)	2 (4.5)
Non-Hematological AE		
Nausea	19 (43.2)	0
Aspartate aminotransferase increased	15 (34.1)	1 (2.3)
Alanine aminotransferase increased	11 (25.0)	1 (2.3)
Diarrhea	13 (29.5)	1 (2.3)
Stomatitis	11 (25.0)	1 (2.3)
Weight decreased	10 (22.7)	0
Hypoalbuminemia	9 (20.5)	1 (2.3)
Blood bilirubin increased	9 (20.5)	0
Alopecia	9 (20.5)	0

Table 7.9. Efficacy in patients with different regimens

	Total	2.5mg/kg D1D8Q3W	3.0mg/kg D1D8Q3W	3.5mg/kg D1D8Q3W
	(N=36)	(N=25)	(N=3)	(N=8)
Prior treatment line, median (range)	2 (0-5)	2 (1-5)	3 (2-4)	2 (0-4)
Best Overall Response (BOR), n				
CR	1	1	0	0
PR	13	7	2	4
cPR	7	4	0	3
PR→Ongoing	2	2	0	0
SD	18	14	1	3
PD	4	3	0	1
ORR, % (95% CI)	38.90% (23.1-56.5)	32.00% (14.9-53.5)	66.7 (9.4-99.2)	50.00% (15.7-84.3)
cORR, % (95% CI)	22.20% (10.1-39.2)	20.00% (6.8-40.7)	0% (0.0, 70.8)	37.50% (8.5-75.5)
DCR, % (95% CI)	88.90% (73.9-96.9)	88.00% (68.8-97.5)	100% (29.2-100.0)	87.50% (47.3~99.7)
mPFS (months, 95% CI)	4.2 (2.8, 7.1)	4.3 (2.7, NR)	3.5 (2.8, NR)	3.4 (1.3, 7.1)
mDOR (months, 95% CI)	5.9 (4.2, NR)	7.3 (NR, NR)	NE	5.8 (4.2, NR)

Table 7.10. Enrollment of patients with previously treated locally advanced or metastatic urothelial carcinoma (UC)

	Total (N = 41)	2.2 mg/kg D1D8Q3W (N = 34)	2.5 mg/kg D1D8Q3W (N = 4)	2.75 mg/kg D1D8Q3W (N = 3)
Sex (Male), n (%)	32 (78.0)	26 (76.5)	4 (100)	2 (66.7)
Age, median (range)	62.0 (42.0, 74.0)	61.5 (42.0, 74.0)	56.5 (51.0, 68.0)	70.0 (68.0, 72.0)
BMI, mean (SD)	23.3 (3.2)	23.3 (3.1)	22.6 (3.9)	23.6 (4.8)
ECOG-PS Score, n (%)				
0	17 (41.5)	15 (44.1)	1 (25.0)	1 (33.3)
1	24 (58.5)	19 (55.9)	3 (75.0)	2 (66.7)
Primary tumor sites, n(%)				
Bladder	22 (53.7)	17 (50.0)	3 (75.0)	2 (66.7)
Upper urinary tract	19 (46.3)	17 (50.0)	1 (25.0)	1 (33.3)
Histologic type, n(%)				
Urothelial only	34 (82.9)	27 (79.4)	4 (100)	3 (100)
Urothelial carcinoma with squamous differentiation	5 (12.2)	5 (14.7)	0	0
Urothelial with other components ^a	2 (4.9)	2 (5.9)	0	0
Prior line of chemotherapy, n (%)				
1	18 (43.9)	16 (47.1)	0	2 (66.7)
PBC	15 (36.6)	13 (38.2)	0	2 (66.7)
ADC	2 (4.9)	2 (5.9)	0	0
PD(L)-1+ chemo	1 (2.4)	1 (2.9)	0	0
2+	33 (56.1)	18 (52.9)	4 (100)	1 (33.3)
Prior anti-PD(L)-1, n (%)	38 (92.7)	31 (91.2)	4 (100)	3 (100)

*: One urothelial carcinoma with sarcomatoid variant and one urothelial carcinoma with glandular differentiation.

BMI: body mass index; ADC: antibody-drug conjugates.

Table 7.11. Primary efficacy in patients with locally advanced or metastatic urothelial carcinoma (UC)

	2.2 mg/kg D1D8Q3W	
	Total	1 Prior line of chemo (PBC or ADC)
	(N = 27)^[1]	(N=12)^[2]
Prior line of therapy, median (range)	2 (1-7)	1 (1-2)
Best Overall Response (BOR), n		
PR	11	9
Confirmed PR	9	9
SD	15	3
PD	0	0
NE	1	0
ORR, % (95%CI)	40.7 (22.4, 61.2)	75.0 (42.8, 94.5)
cORR, % (95%CI)	33.3 (16.5, 54.0)	75.0 (42.8, 94.5)
DCR, % (95%CI)	96.3 (81.0, 99.9)	100 (73.5, 100.0)
Median DOR (months) (95% CI)	NR (NR, NR)	NR (NR, NR)
6-month DOR rate, %, (95% CI)	100 (100.0, 100.0)	100 (100.0, 100.0)
Median PFS (months) (95% CI)	NR (4.2, NR)	NR (NR, NR)
6-month PFS rate, %, (95% CI)	62.4 (32.2, 82.2)	100 (100.0, 100.0)

^[1] Among of the 27 patients, 24 patients had received anti-PD-(L)1, 24 patients had received PBC, and 14 patients had received 1-2 prior lines of ADCs. ^[2] Among of the 12 patients, 11 patients had received anti-PD-(L)1, 9 patients had received PBC, 2 patients had received ADCs, and 1 patient had received anti-PD-(L)1 + gemcitabine. ORR was calculated based on response evaluable population defined as at least 1 post-baseline scan; CI: confidence interval; cORR: confirmed objective response rate; NE: not evaluable; NR: not reached; PD: progressive disease; PR: partial response; SD: stable disease.

Table 7.12. Summary of overall safety

TRAEs, n(%)	2.2 mg/kg D1D8Q3W
	(N = 34)
Median Follow-up (months)	4.6
Treatment Related AE (TRAE)	34 (100)
TRAE leading to death	0
TRAE leading to discontinuation	2 (5.9)
TRAE leading to dose reduction	5 (14.7)
Grade ≥ 3 TRAE	18 (52.9)
Treatment Related-SAE	12 (35.3)

AE: adverse event; SAE: serious adverse event; TRAE: treatment related adverse event.

Table 7.13. Summary of treatment-related adverse events (TRAE frequency >15%)

2.2 mg/kg D1D8Q3W (N = 34)			
Preferred Term (PT), n(%)	All Grade	Grade 3	Grade 4
Hematological AE			
Anemia	28 (82.4)	9 (26.5)	0
Leukopenia	24 (70.6)	6 (17.6)	4 (11.8)
Thrombocytopenia	21 (61.8)	4 (11.8)	5 (14.7)
Neutropenia	19 (55.9)	7 (20.6)	4 (11.8)
Lymphocyte count decreased	7 (20.6)	2 (5.9)	0
Non-Hematological AE*			
Decreased appetite	16 (47.1)	1 (2.9)	0
Nausea	15 (44.1)	1 (2.9)	0
Hypoalbuminemia	9 (26.5)	0	0
Vomiting	9 (26.5)	0	0
Alopecia	8 (23.5)	0	0
Asthenia	6 (17.6)	0	0
Constipation	6 (17.6)	0	0
Diarrhea	6 (17.6)	0	0
Stomatitis	6 (17.6)	0	0

* Rash was 11.8 (4/34). All cases were G1

Sequence listing

SEQ ID NO.	Sequence Description
1	Light chain amino acid sequence of antibody SI-1 × 6.4 <u>DILLTQSPVILSVSPGERVSFSCRASOSIGTNIH</u> WYQORTNGSPRLLIK <u>YASESISIPSRFSGSGSGTDFTL</u> SINSVESEDIADYYC <u>QONNNWPTTFGA</u> <u>GTKLEL</u> KRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQ WKVDNALQSGNSQESVTEQDSKDSTYLSSTLTLSKADYEKHKVY ACEVTHQGLSPVTKSFNRGEC
2	Amino acid sequence of the light chain variable region of antibody SI-1×6.4 Amino acid sequence of the light chain variable region of antibody SI-1×24 <u>DILLTQSPVILSVSPGERVSFSCRASOSIGTNIH</u> WYQORTNGSPRLLIK <u>YASESISIPSRFSGSGSGTDFTL</u> SINSVESEDIADYYC <u>QONNNWPTTFG</u> <u>AGTKLEL</u> K
3	Amino acid sequence of antibody SI-1 × 6.4 light chain variable region CDR1 Amino acid sequence of the antibody SI-1×2 light chain variable region CDR1 Amino acid sequence of the antibody SI-1×22 light chain variable region CDR1 Amino acid sequence of the antibody SI-1×25 light chain variable region CDR1 <u>RASOSIGTNIH</u>
4	Amino acid sequence of antibody SI-1 × 6.4 light chain variable region CDR2 Amino acid sequence of the antibody SI-1×2 light chain variable region CDR2 Amino acid sequence of the antibody SI-1×22 light chain variable region CDR2 Amino acid sequence of the antibody SI-1×25 light chain variable region CDR2 <u>YASESIS</u>
5	Amino acid sequence of antibody SI-1 × 6.4 light chain variable region CDR3 Amino acid sequence of the antibody SI-1×2 light chain variable region CDR2 Amino acid sequence of antibody SI-1×22 light chain variable region CDR3 Amino acid sequence of the antibody SI-1×25 light chain variable region CDR3 <u>QONNNWPTT</u>
6	Amino acid sequence of the construct of antibody SI-1 × 6.4 heavy chain with single chain Fv (scFv) structural domains <u>QVQLKQSGPGLVQPSSQSLTCTVSGFSLTNYGVHWVRQSPGKGLEW</u> <u>LGVIWSSGGNTDYNTPFTSRLSINKDNSKSOVFFKMNSLQSNDAIYYC</u> <u>ARALTYDYEFAYWGQGLVTVSSASTKGPSVFPLAPSSKSTSGGTA</u> ALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVV TVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAP ELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWY VDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKC KVSNNKALPAIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCL

	VKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKLTVDK SRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGSGGGGSGGGGSGQV <u>QLOESGGGLVKPGGSLRLS</u>CAASGFTFSSYWMSWVRQAPGKGLEWV <u>ANINRDGSASYYVDSVKGRFTISRDDAKNSLYLOMNSLRAEDTAVYYC</u> <u>ARDRGVGYFDLWGRGTLVTVSSGGGGSGGGGSGGGGSGSALTQPAS</u> <u>VSGSPGQSITISCTGTSSDVGGYNFVSWYQOHPGKAPKLMYDVSDR</u> <u>PSGVSDRFSGSKSGNTASLIISGLQADDEADYYCSSYGSSTHVI</u>FGGG <u>TKVTVL</u>
7	Amino acid sequence of the heavy chain variable region in the construct of antibody SI-1×6.4 heavy chain and single chain Fv (scFv) structural domains Amino acid sequence of the heavy chain variable region in the construct of the antibody SI-1×24 heavy chain and single chain Fv (scFv) structural domains <u>QVQLKQSGPGLVQPSQSLITCTVSGFSLTNYGVHWVRQSPGKGLEW</u> <u>LGVIWSSGGNTDYNTPFTSRLSINKDNSKSQVFFKMNSLQSNDAIYYC</u> <u>ARALTYDYEFAYWGQGLVTVSS</u>
8	Amino acid sequence of the heavy chain variable region CDR1 in the construct of antibody SI-1 × 6.4 heavy chain and single chain Fv (scFv) structural domains Amino acid sequence of the heavy chain variable region CDR1 of antibody SI-1×22 Amino acid sequence of the heavy chain variable region CDR1 in the construct of the antibody SI-1×24 heavy chain and single chain Fv (scFv) structural domains Amino acid sequence of the heavy chain variable region CDR1 of antibody SI-1×25 <u>NYGVH</u>
9	Amino acid sequence of the heavy chain variable region CDR2 in the construct of antibody SI-1 × 6.4 heavy chain and single chain Fv (scFv) structural domains Amino acid sequence of the heavy chain variable region CDR2 of antibody SI-1×22 Amino acid sequence of the heavy chain variable region CDR2 in the construct of the antibody SI-1×24 heavy chain and single chain Fv (scFv) structural domains Amino acid sequence of the heavy chain variable region CDR2 of antibody SI-1×25 <u>VIWSSGGNTDYNTPFTS</u>
10	Amino acid sequence of the heavy chain variable region CDR3 in the construct of antibody SI-1×6.4 heavy chain and single chain Fv (scFv) structural domains Amino acid sequence of the heavy chain variable region CDR3 of antibody SI-1×22 Amino acid sequence of the heavy chain variable region CDR3 in the construct of the antibody SI-1×24 heavy chain and single chain Fv (scFv) structural domains Amino acid sequence of the heavy chain variable region CDR3 of antibody SI-1×25 <u>ALTYDYEFAY</u>

11	Amino acid sequence of the light chain variable region in the structural domain of antibody SI-1×6.4 single chain Fv (scFv) Amino acid sequence of the light chain variable region in the structural domain of antibody SI-1×24 single chain Fv (scFv) Amino acid sequence of the light chain variable region in the structural domain of antibody SI-1×4 single chain Fv (scFv) <u>QSALTQPASVSGSPGQSITISCTGTSSDVGGYNFVSWYQQHPGKAPKL</u> <u>MIYDVSDRPSGVSDRFGSGSKSGNTASLIISGLQADDEADYYC</u><u>SSYGSSS</u> <u>THVIFGGGTKVTVL</u>
12	Amino acid sequence of the light chain variable region CDR1 in the structural domain of antibody SI-1 × 6.4 single chain Fv (scFv) Amino acid sequence of the light chain variable region CDR1 in the structural domain of antibody SI-1×22 single chain Fv (scFv) Amino acid sequence of the light chain variable region CDR1 in the structural domain of antibody SI-1×24 single chain Fv (scFv) Amino acid sequence of the light chain variable region CDR1 in the structural domain of antibody SI-1×4 single chain Fv (scFv) Amino acid sequence of the light chain variable region CDR1 in the structural domain of antibody SI-1×25 single chain Fv (scFv) Amino acid sequence of the light chain variable region CDR1 in the structural domain of antibody SI-1×26 single chain Fv (scFv) <u>TGTSSDVGGYNFVS</u>
13	Amino acid sequence of the light chain variable region CDR2 in the structural domain of antibody SI-1×6.4 single chain Fv (scFv) Amino acid sequence of the light chain variable region CDR2 in the structural domain of antibody SI-1×22 single chain Fv (scFv) Amino acid sequence of the light chain variable region CDR2 in the structural domain of antibody SI-1×24 single chain Fv (scFv) Amino acid sequence of the light chain variable region CDR2 in the structural domain of antibody SI-1×4 single chain Fv (scFv) Amino acid sequence of the light chain variable region CDR2 in the structural domain of antibody SI-1×25 single chain Fv (scFv) Amino acid sequence of the light chain variable region CDR2 in the structural domain of antibody SI-1×26 single chain Fv (scFv) <u>DVSDRPS</u>
14	Amino acid sequence of the light chain variable region CDR3 in the structural domain of antibody SI-1×6.4 single chain Fv (scFv) Amino acid sequence of the light chain variable region CDR3 in the structural domain of antibody SI-1×22 single chain Fv (scFv) Amino acid sequence of the light chain variable region CDR3 in the structural domain of antibody SI-1×24 single chain Fv (scFv) Amino acid sequence of the light chain variable region CDR3 in the structural domain of antibody SI-1×4 single chain Fv (scFv) Amino acid sequence of the light chain variable region CDR3 in the structural domain of antibody SI-1×25 single chain Fv (scFv) Amino acid sequence of the light chain variable region CDR3 in the structural domain of antibody SI-1×26 single chain Fv (scFv) <u>SSYGSSSTHVI</u>
15	Amino acid sequence of the heavy chain variable region in the structural domain of antibody SI-1×6.4 single chain Fv (scFv)

	Amino acid sequence of the heavy chain variable region in the structural domain of antibody SI-1×24 single chain Fv (scFv) Amino acid sequence of the heavy chain variable region in the structural domain of antibody SI-1×4 single chain Fv (scFv) <u>QVQLQESGGGLVKPGGSLRLSCAASGFTFSSYWMSWVRQAPGKGLE</u> <u>WVANINRDGSASYVDSVKGRFTISRDDAKNSLYLOMNSLRAEDTAVY</u> <u>YCARDRGVGYFDLWGRGTLTVSS</u>
16	Amino acid sequence of the heavy chain variable region CDR1 in the structural domain of antibody SI-1×6.4 single chain Fv (scFv) Amino acid sequence of the heavy chain variable region CDR1 in the structural domain of antibody SI-1×22 single chain Fv (scFv) Amino acid sequence of the heavy chain variable region CDR1 in the structural domain of antibody SI-1×24 single chain Fv (scFv) Amino acid sequence of the heavy chain variable region CDR1 in the structural domain of antibody SI-1×4 single chain Fv (scFv) Amino acid sequence of the heavy chain variable region CDR1 in the structural domain of antibody SI-1×25 single chain Fv (scFv) Amino acid sequence of the heavy chain variable region CDR1 in the structural domain of antibody SI-1×26 single chain Fv (scFv) <u>SYWMS</u>
17	Amino acid sequence of the heavy chain variable region CDR2 in the structural domain of antibody SI-1×6.4 single chain Fv (scFv) Amino acid sequence of the heavy chain variable region CDR2 in the structural domain of antibody SI-1×22 single chain Fv (scFv) Amino acid sequence of the heavy chain variable region CDR2 in the structural domain of antibody SI-1×24 single chain Fv (scFv) Amino acid sequence of the heavy chain variable region CDR2 in the structural domain of antibody SI-1×4 single chain Fv (scFv) Amino acid sequence of the heavy chain variable region CDR2 in the structural domain of antibody SI-1×25 single chain Fv (scFv) Amino acid sequence of the heavy chain variable region CDR2 in the structural domain of antibody SI-1×26 single chain Fv (scFv) <u>NINRDGSASYVDSVKG</u>
18	Amino acid sequence of the heavy chain variable region CDR3 in the structural domain of antibody SI-1×6.4 single chain Fv (scFv) Amino acid sequence of the heavy chain variable region CDR3 in the structural domain of antibody SI-1×22 single chain Fv (scFv) Amino acid sequence of the heavy chain variable region CDR3 in the structural domain of antibody SI-1×24 single chain Fv (scFv) Amino acid sequence of the heavy chain variable region CDR3 in the structural domain of antibody SI-1×4 single chain Fv (scFv) Amino acid sequence of the heavy chain variable region CDR3 in the structural domain of antibody SI-1×25 single chain Fv (scFv) Amino acid sequence of the heavy chain variable region CDR3 in the structural domain of antibody SI-1×26 single chain Fv (scFv) <u>DRGVGYFDL</u>
19	Amino acid sequence of a construct of the structural domain of antibody SI-1×22 light chain and single chain Fv (scFv) <u>DILLTQSPVILSVSPGERVSEFCRASQSIGTNIHWYQORTNGSPRLIKY</u> <u>ASESISGIPSRFSGSGTDFTLINSVESEDIADYYCOONNNWPTTFG</u>

	<u>CGTKLELK</u>KRTVAAPSASFVFIPPSSDEQLKSGTASVVCLLNNFYPREAK VQWKVDNALQSGNSQESVTEQDSKDYSLSSSTLTLSKADYEKHK KVYACEVTHQGLSPVTKSFNRGECGGGGSGGGGSGGGGSGVQL <u>QESGGGLVKPGGSLSLSCAASGFTFSSYWM</u>SWVRQAPGKGLEWVANI <u>NRDGSASYYYVDSVKGRFTISRDDAKNSLYLQMN</u>SLRAEDTAVYYCAR <u>DRGVGYFDLWGRGTLTVTSSGGGGSGGGGSGGGG</u>QSALTQPASV <u>GSPGQSITISCTGTSSDVGGYNFVSWYQOHPGKAPKLMYDVSDRPS</u> <u>GVSDRFSGSKSGNTASLIISGLQADDEADYYCSSYGSSTHVI</u>FGGGTK <u>VTVL</u>
20	Amino acid sequence of the light chain variable region of antibody SI-1×22 Amino acid sequence of the light chain variable region of antibody SI-1×25 <u>DILLTQSPVILSVSPGERVFSFCRASOSIGTNIH</u>WYQQRTNGSPRLLIK <u>ASESISGIPSRFSGSGSGTDFTLSINSVESEDIADYYCQONNNWPTTFG</u> <u>CGTKLELK</u>
21	Amino acid sequence of the light chain variable region in the structural domain of antibody SI-1×22 single chain Fv (scFv) Amino acid sequence of the light chain variable region in the structural domain of antibody SI-1×25 single chain Fv (scFv) Amino acid sequence of the light chain variable region in the structural domain of antibody SI-1×26 single chain Fv (scFv) <u>QSALTQPASVSGSPGQSITISCTGTSSDVGGYNFVSWYQOHPGKAPKL</u> <u>MIYDVSDRPSGVSDRFSGSKSGNTASLIISGLQADDEADYYCSSYGSSTHVI</u>FGGGTKVTVL
22	Amino acid sequence of the heavy chain variable region in the structural domain of antibody SI-1×22 single chain Fv (scFv) Amino acid sequence of the heavy chain variable region in the structural domain of antibody SI-1×25 single chain Fv (scFv) Amino acid sequence of the heavy chain variable region in the structural domain of antibody SI-1×2 single chain Fv (scFv) <u>QVQLQESGGGLVKPGGSLSLSCAASGFTFSSYWM</u>SWVRQAPGKGLE <u>WVANINRDGSASYYYVDSVKGRFTISRDDAKNSLYLQMN</u>SLRAEDTAV <u>YYCARDRGVGYFDLWGRGTLTVTSS</u>
23	Heavy chain amino acid sequence of antibody SI-1×22 <u>QVQLKQSGPGLVQPSQSL</u>SITCTVSGFSLTNYGVHWVRQSPGKCLEW <u>LGVIWSSGGNTDYNTPFTSRLSINKD</u>NSKSQVFFKMNSLQSNDAIYYC <u>ARALTYDYEFAYWGOGLTVTVSA</u>ASTKGPSVFPLAPSSKSTSGGTA ALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSV VTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCTCPCPA PELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNW YVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYK CKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLT CLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKLTV DKSRWQQGNVFCFSVMHEALHNHYTQKSLSLSPG
24	Amino acid sequence of the variable region of the heavy chain of antibody SI-1×22 Amino acid sequence of the variable region of the heavy chain of antibody SI-1×25 <u>QVQLKQSGPGLVQPSQSL</u>SITCTVSGFSLTNYGVHWVRQSPGKCLEW <u>LGVIWSSGGNTDYNTPFTSRLSINKD</u>NSKSQVFFKMNSLQSNDAIYYC <u>ARALTYDYEFAYWGOGLTVTVSA</u>

25	Light chain amino acid sequence of antibody SI-1×24 <u>DILLTQSPVILSVSPGERVSFSCRASQSIGTNIHWYQORTNGSPRLLIKY</u> <u>ASESISGIPSRFSGSGSGTDFTLINSVESEDIADYYCOONNNWPTTFG</u> <u>AGTKLELKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKV</u> QWKVDNALQSGNSQESVTEQDSKDYSLSTLTLSKADYEKHKV YACEVTHQGLSSPVTKSFNRGEC
26	Amino acid sequence of the construct of antibody SI-1×24 heavy chain with single chain Fv (scFv) structural domains <u>QVQLQESGGGLVKPGGSLRLSCAASGFTFSSYWMSWVRQAPGKGLE</u> <u>WVANINRDGSASYYVDSVKGRFTISRDDAKNSLYLQMNSLRAEDTAVY</u> <u>YCARDRGVGYFDLWGRGTLVTVSSGGGGSGGGGSGGGGSQSALTQP</u> <u>ASVSGSPGQSITISCTGTSSDVGGYNFVSWYQQHPGKAPKLMYDVSD</u> <u>RPSGVSDRFSGSKSGNTASLIISGLQADDEADYYCSSYGSSTHVFEGG</u> <u>GTKVTVLGSGGGSGGGGSGVQLKQSGPGLVQPSQSLITCTVSGFSLTN</u> <u>YGVHWVRQSPGKGLEWLGVIWSSGGNTDYNTPFTSRLSINKDNSKSO</u> <u>YFFKMNSLQSNDAIYYCARALTYDYEFAYWGOGTLVTVSSASTKGP</u> SVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHT FPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTKVDKRVE PKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLT VLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTL PSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVL DSDGSFFLYSKLTVDKSRWQQGNVFSFSVMHEALHNHYTQKSLSL SPG
27	Light chain amino acid sequence of antibody SI-1×4 <u>DIQMTQSPSSLSASVGDRVTITCRSSONIVHSNGNTYLDWYQQTPGKA</u> <u>PKLLIYKVSNRFSGVPSRFSGSGSGTDFFTISSLOPEDATYYCFQYSH</u> <u>VPWTFGOGTKLOITRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFY</u> PREAKVQWKVDNALQSGNSQESVTEQDSKDYSLSTLTLSKAD YEKHKVYACEVTHQGLSSPVTKSFNRGEC
28	Amino acid sequence of the variable region of the light chain of antibody SI-1×4 <u>DIQMTQSPSSLSASVGDRVTITCRSSONIVHSNGNTYLDWYQQTPGKA</u> <u>PKLLIYKVSNRFSGVPSRFSGSGSGTDFFTISSLOPEDATYYCFQYSH</u> <u>VPWTFGOGTKLOIT</u>
29	Amino acid sequence of the antibody SI-1×4 light chain variable region CDR1 Amino acid sequence of antibody SI-1×26 light chain variable region CDR1 <u>RSSONIVHSNGNTYLD</u>
30	Amino acid sequence of the antibody SI-1×4 light chain variable region CDR2 Amino acid sequence of antibody SI-1×26 light chain variable region CDR2 <u>KVSNRES</u>
31	Amino acid sequence of antibody SI-1×4 light chain variable region CDR3 Amino acid sequence of antibody SI-1×26 light chain variable region CDR3 <u>FOYSHVPWT</u>
32	Amino acid sequence of a construct of the structural domain of antibody SI-1×4 heavy chain and single chain Fv (scFv) <u>QVQLQQSGAEVKKPGSSVKVSKASGYTFNYYIYVWRQAPGQGLEW</u> <u>IGGINPTSGGSNFNEKFKTRVTTTADESSTTAYMELSSLRSEDTAFYFCT</u>

	<u>ROGLWFDS DGRGFDFWGO GTTVTVSS</u>ASTKGPSVFPLAPSSKSTSG GTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLS SVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVPEPKSCDKTHTCPPC PAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFN WYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEY KCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLT CLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSKLTV DKSRWQQGNV FSCSV MHEALHNHYTQKSLSLSPGGGGGSGGGGS <u>QVQLQESGGGLVKPGGSLRLS</u>CAASGFTFSSYWMSWVRQAPGKGLE <u>WVANINRDGSASYYVDSVKGRFTISRDDAKNSLYLQMNSLRAEDTAVY</u> <u>YCARDRGVGYFDLWGRGTLVTVSS</u>GGGGSGGGGSGGGGSQSAITQP <u>ASVSGSPGOSITISCTGTSSDVGGYNFVSWYQQHPGKAPKLMYDVSD</u> <u>RPSGVSDRFSGSKSGNTASLIISGLQADDEADYYC</u>SSYGSSSTHVIFFG <u>GTKVTVL</u>
33	Amino acid sequence of the heavy chain variable region in the construct of the antibody SI-1×4 heavy chain and single chain Fv (scFv) structural domains <u>QVQLQESGA EVKKPGSSVKV SCKASGYTFTNYYIWVRQAPGQGLEW</u> <u>IGGINPTSGGSNFNEKFKTRVTTT</u>ADESSTTAYMELSSLRSEDTAFYFCT <u>ROGLWFDS DGRGFDFWGO GTTVTVSS</u>
34	Amino acid sequence of the heavy chain variable region CDR1 in the construct of the antibody SI-1×4 heavy chain and single chain Fv (scFv) structural domains Amino acid sequence of antibody SI-1×26 heavy chain variable region CDR1 <u>NYYIY</u>
35	Amino acid sequence of the heavy chain variable region CDR2 in the construct of the antibody SI-1×4 heavy chain and single chain Fv (scFv) structural domains Amino acid sequence of antibody SI-1×26 heavy chain variable region CDR2 <u>GINPTSGGSNFNEKFKT</u>
36	Amino acid sequence of the heavy chain variable region CDR3 in the construct of the antibody SI-1×4 heavy chain and single chain Fv (scFv) structural domains Amino acid sequence of antibody SI-1×26 heavy chain variable region CDR3 <u>ROGLWFDS DGRGFDF</u>
37	Amino acid sequence of a construct of the structural domain of antibody SI-1×25 light chain and single chain Fv (scFv) <u>QVQLQESGGGLVKPGGSLRLS</u>CAASGFTFSSYWMSWVRQAPGKGLE <u>WVANINRDGSASYYVDSVKGRFTISRDDAKNSLYLQMNSLRAEDTAVY</u> <u>YCARDRGVGYFDLWGRGTLVTVSS</u>GGGGSGGGGSGGGGSQSAITQP <u>ASVSGSPGOSITISCTGTSSDVGGYNFVSWYQQHPGKAPKLMYDVSD</u> <u>RPSGVSDRFSGSKSGNTASLIISGLQADDEADYYC</u>SSYGSSSTHVIFFG <u>GTKVTVL</u>GGGGSGGGGS<u>DILLTQSPVILSVSPGERV</u>SFSCRASOSIGTN <u>IHWYQQR</u>INGSPRLLIKYASESISGIPSRISGSGSGTDFTLINSVESEDI <u>ADYYCQONNNWPTTF</u>CGTKLELKRTVAAPSVFIFPPSDEQLKSGTA SVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDESTYS LSSTLTLSKADYEKHKVYACEVTHQGLSPVTKSFNRGEC

38	Amino acid sequence of the heavy chain of antibody SI-1×25 <u>QVQLKQSGPGLVOPSSQLSITCTVSGFSLTNYGVHWVROSPGKC</u> <u>LEWLGVITWSSGGNTDYNTPFTSRLSINKDNSKSOVFFKMNSLOSNDTA</u> <u>IYYCARALTYDYEFAYWGOGLVTVSA</u>ASTKGPSVFPLAPSSKSTSG GTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSL SSVTVTPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPP CPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVK FNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGK EYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQV SLTCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSK LTVDKSRWQQGNVFCFSVMHEALHNHYTQKSLSLSPG
39	Amino acid sequence of a construct of the structural domain of antibody SI-1×26 light chain and single chain Fv (scFv) <u>DIQMTQSPSSLSASVGDRTTTCRSSONIVHSNGNTYLDWYQOTPGKA</u> <u>PKLLIYKVSNRFSGVPSRFSGSGTDFTFITSSLOPEDIATYYCFQYSH</u> <u>VPWTFGCGTKLQITRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFY</u> PREAKVQWKVDNALQSGNSQESVTEQDSKDYSLSTLTLSKAD YEKHKVYACEVTHQGLSSPVTKSFNRGECGGGGSGGGGSGGGGS <u>QVQLQESGGGLVKPGGSLSLSCAASGFTFSSYWMWVRQAPGKGLE</u> <u>WVANINRDGSASYVDSVKGRFTISRDDAKNSLYLOMNSLRADTAVY</u> <u>YCARDRGVGYFDLWGRGTLVTVSSGGGGSGGGGSGGGGSQSALTQP</u> <u>ASVSGSPGOSITISCTGTSSDVGGYNFVSWYQOHPGKAPKLMYDVS</u> <u>RPSGVSDRFSGSKSGNTASLIISGLQADDEADYYCSSYGSSTHVIFFGG</u> <u>GTKVTVL</u>
40	Amino acid sequence of the light chain variable region of antibody SI-1×26 <u>DIQMTQSPSSLSASVGDRTTTCRSSONIVHSNGNTYLDWYQOTPGKA</u> <u>PKLLIYKVSNRFSGVPSRFSGSGTDFTFITSSLOPEDIATYYCFQYSH</u> <u>VPWTFGCGTKLQIT</u>
41	Amino acid sequence of the heavy chain of antibody SI-1×26 <u>QVQLQQSGAEVKKPGSSVKVSKASGYTFTNYYIYWVRQAPGQCLEW</u> <u>IGGINPTSGGSNENEFKFKTRVTITADESSTAYMELSSLRSEDTAFYFCT</u> <u>ROGLWFDSGGRGFDFWGOGLTVTVSS</u>ASTKGPSVFPLAPSSKSTSG GTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLS SVVTVTPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPC PAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFN WYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEY KCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLT CLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKLT DKSRWQQGNVFCFSVMHEALHNHYTQKSLSLSPG
42	Amino acid sequence of the heavy chain variable region of antibody SI-1×26 <u>QVQLQQSGAEVKKPGSSVKVSKASGYTFTNYYIYWVRQAPGQCLEW</u> <u>IGGINPTSGGSNENEFKFKTRVTITADESSTAYMELSSLRSEDTAFYFCT</u> <u>ROGLWFDSGGRGFDFWGOGLTVTVSS</u>

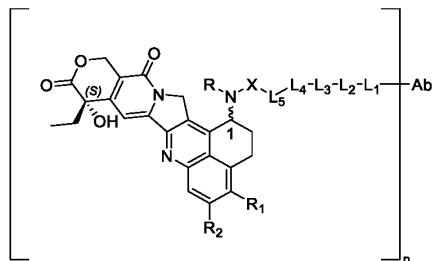
METHODS AND COMPOSITIONS FOR TREATING TUMORS USING ANTIBODY
CAMPTOTHECIN DRUG CONJUGATES

CLAIMS

WHAT IS CLAIMED IS:

1. A method of treating cancer or a tumor, comprising administering to a subject in need thereof a ligand-camptothecin conjugate of Formula I, or a pharmaceutically acceptable salt or solvate thereof, wherein the method comprises administering to the subject at a treatment dose per administration from about 0.1 mg/kg to 15.0 mg/kg,

wherein the Formula I has the following structure:

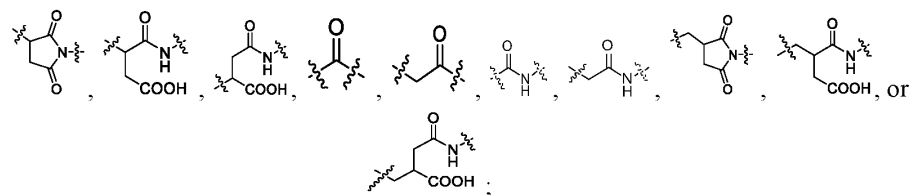


Formula I

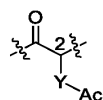
wherein:

Ab is a bispecific antibody or antigen-binding fragment thereof having a binding affinity to EGFR and HER3;

L₁ is:



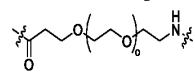
L₂ has the structure shown in Formula A,



Formula A

wherein Y is a scaffold selected from C1-C6 alkyl, substituted C1-C6 alkyl, or C3-C8 cycloalkyl; Ac is a hydrophilic structural unit; and the carbon 2 attached to Y is absolutely chiral in either the R configuration or the S configuration;

L₃ is present or absent, and when present, L₃ is selected from PEG hydrophilic units:



, o is selected from an integer of 1-10;

L₄ is an enzymatically cleavable unit;

L₅ is a connection unit;

the chiral carbon atom No. 1 attached to N in Formula I has absolute chirality in either the R configuration or the S configuration;

R is selected from hydrogen atom, deuterium atom, halogen, C1-C6 alkyl, substituted C1-C6 alkyl, deuterated C1-C6 alkyl, C3-C8 cycloalkyl C1-C6 alkyl, C1-C6 alkoxy C1-C6 alkyl, C6-C10 aryl, substituted C6-C10 aryl, 5-10 heteroaryl, substituted 5-10 heteroaryl;

R_1 is selected from hydrogen atom, deuterium atom, halogen, C1-C6 alkyl, substituted C1-C6 alkyl, deuterated C1-C6 alkyl, C3-C8 cycloalkyl C1-C6 alkyl, C1-C6 alkoxy C1-C6 alkyl, carboxyl, 3-7 heterocyclic, substituted 3-7 heterocyclic, C6-C10 aryl, substituted C6-C10 aryl, 5-10 heteroaryl, substituted 5-10 heteroaryl;

R_2 is selected from hydrogen atom, deuterium atom, halogen, C1-C6 alkyl, substituted C1-C6 alkyl, deuterated C1-C6 alkyl, C3-C8 cycloalkyl C1-C6 alkyl, C1-C6 alkoxy C1-C6 alkyl, carboxyl, 3-7 heterocyclic, substituted 3-7 heterocyclic, C6-C10 aryl, substituted C6-C10 aryl, 5-10 heteroaryl, substituted 5-10 heteroaryl;

X selected from $-C(O)-CR_aR_b-(CR_3R_4)_m-O-$, $-C(O)-CR_aR_b-(CR_3R_4)_m-NH-$ or $-C(O)-CR_aR_b-(CR_3R_4)_m-S-$;

R_a and R_b are each independently selected from hydrogen atoms, deuterium atom, halogens, C1-C6 alkyl, deuterated C1-C6 alkyl, halogenated C1-C6 alkyl, C3-C8 cycloalkyl, C3-C8 cycloalkyl C1-C6 alkyl, C6-C10 aryl C1-C6 alkyl, C1-C6 alkoxy C1-C6 alkyl, 3-7 heterocyclic group, substituted 3-7 heterocyclic group, C6-C10 aryl, substituted C6-C10 aryl, 5-10 heteroaryl, substituted 5-10 heteroaryl;

R_3 , R_4 are the same or different and are independently hydrogen atoms, deuterium atoms, halogens, C1-C6 alkyl, halogenated C1-C6 alkyl, deuterated C1-C6 alkyl, C1-C6 alkoxy, hydroxyl, amino, cyano, nitro, hydroxy C1-C6 alkyl, C3-C8 cycloalkyl, 3-7 heterocyclic, substituted 3-7 heterocyclic, respectively;

m is selected from integers 0-4; n is selected from integers 1-10.

2. The method of Claim 1, wherein the method comprises:

(a) a treatment cycle comprising a 4-week period with weekly dosing, wherein the treatment dose per administration is from about 0.25 mg/kg to about 10 mg/kg.

(b) a treatment cycle comprising a 4-weeks period with dosing on the first day of the first, second, and third weeks, and no dosing in the fourth week, wherein the treatment dose per administration is from about 1.5 mg/kg to about 15 mg/kg.

(c) a treatment cycle comprising a 4-week period with biweekly dosing, wherein the treatment dose per administration from about 2.0mg/kg to about 15mg/kg,

(d) a treatment cycle comprising 3-week period with weekly dosing, wherein the treatment dose per administration from about 0.25mg/kg to about 10mg/kg,

(e) a treatment cycle comprising a 3-week period with dosing on the first day of the first week and no dosing in the second and third weeks, wherein the treatment dose per administration from about 1.5mg/kg to about 6mg/kg,

(f) a treatment cycle comprising a 3-week period with dosing on the first day of the first and second weeks and no dosing in the third week, wherein the treatment dose per administration from about 2.0mg/kg to about 4.5mg/kg,

or a combination thereof.

3. The method of Claim 1-2, wherein the treatment dose per administration is from about 1.5 mg/kg to 5 mg/kg.

4. The method of Claim 1-3, wherein the treatment dose per administration is about 2.5mg/kg, 3 mg/kg or 3.5mg/kg.

5. The method of Claim 1-3, wherein the treatment dose per administration is about 2.0mg/kg, 2.2mg/kg, 2.5 mg/kg, or 2.75mg/kg.

6. The method of Claim 1-6, wherein the cancer or tumor comprises a cancer expressing EGFR, HER3, or a combination thereof.

7. The method of Claim 1-5, wherein the cancer or tumor comprises non-small cell lung cancer or small cell lung cancer, EGFR wild-type non-small cell lung cancer, EGFR mutant non-small cell lung cancer, head and neck squamous carcinoma, triple negative breast cancer, urothelial carcinoma (bladder cancer), esophageal squamous cell carcinoma (ESCC), or metastatic biliary track carcinoma (BTC).

8. The method of Claim 1, wherein the subject is a human.

9. The method of Claim 1-8, wherein the ligand-camptothecin derivative conjugate of Formula I, or a pharmaceutically acceptable salt or solvate thereof, is administered to the subject in the form of an injectable solution derived from a lyophilized powder injection formula, wherein the lyophilized powder injection formula comprises the ligand-camptothecin derivative conjugate of Formula I, or a pharmaceutically acceptable salt or solvent compound thereof, and a pharmaceutical carrier composition.

10. The method of Claim 9, wherein the pharmaceutical carrier composition consists essentially of histidine, histidine hydrochloride, mannitol, sucrose, and polysorbate 80.

11. The method of Claim 9, the injectable solution is given to the subject intravenously.

12. The method of Claim 1-11, further comprising administering a second treatment to the subject before, after, or concurrently with the administration of the ligand-camptothecin derivative conjugate of Formula I, or a pharmaceutically acceptable salt or solvent compound thereof, wherein the second treatment comprises hormonal treatment, chemotherapy, immune checkpoint inhibitor therapy, EGFR-TKI (epidermal growth factor receptor-lysine kinase inhibitor) therapy, immunotherapy, a targeted therapy, or a combination thereof.

13. The method of Claim 12, wherein the immune checkpoint inhibitor therapy comprises administering an immune checkpoint inhibitor, wherein the immune checkpoint inhibitor comprises anti-PD-1 mAb, anti-PD-L1 mAb, a combination of anti-PD-1 mAb and anti-PD-L1 mAb, anti-CTLA-4 mAb, anti-LAG3 mAb, anti-TIGIT mAb, or a combination thereof, and wherein the chemotherapy comprises administering platinum-containing or non-platinum-containing chemotherapeutic agents.

14. The method of Claim 13, wherein the subject is a patient with EGFR wild-type non-small cell lung cancer, a patient with small cell lung cancer, a patient with nasopharyngeal cancer, or a patient with head and neck cancer, and wherein the second treatment comprises the chemotherapy, the immune checkpoint inhibitor therapy, or a combination thereof.

15. The method of Claim 13, wherein the subject is a patient with EGFR-mutant non-small cell lung cancer, and wherein the second treatment comprises the EGFR-TKI therapy, the chemotherapy, the immune checkpoint inhibitor therapy, or a combination thereof.

16. The method of Claim 1, wherein the Ab comprises two IgG1 heavy chains, two κ light chains, and two scFv domains, wherein each scFv domain is connected to each of the IgG1 heavy chain or κ light chain through a linker, wherein the linker comprises an amino acid sequence of (gly-gly-gly-ser)_n, and wherein n is an integer from 1 to 10.

17. The method of Claim 1, wherein Ab comprises,
an IgG1 heavy chain (HC), a, and a single-chain Fv (scFv) domain,
the IgG1 HC and κ LC form a Fab domain having a binding specificity for EGFR, and
the scFv domain has a binding specificity for HER3, wherein the scFv domain is connected to the IgG1 HC or the κ light chain (LC) through a linker to provide an IgG1 HC-linker-scFv or a κ LC-linker-scFv, wherein the linker is attached to the C-terminus or the N-terminus of the IgG1 HC or the C-terminus or the N-terminus of the κ LC, and wherein the scFv domain has a structural order of N-terminus-HC variable region-joint-LC variable region-C-terminus, or N-terminus-LC variable region-joint-HC variable region-C-terminus.

18. The method of Claim 17, wherein the linker comprises an amino acid sequence of (gly-gly-gly-gly-ser)_n, and wherein n is an integer from 1 to 10.

19. The method of Claim 17, wherein
the κ LC comprises a CDR as shown in SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5,
the IgG1 HC comprises a CDR as shown in SEQ ID NO: 8, SEQ ID NO: 9, SEQ ID NO: 10, and
the scFv domains comprises HC variable region CDRs as shown in SEQ ID NO: 16, SEQ ID NO: 17, SEQ ID NO: 18, and LC variable region CDRs as shown in SEQ ID NO: 12, SEQ ID NO: 13, SEQ

ID NO: 14.

20. The method of Claim 17, wherein the Ab comprises
the κ LC variable region as shown in SEQ ID NO: 2,
the IgG1 HC comprises a variable region as shown in SEQ ID NO: 7, and
the scFv domain contains a HC variable region as shown in SEQ ID NO: 15 and a LC variable region as shown in SEQ ID NO: 11.

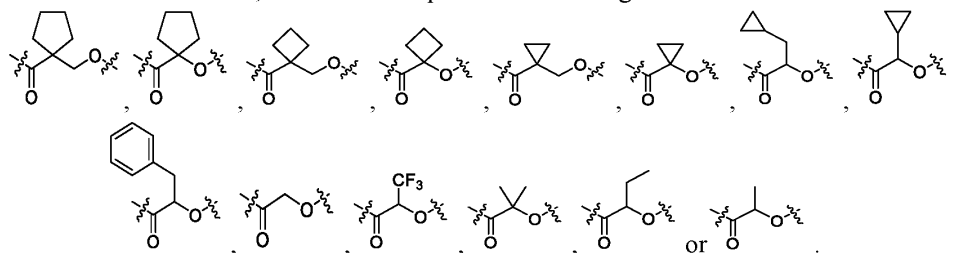
21. The method of Claim 17, wherein
the κ LC comprises CDRs as shown in SEQ ID NO: 29, SEQ ID NO: 30, SEQ ID NO: 31,
the IgG1 HC comprises CDRs as shown in SEQ ID NO: 34, SEQ ID NO: 35, SEQ ID NO: 36 shown, and
the scFv domain contains the HC variable region CDRs as shown in SEQ ID NO: 16, SEQ ID NO: 17, SEQ ID NO: 18, as the LC variable region CDRs as shown in SEQ ID NO: 12, SEQ ID NO: 13, SEQ ID NO: 14.

22. The method of Claim 17, wherein
the κ LC comprises a variable region as shown in SEQ ID NO: 28,
the IgG1 HC comprises a variable region as shown in SEQ ID NO: 33, and
the scFv domain comprising a HC variable region as shown in SEQ ID NO: 15 and a LC variable region as shown in SEQ ID NO: 11.

23. The method of Claim 17, wherein the Ab comprises,
the κ LC having a variable region as shown in SEQ ID NO: 20,
the IgG1 HC having a variable region as shown in SEQ ID NO: 24, and
the scFv domain comprising a HC variable region as shown in SEQ ID NO: 22 and a LC variable region as shown in SEQ ID NO: 21.

24. The method of Claim 17, wherein the Ab comprises,
a variable region as shown in SEQ ID NO: 40,
the IgG1 HC comprising a variable region as shown in SEQ ID NO: 42, and
the scFv domain comprising a HC variable region as shown in SEQ ID NO: 50 and a LC variable region as shown in SEQ ID NO: 21.

25. The method of Claim 1, wherein X comprises the following structures or isomers thereof:



where the left wavy line is connected to the camptothecin derivative, and the right wavy line is connected to L₅.

26. The method of Claim 1, wherein L₄ is selected from peptide residues comprising glycine (G) - glycine (G) -phenylalanine (F) -glycine (G).

27. The method of Claim 1, wherein,

L₅ is selected from -NR₅ (CR₆R₇)_q- or a chemical bond, and q is selected from integers 0-6; and

R₅, R₆ and R₇ are the same or different and are each independently selected from hydrogen atoms, deuterium atoms, halogens, C1-C6 alkyl group, substituted C1-C6 alkyl group, deuterated C1-C6 alkyl group, C3-C8 cycloalkyl group, C3-C8 cycloalkyl C1-C6 alkyl group, C1-C6 alkoxy C1-C6 alkyl group, 3-7 heterocycloheteroaryl group, substituted 3-7 heterocycloheteroaryl group, C6-C10 aryl group, substituted C6-C10 aryl, 5-10 heteroaryl, substituted 5-10 heteroaryl, or a combination thereof.

28. The method of Claim 26, wherein R_5 , R_6 and R_7 are each independently selected from hydrogen atoms or C1-C6 alkyl group.

29. The method of Claim 1-15, wherein:



L_1 is ,

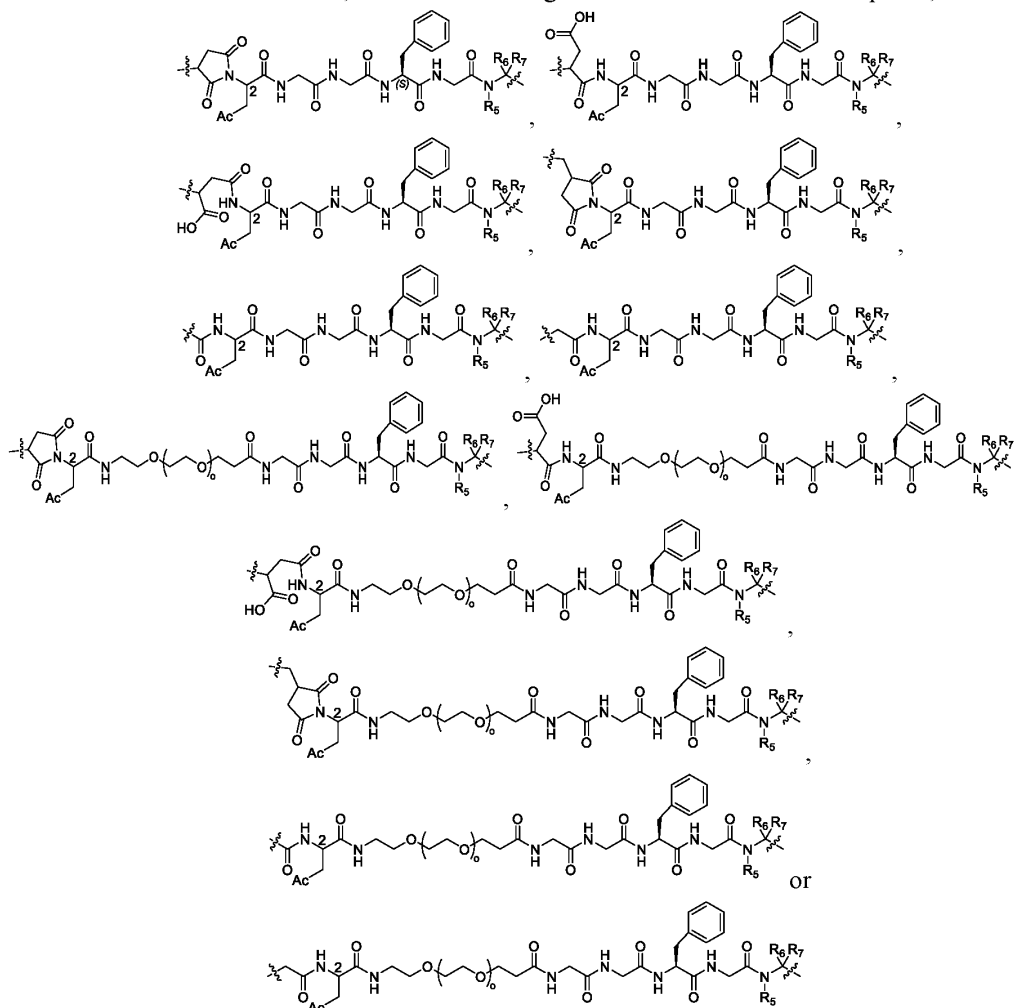
Y is C1-C6 alkyl, and the carbon 2 attached to Y is absolutely chiral in the S configuration,

R is hydrogen, R_1 is C1-C6 alkyl, R_2 is halogen, and

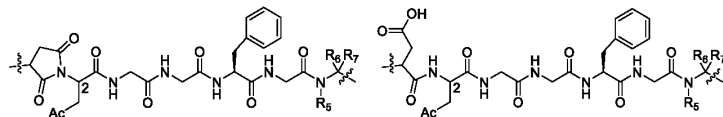
X selected from $-C(O)-CR_aR_b-(CR_3R_4)_m-O-$, wherein R_a and R_b are each independently selected from hydrogen and C1-C6 alkyl, and wherein m is 0.

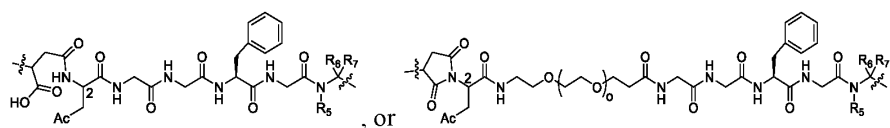
30. The method of Claim 28, wherein R_1 is methyl, R_2 is F, R_a and R_b are H and methyl.

31. The method of Claim 1-15, wherein the linking unit $-L_1-L_2-L_3-L_4-L_5-$ comprises,



32. The method of Claim 1-15, wherein the linking unit $-L_1-L_2-L_3-L_4-L_5-$ comprises,





wherein:

Ac is a hydrophilic structural unit,

R₅, R₆ and R₇ are the same or different and are each independently selected from hydrogen atom, deuterium atom, halogen, C1-C6 alkyl, substituted C1-C6 alkyl, deuterated C1-C6 alkyl, C3-C8 cycloalkyl, C3-C8 cycloalkyl C1-C6 alkyl, C1-C6 alkoxy C1-C6 alkyl, 3-7 heterocyclic, substituted 3-7 heterocyclic, C6-C10 aryl, substituted C6-C10 aryl, 5-10 heteroaryl, substituted 5-10 heteroaryl,

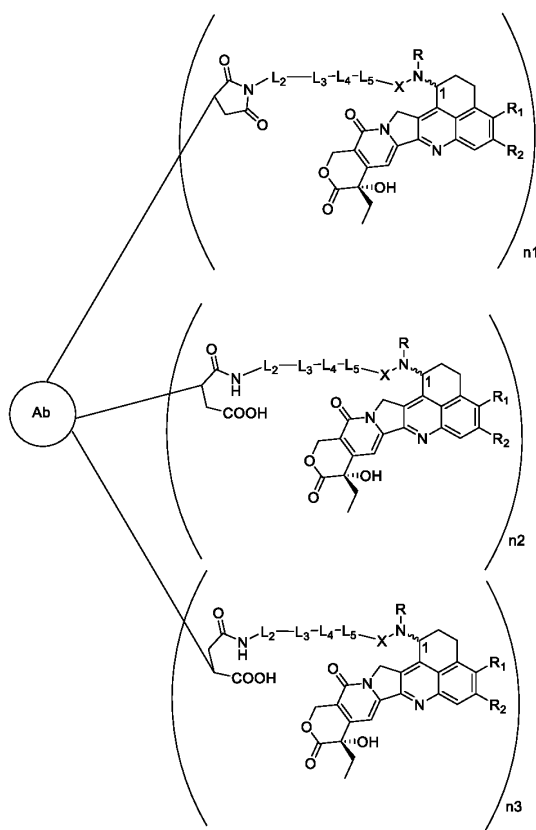
the carbon atom #2 attached to N has absolute chirality in either the R configuration or the S configuration,

the left wavy line is connected to the antibody or its antigen-binding fragment portion, and the right wavy line is connected to the X; and

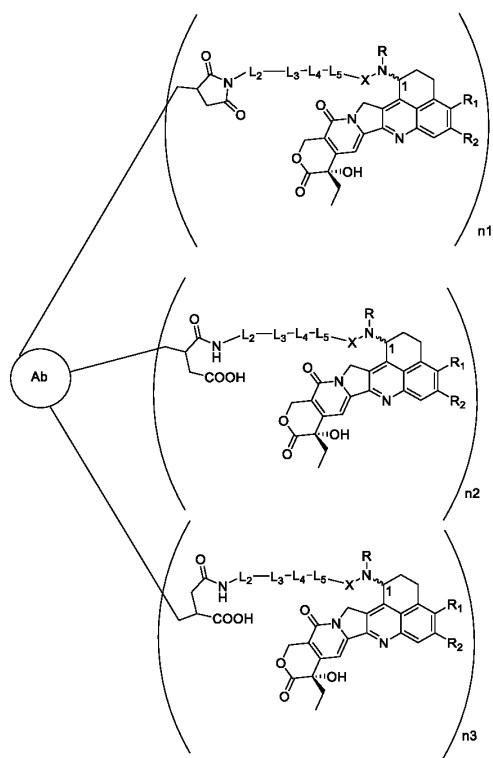
o is selected from integers 1-10.

33. The method of Claim 32, wherein R₅, R₆ and R₇ are each independently selected from a hydrogen atom or a C1-C6 alkyl group.

34. The method of Claim 1-15, wherein the ligand-camptothecin derivative conjugate of Formula I, or a pharmaceutically acceptable salt or solvent compound thereof, has a structure as shown in Formula I-1 or I-2.



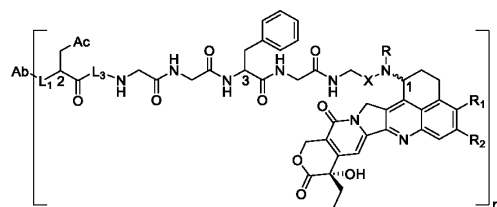
Formula I-1



Formula I-2

wherein n_1, n_2, n_3 are each independently selected from any integer or any decimal number from 0-10, n_1, n_2, n_3 are not simultaneously 0, and $1 \leq n_1 + n_2 + n_3 \leq 10$.

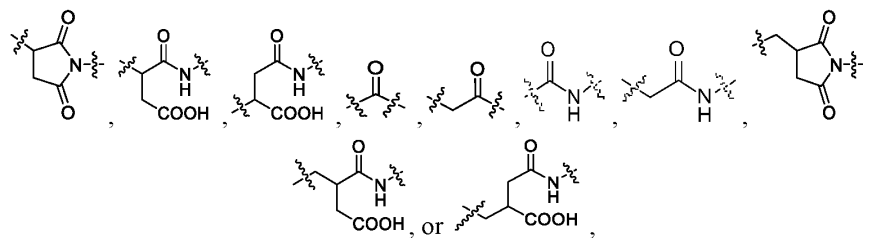
35. The method of Claim 1-15, wherein the ligand-camptothecin derivative conjugate of Formula I, or a pharmaceutically acceptable salt or solvent compound thereof, has a structure as shown in Formula II:



Formula II

wherein:

L₁ is a connection unit connected to Ab, comprising:



L₃ is present or absent, and when L₃ is present, L₃ is selected from , o is selected

from an integer from 1-10,

Ac is a hydrophilic structural unit,

the 1-position, 2-position and 3-position chiral carbon atoms have two chiral configurations, the R-absolute configuration or the S-absolute configuration,

R is selected from hydrogen atoms, deuterium atoms, halogens, C1-C6 alkyl, substituted C1-C6 alkyl, deuterated C1-C6 alkyl, C3-C8 cycloalkyl C1-C6 alkyl, C1-C6 alkoxy C1-C6 alkyl, C6-C10 aryl, substituted C6-C10 aryl, 5-10 heteroaryl, substituted 5-10 heteroaryl,

R₁ is selected from hydrogen atoms, deuterium atoms, halogens, C1-C6 alkyl, substituted C1-C6 alkyl, deuterated C1-C6 alkyl, C3-C8 cycloalkyl C1-C6 alkyl, C1-C6 alkoxy C1-C6 alkyl, carboxyl, 3-7 heterocyclic, substituted 3-7 heterocyclic, C6-C10 aryl, substituted C6-C10 aryl, 5-10 heteroaryl, substituted 5-10 heteroaryl,

R₂ is selected from hydrogen atoms, deuterium atoms, halogens, C1-C6 alkyl, substituted C1-C6 alkyl, deuterated C1-C6 alkyl, C3-C8 cycloalkyl C1-C6 alkyl, C1-C6 alkoxy C1-C6 alkyl, carboxyl, 3-7 heterocyclic, substituted 3-7 heterocyclic, C6-C10 aryl, substituted C6-C10 aryl, 5-10 heteroaryl, substituted 5-10 heteroaryl,

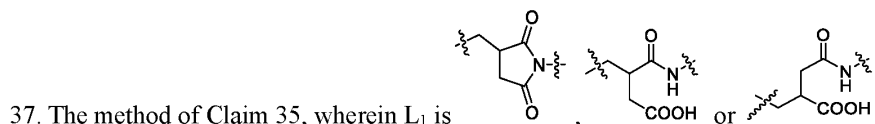
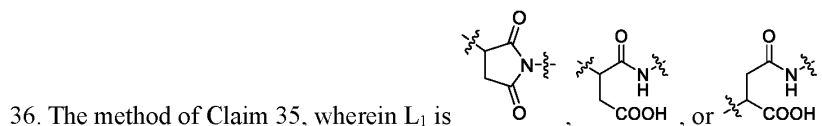
X selected from -C(O)-CR_aR_b-(CR₃R₄)_m-O-, -C(O)-CR_aR_b-(CR₃R₄)_m-NH- or -C(O)-CR_aR_b-(CR₃R₄)_m-S-,

R_a and R_b are each independently selected from a hydrogen atom, a deuterium atom, a halogen, a C1-C6 alkyl, a deuterated C1-C6 alkyl, a halogenated C1-C6 alkyl, a C3-C8 cycloalkyl, a C3-C8 cycloalkyl C1-C6 alkyl, a C1-C6 alkoxy C1-C6 alkyl, a 3-7 heterocyclic group, a substituted 3-7 heterocyclic group, a C6-C10 aryl, a substituted C6-C10 aryl, a 5-10 heteroaryl, substituted 5-10 heteroaryl,

R₃, R₄ are the same or different and are independently hydrogen atoms, deuterium atoms, halogens, C1-C6 alkyl, halogenated C1-C6 alkyl, deuterated C1-C6 alkyl, C1-C6 alkoxy, hydroxyl, amino, cyano, nitro, hydroxy C1-C6 alkyl, C3-C8 cycloalkyl, 3-7 heterocyclic, substituted 3-7 heterocyclic, respectively,

m is selected from the integers 0-4, and

n is chosen from the integers 1-10.



38. The method of Claim 35, wherein

R is hydrogen or C1-C6 alkyl.

R₁ is hydrogen or C1-C6 alkyl.

R₂ is hydrogen, halogen, or C1-C6 alkyl.

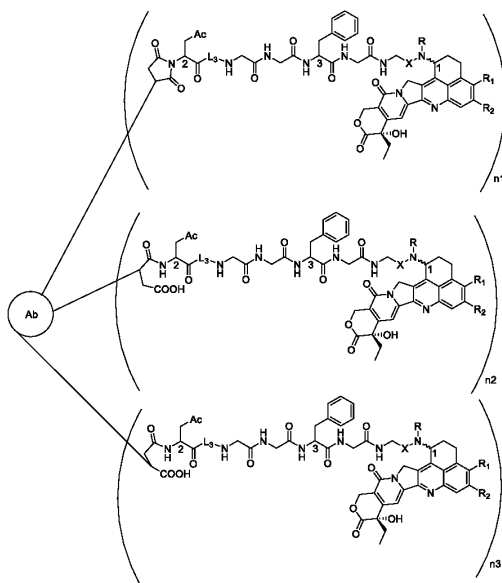
X is -C(O)-CR_aR_b-(CR₃R₄)_m-O-,

wherein R_a and R_b are each independently selected from a hydrogen atom, a C1-C6 alkyl, a halo-C1-C6 alkyl, a C3-C8 cycloalkyl C1-C6 alkyl or a C6-C10 aryl C1-C6 alkyl, or wherein R_a, R_b and the carbon atoms to which they are attached constitute C3-C8 cycloalkyl group, C3-C8 cycloalkyl C1-C6 alkyl group, 3-7 heterocycloalkyl group, substituted 3-7 heterocycloalkyl group, and

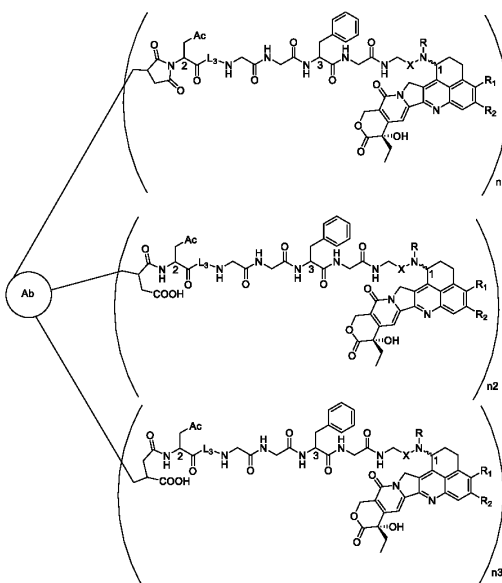
wherein R₃, R₄ are independently hydrogen or C1-C6 alkyl, or wherein R₃, R₄ and the carbon atoms attached thereto constitute a C3-C8 cycloalkyl group, a C3-C8 cycloalkyl C1-C6 alkyl group, a 3-7 heterocyclic group, a substituted 3-7 heterocyclic group.

39. The method of Claim 35, wherein R_a , R_b and the carbon atoms to which they are attached constitute C3-C8 cycloalkyl group.

40. The method of Claim 35, wherein the ligand-camptothecin derivative conjugate of Formula I, or a pharmaceutically acceptable salt or solvent compound thereof, has a structure as shown in Formula II-1 or II-2:



Formula II-1



Formula II-2

wherein n_1 , n_2 , and n_3 are each independently selected from any integer or any decimal number from 0 to 10, n_1 , n_2 , and n_3 are not simultaneously 0, and $1 \leq n_1 + n_2 + n_3 \leq 10$.

41. The method of Claim 1, wherein the Ac has the structure shown in Formula B below.



Formula B

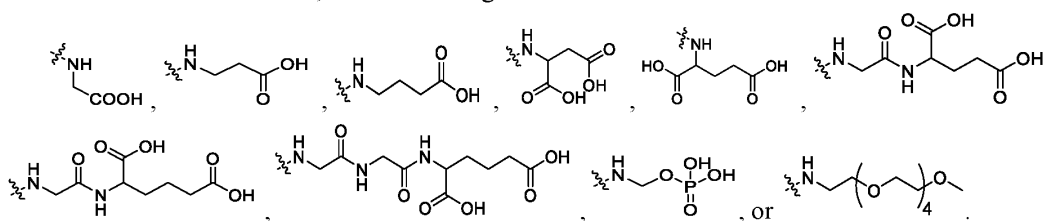
wherein:

Z comprises one or more of hydrophilic structural carboxyl group, phosphoric acid, polyphosphoric acid, phosphite, sulfonic acid, sulfinic acid, or polyethylene glycol (PEG),

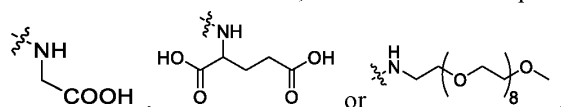
Y' is optionally a scaffold connecting the amino group to Z, wherein Y' is C1-C6 alkyl and Z is selected from hydrophilic structural carboxylates and phosphoric acid or polyethylene glycol (PEG), and

Ac is connected to the 2-position carbon that has been labeled in structural formula I by means of a bracket Y.

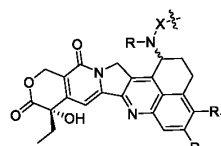
42. The method of Claim 1-15, wherein the Ac comprises glycine, (*D/L*) alanine, (*D/L*) leucine, (*D/L*) isoleucine, (*D/L*) valine, (*D/L*) phenylalanine, (*D/L*) proline, (*D/L*) tryptophan, (*D/L*) serine, (*D/L*) tyrosine, (*D/L*) cysteine, (*D/L*) cystine, (*D/L*) arginine, (*D/L*) histidine, (*D/L*) methionine, (*D/L*) asparagine, (*D/L*) glutamine, (*D/L*) threonine, (*D/L*) aspartic acid, (*D/L*) glutamic acid, natural or non-natural amino acid derivatives, or the following structures or isomers thereof:



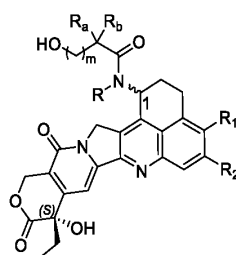
43. The method of Claim 42, wherein the Ac comprises



44. The method of Claim 1, wherein the Ac comprises a glycine, phosphoric acid, (*D/L*) glutamic acid, or polyethylene glycol hydrophilic structure.



45. The method of Claim 1-15, wherein the Formula D below:



Formula D

wherein:

R is selected from hydrogen atom, deuterium atom, halogen, C1-C6 alkyl, substituted C1-C6 alkyl, deuterated C1-C6 alkyl, C3-C8 cycloalkyl C1-C6 alkyl, C1-C6 alkoxy C1-C6 alkyl, C6-C10 aryl, substituted C6-C10 aryl, 5-10 heteroaryl, substituted 5-10 heteroaryl,

R_1 is selected from hydrogen atoms, deuterium atoms, halogens, C1-C6 alkyl, substituted C1-C6 alkyl, deuterated C1-C6 alkyl, C3-C8 cycloalkyl C1-C6 alkyl, C1-C6 alkoxy C1-C6 alkyl, carboxyl, 3-7 heterocyclic, substituted 3-7 heterocyclic, C6-C10 aryl, substituted C6-C10 aryl, 5-10 heteroaryl, substituted 5-10 heteroaryl,

R_2 is selected from hydrogen atoms, deuterium atoms, halogens, C1-C6 alkyl, substituted C1-C6 alkyl, deuterated C1-C6 alkyl, C3-C8 cycloalkyl C1-C6 alkyl, C1-C6 alkoxy C1-C6 alkyl, carboxyl, 3-7 heterocyclic, substituted 3-7 heterocyclic, C6-C10 aryl, substituted C6-C10 aryl, 5-10 heteroaryl, substituted 5-10 heteroaryl,

R_a and R_b are each independently selected from a hydrogen atom, a deuterium atom, a halogen, a C1-C6 alkyl, a deuterated C1-C6 alkyl, a halogenated C1-C6 alkyl, a C3-C8 cycloalkyl, a C3-C8 cycloalkyl C1-C6 alkyl, a C1-C6 alkoxy C1-C6 alkyl, a 3-7 heterocyclic group, a substituted 3-7 heterocyclic group, a C6-C10 aryl, a substituted C6-C10 aryl, a 5-10 heteroaryl, substituted 5-10 heteroaryl,

the 1-position chiral carbon atom has two chiral configurations, the R absolute configuration or the S absolute configuration, and

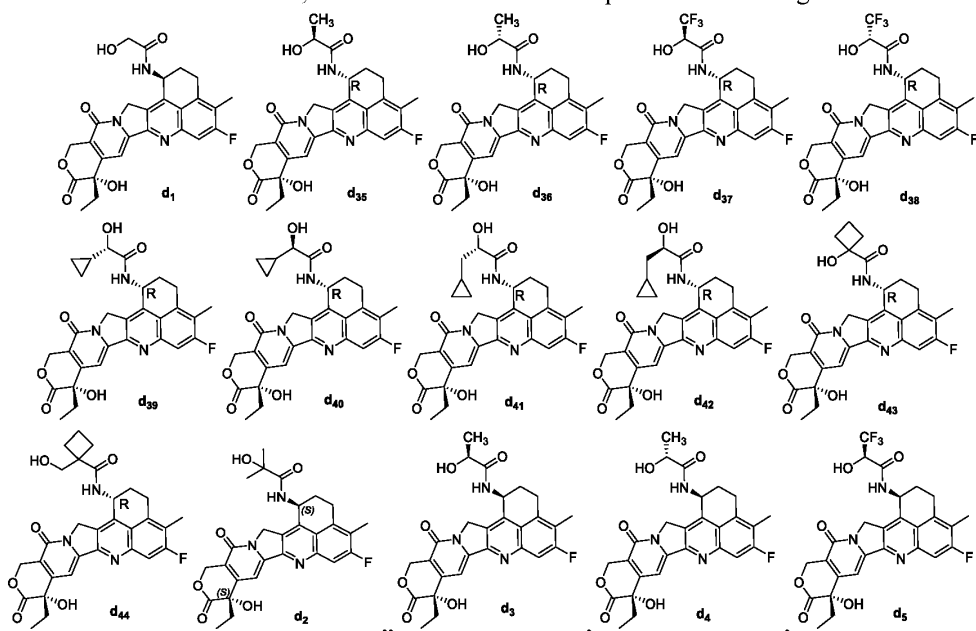
m is selected from 0 or 1.

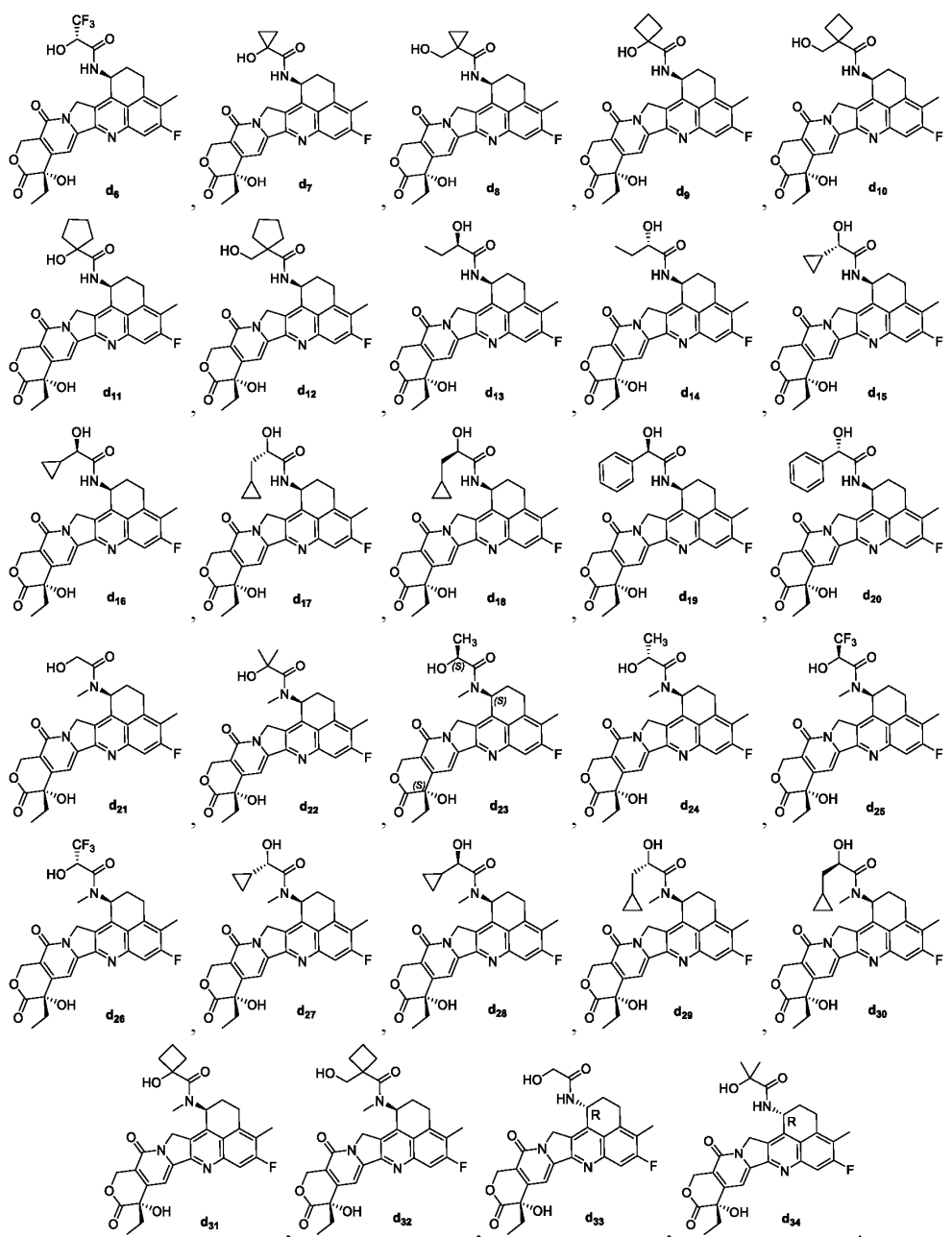
46. The method of Claim 45, wherein R is hydrogen atom or C1-C6 alkyl, R_1 is C1-C6 alkyl, R_2 is halogen.

47. The method of Claim 45, wherein R_a and R_b are each independently selected from hydrogen, C1-C6 alkyl, halo-C1-C6 alkyl, C3-C8 cycloalkyl, C1-C6 alkyl, C6-C10 aryl, or wherein R_a , R_b and the carbon atoms to which they are attached constitute C3-C8 cycloalkyl, C3-C8 cycloalkyl, C1-C6 alkyl, 3-7 heterocycloalkyl, substituted 3-7 heterocycloalkyl;

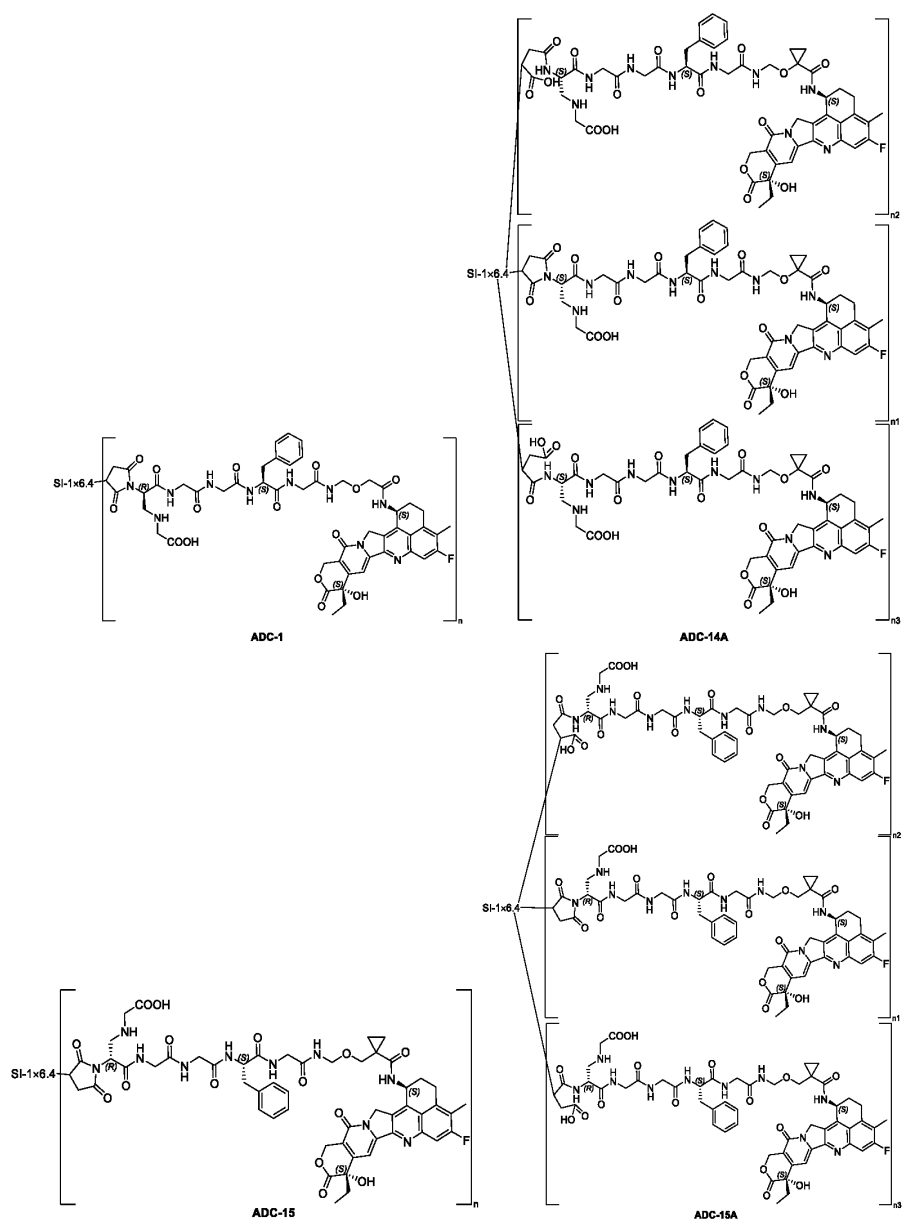
48. The method of Claim 45, wherein R_a , R_b and the carbon atoms to which they are attached constitute a C3-C8 cycloalkyl group.

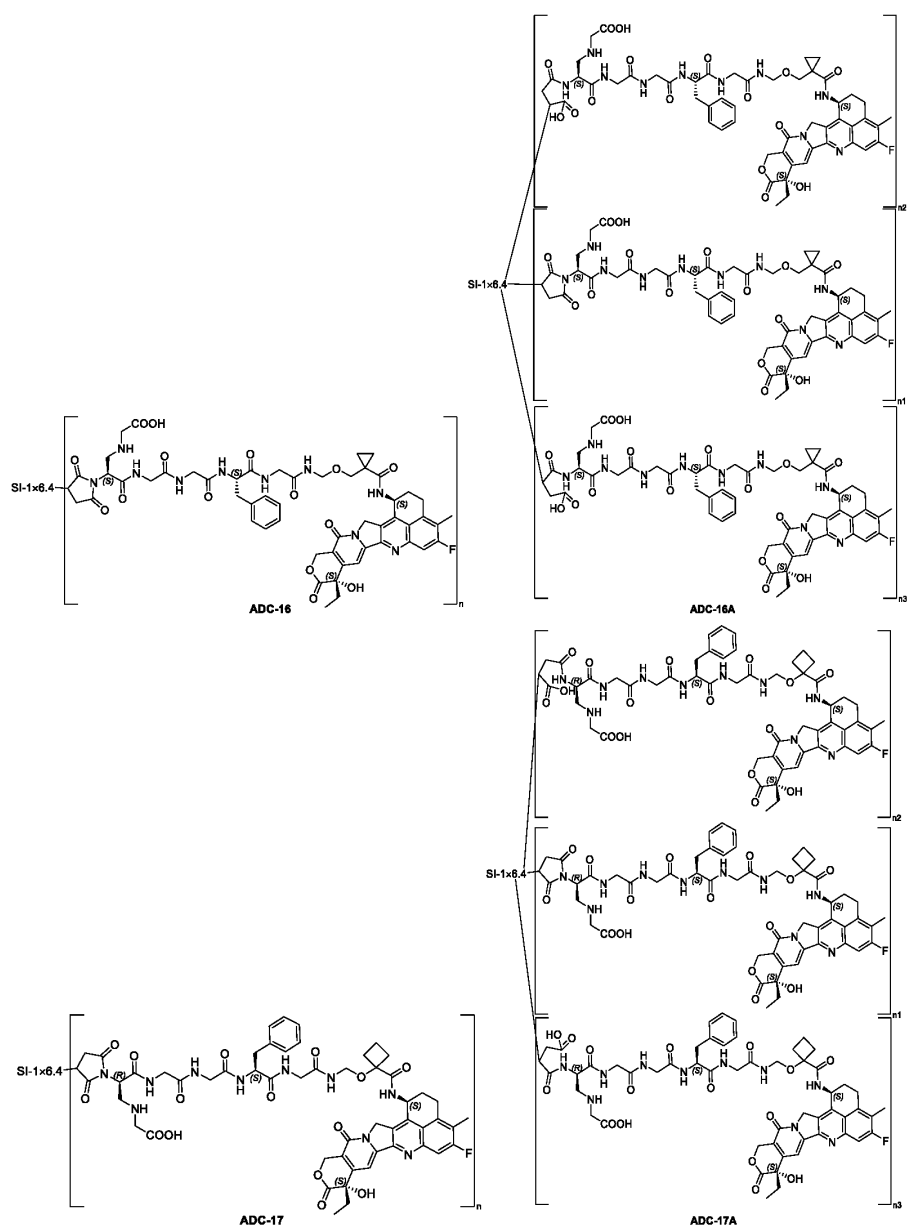
49. The method of Claim 45, wherein the Formula D comprises the following:

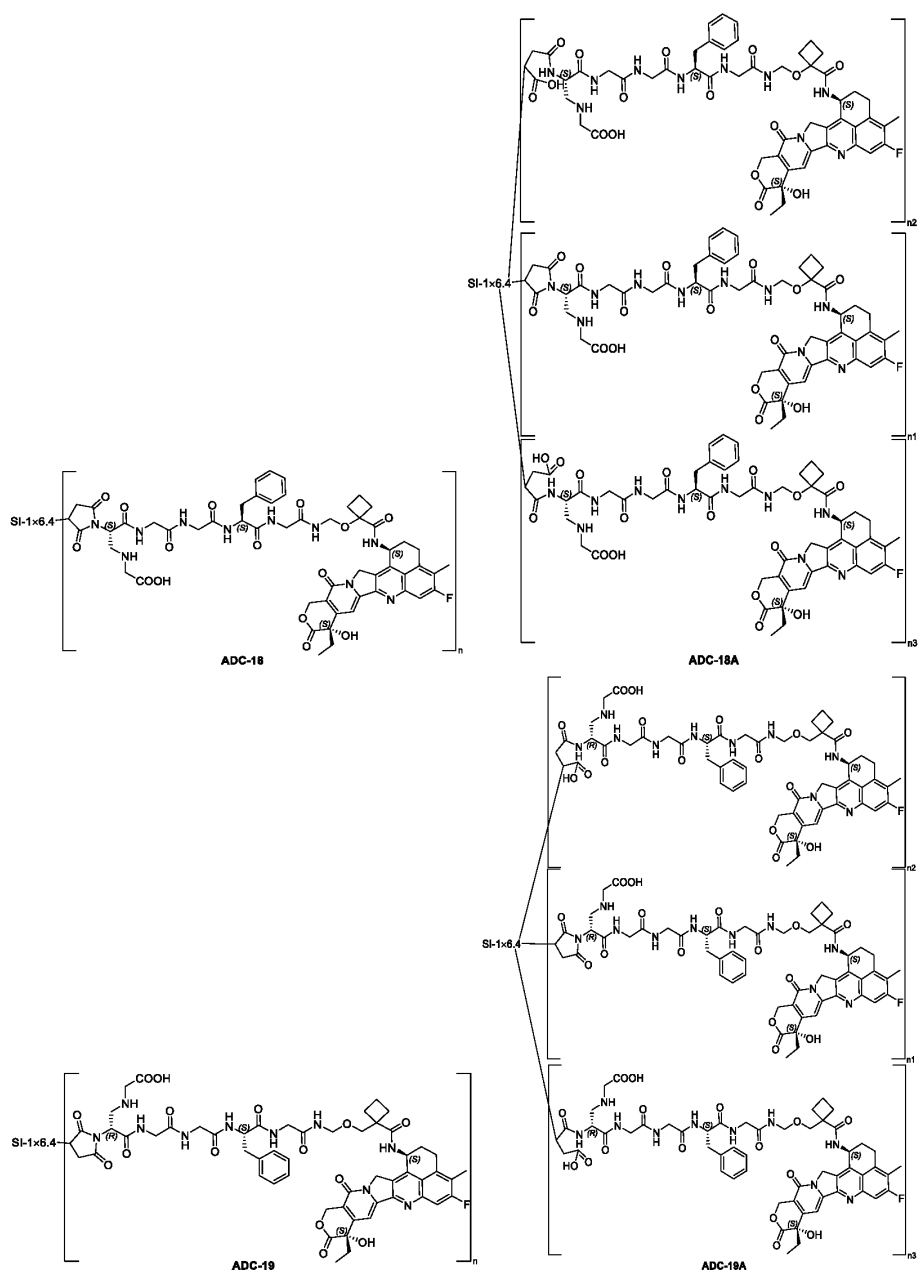


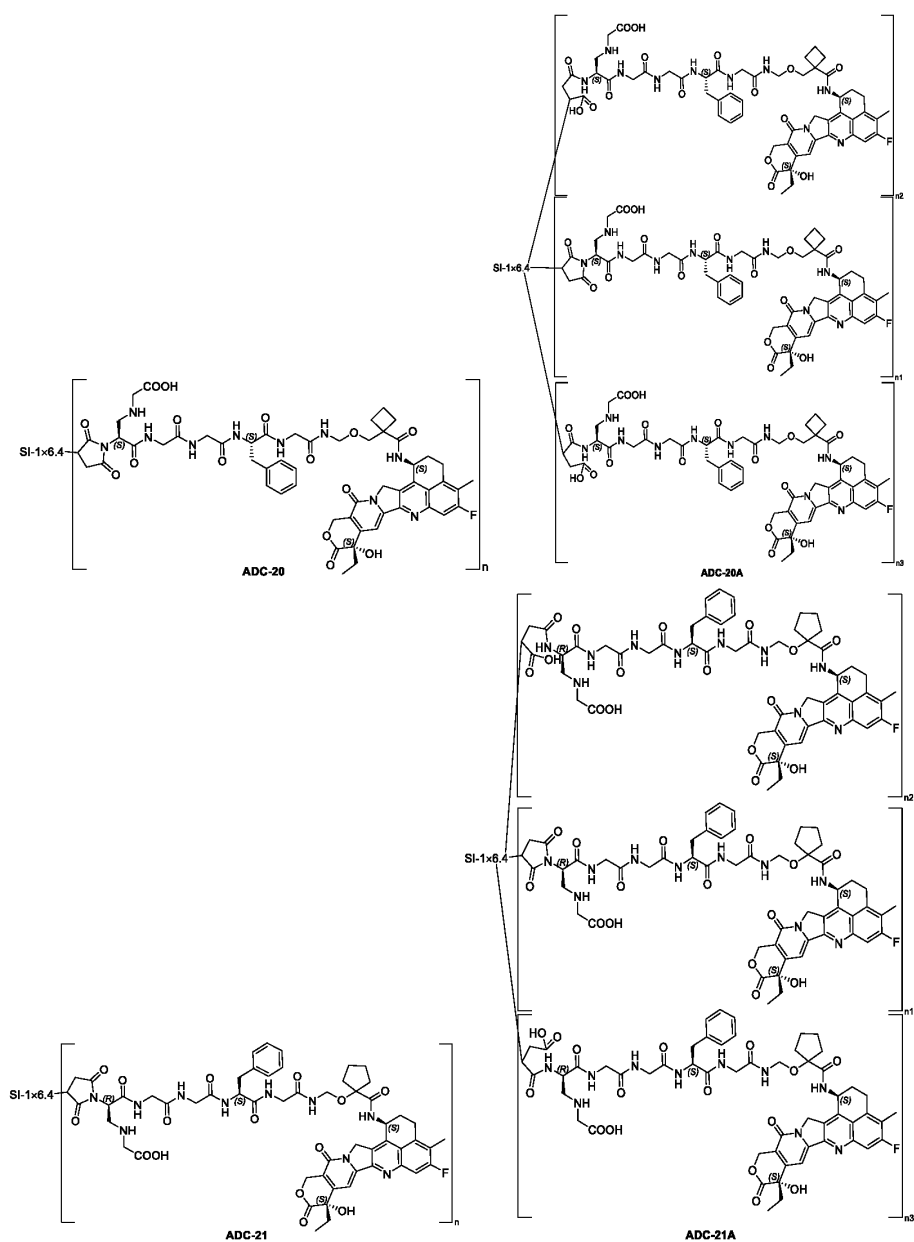


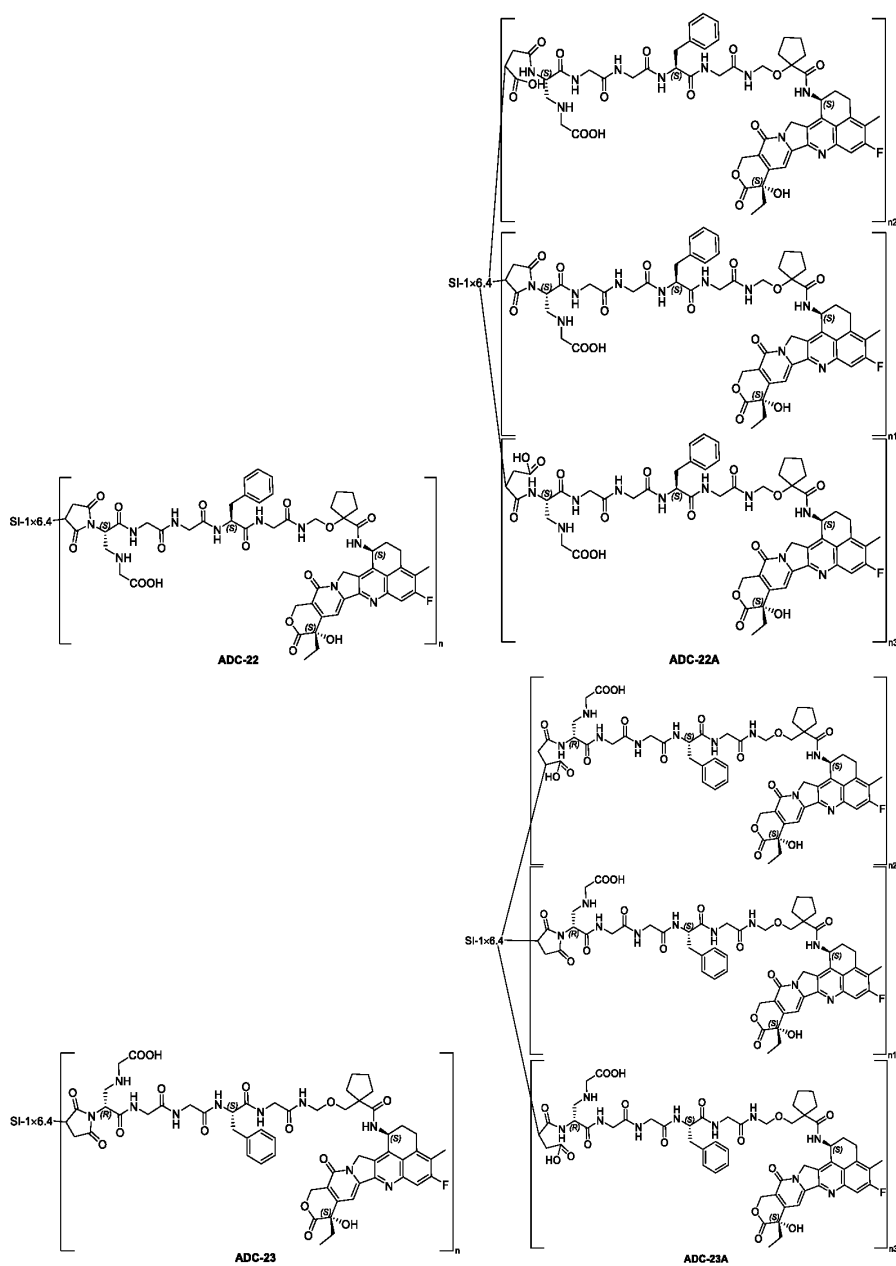
50. The method of Claim 1-15, wherein the ligand-camptothecin derivative conjugate of Formula I, or a pharmaceutically acceptable salt or solvent compound thereof, comprises the following structure or a butanediimide ring-opening structure thereof or an isomer thereof:

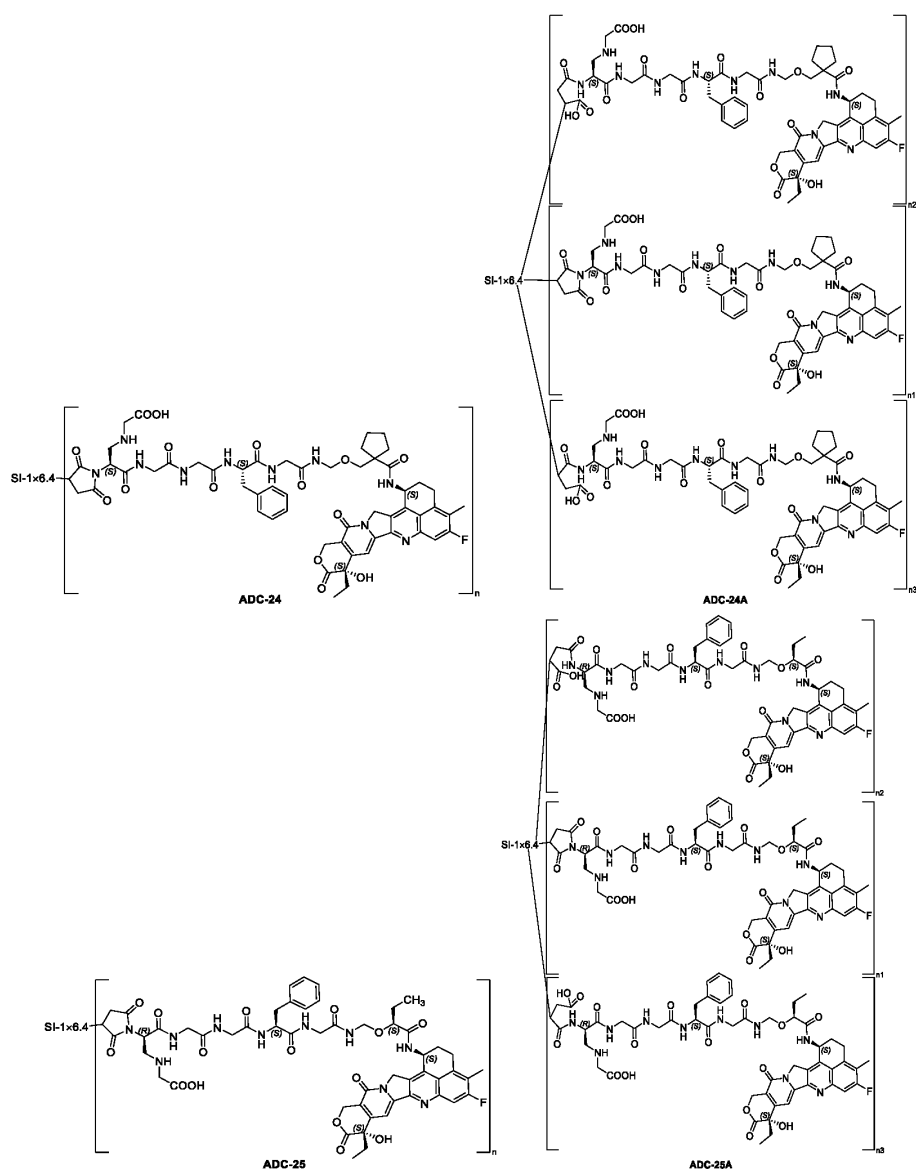


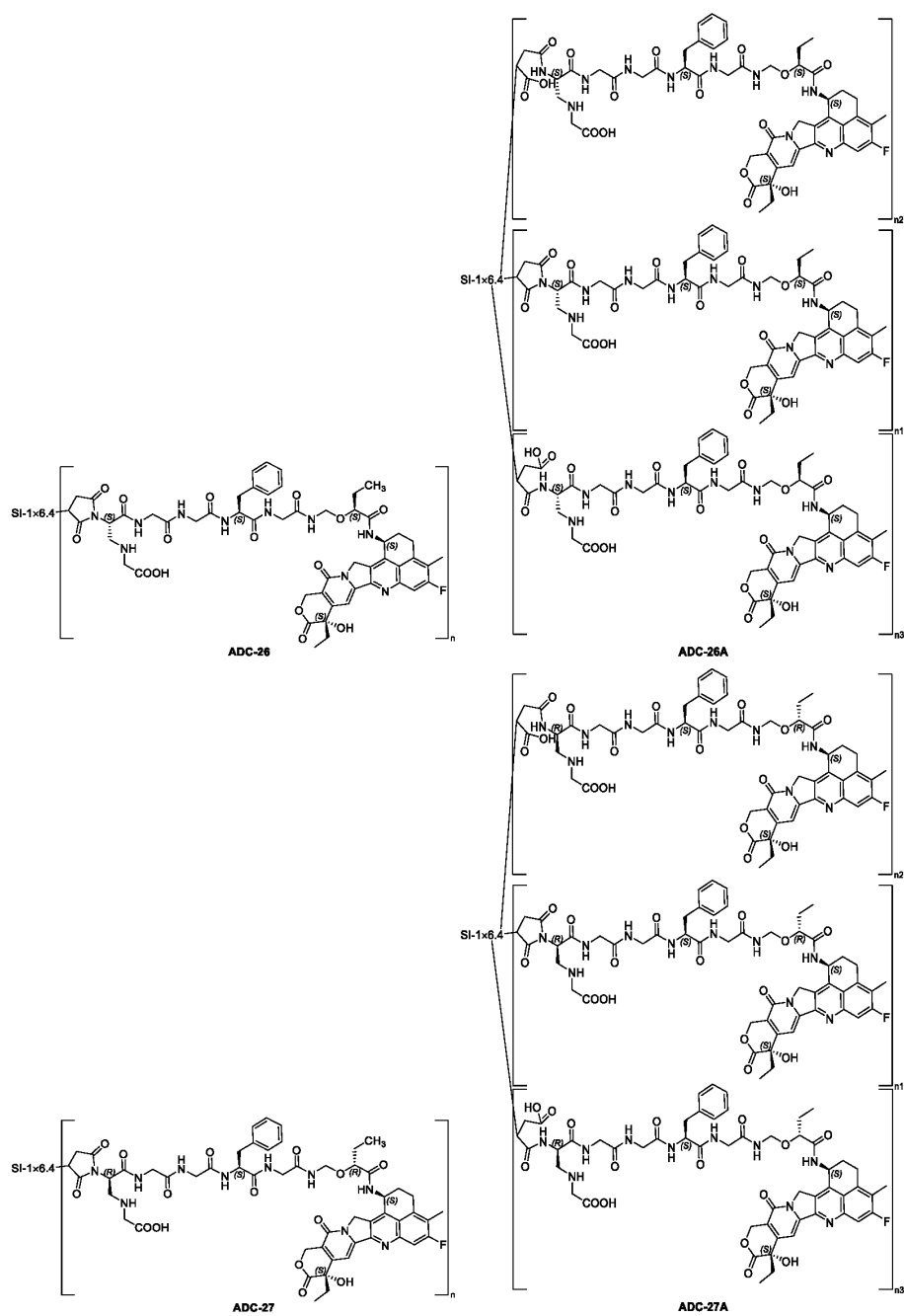


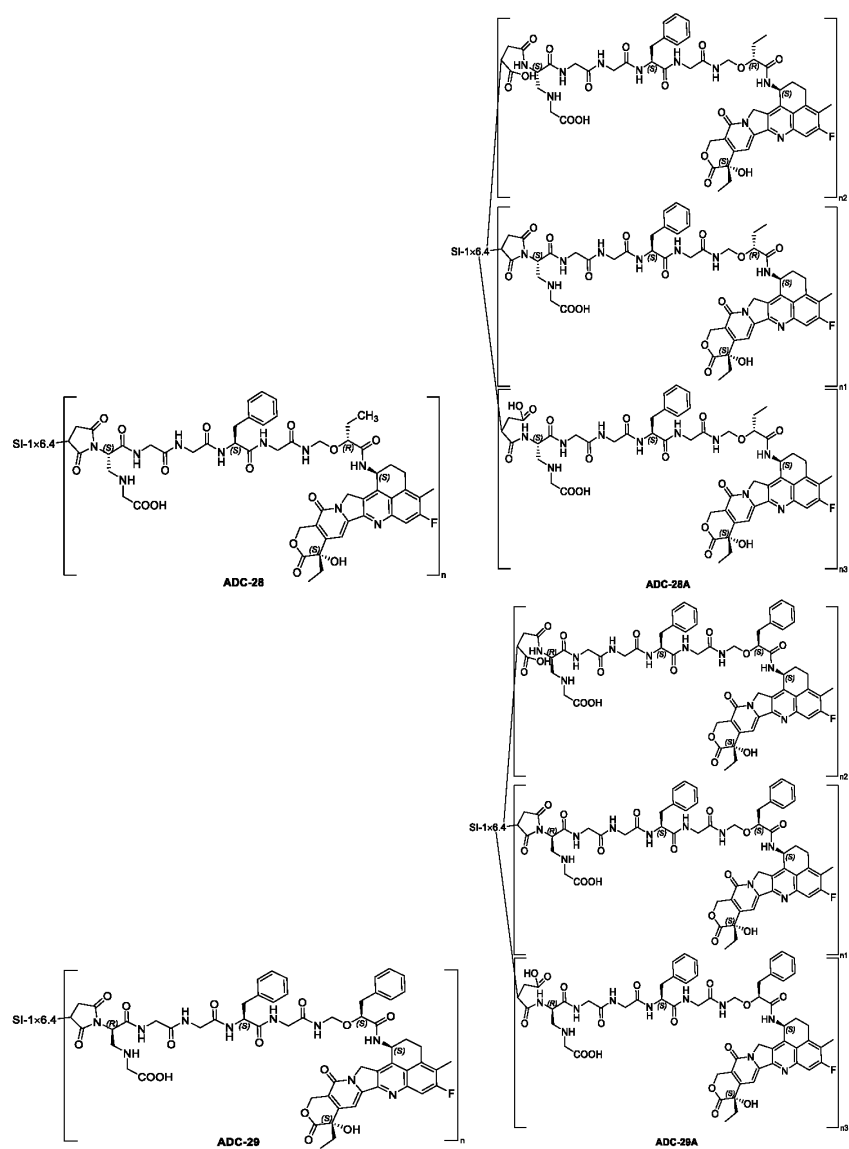


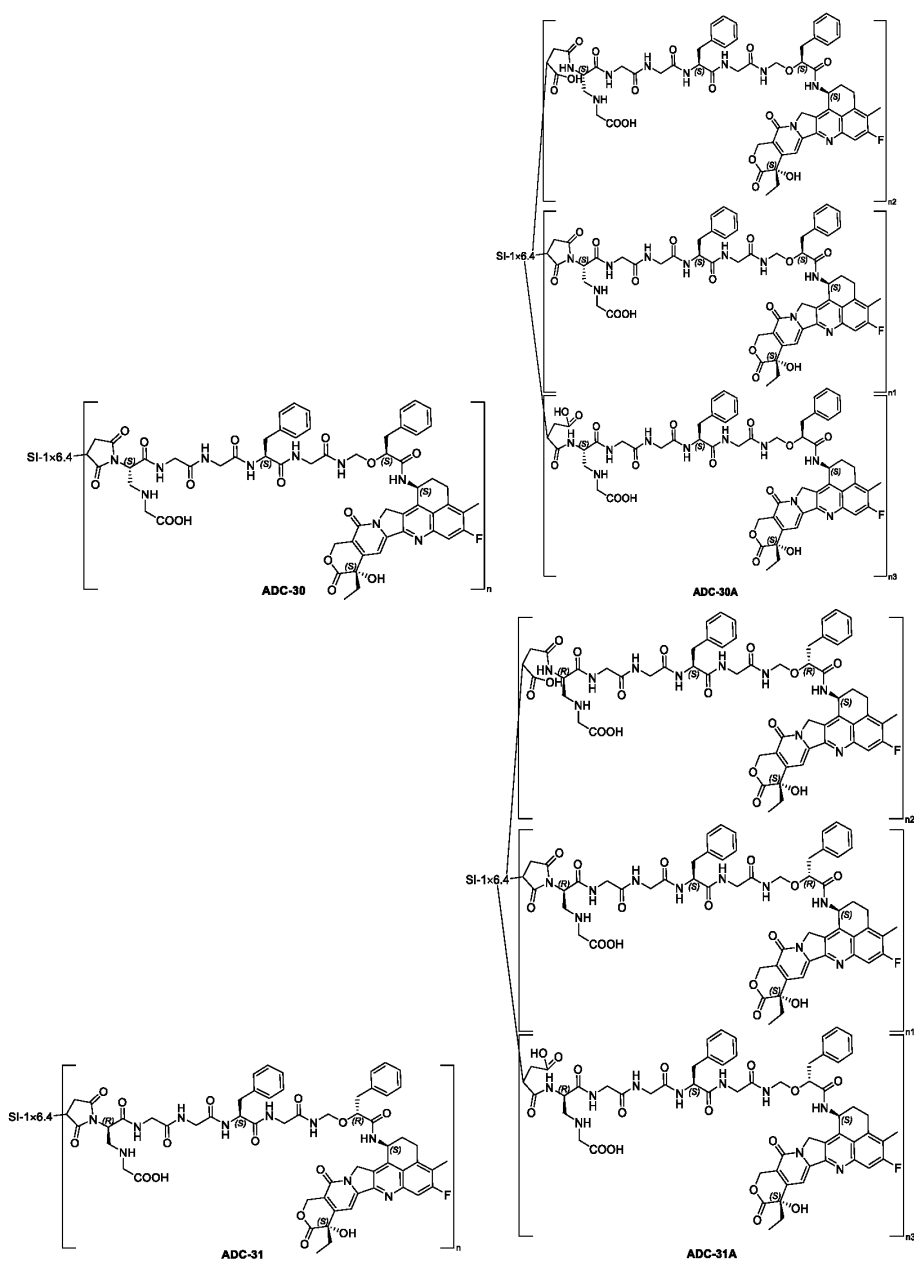


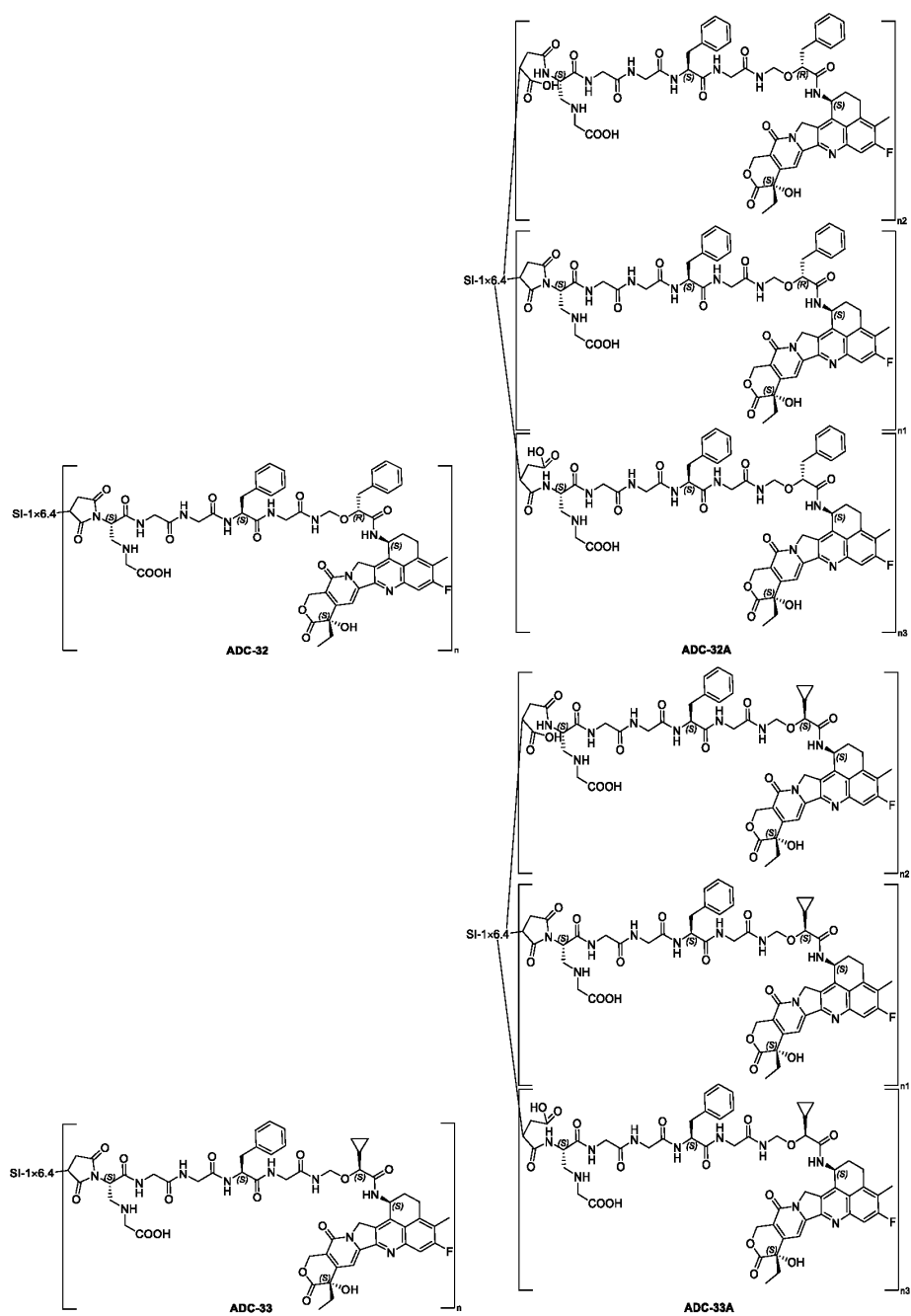


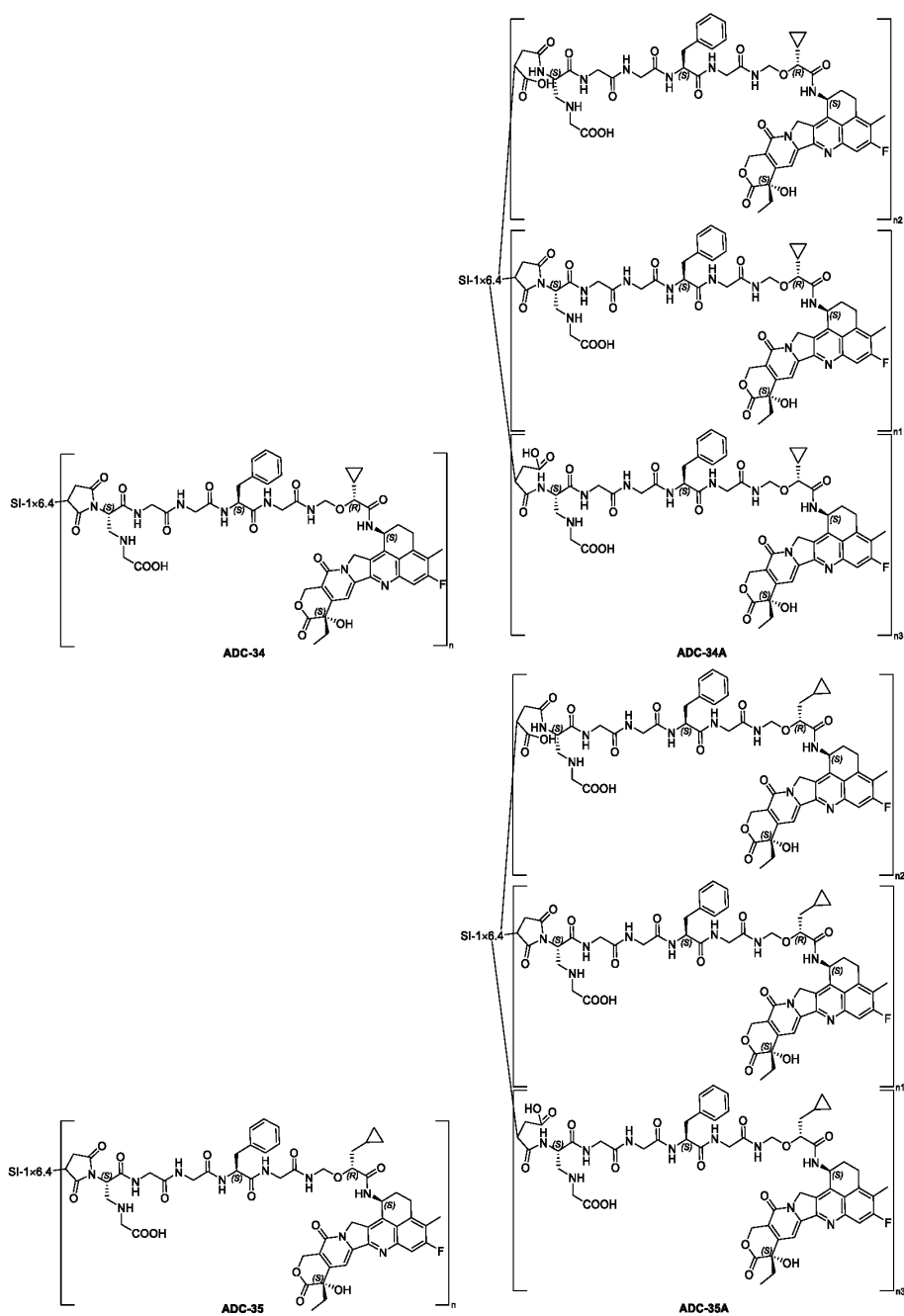


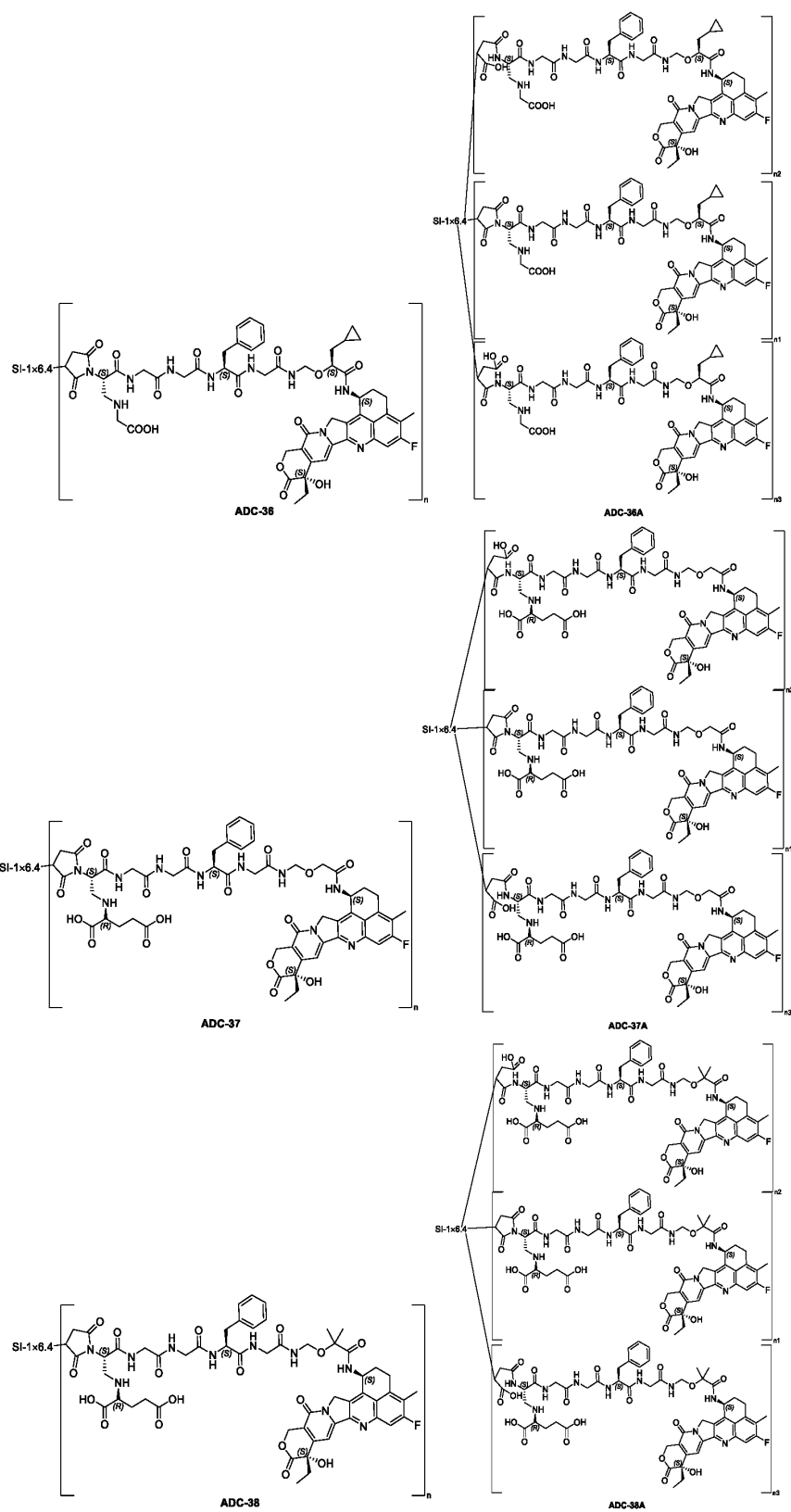


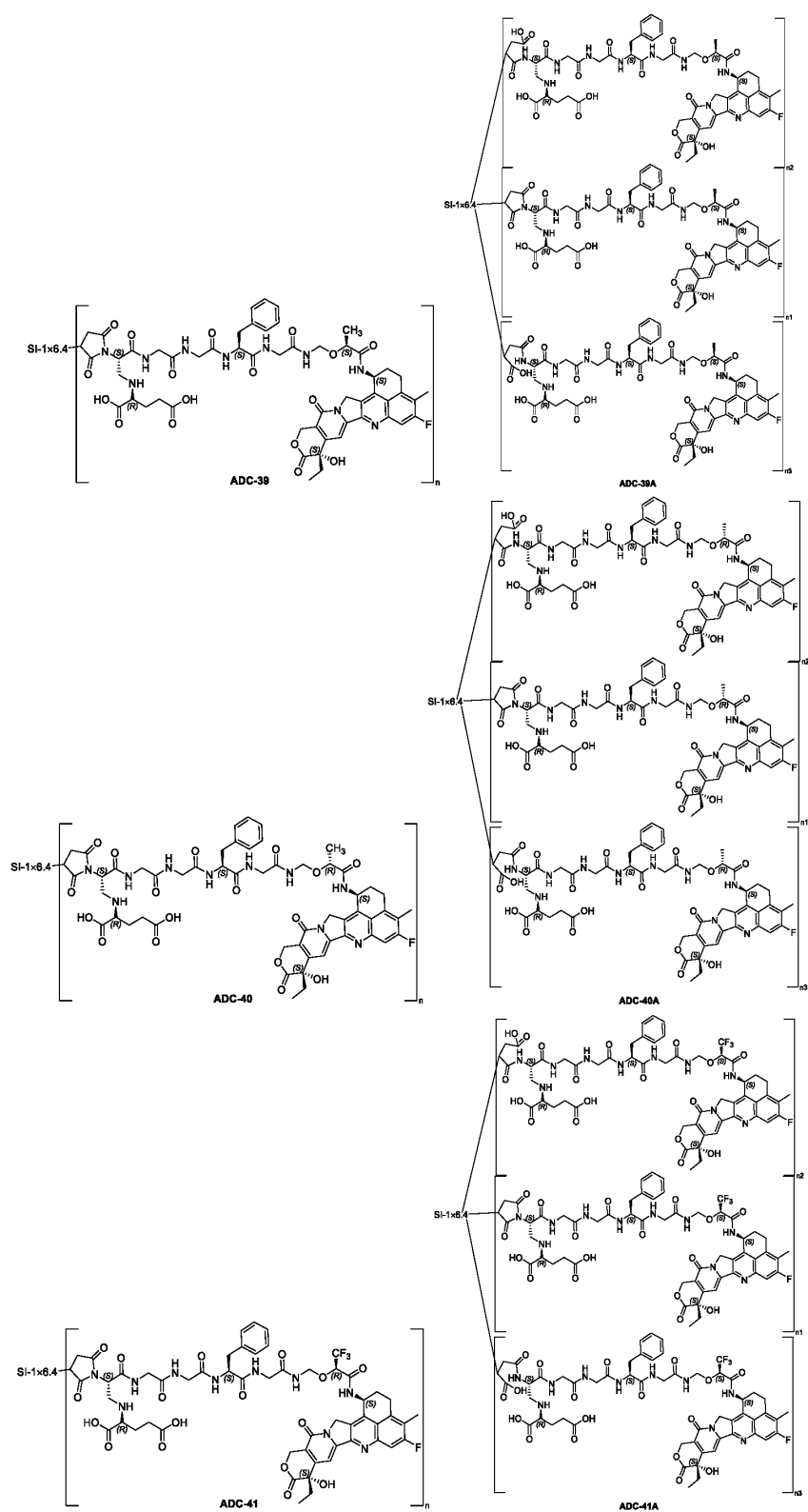




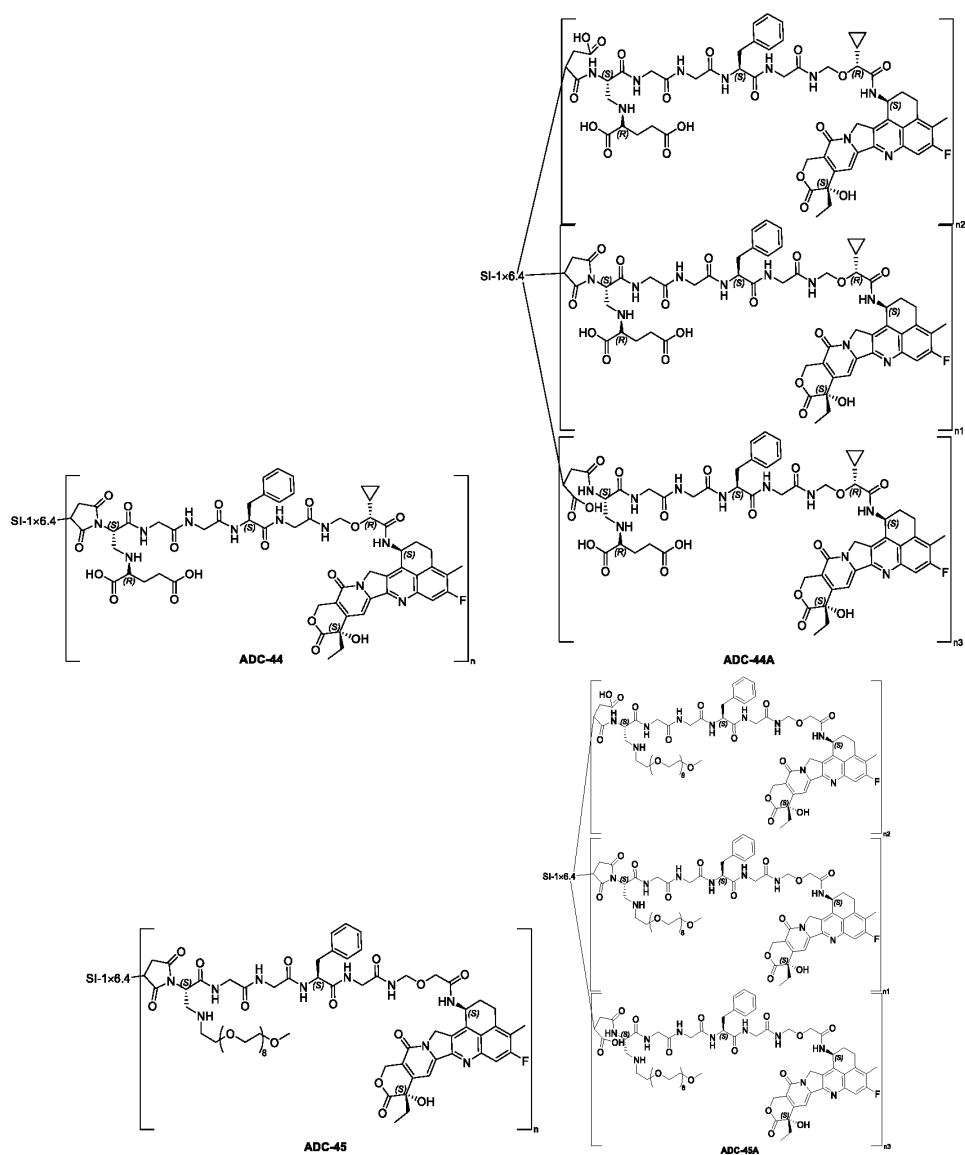


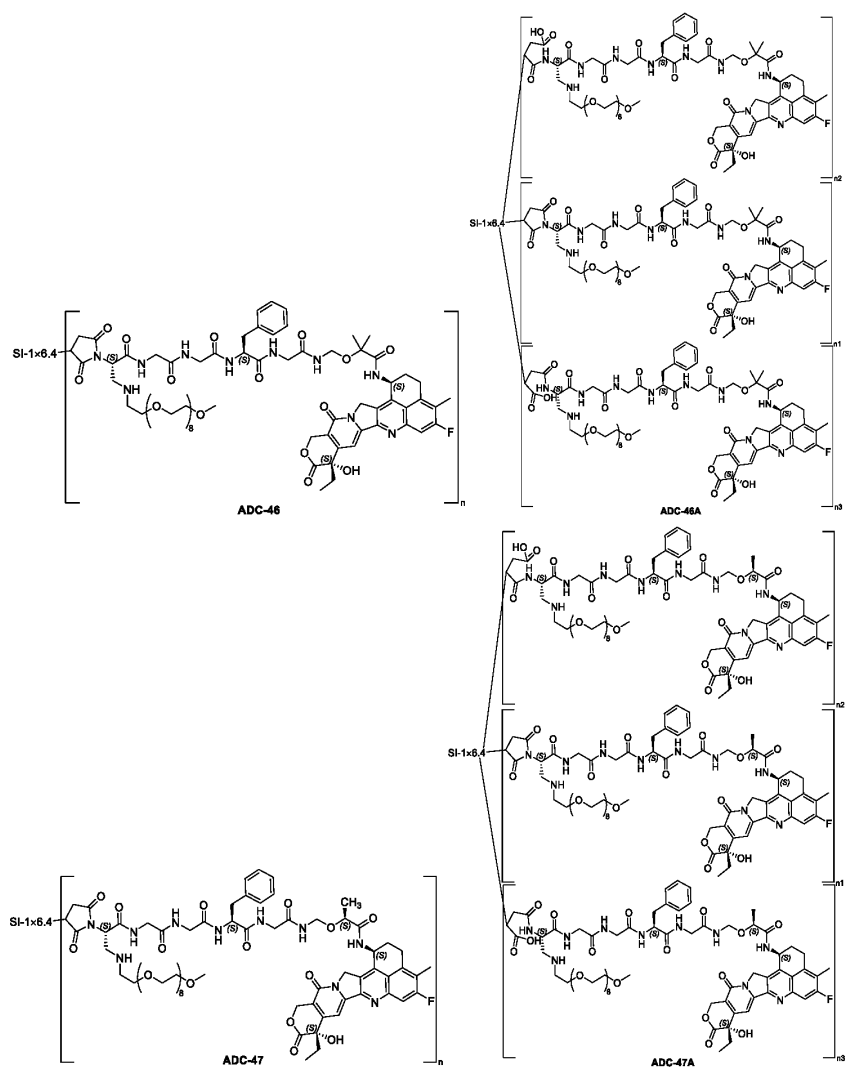


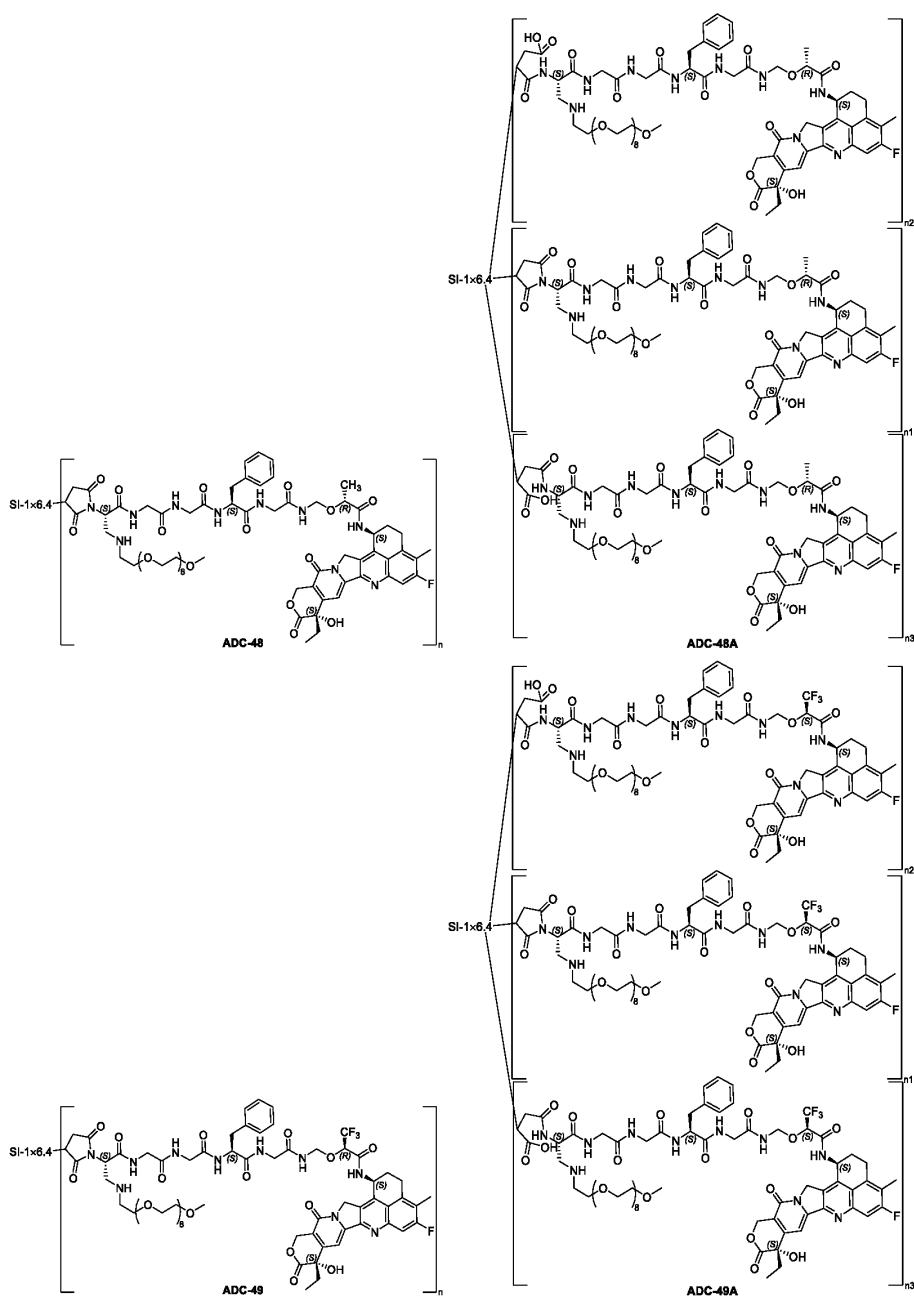


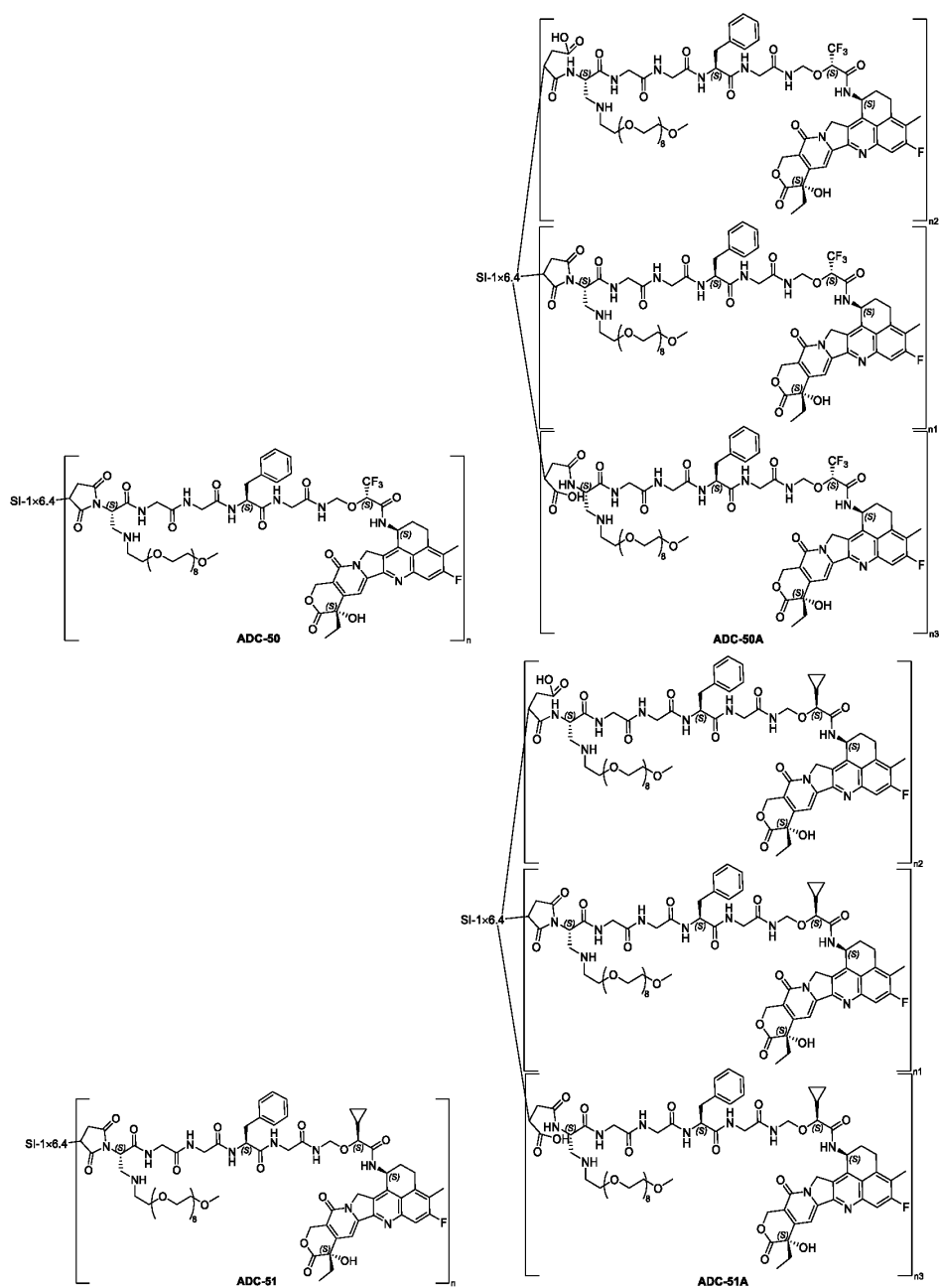


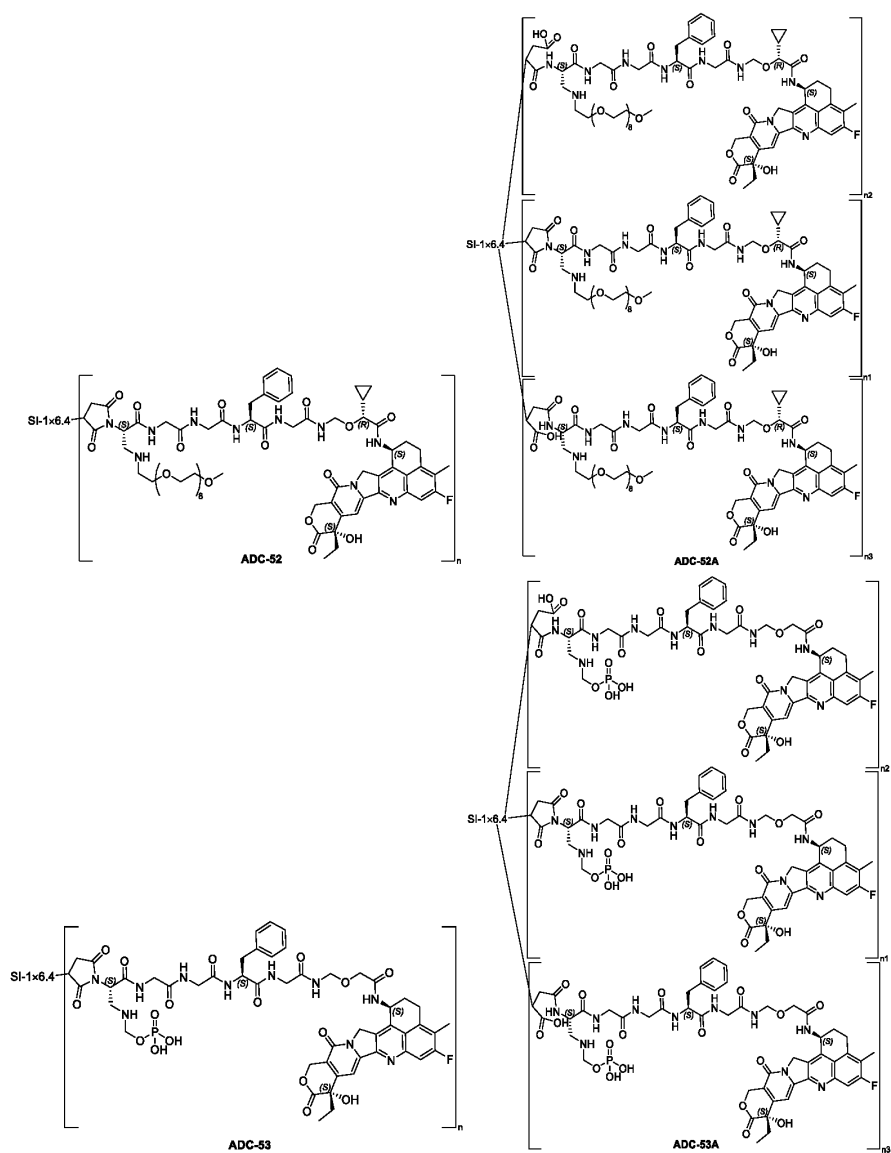


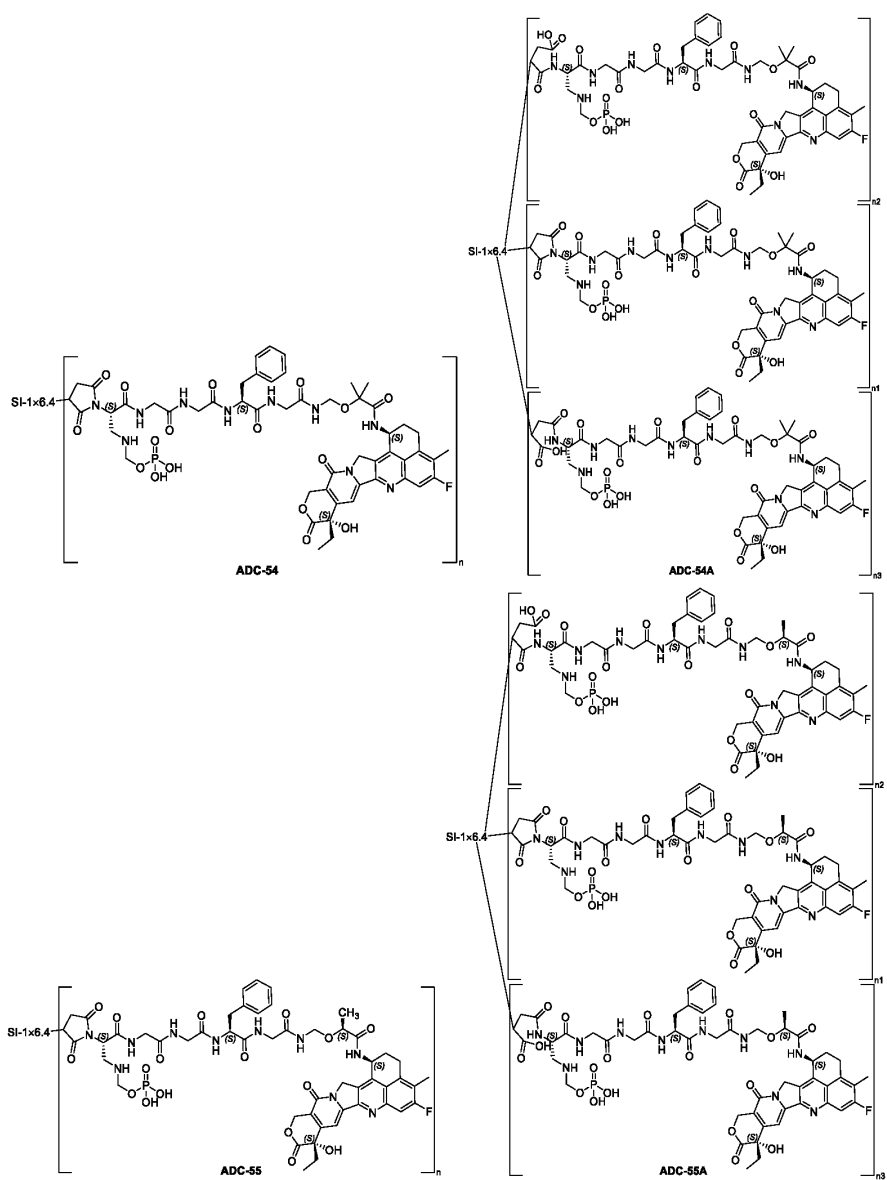


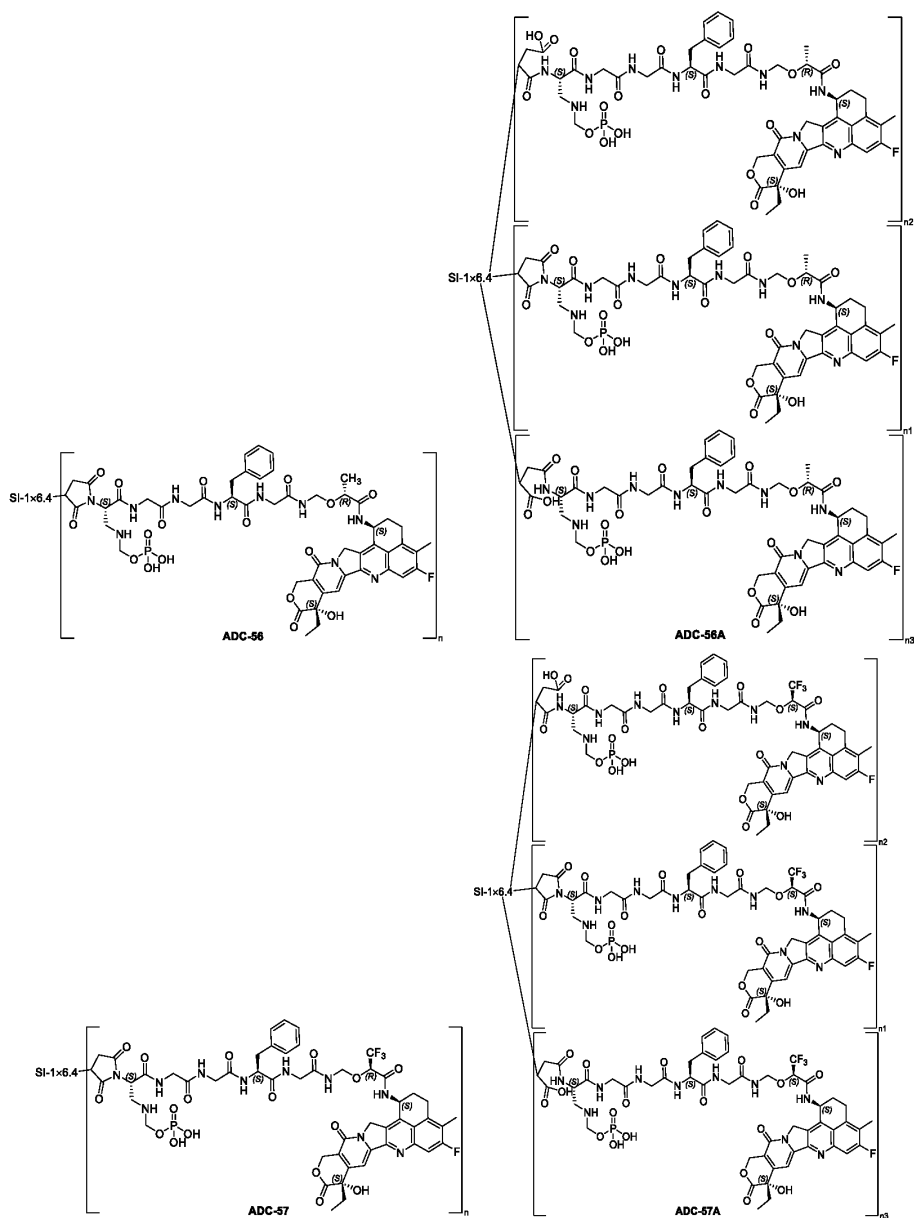


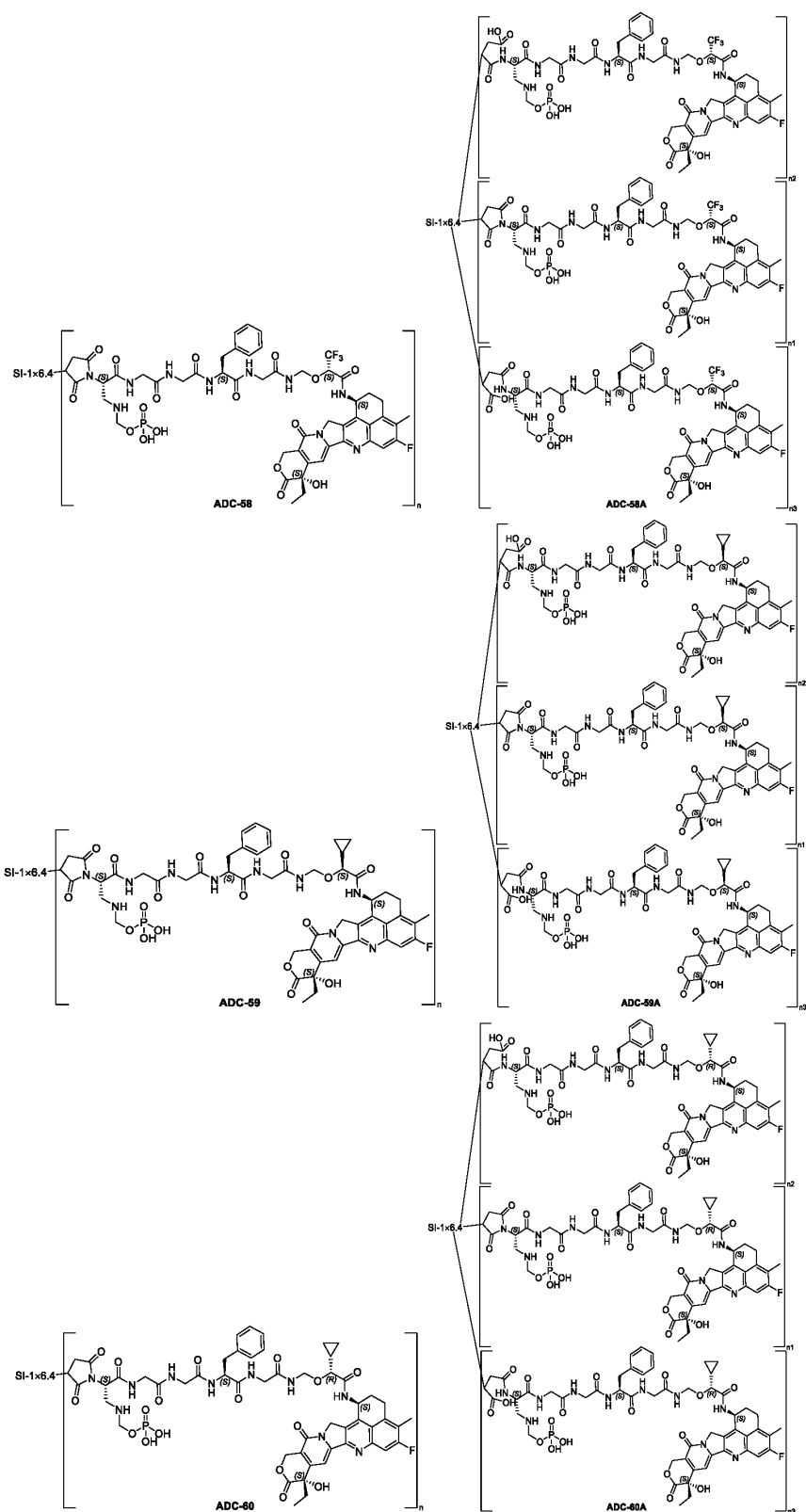


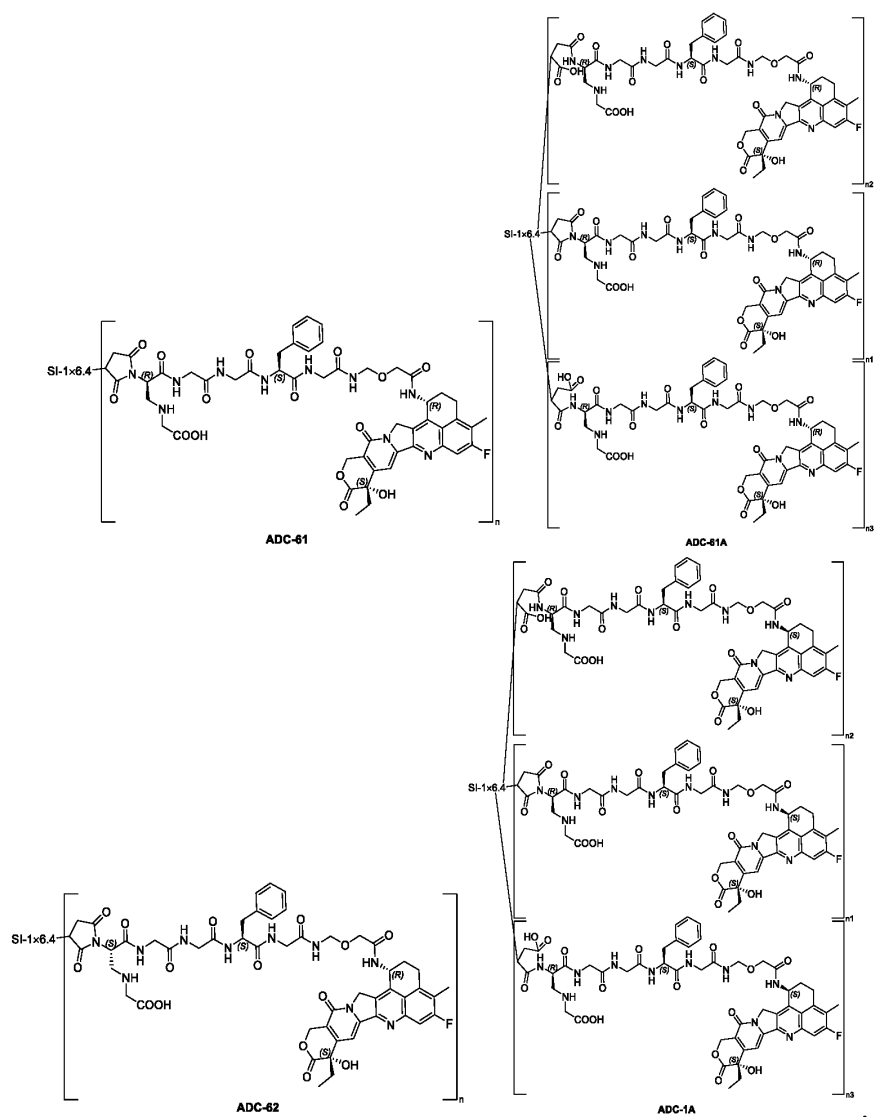


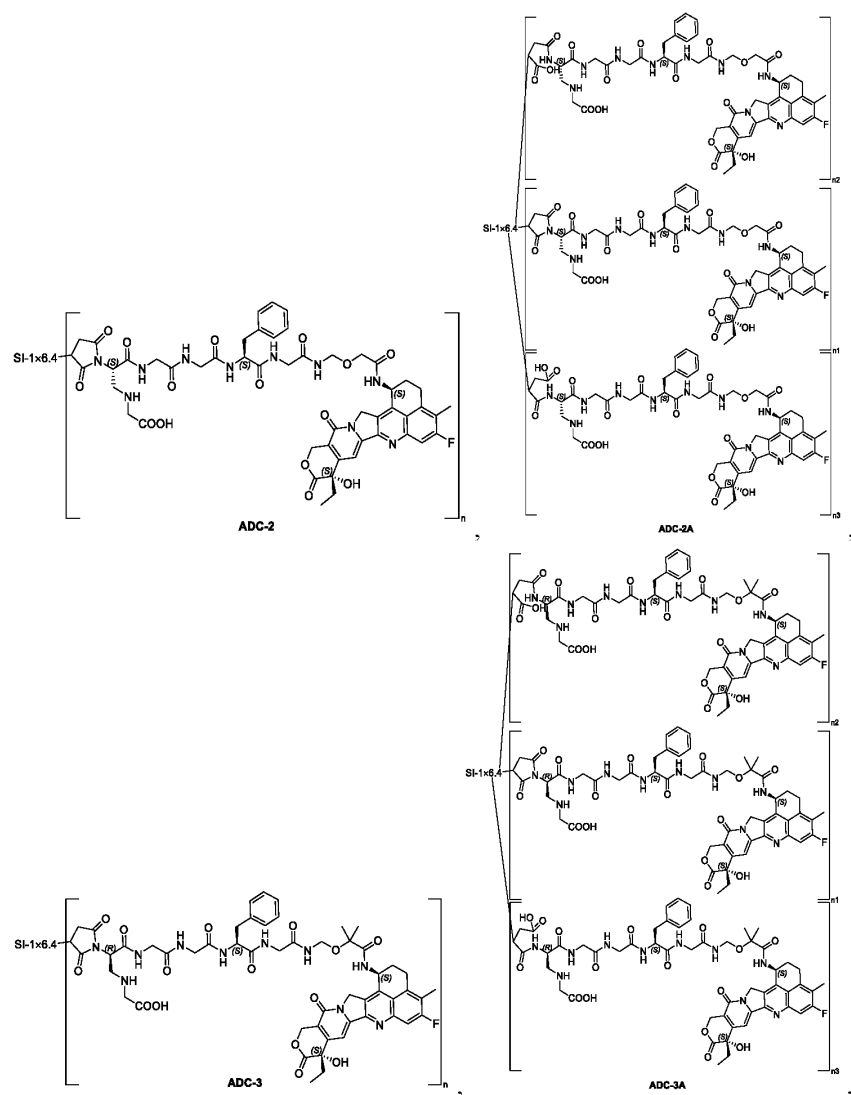


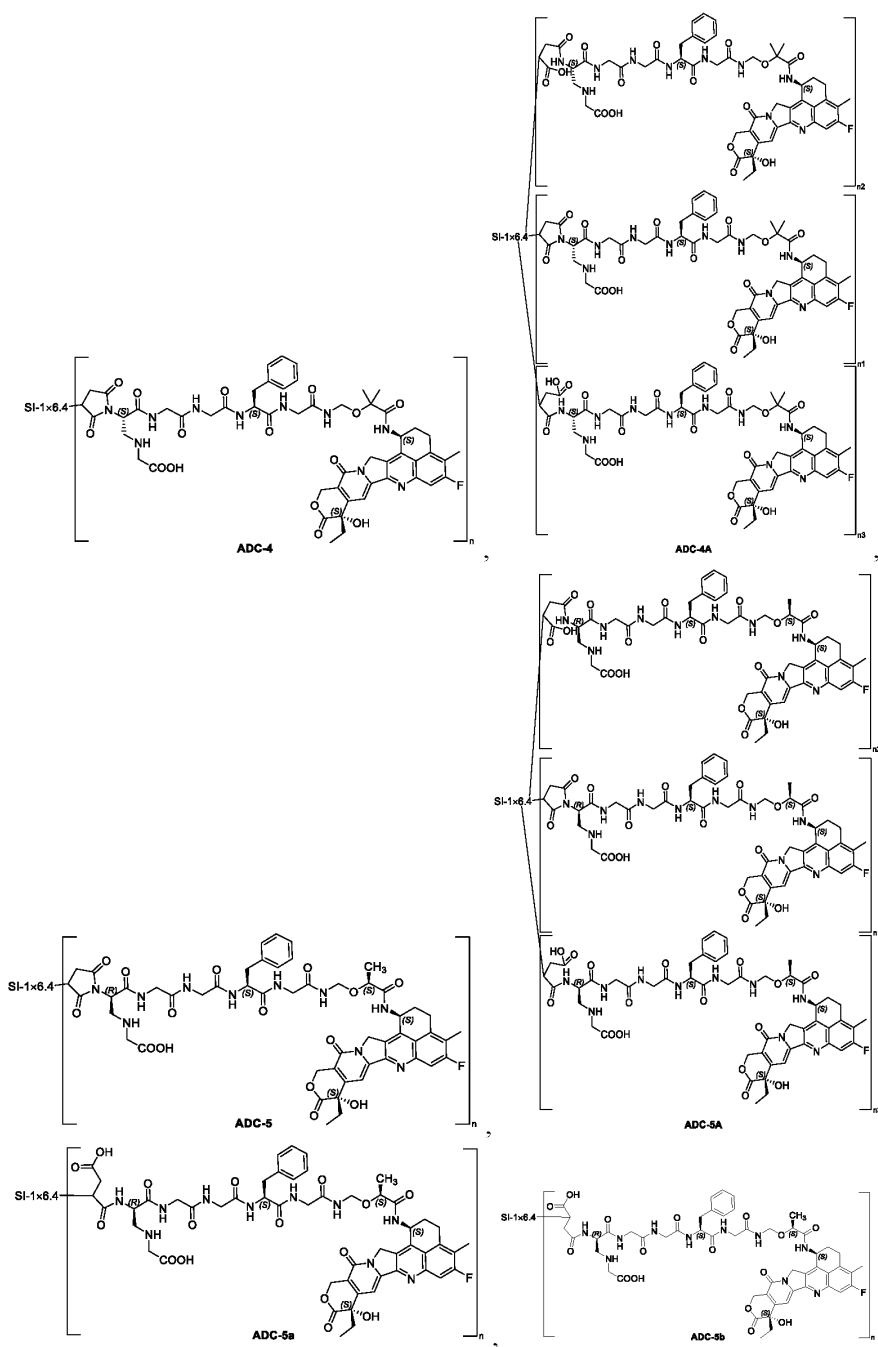


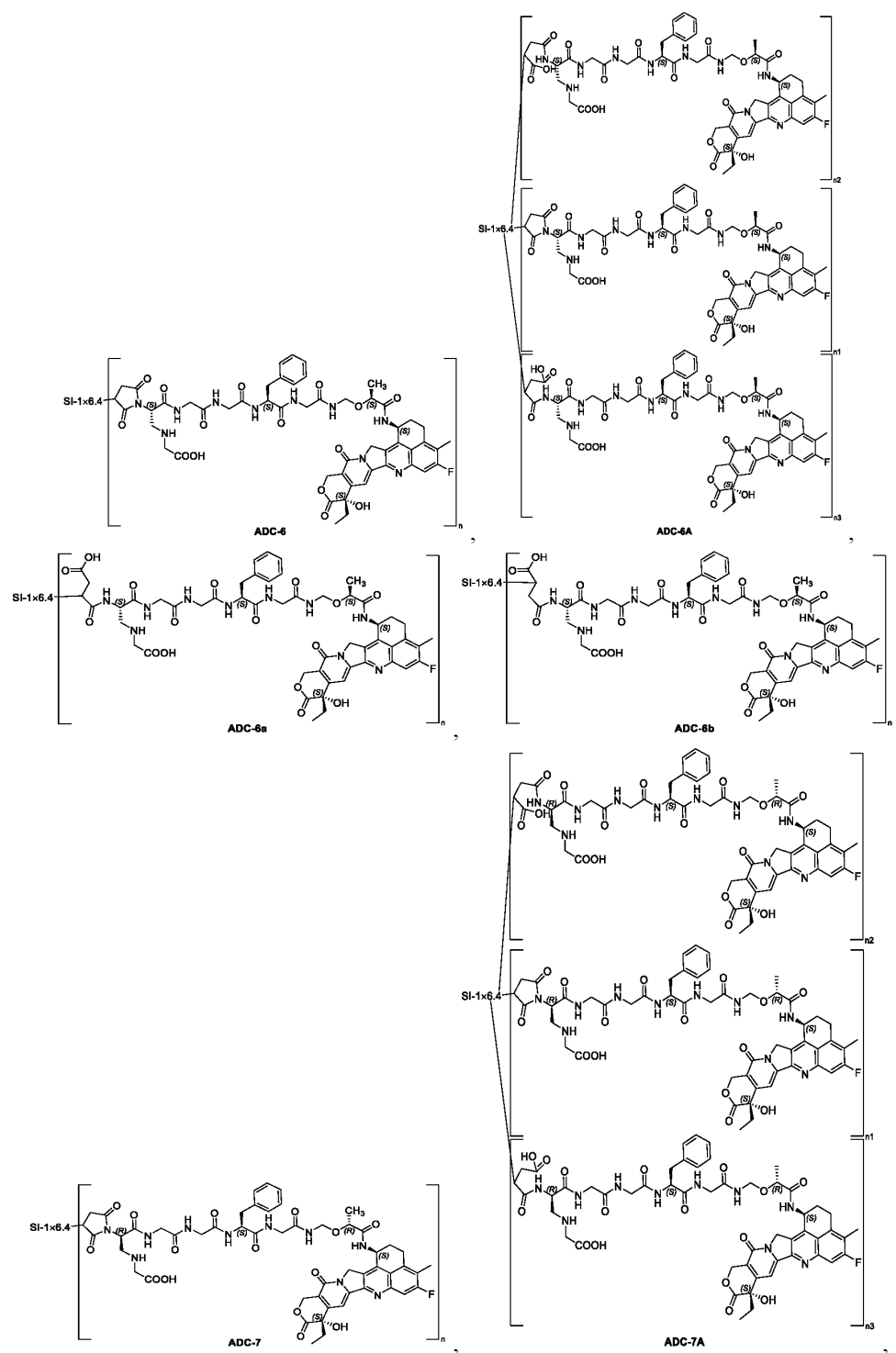


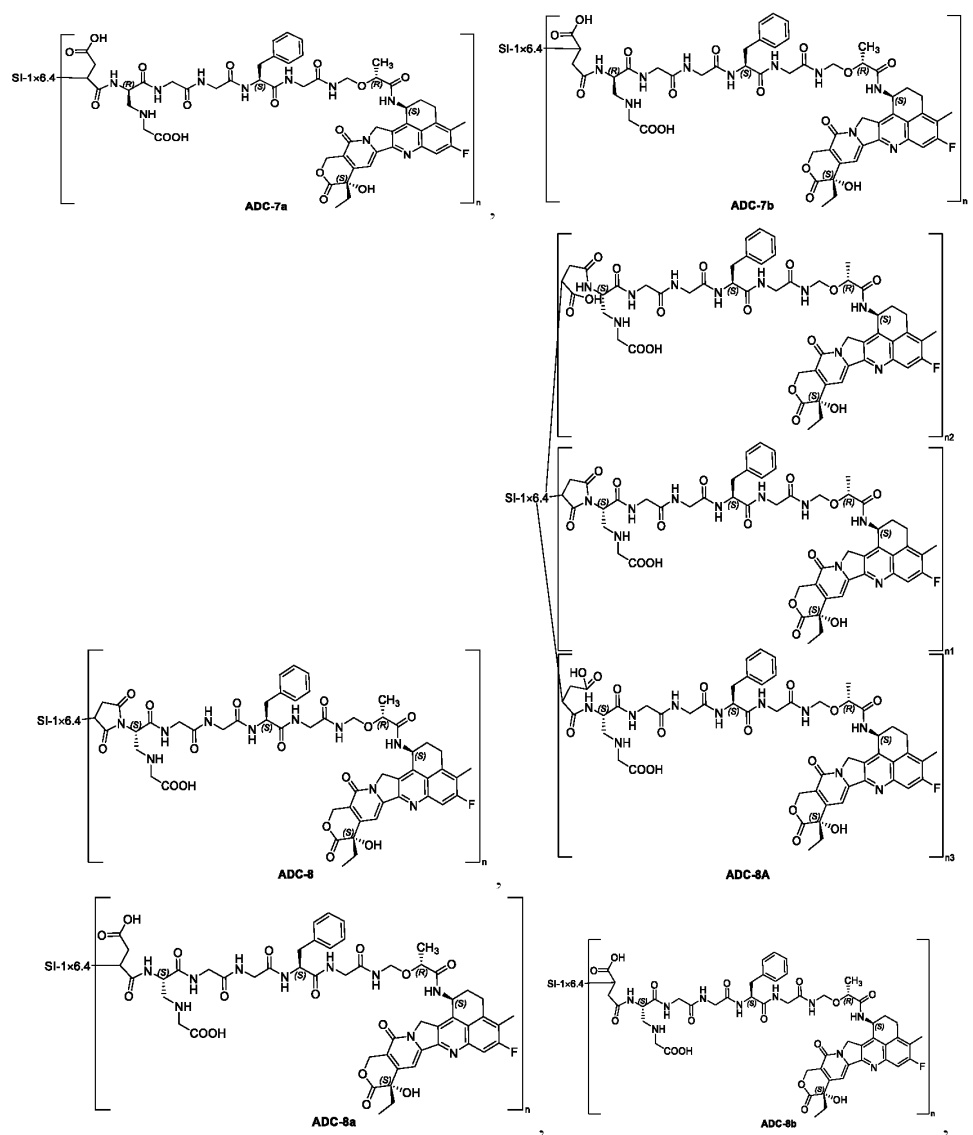


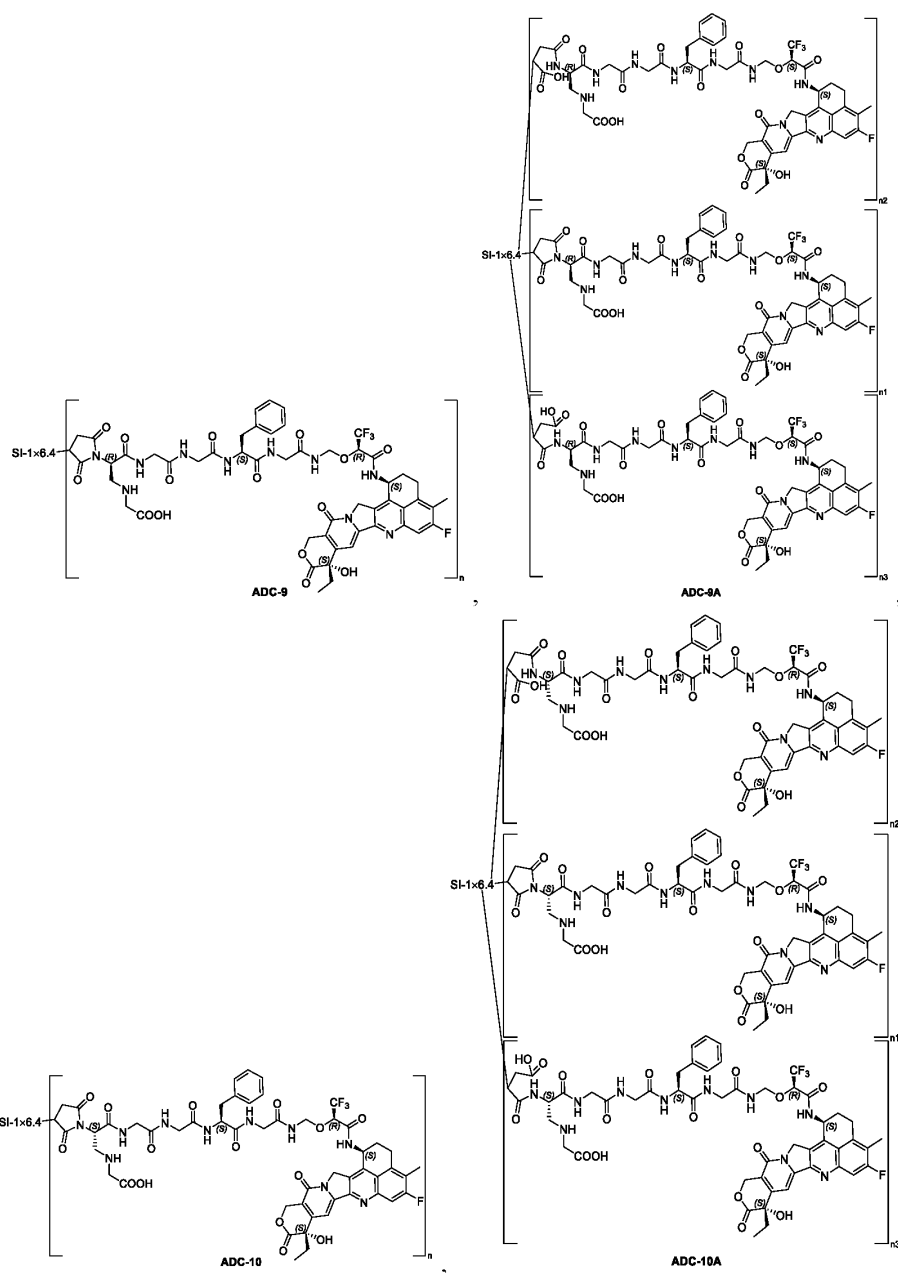


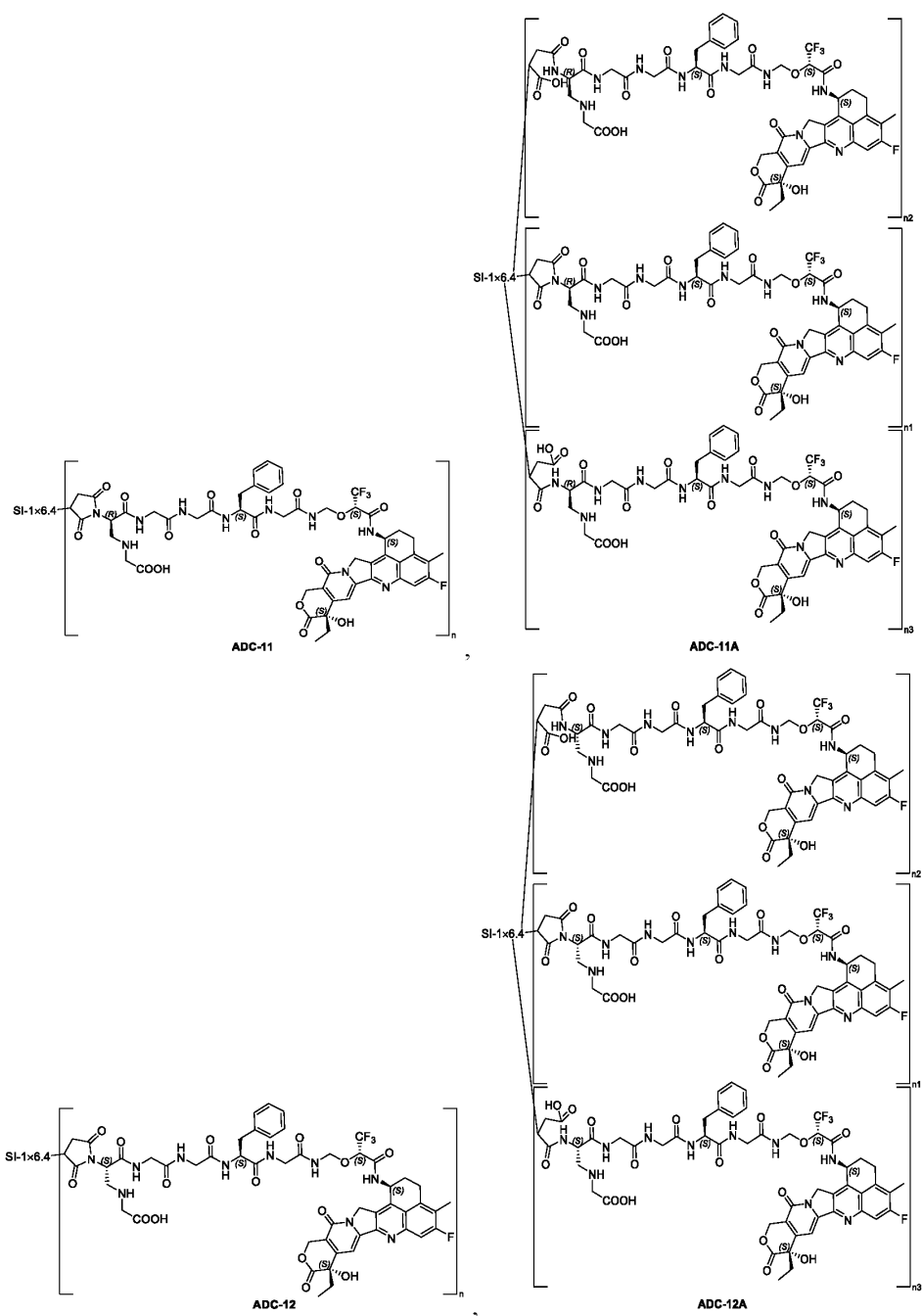


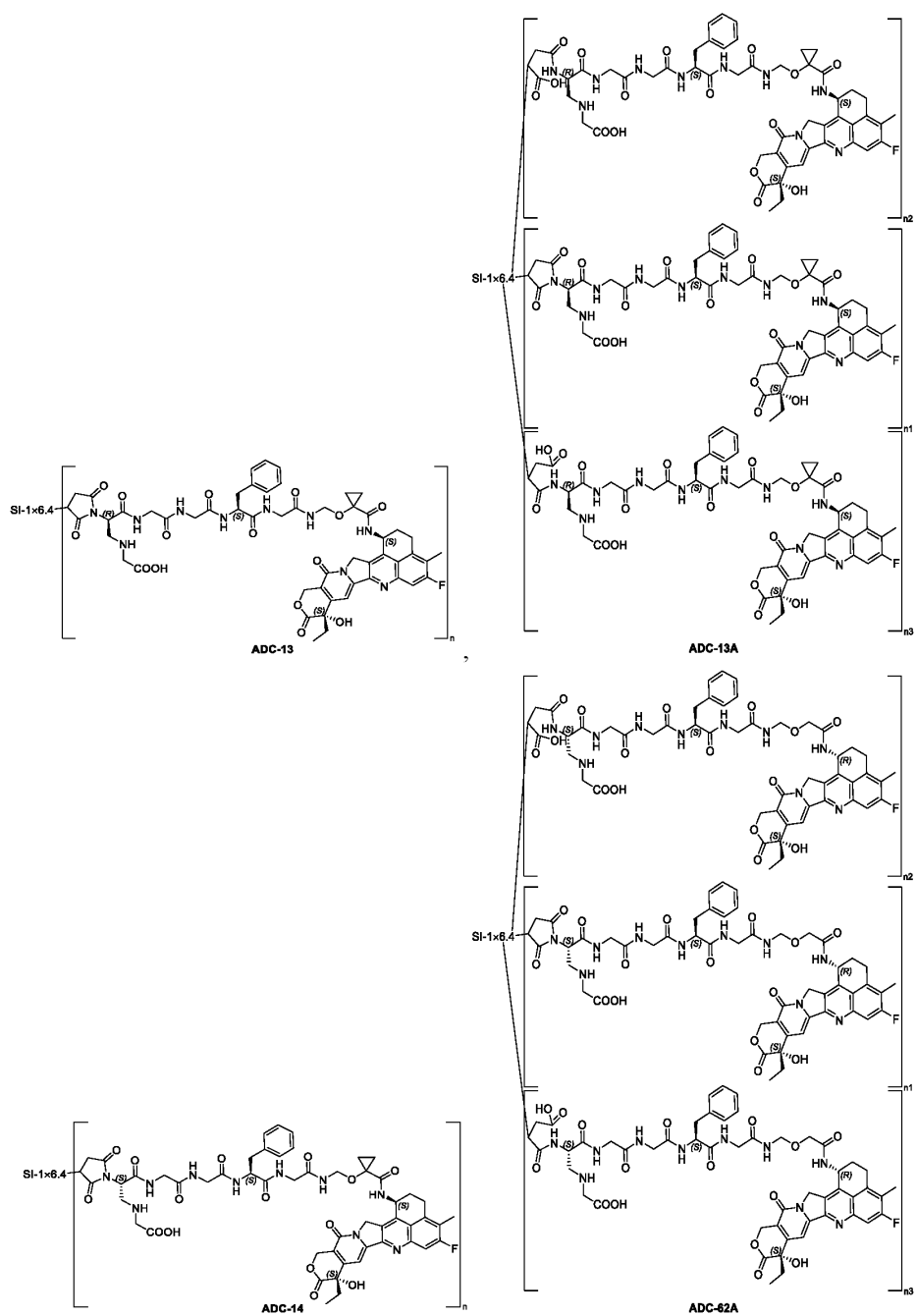


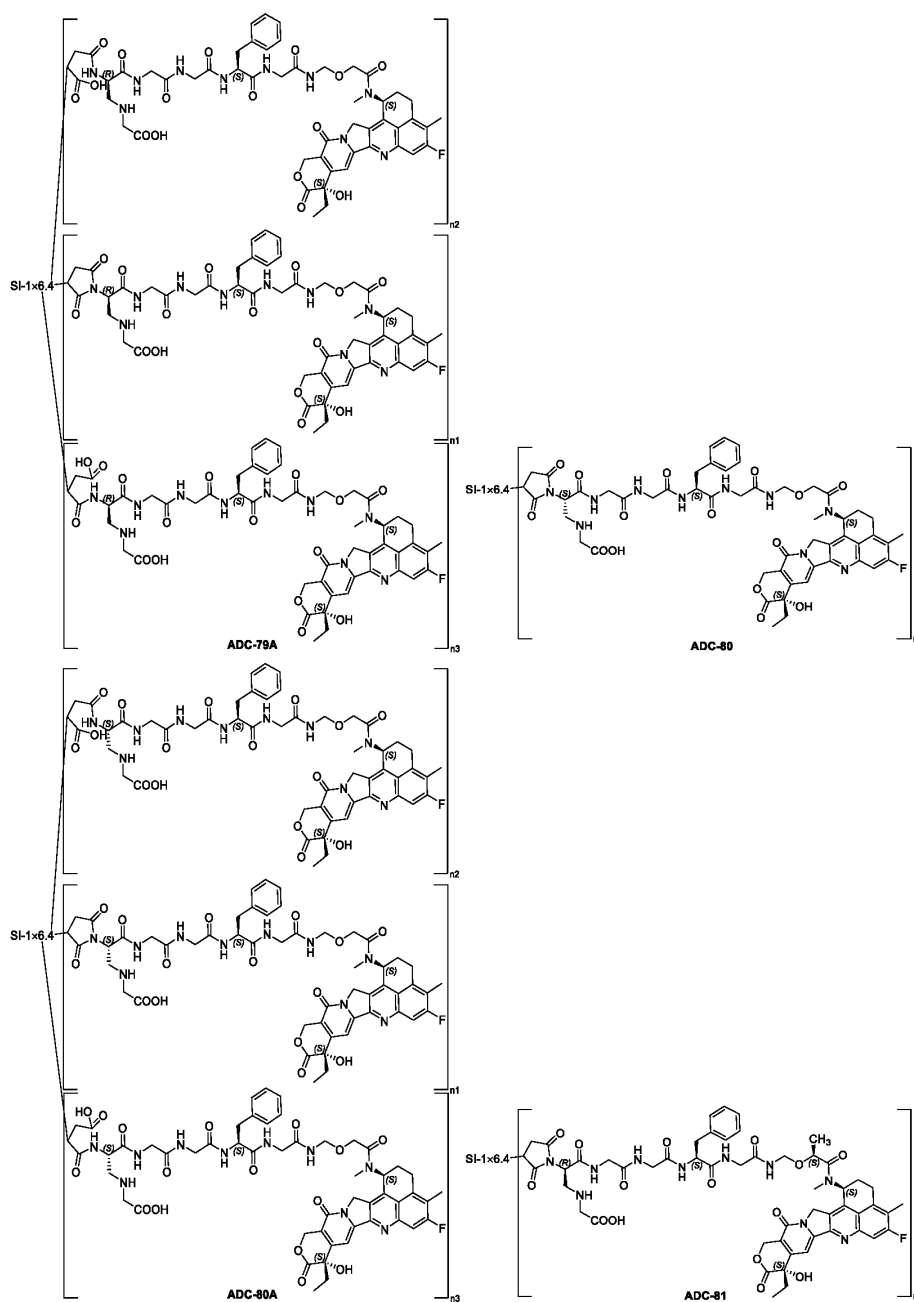


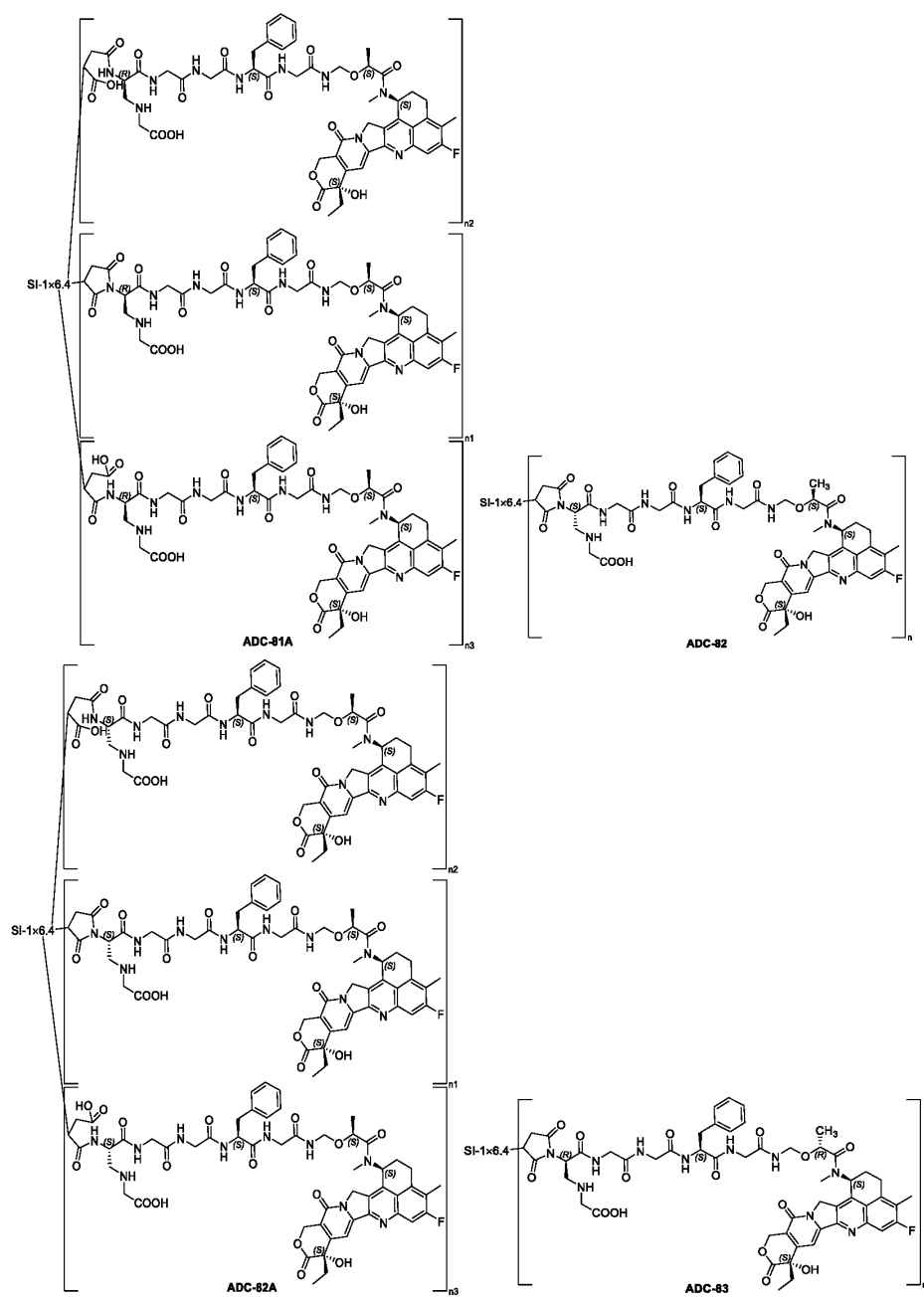


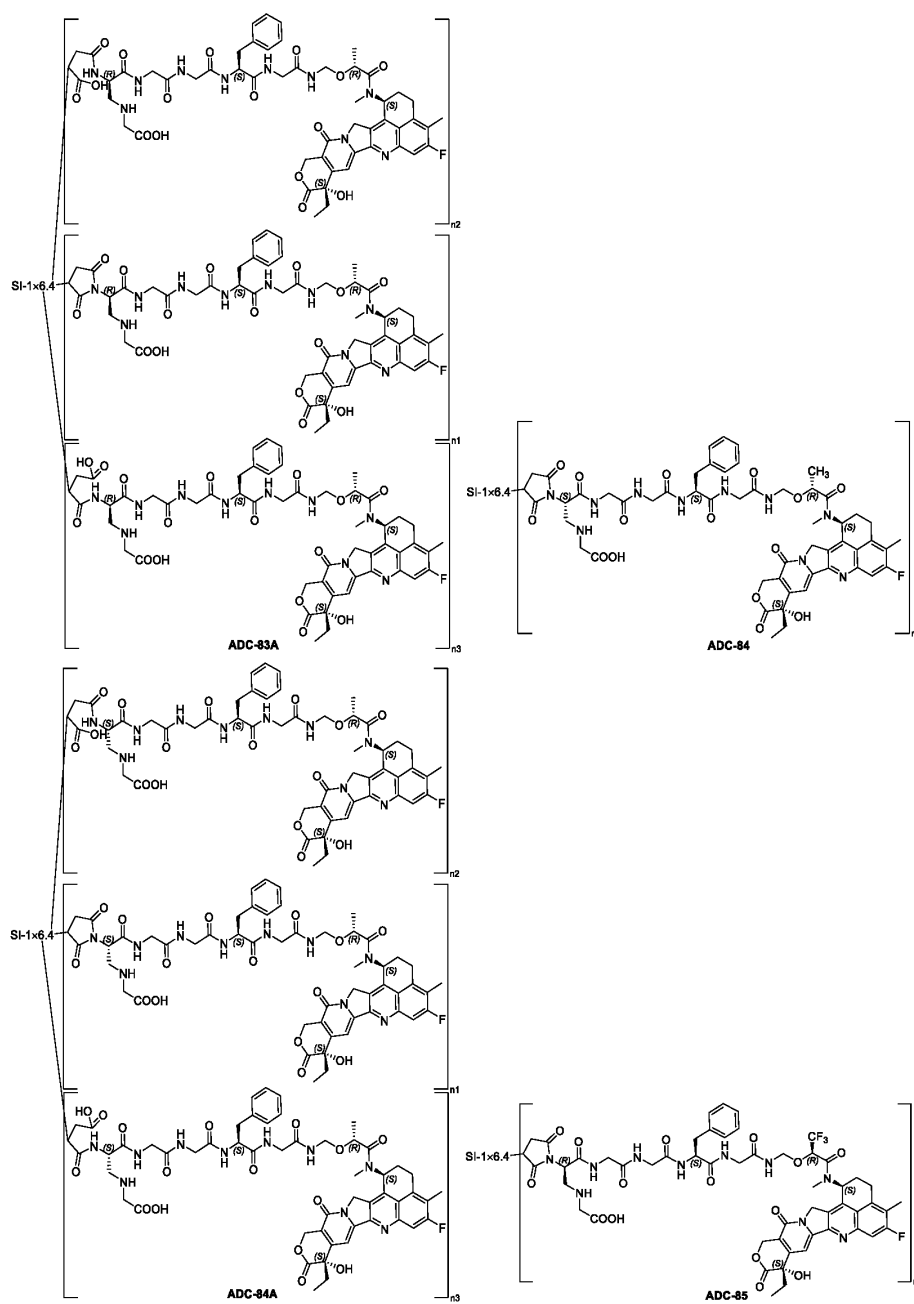


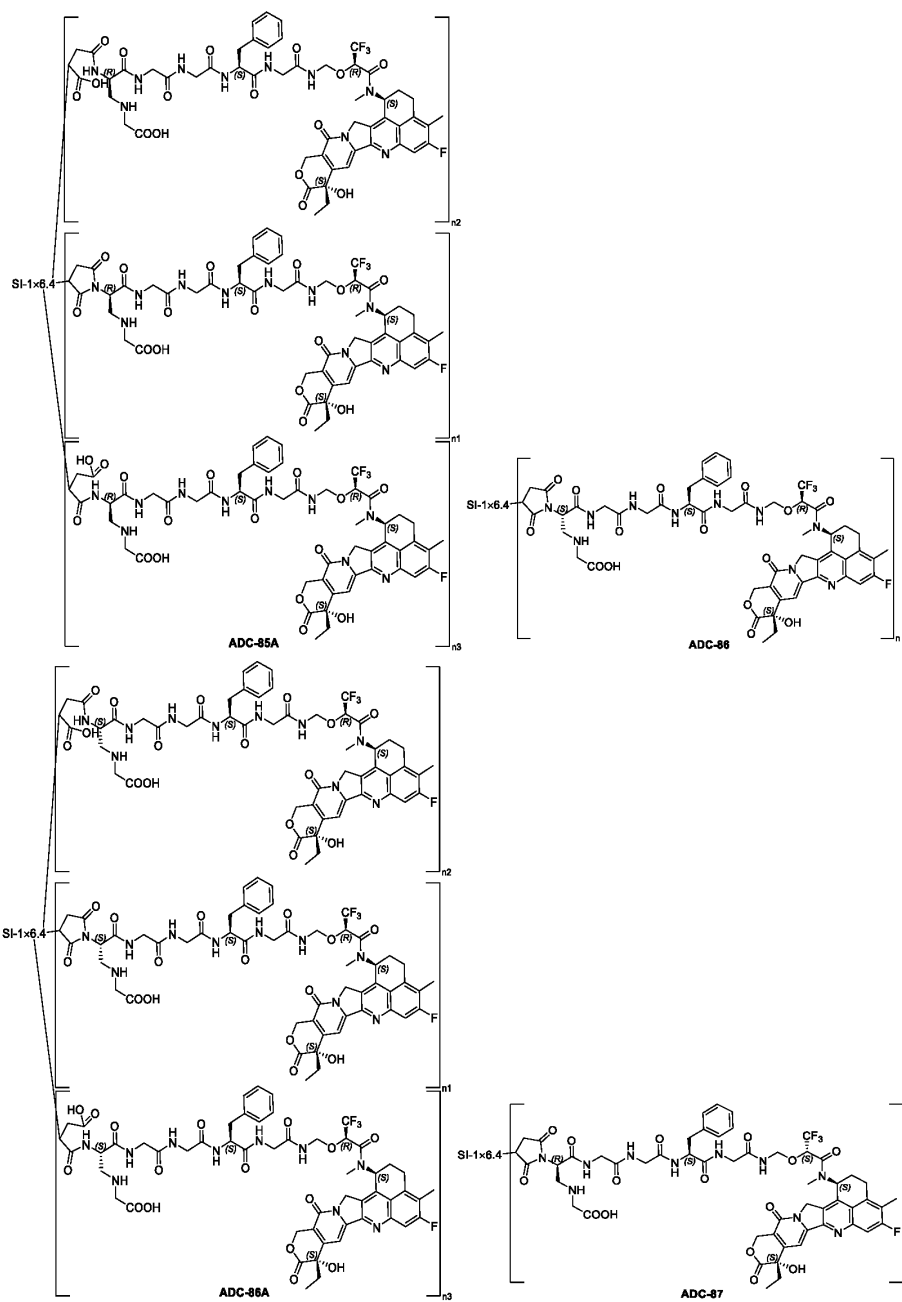


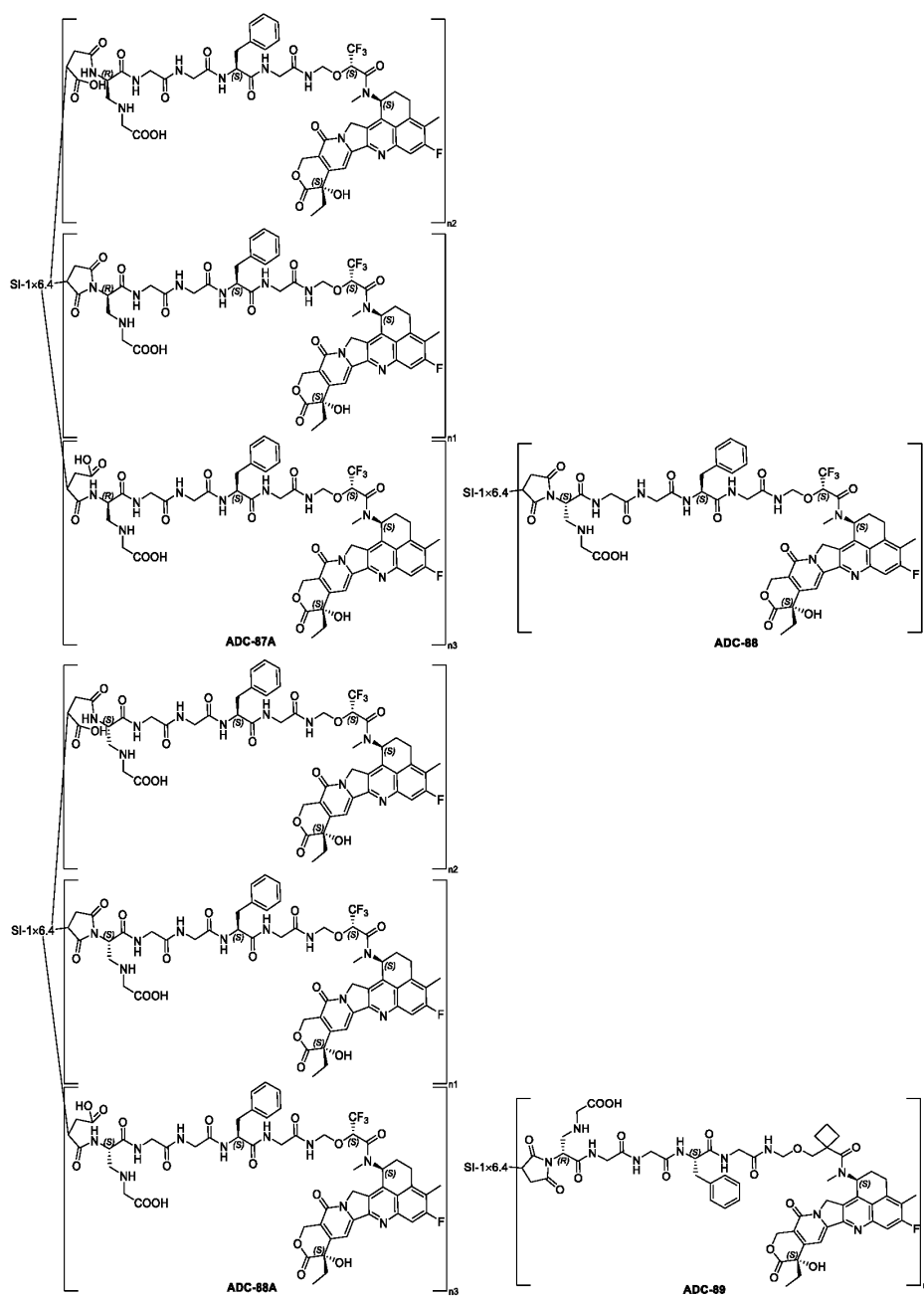


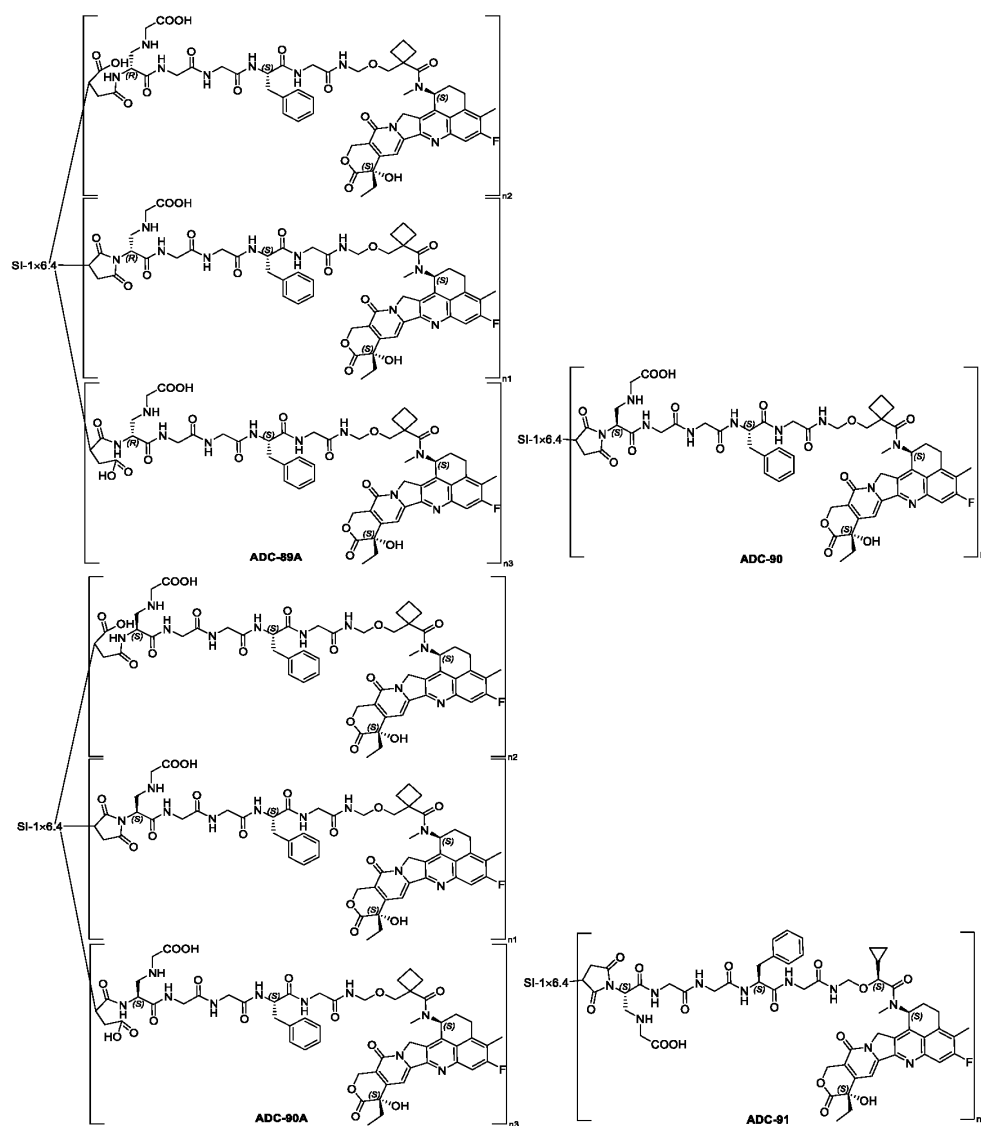


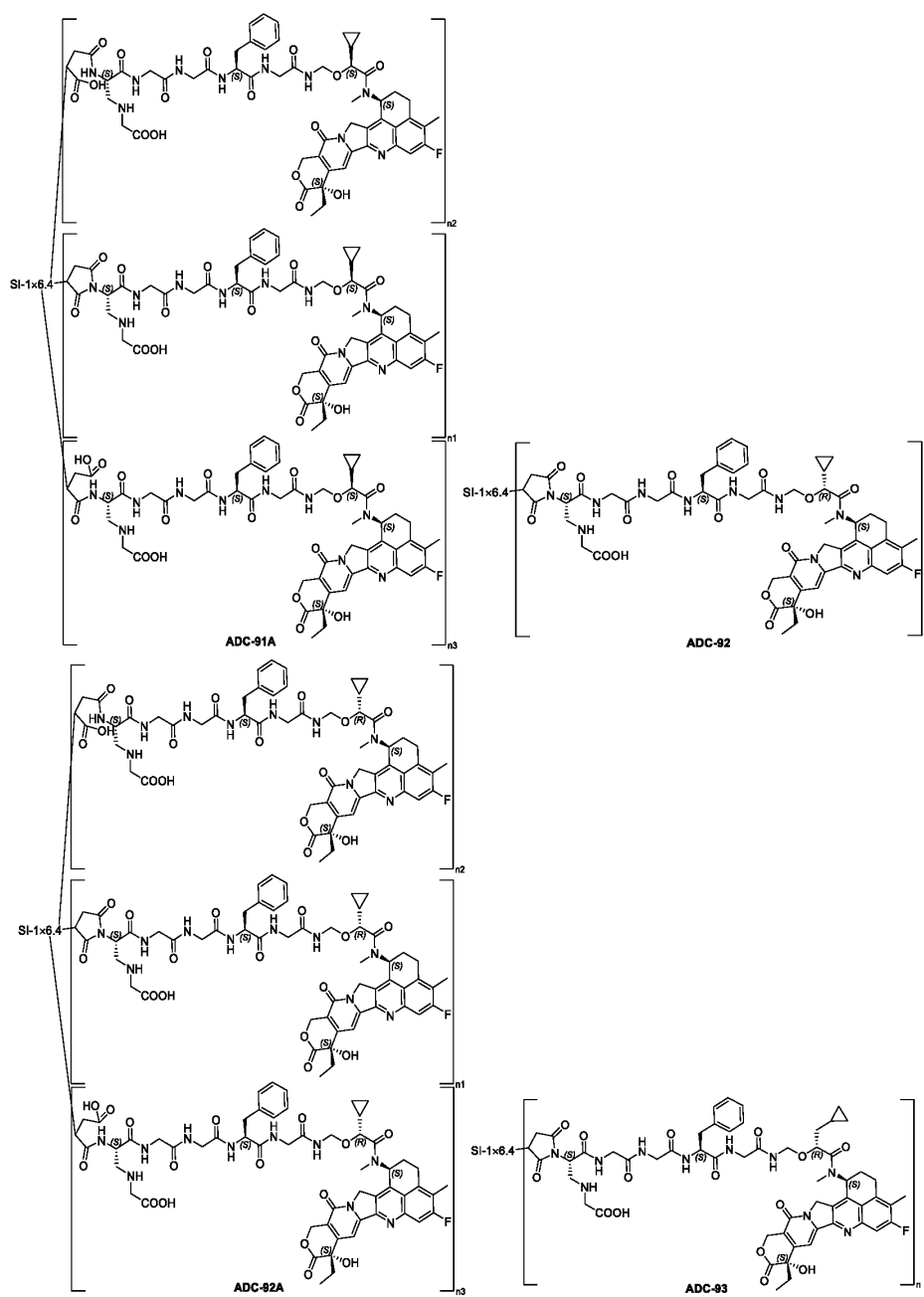


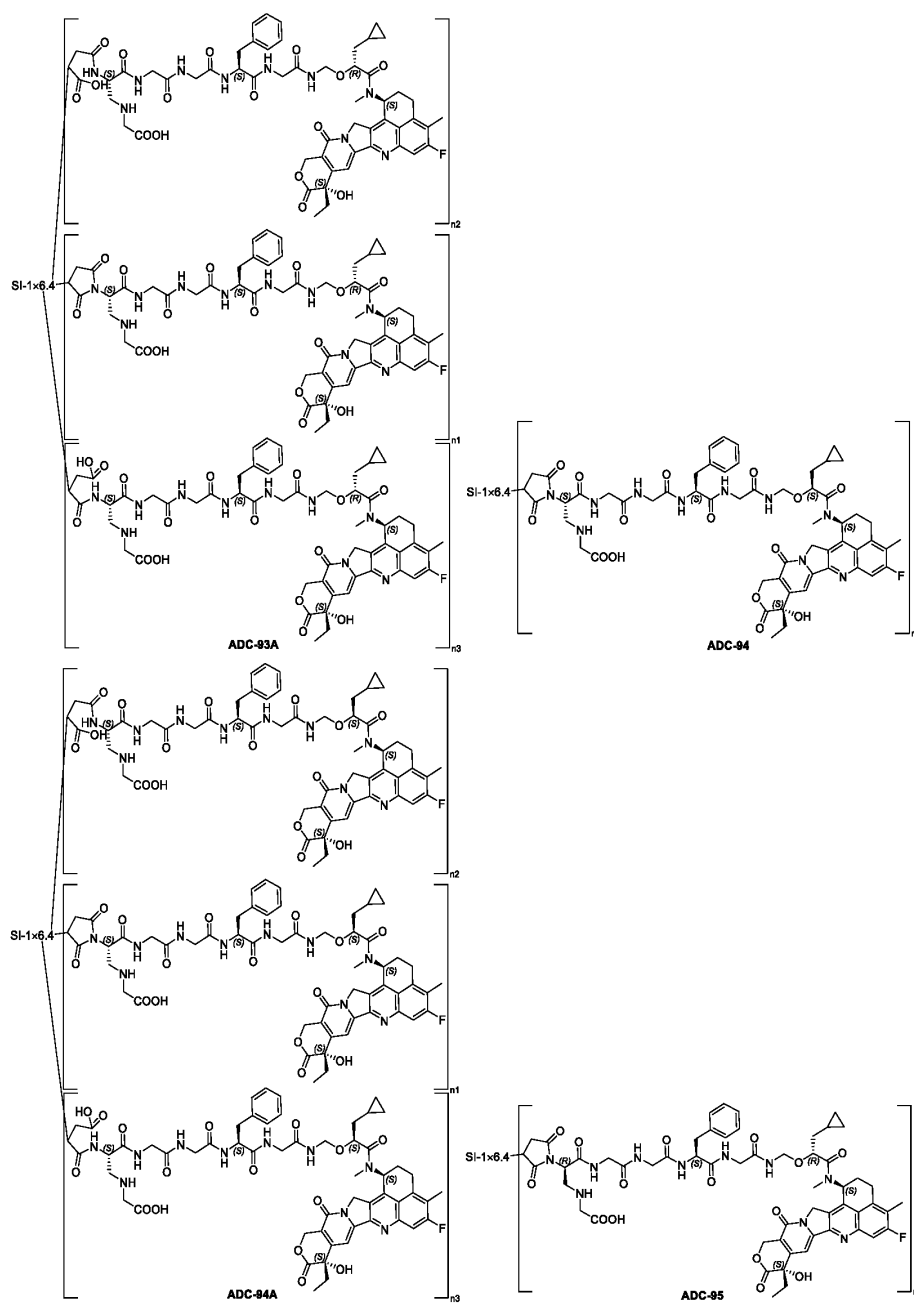


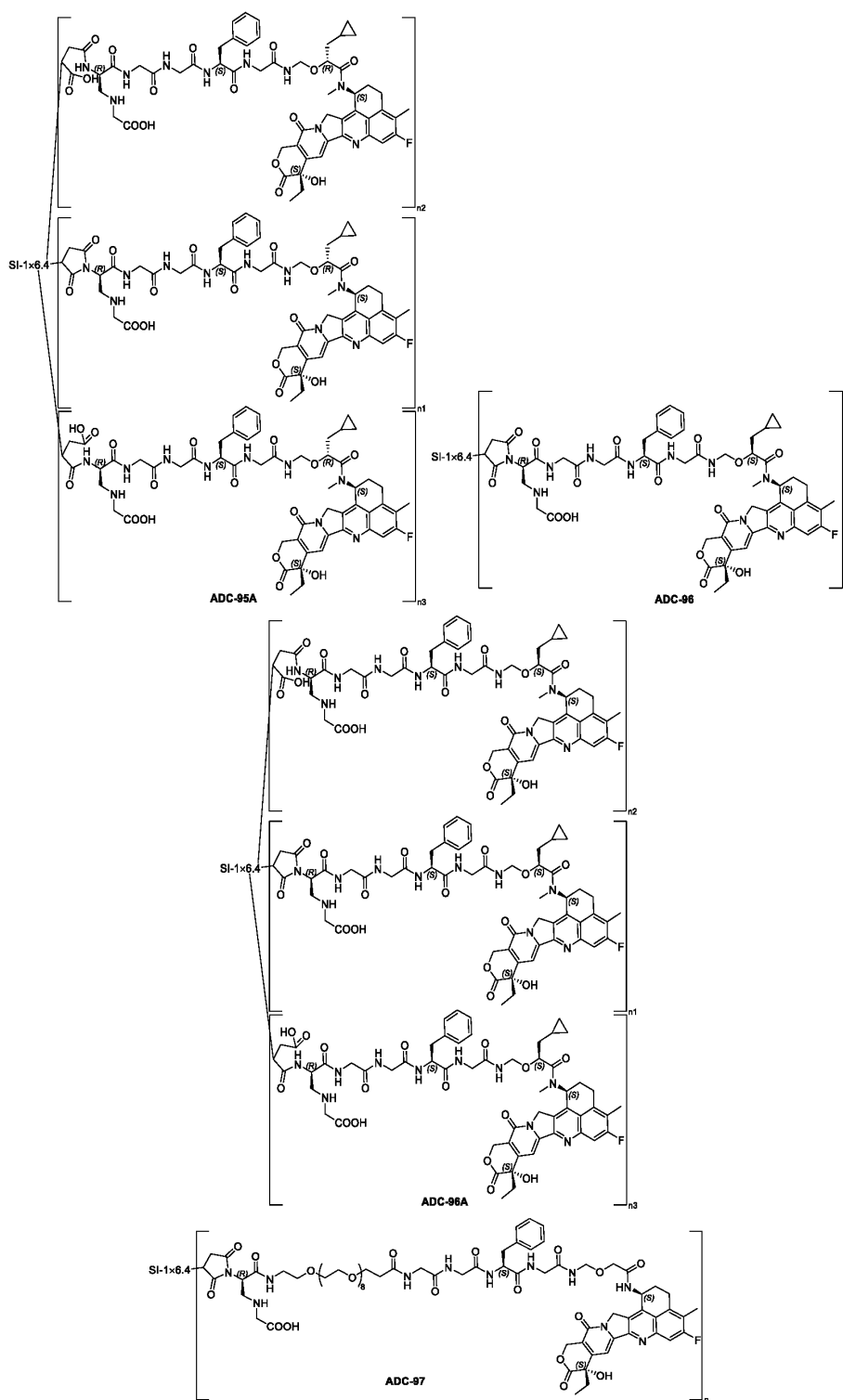


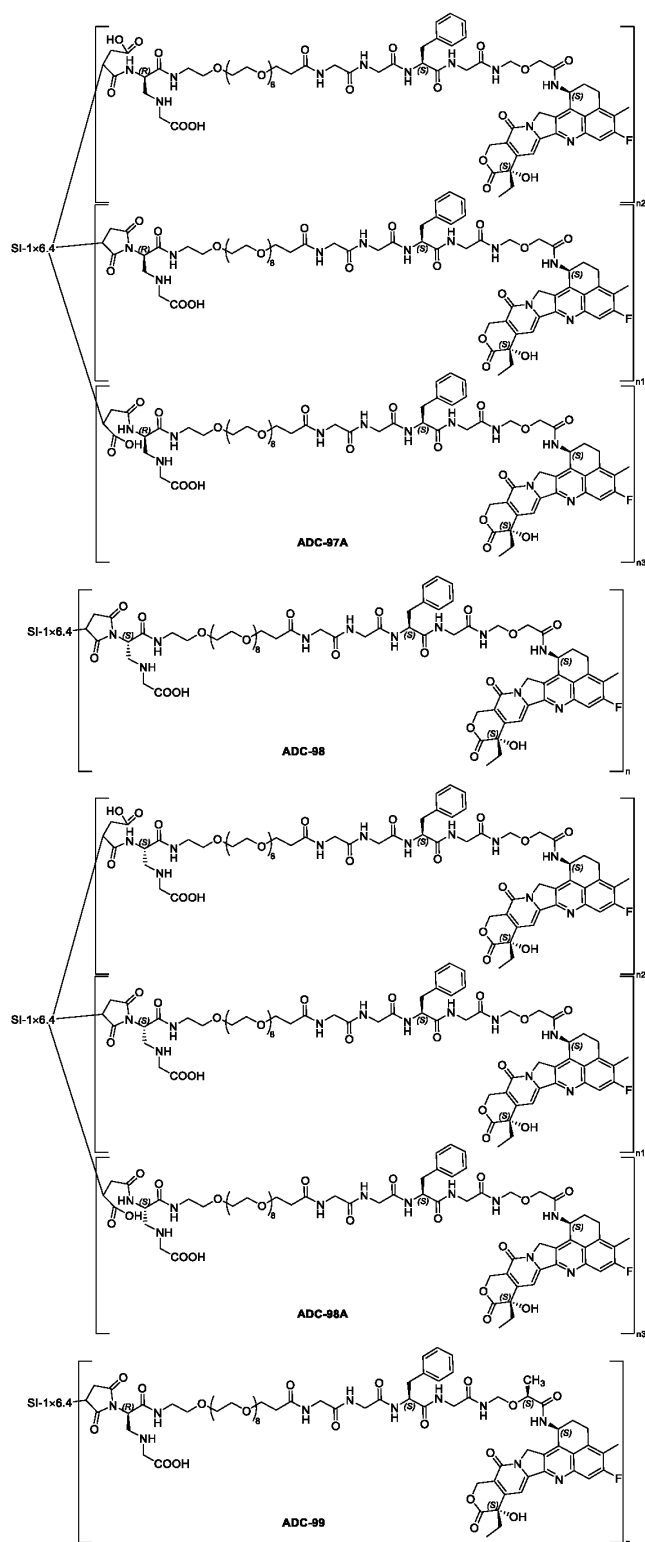


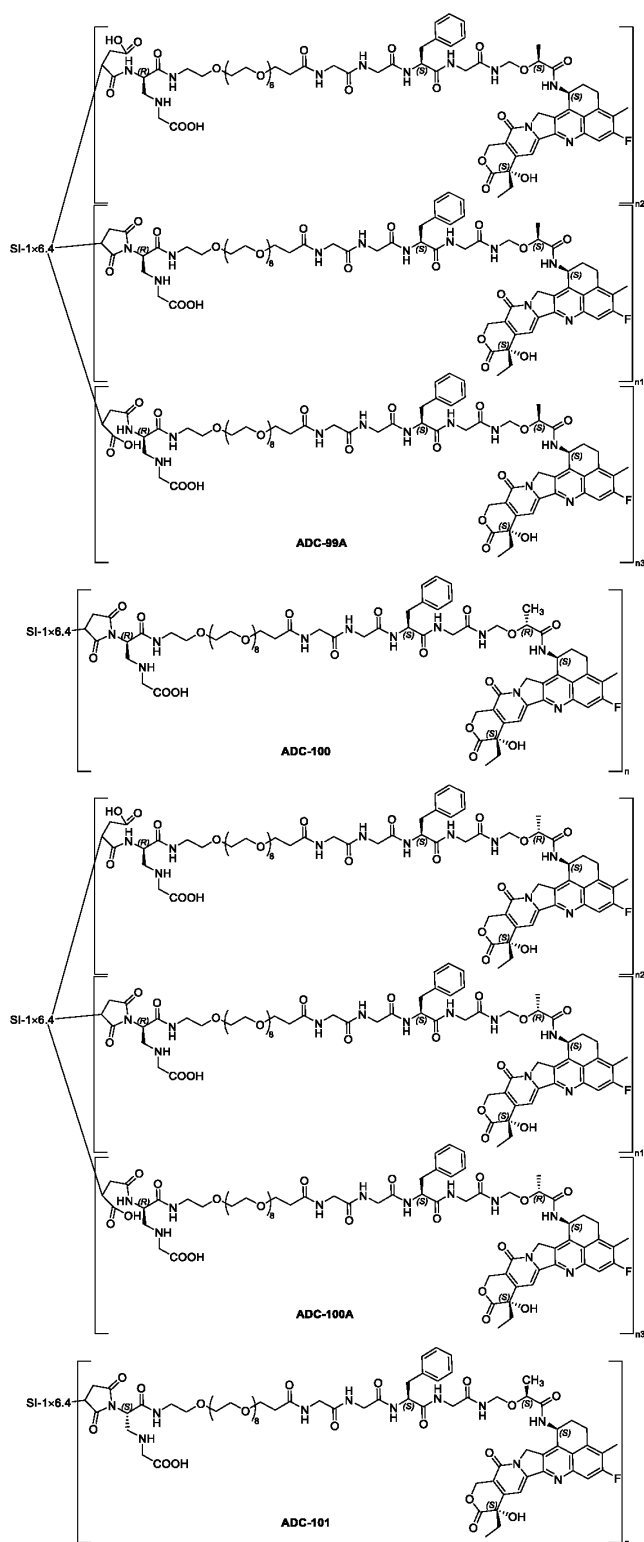


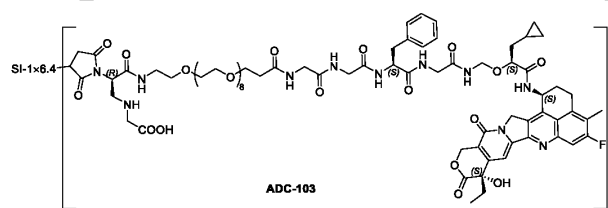
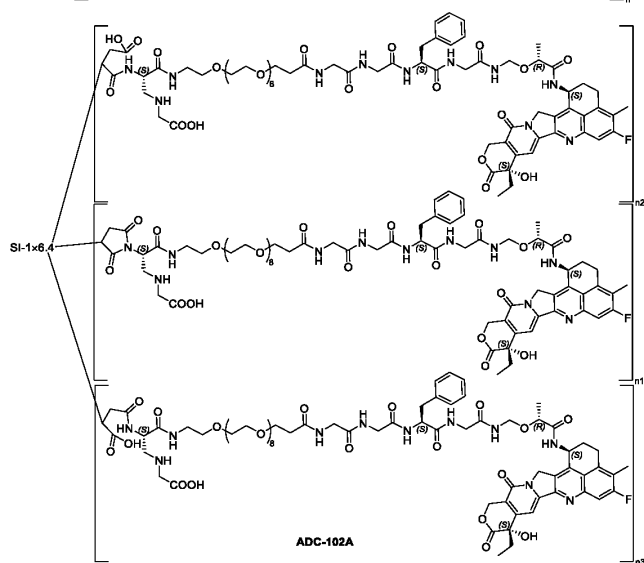
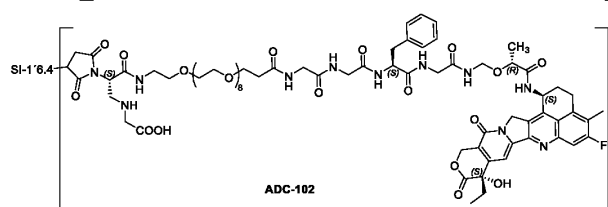
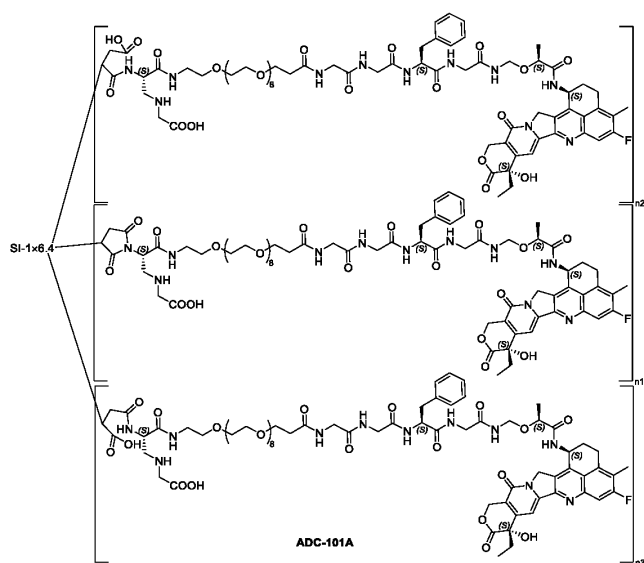


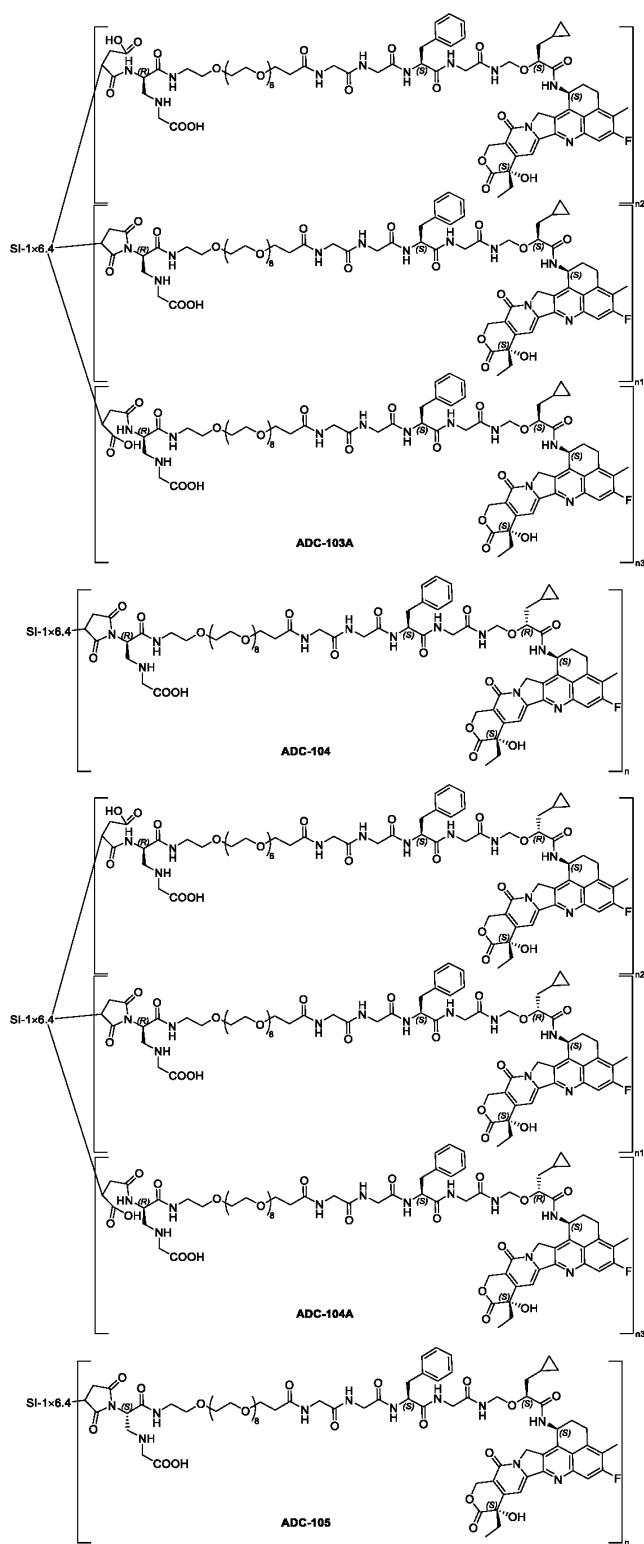


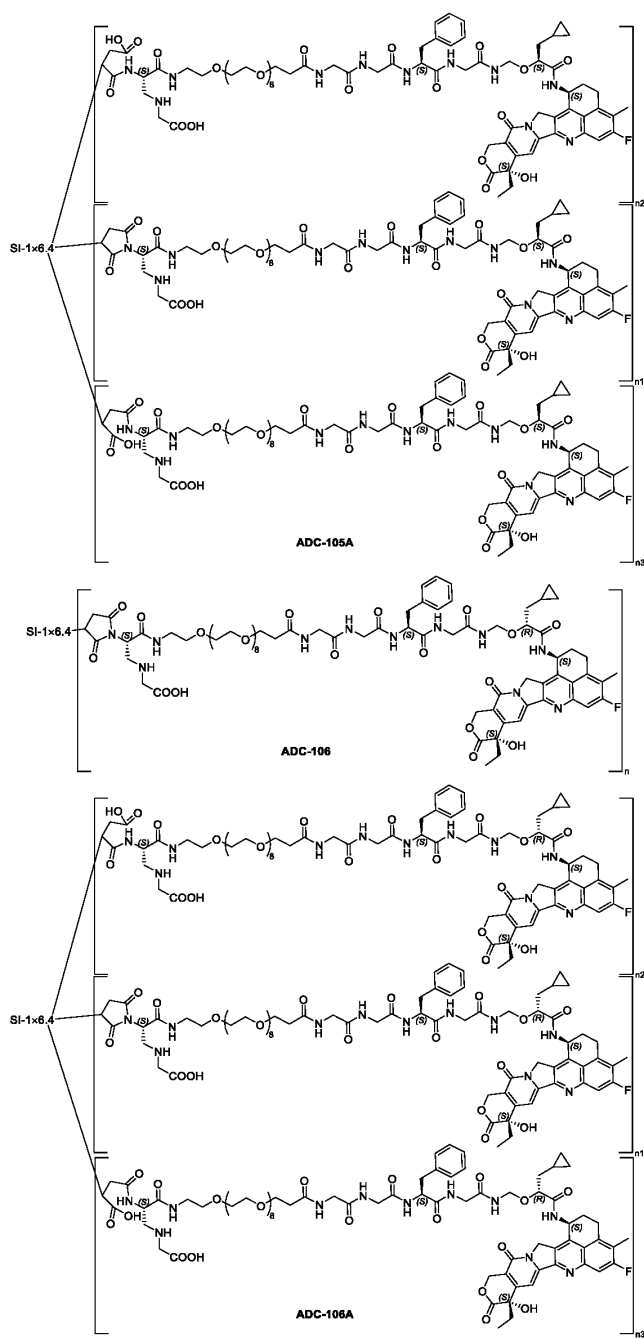


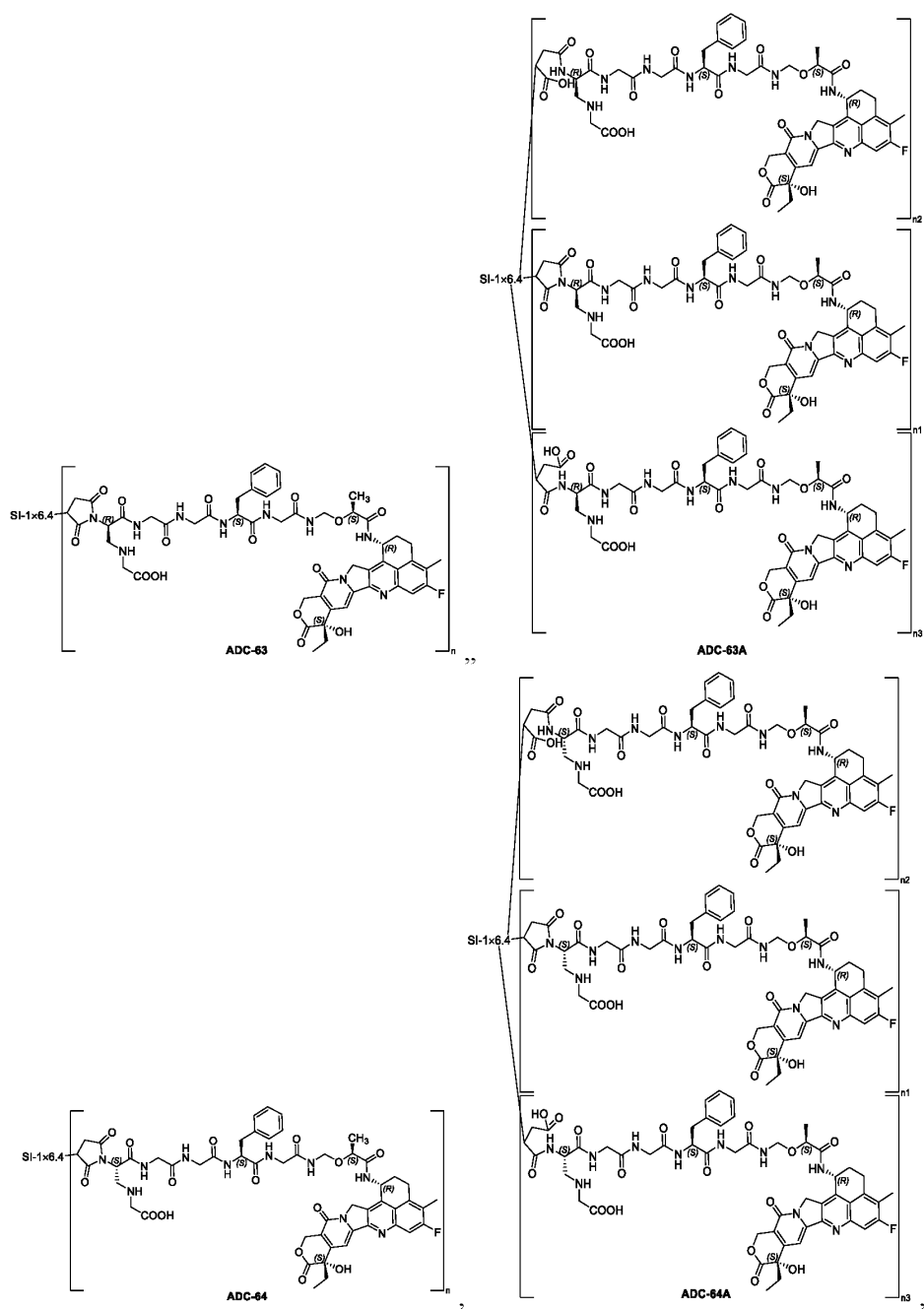


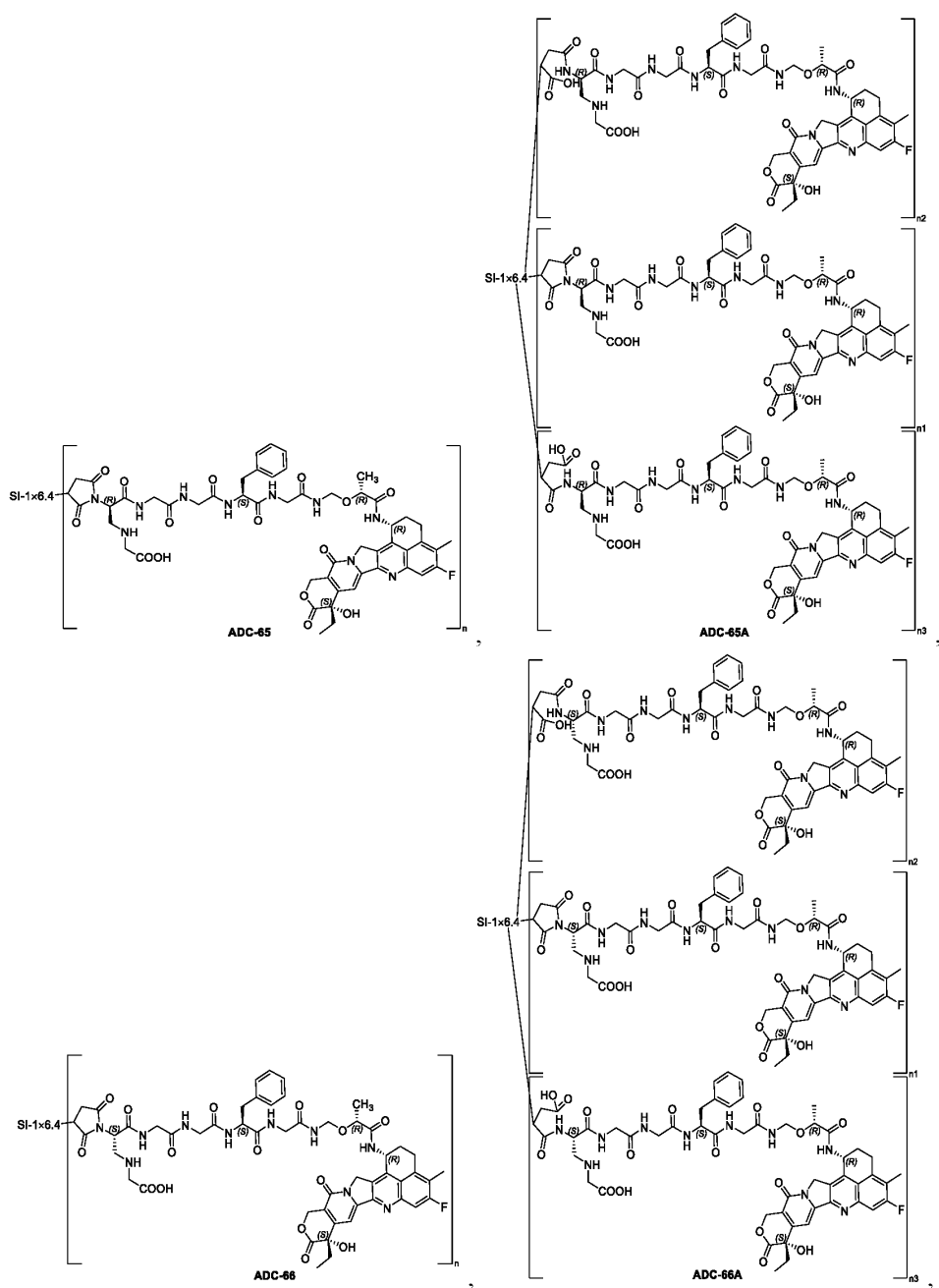


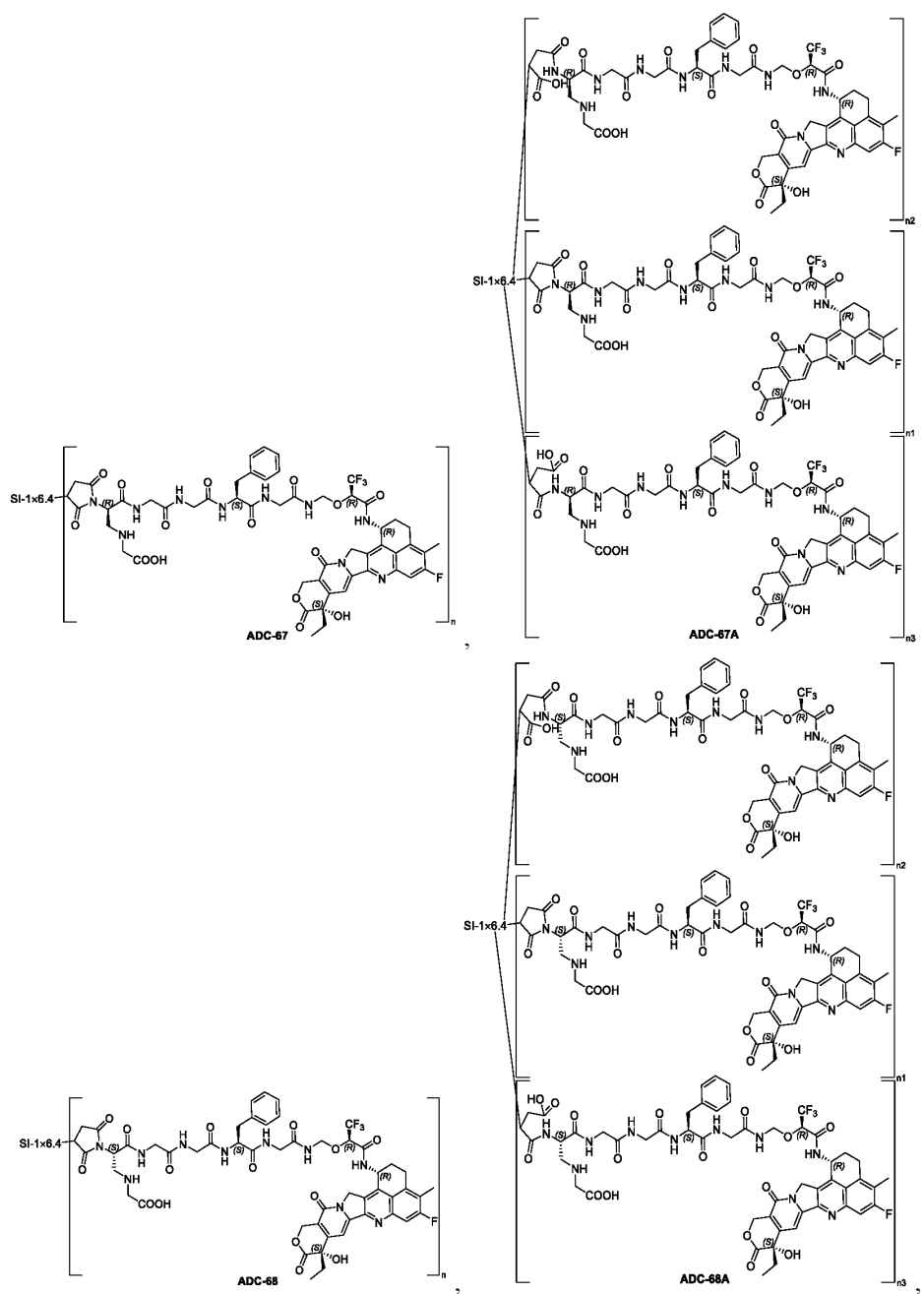


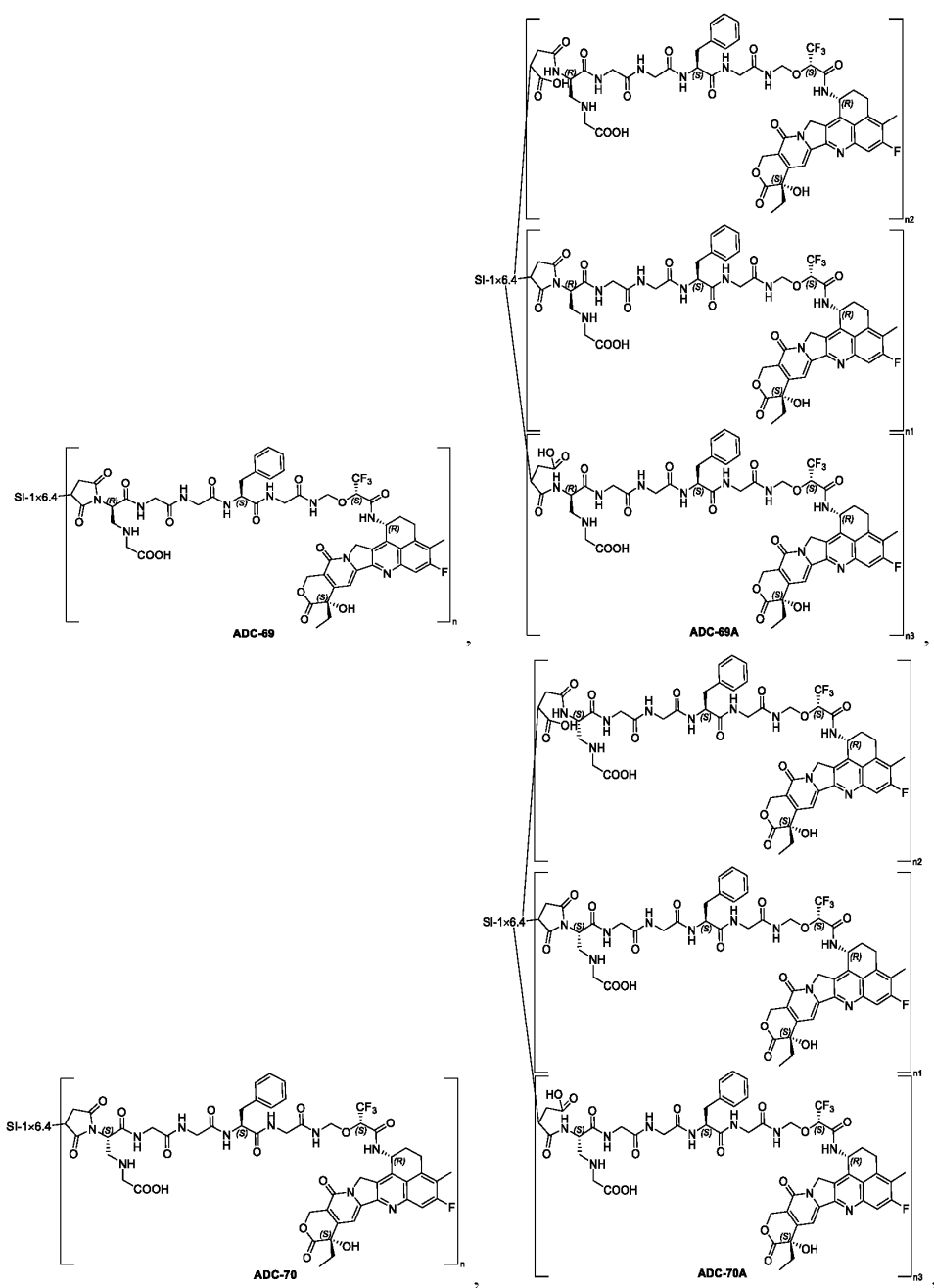


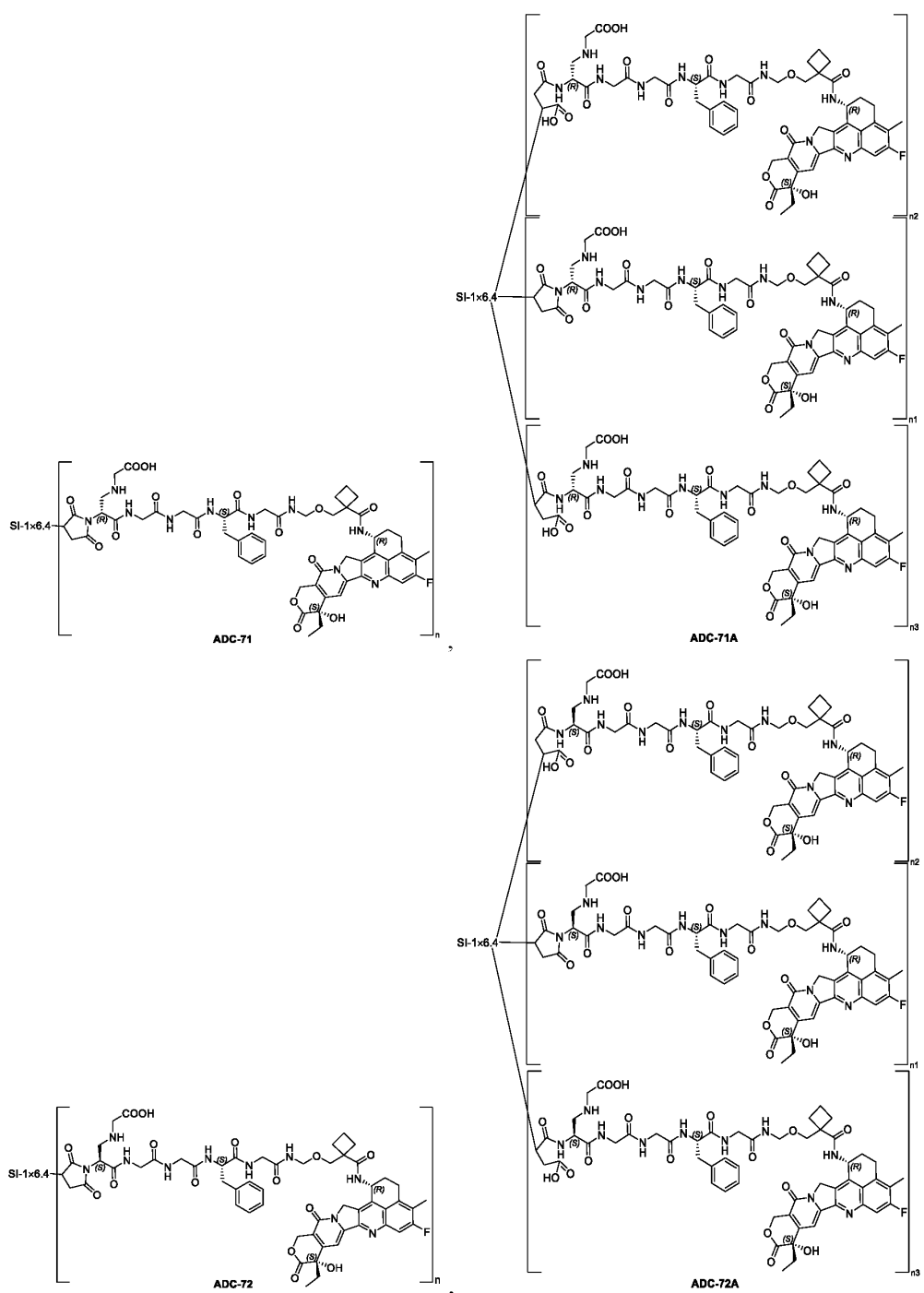


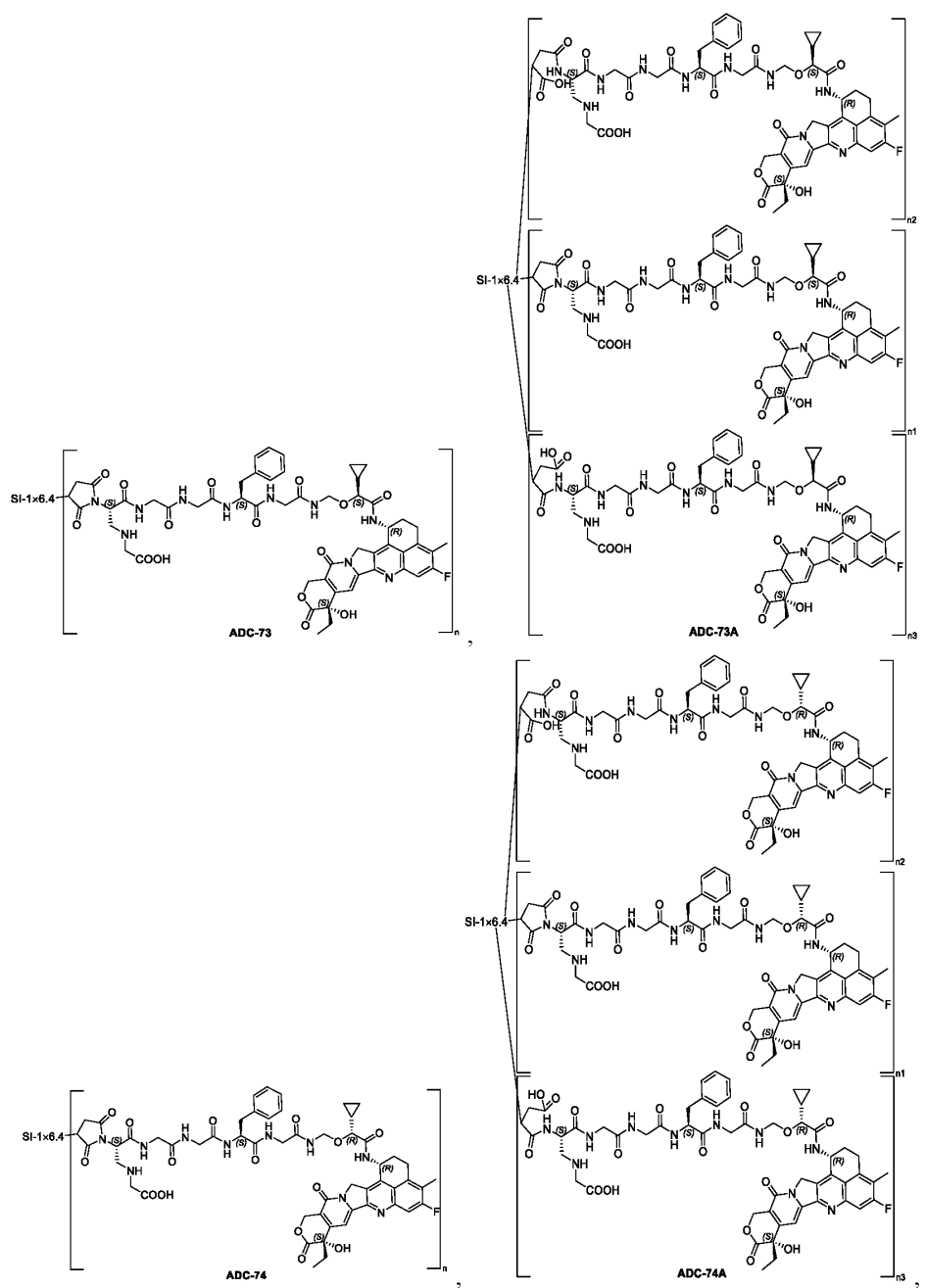


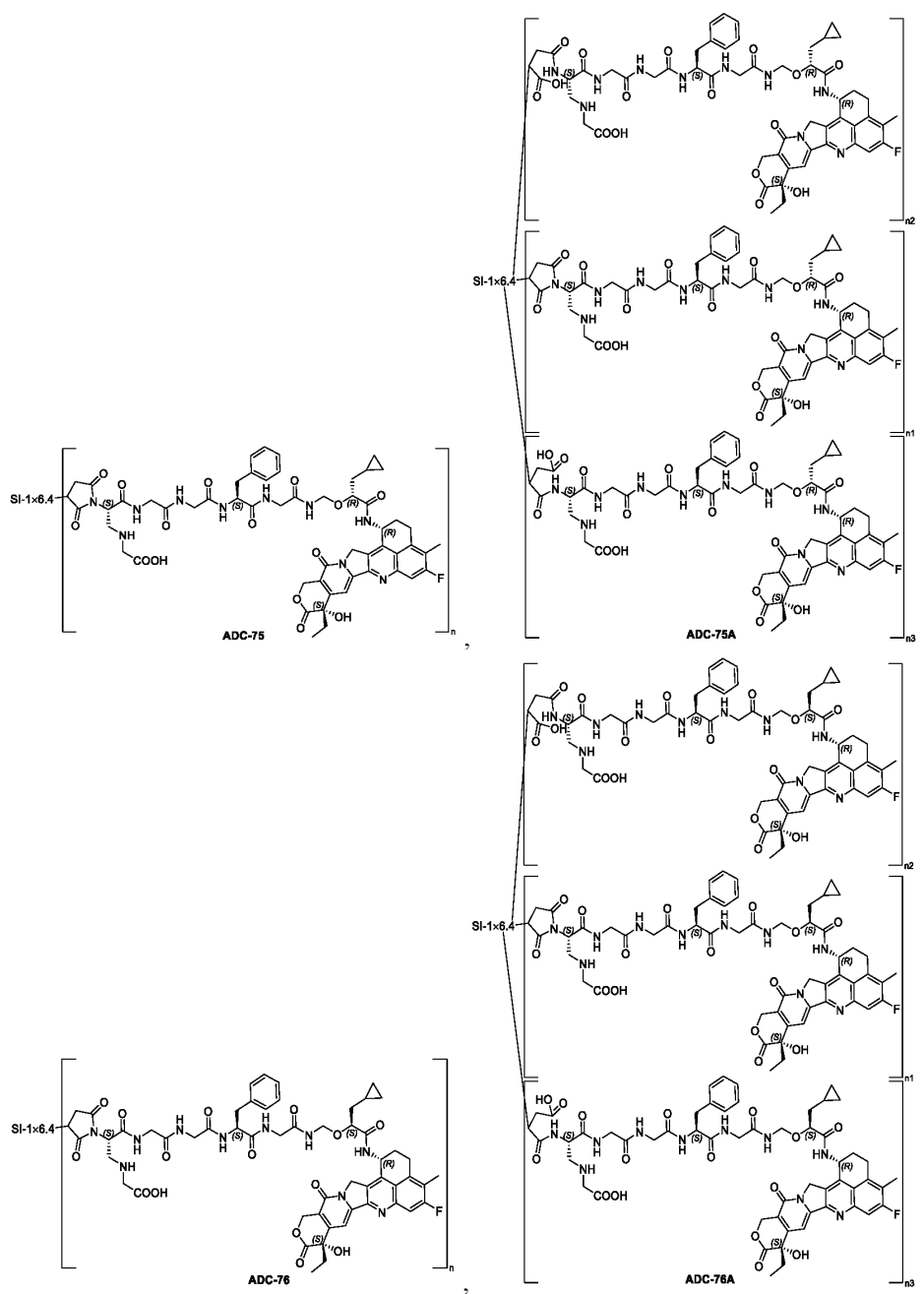


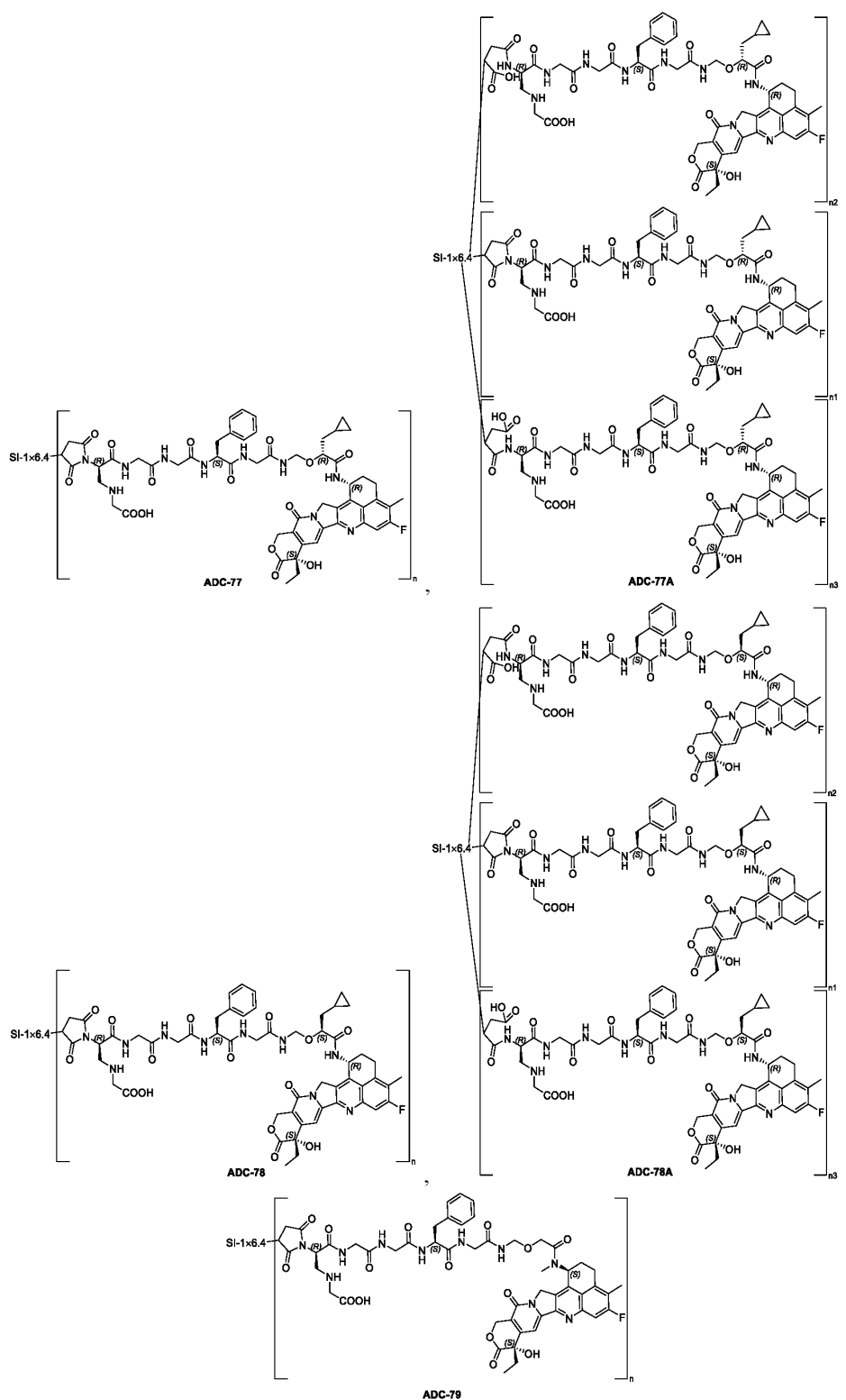












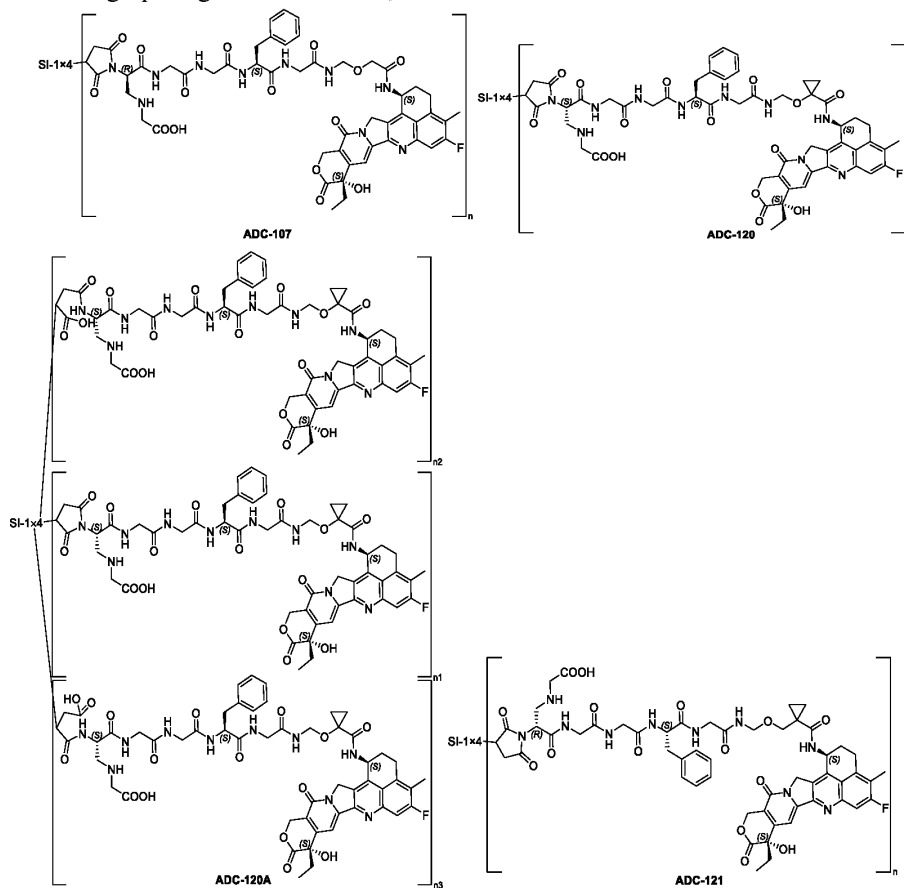
wherein:

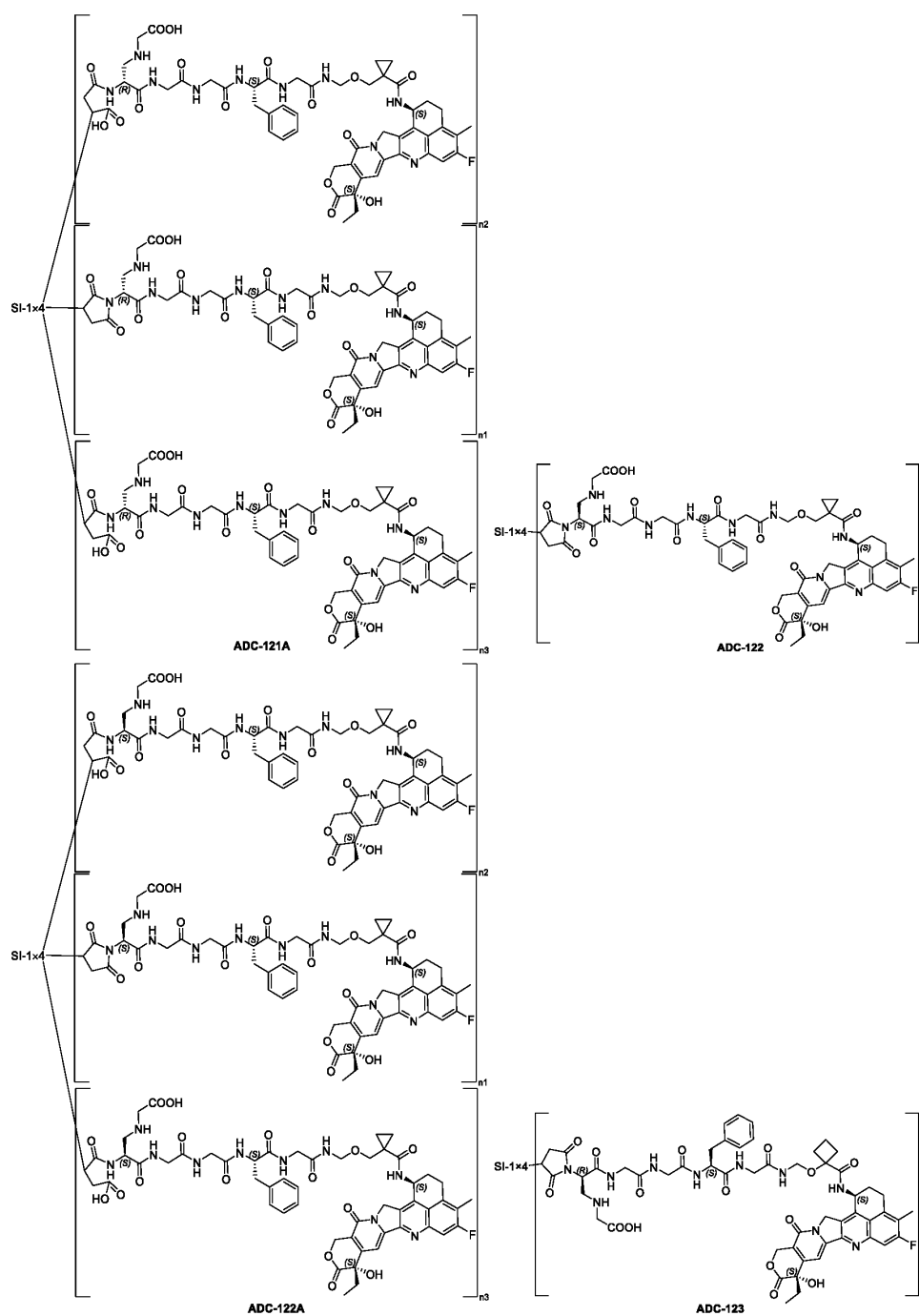
SI-1 x 6.4 is a bispecific antibody or antigen-binding fragment thereof having a binding affinity

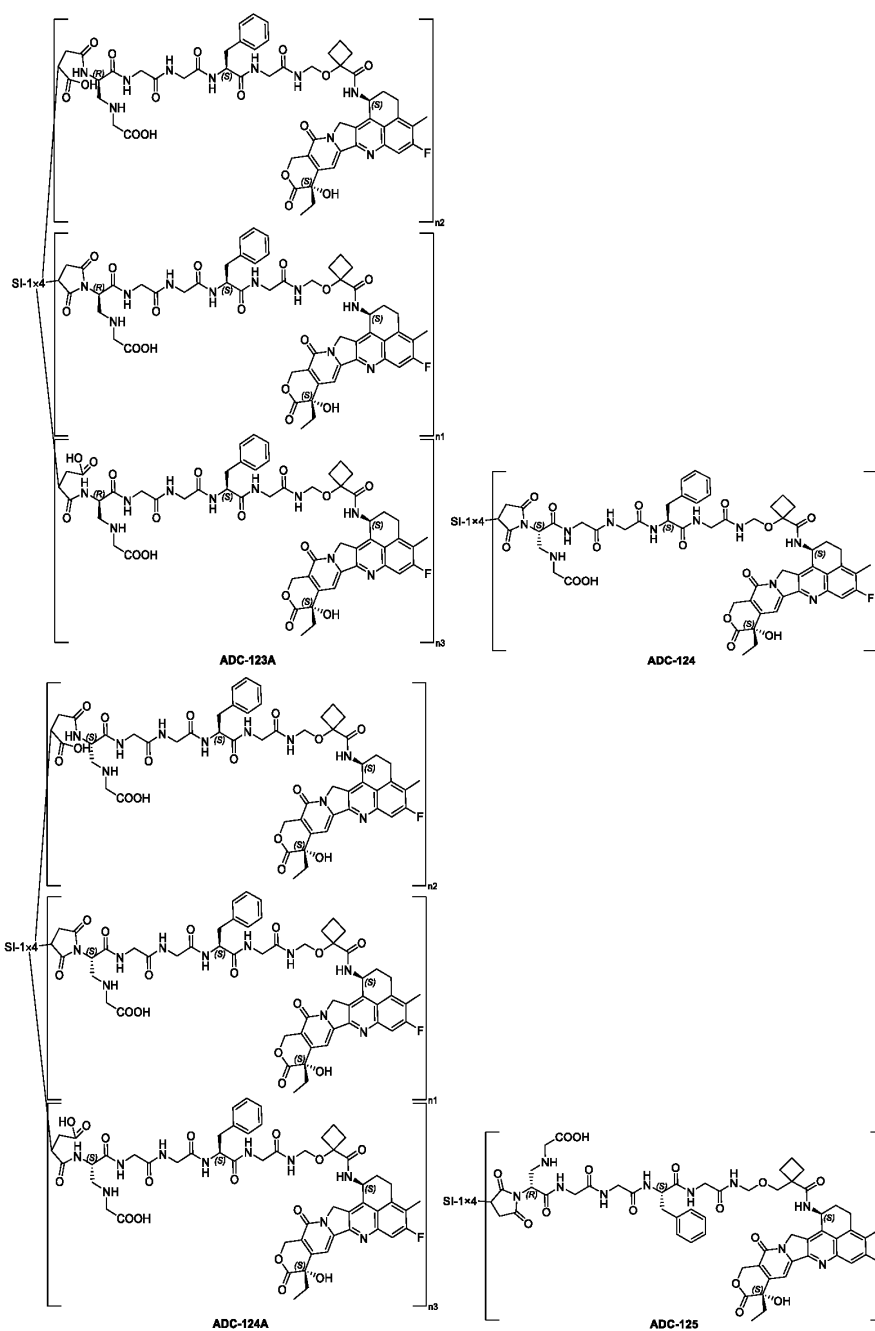
to EGFR and HER3,

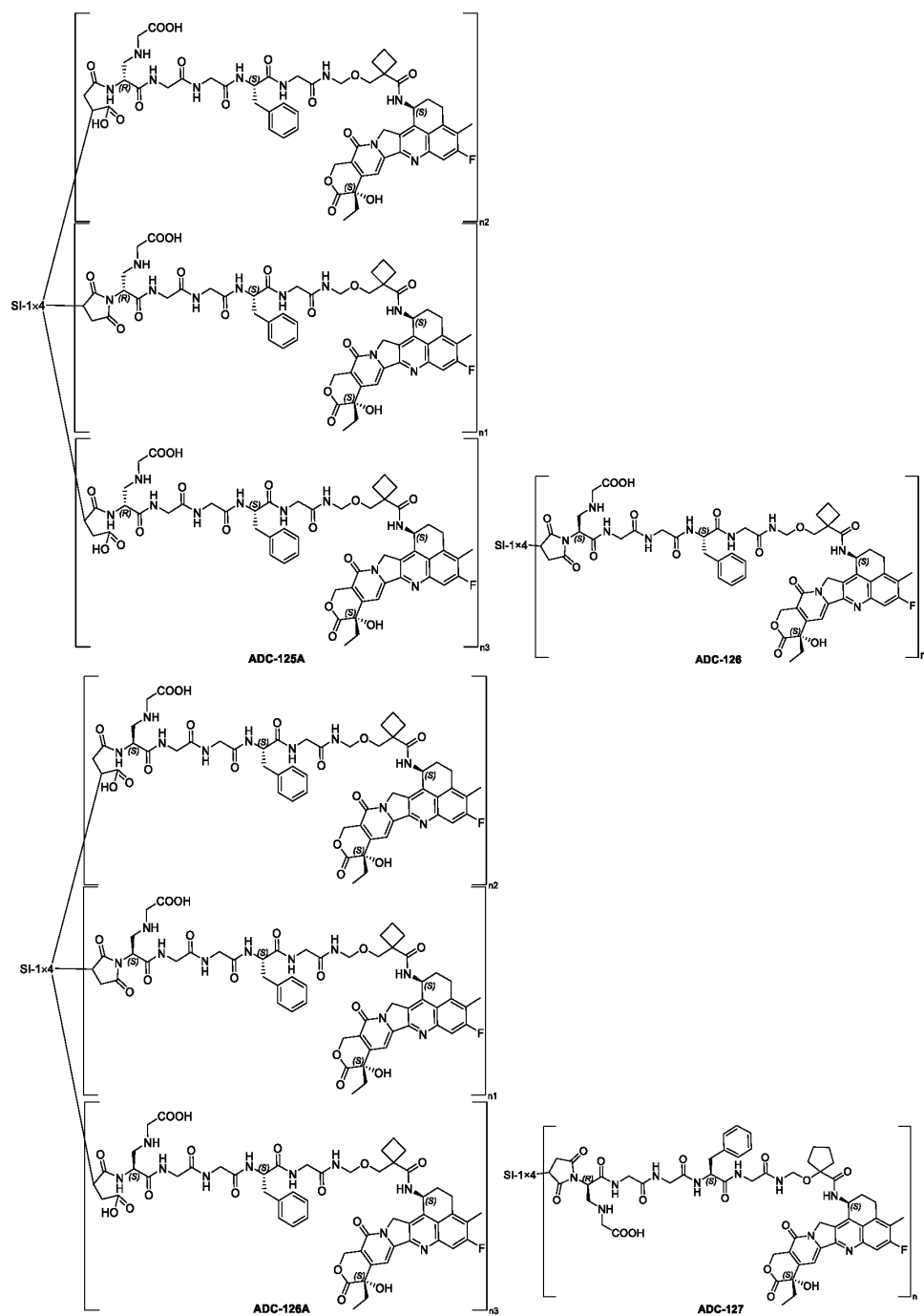
n is an integer of 1-10, n1, wherein n2, and n3 are each independently chosen from any integer or any decimal number from 0-10, n1, n2, and n3 are not simultaneously 0, and $1 \leq n1 + n2 + n3 \leq 10$.

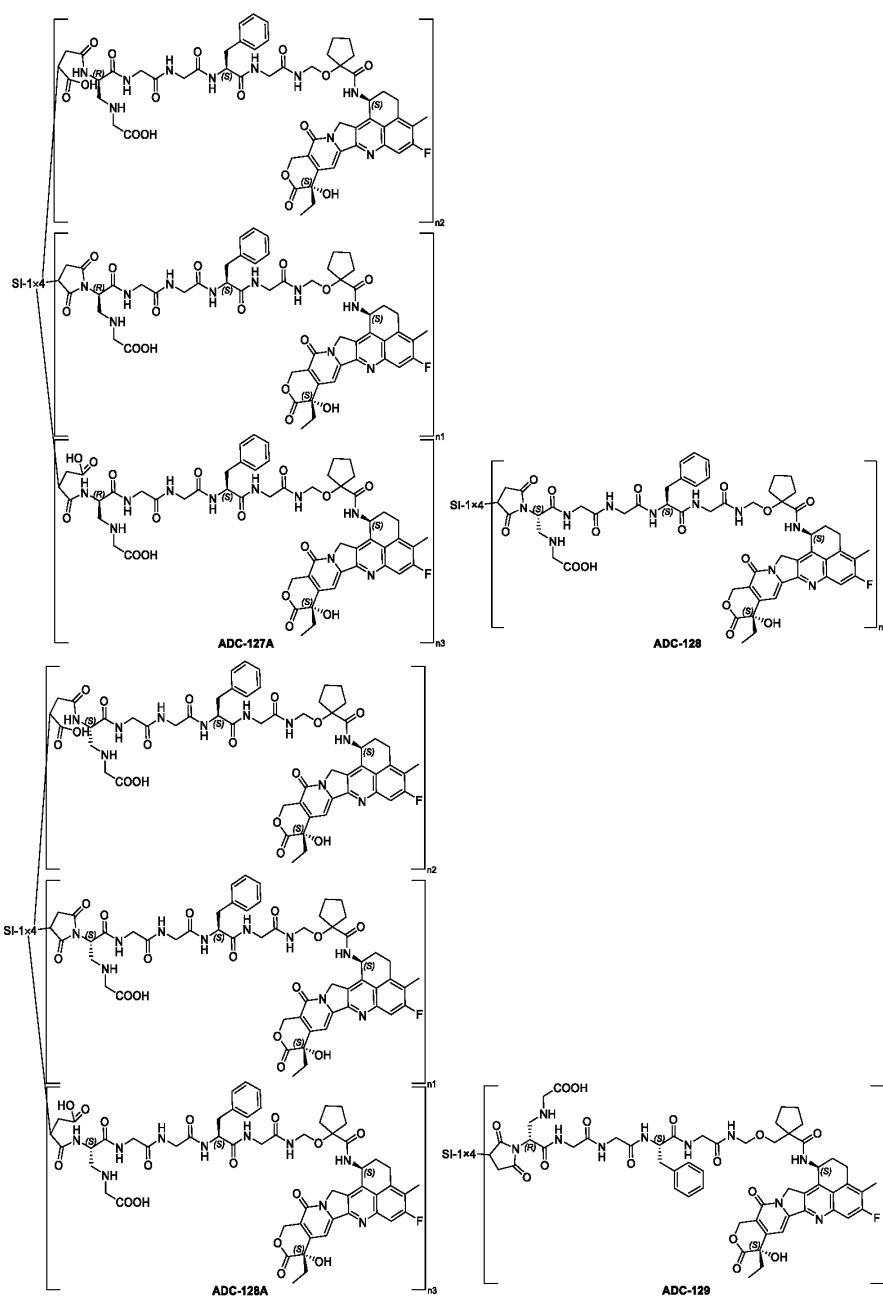
51. The method as Claim 1-15, wherein the ligand-camptothecin derivative conjugate, or a pharmaceutically acceptable salt or solvate thereof, comprises the following structure, or a butanediimide ring-opening structure thereof, or an isomer thereof:

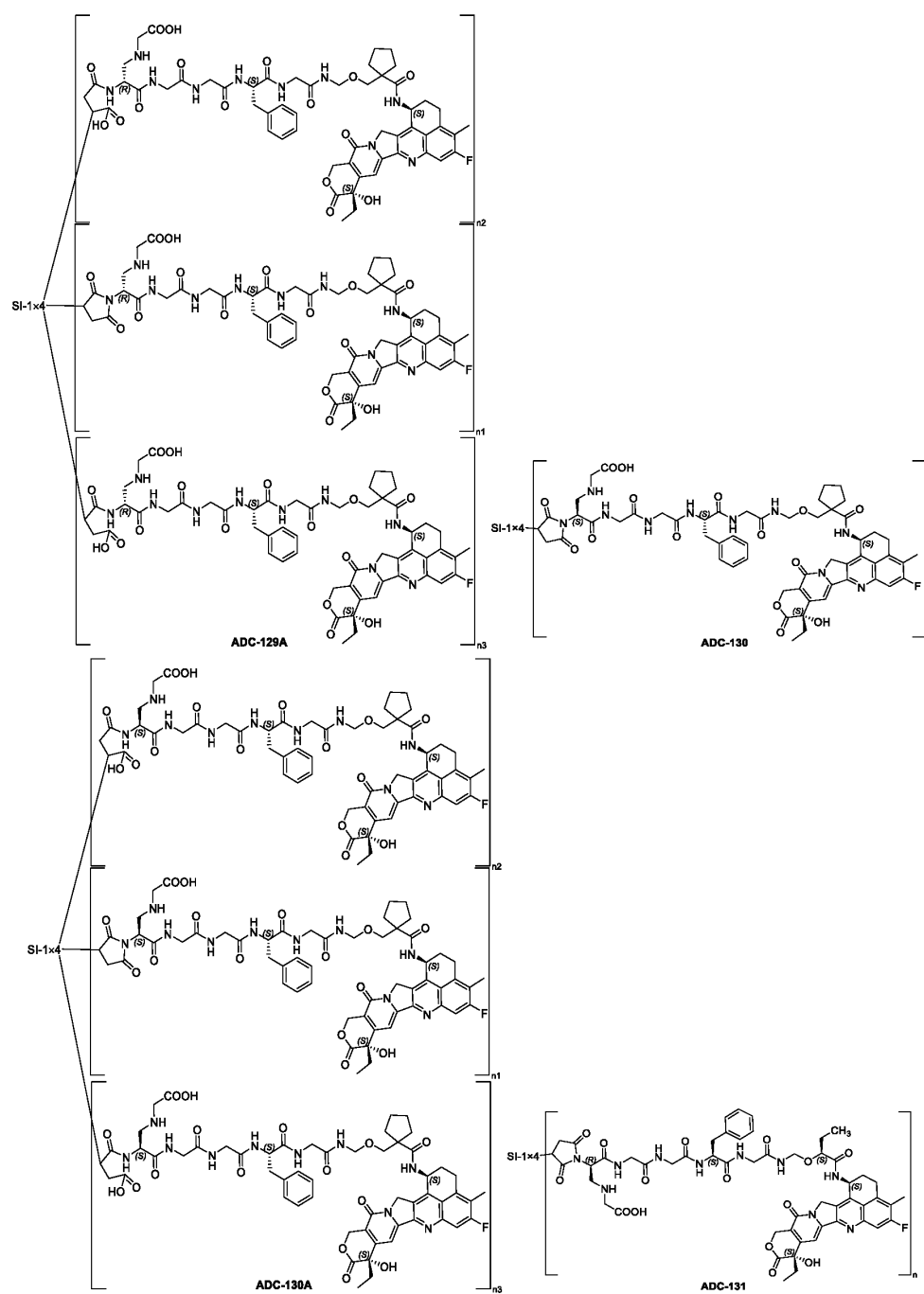


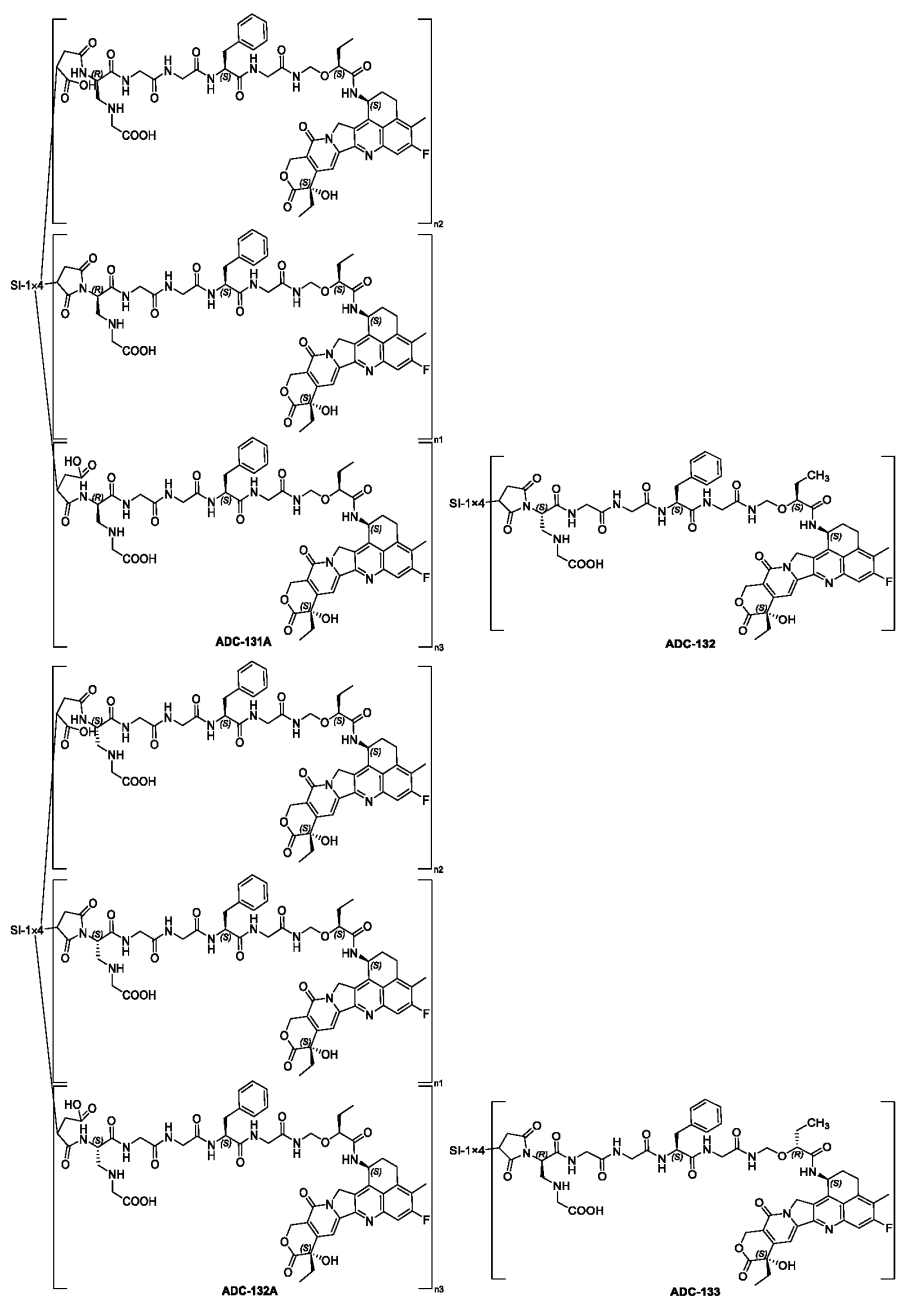


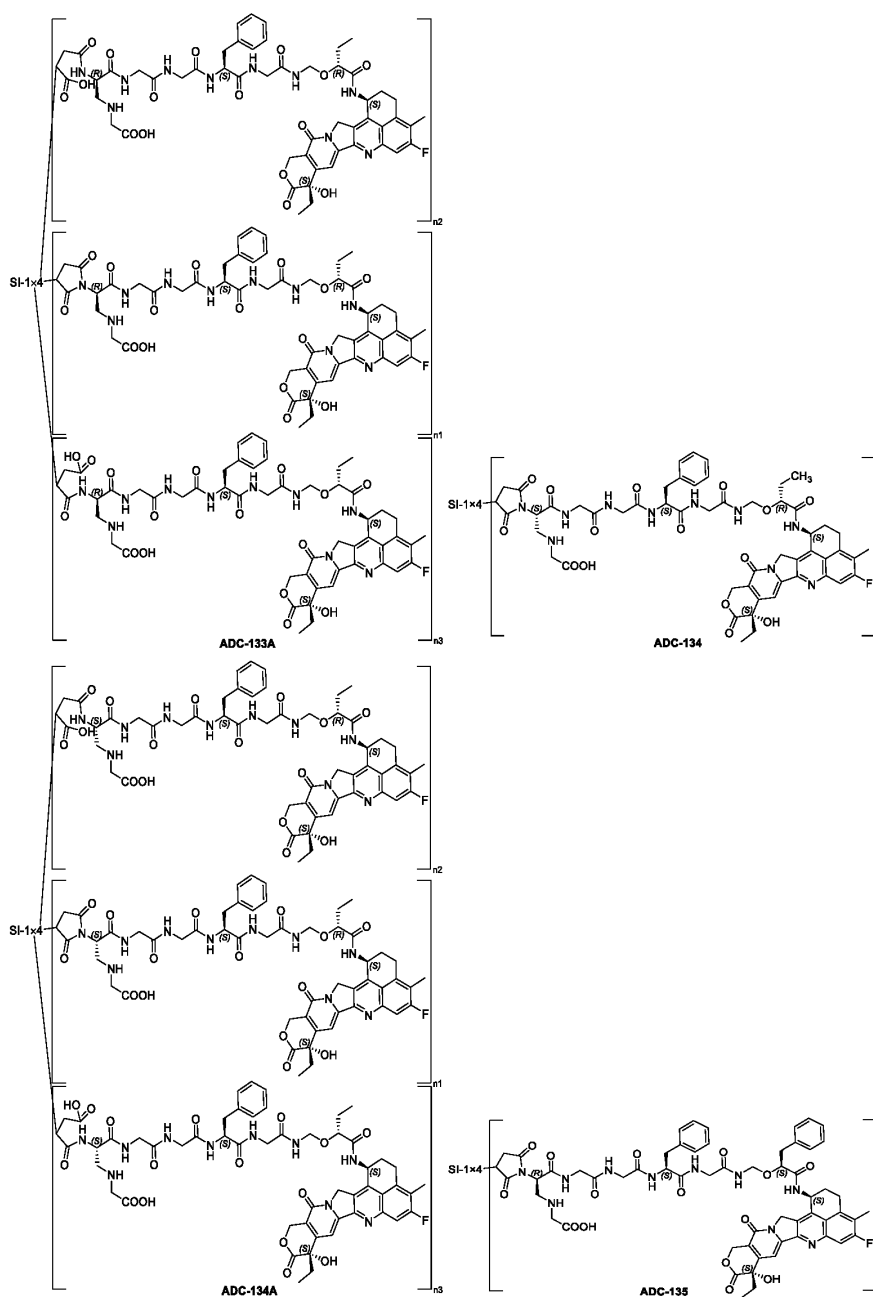


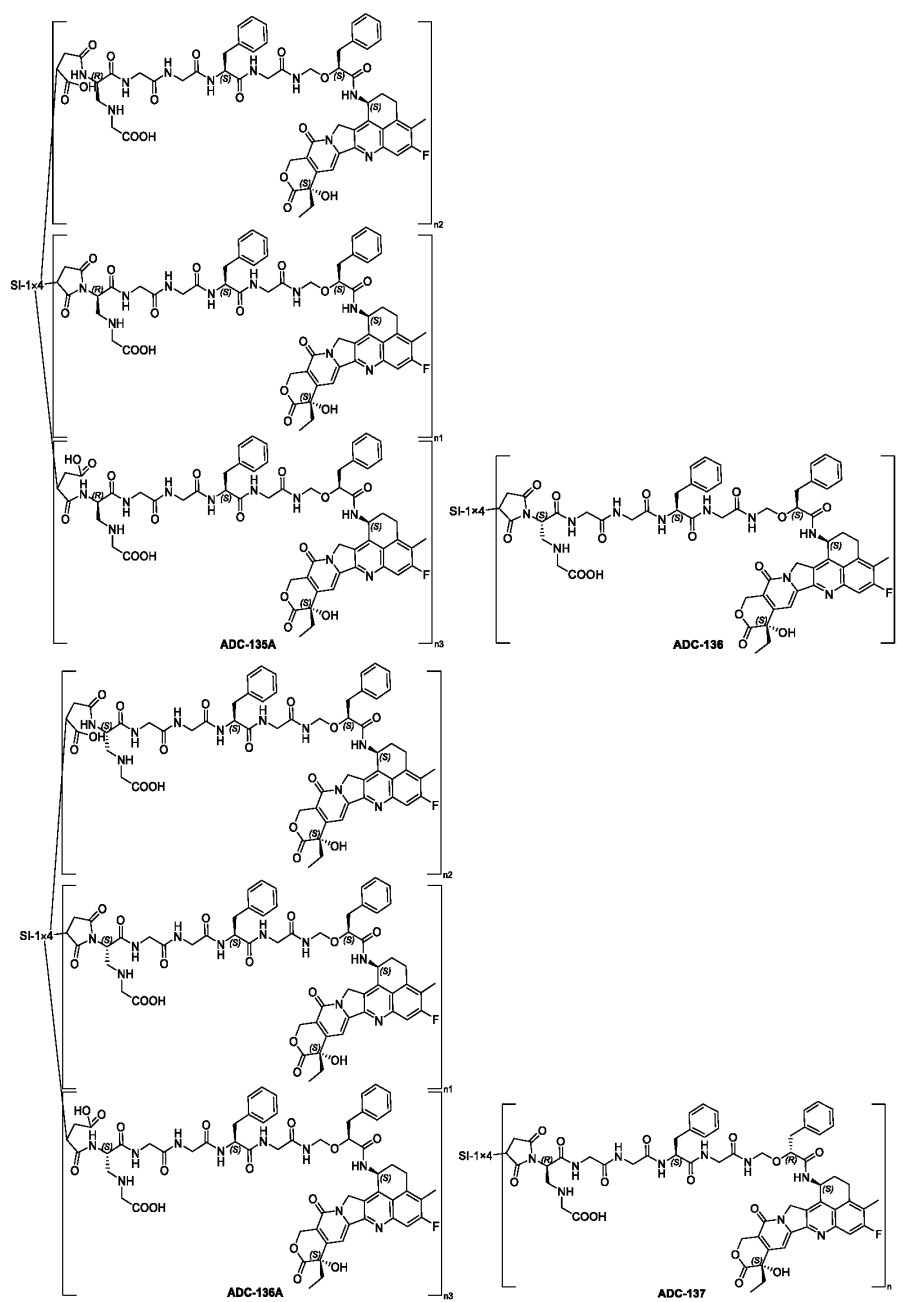


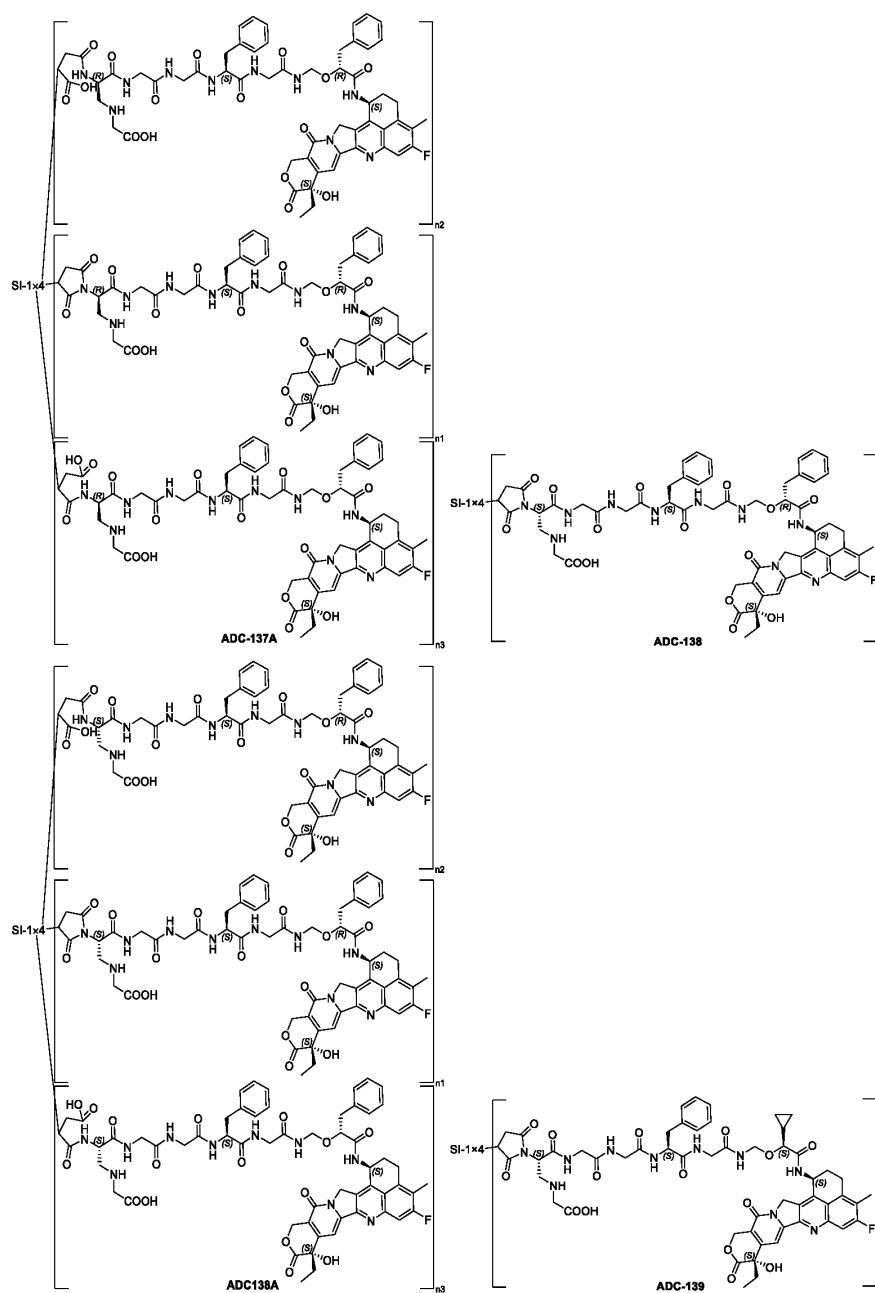


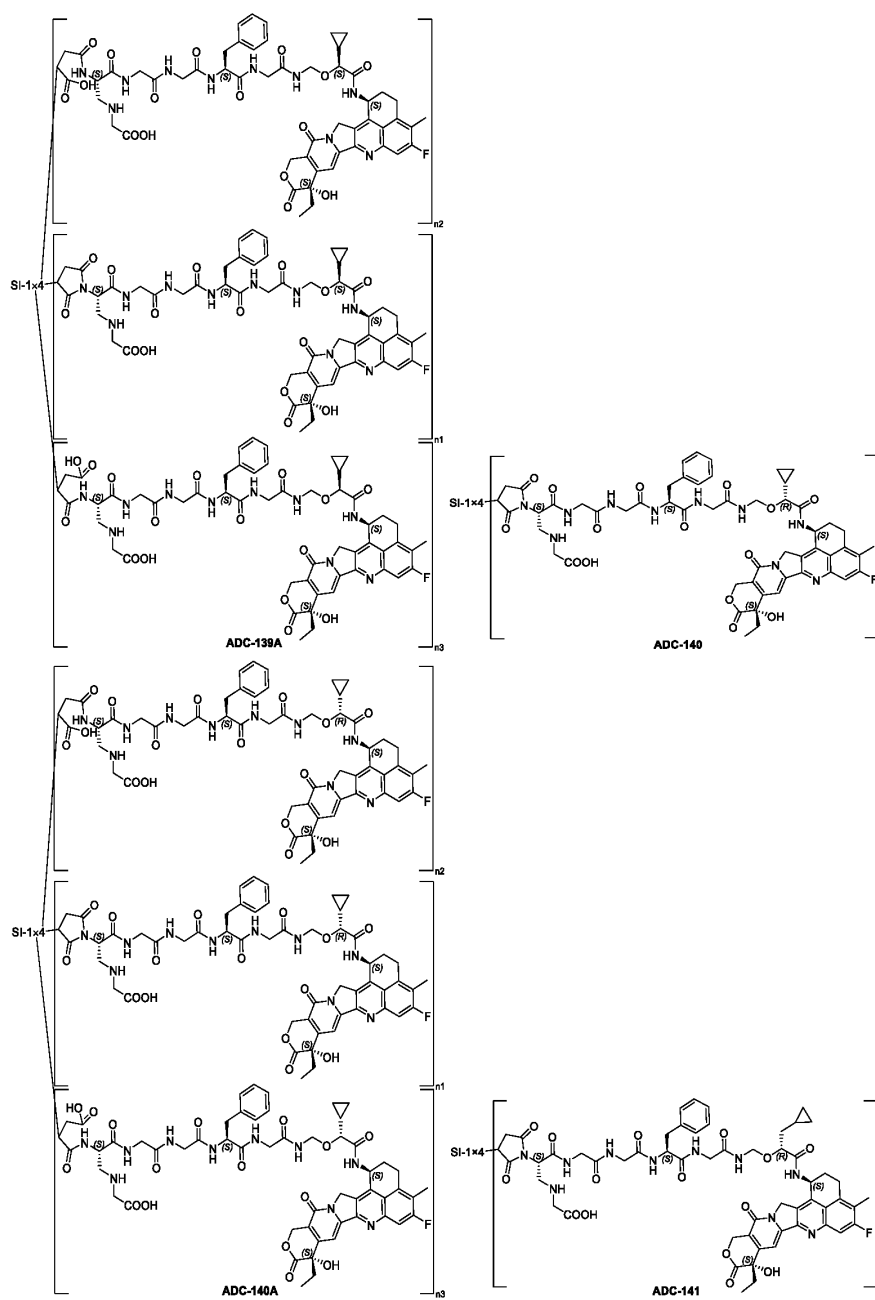


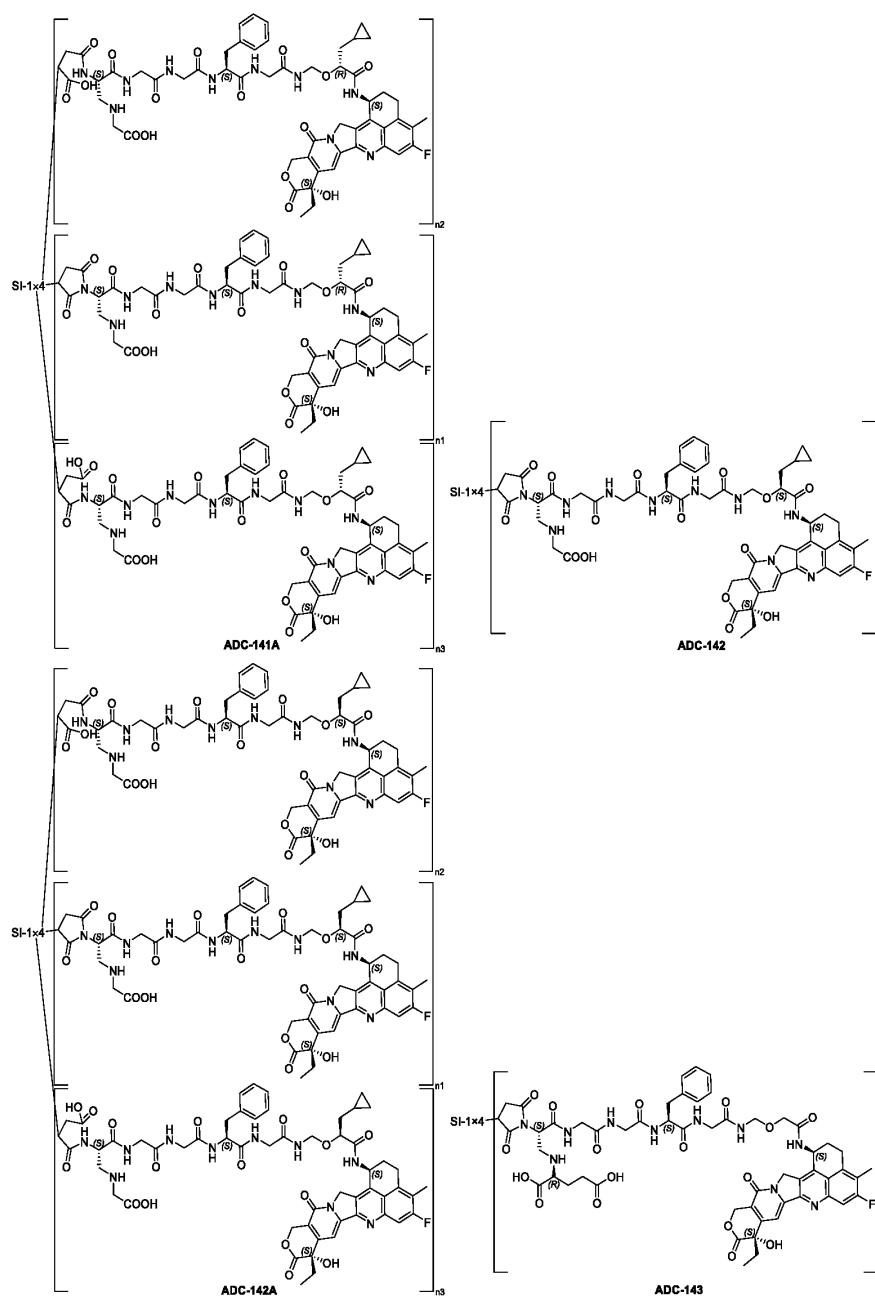


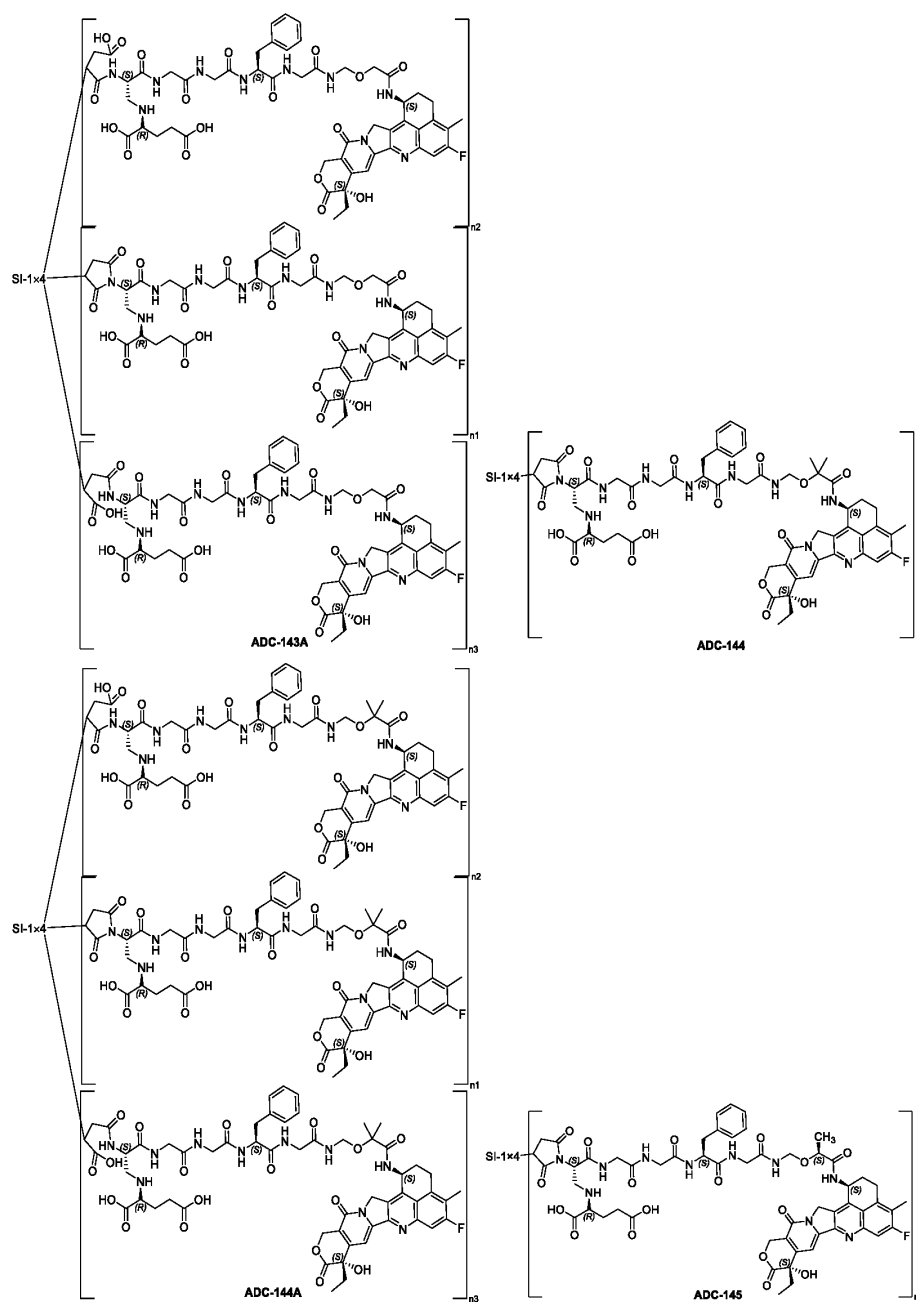


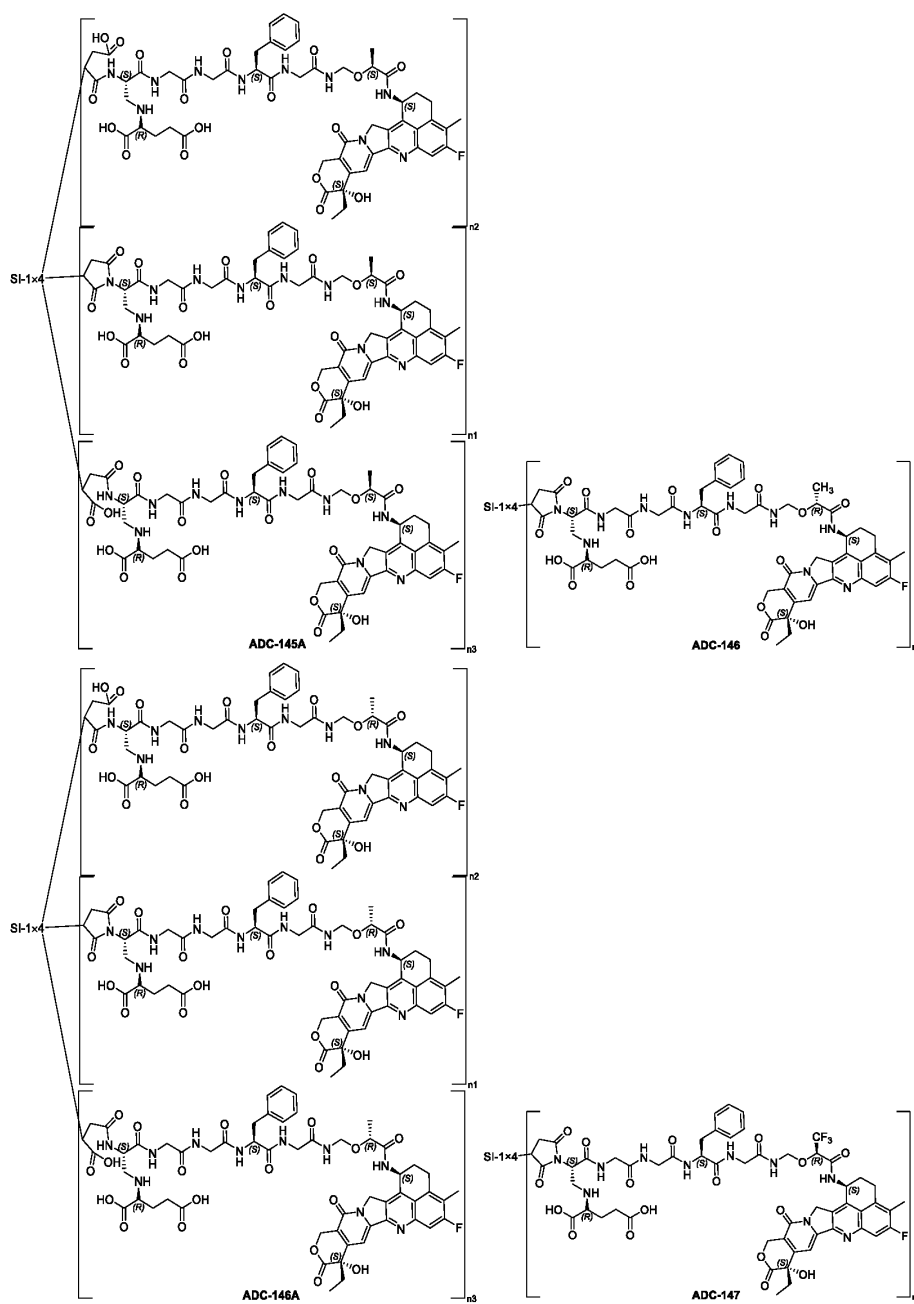


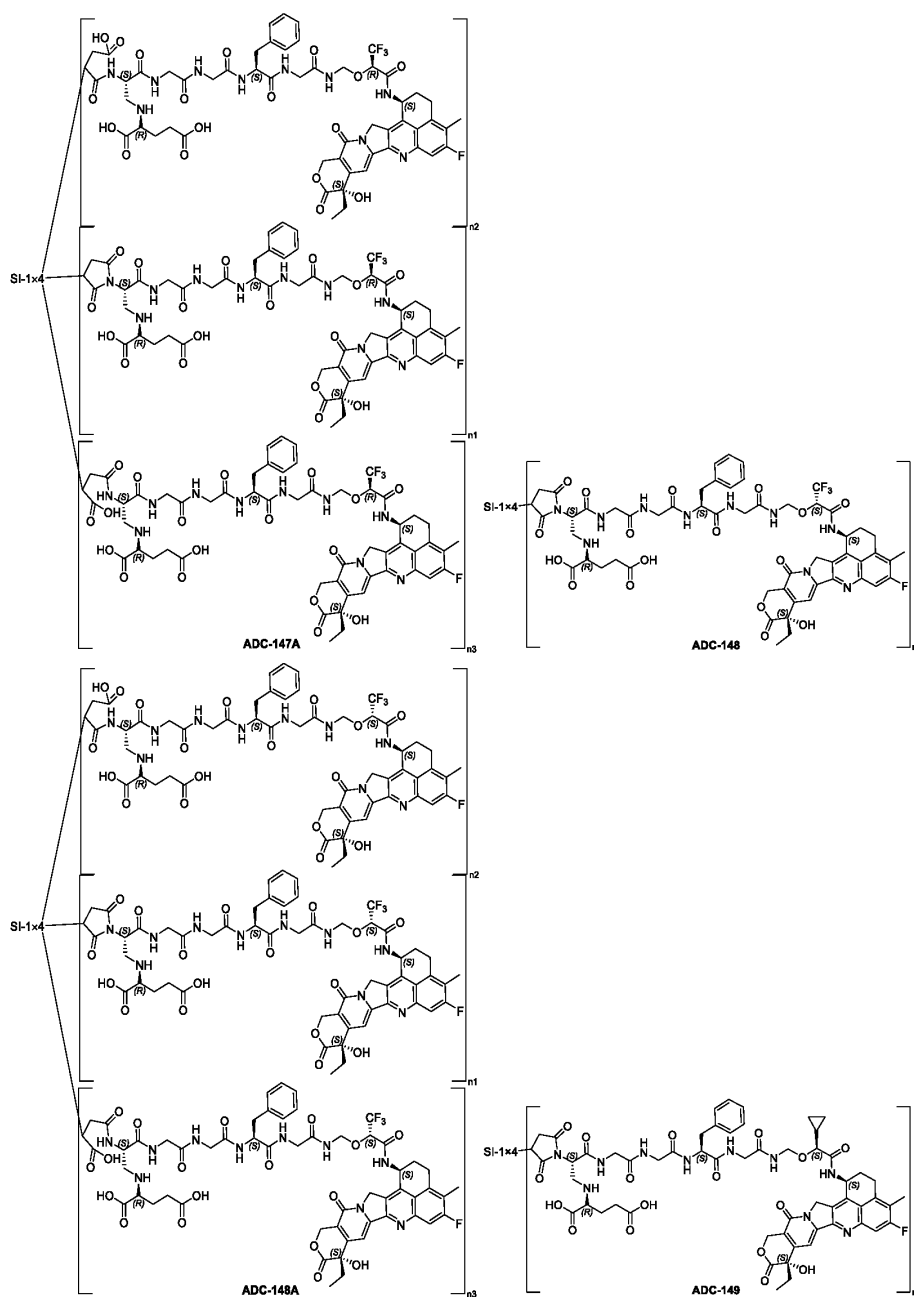


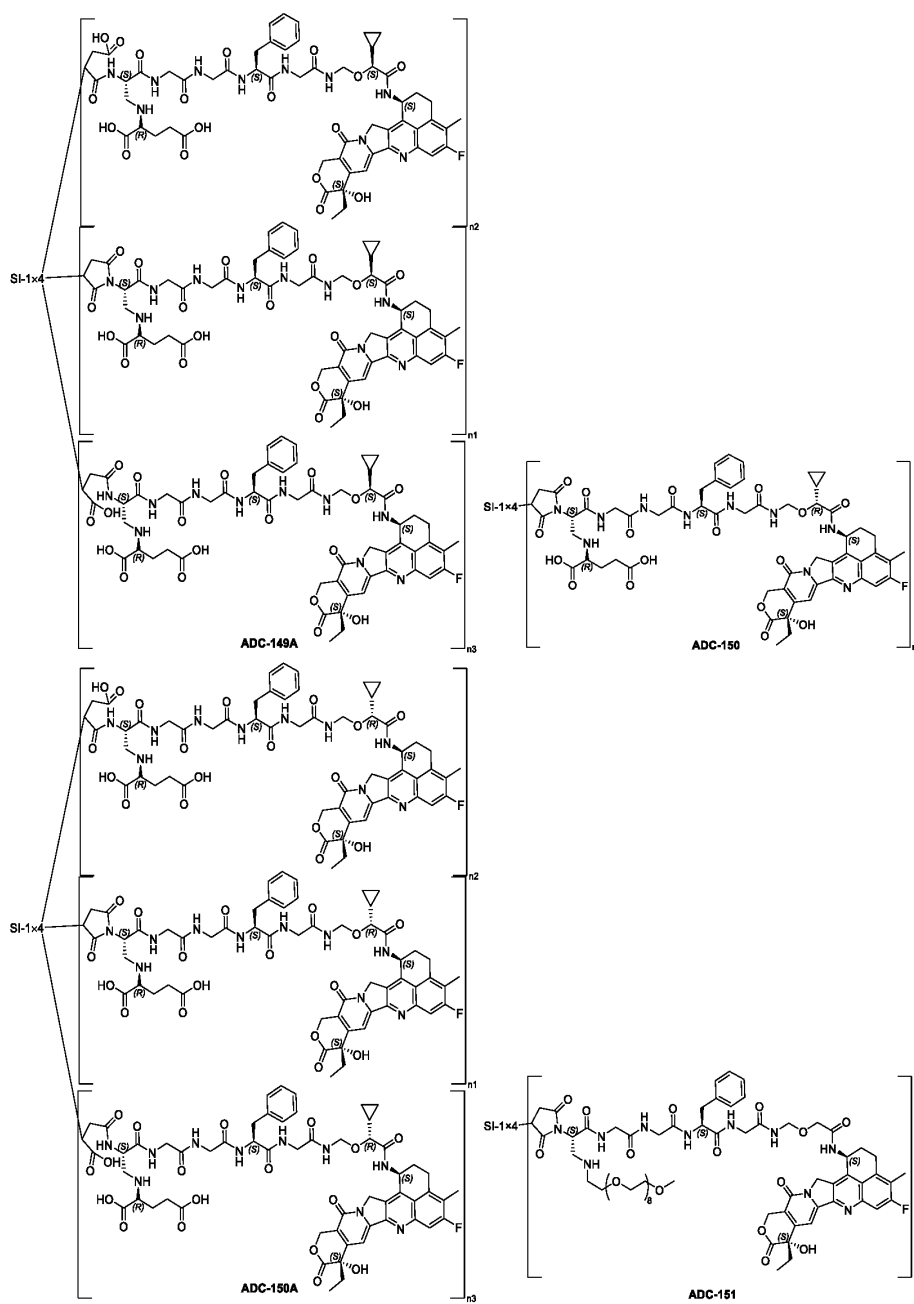


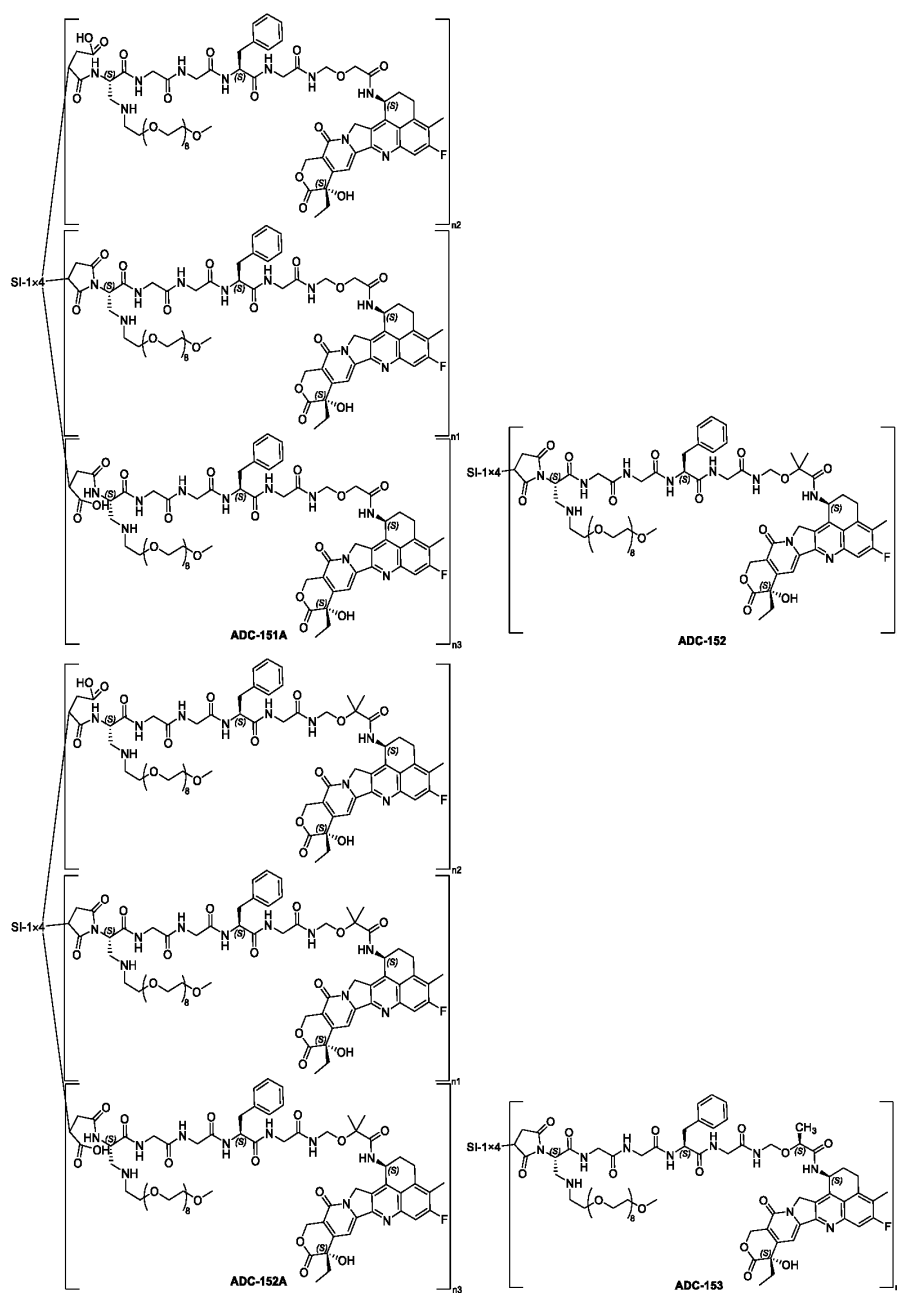


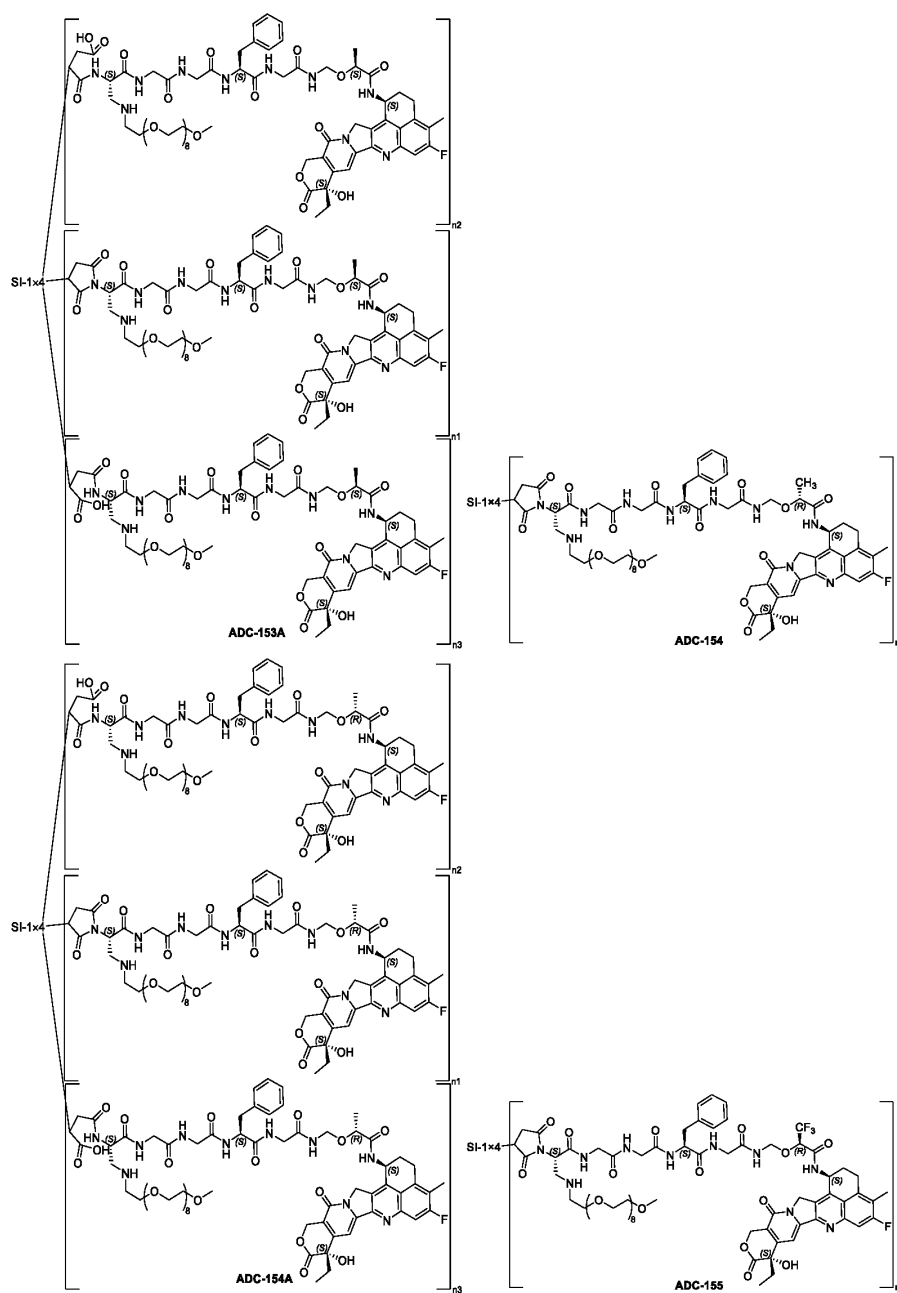


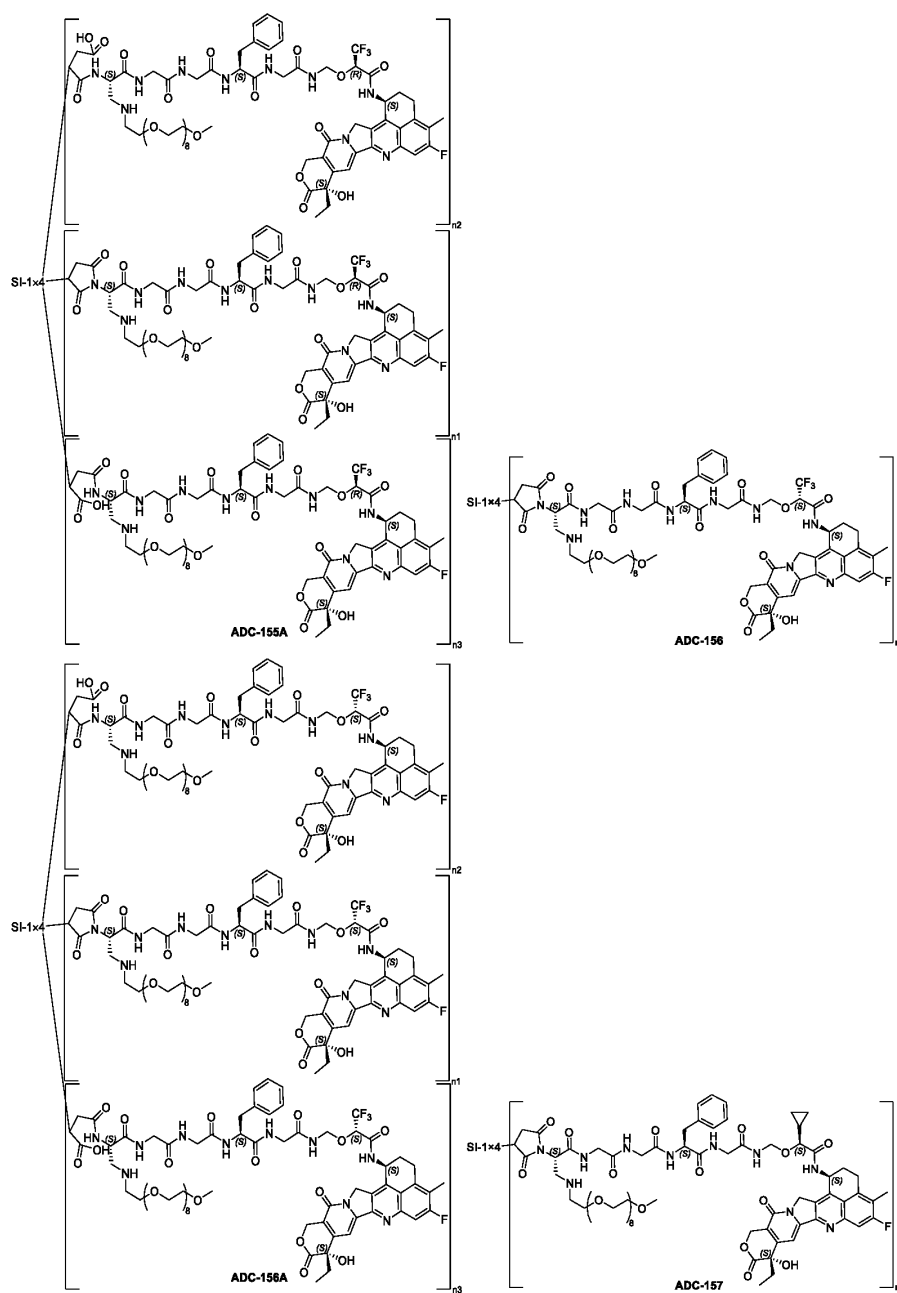


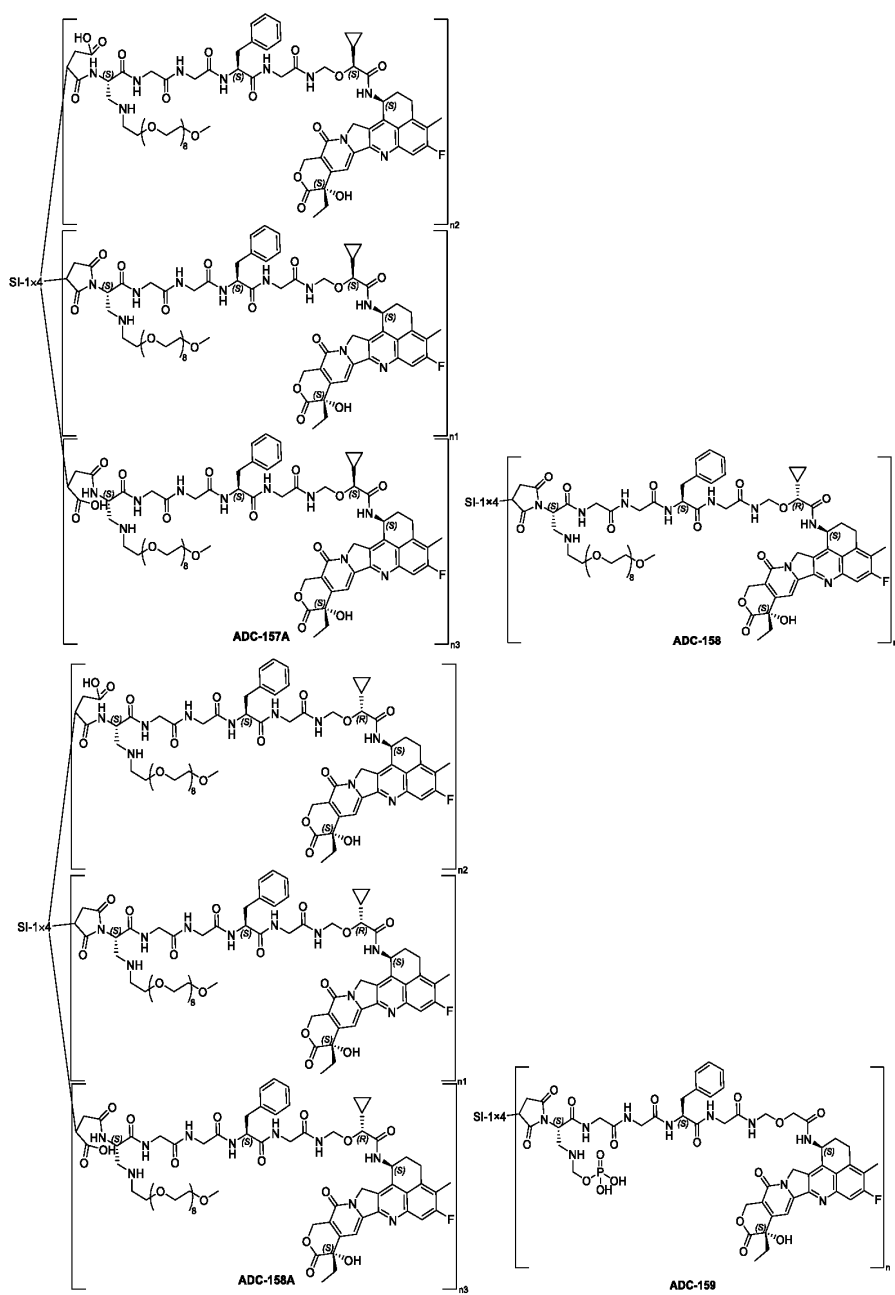


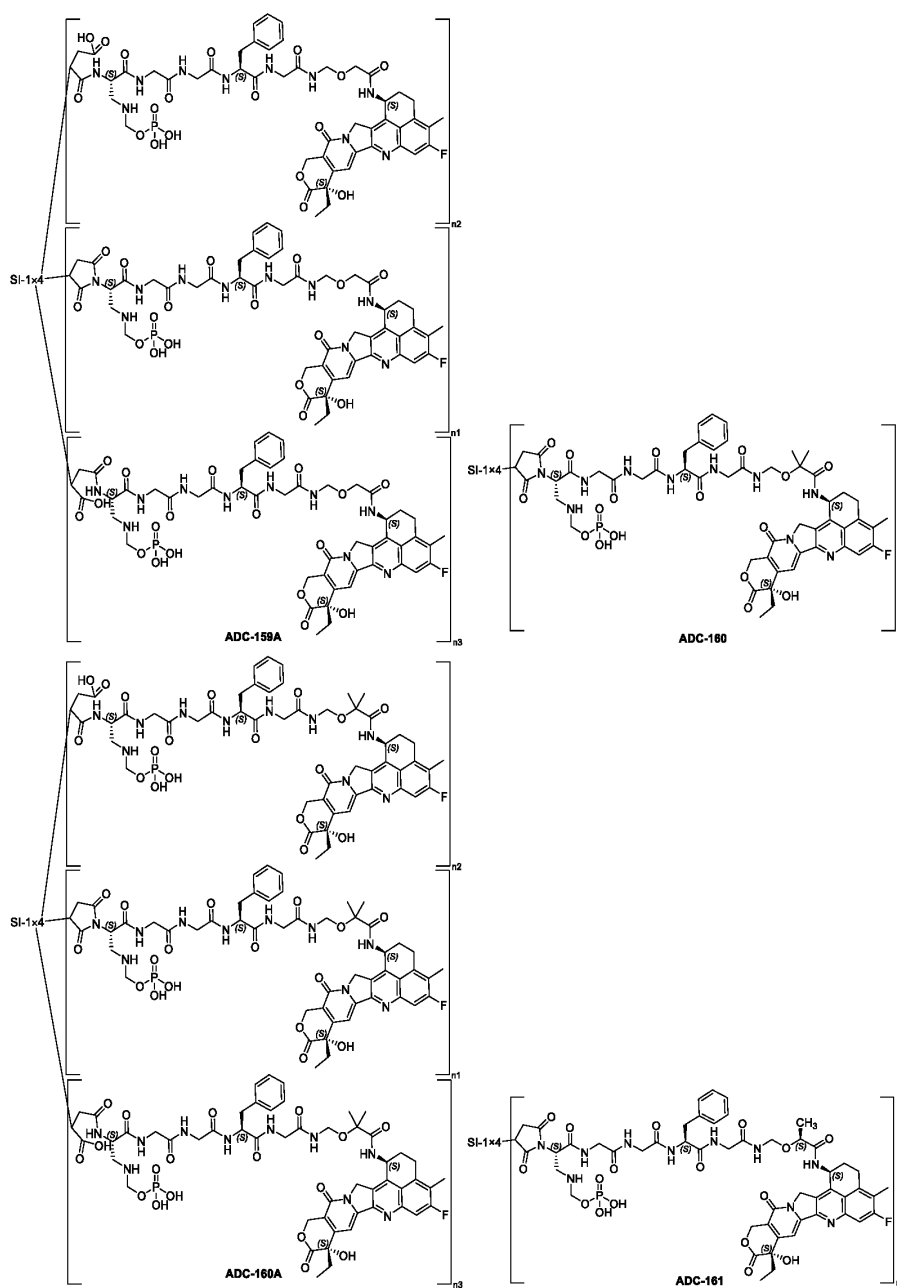


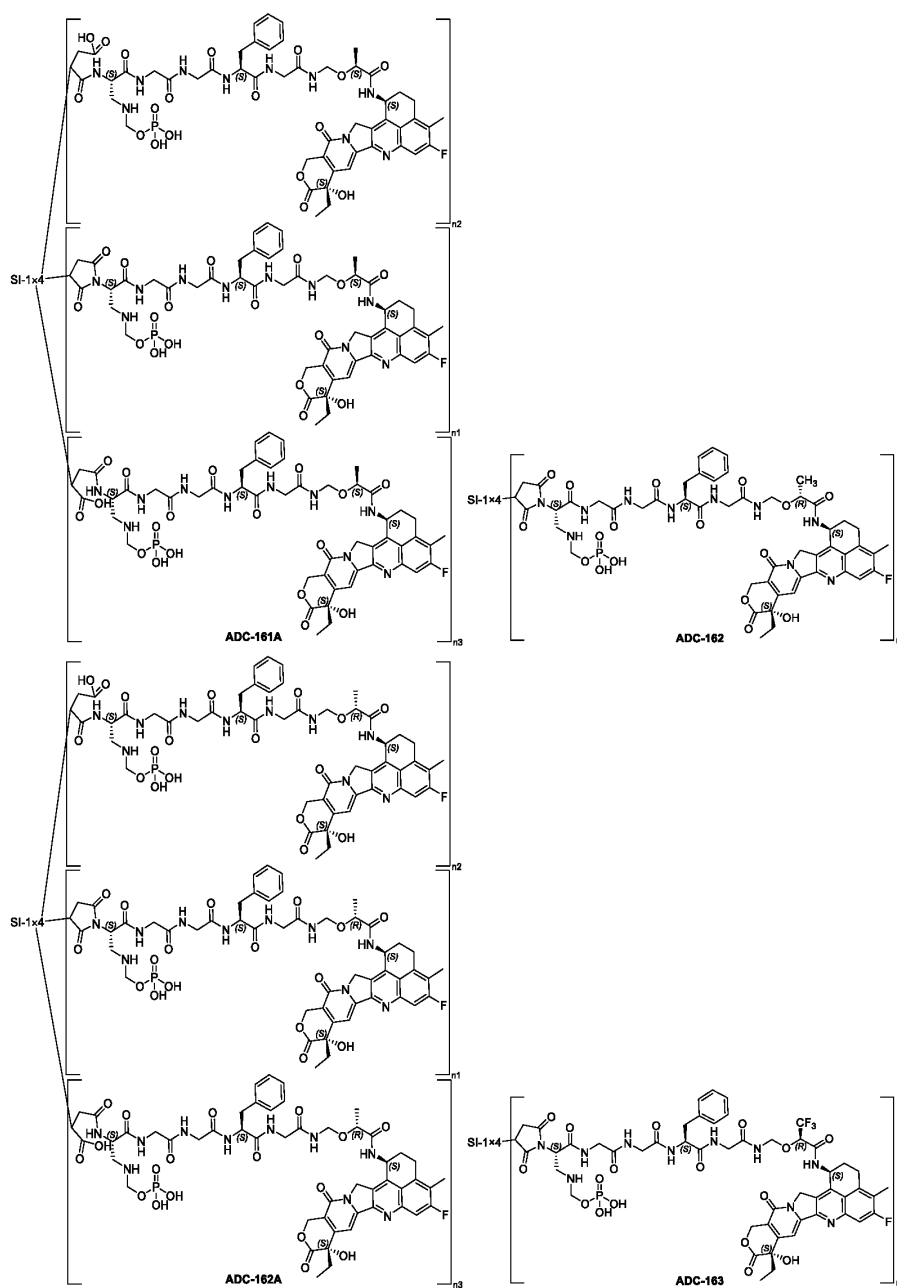


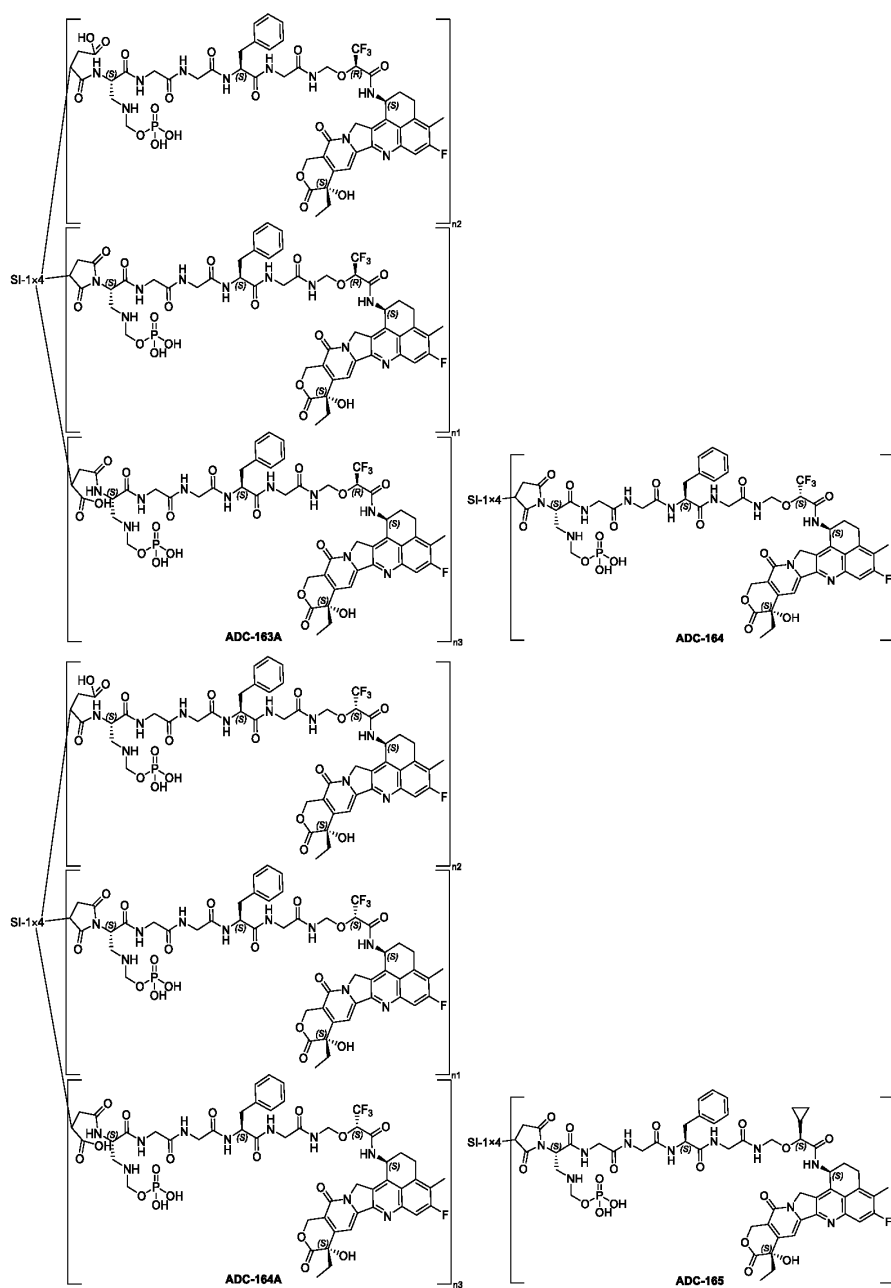


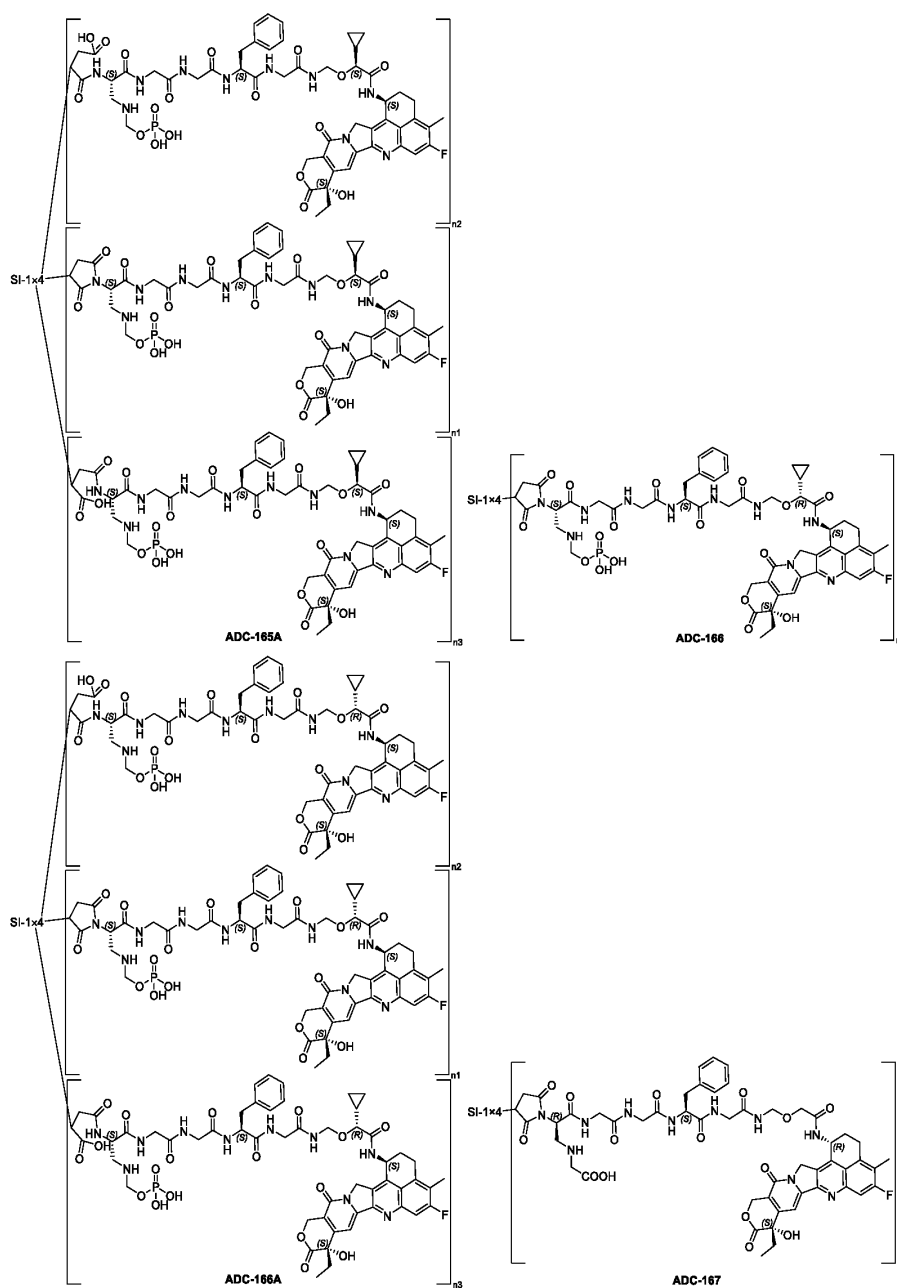


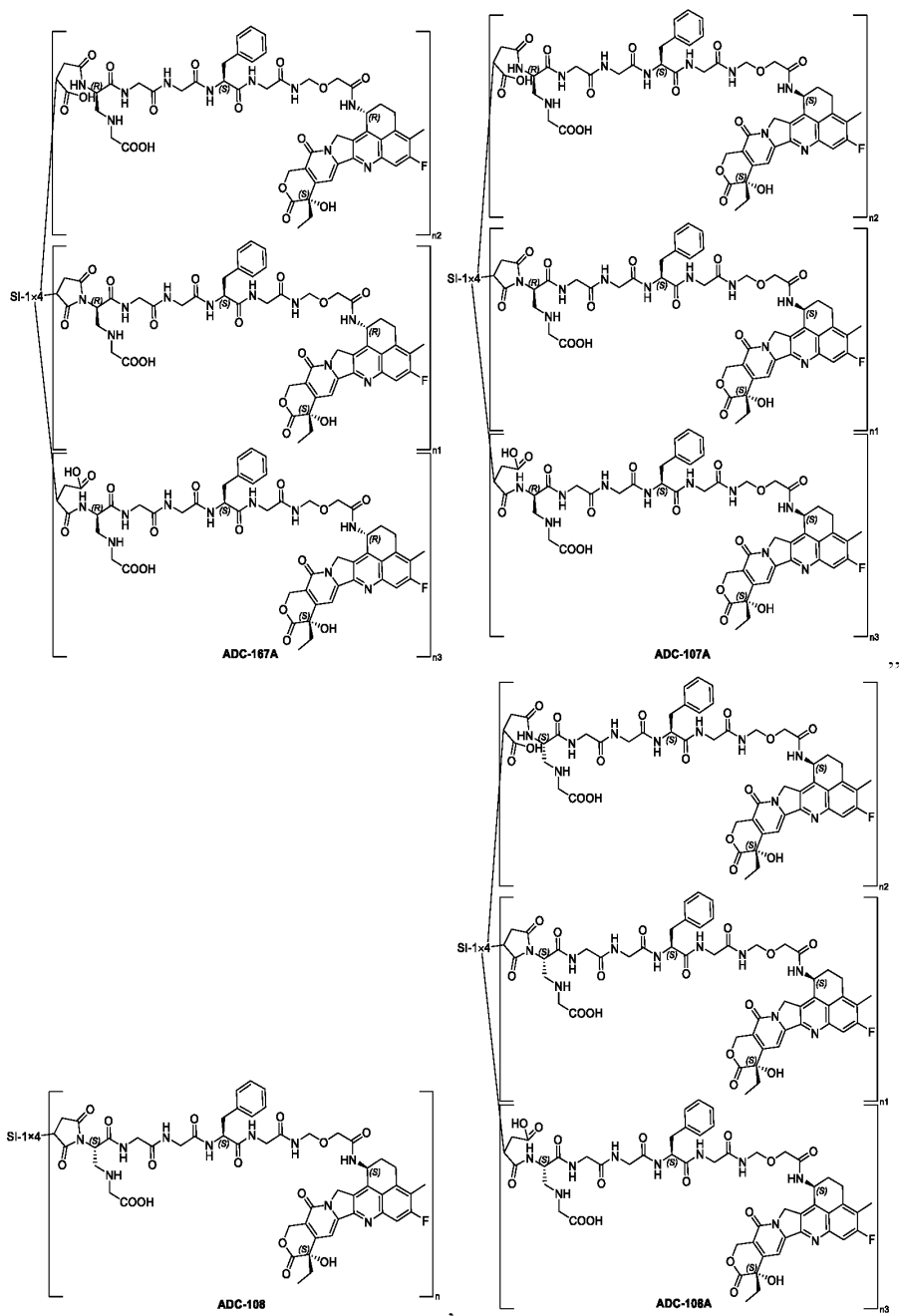


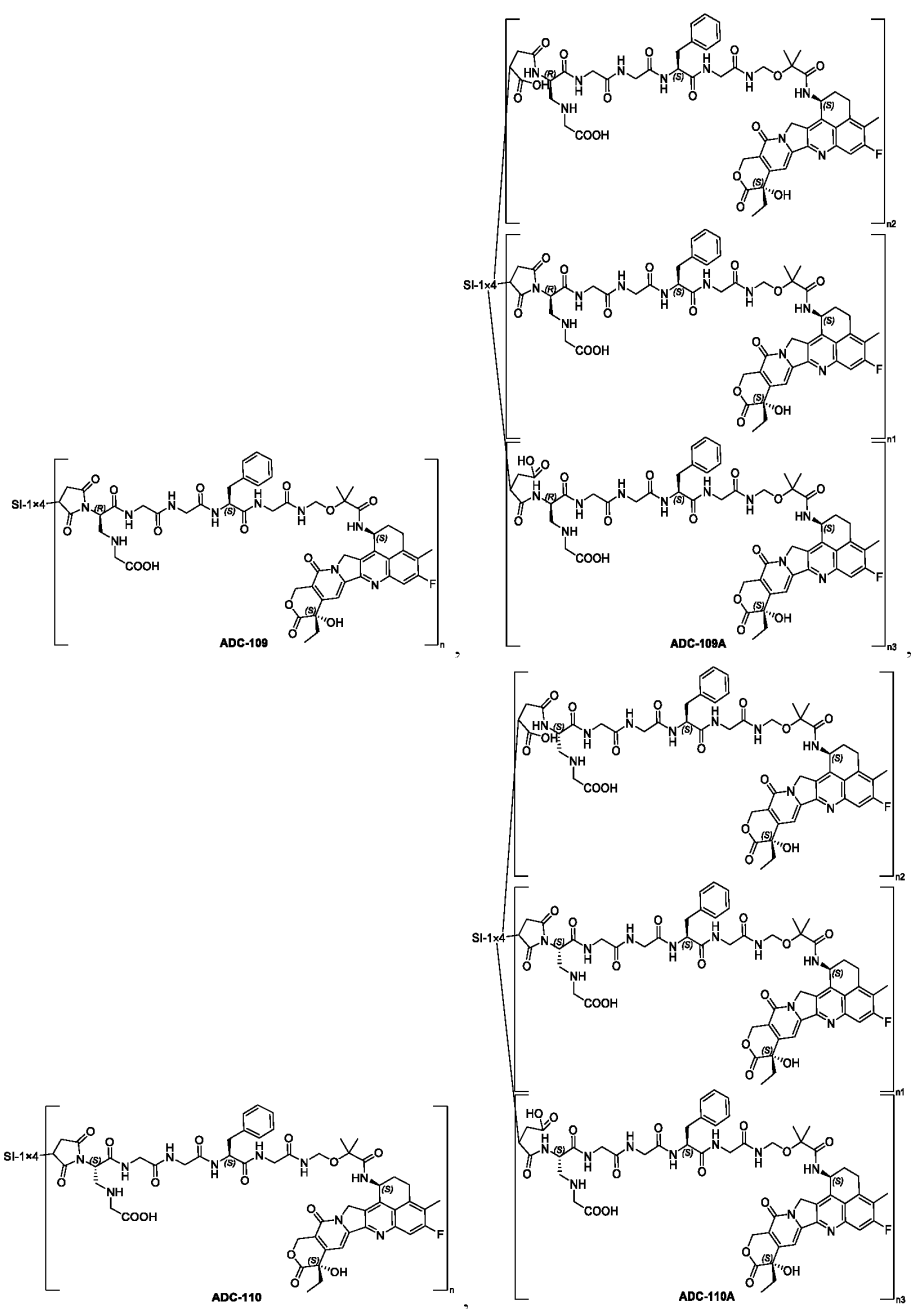


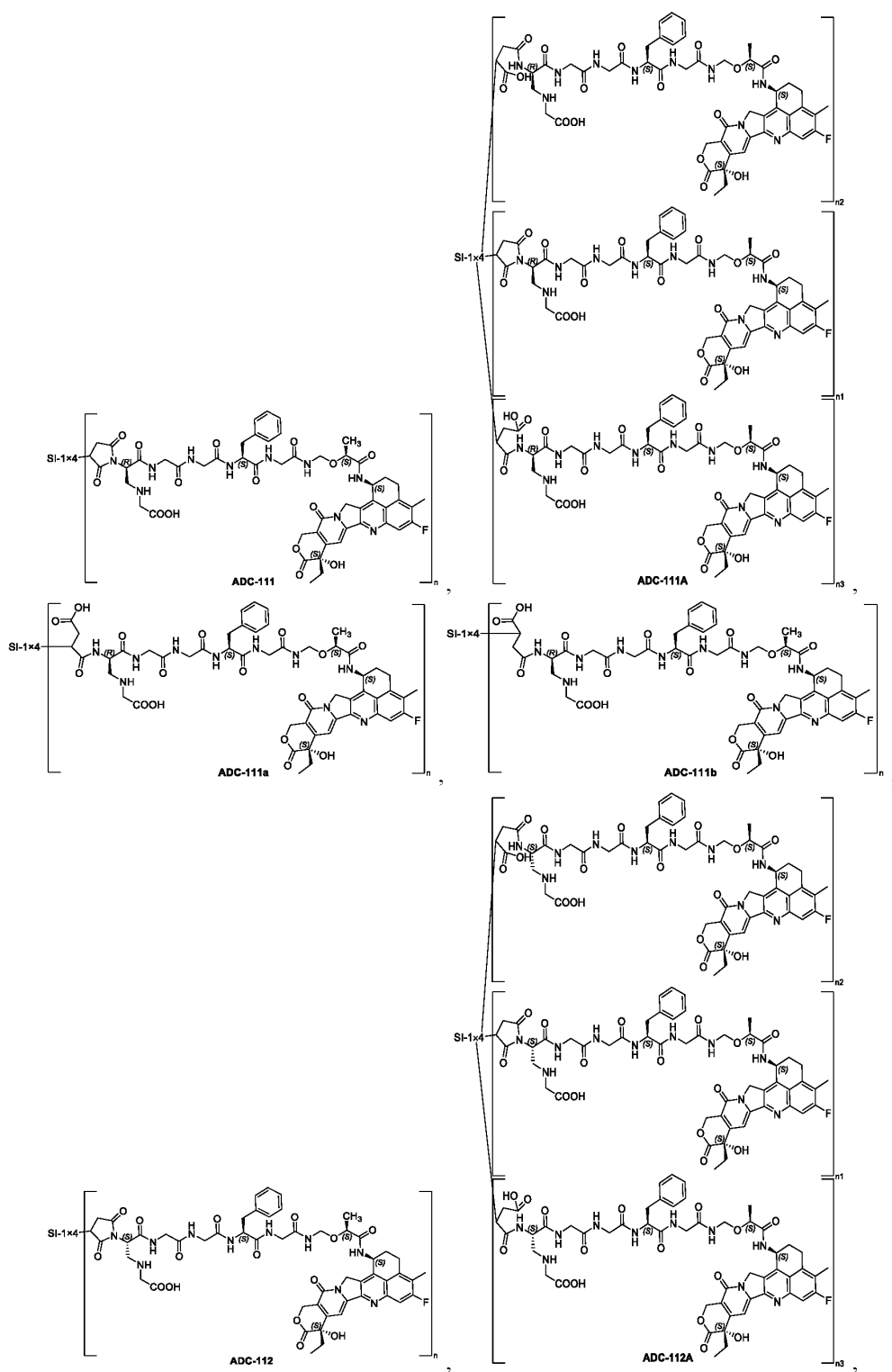


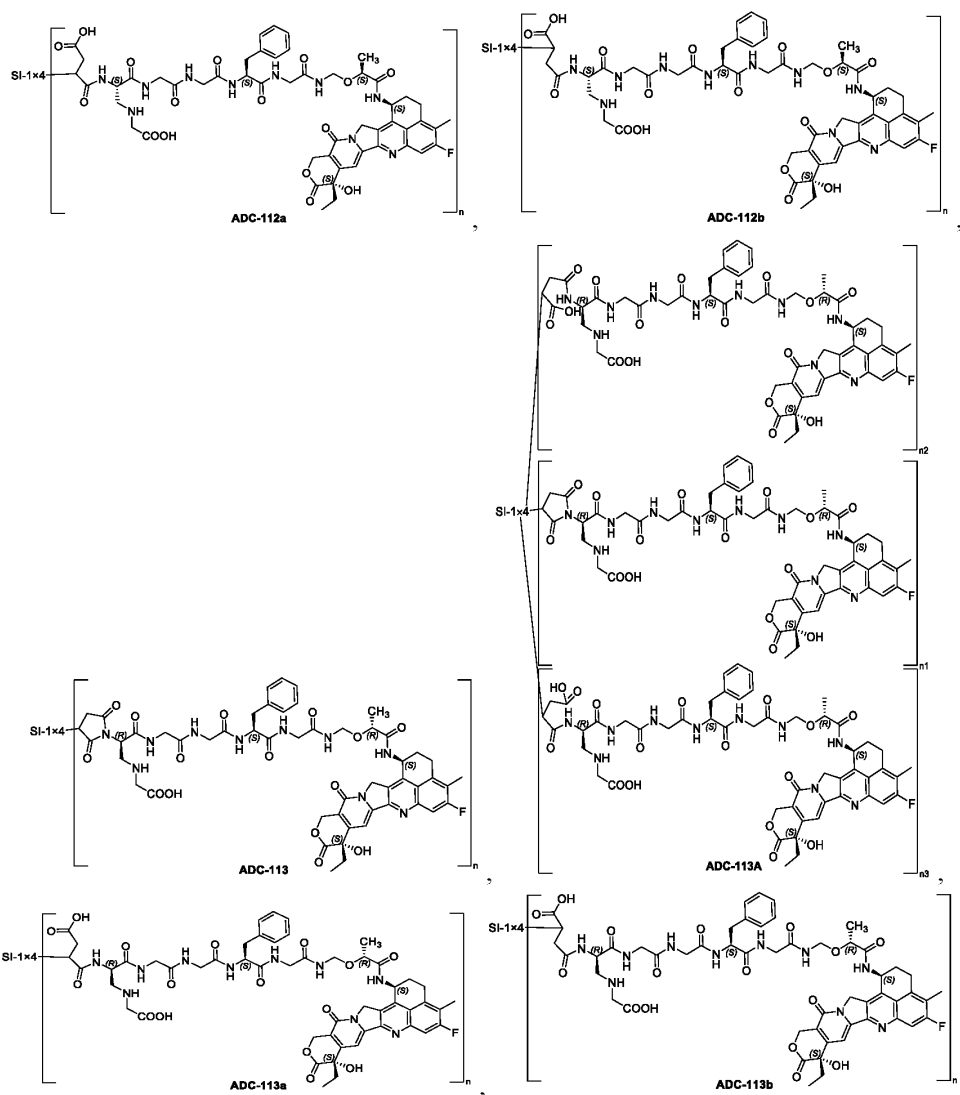


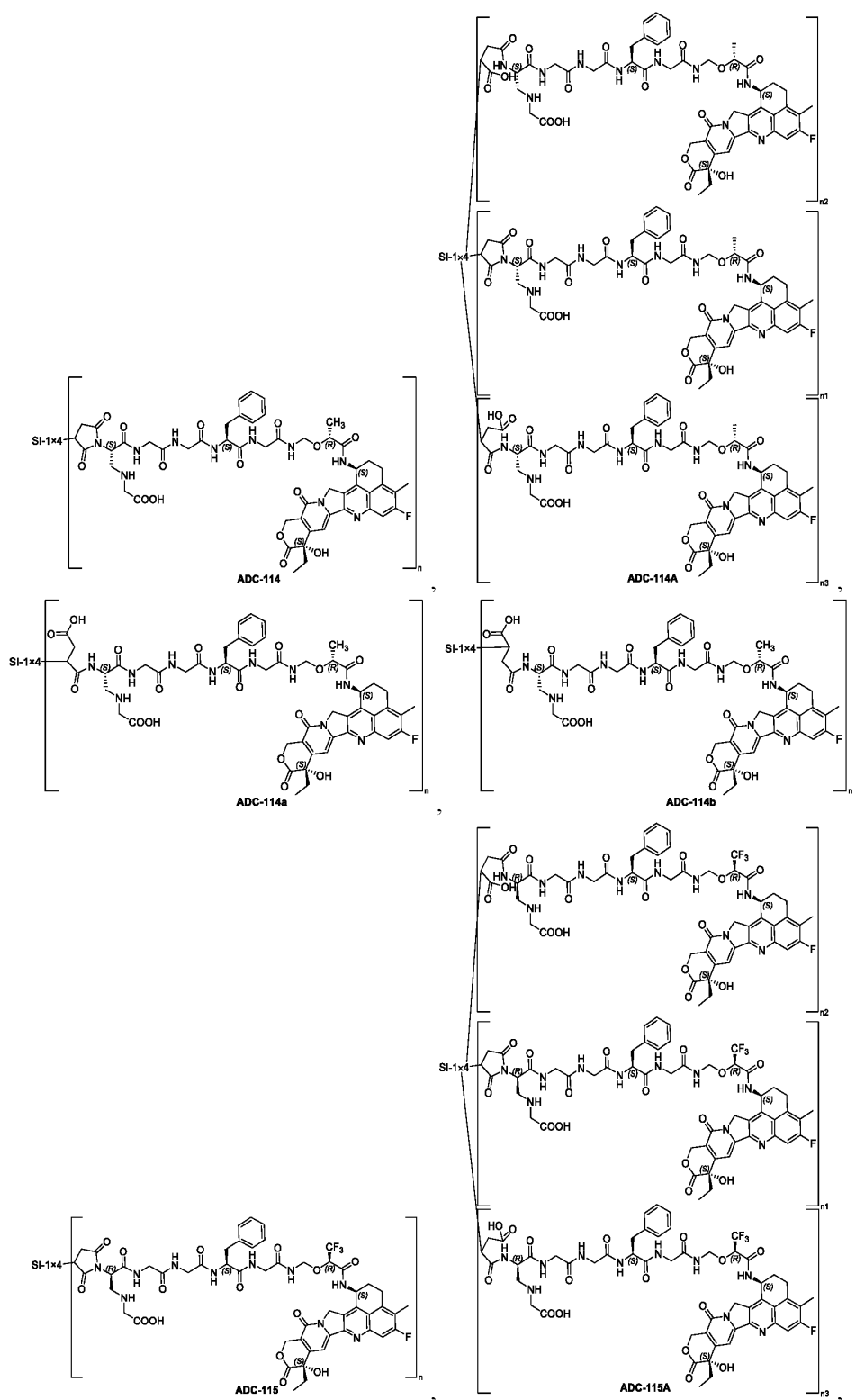


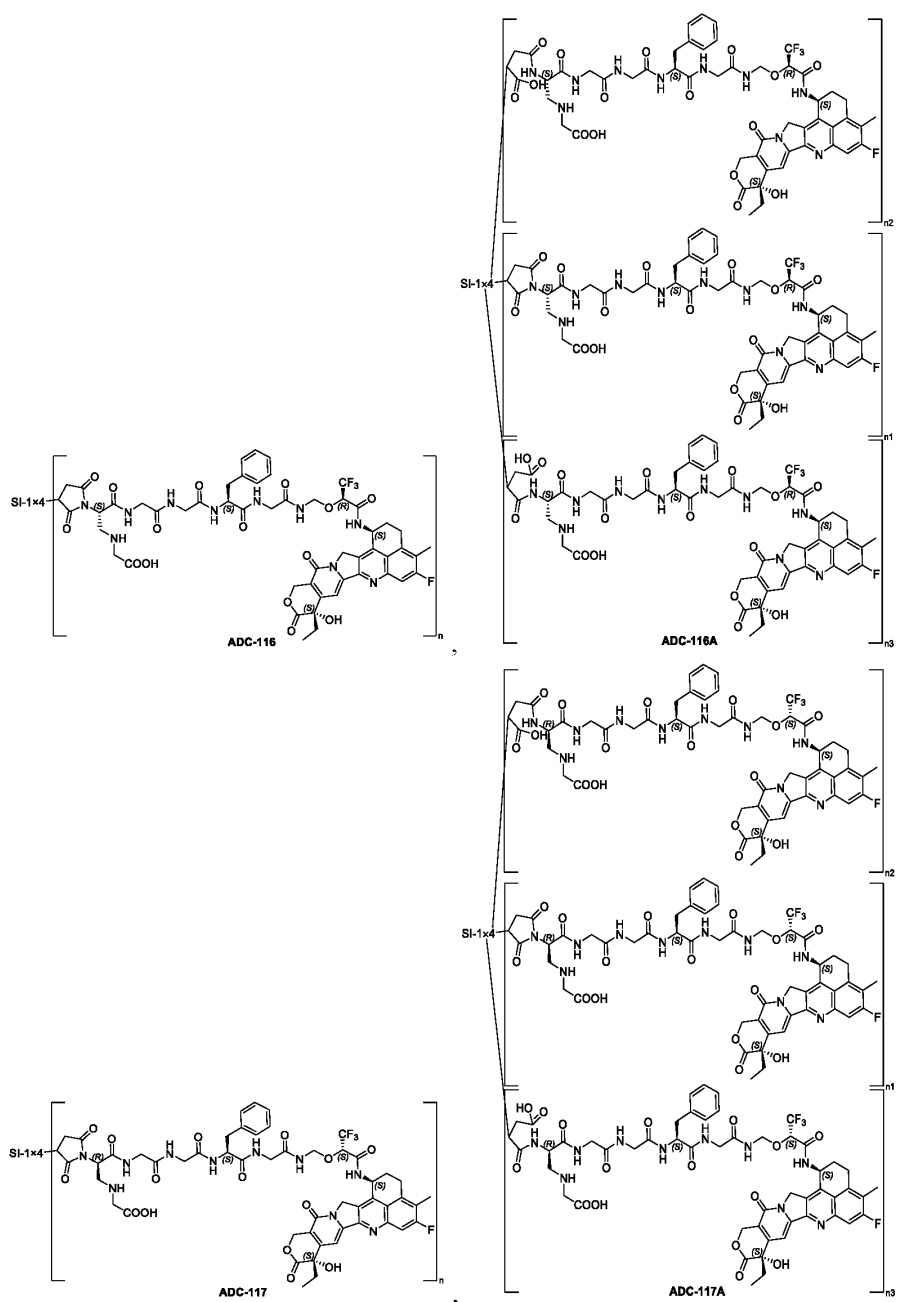


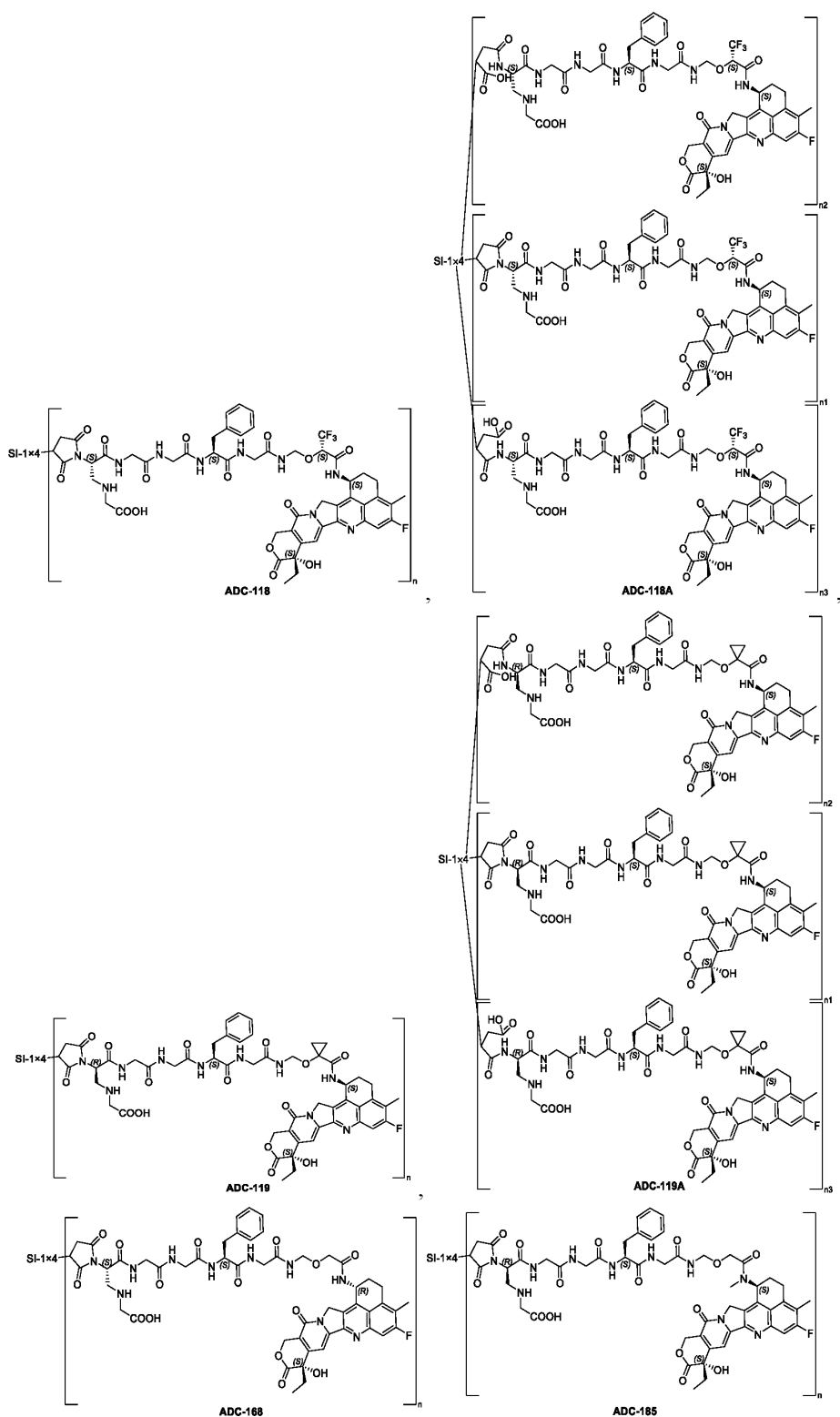


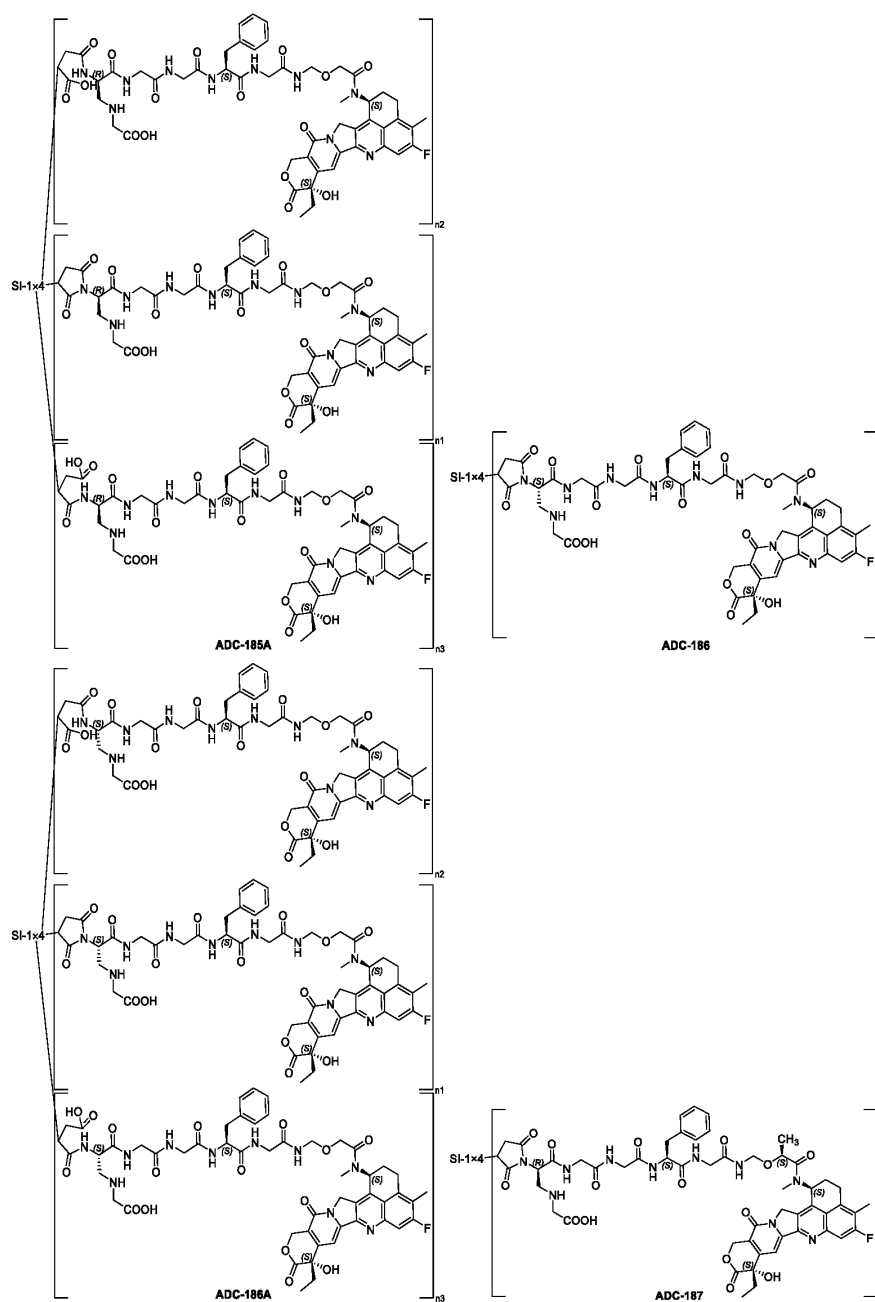


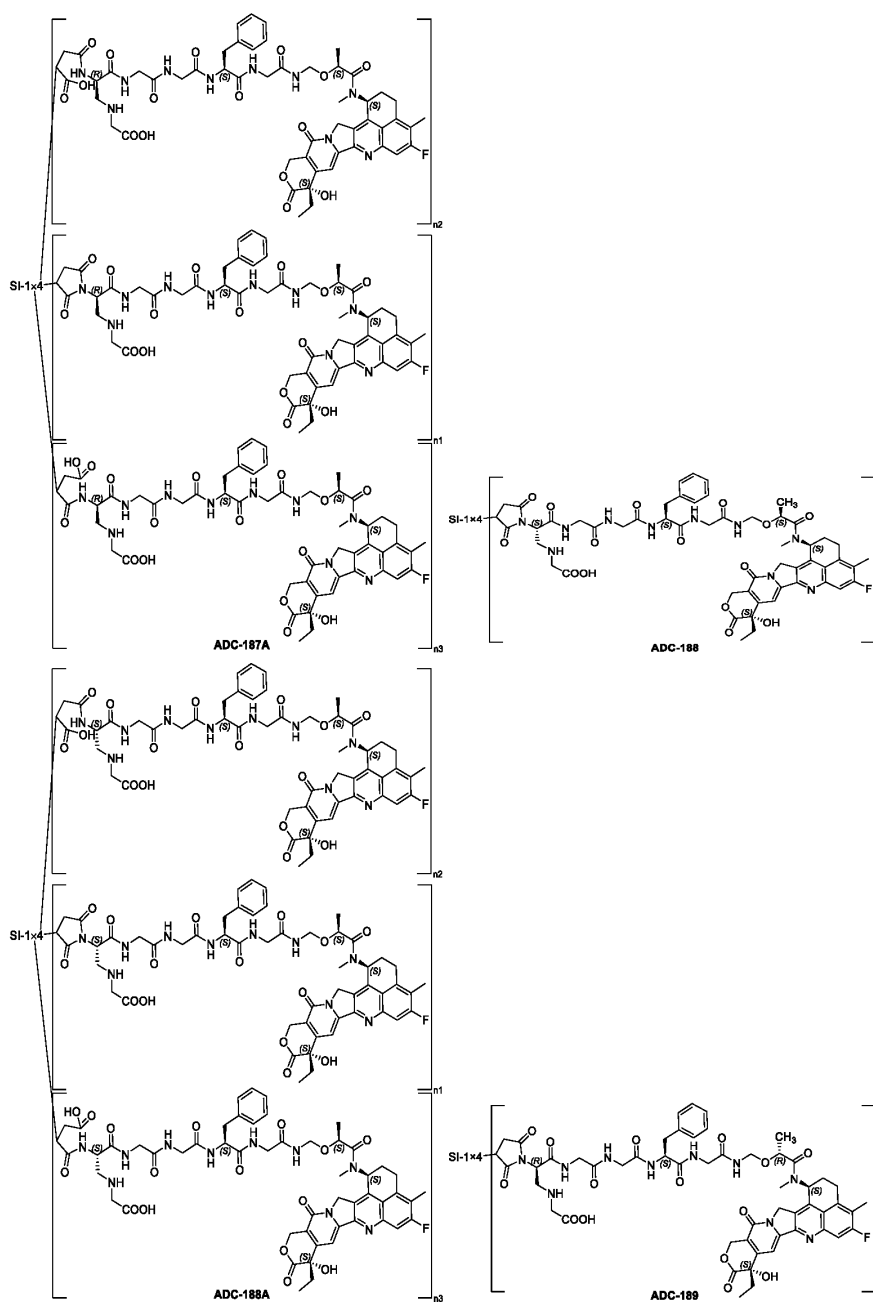


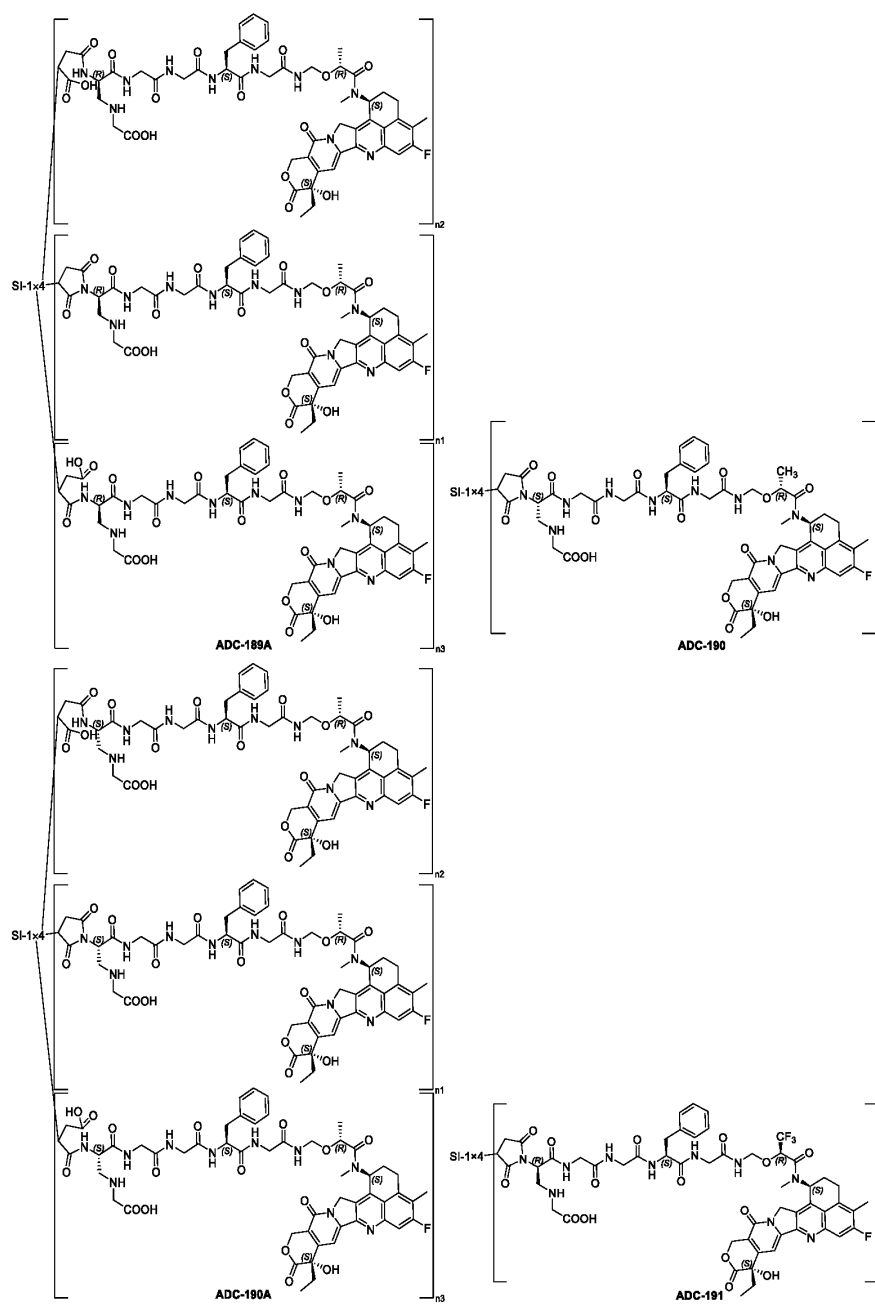


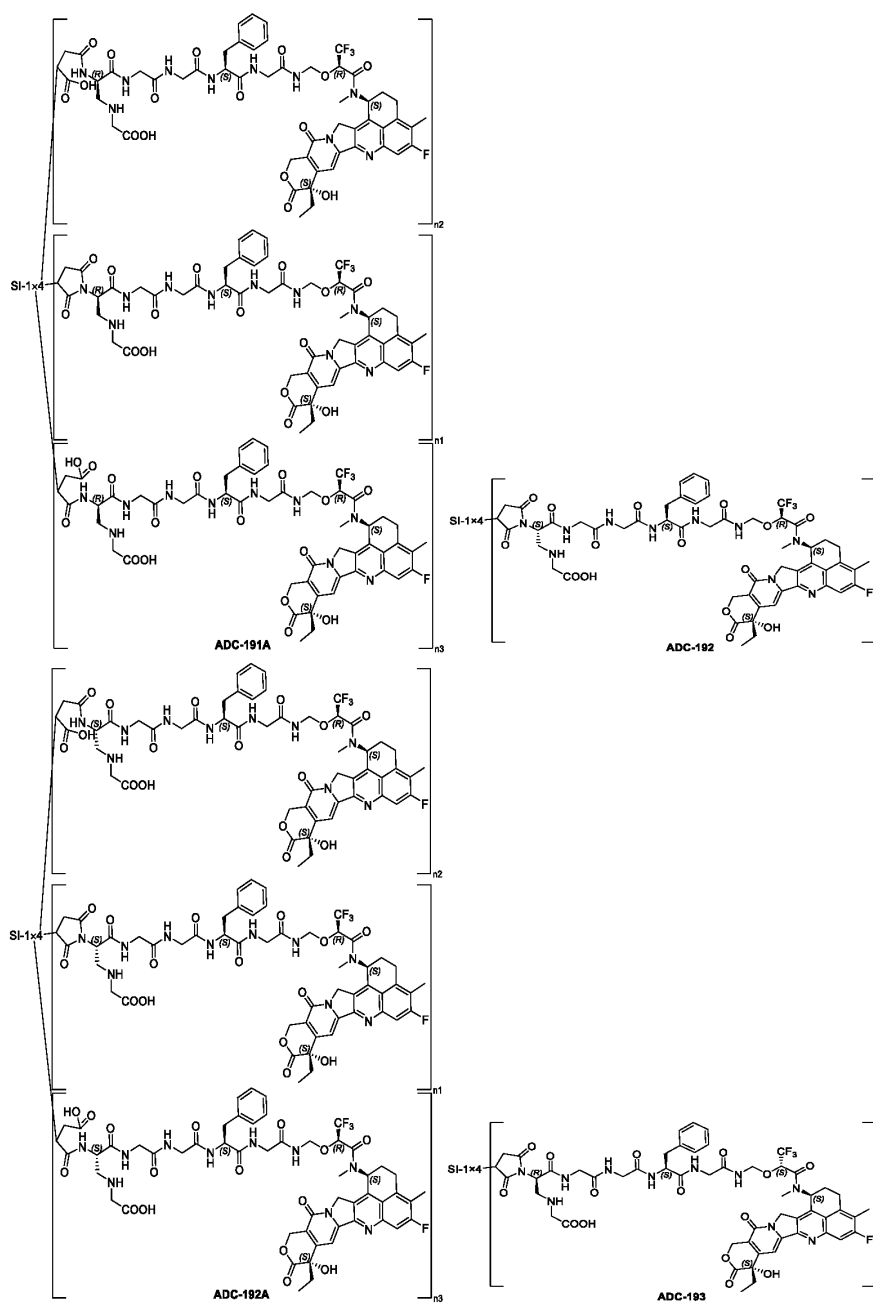


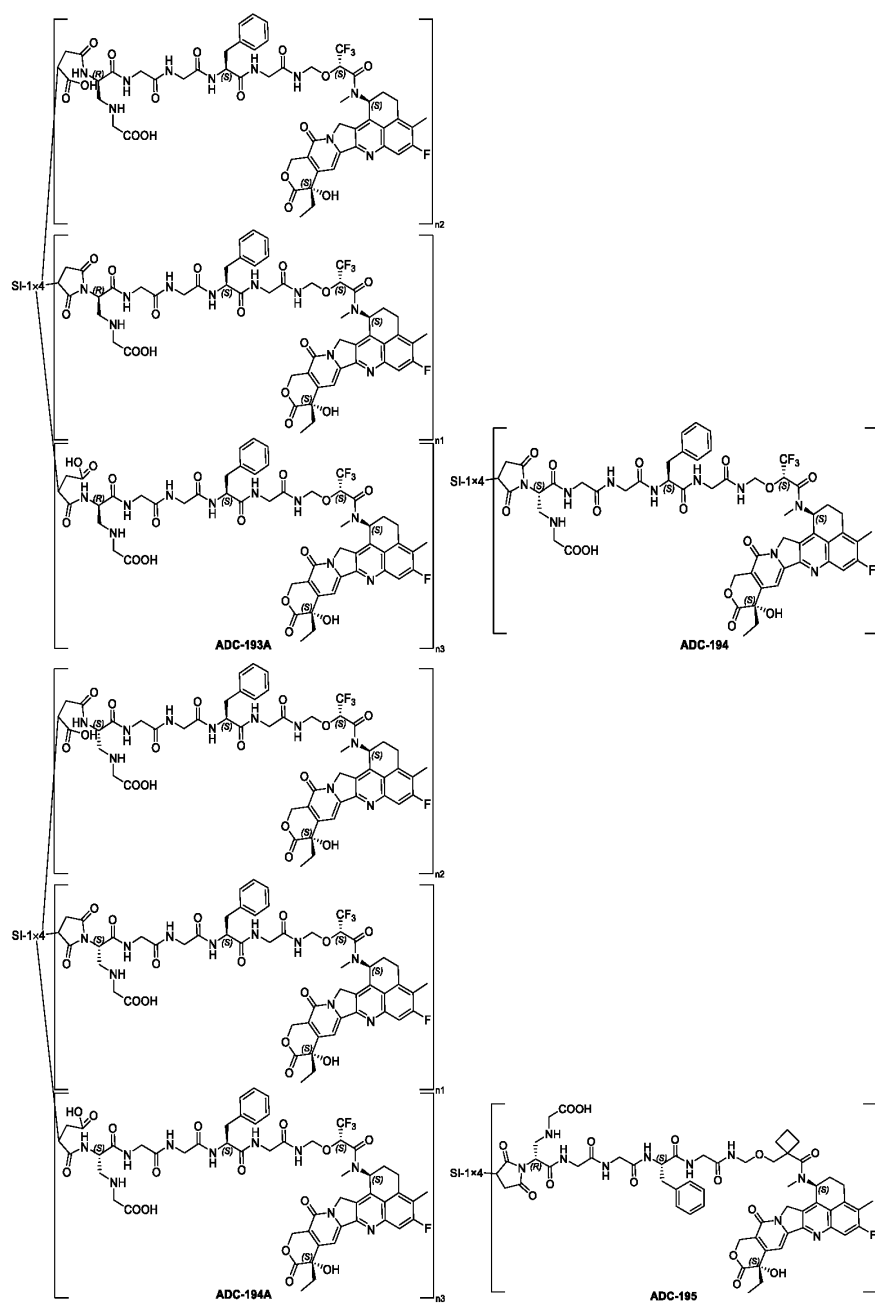


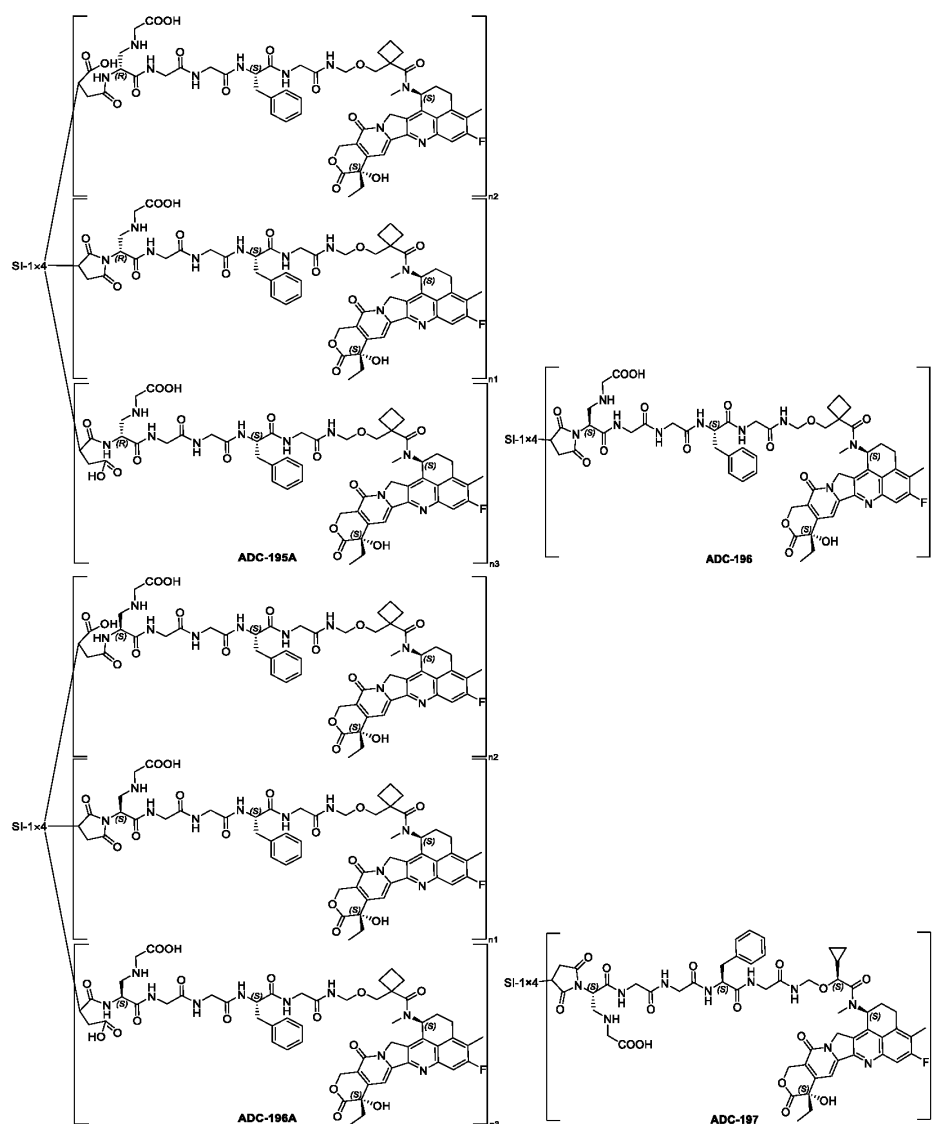


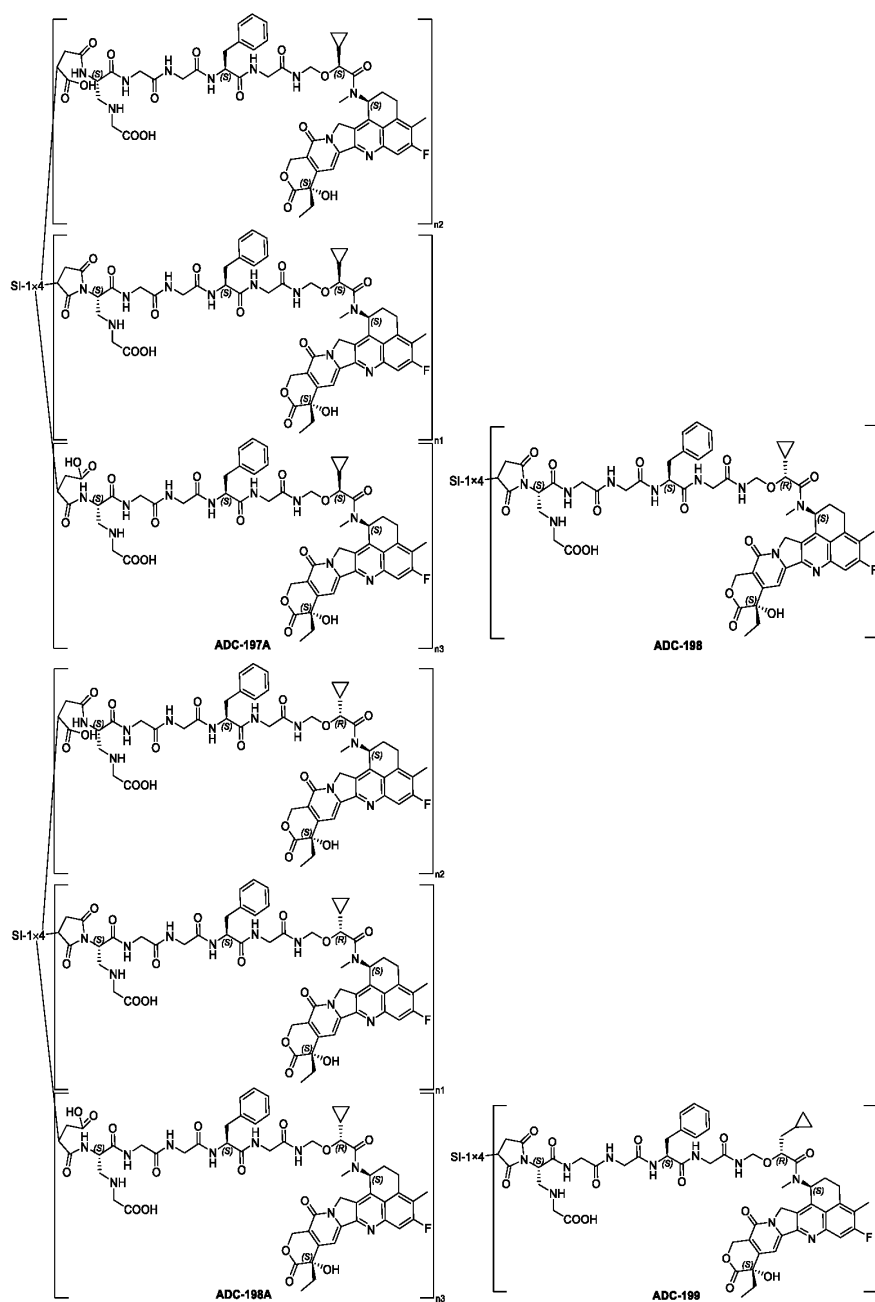


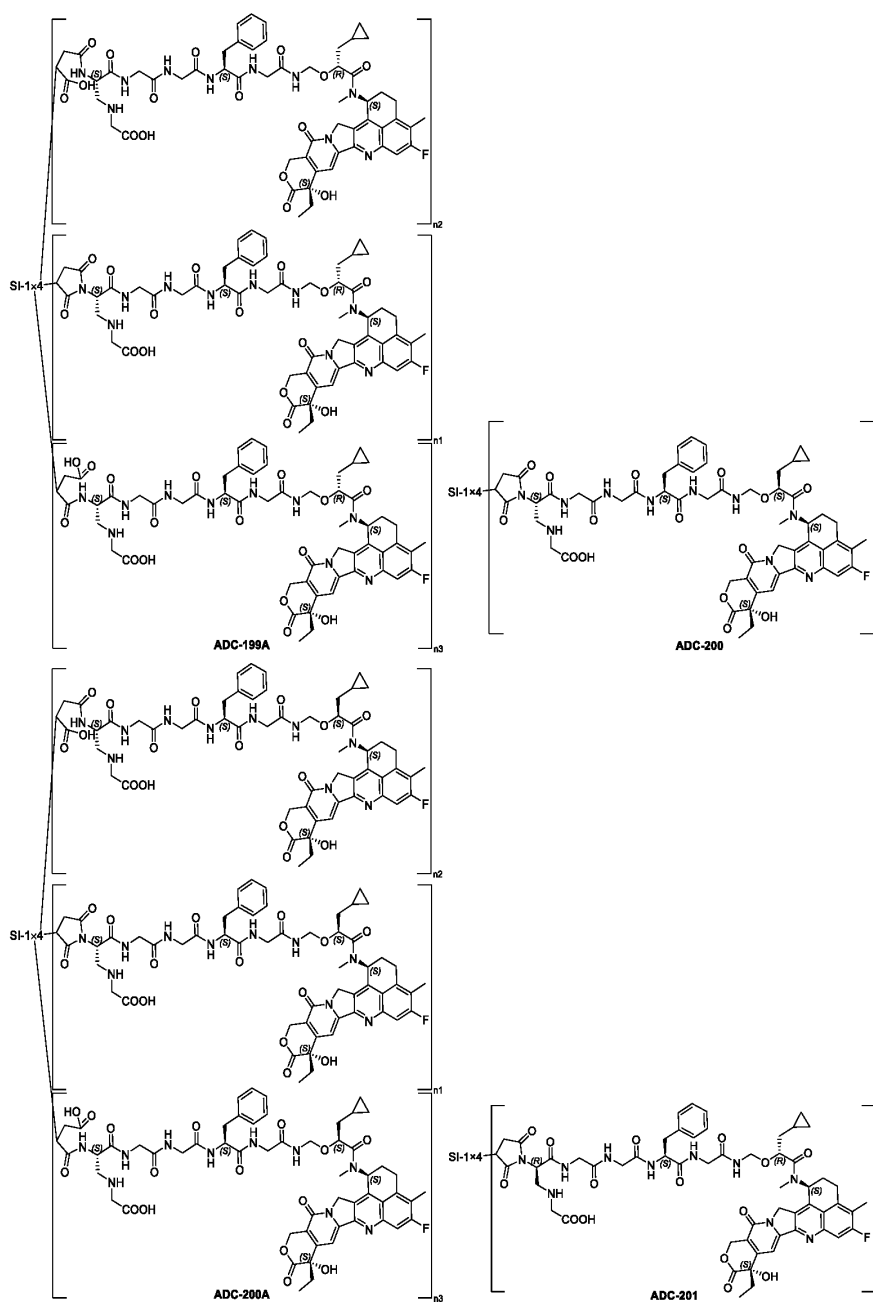


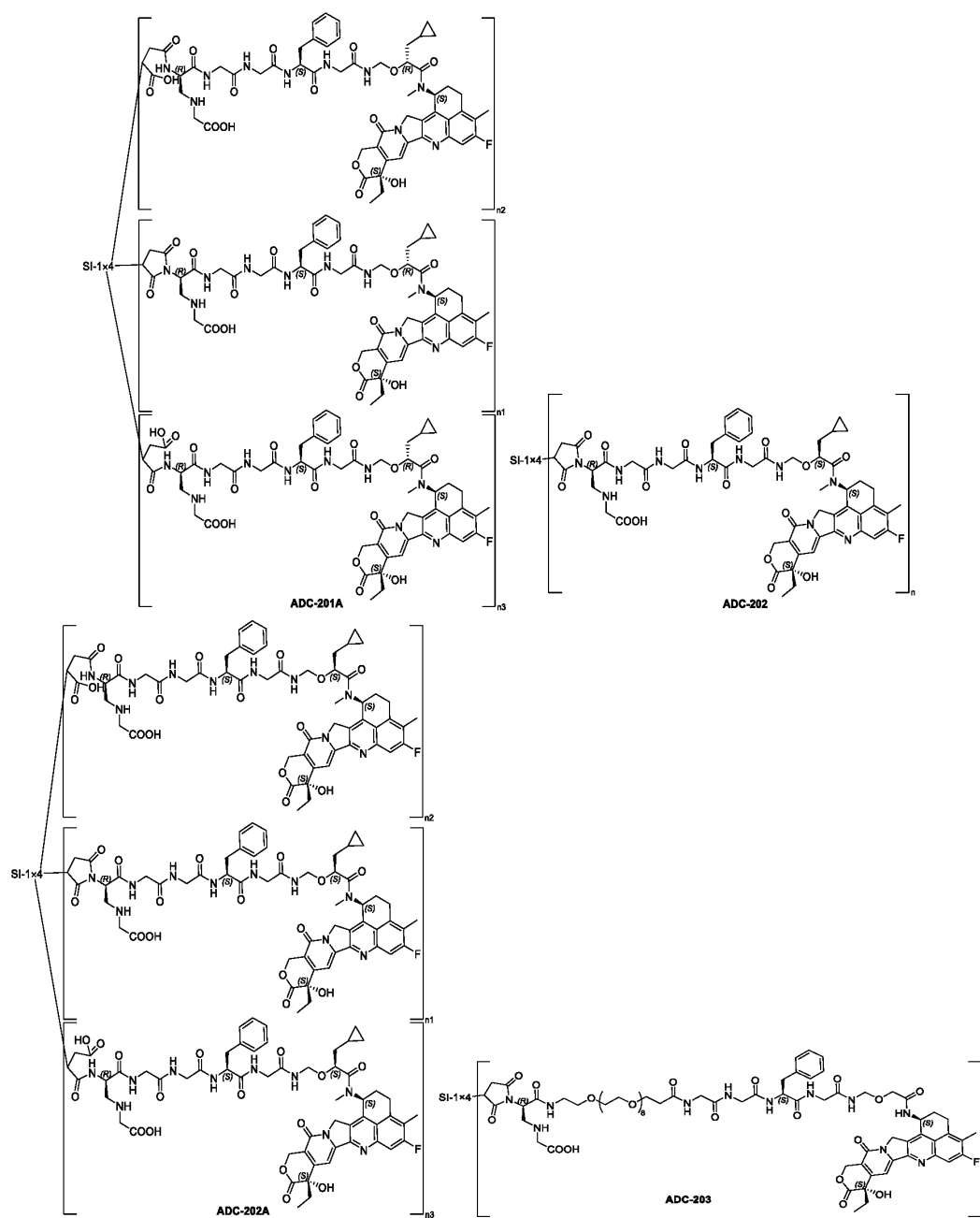


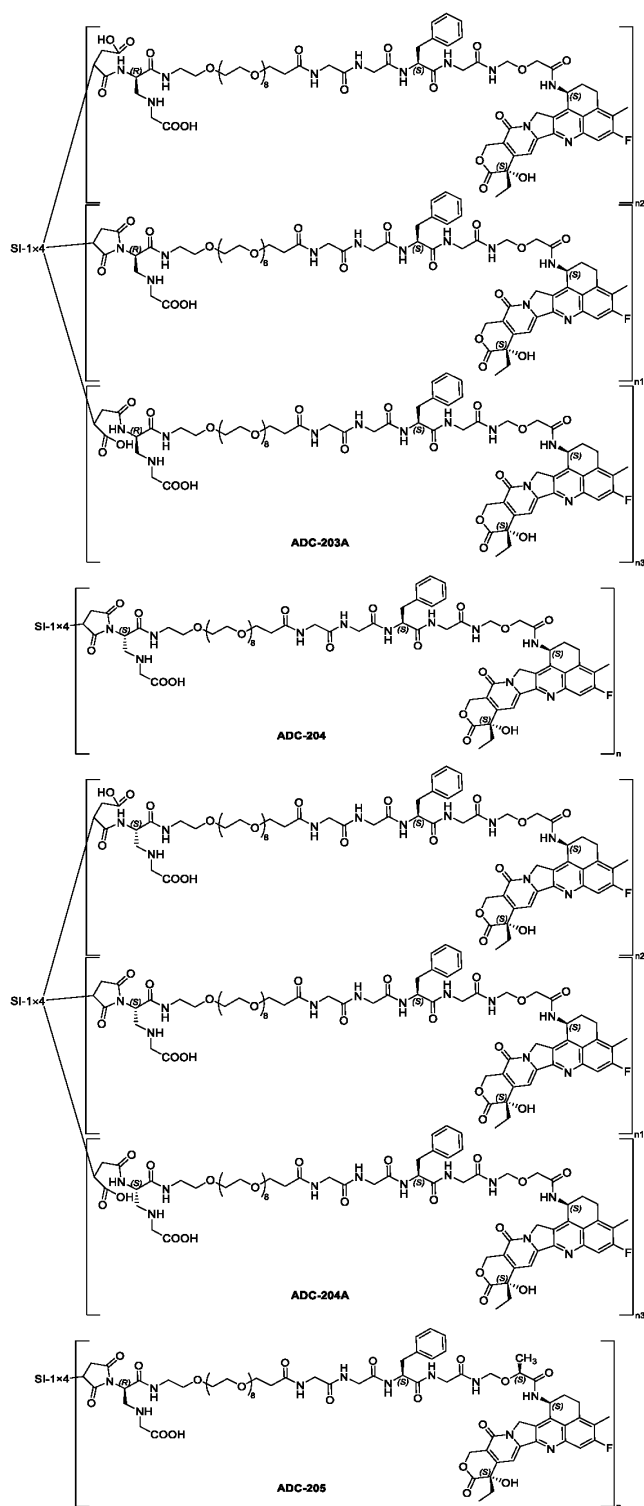


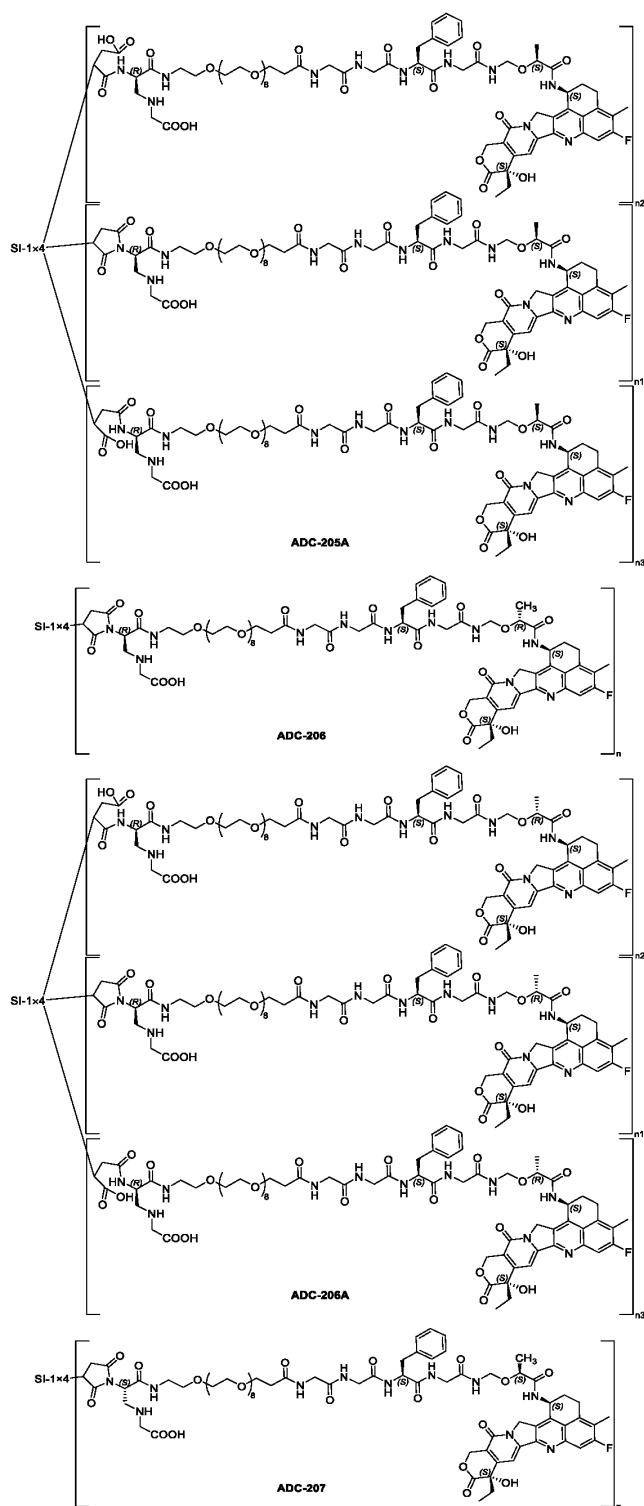


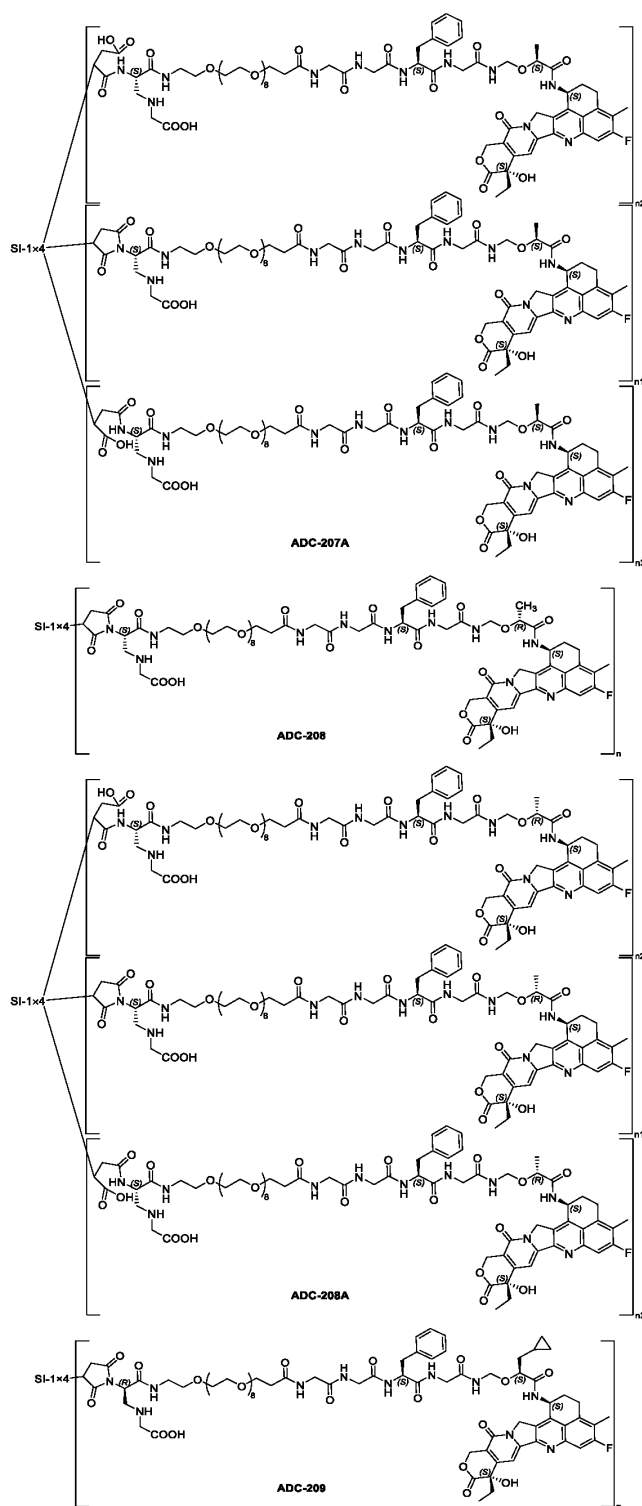


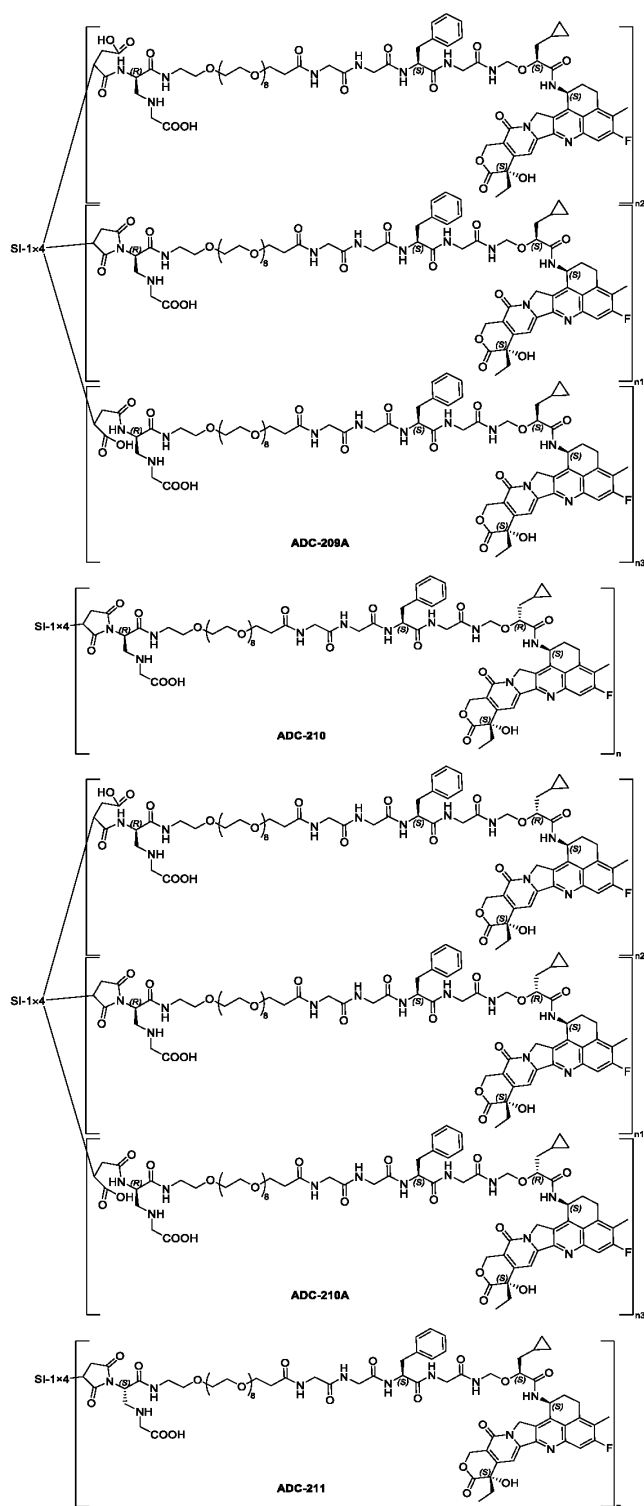


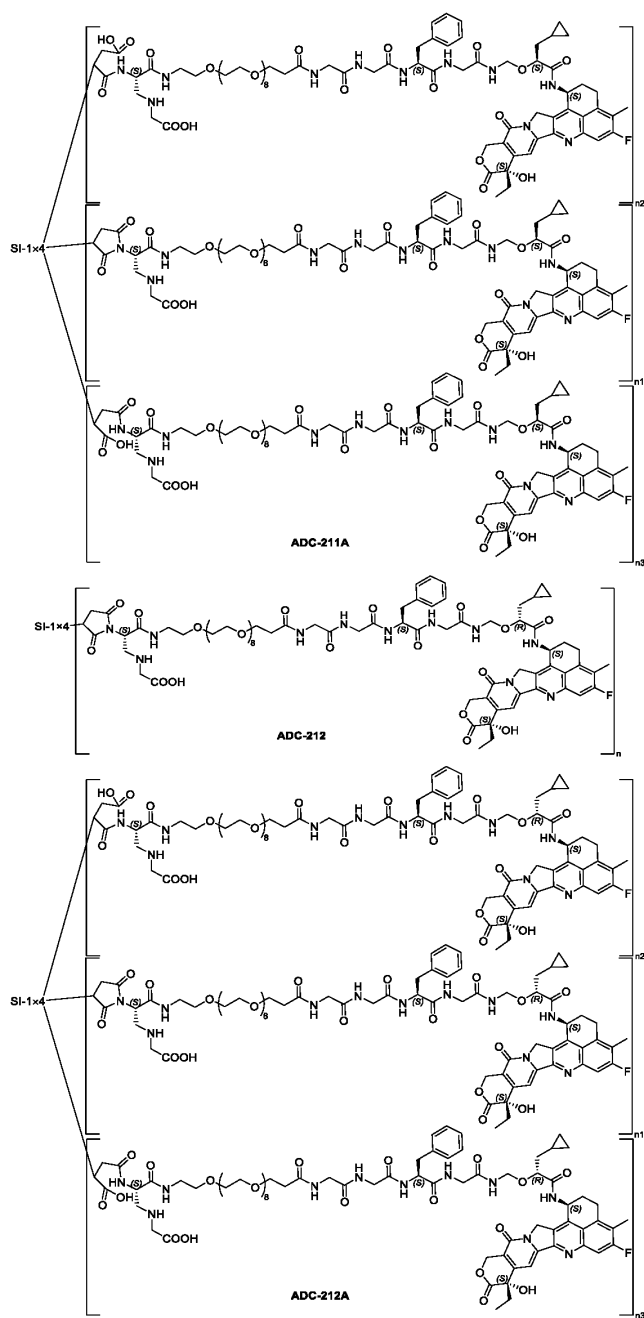


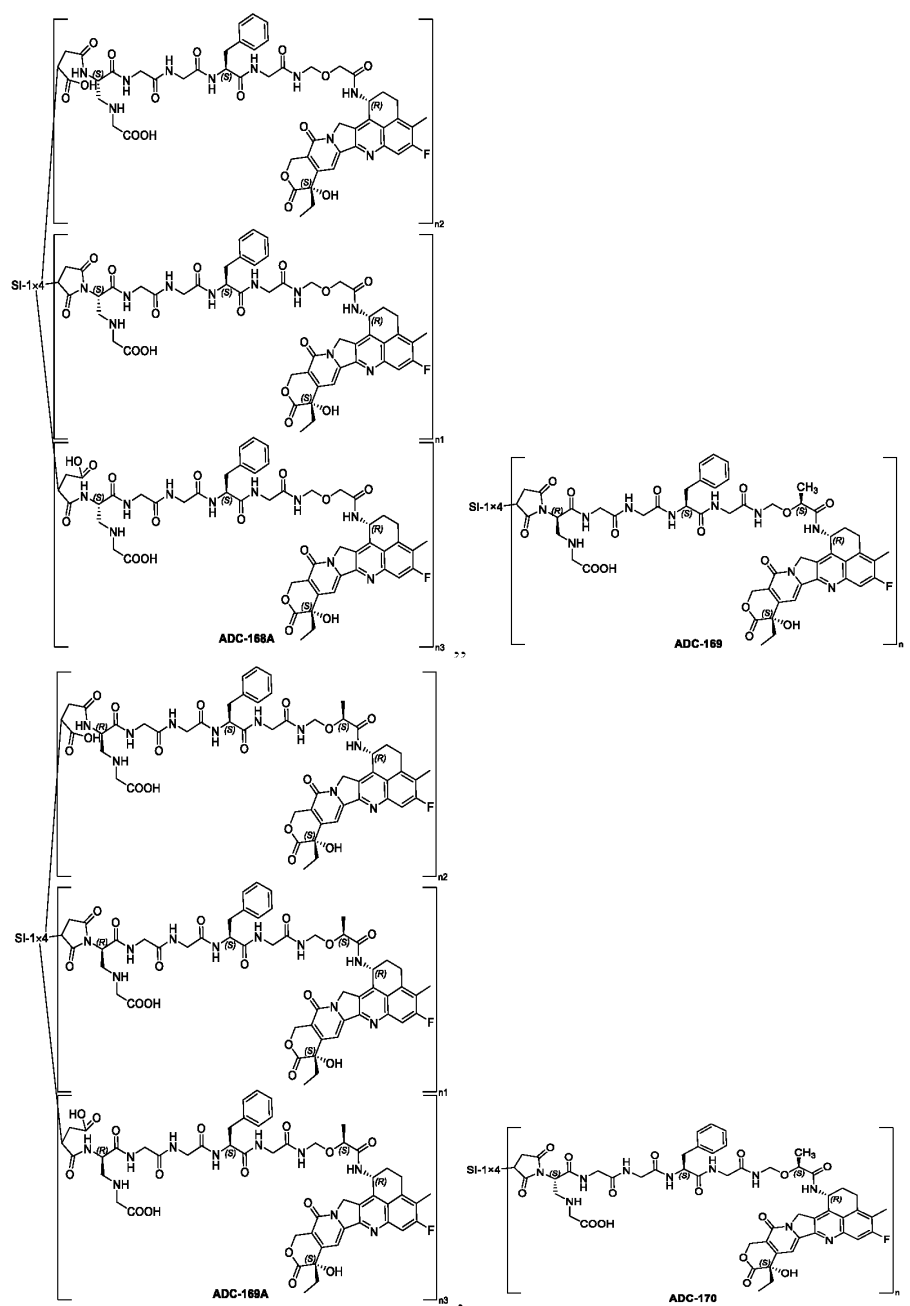


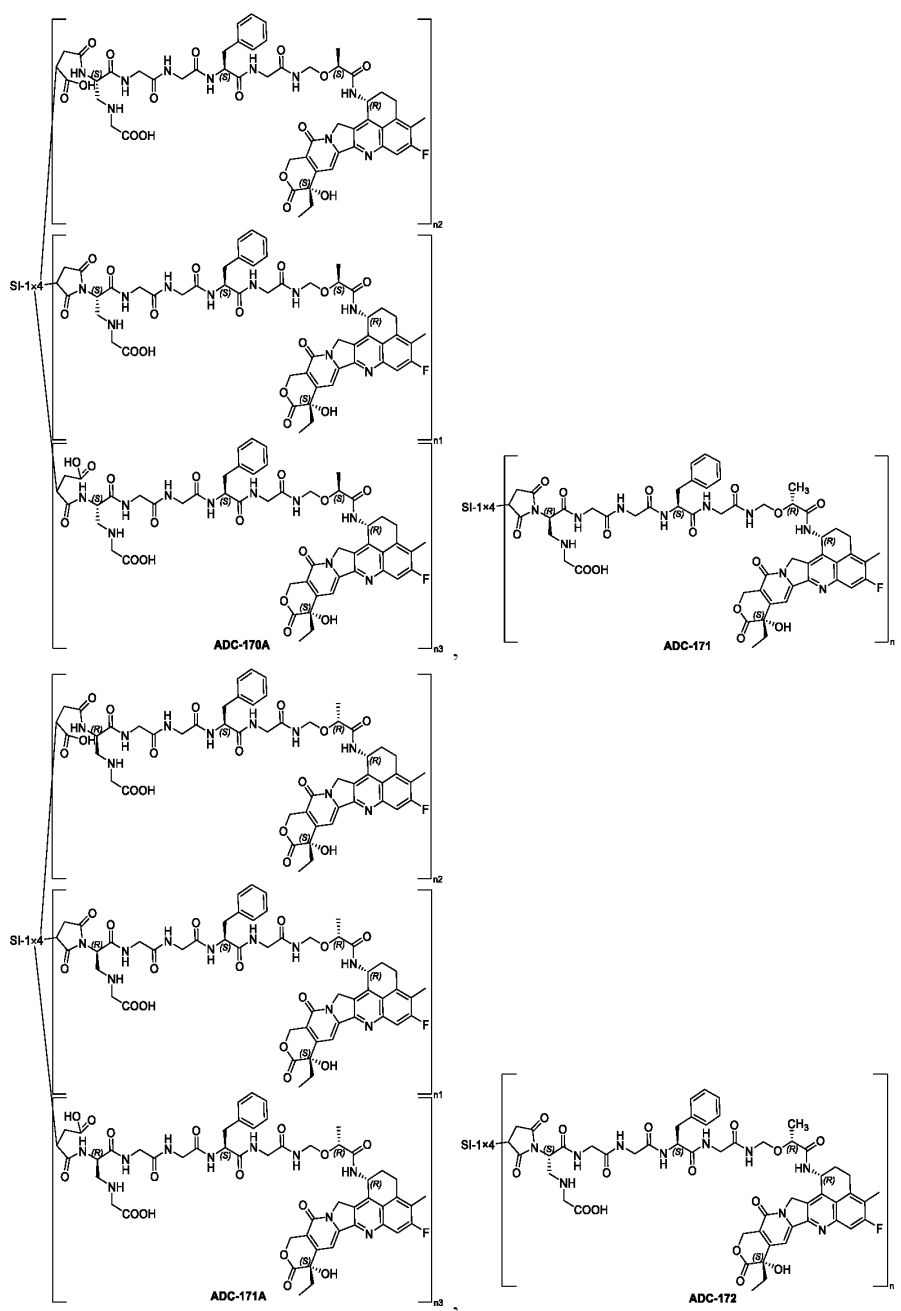


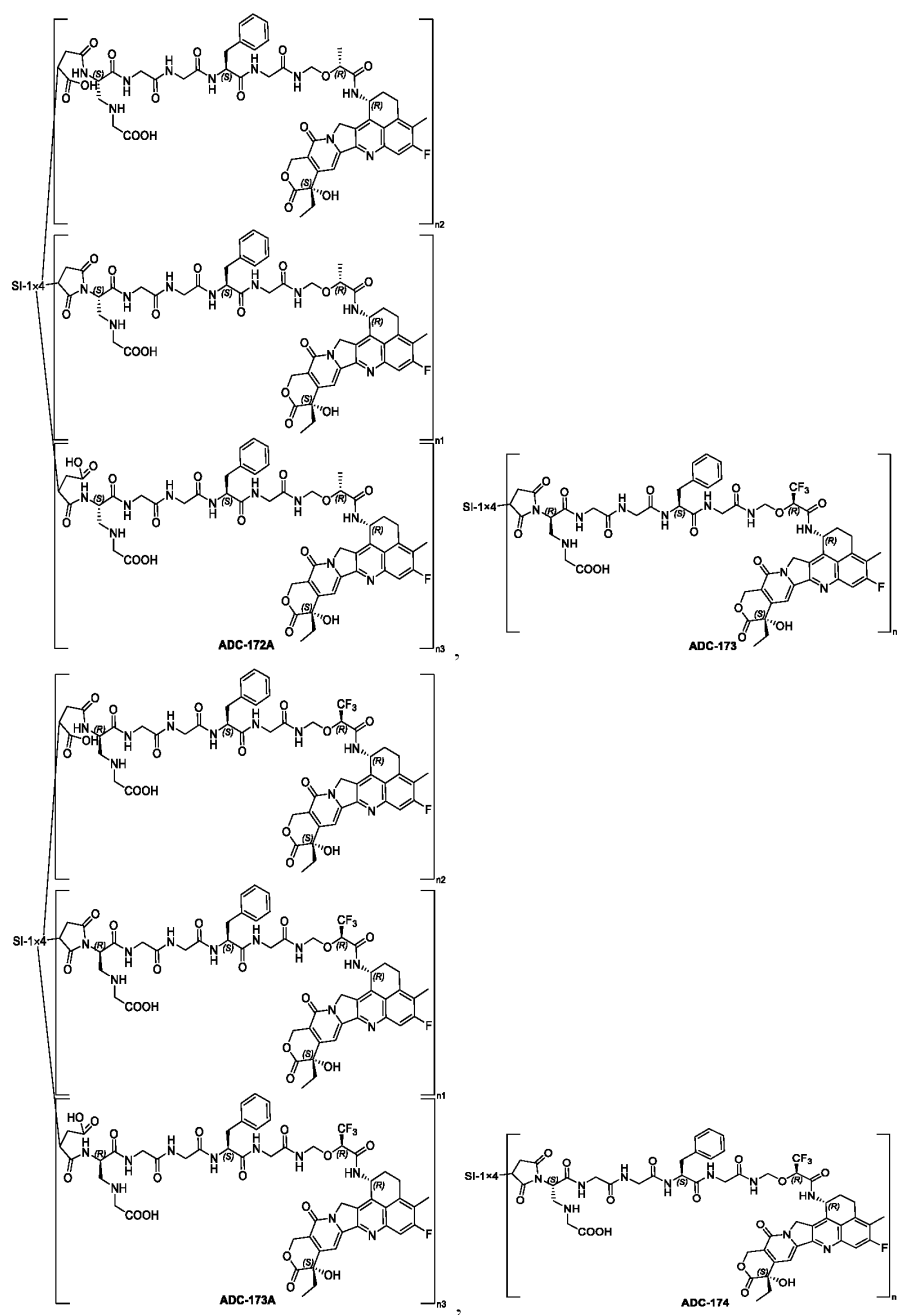


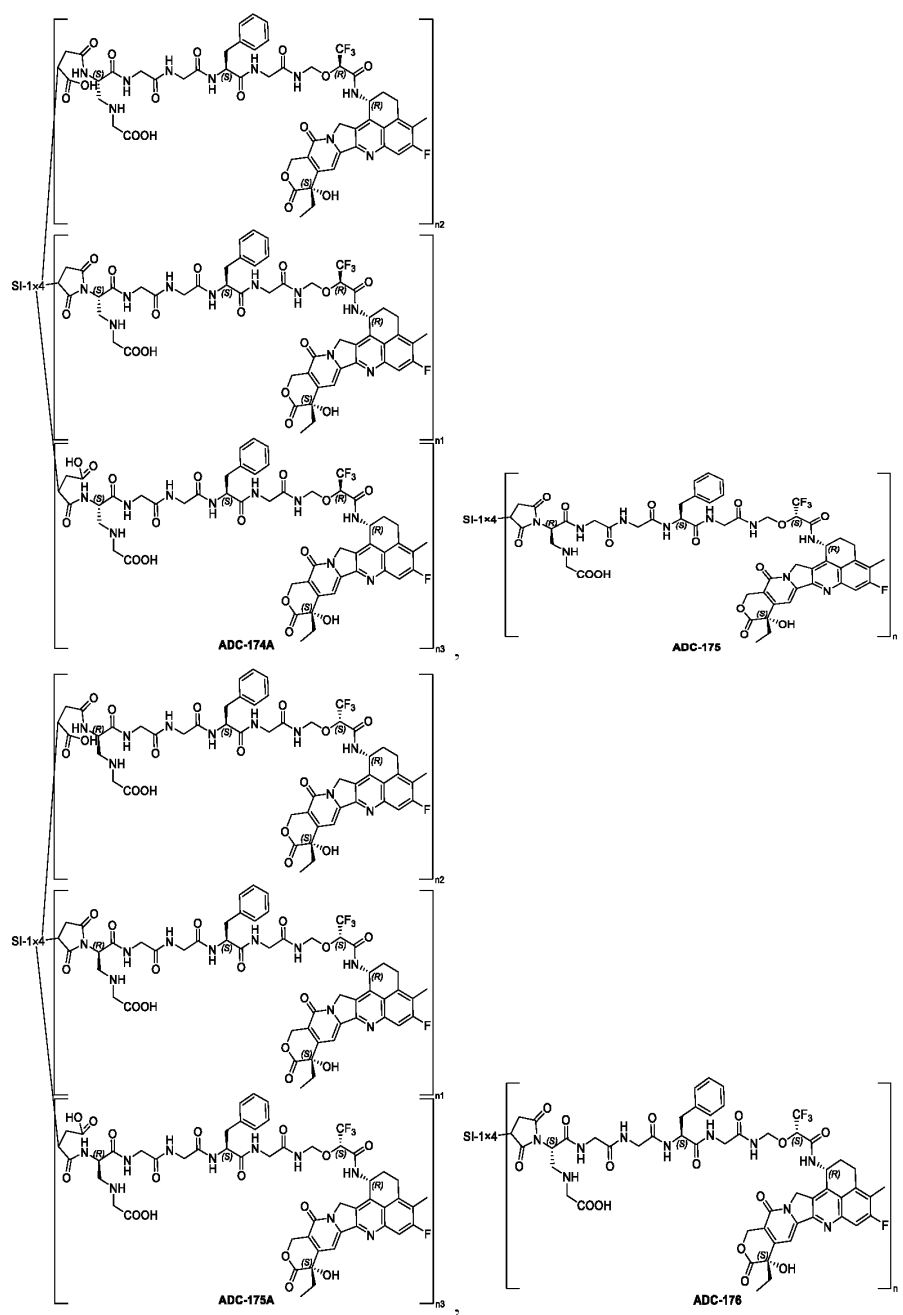


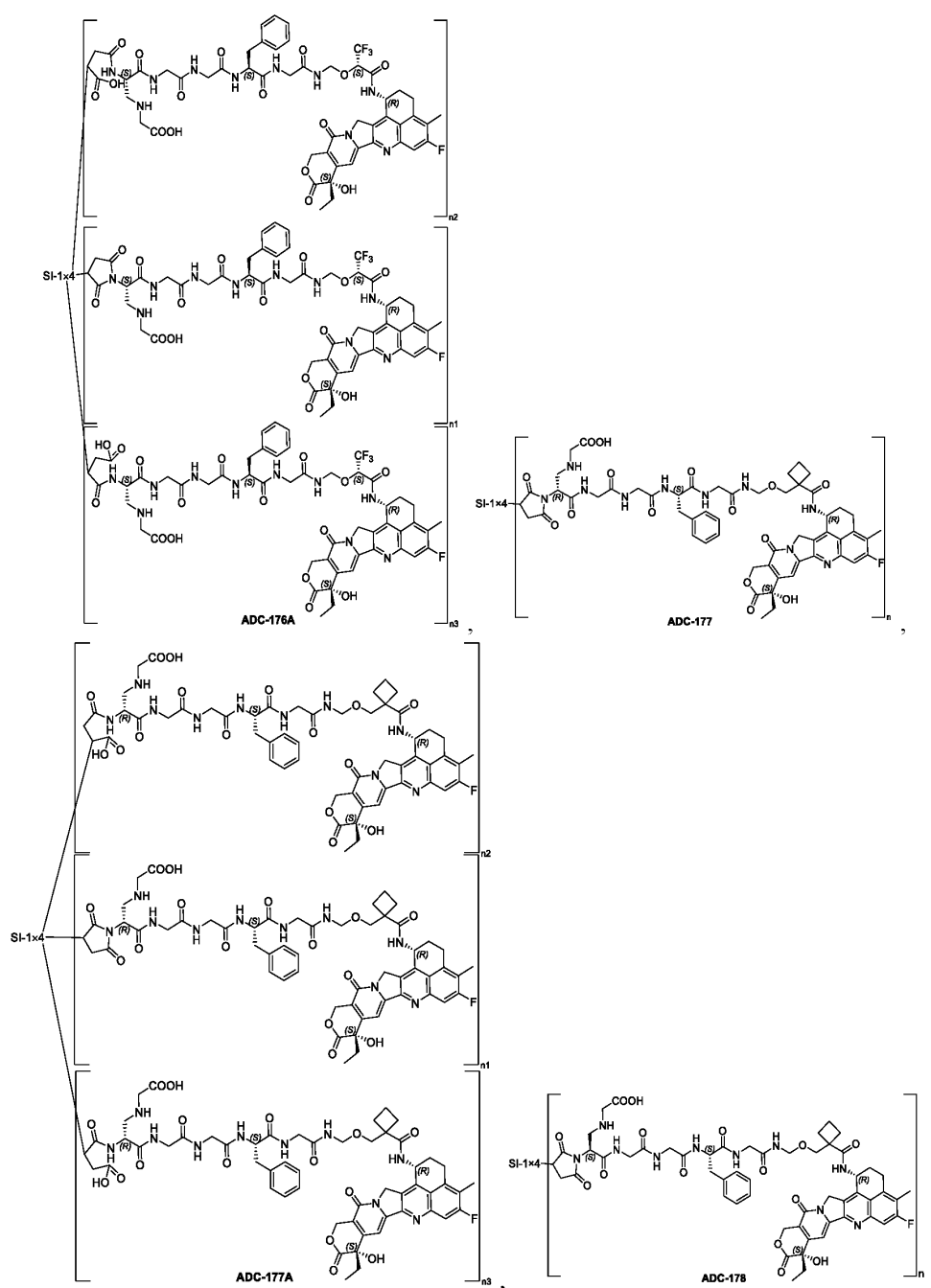


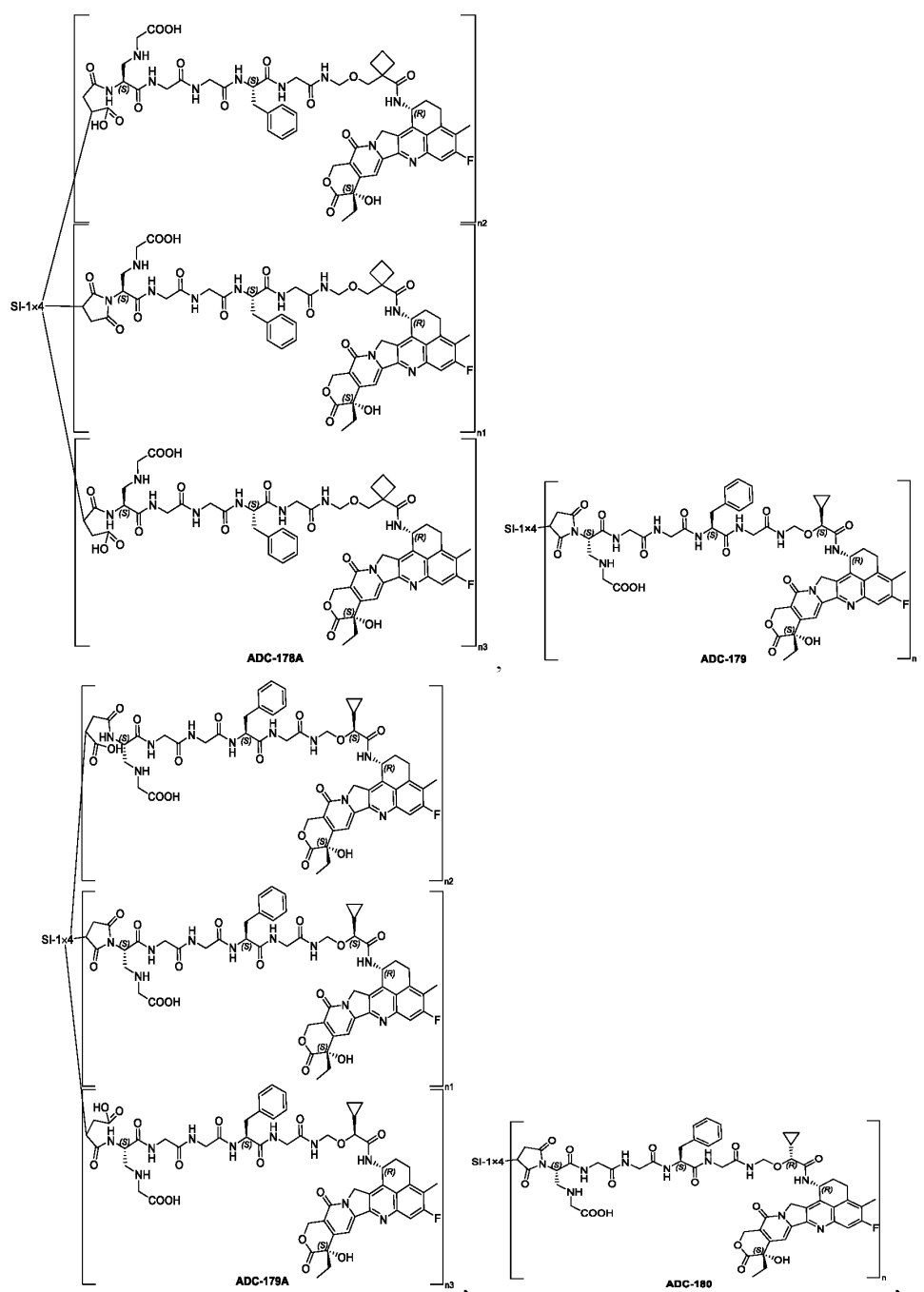


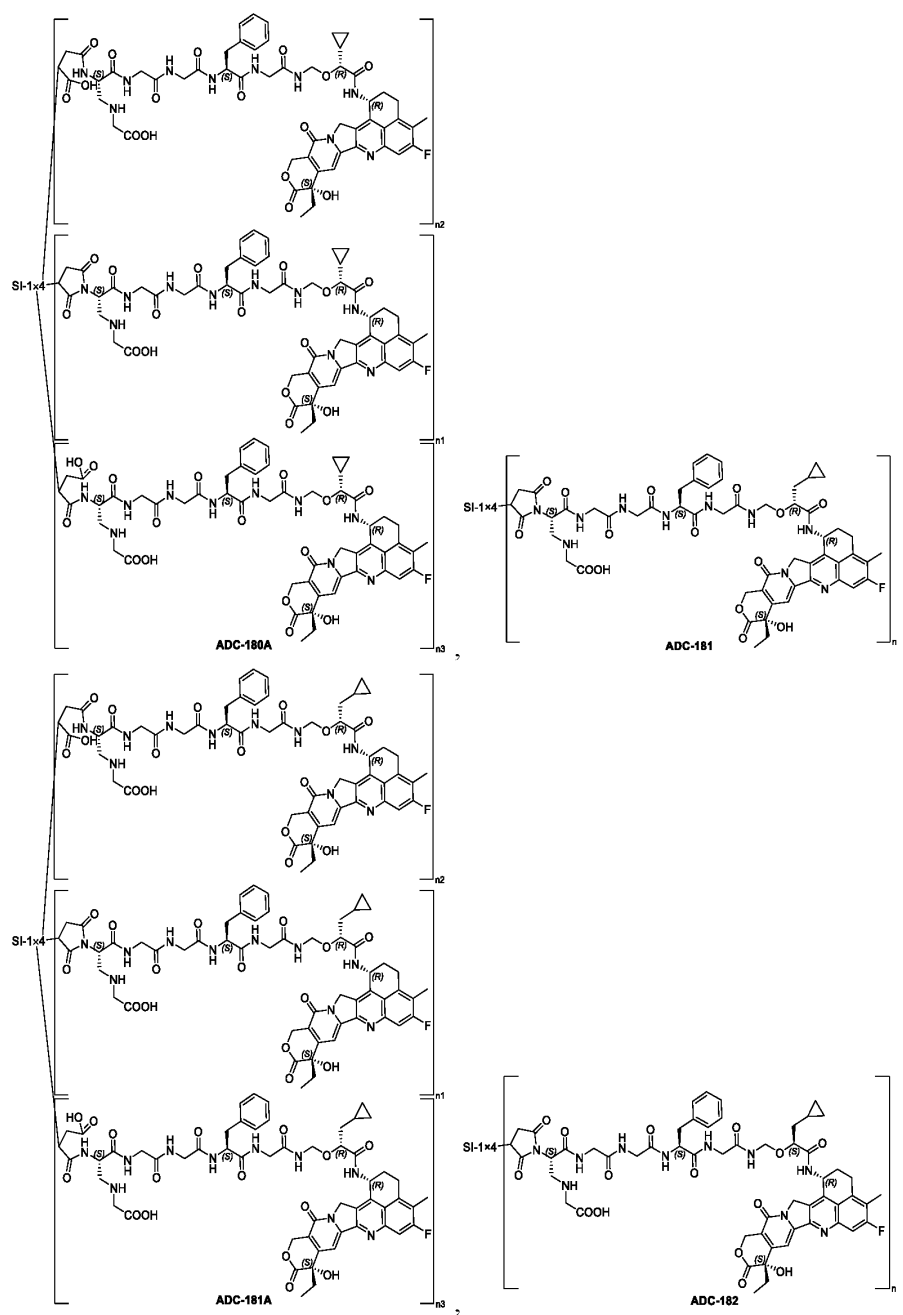


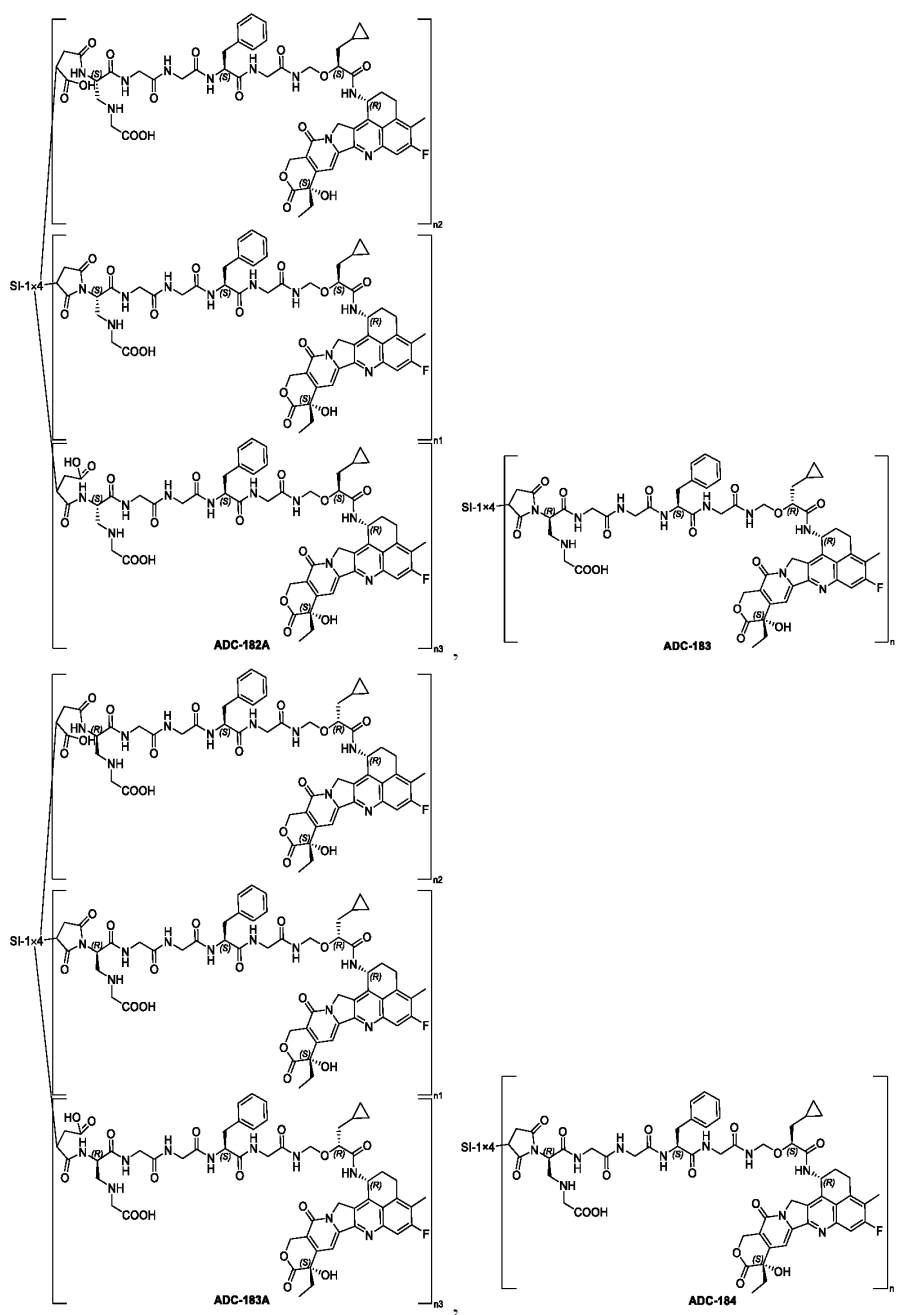


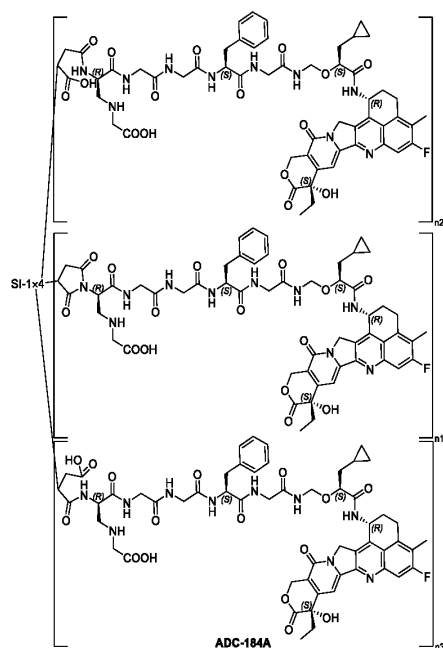










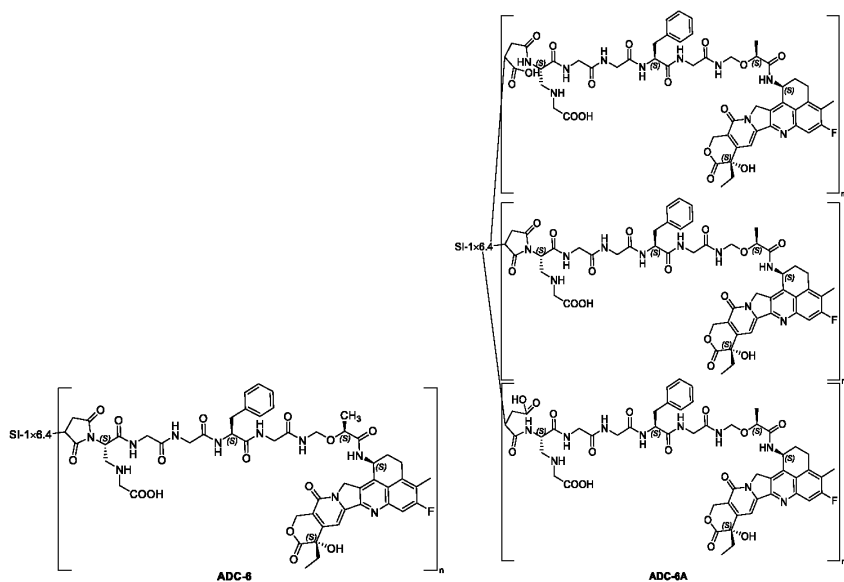


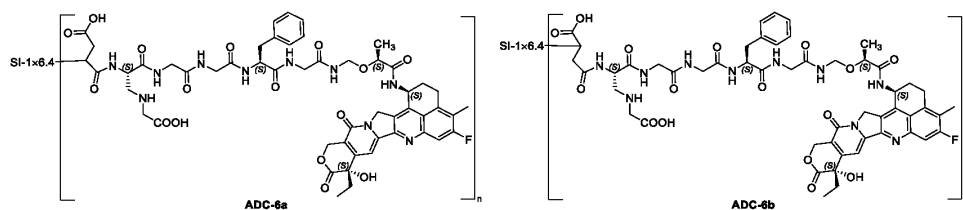
wherein:

SI-1 x 4 is a bispecific antibody or antigen-binding fragment thereof having a binding specificity to both EGFR and HER3,

n is an integer of 1-10, wherein n1, n2, and n3 are each independently chosen from any integer or any decimal number from 0-10, n1, n2, and n3 are not simultaneously 0, and $1 \leq n1 + n2 + n3 \leq 10$.

52. The method of Claim 1-15, wherein the ligand-camptothecin derivative conjugate of Formula I, or a pharmaceutically acceptable salt or solvent compound thereof, comprises the following structure or a butanediimide ring-opening structure thereof or an isomer thereof:



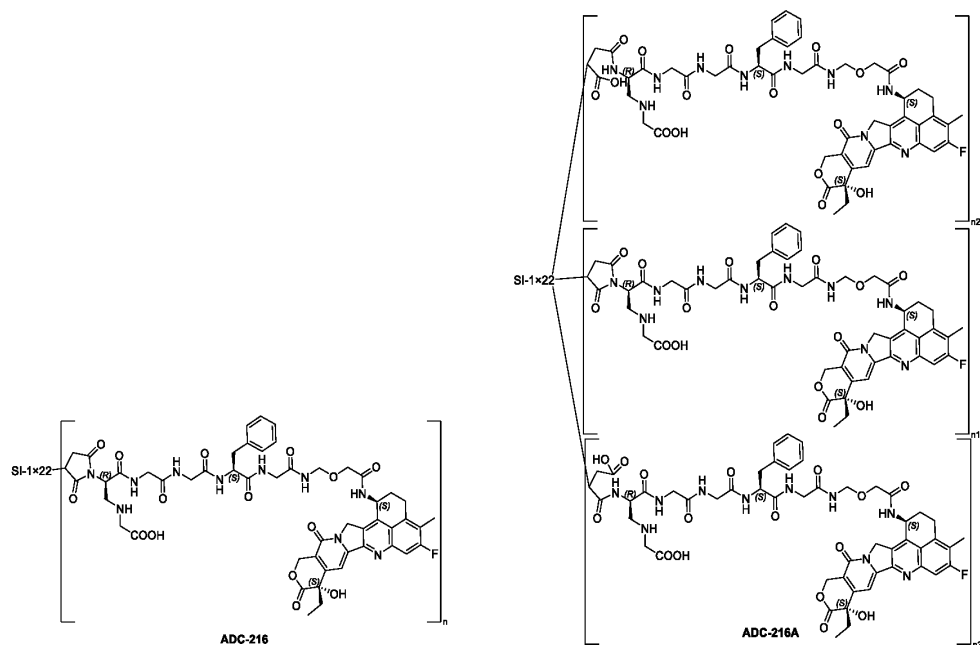


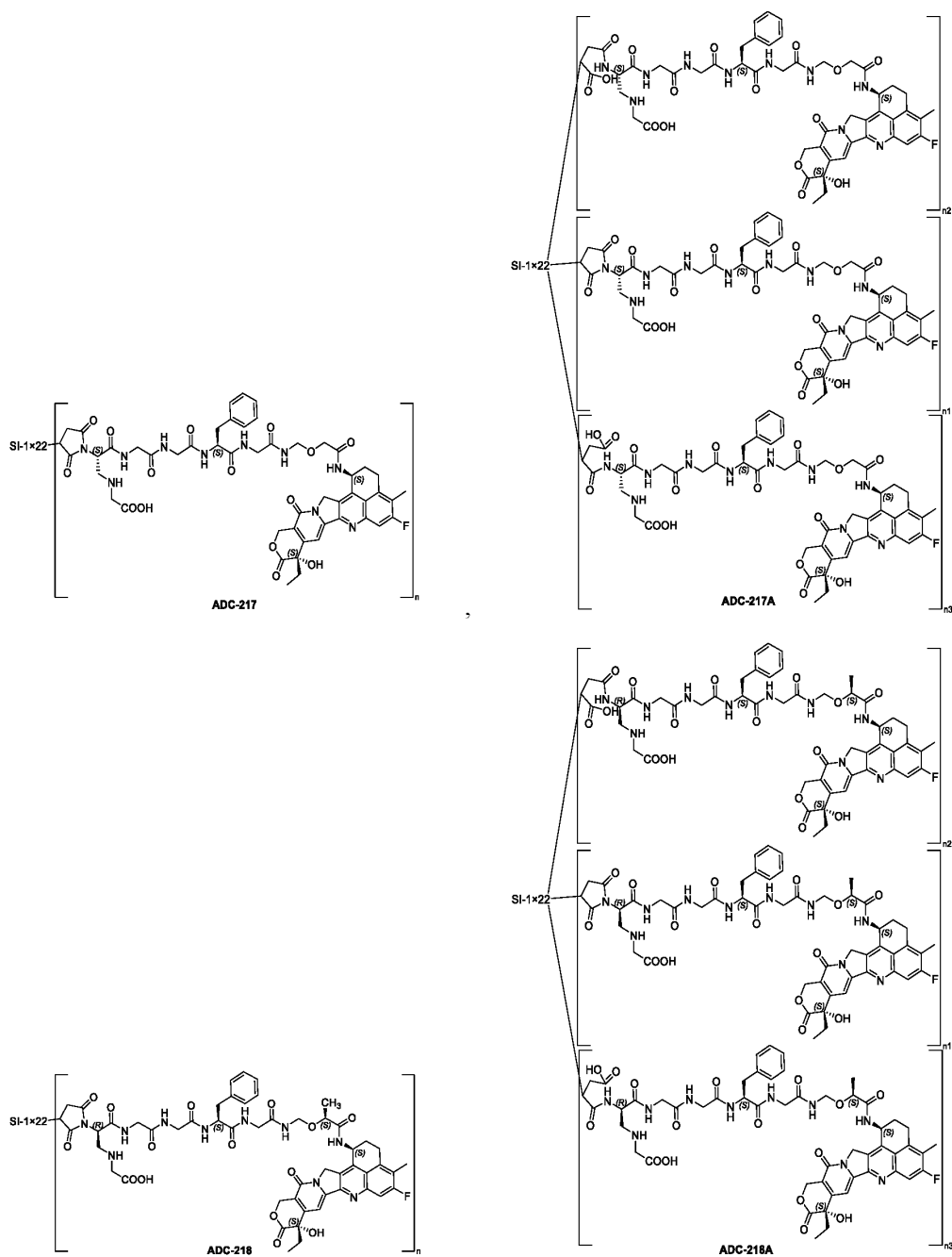
wherein:

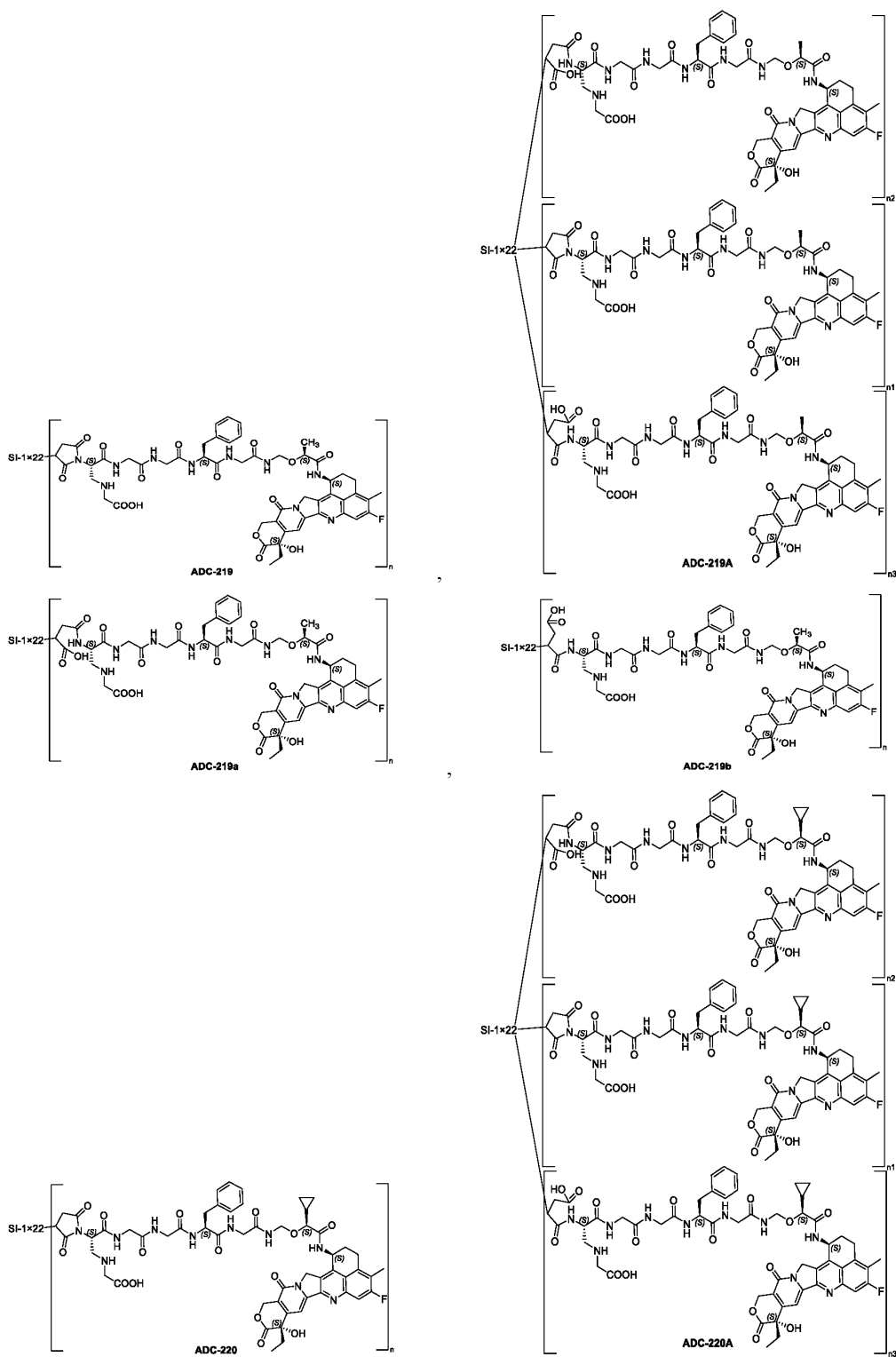
SI-1 x 24 is a bispecific antibody or antigen-binding fragment thereof having a binding specificity to both EGFR and HER3;

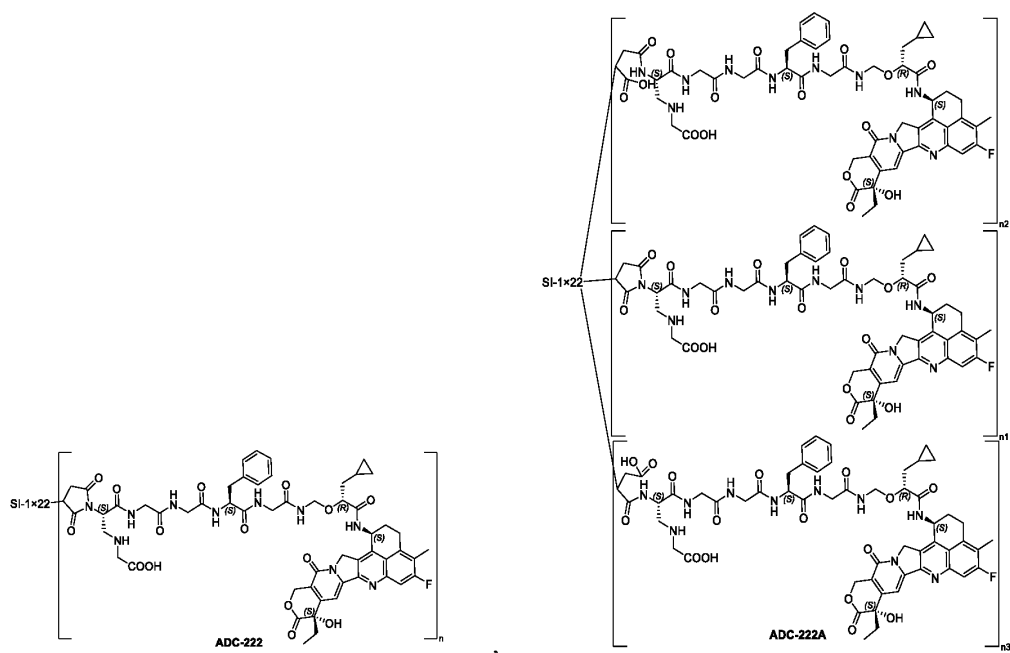
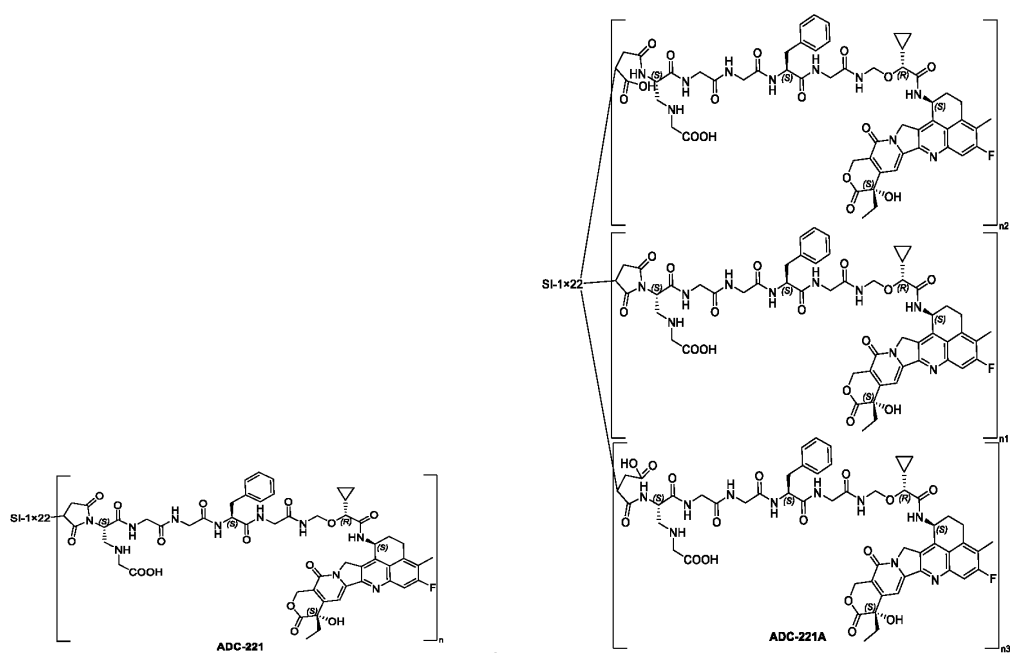
n is an integer of 1-10, wherein n1, n2, and n3 are each independently chosen from any integer or any decimal number from 0-10, n1, n2, and n3 are not simultaneously 0, and $1 \leq n1 + n2 + n3 \leq 10$.

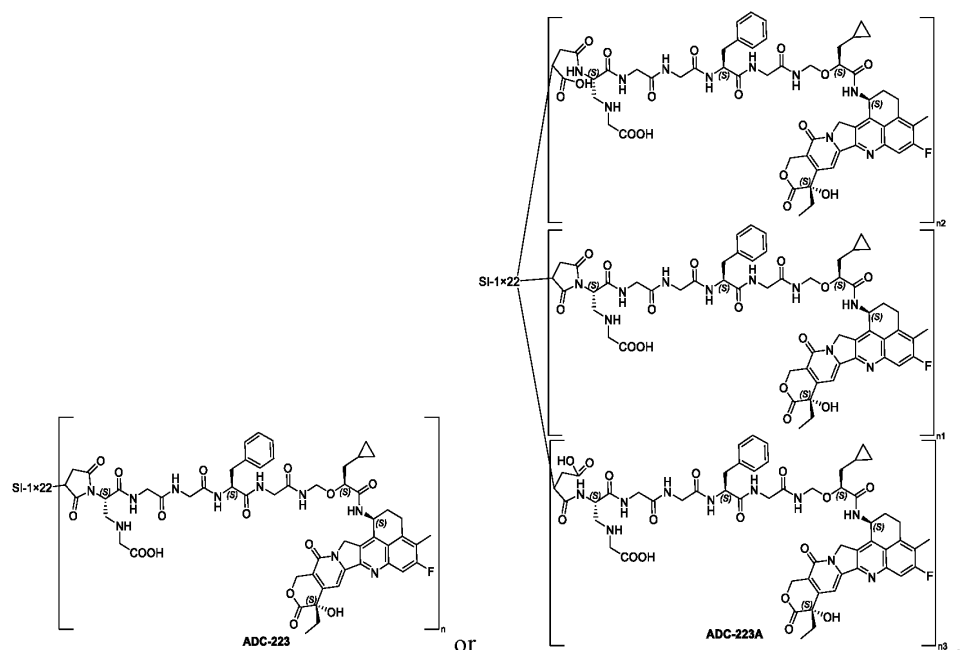
53. The method of Claim 1-15, wherein the ligand-camptothecin derivative conjugate of Formula I, or a pharmaceutically acceptable salt or solvent compound thereof, comprises the following structure, or a butanediimide ring-opening structure thereof, or an isomer thereof:









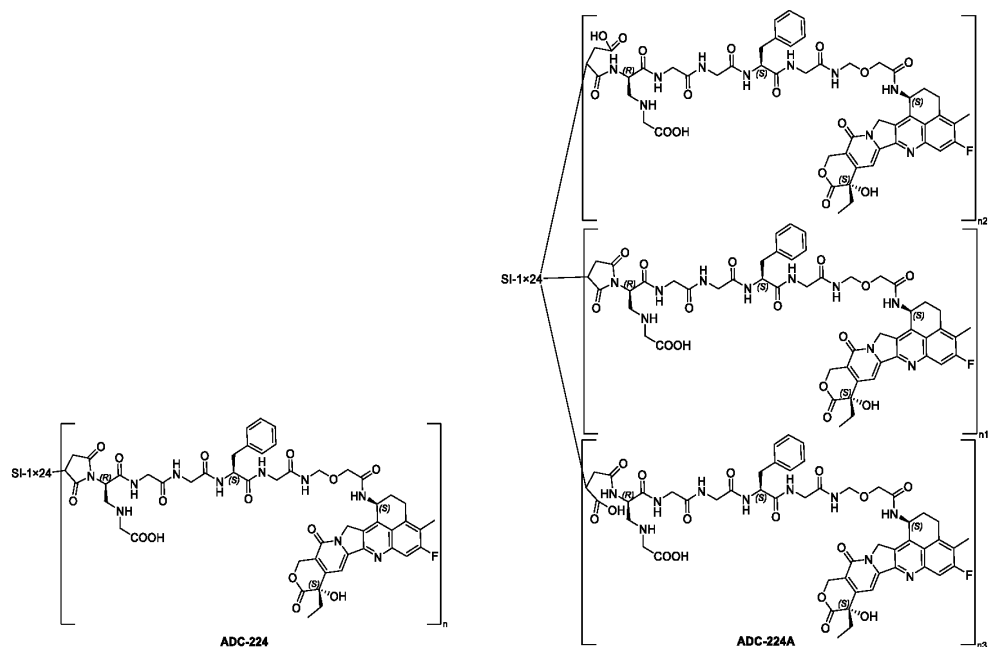


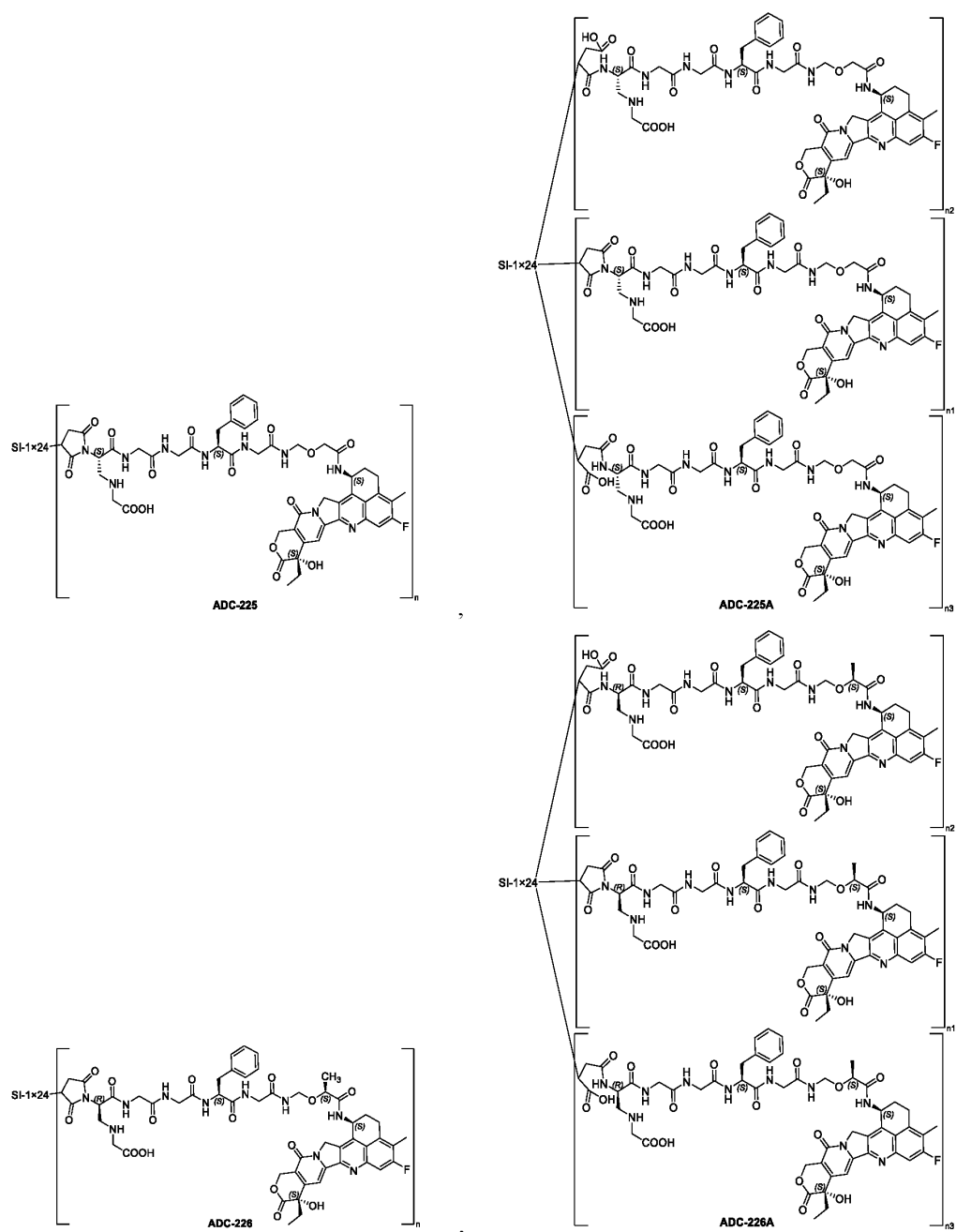
wherein:

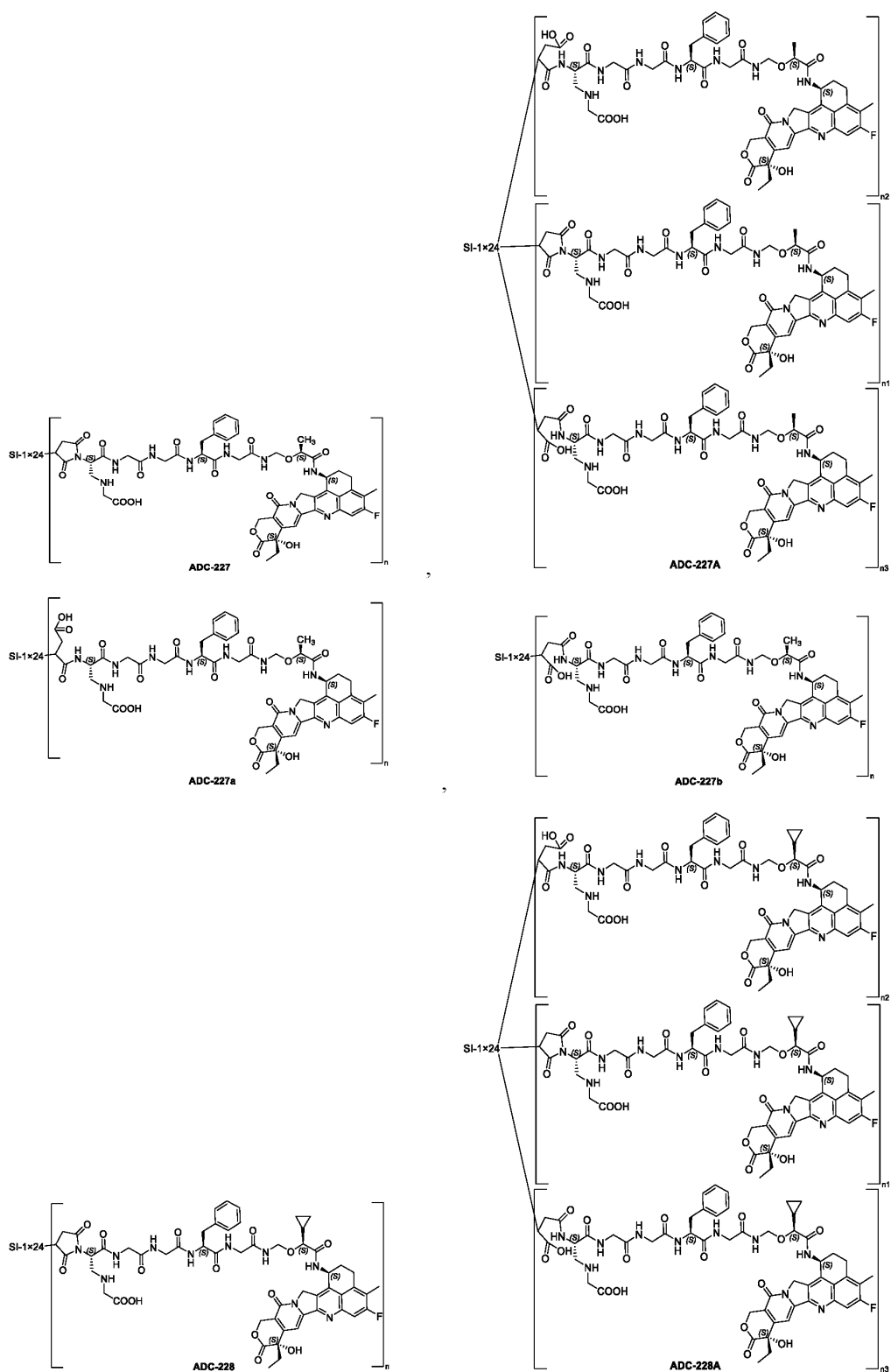
SI-1 x 22 is a bispecific antibody or antigen-binding fragment thereof having a binding specificity to both EGFR and HER3;

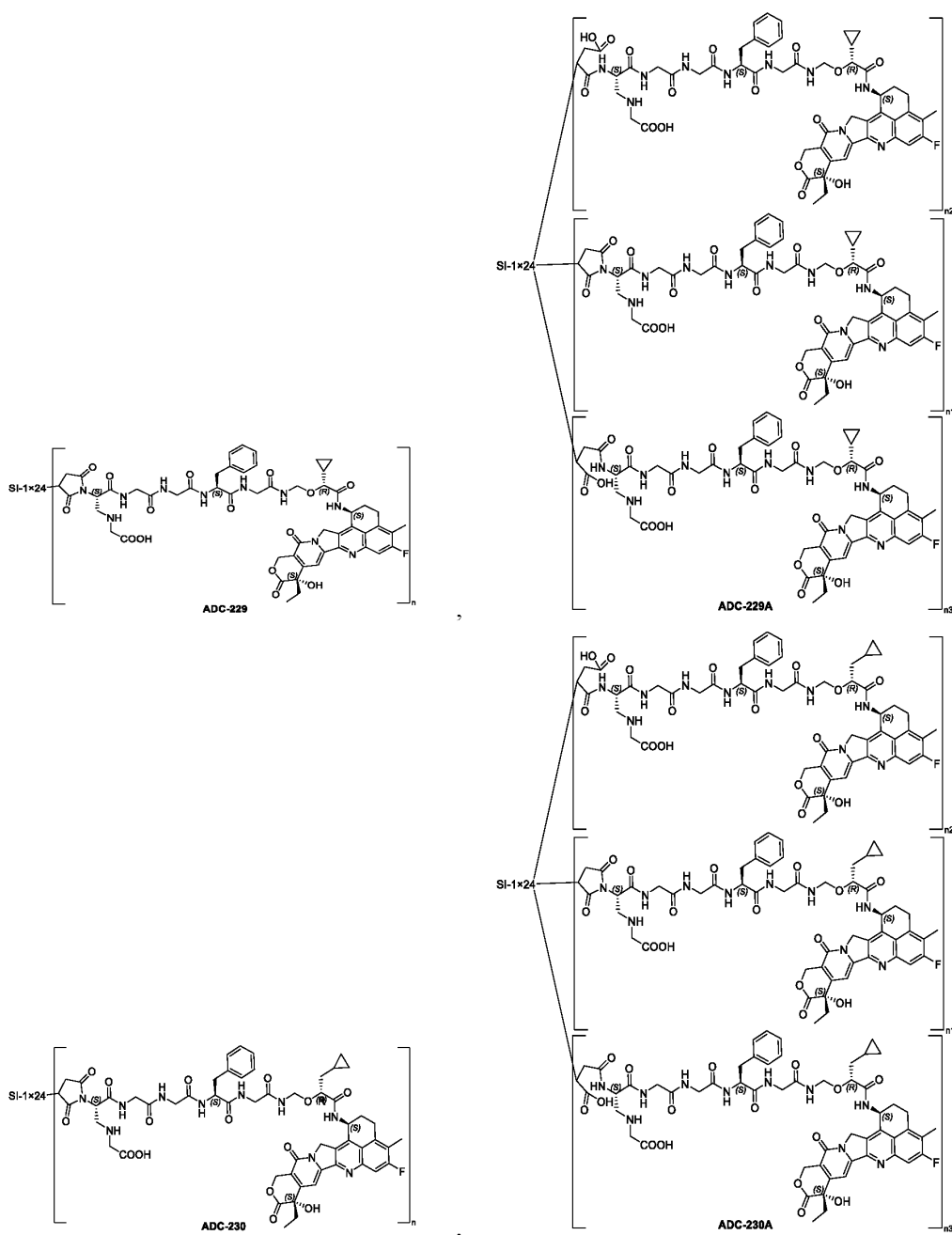
n is an integer of 1-10, wherein n1, n2, and n3 are each independently chosen from any integer or any decimal number from 0-10, n1, n2, and n3 are not simultaneously 0, and $1 \leq n1 + n2 + n3 \leq 10$.

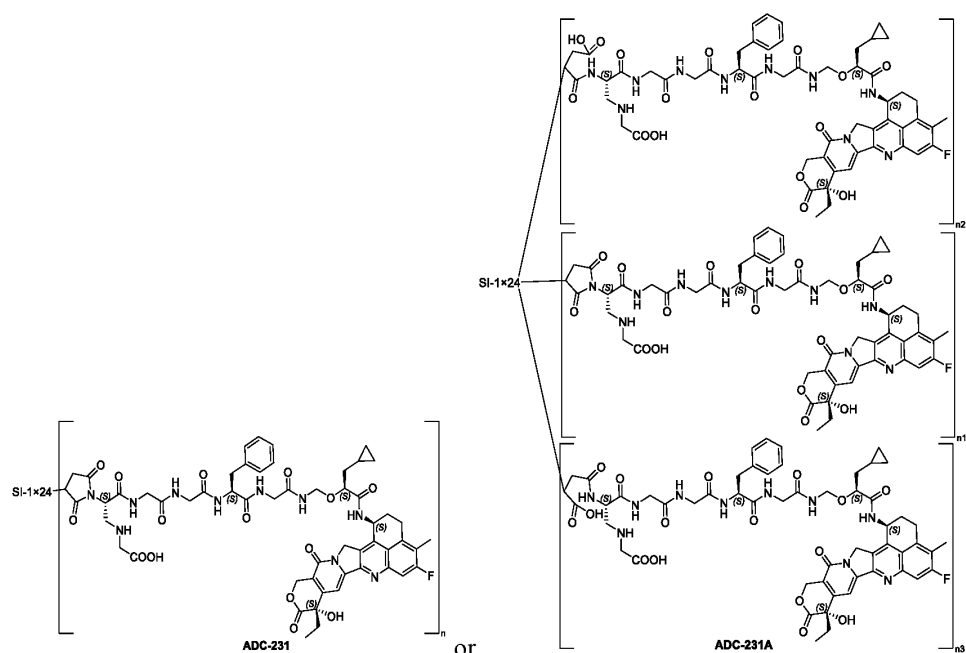
54. The method of Claim 1-15, wherein the ligand-camptothecin derivative conjugate of Formula I, or a pharmaceutically acceptable salt or solvent compound thereof, comprises the following structure, or a butanediimide ring-opening structure thereof, or an isomer thereof:









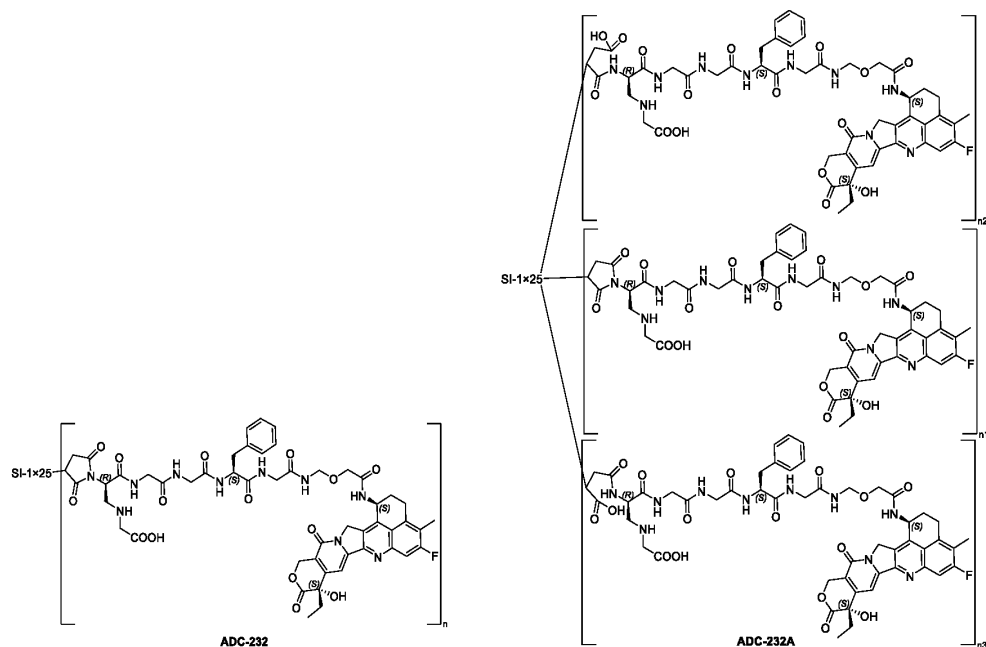


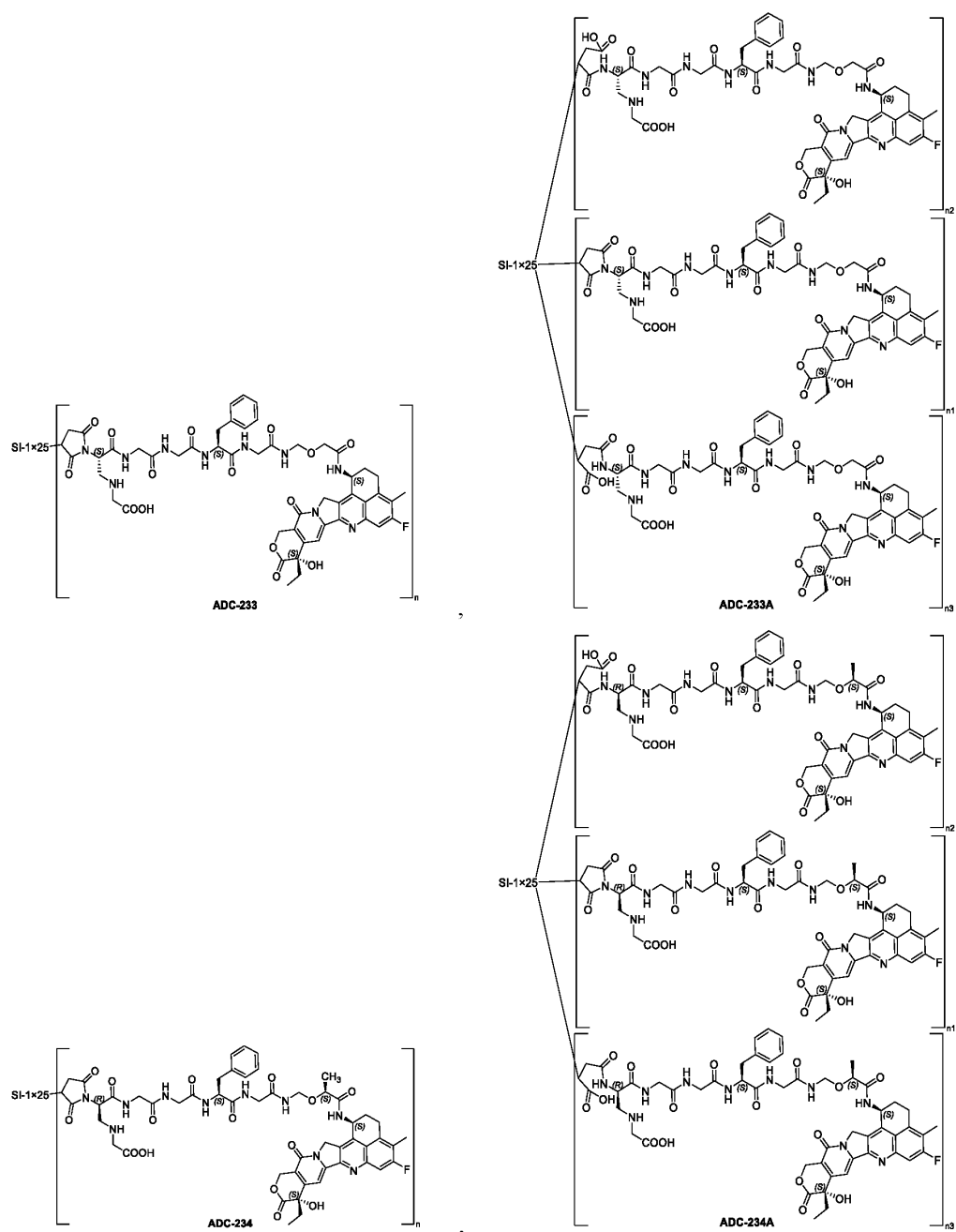
wherein:

SI-1 x 24 is a bispecific antibody or antigen-binding fragment thereof having a binding specificity to both EGFR and HER3;

n is an integer of 1-10, wherein n_1 , n_2 , and n_3 are each independently chosen from any integer or any decimal number from 0-10, n_1 , n_2 , and n_3 are not simultaneously 0, and $1 \leq n_1 + n_2 + n_3 \leq 10$.

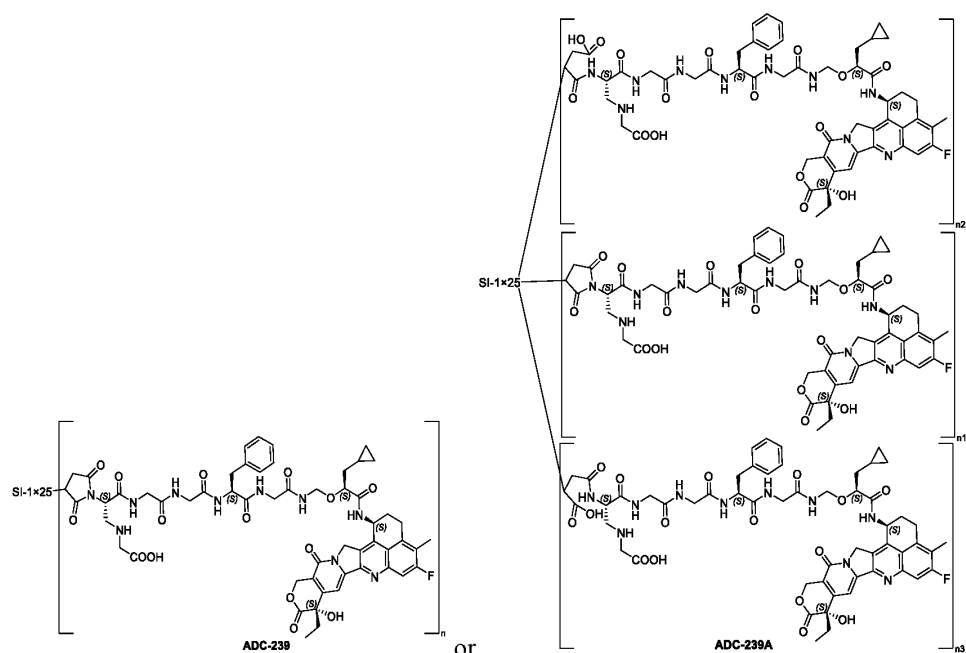
55. The method of Claim 1-15, wherein the ligand-camptothecin derivative conjugate of Formula I, or a pharmaceutically acceptable salt or solvent compound thereof, comprises the following structure, or a butanediimide ring-opening structure thereof, or an isomer thereof.









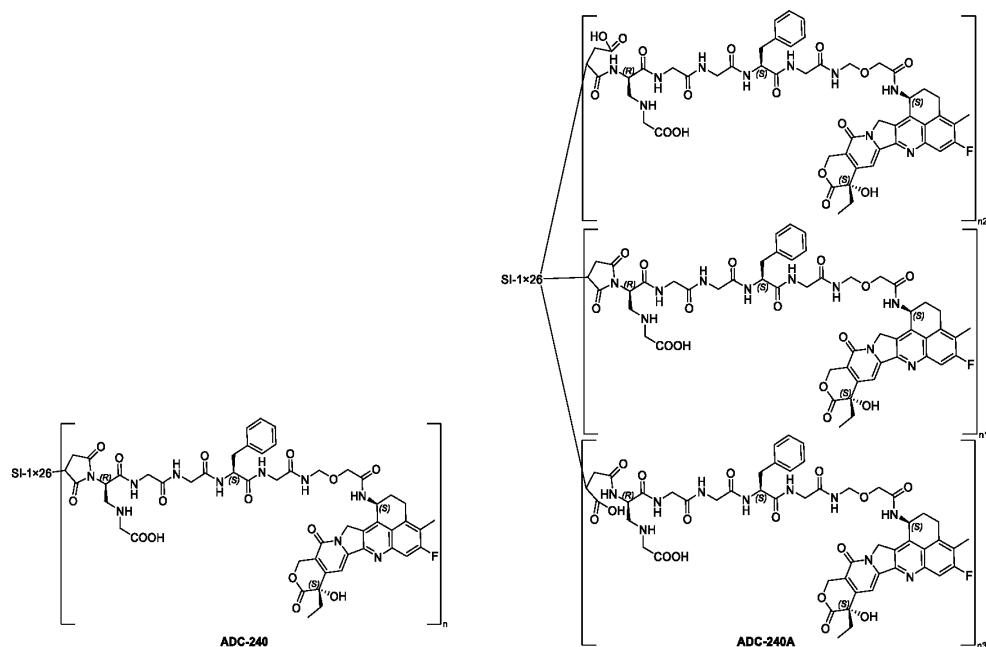


wherein:

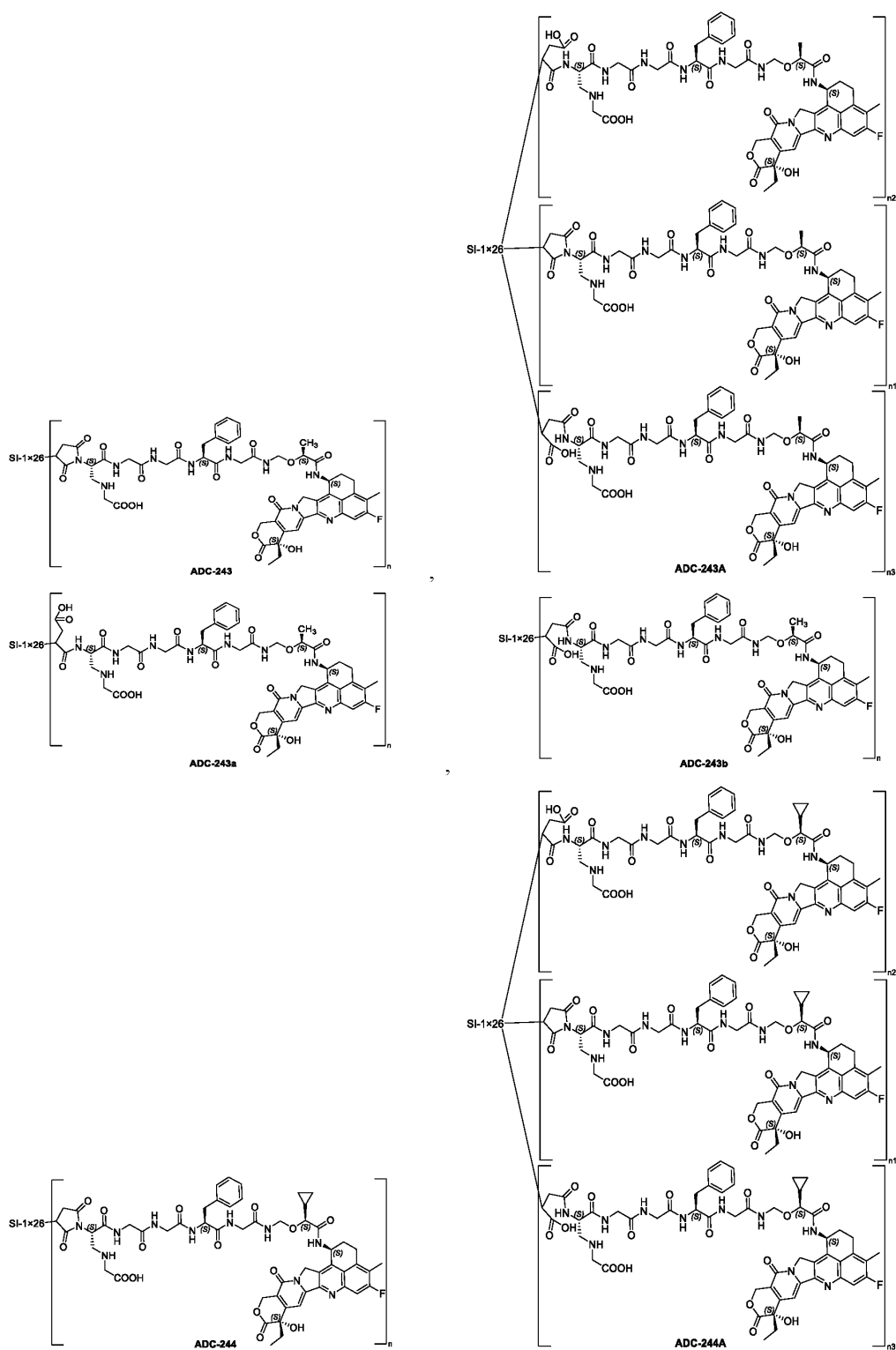
SI-1 x 25 is a bispecific antibody or antigen-binding fragment thereof having a binding specificity to both EGFR and HER3,

n is an integer of 1-10, wherein n1, n2, and n3 are each independently chosen from any integer or any decimal number from 0-10, n1, n2, and n3 are not simultaneously 0, and $1 \leq n1 + n2 + n3 \leq 10$.

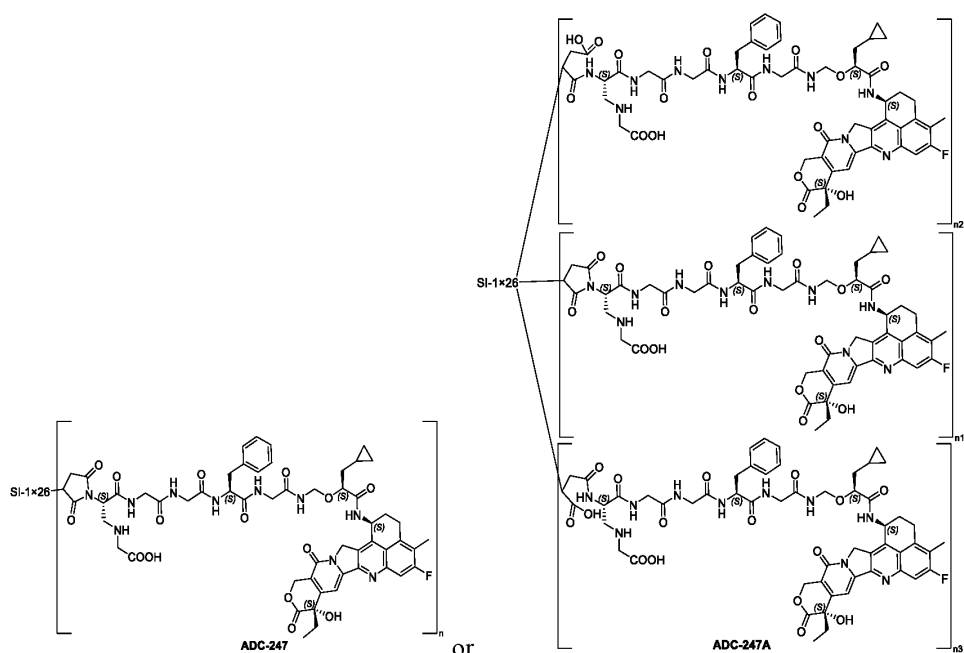
56. The method of Claim 1-15, wherein the ligand-camptothecin derivative conjugate of Formula I, or a pharmaceutically acceptable salt or solvent compound thereof, comprises the following structure, or a butanediimide ring-opening structure thereof, or an isomer thereof:











wherein:

SI-1 x 26 is a bispecific antibody or antigen-binding fragment thereof targeting having a binding specificity to both EGFR and HER3,

n is an integer of 1-10, wherein n_1 , n_2 , and n_3 are each independently chosen from any integer or any decimal number from 0-10, n_1 , n_2 , and n_3 are not simultaneously 0, and $1 \leq n_1 + n_2 + n_3 \leq 10$.

57. The method of Claim 1, wherein the pharmaceutically acceptable salt comprises a sodium, potassium, calcium, or magnesium salt formed with an acidic functional group in the structural formula, and acetate, trifluoroacetate, citrate, oxalate, oxalate, tartrate, malate, nitrate, chloride, bromide, iodide, sulphate, bisulfate, phosphate, lactate, oleate, ascorbate, salicylic acid, tartrate, malate, nitrate, chloride, bromide, iodide, sulfate, bisulfate, phosphate, lactate, oleate, ascorbate, salicylate, formate, glutamate, methanesulfonate, ethanesulfonate, benzenesulfonate, p-toluenesulfonate, or a combination thereof.

58. A pharmaceutical composition, comprising a lyophilized powder injection formula, wherein the lyophilized powder injection formula comprises the ligand-camptothecin derivative conjugate of Formula I, or a pharmaceutically acceptable salt or solvate thereof, of Claim 1 and a pharmaceutical carrier composition.

59. The pharmaceutical composition of Claim 58, wherein the lyophilized powder injection formula comprises the ligand-camptothecin conjugate of Formula I, or a pharmaceutically acceptable salt or solvate thereof, in an amount from about 10% to about 20% w/w, from about 12% to about 16% w/w, or from about 14% to about 15% w/w.

60. The pharmaceutical composition of Claim 58, wherein the pharmaceutical carrier composition comprises a buffer composition, an excipient, a preservative, an emulsifier, or a combination thereof.

61. A method for making the pharmaceutical composition of Claim 58, comprising combining the ligand-camptothecin derivative conjugate of Formula I, or a pharmaceutically acceptable salt or solvent thereof, of Claim 1 and a pharmaceutical carrier composition to provide a pharmaceutical mixture, and

lyophilizing the pharmaceutical mixture to provide the lyophilized powder injection formula.

62. The method of Claim 61, further comprising combining the lyophilized powder injection formula with water to provide an injection solution.

63. A treatment kit, comprising a first container and a package insert, wherein the first container comprises at least one dose of the pharmaceutical composition of Claim 58, and wherein the package insert comprises instructions for treating the subject using the pharmaceutical composition.

64. The treatment kit of Claim 63, further comprising a second container, wherein the second container comprises at least one dose of a second treatment composition, wherein the second treatment composition comprises a platinum-containing or platinum-free chemotherapeutic agent, an immune checkpoint inhibitor, an EGFR-TKI, or a combination thereof.

65. The treatment kit of Claim 63, wherein the instructions state that the treatment kit is intended for use in treating the subject having cancer or tumor that tests positive for EGFR, HER3 or both.

66. The treatment kit of Claim 63, wherein the instructions state that the treatment kit is intended for use in treating the subject having non-small cell lung cancer, small cell lung cancer, head and neck squamous carcinoma, nasopharyngeal cancer, breast cancer, bladder cancer, esophageal squamous cell carcinoma, or biliary tract carcinoma.